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Palladium-Catalyzed *ortho*-CH-Bond Oxygenation of Aromatic Ketones

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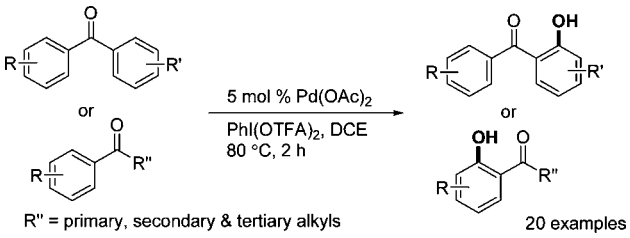
ABSTRACT



A palladium-catalyzed $C_{(sp2)}$–H bond oxygenation reaction is described. This protocol represents the first example of a C–H bond cleavage/C–O bond formation sequence, by employing a ketone moiety as the directing group. With this new catalytic method, a variety of *ortho*-acylphenols can be easily accessed from arylketones.

Phenols bearing an acyl group are an important and commonly found subunit in a number of drug-relevant and bioactive molecules (Figure 1).[1] In particular, *ortho*-acylphenols are versatile synthetic building blocks for preparing various pharmaceuticals and natural products.[2] Thus, method development for accessing this structural motif is of high interest.

A classical protocol for the synthesis of an *ortho*-acylphenol scaffold is the Fries rearrangement of phenyl esters (Scheme 1A).[3] Yet, this route suffers from a regioselective drawback, and thus an undesirable *para*-substituted product would be formed. Moreover, this anionic protocol is not compatible with enolizable ketones. Traditional Friedel–Crafts acylation[4] of phenols and direct hydroxylation of arylketones using a radical approach[5] lack site selectivity, and possible *ortho*-, *meta*-, and *para*-isomers of acylphenol are usually generated. These regiomixtures are generally difficult to purify.

Palladium-catalyzed aromatic C–O bond formation has emerged as an alternative route for preparing site-selective phenolic compounds.[6] Successful hydroxylation of aryl halides has been reported recently (Scheme 1B).[7] Apart from this development, we envisioned that the direct C–H bond functionalization would be even more attractive.[8]

Figure 1. Pharmaceuticals and natural products bearing *ortho*-acylphenol skeleton.

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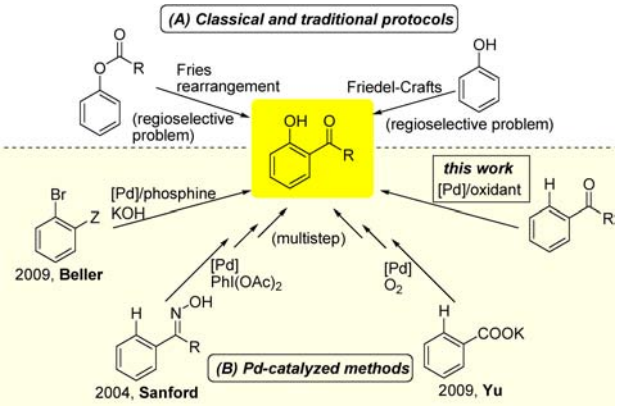
Hence, Pd-catalyzed directed $C_{(sp2)}$−H bond cleavage/$C_{(sp2)}$−O bond formation sequence is a desirable approach. In 2004, Sanford reported oxime as a directing group for *ortho*-acetoxylation of aromatic/aliphatic C−H bonds.[9] Later, Yu disclosed a Pd-catalyzed *ortho*-hydroxylation of carboxylic acid salts at 115 °C (Scheme 1B).[10] Apart from Pd catalysis, the Rao and Lei groups recently showed that Ru and Cu complexes could be applied in the hydroxylation of benzoate esters and electron-deficient arenes, respectively.[11,12] These establishments potentially provide a synthetic method to access an *ortho*-acylphenol moiety. However, additional steps are necessary to retrieve the phenol or obtain the ketone moiety (Scheme 1B). Therefore, it would be attractive to access *ortho*-acylphenols if the ketone group could be directly employed as the directing group for direct $C_{(sp2)}$−H bond oxygenation.

