# Chapter 7
# Recent Advances in Cross-Coupling Reactions with Aryl Chlorides, Tosylates, and Mesylates

**Shintaro Noyori and Yasushi Nishihara**

**Abstract** In the past 10 years, the cross-coupling reactions of the relatively unreactive electrophilic aryl chlorides, -tosylates, and -mesylates have been extensively investigated. Strategies to promote oxidative addition toward inert chemical bonds have included the use of bulky, electron-rich ligands.

**Keywords** Aryl chlorides · Aryl tosylates · Aryl mesylates · Activation of unactivated bonds

## 7.1 Introduction

The palladium-catalyzed cross-coupling reactions of organometallic reagents with aryl halides are widely used in the field of synthetic organic chemistry. These reactions are very important for creating novel functional materials and bioactive substances [1, 2]. Although numerous cross-coupling reactions have achieved the formation of carbon–carbon bonds via the cleavage of the comparatively weak bonds of aryl iodides, bromides, and triflates (C($sp^2$)-I, -Br, and -OTf), the synthetic success of the cross-coupling reactions cleaving the more inert bonds such as aryl chlorides, tosylates, and mesylates (C($sp^2$)-Cl, OTs, and OMs) has lagged behind [3, 4]. In regard to the reaction mechanism, one of the reasons why the latter substrates have not been utilized in cross-couplings is that oxidative addition of aryl chlorides, tosylates, and mesylates to the palladium center does not readily

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S. Noyori · Y. Nishihara (✉)
Division of Earth, Life, and Molecular Sciences, Graduate School of Natural Science and Technology, Okayama University, 3-1-1 Tsushimanaka, Kita-ku,
Okayama 700-8530, Japan
e-mail: ynishiha@okayama-u.ac.jp

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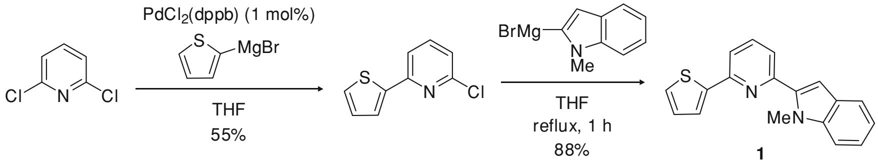
occur under standard conditions. However, around 2000 it began to be reported that the appropriate combination of certain ligands with the transition metal catalysts enables cross-coupling reactions of aryl chlorides, tosylates, and mesylates as coupling partners [5–7]. This chapter outlines the examples of the Ni and Pd-catalyzed cross-coupling reactions of the relatively inactive aryl electrophiles reported in recent years, as shown in Eq. 7.1.

$$\underset{\text{X = Cl, OTs, OMs}}{\text{Aryl—X}} \quad + \quad \underset{\substack{\text{R = Alkyl, Aryl, Alkynyl etc.} \\ \text{M = Mg, Zn, Sn, B, Si, etc.}}}{\text{M—R}} \quad \xrightarrow{\text{Ni, Pd catalyst}} \quad \text{Aryl—R} \tag{7.1}$$

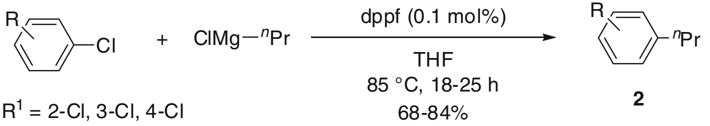
## 7.2 Kumada–Tamao–Corriu Coupling

In 1984, Tamao and Kumada synthesized the coupled product **1** by using 2,6-chloropyridine and two different heteroaryl Grignard reagents as coupling partners under palladium catalysis (Scheme 7.1) [8].



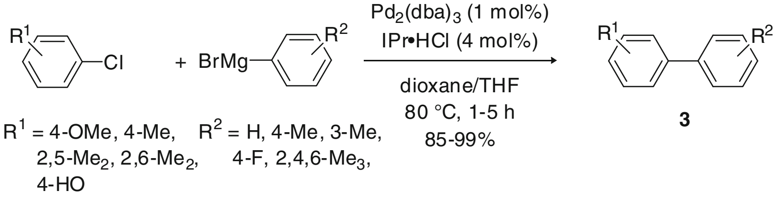
**Scheme 7.1** Kumada-Tamao-Corriu coupling of 2,6-chloropyridine with two different heteroaryl Grignard reagents

Later, Umeno and Katayama succeeded in the first cross-coupling reactions of alkyl Grignard reagents with aryl chlorides, rather than heteroaryl chlorides. The reactions of dichloroarenes with alkyl Grignard reagents afforded the corresponding monoalkylated products **2**. The double alkylated products were formed, but only in very small amounts (Eq. 7.2) [9].



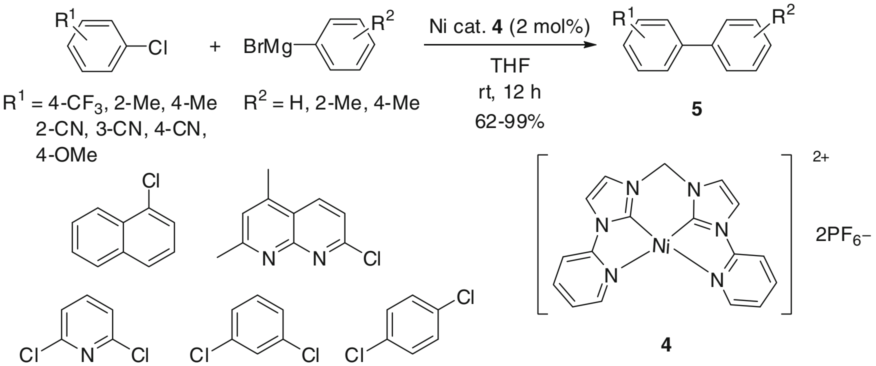
(7.2)

In 1999, Nolan et al. reported that Kumada–Tamao–Corriu coupling reactions, catalyzed by the palladium complexes having the *N*-heterocyclic carbene (NHC) ligands, took place across aryl chlorides bearing electron-donating groups to afford the corresponding biaryls **3** (Eq. 7.3) [10]. However, they also reported that the reaction of a bulky 2,6-dimethylphenyl chloride with 2,4,6-trimethylphenyl Grignard reagents did not generate a corresponding product at all due to the steric hindrance.



