TUTORIAL REVIEW

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Transition metal-catalyzed carbon–carbon bond activation

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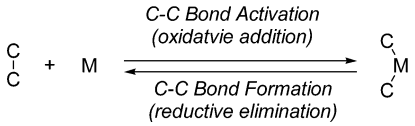
This *tutorial review* deals with recent developments in the activation of C–C bonds in organic molecules that have been catalyzed by transition metal complexes. Many chemists have devised a variety of strategies for C–C bond activation and significant progress has been made in this field over the past few decades. However, there remain only a few examples of the catalytic activation of C–C bonds, in spite of the potential use in organic synthesis, and most of the previously published reviews have dwelt mainly on the stoichiometric reactions. Consequently, this review will focus mainly on the catalytic reaction of C–C bond cleavage by homogeneous transition metal catalysts. The contents include cleavage of C–C bonds in strained and unstrained molecules, and cleavage of multiple C–C bonds such as C≡C triple bonds in alkynes. Multiple bond metathesis and heterogeneous systems are beyond the scope of this review, though they are also fascinating areas of C–C bond activation. In this review, the strategies and tactics for C–C bond activation will be explained.

1 Introduction

Selective C–H and C–C bond activation (cleavage) by transition metal complexes has attracted many organometallic chemists, due not only to its fundamental scientific interest but also to its potential utility in organic synthesis.[1–4] In particular activation of C–C bonds is a challenging subject in spite of their inertness. This topic has been well reviewed until up to 1999 with the focus mainly on stoichiometric reactions.[5,6] Therefore, before looking into the catalytic reaction, we shall briefly consider the stoichiometric reaction of C–C bond activation.

It is quite reasonable to note that C–C bond activation by a metal (oxidative reaction) is the reverse reaction of C–C bond formation (reductive elimination), from the viewpoint of microscopic reversibility (Scheme 1).

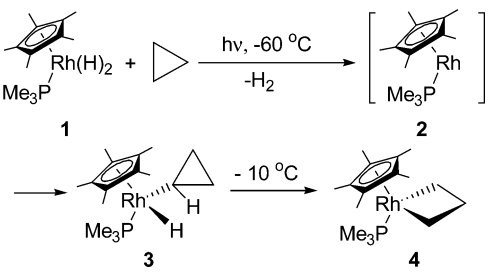
The former has been rarely developed compared with the latter, which is commonly used in many organometallic reactions for organic synthesis, because two weak metal–carbon bonds (20–30 kcal mol^{-1} per bond) are formed at the expense of a relatively stable C–C bond (90 kcal mol^{-1}).[7] This is one of the reasons why C–C bond activation is thermodynamically much less favored than the C–C bond formation.



Scheme 1

In order to facilitate C–C bond activation two basic strategies can be applied. One is to increase the energy state of the starting materials, and the other is to lower the energy state of the C–C bond cleaved complexes. The first strategy is to use high energy starting materials such as strained 3- or 4-membered ring compounds. Relief of the ring-strain in these strained molecules can compensate for the thermodynamic disadvantage of the C–C bond activation by forming more stable ring expanded metallacyclic complexes through metal insertion into the strained C–C bond in cyclopropane, cubane, quadricyclene, *etc*.[8] For this reason, coordinatively unsaturated 14e or 16e transition metal complexes (high energy active metal complexes) could also be used as good reacting partners.

Ultraviolet irradiation of the rhodium dihydride complex **1** generated the coordinatively unsaturated 16 electron species **2** with the liberation of H_2, which reacted with liquid cyclopropane to give the hydrido cyclopropyl rhodium(III) complex **3** through C–H bond activation (Scheme 2).[9] Upon heating,



Scheme 2

Professor Chul-Ho Jun was born in 1953, and grew up in Seoul, Korea. He received his BSc degree in Chemistry at Yonsei University, Seoul in 1976. He then went on to complete his PhD studies in the area of C–C bond activation of 8-acylquinoline derivatives at Brown University in 1987 under the supervision of Professor J. W. Suggs. From 1991–1992, he worked at Yale University as a post-doctoral research fellow under the guidance of Professor R. H. Crabtree. Between 1976 and 1993, he worked as a research scientist at the Agency for Defence Development in Korea. In 1993 he moved to Yonsei University as an Associate Professor, and then, in 1995 he was promoted to full Professor. He is also one of the directors of the National Research Laboratory of Korea. His current research interests include the design and synthetic applications of transition metal-catalyzed chelation-assisted C–H and C–C bond activation and recyclable catalysts.

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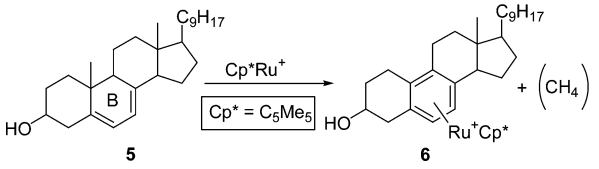
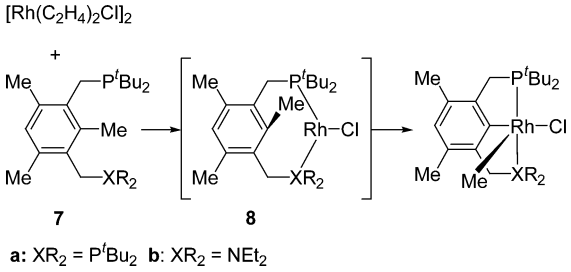
rearrangement of **3** occurred, leading to a thermodynamically more stable C–C bond cleaved 4-membered ring metallacyclic complex **4**.

However, for the reaction of unstrained molecules, special driving forces for C–C bond activation are required to generate stable metal complexes, which is a strategy for lowering the energy state of the C–C bond cleaved complexes. For example, Chaudret *et al.* applied the aromatic stabilization strategy, previously developed by Crabtree *et al.*[10] to eliminate the methyl group in a series of steroid compounds (Scheme 3).[11] Through C–C bond activation by Cp^*Ru^+, the B-ring of ergosterol **5** is aromatized to give **6** with the evolution of CH_4.



