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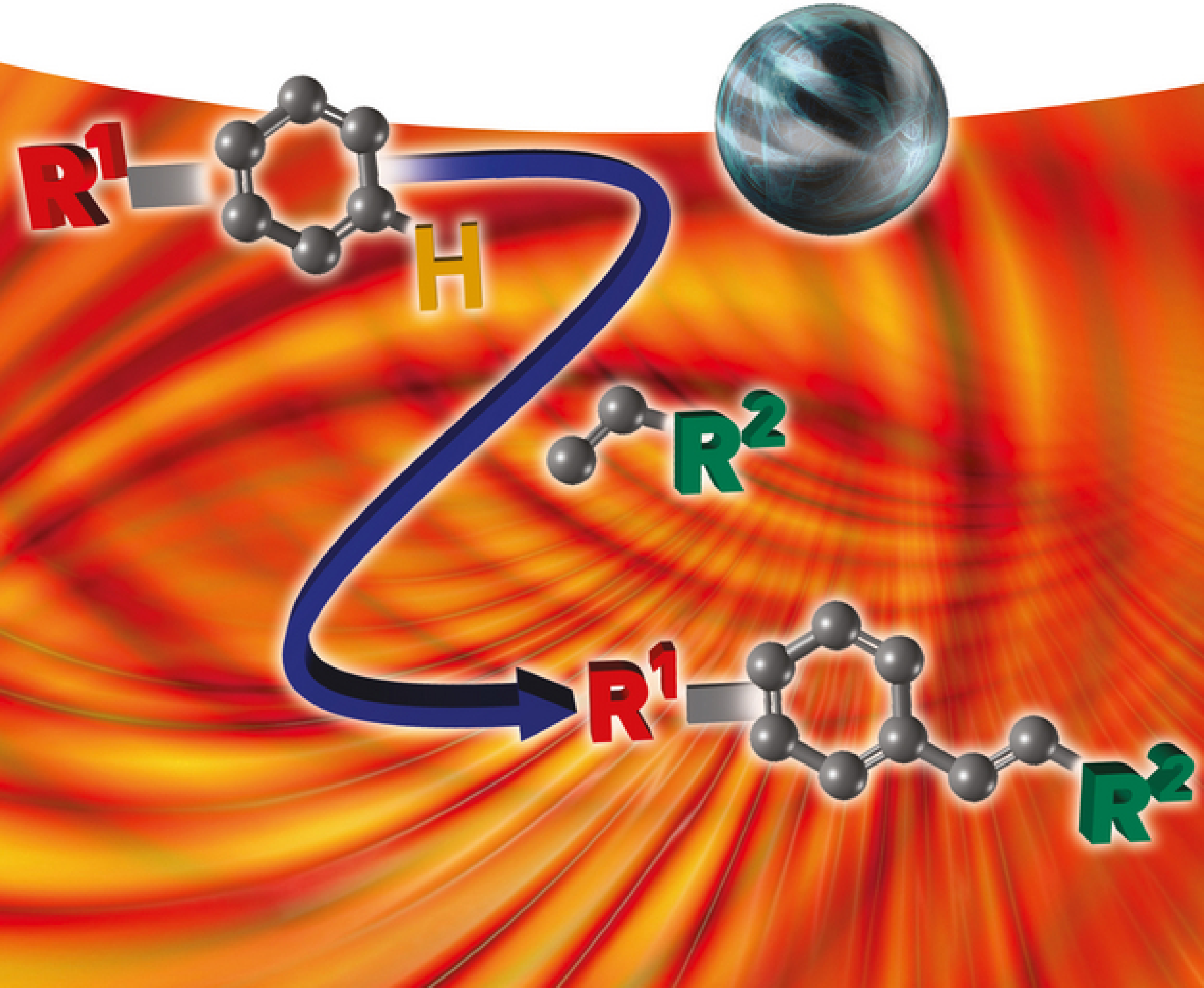

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Contents

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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Hua Zhang, and Chuan He.

