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Four Tandem C–H Activations: A Sequential C–C and C–O Bond Making via a Pd-Catalyzed Cross Dehydrogenative Coupling (CDC) Approach

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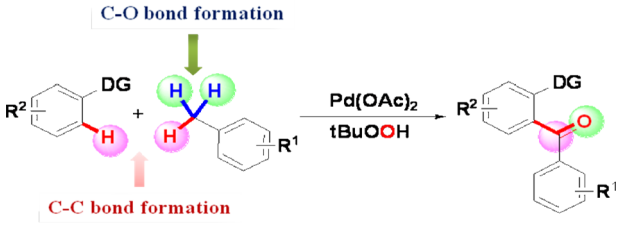
ABSTRACT



An unprecedented aroylation at the *ortho* C–H bond with respect to a directing group has been accomplished via a Pd(II)-catalyzed cross dehydrogenative coupling approach using alkylbenzene as the synthetic equivalent of an aroyl moiety. The reaction proceeds through sequential C–C and C–O bond making at the expense of four consecutive C–H bond cleavages (three sp^3 benzylic C–H's and one sp^2 arene C–H) to selectively install an aroyl functionality at the proximal site of substrates containing various directing groups.

The modern era of organic chemistry has brought about many appealing results pertaining to transition-metal-catalyzed C–H bond activations with subsequent functionalizations.[1] Foundations to most C–H activation processes generally rely on the strategies of directing group assisted C–H bond functionalization[2] and cross dehydrogenative coupling (CDC).[3] These two techniques are highly appreciable due to being atom and step economic. Pertinent to these seminal achievements, protocols for the direct conversion of C–H bonds to C–C bonds stand out to be the key pillar in providing a great impetus to modern synthetic chemistry, as C–C bond formation is regarded as the "holey grail" of organic chemistry.[4] Oxidative C–H bond functionalizations have been successfully applied to construct C–C bonds involving sp, sp^2, or sp^3 hybridized carbons as mutual cross-coupling partners.[5]

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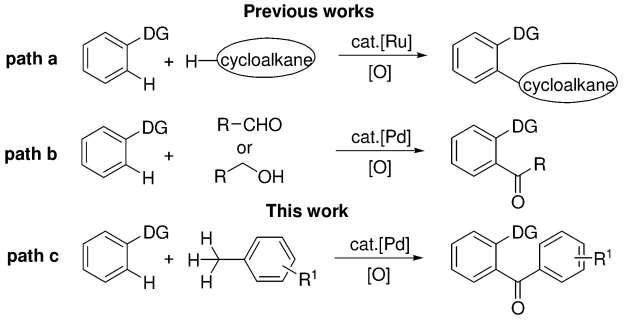
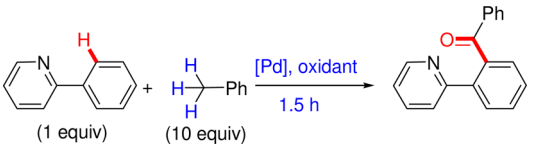
Despite the significant progress made in this area the more challenging arene−alkane couplings remain scarce which is due to the inertness of sp^3 C−H bonds;[6] thus much of it is yet to be explored. Very specifically pertaining to the substrate directed arene−alkane coupling there is only a single precedence where 2-phenylpyridine or analogous substrates have undergone direct C−H alkylation using unreactive cycloalkane as the other coupling partner (path a, Scheme 1).[6a] However, the susceptibility of benzylic C−H bonds toward radical promoted functionalizations by a single electron transfer (SET) have led to them being the subject of further exploration.[7]

