Transition-Metal-Catalyzed Carbon–Carbon Bond Formation via Carbon–Hydrogen Bond Cleavage

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Abstract: Catalytic functionalization of unreactive C–H bond has become one of the most attractive research subjects in modern organic chemistry. To date, a variety of catalytic reactions involving C–H bond cleavage have been reported. In this review, we briefly survey the reported research with respect to efficient and selective transition-metal-catalyzed C–C bond formation via C–H bond cleavage.

1 Introduction

Transition-metal-catalyzed reactions are indispensable to modern organic synthesis because the unique reactivity of transition metals allows access to unconventional transformations with high selectivity and efficiency. To date, a large number of catalytic reactions have been developed. In general, these reactions are initiated by interaction of metals with reactive functional groups. For example, in most of the cross-coupling reactions, aryl halides, triflate, and diazonium salts are required to form carbon–metal bonds, important intermediates to introduce functional groups on the carbon atom due to their high reactivity. In these cases, however, several reaction steps are necessary to synthesize the substrates from readily available starting materials.

If C–H bonds can be used as a functional group, similar to these activated carbon bonds, it becomes one of the most valuable and straightforward methods for synthesis of complex molecules. Therefore, direct catalytic functionalization of C–H bonds has been a highly intriguing research subject for a long time. However, the bond dissociation energy of C–H bonds is usually large (105 kcal/mol for H–CH₃, and 110 kcal/mol for H–C₆H₅). In 1963, Kleiman and Dubek reported a stoichiometric reaction of a nickel complex where an ortho C–H bond of azobenzene was cleaved to form a five-membered chelate. Subsequently, Chatt and co-workers described the first observation of oxidative addition of an unactivated C–H bond using a ruthenium(0) complex (Scheme 1).

[Scheme 1]

After these pioneering works, a large number of studies of C–H bond cleavage using a stoichiometric amount of transition-metal complexes were reported and revealed the fundamental features of the C–H bond cleavage with low-valent transition-metal complexes. Almost all of these studies focused on direct observation of oxidative addition of C–H bonds to transition metals.

In 1969, Fujiwara and Moritani reported the first catalytic conversion of C–H bonds into C–C bonds using palladium and copper catalysts. In this case, C–H bonds are cleaved via an electrophilic substitution pathway. Rhodium-catalyzed C–H addition to diphenyl ketene, developed in 1978 by Hong, Yamazaki, Sonogashira, and Hagihara, should be considered the first catalytic C–H functionalization via oxidative addition. However, the reaction of monosubstituted arenes afforded a mixture of three possible regioisomers.

The first regioselective alkylation of C–H bonds with alkenes was reported by Lewis and Smith. A few examples of regioselective C–H functionalization with olefins were found within several years, but the scope of at least one of two substrates is apparently very limited and a large excess of those substrates was necessary.

In late 1993, Murai and co-workers reported a highly efficient, regioselective alkylation of C–H bonds in aromatic ketones with alkenes using RuH₂(CO)(PPh₃)₃ (1) as a catalyst. This reaction should be regarded as the first gener-
al method for catalytic regioselective C–H functionalization, because of the reasonably wide scope of both substrates, ketones and olefins, and the quantitative yields obtained even with 1:1 ratio of substrates for many examples. The authors proposed the ‘chelation-assistance’ with a heteroatom as a basic principle to attain high regioselectivity and efficiency.

In the wake of their findings, the chemistry of ‘chelation-assisted’ regioselective C–H functionalization by transition-metal catalysts has rapidly expanded. Since then, catalytic C–H functionalization has become one of the most attractive research subjects in organic and organometallic chemistry. To date, a variety of catalytic methods to functionalize C–H bonds have been developed and many review articles have been published.9

This review article broadly surveys the literature dealing with the catalytic C–C bond formation via cleavage of otherwise unreactive sp² and sp³ C–H bonds up to the year 2007. However, several areas, such as hydroacylation using aldehydes and related compounds, Michael- and aldol-type additions of active methylene compounds, reactions involving transition-metal-carbenoids, catalytic reactions via sp C–H bond cleavage, and reactions with heterogeneous catalysts, are not included because these catalytic reactions have already matured in modern organic synthesis. Furthermore, formation of bonds other than C–C bonds, such as C–B, C–Si, C–O, C–N, C–X (X = halogen) bonds, is not covered. In this review, only a limited number of C–C formation reactions – those involving unusual significance, originality, or complexity – are presented schematically.

2 Addition of C–H Bonds to C–C Multiple Bonds

Among the catalytic reactions involving C–H bond cleavage, C–H addition to C–C multiple bonds to provide the corresponding alkylation and alkenylation products can be regarded as the simplest atom-economical reactions.

2.1 Intermolecular Addition of Aromatic and Heteroaromatic C–H Bonds to Alkenes

Reaction of benzene, used as a solvent, with diphenylketene (2) in the presence of Rh₄(CO)₁₂ catalyst gives ketone 3 in good yield (Scheme 2).6 This is the first example of transition-metal-catalyzed reaction via oxidative addition of C–H bonds. Electron-deficient arenes, such as fluorobenzene, are more reactive in this reaction than electron-rich arenes like toluene.

![Scheme 2](image)

Regioselective C–H functionalization of phenol with ethylene using ruthenium phosphite complex 4 as a catalyst was developed in 1986 (Scheme 3).7 Coordination of the phosphorus atom in the triphenylphosphite is important for the C–H bond cleavage. It is essential to use potassium phenoxy, which induces exchange of the alkylated phenoxy moiety on the phosphite with phenol.

Biographical Sketches

**Fumitoshi Kakiuchi** was born in Hyogo, Japan, in 1965 and received his BSc in 1988 and PhD in 1993 from Osaka University under the guidance of Prof. Shinji Murai. He was appointed as Assistant Professor at Osaka University in 1993. He did his postdoctoral work with Professor E. N. Jacobsen at Harvard University in 1996–1997. In 2000, he was promoted to Associate Professor at Osaka University. In 2005, he moved to Keio University as Professor. His research interests include the development of new transition-metal-catalyzed reactions.

**Takuya Kochi** was born in Tokyo, Japan in 1975. He received his undergraduate and master’s degrees from the University of Tokyo, working with Professors Masanobu Hidai and Youichi Ishii, and his PhD in chemistry from the University of California at Berkeley, working with Professor Jonathan A. Ellman. After carrying out postdoctoral research with Professor Kyoko Nozaki at the University of Tokyo, he joined the group of Professor Fumitoshi Kakiuchi at Keio University as an Assistant Professor in 2007. His research interests include the development of new reactions and their application to the synthesis of a wide range of organic molecules.
In 1989, α-alkylation of α-picoline (5) with terminal alkenes using cationic zirconium catalyst 6 was reported. The use of H₂ is essential for regeneration of the catalytically active species (Scheme 4).

Scheme 4

At the end of 1993, Murai and co-workers reported the first general method for highly efficient and selective C–H functionalization, in which alkylation of aromatic ketones with alkenes is catalyzed by 1. In this reaction, coordination of a carbonyl oxygen to a ruthenium center is proposed to facilitate the approach of the ruthenium to an ortho C–H bond and to stabilize the ruthenacycle intermediate 8 (Scheme 5). Various combinations of aromatic or heteroaromatic ketones and terminal alkenes can be used and the reaction shows high functional group compatibility. Both electron-donating and electron-withdrawing groups such as –NMe₂, –OMe, –F, –NEtC(O)Me, –CF₃, –CO₂Et, –CN, acetals, and –OC(O)Me remain in the product. Steric hindrance of a substituent on the aromatic ring is critical in determining the regioselectivity of the C–C bond formation. The C–C bond is usually formed at the less congested ortho position (6-position) (Figure 1a), but interestingly, the reaction of m-methoxyacetophenone occurs at the more congested 2-position (Figure 1b). When an electron-withdrawing CF₃ group, which decreases the electron density of the adjacent atom, is introduced on the ether oxygen, alkylation takes place preferentially at the less congested position. These results suggest that heteroatoms may additionally affect the regioselectivity of the C–C bond formation.

Ruthenium phosphine complexes such as 1, Ru(CO)₂(PPh₃)₃, and RuH₂(PPh₃)₄ exhibit high activity for the alkylation of aromatic ketones. The major drawback of this reaction is that the applicable alkenes are limited to terminal alkenes and strained internal alkenes such as cyclopentene and norbornene.

Several related examples of transition-metal-catalyzed addition of C–H bonds in ketones to alkenes have been reported. Weber and co-workers reported that the RuH₂(CO)(PPh₃)₃-catalyzed copolymerization of aromatic ketones having two vacant ortho positions with 1,4-dienes provides high molecular weight polymers (Scheme 6). The fact that this step-growth polymerization gives higher molecular weight polymers implies that the C–H addition proceeds virtually quantitatively.

