Review

Transition metal catalyzed manipulation of non-polar carbon–hydrogen bonds for synthetic purpose

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Abstract: The direct addition of ortho C–H bonds in various aromatic compounds such as ketones, esters, imines, imidates, nitriles, and aldehydes to olefins and acetylenes can be achieved with the aid of transition metal catalysts. The ruthenium catalyzed reaction is usually highly efficient and useful as a general synthetic method. The coordination to the metal center by a heteroatom in a directing group such as carbonyl and imino groups in aromatic compounds is the key step in this process. Mechanistically, the reductive elimination to form a C–C bond is the rate-determining step, while the C–H bond cleavage step is not.

Keywords: transition-metal catalyst, catalytic reaction, carbon–hydrogen bond, C–H activation, ruthenium complex, addition to olefin

Introduction

Synthetic organic chemistry is a field of endeavor that is concerned with transformations of organic molecules. In general, such transformations involve converting a relatively simple molecule to a more complex one, thus creating a more value-added molecule from a readily available molecule. This constitutes a synthetic operation. To achieve such a conversion, operations heavily rely upon the characteristics of various polar functional groups, e.g. a halogen atom bonded to a carbon.

In contrast to these reactive functional groups, a hydrogen bonded to a carbon, i.e., a C–H bond, is usually not reactive except when it is in a polar environment or has acidic characteristics. A typical organic molecule consists of a carbon skeleton and (usually) some additional functional groups. The remainder of the carbon framework in the molecule is covered with hydrogen atoms, which, of course, are usually inert and are generally unreactive. If a synthetic method could be developed that allows the direct use of normally “unreactive” C–H bonds, an entirely new opportunity in the field of synthetic organic chemistry would be opened. This report deals with such an innovation, largely developed by our research group.

The finding that transition metal complexes are able to cleave unactivated C–H bonds was reported in the 1960’s. Azobenzene was found to undergo cleavage at the ortho C–H bond in a reaction with a nickel complex to give the ortho-nickelated complex 1 (Scheme 1(a)). In 1965, naphthalene was reported to undergo a remarkable reaction with a Ru(0) complex (Scheme 1(b)). In 1965, an X-ray analysis of a ruthenium complex having “five ligands” showed, unexpectedly, that it was “six-coordinated” with a C–H bond as the sixth ligand (Fig. 1). These findings stimulated widespread interest in an entirely novel field of organic synthesis where the manipulation of unreactive C–H bonds became a possibility. Extensive progress has been made during the following thirty years and, as a result, more than fifty review articles have appeared, mostly dealing with the stoichiometric cleavage of C–H bonds by metal complexes. To be useful in organic synthesis the reaction must be catalytic. However, the development of catalytic reactions using this type of chemistry has been very slow. Two early examples (Scheme 1(c) and (d)) and two later examples (Scheme 1(e) and (f)) are shown. The catalytic linear dimerization of acrylonitrile reported in the late
1960’s\textsuperscript{8,9)} has been later proposed by us\textsuperscript{10)} to involve the oxidative addition of a C–H bond to the CN group onto the ruthenium, to give an intermediate such as 2 (Scheme 1\textsuperscript{(c)}).

The addition of an aromatic C–H bond to an unsaturated function reported in 1978\textsuperscript{11)} (Scheme 1\textsuperscript{(d)}) likely involves an intermediate rhodium complex such as 3. Catalytic reactions involving the cleavage of the C–H bond at the α-position of pyridine (Scheme 1\textsuperscript{(e)} and \textsuperscript{(f)}) have been reported.\textsuperscript{12\textendash}15) Although these reactions are exceptionally efficient, the former suffered from a side reaction (hydrogenation of the olefin used)\textsuperscript{12\textendash}13) and the latter frequently required the use of a large excess of one of the reactants.\textsuperscript{14\textendash}15) Another interesting example of the catalytic cleavage of a C–H bond was demonstrated by Jones and Kosar, as shown in Scheme 1\textsuperscript{(g)}. They reported that 2,6-xylylisocyanide could be catalytically converted into indoles.\textsuperscript{16\textendash}17)

It should be noted that various types of C–H bonds can participate when aided by transition metals through a variety of mechanisms ranging from oxidative additions to deprotonation. Some of these reactions can be very useful in organic synthesis. Some selected examples are the Pd-catalyzed functionalization of unsaturated and allylic C–H bonds,\textsuperscript{18\textendash}20)} the Ru-catalyzed functionalization of C–H bonds to heteroatoms,\textsuperscript{21\textendash}24)} the Ru-, Rh-, and Pd-catalyzed addition of active methylene compounds to unsaturated functions,\textsuperscript{25\textendash}31)} the Rh- and Ru-catalyzed hydroacylation of olefins with aldehydes,\textsuperscript{32\textendash}37)} the Rh-catalyzed decarbonylation of aldehydes,\textsuperscript{38)} and the catalytic funcntionalization of olefins via an addition–elimination sequence.\textsuperscript{39\textendash}41)}

One of the most important goals of these efforts has been to achieve the one-step addition of a C–H bond across a double bond of an olefin (Scheme 2). If a non-polar C–H bond could participate in such a reaction without being converted into a reactive but sacrificing functional group such as a halogen, the overall transformation would find great utility.
in organic synthesis. In this paper, we report on our findings with respect to the catalytic use of C–H bonds in organic synthesis.42–64)

Addition of C–H bond in aromatic ketones to olefins

In the early 1990’s, we initiated studies directed to discovering efficient catalytic reactions involving C–H bond cleavage or what is commonly referred to as C–H activation. Our numerous initial attempts were unsuccessful, the only exception being the case of using a new Sn–Ru catalyst system10,42 for the dimerization of acrylonitrile (Scheme 1(c)). During the course of our various attempts to find catalytic reactions in which Ru–Ho or Ru–Si should play a key role, we have discovered a new reaction involving the addition of a C–H bond to an olefin, the Holy Grail to us, in 1991.

