Pd(II)-Catalyzed Direct *ortho*-C–H Acylation of Aromatic Ketones by Oxidative Decarboxylation of α-Oxocarboxylic Acids

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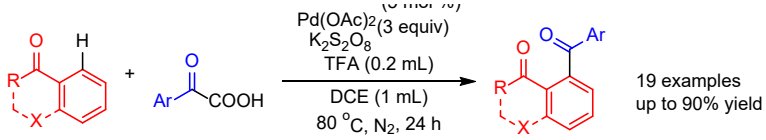
Supporting Information Placeholder



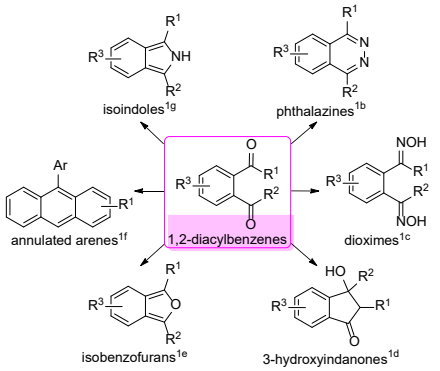
ABSTRACT: A Pd-catalyzed decarboxylative acylation of aromatic ketones with α-oxocarboxylic acids was developed, and 1,2-diacylbenzenes were formed in up to 90% yield with excellent *ortho*-selectivity. This work demonstrates the first successful attempt to direct C–H acylation of aromatic ketones without the need for pre-derivatization to imines. The acylation reaction was inhibited by radical scavengers such as TEMPO, and 2,2,6,6-tetramethylpiperidin-1-yl benzoate, the adduct of TEMPO and benzoyl radical, has been isolated and characterized. This finding is compatible with the intermediacy of acyl radicals. A mechanism involving the reaction of the palladacyclic complexes of aryl ketones with acyl radicals is proposed.

1,2-Diacylbenzenes are versatile precursors for some medicinally important heterocycles such as phthalazines, isobenzofurans and isoindoles (Scheme 1).[1] Moreover, 1,2-diacylbenzenes are also employed as fluorescent reagents for amino acids and peptide analysis.[2] Notably, Friedel-Crafts acylation of aryl ketones with acid chlorides is ineffective for 1,2-diacylbenzene synthesis because of the *meta*-directing properties of the keto substituent. Indeed, many currently available methods for 1,2-diacylbenzene synthesis are laborious with poor generality.[3] For instance, oxidation of 1,3-diarylisobenzofurans by lead(IV) tetraacetate is known to afford 1,2-diacylbenzenes in good yields.[3e] However, the rather high reactivity and toxicity of the lead(IV) tetraacetate hamper any widespread usage of this method.

In 2010, we reported a Pd-catalyzed, direct *ortho*-C–H acylation of aryl ketone *O*-methyl oximes by cross dehydrogenative coupling with aldehydes using *tert*-butyl hydroperoxide (TBHP) as oxidant.[4a] The ortho-selectivity was accomplished by the oxime-directed *ortho*-C–H arene palladation, affording palladacyclic complexes. Subsequent coupling of the palladacyclic complexes with acyl radicals (generated *in situ* via hydrogen atom abstraction of the aldehyde by *tert*-butoxy radicals)[4-5] furnished the *ortho*-acylated ketone oximes. The 1,2-diacylbenzenes were readily obtained by simple oxime deprotection with HCl (Scheme 3a). Recently, Kim and co-workers developed a one-step protocol for palladium-catalyzed acylation of *N*-Boc hydrazones, and 1,2-diacylbenzenes can be obtained in good yields without the oxime deprotection step (Scheme 3b).[6-7]

Despite these advances, the necessity of a strong *N*-directing group for successful transformations remains the inherent limitation. It is envisaged that direct C–H acylation of aryl ketones[8] without the need of pre-derivatization to imines – followed by deprotection – would be highly valuable. Here, we present the

Scheme 1. Some medicinally important heterocycles derived from 1,2-diacylbenzenes



