

# Catalytic Methods for C–H Bond Functionalization: Application in Organic Synthesis

Fumitoshi Kakiuchi\*, Naoto Chatani

Department of Applied Chemistry, Faculty of Engineering, Osaka University, Suita, Osaka 565-0871, Japan  
Fax: +81-6-6879-7396, e-mail: kakiuchi@chem.eng.osaka-u.ac.jp

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**Abstract:** The development of catalytic reactions involving carbon-hydrogen bond cleavage is currently one of the most attractive research subjects in organic and organometallic chemistry. About 40 years have past since the pioneering report of the cleavage of C–H bonds with transition metal complexes. Since that time, a vast number of studies of the cleavage of C–H bonds, using stoichiometric amounts of transition metal complexes has appeared. In the last decade, a variety of catalytic reactions involving C–H bond cleavage has been reported. In this review we briefly survey the results of these research activities with respect to the catalytic use of unreactive C–H bonds in organic synthesis.

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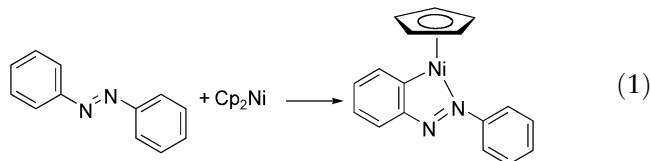
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**Keywords:** alkenylation; alkylation; borylation; carbonylation; C–C bond formation; C–H activation; silylation; transition metal catalysts

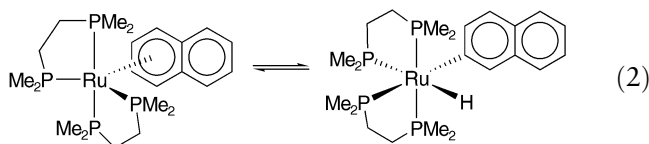
## 1 Introduction

Carbon-hydrogen bonds (abbreviated to C–H bonds hereafter) are ubiquitous in organic compounds. If the C–H bonds could be used as a functional group, similar to a carbon-halogen bond, it would become one of the most powerful, valuable, straightforward methods for producing complex molecules and for the construction of C–C bond frameworks. However, the bond dissociation energy of a C–H bond is usually large, e.g., 105 kcal/mol for H–CH<sub>3</sub>, and 110 kcal/mol for H–C<sub>6</sub>H<sub>5</sub>.<sup>[1]</sup> Therefore, such a C–H bond cleavage was generally believed to be difficult.

In 1963, Kleiman and Dubeck reported the possibility of C–H bond cleavage in azobenzene by the Cp<sub>2</sub>Ni complex, Eq. (1).<sup>[2]</sup> The reaction mechanism for this metalation reaction has not been elucidated, but the *ortho*-C–H bond was apparently cleaved.



Two years later, in 1965, Chatt and Davidson reported on the first example of the oxidative addition of a C–H bond to the zero-valent ruthenium center to give the Ru(H)(2-naphthyl)(dmpe)<sub>2</sub> [dmpe = 1,2-bis(dimethylphosphino)ethane] complex, which is in equilibrium with a  $\pi$ -coordinated naphthalene ruthenium complex, Ru(naphthalene)(dmpe)<sub>2</sub>, Eq. (2).<sup>[3]</sup> They also reported that the *sp*<sup>3</sup> C–H bond of the methyl group in the dmpe ligand can be cleaved by the ruthenium(0) complex.



After these pioneering studies, many research groups have reported on the cleavage of C–H bonds *via* the use of a stoichiometric amount of transition metal complexes.<sup>[4]</sup> To date, a large number of review articles is available and the fundamental features of the C–H bond cleavage reactions have been elucidated.<sup>[4,5]</sup> Nearly all of these review articles deal with studies of the stoichiometric cleavage of C–H bonds by transition metal

*Fumitoshi Kakiuchi* was born in Hoyogo, Japan, in 1965 and received his B.Sc. in 1988 and Ph.D. in 1993 from Osaka University under the guidance of Prof. Shinji Murai. He was appointed as an Assistant Professor at Osaka University in 1993. He did his postdoctoral work with Prof. E. N. Jacobsen at Harvard University in 1996–1997. In 2000, he was appointed as an Associate Professor at Osaka University. His research interests include the development of new transition metal-catalyzed reactions.



*Naoto Chatani* was born in Hyogo, Japan, in 1956. He studied chemistry at Osaka University and received his Ph.D. in 1984 under the guidance by Profs. Noboru Sonoda and Shinji Murai. In 1984 he joined the Institute of Scientific and Industrial Research at Osaka University and worked in the laboratory of Prof. Terukiyo Hanafusa. After postdoctoral studies (1988–1989 under Prof. Scott E. Denmark, the University of Illinois, Urbana-Champaign), he moved back to Osaka University and was promoted to Associate Professor in 1992 and Professor in 2003. His research interests center on the area of catalysis.



complexes.<sup>[4]</sup> On the contrary, as for the transition metal-catalyzed functionalization of C–H bonds, the chemistry is considered to be still in its early stages and the only examples have appeared in the literature in the early 1990s.<sup>[6–8]</sup>

In 1989, Jordan reported on the Zr-catalyzed addition of a C–H bond in  $\alpha$ -picoline to an olefin.<sup>[6]</sup> Moore found in 1992 that the Ru-catalyzed three-component coupling of pyridine, carbon monoxide, and olefin provides the corresponding  $\alpha$ -acylpyridines in good yields.<sup>[7]</sup> Subsequently, in 1993 Murai reported on the highly efficient, selective functionalization of C–H bonds in aromatic ketones with olefins in the presence of a ruthenium catalyst.<sup>[8]</sup> Since these discoveries, the chemistry of the catalytic use of C–H bonds in organic synthesis has rapidly expanded.

This review article will broadly survey the literature dealing with the catalytic use of otherwise unreactive  $sp^2$  and  $sp^3$  C–H bonds in organic synthesis until early in the

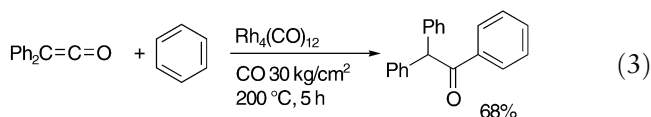
year 2003. However, several areas, e.g., hydroacylation of olefins and acetylenes with aldehydes, Michael addition and aldol reactions using active methylene compounds, reactions involving transition metal-carbenoids, reactions using aryl halides, acetylenes, and palladium complexes, and reactions in the presence of heterogeneous catalysts, will not be dealt with. In this review, only limited numbers of examples which involve unusual significance, originality, or complexity will be presented in equation form.

## 2 Catalytic C–C Bond Formation *via* a C–H Bond Cleavage

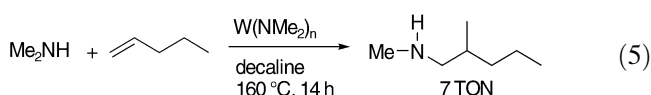
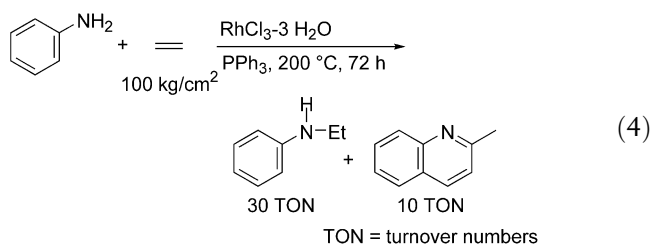
Carbon-carbon bond formation is one of the most important reactions in organic synthesis.<sup>[9]</sup> A large number of methods has been published in the literature and this chemistry continues to grow. When the C–C bond formation is carried out catalytically, relatively reactive functional groups such as halogen and triflates are usually used.<sup>[10]</sup> The important step for these reactions is the generation of metal-carbon bonds *via* oxidative addition of the C–X bond (X = halogen, triflate) to low-valent transition metal complexes. The insertion of small molecules such as olefins, acetylenes, and carbon monoxide into the metal-carbon bond is followed by a reductive elimination, resulting in C–C bond formation. If C–H bonds can be used like carbon-halogen bonds for constructing a C–C bond, the reaction becomes one of the most valuable, powerful, straightforward procedures in organic synthesis. In this section, transition metal-catalyzed C–C bond formation through a C–H bond cleavage will be discussed.

### 2.1 Addition of C–H Bonds to C/C Double Bonds

The catalytic addition of C–H bonds to olefins constitutes one of the most efficient, economical methods for constructing C–C bond frameworks. In 1978, Yamazaki reported on some pioneering studies in this area.<sup>[11]</sup> The reaction of benzene, used as a solvent, with diphenylketene in the presence of  $Rh_4(CO)_{12}$  as a catalyst gives diphenylmethyl phenyl ketone in good yield with moderate selectivity, Eq. (3). The use of a CO atmosphere is essential in achieving a catalytic reaction although no CO incorporation occurs, probably because carbon monoxide maintains the catalyst in an active form. In the examination of the relative reactivities of several aromatic compounds, they found that fluorobenzene is more reactive than toluene. On the basis of these results, they proposed that the C–H bond cleavage step by the rhodium complex appears to be nucleophilic in nature. The rhodium catalyst is also effective for the dehydrogenative vinylation of benzenes with ethylene to give styrenes.<sup>[12]</sup>

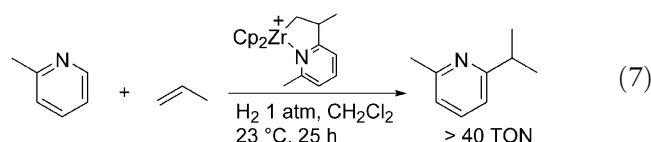
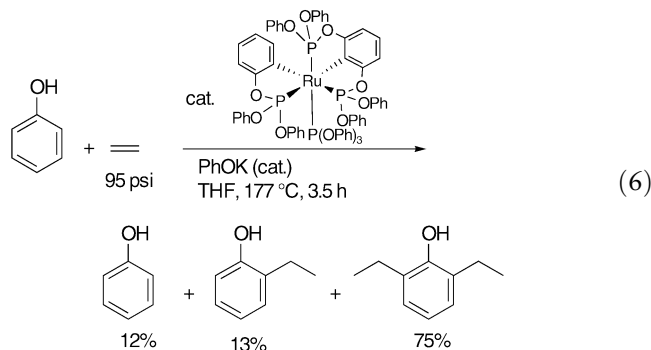


The double insertion of ethylene into aniline with the aid of rhodium(III) chloride hydrate gives the cyclization product, 2-methylquinoline, Eq. (4).<sup>[13]</sup> Forcing reaction conditions (a high ethylene pressure, 100 kg/cm<sup>2</sup>, and a high temperature, 200 °C) and the use of an excess of aniline are required for this catalytic reaction to proceed efficiently. The addition of an *sp*<sup>3</sup> C–H bond adjacent to a nitrogen atom in dimethylamine to 1-pentene is catalyzed by the tungsten amide complex  $\text{W}(\text{NMe}_2)_n$ ,<sup>[14]</sup> which is a 2:1 adduct of  $\text{W}_2(\text{NMe}_2)_6/\text{W}(\text{NMe}_2)_6$ , to give *N*-methyl-*N*-(2-methylpentyl)amine, Eq. (5).<sup>[15]</sup> The similar type of reaction involving an  $\alpha$  C–H bond adjacent to oxygen with *tert*-butyl-ethylene is catalyzed by  $\text{IrH}_5(\text{P}^i\text{Pr}_3)_2$  under relatively mild reaction conditions (50 °C).<sup>[16]</sup> This reaction is formally a dehydrogenative coupling. Hydrogenation of the olefin is the key for regenerating the catalytically active species since the generation of molecular hydrogen by reductive elimination from an H–M–H species is usually a thermally unfavorable pathway.<sup>[17]</sup> Thus, in this reaction, the olefin functions as an acceptor of the C–H bond and also as a scavenger of two hydrogen atoms from the metal center.

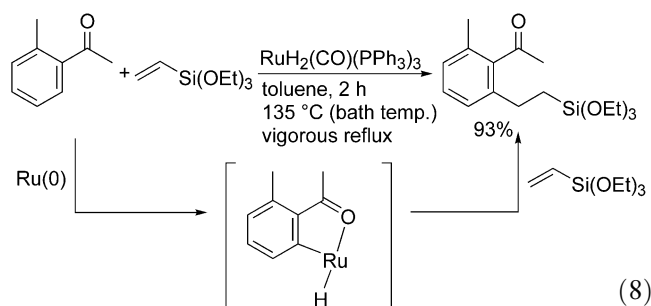


The heteroatom-directed ethylation of a phenol on the benzene ring is catalyzed by a ruthenium(II)-phosphite complex. This alkylation takes place exclusively at the position *ortho* to the hydroxy group, and the corresponding 1:2 addition product is the major product, Eq. (6).<sup>[18]</sup> The alkylation of  $\alpha$ -picoline with a terminal olefin occurs at a position  $\alpha$  to the nitrogen with the aid of a cationic zirconium catalyst, Eq. (7).<sup>[6]</sup> For this reaction, the protection of one  $\alpha$  C–H bond of the pyridine ring with an alkyl group is required to conduct this reaction in a catalytic manner. This reaction can be extended to an asymmetric version. An example of the asymmetric  $\alpha$ -alkylation of the picoline *via* C–H bond cleavage reaction using a chiral tetrahydroindenyl-zirconium complex has been reported by Jordan.<sup>[6b]</sup>

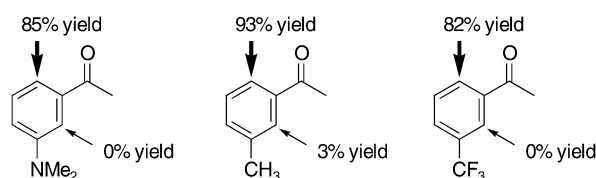
The enantiomeric excess of the product is up to 58% ee. Another type of coupling reaction was reported by Jones:<sup>[19]</sup> the  $\text{RuH}_2(\text{dmpe})_2$ -catalyzed intramolecular insertion of isocyanide into the benzylic C–H bond in 2,6-xylyl isonitrile leading to indole derivatives.



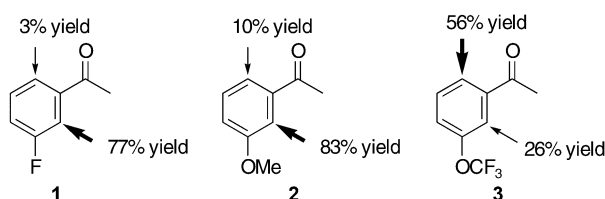
In 1993, Murai found the first example of a highly efficient, selective C–H/olefin coupling reaction.<sup>[8]</sup> The reaction of aromatic ketones with olefins in the presence of  $\text{RuH}_2(\text{CO})(\text{PPh}_3)_3$  gave the corresponding *ortho*-alkylated compounds in quite high yields, Eq. (8). Various combinations of aromatic ketones and olefins are applicable to this reaction. Carbon-carbon bond formation occurred exclusively at the position *ortho* to the carbonyl group. The important feature of this reaction is the coordination of the carbonyl group to the ruthenium, bringing the ruthenium closer proximity to the *ortho* C–H bonds.