A representative example of the addition of a C–H bond to an olefin is given (Scheme 3).43,44) The reaction involves the cleavage and addition of an ortho C–H bond of acetophenone to an olefin. The reaction is operationally very simple, a simple mixing and heating, and generally results in nearly quantitative yields. Consequently, the new catalytic reaction satisfied the general requirements for a tool in organic synthesis, which was quite exceptional for this type of reaction involving the direct manipulation of C–H bonds.

Selected examples of some aromatic C–H-to-olefin addition reactions are given in Scheme 4. Ruthenium complexes containing three triphenylphosphine ligands such as RuH2(CO)(PPh3)3 (6) or Ru(CO)2(PPh3)3 are the best catalysts (or catalyst precursor). We frequently use triethoxyvinylsilane (5) in a test of the reactivity of a ketone, because of its high reactivity and the utility of the product. The 1:1 addition products are obtained in excellent yields. In many cases, the yields are quantitative with respect to both starting materials. Olefins such as tert-butylenethylene, styrene derivatives, vinylsilanes, allylisilanes, and 1,1-disubstituted olefins can be used. Ethylene also reacts nicely. In contrast, olefins with allylic hydrogens rapidly isomerize and give low yields of desired products. A large number of reactions including reactions of various substituted acetophenones have been examined.45,54)

Heteroaromatic ketones react with the vinylsilane 5 to afford the corresponding addition product (Fig. 2). Site selectivity for the reaction of 3-acetylthiophene is complete at the 2-position and not the 4-position. This result suggests the importance of the existence of a conjugated enone characteristic for this C–H bond cleavage.43,44) The effect of various substituents on the aromatic ring was examined, in order to better understand the new ruthenium-catalyzed reaction of C–H bonds in aromatic ketones with olefins. The present C–H-to-olefin addition reaction tolerates both electron-donating (e.g., NMe2, OMe, CH3, NEtC(O)CH3, and OC(O)CH3) and electron-withdrawing (e.g., CF3, CN, CO2Me, F, and OCF3) groups.54,65)

Meta-Substituted acetophenones have two different reaction sites. In this case, C–C bond formation usually occurs at the least congested position (Scheme 5). Steric crowding may prevent the ruthenium from approaching the C–H bond at the 2-position. Interestingly, however, when the substituent is a methoxy or fluoro group, the reaction occurs at the sterically less favorable position, i.e., the 2-position. This unusual site selectivity can be attributed to electronic interactions between the ruthenium and the lone pair of electrons of the methoxy oxygen or the fluoro atom.66)

Addition of olefinic C–H bonds to olefins

Olefinic C–H bonds can also be added to olefins with the aid of ruthenium-catalysts.57) The reaction of
acetylcyclohexene with the vinylsilane 5 in the presence of the same catalyst 6 gave the expected 1:1 olefinic C–H-to-olefin addition product but in low yield (50%) (Scheme 6). Interestingly and unexpectedly, a more bulky ketone, i.e., pivaloylcyclohexene, reacted much faster and the yield was excellent. The reason for this rate enhancement is not completely understood at this time. Various olefins such as α-methylstyrene, vinylcyclohexene, and methyl methacrylate, which gave almost no addition products in the reaction of aromatic ketones, are applicable to the addition of the C–H bond of pivaloylcyclohexene to an olefin.

The use of acyclic enones for C–H-to-olefin addition typically resulted in the production of a complex mixture of products. For chelation-assisted C–H bond cleavage, the s-cis conformation of the enone moiety is important (Fig. 3), in terms of five-membered metalacycle formation. In the case of enone 7, in which the corresponding s-trans conformation is destabilized by allylic strain between the olefinic C–H and the bulky tert-butyl group (Fig. 3), the expected coupling product was obtained in high yield (Scheme 7).

These reactions provide a new route to olefin-to-olefin addition reactions. Trost also reported a similar strategy for the cross coupling of acrylic esters with olefins using the same catalyst 6.67)

Addition of C–H bonds to acetylenes

In addition to olefins, acetylenes also work well.48),64) Thus, all four combinations, i.e., aromatic ketone-to-olefin addition, olefinic ketone-to-olefin addition, aromatic ketone-to-acetylene addition (Scheme 8), and olefinic ketone-to-acetylene addition (Scheme 9), can be used in this reaction. The catalyst used was RuH₂(CO)(PPh₃)₃ (6).

As shown in Scheme 8, the C–H bond of α-tetralone, which is one of the most reactive ketones in the coupling with olefins,45) underwent addition to the triple bond of 1-trimethylsilyl-1-propyne in a completely regioselective, stereoselective manner in 83% yield. This indicates that the addition of a Ru–H (or, less likely, a Ru–C) bond to the acetylene proceeds in a syn fashion. 4-Octyne reacted in a similar manner with a high stereoselectivity (E/Z = 94/6). As shown in Scheme 9, the olefinic C–H bond at the β-carbon atom of an α,β-unsaturated ketone is
cleaved and catalytically added to triple bonds. An aryl group on the acetylene carbon appears to be essential for the success of this reaction, although the roles of the aryl group are not clear at present. Highly congested trisubstituted olefins become available, as the result of these findings.

Generally, acetylenes react with transition metal complexes in various ways, which include C–H oxidative addition, vinylidene complex formation, the formation of metalacyclopentadiene, and cyclotrimerization. Nevertheless, the desired C–H-to-acetylene addition competes successfully with these known reactions. It was, however, not unexpected that terminal acetylenes were completely unreactive. Internal acetylenes underwent smooth addition under reaction conditions that were similar to those used for coupling with olefins.

