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Catalytic Formation of α-Aryl Ketones by C−H Functionalization with Cyclic Alkenyl Carbonates and One-Pot Synthesis of Isocoumarins

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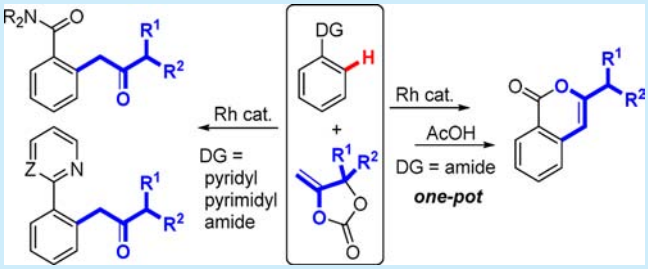
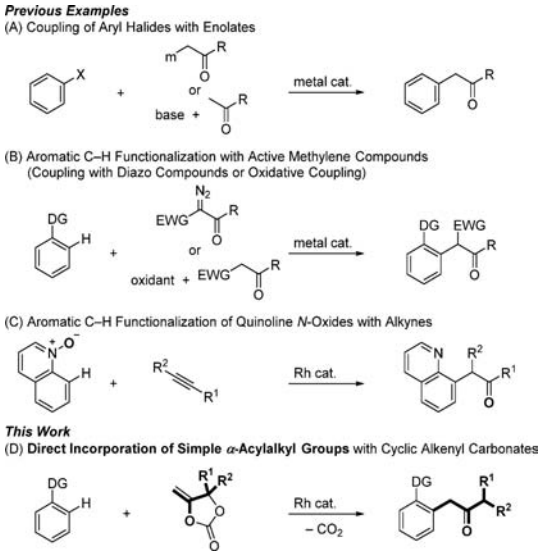
Supporting Information

ABSTRACT: We report here a method for direct catalytic introduction of simple α-acylalkyl groups via rhodium-catalyzed C−H functionalization with cyclic alkenyl carbonates, synthetic equivalents to enolates bearing leaving groups. The reaction proceeded smoothly without using bases to give α-aryl ketones in high yields. Various nitrogen-containing aromatic rings and amide groups serve as directing groups. 3-Substituted isocoumarins can also be prepared by one-pot C−H functionalization/cyclization.



Synthesis of α-aryl ketones by catalytic cross-coupling of aryl halides or pseudohalides with enolates has been extensively studied because the core structure of the products can be found in many molecules of biological interest (Scheme 1A).[1] Direct introduction of α-acylalkyl groups to arenes by transition-metal-catalyzed C−H functionalization can be an alternative method to prepare α-aryl ketones in an efficient way, but the scope of the α-acylalkyl groups introduced by the current methods is limited to specially functionalized ones,[2] and new methods to incorporate simple α-acylalkyl groups effectively are still desired. Therefore, we investigated the C−H functionalization methods to convert hydrogens on aromatic rings to simple α-acylalkyl groups.

Scheme 1. Catalytic Syntheses of α-Aryl Ketones by α-Acylalkylation



There have been several methods for introduction of α-acylalkyl groups by metal-catalyzed C−H functionalization.[2−7] For example, coupling with active methylene compounds using diazo compounds[2] or oxidants[3] has been achieved, but in this case, an additional electron-withdrawing group is attached to the α-position (Scheme 1B).[4] Recently, Li and Chang independently developed methods to introduce α-acylalkyl groups via C−H bond cleavage of quinoline *N*-oxides using alkynes (Scheme 1C),[5] but the *N*-oxide moiety was used as an internal oxidant in these cases, which means that the substrate core structure is altered by the reaction. Glorius and co-workers also reported a C−H functionalization reaction using ketones bearing leaving groups at the α-positions and proposed the formation of simple α-aryl ketone intermediates, but the products of the reaction are N-heterocycles formed via further condensation of the carbonyl moiety with the directing group.[6]

Here, we report a new method for direct catalytic introduction of simple α-acylalkyl groups via C−H bond cleavage by a rhodium catalyst (Scheme 1D). Cyclic alkenyl carbonates[8] are used as synthetic equivalents to enolates bearing leaving groups, and the reaction smoothly proceeded without using bases. In addition to nitrogen-containing aromatic rings, various amide groups function as directing groups, and in this case, one-pot formation of isocoumarins is also achieved.