Scheme 3

In addition, the cyclometallation strategy of employing chelating compounds is another way towards the C–C bond activation of unstrained organic molecules. It is known that a 5-membered ring metallacyclic complex has a special stability in many organometallic complexes.[12] Milstein has devised a series of pincer-type chelating ligands **7** to cleave a strong aryl-C–C bond.[3] Reactions between many different pincer-type model compounds and various transition metal complexes have shown C–C bond activation under very mild conditions.[3,6] The C–C bond activation of **7** by Rh(I) is thermodynamically and kinetically preferred over the competing C–H bond activation (Scheme 4). With **7b** the intermediate complex **8b** was directly observed confirming a single step C–C bond activation.[13]



Scheme 4

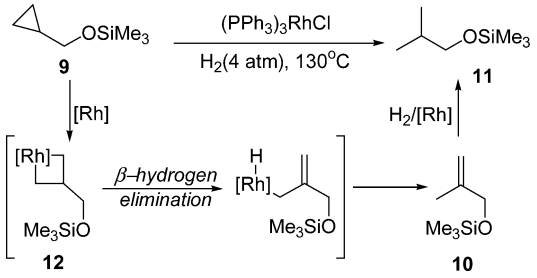
Despite significant developments in C–C bond activation, most of these reactions belong to the stoichiometric reactions as described above. Only a few catalytic reactions have been reported and suitable substrates are strictly limited. The high stability of the intermediate organometallic species might be responsible for the difficulty in converting the stoichiometric reaction to a catalytic one. Therefore, in order to be a catalytic reaction, an energy releasing step such as hydrogenolysis is required at the C–C bond cleaved metal complexes, producing stable organic compounds. Generally speaking, to make an overall catalytic reaction thermodynamically feasible, the final organic products should be more stable than the starting substrates. In this review, the basic principle and mechanism of the transition metal catalyzed C–C bond cleavage reactions in solution will be discussed. Alkene and alkyne metatheses are beyond the scope of this review in spite of their abundant applications and impact on organic synthesis.

2 C–C Bond activation of strained molecules

2.1 Direct cleavage of the C–C bond by transition metal catalysts

There are many more reports about catalytic C–C bond activation of ring-strained molecules compared to those on unstrained molecules. Most of these examples were demonstrated by relieving the ring-strain energy of the 3- or 4-membered ring to make the more stable 4- or 5-membered metallacyclic intermediates through the direct insertion of a metal into the C–C bond of cyclopropyl or cyclobutyl skeletons. Throughout the catalytic reaction, ring-opened or 5- to 6-membered ring organic compounds are produced.

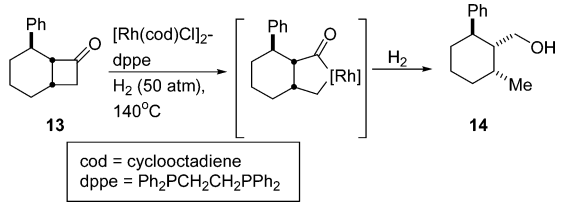
Recently, Bart and Chirik reported a selective carbon–carbon bond activation of a cyclopropane derivative **9** using Rh(I) as a catalyst. (Scheme 5).[14] The reaction proceeds with or



Scheme 5

without H_2 to produce **10** or **11**. Initially, a non-sterically hindered C–C bond in **9** is cleaved by $(PPh_3)_3RhCl$ to generate the rhodacyclobutane complex **12**, and β-hydrogen elimination followed by reductive elimination gives a branched alkene derivative **10**.

Cyclobutanone **13** is another good substrate for a similar type of C–C bond activation, developed by Murakami *et al.*[15] The reaction proceeded regioselectively and stereoselectively to give ring-opened alcohol **14** through the oxidative addition of Rh(I) into cyclobutanone derivatives and successive hydrogenolysis under the high pressure of H_2 (Scheme 6).

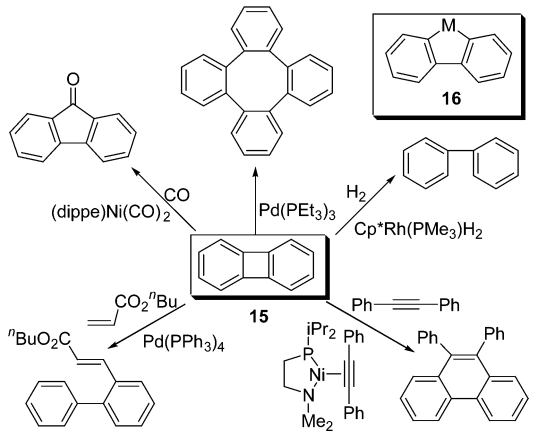


Scheme 6

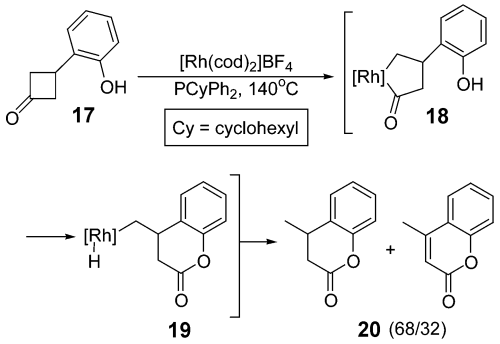
A variety of late transition metal complexes have been found to cleave the C–C bond of biphenylene **15** giving insertion complexes **16** to relieve ring-strain energy.[16] These metal complexes participate in various insertion reactions with small unsaturated molecules, such as CO, olefin, and alkyne, to give functionalized products (Scheme 7). All these products are more stable than biphenylene itself through conjugation, aromatization, ring-expansion, *etc.*

The following two examples are synthetic applications of the ring-cleavage of cyclobutanone derivatives, **17** and **21**, bearing *o*-phenol and the *o*-styryl groups (Scheme 8 and Scheme 9).

