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Copper-Catalyzed Esterification of Alkylbenzenes with Cyclic Ethers and Cycloalkanes via C(sp^3)−H Activation Following Cross-Dehydrogenative Coupling

Saroj Kumar Rout,[†] Srimanta Guin,[†] Wajid Ali, Anupal Gogoi, and Bhisma K. Patel*

Department of Chemistry, Indian Institute of Technology Guwahati, North Guwahati 781039, India

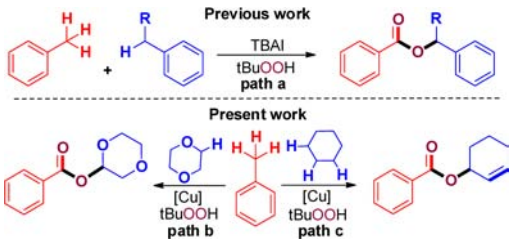
Supporting Information

ABSTRACT: A copper-catalyzed cross-dehydrogenative coupling strategy has been developed for the synthesis of two classes of esters from simple solvents. The reaction of methylarenes with cyclic ethers resulted in α-acyloxy ethers involving four sp^3 C−H cleavages, while treatment of methylarenes with cycloalkanes led to the formation of allyl esters at the expense of six consecutive sp^3 C−H bonds.

The direct C−H activation path has streamlined the synthesis of functionalized molecules by minimizing the number of synthetic steps, and the processes are more atom economic. One such strategy, cross-dehydrogenative coupling (CDC), has played a vital role by providing synthetic values to such methodologies.[1] The CDC protocols have been employed to access a diverse array of C−C and C−heteroatom bonds, by functionalizing C−H bonds of all types (sp, sp^2, sp^3).[2] The extreme reluctance of sp^3 C−H bonds to enter into the periphery of chemical reactions makes their selective functionalization a formidable challenge. The solutions to these problems have resulted in some appealing results on sp^3 C−H functionalizations.[1a,b] In a limited hemisphere of sp^3 C−H functionalizations via CDC, the alkylbenzenes are found to be useful precursors and have been used as ArCOO−, ArCO−, ArCH$_2$O−, and ArCH$_2$− surrogates;[3] most of which have ultimately led to the synthesis of esters.[3a−d]

Esters are important building blocks in organic synthesis, so the most revisited strategies are the ones where the installation of ester C−O bonds are via C−H activation.[3a−d,4] Hence, syntheses of different classes of esters by unconventional approaches are always appreciable, particularly through functionalizations of inert C−H bonds. In this regard, our group has developed a protocol for the synthesis of benzylic esters involving only alkylbenzene(s) as the self- or cross-coupling partners under metal-free conditions (path a, Scheme 1).[3a] The most remarkable outcome that has emerged out of this ester synthesis is the involvement of solvents (methylarenes) as substrates for sp^3 C−H functionalizations via CDC. In pursuit of utilizing this "solvent chemistry" in a CDC reaction, cyclic ether (1,4-dioxane) was attempted as the potential coupling partner with alkylbenzenes. Cyclic ethers are widely used as solvents and are also amenable to functionalizations at sp^3 C−H α to the ethereal oxygen.[5] A relatively weak bond dissociation energy of α sp^3 C−H helps generate a radical center under oxidative conditions, thereby allowing a radical/nucleophile to attack at that position.[1a,6] This leads to the question of how these two (alkylbenzene and cyclic ether) solvents cum reagents can behave as mutual cross-coupling partners under favorable conditions.

Scheme 1. Representative Examples of Ester Synthesis



To give a practical shape to the above-mentioned concept, toluene (**1**) and 1,4-dioxane (**a**) were allowed to react under conditions similar to the coupling between alkylbenzene(s).[3a] However, an attempt to achieve the desired cross coupling was not so fruitful as the reaction gave predominantly benzyl benzoate obtained by the self-coupling of toluene along with a trace (<10%) of the desired α-acyloxy ether (**1a**) (entry 1, Table S1, Supporting Information, SI). Hence, for the exclusive formation of α-acyloxy ether it was necessary to avoid the competing self-coupling of toluene by changing the reaction conditions. During the self-coupling of alkylbenzene, the use of Cu(II)/TBHP combination instead of metal-free conditions (Bu_4NI/TBHP) was unproductive. Interestingly, in the present case the use of Cu(II)/TBHP changed the course of reaction, giving the desired cross-coupled ester (**1a**) exclusively without any trace of benzyl benzoate (entry 2, Table S1, SI).