Addition of C–H bonds in aromatic esters to olefins

An ester group can participate in chelation-assisted C–H-to-olefin addition. The reaction of methyl benzoate with completely failed to give the expected C–H-to-olefin addition product. Interestingly, however, the introduction of an electron-withdrawing group in the aromatic ring dramatically changed the reactivity (Scheme 10). Selected results for other esters that contain an electron-withdrawing group at the meta position are listed in Scheme 11.

Nitrile and ester groups can be used as a rate-accelerating substituent. While it might be expected that an electron-withdrawing group would have facilitated the C–H bond cleavage step, this appears not to be correct (vide infra). Compared with the reactivity among the m- and p-substituted esters, the meta substituent reacts much easier with olefins. This different reactivity may stem from the nature of the proposed intermediate, which will be discussed later.

Addition of aromatic imines to olefins

A nitrogen atom can also function as a directing group. The catalytic reaction of aromatic imines with the olefin gave the corresponding 1:1 addition product (Scheme 12). The unsaturated coupling product, was obtained as a side reaction product. Although the phosphine complex also shows catalytic activity, Ru(OC) (8), which was an ineffective catalyst for the reaction of ketones with olefins, showed the highest activity of the various transition metal complexes screened. Aldimines react also with other types of vinylsilanes, ethylene, tert-butylethylene, and aromatic olefins.

Jun et al. have reported a similar addition reaction of aromatic ketimines with olefins using a rhodium catalyst.

Addition of aromatic nitriles to olefins

Interestingly, a nitrile group can also serve as a directing group in C–H-to-olefin addition reactions. In this case, however the π-electrons, but not the lone-pair electrons of the nitrile group appear to participate in positioning the ruthenium in close proximity to the ortho C–H bond. The reaction of benzonitrile with using 6 as a catalyst gave the corresponding 1:2 addition product in 97% yield as the predominant product (Scheme 13). This exclusive ortho selectivity implies that a nitrile group is capable of directing the ruthenium to the ortho C–H bond. When the reaction was conducted using one equivalent of the vinylsilane 5, both the 1:1 addition product and the 1:2 addition product were obtained.
in 18% and 19% yields, respectively. This unusually high yield of the 1:2 adduct suggests that the second C–H bond cleavage takes place, to a great extent, prior to the dissociation of the 1:1 adduct from the ruthenium center.

**Addition of β-C–H bonds in aromatic and α,β-unsaturated aldehydes to olefins**

The use of a formyl group as a directing functionality was our next interest. When aldehydes are exposed to low-valent ruthenium and rhodium complexes, decarbonylation usually takes place. In addition, the hydroacylation of olefins becomes another competitor against formyl group-directed C–H-to-olefin addition. To suppress these problems, the following two procedures were devised: one being steric (Fig. 4) and the other electronic in nature (Fig. 5).

Steric hindrance around the formyl moiety inhibits the approach of the ruthenium to the carbonyl carbon. Actually, the reaction of aldehydes that contain a sterically bulky group at a position ortho to the formyl group, i.e., 2,4-di-tert-butylbenzaldehyde and 2-trimethylsilylbenzaldehyde, gave the corresponding ortho addition product in good yield (Scheme 14). As shown in Fig. 4, it is difficult for the catalyst metal center to attack the carbonyl carbon leading to decarbonylation. As a result, decarbonylation suffers from steric hindrance in the preferred conformation of the formyl group. As an electronic control, the electron donating characteristics of a heteroatom at a position β to the formyl group decreases the electrophilicity at the formyl carbon atom, due to the contribution of resonance form B, and, as a result, the formyl group is not attacked by the nucleophilic ruthenium center (Fig. 5). The reaction of an aldehyde having a dihydropyran framework resulted in the selective production of the alkylation product (Scheme 15). These results indicate that both steric and electronic effects are important factors in preventing decarbonylation and in achieving C–H-to-olefin addition.

**Intramolecular cyclization of 1,α-dienes via C–H bond cleavage**

The intramolecular cyclization of 1,5- and 1,6-dienes can be achieved, provided the dienes contain pyridyl, imidazolyl, or oxazolyl rings. This provides a new route for the construction of 5- or 6-membered carbocycles. The intramolecular cyclization of 1,5-dienylpyridine proceeded in the presence of RhCl(PPh₃)₃ as the catalyst to give high yields of the desired 5-membered ring compound (Scheme 16). Some 1,6-dienes containing a pyridyl moiety are also applicable to this reaction. The M–H bond formed from the C–H bond and the rhodium complex adds to both terminal and internal olefins resulting in the formation of five- or six-membered carbocycles.
This catalytic cyclization can be extended to an asymmetric version.\textsuperscript{53} When the [RhCl(coe)\textsubscript{2}]/(R)-(S)-PFOMe catalyst system (coe = cyclooctene; (R)-(S)-PFOMe = (R)-1-[(S)-2-(diphenylphosphino)-ferrocenyl]ethyl methyl ether), was employed in place of [RhCl(coe)\textsubscript{2}]/PCy\textsubscript{3} catalyst system, in the reaction of 1,5-dienylimidazoles, the corresponding five-membered carbocycle was obtained in 75\% yield with 82\% ee.

Mechanistic aspect of C–H-to-olefin addition

The reaction mechanism for ruthenium-catalyzed C–H-to-olefin addition reactions has been studied primarily by us\textsuperscript{44),45} but other groups have also contributed.\textsuperscript{79),80} These studies suggest that the initial hydrogenation of an olefin with the dihydriderruthenium catalyst 6 gives a zerovalent ruthenium species, such as Ru(CO)(PPh\textsubscript{3})\textsubscript{3}.

