

Lecture Notes in Chemistry 102

Aiwen Lei *Editor*

# Transition Metal Catalyzed Oxidative Cross-Coupling Reactions

 Springer

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Aiwen Lei  
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# Transition Metal Catalyzed Oxidative Cross-Coupling Reactions

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# Chapter 1

## Introduction



Chao Liu

### 1.1 The Concept of Oxidative Coupling

Synthetic chemistry has been considered as one of the central topics in modern novel material creations. Therefore, the development of novel synthetic concepts and synthetic methods is always appealing. Among various synthetic approaches, transition metal-catalyzed cross-coupling has been considered as one of the great discoveries in the last century. It has been demonstrated as a powerful tool for the construction of various chemical bonds [13]. Several named reactions in this field such as Heck reaction, Negishi reaction, Suzuki reaction, Stille reaction, Hiyama reaction, the Buchwald-Hartwig reaction, etc. have been explored [1, 4–6, 14, 15]. The Nobel Prize in chemistry has been awarded to this area in 2010. The model of those coupling reactions usually involves a nucleophile and an electrophile as the partner in the presence of a catalyst (Scheme 1.1, eq. 1). Overall, this is a redox-neutral process, and no extra redox reagents are required for achieving the bond formation (Scheme 1.1, eq. 1) [10].

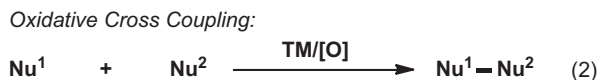
In those classic cross-coupling, the electrophiles are usually obtained from the pre-functionalization of their corresponding nucleophiles, thus decreasing the reaction step-economy of the whole bond forming process. It restricted the development and application of those traditional cross-coupling reactions in organic synthesis. The traditional cross-couplings faced with great challenges for their inevitable drawbacks such as low atom economy, considerable useless by-products generation, etc.; thus, it gradually cannot meet the development of modern synthetic methodology and the urgent demand for green and economical synthesis.

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**Scheme 1.1** Bond formation modes of classic cross-coupling and oxidative cross-coupling



Therefore, new form of coupling with higher atom economy and less overall reaction steps is highly demanding. Oxidative coupling, a concept which has been classically used in heterogeneous system for methane conversion, was introduced in homogeneous system for bond formations between two nucleophiles. Along with the development of synthetic chemistry and green chemistry, oxidative coupling reactions between two nucleophiles can meet the requirement of current development of chemical science; due to that both nucleophiles can be accessible from C-H, N-H, O-H, etc. compounds which are widely available.

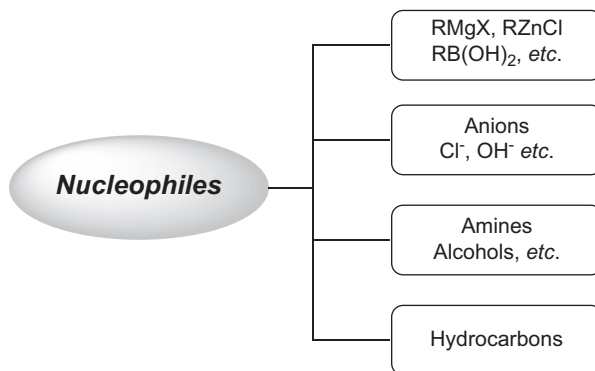
Conceptually, oxidative coupling, as stated in its name, is a coupling strategy through an oxidative process (Scheme 1.1, eq. 2) [10]. In this strategy, the coupling partners are usually two nucleophiles which are electron-rich. To make those nucleophiles forming chemical bonds, an extra oxidant has to be used to take two redundant electrons away to promote the bond formation.

Therefore, to achieve a proper oxidative coupling, two aspects are needed to take into consideration. One is to find two suitable nucleophiles for bond formations; another is to provide a providential oxidant to accept the extra electrons. O<sub>2</sub>, H<sub>2</sub>O<sub>2</sub>, and high-valent metals and organohalides are usually used in oxidative coupling reactions. With the development of current catalysis science, transition metals were applied in the classic cross-coupling to improve the reaction efficiency. On this occasion, the oxidative cross-coupling reaction would be an ideal alternation. Compared with electrophiles, nucleophilic reagents are far more diverse than electrophilic reagents. Most of the organometal reagents, anions, amines, alcohols, and widely existing hydrocarbons are nucleophiles that can all be used in oxidative couplings for the construction of various chemical bonds (Scheme 1.2). It is worthy of note that the application of hydrocarbons, amines, and alcohols as the nucleophiles will provide an atom-economy strategy for bond formations, as usually only hydrogen atoms are lost in the whole process. Nowadays, more and more attentions are paid in this topic to make cross-couplings greener.

