Chapter 8
Recent Advances in Cross-Coupling Reactions with Alkyl Halides

Arisa Yamamoto, Yugo Nishimura and Yasushi Nishihara

Abstract The alkyl electrophiles with β-hydrogens have been scarcely employed in the transition-metal-catalyzed cross-coupling reactions until recently. This is due to their low electrophilicity and the facile occurrence of β-hydrogen elimination under standard conditions. However, in recent years, the alkyl electrophiles have received a marked increase in attention; numerous synthetic examples using the alkyl electrophiles as coupling partners have been reported. This chapter classifies the recently reported cross-coupling reactions of these alkyl electrophiles, grouping the reactions by organometallic reagent. Introductions to representative synthetic examples are given.

Keywords Alkyl electrophiles · Alkyl metal species · β-hydrogen elimination · Bulky and electron-rich ligands · *N*-heterocyclic carbene (NHC) ligands · Asymmetric synthesis

8.1 Introduction

The development of various types of new reactions that form carbon–carbon bonds with high efficiency and selectivity is one of the most important goals in modern synthetic organic chemistry. As described in previous chapters, the catalytic cross-coupling reactions excel in regio- and stereoselectivities. They also enjoy a wide coverage of substrates; therefore, they have been recognized as powerful methods for carbon–carbon bond construction. Furthermore, as described in Chap. 7,

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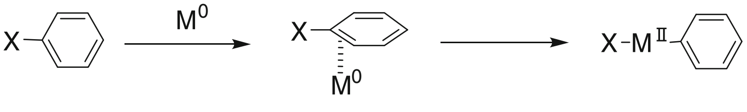
various inert carbon electrophiles such as organic chlorides, as well as mesylates and tosylates converted from a hydroxyl group, have become available as coupling partners in this catalyst system.

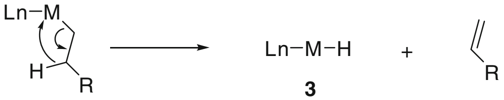
However, these cross-couplings have not been able to utilize unreactive electrophiles for the construction of any hybridized carbon–carbon bonds. Thus, the commonly used carbon electrophiles had to have π-electrons, e.g., aryl, alkenyl (sp^2), or alkynyl (sp) carbons. As described in Chap. 2, the nickel- and palladium-catalyzed cross-coupling reactions proceed according to the catalytic cycle, including: oxidative addition, transmetalation, and reductive elimination. Among these steps, oxidative addition easily occurs because the carbon electrophile's π-electrons can coordinate to the metal centers to generate the π-complex **1**, which undergoes oxidative addition to form complex **2** (Scheme 8.1). Therefore, when the substrates with an sp^2 or an sp-hybridized reaction site are used as carbon electrophiles, the cross-coupling reactions occur under much milder conditions.



1 **2**

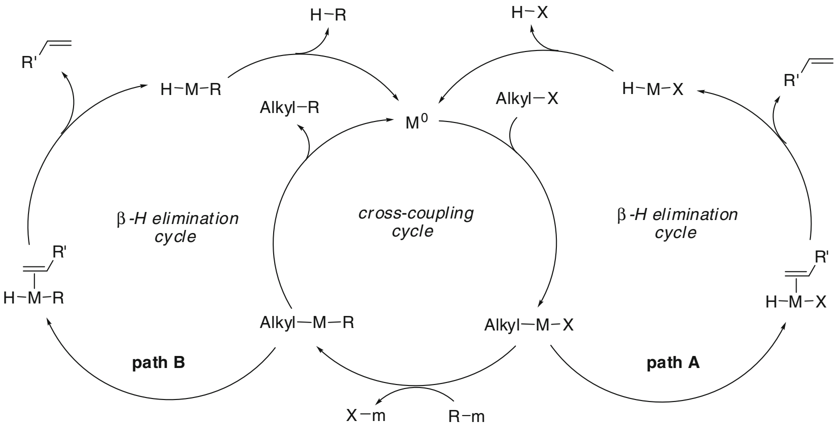
Scheme 8.1 Oxidative addition of aryl halides through the generation of the π-complex **1**

In sharp contrast to the molecules bearing π-bonds, the alkyl electrophiles bearing the β-hydrogens have scarcely been used as carbon electrophiles in the catalytic cross-coupling reactions. The main reasons for the poor success of cross-coupling reactions of the alkyl halides are as follows: (1) the saturated carbon electrophiles have no π-electron that can coordinate to the metal center and (2) the weak electronic attraction of the sp^3 hybridized carbons at a carbon–halogen bond results in slow oxidative addition. Furthermore, when the alkyl electrophiles have β-hydrogens, the d orbital of the transition metals and the C–H σ-bond have an electronic interaction; β-hydrogen elimination in the alkyl complexes occurs smoothly to give the hydrido complexes **3** along with olefins derived from oxidative addition (Eq. 8.1).



3 (8.1)

Therefore, before the desired cross-coupled products are formed, the thermodynamically favored, rapid β-hydrogen elimination competitively proceeds after either oxidative addition (path A) or transmetalation (path B), generating olefin by-products (Scheme 8.2). Although a large amount of research has been elucidated for the widely applicable and reliable cross-coupling reactions of aryl and alkenyl electrophiles, development of the cross-coupling reactions of the alkyl electrophiles as synthetic methods was thus forsaken for a long time.



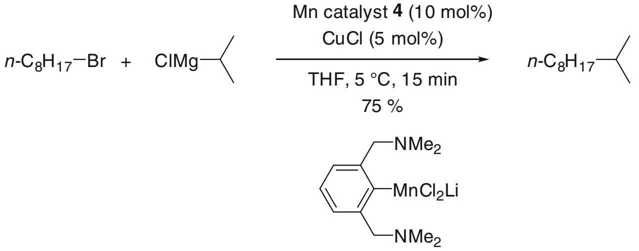
Scheme 8.2 Catalytic cycles involving alkyl electrophiles

However, in the late 1990s, growing concern over this undeveloped field in the catalytic cross-coupling reactions of alkyl electrophiles prompted examination and advancement from the viewpoints of development of new ligands and the use of unprecedented transition-metal catalysts. Gradually, new cross-coupling reactions including the alkyl groups as coupling partners were reported, by retarding *β*-hydrogen elimination. This chapter presents the cross-coupling reactions of the alkyl electrophiles, focusing on representative examples found after 2000.

8.2 Kumada-Tamao-Corriu Coupling

The first Kumada–Tamao–Corriu coupling of alkyl halides was the reaction with Grignard reagents catalyzed by silver, reported by Kochi and Tamura in the early 1970s [1–3]. Although a few similar reactions catalyzed by transition metals such as copper and nickel had been reported over the ensuing 20 years, chemical yields of the products were unsatisfactory [4, 5].

After many years of effort, in 1986 Castle and Widdowson finally reported that the desired cross-coupled products could be obtained from the reactions of primary and secondary alkyl iodides with alkyl magnesium bromides in high yields, in the presence of $PdCl_2$(dppf) [6]. In 1998 Koten and Cahiez reported Kumada–Tamao–Corriu cross-couplings of primary, secondary, and tertiary alkyl Grignard reagents with *n*-alkyl bromides caused by a paramagnetic manganese (II) catalyst **4** bearing a tridentate ligand and CuCl as a co-catalyst (Eq. 8.2) [7].



