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Ruthenium-Catalyzed *Ortho*-Alkenylation of Aromatic Ketones with Alkenes by C−H Bond Activation

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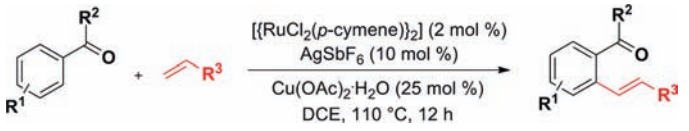
ABSTRACT



A ruthenium-catalyzed chelation-assisted C−H bond activation of aromatic ketones and the reaction with olefins to provide Heck-type products in good to excellent yields with a high regio- and stereoselective manner is described.

Chelation-assisted alkenylation at the *ortho* position of the aromatic ring with alkenes through a metal-catalyzed C−H bond activation reaction is a highly efficient and beneficial method in organic synthesis.[1,2] In 1968, Fujiwara's group reported the first example of alkenylation of electron-rich aromatics with alkenes catalyzed by palladium complexes.[3a,b] After that, several research groups have devoted substantial effort in the area of alkenylation of electron-rich aromatics and heteroaromatics with alkenes.[1,3] In 1979, Diamond and his co-workers revealed a palladium-catalyzed chelation-assisted alkenylation at the *ortho* position of aromatic amines with alkenes.[4] Carboxyl-directed lactonization of sp^3 and sp^2 C−H bonds catalyzed by platinum and palladium complexes has been observed by Sen, Miura, and others previously.[5] Meanwhile, Miura et al. demonstrated the phenol-directed alkenylation of sp^2 C−H bonds in the presence of a palladium complex.[5b,c] Yu and co-workers disclosed the palladium-catalyzed COOH, OH and carbonyl assisted C−H activation/C−C coupling reactions of the substituted arenes and alkanes.[6] van Leeuwen and others studied alkenylation at the *ortho* position of the acetanilide C−H bond in the presence of palladium complexes.[7] Recently, enormous effort has been expended, by the groups of Miura, Satoh, Fagnou, Glorius, and others, to the development of a rhodium-catalyzed chelation-assisted oxidative alkenylation at the *ortho* position of the aromatic C−H bonds.[8] For the chelation-assisted

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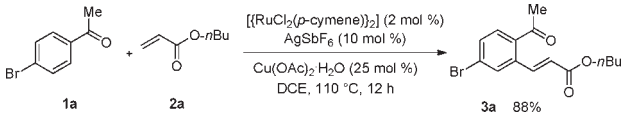
Heck-type alkenylation reactions, only palladium and rhodium complexes have been widely used until now. On the other hand, the use of a less-expensive ruthenium complex as a catalyst has not been explored in detail for the oxidative alkenylation at the *ortho* position of the aromatic C−H bond.[9] While the C−H bond activation reaction in the presence of strong coordinating groups is well documented and facile, activation in the presence of weak-coordinating groups such as aldehydes, esters, and ketones is still a challenging task. In 1993, Murai's group reported one of the first papers in the ruthenium-catalyzed chelation-assisted C−H bond functionalization of aromatic ketones with olefins.[10a,b] However, in the reaction only alkylated products were observed. Later, several other research groups also reported an addition reaction of aromatic ketones with alkenes by using the different ruthenium complexes.[10c−i] In all these reactions only alkylated products were observed. Very recently, Ackermann's group has reported a ruthenium-catalyzed C−H bond activation reaction in which aromatic acids undergo oxidative cyclization with alkenes to give the cyclic phthalides.[11] Herein, we wish to report a ruthenium-catalyzed reaction of aryl ketones with olefins, giving *ortho*-alkenylated aryl ketones through a C−H bond activation reaction in a highly regio- and stereoselective fashion.[12,13]

Scheme 1



The reaction of 4-bromoacetophenone (**1a**) with *n*-butyl acrylate (**2a**) in the presence of $[\{RuCl_2(p\text{-cymene})\}_2]$ (2 mol %), $AgSbF_6$ (10 mol %), and $Cu(OAc)_2 \cdot H_2O$ (25 mol %) in 1,2-dichloroethane (DCE) at 110 °C for 12 h provided a Heck-type product **3a** in 88% isolated yield with excellent *E*-stereoselectivity (Scheme 1). It is important to note that, in most of the rhodium-catalyzed C−H activation reactions, a stoichiometric amount of oxidant has been used.[8] However, only 25 mol % of oxidant is used in the present reaction. It is also whorthwhile to mention that only the catalytic amount of oxidants (Ag salts or Cu salts or air) were used in the palladium-catalyzed alkenylation reactions.[1d] Control experiments revealed that no **3a** was obtained in the absence of a ruthenium catalyst, silver salt, or copper salt (for the detailed optimization studies, see Supporting Information (SI)).

