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Ruthenium-catalyzed Acylation of Arylpyridines with Acyl Chlorides via *ortho*-Selective C–H Bond Cleavage

Takuya Kochi, Aoi Tazawa, Kazuki Honda, and Fumitoshi Kakiuchi*
Department of Chemistry, Faculty of Science and Technology, Keio University, 3-14-1 Hiyoshi, Kohoku-ku, Yokohama, Kanagawa 223-8522

(Received June 29, 2011; CL-110547; E-mail: kakiuchi@chem.keio.ac.jp)

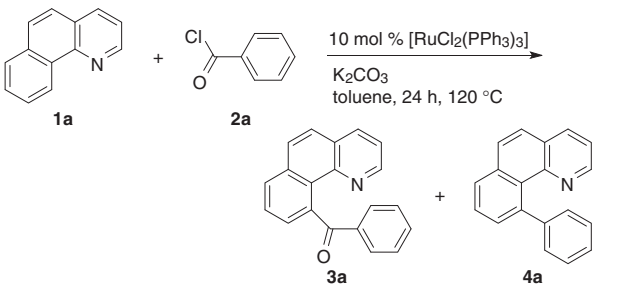
Ruthenium-catalyzed *ortho*-selective acylation of arylpyridines with acyl chlorides via C–H bond cleavage is described. Aromatic acyl chlorides as well as α,β-unsaturated acyl chlorides were coupled with arylpyridines to give aromatic ketones in the presence of $[RuCl_2(PPh_3)_3]$ as a catalyst and potassium carbonate as a base.

Direct functionalization of arenes via regioselective C–H bond cleavage by transition-metal catalysts has been one of the most extensively studied areas in organometallic catalysis in the past decade.[1] Although selective introduction of carbonyl functionalities onto aromatic rings would be valuable in organic synthesis, the scope of such reactions via transition-metal-catalyzed C–H bond cleavage is still limited. For example, C–H acylation has been achieved using several strategies. Rhodium-catalyzed coupling of diphenylketene with benzene was reported in 1978.[2] Three-component coupling of aromatic and heteroaromatic compounds with carbon monoxide and olefins have been studied extensively,[3,4] but these methods can only allow for the introduction of aliphatic acyl groups. In contrast, introduction of aroyl groups via C–H bond cleavage by transition metals had not been known until Cheng and co-workers developed palladium-catalyzed oxidative acylation of arenes with benzaldehyde derivatives in 2009.[5a] Since then, several reports have been made on catalytic C–H aroylation using aldehydes and alcohols in the presence of oxidizing agents.[5b–5f] In early 2009, our group reported that ruthenium-catalyzed introduction of amide and ester groups via aromatic C–H bond cleavage proceeds using chlorocarbonyl compounds such as carbamoyl chlorides and alkyl chloroformates.[6] We envisioned that catalytic C–H acylation may be achieved when acyl chlorides are used as coupling partners. The reaction of aromatic compounds with acyl chlorides in the presence of Lewis acids, Friedel–Crafts acylation, is widely known as a general method for acylation of arenes. However, if chelation-assisted C–H bond cleavage can be employed for the acylation, unlike Friedel–Crafts methods, the reaction should be *ortho*-selective and relatively electron-deficient arenes may also be used as substrates.

Herein we report ruthenium-catalyzed acylation of arylpyridines with acyl chlorides via aromatic C–H bond cleavage. Direct introduction of aroyl and alkenoyl groups without oxidizing agents was achieved using the corresponding aroyl and alkenoyl chlorides.

The acylation was first examined with benzo[*h*]quinoline (**1a**) and benzoyl chloride (**2a**) as substrates. When the reaction of **1a** with **2a** using $[RuCl_2(PPh_3)_3]$ was conducted following our previously reported aminocarboxylation procedure, the desired acylation product **3a** was obtained in 58% GC yield (Table 1, Entry 1). Phenylation product **4a** was also formed in 7% yield by decarbonylation. Reduction of the amount of toluene solvent to 3 mL improved the yield of **3a** to 76% (Entry 2), but further decrease to 2 mL resulted in 68% yield (Entry 3). The amount of potassium carbonate was then investigated. When the amount of the base was lowered to 1.2 equiv, slight decrease of the product yield was observed (Entry 4). In contrast, the use of 5.0 equiv of potassium carbonate led to 97% GC yield of acylation product **3a** (Entry 5).[7] Using these conditions, product **3a** was isolated by silica gel column chromatography in 95% yield in a pure form, which does not contain arylation product **4a**. It is worthy to note that Rh(I)-catalyzed coupling of **1a** with **2a** was reported by Yu,[8] but phenylation product **4a** was obtained exclusively via decarbonylation. In contrast, decarbonylation is surpressed in our system to give acylation product **3a** as a major product.

