ORGANIC LETTERS

2012
Vol. 14, No. 3
906–909

Tandem Rh(III)-Catalyzed Oxidative Acylation of Secondary Benzamides with Aldehydes and Intramolecular Cyclization: The Direct Synthesis of 3-Hydroxyisoindolin-1-ones

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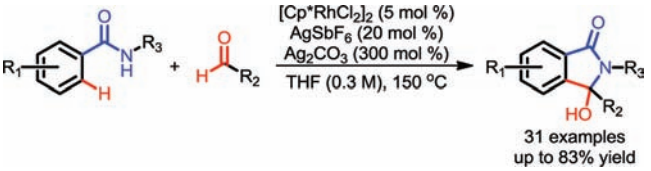
Received December 22, 2011

ABSTRACT



The rhodium-catalyzed oxidative acylation between secondary benzamides and aryl aldehydes via sp^2 C−H bond activation followed by an intramolecular cyclization is described. This method results in the direct and efficient synthesis of 3-hydroxyisoindolin-1-one building blocks.

3-Hydroxyisoindolin-1-ones are ubiquitous structural motifs in a number of synthetic and naturally occurring bioactive compounds, such as the synthetic diuretic and antihypertensive agent chlorthalidone,[1] the natural product isoquinoline fumadensine,[2] and isoindolobenzazepine chilenine,[3] and a synthetic antibacterial compound.[4] 3-Hydroxyisoindolin-1-ones are conventionally synthesized by the site-selective addition of organometallic reagents or other nucleophilic agents to phthalimide derivatives.[5] The condensation of pseudo acid chlorides (Ψ-acid chlorides) with amines provides an efficient protocol for the synthesis of 3-hydroxyisoindolin-1-ones.[6] Friedel−Crafts acylation of compounds containing secondary amide moieties with carboxylic acid derivatives (e.g., acid chlorides) followed by intramolecular cyclization has also been reported.[7] Recently, Liu et al. described a tandem transformation for the construction of 3-hydroxyisoindolin-1-ones from *o*-(substituted ethynyl)benzoic acids and primary amines using a phase transfer catalyst.[8] However, from a synthetic point of view, these approaches have intrinsic drawbacks, which include strict handling requirements for the organometallic reagent (e.g., Grignard reagents), poor functional group tolerance, harsh reaction conditions, and the need for prefunctionalization of the coupling partners. Therefore, it is highly desirable to develop novel and efficient protocols that involve fewer synthetic steps and

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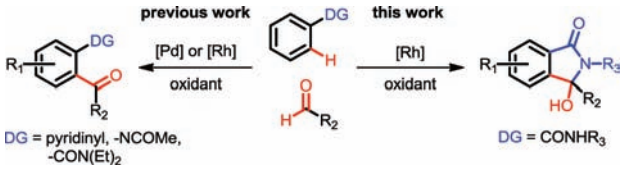
10.1021/ol2034228
Published on Web 01/20/2012

readily available starting materials for the synthesis of 3-hydroxyisoindolin-1-ones.

Scheme 1. Transition-Metal-Catalyzed Oxidative Acylation and Intramolecular Cyclization



Transition-metal-catalyzed C−H bond functionalizations have emerged as powerful tools in organic synthesis, since such methods avoid the necessity of multistep preparation of preactivated starting materials and lead to an improved overall efficiency of the desired transformation.[9] In particular, the combination of transition metals and directing groups is a useful strategy for facilitating C−H bond cleavage[10] and has provided valuable conversions of C−H bonds to C−X (X = carbon,[11] oxygen,[12] nitogen,[13] and halogen[14]) bonds. Recently, remarkable progress has been made in the transition-metal-catalyzed oxidative coupling of two different aryl C−H bonds for the construction of arene−arene linkages.[15] However, cross-coupling reactions between aryl C−H and aldehyde C−H bonds to form corresponding aryl ketones remain relatively unexplored.[16] Cheng et al. described a palladium-catalyzed cross-coupling reaction of aromatic compounds containing a pyridine directing group and aldehydes to afford aryl ketones.[16a] Li and co-workers reported the palladium-catalyzed sp^2−sp^2 coupling of 2-phenylpyridine with aliphatic aldehydes.[16b] Deng and Li demonstrated a palladium-catalyzed oxidative acylation reaction of 2-arylpyridines and alcohols in the presence of *tert*-butyl hydroperoxide as an oxidant.[16c] Li and Kwong also reported a palladium-catalyzed oxidative coupling of acetanilides and aldehydes to provide *ortho*-acyl acetanilides.[16d] Recently, we described the rhodium-catalyzed oxidative acylation of tertiary benzamides and aldehydes to afford aryl ketones (Scheme 1).[17]

As part of an ongoing research program directed toward the development of transition-metal-catalyzed carbon−carbon bond forming reactions,[18] we became interested in developing an efficient synthetic route to 3-hydroxyisoindolin-1-ones from secondary benzamides and aldehydes via C−H bond activation followed by aminocyclization. In this paper, we report the rhodium-catalyzed regioselective *ortho*-acylation and intramolecular cyclization sequence in the presence of silver carbonate as an oxidant to prepare 3-hydroxyisoindolin-1-ones in good to high yields.