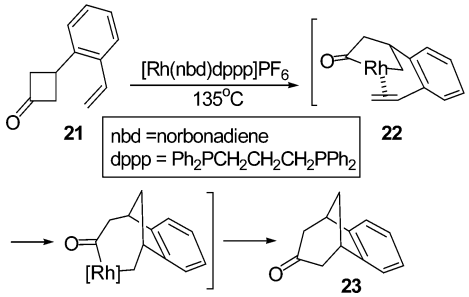
Initially-formed 5-membered acylrhodium intermediates, **18** and **22**, react with the phenolic hydroxyl group and the vinyl of the styryl group to give a six-membered ring lactone **19**[17] and the bicyclo[3.2.1]octanone derivative **23**,[18] respectively. Direct reductive elimination of **19**, or β-hydride elimination followed



Scheme 7



Scheme 8



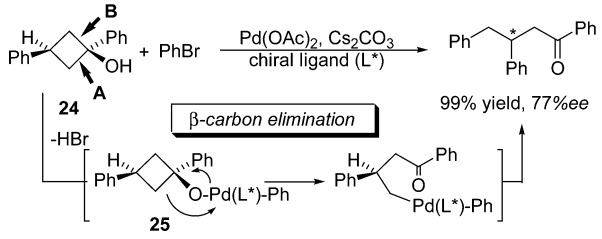
Scheme 9

by isomerization, gives lactones **20**. In the reaction of cyclobutanone bearing an *o*-styryl group with the rhodium complex, the resulting acylrhodium intermediate **22** undergoes an intramolecular olefin insertion into the styryl group and reductive elimination to give **23**. This type of insertion reaction of olefin into the C–C single bond is very rare in organometallic reactions.

2.2 β-Alkyl elimination of a strained molecule

When a strained molecule is bonded to a metal through a carbon, nitrogen, or oxygen atom, β-alkyl elimination commonly occurs to give ring-opened alkyl–metal intermediates. This is another way of relieving the ring-strain energy of a strained molecule.

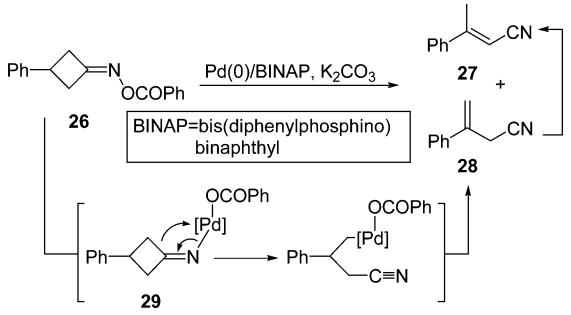
Uemura and co-workers reported that palladium-catalyzed arylation of *tert*-cyclobutanol **24** with an arylating reagent involving the enantioselective C–C bond cleavage afforded an optically active γ-arylated ketone in excellent yields with high enantioselectivity (Scheme 10).[19] In this reaction, the key step is the β-alkyl elimination of Pd(II) alcoholate **25** formed *in situ*. The chiral bidentate ligand plays an important role in



Scheme 10

controlling the direction of the enantioselective C–C bond cleavage, either A or B in **24**.

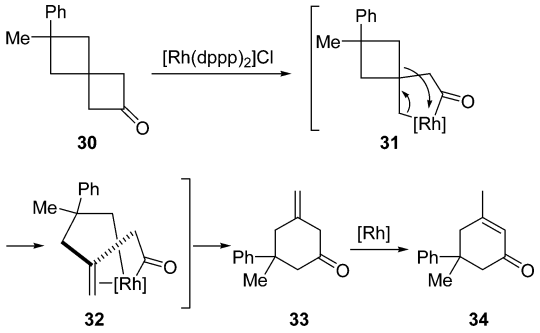
Another interesting example of β-alkyl elimination of a strained molecule is the transformation of cyclobutanone *O*-acyloxime **26** into nitriles (Scheme 11).[20] The cyclobutani-



Scheme 11

minopalladium(II) complexes **29**, which are generated from an oxidative addition of Pd(0) species to the N–O bond of *O*-acyloximes **26**, undergo β-alkyl elimination and successive β-hydrogen elimination to give nitriles, **27** and **28**.

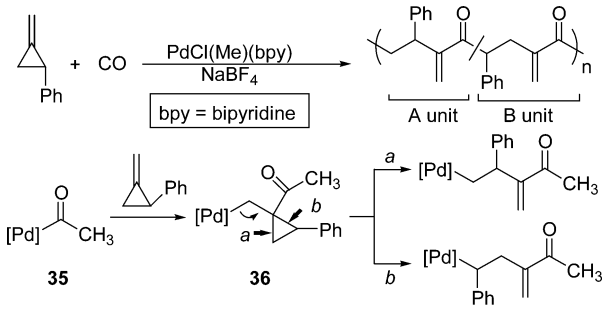
Spirocyclobutanone **30** is a very interesting molecule since the double C–C bond activations take place through an initial oxidative addition followed by β-alkyl elimination (Scheme 12).[21] Initially, a 5-membered ring acylrhodium(III)



Scheme 12

complex **31** is formed through the C–C bond cleavage of cyclobutanone **30**. Subsequent β-alkyl elimination of another cyclobutyl group in **31** and reductive elimination of **32** lead to a stable cyclohexenone derivative **34** after isomerization of the resulting β,γ-unsaturated methylenecyclohexanone **33**.