Table 1. Ruthenium-catalyzed regioselective acylation of **1a** with **2a**[a]

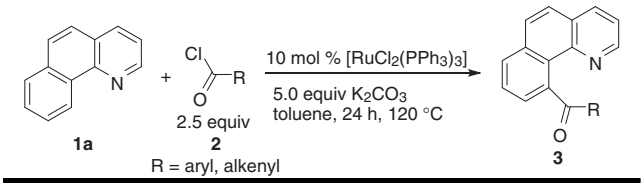


Entry	K_2CO_3 /equiv	Toluene /mL	GC yield/%	
			3a	**4a**
1	2.5	6	58	7
2	2.5	3	76	4
3	2.5	2	68	3
4	1.2	3	71	3
5	5.0	3	97 (95)[b]	3

[a]Reaction conditions: **1a** (1 mmol), **2a** (2.5 mmol), K_2CO_3, $[RuCl_2(PPh_3)_3]$ (0.1 mmol), toluene, 120 °C, 24 h. [b]Isolated yield (%).

The acylation of **1a** with various benzoyl chloride derivatives was then examined (Table 2). The reactions with benzoyl chlorides bearing electron-donating Me and OMe groups at para position (**2b** and **2c**) provided the corresponding acylation products **3b** and **3c** in 81% and 88% yields, respectively (Entries 1 and 2). The structure of **3b** was confirmed by X-ray crystallography, and the result clearly showed that the 10-position of **1a** was selectively acylated. The reaction with benzoyl chloride with a *p*-CF_3 group (**2d**) afforded 63% yield of **3d** (Entry 3), but the use of 20 mol % of triphenylphosphine as

Table 2. Ruthenium-catalyzed regioselective acylation of **1a** with various acyl chlorides[a]



1a **2** **3**

Entry	2	R	3	Isolated yield/%
1	**2b**	*p*-MeC_6H_4	**3b**	81
2	**2c**	*p*-$MeOC_6H_4$	**3c**	88
3	**2d**	*p*-$CF_3C_6H_4$	**3d**	63
4[b]	**2d**	*p*-$CF_3C_6H_4$	**3d**	86
5	**2e**	*o*-MeC_6H_4	**3e**	84
6	**2f**	*o*-$MeOC_6H_4$	**3f**	23
7[c]	**2g**		**3g**	54
8[c]	**2h**		**3h**	33

[a]Reaction conditions: **1a** (1 mmol), **2a** (2.5 mmol), K_2CO_3 (5.0 mmol), $[RuCl_2(PPh_3)_3]$ (0.1 mmol), toluene 3 mL, 120 °C, 24 h. [b]20 mol % of PPh_3 was used as an additive. [c]Reaction was performed for 48 h in 6 mL of toluene.

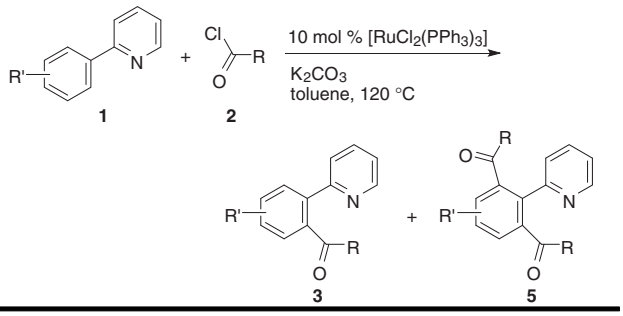
an additive improved the yield to 86% (Entry 4). While benzoyl chloride with an *o*-Me group (**2e**) provided product **3e** in 84% yield (Entry 5), the use of an *o*-OMe group resulted in 23% yield of product **3f** (Entry 6).

The acylation can also be performed with α,β-unsaturated acyl chlorides. When the reaction of **1a** was performed with tigloyl chloride (**2g**) in 6 mL of toluene, the corresponding enone product **3g** was obtained in 54% yield, and the olefin geometry in **2g** was maintained in product **3g** (Entry 7). The acylation with 1-cyclohexenecarbonyl chloride (**2h**) also provided product **3h** in 33% yield (Entry 8). To our knowledge, only one example of direct introduction of alkenoyl groups via metal-catalyzed C–H bond cleavage has been reported by Li and co-workers for one set of substrates, which gave moderate yield (29%) of the acylation product.[5b]

The acylation was also applicable for other arylpyridines. When the ruthenium-catalyzed acylation of *m*-tolylpyridine **1b** with 1.2 equiv of **2e** was performed using 2.4 equiv of potassium carbonate, monoacylation product **3i** was obtained in 67% yield (Table 3, Entry 1). The acylation of *m*-trifluoromethylpyridine **1c** gave 38% yield of monoacylation product **3j**, but extension of the reaction time to 48 h improved the yield to 51% (Entry 2). The reaction of phenylpyridine **1d** with **2e** gave a mixture of mono- and diacylation products **3k** and **5k** (Entry 3). The use of *p*-fluorophenylpyridine **1e** showed lower reactivity, but after 48 h, product **3l** was obtained in 68% yield (Entry 4). The reaction with α,β-unsaturated acyl chloride **2g** was also examined. *meta*-Substituted 2-phenylpyridines, **1b** and **1c**, were converted to the corresponding monoacylation products in 58% and 68% yields, respectively (Entries 5 and 6). The reaction of phenylpyridine **1d** with **2g** also gave a mixture of mono- and diacylation products (Entry 7).

