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Palladium-Catalyzed Oxidative C−H Bond Coupling of Steered Acetanilides and Aldehydes: A Facile Access to *ortho*-Acylacetanilides

Yinuo Wu,[†] Baozhu Li,[‡] Fei Mao,[†] Xingshu Li,*[,†] and Fuk Yee Kwong*[,‡]

School of Pharmaceutical Sciences, Sun Yat-sen University, Guangzhou 510006, China, and State Key Laboratory of Chirosciences and Department of Applied Biology and Chemical Technology, The Hong Kong Polytechnic University, Kowloon, Hong Kong

lixsh@mail.sysu.edu.cn; bcfyk@inet.polyu.edu.hk

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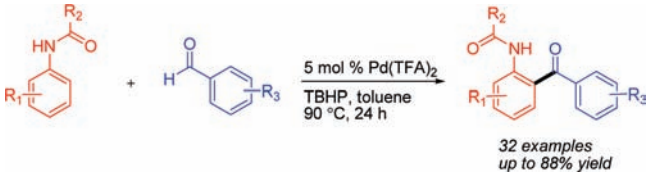
ABSTRACT



A palladium-catalyzed oxidative C−H bond functionalization/*ortho*-acylation of acetanilides using easily accessible aldehyde as the acyl source is described. In the presence of a $Pd(TFA)_2$ catalyst and *tert*-butylhydroperoxide at 90 °C in general, an array of *ortho*-acylacetanilides can be afforded in good yields.

Transition-metal-catalyzed direct C−H bond functionalization/cross-coupling have been successful as a valuable tool for the modular and facile synthesis of structurally similar, yet diversified organic molecules.[1] With the assistance of a directing group, the *ortho*-$C_{(sp2\ or\ sp3)}$−H bond cleavage (*ortho*-metalation) can be facilitated in the presence of transition metals (e.g., Pd, Ir, Rh, Ru, Cu, Fe, etc.), leading to a versatile C−H bond functionalization upon trapping with appropriate electrophiles or nucleophiles under basic or oxidative conditions, respectively.[2] Recent advancements of palladium catalysis demonstrated that a number of *ortho*-chelating groups such as pyridyl,[3] acyloxy/acyl,[4] carbamoyl,[5] oxazolyl,[6] *N*-methoxy,[7] and acetamido[8]

[†] Sun Yat-sen University.
[‡] The Hong Kong Polytechnic University.

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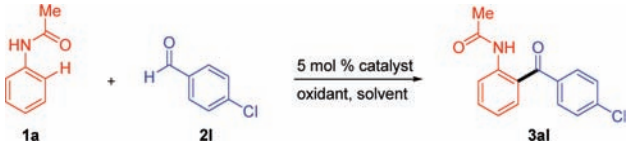
moieties are favorable for assisting the C−H bond activation/functionalization. In view of direct synthesis being able to minimize waste/side product formation, the oxidative coupling of two C−H bonds from two coupling partners is highly attractive.[9]

ortho-Acylacetanilides are important structural motifs and resourceful intermediates for preparing natural products and pharmaceutically useful compounds.[10] Earlier organic syntheses for preparing these *ortho*-amino/acetamido diaryl ketone derivatives were from lithiation of aryl bromides with subsequent acylation by anthranilic acid *N*-methoxy-*N*-methylamide at −78 to −100 °C;[11] the reaction of anilines with acyl chlorides in the presence of $ZnCl_2$;[12] the reduction of the corresponding azide substituted diaryl ketones;[13] or the conversion of 2-acylphenols to 2-acylanilines *via* Smiles rearrangement.[14] Recently, Li reported an acylation of 2-arylpyridine with aldehyde.[15] In 2010, Ge and co-workers reported a Pd-catalyzed decarboxylative *ortho*-acylation of acetanilides using α-oxocarboxylic acid as the acyl sources.[16] Despite this decarboxylative acylation protocol, we report a new oxidative approach for accessing these acylacetanilides using readily available and inexpensive aldehydes as the acyl coupling partners.

