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Room-Temperature Regioselective C−H/Olefin Coupling of Aromatic Ketones Using an Activated Ruthenium Catalyst with a Carbonyl Ligand and Structural Elucidation of Key Intermediates

Fumitoshi Kakiuchi,[†,*] Takuya Kochi,[†] Eiichiro Mizushima,[‡] and Shinji Murai*[,§]

Department of Chemistry, Faculty of Science and Technology, Keio University, 3-14-1 Hiyoshi, Kohoku-ku, Yokohama, Kanagawa 223-8522, Japan, PRESTO, JST, 4-1-8 Honcho Kawaguchi, Saitama 332-0012, Japan, and Nara Institute of Science and Technology, 8916-5 Takayama, Ikoma, Nara 630-0019, Japan

Received June 5, 2010; E-mail: kakiuchi@chem.keio.ac.jp

Abstract: Mechanistic studies of the ruthenium-catalyzed reaction of aromatic ketones with olefins are presented. Treatment of the original catalyst, $RuH_2(CO)(PPh_3)_3$, with trimethylvinylsilane at 90 °C for 1−1.5 h afforded an activated ruthenium catalyst, $Ru(o\text{-}C_6H_4PPh_2)(H)(CO)(PPh_3)_2$, as a mixture of four geometric isomers. The activated complex showed high catalytic activity for C−H/olefin coupling, and the reaction of 2′-methylacetophenone with trimethylvinylsilane at room temperature for 48 h gave the corresponding ortho-alkylation product in 99% isolated yield. The activated catalyst was thermally robust and showed excellent catalytic activity under refluxing toluene conditions. ^1H and ^{31}P NMR studies of the C−H/olefin coupling at room temperature suggested that an ortho-ruthenated complex, *P*,*P*′-*cis*-*C*,*H*-*cis*-Ru(2′-(6′-MeC_6H_4C-(O)Me))(H)(CO)$(PPh_3)_2$, participated in the reaction as a key intermediate. Isotope labeling studies using acetophenone-d_5 indicated that the rate-limiting step was the C−C bond formation, not the C−H bond cleavage, and that each step prior to the reductive elimination was reversible. The rate of C−H/olefin coupling was found to exhibit pseudo first-order kinetics and to show first-order dependence on the ruthenium complex concentration.

Introduction

Transition-metal-catalyzed regioselective functionalizations via cleavage of normally unreactive carbon−hydrogen bonds have attracted much attention due to their synthetic utility and are now regarded as powerful tools in organic synthesis.[1] In the catalytic cycles of the reactions, carbon−hydrogen bond cleavage by transition metal catalysts is, of course, one of the key steps. Several mechanisms for this step are considered to be involved in catalytic C−H functionalizations, and oxidative addition of C−H bonds is one such mechanism. A variety of catalytic functionalizations have been developed via oxidative addition of C−H bonds, such as alkylations,[2−5] alkenylations,[6,7] acylations,[8] arylations,[9] silylations,[10] and borylations.[11]

Oxidative addition of C−H bonds plays a particularly valuable role in catalytic C−H addition to C−C multiple bonds, because after C−H bond cleavage, a hydride ligand remains on the metal and can be directly used for C−H bond formation. In 1993, highly efficient, catalytic, regioselective alkylation of aromatic ketones via oxidative addition of ortho C−H bonds or equivalent processes was reported.[2a] The multiple step processes gave overall results equivalent to direct oxidative addition. The reaction employed $RuH_2(CO)(PPh_3)_3$ (**1**) as a catalyst and showed a reasonably wide substrate scope and high functional group compatibility, providing excellent yields of products. Since then, the chemistry of transition-metal-catalyzed regioselective functionalization via unreactive C−H bond cleavage has been explored rapidly and intensively, and a huge number of methods have been developed for catalytic C−H functionalization.[1] On the other hand, ruthenium-catalyzed

† Keio University.
‡ PRESTO, JST.
§ Nara Institute of Science and Technology.

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aromatic ketone/olefin coupling has also been studied by many researchers, and ruthenium catalysts other than complex **1** have been found for C−H/olefin coupling. In addition, several suggestions have been provided for the catalytic intermediates of ruthenium-catalyzed coupling.

In an early investigation, transfer of the hydride ligands of $RuH_2(CO)(PPh_3)_3$ (**1**) to an olefin gave a catalytically active species, and it was proposed that the dehydrogenation of **1** is the key step for the generation of an active catalyst.[2c] Concurrently, Weber and co-workers also observed partial hydrogenation of olefins in the application of C−H/olefin coupling to step-growth polymerization and suggested that the reduction of the olefin may be involved in the formation of catalytically active species.They also found that treatment of **1** with a stoichiometric amount of styrene (**2**) prior to step-growth polymerization provided a catalytically active species. In both studies, coordinatively unsaturated ruthenium(0) species were considered to be the active catalyst, but the structure was not experimentally determined.

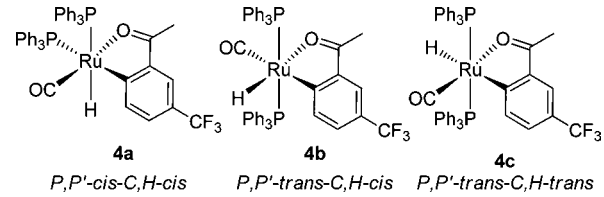

Figure 1. Structures of ortho-ruthenated intermediates.

NMR studies carried out by Hiraki and co-workers suggested that treatment of **1** with **2** and 3′-trifluoromethylacetophenone (**3**) generates several ruthenium complexes involving *P,P′-cis-C,H-cis*-$Ru(C_6H_3(CF_3)C(O)CH_3)(H)(CO)(PPh_3)_2$ (**4a**), *P,P′-trans-C,H-cis*-$Ru(C_6H_3(CF_3)C(O)CH_3)H(CO)(PPh_3)_2$ (**4b**), and *P,P′-trans-C,H-trans*-$Ru(C_6H_3(CF_3)C(O)CH_3)H(CO)(PPh_3)_2$ (**4c**) (Figure 1).[13] The structures of these complexes were not determined solely by the NMR analyses, but were proposed

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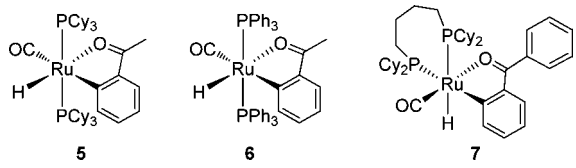


Figure 2. Structures of previously synthesized ortho-ruthenated complexes.

taking the electronic effects of the ligands into account.[13] Under their reaction conditions, ortho-ruthenated acetophenone complexes **4a**−**c** were observed as minor isomers, along with a large amount of starting complex **1**, and **4b** was considered more active as a catalyst than **4a** and **4c**. The authors speculated that one carbonyl ligand was attached to the catalytically active species, but the presence was not confirmed spectroscopically.

