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Directing Group Assisted Copper-Catalyzed Chemoselective *O*-Aroylation of Phenols and Enols Using Alkylbenzenes

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ABSTRACT

By using alkylbenzenes as aroyl surrogates, copper(II) catalyzed chemoselective *O*-aroylations of 1,3-dicarbonyl compounds and phenolic −OH ortho to carbonyl (−CHO, −COR) groups have been achieved. A dual mechanism operating in tandem for these transformations has been supported by a crossover experiment.

Esterifications are traditionally achieved by reacting alcohols with carboxylic acids or its derivatives which often require auxiliary chemicals.[1] Besides the recently improved traditional esterification of alcohols,[2] the oxidative esterification of aldehydes[3] and carbonylation of hydrocarbons are some alternative approaches to ester synthesis.[4] Of late, the construction of C−C and C−X bonds via cross dehydrogenative couplings (CDC) is attractive because it does not require substrate prefunctionalizations and is atom economic.[5] The importance of C−O bonds in synthetic organic chemistry has resulted in the development of a variety of C−H bond functionalization methods mediated by various transition metals.[6] In this context the ester synthesis is in the vanguard. Recent synthesis of esters involve reactions of acids with cyclic

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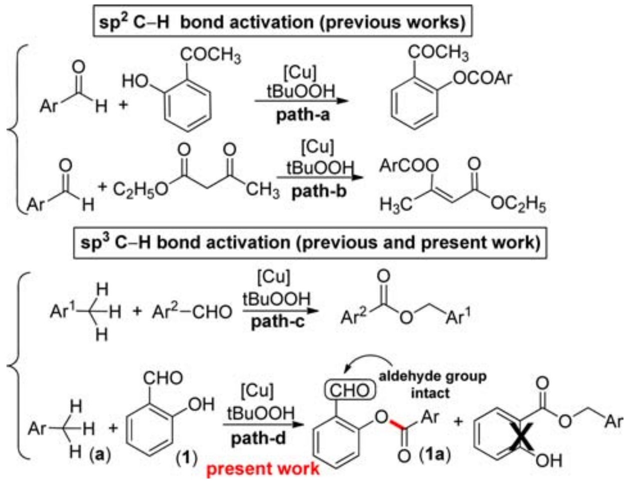
ethers where the C−O bond formation takes place at the sp^3 carbon atoms α to the ethereal oxygen.[7] Besides these a number of CDC based approaches employing metal catalysts such as Cu,[3k] Ru,[8] Rh,[9] Ir,[10] Pd,[11] and Fe[12] have been reported. Pushing the ester synthesis to an extreme limit of C−H activation we have developed a metal-free (Bu_4NI and TBHP) CDC approach for the synthesis of benzylic esters involving only alkylbenzene(s) as a self- or a cross-coupling partner(s).[13] Very specifically regarding the substrate directed coupling for the synthesis of esters via *O*-aroylation processes, there are only two reports where 2-acetylphenols and *β*-dicarbonyl derivatives or their analogs have undergone directed *O*-aroylation using aldehydes as the coupling partners (Scheme 1, path a and b).[3d,14]

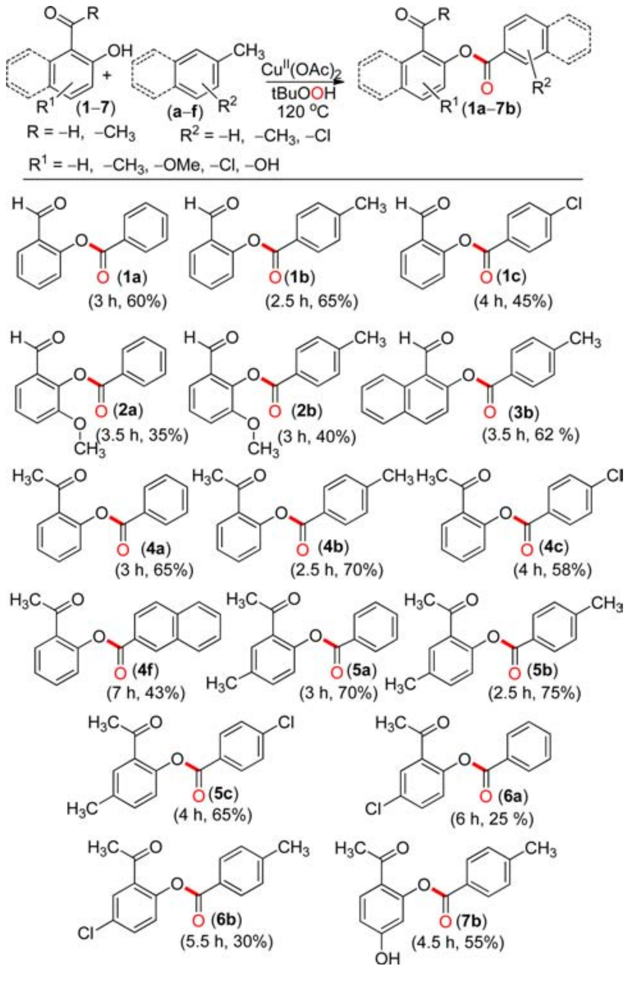
Scheme 1. CDC Protocols for C−O Bond Formation via C−H Activations