Recently, Osakada *et al.* reported that the transition metal catalyzed ring-opening of methylenecyclopropane could be applied to the polymerization reaction (Scheme 13).[22] In this reaction polyketone can be obtained by ring-opening copolymerization of methylenecyclopropane associated with CO under the palladium catalyst. *In situ* generated palladium(II)-acetyl complex **35** is inserted into a methylenecyclopropane derivative to give a cyclopropylmethyl palladium complex **36** as an intermediate, which undergoes two different types of



Scheme 13

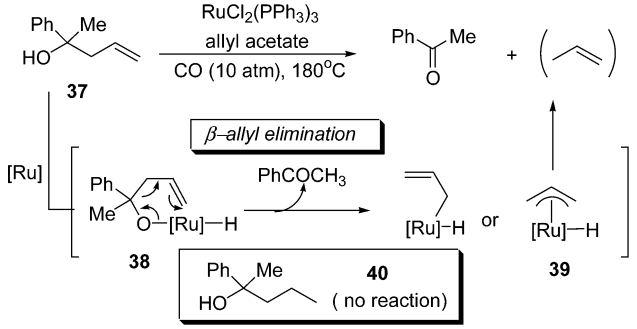
ring-openings, *a* and *b*, in the phenylcyclopropanyl group leading to A and B units, respectively. As a result, the reaction produces copolymers consisting of A and B units.

3 C–C Bond activation of unstrained molecules

3.1 β-Alkyl elimination of unstrained molecules

In the previous section, we have seen that β-alkyl elimination is a good way to relieve the ring-strain energies in the ring-strained molecules. However, even with unstrained molecules it is possible to cleave the C–C bond through β-alkyl elimination. Tertiary alcohols are one of the successful substrates for this selective C–C bond cleavage.

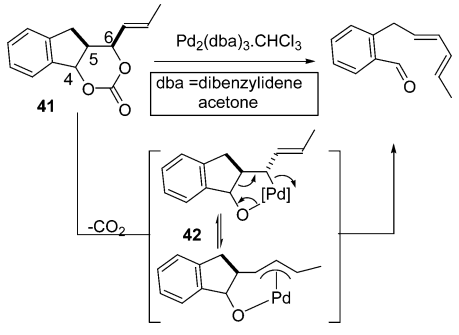
A ruthenium-catalyzed deallylation of unstrained homoallylic alcohol **37**, developed by Mitsudo *et al.*, was achieved *via* the oxidative addition of a hydroxyl group and subsequent β-allyl elimination of **38** to afford acetophenone and propene (Scheme 14).[23] The driving force of this reaction might be the



Scheme 14

formation of a stable η^3-allyl ruthenium(II) species **39** as an intermediate, because the tertiary alcohol **40** bearing no homoallylic functionality did not give any C–C bond cleaved product.

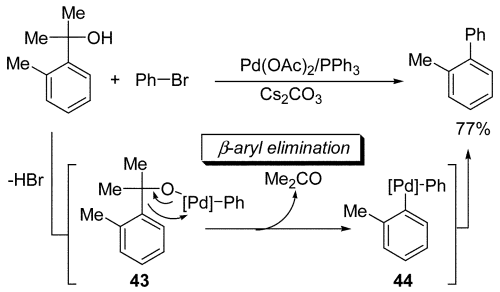
This type of π-allylic stabilization is also utilized in the palladium(0)-catalyzed C–C bond cleavage of 6-vinyl cyclic carbonate **41** to furnish ω-diene aldehyde (Scheme 15).[24] The



Scheme 15

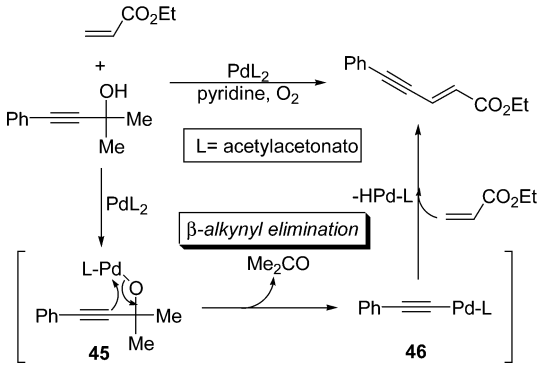
intermediate complex **42** is stabilized by π-allyl coordination to the metal catalyst. This reaction is believed to proceeds *via* a β-decarbopalladation, not *via* a β-alkyl elimination.

Miura and co-workers reported that the reaction of 2-methylphenyl-2-propanol with bromobenzene under the palladium catalyst produced 2-methylphenylbiphenyl (Scheme 16).[25] The β-aryl elimination of Pd(II) alcoholate **43** formed *in situ* is an important step in which a strong aryl sp^2-carbon–palladium bond in **44** is generated as an intermediate.



Scheme 16

One of the most interesting substrates among tertiary alcohols is tertiary propargylic alcohol because it reacts with ethyl acrylate to give enyne compounds under the palladium catalyst (Scheme 17).[26] During the reaction, a very strong

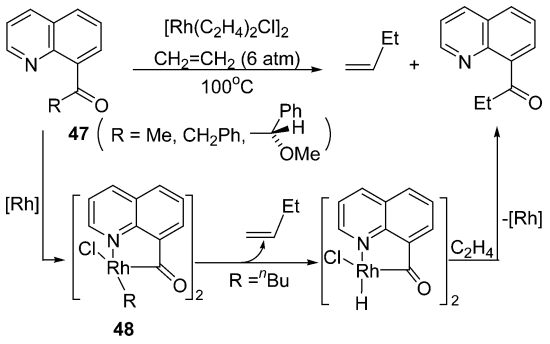


Scheme 17

alkynyl sp-carbon–palladium bond in **46** is also generated by β-alkynyl elimination of **45**. Therefore, tertiary propargylic alcohol can be used as a convenient source of acetylene.

