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Unique Effect of Coordination of an Alkene Moiety in Products on Ruthenium-Catalyzed Chemoselective C−H Alkenylation

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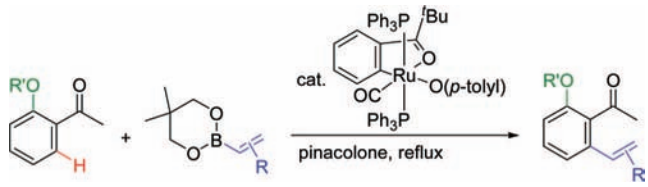
ABSTRACT



Ruthenium-catalyzed alkenylation of 2′-alkoxyacetophenones with alkenylboronates provides *ortho* C−H alkenylation products without sacrificing an ether functional group at the other *ortho* position. Both excellent chemoselectivity and high product yields are achieved with an aryloxo ruthenium complex. The effective suppression of the C−O bond cleavage was attained by coordination of the alkenyl moiety in the C−H alkenylation product to the ruthenium center.

Chelation-assisted transition-metal-catalyzed carbon−carbon bond formation via cleavage of unreactive C−H bonds has been an attractive research subject[1] because excellent regioselectivity can be achieved for a variety of transformations such as alkylation,[2] alkenylation,[3] arylation,[4,5] and acylation.[6] These methods have also become powerful tools for regioselective introduction of functional groups in modern organic synthesis. Chelation-assisted control of regioselectivity in catalytic reactions has not only been applied for functionalization of C−H bonds but also for that of other bonds including C−O and C−N bonds.[7,8]

However, chemoselective functionalization of C−H bonds over those other cleavable bonds has not been a trivial task. For example, the coupling reaction of 2′-methoxyacetophenone (**1**) with triethoxyvinylsilane catalyzed by $RuH_2(CO)(PPh_3)_3$ (**2**) affords only 11% of the C−H/olefin coupling product as a result of competing cleavage of the C−O bond (eq 1),[2d] which is considered thermodynamically easier to cleave than the C−H bond.[7b]

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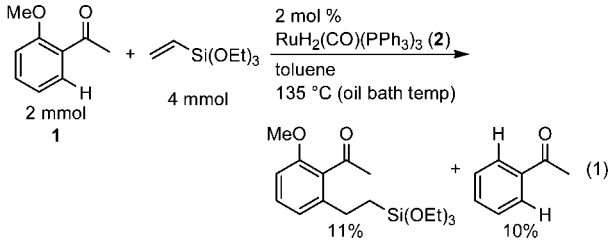
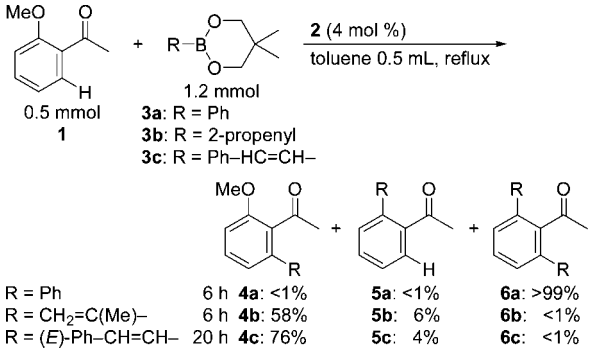


In this communication, we report a highly C−H selective alkenylation of *o*-alkoxyacetophenones such as **1** with alkenylboronates using ruthenium catalysts. The unique effect of an introduced alkenyl substituent in the product on the chemoselectivity is also described.

Previously we reported $RuH_2(CO)(PPh_3)_3$-catalyzed arylation of *o*-alkoxyphenyl ketones with arylboronates via C−O bond cleavage.[7] When aryl ketone **1** was subjected to the conditions with phenylboronic ester **3a**, 2′,6′-diphenylacetophenone **6a** was obtained in quantitative yield (Scheme 1) and no monophenylated products, **4a** and **5a**, were

Scheme 1. Coupling of **1** with Aryl- and Alkenylboronates



observed throughout the reaction. Thus, both C−H and C−OMe bonds were phenylated efficiently under the reaction conditions. In contrast to the phenylation, however, alkenylation of **1** proceeds preferentially at C−H bonds to afford monoalkenylated products. The reaction of **1** with 2-propenylboronic ester **3b** afforded monoalkenylation product **4b** in 58% yield. In this case, the corresponding C−O alkenylation product **5b** was formed only in 6% yield. The reaction with *β*-styrylboronate **3c** for 20 h also provided the corresponding C−H alkenylation product **4c** in 76% yield along with 4% yield of **5c**.