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(8.2)

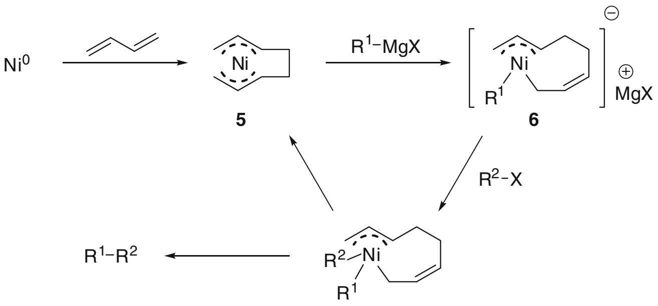
In addition, in 2000 Cahiez reported the cross-coupling reactions of alkyl halides with alkyl or aryl magnesium reagents by using the copper catalysts (Eq. 8.3) [8]. When alkyl magnesium compounds were used as nucleophiles in this reaction, *N*-methylpyrrolidone (NMP) solvent promoted the reaction; on the contrary, when the aryl magnesium reagents were employed, NMP suppressed the reaction progress. Unfortunately, secondary and tertiary alkyl halides and a series of alkyl chlorides were found not to be applicable to this reaction.

$$\mathrm{R_{alkyl}{-}X} \; + \; \underset{\text{R = alkyl, aryl}}{\mathrm{XMg{-}R}} \xrightarrow[\substack{\text{THF, 20 °C} \\ \text{56-92\%}}]{\substack{\mathrm{Li_2CuCl_4}\text{ (3 mol\%)} \\ \text{NMP (4 equiv)}}} \mathrm{R_{alkyl}{-}R} \tag{8.3}$$

Terao and Kambe reported in 2002 the nickel-catalyzed Kumada-Tamao-Corriu coupling reactions of alkyl Grignard reagents with alkyl chlorides or bromides (Eq. 8.4) [9]. This reaction protocol also enabled the application to alkyl tosylates. A small catalyst loading with the assistance of 1,3-butadiene as the ligand gave the corresponding cross-coupled products in good to excellent yields.

$$\underset{\text{X = Cl, Br, OTs}}{\mathrm{R_{alkyl}{-}X}} \; + \; \mathrm{BrMg{-}R_{alkyl}} \xrightarrow[\substack{\text{THF, 0-25 °C, 0.5-20 h} \\ \text{56-100\%}}]{\substack{\mathrm{NiCl_2}\text{ (1-3 mol\%)} \\ \text{1,3-butadiene (10-100 mol\%)}}} \mathrm{R_{alkyl}{-}R_{alkyl}} \tag{8.4}$$

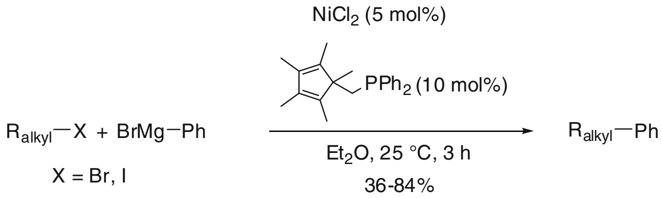
Moreover, Terao and Kambe showed that the 1,3-butadiene ligand stabilized the active species and promoted reductive elimination. The proposed reaction mechanisms are shown in Scheme 8.3. First, $NiCl_2$ is reduced by R^1MgX, and then two molar equivalents of 1,3-butadiene react with the generated Ni(0) species to form the bis(π-allyl)nickel complex **5**. This complex **5**, which is inert toward oxidative addition of the alkyl halides, selectively reacts with Grignard reagents to afford the nickelate complex **6**. The subsequent oxidative addition of alkyl halides and reductive elimination give the desired cross-coupled products. In addition, in 2003 Terao and Kambe also reported the cross-coupling reactions of alkyl



Scheme 8.3 Ni-catalyzed alkyl-alkyl coupling by using 1,3-butadiene ligand

tosylates or bromides with alkyl magnesium reagents, accelerated by the combination of the palladium catalyst with the 1,3-butadiene ligands [10].

Very recently, several examples of Kumada–Tamao–Corriu coupling reactions catalyzed by nickel have been reported using $Cp^*CH_2PPh_2$ ($Cp^* = C_5Me_5$) as the ligand (Eq. 8.5) [11]. Also, the pincer-type tridentate amido ligands of the nickel (II) complex **7** have been recently described (Eq. 8.6) [12].



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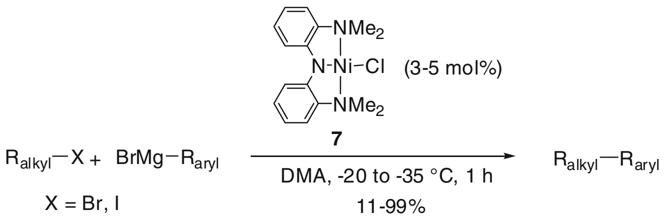

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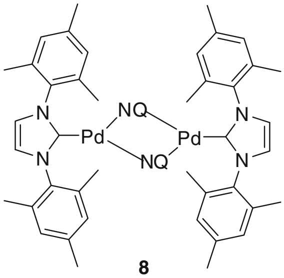
An example with palladium catalysis (involving the palladium(II) acetate-tricyclohexylphosphine catalyst system) was reported by Beller in 2002 utilizing the alkyl-aryl-type Kumada–Tamao–Corriu coupling reactions (Eq. 8.7) [13].

$$R_{alkyl}{-}Cl \;+\; BrMg{-}R_{aryl} \xrightarrow[\text{NMP, rt, < 20 h}]{\substack{\text{Pd(OAc)}_2\text{ (4 mol\%)} \\ \text{PCy}_3\text{ (4 mol\%)}}} R_{alkyl}{-}R_{aryl} \tag{8.7}$$

In addition, Beller reported for the first time in 2003 the analogous Kumada–Tamao–Corriu coupling reactions using the palladium naphthoquinone catalysts **8** ligated with *N*-heterocyclic carbene (NHC) ligands (Eq. 8.8) [14].

$$R_{alkyl}—Cl \quad + \quad BrMg—R_{aryl} \xrightarrow[\text{THF, rt, 1 h}\atop\text{33-99\%}]{\text{Pd catalyst }\mathbf{8}\text{ (2 mol\%)}} R_{alkyl}—R_{aryl} \tag{8.8}$$



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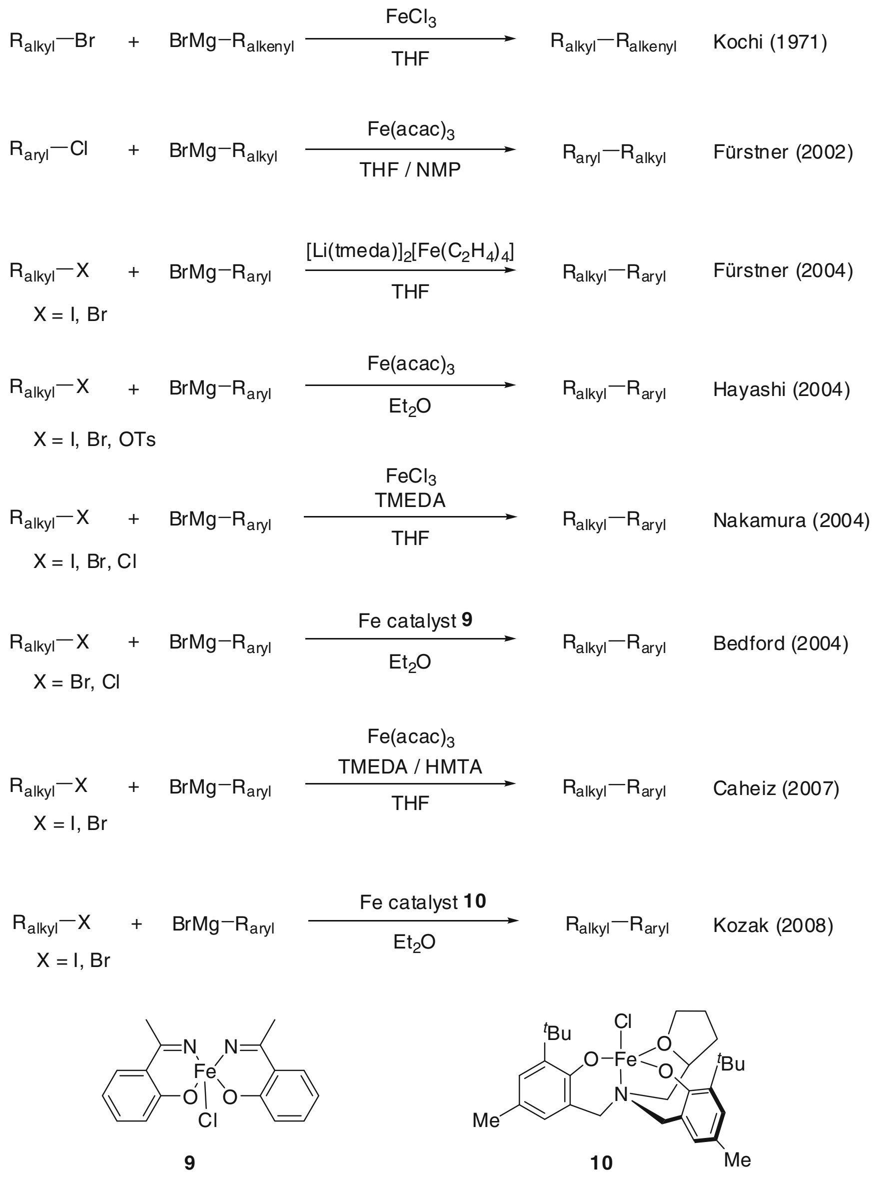
NQ = naphthoquinone