Further mechanistic studies by means of deuterium-labeling experiments and the measurement of \textsuperscript{13}C kinetic isotope effects (KIEs) have been done.\textsuperscript{63),81}

A deuterium-labeling experiment using methyl benzoate (9-\textsubscript{d5}) with 5 was carried out in the presence of 6 as catalyst at 135 °C for 24 h (Scheme 17). Seemingly no reaction occurred under these conditions, but the \textsuperscript{1}HNMR spectra of the recovered starting materials indicate that a complete scrambling occurred among the two ortho positions of the ester and three vinylic positions of the vinylsilane.

For the reaction of esters, we measured the experimental \textsuperscript{13}C kinetic isotope effects (KIEs) at natural abundance.\textsuperscript{53),81} If the C–C bond formation step is rate-determining, the relative intensity of the ortho-\textsuperscript{13}C in the recovered starting material should be increased compared with those at natural abundance. The observed KIE for the ortho carbon was 1.033, while those of the other aromatic carbons were nearly 1.000 for each carbon atom. This result strongly suggests that C–C bond formation is the rate-determining step in the catalytic reaction of aromatic esters.

A plausible reaction pathway for the ruthenium-catalyzed reactions of aromatic compounds with olefins is proposed in Scheme 18.

The H/D exchange occurring only at the ortho position indicates that chelation assistance is critically important for the formation of the ruthenium-hydride (Ru–H) species. The addition of the Ru–H bond to olefins occurs in both directions, and the reverse of these reactions, i.e., β hydride elimination, also take place. In the present case, 14 can only return to 12. In the case of the reaction of acetophenone, intermediate 13 undergoes reductive elimination to the addition product, but in the case of methyl benzoate, 13 does not. The hydride 12 returns to 11 and then to 9. The deuterium scrambling experiments show that these equilibrium processes are occurring well ahead of reductive elimination, which was a surprise. In contrast to the generally accepted view, the C–H bond cleavage step is an easy step in the present catalytic reactions. It is also suggested that an alternative step involving the carbo-metallation from 12 (not shown) can be eliminated since the reverse decarbo-metallation to establish equilibrium is unlikely.

The \textsuperscript{13}C kinetic isotope effects verify that reductive elimination, resulting in C–C bond formation, is the rate-determining step in the RuH\textsubscript{2}(CO)(PPh\textsubscript{3})\textsubscript{3} catalyzed reactions.

An electron-withdrawing group on the leaving ligand (e.g., aromatic ring) is known to retard the rate of the reductive elimination step.\textsuperscript{82} Interestingly, however, in the reaction of aromatic esters with olefins, the presence of electron-withdrawing groups...
appeared to facilitate reductive elimination. We propose that a migration mechanism (15 to 16, Scheme 19), i.e., $\sigma-\pi$ coupling, is favorable for reductive elimination, rather than the usual $\sigma-\sigma$ coupling mechanism. In the case of $\sigma-\pi$ coupling, an alkyl group on the ruthenium first undergoes a 1,2-shift to the aromatic ring without extensive cleavage of the aromatic carbon-metal $\sigma$-bond (15 to 16). The role of the electron-withdrawing groups in the reaction of aromatic esters with 5 (Scheme 11) can be attributed to an acceleration of this Michael addition-type migration. A meta-electron-withdrawing group is more efficient than ortho and para groups.

These results demonstrate the very important features of the present C–H-to-olefin addition. C–H bond cleavage, which has been often considered to be a rate-determining step, is a facial step compared with the C–C bond formation step and a pre-equilibrium prior to reductive elimination occurs in this catalytic cycle. A theoretical study of the present catalytic reaction was reported by Morokuma et al. Their results are in agreement with the mechanism proposed.

**Further extension of the catalytic conversion of C–H bonds**

Since the discovery of the highly efficient catalytic conversion of C–H bonds, a number of related synthetic transformations have been reported by us and others. Some early examples of new reactions developed by our group are discussed below. These involve reactions with organosilicon compounds, organoboranes, and carbon monoxide.

The direct silylation of aromatic C–H bonds can be achieved by reaction with a trialkylsilane in the presence of an olefin as the hydrogen scavenger using $\text{Ru}_3(\text{CO})_{12}$ (8) as the catalyst. An example is shown in Scheme 20. During the catalytic reaction, two hydrogen atoms must be removed. The reductive elimination of molecular hydrogen from a ruthenium center is a thermally unfavorable step (by ca. +20 kcal/mol). The use of an olefin (e.g. tert-butylethene) was found to be an effective scavenger of hydrogen.

The catalytic borylation of C–H bonds (especially sp$^3$-C–H bonds) is a highly active research subject in the catalytic use of C–H bonds. In contrast, we found that an aromatic group on an organoborane can be transferred to the carbon atom with cleavage of the C–H bond. As shown in Scheme 21, we found that the ruthenium catalyzed arylation of aromatic ketones with arylboronates provides the ortho product exclusively. Catalytic carbonylation at C–H bonds also takes place. A representative example is given in Scheme 22. When the reaction of phenylpyridine with carbon monoxide (20 atm) and ethylene was conducted at 160 °C in the presence of a catalytic amount of $\text{Ru}_3(\text{CO})_{12}$ (8) the ortho C–H bond underwent carbonylation. A similar but less efficient reaction had been reported with pyridine, which was used both as a reactant and solvent.

![Scheme 19](image1.png)

![Scheme 20](image2.png)

![Scheme 21](image3.png)

![Scheme 22](image4.png)
Conclusion

It had long been thought impossible to utilize C–H bonds for selective organic synthesis. The situation has now been completely changed. It is now thought that highly selective reactions at C–H bonds are both possible and useful, as demonstrated by the catalytic addition of C–H bonds to multiple bonds. We also have shown that the hydrogen at a C–H bond can be catalytically displaced. This aspect is not discussed in detail here. The early works reported by other groups have been cited in our reviews.91)

The subject of this research area is often referred to C–H bond activation studies. Because direct use of C–H bonds promises to result in most economic synthetic pathway, this area has attracted intensive interest. We are also continuing our efforts actively for further development of this new chemistry.94) This research area is not only important in terms of the science involved but also in attaining a sustainable society in the future. The remarkable progress now ongoing in this field is exemplified by the fact that the entire volume of the number two issue of Chemical Reviews (London) of 2010 has been devoted to “C–H bond activation,” including sixteen reviews in this field.