Under the optimized reaction conditions, several substituted acetophenones **1b**−**m** reacted efficiently with *n*-butyl acrylate (**2a**) to give the corresponding alkene derivatives **3b**−**m** in good to excellent yields with complete *E*-stereoselectivity (Table 1). Thus, acetophenone (**1b**), 4-fluoroacetophenone (**1c**), and 4-iodoacetophenone (**1d**) gave the Heck-type products **3b**−**3d** in 86%, 89%, and 83% yields, respectively (entries 1−3). It is interesting to note that the catalytic reaction is compatible with very sensitive halogen groups such as I and Br (Table 1, entry 3 and Scheme 1). Similarly, 4-methylacetophenone (**1e**) and 4-methoxyacetophenone

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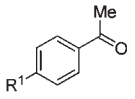
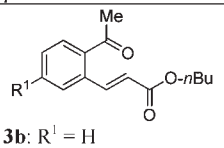
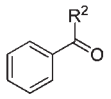
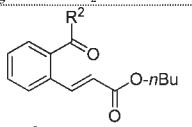
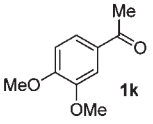
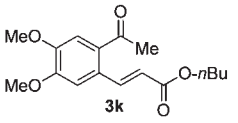
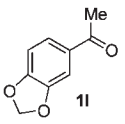
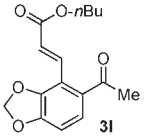
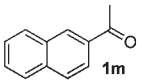
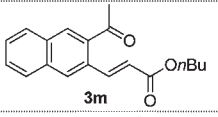
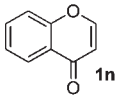
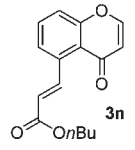
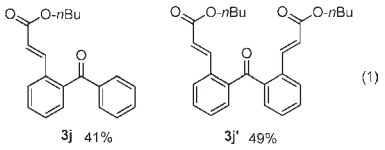
Table 1. Results of the Reaction of Aromatic Ketones **1** with *n*-Butyl Acrylate (**2a**)[a]

entry	1	product 3	yield (%)[b]
			
1	**1b**: R^1 = H	**3b**: R^1 = H	86
2	**1c**: R^1 = F	**3c**: R^1 = F	89
3	**1d**: R^1 = I	**3d**: R^1 = I	83
4	**1e**: R^1 = Me	**3e**: R^1 = Me	79
5	**1f**: R^1 = OMe	**3f**: R^1 = OMe	77
6	**1g**: R^1 = CO_2Me	**3g**: R^1 = CO_2Me	85
			
7	**1h**: R^2 = Et	**3h**: R^2 = Et	85
8	**1i**: R^2 = *i*-Pr	**3i**: R^2 = *i*-Pr	79
9			72
10			75
11			77
12			88

[a] All reactions were carried out using aromatic ketones **1** (1.0 mmol), *n*-butyl acrylate (**2a**) (1.5 mmol), [{$RuCl_2$(*p*-cymene)}$_2$] (2 mol %), $AgSbF_6$ (10 mol %), and $Cu(OAc)_2 \cdot H_2O$ (25 mol %) in DCE (1,2-dichloroethane) (3.0 mL) at 110 °C for 12 h. [b] Isolated yields.