Scheme 1. Synthetic Pathways for *ortho*-Acylphenol Motifs



Ketone-directed C−H bond functionalization has been established since Murai's initial work on Ru-catalyzed olefin coupling.[13] Apart from the significant development of the ketone-directed C−H bond cleavage/C−C bond-forming strategy,[14] there have been very limited examples on C−X bond formation. Until very recently, Liu[15] and Glorius[16] reported ketone-directed C−N and C−Br bond formation by employing Pd and Rh catalysts, respectively. Pal reported the hydroxylation of benzophenone under UV photoactivation conditions, leading to a mixture of regioisomers.[17] Yet, there has been no report on ketone-directed arene oxidation (C−O bond formation) to date. Presumably the weaker coordinating ability (with respect to amides, oximes, carboxylic salts/esters, and 2-phenylpyridine)[18] likely gives lower reactivity at the initial *ortho*-directed electrophilic palladation, and consequently more forcing conditions are needed, in which these conditions would lead to substrate decomposition or undesired product formation. Inspired by the need for efficient synthesis of *ortho*-acylphenol motifs from arylketones, we started to embark on this challenge by using a Pd-catalyzed arene oxygenation approach. In continuing our research program on Pd-catalyzed *ortho*-acylaniline synthesis[19] and direct C−H acetoxylation,[20] herein, we report our investigation on the ketone-directed *ortho*-oxygenation of aromatic ketones. This protocol presents a straightforward access of *ortho*-acylphenol frameworks and also allows enolizable ketones to react smoothly. In particular, halo groups are found to be compatible under these mild reaction conditions (80 °C).

We initially started our investigation by using benzophenone as the model substrate (Table 1). Commonly used oxidants were examined (entries 1−4). A more electrophilic oxidant, $PhI(OTFA)_2$, was found to be significantly better than $PhI(OAc)_2$ (entry 3 vs 4). However, there was no essential difference between $Pd(OAc)_2$ and $Pd(OTFA)_2$ when they were used as the precatalysts (entry 4 vs 12). A screening of solvents revealed that DCE was the solvent of choice (entries 4−7). Also, 5 mol % Pd was found to be the lowest level of catalyst loading to provide a good yield (entries 8−10). Indeed, the initial product formed from this reaction was the 2-trifluoroacetoxylbenzophenone. Upon aqueous workup, the hydrolyzed phenolic product **1a** was obtained.

With our optimized reaction conditions in hand, we next tested the substrate scope of this oxgyenation reaction (Table 2). The aromatic ketones proceeded smoothly to give the corresponding product in good yields. Fluoro, chloro, and bromo groups were compatible under these reaction conditions (entries 3, 9−10). This halo group tolerance is versatile for further modification of *ortho*-acylphenol using traditional cross-coupling technology.[21] Apart from the symmetrical diarylketones, we also probed the hydroxylation regioselectivity of the unsymmetrical

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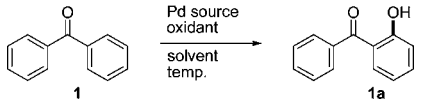
Table 1. A Screening of Pd-Catalyzed *ortho*-Oxygenation Reaction Conditions[a]



entry	Pd (mol %)	oxidant	solvent	temp (°C)	yield[b] (%)
1	$Pd(OAc)_2$ (10)	BQ	DCE	80	0
2	$Pd(OAc)_2$ (10)	$K_2S_2O_8$	DCE	80	0
3	$Pd(OAc)_2$ (10)	$PhI(OAc)_2$	DCE	80	0
4	$Pd(OAc)_2$ (10)	$PhI(OTFA)_2$	DCE	80	82
5	$Pd(OAc)_2$ (10)	$PhI(OTFA)_2$	toluene	110	0
6	$Pd(OAc)_2$ (10)	$PhI(OTFA)_2$	dioxane	80	4
7	$Pd(OAc)_2$ (10)	$PhI(OTFA)_2$	THF	80	6
8	$Pd(OAc)_2$ (1)	$PhI(OTFA)_2$	DCE	80	5
9	$Pd(OAc)_2$ (2)	$PhI(OTFA)_2$	DCE	80	45
10	$Pd(OAc)_2$ (5)	$PhI(OTFA)_2$	DCE	80	79 (71)
11	$Pd(OAc)_2$ (10)	$PhI(OTFA)_2$	DCE	50	10
12	$Pd(TFA)_2$ (5)	$PhI(OTFA)_2$	DCE	80	80
13	$Pd(TFA)_2$ (5)	$PhI(OAc)_2$	DCE	80	0
14[c]	$Pd(OAc)_2$ (10)	$PhI(OAc)_2$	CH_3CN	80	0

[a] Reaction conditions: Benzophenone (0.5 mmol), Pd source (mol % as indicated), oxidant (1.0 mmol), and solvent (2.0 mL) were stirred at specified reaction temperature for 2 h under air. [b] Calibrated GC yields were reported using dodecane as the internal standard. Isolated yield in parentheses. [c] KOAc was added as base.

diarylketones (entries 3−5, 8−10). The steric effect allowed regioselective hydroxylation of the unsubstituted phenyl ring (entries 4−5). The electron-withdrawing group on the unsymmetrical diarylketones offered a regioselective electrophilic palladation on the other phenyl ring (see proposed mechanism). Essentially complete regioselectivity was observed when 4-fluorobenzophenone was employed (entry 3). Less electron-withdrawing groups (e.g., −Cl and −Br) provided a regioselectivity as high as 20 to 1 (entries 9−10). In contrast, no regioselective hydroxylation was observed when tolylphenylketone was used (entry 8). Addition of 2.4 equiv of $PhI(OTFA)_2$ promoted the dihydroxylation product (entry 7).