Murai reported on the successful use of a variety of directing groups including ketones,<sup>[20]</sup> esters,<sup>[21]</sup> aldehydes,<sup>[22]</sup> aldimines,<sup>[23]</sup> ketimines,<sup>[23]</sup> amidinates,<sup>[24]</sup> hydrazones,<sup>[25]</sup> and nitriles.<sup>[26]</sup> The ruthenium-catalyzed coupling of aromatic ketones with olefins is tolerant of several functional groups [e.g.,  $\text{NMe}_2$ ,  $\text{OMe}$ ,  $\text{F}$ ,  $\text{NEt-C(O)Me}$ ,  $\text{CF}_3$ ,  $\text{CO}_2\text{Et}$ ,  $\text{CN}$ , acetals,  $\text{OC(O)CH}_3$ ]. As shown in Figure 1, the regioselectivity is basically controlled by steric factors. In the case of the reaction



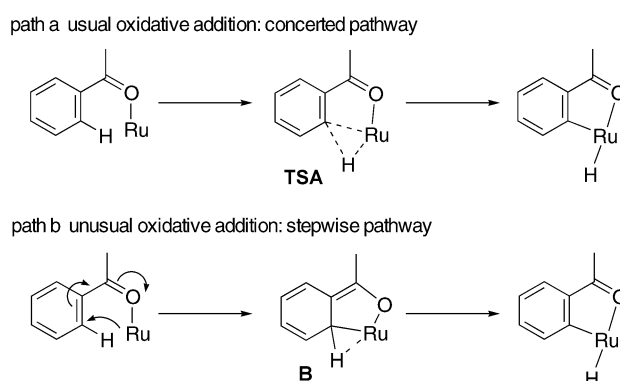
**Figure 1.** Site-selective alkylation controlled by a steric congestion.



**Figure 2.** Effect of the substituents toward the site-selectivity.

of *m*-substituted acetophenones, the corresponding 6'-alkylated products are obtained as the major product (Figure 1). Interestingly, however, the reactions of *m*-fluoro- and *m*-methoxyacetophenones with triethoxyvinylsilane take place at the more congested *ortho* position, i.e., 2'-position (Figure 2; **1** and **2**, respectively). When a strong electron-withdrawing CF<sub>3</sub> group, which should decrease the electron density of the adjacent atom, is introduced on the ether oxygen as in **3**, the alkylation takes place preferentially at the less congested position. These results suggest that heteroatoms may additionally assist in the regioselectivity determination step.

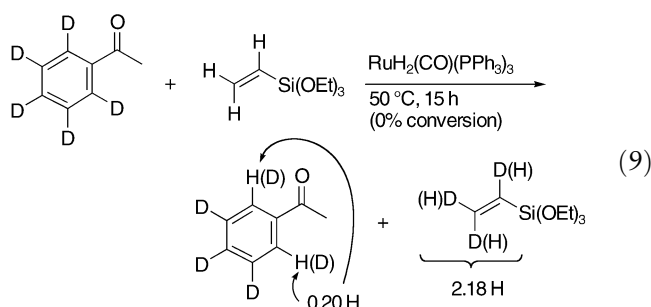
Murai has claimed that there are two plausible mechanisms with respect to the C–H bond cleavage step (Scheme 1).<sup>[20b]</sup> One is a usual oxidative addition of the C–H bond to the ruthenium center which proceeds through transition state **TSA** (path a, concerted pathway). In the other case, the C–H bond cleavage through intermediate **B** occurs in two steps (path b, stepwise pathway). Therefore, in the first step the ruthenium-carbon bond is formed without C–H bond cleavage and in the second step the hydrogen at the *ortho* position is transferred to the ruthenium atom. Both mechanisms satisfactorily explain the *ortho* selectivity. Morokuma and Koga reported that the latter mechanism (path b) is reasonable for the C–H bond cleavage by the ruthenium complex on the basis of *ab initio* theoretical calculations.<sup>[27]</sup> For their theoretical calculation, they used benzaldehyde and ethylene as models of aromatic ketone and olefin. Their calculation revealed that the highly selective *ortho* C–H bond cleavage of the aromatic ketones stems from the coordination of the carbonyl oxygen to the ruthenium center. If the reaction passes through the conventional three-centered transition state (path a), a much larger activation energy (20.1 kcal/mol) would be required. On the contrary, if the C–H bond is cleaved through novel metalacycle



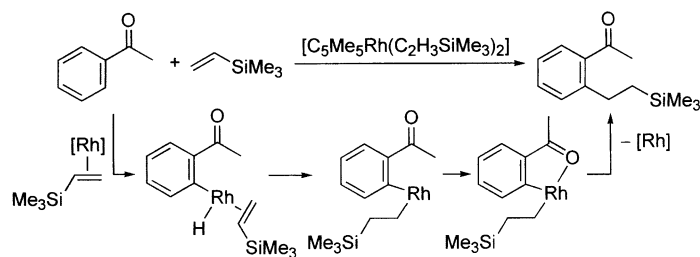
**Scheme 1.** Possible reaction pathways for the C–H bond cleavage step.

intermediate **B**, the reaction proceeds with an extremely small activation energy (1.8–3.0 kcal/mol). Therefore, their calculation suggests that the coordination of the carbonyl oxygen to the ruthenium center is the key for the success of the ruthenium-catalyzed C–H/olefin coupling and the reductive elimination, i.e., C–C bond formation is rate-determining.

Deuterium-labeling experiments and <sup>13</sup>C kinetic isotope effects (KIE) for the RuH<sub>2</sub>(CO)(PPh<sub>3</sub>)<sub>3</sub>-catalyzed reaction of aromatic ketones with olefins provide significant information concerning the rate-determining step. The catalytic reaction of acetophenone-*d*<sub>5</sub> with triethoxyvinylsilane is carried out in presence of RuH<sub>2</sub>(CO)(PPh<sub>3</sub>)<sub>3</sub> as the catalyst at 50 °C for 15 h (0% conversion), Eq. (9).<sup>[20b]</sup> Even though the C–H/olefin coupling reaction does not proceed at all under these reaction conditions, H/D scrambling among the two *ortho* positions of the ketone and the three vinylic positions of the olefin takes place to some extent. These results indicate that a rapid equilibrium exists prior to the reductive elimination step leading to C–C bond formation. These results indicate that the C–H bond cleavage step is quite facile and that the later step of the catalytic cycle is rate-determining. The studies of <sup>13</sup>C KIE for this coupling reaction also provide support that the reductive elimination step is rate-determining.<sup>[28]</sup> Thus, Murai's experimental results are consistent with Morokuma's theoretical calculation.<sup>[27]</sup>



Brookhart found another important phenomenon for the chelation-assisted C–H/olefin couplings.<sup>[29]</sup> In the



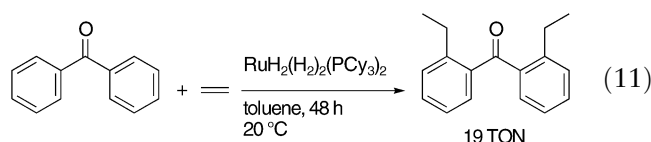
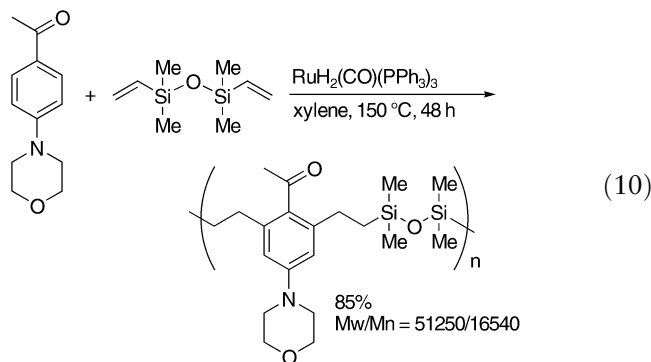
**Scheme 2.** Coordination of carbonyl group prior to the reductive elimination.

case of the reaction of acetophenones with olefins such as trimethylvinylsilane using  $\text{Cp}^*\text{Rh}(\text{C}_2\text{H}_3\text{SiMe}_3)_2$  as a catalyst, the C–H bond cleavage proceeds without the coordination of the carbonyl group to the rhodium. By means of deuterium labeling experiments, they revealed that each C–H bond at the aromatic ring added to the ruthenium atom. These results indicate that the C–H bond cleavage occurs without the coordination of the ketone carbonyl group. Interestingly, however, the C–C bond formation occurred only at the *ortho* position. This result suggests that in the C–C bond formation step the coordination of the carbonyl group is essential (Scheme 2). Brookhart's observations provide a significant working hypothesis for developing new types of C–H/olefin coupling reactions.

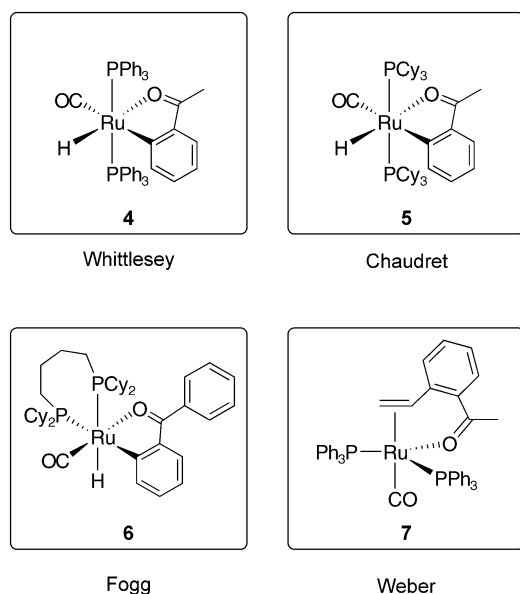
Several related examples of transition metal-catalyzed addition of C–H bonds in ketones to olefins have been reported.<sup>[30–34]</sup> Application of C–H/olefin coupling to polymer chemistry has been reported by Weber's group.<sup>[30]</sup> They prepared a variety of polymers by reactions of aromatic ketones having two free *ortho* C–H bonds with  $\alpha,\omega$ -dienes such as 1,1,3,3-tetramethyl-1,3-divinylsiloxane with the aid of  $\text{RuH}_2(\text{CO})(\text{PPh}_3)_3$  complex as a catalyst, Eq. (10). The fact that this step growth polymerization gives higher molecular weight polymers implies that each step proceeds virtually quantitatively. In particular, acetophenones having an electron-donating group, e.g., methoxy and amino groups, exhibit higher reactivities. Woodgate applied the  $\text{RuH}_2(\text{CO})(\text{PPh}_3)_3$ -catalyzed coupling of aromatic ketones with olefins to the alkylation of aromatic diterpenoids.<sup>[31]</sup> The alkylation of phenyl 3-pyridyl ketone proceeds with the aid of  $\text{RuH}_2(\text{CO})(\text{PPh}_3)_3$  as catalyst.<sup>[32]</sup> The alkylation selectively proceeds at the pyridine ring. Chaudret prepared a reactive ruthenium complex,  $\text{RuH}_2(\text{H}_2)(\text{CO})(\text{PCy}_3)_2$ , and examined the catalytic activity of the complex in a reaction of benzophenone with ethylene.<sup>[33]</sup> The desired C–H/olefin coupling reaction giving the bis(alkylation) product proceeded at room temperature and up to 19 turnover numbers were achieved in 48 h, Eq. (11). Leitner subsequently reported the similar room-temperature C–H/olefin coupling reaction using Chaudret's catalyst.<sup>[34]</sup>

Several attempts have been made to understand the mechanism and the intermediate involved in the cata-

lytic reaction. Trost reported that the catalytic active species does not contain a CO ligand because the  $\text{RuH}_2(\text{CO})(\text{PPh}_3)_3$ -catalyzed C–H/olefin coupling reaction is strongly inhibited under a CO atmosphere.<sup>[35]</sup> Whittlesey prepared some *ortho* metalated complexes by the reaction of  $\text{Ru}(\text{H}_2)\text{H}_2(\text{PPh}_3)_3$  with acetophenone.<sup>[36]</sup> Among the complexes, the most likely *ortho* metalated complex  $\text{RuH}(\text{o-C}_6\text{H}_4\text{C}(\text{O})\text{CH}_3)(\text{CO})(\text{PPh}_3)_2$  (**4**) (Figure 3) showed essentially no catalytic activity.



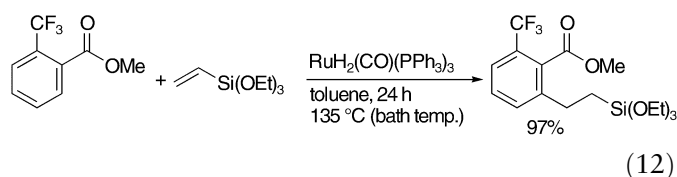
Chaudret prepared a  $\text{PCy}_3$  analogue of the *ortho* metalated complex,  $\text{RuH}(\text{o-C}_6\text{H}_4\text{C}(\text{O})\text{CH}_3)(\text{CO})(\text{PCy}_3)_2$  (**5**) (Figure 3), and observed that the complex does not show any reactivity for the C–H/olefin coupling reaction.<sup>[33]</sup> They also concluded that the ruthenium complex having a CO ligand is not the intermediate in the catalytic reaction, similar to Trost's proposal. The authors of this review are skeptical about this discussion because several ruthenium complexes, including  $\text{RuH}_2(\text{CO})(\text{PPh}_3)_3$ , are known to be converted to  $\text{Ru}(\text{CO})_3(\text{PPh}_3)_2$  under an atmosphere of carbon monoxide,<sup>[37]</sup> which was reported by Murai to be a poor catalyst for the C–H/olefin coupling.<sup>[8,20b]</sup> Fogg reported an *ortho* metalated ruthenium complex,  $\text{RuH}(\text{o-C}_6\text{H}_4\text{C}(\text{O})\text{Ph})(\text{CO})(\text{dcpb})$  (**6**) [ $\text{dcpb} = \text{Cy}_2\text{P}(\text{CH}_2)_4\text{PCy}_2$ ], which was prepared by a reaction of  $\text{RuH}_2(\text{dcpb})(\text{CO})$  with benzophenone (Figure 3).<sup>[38]</sup> In this complex, the hydride ligand is bound at the apical position. This stereochemistry is different from those of Whittlesey's and Chaudret's complexes. Fogg examined the catalytic activity of **6** for the reaction of aromatic ketones with olefin. However, **6** did not exhibit catalytic activity. Hiraki reported an NMR study of the  $\text{RuH}_2(\text{CO})(\text{PPh}_3)_3$ -catalyzed C–H/olefin coupling.<sup>[39]</sup> In this study, they found that several ruthenium-hydride species were present during the catalytic reaction on the basis of  $^1\text{H}$  and  $^{31}\text{P}$  NMR spectroscopy. They concluded that the carbonyl ligand is bound to the ruthenium



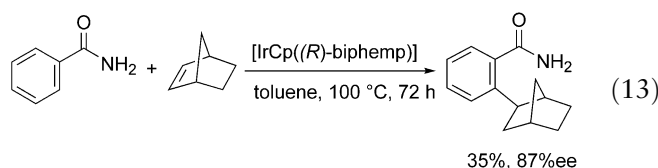
**Figure 3.** Plausible intermediates of C–H/olefin coupling.

throughout the catalytic reaction. However, they did not isolate the corresponding complexes like **4–6**. They discussed the reaction mechanism only on the basis of the NMR studies. Weber synthesized a zero-valent ruthenium complex,  $\text{Ru}(o\text{-vinylacetophenone})(\text{CO})(\text{PPh}_3)_2$  (**7**) (Figure 3).<sup>[40]</sup> Interestingly, this complex has catalytic activity for the co-polymerization of acetophenone with 1,3-divinyltetramethyldisiloxane, although it has a CO ligand. The studies mentioned above indicate that the relation between the structures of the catalyst precursor and the catalyst activity is currently poorly understood and it is premature to conclude that the presence of a CO ligand on the ruthenium center retards catalytic activity.<sup>[40]</sup> Further studies to elucidate the structure of the actual active species should be awaited.