Although the detailed mechanism of the acylation is yet unclear, we propose the catalytic cycle of the acylation as shown

Table 3. Ruthenium-catalyzed regioselective acylation of arylpyridines with acyl chlorides



1 **2** **3** **5**

Entry	1	R′	2	Products			
				3	Yield of 3/%	5	Yield of 5/%
1[a]	**1b**	*m*-Me	**2e**	**3i**	67	—	nd[d]
2[a,b]	**1c**	*m*-CF_3	**2e**	**3j**	51	—	nd[d]
3[a]	**1d**	H	**2e**	**3k**	56	**5k**	6
4[a,b]	**1e**	*p*-F	**2e**	**3l**	68	—	nd[d]
5[c]	**1b**	*m*-Me	**2g**	**3m**	58	—	nd[d]
6[c]	**1c**	*m*-CF_3	**2g**	**3n**	68	—	nd[d]
7[c]	**1d**	H	**2g**	**3o**	40[e]	**5o**	20[e]

[a]Reaction conditions: **1** (1 mmol), **2e** (1.2 mmol), K_2CO_3 (2.4 mmol), $[RuCl_2(PPh_3)_3]$ (0.1 mmol), toluene 3 mL, 120 °C, 24 h. [b]Reaction was performed for 48 h instead of 24 h. [c]Reaction conditions: **1** (1 mmol), **2g** (2.5 mmol), K_2CO_3 (5.0 mmol), $[RuCl_2(PPh_3)_3]$ (0.1 mmol), toluene 6 mL, 120 °C, 48 h. [d]Not detected. [e]Two products **3o** and **5o** were isolated as a mixture and the yields were determined by ^1H NMR analysis.

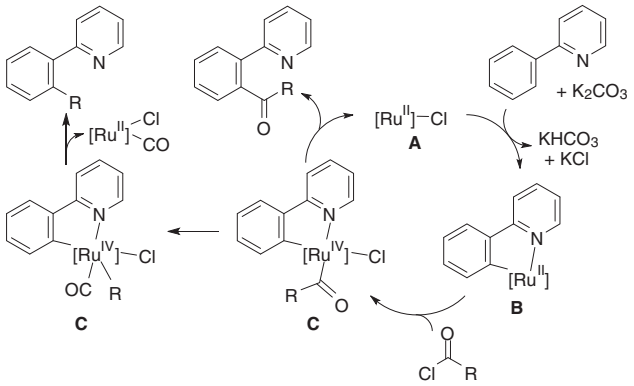
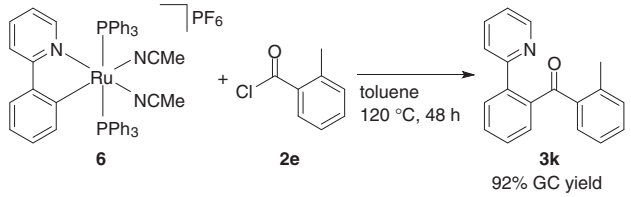


Figure 1. Proposed mechanisms of the catalytic C–H acylation and the decarbonylative functionalization.

in Figure 1.[9,10] First, Ru(II) species **A** reacts with arylpyridine to give five-membered ruthenacycle **B**. Due to the relatively electron-rich nature of the chelate containing a carbanion ligand, acyl chloride can undergo oxidative addition to **B** to form Ru(IV) species **C**. Decarbonylation may occur from acylruthenium complex **C**, but the highly oxidized ruthenium center may disfavor a CO ligand formed by decarbonylation and facilitate the reductive elimination to give the acylation product.

To gain understanding of the mechanism, we examined a reaction of ruthenacycle species **6**, reported by Sirlin, Pfeffer,



Scheme 1. Reaction of ruthenacycle **6** with **2e**.

and co-workers,[11] with acyl chloride **2e** (Scheme 1). When complex **6** was heated at 120 °C for 48 h in a 0.4 M toluene solution of **2e** (under the conditions used for Table 3, Entry 3), the corresponding acylation product **3k** was obtained in 92% GC yield. The result shows it is possible to form acylation products by the reaction of acyl chlorides with ruthenacycle(II) species generated from arylpyridines.

In summary, ruthenium-catalyzed *ortho*-selective acylation of arylpyridines with acyl chlorides via C–H bond cleavage was achieved under oxidant-free conditions. Aromatic acyl chlorides as well as α,β-unsaturated acyl chlorides were used for the acylation to obtain the corresponding aromatic ketone products. Only little decarbonylative coupling was observed in our catalyst system to give ketones in good yields.[12]

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