Recently, much attention has been paid to the development of the cross-coupling reactions catalyzed by the less expensive, ubiquitous transition-metal catalysts rather than nickel and palladium as the catalysts. Since the report by Kochi in 1971 of iron(III) chloride-catalyzed Kumada–Tamao–Corriu coupling [15], satisfying results using the iron catalysts had not been obtained for decades. But, Fürstner found in 2002 that acetylacetonato iron could be an effective catalyst for the Kumada–Tamao–Corriu coupling of aryl chlorides with alkyl magnesium reagents [16].

After this pioneering work, a great deal of research on the Kumada–Tamao–Corriu coupling promoted by the iron catalysts has led to utilization of this chemistry by many other researchers in the recent years [17–24]. Representative synthetic examples of such are shown in Scheme 8.4.

In addition to the iron catalysts, cobalt and vanadium complexes were found by Oshima to be highly effective for catalysis of the alkyl-aryl Kumada–Tamao–Corriu coupling of the alkyl electrophiles with aryl magnesium reagents (Scheme 8.5) [25–27].

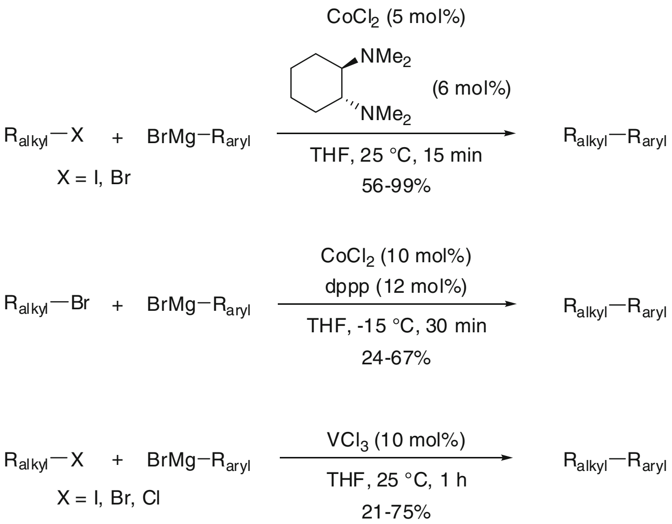
As described herein, it seems that the catalysts for Kumada–Tamao–Corriu coupling reactions of the alkyl electrophiles are no longer limited to palladium and nickel. In the iron-catalyzed reactions the anionic iron complex is postulated to be the active species, while in the reactions catalyzed by cobalt and vanadium a radical mechanism has been proposed. Therefore, these catalytic cycles might proceed in different manners from the established palladium and nickel-catalyzed cross-couplings. However, the aryl nucleophiles applicable to the cobalt- and vanadium-catalyzed cross-coupling reactions are limited to Grignard reagents, significantly limiting the types of coupled products due to poor functional group tolerance. It is noteworthy that the catalytic activities were found to be superior to palladium and nickel in some of the reaction systems mediated by cobalt and vanadium.



Scheme 8.4 Fe-catalyzed Kumada-Tamao-Corriu coupling of alkyl electrophiles

8.3 Negishi Coupling

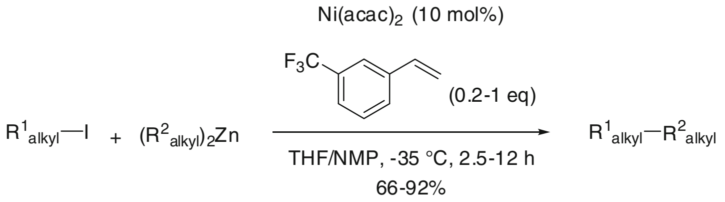
Tucker and Knochel reported the first account of Negishi coupling using alkyl halides in 1993; this work dealt with the reactions of alkyl iodides and dialkyl zinc reagents, mediated by a stoichiometric amount of [Cu(CN)Me$_2$(MgCl$_2$)] [28]. Two



Scheme 8.5 Co- and V-catalyzed Kumada-Tamao-Corriu coupling of alkyl electrophiles

years later, using a nickel catalyst, Knochel also reported the alkyl–alkyl Negishi coupling of the alkyl zinc reagents with alkyl iodides functionalized with a double bond in the 4- or 5-positions [29]. However, because severe substrate limitations were observed in these reactions, they were not generally exploited.

Finally, Knochel found in 1998 the more preparative Negishi coupling reactions of alkyl iodides (sans double bonds) with organozinc reagents, by adding styrene additives with an electron-withdrawing trifluoromethyl group, under nickel catalysis (Eqs. 8.9, 8.10) [30–32].



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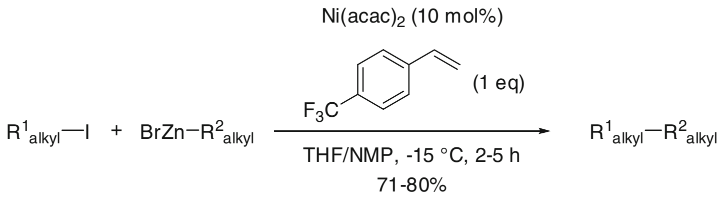


(8.10)

In 2003, Zhou and Fu reported Negishi coupling reactions with alkyl electrophiles by using a palladium catalyst ligated with tricyclopentylphosphine (Eq. 8.11) [33]. The reaction efficiently took place with unactivated primary alkyl iodides, bromides, chlorides, and even tosylates. In addition, it was clarified that the addition of *N*-methylimidazole (NMI) promoted transmetalation from zinc to palladium and that the product yields were dramatically improved.

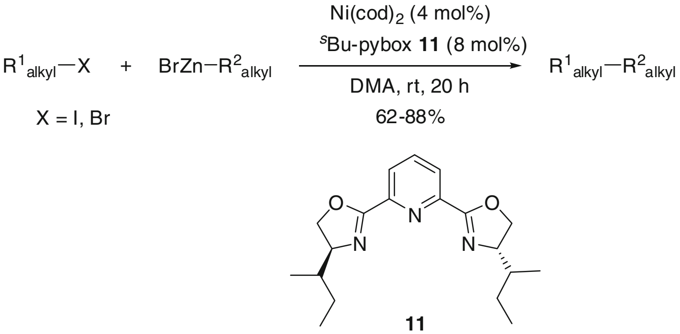
$$R_{alkyl}{-}X \quad + \quad BrZn{-}R \xrightarrow[\substack{\text{THF/NMP} \\ 80\ ^\circ\text{C, 12-14 h} \\ 48\text{-}98\%}]{\substack{Pd_2(dba)_3\ (2\ \text{mol\%}) \\ P(c\text{-}C_5H_9)_3\ (8\ \text{mol\%}) \\ \text{NMI}}} R_{alkyl}{-}R \tag{8.11}$$

X = I, Br, Cl, OTs

R = alkyl, aryl, alkenyl

NMI = *N*-methylimidazole

In addition, Fu has also succeeded in an extension of these reactions to include the cross-coupling reactions of secondary alkyl bromides and iodides (Eq. 8.12) [34]. These newer reactions smoothly proceed at room temperature with the aid of the nickel catalyst bearing the bis(oxazolinyl)pyridine (pybox) ligand **11**.