## 1.2 The History of Oxidative Coupling

Actually, bond formations between two nucleophiles have been demonstrated for a long time. For example, the homo-coupling of terminal alkynes to prepare conjugated 1,3-diyne has been firstly demonstrated in 1869 [3]. In this transformation,

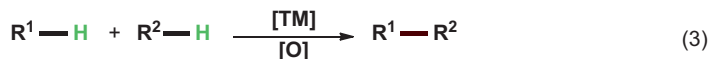
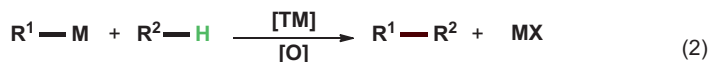
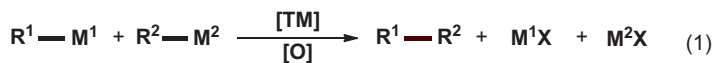




**Scheme 1.2** Nucleophiles in oxidative couplings

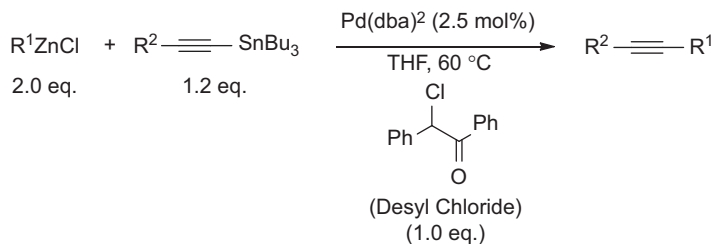
CuCl was used as catalyst; ammonia and EtOH acted as the co-solvent, under O<sub>2</sub> atmosphere; and phenyl acetylene transformed to 1,3-dienes. This transformation is now called Glaser coupling. However, the term “oxidative coupling” has been rarely used in homogeneous system during the twentieth century. Before the year of 2005, the term oxidative coupling was majorly used in heterogeneous catalytic system for the oxidative coupling of methane (OCM). As early as 1982, since the report by Keller and Bhasin on the oxidative coupling of methane reaction to synthesis ethylene and ethane [7]. Subsequently, more and more attention has been paid on the study of the catalysts’ preparation and reaction mechanism [2, 20]. It can be seen that both the homogeneous and heterogeneous systems have been majorly focused on the oxidative coupling between two identical nucleophiles. Those reactions can be termed as oxidative homo-couplings. In this case, it is highly restricted on the substrate scope. Therefore, the oxidative coupling was developed with a slow progress.

The oxidative coupling between two different nucleophiles will obviously enlarge the scope of nucleophiles; thus, it can broaden the type of the products. However, the selectivity is difficult to control, for both homo-couplings and cross-couplings of two different nucleophiles may occur in one reaction system. It seemed unreachable for achieving the selective oxidative cross-couplings. Thanks to those early developments on the oxidative cross-couplings between two nucleophiles at the beginning of this century. Those breakthroughs bring the light of such appealing chemistry into the front of people. Since then, the oxidative cross-coupling between two different nucleophiles sprung up throughout the last 10 years, due to their great potential for green and economic synthesis as well as considerable advantages over traditional cross-couplings, especially for those cross-couplings between two C-H nucleophiles. Normally, nucleophiles could be divided into several classes: MX, C-M, CH, or X-H (X = N, O, S, etc.). In the MX group, salts such as metal halides are employed as reactants to form carbon-halogen bonds. In the C-M group, organo-metallic reagents serve as the efficient carbon nucleophiles which have been widely applied in transition metal-catalyzed coupling reactions.



