# 1
# Oxidative Coupling – Bonding between Two Nucleophiles

## 1.1
## Introduction/General

### 1.1.1
### What is Oxidative Cross-Coupling?

Transition-metal-catalyzed cross-coupling reactions have been developed to be a powerful tool for the construction of various chemical bonds since its initial discovery in the last century [1]. Owing to their great capacity for different types of bond formation, they have been widely applied in the areas of pharmaceuticals, agriculture, food industries, materials sciences, and so on [2]. Normally, in those classical cross-coupling reactions, bond formations occur between an electrophile and a nucleophile in the presence of a transition metal catalyst (Scheme 1.1, Eq. (1.1)) [3], in which no extra redox reagents are required for achieving the bond formation [4]. Both the electrophiles and the organometallic nucleophiles are usually obtained from pre-functionalization of their corresponding R–Hs (R equals C, N, O, S, etc.). However, with the development of modern synthetic methodology and the urgent demand for green and economical synthesis, traditional cross-couplings face great challenges on account of their inevitable drawbacks such as low atom economy and considerable generation of useless by-products [1, 5, 6]. At this point, direct bond formation between two nucleophiles, especially two hydrocarbons, would be an ideal alternative. As the coupling between two nucleophiles has to use an extra oxidant to promote bond formation, this type of couplings are named as oxidative cross-coupling (Scheme 1.1, Eq. (1.2)) [4, 7].

### 1.1.2
### Why Oxidative Cross-Coupling?

Oxidative cross-couplings have gone through an extremely rapid development over the past decades, owing to their great potential for green and economic synthesis as well as considerable advantages over traditional cross-couplings, especially those couplings between two CH nucleophiles [8, 9]. Normally, nucleophiles can be divided into several classes: MX, CM, CH, or XH (X = N, O, S, etc.). In the MX group, salts such as metal halides are employed as reactants to

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Classic cross-coupling:

$$\mathrm{Nu} + \mathrm{E} \xrightarrow{\mathrm{TM}} \mathrm{Nu{-}E} \qquad (1)$$

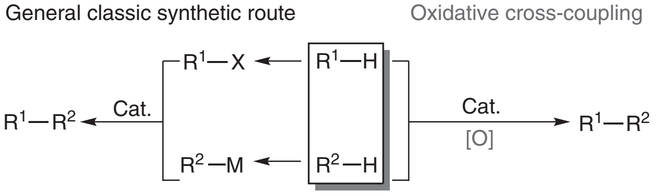
Oxidative cross-coupling:

$$\mathrm{Nu^1} + \mathrm{Nu^2} \xrightarrow{\mathrm{TM/[O]}} \mathrm{Nu^1{-}Nu^2} \qquad (2)$$

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

form carbon–halogen bonds. In the C–M group, organometallic reagents serve as efficient carbon nucleophiles, which have been widely applied in transition-metal-catalyzed coupling reactions. Notably, CH or XH (X = N, O, S, etc.) nucleophiles exist extensively in nature, and they represent the most abundant nucleophiles. In the beginning, oxidative couplings focused on bond formations between two organometallic reagents under transition metal catalysis [10]. However, this bond formation mode does not meet the requirement of modern sustainable chemistry [11], since the organometallic reagents need to be derived from the corresponding hydrocarbons. In the following several years, replacing the organometallic reagents with various C–H or X–H nucleophiles to achieve greener oxidative couplings such as $R^1$–H/$R^2$–$M^2$ and $R^1$–H/$R^2$–H dominated the research area, in which numerous outstanding works have been reported [12–15]. Especially, transition-metal-catalyzed oxidative $R^1$–H/$R^2$–H coupling with air or $O_2$ as the oxidant is no doubt an ideal approach for bond formations [16, 17].