Classic cross-coupling:

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

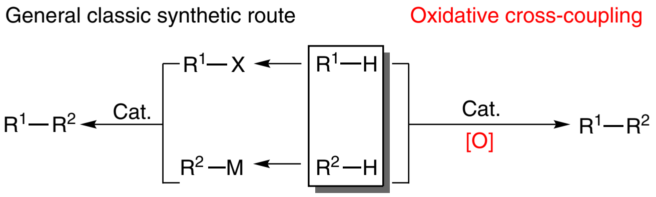
Oxidative cross-coupling:

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

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

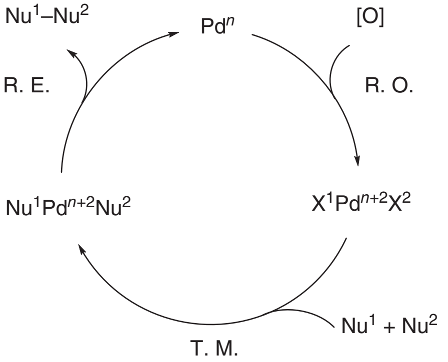


Scheme 1.2 Comparison between classic synthetic route and oxidative cross-coupling.

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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2
Organometals as Nucleophiles

2.1
Classification and Applications of Organometallic Reagents

It is noteworthy that “organometallic reagents” are slightly different from “organometallic compounds.” Generally, in the narrow sense, organometallic reagents are compounds that include “meta”-organic σ-bonds and they are widely used in organic synthesis as an initial reactant, for example, the Grignard reagent. Here, the term “metals” usually also includes non-metal elements such as Si, Te, Se, and B. These elements can also exhibit properties similar to other widely used metal elements in organic synthesis.

The different metals are classified into several kinds. It is known that more than 80% of the elements are metals, and theoretically most of them can form organometallic compounds. However, among all these metals, those widely used in organic synthesis are only a few. The metals typically used in organic synthesis are listed in Scheme 2.1.

Many of the organometallic compounds are named reagents, for example, the Grignard reagents. As Grignard reagents are also used in Kumada-C cross-coupling reactions, they are also named as Kumada reagents. Table 2.1 lists some common named reagents.

Organometallic reagents are widely used in organic synthesis. This is due to their relatively high reactivity. Most organometallic reagents are good nucleophiles, and many of them are air or moisture sensitive. Other ones are designed to be stable to oxygen and water, such as the Hiyama reagents, the Stille reagents, and the Suzuki reagents. These reagents are easy to handle and the reaction proceeds under mild conditions, and have been developing fast in the recent several decades. In 2010, Negishi and Suzuki were awarded the Nobel Prize in Chemistry, shared with Heck, for their contribution to palladium-catalyzed cross-coupling reactions.

It should also be mentioned that some organometallic reagents are toxic, particularly those containing heavy metals, such as organolead reagents, organotin reagents, and organomercury reagents. Although some of them were widely used, such as the organotin reagents in Stille coupling, the application of these reagents is strictly limited in the recent years.

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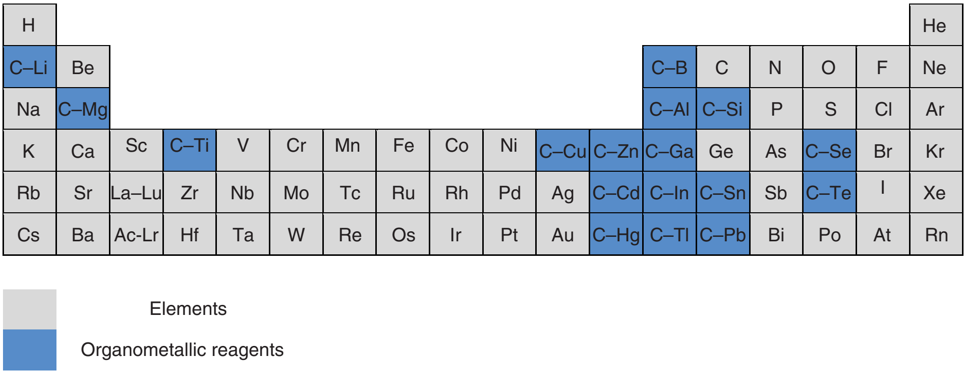


H																	He
C–Li	Be											C–B	C	N	O	F	Ne
Na	C–Mg											C–Al	C–Si	P	S	Cl	Ar
K	Ca	Sc	C–Ti	V	Cr	Mn	Fe	Co	Ni	C–Cu	C–Zn	C–Ga	Ge	As	C–Se	Br	Kr
Rb	Sr	La–Lu	Zr	Nb	Mo	Tc	Ru	Rh	Pd	Ag	C–Cd	C–In	C–Sn	Sb	C–Te	I	Xe
Cs	Ba	Ac-Lr	Hf	Ta	W	Re	Os	Ir	Pt	Au	C–Hg	C–Tl	C–Pb	Bi	Po	At	Rn

Scheme 2.1 Typical elements in organometallic reagents.