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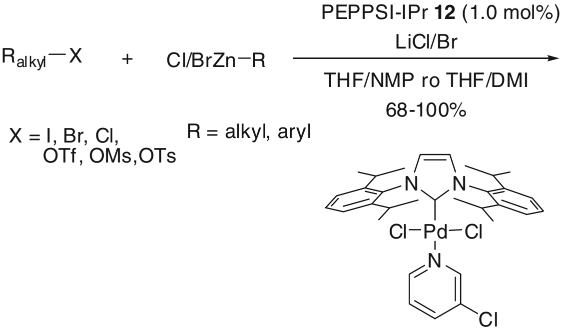
(8.12)

Recently, Organ further expanded the range of the substrate scope in Negishi coupling reactions of alkyl electrophiles involving alkyl chlorides, mesylates, and tosylates by the palladium complexes (PEPPSI) **12** having *N*-heterocyclic carbene (NHC) and 3-chloropyridine as auxiliary ligands (Eq. 8.13) [35].



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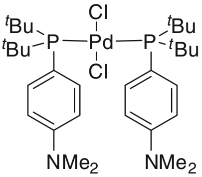
Lipshutz reported reactions of alkyl halides at room temperature in water using the organozinc reagents generated in situ from zinc-diamine complexes and the commercially available amphiphile polyoxyethanyl α-tocopheryl sebacate (PTS); these reactions were catalyzed by palladium complex **13** having bulky and electron-rich phosphine ligands (Eq. 8.14) [36].

$$R_{alkyl}-X \;+\; Br-R_{aryl} \xrightarrow[\substack{\text{PTS/}H_2O\text{, rt, 12-24 h} \\ \text{65-92\%}}]{\substack{\text{Pd catalyst } \mathbf{13} \text{ (2 mol\%)} \\ \text{Zn-diamine}}} R_{alkyl}-R_{aryl}$$

PTS = polyoxyethanyl α-tocopheryl sebacate



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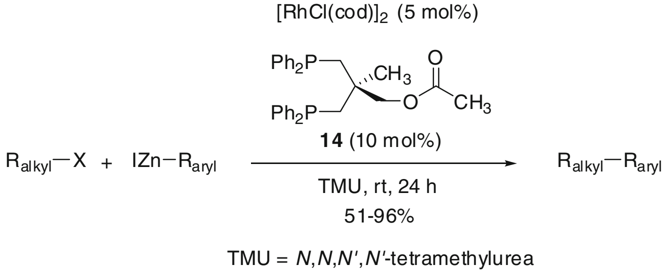
(8.14)

The Negishi coupling reactions of alkyl electrophiles catalyzed by the other transition metals (rather than palladium and nickel) have been recently exploited. For instance, in 2005 Nakamura et al. reported the alkyl-aryl Negishi coupling of primary and secondary alkyl halides with aryl zinc reagents, catalyzed by iron(III) chloride in high to excellent yields (Eq. 8.15) [37].

$$R_{alkyl}-X \;+\; XZn-R_{aryl} \xrightarrow[\substack{\text{THF, 50 °C, 30min} \\ \text{72-98\%}}]{\substack{FeCl_3 \text{ (5 mol\%)} \\ \text{TMEDA}}} R_{alkyl}-R_{aryl} \qquad (8.15)$$

Very recently, Takagi et al. found that the rhodium complexes ligated with 3-diphenylphosphino-2-(diphenylphoshino)methyl-2-methylpropyl acetate **14** (a tripodal ligand) showed excellent catalytic activity in the alkyl-aryl Negishi coupling reactions. This provides a facile and useful synthetic method for polyfunctionalized alkylbenzenes (Eq. 8.16) [38].



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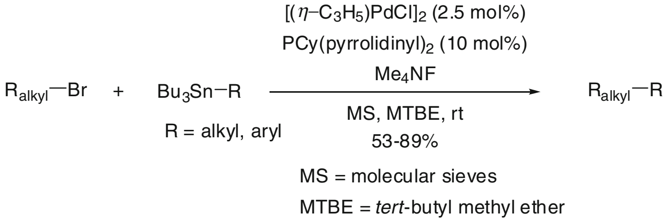
8.4 Migita–Kosugi–Stille Coupling

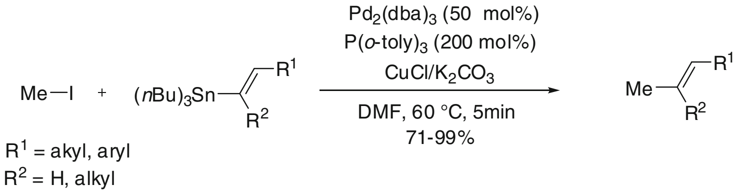
Migita–Kosugi–Stille coupling reactions of alkyl halide electrophiles were reported by Fuchikami in 1996, using $PdCl_2(PPh_3)_2$ as the catalyst [39]. In these reactions, alkyl iodides substituted with an electron-deficient fluorine atom in the β-position reacted with organotin compounds. However, the yields of the coupled products were not satisfactory and heavy catalyst loading was necessary. Later, research disclosed that electron-rich alkyldimonophosphine ligands (rather than simple trialkylphosphines) are effective, especially for Migita–Kosugi–Stille coupling of alkyl electrophiles in the palladium-phosphine catalyst system. In 2001, Fuchikami et al. reported Migita–Kosugi–Stille-type coupling reactions of alkynyl stannanes with alkyl iodides bearing a fluorine atom in the γ- or δ-position, catalyzed by $Pd(PPh_3)_4$. It has been hypothesized that the oxidative addition of these fluorinated alkyl halides generates an alkyl palladium complex, which is stabilized by an internal coordination of fluorine to the metal center, suppressing the undesired β-hydrogen elimination [40].

Fu reported in 2003 that Migita–Kosugi–Stille coupling reactions of tributyl stannanes with primary alkyl bromides bearing substituents in the ω-position smoothly occurred at room temperature by using cyclohexyl di pyrrolidinyl phosphine as the ligand in the presence of tetramethylammonium fluoride as an activator (Eq. 8.17) [41].



(8.17)

In 2006, the palladium-catalyzed methylation of alkenyl stannanes was carried out by incorporating a short-lived ^{11}C-labeled methyl group into biologically significant methylated alkenes with the aim of synthesizing a positron emission tomography (PET) tracer (Eq. 8.18) [42]



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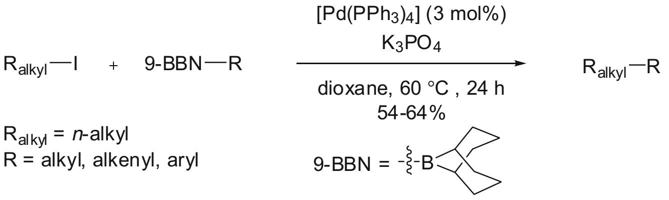
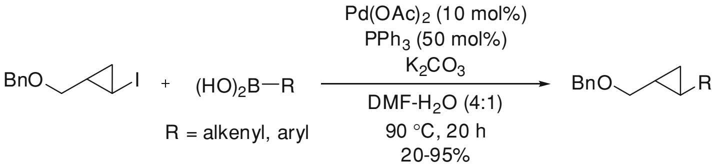
8.5 Suzuki–Miyaura Coupling

The first palladium-catalyzed alkyl–alkyl-type coupling reactions of primary alkyl iodides with alkyl boron compounds were reported by Suzuki and Miyaura in 1992 (Eq. 8.19) [43]. These reactions can be catalyzed by $Pd(PPh_3)_4$; 9-BBN (9-borabicyclononane)-containing alkyl boron compounds were employed as the substrates, but only primary alkyl iodides were successfully applicable to this protocol.



(8.19)

Subsequently, Charette reported Suzuki–Miyaura coupling reactions in 1996 of aryl and alkenyl boronic acids with the alkyl electrophile iodo cyclopropane under palladium catalysis (Eq. 8.20) [44]. However, the range of applicable alkyl electrophiles was found to be rather limited.