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References

1) Kleiman, J.P. and Dubcek, M. (1963) The preparation of cyclopentadienyl [o-(phenylazo)phenyl]nickel. J. Am. Chem. Soc. 85, 1544–1545.
2) Chatt, J. and Watson, H.R. (1962) Complexes of zerovalent transition metals with the diterary phosphine, Me₂PCH₂CH₂PMe₂. J. Chem. Soc., 2545–2549.
3) Chatt, J. and Davidson, J.M. (1965) The tautomerism of arene and diterary phosphine complexes of ruthenium(0), and the preparation of new types of hydrido-complex of ruthenium(II). J. Chem. Soc., 843–855.
4) La Placa, S.J. and Ibers, J.A. (1965) Five-coordinate d⁶ complex: structure of dichlororotris(triphenylphosphine)ruthenium(II). Inorg. Chem. 4, 778–783.
5) Bergman, R.G. (1984) Activation of alkanes with organotransition metal complexes. Science 223, 902–908.
6) Shilov, A.E. and Shul’pin, G.B. (1997) Activation of C–H bonds by metal complexes. Chem. Rev. 97, 2879–2932.
7) Jones, W.D. (1999) Activation of C–H bonds: stoichiometric reactions. In Topics in Organometallic Chemistry Vol. 3 (ed. Murai, S.). Springer, Berlin, pp. 9–46.
8) Rhone-Poulenc (1967) Dimerization of acrylonitrile to 1,4-dicyanobutene and (or) adiponitrile. Neth. Patent 6,603,115; Rhone-Poulenc (1967) Chem. Abstr. 66, 85483.
9) Tsou, D.T., Burrington, J.D., Maher, E.A. and Grasselli, R.K. (1985) Mechanism of ruthenium-catalyzed linear dimerization of acrylonitrile: a kinetic study. J. Mol. Catal. 30, 219–239.
10) Kashihwa, K., Sugise, R., Shimakawa, T., Matuura, T., Shirai, M., Kakiuchi, F. and Murai, S. (1997) Catalytic dimerization of acrylonitrile. Organometallics 16, 2233–2235.
11) Hong, P., Yamazaki, H., Sonogashira, K. and Hagiwara, N. (1978) Rhodium carbonyl cluster catalyzed addition of arenes to diphenylketene and aryl isocyanates. Chem. Lett., 535–538.
12) Jordan, R.F. and Taylor, D.F. (1989) Zirconium-catalyzed coupling of propene and α-picoline. J. Am. Chem. Soc. 111, 778–779.
13) Rodewald, S. and Jordan, R.F. (1994) Stereoselective olefin insertion reactions of chiral (EBI)Zr(η⁵-pyrid-2-vl)⁺ and (EBTHI)Zr(η⁵-pyrid-2-vl)⁺ complexes. J. Am. Chem. Soc. 116, 4491–4492.
14) Moore, E.J., Pretzer, W.R., O’Connel, T.J., Haris, J., LaBounty, L., Chou, L. and Grimmer, S.S. (1992) Catalytic and regionselective acylation of aromatic heterocycles using carbon monoxide and olefins. J. Am. Chem. Soc. 114, 5888–5890.
15) Moore, E.J. and Pretzer, W.R. (1992) Regioselective carboxylation process for making acyl compounds from aromatic heterocycles and olefins. US Patent, US 5,081,250.
16) Jones, W.D. and Kosar, W.P. (1986) Carbon–hydrogen bond activation by ruthenium for the catalytic synthesis of indoles. J. Am. Chem. Soc. 108, 5640–5641.
17) Hsu, G.C., Kosar, W.P. and Jones, W.D. (1994) Functionalization of benzylc carbon–hydrogen bonds. Mechanism and scope of the catalytic synthesis of indoles with [Ru(dmpu)₂]³⁻. Organometallics 13, 385–396.
18) Colequhoun, H.M., Holton, J., Thompson, D.J. and Twigg, M.V. (1984) New Pathways for Organic synthesis. Plenum, New York.
19) Heck, R.F. (1985) Palladium Reagents in Organic Synthesis. Academic Press, London.
20) Fujiiwara, Y., Jintoku, T. and Takaki, K. (1990) Look what Pd catalyzes. Chemtech 20, 636–640.
21) Murahashi, S.-I., Naota, T. and Taki, H. (1985) Ruthenium-catalysed oxidation of secondary-
amines to imines using tert-butyl hydroperoxide. J. Chem. Soc. Chem. Commun., 613–614.

22) Murahashi, S.-I., Naota, T. and Yonemura, K. (1988) Ruthenium-catalyzed cytochrome-P-450 type oxidation of tertiary-amines with alkyl hydroperoxides. J. Am. Chem. Soc. 110, 8256–8258.

23) Murahashi, S.-I., Naota, T., Kuwabara, T., Saito, T., Kumobayashi, H. and Akutagawa, S. (1990) Ruthenium-catalyzed oxidation of amides and lactams with peroxides. J. Am. Chem. Soc. 112, 7820–7822.

24) Murahashi, S.-I., Saito, T., Naota, T., Kumobayashi, H. and Akutagawa, S. (1991) Ruthenium-catalyzed oxidation of $\beta$-lactams with molecular oxygen and aldehydes. Tetrahedron Lett. 32, 5991–5994.