**Scheme 1.3** The development of oxidative cross-coupling reactions

The development of oxidative coupling can be divided into four generations (Scheme 1.3). At the beginning, oxidative couplings focused on the bond formations between two organometallic reagents (C-M, M = Zn, Mg, In, Sn, Cu, etc.) under transition metal catalysis (Scheme 1.3, eq. 1), and many excellent results with high selectivity and yield have been reported in this field. In this type of transformation, the organometallic reagents have high reactivity, the challenge is selectivity control, homo-coupling of the organometallic reagents that is often involved occurs, and the organometallic reagents can also react with oxidants that result in poor yields. And these organometallic reagents were sensitive to air and water; some of them are also very toxic. Besides, after the reaction complication, two kinds of metal salts were wastes. Therefore, this kind of bond formation mode does not meet the requirement of modern sustainable chemistry; more greener method is urgent to development [16]. While science is always in progress, in the following several years, taking the place of one of the organometallic reagents with a X-H compound is a greener design and makes the oxidative cross-coupling cleaner (Scheme 1.2, eq. 2), which is the second generation of oxidative cross-coupling. Notably, CH or XH (X = N, O, S, etc.) nucleophiles extensively exist in nature, which represent the most abundant nucleophiles. Thus, the best choice of oxidative coupling was the  $R^1-H/R^2-H$  coupling (Scheme 1.3, eq. 3), the third generation of oxidative cross-coupling, which can construct C-C and C-heteroatom bond toward sustainable synthesis; it can greatly enlarge the scope of organic synthesis, and numerous outstanding works have been reported [12]. Undoubtedly, air or  $O_2$  is a green oxidant, in the transition metal-catalyzed oxidative  $R^1-H/R^2-H$  coupling reactions; if air or  $O_2$  can be used as the oxidant, it will be an ideal approach for bond formations. Compared to the traditional cross-couplings, in oxidative  $R^1-H/R^2-H$  couplings, the substrates don't need to be pre-functionalized, and the generation of waste is largely diminished with only  $H_2O$  as the by-product; thus, the synthetic procedure is greatly shortened, and atom economy is considerably enhanced, demonstrating great potential for pharmaceutical and industrial application. However, in these transformations, noble transition metals such as Pd, Ru, Rh, and others were used as the catalysts. In recent years, there has been an increase in number of oxidative cross-coupling reactions with first-row transition metal salts (Fe, Co, etc.) as catalysts or even no metal. Since first-row transition metals often can go through multiple



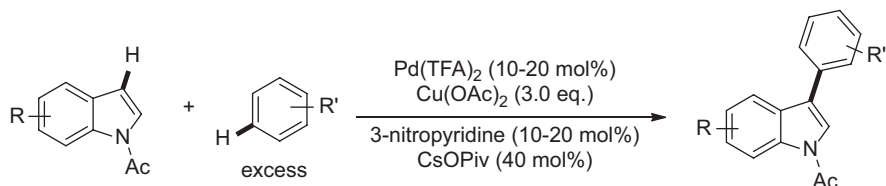
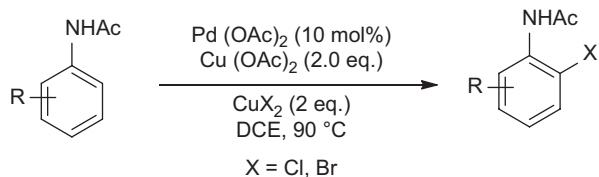
**Scheme 1.4** The oxidative cross-coupling reaction between two different nucleophiles

chemical valence changes, those oxidative cross-couplings can involve single-electron transfer processes. Radical oxidative coupling reactions represent a promising development in green chemistry [11]. Recently, an external oxidant-free oxidative coupling was developed, which no oxidant was needed and only  $\text{H}_2$  was generated as a side product (Scheme 1.3, eq. 4), which could be called the fourth-generation oxidative coupling reactions. In this transformation, no oxidants and proton acceptors were applied as the sacrificial reagents, with no wasteful by-products or oxidation side reactions. This was no doubt the most ideal mode to construct C-C and C-heteroatom bond. The field holds significant potential for the applications to a series of organic reactions, and scientists paid more and more attention on this field.