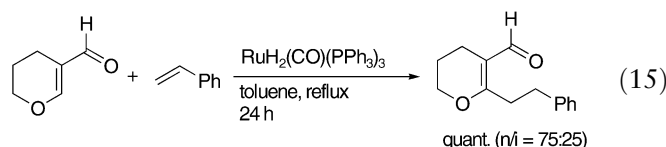
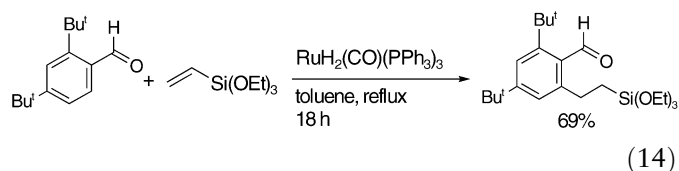
Chelation-assisted C–H/olefin coupling is also applicable to aromatic esters.<sup>[21]</sup> In the case of aromatic esters, electron-withdrawing groups such as  $\text{CF}_3$  and CN groups facilitate the C–H/olefin coupling reaction, Eq. (12). In this alkylation, trimethylvinylsilane showed a higher reactivity (100% yield for 1 h) than triethoxyvinylsilane (97% yield for 24 h). The use of an amide group is also effective for the regioselective alkylation. Togni reported that the addition of a C–H bond of benzamide to norbornene takes place in the presence of an  $\text{Ir}(\text{Cp})(R)\text{-biphemp}$  complex [biphemp = 2,2'-bis(diphenylphosphino)-6,6'-dimethyl-1,1'-biphenyl], Eq. (13).<sup>[41]</sup> This re-



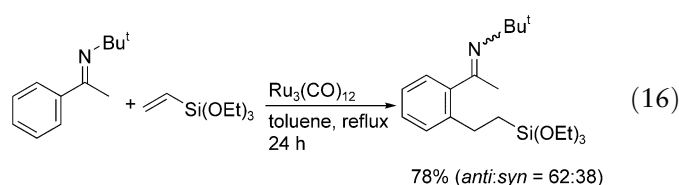
action gives the optically active alkylation product in moderate yields with high enantiomer excess.



For the alkylation of aromatic aldehydes and conjugated enals with olefins using the  $\text{RuH}_2(\text{CO})(\text{PPh}_3)_3$  catalyst, a sterically bulky substituent on the *ortho* position or a heteroatom at the  $\beta$  position of the enals is essential for the reaction to proceed catalytically. These substituents are believed to suppress undesired decarbonylation reactions by steric or electronic effects, Eqs. (14) and (15).<sup>[22]</sup>



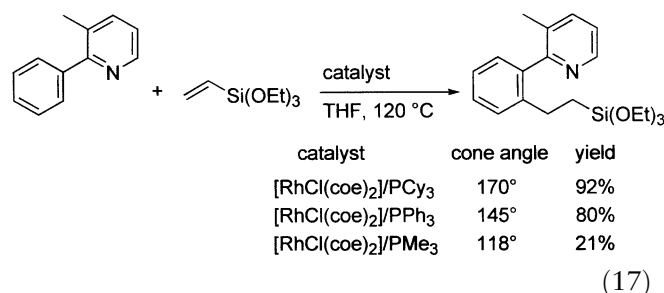
A nitrogen functionality can also function as a directing group. In the cases of reactions of aromatic imines,  $\text{Ru}_3(\text{CO})_{12}$  exhibits a higher catalytic activity than  $\text{RuH}_2(\text{CO})(\text{PPh}_3)_3$ . Interestingly, the reaction of aromatic ketimines derived from acetophenone gave the corresponding 1:1 coupling product as a single product, Eq. (16).<sup>[23]</sup>



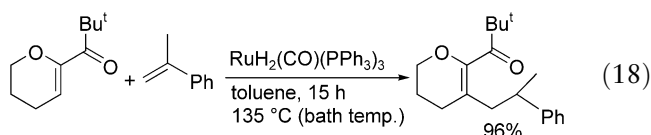
Lim reported a similar alkylation of aromatic imines with olefins using the  $\text{RhCl}(\text{coe})_2/\text{PCy}_3$  catalyst system.<sup>[42]</sup> Later, Jun also reported the  $\text{RhCl}(\text{PPh}_3)_3$ -catalyzed coupling of aromatic imines with olefins.<sup>[43]</sup> Both aromatic aldimines and ketimines smoothly reacted with the olefin to give the corresponding alkylation products. Interestingly, in the case of aromatic ketimines, the 1:1 coupling product is obtained as a single isomer. On the other hand, in the case of the reaction of the hydrazone derived from acetophenone, the corresponding 1:1 and 1:2 coupling products are

obtained,<sup>[25]</sup> although the reactions of aromatic ketimines do not give the 1:2 coupling products. Steric repulsion between the methyl group in the imine moiety and the alkyl group at the *ortho* position does not appear to be important for product selectivity.

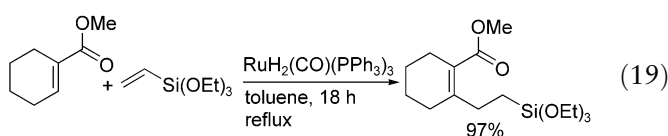
The  $sp^2$  nitrogen in a pyridine ring can also function as a directing functionality. The alkylation reaction of 2-arylpyridines is catalyzed by rhodium catalysts.<sup>[44]</sup> Introduction of a methyl group at the 3-position of the pyridyl ring suppresses the incorporation of the second olefin into another *ortho* C–H bond. For the alkylation of 3-methyl-2-phenylpyridine, the cone angles of the phosphine ligands largely affect reactivity rather than electronic factors, Eq. (17).<sup>[42b]</sup> The pyridyl group-directed C–H/olefin coupling can be extended to atrop-selective alkylation.<sup>[45]</sup> The coupling of 2-(1-naphthyl)-3-methylpyridine with ethylene using  $[\text{RhCl}(\text{coe})_2]_2$  (*R*), (*S*)-PPFOMe as catalyst  $\{(\text{R}), (\text{S})\text{-PPFOMe} = (\text{R})\text{-1-}[(\text{S})\text{-2-diphenylphosphino}] \text{ferrocenyl} \text{ ethyl methyl ether}\}$  gives the alkylation product in 37% yield with 49% ee.



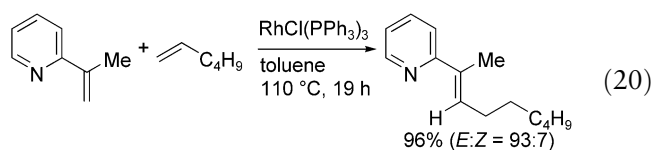
Murai reported that olefinic C–H bonds in conjugated enones can add across C/C double bonds with the aid of the  $\text{RuH}_2(\text{CO})(\text{PPh}_3)_3$  catalyst, Eq. (18).<sup>[20c, g]</sup> Among the acylcyclohexenes investigated, 1-pivaloyl-1-cyclohexene exhibits a high reactivity and the presence of an oxygen atom at the allylic position in the 6-membered ring increases the reactivity of the enones. Some terminal olefins, e.g., triethoxysilane, allyltrimethylsilane, methyl methacrylate, and vinylcyclohexane, are applicable to this reaction. Acyclic enones are also effective for this C–H/olefin coupling.<sup>[20 g]</sup>

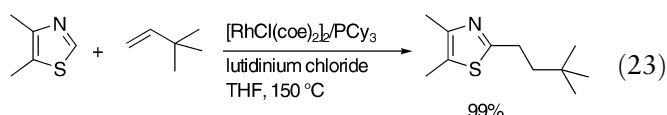
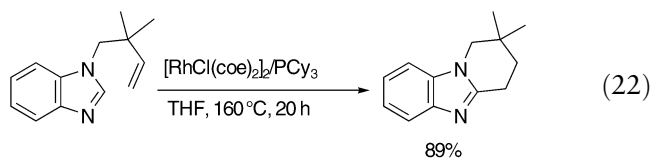
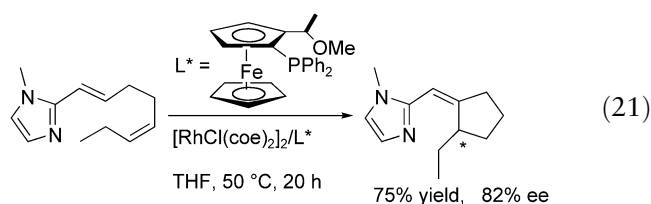


Trost reported on a similar coupling reaction of a conjugated ester with olefins using  $\text{RuH}_2(\text{CO})(\text{PPh}_3)_3$ , Eq. (19).<sup>[35]</sup> Both cyclic and acyclic conjugated esters can be applied to the coupling reaction. This coupling reaction tolerates various functional groups on the ester moiety.

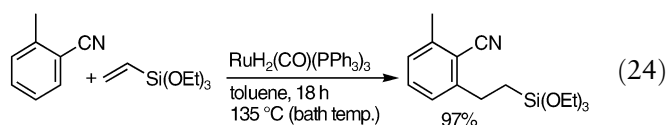


The rhodium-catalyzed alkylation of 2-isopropenylpyridine gives the addition product, in which the stereochemistry around the double bond is inverted with respect to the thermodynamically favorable *E*-isomer, Eq. (20).<sup>[46]</sup> This olefinic C–H/olefin coupling can be applied to several substrates. The reaction of 2-vinylpyridines with 1,ω-dienes results in a double C–H/olefin coupling reaction affording carbocycles with good efficiency, albeit in low-product selectivity.<sup>[46c]</sup> Murai found that intramolecular C–H/olefin coupling provides a new entry to the carbocyclic compounds.<sup>[47]</sup> The cyclization of 1-methyl-2-octa-1,5-dienyl-1*H*-imidazole giving a 5-membered carbocycle is catalyzed by a ruthenium or a rhodium complex, Eq. (21). A pyridyl group is also effective as a directing group for this type of cyclization of 1,ω-dienes. Deuterium labeling experiments indicate that this reaction proceeds *via* a direct C–H bond cleavage pathway and that the reductive elimination step is rate-determining. This cyclization reaction proceeds in an asymmetric fashion.<sup>[47b]</sup> When the reaction is conducted in the presence of a monodentate chiral ferrocenylphosphine and  $[\text{RhCl}(\text{coe})_2]_2$ , enantiomerically enriched carbocycles are obtained.<sup>[47b]</sup> In the case of the reaction of an imidazolyldiene, the product is obtained in 75% chemical yield with 82% ee at 50 °C, Eq. (21). Ellman and Bergman recently reported on a similar intramolecular cyclization reaction.<sup>[48]</sup> The conversion of *N*-alkenylbenzimidazoles yielding carbocycles proceeded with the aid of  $[\text{RhCl}(\text{coe})_2]_2$  and  $\text{PCy}_3$ , Eq. (22). They proposed that the *N*-heterocyclic carbene complex may participate in this cyclization as an intermediate and theoretical calculations supported the intermediacy of this carbene complex.<sup>[48c]</sup> An imino group is also effective as a directing group for the intramolecular cyclization, giving carbocycles.<sup>[48b]</sup> The intramolecular cyclization reactions described above provide new routes for the synthesis of carbocycles. The C–H bond in the  $\text{CH}=\text{N}$  moiety in five-membered heteroaromatic compounds such as thiazoles, benzimidazoles, and -oxazoles also adds to C/C double bonds, Eq. (23).<sup>[49]</sup> The use of Lewis acids such as lutidum chloride and  $\text{MgBr}_2$  dramatically increases the efficiency of the reaction, although the role of the Lewis acids employed is not clear.



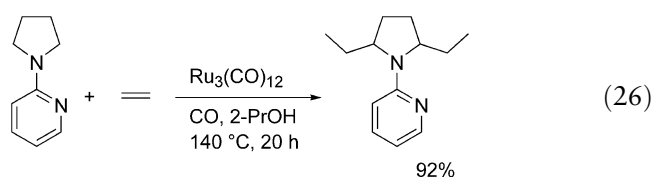
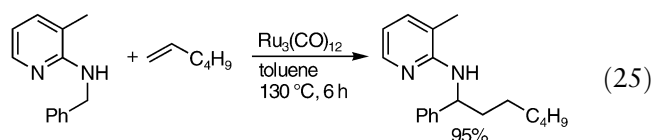


Dimerization of acrylonitrile is a cheaper way to synthesize highly valuable hexamethylenediamine which is one component of the starting materials for Nylon-6,6.<sup>[50,51]</sup> In some cases of the dimerizations of acrylic acid esters, acrylonitriles, and acroleins, a direct C–H bond cleavage step is believed to be involved in the catalytic reaction. At the early stage of the catalytic dimerization of acrylonitrile, *cis*-1,4-dicyanobut-1-ene is formed as the major product, not the *trans*-isomer.<sup>[50,51]</sup> It has been proposed that this high *cis*-selectivity indicates the selective cleavage of the C–H bond *cis* to CN by the metal coordinated to nitrile group with a side-on fashion.<sup>[52]</sup> However, the participation of  $\pi$ -bonded nitrile is still disputable because several possible reaction pathways exist. The ruthenium-catalyzed alkylation of benzonitriles with triethoxysilane proceeds at the *ortho* position predominantly, Eq. (24).<sup>[26]</sup> This regioselectivity indicates the possibility of  $\pi$ -coordination of the CN group to the ruthenium in the catalytic cycle.

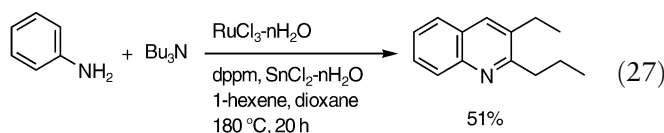


Catalytic C–C bond formation *via*  $sp^3$  C–H bond cleavage is the ultimate reaction in organic synthesis. A relatively ideal catalytic reaction system involves the use of  $sp^3$  C–H bonds adjacent to a heteroatom such as nitrogen and oxygen. Early examples using tungsten or iridium complexes have already been mentioned above.<sup>[15,16]</sup> Recently, Jun succeeded in the  $Ru_3(CO)_{12}$ -catalyzed alkylation of an  $sp^3$  C–H bond  $\alpha$  to the nitrogen atom in benzyl(3-methylpyridin-2-yl)amine by means of chelation assistance, Eq. (25).<sup>[53]</sup> In this case, the coordination of the pyridine nitrogen to the ruthenium complex followed by the C–H bond cleav-

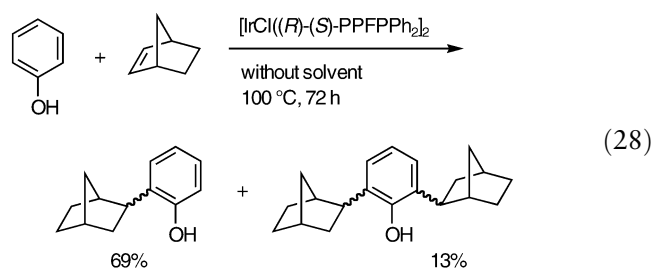
age, which allows the formation of a five-membered ruthenacycle, was proposed to be important in this catalytic reaction. Murai also reported on the ruthenium-catalyzed coupling of 2-*N*-pyridyldialkylamines, Eq. (26).<sup>[54]</sup> The use of 2-propanol as a solvent dramatically improves the yield of the product. The reaction is not limited to a benzylic system when 2-propanol is used as a solvent.