Scheme 6

The reaction of phenyl 3-pyridyl ketone (9) with 7 proceeds only at the pyridyl ring (Scheme 7). This indicates that the C–C bond formation takes place preferentially at the more electron-deficient aromatic ring.

Scheme 7

The alkylation of aromatic ketones having a terpene framework proceeds regioselectively. In this case, Ru(CO)₂(PPh₃)₃ functions better as a catalyst than 1.
Some other ruthenium complexes have been screened as a catalyst. Acetophenone undergoes ethylation with ethylene at room temperature when RuH₂(H₂)(PCy₃)₂ is used as a catalyst. In this case, turnover numbers of up to 19 can be achieved in 48 hours (Scheme 8). The catalyst activity is sensitive to the reaction temperature: high reaction temperature suppresses the reaction due to decomposition of the complex.

![Scheme 8](image-url)

A convenient protocol for in situ generation of low-valent ruthenium species by reaction of [RuCl₂(p-cymene)]₂ with sodium formate and triphenylphosphine was developed by Genêt and co-workers (Scheme 9). This system is applicable to the alkylation of aromatic and heteroaromatic ketones such as 10, conjugate enones, and aromatic imines.

![Scheme 9](image-url)

Several attempts have been made to understand the mechanism of the alkylation of aryl ketones catalyzed by 1. Studies of the relationship between the structures of the ketones and their activity toward the alkylation suggest that α,β-conjugate enone frameworks are important in both the C–H bond cleavage and the C–C bond formation steps. Morokuma, Koga and co-workers studied the reaction mechanism by density functional theory (DFT) calculations using benzaldehyde and ethylene as models of the aromatic ketone and alkene (Scheme 10). Based on their calculations, if the reaction passes through conventional three-centered transition state (path a), a much larger activation energy (20.1 kcal/mol) is required. On the other hand, if the C–H bond is cleaved through novel metallacycle intermediate 12 (path b), the reaction proceeds with extremely small activation energy (1.8–3.0 kcal/mol). The C–H bond cleavage proceeds via nucleophilic attack of ruthenium(0) onto the ortho carbon atom, followed by migration of hydrogen to the ruthenium center. The C–C bond is formed by nucleophilic attack of the alkyl group on the ruthenium to give intermediate 13.

Brookhart and Lenges found another important phenomenon for the chelation-assisted alkylation of C–H bonds. For the reaction of acetophenones with alkenes such as 14 using Cp*Rh(C₂H₃SiMe₃)₂ as a catalyst, they revealed that the C–H bond of the aromatic ring adds to the rhodium atom without pre-coordination of the ketone carbonyl group (Scheme 11). The regioselectivity of the products suggests that the coordination of the carbonyl group is essential in the C–C bond-formation step, but not in the C–H bond-cleavage step. This result clearly shows that reactivity of the products in the chelation-assisted alkylation does not always indicate the coordination of a heteroatom to the metal prior to the C–H bond cleavage.

![Scheme 11](image-url)

The catalytic activity of several ortho-ruthenated aryl ketone complexes such as 15–19 (Figure 2) has also been examined. While carbonyl complex 17, which appears to be an intermediate of the alkylation catalyzed by 1, is ineffective for this reaction, 15, which bears no CO ligand, and carbonyl complex 16 exhibit the catalytic activity. The relationship between the structures of the catalysts and their activity is still not clearly understood and remains to be explored.

Some aromatic esters can also be alkylated, but the substituents on the aromatic ring strongly affect the reactivity. The reaction of methyl benzoate with 7 using 1 as a catalyst does not give alkylation product 20; however, introduction of an electron-withdrawing group such as –CF₃, –CN, and –CO₂Et leads to the formation of the ortho alkylation products 21–23 in good yields (Figure 3).

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position was selectively alkylated with 7 at the other ortho position.\textsuperscript{23} Ethylation of 24, where the electron-donating nitrogen reduces the electrophilicity of the carbonyl, proceeds in quantitative yield (Scheme 12).

![Scheme 12](image)

In the reaction of aromatic imines, Ru\(_3\)(CO)\(_{12}\), ineffective for the alkylation of aromatic ketones, serves as a good catalyst (Scheme 13).\textsuperscript{26} The product selectivity differs between aromatic aldimes and ketimines. The reaction using aldimine 25a usually provided a mixture of 26a and 27a. On the other hand, the reaction using ketimine 25b gave alkylation product 26a exclusively.

![Scheme 13](image)

Lim and co-workers reported a similar alkylation of aromatic imines with alkenes using a [RhCl(coe)\(_2\)]\(_2\)/PCy\(_3\) catalyst system.\textsuperscript{27} Subsequently, Jun reported the RhCl(PPh\(_3\))\(_3\)-catalyzed coupling of aromatic imines with alkenes.\textsuperscript{28} Both aromatic aldimes and ketimines reacted smoothly with the alkenes to give the corresponding alkylation products. Aromatic hydrazones derived from aromatic ketones can also be used in the catalytic alkylation of C–H bonds.\textsuperscript{29} The directing groups affect the regioselectivity of the C–C bond formation and the product selectivity of the coupling reaction.

Jun and co-workers developed a catalyst recycling system for the rhodium-catalyzed alkylation of aromatic ketimines with alkenes. Use of self-assembly consisting of decylbarbiturate-substituted triarylporphine and 5-ethyl-2,4,6-triaminopyrimidine was found to be effective for catalyst recovery after the reaction. No significant decrease in yield was observed after eight runs.\textsuperscript{28c}

Pyridine rings also function as directing groups via coordination of the sp\(^2\) nitrogen.\textsuperscript{30} Alkylation of 28 is catalyzed by rhodium catalysts (Scheme 14). Introduction of a methyl group at the 3-position of the pyridine ring suppresses incorporation of the second alkene into the other

From deuterium-labeling experiments using methyl benzozate-d\(_{2}\) and 7 and \(^{13}\)C kinetic isotope effect using methyl 2-toluene and 14, it was revealed that there is a rapid equilibrium among the intermediates prior to the rate-determining C–C bond formation.\textsuperscript{21b} These experimental results are consistent with theoretical calculations.\textsuperscript{17} In general, reductive elimination to form an aryl–carbon bond is accelerated by introduction of an electron-releasing group on the aromatic moiety. Interestingly, however, in this case, the C–C bond formation is facilitated by an electron-withdrawing group. It is proposed that the electron-withdrawing groups assist the nucleophilic attack of the ruthenium(0) species to the carbonyl carbon; 1) introduction of a heteroatom in an appropriate position on the aromatic ring would also suppress the nucleophilic attack by electron donation to the carbonyl. Indeed, benzaldehyde with a bulky trimethylsilyl group at one ortho.

For the alkylation of aromatic amides, CpIr(R)-biphemp complex \([\text{biphemp} = 2,2’\text{-bis}(\text{diphenylphosphino})-6,6’\text{-dimethyl-}1,1’\text{-biphenyl}]\) functions as a catalyst.\textsuperscript{22} The reaction of benzamide with norbornene gives the optically active alkylation product in 35% yield with 85% ee.

The use of a formyl group as a directing group is challenging because aldehydes are prone to undergo decarbonylation\textsuperscript{23} or hydroacylation of the alkenes.\textsuperscript{24} To achieve these reactions, the following two hypotheses to suppress the decarbonylation were investigated, one being steric and the other electronic in nature: 1) increased sterics around the formyl group would retard the nucleophilic attack of the ruthenium(0) species to the carbonyl carbon; 2) introduction of a heteroatom in an appropriate position on the aromatic ring would also suppress the nucleophilic attack by electron donation to the carbonyl. Indeed, benzaldehyde with a bulky trimethylsilyl group at one ortho.

![Figure 2](image)

![Figure 3](image)
ortho C–H bond. Cone angles of the phosphine ligands have a large influence on the reactivity.30b

The pyridyl-group-directed alkylations were extended to an atropselective reaction (Scheme 15).31 The coupling of 29 with ethylene using \([\text{RhCl}(\text{coe})_2]/(R),(S)-\text{PPFOMe}\) catalyst \([(R),(S)-\text{PPFOMe} = (R)-1-((S)-2\text{-diphenylphosphino})\text{ferrocenyl})\text{ethyl methyl ether}]\) gives optically active product 30 in 37% yield with 49% ee.

Scheme 15

In the reactions of arylimidates, ring size of the N,O-heterocycles affects the product selectivity.32 The reaction of aryloxazine 31 provides alkylation product 32 selectively (Scheme 16). In contrast, the reaction of the aryloxazolines (five-membered ring) mainly affords the dehydrogenative alkenylation product.