In 2006, Lei firstly used the concept “oxidative cross-coupling” in a  $\text{Csp}^3\text{-Csp}^3$  bond formation between two different organometal nucleophiles (Scheme 1.4) [21]. In this transformation, alkynylstannanes and alkylzinc reagents were used as the two nucleophiles, 2-chloro-2-phenylacetophenone (Desyl chloride) was applied as the oxidant, and the desired  $\text{Csp}^3\text{-Csp}^3$  cross-coupled products were produced with high selectivity and yields in the presence of  $\text{Pd(dba)}_2$  without an extra ligand. In this reaction, the  $\text{Csp}^3\text{-Csp}^3$  homo-coupling of alkylzinc reagent is very slow; the homo-coupling of alkynylstannane did not occur under the standard conditions. The reaction started from the low-valent  $\text{Pd(0)}$ , Desyl chloride used as the oxidant which was reoxidize  $\text{Pd(0)}$  to regenerate the  $\text{Pd(II)}$  species, and then two transmetalations of alkynylstannane and alkylzinc reagent with the  $\text{Pd(II)}$  species followed by reductive elimination to get the desired cross-coupling product. In addition, the mechanism was investigated by *situ* IR; the result indicated that the alkylzinc reagent transmetalated with the  $\text{Pd-enolate}$  bond and the alkynylstannanes reagent transmetalated with the  $\text{Pd-Cl}$  bond selectively. After that, this type of oxidative cross-coupling was further developed [9, 10, 12, 17].

At the same time, C-H functionalization has also developed. In 2006, Shi reported the C-H functionalization/halogenation of acetanilide (Scheme 1.5) [19]. In this reaction, acetanilide and halides (Cl or Br) can be considered as the two different nucleophiles;  $\text{Pd(OAc)}_2$  acted as the catalyst and  $\text{Cu(OAc)}_2$  as the oxidant; in DCE, acetanilides were transformed to halogenated acetanilides with high regioselectivity. In this transformation, the acetyl group was used as the directing group, which was important for this reaction; when changed to formyl, benzoyl, tosyl, and trifluoroacetyl, only trace amount of products (<5%) were observed. Pivaloyl group could

**Scheme 1.5** C-H functionalization/halogenation of acetanilide



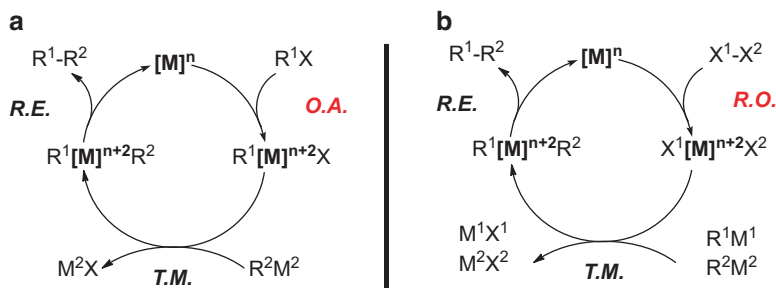
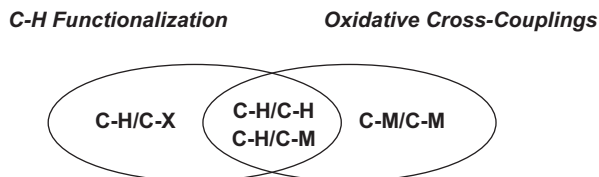
**Scheme 1.6** Oxidative cross-coupling of C-H/C-H bonds

be utilized as a directing group but yield with a slight decrease. In the mechanism studies, cyclopalladation of acetanilide which has C-Pd bond could be the active species during this catalytic cycle. Subsequently, other directing groups such as O-alkyl oximes, carboxylic acids, 2-aryl or alkyl pyridines, oxazolines, O-methyl hydroxamic acids, cyano, etc. and even common electron-rich (hetero)arenes without directing groups have been successfully introduced into C-H functionalization. Even through this chemistry has been demonstrated as C-H functionalization, it is clear that this chemistry is an oxidative cross-coupling process between two nucleophiles.

In 2007, Fagnou and co-workers reported a Pd-catalyzed oxidative cross-coupling of unactivated arenes (Scheme 1.6) [18]. In this reaction,  $\text{Pd(TFA)}_2$  was used as the catalyst; 3-nitropyridine as the ligand, in conjunction with  $\text{Cu(OAc)}_2$  as the oxidant; cesium pivalate ( $\text{CsOPiv}$ ) acted as the base and can catalyze the cross-coupling of *N*-acetylindoles and benzenes in high yield and high regioselectivity. These reactions are completely selective for arene cross-coupling, with no products arising from *N*-acetylindole or benzene homo-coupling products. Though the reaction conditions are a litter harsh, and the substrate scope is narrow, that free N-H indole did not react and *N*-methylindole produced self-dimerization predominantly, it still was an important report to promote the science progress. Obviously, this is a C-H/C-H oxidative cross-coupling reaction.

