

## Catalytic addition of C–H bonds to multiple bonds

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**Abstract:** Some ruthenium complexes have been found to catalyze the direct addition of *ortho* carbon-hydrogen bonds in aromatic ketones, olefins, aromatic esters, and imines to unsaturated compounds with high efficiency and selectivity.

### Introduction

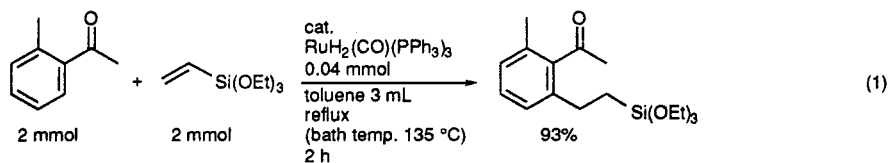
In contrast to a number of examples of stoichiometric reactions involving C-H bond cleavage by transition metal complexes, the use of this chemistry in practical catalytic reactions is still rare. The catalytic reactions of this type generally suffer from low efficiency (low chemical yields, low catalyst turnover, necessity of the use of one of the reactants in large excess, often as the solvent, and necessity of extra energy input by photo irradiation etc.), low selectivity, and lack generality. During the past 30 years, the research in these fields has been very active and as much as 50 review articles have been published (refs. 1 and 2).

Recently, exceptionally efficient catalytic reactions involving C-H bond cleavage were reported. Jordan and Taylor found a Zr-catalyzed addition of  $\alpha$ -picoline to olefins in 1989 (ref. 3). Although the presence of molecular hydrogen was necessary to keep the catalyst turnover high and thus it inevitably forced the consumption of olefin by hydrogenation as a competing reaction, a quantitative yield of the product could be obtained. In 1992, Moore and co-workers reported on the coupling together of three reactants, pyridine, CO, and an olefin, using  $\text{Ru}_3(\text{CO})_{12}$  as the catalyst (ref. 4). The oxygen atom of CO could not carry a substituent at the oxygen but the nitrogen in isoelectronic isonitrile could be envisioned to bear such and the plausibility of an intramolecular  $\alpha$ -addition can be thus recognized. This was realized by Jones and Kosar (ref. 5).

It should be noted that various types of C-H bonds can react with the aid of transition metals through a variety of mechanisms ranging from oxidative addition to deprotonation. Some of these reactions are useful in organic synthesis. The selected examples are Pd-catalyzed functionalization of unsaturated and allylic C-H bonds (ref. 6), Ru-catalyzed functionalization of C-H bonds  $\alpha$  to hetero atoms (ref. 7), Ru-, Rh-, and Pd-catalyzed addition of active methylene compounds to unsaturated functions (ref. 8), Rh- and Ru-catalyzed hydroacylation of olefins with aldehydes (ref. 9), Rh-catalyzed decarbonylation of aldehydes (ref. 10), and catalytic functionalization of olefins via addition-elimination mechanism (ref. 11).

### Ru-Catalyzed Aromatic C-H/Olefin Coupling

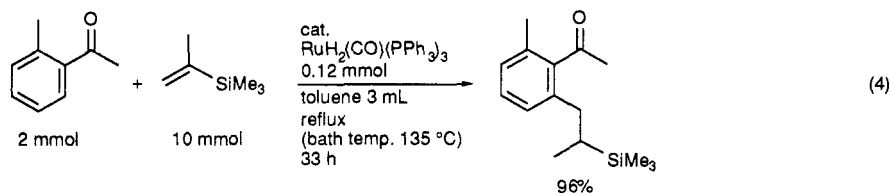
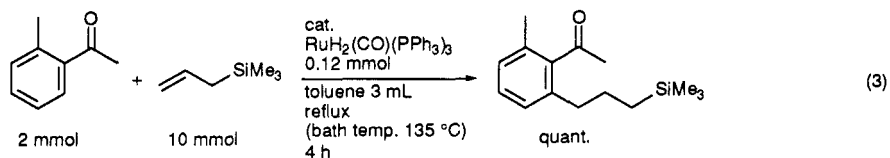
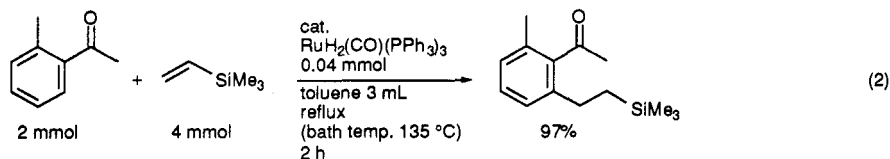
Very recently, we reported a new transition metal-catalyzed reaction that enabled addition of aromatic C-H bonds to olefins (refs. 12 and 13). The new Ru-catalyzed reaction could bring about the addition of C-H bonds in a broad range of substrates from aromatic ketones to double bonds of olefins. A C-C bond could be formed from a C-H bond in a single step high in an efficiency that had never been attained hitherto. A representative example is given in eq. 1.