Scheme 16

In addition to the chelation assistance by the heteroatoms, coordination of \(\pi\)-electrons in the nitrile group is also applicable to the regioselective alkylation of C–H bonds.33 The participation of the nitrile \(\pi\)-bond is somewhat disputable, but the regioselectivity suggests the possible side-on coordination of the nitrile group, to the ruthenium in the catalytic cycle (Scheme 17).

The addition of C–H bonds adjacent to \text{sp}^2 nitrogen in heterocycles to alkenes proceeds with the aid of a rhodium catalyst. Bergman and Ellman developed an efficient alkylation of imidazoles and benzimidazoles with alkenes using \([\text{RhCl}(\text{coe})_2]/\text{PCy}_3\) catalyst.34 In the case of intermolecular couplings of heteroaromatic compounds with alkenes, the addition of Lewis or Brønsted acids such as magnesium bromide, lutidinium chloride, and tricyclonexyphosphine hydrochloride dramatically increased the rate and the yield of the product (Scheme 18). This reaction can also be applied to other aromatic and non-aromatic heterocycles such as thiazoles, benzoazolone, oxazolines, and 3,4-dihydroquinazolines.

Scheme 17

The detailed reaction mechanism of the C–H bond-cleavage step governing the rhodium(I)-catalyzed coupling reactions of N-heterocycles was examined. In addition to experimental studies including stoichiometric reactions of \([\text{RhCl}(\text{coe})_2]/\text{PCy}_3\) catalyst with heterocycle substrates and with isotope-labeled 3,4-dihydroquinazoline derivatives, DFT calculations were performed.34a,c,f The most important mechanistic aspect of this coupling is that rhodium-mediated 1,2-hydride shift to form N-heterocyclic carbene intermediate 33 is responsible for the C–H bond cleavage (Scheme 19).

Periana and co-workers developed a new entry for alkylation of arenes with alkenes using an iridium(III) catalyst.35 The authors proposed that the C–H bond cleavage takes place via a \(\sigma\)-bond metathesis-like transition state. An iridium hydride species does not participate in the catalytic cycle (Scheme 20).35 Gunnoe and co-workers also reported a similar alkylation reaction of arenes with alkenes using \(\text{TpRu(CO)}(\text{NCMe})(\text{Ph})\) \([\text{Tp} = \text{hydridotris(pyrazolyl)}\text{borate}]\) as a catalyst.36
2.2 Intermolecular Addition of sp² C–H Bonds Other than Aromatic C–H Bonds to Alkenes

Olefinic C–H bonds can be regioselectively alkylated with alkene via chelation assistance. Trost and co-workers reported the RuH₂(CO)(PPh₃)₃-catalyzed reaction of conjugate esters with alkenes (Scheme 21). Both cyclic and acyclic conjugated esters such as 36 can be applied to the coupling reaction. This coupling reaction tolerates various functional groups on the ester moiety.

Murai and co-workers reported the addition of C–H bonds in α,β-enones to alkenes using I as a catalyst. In this reaction, 1-acylcyclohexene and related compounds show high reactivity. The authors proposed that at least three possible reaction pathways are present for acyclic enones and the structure of the substrates dramatically affects the reaction pathway (Scheme 22).

The reaction of β-phenyl enone 37a with styrene selectively gives the coupling product with retained stereochemistry (38a) (run 1 in Scheme 23, via path a). On the other hand, in the reaction of β-methyl enone 37b, the regiosomeric product with inverted stereochemistry (39b) is formed (run 2 in Scheme 23, via path b or c). From these results, products 38a and 39b are considered to be formed via different pathways.

2.3 Intermolecular Addition of sp³ C–H Bonds to Alkenes

Catalytic C–C bond formation via sp³ C–H bond cleavage is one of the ultimate goals in organic synthesis. Among the reactions in this area, a relatively viable catalysis involves the use of sp³ C–H bonds adjacent to a nitrogen or an oxygen atom.

Double insertion of ethylene into aniline with the aid of a rhodium(III) catalyst gives cyclization product 42 (Scheme 25). A similar cyclization of anilines with styrenes using [Rh(cod)₂]BF₄ catalyst was also reported. Use of tertiary amines for transition-metal-catalyzed annulation with anilines is another strategy for the catalytic functionalization of sp³ C–H bonds. While several intermolecular coupling reactions affording quinoline derivatives were developed, an intramolecular version of this quinoline synthesis using α-allylanilines and Co₂(CO)₈ catalyst was also demonstrated by Jones.

Scheme 20

Scheme 21

Scheme 22

Scheme 23

Scheme 24

Scheme 25
The addition of an sp³ C–H bond adjacent to a nitrogen atom in dimethylamine to pent-1-ene was catalyzed by W(NMe₂)₆ to give N-methyl-N-(2-methylpentyl)amine.⁴⁴ Jun and co-workers succeeded in the Ru₃(CO)₁₂-catalyzed alkylation of a benzylic C–H bond to a nitrogen atom in \(43\) to afford \(44\) in good yield (Scheme 26).⁴⁵

Murai and co-workers developed a pyridyl-group-directed alkylation of sp³ C–H bonds in N-2-pyridyldialkylamines such as \(45\) using Ru₃(CO)₁₂ as a catalyst (Scheme 27).⁴⁶ Use of propan-2-ol as a solvent dramatically improved the efficiency.

### 2.4 Intramolecular Addition of C–H Bonds to Alkenes

Intramolecular variants of the chelation-assisted addition of C–H bonds in alkenes to other alkenes enable the one-step synthesis of carbo cyclic compounds. Imidazolyl and pyridyl groups have served as effective directing groups for this carbo cyclization.⁴⁷ The asymmetric cyclization of \(46\) giving five-membered carbocycle \(47\) is catalyzed by a rhodium complex with a monodentate chiral ferrocenyl phosphine (Scheme 28).⁴⁷b In the reaction of imidazolyl diene, the product was obtained in 75% yield with 82% ee at 50 °C.

Bergman and Ellman have reported several types of intramolecular cyclizations.⁴⁸ Reactions of N-alkenylbenzimidazoles such as \(48\) via N-heterocyclic carbene intermediates using [RhCl(coe)₂]₂/PCy₃ afford carbocycle products (Scheme 29).⁴⁸a,b,c,d Asymmetric intramolecular cyclization of aromatic imines bearing an alkene moiety at the meta position, such as in \(49\), was also developed using [RhCl(cod)]₂ with a chiral phosphoramidite ligand (Scheme 30).⁴⁸b,c This cyclization proceeds with quite high enantioselectivity. In addition, intramolecular alkylation of C–H bonds has been used in the synthesis of bioactive compounds such as vasicoline³⁴e and c-jun N-terminal kinase inhibitors.⁴⁸d Their approach provides a new synthetic protocol in the synthesis of bioactive compounds.

### 2.5 Addition of C–H Bonds to C–C Triple Bonds

Catalytic addition of sp² C–H bonds in arenes and alkenes to alkynes affords the corresponding styrenes and conjugate dienes, respectively. This method is one of the simplest protocols for the synthesis of the alkenylation products with 100% atom efficiency. To date, three types of alkenylation reactions with alkynes have been developed.⁵⁰–⁶³ One involves the oxidative addition of C–H bonds to transition-metal complexes.⁵⁰–⁶¹ In another, the C–H bond cleavage takes place via electrophilic substitution with metal complexes.⁵² In the third case, the C–H
bond cleavage proceeds via electrophilic substitution with alkenyl cation-like species which is generated by coordination of a C–C triple bond to a metal ion. In this section, this third type of reaction is not dealt with because the metal complex does not participate in the C–H bond cleavage step.

In 1979, Hong and co-workers reported a pioneering work on the alkenylation of C–H bonds in arenes and heteroarenes with alkynes. Rh₄(CO)₁₂-catalyzed alkenylation of arenes with diphenylacetylene gave alkenylation product 51. Interestingly, the reactions of anisole and fluorene with alkynes gave the ortho alkenylation products as a major product (Scheme 32). The relative reactivity of aromatic and heteroaromatic compounds was estimated based on the yields of the coupling products as follows: furan > thiophene > N-methylpyrrole > benzene.

Scheme 32

Regioselective alkenylation of C–H bonds with alkynes by means of chelation assistance was developed by Kisch and co-workers. RhCl(PPh₃)₃-catalyzed reaction of azobenzene (52) with diphenylacetylene gives 53 in good yield (Scheme 33). Electron-withdrawing groups on the acetylene retard this coupling reaction.

Scheme 33

In the reaction of aromatic ketones with 54 catalyzed by 1, perfect regio- and stereoselectivity is observed (Scheme 34). The fact that the E-isomer, such as 55, is obtained as the sole product indicates that C–H addition to the C–C triple bond proceeds with syn selectivity. The coupling of α,β-unsaturated ketones and esters with alkynes provides highly substituted and conjugated carbonyl compounds. Terminal alkynes cannot be used due to facile dimerization of the alkynes under the reaction conditions.