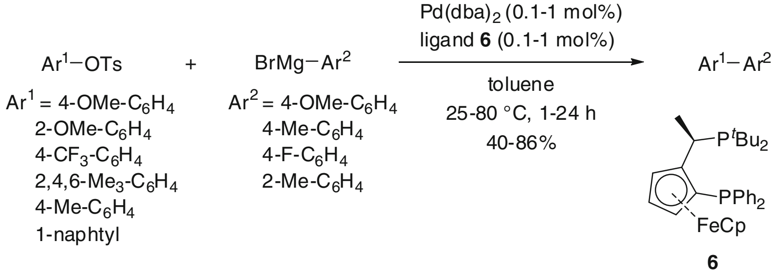
(7.3)

In addition, in 2007 Organ et al. reported that a wide variety of the substrates could be applied to Kumada–Tamao–Corriu coupling reactions with various heteroaryl and aryl chlorides [11]. Recently, Kumada–Tamao–Corriu coupling reactions of aryl chlorides using nickel catalysts, rather than palladium, have been reported [12, 13]. Along that trend, Chen revealed that the nickel complexes **4**, ligated by a tetradentate ligand for the Kumada–Tamao–Corriu coupling reactions, showed a high catalytic activity to generate the desired cross-coupled products **5** (Eq. 7.4) [14, 15].



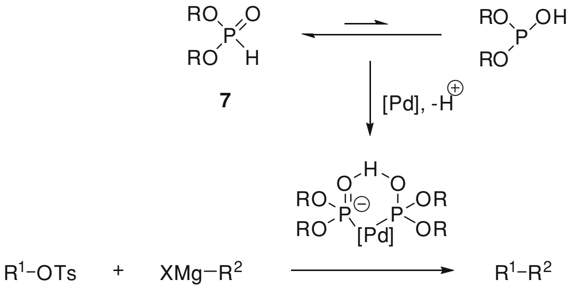
(7.4)

Endeavors to perform Kumada–Tamao–Corriu coupling reactions with aryl tosylates have been underway in recent years. For instance, Kumada–Tamao–Corriu couplings of electron-deficient aryl tosylates with arylmagnesium reagents were demonstrated by the research group of Leitner in 2002 [16]. Later, Hartwig et al. reported coupling reactions with the aryl tosylates having various substituents in 2005 (Eq. 7.5) [17, 18]. Using palladium catalysts ligated by the bidentate ligand **6**, they clarified the mechanism details of these reactions by elucidating stoichiometric reactions of the palladium complexes.



(7.5)

In 2006, Althammer et al. succeeded in Kumada–Tamao–Corriu coupling reactions of aryl tosylates under palladium catalysis by using the air-stable phosphonate ligands [19]. It is postulated that an equilibrium (shown in Scheme 7.2) exists for the phosphonate **7**, and the active species can be stabilized through a hydrogen bond in the reaction system [20].



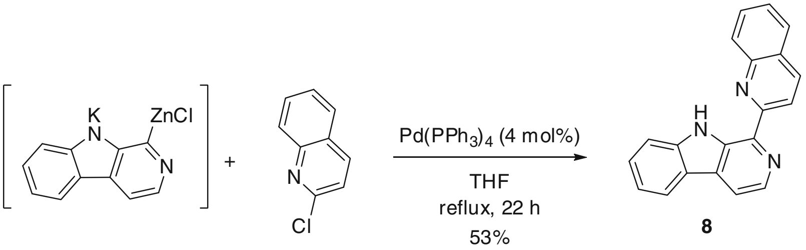
**Scheme 7.2** Kumada-Tamao-Corriu coupling of aryl tosylates using the air-stable phosphonate ligands

Knochel et al. have accomplished the cobalt(II)-catalyzed Kumada–Tamao–Corriu coupling reactions of aryl tosylates [21] and heteroaryl tosylates [22] with directing groups, achieving the in situ generation of arylcuprates from aryl bromides, Grignard reagents, and copper(I) cyanide.

## 7.3 Negishi Coupling

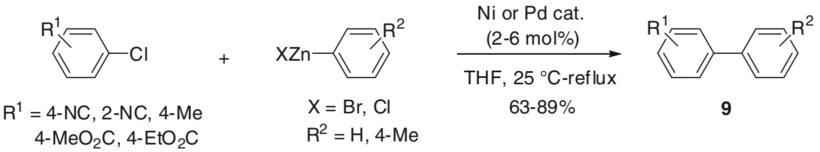
Negishi coupling reactions of organozinc compounds with aryl chlorides have been actively researched as well. In the 1980s, the studies started with the reactions of a variety of activated heteroaryl chlorides such as pyridines [23].

In 1994, Bracher and Hildebrand achieved the synthesis of nitramarine (**8**) by Negishi coupling of heteroaryl chlorides (Eq. 7.6) [24]. Negishi coupling of heteroaryl chlorides is a viable tool in various natural product syntheses to construct an array of carbon–carbon bonds (see Chap. 3).



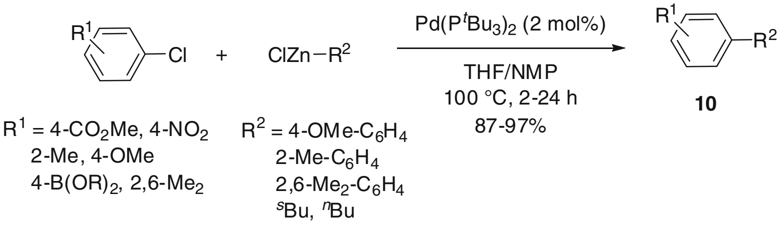
(7.6)

Negishi coupling reactions of the activated aryl chlorides bearing electron-withdrawing substituents was reported by Miller and Farrell in 1998 (Eq. 7.7) [25]. They accomplished Negishi coupling reactions of aryl chlorides substituted by cyano and ester groups catalyzed by palladium and nickel as the catalysts, giving rise to the corresponding biaryls **9**.



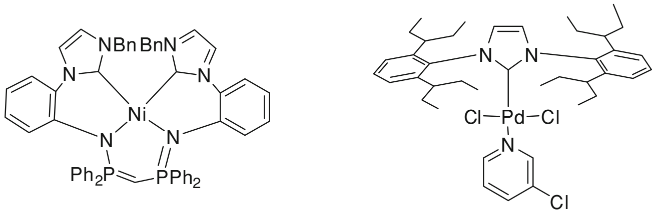
(7.7)

Dai and Fu explored Negishi couplings of electron-rich aryl chlorides with aryl- and alkylzinc reagents by using an electron-donating and bulky tri-*tert*-butylphosphine as the ligand under the palladium catalysis, giving rise to the corresponding biaryls and alkylated arenes **10** (Eq. 7.8) [26].



(7.8)

The analogous Negishi coupling reactions were found to take place, not only with the palladium catalysts [27–29], but also with the nickel catalysts [30]. For instance, Wang synthesized the NHC-ligated nickel complex **11** and applied this to Negishi coupling reactions with a variety of aryl chlorides [31, 32]. Recently, it was also reported that Negishi coupling of more inert aryl chlorides were smoothly accelerated under mild conditions by the palladium complex **12** bearing the NHC ligand (Fig. 7.1) [33, 34].