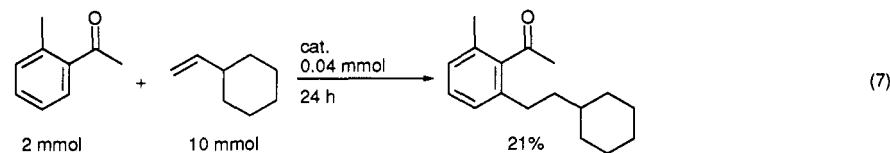
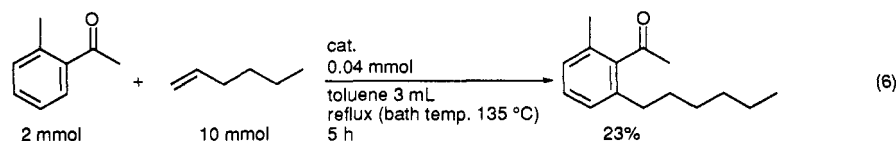
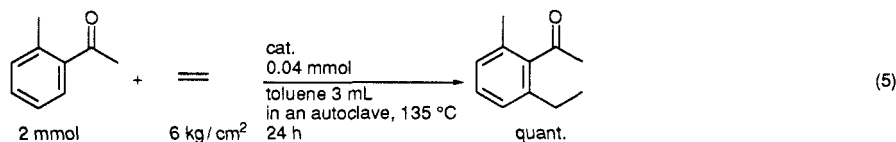
The reaction gave a 1:1 adduct in almost quantitative yield based on both starting materials. Only the C-H bond *ortho* to the carbonyl group had been reacted. Various transition metal complexes were

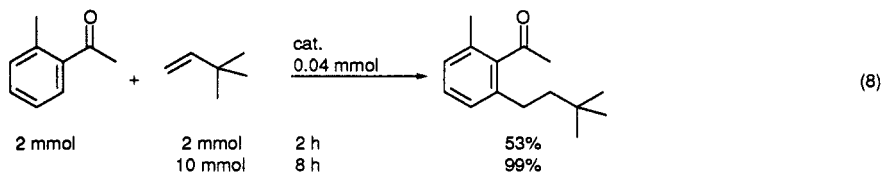
examined for their catalytic activities.  $\text{RuH}_2(\text{CO})(\text{PPh}_3)_3$  and  $\text{Ru}(\text{CO})_2(\text{PPh}_3)_3$  were found to be most effective while  $\text{RuH}_2(\text{PPh}_3)_4$  and  $\text{Ru}(\text{CO})_3(\text{PPh}_3)_2$  were moderate and  $\text{RuHCl}(\text{CO})(\text{PPh}_3)_3$ ,  $\text{RuCl}_2(\text{PPh}_3)_3$ ,  $\text{RuCl}_2(\text{CO})_2(\text{PPh}_3)_2$ , and  $\text{Ru}_3(\text{CO})_{12}$  were inactive. Interestingly, the ruthenium complex  $\text{RuCl}(\text{OAc})(\text{CO})(\text{PPh}_3)_2$  that was known to undergo cyclometallation of acetophenone (ref. 14) with cleavage of the *ortho* C-H bond did not show any catalytic activity for the present reaction.

Vinylsilanes and allylsilanes gave coupling products with *o*-methylacetophenone in excellent yields (eqs. 2-4). Trimethylvinylsilane was used in excess because of its low boiling point. For less reactive olefins such as allyltrimethylsilane and isopropenyltrimethylsilane, high yields were obtained when the five equivalents of olefins were used. Triethoxyvinylsilane seemed to be the olefin of choice for the examination of reactivities of different ketones (*vide infra*).