Scheme 34

The alkenylation of diterpenoid analogues also proceeds regio- and stereoselectively under similar reaction conditions. The alkenylations catalyzed by 1 have been applied extensively to step-growth copolymerization of aromatic ketones with alkynes, providing cross-conjugated polymers with copoly(arylene/1,2-vinylene) backbones.

The phenolic hydroxy group can also function as a directing group for the alkenylation of C–H bonds in naphthols. Reaction of 56 with oct-4-yne using [IrCl(cod)]₂/P(t-Bu)₃ catalyst gives 57 in 84% yield (Scheme 35). The nature of the phosphine ligand strongly affects the product yields; tri(tert-butyl)phosphine is suitable, while triphenylphosphine gives only 2% yield of the product.

Scheme 35

Addition of ortho C–H bonds in aromatic imines such as 58 to terminal alkynes catalyzed by RhCl(PPh₃)₃ affords (E)-styrene derivatives (Scheme 36). After hydrolysis of the products, ortho-alkenylated ketones can be obtained.

Scheme 36

Lim reported that reaction of 2-phenylpyridines with internal alkynes using RhCl(PPh₃)₃ as catalyst also gives ortho alkenylation products in high yields. Recently, a unique entry of alkenylation of aromatic aldines with internal alkynes using [ReBr(CO)₃(thf)]₂ as a catalyst to afford indene derivatives was developed (Scheme 37). The authors proposed that the Re–C bond in intermediate 59 can add to a C = N bond because of its high nucleophilicity. Internal alkynes bearing at least one aryl group are essential to accomplishing this reaction. The [Cp*RhCl₂]₂/Cu(OAc)₂-catalyzed oxidative coupling of benzoic acids with alkynes yields isocoumarin deriva-
tives such as 60 (Scheme 38). The choice of oxidant is an important factor for product selectivity. When Ag₂CO₃ is used as an oxidant in place of Cu(OAc)₂/O₂, 1,2,3,4-tetrasubstituted naphthalene derivatives, formed via decarboxylation and double insertion of alkynes, are obtained selectively.

Non-chelation-assisted alkenylation of C–H bonds in arenes with alkynes takes place in the presence of palladium amidate catalyst 61 (Scheme 39). The C–H bond cleavage is proposed to proceed via oxidative addition because electron-deficient arenes are more reactive than electron-rich heteroarenes and the C–H addition to C–C triple bonds occurs in a cis fashion. Both terminal and internal alkynes can be used for this reaction.

Reactions of indoles, benzimidazoles, and related compounds, including 62, with internal alkynes using Ni(cod)₂/PCyp₃ as a catalyst provides α-alkenylation products such as 63 in high yields (Scheme 40).

An sp³ C–H bond adjacent to an imino nitrogen is alkenylated with terminal alkynes (Scheme 41). C–C bond formation takes place at the internal carbon of the alkyne.

While catalytic addition of C–H bonds to alkynes is the simplest protocol for alkenylation, use of alkene and related compounds also provides efficient methods. Three types of this alkenylation reaction have been developed (Scheme 42). One is dehydrogenative C–H alkenylation with alkenes (method a). In this case, alkenes function not only as substrates, but also as hydrogen acceptors. Another example is oxidative alkenylation (method b), in which high-valent transition-metal complexes are regenerated by oxidants. In the third case, alkenylations are accomplished by reaction with functionalized alkenes such as alkynyl halides and acetates, and alkynylboronates (method c).

3 Alkenylation of C–H Bonds via Substitution Reactions

3.1 Alkenylation of C–H Bonds with Alkenes via Dehydrogenation

The first dehydrogenative alkenylation of aromatic C–H bonds with alkenes was reported using Rh₄(CO)₁₂ as a catalyst in 1979. Dehydrogenative alkenylation of sp³ C–H bonds adjacent to an oxygen in 64 with tert-butyl ethylene was also achieved using IrH₃[P(i-Pr)₃]₂ catalyst (Scheme 43). These early results were intriguing, but improvements in the yields and the selectivities were desired.
The Ru\(_3\)(CO)\(_{12}\)-catalyzed reaction of aryloxazoline 65 with styrene provides dehydrogenative alkenylation product 66, along with a nearly equimolecular amount of ethyl benzene, which shows that alkenes also function as scavengers of H\(_2\) (Scheme 44).\(^32\)

\[ \text{Scheme 44} \]

### 3.2 Alkenylation of C–H Bonds with Alkenes with the Aid of Oxidant

In 1969, the first oxidative alkenylation of arenes with alkenes was developed using palladium(II) acetate and copper(II) acetate as the catalyst system and molecular oxygen as a terminal oxidant (Scheme 45).\(^5\) Monosubstituted and 1,1-disubstituted aromatic alkenes, as well as electron-deficient alkenes such as acrylates and acroleins, showed high reactivity.\(^65\) A similar palladium-catalyzed oxidative alkenylation was attained using heteropolyoxometalate 67 and molecular oxygen (Scheme 46).\(^66\) Solvent-free direct oxidative alkenylation was also achieved under oxygen pressure.\(^67\) Use of a rhodium\(^{68a,b}\) or ruthenium catalyst\(^68c\) for the alkenylation has also been demonstrated by several researchers.

\[ \text{Scheme 45} \]

Mikami and co-workers reported an asymmetric coupling of benzene with cyclohexene carbonitrile in the presence of palladium(II) acetate, tert-butyl perbenzoate, and a chiral oxazoline ligand.\(^69\) Chemical and optical yields are moderate (25% yield, 44% ee), but it provides a prospective method for enantioselective construction of C–C bonds.

Regioselective alkenylation of 2-phenylphenols with alkyl acrylates gives 6H-dibenzo\([b,d]\)pyrans, formed by intramolecular Michael-type addition of the phenolic OH group to the C–C double bond of the alkenylation product.\(^70\) A similar oxidative coupling of a C–H bond in arenesulfonamides such as 68 and benzoic acid derivatives was also developed, using a palladium(II) acetate, copper(II) acetate and air catalyst system (Scheme 47).\(^71\)

\[ \text{Scheme 46} \]

For the reaction of anilide 69, the palladium(II) acetate and benzoquinone system led to alkenylation product 70 in high yield (Scheme 48).\(^72\) A palladium(II) chloride and copper(II) acetate system exhibited high activity for \(N,N\)-dimethylbenzylamines.\(^73\)

\[ \text{Scheme 47} \]

When indole is used for the palladium(II) acetate catalyzed oxidative alkenylation, regioselectivity of C–C bond formation is controlled by the solvent (Scheme 49).\(^74\) In an aprotic solvent such as DMF–DMSO, the alkenylation takes place at the \(\beta\)-position to give 71 because generation of the less polar intermediate 72 is favorable. On the other hand, in a protic solvent such as dioxane–acetic acid, \(\alpha\)-alkenylation product 73 is obtained because polar intermediate 74 is stabilized in this media.

\[ \text{Scheme 48} \]

\[ \text{Scheme 49} \]
3.3 Alkenylation of Aromatic C–H Bonds Using Other than Simple Alkenes

Oi and co-workers developed ruthenium-catalyzed regioselective alkenylation of arylpyridines (such as 75), arylimines, and arylxazolines with alkenyl bromides (Scheme 50). The authors propose the following two mechanisms for the initiation step: 1) oxidative addition of an alkenyl bromide to the ruthenium(II) species; and 2) electrophilic substitution with the ruthenium(II) species. In both cases, the reaction is proposed to proceed via a ruthenium(IV) intermediate.

Scheme 50

Anilides such as 76 can be alkenylated with haloalkenes bearing an electron-withdrawing group by a palladium(II) chloride and silver(I) triflate catalyst system. This reaction starts with formation of ortho-palladated intermediate 77 by electrophilic substitution with palladium(II) species. Carbopalladation of a haloalkene provides 78, and β-halide elimination takes place to release the product (Scheme 51).

Scheme 51

Alkenylation of arenes having an sp² nitrogen atom such as 79 with alkenyl acetates is catalyzed by Ru(cod)(cot) (Scheme 52). The C–C bond formation takes place between the ortho carbon and the vinylic carbon adjacent to the acetoxy group. In many cases, addition of base is not necessary to conduct this alkenylation.

Scheme 52

Reaction of aromatic ketones such as 80 with alkenylboronates provides ortho-alkenylationated compounds (Scheme 53). The C–C bond is formed between the ortho carbon and the alkenyl carbon next to the boron atom. The proposed mechanism is described in section 5.4.

Scheme 53

4 Carbonylation and Acylation of C–H Bonds Using Carbon Monoxide

There are two methods for direct carbonylation of C–H bonds using carbon monoxide (CO). One is insertion of CO into C–H bonds leading to aldehydes (carbonylation) and the other is three-component coupling of C–H bonds, CO, and alkenes leading to ketones (acylation). The former reaction should be carried out under photo-irradiation conditions because it is endothermic. On the other hand, acylation is an exothermic reaction.