With our previous findings indicating that aldehyde could undergo C−H activation for generating a Rh-acyl complex,[17] we began to investigate the feasibility of using aldehyde as the acyl source in this oxidative coupling reaction. Acetanilide and *para*-chlorobenzaldehyde were used as the prototypical substrates in the model reaction. In the initial trial, we were delighted that the desired product **3al** was obtained in 42% yield in the presence of oxidant TBHP (Table 1, entry 1). A screening of catalysts showed that $Pd(TFA)_2$ gave the best results while $Ni(acac)_2$ and $Rh(PPh_3)_3Cl$ were found to be inferior (entries 1−6). The effectiveness of the oxidant was also examined (entries 6−11). TBHP was the most suitable oxidant in this reaction. Increasing the stoichiometry of TBHP offered a better yield of the desired product (entries 6 and 12−14). The optimal TBHP added to the reaction was 4−6 equiv. Commonly used organic solvents were screened. Toluene gave the best yield while other solvents such as DCE, DMF, MeCN, dioxane, and *t*-BuOH afforded poor results (entries 6 and 15−19). Lowering the reaction temperatures to 80−90 °C was feasible (entries 20−21). The reaction proceeded smoothly at 40 °C in the presence of 15 mol % $Pd(TFA)_2$ with an extended reaction time (entry 22).

Table 1. Optimization of Reaction Conditions[a]



1a 2l 3al

Entry	Metal precursor	Oxidant (equiv)	Temp (°C)	Yield (%)[b]
1	$Pd(OAc)_2$	TBHP (2)	120	42
2	$PdCl_2$	TBHP (2)	120	28
3	$Pd(MeCN)_2Cl_2$	TBHP (2)	120	31
4	$Ni(acac)_2$	TBHP (2)	120	0
5	$Rh(PPh_3)_3Cl$	TBHP (2)	120	0
6	$Pd(TFA)_2$	TBHP (2)	120	50
7	$Pd(TFA)_2$	air	120	4
8	$Pd(TFA)_2$	$K_2S_2O_8$ (2)	120	5
9	$Pd(TFA)_2$	$PhI(OAc)_2$ (2)	120	0
10	$Pd(TFA)_2$	Ag_2O (2)	120	0
11	$Pd(TFA)_2$	(*t*-BuO)$_2$ (2)	120	5
12	$Pd(TFA)_2$	TBHP (3)	120	68
13	$Pd(TFA)_2$	TBHP (4)	120	76
14	$Pd(TFA)_2$	TBHP (6)	120	79
15[c]	$Pd(TFA)_2$	TBHP (4)	120	15
16[d]	$Pd(TFA)_2$	TBHP (4)	120	0
17[e]	$Pd(TFA)_2$	TBHP (4)	120	6
18[f]	$Pd(TFA)_2$	TBHP (4)	120	10
19[g]	$Pd(TFA)_2$	TBHP (4)	120	0
20	$Pd(TFA)_2$	TBHP (4)	90	81
21	$Pd(TFA)_2$	TBHP (4)	80	80
22[h]	$Pd(TFA)_2$	TBHP (4)	40	76

[a] Reaction conditions: **1a** (1.0 mmol), **2l** (2.0 mmol), metal precursor (0.05 mmol, 5 mol %), oxidant (as indicated), toluene (2.0 mL) for 18 h under air. [b] Isolated yields. [c] DCE as solvent. [d] DMF as solvent. [e] MeCN as solvent. [f] Dioxane as solvent. [g] *t*-BuOH as solvent. [h] $Pd(TFA)_2$ (0.15 mmol) was used, for 48 h.

With our optimized reaction conditions in hand, we next tested the scope of aldehyde as the acyl source (Scheme 1). 1- and 2-naphthyl aldehydes gave good yields of the corresponding products (**3ab** and **3ac**). It is worth noting that *ortho*-hindered aldehydes were feasible coupling partners (**3ae** and **3af**).[18] Strongly electron-donating *para*-methoxybenzaldehyde gave a slightly lower yield of the product **3ag** presumably due to the difficult C−H bond