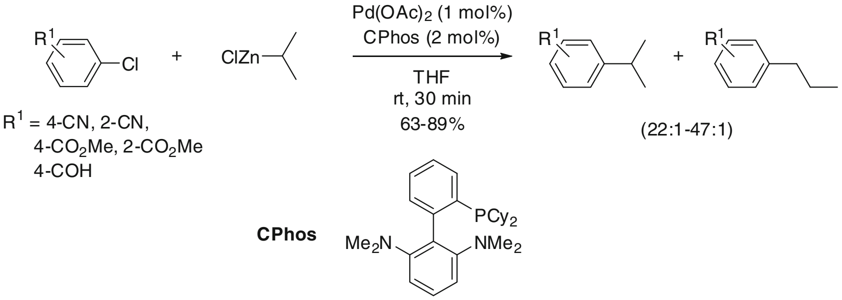


**11**

**12**: Pd-PEPPSI-IPent

**Fig. 7.1** Active catalysts for Negishi coupling reactions of various aryl chlorides

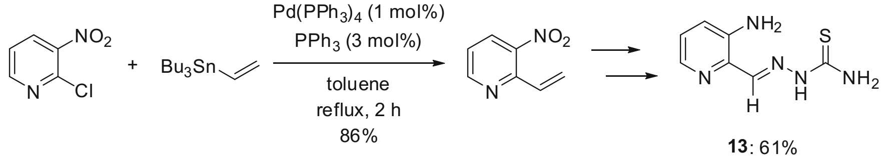
In contrast to the large number of Negishi coupling reactions of arylzinc reagents and aryl chlorides reported, in 2009 Buchwald succeeded in Negishi coupling reactions of secondary alkylzinc compounds and a variety of aryl chlorides by using CPhos as the ligand of the palladium catalyst (Eq. 7.9) [35].



(7.9)

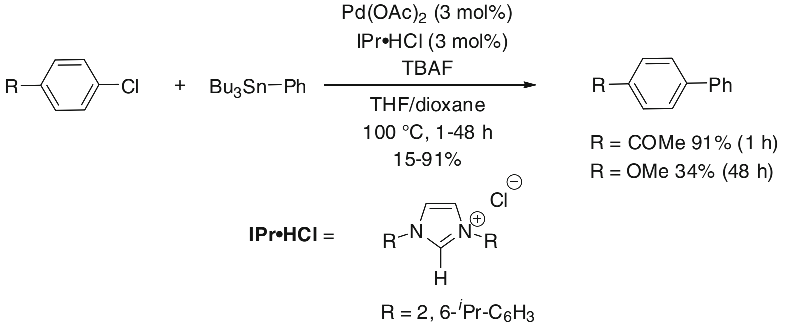
## 7.4 Migita–Kosugi–Stille Coupling

In 1998, Li et al. achieved the vinylation reactions of chloropyridine with the organotin compounds in the presence of the palladium catalyst; this was the key reaction in the synthesis of 3-AP (3-aminopyridine-2-carboxaldehyde thiosemicarbazonea) **13**, the ribonucleotide reductase inhibitor (Scheme 7.3) [36].



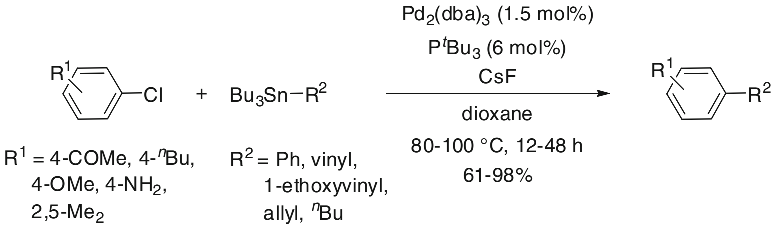
**Scheme 7.3** Vinylation reactions of chloropyridine by Migita-Kosugi-Stille coupling

In 2001, Grasa and Nolan succeeded in the synthesis of the corresponding biaryls by the Migita–Kosugi–Stille coupling reactions of aryl chlorides bearing electron-poor substituents with aryltin compounds, using the palladium catalysis ligated by NHC. However, a decrease in yield was observed in the coupling reactions with aryl chlorides having the electron-donating substituents (Eq. 7.10) [37].



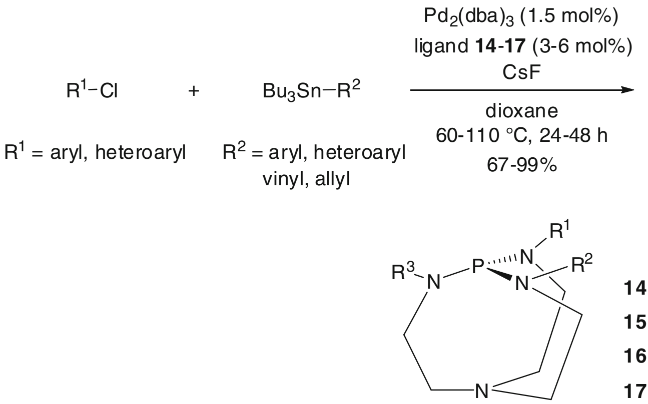
(7.10)

In 1999, Fu and Littke succeeded in the Migita–Kosugi–Stille coupling of aryl chlorides bearing electronic-rich substituents under palladium catalysis by using an electron-donating and bulky tri-*tert*-butylphosphine as the ligand. In addition, it was disclosed that not only aryltin compounds but also alkenyltin and alkyltin compounds could be used as the substrates (Eq. 7.11) [38, 39].



(7.11)

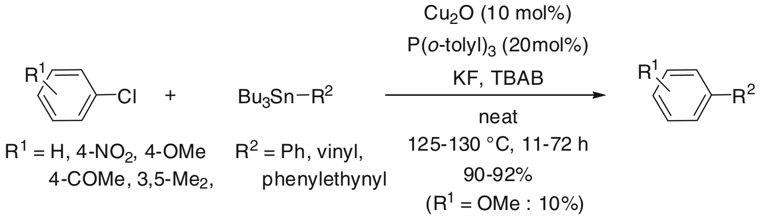
In 2004 Verkade et al. reported active catalyst systems to accelerate the coupling reactions of more inert aryl chlorides [40]. The electronic density on the phosphorus atom of the proazaphosphatrane ligands **14**–**17** (as shown in Eq. 7.12) is rather large because: (1) the three nitrogen atoms around the phosphorus atom share the same plane with phosphorus, and (2) the phosphorus atom has an interaction with the unpaired electron of the nitrogen atom at the bridgehead. As a result, the palladium catalysts having this ligand generally show high catalytic activity toward inert aryl chlorides.