4.1 Carbonylation at C–H Bonds under Photo-irradiation Conditions

Aldehydes are very important compounds because of their high reactivity and wide utility in the synthesis of complex organic compounds. If aldehydes can be obtained via direct carbonylation of the C–H bonds, it becomes a highly valuable protocol in organic synthesis.

In 1983, Eisenberg and co-workers reported the first example of the carbonylation of benzene using IrH3(CO)(dppe) complex (dppe = Ph2PCH2CH2PPh2) under photo-irradiation conditions. Although the efficiency of this carbonylation was low, their work opened a new opportunity for direct carbonylation at C–H bonds. Related photochemical carbonylation of benzene catalyzed by RhCl(CO)(PMe3)2 (81) led to an improvement in the yield. Lowering the catalyst concentration also increased the yields (Scheme 54). Aromatic compounds with an electron-donating substituent showed good reactivity, but electron-withdrawing groups (Cl and CN) retarded the reaction.

Scheme 54

Alkanes are also carbonylated under photo-irradiation conditions. The wavelengths of light used are important for the photoassisted carbonylation of decane. The selec-
tivity of the carbonylation product, \( \text{C}_{11} \) aldehydes, is altered by cutting off the short-wavelength region (\( \lambda < 325 \) nm) of the light, because of the complete suppression of Norrish type II reaction. In the case of photo-irradiation with light including the short-wavelength region (\( 295 < \lambda < 420 \) nm), the carbonylation occurs preferentially at the terminal carbon (86\% selectivity), whereas it takes place almost equally at the internal carbons (5\%, 4\%, 2\%, and 3\% selectivity).

Several research groups have reported the mechanism of the rhodium-catalyzed photochemical carbonylation of benzene. Sakakura and Tanaka proposed that the \( \text{Rh} \) complex 82 via dissociation of CO ligand. In 1994, Field and co-workers revealed the presence of CO ligand in the irradiated products by \( ^{13} \)C NMR using trans-RhCl\((\text{CO})(\text{PMe}_3)_2\). Goldman and co-workers reported that the primary photo process does not involve ligand loss and the C–H bond cleavage step proceeds predominantly via an associative process (Scheme 55). Ford and co-workers reported another possibility for the photo-induced oxidative addition of CO to give \( \text{Rh} \) by direct reaction of 81 in the excited state with benzene. The second is a stepwise process, involving CO photo-dissociation to give 82, followed by oxidative addition of benzene and CO addition to form 83. The two mechanisms are not mutually exclusive and both are operative if the reaction is performed under appropriate conditions.

Isocyanides are often used as the isoelectronic compound of CO. Ruthenium-catalyzed intramolecular insertion of isocyanide into an sp\(^2\) C–H bond of 84 gives indole derivative 85 (Scheme 56). This reaction was extended to photo-assisted insertion of isocyanide into C–H bonds using Fe(\( \text{PMe}_3 \))\(_2\)(CNCH\(_2\)\( \text{t-Bu} \)) as catalyst.

### 4.2 Acylation at C–H Bonds Using Alkenes and Carbon Monoxide

Hong and co-workers reported that acylation of benzene was observed when a reaction was performed with ethylene and CO in the presence of \( \text{Rh}_3(\text{CO})_12 \) as catalyst. In 1992, \( \text{Ru}_3(\text{CO})_12 \) was found to catalyze the highly selective acylation at \( \alpha \)-C–H bonds in pyridines using alkene and CO to give 2-acylpyridines such as 86. A variety of terminal alkenes, such as ethylene, 1-hexene, and 1-eicosane, can be used in this reaction (Scheme 57).

Subsequently, the \( \text{Ru}_3(\text{CO})_12 \)-catalyzed regioselective acylation of C–H bonds in imidazoles such as 87 was reported (Scheme 58). A wide range of alkenes bearing ester, ketal, nitrile, and silyl groups can be utilized in this reaction. Other five-membered N-heteroaromatic compounds, such as pyrazoles, oxazoles, and thiazoles, are similarly acylated, and in all cases, the reaction takes place exclusively at a C–H bond to the sp\(^3\) nitrogen.

Chatani and co-workers studied the sp\(^3\) nitrogen-directed acylation using ruthenium or rhodium catalysts and were able to effect acylation at positions other than the sp\(^3\) N of several other compounds, including benzimidazole 88 (\( \gamma \) to the sp\(^3\) N), 91, aryloxazoline 90, \( \alpha \)-aromatic imine 91, and \( \gamma \) to the sp\(^2\) N, and \( \beta \) to the sp\(^2\) N (Figure 4). Several types of alkenes, such as ethylene, trimethylvinylsilane, 1-hexene, 2-methylsterecne, and cyclohexene, can be used in the acylation at a C–H bond to the sp\(^2\) nitrogen, but the C–H bond in pyridine ring does not react at all. The product selectivity of mono- and diacylation...
products is largely affected by the substituent on the pyridine ring. The acylation of 28 leads to exclusive formation of monoacylation product 93 (Scheme 59).

Aromatic aldimine 94 undergoes acylation at the ortho C–H bond. In this reaction, the presumed primary product 95 is not isolable, owing to its high tendency for cyclization, and instead converted into indenone derivative 96 via intramolecular aldol condensation (Scheme 60).94

For efficient screening of the Ru3(CO)12-catalyzed acylation of C–H bonds with alkenes and CO, Bergman and Ellman developed a mass spectrometric labeling strategy for the high-throughput evaluation of many substrates.96 The acylation of sp3 C–H bonds adjacent to nitrogen in cyclic amines such as 97 can be attained using [RhCl(cod)]2 catalyst and propan-2-ol (Scheme 61).97

Dehydrogenative acylation of sp3 C–H bonds in N-(2-pyridyl)piperazines takes place when Rh4(CO)12 is used as a catalyst.98 The presence of an additional nitrogen functionality at the 4-position of the piperazine ring is essential for the reaction. The reaction involves two discrete processes: i) dehydrogenation of the piperazine ring; ii) carbonylation at a C–H bond. In place of the pyridyl group, an acyl group can also function as a directing group for the dehydrogenative acylation.99

5  Arylation of C–H Bonds

Among the various catalytic functionalizations of C–H bonds, the arylation of arenes has been one of the most extensively studied research subjects, because the reaction provides π-conjugated aromatic compounds, which are found in many organic electronic and optical devices, and bioactive compounds. To date, a large number of direct arylations of arenes have been reported.100 The arylations can be classified mainly into three types: one is electrophilic substitution of arenes with aryl-metal species formed by oxidative addition of aryl halides to transition metals; the second is aryl C–H/aryl C–H coupling using oxidants, and the third involves the oxidative addition of C–H bonds, followed by transmetalation with organometallic reagents. In this section, only a limited number of examples concerning the arylation are described, owing to the large number of reactions in this category.100

5.1  Intermolecular Direct Arylation of C–H Bonds Using Aryl Halides and Pseudohalides

In 1982, Tajima and co-workers reported a pioneering work with respect to catalytic intermolecular direct arylation of C–H bonds with aryl halides.101 The reaction of 3-tosyl-5-methylisooxazole with phenyl iodide in HMPA using palladium(II) acetate or palladium-on-carbon as a catalyst afforded 4-phenylisooxazolines in moderate yields. In 1985, Chiusoli and co-workers demonstrated that the palladium-catalyzed reaction of bromobenzene with norbornene gives hexahydromethanotriphenylenes via C–H bond cleavage.102 A similar reaction was reported subsequently by de Meijere.103 Palladium-catalyzed arylation of 1-naphthol with aryl iodides affords 8-aryl-1-naphthols selectively (Scheme 62).104 Use of cesium carbonate and molecular sieves is essential for an efficient reaction. Treatment of phenol with aryl bromides using a palladium catalyst gives multiarylation products.105

Figure 4

Scheme 59

Scheme 60

Scheme 61

Scheme 62
Another type of heteroatom-directed arylation of phenols was developed by Bedford and co-workers. Reaction of \( \text{99} \) with aryl bromides using phosphinite \( \text{100} \) as a co-catalyst provides ortho-arylated phenols \( \text{101} \) (Scheme 63).106 The important steps in this reaction are: i) coordination of \( \text{100} \) to the rhodium; ii) dissociation of arylated phosphinite \( \text{102} \); and iii) transesterification of the arylated ligand with \( \text{99} \) to regenerate co-catalyst \( \text{100} \) and to liberate arylation product \( \text{101} \). Oi and Inoue found a more convenient and practical protocol for the ortho arylation of phenols with aryl bromides. The authors used P(NMe\(_2\))\(_3\) as a co-catalyst to generate arylphosphite equivalents in situ by reaction with phenols (Scheme 64).107 Bedford and co-workers subsequently reported a similar rhodium(I) and P(NMe\(_2\))\(_3\)-catalyzed ortho arylation of phenols.108 Bergman and Ellman also reported a similar phosphorus-compound-mediated ortho-selective alkylation of phenols using a rhodium catalyst.109

Miura and co-workers developed the palladium-catalyzed arylation of aromatic carbonyl compounds such as ketones109, amides (e.g., \( \text{103} \)),110 and aldehydes111 with aryl bromides and triflates (Scheme 65). In this reaction, coordination of the enolate anion generated from the ketone or aldehyde with the amide anion generated from the benzanilide is key to attaining the regioselective C–H bond cleavage. N-Acyl anilines, benzylamines, and benzoic acids are also arylated using palladium(II) acetate as catalyst in the presence of silver(I) acetate as a base.112 Aryl chlorides can be used as an arylating reagent when the palladium(II) acetate and n-BuAd\(_3\)P catalyst system is employed.