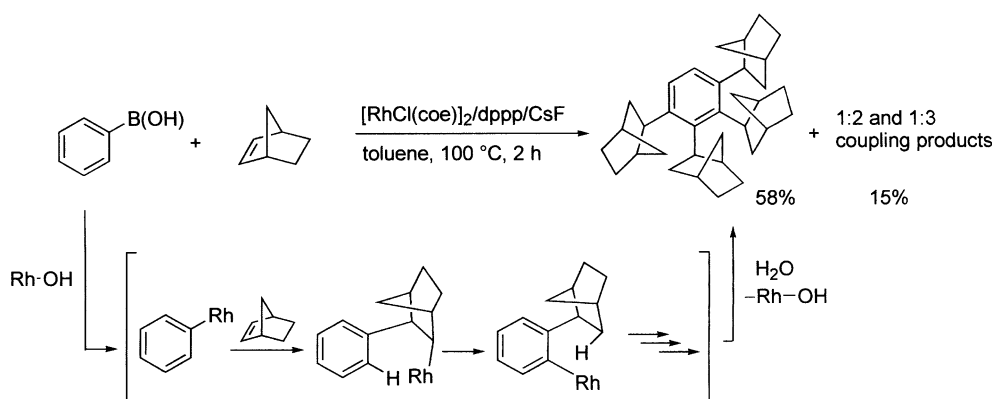
Transition metal-catalyzed annulation reactions of anilines with tertiary amines is another protocol for the catalytic functionalization of  $sp^3$  C–H bonds, Eq. (27). Recently, several reaction systems resulting in the formation of heteroaromatic compounds which are modifications of the preceding annulation reaction using aniline and ethylene with the aid of rhodium catalyst have been developed.<sup>[55]</sup> An intramolecular version of this quinoline synthesis using *o*-allylanilines and  $Co_2(CO)_8$  catalyst has also been demonstrated by Jones.<sup>[56]</sup>



Some other types of C–H/olefin coupling reactions have also been reported. The reaction of phenols with norbornenes using  $[IrCl((R)-(S)-PPFPPh_2)_2]$   $\{(R)-(S)-PPFPPh_2 = (R)-1-[(S)-2-(diphenylphosphino)ferrocenyl]ethyldiphenylphosphine\}$  gives the corresponding *ortho* alkylation products, Eq. (28).<sup>[57]</sup> Miura found that the reaction of phenylboronic acid with excess amounts of norbornene using  $[RhCl(cod)]_2$ /DPPP [DPPP = 1,2-



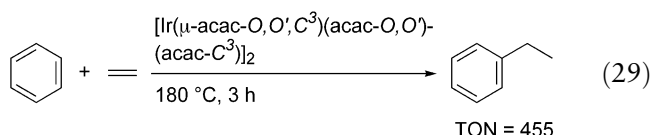




**Scheme 3.** Plausible pathway for the multi alkylation *via* 1,4-rhodium shift.

bis(diphenylphosphino)propane] as catalyst results in multiple substitution with norbornene on aromatics in high yield (Scheme 3).<sup>[58]</sup> The important step in this multiple alkylation involves cyclometalation *via* C–H bond cleavage followed by the reductive elimination of the C–H bond giving an (aryl)rhodium intermediate.

Obviously, non-chelation-assisted C–H/olefin couplings are more ideal than chelation-assisted ones. Recently, the alkylation of benzene with olefins has been accomplished with the aid of  $[\text{Ir}(\mu\text{-acac-}O,O',C^3)(\text{acac-}O,O')(\text{acac-}C^3)]_2$ , Eq. (29). Although interesting, the reaction does not overcome the regioselectivity. Thus, the reaction of substituted arenes with olefins provides a mixture of regioisomers.<sup>[59]</sup> For example, the reaction of toluene with ethylene affords *m*- and *p*-isomers in 63% and 37% selectivity, respectively.

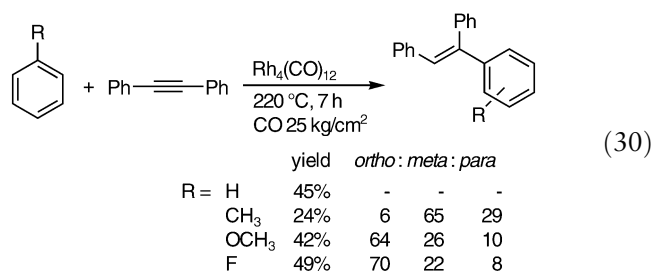


## 2.2 Addition of C–H Bonds to C/C Triple Bonds

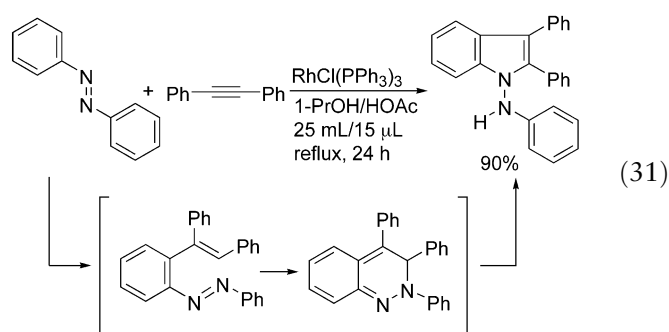
Substituted styrenes and vinylic compounds are versatile intermediates in organic synthesis, and various methods for accomplishing this have been published in the literature.<sup>[9,60,61]</sup> Among the catalytic approaches, transition metal-catalyzed coupling reactions using organometallic reagents<sup>[62]</sup> and dehydrohalogenative vinylation reactions between organic halides and olefins (the so-called Mizoroki–Heck reaction)<sup>[63,64]</sup> are frequently used to obtain the desired compounds. For these reactions, however, the use of a C–X (e.g., X = halogen, triflate) bond is required for producing C–C bonds. If the direct addition of an otherwise unreactive C–H bond to acetylenes takes place, the method promises to become one of the simplest methods for the preparation of vinylic compounds with 100% atom efficiency. In this

section, we will describe the transition metal-catalyzed vinylation of aromatic compounds using acetylenes.

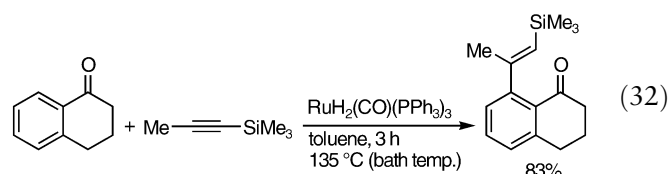
The pioneering work on a coupling of aromatic and heteroaromatic compounds with acetylenes has been reported by Yamazaki.<sup>[11b,65]</sup> Reaction of benzene with diphenylacetylene gives triphenylethene in 45% yield based on the acetylene employed. The presence of carbon monoxide is an essential factor in accomplishing this coupling in a catalytic fashion. In the case of the monosubstituted benzene, the low regioselectivity is an inevitable problem. The reaction of toluene gives a mixture of *o*-, *m*-, and *p*-isomers in a ratio of 6:65:29, Eq. (30). Heteroaromatic compounds, such as furan, thiophene and *N*-methylpyrrole, are also applicable to this vinylation reaction, giving the corresponding coupling products in 80%, 48%, and 31% yields, respectively.<sup>[11b,66]</sup> The order of the relative reactivities of these compounds are estimated as follows: furan > thiophene > *N*-methylpyrrole > benzene.



The addition of C–H bonds in azobenzenes to diphenylacetylene is catalyzed by  $\text{CoH}(\text{N}_2)(\text{PPh}_3)_3$ ,  $\text{CoH}_3(\text{PPh}_3)_3$ , or  $\text{RhCl}(\text{PPh}_3)_3$ .<sup>[67]</sup> When  $\text{RhCl}(\text{PPh}_3)_3$  is used as the catalyst, this coupling reaction gives 1-(arylamino)indole in good yields, Eq. (31). Electron-withdrawing groups on the acetylene retard the coupling reaction. On the basis of this result, it was proposed that the C–H bond cleavage step is rate-determining. There are several alternative mechanisms and these wait further studies.

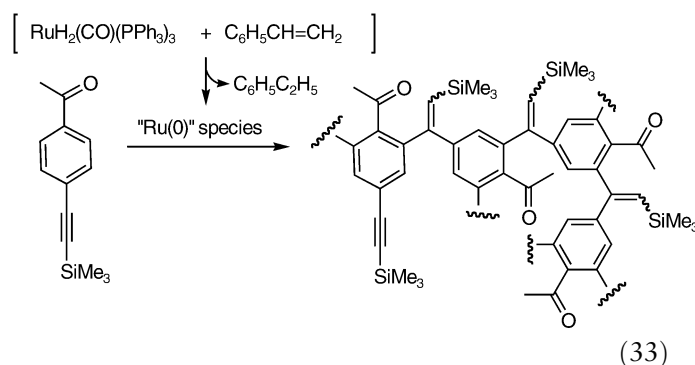


Methodology in which the directing group promotes the regioselective cleavage of C–H bonds is applicable to the addition of aromatic C–H bonds in aromatic ketones to acetylenes, Eq. (32).<sup>[68]</sup> When trimethylsilyl-substituted acetylenes are employed in the reaction, the desired coupling products are obtained with high regioselectivity in excellent yields.<sup>[68a]</sup> In the case of the reaction with 1-trimethylsilylpropyne, the regio- and stereochemical outcome is perfect. The *E*-isomer is the predominant product. These results indicate that the addition of C–H bonds to the C/C triple bond proceeds with *syn* selectivity. This C–H/olefin coupling is applicable to conjugated enones, and highly substituted dienes are obtained in high yields with a high stereoselectivity.<sup>[68b]</sup> Miura reported regioselective alkenylation of 1-naphthols with alkynes.<sup>[69]</sup> In this case, the C–C bond formation takes place exclusively at the *peri* position (8 position).

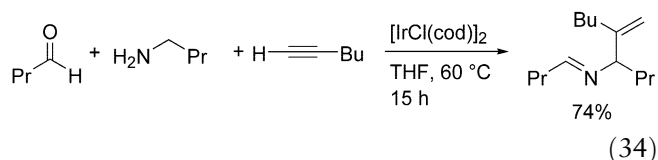


Extensive reactions of ruthenium-catalyzed C–H/alkyne coupling have been studied with respect to the step growth copolymerization of aromatic ketones and acetylenes, resulting in the formation of cross-conjugated polymers, copoly(arylene/1,2-vinylene) backbone,

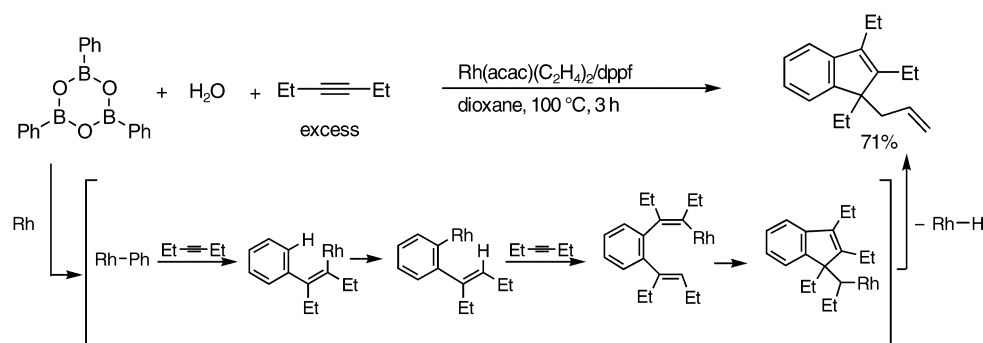
Eq. (33),<sup>[70]</sup> which have received considerable attention because of their potential utility in a number of applications such as light emitting diodes.<sup>[71]</sup> Woodgate demonstrated a similar alkenylation reaction of diterpenoid analogues with acetylenes.<sup>[72]</sup> The regio- and stereoselectivities are nearly the same as that in the reaction of Eq. (32). Lim reported that the reaction of 2-phenylpyridines with internal acetylenes using RhCl(PPh<sub>3</sub>)<sub>3</sub> catalyst also gives *ortho* alkenylation products in high yields.<sup>[73]</sup>



Quite recently, the iridium-catalyzed addition of *sp*<sup>3</sup> C–H bond adjacent to the imino nitrogen to acetylenes was reported by Ishii, Eq. (34).<sup>[74]</sup> Terminal acetylenes can be used for this reaction. Carbon-carbon bond formation takes place at the internal carbon atom of the alkyne moiety.