**14**: $R^1$, $R^2$, $R^3$ = $^i$Bu
**15**: $R^1$, $R^2$ = $^i$Bu, $R^3$ = Bn
**16**: $R^1$, $R^2$ = Bn, $R^3$ = $^i$Bu,
**17**: $R^1$, $R^2$, $R^3$ = Bn

(7.12)

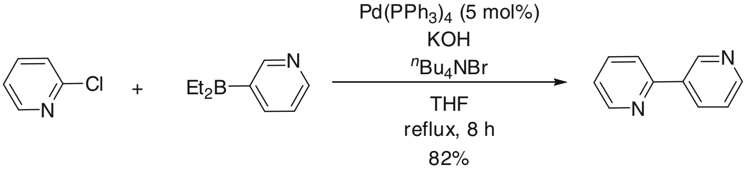
Although the use of palladium as a catalyst is frequent in the cross-coupling reactions of aryl chlorides [41–43], in 2006 Zhang reported that copper(I) oxide can catalyze the coupling reactions of aryl chlorides and aryltin compounds through the assistance of appropriate activators (Eq. 7.13) [44].



(7.13)

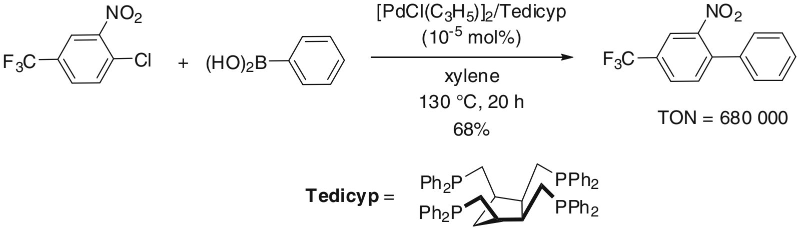
## 7.5 Suzuki–Miyaura Coupling

In the 1980s, Suzuki–Miyaura coupling reactions of aryl chlorides with organoboron compounds were reported for the first time by Terashima (Eq. 7.14) [45]. In this reaction, the desired bipyridine was obtained from 2-chloropyridine as a coupling partner by using $Pd(PPh_3)_4$ as the catalyst.



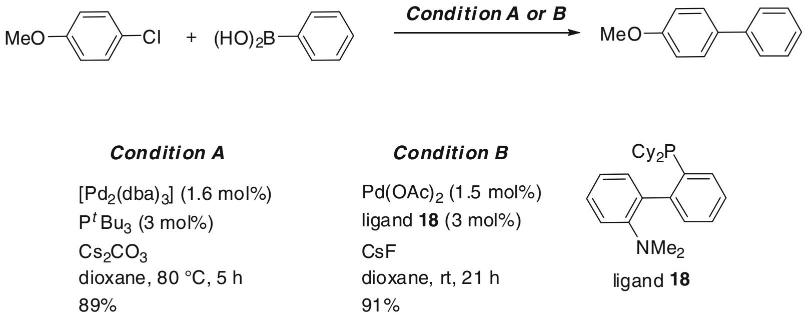
(7.14)

Through the use of palladium with triarylphosphine ligands, the cross-coupling reactions of a variety of heteroaromatic chlorides were achieved. In the 1990s, it began to be reported that the cross-coupling reactions of arylboronic acids with aryl chlorides afforded the target biaryls utilizing a substrate bearing electron-withdrawing groups, such as nitro, cyano, and acetyl groups, in the presence of the palladium catalysts ligated with arylphosphines [46]. Moreover, reactions using the catalysts with high turnover numbers (TONs) were reported (Eq. 7.15) [47]



(7.15)

Pioneering research in this field was reported in 1998. Fu accomplished the cross-coupling of electron-rich aryl chlorides utilizing a bulky alkylated phosphine ligand (Eq. 7.16, condition A) [48]. Meanwhile, Buchwald succeeded in obtaining the cross-coupled products in high yields from unactivated aryl chlorides by using the phosphine ligand **18**, consisting of a biaryl backbone (Eq. 7.16, condition B) [49–52].



(7.16)

Since the initial discovery, a large number of researchers have created a myriad of these catalysts for effective Suzuki–Miyaura coupling reactions of aryl chlorides (Fig. 7.2). In recent years, copious examples of the Suzuki–Miyaura coupling reactions accomplished with highly electron-donating, bulky phosphorus-containing ligands [53–60], the biaryl-type phosphine ligands [61–63], and the NHC (*N*-hetrocyclic carbene) ligands [64–67] of the palladium catalysts have been reported [53, 54, 63, 68].

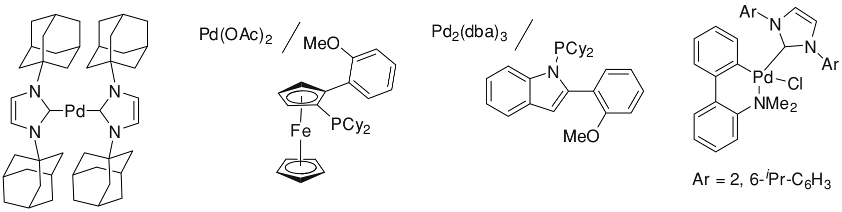
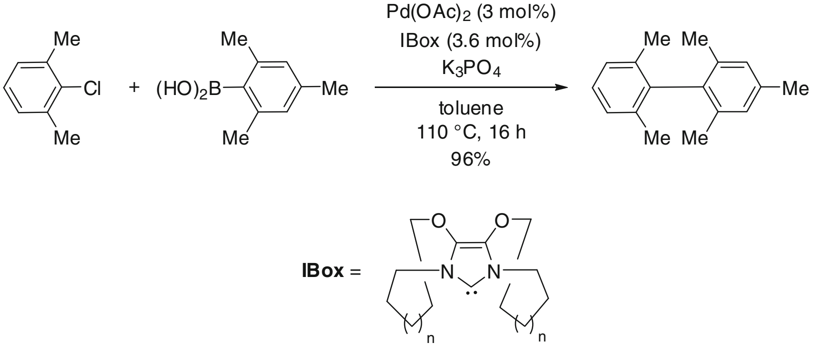


**Fig. 7.2** Various palladium catalysts effective for Suzuki–Miyaura couplings of aryl chlorides

Enhancements such as milder reaction conditions have also been attained; for instance, the room-temperature reactions of highly active catalysts have been developed. In 2004, the NHC ligands with a powerful ability to accelerate Suzuki–Miyaura coupling reactions toward the bulky and electron-rich substrates were synthesized (Eq. 7.17) [69]. In these reactions, even if both the aryl chlorides and the arylboronic acids were sterically congested, the corresponding biaryl compounds were obtained in high yields.



(7.17)

In 2005, Buchwald similarly reported that the Suzuki–Miyaura couplings occured for the bulky substrates in water by introducing sodium sulphonate into the aryl group of the biaryl-type ligands [70]. It was reported that other ligands involving polymers such as the silica gel, tetraethylene glycol, and polystyrenes also showed a high performance [58, 71–74]. In the reactions reported by Tsuji, the TEG-containing ligand **19** captures the metal catalysts, generating coordinatively unsaturated catalyst species (Fig. 7.3). The formed active catalysts accelerate oxidative addition of the carbon-chlorine bond, leading to the smooth cross-coupling reactions of the electron-rich aryl chlorides [75–78].