During our investigation of C−H functionalization with alkenyl esters and carbonates,[9] we examined the reaction of arylpyridines with cyclic alkenyl carbonates,[10] which are readily prepared from propargyl alcohols and carbon dioxide or Boc-protected propargyl alcohols.[11] When the reaction of 2-(*o*-

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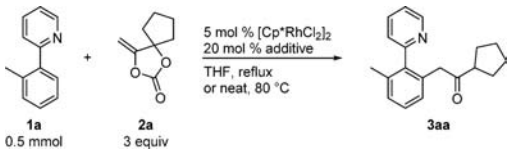
tolyl)pyridine (**1a**) with cyclic alkenyl carbonate **2a** was performed in the presence of 5 mol % of $[Cp^*RhCl_2]_2$ and 20 mol % of $AgBF_4$ under THF refluxing conditions for 24 h,[12] ortho-selective α-acylalkylation proceeded to give α-aryl ketone **3aa** in 63% GC yield (Table 1, entry 1). Other additives including

Table 1. Rhodium-Catalyzed α-Acylalkylation of Arylpyridine 1a with Cyclic Alkenyl Carbonate 2a[a]



entry	additive	solvent	time (h)	GC yield (%)
1	$AgBF_4$	THF (0.5 mL)	24	63
2	$AgSbF_6$	THF (0.5 mL)	24	54
3	AgOTf	THF (0.5 mL)	24	50
4	$NaBF_4$	THF (0.5 mL)	24	nd[b]
5	$AgBF_4$	THF (0.5 mL)	48	76
6	$AgBF_4$	THF (0.25 mL)	48	88
7[c]	$AgBF_4$	neat	48	88 (73)[d]

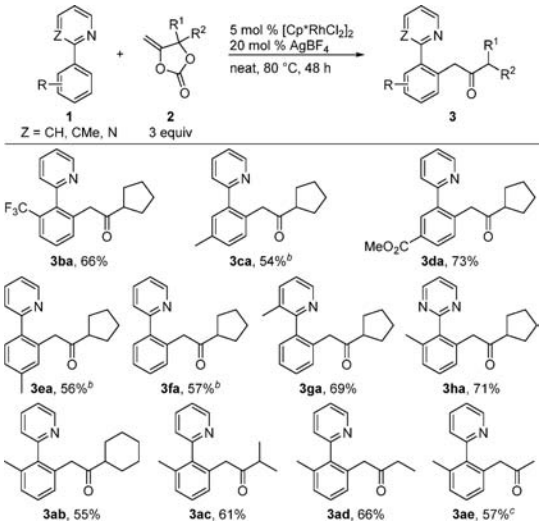
[a]Reaction conditions: **1a** (0.5 mmol), **2a** (1.5 mmol), $[Cp^*RhCl_2]_2$ (0.025 mmol), additive (0.1 mmol), THF, reflux. [b]Not detected. [c]Performed with no solvent at 80 °C. [d]Isolated yield is shown in parentheses.

$AgSbF_6$, AgOTf, and $NaBF_4$ were examined but resulted in lower yields or no product formation (entries 2−4). Extension of the reaction time to 48 h improved the yield to 76% (entry 5), and reduction of the solvent amount further increased the yield to 88% (entry 6). The reaction without using the solvent at 80 °C also gave 88% GC yield of **3aa**,[13] and using these reaction conditions, product **3aa** was isolated in 73% yield (entry 7).