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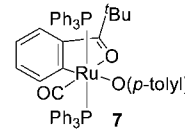
Then the catalysts for the C−H alkenylation were screened to improve both the chemoselectivity and the activity (Table 1).

Table 1. Screening of Catalysts for C−H Selective Alkenylation[a]

entry	catalyst	GC yields 4c	5c	6c
1	$RuH_2(CO)(PPh_3)_3$ (**2**)	55%	3%	<1%
2	$Ru(CO)_2(PPh_3)_3$	17%	<1%	<1%
3	$Ru_3(CO)_{12}$	7%	<1%	<1%
4	Ru(cod)(cot)	4%	<1%	<1%
5	$RuHCl(CO)(PPh_3)_3$	<1%	<1%	<1%
6	 **7**	76%	<1%	<1%
7	$RhCl(PPh_3)_3$	<1%	<1%	<1%
8	$Cp^*Rh(C_2H_3SiMe_3)_2$	<1%	<1%	<1%

[a] Reaction conditions: ketone **1** (0.5 mmol), *β*-styrylboronate **3c** (0.6 mmol), pinacolone (0.5 mL), catalyst (0.02 mmol of Ru), reflux, 10 h.

Initially, catalysts that have been used for C−H functionalization were examined for this reaction. Although $Ru(CO)_2(PPh_3)_3$ exhibited excellent catalytic activity for addition of C−H bonds to alkenes,[2a,b] the C−H alkenylation product was obtained in low yield (entry 2 in Table 1). The alkenylation using other known ruthenium catalysts also resulted in poor yields or no product formation (entries 3−5). However, when Ar−Ru−OAr′ complex **7**, synthesized by reaction of **1** with 2′-(4-methylphenoxy)pivalophenone,[7b] was used as a catalyst for 10 h, C−H alkenylation product **4c** was obtained in 76% yield (entry 6). Catalyst **7** showed both higher activity and higher chemoselectivity compared to those of **2** (entry 1), and only a trace amount of **5c** was detected by GC/MS. Catalytic activities of rhodium complexes[2e,f] were also examined, but the alkenylation reaction did not take place (entries 7 and 8).

(4) Representative reviews, see: (a) Satoh, T.; Miura, M.; Nomura, M. *J. Organomet. Chem.* **2002**, *653*, 161. (b) Catellani, M. *Synlett* **2003**, 298. (c) Campeau, L.-C.; Fagnou, K. *Chem. Commun.* **2006**, 1253. (d) Daugulis, O.; Zaitsev, V. G.; Shabashov, D.; Pham, Q. N.; Lazareva, A. *Synlett* **2006**, 3382. (e) Satoh, T.; Miura, M. *Chem. Lett.* **2007**, *36*, 200. (g) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, 174. (h) Ackermann, L. *Synlett* **2007**, 507. (i) Pascual, S.; de Mendoza, P.; Echavarren, A. M. *Org. Biomol. Chem.* **2007**, *5*, 2727.

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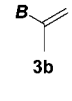
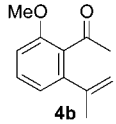
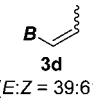
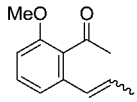
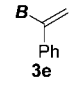
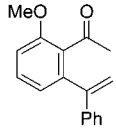
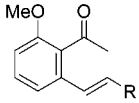
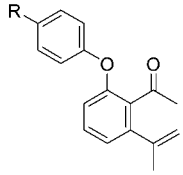
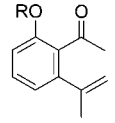
(7) (a) Kakiuchi, F.; Usui, M.; Ueno, S.; Chatani, N.; Murai, S. *J. Am. Chem. Soc.* **2004**, *126*, 2706. (b) Ueno, S.; Mizushima, E.; Chatani, N.; Kakiuchi, F. *J. Am. Chem. Soc.* **2006**, *128*, 16516.

(8) Ueno, S.; Chatani, N.; Kakiuchi, F. *J. Am. Chem. Soc.* **2007**, *129*, 6098.

With catalyst **7** in hand, C−H selective alkenylation of 2′-alkoxyacetophenone with several alkenylboronates was investigated to determine the generality of the reaction (Table 2).