25) Naota, T., Taki, H., Mizuno, M. and Murahashi, S.-I. (1989) Ruthenium-catalyzed aldol and Michael reactions of activated nitriles. J. Am. Chem. Soc. 111, 5954–5955.

26) Paganelli, S., Schionato, A. and Botteghi, C. (1991) Rhodium-catalyzed Michael additions of activated nitriles to $\alpha$,$\beta$-unsaturated esters. Tetrahedron Lett. 32, 2807–2810.

27) Sawamura, M., Hamashima, H. and Ito, Y. (1992) TRAP-rhodium-catalyzed asymmetric Michael addition of $\alpha$-cyano carboxylates. J. Am. Chem. Soc. 114, 8295–8296.

28) Yamamoto, Y., Kubota, Y., Honda, Y., Fuku, H., Asao, N. and Nemoto, H. (1994) Transition-metal-catalyzed addition of certain nitriles to imines. J. Am. Chem. Soc. 116, 3161–3162.

29) Nemoto, H., Kubota, Y. and Yamamoto, Y. (1994) Palladium-catalyzed addition of masked formyl cyanides ROCH(CN)$_2$ to aldehydes. J. Chem. Soc. Chem. Commun., 1665–1666.

30) Yamamoto, Y., Al-Masum, M. and Asao, N. (1994) Palladium-catalyzed addition of activated methylene and methylene compounds to allenes. J. Am. Chem. Soc. 116, 6019–6020.

31) Murahashi, S.-I., Naota, T., Taki, H., Mizuno, M., Takaya, H., Komiya, S., Mizuho, Y., Oyasato, N., Hiraoka, M., Hirano, M. and Fukunoka, A. (1995) Ruthenium-catalyzed aldol and Michael reactions of nitriles. Carbon–carbon bond formation by $\alpha$–C–H activation of nitriles. J. Am. Chem. Soc. 117, 12436–12451.

32) Sakai, K., Ide, J., Oda, O. and Nakamura, N. (1972) Synthetic studies on prostanoids 1. Synthesis of methyl 9-oxoprostanolate. Tetrahedron Lett. 13, 1287–1290.

33) Kondo, T., Tsuji, Y. and Watanabe, Y. (1987) Ruthenium complex catalyzed intermolecular hydroacylation of olefins. Tetrahedron Lett. 28, 6229–6230.

34) Marder, T.B., Roe, C. and Milstein, D. (1988) Transition-metal-catalyzed carbon–carbon bond formation via carbon–hydrogen activation, intermolecular hydroacylation: the addition of aldehydes to allenes. Organometallics 7, 1451–1453.

35) Kondo, T., Akazome, M., Tsuji, Y. and Watanabe, Y. (1990) Ruthenium complex catalyzed intermolecular hydroacylation and transhydroformylation of olefins with aldehydes. J. Org. Chem. 55, 1286–1291.

36) Watanabe, Y., Mitsudo, T. and Kondo, T. (1992) A new development of ruthenium complex catalysts. Carbon–carbon bond forming reactions. Shokubai 34, 173–181; Watanabe, Y., Mitsudo, T. and Kondo, T. (1992) Chem. Abstr. 117, 19104G.

37) Barnhart, R.W., Wang, X., Noheca, P., Bergens, S.H., Whelan, J. and Bosluch, B. (1994) Asymmetric catalysis. Asymmetric catalytic intramolecular hydroacylation of 4-pentenals using chiral rhodium diphosphine catalysts. J. Am. Chem. Soc. 116, 1821–1830.

38) Colequhou, H.M., Thompson, D.J. and Twigg, M.V. (1991) Decarbonylation. In Carbylation. Plenum, New York, pp. 205–226.

39) Collman, J.P., Hegedus, L.S., Norton, J.R. and Finke, R.G. (1982) Principles and Applications of Organotransition Metal Chemistry. University Science Books, Mill Valley.

40) Wilkinson, G., Stone, F.G.A. and Abel, E.W. (1982) Comprehensive Organometallic Chemistry. Pergamon, Oxford.

41) For a latest example, Trost, B.M., Romeroand, D.L. and Rive, F. (1994) Palladium-catalyzed cycloisomerization to 1,2-diarylidenecycloalkanes. 2. Alternative catalyst system. J. Am. Chem. Soc. 116, 4268–4278.

42) Murai, S., Oodan, K., Sugise, R., Shirai, M. and Shimakawa, T. (1994) Preparation of acrylnitrile. Jpn. Kokai Tokkyo Koho JP 06,009,531; Murai, S., Oodan, K., Sugise, R., Shirai, M. and Shimakawa, T. (1994) Chem. Abstr. 120, 191146.

43) Murai, S., Kakiuchi, F., Sekine, S., Tanaka, Y., Kamatani, A., Sonoda, M. and Chatani, N. (1993) Efficient catalytic addition of aromatic carbon–hydrogen bonds to olefins. Nature 366, 529–531.

44) Murai, S., Kakiuchi, F., Sekine, S., Tanaka, Y., Kamatani, A., Sonoda, M. and Chatani, N. (1994) Catalytic C–H/olefin coupling. Pure Appl. Chem. 66, 1527–1534.

45) Kakiuchi, F., Sekine, S., Tanaka, Y., Kamatani, A., Sonoda, M., Chatani, N. and Murai, S. (1995) Catalytic addition of substituted acephenones to an olefin. J. Organomet. Chem. 504, 151–152.

46) Sonoda, M., Kamiuchi, F., Chatani, N. and Murai, S. (1995) Directing effect of functional groups in ruthenium-catalyzed addition of substituted acephenones to an olefin. J. Organomet. Chem. 504, 151–152.

47) Kamiuchi, F., Tanaka, Y., Sato, T., Chatani, N. and Murai, S. (1995) Catalytic addition of olefinic C–H bonds to olefins. Chem. Lett., 679–680.