Alkylbenzenes have been excellent aroyl surrogates[15] and are the best alternatives to Friedel−Crafts aroylations. Benzylic esters are obtained by the CDC coupling of aldehydes and alkylbenzenes using the Cu(II) catalyst (Scheme 1, path c).[3k] Under similar conditions 2-hydroxyacetophenones gave phenol esters (Scheme 1, path a).[14] Thus it would be interesting to see if salicaldehyde (**1**) possessing both phenolic −OH and aldehydic functionalities when treated with an alkylbenzene would give benzylic ester (Scheme 1, path c)[3k] or a phenol ester (Scheme 1, path a).[14] Phenolic ester (Scheme 1, path a) is indeed obtained whether the aldehydic function would survive the oxidative conditions or not.

With the above possibilities in mind under the identical reaction conditions,[3k] when salicaldehyde (**1**) was treated with toluene (**a**) the product isolated (35%) was found to be a phenolic ester (**1a**) with the aldehydic group remaining intact. This is the first observation of its kind where alkylbenzene serves as an aroyl source in the *O*-aroylation of the −OH group for a substrate possessing an ortho −CHO

Scheme 2. Substrate Scope for the Synthesis of Esters[a,b]



[a] Reaction conditions: phenols (**1**−**7**) (1 mmol), alkylbenzenes (**a**−**c**) (5 mmol), $Cu(OAc)_2 \cdot 2H_2O$ (0.2 mmol), TBHP (2 mmol), 120 °C, time 3−7 h. [b] Reactions were monitored by TLC. Confirmed by spectroscopic analysis. Yield of isolated pure product reported.

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group. Yet, under the identical conditions phenol failed to give any trace of ester, confirming the need for the ortho carbonyl (−CHO) functionality for this esterification.

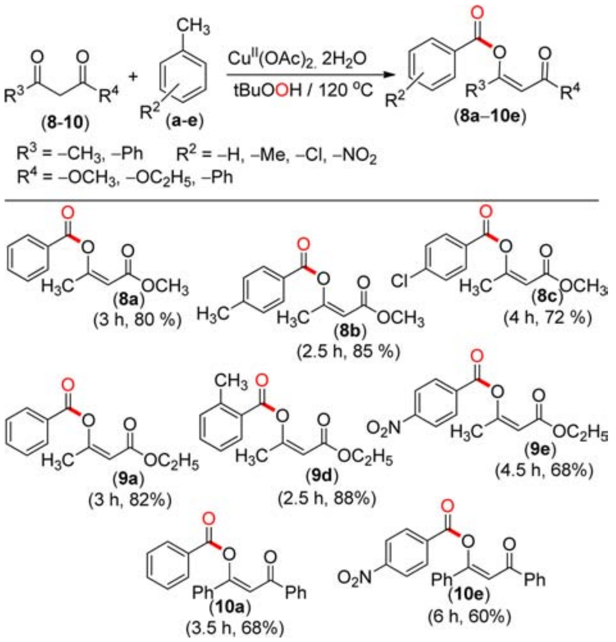
Encouraged by this unprecedented result, further optimizations were carried out to achieve a better yield of the product (**1a**). Details of optimizations are shown in Table S1 (see Supporting Information [SI]). Substrate salicaldehyde (**1**) (1 equiv), toluene (5 equiv), catalyst $Cu(OAc)_2 \cdot 2H_2O$ (20 mol %), and oxidant TBHP in decane (5−6 M) (2 equiv) at a temperature of 120 °C gave the best possible yield after 3 h (Table S1, SI). These optimized conditions were used for all other reactions.