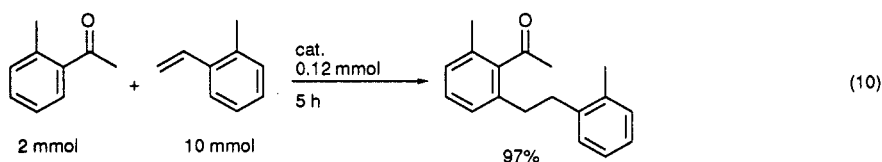
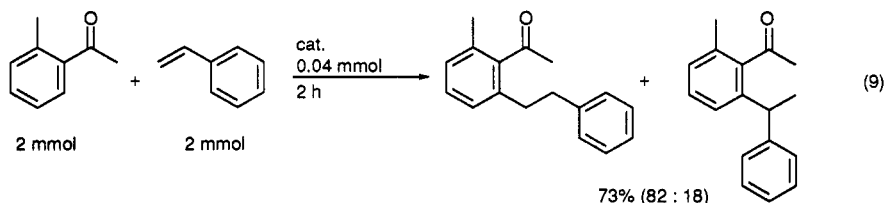


The results obtained for ethylene and substituted ethylenes are given in eqs. 5-8. In the cases of primary and secondary alkyl substituents (eqs. 6 and 7), the addition products were obtained only in low yields due to the isomerization of the starting olefins during the reaction. From *tert*-butylethylene, in which isomerization is impossible, the 1:1 coupling product was formed quantitatively (eq. 8). It should be noted that these products are of the type that are not easily obtainable by conventional synthetic methods. Acylation of an alkylbenzene would give a mixture of *ortho*- and *para*-isomers with the latter predominating. Alkylation of acylbenzenes as an alternative synthetic route would be even more difficult since the electron deficient aromatic ring is usually unreactive to known alkylating reagents.

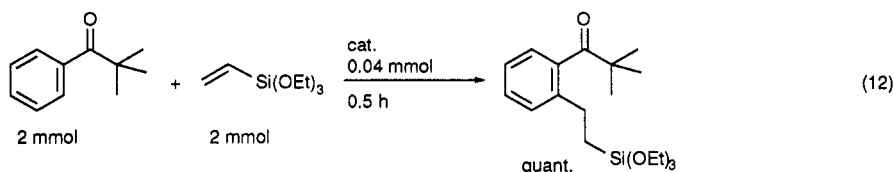
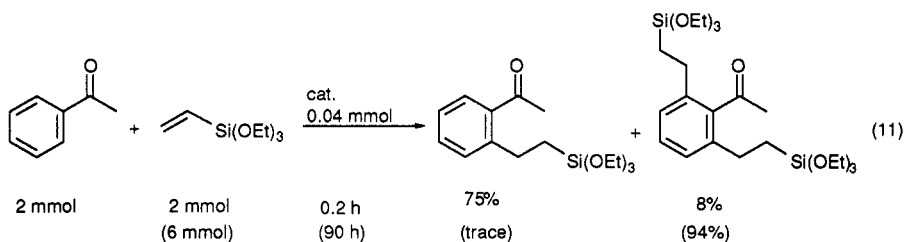




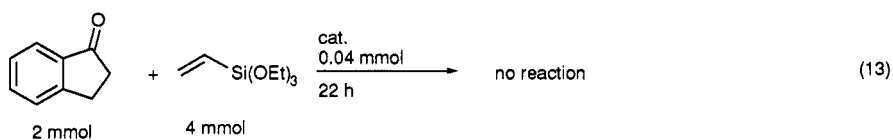
Styrene gave a mixture of regioisomers in a 4:1 ratio (eq. 9). The regioselectivity became complete when a small alkyl group was introduced to the ortho position of styrene (eq. 10).

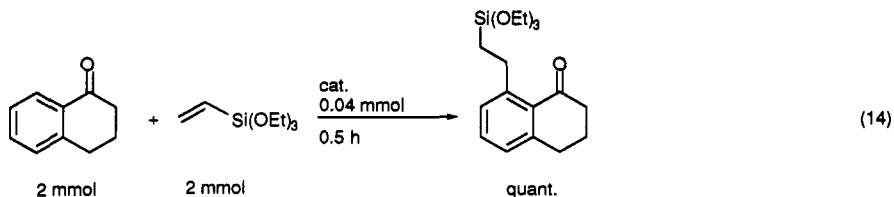


Various aromatic ketones have been subjected to the catalytic reaction using triethoxyvinylsilane as the olefin. Acetophenone has two ortho hydrogens and indeed 1:1 and 1:2 coupling products were obtained. By employing an excess amount of the olefin and prolonged reaction time, the 1:2 adduct was produced almost exclusively (eq. 11). A 1:2 adduct was no longer formed even under the forcing conditions in the case of *tert*-butyl phenyl ketone (eq. 12).