Scheme 2. Selected examples for ketone-directed *ortho*-C–H functionalization

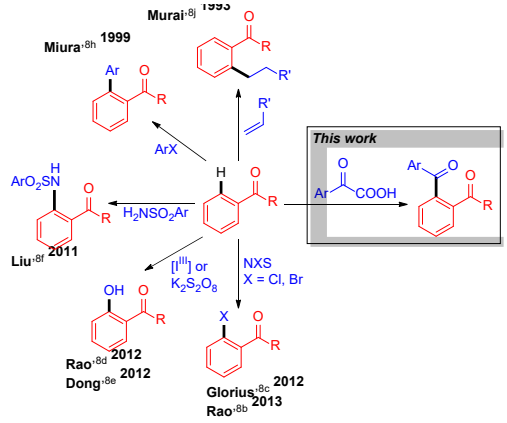
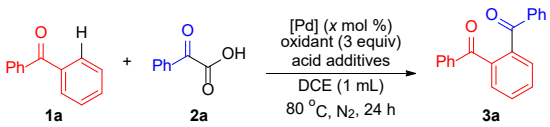


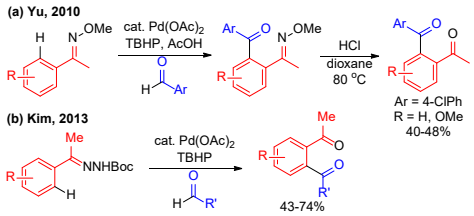
Table 1. Reaction optimization[a]



entry	[Pd] (mol %)	oxidant (equiv)	acid additives (mL)	1a (equiv)	2a (equiv)	yield (%)[b]
1	$Pd(TFA)_2$ (10)	$(NH_4)_2S_2O_8$ (3.0)	TFA (0.5)	1.0	3.0	46
2[c]	$Pd(TFA)_2$ (10)	$(NH_4)_2S_2O_8$ (3.0)	TFA (0.5)	1.0	3.0	31
3	$Pd(OAc)_2$ (5)	$K_2S_2O_8$ (3.0)	TFA (0.5)	1.0	3.0	56
4	$Pd(OAc)_2$ (5)	$K_2S_2O_8$ (3.0)	TFA (0.2)	1.0	3.0	50
5	$Pd(OAc)_2$ (5)	$K_2S_2O_8$ (3.0)	AcOH (0.5)	1.0	3.0	trace
6	$Pd(OAc)_2$ (5)	$K_2S_2O_8$ (3.0)[d]	TFA (0.2)	1.0	1.0[d]	41
7	$Pd(OAc)_2$ (5)	$K_2S_2O_8$ (3.0)[d]	TFA (0.2)	3.0	1.0[d]	72
8	$Pd(OAc)_2$ (5)	$K_2S_2O_8$ (3.0)[d]	TFA (0.2)	4.0	1.0[d]	84
9	$Pd(OAc)_2$ (5)	$K_2S_2O_8$ (3.0)[d]	TFA (0.2)	6.0	1.0[d]	86
10	$Pd(OAc)_2$ (5)	$K_2S_2O_8$ (3.0)	TFA (0.2)	4.0	1.0	74

[a] Reaction conditions: **1a**, **2a**, Pd catalyst, oxidant (3 equiv), acid additives, DCE (1 mL) at 80 °C for 24 h, under N_2 atmosphere. [b] Isolated yield. [c] Performed in undegassed conditions. [d] $K_2S_2O_8$ (3 × 1.0 equiv / h) and **2a** (3 × 0.33 equiv / h) were added in a batch-wise fashion.

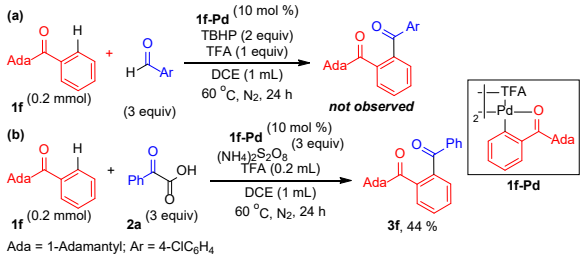
Scheme 3. Synthesis of 1,2-diacylbenzenes by Pd-catalyzed oxidative C–H acylation of aryl ketoimines



Pd-catalyzed direct ortho-C–H acylation of aryl ketones by decarboxylative coupling with α-oxocarboxylic acids to produce 1,2-diacylbenzenes directly without the pre-derivatization-deprotection step. The reaction is probably initiated by ketone-directed ortho-C–H palladation, followed by decarboxylative coupling of the α-oxocarboxylic acids.

