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Rhodium-Catalyzed Oxidative *ortho*-Acylation of Benzamides with Aldehydes: Direct Functionalization of the sp^2 C–H Bond

Jihye Park,[†] Eonjeong Park,[†] Aejin Kim,[†] Youngil Lee,[†] Ki-Whan Chi,[†] Jong Hwan Kwak,[‡] Young Hoon Jung,[‡] and In Su Kim*,[†]

Department of Chemistry, University of Ulsan, Ulsan, 680-749, Republic of Korea, and School of Pharmacy, Sungkyunkwan University, Suwon 440-746, Republic of Korea

insukim@ulsan.ac.kr

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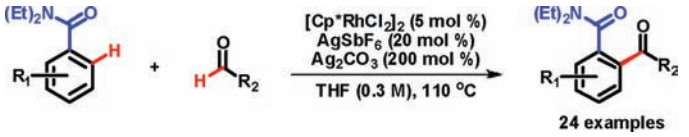
ABSTRACT



A rhodium-catalyzed oxidative acylation of benzamides with aryl aldehydes via direct sp^2 C–H bond cleavage is described. In the presence of $[Cp^*RhCl_2]_2$, $AgSbF_6$, and silver carbonate as an oxidant, *N,N*-diethyl benzamides can be effectively carbonylated to yield *ortho*-acyl benzamides.

Transition-metal-catalyzed direct transformation of inactive C—H bonds has emerged as a powerful tool for the facile production of structurally diverse organic molecules.[1] Since the pioneering efforts of Murai,[2] great progress has been made in transition-metal-catalyzed C—H bond functionalization upon trapping with appropriate electrophiles or nucleophiles under oxidative or basic conditions, respectively.[3] In particular, reactions involving the activation of C—H bonds by a neighboring directing

[†] University of Ulsan.
[‡] Sungkyunkwan University.

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group have been extensively investigated. As a result, the combination of transition metals and directing groups provides efficient conversion of C—H bonds to C—C,[4,5] C—X,[6] C—O,[7] and C—N bonds.[8] Although carbon–carbon bond formation reactions using C=C[4] or C≡C[5] bonds as the coupling partners have been well established, the reactions between C—H bonds and C—heteroatom unsaturated bonds (e.g., C=O and C=N bonds) remain relatively unexplored. In 2009, Cheng reported a palladium-catalyzed coupling reaction between arene compounds containing a pyridine-directing group and aryl aldehydes to afford aryl ketones.[9] Li and coworkers described the palladium-catalyzed oxidative sp^2 C—H bond acylation of 2-phenylpyridine or benzo[*h*]quinoline with aliphatic aldehydes in the presence of $Pd(OAc)_2$ with *tert*-butyl hydroperoxide as an oxidant.[10] Deng and Li also demonstrated a palladium-catalyzed sp^2–sp^2 coupling reaction of 2-arylpyridines and benzylic or aliphatic alcohols from the alcohol oxidation level.[11] Ge developed palladium-catalyzed decarboxylative C—H bond acylation of arylpyridines or acetanilides using α-oxocarboxylic acids as the acyl surrogates to yield *ortho*-acyl arylpyridine[12] or *ortho*-acyl acetanilides,[13] respectively. Also, Li and Kwong reported palladium-catalyzed oxidative coupling of acetanilides and aldehydes to provide *ortho*-acyl acetanilides.[14] Recently, the Ellman[15] and Shi groups[16] described very similar results, which included rhodium-catalyzed direct addition of the C—H bond of arylpyridines to the C=N bond of *N*-sulfonyl aldimines or *N*-Boc aldimines providing the corresponding amine compounds. However, from a synthetic point of view, the introduction of a pyridine-directing group[9−12,15,16] can pose additional barriers to their use due to the difficulty of further manipulations to the desired functional groups.

Aryl ketones are crucial structural motifs in biologically active compounds and functional materials.[17] Traditional methods for the preparation of aryl ketones rely primarily on Friedel–Crafts acylation[18] or the reaction of activated carboxylic acid derivatives, (e.g., Weinreb amides), with organometallic reagents prepared by halogen–metal exchange reactions of aryl halides.[19] However, these approaches present intrinsic drawbacks, namely, the deficiency of regioselectivity and the need for prefunctionalization of both coupling partners. Therefore, it is highly desirable to develop more efficient methodologies for synthesizing aryl ketones with fewer synthetic steps that avoid waste formation.