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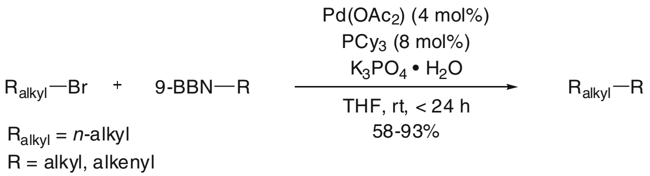
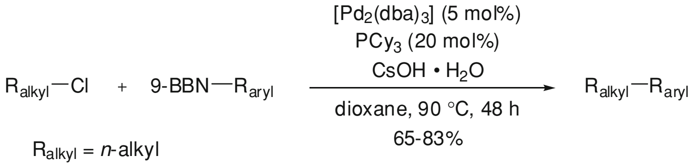
Since 2000, many innovative alkyl–alkyl Suzuki–Miyaura coupling reactions have been reported by Fu et al. In 2001, they succeeded in the coupling reactions of primary alkyl bromides with alkyl boron compounds using potassium phosphate as the base and tricyclohexylphosphine as the ligand of a palladium catalyst (Eq. 8.21) [45]. Because of the mild conditions, this reaction has tolerance of a wide variety of substituents, with not only the double and triple bonds, but also the polar functional groups such as esters, nitriles, and amides.



$$R_{alkyl}{-}Br \quad + \quad 9\text{-}BBN{-}R \xrightarrow[\substack{THF,\ rt,\ <24\ h \\ 58\text{-}93\%}]{\substack{Pd(OAc_2)\ (4\ mol\%) \\ PCy_3\ (8\ mol\%) \\ K_3PO_4 \bullet H_2O}} R_{alkyl}{-}R \tag{8.21}$$

$R_{alkyl} = n\text{-alkyl}$
R = alkyl, alkenyl

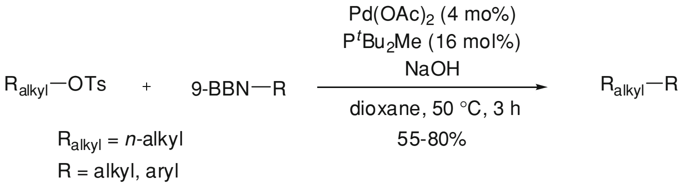
In 2002, Fu discovered that the palladium-catalyzed Suzuki–Miyaura coupling of primary alkyl chlorides with alkyl boron compounds can proceed with cesium hydroxide as the base (Eq. 8.22) [46]. Those reaction conditions are also compatible with a variety of functional groups, including nitriles and amines.



$$R_{alkyl}{-}Cl \quad + \quad 9\text{-}BBN{-}R_{aryl} \xrightarrow[\substack{dioxane,\ 90\ ^\circ C,\ 48\ h \\ 65\text{-}83\%}]{\substack{[Pd_2(dba)_3]\ (5\ mol\%) \\ PCy_3\ (20\ mol\%) \\ CsOH \bullet H_2O}} R_{alkyl}{-}R_{aryl} \tag{8.22}$$

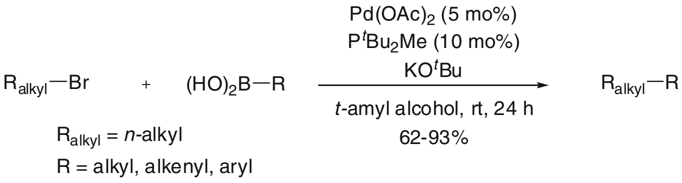
$R_{alkyl} = n\text{-alkyl}$

Subsequently, Fu reported Suzuki–Miyaura coupling reactions of primary alkyl tosylates (Eq. 8.23) [47] and bromides (Eq. 8.24) [48] with alkyl boron reagents, based on the palladium catalyst systems involving the ligand P^tBu_2Me under various reaction conditions (bases, solvents, etc.); the structures of the alkyl palladium complexes formed by oxidative addition of alkyl bromides to $Pd(P^tBu_2Me)_2$ were determined by X-ray structural analyses.



$$R_{alkyl}{-}OTs \quad + \quad 9\text{-}BBN{-}R \xrightarrow[\substack{dioxane,\ 50\ ^\circ C,\ 3\ h \\ 55\text{-}80\%}]{\substack{Pd(OAc)_2\ (4\ mo\%) \\ P^tBu_2Me\ (16\ mol\%) \\ NaOH}} R_{alkyl}{-}R \tag{8.23}$$

$R_{alkyl} = n\text{-alkyl}$
R = alkyl, aryl



$$R_{alkyl}{-}Br \quad + \quad (HO)_2B{-}R \xrightarrow[\substack{t\text{-amyl alcohol, rt, 24 h} \\ 62\text{-}93\%}]{\substack{Pd(OAc)_2\ (5\ mo\%) \\ P^tBu_2Me\ (10\ mo\%) \\ KO^tBu}} R_{alkyl}{-}R \tag{8.24}$$

$R_{alkyl} = n\text{-alkyl}$
R = alkyl, alkenyl, aryl

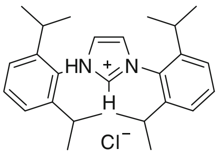


Fig. 8.1 A precursor of the NHC ligand **15**

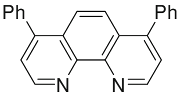
In 2004, Caddick and Cloke reported the alkyl–alkyl-type Suzuki–Miyaura coupling reactions of primary alkyl bromides with alkyl boron compounds by using the palladium catalyst with *N*-heterocyclic carbene ligand **15** (Fig. 8.1) [49]. However, yields of the coupled products were below 60% and not satisfactory.

Suzuki–Miyaura couplings of primary alkyl halides with organoboron compounds were successful; whereas until recently, secondary and tertiary alkyl halides had been assumed to be improper substrates for the analogous cross-coupling reactions due to their difficulty of oxidative addition caused by the large steric hindrances [50, 51]. But, Fu has succeeded in Suzuki–Miyaura coupling of inert secondary alkyl iodides and bromides by using nickel (0) complexes with the bathophenanthroline ligand **16** (Eq. 8.25) [52]. Duncton et al. have applied this type of reaction to the cross-coupling reactions of oxetane iodides with azetidine; and they have synthesized the corresponding aromatic azetidines, which are known to be important motifs of the pharmaceuticals [53].

$$\mathrm{R_{alkyl}{-}X} + \mathrm{(HO)_2B{-}R} \xrightarrow[\text{2-butanol, 60 °C, 5 h}]{\text{Ni(cod)}_2\text{ (4 mol\%), ligand }\mathbf{16}\text{ (8 mol\%), KO}^t\text{Bu}} \mathrm{R_{alkyl}{-}R} \qquad (8.25)$$

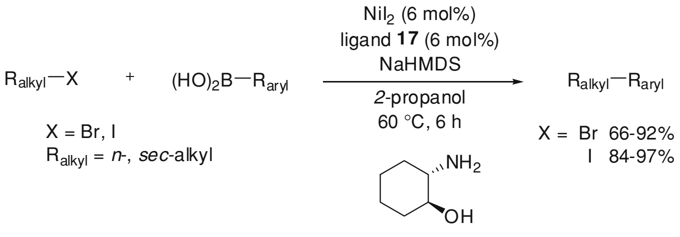
X = Br 44-90%
I 62-75%

X	R_{alkyl}	R
Br	*sec*-alkyl	aryl
I	*n*-, *sec*-alkyl	aryl, alkenyl



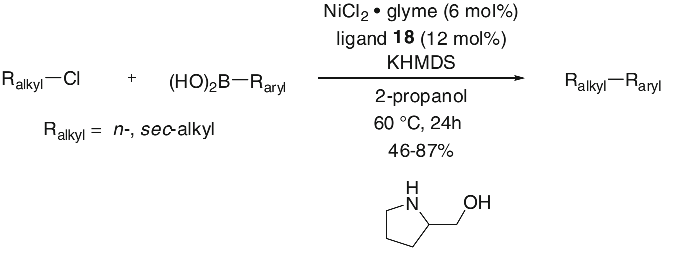
16

In 2006, Fu enabled the reactions of primary and secondary alkyl bromides (Eq. 8.26) and primary and secondary alkyl chlorides (Eq. 8.27), which were previously reported to be unreactive substrates. Fu catalyzed these reactions via nickel incorporated with the amino alcohol ligands **17** and **18** [54]. In these protocols, an advantageous feature is the use of the air-stable nickel (II) salts as precursors of the nickel catalysts—unlike the highly unstable Ni(cod)$_2$.