Table 2. C−H Selective Alkenylation of 2′-Alkoxyacetophenones with Alkenylboronates[a]

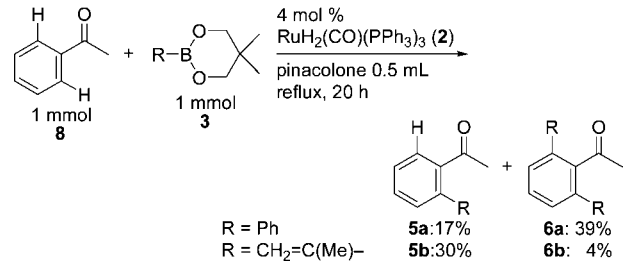
entry	alkenyl-boronate[b]	product		isolated yield (time)
1	 **3b**	 **4b**		88% (10 h)
2	 **3d** (*E*:*Z* = 39:61)			82% (10 h) (*E*:*Z* = 95:5)
3	 **3e**			82% (10 h)
4	 **3c,f**		R = Ph	73% (10 h)
5			R = *p*-tolyl	71% (10 h)
6	**3b**		R = OMe	75% (10 h)
7	**3b**		R = Me	77% (10 h)
8	**3b**		R = F	84% (20 h)
9	**3b**		R = ^{i}Pr	91% (20 h)
10	**3b**		R = TBDMS	75% (20 h)

[a] Reaction conditions: aromatic ketone (0.5 mmol), alkenylboronate (0.6 mmol), pinacolone (0.5 mL), ruthenium complex **7** (0.02 mmol), reflux, 10 or 20 h. [b] ***B*** = B(OCH$_2$CMe$_2$CH$_2$O).

The C−H alkenylation with various alkenylboronates provides quite high yields of the desired products. It is noteworthy that this alkenylation of alkoxyacetophenones generally presents yields markedly higher than those of our previously reported C−H alkenylation of aromatic ketones.[3i] For example, the alkenylation of **1** with 2-propenylboronic ester **3b** offered desired product **4b** in 88% yield (entry 1). The reaction with 1-propenylboronate (**3d**, *E*:*Z* = 39:61) afforded propenylation product **4d** in 82% yield with the *E*:*Z* isomer ratio of 95:5 (entry 2). Use of α- and *β*-arylvinylboronates is also effective for the alkenylation, and the products were obtained in good yields (entries 3−5). Aromatic ketones bearing aryloxy groups instead of methoxy groups similarly reacted to give the corresponding C−H alkenylation products, and electronically diverse substituents (OMe, Me, and F groups) on the aryloxy group remained in the coupling products (entries 6−8). The reactions of the substrates with electron-donating substituents such as methyl and methoxy groups on the aryloxy group afforded the products with 75% and 77% yields. On the other hand, in the case of 2′-(4-fluorophenoxy)acetophenone, a longer reaction period was required to attain a comparable yield (entry 8). Introduction of bulkier substituents such as isopropoxy and *tert*-butyldimethylsiloxy groups as the alkoxy group on the substrate also retarded the reaction, but the reaction for 20 h offered the desired C−H alkenylation products in 91% and 75% yields, respectively.

The sharp contrast in the product selectivity between phenylation and alkenylation and the selective formation of monoalkenylation products were also observed for the reaction of acetophenone (**8**) (Scheme 2). As reported for

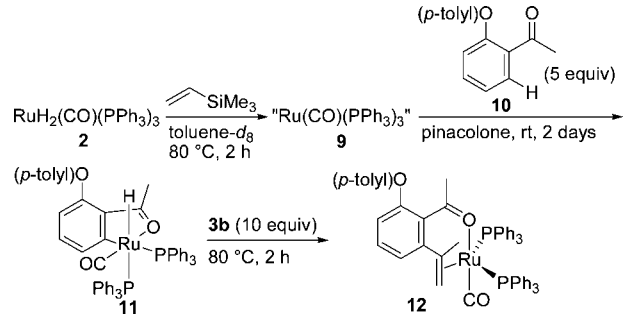
Scheme 2. Selective Monoalkenylation of Acetophenone



the ruthenium-catalyzed arylation, diphenylation product **6a** was obtained as a major product for the reaction of **8** with **3a**.[5b] On the other hand, the reaction of **8** with 2-propenylboronate **3b** afforded the corresponding 1:1 coupling product **5b** as a major product.[3i]

To investigate the origin of the product selectivity toward monoalkenylated aryl ketones, a stoichiometric reaction of ruthenium complex **2** with aryl ketones and alkenylboronate **3b** was examined in an NMR tube (Scheme 3). To conduct

Scheme 3. Stoichiometric Reactions of Complex **9**



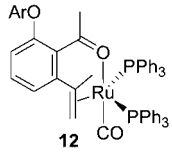
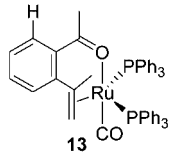
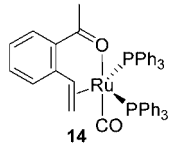
the reaction under mild reaction conditions, complex **2** was converted to the activated ruthenium complex Ru(CO)(PPh$_3$)$_3$ (**9**) by reduction of **2** with trimethylvinylsilane.[2b,9] A reaction