Enolizable arylalkylketones were also examined in this Pd-catalyzed *ortho*-oxygenation reaction (Scheme 2). Tetralone reacted smoothly to give the corresponding product in good yield (**10a**). Cyclohexylphenylketone and cyclopropylarylketones furnished the hydroxylated products without being affected by the substituted groups at the *para*-position (**13a**−**15a**, with respect to the acyl group). Primary alkyl arylketone (e.g., acetophenone and *p*-OMe-acetophenone) proceeded to form the desired products **16a** and **17a**. These products are versatile materials for synthesizing various substituted flavones through a modular assembly with arylaldehydes (Scheme 3).[22] Importantly, the *tert*-butylphenyl ketone was applicable in this reaction. This substrate was found to be problematic in Fries rearrangement.[23]

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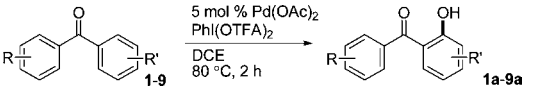
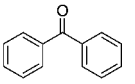
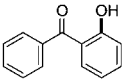
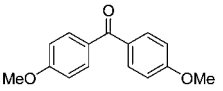
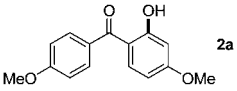
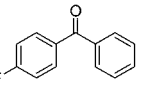
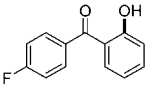
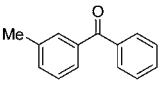
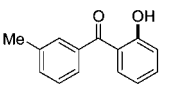
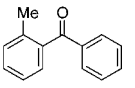
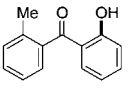
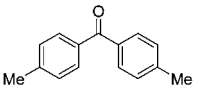
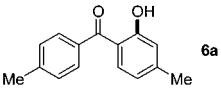
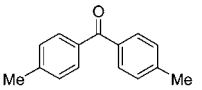
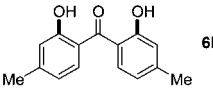
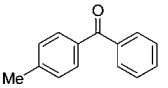
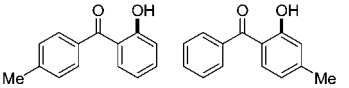
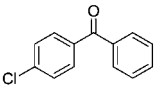
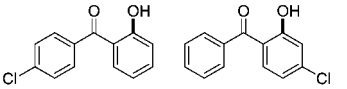
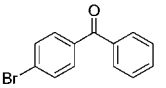
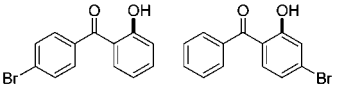
Table 2. Pd-Catalyzed *ortho*-Oxygenation of Benzophenone Derivatives[a]



entry	ArC(O)Ar'		product		% yield[b]
1		1		1a	81
2		2		2a	70
3		3		3a	88
4		4		4a	72
5		5		5a	71
6[c]		6		6a	86
7[d]		6		6b	68
8		7		7a:7b = 1:1	86
9		8		8a:8b = 20:1	73
10		9		9a:9b = 20:1	85

[a] Reaction conditions: Substituted benzophenones **1**−**9** (0.5 mmol), $Pd(OAc)_2$ (5 mol %), $PhI(OTFA)_2$ (1.0 mmol), and DCE (2.0 mL) were stirred at 80 °C for 2 h under air (see Supporting Information for details). [b] Isolated yields were reported. [c] 0.75 mmol of $PhI(OTFA)_2$ was used. [d] 1.2 mmol of $PhI(OTFA)_2$ was used.

A plausible mechanism for this reaction is shown in Scheme 4. The reaction begins with the ligand exchange followed by the ketone carbonyl oxygen coordination with Pd(II) species. Then, the electrophilic palladation (C−H bond cleavage) occurs to generate the palladacyclic intermediate.[24] The Hammett investigation indicated that