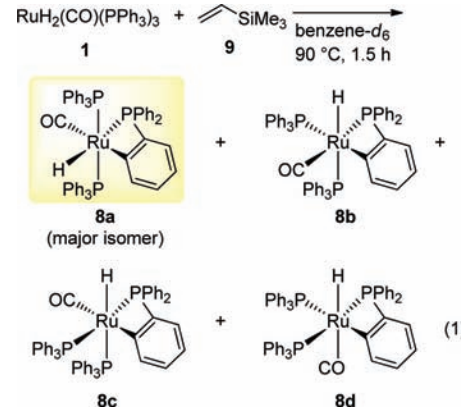
Several related ortho-ruthenated aromatic ketone complexes have also been synthesized by other research groups (Figure 2).[4,14,15] Chaudret and co-workers synthesized an ortho-ruthenated benzophenone complex, *P*,*P*′-*cis*-*C*,*H*-*trans*-Ru(*o*-$C_6H_4C(O)Ph)(H)(CO)(PCy_3)_2$ (**5**), having tricyclohexylphosphine as axial ligands (Figure 2).[4] Complex **5** showed essentially zero catalytic activity, and on the basis of this observation and Trost's results on a related C−H/olefin coupling, using conjugated alkenes instead of aromatic ketones,they proposed that the binding of the CO ligand to the ruthenium suppressed the catalytic activity of the ruthenium complex. Subsequently, Whittlesey and co-workers synthesized *P*,*P*′-*trans*-*C*,*H*-*cis*-Ru(*o*-$C_6H_4C(O)Me\}(H)(CO)(PPh_3)_2$ (**6**) and determined its structure by X-ray crystallography.[14] Complex **6** did not catalyze C−H/olefin coupling, and the authors stated it was highly likely that alternative isomers of **6** could be involved in the catalytic pathways, although their results did not provide definitive evidence for or against the coordination of a CO ligand in metalated species. Fogg and co-workers prepared an ortho-ruthenated benzophenone complex, $Ru(C_6H_4C(O)Ph)(H)(CO)$-(dcypb) (**7**) (dcypb = 1,4-bis(dicyclohexylphosphino)butane; $Cy_2P(CH_2)_4PCy_2$) (Figure 2) and examined its catalytic activity for alkylation of aromatic ketones.[15] However, complex **7** showed only low catalytic activity, and they proposed that it was in the catalytic sink for the alkylation of aromatic ketones.

Koga, Morokuma, and co-workers conducted theoretical calculations on ruthenium-catalyzed C−H/olefin coupling.[12] They used benzaldehyde and ethylene as substrates and $Ru(CO)(PH_3)_n$ as a catalyst and showed that the coordination of the carbonyl oxygen to the ruthenium center decreased the activation energy of the C−H bond cleavage step. Based on their calculation using the carbonyl complex, the C−H bond is so easily cleaved that the rate-determining step is the C−C bond formation, not the C−H bond cleavage.

This Article describes a detailed investigation of the $RuH_2(CO)$-$(PPh_3)_3$-catalyzed coupling of aromatic ketones with alkenes, including spectroscopic analyses of intermediates and kinetic studies. Several features of C−H/olefin couplings were revealed: (1) Catalytically active intermediates possess a carbonyl ligand during catalysis; (2) reaction of $RuH_2(CO)(PPh_3)_3$ with an olefin provides a catalytically active species, Ru(*o*-$C_6H_4PPh_2$)(H)-$(CO)(PPh_3)_2$ (**8**); and (3) the activated ruthenium catalyst **8** with a carbonyl ligand shows excellent catalytic activity for C−H/olefin coupling and even catalyzes the reaction at room temperature.

Results and Discussion

Generation of Highly Active Species for Alkylation of C−H Bonds with Olefins. This study was initiated with the reaction of ruthenium catalyst **1** with olefins to determine the structure of the activated ruthenium complex. On the basis of the accumulated results concerning $RuH_2(CO)(PPh_3)_3$-catalyzed coupling reactions of aromatic compounds with olefins, trimethylvinylsilane (**9**), which is the most reactive among the olefins screened, was chosen as an activator of **1**. When the reaction of **1** with **9** was carried out in benzene-d_6 at room temperature, a significant amount of a white precipitate was formed, and the only ruthenium species observable by ^{31}P NMR was **1**, remaining in the solution even after 7 days. By contrast, the reaction at 90 °C provided several new ruthenium species, and the resulting mixture was analyzed by ^1H and ^{31}P NMR spectroscopy (eq 1).



Two hydride signals of **1** at −8.60 (ddt, J_{HP} = 75.1, 5.8, 29.2 Hz) and at −6.76 ppm (ddt, J_{HP} = 14.8, 5.8, 31.1 Hz)

(10) (a) Gustavson, W. A.; Epstein, P. S.; Curtis, M. D. *Organometallics* **1982**, *1*, 884–885. (b) Ishikawa, M.; Sakamoto, H.; Okazaki, S.; Naka, A. *J. Organomet. Chem.* **1992**, *439*, 19–21. (c) Uchimaru, Y.; El Sayed, A. M. M.; Tanaka, M. *Organometallics* **1993**, *12*, 2065–2069. (d) Djurovich, P. I.; Dolich, A. R.; Berry, D. H. *J. Chem. Soc., Chem. Commun.* **1994**, 1897–1898. (e) Ishikawa, M.; Naka, A. *Synlett* **1995**, 794–802. (f) Williams, N. A.; Uchimaru, Y.; Tanaka, M. *J. Chem. Soc., Chem. Commun.* **1995**, 1129–1130. (g) Kakiuchi, F.; Matsumoto, M.; Sonoda, M.; Fukuyama, T.; Chatani, N.; Murai, S.; Furukawa, N.; Seki, Y. *Chem. Lett.* **2000**, 750–751. (h) Kakiuchi, F.; Igi, K.; Matsumoto, M.; Chatani, N.; Murai, S. *Chem. Lett.* **2001**, 422–423. (i) Kakiuchi, F.; Igi, K.; Matsumoto, M.; Hayamizu, T.; Chatani, N.; Murai, S. *Chem. Lett.* **2002**, 396–397. (j) Kakiuchi, F.; Matsumoto, M.; Tsuchiya, K.; Igi, K.; Hayamizu, T.; Chatani, N.; Murai, S. *J. Organomet. Chem.* **2003**, *686*, 134–144. (k) Williams, N. A.; Uchimaru, Y.; Tanaka, M. *Dalton Trans.* **2003**, 236–243. (l) Ishiyama, T.; Sato, K.; Nishio, Y.; Miyaura, N. *Angew. Chem., Int. Ed.* **2003**, *42*, 5346–5348. (m) Tsukada, N.; Hartwig, J. F. *J. Am. Chem. Soc.* **2005**, *127*, 6022–6023. (n) Ishiyama, T.; Sato, K.; Nishio, Y.; Saiki, T.; Miyaura, N. *Chem. Commun.* **2005**, 5065–5067. (o) Saiki, T.; Nishio, Y.; Ishiyama, T.; Miyaura, N. *Organometallics* **2006**, *25*, 6068–6073. (p) Murata, M.; Fukuyama, N.; Wada, J.-I.; Watanabe, S.; Masuda, Y. *Chem. Lett.* **2007**, *36*, 910–911.

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Table 1. ^{1}H and ^{31}P NMR Spectral Data (benzene-d_6, 22 °C) for Complexes **8a**−**d**

complex	^{1}H NMR spectral data	^{31}P NMR spectral data
8a	δ −8.18 (dt, J_{HP} = 83.6, 26.5 Hz)	δ −35.3 (t, J_{PP} = 15.2 Hz) δ 52.1 (d, J_{PP} = 15.2 Hz)
8b	δ −5.82 (ddd, J_{HP} = 84.9, 30.2, 21.4 Hz)	δ −36.3 (dd, J_{PP} = 26.9, 21.9 Hz) δ 31.4−31.9 (overlapped with signals of **8c**) δ 42.2 (dd, J_{PP} = 21.9, 18.5 Hz)
8c	δ −5.57 (ddd, J_{HP} = 85.6, 28.5, 19.9 Hz)	δ −28.1 (dd, J_{PP} = 242.2, 18.3 Hz) δ 31.4−31.9 (overlapped with signals of **8b**) δ 54.4 (dd, J_{PP} = 242.2, 17.4 Hz)
8d	δ −3.15 (td, J_{HP} = 25.9, 18.6 Hz)	δ −34.0 (dd, J_{PP} = 242.4, 23.9 Hz) δ 49.7 (dd, J_{PP} = 23.9, 16.2 Hz) δ 60.7 (dd, J_{PP} = 242.4, 16.2 Hz)