Scheme 1. CDC Approaches for C−C Bond Forming Reactions via C−H Bond Cleavage



In light of the above-mentioned, an initial foray was intended toward C−H benzylation using 2-phenylpyridine (**1**) (1 equiv) and toluene (**a**) (10 equiv) as the prototypical substrates using $Pd(OAc)_2$ (5 mol %) and TBHP in decane (5−6 M) (1 equiv). Interestingly, the reaction of the aforementioned combinations at 120 °C resulted in an unprecedented formation of phenyl(2-(pyridine-2-yl)phenyl)-methanone (**1a**), an aroylated product (53%) instead of the expected benzylated product (Table 1, entry 1). Thus, toluene could be perceived as a new synthetic equivalent or surrogate of the benzoyl functionality. In this case, incorporating a benzoyl functionality at the proximal site is at the expense of four consecutive C−H bond (three sp^3 benzylic C−H bonds and one sp^2 arene C−H bond) cleavages. Prior to this report, the directed C−H *ortho*-acylation has been accomplished via two distinct approaches with substrates possessing various N and O donor atoms. The first invokes a CDC approach[8] that uses aldehydes or alcohols as the acylating equivalent (path b, Scheme 1) while the second strategy proceeds through a substrate-directed decarboxylation of α-keto carboxylic acids.[9] However, the present protocol (path c, Scheme 1) demonstrates an unprecedented arene−alkane coupling (C−C bond formation) with a subsequent C−O bond formation via four tandem C−H bond activations to selectively install an aroyl moiety at the proximal site of directing group containing substrates.

Table 1. Screening of Reaction Conditions



entry	catalyst (mol %)	oxidant	temp (°C)	yield (%)[a,b]
1	$Pd(OAc)_2$ (5)	TBHP[c,f]	120	53
2	$Pd(TFA)_2$ (5)	TBHP[c,f]	120	15
3	$PdCl_2$ (5)	TBHP[c,f]	120	30
4	$PdBr_2$ (5)	TBHP[c,f]	120	42
5	$Pd(OAc)_2$ (10)	TBHP[c,f]	120	73
6	**$Pd(OAc)_2$ (10)**	**TBHP[c,g]**	**120**	**85**
7	$Pd(OAc)_2$ (10)	TBHP[d,g]	120	20
8	$Pd(OAc)_2$ (10)	H_2O_2[e,g]	120	00
9	$Pd(OAc)_2$ (10)	TBHP[c,g]	100	77
10	$Pd(OAc)_2$ (10)	Nil	120	00
11	nil	TBHP[c]	120	00

[a] Isolated yield. [b] Reaction time: 1.5 h. [c] Decane solution (5−6 M). [d] 70% aqueous solution. [e] 30% aqueous solution. [f] 1 equiv. [g] 2 equiv.

Further optimizations were carried out by varying the reaction parameters in a quest to improve the overall yield. Other potential Pd catalysts such as $Pd(TFA)_2$, $PdCl_2$, and $PdBr_2$ were evaluated (Table 1, entries 2−4), and $Pd(OAc)_2$ was the most effective catalyst giving superior results (Table 1, entry 1). The use of $Pd(TFA)_2$ gave poor conversion (15%) along with the formation of multitudes of side products (Table 1, entry 2). Although the reactions with $PdCl_2$ and $PdBr_2$ (Table 1, entries 3−4) were clean and smooth, the yields were modest as compared to that for $Pd(OAc)_2$ (Table 1, entry 1). An increase in the catalyst loading to 10 mol % and in the TBHP quantity by 2-fold provided substantial improvement in the isolated yield (85%) (Table 1, entry 6). The nature of peroxides and their medium of storage had a marked influence on the product yield. For instance the use of either aqueous TBHP or aqueous H_2O_2 as the oxidants proved to be ineffective (Table 1, entries 7−8). A decrease in the reaction temperature (100 °C) reduced the product yield to 77% (Table 1, entry 9). Control experiments carried out in the absence of either $Pd(OAc)_2$ or TBHP failed to give the desired product (Table 1, entries 10−11) suggesting the