3.2 C–C Bond activation by chelation assistance

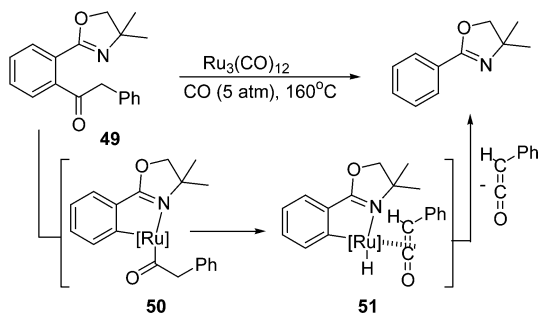
For the C–C bond activation of unstrained molecules, the cyclometallation strategy is one of the promising methods as described in the introductory section. One of the representative examples of this strategy is the activation of the α-C–C bond to the carbonyl group in 8-quinolinyl alkyl ketone **47**, developed by Suggs and Jun (Scheme 18).[27] The C–C bond activation by the Rh(I) proceeds with retention at the chiral carbon atom.[28] By employing **47**, the activation energy for C–C bond cleavage is lowered, since a stable 5-membered metallacyclic complex **48** is formed. If an alkyl group in **47** has β-hydrogens, this stoichiometric reaction can be further developed to the catalytic reaction by reacting with alkene. For example, when the reaction of 8-quinolinyl butyl ketone and ethylene gas was carried out under the Rh(I) catalyst, 8-quinolinyl ethyl ketone and 1-butene were obtained.[29] In this reaction, a β-hydrogen elimination occurs in the acylrhodium(III) butyl complex **48**, generated from the cleavage of the α-C–C bond, to give an acylrhodium(III) hydride and 1-butene. Further reaction



Scheme 18

of the acylrhodium(III) hydride with ethylene leads to 8-quinolinyl ethyl ketone as a final product.

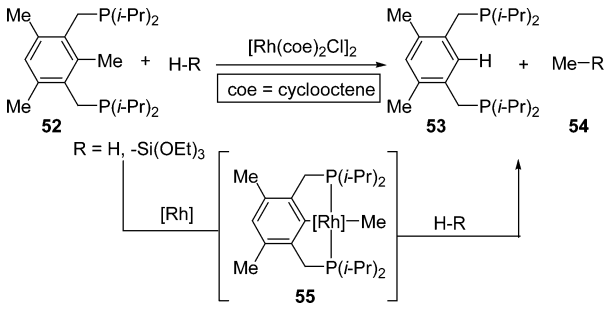
A similar type of decarbonylative C–C bond activation has been demonstrated by Murai *et al.* with ketone **49** bearing an oxazoline group as a directing group for a facile C–C bond activation (Scheme 19).[30] In this reaction, the removal of the



Scheme 19

acyl group in **50** might take place *via* β-hydrogen elimination and reductive elimination of the resulting ruthenium(II)hydride complex **51**.

It has already been demonstrated that a pincer-type ligand could be used for the C–C bond activation. This reaction could be further applied to the catalytic reaction associated with an energy releasing step such as hydrogenolysis. The reaction of $[\{Rh(coe)_2Cl\}_2]$ (coe = cyclooctene) with a P–C–P pincer-type ligand **52** under H_2 pressure or silane resulted in catalytic cleavage of the aryl C–C bond of **52** giving **53** and **54**, in spite of the high stability of the C–C bond cleaved metal complex **55** (Scheme 20).[31] When a similar type of catalytic reaction was performed with a P–C–N ligand instead of a P–C–P ligand **52**, an exclusive C–N bond activation was observed.[32]



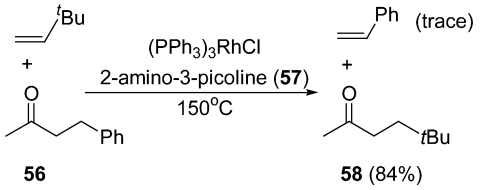
Scheme 20

As seen in the previous examples, all good substrates for C–C bond activation should satisfy geometrical requirements by making a 5-membered ring metallacyclic complex as an intermediate after C–C bond activation. This type of cyclometallation strategy can be further applied to the temporary chelation-assisted C–C bond activation of non-chelating compounds.

3.3 C–C Bond activation by temporary chelation assistance

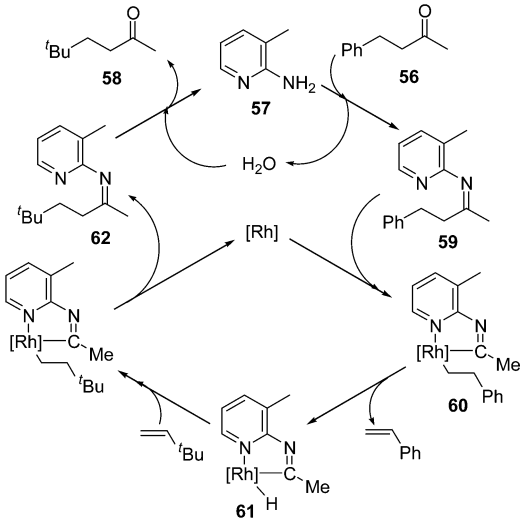
In this section, we will see the C–C bond activation of unstrained molecules bearing non-coordinating functionalities. C–C Bond activation of these molecules can be achieved through the temporary installation of an appropriate chelation auxiliary, which can be easily removed from the product by a simple manipulation such as hydrolysis.[33]

Recently, we reported a C–C bond activation of unstrained ketones utilizing a chelation-assisted protocol, developed in the course of studies on a chelation-assisted hydroacylation using 2-amino-3-picoline as a temporary chelating auxiliary.[34] Interestingly, benzylacetone (**56**) reacted with excess olefin, *tert*-butylethylene, under cocatalysts of Wilkinson's complex and 2-amino-3-picoline (**57**) to give an alkyl group-exchanged ketone **58** and a trace of styrene (Scheme 21).[35]