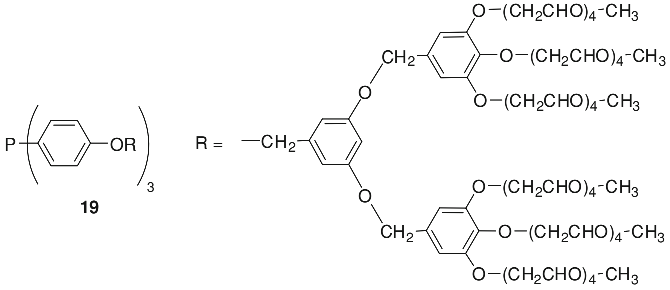
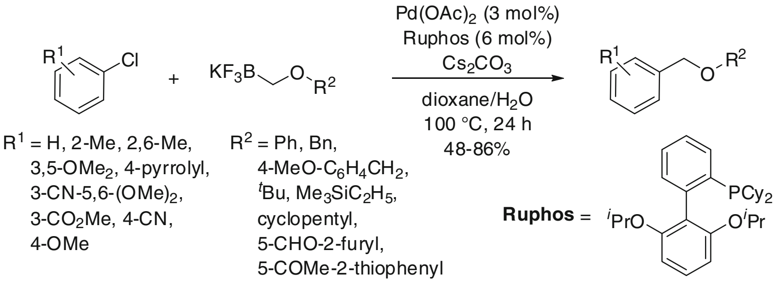


**Fig. 7.3** Active ligand containing the TEG moieties

In addition to the aforementioned active catalysts, recently recyclable heterogeneous catalysts were synthesized for use in Suzuki–Miyaura couplings [79]. This new type of catalyst consists of nano particles of iron oxide ($Fe_3O_4$) on silica gel; the film-supported catalysts have been used for the Suzuki–Miyaura couplings. The catalysts were found to be easily separable from the reaction mixtures with a magnet after completion of the reactions, and they can be recycled many times. Moreover, the catalysts can be applicable to Sonogashira–Hagiwara as well as Migita–Kosugi–Stille couplings under slightly modified reaction conditions.

Although arylboronic acids have been widely utilized as coupling partners in the Suzuki–Miyaura coupling reactions of aryl chlorides, in 2004 Buchwald reported coupling reactions utilizing potassium aryltrifluoroborates [80]. Furthermore, Molander reported Suzuki–Miyaura coupling reactions of aryl chlorides with alkoxymethyltrifluoroborates (Eq. 7.18) [81] and with cyclopropyl- and cyclobutyltrifluoroborates (Scheme 7.4) [82].



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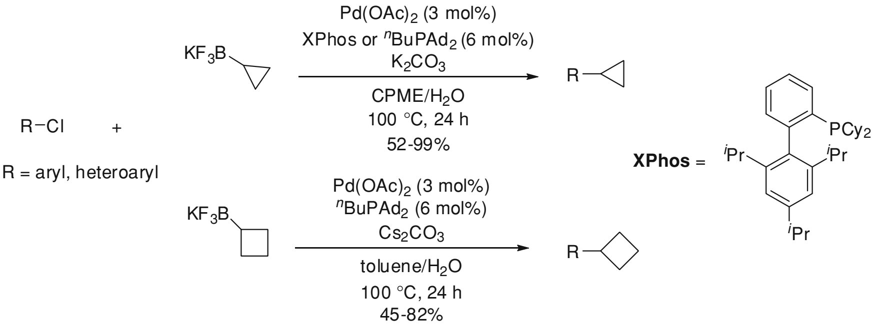
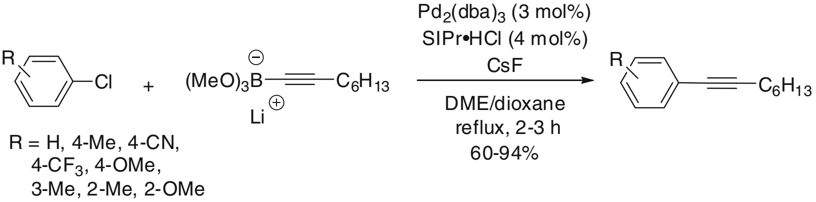


**Scheme 7.4** Suzuki-Miyaura coupling of aryl chlorides with cyclopropyl- and cyclobutyltrifluoroborates

Colobert reported the NHC-ligated-palladium-catalyzed Suzuki–Miyaura cross-coupling reactions of aryl chlorides with lithium alkynylborates as coupling partners to give the corresponding internal ethynes (Eq. 7.19) [83].



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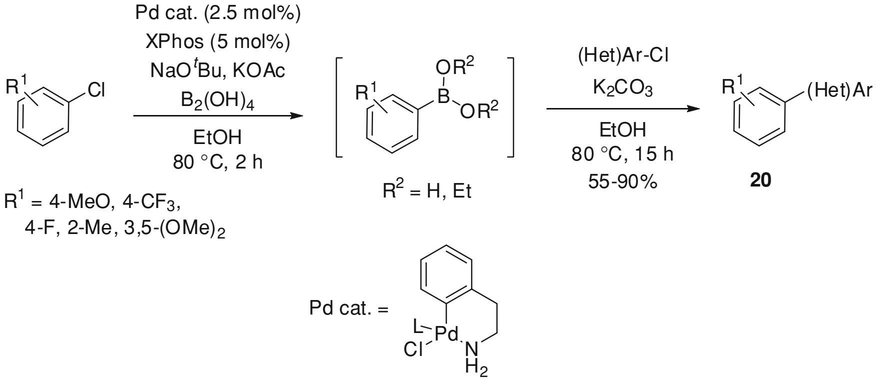
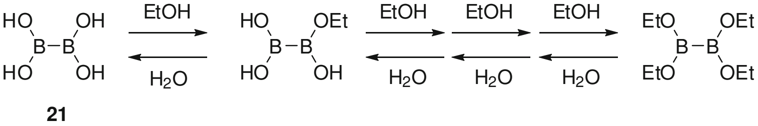


**Scheme 7.5** Suzuki-Miyaura coupling of tetrahydroxydiborane with two different aryl chlorides

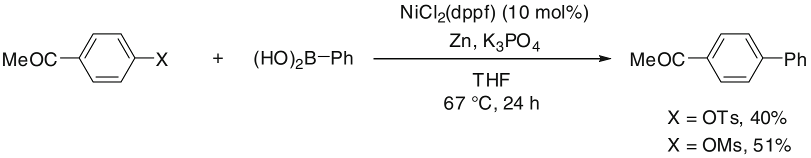
In 2010, Dreher synthesized the corresponding biaryls **20** from the subsequent Suzuki–Miyaura cross-coupling reactions of tetrahydroxydiborane with two different aryl chlorides in one pot (Scheme 7.5) [84].

In this reaction, it is thought that solubility and reactivity are enhanced by using ethanol as the solvent. The equilibrium between tetrahydroxydiborane (**21**) and ethanol creates a variety of ethyl ethers to generate dipinacolboron-like species, as shown in Scheme 7.6.