Existing methods to α-acyloxy ethers can be broadly classified into five main categories: (i) addition of a carboxylic acid to an alkenyl ether,[7] (ii) α-halo substitution of an ether with a carboxylic acid,[8] (iii) treatment of a hemiacetal with an acid or its derivatives,[9] (iv) CDC reaction between a carboxylic acid and an

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ether,[10] and (v) miscellaneous methods comprising of two-step synthesis.[11] The present method on synthesis of α-acyloxy ether with a higher degree of C−H activation (four sp^3 C−H cleavages) from solvents is unprecedented (path b, Scheme 1).

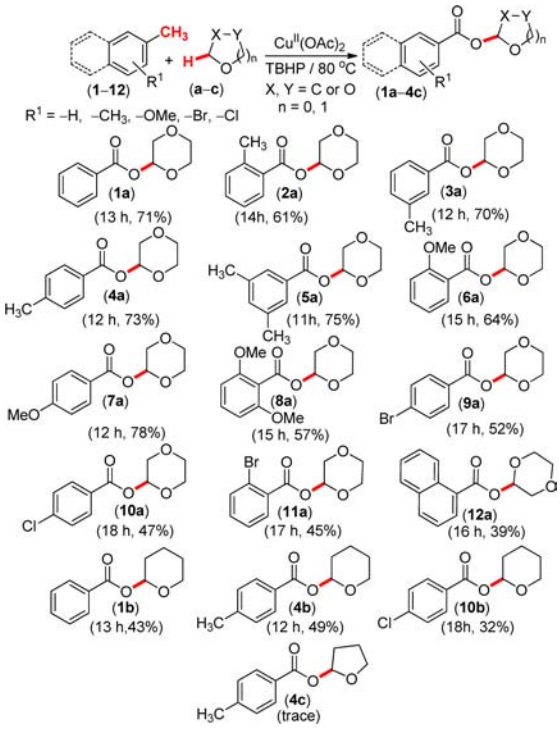
Inspired by this unique α-esterification of ether originating from solvent−solvent coupling, we examined other Cu catalysts in a quest to improve the yield (Table S1, SI). Among all other Cu(I) [CuBr, CuCl, and CuI] (Table S1, entries 3−5, SI) and Cu(II) [$CuBr_2$, $CuCl_2$, and $Cu(OTf)_2$] salts (Table S1, entries 6−8, SI) tested, $Cu(OAc)_2$ was found to be the best (Table S1, entry 2, SI). By increasing the $Cu(OAc)_2$ quantity from 10 to 20 mol %, the yield improved from 63% to 71% (Table S1, entry 9, SI). No significant improvement in the product yield was observed with 30 mol % of the catalyst (Table S1, entry 10, SI). Even when the oxidant quantity was increased from 6 to 7 equiv, the yield could not be enhanced further (Table S1, entry 11, SI). Unexpectedly the yield decreased when the reaction was performed at 100 °C instead of 80 °C (Table S1, entry 12, SI). The use of a decane solution of TBHP (5−6 M) (Table S1, entry 13, SI) was found to be slightly ineffective compared to its aqueous solution (70%). Control experiments suggest that a catalyst-oxidant combination is indeed essential to bring about the desired transformation (Table S1, entries 14 and 15, SI).