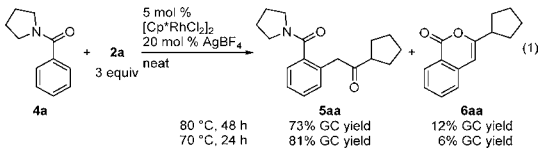
Substrate scope was examined for the rhodium-catalyzed C−H α-acylalkylation using arenes bearing nitrogen-containing aromatic directing groups and cyclic alkenyl carbonates (Scheme 2). The α-acylalkylation of an arylpyridine bearing a trifluoromethyl group at the ortho position proceeded at the other ortho position to give **3ba** in 66% isolated yield. When arylpyridines possessing methyl and methoxycarbonyl groups at the meta positions were used as substrates, the less sterically congested ortho positions were selectively functionalized to give α-aryl ketones **3ca** and **3da** in 54 and 73% yields, respectively. The reaction of arylpyridines bearing only para substituents or no substituents gave only mono-α-acylalkylation products such as **3ea** and **3fa**. The α-acylalkylation was also observed for the reaction of 2-phenyl-3-picoline and 2-(*o*-tolyl)pyrimidine to provide **3ga** and **3ha** in 69 and 71% yields, respectively. In addition to **2a**, various other cyclic alkenyl carbonates were used as substrates to afford cyclohexyl (**3ab**), isopropyl (**3ac**), ethyl (**3ad**), and methyl (**3ae**) ketones in 55−66% yields.

Benzamide derivatives were also found to be applicable for the rhodium-catalyzed C−H α-acylalkylation. When pyrrolidine amide **4a** was reacted with cyclic alkenyl carbonate **2a** at 80 °C for 48 h, the reaction went to full conversion and the corresponding α-acylalkylation product **5aa** was obtained in 73% GC yield along with 12% GC yield of isocoumarin **6aa**, which is considered to be formed by intramolecular condensation of **5aa** (eq 1). Lowering of the reaction temperature to 70 °C and shortening of the reaction time to 24 h improved the GC yield of **5aa** to 81% while suppressing the formation of **6aa** to 6%.

Scheme 2. Nitrogen-Directed Rhodium-Catalyzed α-Acylalkylation of Arenes 1 with Cyclic Alkenyl Carbonate 2[a]

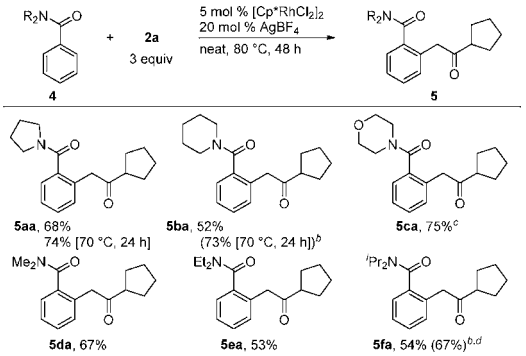


[a]Reaction conditions: **1** (0.5 mmol), **2** (1.5 mmol), $[Cp^*RhCl_2]_2$ (0.025 mmol), $AgBF_4$ (0.1 mmol), neat, 80 °C. [b]Performed with 5 equiv of **2**. [c]Performed using 10 mol % (0.05 mmol) of $[Cp^*RhCl_2]_2$ and 40 mol % (0.2 mmol) of $AgBF_4$.



The C−H α-acylalkylation was examined using various benzamide derivatives (Scheme 3). In addition to pyrrolidine

Scheme 3. Carbonyl-Directed Rhodium-Catalyzed α-Acylalkylation of Various Amides 4 with 2a[a]



[a]Reaction conditions: **4** (0.5 mmol), **2a** (1.5 mmol), $[Cp^*RhCl_2]_2$ (0.025 mmol), $AgBF_4$ (0.1 mmol), neat, 80 °C, 48 h. [b]Numbers in parentheses are isolated yields obtained using 5 equiv (2.5 mmol) of **2a**, 10 mol % (0.05 mmol) of $[Cp^*RhCl_2]_2$, and 40 mol % (0.2 mmol) of $AgBF_4$. [c]Performed with 5 equiv of **2a**. [d]Performed for 72 h.

amide **4a**, other derivatives of cyclic amines such as piperidine and morpholine can be used as substrates and the corresponding products **5ba** and **5ca** were obtained. The reaction of *N*,*N*-dimethyl-, *N*,*N*-diethyl-, and *N*,*N*-diisopropylamides also proceeded to give α-aryl ketones **5da**, **5ea**, and **5fa** in 53−67% yields.