had completely disappeared from the ^{1}H NMR spectrum after 1.5 h, and four new hydride signals having spin−spin coupling with phosphorus nuclei appeared at −8.18 (**8a**), −5.82 (**8b**), −5.57 (**8c**), and −3.15 (**8d**) ppm in a ratio of 2.6:1.0:1.3:1.3 (Table 1). The ^{31}P NMR spectrum also suggested that four ruthenium phosphine complexes were present in the mixture, along with a small amount of triphenylphosphine and triphenylphosphine oxide, and two or three phosphine signals were observed for each complex (Figure 3). The ^{31}P NMR spectral data are listed in Table 1. The high field shifts (−35.3, −36.3, −28.1, and −34.0 ppm) suggested the presence of an ortho-metalated triphenylphosphine (PPh_3) on each ruthenium center.[16] Similar ^{1}H and ^{31}P NMR results were also obtained when the reaction was carried out in toluene-d_8. Investigation into the ^{1}H and ^{31}P NMR area ratios and coupling constants led us to assign the structures of ruthenium complexes **8a**−**d** to be the ones drawn in eq 1. Correlations between hydrides and phosphorus atoms located at trans positions to each other in **8a**−**c** were also observed in the $^{1}H-^{31}P$ HMQC spectrum of the mixture and are in good agreement with the assigned structures. The presence of a carbonyl ligand of major isomer **8a** was confirmed by the ^{13}C NMR spectrum. The signal of the ruthenium-bound aromatic carbon and the CO ligand appeared at 173.6 (td, J_{C-P} = 14.1 and 6.6 Hz) and 207.1 ppm (td, J_{C-P} = 13.2 and 6.6 Hz), respectively, and the assignment was also supported by the $^{1}H-^{13}C$ HMBC analysis. The solution-phase IR spectrum of the mixture showed a peak at 1918 cm^{-1}, supporting the existence of a carbonyl ligand.[17]

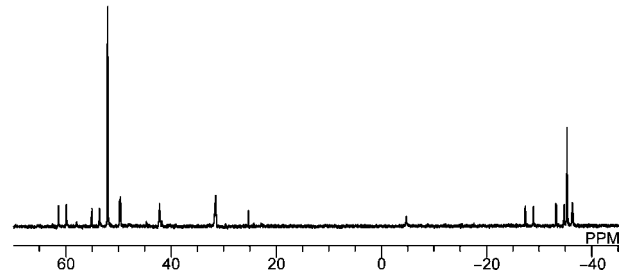
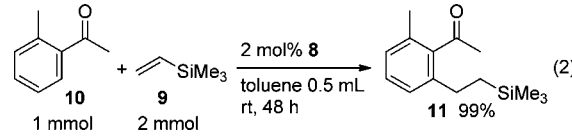


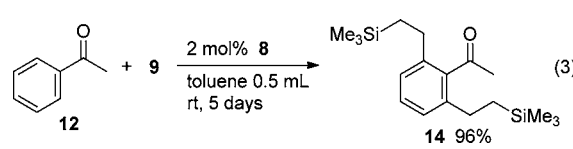
Figure 3. $^{31}P\{^{1}H\}$ NMR spectra of a mixture of complexes **8a**−**d** formed by treatment of **1** with **9** (162 MHz, benzene-d_6, 22 °C).

The observations from the NMR and IR experiments suggested that the reaction of **1** with **9** afforded several isomers of ruthenium complex **8**, possibly via dehydrogenation by the olefin and ortho-ruthenation of one of three PPh_3. Attempts were made to isolate complex **8** in a pure form, but were unsuccessful, probably due to its instability. Complex **8** was therefore generated in situ by the treatment of **1** with **9** for use in the following experiments.

Catalytic Addition of C−H Bonds in Aromatic Ketones to Olefins Using Activated Ruthenium Complex 8 as a Catalyst under Mild Reaction Conditions. To examine the catalytic activity of **8** for C−H/olefin coupling, a reaction of 2′-methylacetophenone (**10**) with **9** was carried out at room temperature using in situ-generated complex **8** as a catalyst (eq 2). The coupling reaction of **10** with **9** took place with only 2 mol % of catalyst **8**, even at room temperature, to give the corresponding ortho-alkylation product **11** in 99% isolated yield. On the other hand, when the same reaction of **10** with **9** was conducted using **1** as a catalyst at room temperature, no coupling product was observed. These results suggest that high reaction temperature (90 °C) was necessary for the generation of catalytically active species **8**, but not for the actual C−H/olefin coupling between **10** and **9**, which could be catalyzed by **8** even at room temperature.



Acetophenone (**12**) was also coupled with **9** using in situ-generated **8** at room temperature to give 2,6-dialkylation product **14** in 96% yield (eq 3). In this reaction, the corresponding 1:1 addition product **13** was observed in the early stage, and, as the reaction proceeded, the amount of **13** was decreased and that of 1:2 coupling product **14** was increased. As reported previously, when the reaction of **12** with **9** was conducted in refluxing toluene using **1** as a catalyst, **14** was formed as a major product, even in the early stage of the catalytic reaction.[2b,c]



For the regioselective alkylation of 2-acetylthiophene, complex **8** generated in situ also functioned as an effective catalyst, but a slightly higher reaction temperature (40 °C) and a prolonged reaction period were necessary to attain high product yield (eq 4).

(12) (a) Matsubara, T.; Koga, N.; Musaev, D. G.; Morokuma, K. *J. Am. Chem. Soc.* **1998**, *120*, 12692–12693. (b) Matsubara, T.; Koga, N.; Musaev, D. G.; Morokuma, K. *Organometallics* **2000**, *19*, 2318–2329.
(13) Hiraki, K.; Ishimoto, T.; Kawano, H. *Bull. Chem. Soc. Jpn.* **2000**, *73*, 2099–2108.
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(16) (a) Appleton, T. G.; Bennett, M. A.; Tomkins, I. B. *J. Chem. Soc., Dalton Trans.* **1976**, 439–440. (b) Cole-Hamilton, D. J.; Wilkinson, G. *J. Chem. Soc., Dalton Trans.* **1977**, 797–804. (c) Garrou, P. E. *Chem. Rev.* **1981**, *81*, 229–266. (d) Mohr, F.; Privér, S. H.; Bhargava, S. K.; Bennett, M. A. *Coord. Chem. Rev.* **2006**, *250*, 1851–1888.
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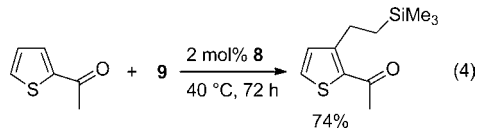
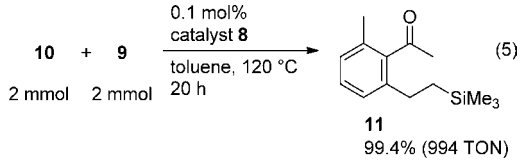


The choice of olefins is an important factor in the achievement of the C−H alkylation reaction. One of the major limitations of $RuH_2(CO)(PPh_3)_3$-catalyzed C−H alkylation is the low reactivity of olefins having allylic hydrogens, due to double-bond isomerization to internal hydrogens, which are unreactive in this reaction.[2c] The use of **8** as the catalyst was expected to suppress the undesired double-bond isomerization because of high catalyst activity, even under the milder reaction conditions. Unfortunately, however, when the reaction of **10** with 1-hexene was carried out at room temperature, isomerization of 1-hexene to 2- and 3-hexenes proceeded, and no coupling product was obtained, even after 7 days. Thus, ruthenium-catalyzed double-bond isomerization is more facile than C−H alkylation, even at room temperature.