Cross-dehydrogenative-coupling (CDC) reactions [8], which combine two C-H bonds under oxidative conditions to form new C-C bonds. In CDC reactions, it could avoid the pre-functionalized materials that make organic synthesis simpler and more efficient. In the presence of simple and cheap catalysts such as copper and iron salts or even no metal catalyst and oxidants such as hydrogen peroxide, dioxygen, *tert*-butylhydroperoxide, 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) etc.,  $\text{Csp}^3\text{-Csp}^3$  bond,  $\text{Csp}^3\text{-Csp}^2$  bond, and  $\text{Csp}^3\text{-Csp}$  bond could be constructed without requiring pre-activation.

**Scheme 1.7** The relationship between C-H functionalization and oxidative cross-couplings



**Scheme 1.8** (a) General catalytic cycle of palladium-catalyzed traditional coupling. (b) General catalytic cycle of palladium-catalyzed oxidative cross-coupling reactions

It can be seen that oxidative cross-couplings and C-H functionalization are two different concepts. However, they have overlaps and differences on the topic of bond formations as shown in Scheme 1.7. C-H functionalization is a type of reaction in which a C-H bond is cleaved and replaced with a new chemical bond. It has three reaction modes: (1) C-H/C-X bond formation, (2) C-H/C-M bond formation, and (3) C-H/C-H bond formation. In C-H bond functionalization, the hydrocarbon is first to react with a metal catalyst to create an organometallic complex, which is the key intermediate. Then, the organometallic complex can undergo subsequent reactions to produce the functionalized product.

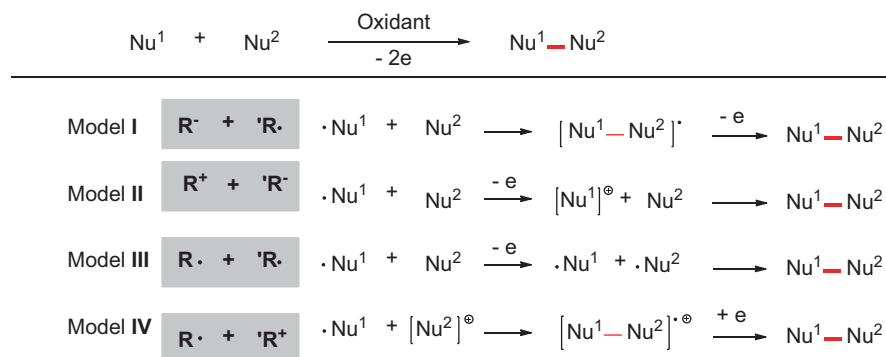
### 1.3 The Principle of Oxidative Coupling

The mechanism for this traditional coupling was showed in Scheme 1.8, the catalytic cycle generally starts from a low-valent  $[M]^n$  species, and it contains three fundamental unit reactions: (1) oxidative addition of C-heteroatom bond of electrophiles  $R^1-X$  to the low-valent transition metal catalyst  $[M]^n$  to form the intermediate  $R^1-[M]^{n+2}-X$ , (2) transmetalation of nucleophiles  $R^2-M^2$  with  $R^1-[M]^{n+2}-X$  to form the intermediate  $R^1-[M]^{n+2}-R^2$ , and (3) reductive elimination of intermediate  $R^1-[M]^{n+2}-R^2$  to release the desired coupling product  $R^1-R^2$  and regenerate the low-valent  $[M]^n$  species, thus completing a catalytic cycle. In this catalytic cycle, the electrophile in the oxidative addition step is usually an organic halide or pseudo-halide; it can be aryl or alkenyl halides and sometimes even alkyl halides. They act

as an oxidant to oxidize the low-valent metal catalyst  $[M]^n$ ; at last their organic group goes on to form part of the final cross-coupling product. As a result, no extra oxidant is required.