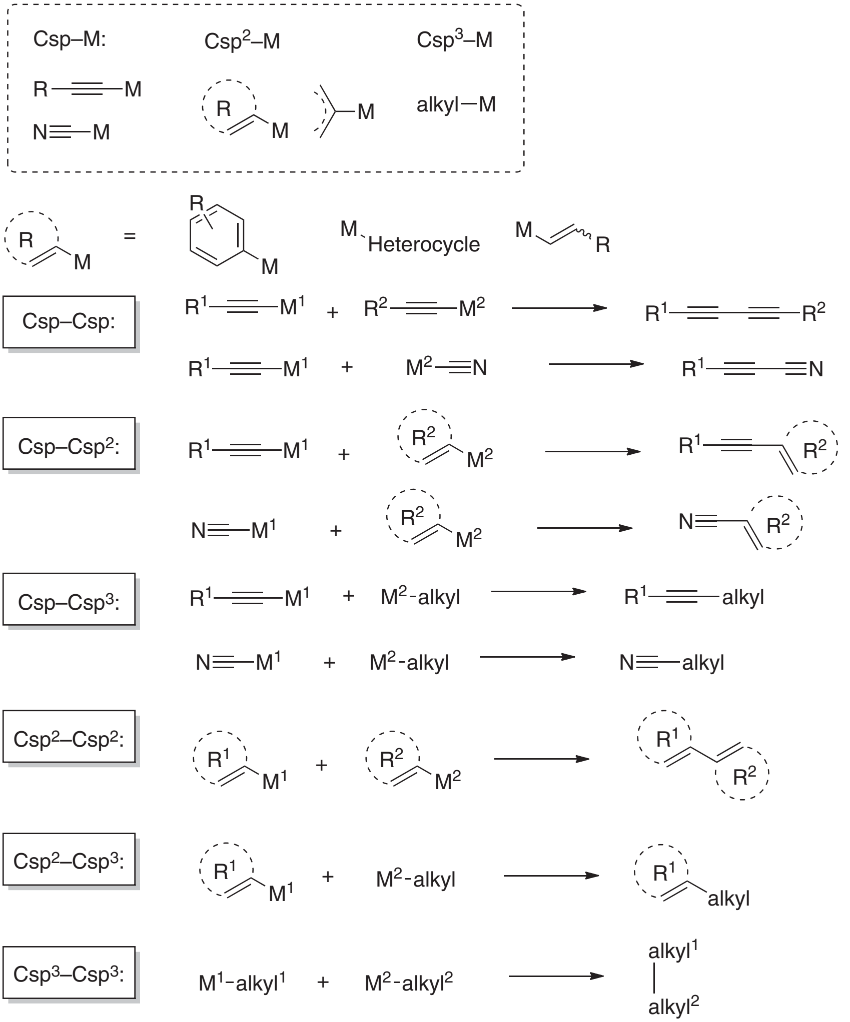
Table 2.1 Common named organometallic reagents.

"Metal" elements	Named reagents
Mg	Grignard/Kumada reagents
B	Suzuki reagents
Si	Hiyama reagents
Sn	Stille reagents
Zn	Negishi reagents

On the other side, organometallic reagents could also be classified according to the status of the carbon atom bonded to the metals. Carbon atoms exhibit three different types of hybridization state, and thus the organometallic reagents are classified into three types: Csp–M, Csp^2–M, and Csp^3–M. Csp carbons include the alkynyl carbon and cyano carbons; Csp^2 carbons include the alkenyl carbons, heterocyclic carbons, and aryl carbons; and Csp^3 carbons refer to the alkyl carbons. Theoretically, oxidative coupling can occur between any of these types of organometallic reagents. Oxidative cross-coupling reactions between these reagents are listed in Scheme 2.2.

2.2
Csp–M and Csp–M as Nucleophiles

Csp carbons represent two major types, the alkyne and cyano group, which means the coupling of Csp–Csp would have at least three forms: coupling of two alkynes, coupling of two cyano groups, and between alkynes and cyano groups. Of these three types, most reports are focused on the coupling between two alkynes.