C−H Alkylation with 9 Using 8 as a Catalyst under Low Catalyst Loading Conditions. Catalytic efficiency (turnover numbers) of in situ-generated complex **8** for C−H alkylation was examined under low catalyst loading conditions. When the reaction of **10** with **9** was conducted at room temperature after 0.1 mol % of **1** was treated with **9** at 90 °C for 1.5 h, C−H alkylation proceeded only sluggishly. When the reaction temperature was increased to 120 °C, **10** was completely consumed after 20 h, and the corresponding ortho-alkylation product **11** was isolated in 99.4% yield (994 turnover numbers) (eq 5).[18]



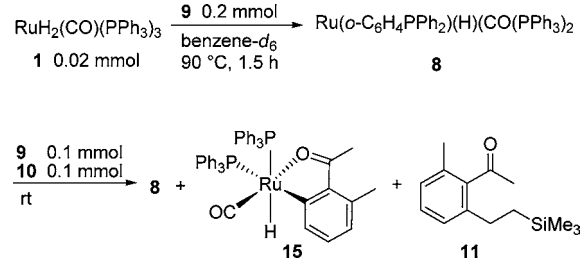
Chaudret's[4] and Leitner's[5a,b] groups independently reported the $RuH_2(H_2)(PCy_3)_2$-catalyzed alkylation of aromatic ketones with ethylene at room temperature. This complex functioned as a catalyst under mild reaction conditions such as room temperature, but at a higher reaction temperature, the complex was decomposed, and the C−H alkylation did not proceed.[4] On the other hand, complex **8** generated in situ showed high catalytic activity at both room and high (120 °C) reaction temperatures and should be considered as a more thermally robust catalyst.

Monitoring of the Catalytic Reaction of 2′-Methylacetophenone (10) with Trimethylvinylsilane (9) by NMR Spectroscopy. To probe the intermediate structures of room-temperature catalytic C−H/olefin coupling using **8**, the reaction of 2′-methylacetophenone (**10**) with vinylsilane **9**, using catalyst **8** generated in situ, was performed at room temperature in benzene-d_6 (Scheme 1).

To a benzene-d_6 solution of **8**, generated by the reaction of **1** (0.02 mmol) with **9** (0.2 mmol, 10 equiv) at 90 °C for 1.5 h (Figure 4a) were added **10** (0.1 mmol) and **9** (0.1 mmol, total 0.3 mmol) at room temperature, and the progress of the reaction was monitored by ^1H and ^{31}P NMR spectroscopy. After 6 h, the C−H alkylation proceeded, but free ketone **10** still remained

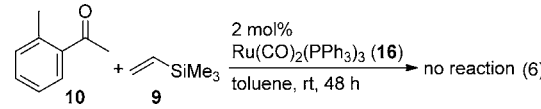
(18) Darses and co-workers recently reported highly efficient C−H alkylation of aromatic ketones using an in situ-generated ruthenium catalyst. See ref 3.

Scheme 1. Detection of an Intermediate in the Reaction of **10** with **9** Using **8** as a Catalyst



in the reaction mixture. The ^{31}P NMR spectrum showed that the amount of **8** was reduced, and a new species **15**, bearing two PPh_3 ligands in a cis configuration (δ 35.1, J_{PP} = 18.3 Hz and δ 39.1, J_{PP} = 18.3 Hz), was observed in the reaction mixture (Figure 4b). Ketone **10** was completely converted to alkylation product **11** after 5 days. At this point, ortho-ruthenated complex **15** disappeared, and all of the peaks corresponding to **8a**−**d** re-emerged on the ^{31}P NMR spectrum (Figure 4c). When 0.2 mmol of ketone **10** was added again to the reaction mixture, the signals of **15** gradually regenerated (Figure 4d). This indicates that complexes **8** and **15** participate in the coupling reaction of **10** with **9** as key intermediates.

The Reaction of 10 with 9 Using $Ru(CO)_2(PPh_3)_3$ (16) as a Catalyst. Previous research has established that $Ru(CO)_2(PPh_3)_3$ (**16**) can also be used as a catalyst for the alkylation of aromatic ketones under refluxing toluene conditions.[2a,c] When C−H alkylation was carried out using catalyst **8** at room temperature, **16** was gradually formed, as shown in Figure 4. Thus, there was a possibility that complex **16** functioned as a catalyst for the alkylation of **10** with **9** at room temperature. To examine the catalytic activity of **16** at room temperature, the reaction of **10** with **9** was conducted in the presence of **16** as a catalyst (eq 6). However, no coupling product was obtained, even after 48 h, and catalytically active species were not generated from **16** at room temperature.



Elucidation of the Structure of the Ortho-Ruthenated 2′-Methylacetophenone Complex by NMR Spectroscopy. The structure of ortho-ruthenated 2′-methylacetophenone complex **15** was determined by ^1H, ^{31}P, ^{13}C, and $^1H-^{13}C$ HMBC NMR spectra in benzene-d_6. As mentioned above, in the $^{31}P\{^1H\}$ NMR spectrum, the two phosphorus atoms are coupled to each other, and their small spin−spin coupling constant (J_{PP} = 17.0 Hz in benzene-d_6) indicates the cis configuration of the two phosphine ligands. The ^1H NMR spectrum of **15** displayed the hydride ligand at −5.82 ppm as a doublet of doublets, due to the coupling with two phosphine ligands (J_{HP} = 91.9, 24.6 Hz). The J_{HP} values suggest that the hydride ligand is located at the trans position of one of the phosphines and the three ligands, and the hydride and the two phosphines coordinate to the ruthenium in a meridional fashion. The structures satisfying the ^1H and ^{31}P NMR observations are shown as complexes **15** and **17** in Figure 5, and, at this point, the relationship between the other three ligands cannot be established. The ^{13}C NMR spectrum showed the signals of the CO ligand, the ketone carbonyl group, and the ruthenium-bound aryl group at 210.3, 209.8, and 208.4, respectively, and the assignment was supported

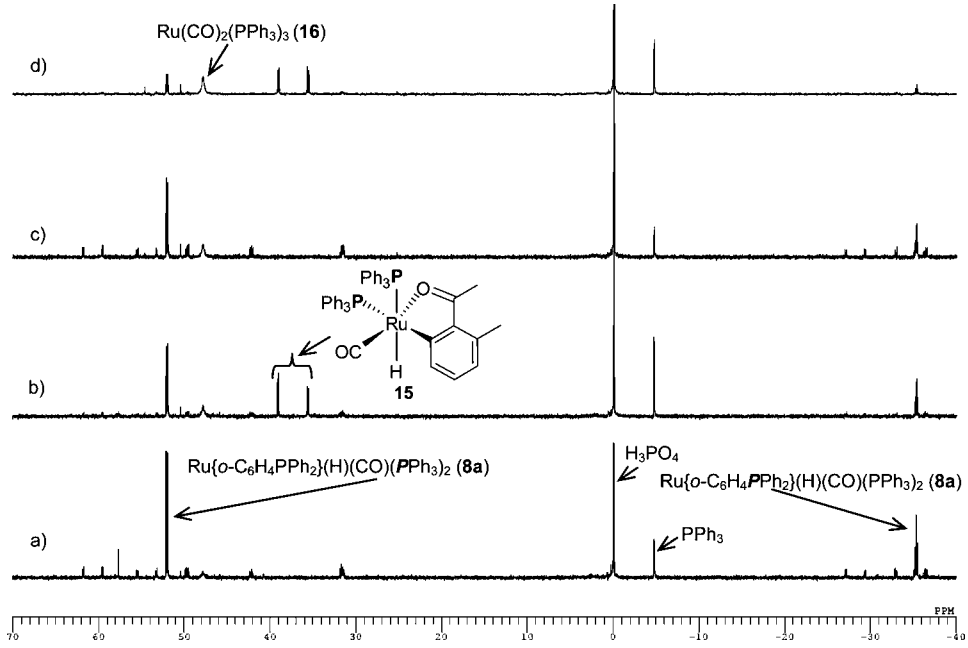


Figure 4. $^{31}P\{^{1}H\}$ NMR monitoring of the catalytic reaction of ketone **10** with vinylsilane **9** using **8** as a catalyst at room temperature. (a) The mixture of **8a**−**d** generated by the reaction of $RuH_2(CO)(PPh_3)_3$ (**1**) with **9**. (b) The reaction mixture at 6 h after addition of **10** and an extra amount of **9**. (c) The reaction mixture after 5 days. (d) The mixture at 3 h after further addition of **10**.