Daugulis and Shabashov reported that, in the palladium-catalyzed arylation of aromatic amides with aryl iodide using silver(I) acetate, bromo and chloro groups remain in the coupling products.112 A competitive reaction using 4-tert-butyl- and 4-acetyl-1-iodobenzenes provides a 2:1 ratio of 4-tert-butylphenylated and 4-acetylphenylated products. Usually, Ar–Br and Ar–I bonds are reactive toward palladium(0) species and the electrophilicity of the arylpalladium(II) species bearing an electron-withdrawing group (acyl) on the aromatic ring is higher than that of the species with an electron-donating group (tert-butyl). On the basis of the observed unusual reactivity, this arylation is proposed to proceed via a palladium(II)/palladium(IV) catalytic cycle. The choice of the solvent greatly affects the reactivity of the primary monoarylated products, and use of a 4:1 mixture of acetic acid to trifluoroacetic acid is advantageous if monoarylation products are desired.112

When the reaction of \( \text{104} \) with bromobenzene is examined in the presence of palladium(II) acetate and a bulky phosphine, P(o-biphenyl)(t-Bu)\(_2\), arylation takes place at the 2-, 3- (or 4-), and 5-positions, via decarbamoylation, to give \( \text{105} \). In the case of 3-carboethoxyfuran, however, the arylation proceeds selectively at the 2-position and the ester moiety is retained in the product.114

A ruthenium(II)–phosphine complex exhibits high catalytic activity for the regioselective arylation of 2-arylpyridines such as \( \text{106} \) using aryl halides (Scheme 66).115 The catalyst system is also effective for the arylation of aryl imines,75b oxazolines, and imidazolines.75c

In place of triphenylphosphine as ligand, the use of the bulky phosphine oxide ligand such as di(1-adaman-
Tyl)phosphine oxide and dianiminophosphine oxide as pre-
ligand of the anionic P-bonded ligand enables the
arylation of arylpyridines and aromatic imines with aryl
chlorides and the arylation of arloxazolines with aryl to-
sylates (Scheme 68). Both electron-withdrawing and
electron-donating groups are tolerated in the reactions.

Product selectivity is greatly affected by the choice of
electrophiles. For example, the arylation of 2-phenylpyri-
dine with phenyl chloride provides the 2,6-diphenylated
product, but the reaction with phenyl tosylate gives the
monoarylation product selectively.

Fagnou and co-workers reported the direct arylation of
perfluoroarenes. In this catalyst system, reactivity of
arenes depends on the acidity of the C–H bonds, not on the
nucleophilicity of the arenes, and pentafluorobenzene is at
least 200-fold more reactive than the 1,4-difluorobenzene.
They also reported the direct arylation of simple arenes
such as benzene using pivalic acid. Competitive exper-
iments for this reaction also showed that electron-defi-
cient arenes possess higher reactivity (Scheme 69). While
a similar benzene arylation reported by Fujita and
Yamaguchi using an iridium catalyst is considered to pro-
ceed via a radical intermediate, a metalation–arylation
pathway was proposed for this arylation; this is described
in section 5.2.

In the preparation of 2-arylated pyridines by catalytic cross-
coupling, 2-pyridyl halides are usually reacted with orga-
nometallic reagents such as organoboron, -zinc, and
-magnesium compounds. Aryl halides are generally not
used to couple with 2-pyridyl organometallic reagents be-
cause these 2-metalated pyridines are often unstable and
difficult to prepare. However, palladium-catalyzed regio-
selective direct arylation of pyridine N-oxide using aryl halides affords 2-arylpyridine N-oxides such as 108
(Scheme 69). Reduction of 108 using palladium-on-
carbon and ammonium formate leads to pyridine deriva-
tive 109. This is a new synthetic procedure for the prepa-
ration of α-arylated pyridines.

The cyclopentadienyl ring in metallocenes such as 110
undergoes arylation with aryl halides using the catalyst
combination of palladium(II) acetate, tri(tert-butyl)phos-
phine and cesium carbonate (Scheme 71). Use of tri(4-fluorophenyl)phosphine or tri(tert-butyl)phosphine as a ligand is important because scrambling
of the aryl moiety of the triarylphosphine into the product
may take place during the reaction with other ligands.

The palladium-catalyzed reaction of 2-arylpyridines such as 28 with [Ar2I]+X– (X = BF4, PF6) affords
ortho arylation products. It is necessary to use [Mes-I-Ar]BF4 in order to attain high product selectivity (Scheme 72).

The β-C–H bond in 2-alkenylpyridine 112 undergoes ary-
lation with aryl bromides regio-and stereoselectively with
the aid of [RuCl2(η5-C5H5)]2 and triphenylophosphine as a
catalyst (Scheme 73). The observed high selectivity

Scheme 67

Scheme 68

Scheme 69

Scheme 70

Scheme 71

Scheme 72
suggests that this reaction proceeds through a chelation-assisted C–H bond-cleavage pathway.

Dyker reported the palladium-catalyzed homocoupling of 1-alkyl- or 1-alkoxy-2-iodobenzenes by way of the arylation of sp³ C–H bonds. 122 For example, 113 is converted into 114 in 75% yield (Scheme 74). An important step is the oxidative addition of the aryl iodide to the palladacycle intermediate, giving the palladium(IV) intermediate 115.122b

Scheme 74

Arylation of 4-alkynitrobenzenes with aryl halides proceeds at the benzyl position. The presence of the strongly electron- withdrawing nitro group or a highly electron-deficient heteroaromatic ring such as pyrimidine is essential in this reaction.123

Daugulis and co-workers reported that the reaction of 8-aminoquinoline amides with aryl iodides with the aid of a palladium(II) catalyst and silver(I) acetate takes place at the C–H bond that is β to the carbonyl group. The authors proposed that the reaction proceeds through cyclopalladated intermediate 118 shown in Scheme 75.124

Scheme 75

One of the most important pioneering works with respect to the direct arylation of heteroaromatic compounds using aryl halides and related compounds is the palladium-catalyzed coupling of thiophenes and furans with aryl bromides that was reported by Ohta and co-workers in 1989.125 To date, a variety of catalytic reactions concerning direct arylations of heteroarenes using aryl halides have been developed.

Miura and co-workers reported that, in the palladium-catalyzed arylation of 119, the use of an excess amount of copper(I) iodide improves the yield to 82% (Scheme 76).126 Several other catalyst systems using palladium complexes, such as PdCl₂/LiCl,127 PdCl₂(dppb),128 Pd(OAc)₂/P(o-biphenyl)(t-Bu)₂,129 and PdCl₂(PPh₃)₂,130 are also effective.

Scheme 76

The arylation of furans and thiophenes with aryl iodides takes place at the α-position.114,130,131 In the arylation of 3-thiophenecarboxylates, two plausible reaction pathways are present (Scheme 77). One involves a Heck-type α,β-insertion reaction proximal to the electron-withdrawing group (path a). The other pathway is an electrophilic substitution pathway (path b). When the reaction is conducted in non-polar solvents using triphenylphosphine, generation of a σ-bonded palladium(II) species is favorable, and the reaction proceeds through path a. On the other hand, in polar solvents and without triphenylphosphine, ionization of the Pd–X σ-bond is promoted. Thus, path b is more reasonable.

Scheme 77

When reaction of 120 with 121 is performed in the presence of a catalyst system made up of palladium(II) acetate and a trisubstituted phosphine, the unprecedented arylation product 122 is obtained via C–C and C–H bond cleavage reactions (Scheme 78).132

The proper ligand choice is an important factor in achieving the rhodium-catalyzed arylation of five-membered heterocyclic arenes. In the rhodium-catalyzed reaction of 123 with 124, a strong π-accepting ligand, such as P(OMe(CF₃)₃), dramatically improves the catalytic ac-
tivity (Scheme 79). The electron-deficient ligand is proposed to increase the electrophilicity of the rhodium center that is suitable for electrophilic substitution on thiophenes.