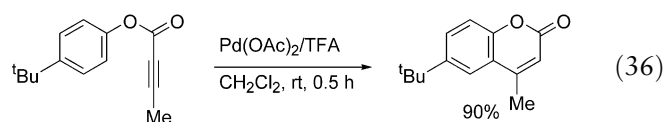
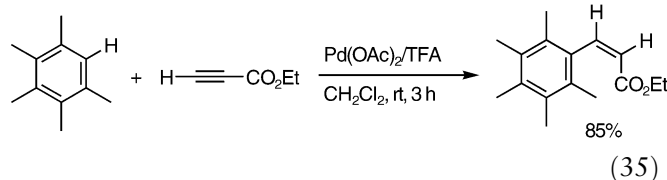
When the rhodium-catalyzed coupling of phenylboronic acid with internal acetylenes is performed, a unique alkenylation reaction involving a 1,4-shift of rhodium, i.e., the isomerization of 2-aryl-1-alkenylrhodium to 2-alkenylarylrhodium, takes place (Scheme 4).<sup>[75a]</sup> This unique 1,4-shift of rhodium is supported by deuterium



**Scheme 4.** A Plausible pathway for the alkenylation of the aromatic C–H bond *via* 1,4-rhodium shift.

labeling experiments. Previously, Miura has already reported a similar 1,4-shift of rhodium in multialkylation of aromatic ring with norbornene (see Scheme 3).<sup>[58]</sup> Although not unprecedented, Larock found that a unique 1,4-shift of palladium takes place in the palladium-catalyzed reaction 2-iodo-4-methylbiaryl with ethyl acrylate.<sup>[75b]</sup>

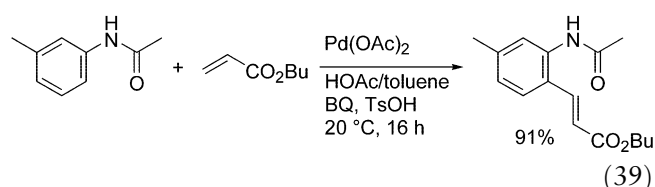
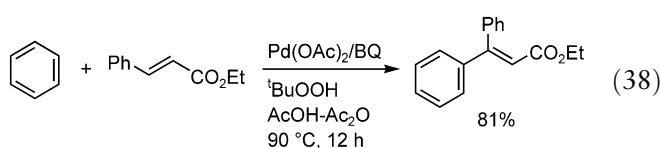
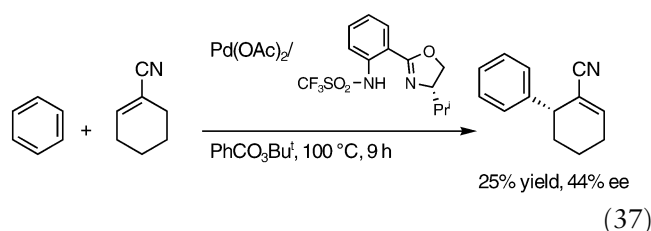
Another approach to the alkenylation of aromatic compounds involves the electrophilic substitution of arenes with transition metal salts such as Pd(OAc)<sub>2</sub> and PtCl<sub>2</sub>. One of the most significant advances in the catalytic addition of C–H bonds to C/C triple bonds was achieved by Fujiwara, Eq. (35).<sup>[76]</sup> Various arenes react with both terminal and internal acetylenes to give the corresponding *trans* hydroarylation products in high yields. It is noteworthy that this coupling reaction occurs at room temperature. The stereoselectivity and efficiency of this coupling reaction are sufficiently high to merit its use as a tool in organic synthesis. When arenes having an acetylene moiety are exposed to the reaction conditions, intramolecular cyclization takes place selectively. For example, in the case of aryl alkynoates, coumarins are obtained in high yields, Eq. (36).<sup>[76c–e]</sup>



### 2.3 Oxidative Coupling of Arenes with Olefins via Electrophilic Substitution by Transition Metal Complexes

The alkenylation of arenes with olefins *via* C–H bond cleavage is the most highly valuable procedure for the preparation of styrene derivatives. The first example of this type of coupling reaction was reported in 1967.<sup>[77]</sup> Later, several efforts have been made to perform this reaction in a catalytic manner.<sup>[78]</sup> Recently, remarkable advances appeared with respect to the transition metal-catalyzed oxidative coupling of arenes with olefins. Mikami reported the asymmetric coupling reaction of benzene with cyclohexenecarbonitrile in the presence of Pd(OAc)<sub>2</sub>, *tert*-butyl perbenzoate as an oxidant, and a chiral oxazoline ligand.<sup>[79]</sup> This reaction gives 6-phenyl-1-cyclohexenecarbonitrile. Chiral induction arises at the 6-position of the cyclohexene ring. The chemical and optical yields are moderate, but this is a prospective procedure for making C–C bonds in an enantioselective

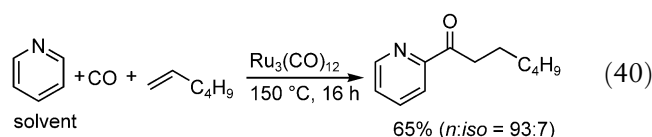
fashion, Eq. (37). Fujiwara achieved the highly efficient palladium-catalyzed addition of arenes to electron-deficient olefins with the aid of benzoquinone and *tert*-butyl hydrogen peroxide as an oxidant, Eq. (38).<sup>[80]</sup> In this case, C–C bond formation took place selectively at the position β to the electron-withdrawing groups. A similar reaction was reported using heteropolyoxometalate and oxygen as a reoxidation reagent by Ishii.<sup>[81]</sup> In these cases, the control of regioselectivity is substantial. The use of chelation-assistance with the amide group improved the regioselectivity. The Pd(OAc)<sub>2</sub>-catalyzed reaction of *N*-acetylanilides with acrylic esters conducted at room temperature using benzoquinone as an oxidant gives the alkenylated product in good to high yields. This observation suggests that chelation-assistance is also effective in electrophilic C–H bond cleavage, Eq. (39).<sup>[82]</sup> Alkenylations of arenes using rhodium<sup>[83]</sup> or ruthenium catalysts<sup>[84]</sup> have also been demonstrated by several research groups.



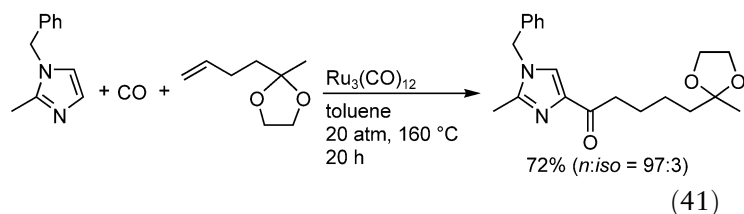
### 2.4 Coupling of C–H Bonds, Carbon Monoxide, and Olefins

There are two categories that involve the direct carbonylation of C–H bonds. One is C–H/CO coupling, and the other is C–H/CO/olefin coupling. Since the former reaction leading to aldehydes is endothermic, the reaction should ideally be conducted under photoirradiation conditions.<sup>[85]</sup> On the other hand, the C–H/CO/olefin coupling reaction leading to ketones can proceed under thermal reaction conditions, because it is exothermic. The photo-assisted carbonylation reaction of C–H bonds will not be dealt with in this review, since there are several leading review articles.<sup>[4]</sup>

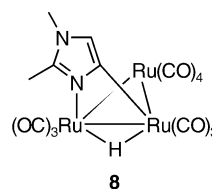
Yamazaki reported the first example of a three-component coupling reaction of C–H bonds in arenes, CO, and olefins using a  $\text{Rh}_4(\text{CO})_{12}$  catalyst.<sup>[12]</sup> This pioneering work reveals that the benzene ring undergoes acylation with CO and olefins under thermal reaction conditions, although the efficiency is not high. In 1992, Moore reported on the highly selective carbonylation of pyridines with the aid of a  $\text{Ru}_3(\text{CO})_{12}$  catalyst.<sup>[7]</sup> The reaction of pyridine, CO, and 1-hexene in the presence of  $\text{Ru}_3(\text{CO})_{12}$  at 150 °C gives  $\alpha$ -acylated pyridines, Eq. (40). A number of olefins can be used in this system. Terminal olefins, as small as ethylene and as large as 1-eicosene, afforded the corresponding linear pyridyl ketones as the major products.



Murai and coworkers reports that the carbonylation of imidazole derivatives using several olefins takes place in high yields with the aid of a  $\text{Ru}_3(\text{CO})_{12}$  catalyst, Eq. (41).<sup>[86]</sup> Carbon-carbon bond formation occurs exclusively at the position  $\alpha$  to the  $sp^2$  nitrogen. A wide range of olefins can be utilized in this reaction, and a variety of functional groups are compatible under the reaction conditions, indicating that C–H bond activation reactions are now on a satisfactory level in organic synthesis. The ( $\mu$ -H)triruthenium clusters **8**, as shown in Scheme 5, are proposed as a key species on the basis of the result in which a triosmium cluster, analogous to complex **8**, is obtained by a stoichiometric reaction of  $\text{Os}_3(\text{CO})_{10}(\text{CH}_3\text{CN})_2$  with 2-methylimidazole.<sup>[87]</sup> Other five-membered *N*-heteroaromatic compounds, such as pyrazoles, oxazoles, and thiazoles, can also be used for the carbonylation, and in all cases, carbonylation takes place exclusively at a C–H bond  $\alpha$  to the  $sp^2$  nitrogen. The reactivity of the five-membered heterocycles corresponds to the  $\text{p}K_a$  values of the conjugate acid of these heterocycles. The higher the  $\text{p}K_a$  of the substrate, the higher is the reactivity. This result also indicates that the coordination of the substrates by the  $sp^2$  nitrogen to the ruthenium center is essential for the reaction to proceed.

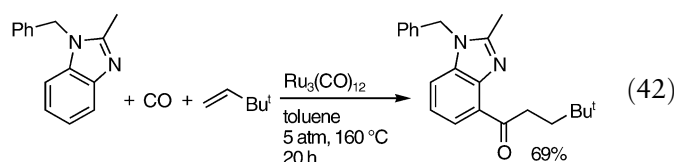


Carbonylation at a C–H bond  $\beta$  to the  $sp^2$  ring nitrogen is also achieved by  $\text{Ru}_3(\text{CO})_{12}$  catalyst.<sup>[88]</sup> The  $\text{Ru}_3(\text{CO})_{12}$ -catalyzed reaction of 1,2-dimethylbenzimidazole with

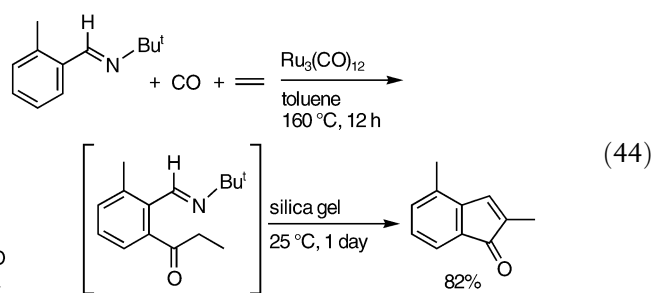
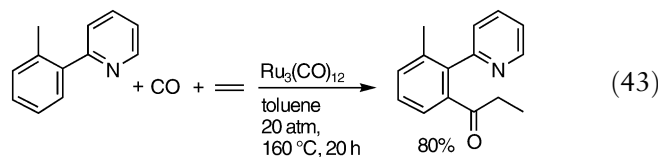


**Scheme 5.** A plausible intermediate.

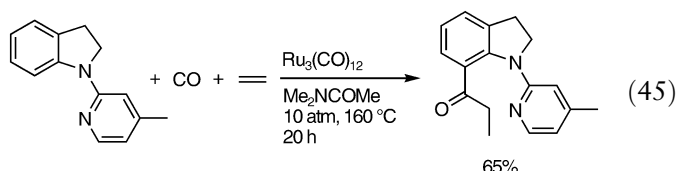
olefin and CO provides the corresponding  $\beta$  acylated product in high yield, Eq. (42).



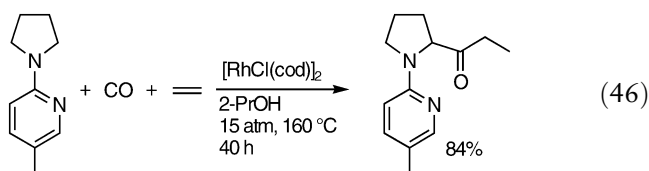
When the reaction of phenylpyridine with CO (20 atm) and ethylene is conducted at 160 °C, the *ortho* C–H bond ( $\gamma$  to the  $sp^2$  nitrogen) in the benzene ring undergoes carbonylation, Eq. (43).<sup>[89]</sup> In this reaction, a C–H bond in the pyridine ring is completely unreactive. In the reaction of *m*-substituted substrates, such as those having Me, OMe,  $\text{CF}_3$ , and  $\text{COOMe}$ , carbonylation takes place exclusively at the less hindered C–H bond, irrespective of the electronic nature of the substituents. An oxazoline ring instead of a pyridine ring is also an effective directing group for the  $\gamma$  selective carbonylation of the benzene ring.<sup>[90]</sup> The reaction of aromatic aldimine gives indenones *via* carbonylation reaction at the *ortho* C–H bond followed by intramolecular aldol-type condensation, Eq. (44).<sup>[91]</sup>



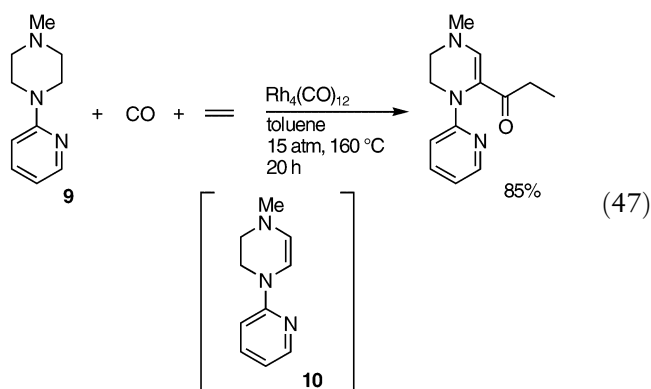
The carbonylation of a C–H bond at the position  $\delta$  to the  $sp^2$  nitrogen proceeds with the aid of  $\text{Ru}_3(\text{CO})_{12}$  as catalyst, Eq. (45).<sup>[92]</sup> The reactivity appears to be sensitive to the polarity of the solvent. The choice of *N,N*-dimethylacetamide as the solvent is crucial for the reaction to proceed efficiently.



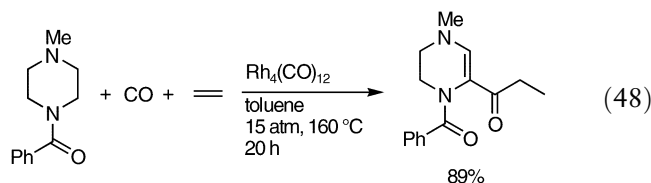
The acylation of the  $sp^3$  C–H bond adjacent to a nitrogen atom can be attained by means of chelation-assisted C–H bond cleavage, Eq. (46).<sup>[93]</sup> The  $[\text{RhCl}(\text{cod})]_2$  complex is superior as a catalyst and 2-propanol is the solvent of the choice. While cyclic amines exhibit a high reactivity (up to 84%), acyclic amines show relatively low reactivity (18%). Although the scope of this reaction is limited, this carbonylation protocol expands the scope of carbonylation reactions. The use of  $\text{Ru}_3(\text{CO})_{12}$  as a catalyst does not result in a carbonylation reaction, but instead the addition of the  $sp^3$  C–H bond across the olefin bond to give an alkylation product, even when the reaction is carried out under CO pressure.<sup>[94]</sup>



The reaction of *N*-(2-pyridinyl)piperazines with CO and ethylene in the presence of a catalytic amount of  $\text{Rh}_4(\text{CO})_{12}$  in toluene at 160 °C results in a novel type of carbonylation reaction, which involves dehydrogenation and carbonylation at a C–H bond, Eq. (47).<sup>[95]</sup> The presence of an additional nitrogen functionality at the 4-position of the piperazine ring is essential for the reaction to proceed. The substitution of both an electron-donating group on the 4-nitrogen and an electron-withdrawing group, e.g., 5-COOMe, 4-COOMe, and 5- $\text{CF}_3$ , on the pyridine ring causes a significant increase in reactivity. It was found that the reaction involves two discrete reactions: i) dehydrogenation of the piperazine ring leading to **10** and ii) carbonylation at a C–H bond in the resulting olefin **10**. Interestingly,



$\text{Ru}_3(\text{CO})_{12}$  is ineffective for the carbonylation of **9**, but effective for the carbonylation of **10** or *N*-(2-pyridinyl)enamines.<sup>[96]</sup> In place of the pyridyl group, an acyl group can also serve as a directing group for carbonylation at an  $\alpha$  C–H bond, Eq. (48).<sup>[97]</sup> This is the first example of a carbonylation at a C–H bond which is directed by a functional group other than a C=N moiety.