In oxidative cross-coupling reactions, the general catalytic cycle could be elucidated as in Scheme 1.8 [9]. As shown in Scheme 1.8, the catalytic cycle generally starts from a high-valent metal species  $X^1-[M]^{n+2}-X^2$ , which has two different leaving groups  $X^1$  and  $X^2$ . Consequent transmetalation of two different nucleophiles  $R^1M^1$  and  $R^2M^2$  with the high-valent metal species  $X^1-[M]^{n+2}-X^2$  affords a  $R^1-[M]^{n+2}-R^2$  intermediate, followed by reductive elimination to afford the desired coupling product  $R^1-R^2$  and release a low-valent metal species  $[M]^n$ . In order to restart the catalytic cycle, a proper oxidant is needed to reoxidize  $[M]^n$  to regenerate the  $X^1[M]^{n+2}X^2$  species. From the catalytic cycle in Scheme 1.8, we can see that both of the two nucleophiles are involved in the final product, while the oxidant only acts as the electron acceptor to reoxidize the  $[M]^n$  species without going into the coupling product. In oxidative cross-coupling, both nucleophiles are electron-rich species, and an appropriate oxidant is required to remove the extra electrons for their chemical bond formation. Therefore,

Along with the development of oxidative cross-couplings, more and more single-electron transfer (SET) processes become common phenomena with first row of transition metals as the catalyst. For radical processes in oxidative cross-couplings between two nucleophiles, it could be classified into four models based on radical intermediates (Scheme 1.9): In model **I**, the bond formation between radical ( $Nu^1\bullet$ ) and anion ( $Nu^2$ ); in model **II**, the bond formation between cation ( $Nu^1+$ ) and anion ( $Nu^2$ ); in model **III**, the bond formation between radical ( $Nu^1\bullet$ ) and radical ( $Nu^2\bullet$ ); and in model **IV**, the bond formation between radical ( $Nu^1\bullet$ ) and cation ( $Nu^2+$ ). In this transformation, most of the examples were classified into model **I** and model **II**, although there are only few examples presented for model **III** and model **IV**.



**Scheme 1.9** Four models for the final bond formations in radical oxidative cross-couplings

## 1.4 Development and Outlook

Currently, tremendous amount of excellent work is still publishing on oxidative cross-couplings between two different nucleophiles especially those C-H nucleophiles. However, challenges still remain in this research area, such as the selective control of the reactive site of hydrocarbons. Moreover, understandings of this concept are still superficial and incomplete, and the mechanistic study in this area is still in its primary stage. Along with the development of transition metal-catalyzed oxidative cross-couplings, especially of those none noble transition metal catalysis system, radical process becomes dominating in the research area. More and more examples will be developed in the future. And there are still many unexplored methods and unknown insightful mechanism left. Therefore, chances and challenges are still remaining, such as finding milder reaction conditions and proper ways to control the reactivity and chemoselectivity of radical species. Thus developing new, greener, and more efficient radical oxidative cross-couplings is still an urgent work in the future. Furthermore, external oxidant-free oxidative cross-coupling between two C-H with the release of hydrogen gas would be a very promising direction for oxidative cross-couplings. This area is more atomic economy and consistent with sustainable development, with no wasteful by-products or oxidation side reactions, and the environment is sustainable. It holds significant potential for the applications to a series of organic reactions, and scientists paid more and more attention on this field.

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# Chapter 2

## Transition Metal-Catalyzed Oxidative Coupling Involving Two Organometallic Compounds



Hua Zhang

### 2.1 Introduction

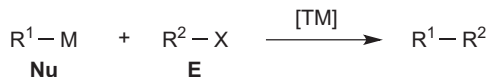
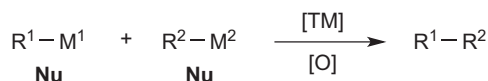
Organometallic compounds are a kind of compounds containing at least one chemical bond between a carbon atom and a metal atom (alkaline, alkaline earth, transition metal, and metalloid), which are widely applied in both research and industrial chemical reactions. These compounds could be used both as homogeneous catalysts and stoichiometric reagents in chemical synthesis to afford pharmaceuticals, agrochemicals, polymers, and many other types of practical products.

Due to their relatively high reactivity, organometallic compounds act as good nucleophiles in numerous organic reactions. Since the first report of Kumada coupling utilizing Grignard reagents, various transition metal-catalyzed cross-coupling reactions employing different organometallic compounds as nucleophiles and organic halides or pseudohalides as electrophiles were developed (Scheme 2.1). During the past several decades, these couplings have been developed to serve as one of the most important methods toward the carbon–carbon bond formation in organic synthesis. Therefore, Heck, Negishi, and Suzuki were awarded the 2010 Nobel Prize in Chemistry for their contribution to palladium-catalyzed cross-coupling reactions.

