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Ruthenium-catalyzed Ortho-selective Aromatic C–H Alkenylation with Alkenyl Carbonates

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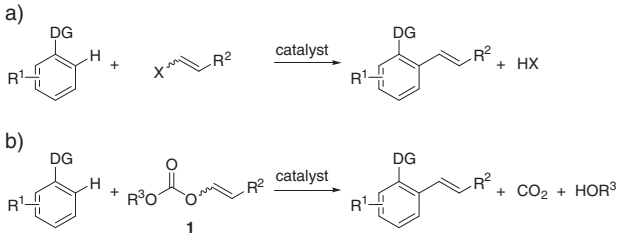
Ortho-selective aromatic C–H alkenylation with alkenyl carbonates proceeds in the presence of a catalytic amount of [Ru(cod)(cot)]. Arylpyridines and an aryloxazoline were regioselectively alkenylated without adding external bases. Aromatic C–H alkylation also occurs depending on the reaction conditions.

Catalytic alkenylation of C–H bonds is a powerful method for the synthesis of styrene derivatives, which can be found in many molecules of biological, pharmaceutical, and industrial interest. There have been several classes of methods developed for catalytic aromatic C–H alkenylation,[1] and one of them is coupling with alkenes bearing halides or pseudohalides as leaving groups (Scheme 1a).[2–7] This class of alkenylation enables the introduction of various types of alkenyl groups by designing appropriate alkenes with leaving groups. However, it produces the corresponding acid originating from the leaving group such as hydrogen halides, and in most cases, addition of a base is necessary to conduct the reaction.

In this context, our group developed aromatic C–H alkenylation with alkenyl esters using ruthenium catalysts.[8] This reaction provides alkenylation products along with carboxylic acids such as acetic acid as by-products. The acidity of the carboxylic acids is weak enough to perform the reaction without adding a base for most of the substrates, including arylpyridines, but more basic substrates such as oxazolines require the addition of 2,6-lutidine to scavenge the acid by-product. In search of an alkenylation reaction under more neutral conditions, we envisioned the use of alkyl alkenyl carbonates **1** as alkenylating agents, because the leaving group, alkylcarbonate, may degrade into carbon dioxide and the corresponding alkoxide, which eventually affords an alcohol as a by-product (Scheme 1b).

Here, we describe a catalytic aromatic C–H alkenylation using alkenyl carbonates. The reaction was catalyzed by [Ru(cod)(cot)] (cod: cyclooctadiene, cot: cyclooctatriene) without any further additives to afford ortho-alkenylation products from aromatic compounds, including arylpyridines and an aryloxazoline. Depending on the reaction conditions, alkylation products can also be prepared.

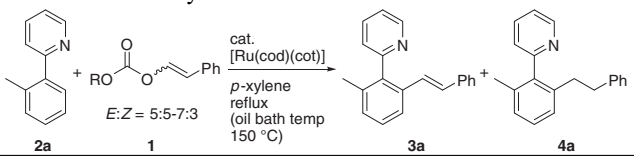


Scheme 1. Catalytic C–H alkenylations of aromatic compounds with (a) alkenyl halides and pseudohalides and with (b) carbonates.

When *o*-tolylpyridine **2a** was reacted with 3 equiv of ethyl β-styryl carbonate (**1a**) in the presence of 5 mol % of [Ru(cod)(cot)] for 24 h in gently refluxing *p*-xylene by heating in an oil bath whose temperature was adjusted to 150 °C, ortho-alkenylation product **3a** was obtained in 51% yield, along with alkylation product **4a** in 2% yield (Table 1, Entry 1). The product yield was improved to 71% by using 10 mol % of the catalyst and 5 equiv of **1a** (Entry 2). The reaction of **2a** and 3 equiv of isopropyl β-styryl carbonate (**1b**) with 5 mol % of [Ru(cod)(cot)] afforded 70% yield of alkenylation product **3a**, but the yield of alkylation product **4a** was also increased to 3% (Entry 3). Examination of the reaction conditions revealed that the reaction with 5 equiv of **1b** for 48 h afforded product **3a** in 90% yield (Entry 4). When the reaction was performed on gram-scale (5 mmol of **2a**), 1.12 g (83%) of **3a** was isolated (Entry 5). The use of methyl, *tert*-butyl, or phenyl carbonate for alkenylation was not effective and afforded low yields of alkenyltion product **3a** (Entries 6–8).