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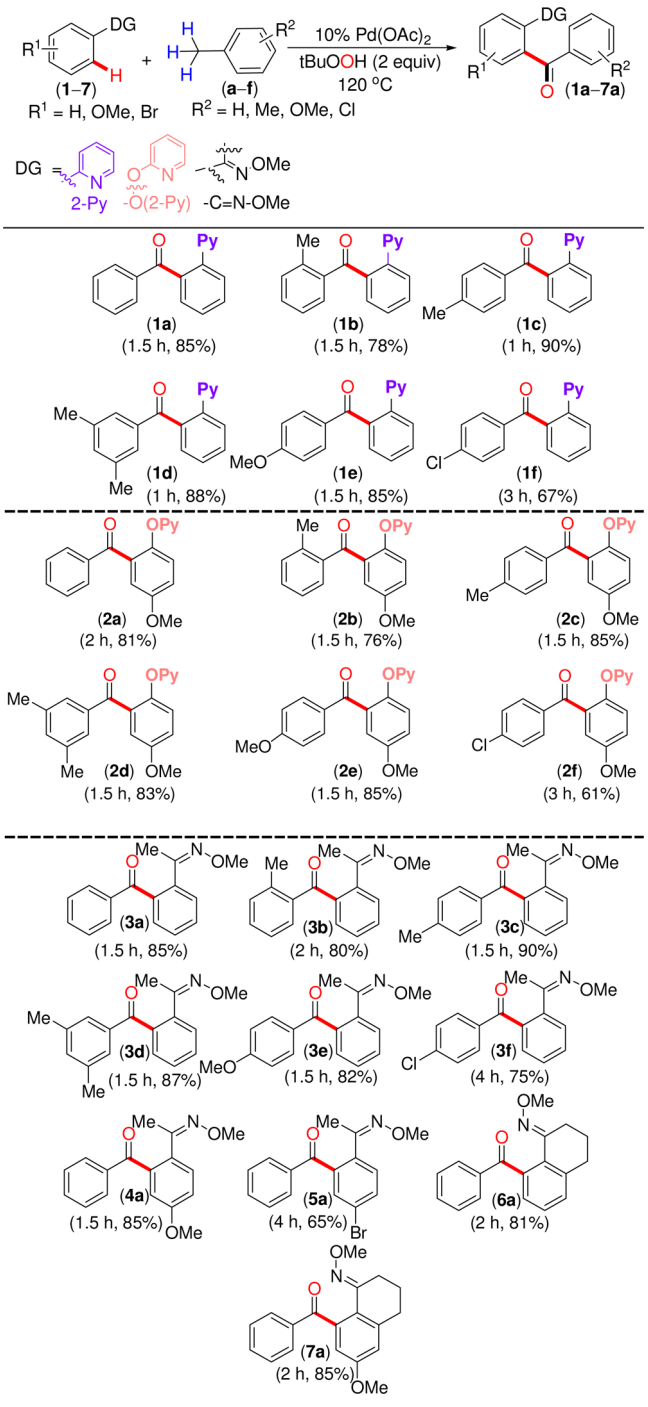
Scheme 2. Substrate Scope for the Synthesis of Ketone via C−H Functionalization[a]



[a] Reaction conditions: arenes (**1**−**7**) (1 mmol), methylbenzenes (**a**−**f**) (10 mmol), $Pd(OAc)_2$ (0.1 mmol), TBHP in decane (5−6 M) (2 mmol), 120 °C, time 1−4 h. Reactions were monitored by TLC. Confirmed by spectroscopic analysis. Yield of isolated pure product reported.

requirement of both the metal catalyst and the oxidant. Solvent optimizations were not carried out as the methylarenes used were liquids which served both the purpose of reactants and the reaction medium for these oxidative aroylations. The results for various trial reactions are summarized in Table 1.

