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Pd-Catalyzed *Ortho*-C−H Acylation/ Cross Coupling of Aryl Ketone *O*-Methyl Oximes with Aldehydes Using *tert*-Butyl Hydroperoxide as Oxidant

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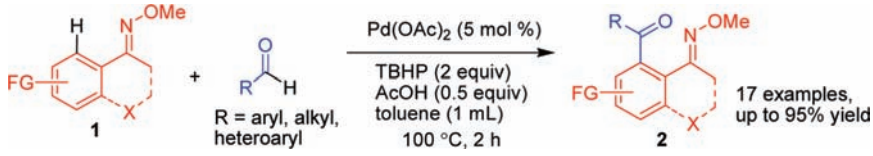
ABSTRACT



A Pd-catalyzed protocol for direct C−H bond acylation by cross coupling of aryl ketone oximes and aldehydes using *tert*-butyl hydroperoxide (TBHP) as oxidant was developed. With oximes as a directing group for the C−H activation, the coupling with aldehydes was achieved with remarkable regioselectivity. The acylation reactions exhibit excellent functional group tolerance, and both aliphatic and heteroaromatic aldehydes can be effectively coupled to the oximes.

Aryl ketones are important motifs in some bioactive and functional materials.[1] Apart from the classical Friedel−Crafts acylation reactions,[2] which often suffer from poor regioselectivity and the use of a stoichiometric amount of reactive acyl halide reagents, transition metal catalyzed cross coupling reactions of aldehydes with arylboronic acids or aryl halides have emerged as an appealing alternative to Friedel−Crafts chemistry.[3] Hartwig and co-workers also reported a convenient synthesis of aryl ketones by Pd-catalyzed coupling of aryl bromides with *N*-*tert*-butylhydrazones as an acyl anion equivalent.[4] Other Pd-catalyzed cross coupling reactions of aryl halides under carbonylative[5] and decarbonylative[6] conditions are also developed. Despite the apparent success of the cross coupling strategy, catalytic reactions that transform unactivated C−H bonds to aryl ketones are sparse in the literature.

Significant progress has been achieved in the Pd-catalyzed regioselective C−H bond arylations and vinylations.[7] How-

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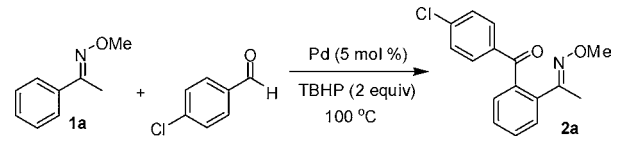
ever, examples of direct arene C−H bond coupling reactions with aldehydes to aryl ketones are less established. Notably, Cheng and co-workers pioneered in developing a Pd-catalyzed coupling of 2-arylpyridines with benzaldehydes to give aromatic ketones using dioxygen as oxidant.[8] During the course of our investigation, Li and co-workers recently reported the oxidative coupling of 2-arylpyridines with aliphatic aldehydes by TBHP.[9] Motivated by Cheng's work and our earlier studies[10] on the Pd-catalyzed *ortho*-selective C−H ethoxycarbonylation of 2-arylpyridines with diethyl azodicarboxylate (DEAD),[10c] we considered that the analogous C−H bond coupling of aryl ketone oxime ethers with aldehydes would be a versatile route to 1,2-diacylbenzenes after the oxime deprotection. 1,2-Diacylbenzenes are useful precursors to isoindoles, isoquinolines, *N*-arylphthalimidines, and phthalazines, which are scaffolds for compounds of biological or pharmaceutical interest.[11] While a general synthetic method is lacking, 1,2-diacylbenzenes can be prepared from 2-hydroxylarylaldehyde/ketone acylhydrazones with $Pb(OAc)_4$ or $PhI(OAc)_2$ as reagent.[12] However, this reaction would be limited by the requirement of prefunctionalized starting materials and use of highly toxic lead compounds.

Our previous investigation implicated that the reaction of organopalladium(II) complexes with carboradicals such as $\bullet CO_2Et$ and Ar• radicals would be a key step for the direct ethoxycarbonylations[10c] and arylations.[10a] Thus, we hypothesized that the analogous coupling of organopalladium(II) with acyl [•C(O)R] radicals would lead to aryl ketone formation.[13] In this regard, hydrogen atom abstraction from aldehydes by reactive oxygen radicals (e.g., *t*BuO•) is known to be the cleanest way to generate acyl radicals.[14] Herein we describe a convenient synthesis of 1,2-diacylbenzene oximes via Pd-catalyzed oxidative arene C−H bond coupling with aldehydes using TBHP as oxidant. Good to excellent yields of the coupled ketones were obtained from aliphatic and heteroaromatic aldehydes.