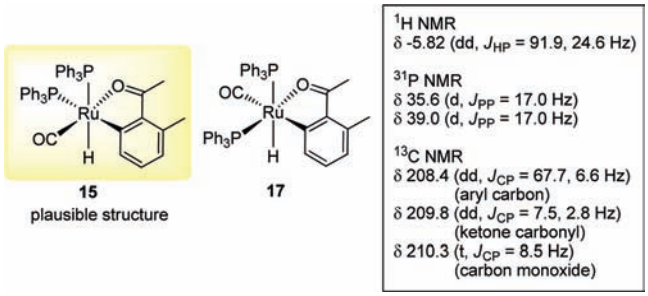
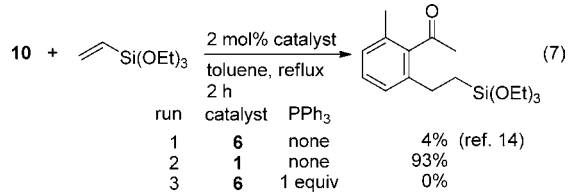


Figure 5. Possible structures of the ortho-ruthenated intermediate.

by the HMBC spectrum. The presence of the coupling (J_{CP} = 67.7 Hz) between the aryl carbon and one of the phosphorus atoms indicates the trans configuration of these two ligands. Therefore, the other two ligands, the ketone carbonyl group and the carbon monoxide, should be located at the cis position of both phosphines, and the structure of **15** was determined as shown in Figure 5.

Comparison of the Catalytic Activities of 6 and 1. Whittlesey and co-workers synthesized an ortho-ruthenated acetophenone complex, *P*,*P*′-*trans*-*C*,*H*-*cis*-Ru(H)(*o*-$C_6H_4C(O)CH_3$)(CO)-$(PPh_3)_2$ (**6**) and examined the catalytic activity of **6** for the alkylation of 2′-methylacetophenone (**10**) with triethoxyvinylsilane, but the product yield was poor, even under toluene reflux conditions (run 1 in eq 7).[14] As reported earlier, the coupling of **10** with triethoxyvinylsilane afforded 93% yield of the product when **1** was used as a catalyst.[2c]

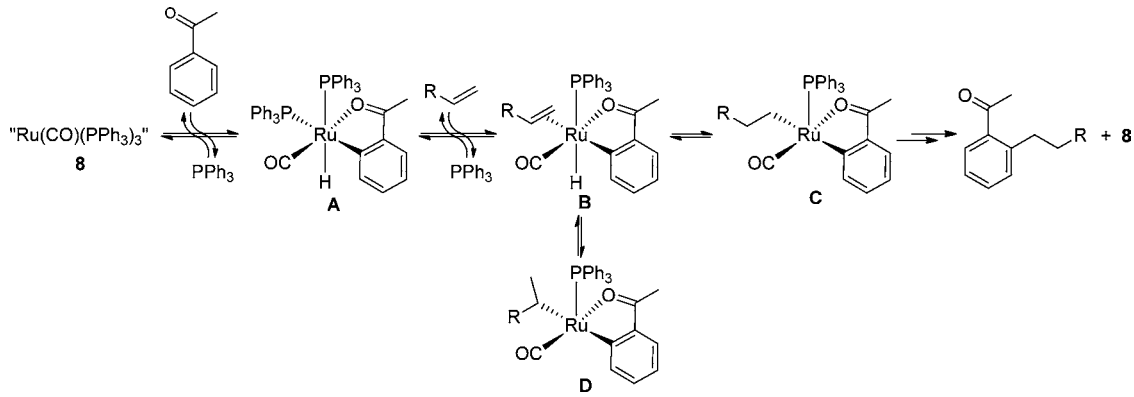


One of the major differences between the two experiments (runs 1 and 2 in eq 7) is that the catalytic reaction was performed in the presence of one more equivalent of PPh_3 than that of Whittlesey and co-workers, because, as compared to **6**, **1** had one more phosphine on the ruthenium. To examine the possibility that the third PPh_3 ligand participates in the catalyst regeneration, C−H alkylation was carried out using **6** as a catalyst in the presence of 1 equiv of PPh_3 (run 3 in eq 7). However, there was no improvement in the observed catalytic efficiency. This result shows that the low catalytic activity of **6** cannot be attributed to the small PPh_3/Ru ratio on the catalyst.

Comparison with Hiraki's Reaction Systems. As mentioned in the Introduction, Hiraki and co-workers previously studied the reaction mechanism of $RuH_2(CO)(PPh_3)_3$-catalyzed C−H alkylation using 3′-trifluoromethylacetophenone (**3**) and styrene (**2**).[13] They examined the reaction of **3** (0.37 mmol) with **2** (0.2 mmol) in the presence of **1** (0.04 mmol) at 70 °C without preactivation of **1**. Several ruthenium complexes were observed by ^{1}H and ^{31}P NMR spectroscopy. In this case, in addition to a large amount of unreacted complex **1**, three ortho-ruthenated acetophenone complexes were observed as minor products. In consideration of the ^{1}H and ^{31}P NMR spectral data and the trans influence of the ligands, they proposed the structures of these three ortho-ruthenated complexes, as shown in Figure 1.[13] While two phosphines on complex **4a** coordinate to the ruthenium at the cis position to each other, **4b** and **4c** possess the phosphines in a trans configuration. The geometry around the ruthenium center of **4a** proposed by Hiraki and co-workers was similar to that of **15** observed in the present NMR studies. Complex **4a** isomerized to *P*,*P*′-*trans*-*C*,*H*-*cis* isomer **4b** during the reaction at high temperature, but they claimed that the geometry of **4b** produced more catalytically active species than **4a**, and the isomerization that occurred only at high temperature is the key step for highly efficient C−H/olefin coupling.

In the present study, however, the kinetically favorable cis-isomer **15** was observed to be involved in the catalytic reaction. In addition, trans-isomer **6** exhibited almost no catalytic activity

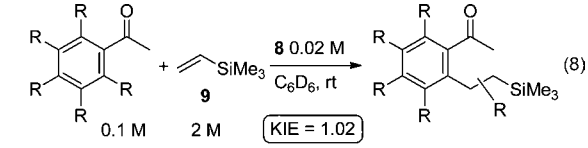
Scheme 2. A Plausible Reaction Pathway for the C−H Alkylation of Aromatic Ketones Using **8**



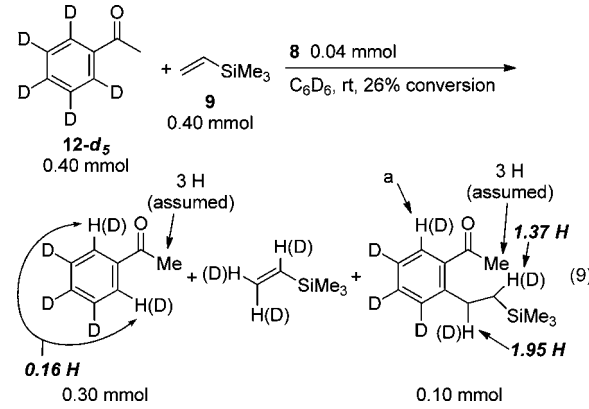
at either room or toluene reflux temperature. This is critically different from Hiraki's proposal, and the intermediacy of the *P,P′-cis-C,H-cis* isomers may explain the discrepancy between the plausibility of the presence of Ru(H)(*o*-$C_6H_4C(O)CH_3$)(CO)$(PPh_3)_2$ in the catalytic cycle and the observed inactivity of the *P,P′-trans-C,H-cis* isomers.

Although a complete understanding of the relationship between the structures of the intermediates and the catalytic activity for the $RuH_2(CO)(PPh_3)_3$-catalyzed C−H alkylation must await further extensive studies, the following features can be addressed: (1) two PPh_3 ligands coordinate to the ruthenium center with cis configuration in the active intermediate; (2) the hydride ligand is bound at the position trans to one of the phosphine ligands and cis to the other; (3) the CO ligand coordinates to the ruthenium throughout the reaction; and (4) the geometry of the coordination of the PPh_3 ligands to the ruthenium center is highly important for the attainment of the efficient catalytic reaction of aromatic ketones with olefins.