Examination of the C–H alkenylation reaction of several arylpyridines was conducted under the conditions described for Entries 2 (conditions A, using carbonate **1a**) and 4 (conditions B, using carbonate **1b**) in Table 1 (Table 2). The alkenylation of

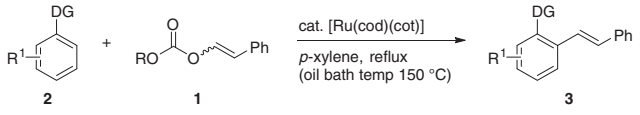
Table 1. Ruthenium-catalyzed C–H alkenylation of arylpyridine **2a** with alkenylcarbonates **1**[a]

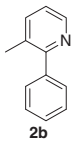
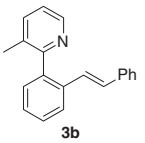
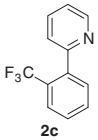
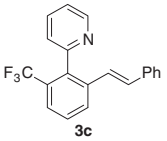
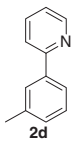
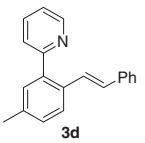
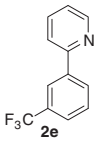
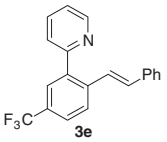
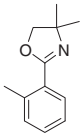
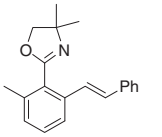


Entry	[Ru(cod)(cot)] /mol %	**1** R	**1** equiv	Time /h	Yields/%[b] **3a**	Yields/%[b] **4a**
1	5	Et (**1a**)	3	24	51	2
2	10	Et	5	24	71	2
3	5	*i*-Pr (**1b**)	3	24	70	3
4	5	*i*-Pr	5	48	90	3
5[c]	5	*i*-Pr	5	48	83[d]	—
6	5	Me (**1c**)	3	24	11	nd[e]
7	5	*t*-Bu (**1d**)	3	24	23	nd[e]
8	5	Ph (**1e**)	3	24	8	nd[e]

[a]Conditions: **2a** (0.5 mmol), **1**, [Ru(cod)(cot)], *p*-xylene (0.1 mL), reflux (oil bath temp 150 °C). [b]GC yields. [c]5 mmol scale. [d]Isolated yield. [e]Not detected.

Table 2. Ruthenium-catalyzed C–H alkenylation of aromatic compounds with alkenylcarbonates **1**[a]



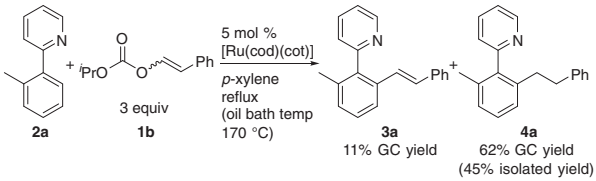
Entry	**2**	Conditions	**3**	GC yield /%
1	 **2b**	A	 **3b**	82
2		B		43
3	 **2c**	A	 **3c**	80
4		B		85
5	 **2d**	A	 **3d**	63
6		B		54
7	 **2e**	A	 **3e**	50
8		B		25
9	 **2f**	A	 **3f**	77
10		B		77

[a]Conditions A: **2** (0.5 mmol), **1a** (2.5 mmol), [Ru(cod)(cot)] (0.05 mmol), *p*-xylene (0.1 mL), reflux (oil bath temp 150 °C), 24 h; conditions B: **2** (0.5 mmol), **1b** (2.5 mmol), [Ru(cod)(cot)] (0.025 mmol), *p*-xylene (0.1 mL), reflux (oil bath temp 150 °C), 48 h.

phenylpicoline **2b** with carbonate **1a** afforded the corresponding ortho-alkenylation product **3b** in 82% yield (Entry 1), and the reaction under conditions B using carbonate **1b** resulted in lower yield (Entry 2). In the case of arylpyridine **2c** bearing a trifluoromethyl group at the ortho position on the phenyl ring, high yields of product **3c** were obtained for reactions under both conditions A and B (Entries 3 and 4). Arylpyridines with meta substituents were also investigated for the alkenylation. For *m*-tolylpyridine **2d**, the C–H alkenylation took place only at the less congested ortho position and afforded the corresponding monoalkenylation product **3d** in 63% and 54% yields under conditions A and B, respectively (Entries 5 and 6). The reaction of arylpyridine **2e** with a *m*-trifluoromethyl group provided monoalkenylation product **3e** in lower yields (Entries 7 and 8), and under conditions A, product **3e** was obtained in 50% yield (Entry 7).

C–H alkenylation was also investigated with *o*-tolyloxazoline **2f**, whose alkenylation using alkenyl acetate requires addition of a base, 2,6-lutidine, to obtain the alkenylation product in good yield (69%) because of the relatively high basicity of the oxazoline ring.[8] To examine if the reaction of **2f** with alkenyl carbonates proceeds without addition of a base because it affords alcohols as by-products, the alkenylation was performed under conditions A and B and indeed proceeded to afford 77% yield of the corresponding alkenylation product **3f** in each case (Entries 9 and 10). In addition to alkenylation products **3**, small amounts of the corresponding alkylation products, **4b**–**4f**, were also detected by GC and GC-MS for all entries in Table 2.