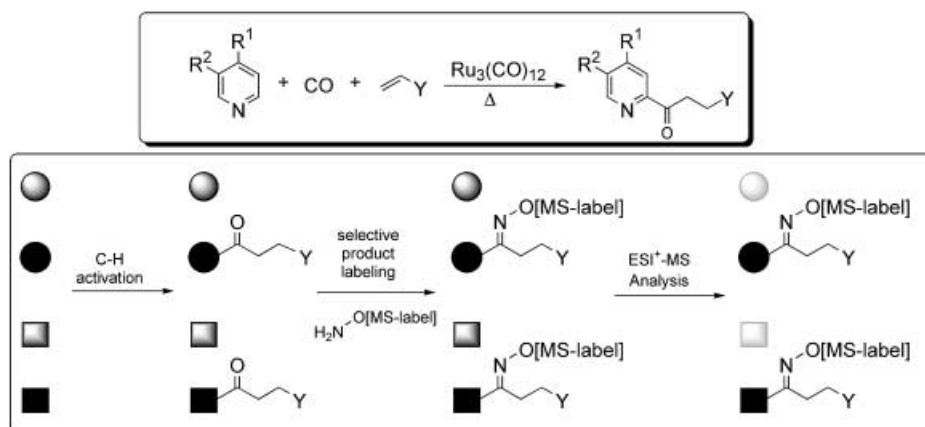


Several high-throughput protocols for examining optimal reaction conditions and applicable substrates have recently been reported. A mass spectrometric labeling strategy is now popular as a rapid screening method to evaluate many substrates. The method can be applied to the direct carbonylation of C–H bonds in *N*-heterocyclic compounds (Scheme 6).<sup>[98]</sup>

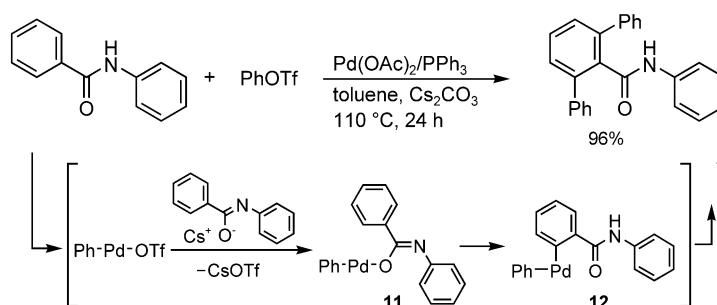
The three-component coupling reaction of a C–H bond, carbon monoxide, and olefins leading to ketones is applicable to a number of *N*-heterocyclic compounds. The carbonylation at  $sp^2$  C–H bonds reported thus far can be classified into four types, depending on the position where the carbonylation takes place;  $\alpha$ ,  $\beta$ ,  $\gamma$ , and  $\delta$  to the  $sp^2$  nitrogen atom. Carbonylation at an  $sp^3$  C–H bond adjacent to a nitrogen atom has also been developed. These methods have already become new synthetic tools for catalytic acylation.

## 2.5 Catalytic Arylation of C–H Bonds

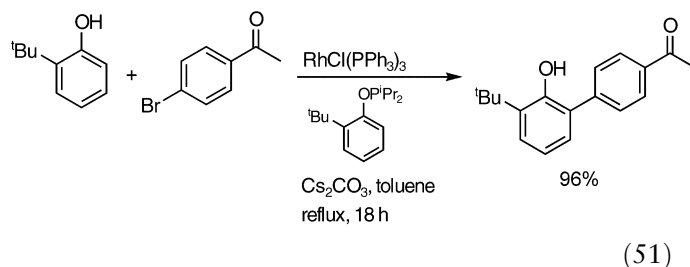
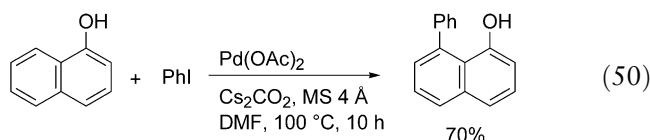
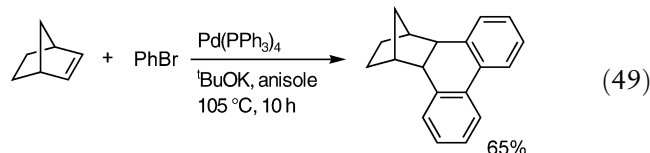
Catalytic arylation *via* C–H bond cleavage is a subject of intense interest.<sup>[99]</sup> Pioneering work in this area was originally reported by Chiusoli in 1985.<sup>[100]</sup> The reaction of bromobenzene with norbornene gives hexahydromethanotriphenylenes, Eq. (49). The biaryl framework is formed *via* C–H bond cleavage. Later de Meijer also reported on a similar coupling reaction of aryl halides with norbornene, to give the multiple arylation product.<sup>[101]</sup> One of the highly important advances in this area is the palladium-catalyzed arylation of 2-phenylphenols and naphthols, Eq. (50).<sup>[102]</sup> The formation of an (aryl)(aryloxy)palladium(II) intermediate is crucial to accomplishing this arylation reaction. Very recently, the  $\text{RhCl}(\text{PPh}_3)_3$ -catalyzed arylation of phenols with aryl halides in the presence of phosphinites  $[\text{PR}_2(\text{OAr})]$  has been reported, Eq. (51).<sup>[103]</sup> The significant point of this reaction is the use of phosphinite as a co-catalyst. The phosphorus atom coordinates to the rhodium atom, then electrophilic substitution with the rhodium(III) species occurs at the *ortho* position.



**Scheme 6.** High-throughput reaction evaluation and optimization: exploring C–H bond activation.



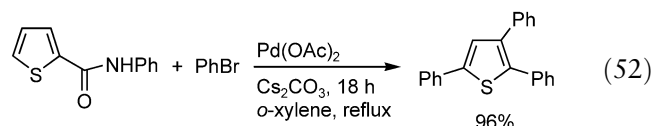
**Scheme 7.** Plausible pathway for the arylation of benzanilides.



The palladium-catalyzed arylations of aromatic carbonyl compounds such as ketones,<sup>[104]</sup> amides,<sup>[105]</sup> and aldehydes<sup>[106]</sup> with aryl halides lead to the multiple arylation products (Scheme 7). A plausible pathway is as follows: an anion exchange between the amido anion

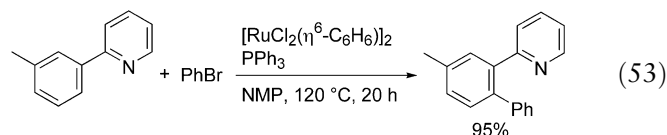
(or enolate) and triflate (or halide) ion in the Ar–Pd–X species leads to the (aryl)(alkoxy)palladium intermediate **11**; electrophilic palladation on the aromatic ring gives the Ar–Pd–Ar' intermediate **12**; the reductive elimination affords the diaryl compounds.

A unique multiphenylation accompanied by formal decarbonylation takes place where the reaction of secondary 2-thiophenecarboxamides with bromobenzene is conducted in the presence of Pd(OAc)<sub>2</sub> and a bulky phosphine [P(*o*-biphenyl)(*t*-Bu)<sub>2</sub>], Eq. (52).<sup>[107]</sup> Interestingly, when the reaction of 3-carboethoxyfuran with an aryl bromide is examined, the arylation proceeds selectively at the 2-position and the ester moiety is retained in the product.<sup>[108]</sup> The arylation of thiazole with aryl iodide occurs at the 2-position with the aid of PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>/CuI as catalyst.<sup>[109]</sup> Tetrabutylammonium fluoride improves the activity of the catalyst.

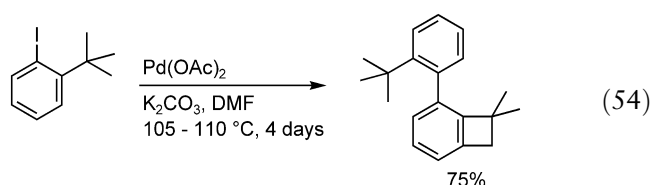


The ruthenium(II)-phosphine complex exhibits a high catalytic activity for the regioselective arylation of 2-arylpyridines using aryl halides, Eq. (53).<sup>[110]</sup> The C–C bond formation occurs at the position *ortho* to the

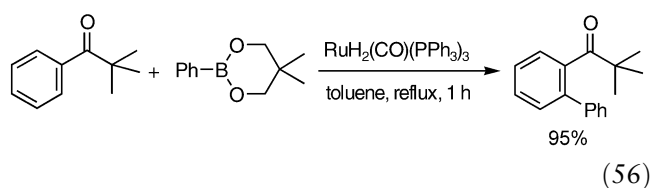
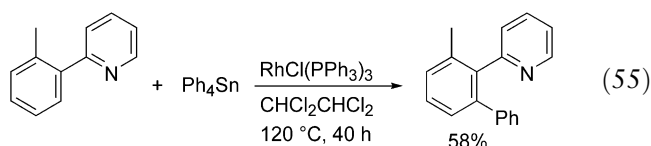
pyridyl group predominantly. The same catalyst system is also effective for the arylation of aromatic imines.<sup>[111]</sup> The authors proposed that the tetravalent arylruthenium complex reacts electrophilically with the arylimines. Therefore, C–H bond cleavage proceeds *via* an electrophilic substitution pathway.



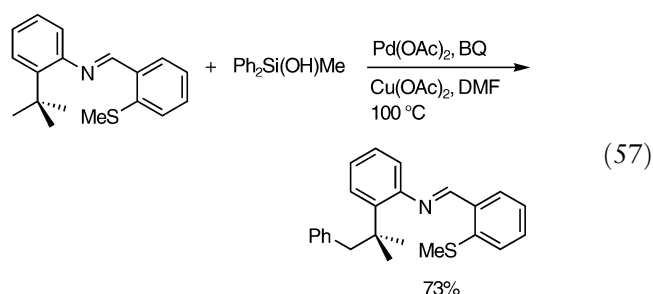
Dyker reported on the intramolecular arylation of C–H bonds.<sup>[112]</sup> In this case, 1-*tert*-butyl-2-iodobenzene is reacted under palladium catalysis to give the 1,2-dihydrocyclobutabenzene derivative in 75% yield, Eq. (54). They proposed that this catalytic cycle is initiated by the oxidative addition of ArI to Pd(0) to give an Ar–Pd–I species, then electrophilic substitution at the *sp*<sup>3</sup> C–H bond with the Pd(II) species results in the formation of the cyclopalladation complex. To this Pd(II) species, another molecule of ArI oxidatively adds, giving the Pd(IV) complex.



There are new entries to the catalytic arylation of aromatic compounds. The utilization of organometallic reagents as an arylating agent is another protocol. Oi reported on the rhodium-catalyzed arylation of arylpyridines using tetraarylstannanes, Eq. (55).<sup>[113]</sup> This reaction required the use of 1,1,2,2-tetrachloroethane as a solvent for attaining a high catalyst activity. Very recently, Kakiuchi found that the ruthenium-catalyzed coupling reaction of aromatic ketones with arylboronates providing the *ortho* arylated aromatic ketones, Eq. (56).<sup>[114]</sup> This arylation can be applied to several combinations of aromatic ketones and arylboronates.



The catalytic arylation and alkenylation of alkane segments has been developed, Eq. (57).<sup>[115]</sup> In this reaction, Ph<sub>2</sub>Si(OH)Me shows a high reactivity. The Pd(OAc)<sub>2</sub>-catalyzed phenylation of a *tert*-butyl group in an aromatic Schiff base with the diphenylsilanol proceeded in good yield. The applicability is relatively limited, but this is a rare example of C–C bond formation using an *sp*<sup>3</sup> C–H bond.

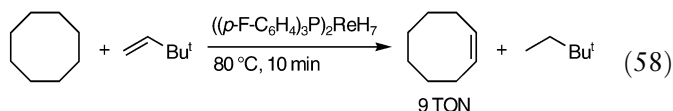


### 3 Catalytic Dehydrogenation of Alkanes

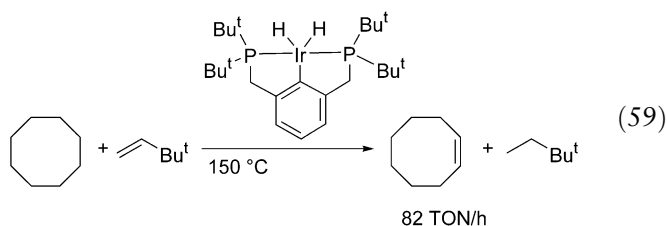
Since various types of functional groups can be made by transformations of C/C double bonds, a large number of methods for the preparation of a C/C double bond have been reported.<sup>[9,66,67]</sup> The simplest way is the direct dehydrogenation of alkanes giving alkenes with the aid of transition metal-catalysts. This reaction is highly valuable, but only a limited number of studies has appeared in the literature. In this section, transition metal-catalyzed dehydrogenations of alkanes yielding alkenes will be described.

In 1979, Crabtree demonstrated the dehydrogenation of alkanes using a stoichiometric amount of an iridium-phosphine complex.<sup>[116]</sup> Several years later, dehydrogenation reactions of alkanes were conducted in the presence of a hydrogen acceptor, i.e., an alkene, because the thermally disfavored alkane dehydrogenation ( $\Delta G = ca. 20 \text{ kcal/mol}$ )<sup>[117]</sup> becomes thermally much more favorable ( $\Delta G = ca. 0 \text{ kcal/mol}$ ) compared with hydrogen acceptor-less conditions by combining hydrogen transfer reactions. The first example with respect to the catalytic dehydrogenation of an alkane under thermal conditions was reported by Baudry using a homogeneous rhenium catalyst.<sup>[118]</sup> The rhenium polyhydride complex is effective for the dehydrogenation of cycloalkanes with the aid of *tert*-butylethylene as a hydrogen acceptor. The turnover number in this system is only 9, but this result indicates the possibility of alkane dehydrogenation by a soluble transition metal catalyst under thermal reaction conditions, Eq. (58). Some other transition metal polyhydride complexes also have shown catalytic activities for the alkane dehydrogenation. Among several iridium complexes, e.g., [IrH<sub>5</sub>(Pr<sub>3</sub>P)<sub>2</sub>], [IrH<sub>5</sub>((*p*-FC<sub>6</sub>H<sub>4</sub>)<sub>3</sub>P)<sub>2</sub>], and [RuH<sub>4</sub>((*p*-FC<sub>6</sub>H<sub>4</sub>)<sub>3</sub>P)<sub>3</sub>], the iridium polyhydride complex having isopropylphosphine shows the highest catalytic activities (23 TON/

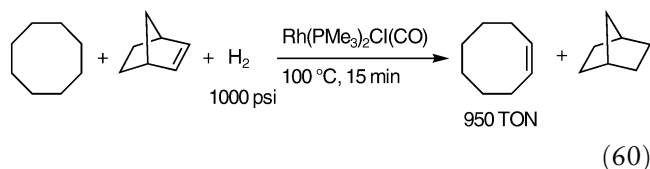
3 h). This protocol has been rapidly applied to various catalytic systems. Crabtree re-examined their previously reported reactions and found that the dehydrogenation of cyclooctane takes place in a catalytic manner.<sup>[119]</sup>



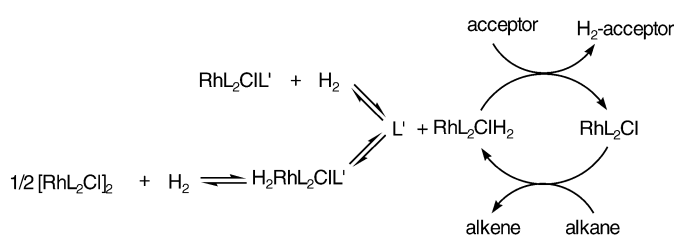
Other types of thermal catalytic alkane dehydrogenation using a hydrogen acceptor have been reported by several research groups.<sup>[119–126]</sup> A variety of iridium complexes, e.g.,  $[\text{IrH}_2(\text{acetone})_2\text{P}(p\text{-FC}_6\text{H}_4)_3]\text{SbF}_6$ ,<sup>[119]</sup>  $\text{IrH}_5(\text{P}^i\text{Pr}_3)_2$ ,<sup>[120,121]</sup>  $[\text{IrH}_2(\text{CF}_3\text{CO}_2)(p\text{-FC}_6\text{H}_4)_2]$ ,<sup>[122,123]</sup> and  $[\text{IrH}_2(\eta^3\text{-C}_6\text{H}_3(\text{CH}_2\text{P}^t\text{Bu}_2)_2-2,6)]$ ,<sup>[124]</sup> can catalyze the dehydrogenation of cycloalkanes giving cycloalkenes in the presence of *tert*-butylethylene as the hydrogen acceptor, Eq. (59). An analogous iridium complex,  $[\text{IrH}_2(\text{acetone})_2\text{PPh}_3]\text{SbF}_6$ ,<sup>[125]</sup> catalyzes the selective dehydrogenation of cyclohexenes to arenes. In this case, the cyclohexenes function as the substrate and also as the hydrogen acceptor.