48) Kamiuchi, F., Yamamoto, Y., Chatani, N. and Murai, S. (1995) Catalytic addition of aromatic C–H bonds to acetylenes. Chem. Lett., 681–682.

49) Sonoda, M., Kamiuchi, F., Kamatani, A., Chatani, N. and Murai, S. (1996) Ruthenium-catalyzed addition of aromatic esters to the ortho C–H bonds to olefins. Chem. Lett., 109–110.
Kakiuchi, F., Yamauchi, M., Chatani, N. and Murai, S. (1996) Ruthenium-catalyzed addition of aromatic imines at the ortho C–H bonds to olefins. Chem. Lett., 111–112.

Fujii, N., Kakiuchi, F., Chatani, N. and Murai, S. (1996) Transition metal-catalyzed intramolecular C–H/olefin coupling. Chem. Lett., 939–940.

Murai, S., Chatani, N. and Kakiuchi, F. (1997) Catalytic addition of C–H bonds to multiple bonds. Pure Appl. Chem. 69, 589–594.

Fujii, N., Kakiuchi, F., Yamada, A., Chatani, N. and Murai, S. (1997) Asymmetric intramolecular C–H/olefin coupling: asymmetric cyclization reactions of 1,5-dienes catalyzed by rhodium complexes. Chem. Lett., 425–426.

Sonoda, M., Kakiuchi, F., Chatani, N. and Murai, S. (1997) Ruthenium-catalyzed addition of carbon–hydrogen bonds in aromatic ketones to olefins. The effect of various substituents at the aromatic ring. Bull. Chem. Soc. Jpn. 70, 3117–3128.

Fujii, N., Kakiuchi, F., Yamada, A., Chatani, N. and Murai, S. (1998) Transition metal-catalyzed intramolecular cyclization of 1,5- and 1,6-dienes via direct cleavage and addition of the carbon–hydrogen bond. Bull. Chem. Soc. Jpn. 71, 285–298.

Sato, T., Kakiuchi, F., Chatani, N. and Murai, S. (1998) Ruthenium-catalyzed reactions of acyclic α,β- enones with olefins and their reaction mechanisms. Chem. Lett., 893–894.

Kakiuchi, F., Sato, T., Tsujimoto, T., Yamauchi, M., Chatani, N. and Murai, S. (1998) New protocol for the site-selective alkylation and vinylation of aromatic compounds. Catalyst-specific reactions. Chem. Lett., 1053–1054.

Kakiuchi, F., Sato, T., Yamauchi, M., Chatani, N. and Murai, S. (1999) Ruthenium-catalyzed addition of aromatic carbon–hydrogen bonds in aromatic imidates with olefins. Chem. Lett., 19–20.

Kakiuchi, F., Sonoda, M., Tsujimoto, T., Chatani, N. and Murai, S. (1999) The ruthenium-catalyzed addition of C–H bonds in aromatic nitriles to olefins. Chem. Lett., 1083–1084.

Kakiuchi, F., Le Gendre, P., Yamada, A., Ohtaki, H. and Murai, S. (2000) Atropselective alkylation of biaryl compounds by means of transition metal-catalyzed C–H/olefin coupling. Tetrahedron Asymmetry 11, 2647–2651.

Kakiuchi, F., Sato, T., Igi, K., Chatani, N. and Murai, S. (2001) The ruthenium-catalyzed addition of 3-C–H bonds in aldehydes to olefins. Chem. Lett., 386–387.

Kakiuchi, F., Tsujimoto, T., Sonoda, M., Chatani, N. and Murai, S. (2001) The transition metal-catalyzed addition of C–H bonds in aromatic hydrazones to olefins. Synlett, 948–951.

Kakiuchi, F., Ohtaki, H., Sonoda, M., Chatani, N. and Murai, S. (2001) Mechanistic study of the Ru(H)(CO)(PPh)_3-catalyzed addition of C–H bonds in aromatic esters to olefins. Chem. Lett., 918–919.

Kakiuchi, F., Uetsuaha, T., Tanaka, Y., Chatani, N. and Murai, S. (2002) Ruthenium-catalyzed addition of olefinic C–H bonds in conjugate enones to acetylenes to give conjugate dienones. J. Mol. Catal. Chem. 182–183, 511–514.

Hansch, C., Leo, A. and Taft, R.W. (1991) A survey of Hammett substituent constants and resonance and field parameters. Chem. Rev. 91, 165–195.

McKinney, R.J., Firestein, G. and Kaez, H.D. (1975) Metallation of aromatic ketones and anthaquinone with methylmanganese and methylrhenium carbonyl complexes. Inorg. Chem. 14, 2057–2061.

Trost, B.M., Imi, K. and Davies, I.W. (1995) Elaboration of conjugated alkenes initiated by insertion into a vinylc C–H bond. J. Am. Chem. Soc. 117, 5371–5372.

Marder, T.B., Zargarian, D., Calabrese, J.C., Herskovitz, T.H. and Milstein, D. (1987) C–H rather than O–H activation: synthesis and molecular structure of a cationic cis-hydrido-α-acetylide complex of rhodium. J. Chem. Soc. Chem. Commun., 1484–1485.

Bruce, M.I. (1991) Organometallic chemistry of vinylidene and related unsaturated carbenes. Chem. Rev. 91, 197–257.

Schore, N.E. (1988) Transition metal-mediated cycloaddition reactions of alkenes in organic synthesis. Chem. Rev. 88, 1081–1119.

Wakatsuki, Y. and Yamazaki, H. (1973) Cobalt-catalyzed insertion of conjugated alkenes to give conjugate dienones. J. Mol. Catal. Chem. 12, 437–440.