Deuterium-Labeling Experiments. Deuterium-labeling experiments were carried out to gain further understanding of C−H/olefin coupling at room temperature. The reactions of acetophenone-d_0 (**12**) and acetophenone-d_5 (**12-*d*$_5$**) with **9** using in situ-generated complex **8** were examined at room temperature under pseudo first-order kinetic conditions, and the rate constants of these reactions were measured. At 25 °C, the observed rate constants were k_{obs}(**12**) = 1.15×10^{-5} s^{-1} (run 1 in eq 8) and k_{obs}(**12-*d*$_5$**) = 1.13×10^{-5} s^{-1} (run 2 in eq 8). The kinetic deuterium isotope effect (KIE), k_{obs}(**12**)/k_{obs}(**12-*d*$_5$**), was 1.02. This small KIE value indicates that the C−H bond cleavage step is not rate-limiting. This result is consistent with a previous study concerning the reaction of **12-*d*$_5$** with triethoxyvinylsilane under toluene reflux conditions.[2c] The C−H bond cleavage is, therefore, facile and not rate-limiting at both room and toluene-reflux temperatures.



The reaction of **12-*d*$_5$** with 1 equiv of **9** was carried out using in situ-generated **8** as a catalyst at room temperature (eq 9). The ^{1}H NMR spectrum of the reaction mixture indicated that partial H/D exchange proceeded among the two ortho C-D bonds in **12-*d*$_5$** and the three vinylic C−H bonds in **9**. Partial incorporation of deuterium atoms in exchange for each of the three vinylic hydrogens was also confirmed by an independent ^{2}H NMR experiment in C_6H_6. Although the material balance with respect to deuterium atoms in the starting materials, as well as to the product, could not be determined due to overlap and the difficulty in quantifying the deuterium in the vinylsilane, the partial H/D exchange among the ketone and the vinylsilane supports the idea that each step prior to reductive elimination is fast even at room temperature, and the reductive elimination, that is, the C−C bond formation, is rate-limiting under the reaction conditions.



On the basis of the results of the NMR studies and the deuterium-labeling experiments, a plausible reaction pathway is proposed, as shown in Scheme 2. The initial step involves the oxidative addition of an ortho C−H bond to the ruthenium center to give the ortho-ruthenated complex **A**. Coordination of an olefin to **A** affords **B**, followed by hydro-ruthenation of the coordinating olefin, and provides alkylruthenium intermediates **C** and **D**. An equilibrium among **A**−**D** leads to H/D exchange among the ortho C−H bonds in acetophenone and the vinyl C−H bonds in the olefin. The coupling product and the catalytically active species **8** are formed from intermediate **C** through several steps.

Kinetic Studies of the Reaction of 10 with 9 at 25 °C. The rate of alkylation of 2′-methylacetophenone (**10**) with trimethylvinylsilane (**9**), using in situ-generated complex **8** as a catalyst, was measured at 25 °C by ^{1}H NMR spectroscopy (eq 10). First, the progress of the reaction with an excess amount of **9** was monitored by measuring the concentration of coupling product **11** (Figure 6a), and the rate of the catalytic C−H addition was found to exhibit pseudo first-order kinetics (Figure 6b). This

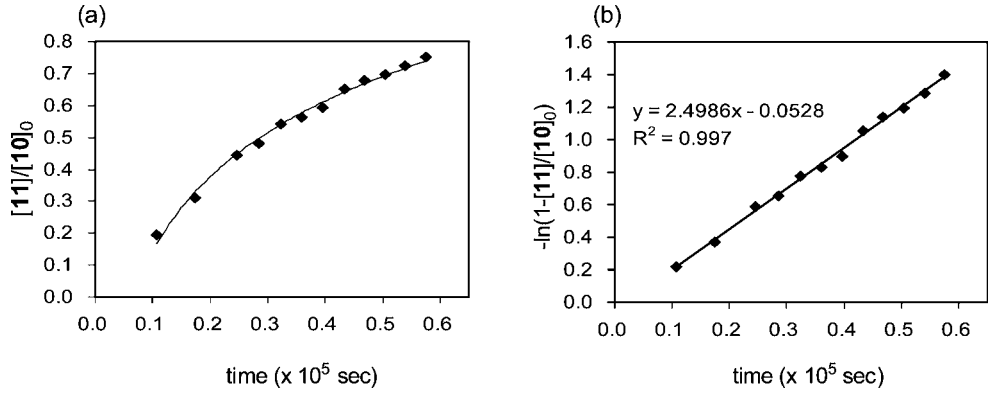
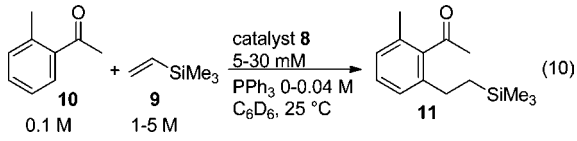


Figure 6. (a) Time−conversion curve and (b) first-order plot for alkylation of **10** with **9**. Reaction conditions: $[\mathbf{10}]_0 = 0.10$ M, $[\mathbf{9}]_0 = 3.0$ M, $[\mathrm{Ru}]_0 = 10$ mM in benzene-d_6, at 25 °C.

Table 2. Kinetic Data in the C−H Alkylation of **10** with **9** Using **8** as a Catalyst

run	$[\mathbf{1}]_0$, M	$[\mathbf{9}]_0$, M	$[PPh_3]$, M	$k_{obs} \times 10^5$, s^{-1}
1	0.005	2.0	0	8.43×10^{-1}
2	0.01	2.0	0	1.27
3	0.02	2.0	0	3.56
4	0.03	2.0	0	5.51
5	0.01	1.0	0	4.61×10^{-1}
6	0.01	2.0	0	1.27
7	0.01	3.0	0	2.50
8	0.01	4.0	0	3.39
9	0.01	5.0	0	3.89
10	0.02	2.0	0.02	2.14
11	0.02	2.0	0.04	2.81×10^{-1}
12	0.01	2.0	0.05	2.16×10^{-2}
13	0.01	4.0	0.05	3.56×10^{-2}
14	0.01	5.0	0.05	5.02×10^{-2}

means that the ketone consumption obeyed the pseudo first-order rate law described as $-\mathrm{d}[\mathbf{10}]/\mathrm{d}t = k_{obs}[\mathbf{10}]$,[19] where k_{obs} is 2.50×10^{-5} s^{-1}, if it is assumed that the amount of the intermediates such as **15** is small enough to be ignored in the calculation.



The rate constants, k_{obs}, were measured using various concentrations of **8**, **9**, and PPh_3 and are listed in Table 2. Because complex **8** was generated in situ by treating complex **1** with an excess amount of **9**, and only the weight of **1** was measured accurately as the ruthenium catalyst used for all the experiments, the initial concentration of **1** $[\mathbf{1}]_0$ was used as the amount of catalyst for the following descriptions. As $[\mathbf{1}]_0$ increased from 5 to 30 mM (runs 1−4), the k_{obs} value became larger, and the plot of the k_{obs} values against $[\mathbf{1}]_0$ shows that the relationship was almost linear (Figure 7a). An increase in the concentration of vinylsilane **9** also accelerated the reaction, but the relationship between the rate constants and the initial concentration $[\mathbf{9}]_0$ appeared to be more complex. At low concentration ($[\mathbf{9}]_0 = 1-3$ M) (runs 5−7), the rate constants appeared to be greater than first-order in $[\mathbf{9}]_0$ (Figure 7b), but the degree of order becomes lower at a higher concentration of $[\mathbf{9}]_0$ ($[\mathbf{9}]_0 = 4-5$ M) (runs 8,9). Although the actual cause of the dependence of the relationship on the olefin concentration is not clear at present, this result may suggest the possible involvement of more than one vinylsilane in a catalytic cycle and an increase in the amount of intermediates containing **9** at high concentrations.