17

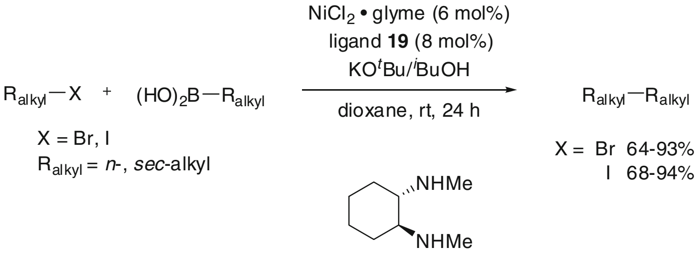
(8.26)



18

(8.27)

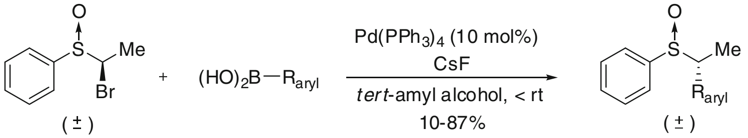
In addition, Fu succeeded in 2007 in the room temperature Suzuki–Miyaura coupling reactions of primary alkyl iodides and bromides by combining the chiral 1, 2-diamine ligands **19** with the nickel (II) salts (Eq. 8.28) [55]. The mild reaction conditions of these reactions made possible the use of the alkyl boron compounds bearing various functional groups (esters, ethers, carbamic acids, etc.).



19

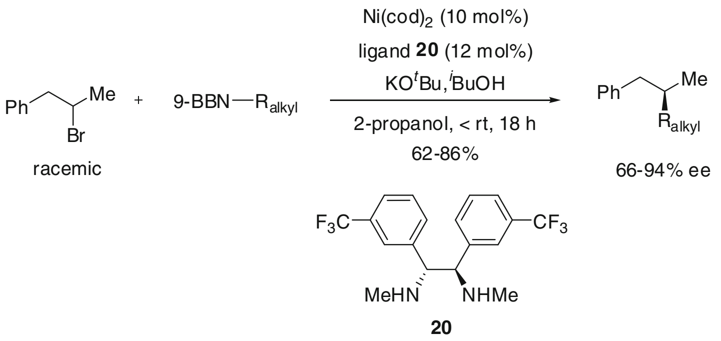
(8.28)

Reports have been compiled concerning the stereochemistry in the Suzuki–Miyaura coupling reactions of a series of alkyl halides. In 2007, Rodríguez et al. reported Suzuki–Miyaura coupling reactions of secondary 1-bromoethyl arylsulfoxides with various arylboronic acids using the palladium catalyst (Eq. 8.29) [56]. In this reaction, the conformational inversion of the stereogenic center occurred in a stereo-specific manner.



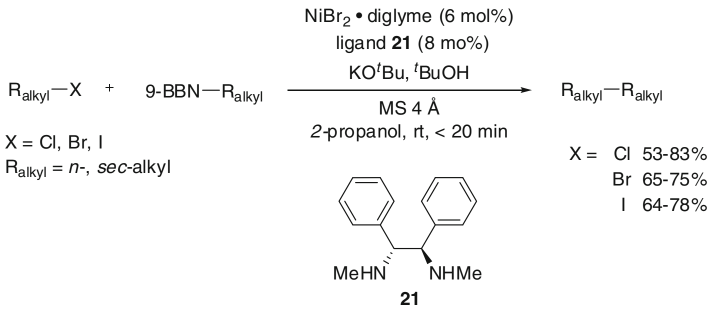
(8.29)

Later, Fu reported highly enantioselective Suzuki–Miyaura coupling reactions of secondary homobenzylic bromides with alkylboranes by using the chiral diamine ligands **20** (Eq. 8.30) [57]. This reaction is the first example of highly enantioselective Suzuki–Miyaura coupling reactions of the alkyl electrophiles.



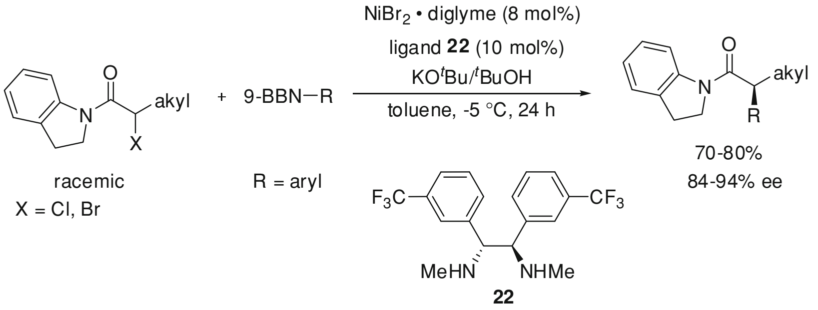
(8.30)

Fu has reported the alkyl–alkyl Suzuki–Miyaura coupling reactions of the inert secondary alkyl chlorides—substrates that had been difficult to employ until very recently (Eq. 8.31) [58]. This reaction proceeded at room temperature, using the nickel (II) salts in the catalyst system with the chiral diamine ligands **21**. This reaction can also be applicable to secondary alkyl bromides and primary alkyl chlorides.



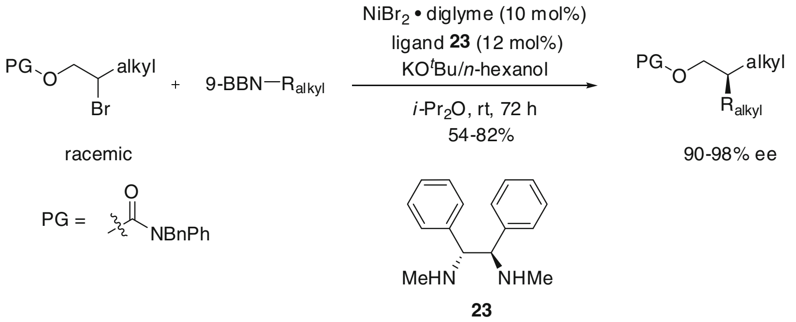
(8.31)

Additionally, Fu succeeded in applying the above-mentioned reactions to enantioselection of the racemic secondary alkyl chlorides, activated by the amide functionalities, with arylboron compounds. The reactions catalyzed by the nickel complex incorporated with the ligand **22** took place under extremely mild reaction conditions at −5 °C and gave optically active alkylamides with up to 94 % (Eq. 8.32) [59].



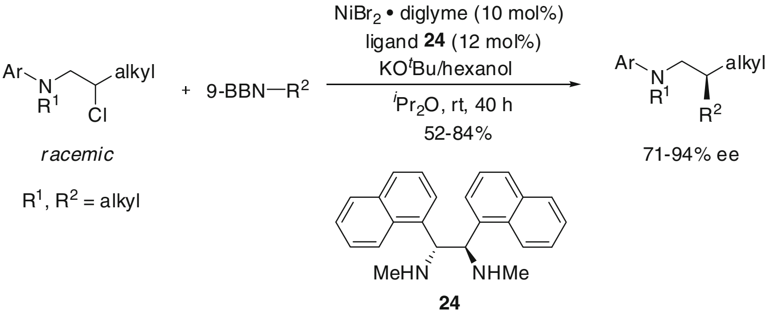
(8.32)

Subsequently, Fu reported the enantioselective alkyl–alkyl-type Suzuki–Miyaura coupling reactions of inert secondary alkyl chlorides with alkylboron compounds (Eq. 8.33) [60]. In this reaction, the chiral coupled products were synthesized from the racemic acylated halohydrins and alkylboron compounds, yielding high enantioselectivity with the assistance of the nickel catalyst ligated with a chiral diamine ligand **23**.