To begin, acetophenone *O*-methyl oxime (**1a**, 0.25 mmol) and 4-chlorobenzaldehyde (0.75 mmol) were treated with TBHP (0.5 mmol) and $Pd(OAc)_2$ (5 mol %) in a toluene−AcOH mixture (2:1 v/v) at 100 °C for 12 h. We were gratified that **2a** was obtained in 47% yield (Table 1, entry 1). A slightly better yield of **2a** (58%) resulted with the use of 0.5 equiv of AcOH as additives (entry 2). The molecular structure of **2a** has been established by X-ray crystallography (see Supporting Information). Presumably, the TBHP serves as a source of reactive oxygen radicals (e.g., *t*BuO•), which would act upon the benzaldehyde to generate acyl radicals in situ. As expected, the **2a** formation was suppressed in the presence of a radical scavenger such as ascorbic acid (see Supporting Information).[15] Employing proprionic acid or benzoic acid as additives produced comparable results; other oxidants such as di-*tert*-butyl peroxide, hydrogen peroxide, and benzoyl peroxide are less effective for the acylaton reaction (see Supporting Information). The catalytic activities of other palladium compounds (5 mol %) have been evaluated; only $Pd(PPh_3)_2Cl_2$ (63%) and $Pd(OAc)_2$ (58%) exhibited significant activities (entries 3−5). After several trials, **2a** was isolated in 71% yield within 2 h by utilizing 6 equiv of benzaldehyde (entry 7). Toluene was found to be the solvent of choice; other solvents such as dioxane, acetonitrile, and DMF failed to yield better results (entries 8−11).

Scheme 1 summarizes the results of the substrate scope studies. With 4-chlorobezaldehyde as reagent, the substituted acetophenone oximes were transformed to the corresponding ketones **2b**, **c**, and **g** in 50−88% yields. In general, electron-withdrawing (F, Cl, Br, $MeSO_2$) and -donating groups (OMe, amide) are tolerated (see for **2a**−**2f**). For **2e**, the aldehyde coupling was selectively directed to the ortho-position of the

Table 1. Reaction Optimization[a]



entry	Pd	aldehyde (equiv)	solvent	% yield[b]
1[c]	$Pd(OAc)_2$	3	toluene	47
2	$Pd(OAc)_2$	3	toluene	58
3	$Pd(CH_3CN)_2(OTs)_2$	3	toluene	-[d]
4	$PdCl_2(PhCN)_2$	3	toluene	53
5	$PdCl_2(PPh_3)_2$	3	toluene	63
6	$Pd(OAc)_2$	6	toluene	76
7[e]	$Pd(OAc)_2$	6	toluene	73 (71)[f]
8[e]	$Pd(OAc)_2$	6	DCE	56
9[e]	$Pd(OAc)_2$	6	dioxane	51
10[e]	$Pd(OAc)_2$	6	acetonitrile	18
11[e]	$Pd(OAc)_2$	6	DMF	11

[a] Conditions: **1a** (0.25 mol), 4-Cl-C_6H_4CHO, Pd catalyst (5 mol %), TBHP (2 equiv), solvent (1 mL) with AcOH (0.5 equiv) as additive, 100 °C, 12 h. [b] Yield determined by GC-FID. [c] 0.5 mL of AcOH was used. [d] No detectable product formation. [e] Reaction run for 2 h. [f] Isolated yield in parentheses.