The highly efficient transfer dehydrogenation of alkanes has been reported by Goldman.<sup>[126]</sup> Their catalyst system is unique. A high pressure (1000 psi) of hydrogen is used for the dehydrogenation reaction.<sup>[126b–d]</sup> Under 1000 psi of  $\text{H}_2$  at 100 °C for 15 min, a cyclooctane solution of  $\text{RhCl}(\text{CO})(\text{PMe}_3)_2$  (0.20 mM) and norbornene (1.2 M) yields 950 turnovers of cyclooctene (0.19 M) and norbornane (1.2 M), Eq. (60). The proposed mechanism for this paradoxical catalytic reaction involves the addition of  $\text{H}_2$ , the loss of CO, and the transfer of  $\text{H}_2$  to a sacrificial acceptor, thereby generating  $\text{RhCl}(\text{PMe}_3)_2$ , which is the same catalytically active species proposed in the photochemical dehydrogenation of alkanes with  $\text{RhCl}(\text{CO})(\text{PMe}_3)_2$  (Scheme 8).

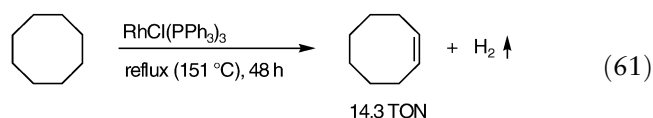


In 1990, Saito reported an extremely interesting result.<sup>[127]</sup> Their finding was that the endoergonic alkane dehydrogenation reactions can be driven by the con-

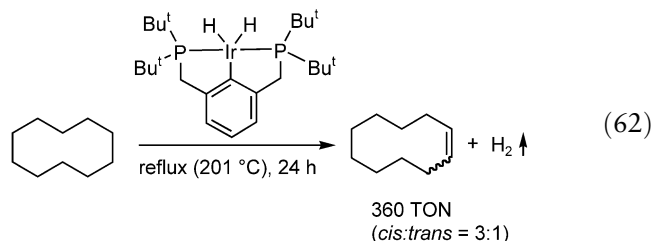


**Scheme 8.** Plausible catalytic cycle of alkane-dehydrogenation in the presence of dihydrogen.

tinuous removal of molecular hydrogen in the refluxing process, Eq. (61). They found that the catalytic reaction of an alkane dehydrogenation under thermal conditions gives an alkene and molecular hydrogen. The important factor in this catalyst system is the continuous removal of molecular hydrogen which is produced by dehydrogenation of the alkane from the reaction mixture by refluxing. Therefore, the continuous removal of molecular hydrogen shifts the equilibrium toward the product, i.e., the alkene. This simple technique has been modified by Crabtree.<sup>[128]</sup> They have assayed the catalytic activities of a variety of transition metal catalysts using the modified reflux method published by Saito's group.

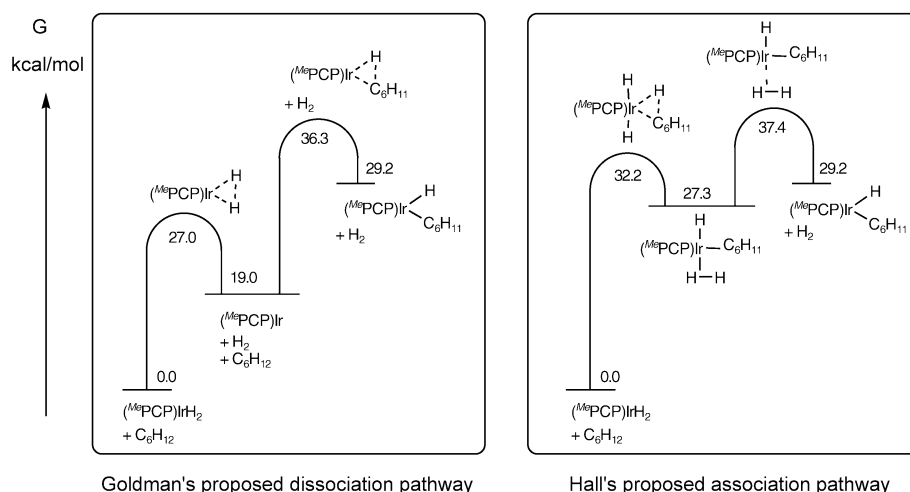


A notable advance has recently been achieved in the acceptor-less dehydrogenation of alkanes. The transition metal-catalyzed highly efficient alkane dehydrogenation proceeds, even in the absence of a sacrificial hydrogen acceptor, under thermal conditions.<sup>[129]</sup> The iridium complex having a  $\eta^3\text{-C}_6\text{H}_3(\text{PBu}^t)_2$ -1,3 (PCP) ligand efficiently catalyzes the dehydrogenation of cyclodecane to give cyclodecene, Eq. (62). When the reaction is carried out at 201 °C in refluxing cyclodecane, 360 turnover numbers were attained after 24 h. The key to their success with respect to the high efficiency observed, appears to be the long-term stability of the Ir-PCP complexes at very high temperatures.



The most attractive recent subject in this area is the elucidation of the reaction mechanism of the acceptor-





**Figure 4.** Free Energy (G) profiles for dissociation and association pathways.

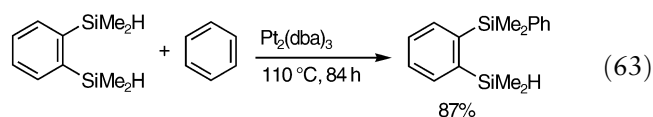
less thermal dehydrogenation of alkanes by means of *ab initio* theoretical calculations.<sup>[130,131]</sup> Hall predicted that the acceptor-less dehydrogenation of alkanes using  $[\eta^3\text{-}2,6\text{-(R}_2\text{PCH}_2)_2\text{C}_6\text{H}_3]\text{IrH}_2$  [abbreviated to  $(^R\text{PCP})\text{IrH}_2$ ] proceeds associatively, specifically *via* the C–H oxidative addition of the  $(^R\text{PCP})\text{IrH}_2$  (Figure 4, right panel).<sup>[130]</sup> On the other hand, Goldman concluded that the dehydrogenation reaction takes place *via* the dissociation of dihydrogen from  $(^R\text{PCP})\text{IrH}_2$ , leading to the  $(^R\text{PCP})\text{Ir}$  (Figure 4, left panel).<sup>[131]</sup> Goldman's results satisfactorily explain the experimental results such as no H/D exchange between the hydrogen in  $(^R\text{PCP})\text{IrH}_2$  and cyclohexane- $d_{12}$ . Although the actual reaction mechanism is still controversial, both studies provide an important consideration in future efforts with respect to the development of related acceptor-less thermal dehydrogenation reactions of alkanes.

#### 4 Catalytic Silylation of C–H Bonds

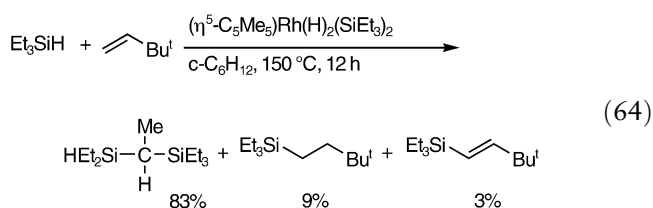
Dehydrogenative silylations of arenes and alkanes with hydrosilane are also a thermally disfavored process. To accomplish these reactions in a catalytic manner, photoirradiation or the co-presence of an efficient hydrogen acceptor is necessary.

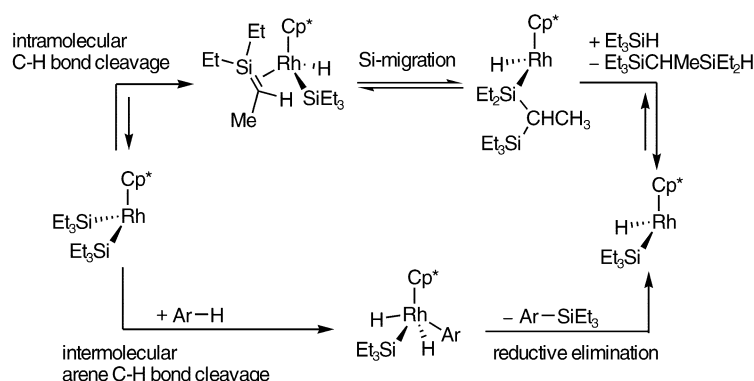
Curtis reported, to the best of our knowledge, the first example of the dehydrogenative silylation of benzene with penatamethyldisiloxane using an  $\text{IrCl}(\text{CO})(\text{PPh}_3)_2$  catalyst under thermal reaction conditions in the absence of a hydrogen acceptor. In this case, a prolonged reaction period (49 days) was required to obtain relatively higher total yields of phenylated products.<sup>[132]</sup> The selective silylation of arenes with *o*-bis(dimethylsilyl)-benzene is catalyzed by  $\text{Pt}_2(\text{dba})_3$  complex, gives the monoarylated hydrosilanes in high yields, Eq. (63).<sup>[133]</sup> In this case, the bis(silyl)platinum appears to function as the active catalyst species. A deuterium-labeling experi-

ment using *o*-bis(deuteriodimethylsilyl)benzene revealed the following results: 1) deuterium remains in the starting hydrosilane; 2) the newly formed Si–H moiety does not contain deuterium. These observations indicate that the origin of the hydrogen of the Si–H moiety in the product is benzene. They proposed the bis(silyl)platinum intermediate as the active catalyst species. In this dehydrogenative silylation, the reactivities of the arenes decrease in the following order: anisole > chlorobenzene > benzene > toluene.



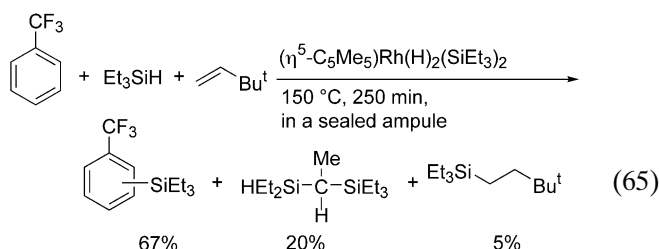
Berry reported on the self-dehydrogenative silylation of triethylsilane in the presence of *tert*-butylethylene as the hydrogen acceptor using  $(\eta^5\text{-C}_5\text{Me}_5)\text{Rh}(\text{H})_2(\text{SiEt}_3)_2$  as catalyst.<sup>[134]</sup> The conversion of the silane is almost quantitative and the dehydrogenative silylated product is obtained, Eq. (64). The  $(\eta^5\text{-C}_5\text{Me}_5)\text{Rh}(\text{H})_2(\text{SiEt}_3)_2$  and  $(\eta^6\text{-C}_6\text{Me}_6)\text{Ru}(\text{H})_2(\text{SiEt}_3)_2$  complexes are also effective for the dehydrogenative silylation of arenes with triethylsilane, Eq. (65).<sup>[135]</sup> In this reaction, the carbosilane dimer,  $\text{Et}_3\text{SiCH}(\text{Me})\text{SiHEt}_2$ , is formed in addition to the arylsilane. In the reaction of  $\alpha,\alpha,\alpha$ -trifluoromethyltoluene with triethylsilane, the selectivity of the desired arylsilane increases as the reaction proceeds. The carbosilane dimer appears to be the kinetic product



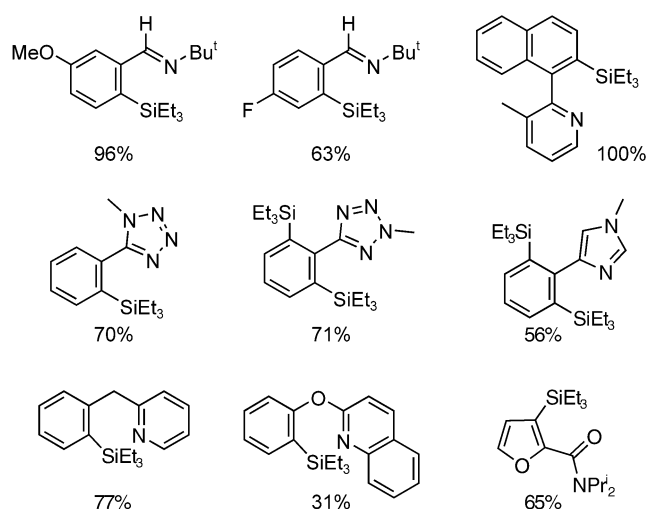


**Scheme 9.** Plausible reaction pathway for the silylation of arenes.

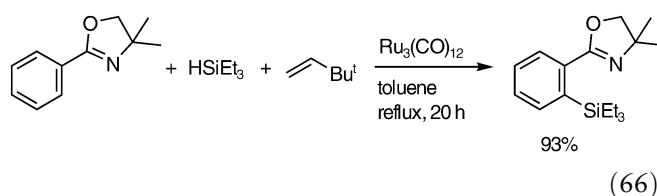
and the arylsilane is the thermodynamic product (Scheme 9).