As an emerging alternative to traditional coupling, transition metal-catalyzed oxidative coupling involving two nucleophiles in the presence of an oxidant has gain rapid development in the past two decades [1–3]. The content of this chapter is focused on transition metal-catalyzed oxidative coupling involving two organometallic compounds to construct carbon–carbon bonds within a context of different chemical oxidants (Scheme 2.2). Therefore, transition metal-mediated oxidative coupling

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**Scheme 2.1** Cross-coupling**Scheme 2.2** Oxidative coupling

[4–12], transition metal-free oxidative coupling [13–20], transition metal-catalyzed electrooxidative coupling [21, 22], and transition metal-catalyzed oxidative coupling without evident oxidants [23–31] are not discussed in this chapter.

## 2.2 Inorganic Oxidants

In the presence of slowly adding iodine as oxidant, oxidative homo-coupling of organostannanes was achieved via copper and manganese catalysis (Scheme 2.3) [32]. Aryl-, alkenyl-, and alkynylstannanes were efficiently converted to symmetrical biaryls, 1,3-dienes, and 1,3-diynes.

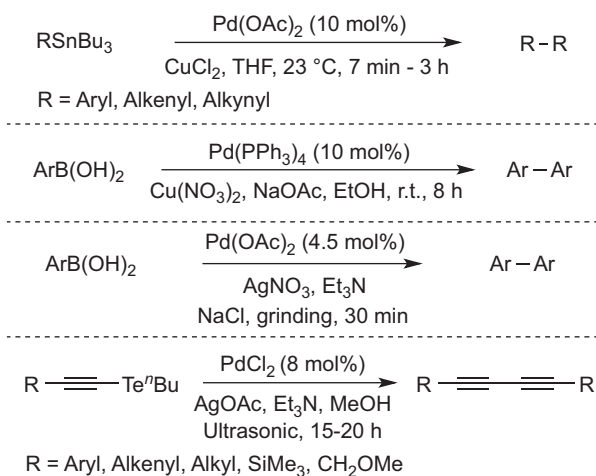
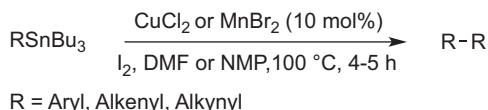
By using copper salts or silver salts as oxidants, palladium-catalyzed oxidative homo-couplings of organostannanes, arylboronic acids, and *n*-butyl alkynyltellurides were achieved to afford various symmetrical biaryls, 1,3-dienes, and 1,3-diynes under mild conditions (Scheme 2.4) [33–36]. Copper(II) salts such as  $\text{CuCl}_2$  and  $\text{Cu}(\text{NO}_3)_2$  and silver(I) salts such as  $\text{AgNO}_3$  and  $\text{AgOAc}$  were effective oxidants in these processes.

In the presence of  $\text{Ag}_2\text{O}$  as oxidant,  $\text{CrCl}_2$  could catalyze oxidative homo-coupling of alkyl-, alkenyl-, and arylboronic acids under mild conditions (Scheme 2.5) [37]. The reaction of an equimolar amount of arylboronic acid and alkyl boronic acid was also tested, in which a 1:1.1 mixture of  $\text{Csp}^2\text{-Csp}^3$  cross-coupling product and  $\text{Csp}^3\text{-Csp}^3$  homo-coupling product was obtained.

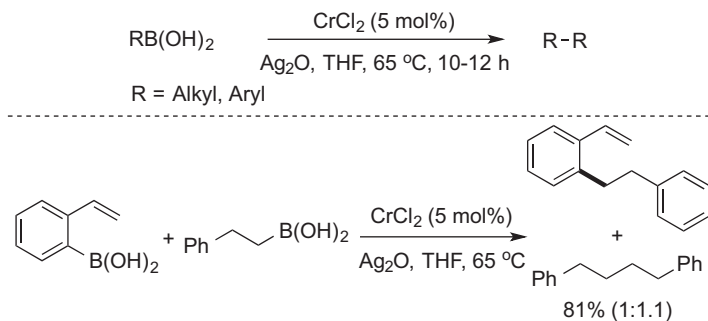
Potassium alkenyltrifluoroborates were also suitable substrates in the palladium-catalyzed oxidative homo-coupling using  $\text{Ag}_2\text{O}$  as oxidant to afford symmetrical 1,3-dienes (Scheme 2.6) [38]. The oxidative cross-coupling of different potassium alkenyltrifluoroborates was also attempted, in which cross-coupling products were obtained as major products in most cases.