Other five-membered heteroaromatic compounds such as pyrroles, thiazoles, imidazoles, benzimidazoles, oxazoles, and purines can be used in palladium-catalyzed direct arylation. Introduction of different aryl groups at the 2- and 5-positions is also possible via stepwise arylation. Interestingly, when 2-phenylthiazole was used, the arylation took place at both the 4- and the 5-position.

The arylation of imidazoles using palladium(II) acetate and triphenylphosphine as catalyst with potassium carbonate in DMF provides 5-arylimidazoles with a significant amount of 2,5-diarylimidazoles. Use of triphenylarsine and cesium fluoride, in place of triphenylphosphine and potassium carbonate, improves the regioselectivity at the 5-position. This direct arylation can be applied to various electron-rich heteroaromatic compounds such as imidazo[1,2-a]pyrimidines, caffeine (125; Scheme 80), and purines.

The arylation of imidazoles using palladium(II) acetate and triphenylphosphine as catalyst with potassium carbonate in DMF provides 5-arylimidazoles with a significant amount of 2,5-diarylimidazoles. Use of triphenylarsine and cesium fluoride, in place of triphenylphosphine and potassium carbonate, improves the regioselectivity at the 5-position. This direct arylation can be applied to various electron-rich heteroaromatic compounds such as imidazo[1,2-a]pyrimidines, caffeine (125; Scheme 80), and purines.

5.2 Intramolecular Arylation of Aromatic C–H Bonds with Aryl Halides

Intramolecular direct arylation is one of the catalytic C–H functionalization methods that have been widely studied and utilized for more than a decade. After pioneering work by Ames and co-workers in the early 1980s, the utility of this reaction was demonstrated by several researchers. Bringmann and co-workers synthesized a number of natural products possessing axially chiral biaryl structures using their 'lactone method'. For example, dioncophylline C (127), which shows high antimalarial activity, was synthesized from 126 via a palladium-catalyzed intramolecular coupling (Scheme 81). Martin developed a short and convergent synthesis of the aglycone of gilvocarcins, antitumor agents, using the intramolecular direct arylation as a key step. This strategy was applied in the first total synthesis of the gilvocarcins by Suzuki and co-workers. While aryl iodide 128a was used for the synthesis of gilvocarcin M, aryl triflate 128b and a hindered base, sodium pivalate, was employed for the construction of the aryl-aryl bond in gilvocarcin V (Scheme 82).

Recently, Fagnou and co-workers extensively studied the intramolecular direct arylation and significantly improved the substrate scope and the catalyst loading. Use of ligands such as alkyl phosphines and N-heterocyclic carbens enabled the direct arylation of aryl chlorides. Particularly, the intramolecular arylation with palladium(II) acetate (1–5 mol%) and tricyclohexylphosphine hydrochloride can be applied for aryl chlorides, bromides, and iodides, and constructs various five- and six-membered rings fused with arenes bearing electron-withdrawing and -donating groups. They also applied the intramolecular coupling of aryl chlorides to the synthesis of biologically active compounds such as allocolchicine.
analogue 129 (Scheme 83)\textsuperscript{141j} and mukonine (130; Scheme 84)\textsuperscript{141k}

By means of the intramolecular arylation of a pyrrole, Trauner and co-workers constructed the nine-membered ring of rhazinilam, which interferes with tubulin polymerization, using 131 as a substrate (Scheme 85).\textsuperscript{141m}

Recent studies on the C–H bond cleavage step in the palladium-catalyzed direct arylation suggested that some direct arylation reactions may proceed via proton abstraction pathways. Maseras, Echavarren, and co-workers\textsuperscript{141n,o} reported that, in an intramolecular direct arylation, a C–H bond is more likely to be cleaved by intermolecular base-assisted abstraction (path a in Scheme 86) than an intramolecular process (path b), because of the following: i) DFT calculations on the intramolecular base-assisted process for substrates with trifluorophenyl and phenyl groups revealed that the difference in activation energies was 3.0 kcal/mol, which implies that the ratio of C–H bond cleavage at the aromatic rings is 40:1, reasonably close to the experimental data of 25:1; and ii) in a related reaction reported by Fagnou and co-workers the nature of the aryl halides affects the regioselectivity significantly,\textsuperscript{141k} which suggests the halides remain on the palladium center. In contrast, Fagnou and co-workers proposed intramolecular base-assisted processes (path b) for intermolecular coupling reactions.\textsuperscript{117,118}

5.3 Oxidative Direct Arene–Arene Coupling

In the transition-metal-catalyzed direct arylation of arenes, Ar–H and Ar–H couplings should be the most straightforward reactions. The direct arene–arene homo- and cross-couplings using a stoichiometric amount of palladium salt appeared in the 1960s.\textsuperscript{142} In 1973, the first palladium-catalyzed direct arene–arene coupling was reported. The reaction of naphthalene using palladium(II) acetate catalyst in refluxing acetic acid for 400 hours provides three types of binaphthyls (132–134) in 670, 790, and 170\% yields based on palladium(II) acetate (Scheme 87).\textsuperscript{143} Subsequently, Itatani and Yoshimoto reported that homo-coupling of arenes proceeds with the palladium(II) acetate and acetylacetone catalyst system under an oxygen atmosphere at 150 °C.\textsuperscript{144} This system can be used for an intramolecular coupling which converts diphenyl ether into diphenylene oxide (30.8 TON based on Pd).

Since the time of these pioneering studies, several types of homo-coupling reactions have been developed.\textsuperscript{145,146} Mori and co-workers reported a palladium-catalyzed homo-coupling at C–H bonds of thiophenes to give bithiophenes such as 135 and oligothiophenes (Scheme 88).\textsuperscript{145} In this case, bromo substituents remained in the coupling products.

![Scheme 88](image)

Sanford and co-workers developed a palladium-catalyzed chelation-assisted oxidative arene–arene homo-coupling using 2-arylpyridines (Scheme 89).\textsuperscript{146} The authors propose that the homo-coupling takes place through an electrophilic substitution of arylpyridines with a palladium(IV) complex formed by oxidation of a palladium(II) complex with Oxone\textsuperscript{6}.

![Scheme 89](image)

A much more challenging subject concerning the direct oxidative arene–arene coupling is an intermolecular cross-coupling reaction.\textsuperscript{147} In 2006, Lu and co-workers succeeded in developing a catalytic method to construct unsymmetrical biaryl frameworks.\textsuperscript{147}\textsuperscript{a} Reaction of naphthalene with \( p \)-xylene using palladium(II) acetate catalyst and potassium persulfate as an oxidant affords 136 in 50\% yield (Scheme 90). The yields of the cross-coupling products are moderate, but this was a highly promising result for the catalytic Ar\textsuperscript{1}–H/Ar\textsuperscript{2}–H cross-coupling reactions.

![Scheme 90](image)

Recently, Fagnou and co-workers reported palladium(II) trifluoroacetate catalyzed arylation of N-acylindoles (e.g., 137) and N-substituted pyrroles with arenes using copper(II) acetate or silver(I) acetate as a terminal oxidant (Scheme 91).\textsuperscript{147b,c} The authors propose the reaction pathway as follows: i) a PdX\textsubscript{2} species attacks an indole via electrophilic substitution to give an Ar\textsuperscript{1}–Pd–X species; ii) reductive elimination from this intermediate provides the biaryl compound and a palladium(0) species; iii) oxidation of the palladium(0) with an oxidant regenerates the electrophilic palladium(II) species.

![Scheme 91](image)

When reaction of benzo furan with benzene is carried out using palladium(II) acetate and \( \text{H}_\text{4}\text{PMo}_{11}\text{VO}_{40} \) as catalyst and molecular oxygen (3 atm) as a terminal oxidant, phenylation of benzo furan takes place in 84\% yield with high selectivity.\textsuperscript{147c} The chelation-assisted protocol for C–H bond cleavage is also effective for oxidative Ar\textsuperscript{1}–H/Ar\textsuperscript{2}–H cross-coupling. Sanford and co-workers reported that reaction of benzoquinoline (138) with 139 using silver carbonate and benzoquinone (BQ) affords 140 in 93\% yield (Scheme 92).\textsuperscript{147d} Addition of DMSO, considered to retard the decomposition of the palladium complex, enhances the yield of 140. The authors also propose that BQ assists the C–H bond cleavage as a ligand, though the actual role is unclear.

![Scheme 92](image)

Development of efficient, selective, and catalytic Ar\textsuperscript{1}–H/Ar\textsuperscript{2}–H cross-couplings has just recently begun. Progress in this field will provide one of the most important protocols for syntheses of biaryl compounds.