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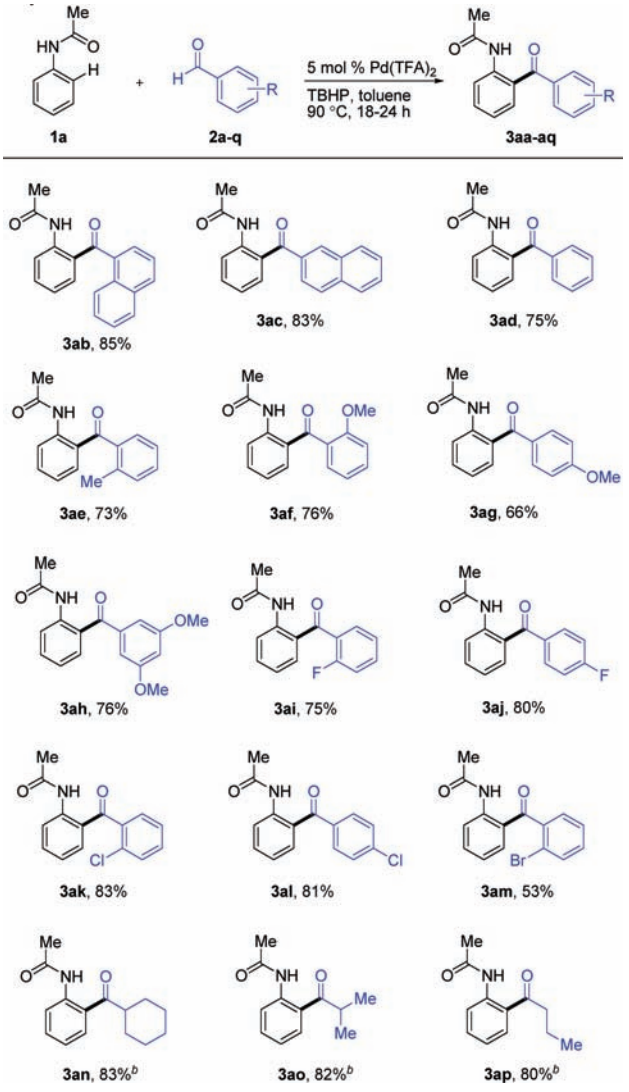
cleavage of aldehdye.[19] *Ortho*- and *para*-fluoro/chloro substituted benzaldehydes were compatible substrates (**3ai**–**3al**). In particular, the bromo group remained intact during the course of the reaction (**3ai**). This entry potentially offers further structural fine-tuning using other traditional cross-coupling reactions.[20] In addition to aromatic aldehdyes, aliphatic aldehydes were applicable in this *ortho*-acylation reaction (**3an**–**3ap**).

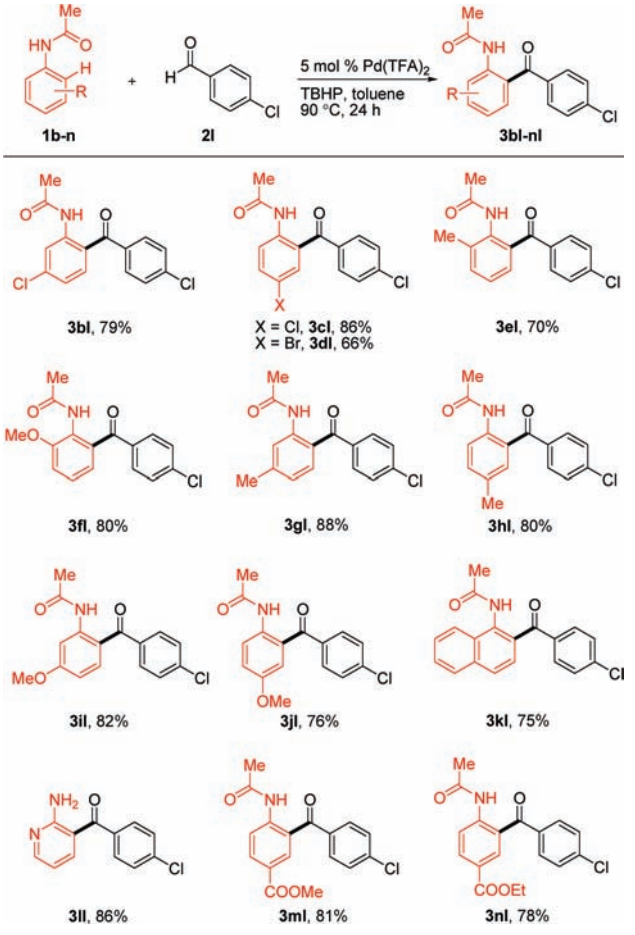
Scheme 1. Scope of Aldehydes in Palladium-Catalyzed *ortho*-Acylation of Acetanilide[a]



[a] Reaction conditions: **1a** (1.0 mmol), **2a**–**q** (2.0 mmol), $Pd(TFA)_2$ (0.05 mmol, 5 mol %), *tert*-butylhydroperoxide TBHP (4.0 mmol), toluene (2.0 mL) at 90 °C under air for 18–24 h. Isolated yields (**3aa**–**3ap**) were reported (reaction times for each substrate were not optimized). [b]Isolated yields based on 60% conversion of acetanilide.