Further reactions were investigated with a set of substituted alkylbenzenes and phenols possessing an ortho −CHO group. The reaction of *p*-xylene (**b**) with 2-hydroxybenzaldehyde (**1**) gave a moderate yield of its mono *O*-aroylated product (**1b**) without affecting the other methyl group (Scheme 2). The structure of the product (**1b**) has been unequivocally confirmed by crystal X-ray crystallography as shown in Figure S1 (see SI). The survival of the aldehydic group and retention of one of the aryl $-CH_3$ groups in the product (**1b**) can be clearly seen in Figure S1. The reaction of *p*-chlorotoluene (**c**) possessing an electron-withdrawing group (−Cl) with **1** proceeded slowly giving product **1c** in 45% yield. This suggests a significant electronic effect on the rates of the reactions and hence on the product yields (Scheme 2). Next a sterically hindered phenol, 2-hydroxy-3-methoxybenzaldehyde (**2**), was reacted with toluene (**a**) and *p*-xylene (**b**), and the reaction provided their *O*-aroylated products, **2a** and **2b**, respectively but in lower yields (Scheme 2). The lesser yields of **2a** and **2b** could be attributed to the steric factor imparted by the adjacent methoxy group in **2**. The naphthoic hyrdoxyl group possessing an aldehydic functionality in its adjacent position as in the case of 2-hydroxy-1-naphthaldehyde (**3**) coupled efficiently with *p*-xylene (**b**) giving *O*-aroylated product **3b** in a modest yield (Scheme 2).

The use of acid as a directing group as in the case of salicylic acid failed to give phenol ester suggesting the poor directing ability of the −COOH group compared to the −CHO group. While the carboxylic group in salicylic acid failed to act as a directing group in providing phenol ester, the aldehydic functionality in *o*-hydroxy aldehydes served as an efficient directing group during the *O*-aroylation process. So the obvious query arises whether the o-$COCH_3$ group can serve as the directing group in this process. The reaction of 2-hydroxyacetophenone (**4**) with a set of methylarenes viz. toluene (**a**), *p*-xylene (**b**), and *p*-chlorotoluene (**c**) gave moderate yields of their respective *O*-aroylated products, **4a**, **4b**, and **4c** (Scheme 2). Besides alkylbenzenes, 2-methylnaphthalene (**f**) could also be employed as an aroyl source in the *O*-aroylation reaction with **4** giving corresponding product **4f** in modest yield (Scheme 2).

The product yields obtained from substrate **4** are better compared to those obtained using substrate **1** which is probably due to the better stability of the acetyl group in **4** under the oxidative conditions compared to the aldehydic functionality in **1** (Scheme 2). The substituent effects present in the aryl ring of 2-hydroxyacetophenone were next investigated. The presence of electron-donating substituents as in the case of 2-hydroxy-5-methylacetophenone (**5**) underwent facile reactions with toluene (**a**), *p*-xylene (**b**), and *p*-chlorotoluene (**c**) giving good to moderate yields of their corresponding *O*-aroylated products, **5a**, **5b**, and **5c** (Scheme 2). However, a substrate possessing an electron-withdrawing group (−Cl) as in the case of 5-chloro-2-hydroxyacetophenone (**6**) coupled with toluene (**a**) and *p*-xylene (**b**) sluggishly provided poorer yields for products **6a** and **6b** respectively. Due to the presence of $-COCH_3$ as the directing group in 2,4-dihydroxyacetophenone (**7**), the *o*-hydroxyl group is selectively aroylated without affecting the *p*-hydroxyl group. Because of the electron-donating ability of the *p*-hydroxyl group the yield of the product **7b** obtained was better compared to the analogous substrate (**6**) possessing an electron-withdrawing group (−Cl) giving product **6b**. Thus it is evident that the presence of electron-donating groups in either of the aryl rings (*o*-hydroxy carbonyl compounds and alkylbenzenes) gives better yields while the presence of electron-withdrawing groups result in inferior yields. However, alkyl heteroaryls such as 2-methylpyridine, 3-methylpyridine, and 2-methylimidazole did not serve as aroyl surrogates in *O*-aroylation reactions.

Scheme 3. Substrate Scope for the Synthesis Enolesters[a,b]



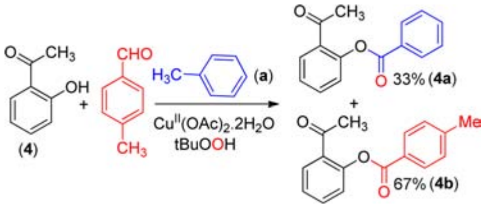
[a] Reaction conditions: 1,3-dicarbonyl (**8**−**10**) (1 mmol), alkylbenzenes (**a**−**e**) (5 mmol), $Cu(OAc)_2 \cdot 2H_2O$ (0.2 mmol), TBHP (2 mmol), 120 °C, time 3−5 h. [b] Reactions were monitored by TLC. Confirmed by spectroscopic analysis. Yield of isolated pure product reported.