Encouraged by this unique arene−alkane coupling, the optimized conditions were implemented in the coupling reactions between a set of substituted alkylbenzenes with arenes possessing directing groups such as 2-pyridyl, 2-oxopyridyl, and ketoxime ether (Scheme 2). The initial investigations were focused on the reactions of 2-phenylpyridine (**1**) with polymethylated benzenes, viz. *o*-xylene (**b**), *p*-xylene (**c**), and mesitylene (**d**). All these coupling reactions proceeded smoothly providing their respective *ortho*-aroylated products (**1b**−**1d**) in excellent yields. The lesser yield observed in the case of *o*-xylene compared to its para (**c**) or meta (**d**) analogues is possibly due to the steric hindrance of the *ortho* methyl group in *o*-xylene (**b**). The main features of these reactions were the exclusive formation of monoaroylated products, with the other methyl group(s) remaining intact. The reaction with *p*-methoxytoluene (**e**) afforded the expected product (**1e**) in an excellent yield. However, when *p*-chlorotoluene (**f**) was used as the coupling partner the product (**1f**) yield dropped considerably (67%). These results imply that the electronic effects of the substituents in the methylarenes affect the reaction rates and the product yields. Substituted toluenes possessing electron-donating groups undergo more facile coupling with arenes than the substrate having an electron-withdrawing group. Furthermore, the same optimized reaction conditions were equally applicable to the 2-aryloxypyridine substrate, such as 2-(4-methoxyphenoxy)-pyridine (**2**) possessing an additional *O*-linker between the pyridyl and the aryl ring. The reaction of 2-(4-methoxyphenoxy)pyridine (**2**) with the same set of methylarenes gave moderate to high yields of their respective monoaroylated products (**2a**−**2e**). Herein, a similar trend in reactivity and selectivity were observed for methylarenes when coupled with 2-(4-methoxyphenoxy)pyridine (**2**) as was the case with substrate 2-phenylpyridine (**1**).

So far as the *ortho*-aroylation is concerned, the aryl ketone oxime ethers as the substrates have significant prospects. The 1,2-diacylarenes generated upon deprotection of oxime ether are useful precursors to a number of biologically important scaffolds such as isoindoles, isoquinolines, *N*-arylpthalimidines, and pthalazines.[10] Thus, a similar aroylation reaction was attempted with the acetophenone *O*-methyl oxime (**3**) and toluene (**a**) employing the above optimized conditions. Encouragingly, the reaction provided an excellent yield of the *o*-aroylated product (**3a**). Subsequent reactions were carried out with acetophenone *O*-methyl oxime (**3**) and other methylarenes as the coupling partners. The yields of coupled products were relatively higher (**3b**−**3e**) with *p*-chlorotoluene being the lone exception giving a modest yield of the product (**3f**). The effects of substituents present in the acetophenone *O*-methyl oxime were investigated. *p*-Methoxyacetophenone *O*-methyl oxime (**4**) underwent a facile aroylation with toluene affording a high yield of the desired product (**4a**). However with *p*-bromoacetophenone *O*-methyl oxime (**5**), the product (**5a**) yield was moderate. The *O*-methyl oxime of bicyclic ketones, viz. α-tetralone analogues (**6**−**7**),

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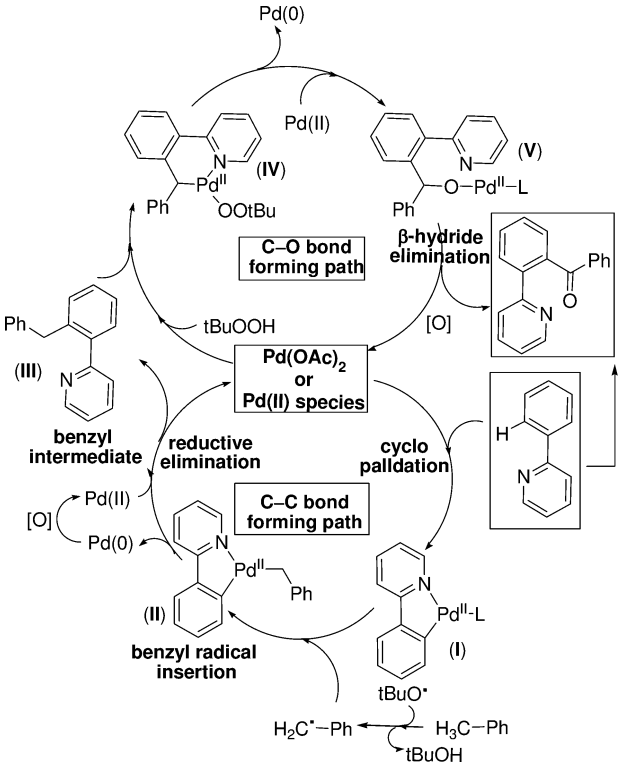
underwent smooth reactions with toluene furnishing their corresponding aryl ketones (**6a**−**7a**) in excellent yields.