The results of substituted acetanilide (**1b**–**m**) compatibility are compiled in Scheme 2. No significant electronic effect of *para*-substituted acetanilides was found (**3cl**, **3dl**, **3hl**, and **3jl**). In particular, the *ortho*-substituted acetanilides were also found to be compatible in this catalyst system (**3el** and **3fl**).[21] These results were in contrast with a previously reported α-oxocarboxylic acid protocol, in which our route may offer a complementary access to *ortho*-substituted products. It is worth noting that the pyridyl substrate allowed one-pot oxidative C–H coupling and deacetylation, giving the *ortho*-amino diaryl ketone product in good yield (86%, **3ll**). Carboxylic ester groups were tolerable under these reaction conditions (**3ml** and **3nl**).

Scheme 2. Scope of Acetanilides[a]



[a] Reaction conditions: **1a** (1.0 mmol), **2a**–**q** (2.0 mmol), $Pd(TFA)_2$ (0.05 mmol, 5 mol %), *tert*-butylhydroperoxide TBHP (4.0 mmol), toluene (2.0 mL) at 90 °C under air for 18–24 h. Isolated yields (**3aa**–**3ap**) were reported (reaction times for each substrate were not optimized).

Apart from the acetamido group, other directing amido moieties were tested in this *ortho*-acylation reaction (Scheme 3). Phenyl and *iso*-propyl groups (e.g., **5** and **6**)

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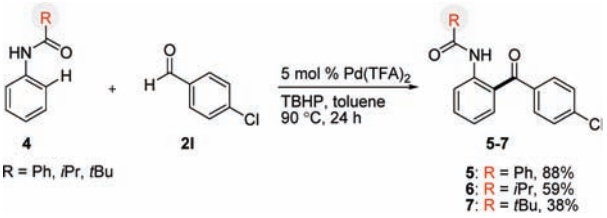
(21) Ge and co-workers reported that *ortho*-substituted acetanilides failed to couple with α-oxocarboxylic acid. See: ref 16.

were applicable in this reaction while a *tert*-butyl moiety gave a low yield of the desired product **7**.

Scheme 3. Pd-Catalyzed *ortho*-Acylation of Amido Substrates



Although a reaction mechanism is not clear at this stage, it is believed that this transformation begins with the *ortho*-palladation of acetanilide with $Pd(TFA)_2$.[22] The resultant complex is subsequently reacted with aldehyde to afford either Pd(IV)[23] or dimeric Pd(III)[24] intermediates.[25] Reductive elimination of acyl and aryl groups provides the *ortho*-acyl-substituted product and regenerates the Pd(II) species. We also attempted to add a radical scavenger (e.g., BHT or ascorbic acid[26]) to the reaction; the rates of reaction were greatly suppressed, and only a trace amount of product was observed from GC-MS analysis. Thus radical intermediates may be involved in this mechanism. In order to eliminate the possibility of the carboxylic acid that could serve as the acyl source, we carried out independent experiments which applies carboxylic acid instead of aldehyde as a coupling partner. However, no desired product was obtained from these control experiments.

In summary, we have succeeded in showing aromatic and aliphatic aldehydes that can act as the acyl sources in the oxidative coupling of two C−H bonds. This efficient Pd-catalyzed *ortho*-acylation process proceeds under mild reaction conditions. Fluoro, bromo, chloro, methoxy, amide, ester, and pyridyl groups at *ortho*-, *meta*-, and *para*-positions are compatible in this catalytic system. We believe this synthetic approach using aldehyde as the acyl source will be useful for generating versatile *ortho*-amino/acetamido diaryl ketone motifs.

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

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(25) A Pd(II) intermediate cannot be ruled out at this stage, since the oxidative addition, carbopalladation of an aldehyde, and β-hydride elimination are precedented transformations for Pd(II) species.

(26) For an attempt to use ascorbic acid as a radical scavenger, see: Warren, J. J.; Mayer, J. M. *J. Am. Chem. Soc.* **2010**, *132*, 7784.