**Scheme 7.6** The equilibrium between tetrahydroxydiborane (**21**) and tetraethoxydiborane

On the other hand, Suzuki–Miyaura coupling reactions of aryl mesylates bearing electron-withdrawing groups, catalyzed by nickel, were reported for the first time by the research group of Hill in 1995 [85]. Moreover, in 1996 Kobayashi et al. similarly reported the Suzuki–Miyaura coupling reactions of aryl tosylates and mesylates with phenylboronic acid in the presence of the nickel catalysts (Eq. 7.20) [86]. Unfortunately, the substrate scope was found to be very narrow, and the reaction only took place with aryl tosylates and mesylates that have electron-withdrawing substituents.



(7.20)

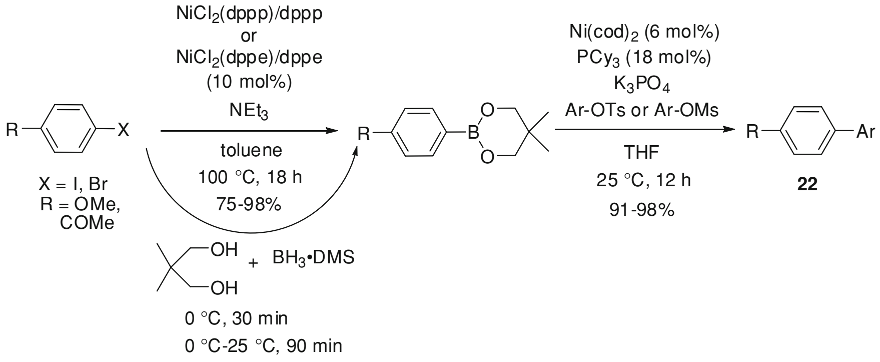
After 2000, Suzuki–Miyaura coupling reactions of aryl tosylates with arylboronic acids bearing various substituents were reported by Monteiro using the alkylphosphine ligands under nickel catalysis [87]. In 2002 Boggess reported the coupling reactions of heteroaryl tosylates with arylboronic acids by using the sterically bulky phosphine ligand, XPhos (see, Scheme 7.4), in the presence of the palladium catalysts [88]. In 2004 Buchwald et al. reported Suzuki–Miyaura coupling reactions of various aryl tosylates, which greatly contributed to the expansion of the substrate scope (Eq. 7.21) [89].

$$\mathrm{Ar^1{-}OTs} \quad + \quad \mathrm{(HO)_2B{-}Ar^2} \xrightarrow[\substack{\text{THF or }^t\text{BuOH} \\ 80\ ^\circ\text{C} \\ 84\text{-}92\%}]{\substack{\mathrm{Pd(OAc)_2}\text{ (2-3 mol\%)} \\ \text{XPhos (5-7 mol\%)}}} \mathrm{Ar^1{-}Ar^2} \tag{7.21}$$

With these nickel catalysts in hand, coupling reactions of a series of aryl mesylates were reported [90]. The analogous coupling reactions with aryl tosylates were attained at room temperature by Hu et al. (Eq. 7.22) [91]. As the result of the precedent works, a large number of reactions were reported using similar ligands [92–95]. Later, improvements of amounts and ease of handling of the catalysts were achieved to realize more coupling reactions [96–99].

$$\mathrm{Ar^1{-}OTs} \quad + \quad \mathrm{(HO)_2B{-}Ar^2} \xrightarrow[\substack{\text{THF} \\ \text{rt, 8 h} \\ 86\text{-}99\%}]{\substack{\mathrm{Ni(cod)_2}\text{ (3 mol\%)} \\ \mathrm{PCy_3}\text{ (12 mol\%)} \\ \mathrm{K_3PO_4}}} \mathrm{Ar^1{-}Ar^2} \tag{7.22}$$

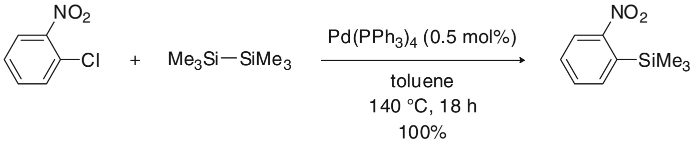
Furthermore, it has been reported that the preparation of the corresponding arylboronic acids from aryl halides, followed by the coupling reactions with aryl tosylates or mesylates can obtain the target biaryl compounds **22** (Scheme 7.7) [100].



**Scheme 7.7** Suzuki-Miyaura coupling with aryl tosylates or mesylates

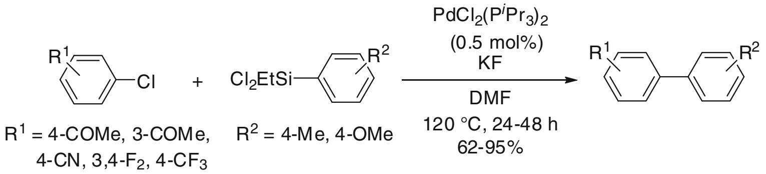
## 7.6 Hiyama Coupling

In 1975 Matsumoto et al. were the first to succeed in the trimethylsilylation of aryl chlorides bearing a nitro group with hexamethyldisilane (Eq. 7.23) [101]. They also proved that the carbon–carbon bonds are easily formed by cleavage of the carbon-chlorine bond in the 2-position, analogous to the reactions with 2,5-dichloronitrobenzene as the coupling partner [102].



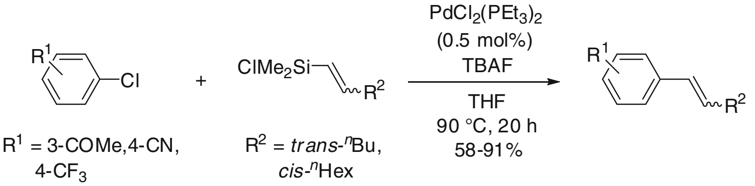
(7.23)

Since the latter half of the 1990s, many researchers have reported coupling reactions for a variety of aryl compounds bearing the silicon functional groups [103–106]. Hatanaka and Hiyama expanded the substrate scope in 1996, reporting the coupling reactions of aryl chlorides bearing various electron-withdrawing groups with arylsilicon compounds (Eq. 7.24) [107].