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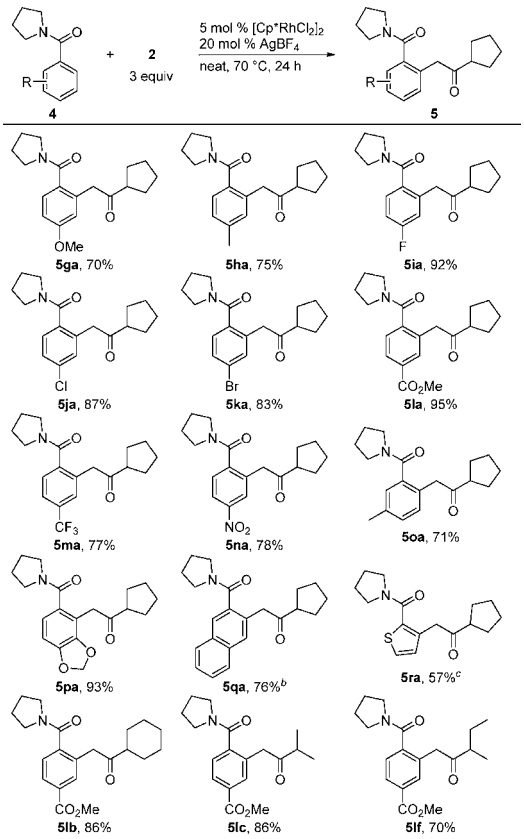
Substrate scope was then investigated for the C−H α-acylalkylation using various pyrrolidine amides and cyclic alkenyl carbonates (Scheme 4). First, benzamides bearing various

Scheme 4. Carbonyl-Directed Rhodium-Catalyzed α-Acylalkylation of Amide 4 with Cyclic Alkenyl Carbonate 2[a]

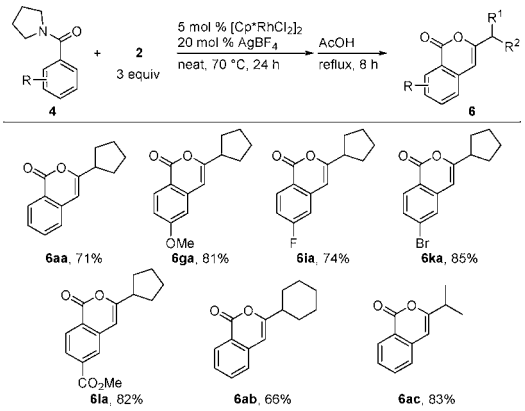


[a]Reaction conditions: **4** (0.5 mmol), **2** (1.5 mmol), $[Cp^*RhCl_2]_2$ (0.025 mmol), $AgBF_4$ (0.1 mmol), neat, 70 °C, 24 h. [b]The product formed by α-acylalkylation at the 1-position was obtained in 9% yield. [c]Performed with 5 equiv (2.5 mmol) of **2a**, 10 mol % (0.05 mmol) of $[Cp^*RhCl_2]_2$, and 40 mol % (0.1 mmol) of $AgBF_4$ (0.1 mmol).

substituents at the para positions were examined, and in all cases, only mono-α-acylalkylation products were observed. The reaction of substrates bearing electron-donating methoxy and methyl groups gave the corresponding α-aryl ketones **5ga** and **5ha** in 70 and 75% yields, respectively. Halogen substituents such as fluoro, chloro, and bromo groups all were tolerated under the reaction conditions to give the mono-α-acylalkylation products **5ia**, **5ja**, and **5ka** in 83−92% yields. The reaction of substrates with electron-withdrawing groups such as methoxycarbonyl, trifluoromethyl, and nitro groups also proceeded smoothly to give products **5la**, **5ma**, and **5na** in high yields, and particularly methoxycarbonyl-substituted α-aryl ketone **5la** was obtained in 95% yield. While the C−H α-acylalkylation of a benzamine derivative with a methyl group at the meta position proceeded at the less sterically congested ortho position to provide **5oa** in 71% yield, only the more sterically congested ortho position was α-acylalkylated in the reaction of the 1,3-benzodioxole-5-carboxamide derivative to give **5pa** in 93% yield.[14] The C−H α-acylalkylation of the 2-naphthalenecarboxamide derivative occurred mainly at the 3-position to afford **5qa** in 76% yield along with 9% of the product formed by α-acylalkylation at the 1-position. Thiophene-2-carboxamide derivative **4r** was also converted to the corresponding ketone **5ra** in 57% yield when 10 mol % of the Rh catalyst and 5 equiv of **2a** were used. Various cyclic alkenyl carbonates were also used for the reaction to give cyclohexyl (**5lb**), isopropyl (**5lc**), and *sec*-butyl (**5ld**) ketones in 70−86% yields.