Having established the standard reaction conditions, the present oxidative esterification of cyclic ether were then implemented on cross couplings between 1,4-dioxane (**a**) and a series of substituted methylarenes. As can be seen in Scheme 2, the developed methodology was applicable to a diverse methylarenes irrespective of the nature of their substituents present. In particular, methylarenes possessing electron-donating groups such as *o*-Me (**2**), *m*-Me (**3**), *p*-Me (**4**), 3,5-diMe (**5**), *o*-OMe (**6**), *p*-OMe (**7**), and 2,6-diOMe (**8**) showed higher reactivities compared to methylarene (**1**), giving their respective α-acyloxy ethers (**2a**−**8a**) in moderate to good yields. Lower yields obtained for *o*-subtituted methylarenes (**2**, **6**, **8**) compared to their *p*- or *m*- analogues (**3**, **4**, **5**, **7**) could be attributed to steric hindrance imparted by the *ortho*-substitutents. The structure of α-acyloxy ether (**8a**) has been confirmed by single-crystal X-ray crystallography as shown in Figure S1 (SI). Note that for polymethylated benzenes (**2**−**5**) one of the −Me groups is functionalized, while the other −Me group(s) remains intact, consistent with the previous esterification processes with alkylbenzenes.[3a,c,d] The presence of electron-withdrawing groups in methylbenzenes such as *p*-Br (**9**) and *p*-Cl (**10**) lowered the yields of their corresponding α-acyloxy ethers (**9a**−**10a**). The yield dropped further when the electron-withdrawing substituent −Br (**11**) was present in the *ortho*-position, which is due to steric as well as electronic factors. The fused bicyclic methylarene viz. 1-methylnaphthalene (**12**) when coupled with **a** provided the desired α-acyloxy ether **12a** in a slightly lower yield.

The successful esterification of 1,4-dioxane (**a**) with various methylarenes led us to examine the feasibility of this approach with other cyclic ethers possessing a single oxygen, such as tetrahydropyran (**b**) and tetrahydrofuran (**c**). Unlike in dioxane (**a**), the oxidative esterifications of tetrahydropyran (**b**) with methylbenzenes (1, 4, and 10) were not so effective, giving α-acyloxy ethers **1b**, **4b**, and **10b** in modest yields. Five-membered cyclic ether tetrahydrofuran (**c**), when reacted with methylbenzene (**4**), gave a negligible amount of α-acyloxy ether **4c**. Lower yields were obtained when tetrahydropyran (**b**) was used instead of 1,4-dioxane (**a**) because in the former there are four equivalent sp^3 C−H's, whereas in the latter the chances are doubled due to the presence of eight equivalent C−H's. A substantial drop in the yield was observed when tetrahydrofuran (**c**) was used, which could be due to the above-mentioned statistical factor as well as the instability of the desired radical intermediate. Acyclic ethers such as dimethoxyethane (DME) was found to be completely inert under the reaction conditions when treated with **4**. In spite of the favorable statistical possibilities, the 18-crown-6 failed to undergo esterification, which may be due to steric crowding or its fluxional nature.

Now the question arises whether cycloalkane possessing no oxygen atom would serve as the coupling partner with alkylbenzenes? The inert cycloalkanes have previously been used as precursors for C−C[1a,b] and C−N[12] bond formations. Pertaining to C−O bond formation at cyclohexane, the Giff process[13] is well-known, although a direct construction of ester C−O bond is unexplored. To reveal the answer to these queries, toluene (**1**) and cyclohexane (**a′**) were reacted under the above optimized conditions. Unfortunately, other than the detection of benzaldehyde originating from **1** no desired coupling product was observed. However, when the reaction was performed at 120 °C formation of an allyl ester (**1a′**) was observed in a mere yield of 10%.[14] We envisaged the formation of an ester C−O bond at cyclohexane (**a′**) with PhCOO− derived from toluene, but the generation of an olefinic system and further formation of C−O bond at its allylic position leading to an allyl ester (**1a′**) is unprecedented (path c, Scheme 1). This process is taking place at the expense of six sp^3 C−H bond cleavages, three each from either of the coupling partners. The dehydrogenative olefination of cyclohexane to cyclohexene has been reported with various Pt, Ir, or Re catalysts.[15] Very recently, Perez et al. have observed dehydrogenative olefination of cyclohexane using hydrogen peroxide and a Cu complex.[16] Prior to this report, such allyl esters

Scheme 2. Substrate Scope of α-Acyloxy Ethers[a−c]



[a]Reaction conditions: **1**−**12** (5 mmol), **a**−**c** (2 mL), $Cu(OAc)_2$ (0.2 mmol), aq TBHP (6 mmol), 80 °C. [b]Isolated yield. [c]Catalyst and oxidant were for 1 mmol of substrates.