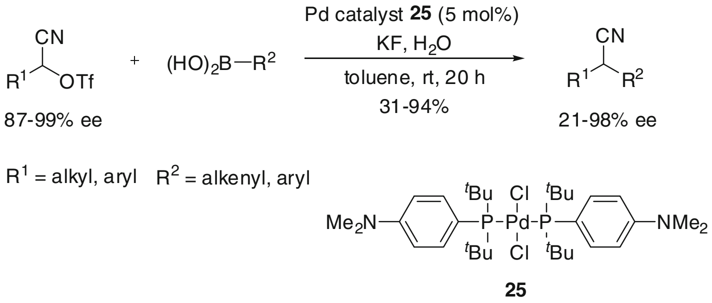
(8.33)

Very recently, Fu et al. reported the stereoconvergent alkyl–alkyl-type Suzuki–Miyaura coupling reactions of inert secondary alkyl chlorides substituted with amines (Eq. 8.34) [61]. Detailed mechanistic studies indicated that the primary site of coordination of the arylamine substrates to the nickel complex having the diamine ligand **24** was the nitrogen, not the aromatic ring. The kinetics for these asymmetric cross-coupling reactions of unactivated alkyl electrophiles was studied for the first time; the data were consistent with transmetalation being the turnover-limiting step of the catalytic cycle.



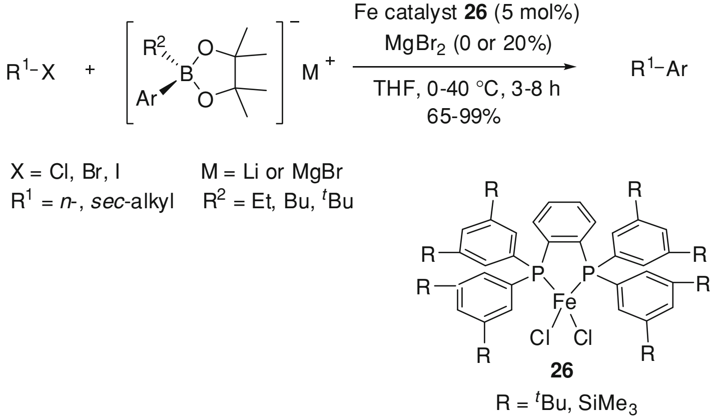
(8.34)

In contrast to their more commonly used nickel catalyst counterparts, the synthetic examples of Suzuki–Miyaura coupling reactions of secondary alkyl electrophile substrates promoted by palladium catalysts are comparatively rare. However, Falck et al. have recently reported the stereo-specific cross-coupling reactions of chiral secondary alkyl-substituted cyanohydrin triflates with the sp^2 hybridized organoboron compounds in the presence of palladium catalyst **25** (Eq. 8.35) [62].



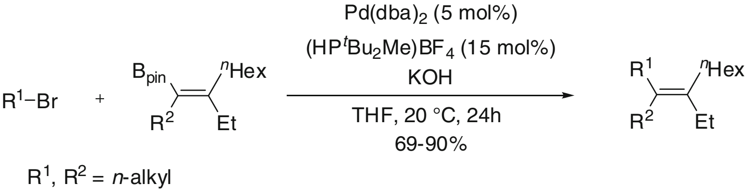
(8.35)

An example of Suzuki–Miyaura coupling reactions of secondary alkyl electrophiles using cheaper transition metals is the iron-catalyzed Suzuki–Miyaura coupling of inert alkyl halides with aromatic pinacolborates, achieved by Nakamura et al. (Eq. 8.36) [63]. Pertinent features of these reactions include the use of the iron catalyst **26** and a magnesium salt as a co-catalyst and the sterically bulky, bidentate phosphine ligands.



(8.36)

The regio- and stereo-selective synthesis of tetra-alkylated olefins has been very recently attained (Eq. 8.37) [64]. The R^2 group was incorporated by Negishi coupling of 1-iodo-1-borylated olefins with primary alkyl bromides through zirconacyclopentene formation (derived from alkynylboronates and the low-valent zirconocene complex). Subsequent Suzuki–Miyaura coupling reactions of trialkyl-substituted alkenyl boronates afforded the tetra-substituted olefins having four different alkyl groups.



(8.37)

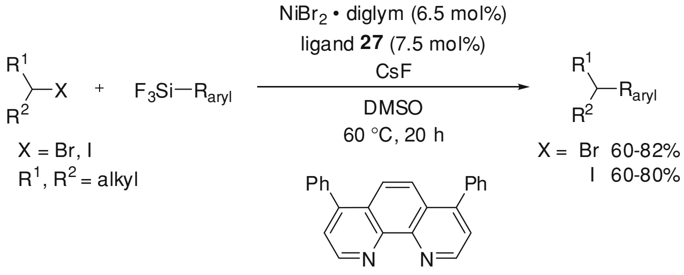
8.6 Hiyama Coupling

The synthetic examples of Hiyama coupling reactions of alkyl halides as the coupling partners are comparatively few, but have gradually increased in number in recent years. For instance, in 2003 Fu et al. reported Hiyama coupling reactions of inert primary alkyl halides with aryl silicon compounds, utilizing palladium with the P^tBu_2Me ligand (Eq. 8.38) [65]. This reaction is based on previously reported Suzuki–Miyaura coupling conditions [45, 48], and is promoted by further adding Bu_4NF as an activator to generate highly nucleophilic, hyper-valent silicon-containing species. As a result, this reaction occurred at room temperature and showed high functional groups tolerance.

$$\mathrm{R_{alkyl}{-}X} + \mathrm{(MeO)_3Si{-}R_{aryl}} \xrightarrow[\text{THF, rt, 14 h; 50-84\%}]{\text{PdBr}_2\text{ (4 mol\%)},\ \text{P}^t\text{Bu}_2\text{Me (10 mol\%)},\ \text{Bu}_4\text{NF}} \mathrm{R_{alkyl}{-}R_{aryl}} \tag{8.38}$$

X = Br, I
R_{alkyl} = *n*-alkyl

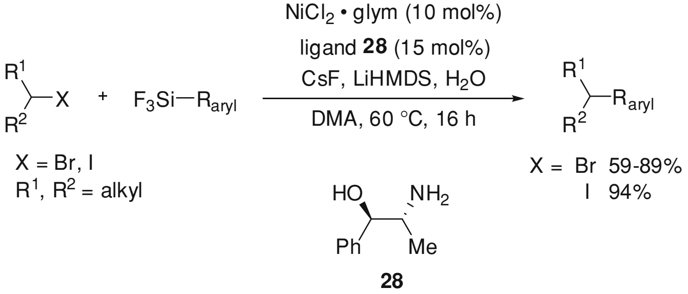
In addition, Fu achieved Hiyama coupling of inert secondary alkyl halides with aryltrifluorosilanes by using nickel having the ligand **27** as the catalyst (Eq. 8.39) [66]. This reaction can also be applicable not only to primary alkyl bromides and chlorides but also to the cyclic and non-cyclic secondary alkyl bromides, as well as the cyclic secondary alkyl iodides. It has also been clarified that these reaction conditions can be effective for the analogous Negishi and Suzuki–Miyaura couplings, employing the same types of the substrates.



27

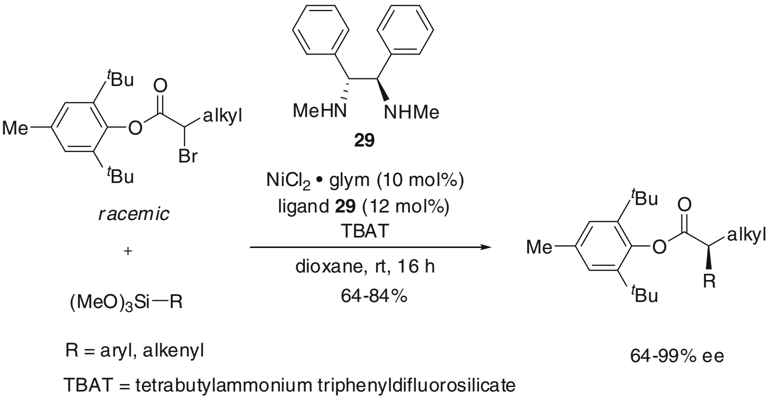
(8.39)

In 2007, Fu reported Hiyama coupling reactions of secondary alkyl bromides and chlorides with the aromatic silicon compounds, with the aid of the nickel catalyst system, i.e., nickel (II) chloride with the norephedrine ligand **28** (Eq. 8.40) [67]. This reaction was modified with the use of new ligands, based on the previously reported Suzuki–Miyaura coupling conditions [54]. It became clear that this reaction was applicable to secondary alkyl bromides and iodides as well as the activated secondary alkyl chlorides, which had not been successfully used as the substrates prior to this work.