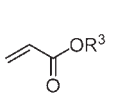
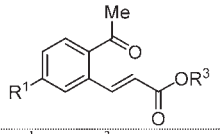
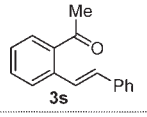
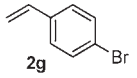
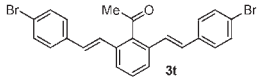
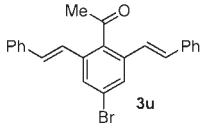
(**1f**) afforded the corresponding alkene derivatives **3e** and **3f** in 79% and 77% yields, respectively (entries 4 and 5). Surprisingly, 4-methylester acetophenone **1g** reacted with **2a** to give the alkenylation product **3g** at the next carbon to the acetyl group in 85% yield (entry 6). The regiochemistry of compound **3g** was established by NOESY experiments (see SI). It is well-known that the ester group serves as an excellent directing group for the ruthenium-catalyzed C−H bond activation reactions.[14] The present result shows that the acetyl group chelates with Ru better than the ester group. The catalytic reaction was also tested with the effect of changing the methyl group in acetophenone to other substituents. Thus, propiophenone (**1h**) and isobutyrophenone (**1i**) efficiently reacted with **2a** to afford **3h** and **3i** in 85% and 79% yields, respectively (entries 7 and 8). However, bulkier benzophenone (**1j**) provided a mixture of monoalkenylated and *bis* alkenylated products **3j** and **3j′** in 41% and 49% yields, respectively (eq 1).



(1)

Next, we studied the regioselectivity of the unsymmetrical acetophenones **1k**−**m** in the reaction (entries 9−11). When 3,4-dimethoxyacetophenone (**1k**) was treated with *n*-butyl acrylate (**2a**), a single regioisomeric product, **3k**, was observed in 72% yield (entry 9). Clearly, it indicates that formation of **3k** is a sterically controlled process. In contrast, 3,4-(methylenedioxy)acetophenone (**1l**) provided a single product **3l** in 75% yield, in which the alkene had been added at the more sterically hindered site (entry 10).

Table 2. Results of the Reaction of 4-Bromoacetophenone (**1a**), Acetophenone (**1b**), or 4-Methylacetophenone (**1e**) with Substituted Alkenes **2b**−**f**[a]

entry	2	3 product	yield (%)[b]
			
1	**2b**: R^3 = Me	**3o**: R^1 = Br, R^3 = Me	86
2	**2c**: R^3 = Et	**3p**: R^1 = Br, R^3 = Et	89
3	**2d**: R^3 = *t*Bu	**3q**: R^1 = Me, R^3 = *t*Bu	75[c]
4	**2e**: R^3 = cyclohexyl	**3r**: R^1 = Br, R^3 = cyclohexyl	83[c]
5			55[c]
6			59[c]
7			62[c]

[a] All reactions were carried out using aromatic ketones **1a**, **1b**, or **1e** (1.0 mmol), alkenes **2** (**2b**−**e** (1.5 mmol), **2f** and **2g** (2.0 mmol)), [{$RuCl_2$(*p*-cymene)}$_2$] (2 mol %), $AgSbF_6$ (10 mol %), and $Cu(OAc)_2 \cdot H_2O$ (25 mol %) in DCE (1,2-dichloroethane) (3.0 mL) at 110 °C for 12 h. [b] Isolated yields. [c] The reaction was carried out in *tert*-butanol (3.0 mL) instead of DCE.

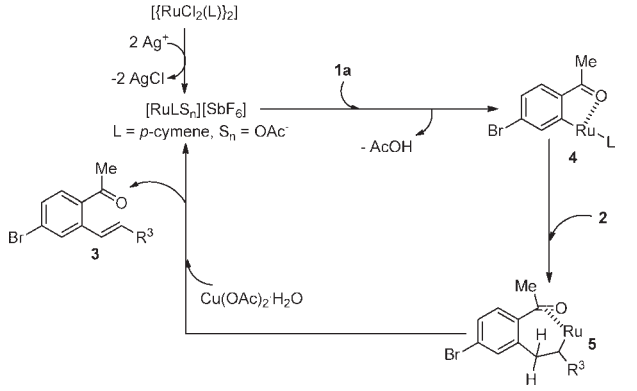
On the other hand, 2-napthophenone (**1m**) afforded **3m**, with the alkene substituent at C3 carbon, exclusively in 77% yield (entry 11). The present methodology can be further extended to the heteroaromatic ketone **1n**. Under the optimized reaction conditions, the reaction of chromone (**1n**) with **2a** afforded **3n** in 88% yields (entry 12). In the reaction, an alkene moiety was incorporated in the C-5

(14) Sonoda, M.; Kakiuchi, F.; Kamatani, A.; Chatani, N.; Murai, S. *Chem. Lett.* **1996**, 109.

carbon of the chromone. The regiochemistry of compound **3n** was established by NOESY experiments (see SI).