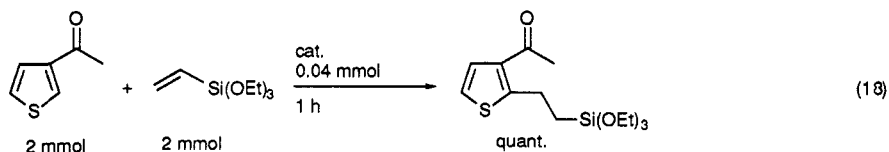
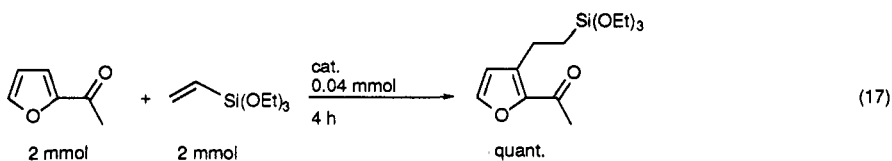
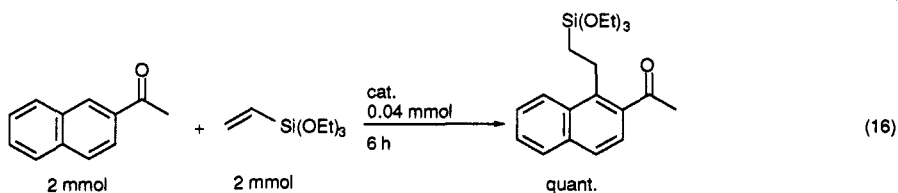
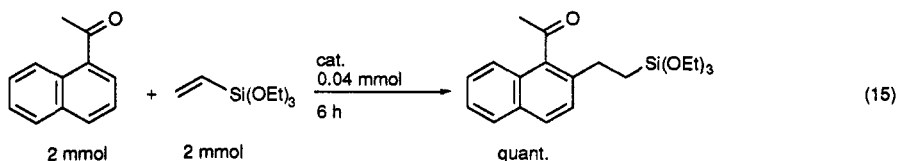


As shown in eqs. 13 and 14, the relative position of the carbonyl group and the C-H bond to each other seems very important.





The catalytic reaction can also be applied to naphthalenes (eqs. 15 and 16) and heteroaromatics (eqs. 17 and 18). The results of eqs. 16 and 18 are worthy of note since, in each case, only one of the two different C-H bonds adjacent to the carbonyl group reacted exclusively.



The new catalytic reaction described above achieves the efficiency, selectivity, and generality to be of general practicality in organic synthesis. Moreover, the catalytic reaction is operationally simple and proceeds cleanly; viz. simply required mixing the reactants and the catalyst in toluene and heating them under vigorous reflux, then simple bulb-to-bulb distillation of the reaction mixture usually allows the isolation of an analytically pure product. That the reaction can be run equally in a larger scale of 10g of reactant, has been confirmed for the reaction of eq. 14.

### Suggested Mechanism

The mechanism of the new Ru-catalyzed C-H/olefin coupling reaction is intriguing and important, but it is far from clear at the present time. We suggest just the possibilities as follows. The course of the catalytic reaction is outlined in Figure 1 with important alternative routes and with simplified structures. The reaction begins with the coordination of a carbonyl group to the Ru atom in the catalyst, bringing the Ru atom close to the ortho C-H bond. By direct interaction of the Ru atom with the C-H bond as in **3** or by 1,4-addition of the Ru species followed by 1,2-H shift via **4**, a cyclometallated intermediate **5** is formed.

After coordination of an olefin to **5**, insertion of the olefin into the Ru-H bond gives **6**, or alternatively insertion into the Ru-C bond gives **7**. The reductive elimination from **6** or **7** leads to **8**, from which

decomplexation of the coupling product **9** regenerates the catalyst **1**. Before the reductive elimination, the chelating carbonyl group can also dissociate (this alternative is not shown in Fig. 1).