Trost, B.M., Martinez, J.A., Kulawiec, R.J. and Indolese, A.F. (1993) Ruthenium-catalyzed addition of allyl alcohols and acetylenes. A simple synthesis of γ,δ-unsaturated ketones. J. Am. Chem. Soc. 115, 10402–10403.

Naota, T., Takaya, H. and Murahashi, S.-I. (1998) Ruthenium-catalyzed reactions for organic synthesis. Chem. Rev. 98, 2599–2660.

Chatani, N., Ishii, Y., Ie, Y., Kakiuchi, F. and Murai, S. (1998) Ruth(III)(CO)_{12} and Ruth(III)(CO)_{12}-catalyzed reactions of pyridylolefin and nitriles. Tetrahedron Lett. 39, 3383–3384.

Jun, C.-H., Hong, J.-B., Kim, Y.-H. and Chung, K.-Y. (2000) The catalytic alkylation of aromatic imides by Wilkinson’s complex: The domino reaction of hydroacylation and ortho-alkylation. Angew. Chem. Int. Ed. 39, 3440–3442.

Ito, T., Horino, H., Koshiro, Y. and Yamamoto, A. (1982) Selective dimerization of aldehyde to esters catalyzed by hydridoruthenium complexes. Bull. Chem. Soc. Jpn. 55, 504–512 and references therein.

Tsuji, J. and Ohno, K. (1969) Decarboxylation reaction using transition metal compounds. Synthesis, 157–169.

Bosnich, B. (1998) Asymmetric catalysis. A comparative study of the mechanisms of intramolecular hydroacylation and hydrosilation. Acc. Chem. Res. 31, 667–674.

Lu, P., Paulasaari, J., Jin, K., Bau, R. and Weber, W.P. (1998) Preparation, characterization, and X-
ray structure of the 1:1 complex of o-acetylstyrene and carbonyl(bis(triphenylphosphine)pentamethylcyclopentadienyl) ruthenium. A new catalyst for the copolymerization of acetophenone and 1,3-divinyltetramethyldisiloxane. Organometallics 17, 584–588.

80) Kawano, H., Tanaka, R., Fujikawa, T., Hiraki, K. and Onishi, M. (1999) Novel dihydrodiorgano ruthenium(II) complexes with chelating diphosphine ligands, RuH2(CO)(diphosphine)(PPh3) (diphosphine = dppe, dppp, dpbb, and dppf). Chem. Lett., 401–402.

81) Singleton, D.A. and Thomas, A.A. (1995) High precision simultaneous determination of d6-organotransition metal complexes. Bull. Chem. Soc. Jpn. 54, 1857–1867.

82) Tatsunami, K., Hoffmann, R., Yamamoto, A. and Stille, J.K. (1981) Reductive elimination of d⇌organotransition metal complexes. Bull. Chem. Soc. Jpn. 54, 1857–1867.

83) Lenges, C.P., Brookhart, M. and Grant, B.E. (1997) H/D exchange reactions between C6D6 and C6Me6Co(CH2=CHR)2 (R = H, SiMe3): evidence for oxidative addition of C6Me6H to the [C6Me6(L)Co] moiety. J. Organomet. Chem. 528, 199–203.

84) Matsubara, T., Koga, N., Musaev, D.G. and Morokuma, K. (1998) Density functional study on activation of ortho-C–H bond in aromatic ketone by Ru complex. Role of unusual five-coordinated d5 metalacyle intermediate with agostic interaction. J. Am. Chem. Soc. 120, 12692–12693.

85) Kakiuchi, F., Igi, K., Matsumoto, M., Chatani, N. and Murai, S. (2001) Ruthenium-catalyzed dehydrogenative silylation of aryloxazolines with hydrosilanes via C–H bond cleavage. Chem. Lett., 422–423.

86) Stull, D.R., Westrum, E.F. and Shinke, G.C. (1987) The Chemical Thermodynamics of Organic Compounds. Robert E. Kreiger Publishing, Malabar, FL.

87) Waltz, K.M., He, X., Muhor, C. and Hartwig, J.F. (1995) Hydrocarbon functionalization by transition metal boryles. J. Am. Chem. Soc. 117, 11357–11358.

88) Chen, H., Schlecht, S., Semple, T.C. and Hartwig, J.F. (2000) Thermal, catalytic, regiospecific functionalization of alkanes. Science 287, 1995–1997.

89) Kakiuchi, F., Kan, S., Igi, K., Chatani, N. and Murai, S. (2003) A ruthenium-catalyzed reaction of aromatic ketones with arylboronates: a new method for the arylation of aromatic compounds via C–H bond cleavage. J. Am. Chem. Soc. 125, 1968–1969.

90) Chatani, N., Ie, Y., Kakiuchi, F. and Murai, S. (1997) Ru3(CO)12-catalyzed reaction of pyridinylbenzenes with carbon dioxide and olefins. Carbonylation at a C–H bond in the benzene ring. J. Org. Chem. 62, 2604–2610.

91) Murai, S. (1999) Activation of unreactive bonds for organic synthesis. Topic in Organometallic Chemistry Vol. 3 (ed. Murai, S.). Springer, Berlin.

92) Kakiuchi, F. and Murai, S. (1999) Activation of C–H bonds: catalytic reactions. In Topics in Organometallic Chemistry Vol. 3 (ed. Murai, S.). Springer, Berlin, pp. 47–79.

93) Kakiuchi, F. and Chatani, N. (2003) Catalytic methods for C–H bond functionalization: application in organic synthesis. Adv. Synth. Catal. 345, 1077–1110.

94) Kakiuchi, F., Kochi, T., Mizushima, E. and Murai, S. (2010) Room temperature regioselective C–H/olefin coupling of aromatic ketones using an activated ruthenium catalyst with a carbonyl ligand and structural elucidation of key intermediates. J. Am. Chem. Soc. 132, 17741–17750.

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Profile

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