Scheme 3. Proposed Mechanism for *o*-Aroylation via Sequential C−C and C−O Bond Formation



The mechanism for these reactions can be depicted in keeping with the observations of the control reactions that were conducted. There was a considerable quenching of the reaction between 2-phenylpyridine (**1**) and toluene (**a**) in the presence of radical scavenger TEMPO giving $< 5\%$ yield of the expected product (**1a**), suggesting a possible radical pathway. This observation indicates that TBHP is possibly playing the role of both an oxidant and a radical initiator. However, a GC-MS analysis of the aliquots taken during an ongoing reaction of **1** with toluene (**a**) showed no presence of either benzaldehyde or benzyl alcohol in the reaction medium that could possibly form via a radical oxidation of toluene (**a**). From these observations and literature reports, a plausible mechanism has been proposed (Scheme 3).[6a,11] Presumably, TBHP generates a radical at the benzylic carbon that undergoes addition to the Pd−substrate complex (**I**) to form the intermediate (**II**).

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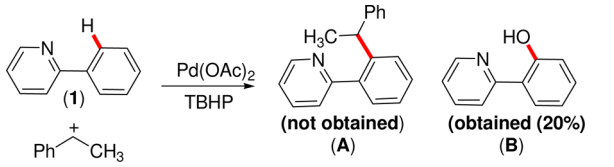
Scheme 4. CDC Approaches for C−C Bond Forming Reactions via C−H Bond Cleavage



Reductive elimination of the Pd catalyst from **II** affords the benzylic product (**III**) which further undergoes rapid oxidation at its benzylic position to generate the keto functionality (**1a**) via intermediates **IV** and **V**.[11h] All our attempts to trap the benzylated product failed due to the fast oxidation kinetics. The benzylic C−H bond cleavage or insertion of the benzyl radical might be involved in the rate-determining step. This fact can be further rationalized from the observations that the reactions worked better with methylarenes possessing electron-donating groups compared to those having electron-withdrawing substituents. In an attempt to isolate the benzylated intermediate and prevent further oxidation, **1** was reacted with ethylarenes (ethylbenzene) instead of methylarenes under the standard conditions (Scheme 4). However, the reaction yielded an *o*-hydroxylated product (**B**) instead of the expected benzylated product (**A**) leaving a major amount of unreacted starting material (**1**) even after 24 h (Scheme 4). Since the mechanistic picture is currently unclear, the usual acylation mechanism proceeding via the *in situ* formation of benzaldehyde or benzyl alcohol cannot be completely ruled out.[8]

In conclusion, an aroylation protocol at the *ortho* C−H bond has been accomplished via sequential C−C/C−O bond formations involving four C−H bond activations. This is the first illustration of an arene−alkane coupling giving an *o*-aroylated product involving activations of a nonreactive benzylic sp^3 C−H of methylarenes and sp^2 C−H bonds of arenes facilitated by the directing groups. With polymethylated arenes, selective monoaroylated products were formed without affecting the other methyl groups. Hence by judging the practicality of the present protocol, it can be an additional alternative to the existing acylation reactions.

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Supporting Information Available. General information, experimental procedures, spectral data, and copies of ^{1}H 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.