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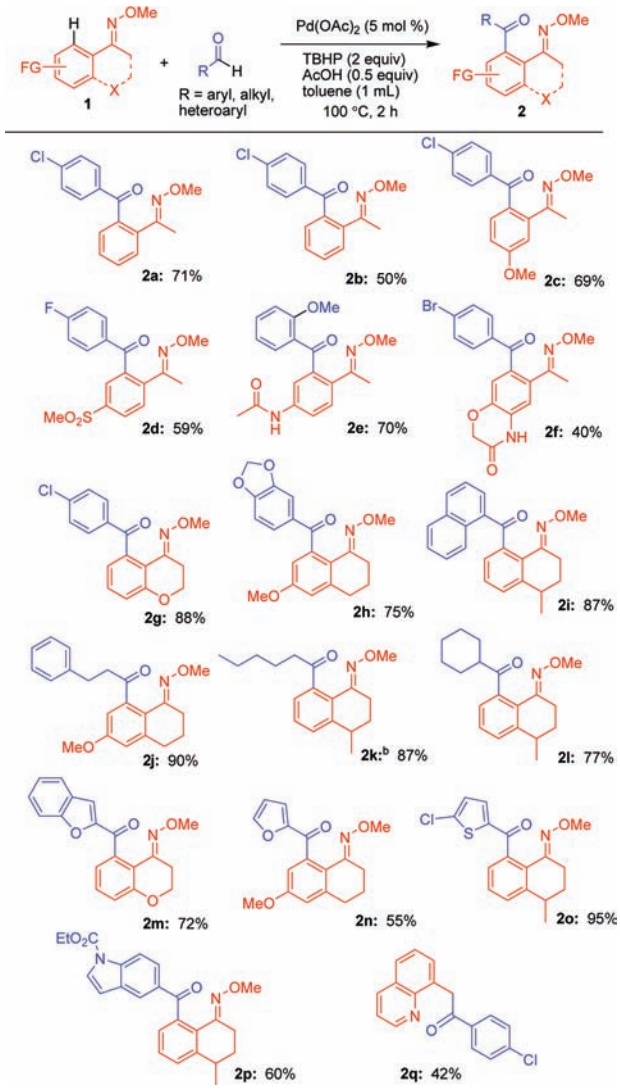
Scheme 1. Pd-Catalyzed Oxidative C−H Bond Coupling with Aldehydes[a]



[a] Isolated yields. [b] DCE as solvent.

oxime group, rather than the amide group. This result reflects the stronger donor ability of the nitrogen than the oxygen atom.[16] Consistent with many related studies,[17] the Pd-catalyzed C−H acylation of meta-substituted arenes was favored at the less hindered site of the aromatic ring (for **2c** and **2f**).

Oximes with a bicyclic scafford would also undergo facile C−H acylation reactions. For instance, 4-chromanone *O*-methyl oxime would react with 4-chlorobenzaldehyde (6 equiv) under the Pd-catalyzed conditions to furnish ketone **2g** in 88% yield. Likewise, effective transformations of the tetralone analogues to **2h** (75%) and **2i** (87%) were also accomplished with piperonal and 2-naphthaldehyde as the coupling partners. Analogous to a recent report by Li and co-workers,[9] aliphatic aldehydes such as 3-phenylpropanal, 1-hexanal, and cyclohexylcarboxyaldehyde can be coupled to the oximes under our experimental conditions to afford ketones **2j** (90%), **2k** (87%), and **2l** (77%), respectively.

Heteroaromatic rings such as indoles are important scaffolds for many pharmaceutically active compounds,[18] 1-aryoylindoles can be readily prepared by direct acylation of the N−H free indole precursors. Other regioisomers were prepared from the indolecarboxyaldehydes by Grignard addition, followed by PDC oxidation.[19] In this work, when the tetralone *O*-methyl oxime was treated with ethyl 5-formyl-1*H*-indole-1-carboxylate under the Pd-catalyzed conditions, ketone **2p** was exclusively isolated in 60% yield, and C3-functionalized products were not detected. Similarly, effective couplings with furfural and 5-chloro-2-thiophenecarboxyaldehyde were also accomplished in 55 and 95% yields. As expected, the catalytic coupling of 4-chromanone oxime with 2-benzofurancarboxyaldehyde gave ketone **2m** in 72% yield. In all cases, no significant oxidation to the heterocycles was observed under our experimental conditions.

In this work, the direct acylation of the sp^3 C−H bond was also pursued. Treatment of 8-methylquinoline with 4-chlorobenzaldehyde using the Pd-catalyzed protocol afforded ketone **2q** in 42% yield. 8-Quinolyl benzil was obtained as a side product (22%) due to overoxidation.

According to Sanford and co-workers, *O*-acetyl oximes were effective directing groups for the Pd-catalyzed C−H acetoxylations, and they can be removed more readily than the oxime ether groups.[20] Despite this apparent advantage, our Pd-catalyzed protocol failed to give ketone products when acetophenone *O*-acetyl oxime was employed as substrate. NMR analysis of the reaction mixture revealed substantial decomposition of the starting oximes.