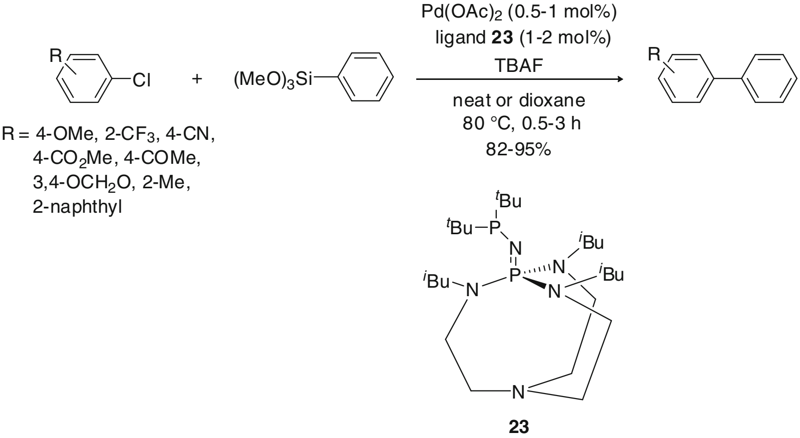
(7.24)

In addition, Hiyama et al. also reported coupling reactions with alkenylsilicon compounds (Eq. 7.25). The reactivity of alkenylchlorosilanes was found to be strongly influenced by the structure of the silyl groups; the cross-coupling reaction of (*E*)-1-octenylchlorosilanes bearing a $SiCl_3$ group was the fastest. It should be noted that these coupling reactions proceeded with the retention of the double bond geometry of the alkenylchlorosilanes.



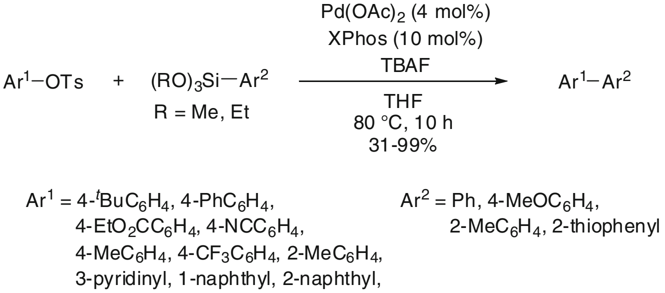
(7.25)

Very recently, Verkade et al. synthesized the new phosphine ligand **23**, with a high electron-donating ability, which was found to smoothly undergo the reactions of various substituted aryl chlorides (Eq. 7.26) [108]. With this catalyst system in hand, the corresponding biaryls were obtained with the electron-rich aryl chlorides.



(7.26)

One of many examples of Hiyama coupling, the reaction of aryl tosylates, has been reported by Wu in 2008 (Eq. 7.27) [109]. Subsequently, the extended coupling reactions with aryl mesylates were reported by the same research group [110]. In 2009 Kwong et al. succeeded in more efficient reactions by using the indole-type ligands under the palladium catalysis [111].

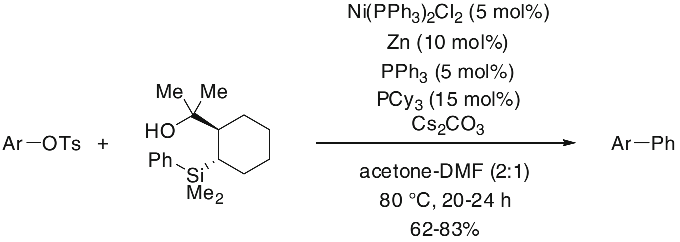


$$\mathrm{Ar^1{-}OTs} + \underset{\mathrm{R = Me,\ Et}}{\mathrm{(RO)_3Si{-}Ar^2}} \xrightarrow[\substack{\mathrm{THF} \\ 80\ ^\circ\mathrm{C},\ 10\ \mathrm{h} \\ 31\text{-}99\%}]{\substack{\mathrm{Pd(OAc)_2}\ (4\ \mathrm{mol\%}) \\ \mathrm{XPhos}\ (10\ \mathrm{mol\%}) \\ \mathrm{TBAF}}} \mathrm{Ar^1{-}Ar^2} \tag{7.27}$$

$\mathrm{Ar^1}$ = 4-$^t\mathrm{BuC_6H_4}$, 4-$\mathrm{PhC_6H_4}$, 4-$\mathrm{EtO_2CC_6H_4}$, 4-$\mathrm{NCC_6H_4}$, 4-$\mathrm{MeC_6H_4}$, 4-$\mathrm{CF_3C_6H_4}$, 2-$\mathrm{MeC_6H_4}$, 3-pyridinyl, 1-naphthyl, 2-naphthyl,

$\mathrm{Ar^2}$ = Ph, 4-$\mathrm{MeOC_6H_4}$, 2-$\mathrm{MeC_6H_4}$, 2-thiophenyl

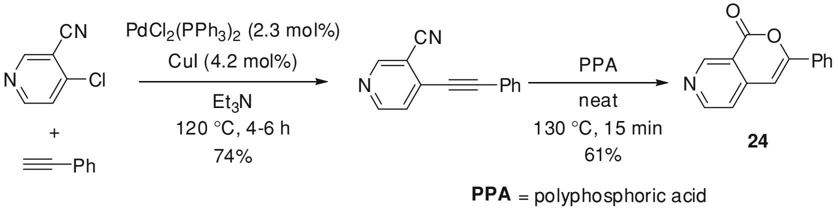
Only one example of a nickel version of coupling reactions of aryl tosylates was reported; Hiyama et al. very recently accomplished this by using the mixed system of two different phosphine ligands (Eq. 7.28) [112]. Importantly, an aryl mesylate also participated in the coupling reaction to give the biaryl.



(7.28)

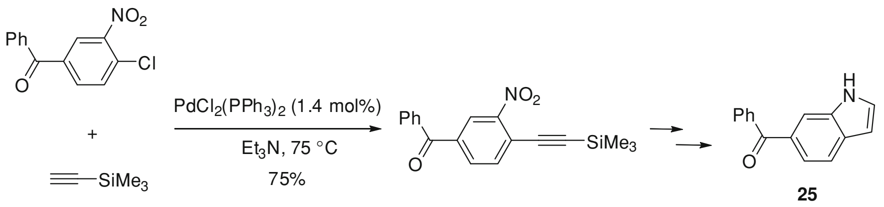
## 7.7 Sonogashira–Hagihara Coupling

The Sonogashira–Hagihara coupling reactions of aryl chlorides with terminal alkynes were ardently researched by many chemists in the latter half of the 1980s. More recently, the Sonogashira–Hagihara coupling reactions of aryl chlorides bearing the electron-withdrawing groups have gradually been investigated (Scheme 7.8) [113, 114]. The coupling reaction of 4-chloro-3-cyanopyridine with phenylethyne gave 4-(phenylethynyl)pyridine, which smoothly underwent the intramolecular cyclization under acidic conditions to afford 3-pheynl-1*H*-pyrano[3,4-c]pyridin-1-one (**24**).