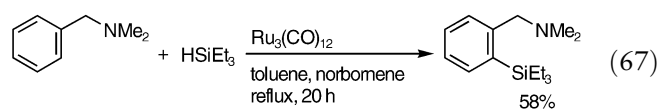
The major drawback of the preceding silylation of C–H bonds is their low regioselectivity.<sup>[132–135]</sup> One of the most reliable protocols for attaining a high regioselectivity is the use of chelation-assisted C–H bond cleavage, which is now popular in catalytic reactions involving C–H bond cleavage. This protocol can also be applied to C–H/SiR<sub>3</sub> coupling.<sup>[136]</sup> In the case of the reaction of aryloxazolines with hydrosilanes, the silylation takes place exclusively at the position *ortho* to the oxazoline ring. As mentioned above, for the dehydrogenative silylation of C–H bond, the use of olefin as a hydrogen scavenger is required to attain the reaction in catalytic manner. Triorganosilanes, especially triethylsilane, show a high reactivity. When the reaction of aryloxazolines with triethylsilane is carried out in the presence of *tert*-butylethylene as a hydrogen acceptor with the aid of Ru<sub>3</sub>(CO)<sub>12</sub> as catalyst, the silylation proceeds at the position *ortho* to the oxazoline group, Eq. (66).<sup>[136a]</sup> The functional group compatibility of this reaction is high. This reaction is tolerant to both electron-donating (Me, OMe, and NMe<sub>2</sub>) and -withdrawing (CF<sub>3</sub> and F) groups. A variety of functional groups such as ester, amide, and imino, groups, and *sp*<sup>2</sup> nitrogen in pyridine, imidazole, pyrazole, triazole, and tetrazole rings can be used as a directing group (Scheme 10). In nearly all cases, the corresponding *ortho* silylation products are obtained in good to excellent yields.



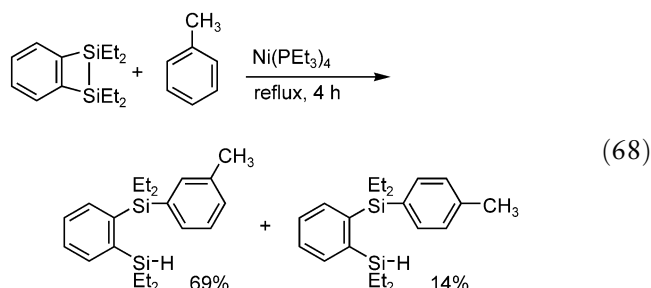
**Scheme 10.** Silylation of a variety of aromatic and hetero-aromatic compounds.



In the chelation-assisted C–H/olefin coupling,  $\pi$ -conjugation between the benzene ring and the directing group is important. This working hypothesis is supported by experimental results<sup>[20b]</sup> and theoretical calculations.<sup>[27]</sup> Interestingly, however, in the case of C–H/SiR<sub>3</sub> coupling,  $\pi$ -conjugation is not essential. The silylation reaction of *N,N*-dimethylbenzylamine with triethylsilane gives the *ortho* silylation product, Eq. (67).<sup>[137]</sup> Some other aromatic compounds in which the directing group is not conjugated with the benzene ring can be silylated under the same reaction conditions.<sup>[137]</sup>

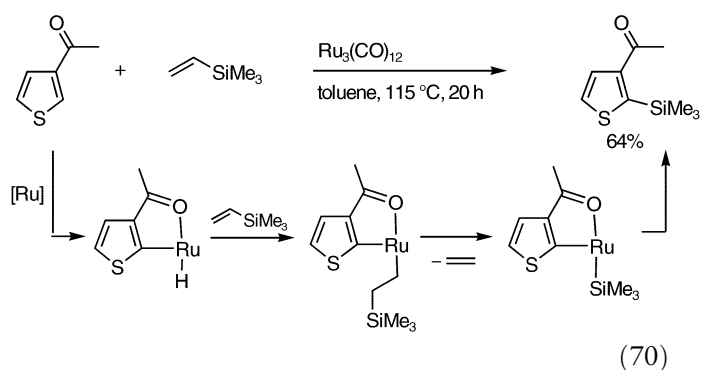
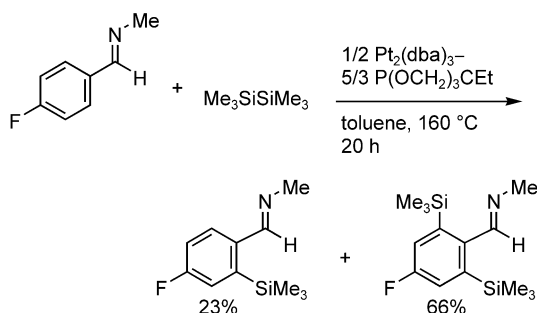


Disilanes are also effective as a silylation reagent. Ishikawa found that the  $\text{Ni}(\text{PEt}_3)_4$ -catalyzed reaction of aromatic compounds with 3,4-benzo-1,1,2,2-tetraethyl-1,2-disilacyclobutene yields the 1-(diethylarylsilyl)-2-(diethylsilyl)benzene, Eq. (68).<sup>[138]</sup> The results of deuterium-labeling experiments suggest that the *o*-quinodisilane-nickel complex, which may produce a bis(silyl)-nickel intermediate, is involved as a key intermediate in this reaction. Later, a similar intermediate was also proposed by Tanaka in the platinum-catalyzed silylation of arenes, Eq. (63).<sup>[133]</sup> In the case of the reaction of mesitylene, interestingly, the benzylic C–H bond can be silylated to afford benzodisilacyclobutene, albeit in low yield (28%). Platinum(0) complexes are effective as catalysts for this silylation reaction.



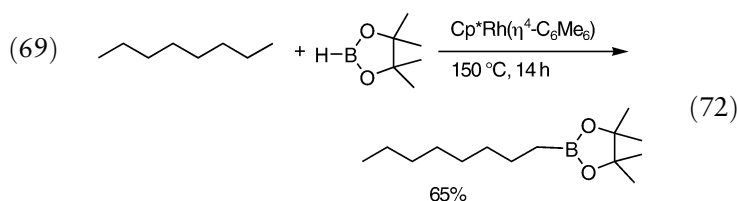
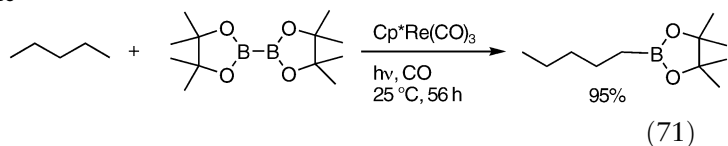
The regioselective silylation of aromatic imines with hexaorganodisilanes proceeds *via* chelation-assisted C–H bond cleavage by a platinum complex.<sup>[139]</sup> The C–H bonds undergo the silylation with exclusive *ortho* selectivity. In the case of the reaction of an imine having an electron-withdrawing group at the *para* position, silylation products are obtained in high yields, Eq. (69).

Murai reported on a unique system for the dehydrogenative silylation of heteroaromatic compounds in which triorganovinylsilane was used as a silylating reagent.<sup>[140]</sup> In this reaction, the vinyl moiety functions as a hydrogen acceptor. Thus, ethylene should be generated after the reaction. When the reaction of 3-acetylthiophene with trimethylvinylsilane is conducted using of  $\text{Ru}_3(\text{CO})_{12}$  as a catalyst, the silylation occurs at the 2-position of 3-acetylthiophene, Eq. (70). The important step of this reaction is a  $\beta$ -silyl elimination, yielding a metal-silyl species.<sup>[141]</sup> This silylation protocol using vinylsilanes can be applied only to heteroaromatic compounds.

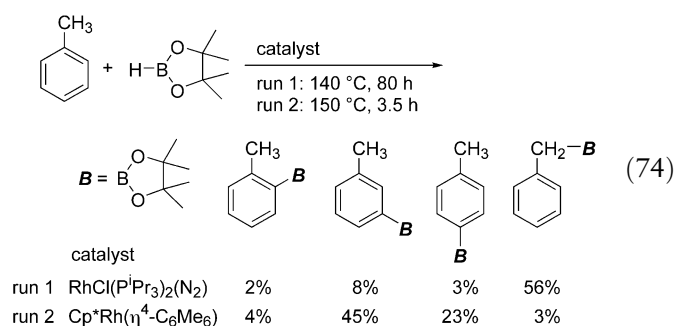
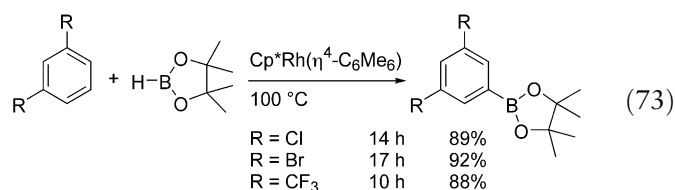


## 5 Catalytic Borylation of C–H Bonds

Direct borylation of C–H bonds is a highly active recent research subject in the catalytic use of C–H bonds. Hartwig reported the first representative result with respect to the borylation of C–H bonds.<sup>[142]</sup> A stoichiometric amount of transition metal boryl complex reacts with arenes under photo-irradiation conditions to give the corresponding arylboron compounds. Subsequently, they succeeded in the borylation of an  $sp^3$  C–H bond in an alkane using  $\text{Cp}^*\text{W}(\text{CO})_2\text{B}(\text{OR})_2$  [(OR)<sub>2</sub> = 1,2- $\text{O}_2(\text{C}_6\text{H}_2-3,5-(\text{CH}_3)_2$ )] under photochemical conditions.<sup>[143]</sup> The first example of the catalytic version of the borylation reaction was accomplished in 1999, Eq. (71).<sup>[144]</sup> When the reaction of pentane with 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi-1,3,2-dioxabobolane ( $\text{B}_2\text{pin}_2$ ) using  $\text{Cp}^*\text{Re}(\text{CO})_3$  as catalyst is conducted under photo-irradiation conditions, C–B bond formation occurs exclusively at the methyl C–H bond. The copresence of carbon monoxide (2 atm) suppresses the deactivation of the catalyst. A remarkable advance was achieved in 2000.<sup>[145]</sup> Hartwig reported on an ideal borylation reaction system. The reaction of octane with  $\text{B}_2\text{pin}_2$  using  $\text{Cp}^*\text{Rh}(\eta^4\text{-C}_6\text{Me}_6)$  as a catalyst, when conducted at 150 °C (*no photo-irradiation*) gives *n*-octylborane with perfect regioselectivity in high yield, Eq. (72). Pinacol-borane (Hbpin) can also be used as a borylating reagent. Hartwig's results indicate that a new research area for alkane functionalization has apparently been created.



In the case of the borylation of arenes, one encounters again the inevitable problem of regioselectivity. The reaction of monosubstituted arenes with hydroboranes yields a mixture of regioisomers as experienced in the non-chelation-assisted silylation of arenes.<sup>[133,135]</sup> When 1,3-disubstituted arenes, e.g., 1,3-dichloro-, 1,3-dibromo-, and 1,3-bis(trifluoromethyl)benzenes, are used in the reaction, C–B bond formation occurs at the 5-position selectively, Eq. (73).<sup>[146]</sup> It is noteworthy that when the reaction of *p*-xylene with pinacol-borane is conducted in the presence of  $\text{RhCl}(\text{P}^i\text{Pr}_3)_2(\text{N}_2)$  as a catalyst, borylation occurs mainly at the benzyl C–H bond [run 1 in Eq. (74)].<sup>[146c, 147]</sup> On the other hand, the use of  $\text{Cp}^*\text{Rh}(\eta^4\text{-C}_6\text{Me}_6)$  as a catalyst results in the formation of a C–B bond at the aromatic ring [run 2 in Eq. (74)].<sup>[146b]</sup> Very recently, Ishiyama reported that the presence of 4,4'-di-*tert*-butyl-2,2'-bipyridine (dtbpy) dramatically improves the activity of the iridium catalyst for aromatic C–H/Bpin<sub>2</sub> coupling.<sup>[148]</sup> Five-membered heteroaromatic compounds are also applicable to the borylation reaction.<sup>[148b]</sup> In this case, 2-boryl heteroaromatic compounds are obtained exclusively in high yields. The anion ligand on the iridium center is sensitive to the activity of the catalyst. The methoxy ligand highly improves the reactivity of the iridium complex. Indeed, the borylation proceeds at room temperature with high efficiency.



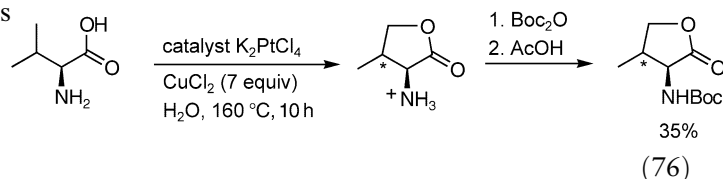
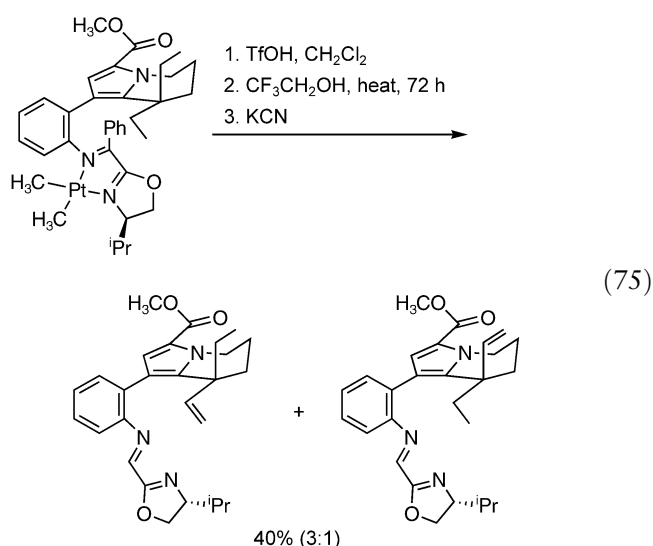
The C–H/B(OR)<sub>2</sub> coupling will certainly become a useful tool in organic synthesis because the boryl moiety can be converted to a hydroxy group by oxidation<sup>[149]</sup> and organoboron compounds are versatile synthetic reagents in the palladium-catalyzed coupling with organohalides (the so-called Suzuki–Miyaura coupling).<sup>[150]</sup>

## 6 Conclusions

The catalytic method for C–H bond functionalization is obviously one of the simplest, most powerful methods in organic synthesis. From the synthetic point of view, C–H/olefin, C–H/acetylene, and C–H/CO/olefin couplings can be regarded as practical tools since these reactions exhibit a high selectivity and efficiency, and a wide applicability, which are essential for practical organic synthesis.

During the past 40 years, C–H bond cleavage, so-called C–H bond activation was an intriguing research subject mainly for inorganic and organometallic chemists. Recently, this situation has dramatically changed. A variety of catalytic reactions involving C–H bond cleavage have become popular and various types of transformation such as C–H/olefin, C–H/acetylene, C–H/CO/olefin, C–H/aryl, C–H/SiR<sub>3</sub>, and C–H/B(OR)<sub>2</sub> couplings, and dehydrogenation of alkanes have appeared in the literature. The growth of this research area has been rapid, but the applicability of this type of coupling reaction to the synthesis of complex molecules is insufficient. Namely, many studies have been focused on investigations of the scope and limitations of these types of reactions.

Quite recently, some promising results have been reported. Sames utilized the C–H bond for the synthesis of rhazinilam using a stoichiometric amount of a palladium complex, Eq. (75).<sup>[151]</sup> They also reported that the palladium-catalyzed oxidative functionaliza-



tion of  $sp^3$  C–H bond in amino acids gives lactones regio- and stereoselectively, Eq. (76).<sup>[152]</sup> This work strongly implies that C–H bonds can now be used as a synthetic tool in the synthesis of complex molecules.

In the past several years, the fundamental features of the catalytic use of C–H bond in organic synthesis have been defined. In the coming decade, it is likely that developments of fascinating synthetic protocols involving unreactive C–H bond cleavage will be reported in organic synthesis.

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