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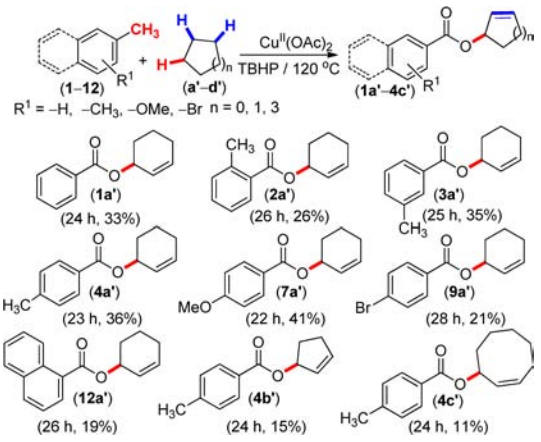
have been synthesized following the Kharasch−Sosnovsky reaction.[17] In the initial attempt, the yield of the allyl ester (**1a′**) obtained was quite low (10%); hence, rigorous optimizations were carried out to arrive at the best conditions leading to maximum possible yield. It was found that the use of $Cu(OAc)_2$ (20 mol %) and TBHP (5−6 M in decane) (8 equiv) at 120 °C gave an improved yield of 33%. Even with this level of optimizations the yield could not be improved beyond this. This is possibly because of the existence of these two solvents in their vapor phase, which limits their opportunity to react at the interface containing the catalyst and oxidant. To prevent the escape of vapors from the flask, a reaction was performed in a Teflon-lined stainless steel autoclave under otherwise similar conditions. Surprisingly, the strategy did not work, and benzaldehyde was the major product detected along with a trace (<5%) of **1a′**. Thus, it seems the poor yield obtained in this esterification is due to the intrinsic low reactivity of sp^3 C−H bonds in cyclohexane.

Proceeding further toward the substrate exploration, cyclohexane (**a′**) was reacted with various methylarenes possessing electron-donating and electron-withdrawing groups (Scheme 3).

Scheme 3. Substrate Scope of Allyl Esters[a,b,c]

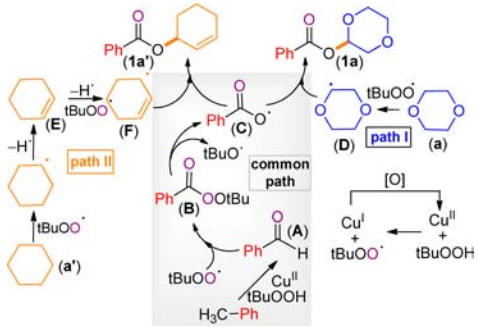


[a]Reaction conditions: **1**−**12** (2.5 mmol), **a′**−**c′** (4 mL), $Cu(OAc)_2$ (0.2 mmol), TBHP (5−6 M) (8 mmol), 120 °C. [b]Isolated yield. [c]Catalyst and oxidant were for 1 mmol of substrates.

For methylbenzenes possessing electron-donating substituents such as *o*-Me (**2**), *m*-Me (**3**), *p*-Me (**4**), and *p*-OMe (**7**), the yields of the corresponding allyl esters **2a′**−**7a′** ranged from 26% to 41%. The allyl ester (**9a′**) derived from methylbenzene, having a moderately electron-withdrawing substituent *p*-Br (**9**), was obtained in 21% yield. The electronic and steric factors in alkylbenzenes have a similar effect on the yields of allyl esters as was observed during synthesis of α-acyloxy ethers. Bicyclic methylarene such as 1-methylnaphthalene (**12**) upon coupling with **a′** afforded its allyl ester **12a′** in a poor yield of 19%. Other cycloalkanes viz. cyclopentane (**b′**) and cyclooctane (**c′**) when reacted with **4** gave their corresponding allyl esters **4b′** and **4c′**, however, in poor yields (Scheme 3). The lower yields obtained in five- and eight-membered cycloalkanes are in part due to instability of their radical and unfavorable strain of their corresponding cycloalkenes. To see if a regioselective esterification could be achieved, methylcyclohexane (**d′**) was reacted with **4**. ^1H and ^{13}C NMR analysis revealed the formation of at least three regioisomeric esters obtained in a combined yield of 30% (Scheme S1, SI).