As part of an ongoing research program directed toward the development of transition-metal-catalyzed carbon–carbon bond formation reactions,[20] we became interested in developing an efficient route to synthesize *ortho*-acyl benzamides from benzamides via C–H bond activation. Herein, we report the rhodium-catalyzed regioselective acylation of sp^2 C–H bonds using aldehydes as the acyl sources in the presence of silver carbonate as an oxidant, affording aryl ketones in moderate to good yields.

Our initial investigation focused on the coupling of *N*,*N*-diethyl benzamide (**1a**) with benzaldehyde (**2a**); selected results are summarized in Table 1. To our delight, the cationic rhodium complex, derived from $[Cp^*RhCl_2]_2$ and $AgSbF_6$, was found to catalyze the coupling of benzamide **1a** and aldehyde **2a** to produce the desired adduct **3a** in 23% yield (Table 1, entry 1). Neutral rhodium complexes did not promote the coupling reaction. Our study focused on the use of oxidants such as Ag_2CO_3, benzoquinone, O_2 gas, $(NH_4)_2S_2O_8$, and $CuCO_3$ (Table 1, entries 5–9). Since aldehydes are sensitive to some oxidants, the choice of oxidants is crucial for this transformation. The use of Ag_2CO_3 as the oxidant resulted in the acylation of a sp^2 C–H bond in *N*,*N*-diethyl benzamide (**1a**) to afford the desired product **3a** as a single regioisomer in 41% yield, as shown in entry 5. However, the combination of isolable catalyst, $[Cp^*Rh(CH_3CN)_3][SbF_6]_2$, and Ag_2CO_3 was relatively ineffective. Solvent screening showed that an improved chemical yield could be obtained using THF as a solvent, providing the *ortho*-acylation product **3a** in 58% yield (Table 1, entry 14), whereas the use of other solvents such as chlorobenzene, toluene, and 1,4-dioxane was less effective (Table 1, entries 11–13). After further optimization, the best results were obtained using a treatment of 5 mol % of $[Cp^*RhCl_2]_2$ and 20 mol % of $AgSbF_6$, in the presence of 200 mol % of Ag_2CO_3 in THF solvent at 110 °C for 20 h, affording the desired aryl ketone **3a** in high yield (70%), as shown in entry 15.

Apart from the *N*,*N*-diethylamide moiety as a directing group, the influence of other directing groups was

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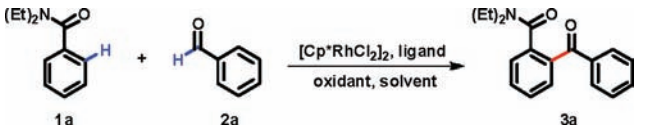
Table 1. Selected Optimization for Reaction Conditions[a]



entry	ligand	oxidant	solvent	yield (%)[b]
1	$AgSbF_6$		CH_2Cl_2	23
2	AgOTf		CH_2Cl_2	trace
3	$AgBF_4$		CH_2Cl_2	4
4	$AgPF_6$		CH_2Cl_2	7
5	$AgSbF_6$	Ag_2CO_3	CH_2Cl_2	41
6	$AgSbF_6$	benzoquinone	CH_2Cl_2	trace
7	$AgSbF_6$	O_2	CH_2Cl_2	7
8	$AgSbF_6$	$(NH_4)_2S_2O_8$	CH_2Cl_2	trace
9	$AgSbF_6$	$CuCO_3$	CH_2Cl_2	8
10[c]	$[Cp^*Rh(CH_3CN)_3]$-$[SbF_6]_2$	Ag_2CO_3	CH_2Cl_2	38
11	$AgSbF_6$	Ag_2CO_3	PhCl	27
12	$AgSbF_6$	Ag_2CO_3	toluene	13
13	$AgSbF_6$	Ag_2CO_3	dioxane	32
14	$AgSbF_6$	Ag_2CO_3	THF	58
15[d]	$AgSbF_6$	Ag_2CO_3	THF	70

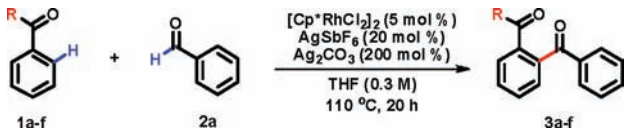
[a] Reaction conditions: **1a** (0.3 mmol), **2a** (0.6 mmol), $[Cp^*RhCl_2]_2$ (2.5 mol %), ligand (10 mol %), oxidant (0.6 mmol), solvent (1 mL) at 110 °C for 20 h under N_2 in 13 × 100 mm^2 pressure tubes. [b] Yield isolated by column chromatography. [c] $[Cp^*Rh(CH_3CN)_3][SbF_6]_2$ (5 mol %) was used as a catalyst. [d] $[Cp^*RhCl_2]_2$ (5 mol %) and $AgSbF_6$ (20 mol %) were used.

examined, as outlined in Table 2. Primary amide **1b** did not yield the desired product (Table 2, entry 2). Dimethylamide **1c** and amide **1e** derived from pyrrolidine were compatible with the reaction conditions (Table 2, entries 3 and 5), whereas sterically hindered dibenzylamide **1d** and less Lewis basic amide **1f** were far more ineffective in this coupling (Table 2, entries 4 and 6).