Scheme 21

The first step might be the formation of ketimine **59** by the condensation of ketone **56** and 2-amino-3-picoline (**57**) (Scheme 22). Then, the C–C bond of ketimine **59** is cleaved

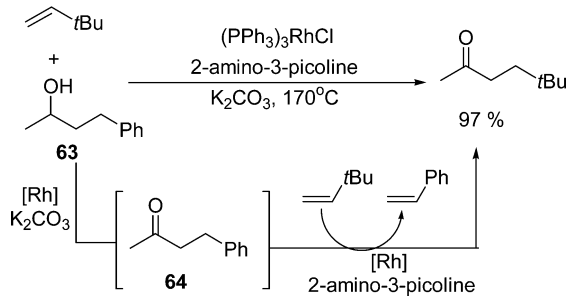


Scheme 22

by the Rh(I) complex to generate an (iminoacyl)rhodium(III) phenethyl **60**, which undergoes β-hydrogen elimination giving an (iminoacyl)rhodium(III) hydride **61** and styrene. At high temperature, styrene is polymerized. The hydrometallation of **61** into *tert*-butylethylene and the subsequent reductive elimination afford ketimine **62**. Hydrolysis of ketimine **62** by H_2O formed during the initial condensation step leads to the formation of ketone **58** with regeneration of **57**. A driving force for this catalytic reaction seems to be the formation of a stable 5-membered ring metallacyclic complex **60**, which undergoes further energy release by β-hydrogen elimination and subsequent hydride insertion of **61** into 1-alkene. Since the reaction is

a thermodynamic equilibrium, the polymerization of styrene, one of the products, might drive a forward reaction.

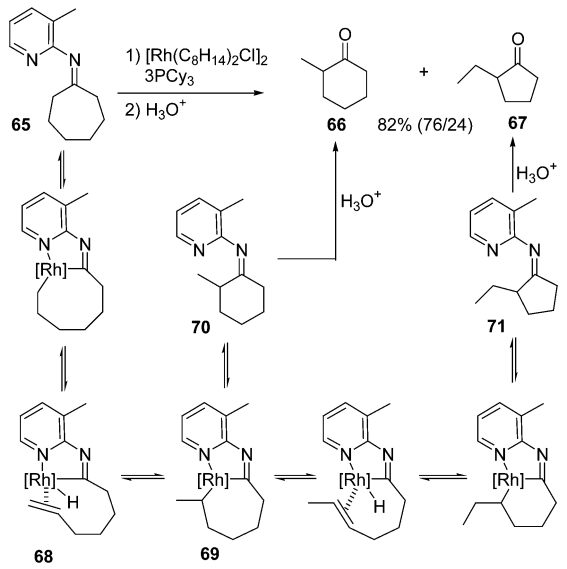
The chelation-assisted strategy was also applied to the C–C bond activation of *sec*-alcohol **63** under a similar catalytic system (Scheme 23).[36] The reaction consists of two consecutive



Scheme 23

reactions, a hydrogen transfer reaction of *sec*-alcohol and a chelation-assisted C–C bond activation of the resulting ketone **64**. Additional K_2CO_3 accelerates the reaction rate, and is supposed to be a cocatalyst for the transfer hydrogenation.

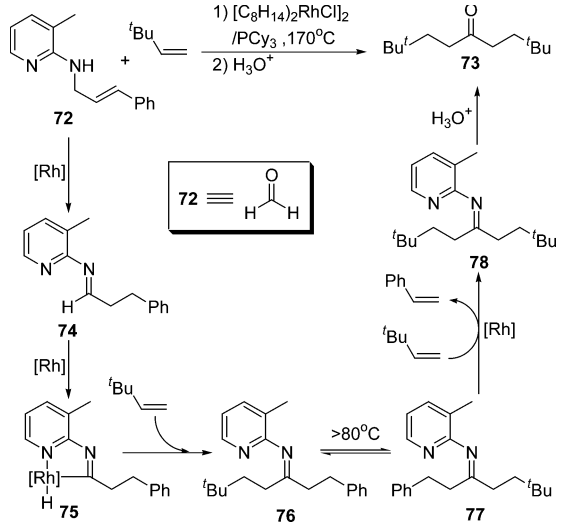
One interesting example of the chelation-assisted C–C bond activation is the skeletal rearrangement of cyclic ketone or its imine form **65**.[37] When cycloheptanoketimine **65** was treated with the Rh(I) complex in the absence of external olefin, a mixture of the ring-contracted cycloalkanones, **66** and **67**, was obtained after hydrolysis (Scheme 24). The C–C bond cleavage



Scheme 24

of ketimine **65** by the Rh(I) complex followed by β-hydrogen elimination leads to an (iminoacyl)rhodium(III) hydride **68**. The intramolecular hydride insertion in **68** gives an (iminoacyl)-rhodium(III) alkyl **69**, which is transformed into **70** through reductive elimination. Likewise, the ketimine **71** is also formed from **69**. Since all these intermediates are in thermodynamic equilibrium, a hydrometallation by Markovnikov's rule (*i.e.* **68** to **69**) is an unfavourable process. However, additional stabilities of 5- and 6-membered rings of ketimines (**70** and **71**) compared with that of the 7-membered ring of cycloheptanoketimine **65**, seem to drive a forward reaction.