To assess the feasibility for the ketone-directed arene acylation reaction, we examined the reaction of adamantyl phenyl ketone (**1f**) with the bimetallic palladacyclic complex **1f-Pd** as catalyst.[9] When subjecting **1f-Pd** (10 mol %) to a mixture of **1f** (0.2 mmol), 4-chlorobenzaldehyde (3 equiv), TBHP (2 equiv) and TFA (1 equiv) in DCE (1 mL), no acylation products were obtained after heating at 80 °C for 24 h with Pd black being formed (Scheme 4a). The failure is likely due to the unfavorable competition between the aromatic ketones and the benzaldehydes for the coordination sites of the palladium complex.

Scheme 4. Preliminary study on acylation of adamantyl phenyl ketone mediated by palladacyclic complex 1f-Pd



Inspired by the Pd-catalyzed decarboxylative acylation reactions with α-oxocarboxylic acids[10] first reported by the research groups of Goossen[10t] and Ge,[10r] we turned to examine α-oxocarboxylic acids as potential acylation reagents for the ketone-directed C–H acylation reaction. Gratifyingly, when **1f** (0.2 mmol) was treated with phenylglyoxylic acid **2a** (3 equiv) and **1f-Pd** (10 mol %) in the presence of $(NH_4)_2S_2O_8$ (3 equiv), TFA

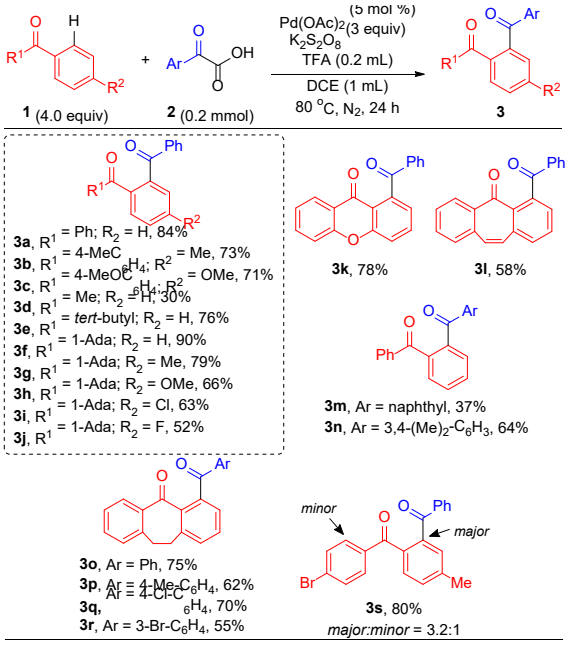
(0.2 mL) and DCE (1 mL) at 60 °C for 24 h, the diketone product **3f** was formed in 44% yield (Scheme 4b).

For further optimization, we surveyed several experimental parameters. Treating **1a** (0.2 mmol) with phenylglyoxylic acid **2a** (0.6 mmol), $Pd(TFA)_2$ (10 mol %), $(NH_4)_2S_2O_8$ (3 equiv) and TFA (0.5 mL) in anhydrous DCE (1 mL) at 80 °C for 24 h, the diketone **3a** was obtained in 46% yield (Table 1, entry 1). A lower yield (31%) was resulted when the reaction was performed in undegassed conditions (entry 2). When $Pd(OAc)_2$ (5 mol %) was the catalyst and $K_2S_2O_8$ (3 equiv) as oxidant, the yield of **3a** was slightly improved to 56% (entry 3). *It should be noted that no **3a** formation was observed in the absence of either the Pd catalyst or the oxidant*. Other oxidants such as $Na_2S_2O_8$, CAN, oxone, O_2 and organic peroxides failed to give better results (see Supporting Information).

With TFA (0.2 - 0.5 mL) as additives, **3a** was furnished in comparable yields (entries 3 and 4). It was noted that employing AcOH (0.5 mL) as additives led to poor results (entry 5). Other acids such as TsOH and TfOH were ineffective as well for the acylation reaction (see Supporting Information).