The present C−H bond functionalization reaction was successfully extended to various alkenes (Table 2). Methyl acrylate (**2b**), ethyl acrylate (**2c**), *tert*-butyl acrylate (**2d**), and cyclohexyl acrylate (**2e**) efficiently reacted with **1a** or **1e** under the optimized reaction conditions to give the corresponding Heck-type products **3o**−**r** in 86%, 89%, 75%, and 83% yields, respectively (Table 2, entries 1−4). The catalytic reaction was also tested with substituted styrenes. Initially, the reaction of styrene (**2f**) with acetophenone (**1b**) was tested with 1,2-dichloroethane under the optimized reaction conditions. However, in the reaction, the corresponding alkenylated product was not observed. The same reaction was tested with other solvents such as THF and *tert*-butanol. Interestingly, *tert*-butanol worked nicely and gave the expected Heck-type product **3s** in 55% yield (entry 5). But, acetophenone (**1b**) reacted with 4-bromostyrene (**2g**) under similar reaction conditions to give *bis* alkenylated product **3t** in 59% yield (entry 6). In a similar fashion, 4-bromoacetophenone (**1a**) also reacted efficiently with styrene (**2f**) to afford *bis* alkenylated product **3u** in 62% yield (entry 7). In these reactions, no monoalkenylated product was observed.

Scheme 2



On the basis of known metal-catalyzed directing group assisted C−H bond activation reactions,[1−8] a possible reaction mechanism is proposed to account for the present catalytic reaction (Scheme 2). The removal of a chloride ligand by a Ag^+ salt from the [{$RuCl_2$(*p*-cymene)}$_2$] complex likely initiates the catalytic reaction. Coordination of the keto oxygen of **1** to the ruthenium cationic species followed by *ortho* metalation gives a five-membered metallacycle **4**.[21] Coordinative insertion of alkene **2** into the Ru−C bond of metallacycle **4** provides an intermediate **5**. β-Hydride elimination from intermediate **5** in the presence of $Cu(OAc)_2 \cdot H_2O$ gives the final product **3** and regenerates the active ruthenium species for the next catalytic cycle. The exact role of the copper source was not clear in the reaction. But, we propose that $Cu(OAc)_2 \cdot H_2O$ provides the OAc^- source to the active ruthenium species in order to accelerate the *ortho*-metalation.

It is interesting to compare the mechanistic differences between the present reactions with the previously reported Murai's type alkylation reaction.[10] The alkylation reaction proceeds via oxidative addition of an ortho C−H bond of acetophenone to the Ru(0) center giving the ruthenium−hydride [(Ar)Ru(II)(H)] species. Coordinative insertion of an alkene into the Ru−H species followed by reductive elimination provides the final alkylated product, whereas, in the present reaction, C−H bond cleavage takes place via a concerted metalation/deprotonation mechanism. Later, coordinative insertion of the olefin into the Ru−C species **4** followed by β-hydride elimination gives the alkenylated product.

In conclusion, we have developed a ruthenium-catalyzed chelation-assisted C−H bond functionalization of an *ortho* C−H bond of aromatic ketones with alkenes to afford substituted alkene derivatives in good to excellent yields. The catalytic reaction is highly regio- and stereoselective. It is interesting to note that acetophenones reacted with alkenes in the presence of $RuH_2(CO)(PPh_3)_3$ to give Michael-type alkylated products, whereas the same reaction provides Heck-type alkenylated products in the presence of a catalytic amount of [{$RuCl_2$(*p*-cymene)}$_2$], $AgSbF_6$, and $Cu(OAc)_2 \cdot H_2O$. Further extension of the C−H bond activation of other chelating group substituted aromatics and functionalization with other π-components and a detailed mechanistic investigation are in progress.

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