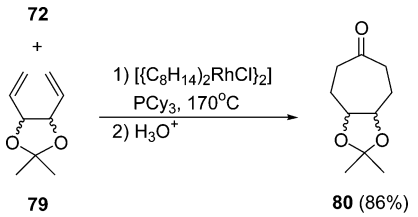
Allylamine **72** can be regarded as a masked form of formaldehyde since it undergoes C–C bond activation as well as C–H bond activation by the Rh(I) catalyst.[38] The reaction of an allylamine **72** and 1-alkene, *tert*-butylethylene, under the Rh(I) catalyst yielded symmetric dialkyl ketone **73** as a major product after hydrolysis of the resulting ketimine **78** (Scheme 25). The first step must be an isomerization of **72** to



Scheme 25

an aldimine **74**, followed by chelation-assisted C–H bond activation. A hydride insertion of the resulting (iminoacyl)-rhodium(III) hydride **75** into olefin and the subsequent reductive elimination of (iminoacyl)rhodium(III) alkyl lead to the formation of ketimine **76**. It is known that above 80 °C an imine like **76** undergoes *syn–anti* isomerization allowing the rhodium catalyst to cleave the C–C bond in **77**. The catalytic C–C bond activation of **77** in the reaction with *tert*-butylethylene results in symmetric dialkyl ketimine **78**.

A further application of allylamine **72** is a facile synthesis of cycloalkanone derivative **80** from diene **79** (Scheme 26).[39] With this synthetic strategy, from 5- to 7-membered ring cycloalkanones could be prepared from 1,3- to 1,5-dienes.



Scheme 26

4 C–C Bond cleavage of triple bond of alkyne

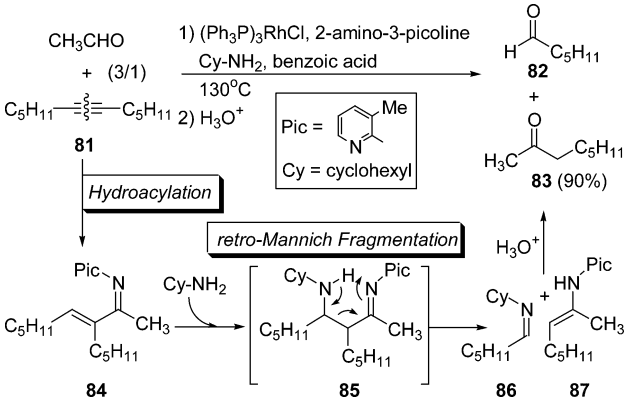
4.1 Retro-Mannich reaction

The triple C≡C bond of alkynes is known to be one of the strongest bonds in organic molecules. The strategy for the C≡C triple bond cleavage of alkynes is as follows. The C≡C triple bond of the alkyne is initially transformed into the CC double bond of an α,β-unsaturated imine through hydroacylation of the alkyne or hydroamination of the diyne. A subsequent retro-Mannich reaction of the α,β-unsaturated imine leads to the formation of the C–C bond cleavage products, aldimines and enamines.

Therefore, the C≡C triple bond cleavage protocol of alkynes needs a mixed catalyst system: a chelation-assisted hydroacylation catalyst and a retro-Mannich fragmentation catalyst. The chelation-assisted hydroacylation catalyst consists of $(Ph_3P)_3RhCl$ and 2-amino-3-picoline, while the retro-Mannich

type fragmentation catalyst is cyclohexylamine associated with benzoic acid, which can also be utilized in the cleavage of the CC double bond of α,β-unsaturated ketones.[40]

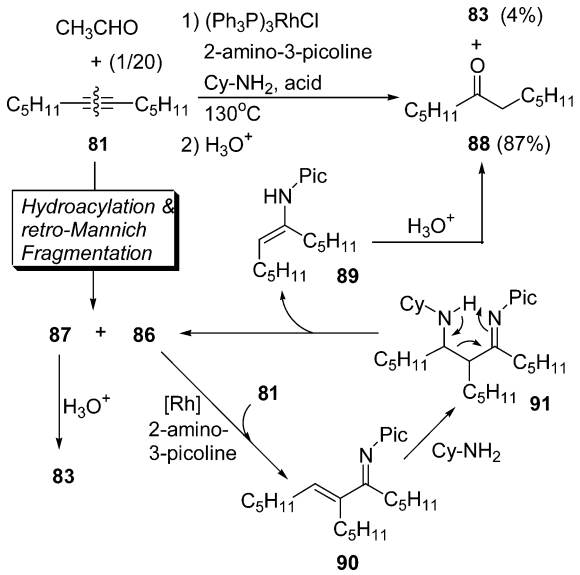
When a 3 : 1 mixture of acetaldehyde and 6-dodecyne (**81**) was heated at 130 °C for 12 h under $(Ph_3P)_3RhCl$, 2-amino-3-picoline, Cy–NH_2 (Cy = cyclohexyl) and benzoic acid, hexanal (**82**) and 2-octanone (**83**) were isolated in very high yields after hydrolysis (Scheme 27).[41] Chelation-assisted hydroacylation of



Scheme 27

alkyne **81** with acetaldehyde, similar to our earlier work,[42] affords α,β-unsaturated ketimine **84**, and 1,4-addition of Cy–NH_2 into the resulting **84** leads to β-aminoketimine **85**, which undergoes a retro-Mannich fragmentation giving a mixture of aldimine **86** and enamine **87**. Hydrolysis of these imines results in aldehyde **82** and ketone **83**. Instead of aldehyde, allylamine **72** could also be applied for the catalytic cleavage of the C≡C triple bond of alkynes.[43]

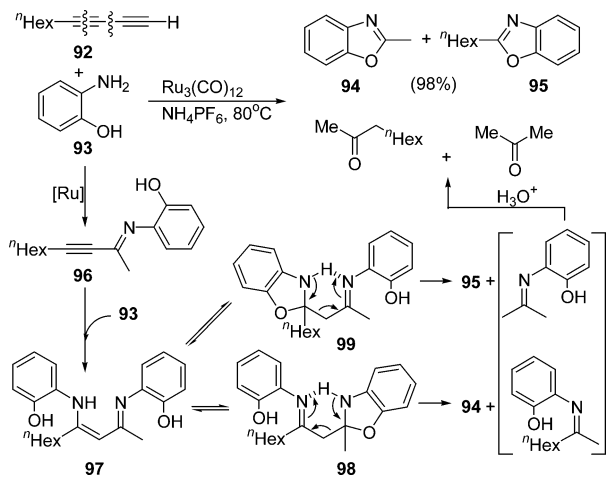
When the ratio of reactants was changed to 1 : 20, 6-dodecanone (**88**) was isolated as a major product (87%), along with a small amount (4%) of 2-octanone (**83**) (Scheme 28).[41]



Scheme 28

This result can be explained by the fact that enamine **87** and aldimine **86** are initially formed until acetaldehyde is completely consumed. Then, the aldimine **86** reacts with 6-dodecyne (**81**), leading to a mixture of enamine **89** and aldimine **86**, which re-enters the catalytic cycle. The catalytic cycle continues until no alkyne **81** is left. In this reaction, acetaldehyde is only used for the initial generation of aldimine **86**.