Figure 7c shows the effect of PPh_3 added to the reaction mixture. The addition of PPh_3 (1−2 equiv to **1**) retarded the reaction, and increasing the equivalent of PPh_3 linearly decreased the rate of the alkylation (runs 3, 10, and 11). To minimize the effect of dissociated PPh_3 on the reaction rates, kinetic studies were performed in the presence of an excess amount of PPh_3 (5 equiv to **1**) (entries 12−14). The rates of the catalytic alkylation still exhibited pseudo first-order kinetics (Figure 8), and the relationship between the rate constants and $[\mathbf{9}]_0$ appeared to be closer to linear (Figure 9). These results suggest that this C−H alkylation obeys first-order kinetics in the ketone concentration and near first-order kinetics in the vinylsilane concentration, even in the presence of 5 equiv of PPh_3.

Summary

Described here is the mechanistic investigation of the coupling of aromatic ketones with alkenes catalyzed by **1**. The presence or absence of a carbonyl ligand on ruthenium during catalysis and the effect on the catalytic activity have previously been discussed by many researchers. The current study revealed that, at least in this system, a carbonyl ligand is present on the ruthenium center during the catalytic reaction, and the ruthenium species with a carbonyl ligand shows excellent catalytic activity. Heating was required for the generation of catalytically active species **8** as a mixture of four geometric isomers, but by using the active catalyst C−H/olefin coupling can be carried out at a much lower temperature, such as room temperature. Catalyst **8** generated in situ also showed excellent catalytic activity at both room and high (120 °C) reaction temperatures or at low catalyst loading (0.1 mol %, 994 TON). The monitoring of the catalytic reaction also showed the presence of an ortho-ruthenated aromatic ketone complex bearing a carbonyl ligand (**15**) during catalysis as an intermediate. The deuterium-labeling experiments using acetophenone and acetophenone-d_5 indicate that C−H (or C−D) bond cleavage is not the rate-limiting step. The H/D exchange reaction between acetophenone-d_5 and vinylsilane **9** suggests that each step prior to the C−C bond formation is in equilibrium. The relationship between the rate constants and the vinylsilane concentrations is not linear, but the kinetic studies under pseudo first-order conditions using an excess amount of

(19) Kitamura, M.; Tsukamoto, M.; Bessho, Y.; Yoshimura, M.; Kobs, U.; Widhalm, M.; Noyori, R. *J. Am. Chem. Soc.* **2002**, *124*, 6649–6667.

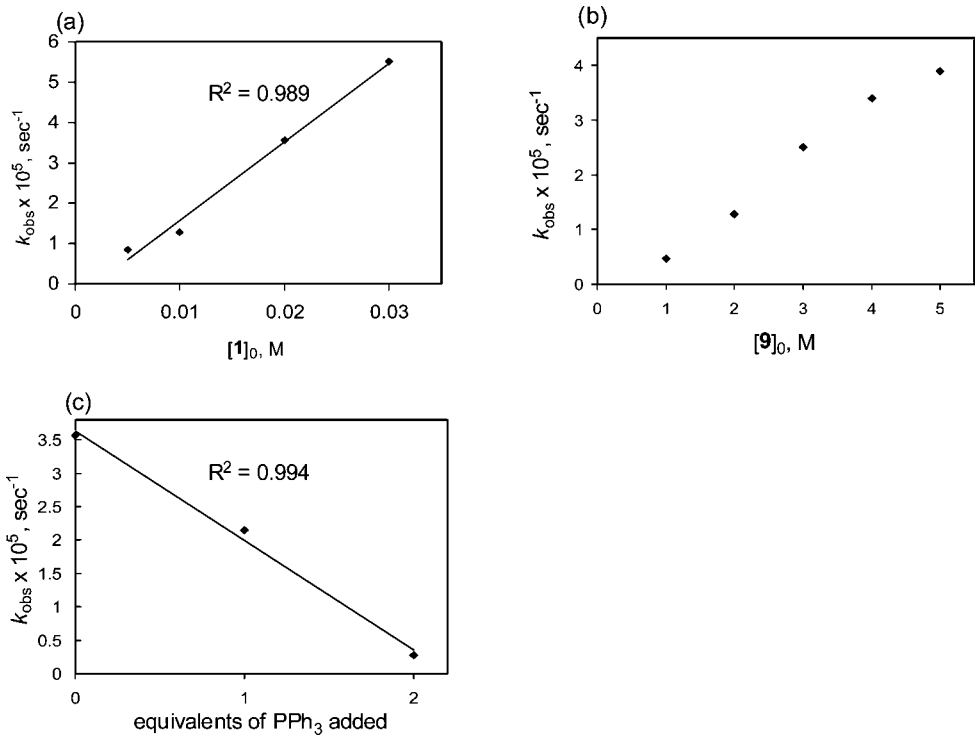


Figure 7. Dependence of the initial concentration of the ruthenium complex ($[\mathbf{1}]_0$), the initial concentration of trimethylvinylsilane **9** ($[\mathbf{9}]_0$), and the concentration of PPh_3 added ($[PPh_3]$) as a rate constant k_{obs} in the alkylation of **10** with **9** at 25 °C. (a) Plotting k_{obs} versus $[\mathbf{1}]_0$. Reaction conditions: $[\mathbf{10}]_0 = 0.10$ M, $[\mathbf{1}]_0 = 5.0-30$ mM, $[\mathbf{9}]_0 = 2.0$ M, benzene-d_6. (b) Plotting k_{obs} versus $[\mathbf{9}]_0$. Reaction conditions: $[\mathbf{10}]_0 = 0.10$ M, $[\mathbf{1}]_0 = 0.01$ M, $[\mathbf{9}]_0 = 1.0-5.0$ M, benzene-d_6. (c) Plotting k_{obs} versus equivalents of PPh_3 added. Reaction conditions: $[\mathbf{10}]_0 = 0.10$ M, $[Ru]_0 = 0.02$ M, $[\mathbf{9}]_0 = 2.0$ M, $PPh_3 = 0-2$ equiv to the ruthenium complex, benzene-d_6.

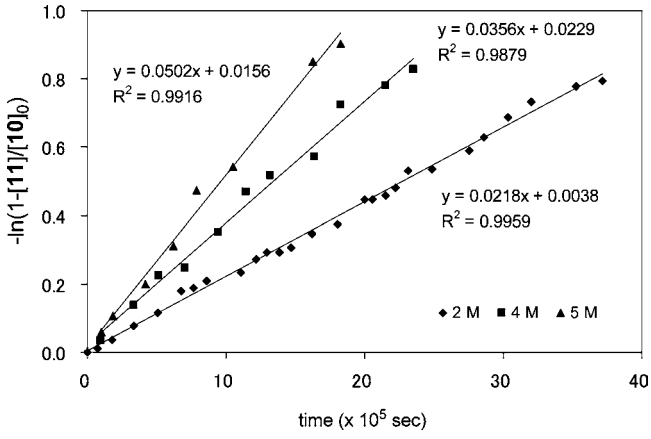


Figure 8. Dependence of initial concentration of trimethylvinylsilane **9** ($[\mathbf{9}]_0$) on the rate constant k_{obs} in alkylation of **10** with **9** at 25 °C in the presence of 5 equiv of PPh_3. Plotting k_{obs} versus $[\mathbf{9}]_0$. Reaction conditions: $[\mathbf{10}]_0 = 0.10$ M, $[\mathbf{1}]_0 = 0.01$ M, $[\mathbf{9}]_0 = 2.0-5.0$ M, $[PPh_3] = 0.05$ M, benzene-d_6, at 25 °C.

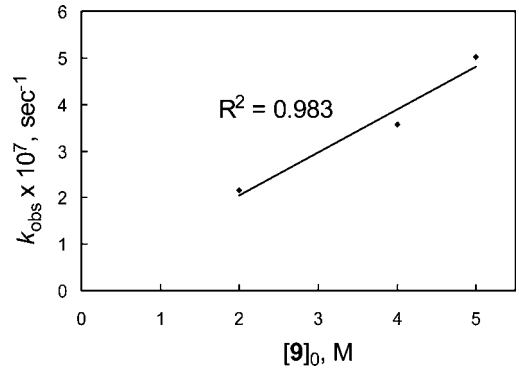


Figure 9. Plotting k_{obs} versus $[\mathbf{9}]_0$. Reaction conditions: $[\mathbf{10}]_0 = 0.10$ M, $[\mathbf{1}]_0 = 0.01$ M, $[\mathbf{9}]_0 = 2.0-5.0$ M, in the presence of 5 equiv of PPh_3, benzene-d_6.

olefin show that the reaction is first-order in ketone and catalyst concentrations.