We initiated our investigation by exploring the coupling of a variety of *N*-substituted benzamides (**1a**−**h**) with 4-(trifluoromethyl)-benzaldehyde (**2a**); selected results are summarized in Table 1. The cationic rhodium complex derived from $[Cp^*RhCl_2]_2$ and $AgSbF_6$ catalyzed the coupling of *N*-methyl benzamide (**1a**) and aryl aldehyde **2a** in the presence of Ag_2CO_3 as an oxidant to yield compound **3a** in 34% yield (Table 1, entry 1). Further screening of *N*-monosubstituted amides indicated that *N*-isopropyl benzamide (**1b**) was the most effective in affording the 3-hydroxyisoindolin-1-one **3b**, as shown in entries 2−8. However, the use of other oxidants, such as AgOAc, $K_2S_2O_8$, benzoquinone, and *t*-BuO_2H, was relatively ineffective in the coupling of **1b** and **2a** (Table 1, entries 9−12). A screening of solvents revealed that the best yield was obtained with THF and that other oxygen-containing solvents, such as 1,4-dioxane and THP, were less effective (Table 1, entries 13 and 14). After further optimization, the best results were obtained by increasing the amount of Ag_2CO_3 (300 mol %) and the reaction temperature (150 °C) to afford the desired 3-hydroxyisoindolin-1-one **3b** in 83% yield, as shown in entry 16.

Having established the optimized reaction conditions, the substrate scope was examined with respect to the aldehyde (Scheme 2). The coupling of benzamide **1b** and aldehydes **2i**−**m** with *para*- or *meta*-substituted electron-withdrawing groups afforded the corresponding products **3i**−**m** in moderate to high yields. This reaction was also compatible with halogen-substituted aldehydes **2n**−**p** furnishing the corresponding products **3n**−**p** in good yields. Particularly noteworthy was the tolerance of the reaction conditions to chloro and bromo groups, which provide a versatile synthetic handle for further functionalization of the products. In addition, 2-naphthaldehyde **2q** and benzaldehyde **2r** also smoothly underwent reaction to generate the corresponding products **3q** and **3r**, respectively.

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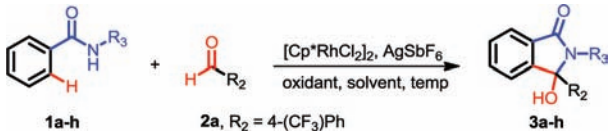
Table 1. Selected Optimization of the Reaction Conditions[a]



entry	R_3	benzamide	oxidant	solvent	yield (%)[b]
1	methyl	**1a**	Ag_2CO_3	THF	34
2	isopropyl	**1b**	Ag_2CO_3	THF	64
3	isobutyl	**1c**	Ag_2CO_3	THF	48
4	*tert*-butyl	**1d**	Ag_2CO_3	THF	23
5	benzyl	**1e**	Ag_2CO_3	THF	35
6	phenyl	**1f**	Ag_2CO_3	THF	12
7	methoxy	**1g**	Ag_2CO_3	THF	0
8	tosyl	**1h**	Ag_2CO_3	THF	0
9	isopropyl	**1b**	AgOAc	THF	0
10	isopropyl	**1b**	$K_2S_2O_8$	THF	0
11	isopropyl	**1b**	benzoquinone	THF	18
12	isopropyl	**1b**	*t*-BuO_2H	THF	0
13	isopropyl	**1b**	Ag_2CO_3	1,4-dioxane	19
14[c]	isopropyl	**1b**	Ag_2CO_3	THP	40
15[d]	isopropyl	**1b**	Ag_2CO_3	THF	72
16[e]	isopropyl	**1b**	Ag_2CO_3	THF	83