(9) A reaction of **2** with trimethylvinylsilane affords dehydrogenated ruthenium complex, which shows high activity for C-H bond cleavage. See, also ref 7b.

of complex **9** with aryloxyacetophenone **10** at room temperature resulted in complete conversion to hydrido complex **11**, and apparently the *ortho* C−H bond of **10** was oxidatively added to the ruthenium. No Ar−Ru−OR type complex, which should be formed by oxidative addition of the C−O bond,[7b] was observed even after 2 days at room temperature. Subsequently, 10 equiv of alkenylboronate **3b** was added to the resulting mixture, and heated at 80 °C. The ^{31}P NMR spectra of this reaction mixture indicated that the alkenylation occurred, but most of complex **11** was converted to ruthenium complex **12** bearing the product as a ligand. When acetophenone (**8**) was used for a similar NMR study without using pinacolone,[10] the corresponding complex bearing the monoalkenylation product (**13**) was formed.

The structures of complexes **12** and **13** were characterized by ^{31}P and ^{1}H NMR spectroscopy (Table 3). The ^{31}P NMR spectrum of **12** showed that the presence of two phosphine ligands (δ 43.7 and 44.6) bound to the ruthenium.[11] In the ^{31}P NMR spectrum of **13**, two phosphine signals were similarly observed at δ 46.2 and 46.6, and in the ^{1}H NMR spectrum, signals corresponding to the alkenyl hydrogens of **13** appeared at δ −0.50 and 3.50. These signals on the ^{31}P and ^{1}H NMR spectra resemble those of the related 2′-vinylacetophenone ruthenium complex **14**, synthesized and structurally characterized by Weber and co-workers.[12] Reported results of X-ray diffraction analysis performed on complex **14** show that both the ketone carbonyl and the alkene moieties coordinate to the ruthenium center. On the basis of these NMR spectra, the alkene moieties in complex **12** and **13** are considered to coordinate to the ruthenium center in a similar manner to **14**.

Table 3. ^{31}P{^{1}H} and ^{1}H NMR Chemical Shifts of Alkene-Coordinated Ruthenium Complexes[a]

ruthenium complex	δ(^{31}P) [ppm][a]	^{2}J (^{31}P,^{31}P)	δ(^{1}H) [ppm][a,b]	^{2}J (^{1}H,^{1}H)	^{2}J (^{1}H,^{31}P)
Our results					
 **12** Ar = *p*-tolyl	43.7 (d)	7.6 Hz	–[c]	–[c]	–[c]
	44.6 (d)	7.6 Hz			
 **13**	46.2 (d)	6.3 Hz	–0.50 (dd)	3.2 Hz	4.9 Hz
	46.6 (d)	6.3 Hz	3.50 (dd)	3.2 Hz	5.9 Hz
Results reported by Weber and co-workers[12]					
 **14**	46.2 (d)	7.5 Hz	0.13 (ddd)	10.1 Hz 3.1 Hz	4.7 Hz
	46.8 (d)	7.5 Hz	3.75 (ddd)	8.5 Hz 3.1 Hz	5.8 Hz
			4.40 (dddd)	10.1 Hz 8.5 Hz	5.0 Hz 2.2 Hz

[a] Multiplicities are in parentheses. [b] Only chemical shifts of vinyl hydrogens are listed. [c] ^{1}H NMR spectrum not measured due to the presence of a large amount of pinacolone.

The origin of the suppression of the second alkenylation can be explained on the basis of the observations described above. The π-acidic alkene moiety in the monoalkenylation product coordinates to the metal as well as the carbonyl oxygen in a bidentate fashion during the reaction. The coordination places the C−O or C−H bond at the other *ortho* position far from the metal center and prevents the bond cleavage from occurring while the monoalkenylation product is on the metal.

In conclusion, we report that ruthenium-catalyzed alkenylation of 2′-alkoxyacetophenones with alkenylboronates provides *ortho* C−H alkenylation products without sacrificing an ether functional group at the other *ortho* position. Particularly, both excellent chemoselectivity and high product yields are achieved with aryloxo complex **7**. The unique effect of the alkene moiety in the C−H alkenylation product to suppress the second alkenylation by its coordination to the metal center is also observed.

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Supporting Information Available: General experimental details and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) In the absence of pinacolone, acetophenone (**8**) not only functions as a substrate, but as a hydride acceptor. See ref 5b for further information.

(11) ^{1}H NMR signals of **12** were not fully assigned, because the presence of an excess amount of pinacolone impeded the characterization.

(12) Lu, P.; Paulasaari, J.; Jin, K.; Bau, R.; Weber, W. P. *Organometallics* **1998**, *17*, 584.