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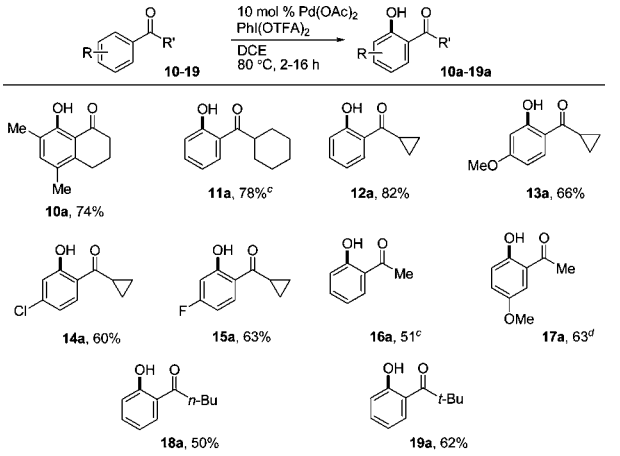
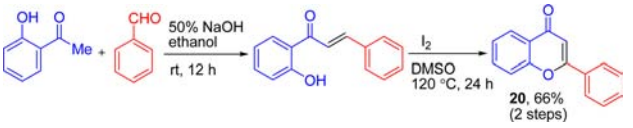
Scheme 2. Pd-Catalyzed *ortho*-Oxygenation of Alkylarylketones[a]



[a] Reaction conditions: Arylalkylketones 10−19 (0.2 mmol), $Pd(OAc)_2$ (10.0 mol %), $PhI(OTFA)_2$ (0.3 mmol), and DCE (1.0 mL) were stirred at 80 °C for 2 h (see Supporting Information for details). [b] Isolated yields were reported. [c] 16 h were used. [d] 5 mol % of $Pd(OAc)_2$ were used, and 0.2 mmol of $PhI(OTFA)_2$ was used.

Scheme 3. Application of the Hydroxylated Product for the Modular Synthesis of Flavones



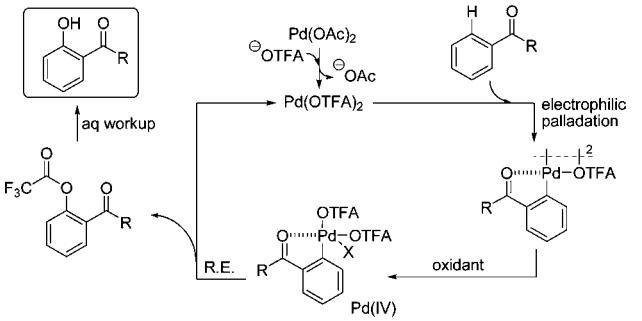
this step obeyed a linear free energy relationship with Hammett constants σ_p (Scheme 5). The palladacyclic intermediate is then oxidized to Pd(IV).[25,26] Subsequent reductive elimination affords the 2-trifluoroacetoxyarylketone and regenerates the Pd(II) complex. The phenolic product is obtained after aqueous workup.

In summary, we have reported the first ketone-directed Pd-catalyzed oxygenation of arenes. This protocol represents a direct and facile approach for accessing a variety of *ortho*-acylphenol compounds from arylketones. In view of the rich feedstock of arylketones in nature, we believe the method reported herein has significant value for organic synthesis. In particular, the success of this research would inspire further explorations of simple ketone-directed C−H bond functionalizations.

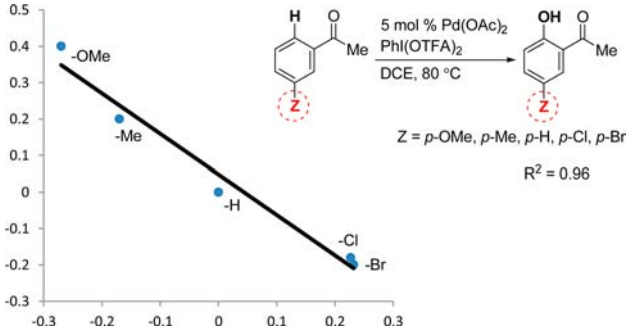
(25) (a) Deprez, N. R.; Sanford, M. S. *J. Am. Chem. Soc.* **2009**, *131*, 11234. (b) Racowski, J. M.; Dick, A. R.; Sanford, M. S. *J. Am. Chem. Soc.* **2009**, *131*, 10974.

(26) We thank a referee for comments. A Pd(III) species may also be a possible pathway; see: (a) Powers, D. C.; Ritter, T. *Acc. Chem. Res.* **2012**, *45*, 840. (b) Powers, D. C.; Ritter, T. *Nat. Chem.* **2009**, *1*, 302.

Scheme 4. Proposed Mechanism



Scheme 5. Hammett Correlation Study



Note Added in Proof. During the reviewing process, two closely related papers appeared. Shan, G.; Yang, X.; Rao, Y. *Angew. Chem., Int. Ed.* **2012**, doi:10.1002/anie.201207458 and Mo, F.; Trzepkowski, L. J.; Dong, G. *Angew. Chem., Int. Ed.* **2012**, doi:10.1002/anie.201207479.

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Supporting Information Available. Detailed experimental procedures, compound characterization data, and copies of ^1H, ^{13}C NMR and HRMS spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.