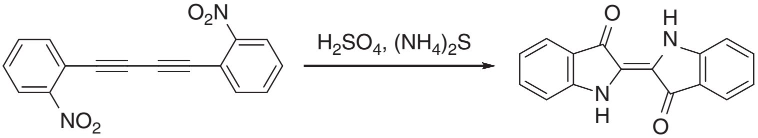
Scheme 2.2 Different oxidative cross-coupling reactions.

2.2.1

Alkyne–Alkyne Oxidative Coupling

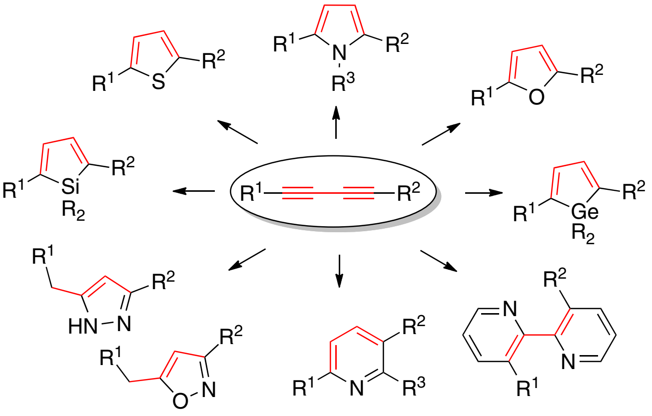
Alkyne–alkyne oxidative coupling reactions have a long history ever since 1869 or earlier, when Carl Glaser had treated copper(I) phenylacetylide generating from phenylacetylene with air to undergo smooth oxidative dimerization, known as the “Glaser coupling” decades later [1]. This coupling reaction gives the 1,3-diyne as the product. The 1,3-diynes, abbreviated as diynes, could be regarded as the basic structures of carbynes – the fourth carbon allotrope besides graphite, diamond, and fullerene, and they have shared some similar characters both in structures and in chemical properties.

Conjugated diynes are a class of compounds that bear the buta-1,3-diyne moieties. This conjugated structure has a rod-like, rigid linear shape, while the carbon atoms are highly unsaturated. Because of these properties, diynes would show both relative stability and reactivity [2, 3]. Applications of diynes can be dated back to 1882, when Baeyer had oxidized the diyne into indigo [1], as shown in Scheme 2.3. Indigo was used as a blue organic dye and was first isolated from plants thousands of years ago, and Baeyer's oxidation of the diyne may be one of the earliest recorded examples in the application of diynes.



Scheme 2.3

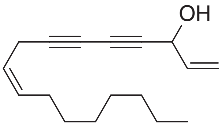
Shi and Lei have summarized the conversion of diynes to various heterocycles in 2014 [3]. Diynes could carry out cycloaddition with nucleophiles with elements such as S, O, and N, to form the corresponding thiophenes, furans, pyrroles, and other cycles, as shown in Scheme 2.4.



Scheme 2.4

Diynes also widely existed in nature, especially in herbal medicines [2, 4]. One of these examples is the (±) falcarinol isolated from *ginseng panax* [5], a famous and genuine tonic Chinese herbal medicine, shown in Scheme 2.5.

Diynes have highly unsaturated carbon chains in their structures, and they have unique spectral properties, such as microwave, infrared, and UV–vis spectra. These properties helped astronomers to confirm the existence of the polyynes in outer space [2]. On the other hand, the rod-like sp hybridized carbon chains are easy to stack in crystal cells and may be applied in functional materials [2].



(±) falcarinol

Scheme 2.5

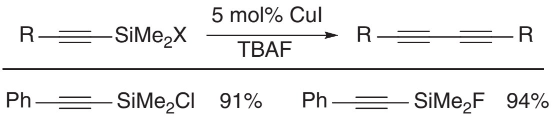
The synthetic chemistry of diyne is also a fast developing field [1]. Most oxidative coupling reactions to form diynes start directly from terminal alkynes. Typically, copper salt was employed as the catalyst to accelerate the reaction, and amines were also used as ligands to stabilize the Cu–acetylene complex. This reaction was first discovered by Glaser, and further improved by Eglinton and Hay, and named as the Glaser–Eglinton–Hay coupling [6–9]. Generally, terminal alkynes would be first activated by Cu salt to form the Cu(I) acetylides as the active intermediates, and the reaction could reach high atom efficiency. Although most of these reactions gave symmetric diynes, recent progress that has achieved unsymmetric diynes has also been reported [10]. Details would be discussed in Chapter 3.