As described previously in eq 1, isocoumarin derivative **6aa** was formed in the reaction of pyrrolidine amide **4a** with **2a** by intramolecular condensation. Because isocoumarin cores are also found in many molecules of biological interest, development of a new method for formation of 3-substituted isocoumarins using a one-pot sequence was examined (Scheme 5).[15,16] When the

Scheme 5. Formation of 3-Substituted Isocoumarin by One-Pot C−H α-Acylalkylation/Deaminative Cyclization[a]



[a]Reaction conditions: **4** (0.5 mmol), **2** (1.5 mmol), $[Cp^*RhCl_2]_2$ (0.025 mmol), $AgBF_4$ (0.1 mmol), neat, 70 °C, 24 h, then AcOH (1 mL), reflux 8 h.

reaction of pyrrolidine amide **4a** with cyclic alkenyl carbonate **2a** was conducted at 70 °C for 24 h and subsequently heated with acetic acid under refluxing conditions,[17] the corresponding isocoumarin derivative **6aa** was obtained in 71% yield. The one-pot reaction of substrates bearing methoxy, fluoro, bromo, and methoxycarbonyl groups at the para positions also proceeded to give isocoumarins **6ga**, **6ia**, **6ka**, and **6la** in 74−85% yields. The one-pot formation of isocoumarin derivatives were also examined using other cyclic alkenyl carbonates and products bearing cyclohexyl (**6ab**) and isopropyl (**6ac**) groups were obtained in 66 and 83% yields, respectively.

Although the mechanism of the rhodium-catalyzed C−H α-acylalkylation is unclear at this point, a possible catalytic cycle is shown in Figure 1. Dicationic rhodium species **A** generated from $[Cp^*RhCl_2]_2$ and $AgBF_4$ reacts with the substrate to form rhodacycle species **B** by chelation-assisted C−H bond cleavage.[18] Coordination of the cyclic alkenyl carbonate gives complex **C**, which undergoes migratory insertion to generate alkylrhodium complex **D**. Then β-oxygen elimination proceeds to give olefin complex **E** and subsequent decarboxylation provides rhodium enolate **F** or oxa-π-allylrhodium **F′**, which is protonated to release the α-aryl ketone product with regeneration of dicationic species **A**.

In summary, a new method is described for direct catalytic introduction of simple α-acylalkyl groups via C−H bond cleavage using a rhodium catalyst. Cyclic alkenyl carbonates were used as synthetic equivalents to enolates bearing leaving groups, and the reaction proceeded without using bases to give α-aryl ketones in high yields. In addition to nitrogen-containing aromatic rings, various amide groups function as directing groups. Aromatic

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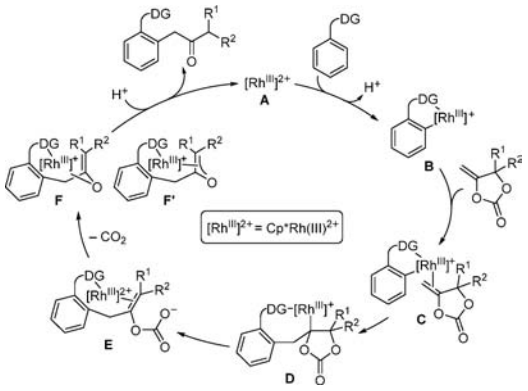

Figure 1. Possible mechanism of the rhodium-catalyzed α-acylalkylation of arenes with cyclic alkenyl carbonates.

compounds bearing a variety of substituents including both electron-donating and withdrawing groups and various cyclic alkenyl carbonates can be applied for this reaction. One-pot formation of isocoumarins by C−H functionalization/cyclization was also achieved.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02414.

Full experimental details and characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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