Hoping to achieve better product yields, we surmised that the diketone formation could be limited by the rate of Pd(II)-mediated C–H activation. Thus, faster radical generation is probably unproductive for diketone formation. With this hypothesis in mind, we adopted a batchwise addition protocol for the phenylglyoxylic acid. In this work, when **1a** (0.2 mmol) was treated with phenylglyoxylic acid **2a** in a batchwise addition manner (0.2 mmol, 3 × 33.3 mol % / h), diketone **3a** was produced in 41% yield (entry 6). Significant yield improvement was achieved by employing 3.0 equiv of **1a**, and **3a** was furnished in 72% yield (entry 7). The yield was further improved

Scheme 5. Substrate scope of the catalytic acylation of aromatic ketones



[a] Reaction conditions: **1** (0.8 mmol), **2** (0.2 mmol; 3 x 33.3 mol % / h), $Pd(OAc)_2$ (5 mol %), $K_2S_2O_8$ (3 x 1 equiv / h), TFA (0.2 mL), DCE (1 mL) at 80 °C for 24 h, under N_2 atmosphere. [b] **2** (0.2 mmol) and $K_2S_2O_8$ (3.0 equiv) were added in a single batch. 1-Ada is 1-adamantyl.

when 4.0 and 6.0 equiv of **1a** were used, and **3a** was isolated in 84% and 86% yields, respectively (entries 8-9). A slightly lower **3a** formation (74%) was encountered when **2a** and $K_2S_2O_8$ were added *all in a single batch* (entry 10). These results are consistent with our hypothesis.

The substrate scope of the Pd-catalyzed decarboxylative acylation was depicted in Scheme 5. Treating benzophenone **1a** (4 equiv), phenylglyoxylic acid **2a** (0.2 mmol, 3 × 33.3 mol % / h) in the presence of $Pd(OAc)_2$ (5 mol %), $K_2S_2O_8$ (3 × 1 equiv / h) and TFA (0.2 mL) in DCE (1 mL) at 80 °C for 24 h afforded **3a** in 84% yield. Benzophenones with methyl and methoxy substituents were transformed to the corresponding diketones in 71-73% yields (**3b** and **3c**). Aromatic ketones bearing alkyl groups such as methyl and *tert*-butyl would undergo *ortho*-C–H acylation to give diketones **3d**-**3e** in 30% and 76% yields, respectively. The apparent low yield of **3d** is attributed to the relatively slow cyclopalladation versus other ketones. As expected, facile transformation of adamantyl aryl ketones with **2a** afforded **3f**-**3j** in good-to-excellent yields. Substrates bearing fused ring structures such as xanthone, 5-dibenzosuberenone and dibenzosuberone were also converted to their diketones (**3k**, **3l** and **3o**) in 58-78% yields under the Pd-catalyzed conditions.

The scope of the α-oxocarboxylic acids was studied with benzophenone and dibenzosuberone as substrates. α-Oxocarboxylic acids with a halogen substituent were effective coupling partners, and diketones **3q** and **3r** were formed in 55-70% yields. Alkyl substituents on α-oxocarboxylic acids such as dimethyl and methyl were tolerated as exemplified by the effective products [**3n** (64%) and **3p** (62%)] formation. 2-(Naphthalen-2-yl)-2-oxoacetic acid containing a bulky substituent would react with benzophenone to give **3m** in 37% yield. Indeed, the reactions involving sterically more demanding 2,3,4,5,6-pentamethylphenylglyoxylic acid were unsuccessful, and no diketone products were obtained. The coupling reactions with some aliphatic and heteroaromatic keto-acids such as pyruvic acid and 2-oxo-2-(thiophen-2-yl) acetic acid were found to be ineffective as well.

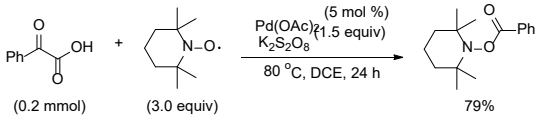
For unsymmetric benzophenones, the regioselectivity of the acylation was examined by performing a competition experiment with (4-bromophenyl)(*p*-tolyl)methanone as substrate. Apparently, the tolyl group would react preferentially versus the bromophenyl group; a product ratio of 3.2:1 with a combined yield of 80% (**3s**) was observed. We are gratified that at 1 mmol-scale transformation of **1a** by the Pd-catalyzed protocol afforded **3a** in 62% yield (see Supporting Information).