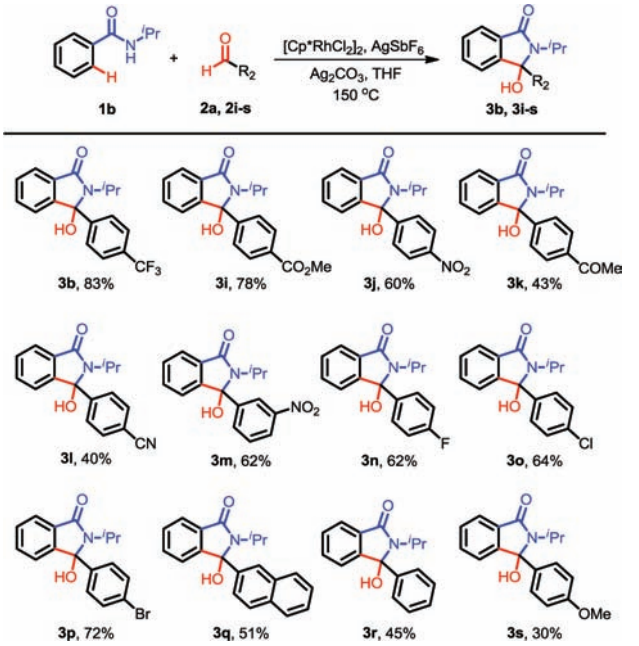
[a] Reaction conditions: **1a**–**h** (0.3 mmol), **2a** (0.6 mmol), $[Cp^*RhCl_2]_2$ (5 mol %), $AgSbF_6$ (20 mol %), oxidant (0.6 mmol), solvent (1 mL) at 110 °C for 20 h under N_2 in 13 × 100 mm^2 pressure tubes. [b] Yield isolated by column chromatography. [c] THP = tetrahydropyrane. [d] Ag_2CO_3 (0.9 mmol) was used. [e] 150 °C.

In contrast, electron-rich aldehyde **2s** was less reactive under the reaction conditions presumably due to the difficulty of metal insertion into the aldehyde C–H bond.[19]

Couplings with a variety of benzamides **1i**–**r** and aldehyde **2a** under identical reaction conditions were examined to further explore the substrate scope and limitations of this process (Scheme 3). Electron-neutral and -donating benzamides **1i**–**m** were readily converted to the corresponding products **4i**–**m**. In particular, the reaction of benzamides **1j**–**m** with a *meta*-substituent preferentially occurred at the more sterically accessible position. In addition, benzamides **1n**–**p** with halogen groups (Br and Cl) in the *para*- or *meta*-positions were found to be favorable in the reaction and provided products which would be amenable to further cross-coupling reactions. However, *ortho*-substituted benzamides **1q** and **1r** showed relatively decreased reactivity since coplanar conformation between the aromatic ring and the amide moiety was not available.

Encouraged by these results, we further examined the influence of both the acetamido and *N*-isopropyl amide

Scheme 2. Scope of Aldehydes[a]



[a] Reaction conditions: **1b** (0.3 mmol), aldehydes **2a** and **2i**–**s** (0.6 mmol), $[Cp^*RhCl_2]_2$ (5 mol %), $AgSbF_6$ (20 mol %), Ag_2CO_3 (0.9 mmol), THF (1 mL) at 150 °C for 20 h under N_2 in 13 × 100 mm^2 pressure tubes. [b] Yield isolated by column chromatography.

directing groups such as in compound **1s**, as shown in Scheme 4. Unfortunately, the Pd-catalyzed oxidative acylation conditions reported by Li and Kwong did not yield *ortho*-acyl acetanilide from the coupling of acetanilide **1s** with aldehyde **2a**.[16d] However, compound **1s** under our optimal reaction conditions was converted to the 3-hydroxyisoindolin-1-one **4s** with excellent regioselectivity in 48% yield. Thus, Rh catalysis could provide efficient regioselectivity in the C–H bond functionalization reaction.

To probe the catalytic mechanism, we carried out a competition experiment between equimolar amounts of *deuterio*-**1b** and benzamides **1b** with aldehyde **2i** under our standard conditions for 10 min, which results in the intermolecular kinetic isotope effect (k_H/k_D) of 1.1 (Scheme 5). Interestingly, the reaction of *deuterio*-**1b** with aldehyde **2i** in THF (condition A) provided significant deuterium loss (27% D) at the *ortho*-position of *deuterio*-**3i** as well as partial deuteration (10% D) of the internal sp^3 C–H bond of the isopropyl group. In addition, the use of either condition B (**2i**-d_1 in THF) or condition C (**2i**-d_1 in THF-d_8) afforded isotope results very similar to those obtained through the use of condition A. These results may arise from a fast and reversible metalation–proto(deutero)demetalation step of *deuterio*-**1b** prior to the cross-coupling reaction