In this section, the oxidative coupling between two alkynyl-metal reagents would be discussed. However, almost all reports in this field are of homocoupling reactions. Although the direct oxidative coupling of terminal alkynes have advantages in atom efficiency and milder reaction conditions, the utility of alkynyl-metal reagents could in some cases show better stability or efficiency under oxidative atmosphere.

2.2.1.1 **Alkynyl-Si**

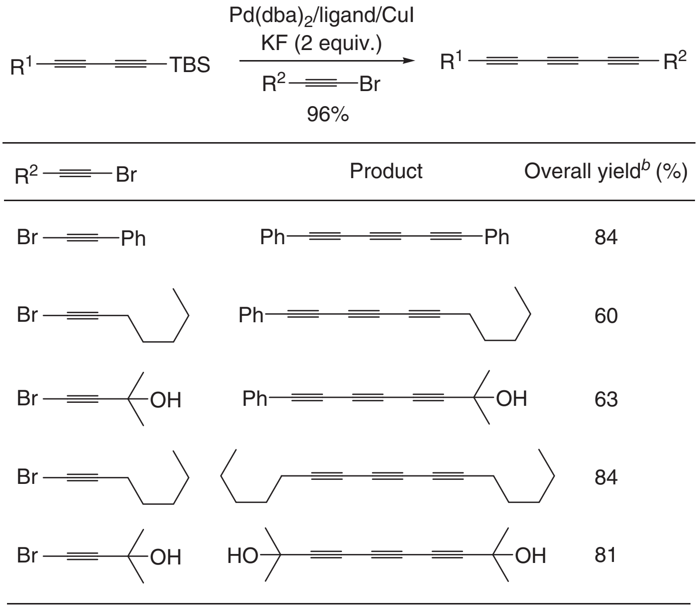
Organosilanes are widely used in Hiyama coupling reactions [11]. Alkynylsilanes are important protected forms of terminal alkynes. Examples include trimethylsilyl (TMS) ethyne in Sonogashira couplings; reactions could occur at the terminal alkyne site, with the silyl group remaining intact. In addition, the silyl protecting groups of alkynylsilanes may be easily removed simply in aqueous NaOH or under the addition of fluoride salt such as KF or TBAF.

One earlier report used TBAF as the activator to promote the homocoupling of organosilicon compounds including two alkynyl structures [12], as shown in Scheme 2.6.



Scheme 2.6

A report by Lei *et al.* utilized TBS (tert-butyldimethylsilyl)-protected diynes to react with 1-bromoalkynes to form the unsymmetric triynes in good yields [5], as shown in Scheme 2.7. KF was used as the activator to promote the reaction.



Scheme 2.7 Triynes from TBS protected diynes.

However, the fluoride ion is not necessary. Mori *et al.* have reported an example where alkynylsilanes could dimerize to form diynes under stoichiometric CuCl without the fluoride salt [13]. The author proposed that CuCl could coordinate with alkynylsilanes, and the alkynyl group may then transfer to copper to generate the alkynylcopper species directly; the alkynylcopper species could then undergo oxidative coupling to form symmetric diynes. Scheme 2.8 lists the substrate scope and yields. Different silyl groups were also tested and have shown significant effects. Oxygen-substituted silyl groups exhibit excellent reactivity, while the more hindered silyl groups such as $SiEt_3$ and Si^iPr_3 lead to zero yield even after 24 h. This method has also been used for the homocoupling of TMS-protected alkynyl tosylamides [14].

Later, Yoshida *et al.* reported an example where only catalytic amounts of metal salts were employed [15]. In this report, Pd-DPPP (1,3-bis(diphenylphosphino)-propane) complex was used in 5 mol% loading, with three examples yielding from 50% to 69%. Oxygen was the sole oxidant. Aryl and aliphatic alkynes showed no significant differences, as shown in Scheme 2.9. In addition, arylsilanes were also found to be good substrates.

2.2.1.2 **Alkynyl-Sn**

Organotin reagents are widely used in organic synthesis and are known as Stille reagents [16–19]. The advantages of alkynyltin reagents include the relative stability to moisture and oxygen and excellent selectivities in some reactions, and the disadvantages include the toxic tin element and high cost. The use of alkynyltrimethyltin to form diynes catalyzed by Pd complex has been reported