Taking the comparison between traditional cross-couplings and oxidative $R^1$–H/$R^2$–H couplings into account, usually, the electrophilic organohalides and the nucleophilic organometal reagents are more or less obtained from their corresponding C–H compounds in order to make the carbon site reactive enough to achieve C–C bond formation under catalytic conditions (Scheme 1.2, *General Classic Synthetic Route*). In this case, more reaction steps and more waste are unavoidable. Along with the development of chemical societies and the requirement for more sustainable chemical process arises the question whether C–C bond formations can be achieved directly from the C–H substrates that do not need to be pre-functionalized. It will greatly shorten the synthetic route and reduce the generation of waste. To form C–H bonds from C–H substrates, only

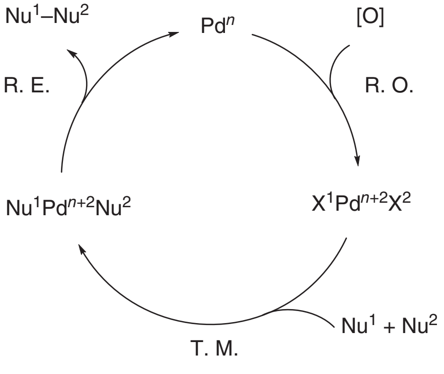


**Scheme 1.2** Comparison between classic synthetic route and oxidative cross-coupling.

hydrogen has to be released. Therefore, atom economy is considerably enhanced, demonstrating great potential for pharmaceutical and industrial application. Usually, an oxidant is required to accept the hydrogen; therefore, it was named as oxidative cross-coupling. Until now, various oxidants have been developed including peroxides, copper salts, silver salts, and so on [4, 7]. Oxygen gas is perhaps the most appealing oxidant for oxidative cross-couplings, as $H_2O$ is usually the side product. Recently, cross-coupling with hydrogen revolution has been demonstrated to achieve C–C and C–heteroatom bond formations in the absence of an external oxidant [18–24]. Those developments put forward the area of oxidative cross-coupling into more practical and more environmentally benign processes.

### 1.1.3
### How Does Oxidative Cross-Coupling Work?

In the initially reported oxidative cross-coupling reactions, palladium catalysis was predominantly used for a long time for achieving various bond formations between two nucleophiles. For the mechanistic aspect, the general catalytic cycle of palladium-catalyzed oxidative coupling reactions can be elucidated from Scheme 1.3 [25]. As shown in Scheme 1.3, the catalytic cycle generally starts from a high valent Pd species. Consequent transmetalation of two different nucleophiles with the Pd species affords a $Nu^1$–Pd–$Nu^2$ intermediate, followed by reductive elimination to afford the coupling product $Nu^1$–$Nu^2$ and release of a low valent palladium species [$Pd^n$], which can be reoxidized by a proper oxidant to regenerate the [$Pd^{n+2}$] species. From the catalytic cycle in Scheme 1.3, we can see that both of the nucleophiles are involved in the final product, while the oxidant only acts as the electron acceptor to reoxidize the [$Pd^n$] species without going into the coupling product. Generally, most of the palladium-catalyzed reactions are not supposed to be radical processes. Along with the development of oxidative cross-couplings, more and more first-row transition metal catalysis



**Scheme 1.3** General catalytic cycle of palladium-catalyzed oxidative cross-coupling reactions.

has been discovered, in which single-electron transfer (SET) processes become common phenomena.

### 1.1.4
### Development and Outlook

Although oxidative cross-couplings between two nucleophiles form a still "young" research field compared to traditional cross-couplings, numerous excellent works have been reported on oxidative cross-couplings between two different hydrocarbons. In addition, several comprehensive reviews have been reported to summarize the recent advances in oxidative couplings between two C–H or X–H nucleophiles. However, challenges still remain in this research area. As hydrocarbons usually have different reactive C–H bonds, achieving chemoselective and regioselective C–H functionalization is still a challenging task. Moreover, understanding of this concept is still superficial and incomplete, and the mechanistic study in this area is still in its primary stage. In addition, developing mild and efficient transition-metal-catalyzed oxidative couplings between two C–H or X–H nucleophiles with air or $O_2$ as the terminal oxidant is still in urgent demand. Further, external-oxidant-free oxidative cross-coupling between two hydrocarbons with liberation of hydrogen gas would also be a promising direction for oxidative cross-couplings.

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