Several control experiments were carried out to elucidate the mechanism of these solvent−solvent couplings. Analysis of the reaction mixture between **1** and **a** divulged the formation of benzaldehyde and benzoic acid, both of which could possibly couple with dioxane to give **1a**. To find the optimal coupling partner among aldehyde and acid, a control experiment was carried out where an equimolar mixture of *p*-methylbenzaldehyde and benzoic acid were reacted with dioxane **a** under identical reaction conditions (Scheme S2, SI). Exclusive formation of **4a** derived from aldehyde and no trace of **1a** (expected from benzoic acid) imply an aldehyde−dioxane coupling. To ascertain the radical nature of the reaction, **4** and **a** were reacted in the presence of radical scavenger 2,2,6,6-tetramethylpyridine *N*-oxide (TEMPO) under otherwise identical conditions. Along with the formation of traces (<10%) of (**4a**), a TEMPO ether (**H**) was isolated, confirming the formation of benzyl radical intermediate (Scheme S3, SI). The trapped benzyl radical (**H**) inhibits the formation of key coupling partner *p*-methylbenzaldehyde, thereby considerably lowering the yield. To determine the possible rate-limiting step in this reaction, an intermolecular competing kinetic isotope effect (KIE) was performed by reacting dioxane **a** with an equimolar mixture of toluene and toluene-d_8. A kinetic isotope effect ($K_H/K_D \sim 1$) ruled out the involvement of a benzylic C−H cleavage as the rate-determining step, thereby indicating dioxane C−H cleavage as the possible rate-limiting step as reported by the Pan group.[10e] The results of the above experiments indicate that esterification of cyclic ethers comprises the following steps. Toluene (**1**) gets converted to benzaldehyde (**A**) via radical oxidation in the presence of Cu/TBHP. The *tert*-butylperoxy radical generated from TBHP adds to benzaldehyde (**A**), providing *tert*-butyl benzoperoxate (**B**). Homolytic cleavage of peroxy species (**B**) affords benzoxy radical (**C**) along with *tert*-butoxyl radical. On the other hand, abstraction of α ethereal hydrogen from dioxane by *tert*-butylperoxy radical gives the radical intermediate (**D**). The radical coupling of **C** and **D** leads to the formation of ester **1a** (path I, Scheme 4). During the

Scheme 4. Proposed Mechanism for Esterification



generation of *tert*-butylperoxy radical from TBHP, Cu(II) gets reduced to Cu(I). Reoxidation of Cu(I) in the medium regenerates Cu(II) for further reaction (Scheme 4). The intermediacy of *tert*-butyl benzoperoxate (**B**) in this transformation has been supported by an independent experiment where the treatment of presynthesized **B** with dioxane **a** under similar reaction conditions afforded the α-acyloxy ether **1a**.

To gain insight into the mechanistic path for the allyl ester formation, various control experiments were again performed. The first query that arose was whether the dehydrogenative olefination of cyclohexane occurs first followed by the

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construction of an allylic ester C−O bond or a reverse sequence operates. To reveal the exact sequence, two independent reactions were performed. In the first reaction, toluene and cyclohexene (**E**) were reacted (Scheme S4, SI), while in the second a presynthesized cyclohexyl benzoate (**G**) was treated under the standard reaction conditions (Scheme S5, SI). The formation of allyl ester (**1a′**) in the former and failure in the latter suggests that dehydrogenative olefination precedes ester C−O bond formation. In another experiment, when **B** was reacted with cyclohexane, formation of **1a′** was observed, suggesting a Kharasch−Sosnovsky-type path. Details of this reaction sequence are depicted in path II, Scheme 4, having common intermediates **A**−**C** as that of path I.

In conclusion, the present protocol demonstrated a copper-catalyzed synthesis of two classes of esters from simple solvents. The combination of methylarenes and cyclic ethers resulted in the formation of α-esterification of ethers via four sp^3 C−H cleavages, while the combination of methylarenes and cycloalkanes led to the synthesis of allyl esters involving six consecutive sp^3 C−H bond cleavages.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details; spectral and analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: patel@iitg.ernet.in.

Author Contributions

†These authors contributed equally.

Notes

The authors declare no competing financial interest.

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