To explore the substrate scope and limitaions of this process, the established reaction conditions were applied to aromatic aldehydes **2a** and **2g**–**2p**, as shown in Scheme 1.

2-Naphthylaldehyde (**2g**) underwent the sp^2–sp^2 coupling reaction to afford a good yield of the *ortho*-arylated product **3g**. The coupling of benzamide **1a** and aldehydes **2h** and **2i** with *para*-substituted electron-donating groups (Me and OMe) gave the corresponding products **3h** and **3i** in high yields. Electron-rich *meta*-anisaldehyde **2j** and piperonal **2k** were also converted to the corresponding products **3j** and **3k**, respectively. Moreover, halogen-substituted aldehydes **2l** and **2m** were compatible under optimal reaction conditions. In particular, the bromo moiety of **3m** remained intact during the course of the reaction, allowing for further cross-coupling reactions to be performed on the products. In contrast, electron-deficient *m*-nitrobenzaldehyde (**2n**) was less reactive under these reaction conditions. Finally, the heterocyclic aldehydes **2o** and **2p** also participated in the oxidative coupling to furnish **3o** and **3p** in slightly decreased yields. It should

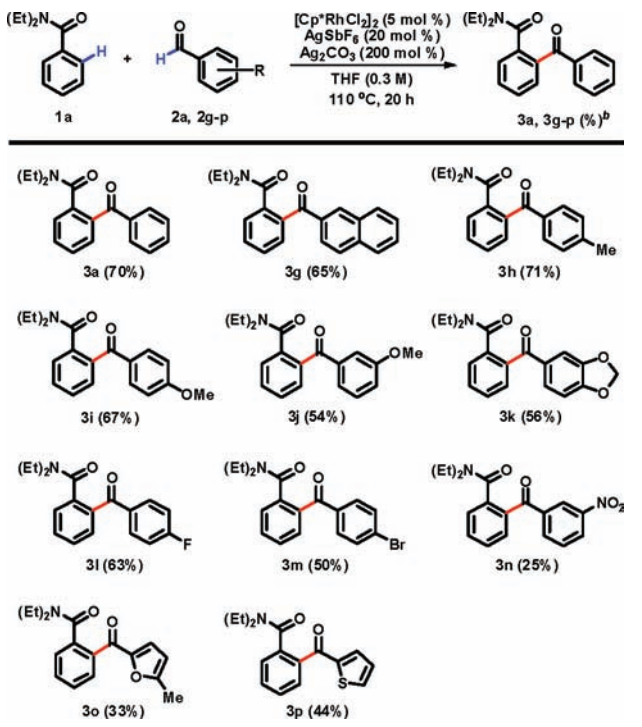
Table 2. Screening of Directing Groups[a]



entry	R		product	yield (%)[b]
1	$N(Et)_2$	**1a**	**3a**	70
2	NHMe	**1b**	**3b**	0
3	$N(Me)_2$	**1c**	**3c**	64
4	$N(Bn)_2$	**1d**	**3d**	6
5	pyrrolidine	**1e**	**3e**	52
6	morpholine	**1f**	**3f**	8

[a] Reaction conditions: **1a**–**f** (0.3 mmol), **2a** (0.6 mmol), 110 °C for 20 h under N_2 in 13 × 100 mm^2 pressure tubes. [b] Yield isolated by column chromatography.