### 5.4 Arylation Using Arylmetal Reagent

Use of organometallic reagents as arylating agents offers another method for the direct arylation. Oi and Inoue reported rhodium-catalyzed arylation of arylpyridines using tetraarylstannanes (Scheme 93).\textsuperscript{148} For this reaction, use of 1,1,2,2-tetrachloroethane as a solvent was effective.
Kakiuchi and co-workers developed a novel type of arylation of C–H bonds using organoboron reagents (Scheme 94). Reaction of aromatic ketones with arylboronates using 1 as a catalyst yields ortho arylation products. When toluene is used as a solvent, a half amount of the starting aromatic ketone is reduced to the corresponding alcohol. Use of pinacolone or acetone as a solvent effectively suppresses the undesired reduction of the starting ketone.

When reaction of benzonitriles with sodium arylboronates is carried out using [RhCl(cod)]/dppe [dppe = 1,2-bis(diphenylphosphino)ethane] as a catalyst, a mixture of biphenyl-2-yl(phenyl)methanimine and dibiphenyl-2-ylmethanimine is obtained. In this case, ammonium chloride is essential for regenerating the Rh–Cl species which react with sodium tetraphenylborate to give the Rh–Ph intermediates.

Catellani and co-workers demonstrated that a variety of new frameworks such as biaryls can be readily constructed by this method using combinations of aryl/alkyl halides and alkenes/alkynes (Scheme 96). These reactions also provided a new synthetic tool to make multiple C–C bonds in one step via C–H bond cleavage.
tandem arylation/alkylation, followed by Mizoroki–Heck coupling.\textsuperscript{152,153} When aryl iodide \textbf{146} is used, tricyclic product \textbf{147} is obtained with almost no loss of stereochemical information (Scheme 98).\textsuperscript{153e} The stereochemistry of the secondary alkyl moiety in the product is inverted. This indicates that the oxidative addition of the secondary alkyl iodide to palladium(II) to form palladium(IV) intermediate \textbf{148} (step a) takes place with inversion of configuration, if the reductive elimination (step b) proceeds with retention. In place of the Mizoroki–Heck reaction in the final step, direct arylation with electron-rich heteroarenes can be used to provide a variety of annulated heteroaromatic compounds.\textsuperscript{154}

![Scheme 97](image)

![Scheme 98](image)

The tandem coupling reaction using aryl iodide \textbf{149}, alkyl halide \textbf{150}, and alkylboronic acid \textbf{151} leads to the formation of \textit{m}-substituted arene \textbf{152} via alkylation, followed by hydride reduction (Scheme 99).\textsuperscript{155} Polycyclic benzonitrile can be synthesized by the reaction of aryl iodides bearing an alkyl bromide moiety with zinc cyanide.

![Scheme 99](image)

Protocols developed by Catellani and Lautens have opened new areas of palladium-catalyzed multi-component coupling involving electrophilic C–H bond cleavage.

7 Conversion of C–H Bonds into C–C Bonds via 1,4- and 1,5-Transition-Metal Migrations

Catalytic reactions involving C–H bond cleavage via 1,n-metal migration (n = 4, 5) have been studied extensively. Larock and co-workers conducted a pioneering work on the coupling of \textit{o}-iodobiaryls with alkenes via 1,4-palladium migration and related reactions (Scheme 100).\textsuperscript{156} The 1,4-shift in isolated arylpalladium complexes was demonstrated by Sharp and Singh.\textsuperscript{157}

![Scheme 100](image)

When the reaction of phenylboronic acid (\textbf{153}) with norbornene using [RhCl(cod)]\textsubscript{2} and DPPP as the catalyst system was performed, multiple substitution with norbornene on aromatics took place via 1,4-shift to afford \textbf{154} (Scheme 101).\textsuperscript{158a}

![Scheme 101](image)

A similar reaction using phenylboronic acid and internal alkynes to give 1-allylindene derivatives was reported.\textsuperscript{158b} The 1,4-rhodium shift is supported for this reaction by deuterium labeling experiments. Several other catalytic reactions via 1,4- and 1,5-transition-metal migrations have also been developed.\textsuperscript{158–160}

8 Addition of C–H Bonds to Polar C=X Bonds

Addition of C–H bonds to polar C=X functional groups such as C=O and C=N bonds is highly intriguing because these reaction enable direct introduction of alkoxy or hydroxy and amino groups on a carbon atom via C–H bond...
cleavage. The first catalytic addition of a C–H bond to C=X bonds was reported in 1978.6 The reaction of benzene with aryl isocyanates such as phenyl, p-tolyl, p-chlorophenyl, and α-naphthyl isocyanates in the presence of Rh₄(CO)₁₂ as catalyst gives the corresponding benzanilides (Scheme 102).

\[
\text{PhN=CO + } \text{Rh}_4(\text{CO})_{12} \xrightarrow{\text{CO (25 atm)}} 220 \degree \text{C}, 6 \text{ h} \quad \text{PhN}^+ \text{CO} \quad 42\% 
\]

Scheme 102

Recently, a similar reaction with respect to the addition of aromatic C–H bonds to aryl isocyanates using [ReBr(CO)₃(thf)]₂ as catalyst was reported (Scheme 103). In this case, the reaction does not stop after the addition of C–H bonds to C=N bond. Further C–C bond formation yielding γ-lactam 155 occurs selectively.⁵⁸b

\[
\text{PhN}^+ \text{Bu} + \text{PhN=CO} \xrightarrow{[\text{ReBr(CO)}_3(\text{thf})]_2} \xrightarrow{\text{DCE reflux, 24 h}} \text{NH}^+\text{Bu} \quad 155 \quad 97\% 
\]

Scheme 103

Rhenium-catalyzed addition of ortho C–H bonds to aryl isocyanates of aromatic and heteroaromatic imines to a carbonyl group in aldehydes yields isobenzofuran derivatives, which are good enophiles in the Diels–Alder reaction. When the reaction is performed in the presence of an alkene as an acceptor of the isobenzofurans, the corresponding cycloaddition products such as 156 are obtained (Scheme 104).³⁶¹ᵃᶜ

\[
\text{Ph}^+ \text{Ph}^+ \text{O} \xrightarrow{[\text{ReBr(CO)}_3(\text{thf})]_2} \xrightarrow{\text{toluene, MS 4A}} 115 \degree \text{C}, 24 \text{ h} \quad \text{Ph}^+ \text{Ph}^+ \text{O} \quad 156 \quad 83\% 
\]

Scheme 104

For addition of C–H bonds in aromatic imidazoles to aldehydes, MnBr(CO)$_n$ is the best catalyst among the transition-metal complexes screened. Use of triethylsilane is essential for the reaction to proceed efficiently. Diastereoselective hydroarylation of the aldehydes also takes place to give the corresponding silyl ether in up to 95% de.¹⁶¹ᵇᵈ

9 Conclusions

During the last decade, transition-metal-catalyzed functionalization of C–H bonds has been widely investigated by organic and organometallic chemists alike. Among these reactions, catalytic C–C bond formations via C–H bond cleavage are the most widely studied subjects. A variety of transformations such as alkylation, alkenylation, carbonylation, acylation, arylation, and dehydrogenation have been developed.

In the 1990s, the scope and limitations of these reactions were explored and several important features of these transformations were uncovered. In particular, catalytic alkylations, alkenylations, and acylations were extensively studied. In the early 2000s, a variety of catalytic reactions concerning transition-metal-catalyzed arylation via an electrophilic metalation of C–H bonds were investigated. Direct non-chelation-assisted arylation of heteroaromatic compounds with aryl halides and pseudohalides was one of the central subjects in this catalytic reaction. In recent years, the transition-metal-catalyzed conversion of C–H bonds into C–C bonds has become useful tools for the synthesis of complex molecules such as natural products, bio-active compounds, pharmaceuticals, and organic electronic devices. These results apparently illustrate that C–H bonds can be used as a functional group like halides.

Although recent advances in the C–H bond functionalization have demonstrated the significant value of this chemistry in organic synthesis, many challenges are still left to overcome. Lowering of the catalyst loading and the reaction temperature is desired in many cases. Optimization of ligands and/or design of new catalysts may be necessary to improve the efficiency of the catalysis. Expensive metals used as catalysts should be displaced by more cost-effective metals. Particularly, in order to avoid the use of the exhaustible noble metals, developments of new catalysts consisting of base metals for C–H functionalization reactions are needed. In addition, there still exists a wide variety of C–C bond-forming reactions via C–H bond cleavage and methods to control the regioselectivity that have not been achieved but would be useful in organic synthesis. Therefore, further developments in these areas may provide more practical methods for the construction of C–C bonds that would have greater impacts on the synthesis of complex organic molecules.

References