Having established a catalytic direct acylation reaction, we turned to develop a straightforward synthesis of phthalazines. It is known that phthalazines and derivatives would exhibit interesting luminescent[21] and anticancer[22] activities. In this work, the oxime deprotection for **2a** and **2c** was

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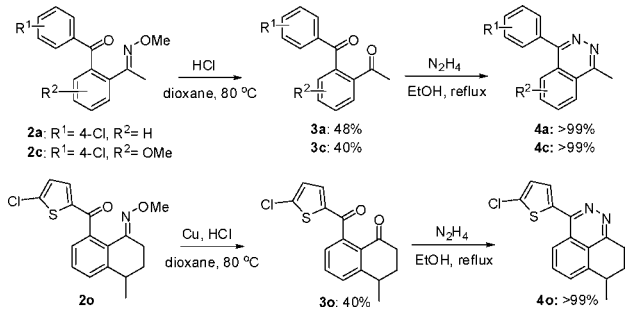
Scheme 2. Phthalazine Synthesis



performed in HCl/dioxane (Scheme 2). After hydrazine condensation, **4a** and **4c** were obtained in ca. 45% overall yield.[23] Yet, treatment of **2o** with HCl/dioxane produced a complicated mixture. However, successful oxime deprotection for **2o** was achieved in the presence of copper powder, and subsequent hydrazine condensation afforded **4o** in 40% overall yield.

A plausible mechanism of the catalytic C−H acylation is depicted in Scheme 3. The reaction is probably initiated by oxime-assisted *ortho*-selective cyclometalation on the arene ring by $Pd(OAc)_2$. The palladacycle would react with the acyl radicals, which were generated in situ by hydrogen atom abstraction of the aldehydes, to afford the product ketones via either reactive Pd(IV)[24] or dimeric Pd(III)[25] intermediates. Direct reaction of the cyclopalladated oximes with aldehydes can be ruled out since stoichiometric reaction of a related palladium complex of 2-phenylpyridine with 4-chlorobenzaldehyde did not produce any acylation products *in the absence of TBHP*. Consistent with the involvement of radical intermediates, the catalytic C−H acylation was suppressed by raical scavengers such as ascorbic acid in a dose-dependent manner.[26]

(23) During the acid deprotection, the reaction mixture developed an intense blue color in several minutes, and TLC analyses revealed formation of some unidentified byproducts.

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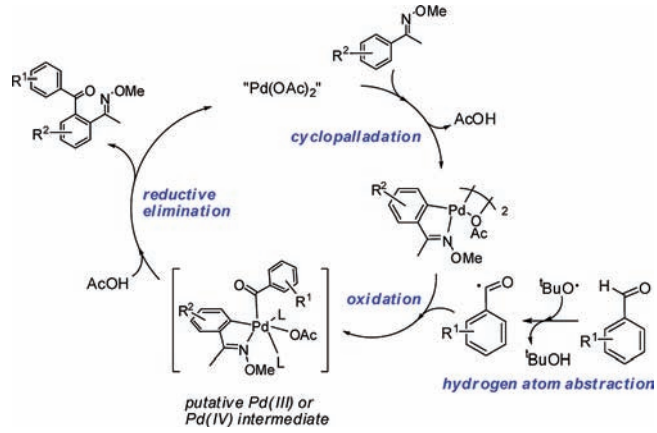
Scheme 3. Plausible Catalytic Cycle



In conclusion, we developed a Pd-catalyzed protocol for an *ortho*-selective C−H acylation reaction of aromatic oximes by oxidative coupling with aldehydes. This protocol constitutes a versatile route to a diverse library of diaryl ketones, which are difficult to obtain by the classical Friedel−Crafts acylation. Simple deprotection of the oxime group would afford 1,2-diacylbenzenes, which can be derivatized to phthalazines and other useful compounds for potential application.

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Supporting Information Available: Details of experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(26) With privaldehyde as the coupling partner, no coupled ketone was obatined with spontaneous palladium black formation. Probably, the *tert*-butylacyl radical was rapidly decarbonylated to form the *tert*-butyl radical, which undergoes β-hydrogen elimination. We thank one of the reviewers for this comment and suggestion.