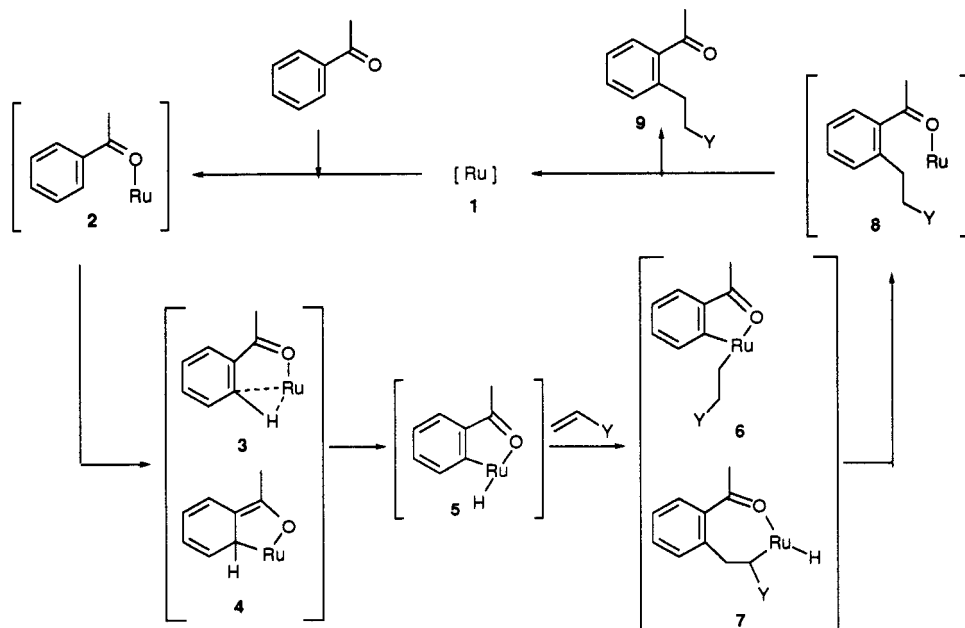
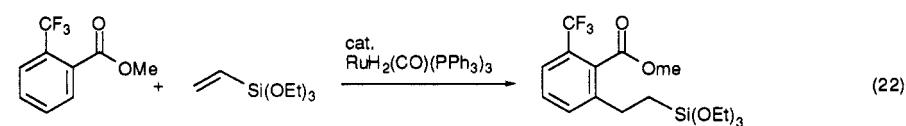
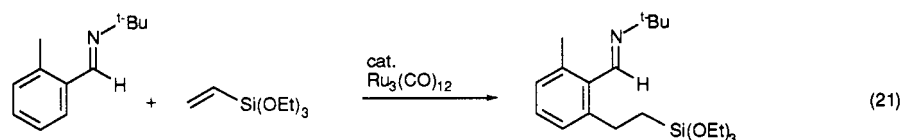
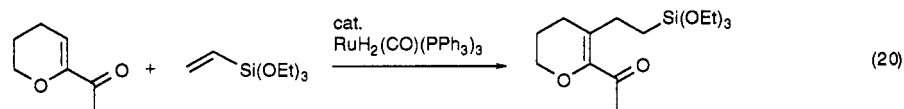
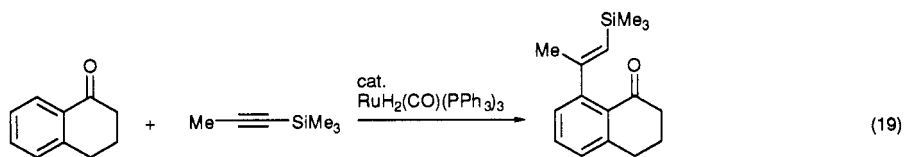


Fig 1. The Outlined Catalytic Cycle with Alternatives

### Manipulation of Other Types of C-H Bonds

The present discovery should open up a myriad of fascinating opportunities in synthetic organic chemistry. Indeed, we have already found that acetylenes instead of olefins participate in the catalytic reaction (eq. 19) (ref. 15) and also that olefinic C-H bonds can be added to different olefins (eq. 20) (ref. 16). In addition, we have found that the new catalytic reaction can be extended to a nitrogen analogue as illustrated in eq. 21 (ref. 17) and also to aromatic esters (eq 22) (ref. 18).



In the coming next few years we anticipate that our efforts will be concentrated in extending the scope of the new Ru-catalyzed C-H/multiple bond coupling, primarily from the synthetic point of view. Also, attempts to find new and different catalytic reactions by making use of the already rich chemistry of C-H bonds cleavage (refs. 4 and 5), will be made. For this purpose, we will rely on the following working hypothesis: the cleavage of C-H bonds is a facile step so that to devise a system in making the last steps such as reductive elimination easier is more important for the construction of a new catalytic cycle (ref. 19).

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- Jones has shown that the slow step in the catalytic formation of indole from 2,6-xylyl isocyanide is not the step of C-H bond cleavage but the last step involving reductive elimination (see ref. 5).