Generally, transition metal-catalyzed oxidative cross-coupling involving two organometallic compounds using inorganic oxidants was considered to proceed via the mechanism shown in Scheme 2.7. Taking palladium catalysis as example, the initial step involves the transmetalation of one organometallic compound with Pd(II) catalyst. The obtained intermediate  $\text{R}^1\text{Pd}(\text{II})\text{X}$  then undergoes a second transmetalation with another organometallic compound to provide  $\text{R}^1\text{Pd}(\text{II})\text{R}^2$ , which undergoes reductive elimination to furnish the cross-coupling product and Pd(0). Finally, the inorganic oxidant oxidizes Pd(0) species to regenerate Pd(II) species.

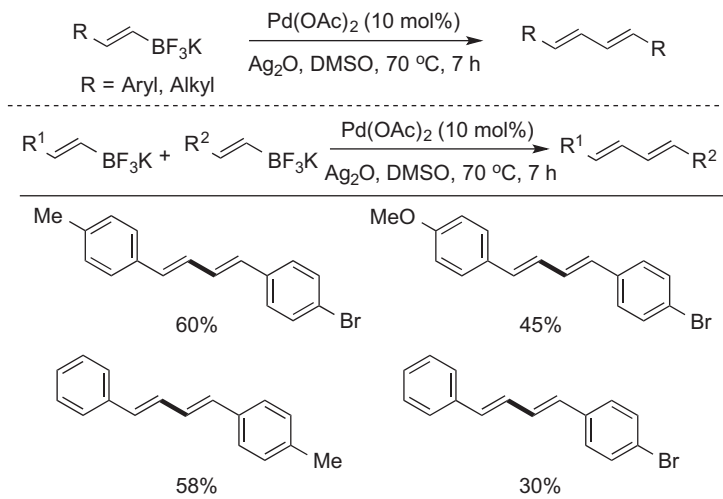
**Scheme 2.3** Cu- and Mn-catalyzed oxidative homo-coupling of organostannanes



**Scheme 2.4** Pd-catalyzed oxidative homo-couplings of organostannanes, arylboronic acids, and *n*-butyl alkynyltellurides

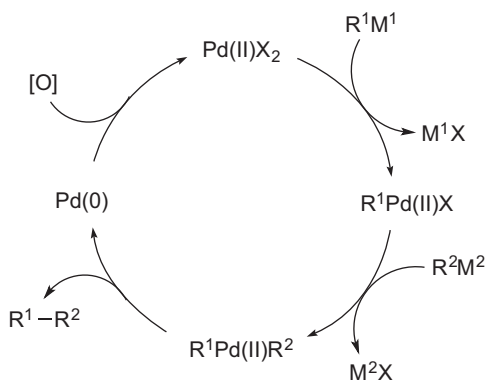


**Scheme 2.5** Cr-catalyzed oxidative homo-coupling of organoboronic acids



**Scheme 2.6** Pd-catalyzed oxidative homo-coupling of potassium alkenyltrifluoroborates

**Scheme 2.7** Proposed mechanism for Pd-catalyzed oxidative cross-coupling involving two organometallic compounds using inorganic oxidants



## 2.3 Organic Oxidant

### 2.3.1 1,2-Dihaloethane Derivatives

#### 2.3.1.1 Homo-coupling

Early in 1997, palladium-catalyzed oxidative homo-coupling of aryl-, vinyl-, and alkynylstannanes was developed in the presence of 1,2-dichloroethane as the oxidant under mild conditions (Scheme 2.8) [39]. Acrylate dibromide derivatives were also suitable oxidants in the palladium-catalyzed oxidative homo-coupling of arylstannanes, arylboronic acids, and arylfluorosilanes to afford biaryls in good yields (Scheme 2.9) [40]. In a similar manner, the palladium-catalyzed oxidative