Retro-Mannich fragmentation is a very powerful method for cleaving α,β-unsaturated ketimine. Recently, Yamamoto reported that the C≡C triple bond cleavage of diyne **92** with *o*-aminophenol **93** could be catalyzed by the Ru or Pd catalyst giving the corresponding 2-substituted benzoxazoles, **94** and **95**, along with ketones after hydrolysis (Scheme 29).[44]



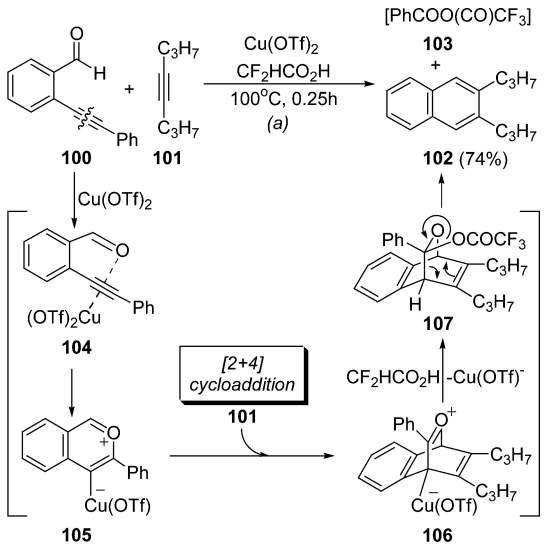
Scheme 29

Transition-metal catalyzed hydroamination[45] of *o*-aminophenol (**93**) into diyne **92** and subsequent tautomerization leads to α,β-unsaturated imine **96**. The conjugate addition of **93** to **96** provides the β-amino unsaturated imine **97**. The intramolecular cyclizations of the iminophenol groups in **97** give hemiaminals, **98** and **99**, of which the final retro-Mannich fragmentations produce the benzoxazoles, **94** and **95**, with the corresponding ketimines.

4.2 [4 + 2] Benzannulation

In the previous section we have seen that the triple C≡C bond of alkynes could be cleaved by consecutive reactions. Yamamoto demonstrated a different cleavage of the triple C≡C bond of the alkynyl group of *o*-alkynylbenzaldehyde through transition metal catalyzed [4 + 2] benzannulation.

When the reaction of *o*-(phenylethynyl)benzaldehyde (**100**) and 4-octyne (**101**) was carried out in the presence of a catalytic amount of $Cu(OTf)_2$ and a stoichiometric amount of a Brønsted acid such as CF_2HCO_2H at 100 °C, naphthalene **102** and anhydride **103** were obtained in high yield (Scheme 30).[46] Throughout the reaction the C≡C bond of the alkynyl group in *o*-alkynylbenzaldehyde is cleaved with an association of alkyne. The proposed mechanism is explained by the fact that the initial coordination of the triple bond to $Cu(OTf)_2$ as in **104** and the subsequent nucleophilic attack of the carbonyl oxygen on the alkynyl group would form the intermediate copper ate complex **105** (Scheme 30). The [4 + 2] cycloaddition of **105** with alkyne **101** generates the intermediate **106**. Then, the protonolysis of the Cu–C bond of **106** with CF_2HCO_2H, and the subsequent attack of $CF_2HCO_2^-$ generates the intermediate **107** and starting catalyst $Cu(OTf)_2$. The retro-Diels–Alder reaction of **107** leads to the formation of the naphthalene derivative **102** and the corresponding anhydride **103** as final products. It was also reported that when the reaction was performed in the presence of a catalytic amount of $AuCl_3$ instead of $Cu(OTf)_2$ without



Scheme 30

Brønsted acid, acylnaphthalene was obtained through the C=O bond cleavage in **100**.[47]

5 Conclusion

In this review, we have tried to explain the recent developments of C–C bond activation by a soluble transition metal catalyst. In spite of the inertness of the C–C bond in organic molecules there has been growing interest in catalytic C–C bond activation. In order to achieve catalytic C–C bond activation several requirements need to be fulfilled. In terms of the thermodynamic stabilities of the organic substrate, the product should be more stable than the starting organic molecules. The intermediate generated from the starting organic molecules and the transition metal catalyst should be moderately stabilized, for example, by generating stable 5-membered metallacyclic complexes, stable π-allyl transition metal complexes, or very strong metal–carbon bonds. The stabilization of intermediate complexes might lower the activation enthalpy in the reaction profile for transformation of the starting molecules to the intermediates. However, if the intermediates are too stable, it is hard to liberate organic molecules and regenerate the catalysts in the next or final step. Therefore, at the final step, to liberate organic molecules and regenerate the catalyst, it is desirable to produce organic molecules bearing very strong bonds such as a carbonyl or aromatic group. If starting molecules and products have similar stabilities, the reaction may not be completed due to the thermodynamic equilibrium. In this case, use of a large excess of one of the starting materials or an irreversible elimination of one of the final products, such as polymerization, might be helpful in forwarding the reaction.

In spite of the many limitations to achieving catalytic C–C bond activation, this area of research is on the threshold of opening up new strategies for organic synthesis.

Acknowledgements

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