o-Hydroxyl carbonyl compounds and the (*Z*)-enol form of 1,3-dicarbonyl compounds have structural analogy so far as the orientation and positioning of carbonyl and hydroxyl groups are concerned. To unravel the potentiality of this approach various 1,3-dicabonyl substrates were reacted with different alkylbenzenes. β-Carbonyl compounds, methylacetoacetate (**8**) when treated with toluene (**a**), *p*-xylene (**b**), and *p*-chlorotoluene (**c**), all gave their enol esters **8a**, **8b**, and **8c** respectively in good yields (Scheme 3). It may be mentioned here that β-carbonyl compounds and C−H bonds adjacent to heteroatoms usually form an $(sp^3)C{-}(sp^3)C$ bond rather than $(sp^3)C{-}O$ bond under various metal catalyzed conditions.[5a,b] Apparently there are few reports on $(sp^3)C{-}O$ bond formations involving β-carbonyl compounds resulting in enol ethers,[16] enol carbamates,[14] and even enol esters.[3d] Moving further, with this strategy other 1,3-dicarbonyl compounds such as ethylacetoacetate (**9**) under the optimized conditions underwent cross dehydrogenative coupling with toluene (**a**), *o*-xylene (**d**), and *p*-nitrotoluene (**e**) giving enol esters **9a**, **9d**, and **9e** respectively in good yields. Alkylbenzenes possessing electron-withdrawing groups gave lesser yields of products compared to those having electron-donating groups, an observation consistent with the results in Scheme 2. Finally, 1,3-diphenyl-1,3-dione (**10**) formed enol esters **10a** and **10e** in modest yields when treated with toluene (**a**) and *p*-nitrotoluene (**e**) (Scheme 3). All these reactions provided highly stereoselective (*Z*)-enol esters with no loss in stereoselectivity (Scheme 3).

From the observations of the control experiments that were performed, a dual mechanism operating in tandem has been proposed for these reactions. The presence of a radical quencher (TEMPO) retards the CDC reaction between 2-hydroxyacetophenone (**4**) and toluene (**a**) giving a $< 10\%$ yield of the product indicating the radical nature of the mechanism. The reagent TBHP is capable of serving as both an oxidant and a radical initiator in these transformations. A large kinetic isotope effect ($K_H/K_D \sim 7.8$) was observed when the reaction of deuterated toluene (d_8 toluene) was carried out with 2-hydroxyacetophenone (**4**) suggesting that benzylic C−H bond cleavage to be the rate-determining step. Based on these observations, two possible mechanisms can be envisaged. The first one possibly involves the radical coupling of the benzylic radical and the phenolic −OH via the Cu complexes **I** and **II** to form *O*-benzylated intermediate **III** as depicted in Scheme S1 (see SI). The *O*-benzylic position of **III** perhaps undergoes oxidation to give corresponding phenol ester (**4a**) as shown in Scheme S1. In an alternative mechanism, the radical coupling of the *in situ* generated benzaldehyde (from toluene) with phenolic O−H cannot be ruled out as shown in Scheme S2 (see SI). Further, the possibility of both mechanisms operating in tandem cannot be ignored.

To ascertain the exact nature of the mechanism, a crossover experiment was performed in which an equimolar mixture of 2-hydroxyacetophenone (**4**), *p*-methylbenzaldehyde, and toluene (**a**) were reacted under the present experimental conditions (Scheme 4). Interestingly, products **4a** and **4b** were formed in the ratio 1:2. This experiment supports the dual nature of the mechanism: one involving the benzyl radical path,[17] and the other, the aroyl radical (Schemes S1 and S2; see SI). Had the reaction proceeded only via the aroyl radical path (Scheme S2), then the product (**4b**) derived from activated aldehyde *p*-methylbenzaldehyde could have been the sole product. The ratio of the product obtained suggests that the reaction proceeded faster with preformed aldehyde (Scheme S2; see SI) than by the benzyl radical insertion path (Scheme S1; see SI). In further support of the mechanism in Scheme S1, when the presynthesized benzyl ether (**III**) was subjected to the present reaction conditions it gave the expected product (**4a**) (Scheme S3; see SI). However, the intermediate (**III**) could not be detected during the GC-MS analysis of the reaction mixture which is possibly due to its rapid oxidation to the phenol ester (**4a**). Detection of traces of benzaldehyde and benzylalcohol by GC-MS analysis of the reaction between **4a** and toluene (**a**) originating possibly via the radical oxidation of toluene supports mechanism S2 (see SI). All other steps and proposed intermediates in Schemes S1 and S2 are similar to the one proposed by Li et al.[3d]

Scheme 4. A Crossover Experiment



In conclusion, a new, efficient Cu-catalyzed directed *O*-aroylation process (esterification) has been accomplished between alkylbenzenes and *o*-carbonylphenols and β-dicarbonyl compounds using TBHP as the oxidant. A dual mechanism operates in tandem for these transformations. This protocol simultaneously installs two C−O bonds at the expense of three benzylic sp^3 C−H bonds. The phenolic group is selectively aroylated (esterified) even in the presence of aldehydic functionality.

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Supporting Information Available. General information, experimental procedures, spectral data, and copies of ^1H and ^{13}C NMR spectra for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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