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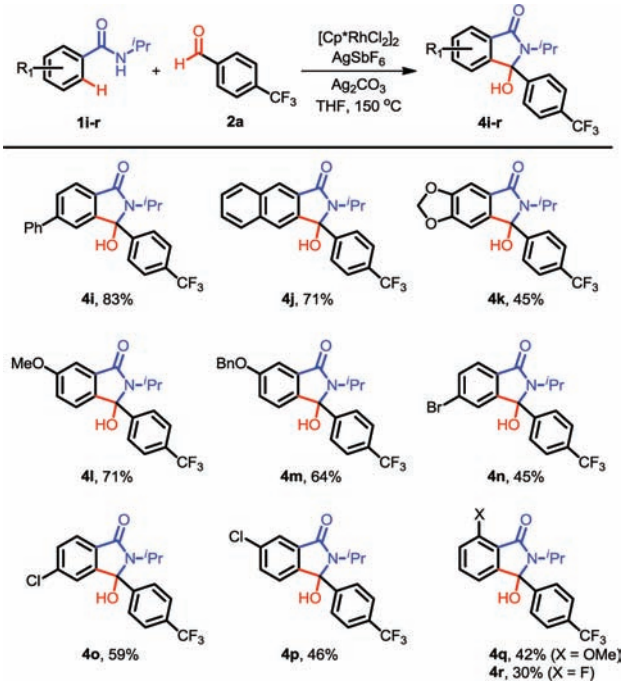
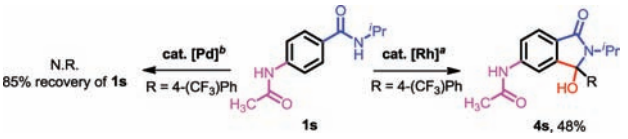
Scheme 3. Scope of Benzamides[a]



[a] Reaction conditions: benzamide **1i**–**r** (0.3 mmol), **2a** (0.6 mmol), $[Cp^*RhCl_2]_2$ (5 mol %), $AgSbF_6$ (20 mol %), Ag_2CO_3 (0.9 mmol), THF (1 mL) at 150 °C for 20 h under N_2 in 13 × 100 mm^2 pressure tubes. [b] Yield isolated by column chromatography.

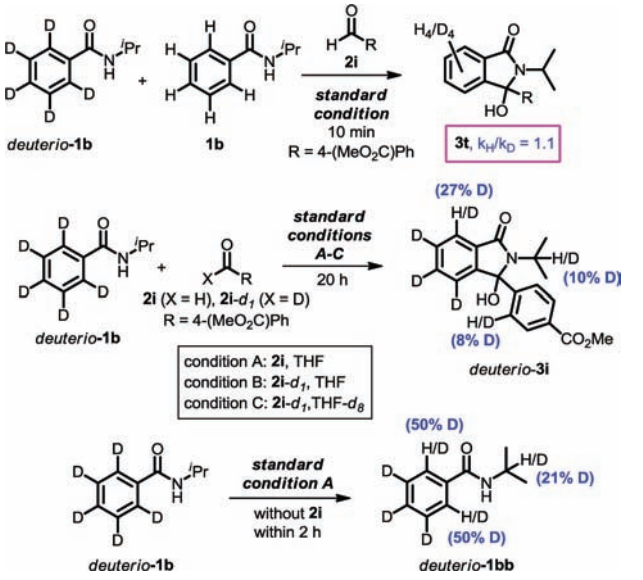
Scheme 4. Regioselectivity of Pd vs Rh



[a] Reaction conditions: **1s** (0.3 mmol), **2a** (0.6 mmol), $[Cp^*RhCl_2]_2$ (5 mol %), $AgSbF_6$ (20 mol %), Ag_2CO_3 (0.9 mmol), THF (0.3 M) at 150 °C for 20 h. [b] Reaction conditions: **1s** (0.3 mmol), **2a** (0.6 mmol), $Pd(TFA)_2$ (5 mol %), *tert*-butyl hydroperoxide (1.2 mmol), toluene (0.5 M) at 90 °C for 18 h.

with aldehyde **2i** or **2i**-d_1.[20] Partial deuteration (8% D) of the aromatic ring sp^2 C–H bond may be the result of a

Scheme 5. Mechanistic Studies



reversible protonation–deuteration step of the aryl ketone intermediate obtained from the oxidative acylation reaction. To gain insight into the catalytic pathway, we again conducted a competition reaction between equimolar amounts of electron-deficient aldehyde **2i** and electron-rich aldehyde **2s** with benzamide **1b** for 1 h, affording about 2.5 times more **3i** than **3s**. Thus, it seems that the insertion of aldehyde to a cyclo-rhodated intermediate is most likely involved in the rate-limiting step of this transformation (see Supporting Information for plausible reaction mechanism).

Acknowledgment. This work was supported by National Research Foundation of Korea (No. 2010-0002465 and 2011-0005400) funded by the Ministry of Education, Science and Technology.

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

The authors declare no competing financial interest.