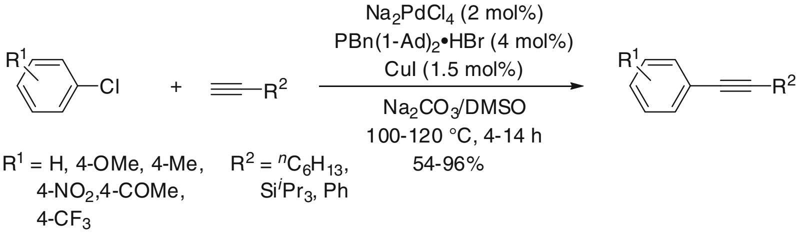
**Scheme 7.8** Sonogashira-Hagihara coupling with aryl chlorides

Meanwhile, Lanza et al. synthesized the corresponding arylethynes from aryl chlorides having a nitro group in the 2-position. They further demonstrated the synthesis of an indole **25** bearing a substituent in the 6-position by four steps (Scheme 7.9) [115].



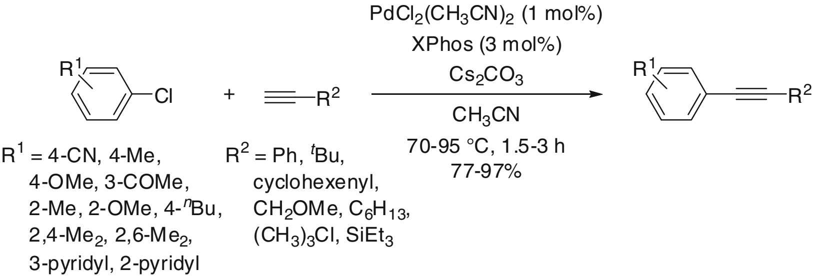
**Scheme 7.9** Synthesis of arylethynes from aryl chlorides having a nitro group in the 2-position

Sonogashira–Hagihara coupling reactions with aryl chlorides that bear various substituents have been manifestly reported since 2000. For instance, in 2003 Plenio reported Sonogashira–Hagihara coupling of the unactivated aryl chlorides without copper (I) salts as a co-catalyst (Eq. 7.29) [116].



(7.29)

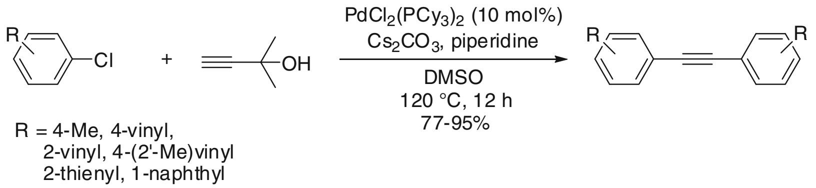
In the same year, Buchwald reported that Sonogashira–Hagihara coupling reactions of a variety of aryl chlorides smoothly proceeded in the presence of the palladium catalysts ligated by XPhos (see Scheme 7.4) (Eq. 7.30) [117]. This reaction overcame the prior limitations of substrates. In the past, coupling reactions of aryl chlorides bearing electron-rich substituents at the ortho position had not taken place easily.



(7.30)

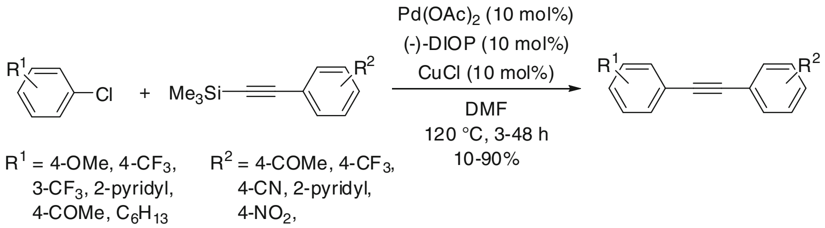
In 2007, Hua et al. reported the reactions of aryl chlorides affording the symmetrical diarylethynes in one pot (Eq. 7.31) [118]. In this reaction, the same aryl groups can be introduced to both ends of the ethyne by using 1,1-

dimethylpropargylalcohol as a substrate. Although most of the reactions reported thus far have employed the palladium catalysts [119–125], Prajapati reported the Sonogashira–Hagihara reactions catalyzed by indium(III) in 2005 [126].



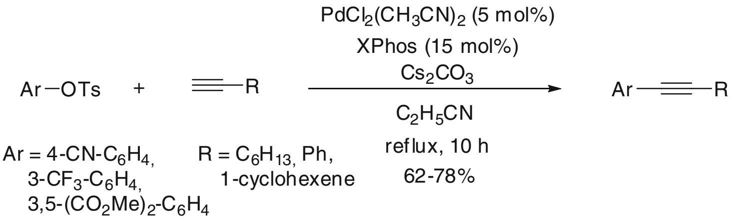
(7.31)

In 2008 the unsymmetrical diarylethynes were synthesized directly by activating the silicon–carbon bond of trimethylsilylethyne derivatives with copper(I) chloride, rather than using the terminal alkynes as the substrates in the classical Sonogashira–Hagihara couplings (Eq. 7.32) [127].



(7.32)

In 2003, for the first time, Sonogashira–Hagihara coupling reactions with aryl tosylates were reported by Buchwald (Eq. 7.33) [128]. In these reactions, slow addition of the alkynes is essential to form the desired products in high yields.

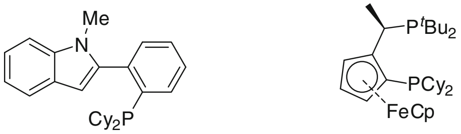


$$\mathrm{Ar{-}OTs} \quad + \quad \equiv\!{-}\mathrm{R} \quad \xrightarrow[\substack{\mathrm{C_2H_5CN} \\ \text{reflux, 10 h} \\ \text{62-78\%}}]{\substack{\mathrm{PdCl_2(CH_3CN)_2}\ \text{(5 mol\%)} \\ \text{XPhos (15 mol\%)} \\ \mathrm{Cs_2CO_3}}} \quad \mathrm{Ar}{-}\!\equiv\!{-}\mathrm{R} \tag{7.33}$$

Ar = 4-CN-$C_6H_4$, 3-$CF_3$-$C_6H_4$, 3,5-$(CO_2Me)_2$-$C_6H_4$

R = $C_6H_{13}$, Ph, 1-cyclohexene

Recently Kwong has reported Sonogashira–Hagihara coupling reactions with aryl mesylates by using the indole-containing phosphine ligand **26** (Fig. 7.4, left) under palladium catalysis [129]. Furthermore, the coupling reactions of aryl mesylates and -tosylates have been attained more efficiently by using ligand **27** (Fig. 7.4, right) [130].



**26**
CM-Phos

**27**
CyPF-*t*-Bu

**Fig. 7.4** Effective ligands **26** and **27** for palladium-catalyzed Sonogashira coupling reactions with aryl tosylates, -mesylates, and -tosylates

## 7.8 Summary

In this chapter, examples of the cross-coupling reactions with aryl chlorides, -mesylates, and -tosylates reported in recent years have been introduced. One can expect to utilize these reactions further for innovative syntheses of natural products and of functional materials with new physical properties. Moreover, in the future, not only the carbon–chlorine bond but also more inert bonds will likely be selectively activated. As a result, the development of new types of cross-coupling reactions that can precisely introduce the desired substituents at the desired position may be achieved.

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