The catalytic C–H acylation is probably initiated by the Pd(II)-mediated arene C–H bond cleavage directed by the adjacent ketone group. This is supported by the fact that the cyclopalladated complex of adamantyl phenyl ketone (**1f-Pd**) was kinetically competent for catalyzing the acylation of **1f** with phenylglyoxylic acid **2a,** and **3f** was formed in 44% yield (Scheme 4b). The Pd-catalyzed C–H acylation reaction exhibits primary kinetic H/D isotope effect (k_H/k_D) = 3.7.[9,11] The KIE were determined by monitoring the acylation reaction by NMR with an equimolar quantity of **1a** and **1a-*d*$_{10}$** as substrates. The significant KIE observed in this work implies that the Pd-mediated C–H cleavage step is likely to be the turnover-limiting step.

The substituent effects of the arene C–H palladation has been studied by examining the acylation reactions of a series of para-substituted adamantyl aryl methanones (Y = OMe, Me, H, F and

Cl). As depicted in Figure S1, a linear relationship of the relative reaction rates with the Hammett constants σ_p was revealed. The ρ value was found to be -4.1.[11b-c,12] Since the arene C–H palladation is the rate-determining step, this finding is consistent with an electrophilic palladation mechanism with development of partial positive charge on the arene.

Scheme 6. Trapping of the acyl radicals by TEMPO

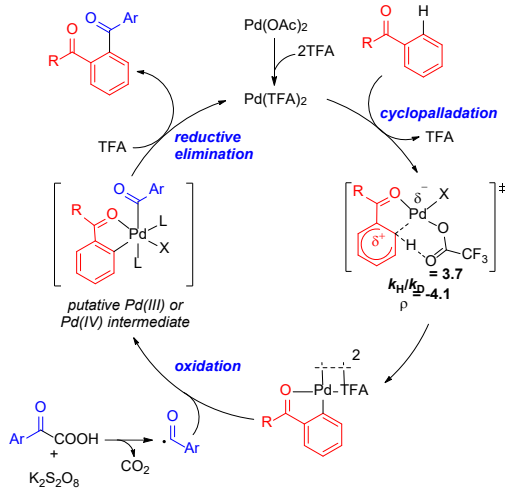


It is likely that the α-oxocarboxylic acids would serve as precursor for acyl radicals, which then mediate the diketone formation via coupling with the palladacyclic intermediates. The involvement of the acyl radicals was scrutinized by employing TEMPO as a radical trapping agent.[13] When **2a** (0.2 mmol) was treated with TEMPO (3 equiv), in the presence of $Pd(OAc)_2$ (5 mol %) and $K_2S_2O_8$ (1.5 equiv), the acyl radical-TEMPO adduct was isolated in 79% yield (Scheme 6). In addition, the diketone formation was also suppressed by TEMPO in a dosage-dependent manner (see Supporting Information).

A plausible mechanism for this Pd-catalyzed C–H acylation is depicted in Scheme 7. In the presence of TFA, $Pd(OAc)_2$ would be transformed to $Pd(TFA)_2$ *in situ*. The acylation is probably initiated by a ketone-directed *ortho*-selective electrophilic palladation on the arene by the $Pd(TFA)_2$. The palladacycle would then undergo oxidative coupling with the acyl radicals, which were *in situ* generated by decarboxylation of α-oxocarboxylic acids.[13] Reductive elimination from the putative Pd(III) or Pd(IV) intermediate[12b,14] would furnish 1,2-diacylbenzenes together with the regeneration of active the Pd(II) catalyst.

In conclusion, we have developed a Pd-catalyzed *ortho*-C–H acylation of aromatic ketones via decarboxylative coupling with α-oxocarboxylic acids. This reaction enables direct synthesis of 1,2-diacylbenzenes from aromatic ketones in high regioselectivity and functional group tolerance. We anticipate that our protocol may be applicable for other C–H coupling reactions.

Scheme 7. Proposed reaction mechanism



ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI:
General experimental procedures, physical characterization data, additional data and NMR spectra of products (PDF)

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

We thank The Hong Kong Research Grants Council (PolyU 153037/14P) for financial support.

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