Experimental Section

General Information. ^1H, $^{13}C\{^1H\}$, $^{31}P\{^1H\}$, and 2D NMR spectra were recorded using JEOL JNM-EX270, JNM-EX400, JNM-GSX400, and JNM ECX400 spectrometers. All manipulations for NMR and kinetic studies were performed under a nitrogen atmosphere in a nitrogen-filled glovebox using dry solvents and glassware.

Solvents and Materials. Toluene was dried over CaH_2 and was distilled under nitrogen. $RuH_2(CO)(PPh_3)_3$ (**1**) (Registry Number: 25360-32-1) and $Ru(CO)_2(PPh_3)_3$ (**16**) (Registry Number: 25360-32-1) were prepared using a method in the literature.[2c] 2′-Methylacetophenone (**10**) (Registry Number: 577-16-2), acetophenone (**12**) (Registry Number: 98-86-2), 2-acetylthiophene (Registry Number: 98-86-2), and acetophenone-d_5 (**12-d_5**) (Registry Number: 28077-64-7) were distilled from $CaSO_4$. Trimethylvinylsilane (**9**) (Registry Number: 754-05-2) was purchased from ShinEtsu Chemical and Industry Co. and distilled from CaH_2.

Generation of Ru(*o*-$C_6H_4PPh_2$)(H)(CO)(PPh_3)$_2$ (8) from $RuH_2(CO)(PPh_3)_3$ (1). $RuH_2(CO)(PPh_3)_3$ (**1**) (0.02 mmol), 1 mL of benzene, and trimethylvinylsilane (**9**) (0.024 mmol) were placed in an oven-dried 10 mL Schlenk flask. The resulting solution was heated at 90 °C. After heating for 1−1.5 h, **1** was completely converted to Ru(*o*-$C_6H_4PPh_2$)(H)(CO)(PPh_3)$_2$ (**8**).

Reaction of 2′-Methylacetophenone (10) with Trimethylvinylsilane (9) at Room Temperature. $RuH_2(CO)(PPh_3)_3$ (**1**) (0.02 mmol), 1 mL of toluene, and trimethylvinylsilane (**9**) (0.2 mmol)

were placed in an oven-dried 10 mL Schlenk flask. The resulting solution was heated at 90 °C for 1 h, and the resulting reaction mixture was then cooled to room temperature. To the solution were added 2′-methylacetophenone (**10**) (1 mmol) and **9** (2 mmol), and the resulting solution was then held at room temperature for 48 h. Volatile materials were evaporated. Silica gel column chromatography of the residue afforded ortho-alkylation product **11** in 99% yield (0.2336 g, 0.997 mmol).

Reaction of Acetophenone (12) with 9 at Room Temperature. In an oven-dried 10 mL Schlenk flask were placed **1** (0.02 mmol), 1 mL of toluene, and **9** (0.4 mmol). The resulting solution was heated at 90 °C for 1 h, and the resulting reaction mixture was then cooled to room temperature. Acetophenone (**12**) (1 mmol) and **9** (6 mmol) were added to the solution, and the resulting solution was then held at room temperature for 120 h. Volatile materials were evaporated. Silica gel column chromatography of the residue afforded **14** in 96% yield (0.3066 g, 0.96 mmol).

Reaction of 2-Acetylthiophene with 9 at 40 °C. In an oven-dried 10 mL Schlenk flask were placed **1** (0.02 mmol), 1 mL of toluene, and **9** (0.2 mmol). The resulting solution was heated at 90 °C for 1 h, and the resulting reaction mixture was then cooled to room temperature. To the solution were added 2-acetylthiophene (1 mmol) and **9** (2 mmol), and the resulting solution was heated at 40 °C for 72 h. Volatile materials were evaporated. Silica gel column chromatography of the residue afforded 3-(2-trimethylsilylethyl)-2-acetylthiophene in 74% yield (0.1676 g, 0.74 mmol).

Reaction of 10 with 9 under Low-Catalyst Loading Conditions. In an oven-dried 10 mL Schlenk flask were placed **1** (0.002 mmol), 1 mL of toluene, and **9** (2 mmol). The resulting solution was heated at 90 °C for 1.5 h, and then the resulting reaction mixture was cooled to room temperature. To the solution was added **10** (2 mmol), and then the resulting solution was heated at 120 °C for 48 h. Volatile materials were evaporated. Silica gel column chromatography of the residue afforded **11** in 99.4% yield (0.466 g, 1.99 mmol).

^{1}H and ^{31}P NMR Monitoring of the Catalytic Reaction of 10 with 9 at Room Temperature Using 8 as a Catalyst. In a benzene-d_6 solution of **8** (0.02 mmol) in a sealable NMR tube, generated according to the procedure described above, were placed **10** (0.1 mmol) and an additional amount of **9** (0.1 mmol). The reaction was carried out at room temperature, and the progress of the reaction was monitored by ^{1}H and ^{31}P NMR spectroscopy. After 5 days, an additional 0.2 mmol of **10** was added to the reaction mixture.

Kinetic Experiments. Kinetic investigations were studied at 25 °C. In an oven-dried Schlenk flask were placed **1** (18 mg, 0.02 mmol, 0.01 M), 1.02 mL of benzene-d_6, and **9** (870 μL, 6.0 mmol, 3.0 M). This mixture was heated at 90 °C for 1.25 h, and the reaction mixture was then cooled to room temperature (25 °C). Into the resulting solution were placed anisole (internal standard for the NMR yield, 11 μL, 0.10 mmol, 0.050 M) and 2′-methylacetophenone **10** (26 μL, 0.20 mmol, 0.10 M). A partial amount (ca. 0.6 mL) of this reaction mixture was transferred into a sealable NMR tube, and this reaction mixture was held at 25 °C. The progress of the reaction was monitored by ^{1}H NMR spectroscopy. The measurement was continued for 960 min. The observed reaction rate was 2.50×10^{-5} s^{-1}. The effects of the initial concentration of catalyst, initial concentration of trimethylvinylsilane, and equivalents of PPh_3 on the reaction rates were measured in a similar fashion.

Kinetic Deuterium Isotope Effect. The rate constants for the reactions of acetophenone-d_0 (**12-d_0**) and -d_5 (**12-d_5**) with trimethylvinylsilane were measured under the following reaction conditions: $[\mathbf{1}]_0 = 0.02$ M, $[\mathbf{12}]_0 = 0.10$ M, $[\mathbf{9}]_0 = 2.0$ M, benzene-d_6, at 25 °C. While the reaction proceeded, the corresponding 1:2 addition product was also formed. To minimize the effect of conversion of the monoalkylation product to the dialkylation product, the rate constant k_{obs} was calculated on the basis of the yield of the corresponding monoalkylation product at the early stage of the catalytic reaction. The rate constants for the reaction of **12-d_0** and **12-d_5** were calculated to be 1.15×10^{-5} and 1.13×10^{-5} s^{-1}, respectively. From these results, the kinetic deuterium isotope effect was calculated to be $k_H/k_D = 1.02$.

Deuterium Labeling Experiment Using 12-d_5. The reaction of **12-d_5** (0.40 mmol) with **9** (0.40 mmol) was carried out in 0.8 mL of benzene-d_6 at room temperature using **8** (0.040 mmol) as a catalyst. The progress of the reaction was monitored by ^{1}H NMR, and, after 80 h, the conversion of the reaction reached 26%. The percentage of the deuterium incorporation into the starting ketone and the product was determined by the ^{1}H NMR spectrum.

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