The reaction of **2a** with isopropyl β-styryl carbonate (**1b**) was also examined to investigate if alkylation product **4a** can be obtained as the major product, and it turned out that harsh refluxing conditions facilitated the alkylation reaction and the reaction at 170 °C (oil bath temperature) afforded 62% GC yield of alkylation product **4a**, which was isolated in 45% yield, along with alkenylation product **3a** in 11% GC yield (eq 1).



(1)

If C–H alkenylation using alkenyl carbonates proceeds in a similar manner to alkenyl esters,[8b] a plausible mechanism is shown in Figure 1.[9] That is, oxidative addition of the ortho C–H bond and hydrometalation of alkenyl carbonate are followed by β-alkoxycarboxy elimination to afford olefin complex **A**. Carbometalation (step a) and β-hydride elimination (step b) then lead to the formation of alkenylation product **3a**. It is not clear at which point decarboxylation occurs, but this process transforms the alkoxycarboxy group into the alkoxy group. The alkoxy intermediates may undergo β-hydride elimination to afford hydrides **B** and **C**, which can be used to produce alkylation product **4a** by either reductive elimination after carbometalation (step a or c) or hydrometalation (step d), or reduction of alkenylation product **3a** (step e).[10] The alkylation reaction may be facilitated by rigorous exclusion of carbon dioxide to assist the decarboxylation process.

In conclusion, we developed a ruthenium-catalyzed ortho C–H alkenylation of aromatic compounds with alkenyl carbonates. Arylpyridines were regioselectively alkenylated by ethyl and isopropyl alkenyl carbonates in the presence of a catalytic amount of [Ru(cod)(cot)]. An aryloxazoline was also identified as an effective substrate for alkenylation with alkenyl carbonates. In this case, addition of a base was unnecessary to achieve high yields, probably because of the low acidity of the alcohol by-products, in contrast to the previously described reaction with alkenyl acetates, which requires the addition of 2,6-lutidine. When the reaction was conducted at 170 °C (oil bath temperature), an alkylation product became the major product. Mechanistic investigations of C–H alkenylation with alkenyl carbonates are still underway.

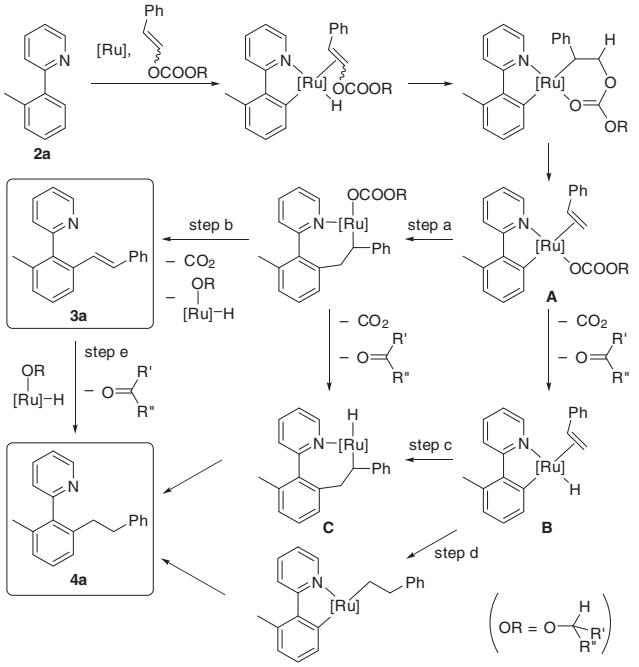


Figure 1. Proposed mechanisms of the catalytic C–H alkenylation and the alkylation.

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8 a) Y. Matsuura, M. Tamura, T. Kochi, M. Sato, N. Chatani, F. Kakiuchi, *J. Am. Chem. Soc.* **2007**, *129*, 9858. b) Y. Ogiwara, M. Tamura, T. Kochi, Y. Matsuura, N. Chatani, F. Kakiuchi, *Organometallics* **2014**, *33*, 402.

9 In the case of the reaction using alkenyl acetate as an alkenylating agent, the *Z*-isomer reacted faster than the *E*-isomer (See ref 8b). Although the difference in reactivity between *E*- and *Z*-carbonate **1** is not clear, when the reaction was performed using **1b** (Table 1, Entry 4), the ratio of the *Z*-isomer in the remaining **1b** slightly decreased from that of the starting **1b** (*E*:*Z* = 32:68 to 36:64).

10 The reduction of **3a** was observed when the reaction of **3a** with **2b** and **1b** was performed in the presence of [Ru(cot)(cot)] as a catalyst. See the Supporting Information for details. Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.