Scheme 1. Scope of Aldehydes in the Oxidative *ortho*-Acylation[a]

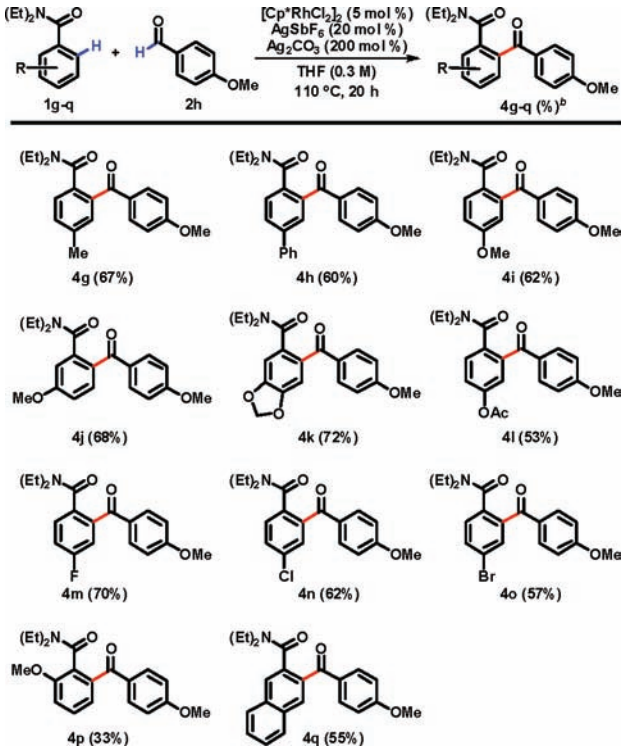


[a] Reaction conditions: **1a** (0.3 mmol), aldehyde (0.6 mmol), 110 °C for 20 h under N_2 in 13 × 100 mm^2 pressure tubes. [b] Yield isolated by column chromatography.

be noted that the reaction exclusively afforded the monoacylated products in all cases, and no bis-acylation products were observed by ^1H NMR or GC-MS analysis.

To further evaluate the scope of this process, the coupling of a variety of benzamides **1g**–**q** and *p*-anisaldehyde (**2h**) under identical reaction conditions was examined (Scheme 2). Electron-neutral and electron-rich benzamides **1g**–**l** were found to be favored in the reaction, whereas substrates with electron-withdrawing groups (e.g., NO_2

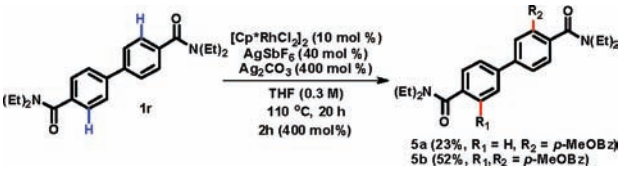
Scheme 2. Scope of *N*,*N*-Diethyl Benzamides in the Oxidative *ortho*-Acylation[a]



[a] Reaction conditions: **1g**−**q** (0.3 mmol), **2h** (0.6 mmol), 110 °C for 20 h under N_2 in 13 × 100 mm^2 pressure tubes. [b]Yield isolated by column chromatography.

and CO_2Et) in *para*- or *meta*-positions failed to deliver the acylation products under these conditions (data not shown). This observation is consistent with the previous results that monoacylated adducts with an electron-withdrawing acyl moiety did not participate in the bis-acylation process. Benzamides **1m**−**o** with halogen functional groups (F, Cl, and Br) were well converted to the corresponding products **4m**−**o**, respectively. However, *ortho*-methoxy substituted benzamide **1p** gave a low yield, presumably due to the increased steric effect preventing the formation of a coplanar conformation between the aromatic ring and the ketone moiety in the *N*,*N*-diethyl amide group. In addition, 2-naphthamide **1q** selectively afforded the corresponding product **4q** in 55% yield. Interestingly, no C-1 acylation adduct was obtained since the C−H bond in the C-8 position of the naphthalene moiety may interfere with the approach of the aldehyde to the C-1 position.

Scheme 3. Oxidative *ortho*-Acylation of Dicarboxamide



Finally, we examined the reaction of dicarboxamide **1r** and *p*-anisaldehyde (**2h**) under optimal reaction conditions. As expected, dicarboxamide **1r** was converted to the monoacylated product **5a** and the bis-acylated product **5b** with an excellent regioselectivity in 23% and 52% yield, respectively (Scheme 3).

In conclusion, we have developed an efficient method for Rh-catalyzed oxidative carbonylation of benzamides with aldehydes via C−H bond activation. The cationic rhodium complex, derived from $[Cp^*RhCl_2]_2$ and $AgSbF_6$, catalyzes the coupling of *N*,*N*-diethyl benzamides and aryl aldehydes in the presence of Ag_2CO_3 to yield *ortho*-monoacylated *N*,*N*-diethyl benzamides. Mechanistic studies and applications for the synthesis of biologically active compounds are currently underway, and the results will be reported in due course.

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Supporting Information Available. Spectroscopic data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.