(8.40)

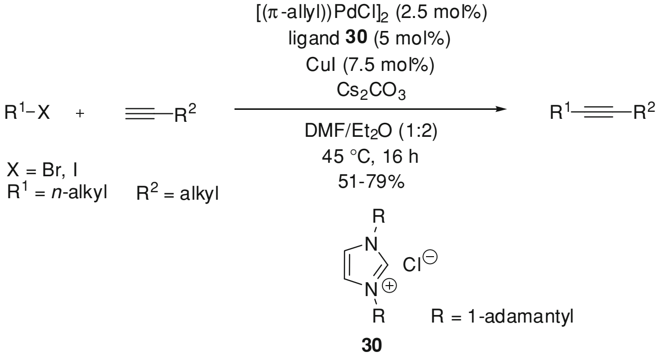
In 2008, Fu et al. reported the nickel-catalyzed asymmetric Hiyama coupling reactions of the racemic secondary α-bromoesters, employing diamine ligands **29** to give the corresponding chiral secondary esters with high enantioselectivity (Eq. 8.41) [68]. Anhydrated tetrabutylammonium triphenyldifluorosilicate (TBAT), as an activator, was the essential component to accelerate this reaction.



(8.41)

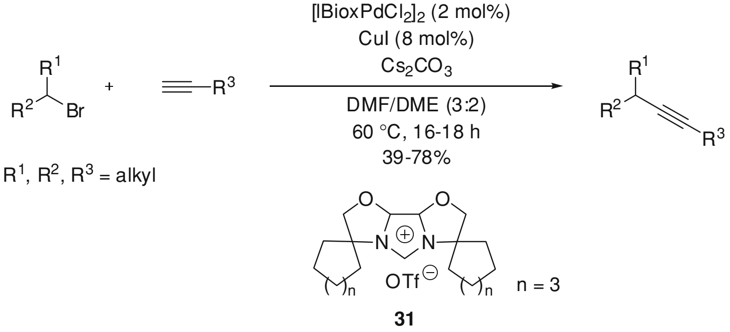
8.7 Sonogashira–Hagihara Coupling

In 2003, Fu reported Sonogashira–Hagihara cross-couplings of alkyl bromides and iodides by using a palladium catalyst ligated with *N*-heterocyclic carbene ligands **30** (Eq. 8.42) [69]. It was found that this reaction could be applicable to primary alkyl bromides and iodides even under mild conditions, but the alkyl chlorides were reported to be unsuitable.



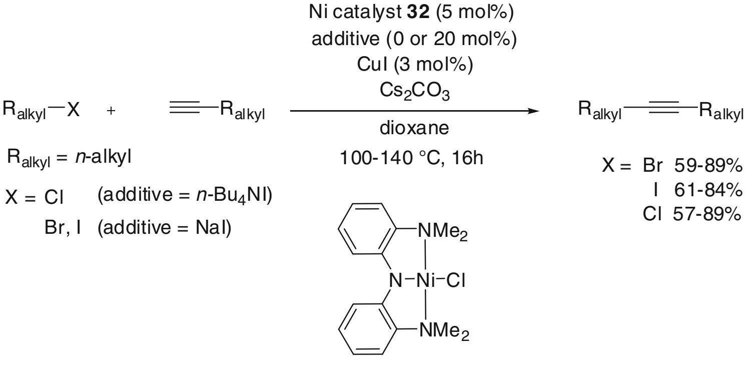
(8.42)

In 2006, Glorius et al. reported the first Sonogashira–Hagihara coupling of secondary alkyl bromides using the palladium catalyst bearing the bioxazoline-derived *N*-heterocyclic carbene ligands **31** (Eq. 8.43) [70]. This reaction could be extended to the use of primary and secondary alkyl bromides, and the reactive functional groups such as esters and epoxides were compatible with these reactions.



(8.43)

Hu et al. reported in 2009 the nickel-catalyzed Sonogashira–Hagihara coupling reactions of inert alkyl halides by using the nickel complex **32** bearing the pincer-type ligands (Eq. 8.44) [71]. In these reactions, a series of alkyl chlorides, bromides, and iodides were used as the substrates. This is the first example for Sonogashira–Hagihara coupling of unactivated alkyl chlorides.



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(8.44)

8.8 Summary

In this chapter, the recently reported examples of the cross-couplings of the alkyl electrophiles are collectively introduced. The cross-coupling reactions of the alkyl electrophiles have expanded the territory of the stereo-specific reactions toward the asymmetric syntheses. Because these reactions are tremendously useful for the synthesis of complicated organic molecules and the natural products bearing the alkyl chains as functional groups, further development of more efficient and selective reactions is highly anticipated. The further achievement of novel reactions by inexpensive and more active catalysts and the expansion to overcome the limitations of organometallic nucleophiles with reactive functional groups will be important future breakthroughs.

References

1. Kochi JK, Tamura M (1971) Mechanism of the silver-catalyzed reaction of Grignard reagents with alkyl halides. J Am Chem Soc 93:1483–1485
2. Kochi JK, Tamura M (1971) Alkylcopper(I) in the coupling of Grignard reagents with alkyl halides. J Am Chem Soc 93:1485–1487
3. Tamura M, Kochi JK (1972) Copper-catalyzed coupling of Grignard reagents and alkyl halides in tetrahydrofuran solutions. J Organomet Chem 42:205–228
4. Nunomoto S, Kawakami Y, Yamashita Y (1983) Cross-coupling reaction of 2-(1,3-butadienyl)magnesium chloride with alkyl or aryl halides by lithium chloride-cupric chloride (Li_2CuCl_4), a superior catalyst. J Org Chem 48:1912–1914
5. Wright ME, Jin M-J (1990) Bis(pyridyl)-silane and -methanol ligands IV. Catalytic application of nickel(II) complexes in the Kumada cross-coupling reaction. J Organomet Chem 287:373–379

6. Castle PL, Widdowson DA (1986) New developments in palladium catalysed cross coupling: the coupling of alkyl iodides with alkyl Grignard reagents. Tetrahedron Lett 27:6013–6016
7. Donkervoort JG, Vicario JL, Jastrzebski JTBH, Gossage RA, Cahiez G, van Koten G (1998) Novel tridentate diamino organomanganese(II) complexes as homogeneous catalysts in manganese(II)/copper(I) catalyzed carbon–carbon bond forming reactions. J Organomet Chem 558:61–69
8. Cahiez G, Chaboche C, Jezequel M (2000) Cu-catalyzed alkylation of Grignard reagents: a new efficient procedure. Tetrahedron 56:2733–2737
9. Terao J, Watanabe H, Ikumi A, Kuniyasu H, Kambe N (2002) Nickel-catalyzed cross-coupling reaction of Grignard reagents with alkyl halides and tosylates: remarkable effect of 1,3-butadienes. J Am Chem Soc 124:4222–4223
10. Terao J, Naitoh Y, Kuniyasu H, Kambe N (2003) Pd-catalyzed cross-coupling reaction of alkyl tosylates and bromides with Grignard reagents in the presence of 1,3-butadiene. Chem Lett 32:890–891
11. Uemura M, Yorimitsu H, Oshima K (2006) Synthesis of $Cp^*CH_2PPh_2$ and its use as a ligand for the nickel-catalyzed cross-coupling reaction of alkyl halides with aryl Grignard reagents. Chem Commun, 4726–4728
12. Vechorkin O, Proust V, Hu X (2009) Functional group tolerant Kumada–Corriu–Tamao coupling of nonactivated alkyl halides with aryl and heteroaryl nucleophiles: catalysis by a nickel pincer complex permits the coupling of functionalized Grignard reagents. J Am Chem Soc 131:9756–9766
13. Frisch C, Shaikh N, Zapf A, Beller M (2002) Palladium-catalyzed coupling of alkyl chlorides and Grignard reagents. Angew Chem Int Ed 41:4056–4059
14. Frisch AC, Rataboul F, Zapf A, Beller M (2003) First Kumada reaction of alkyl chlorides using *N*-heterocyclic carbene/palladium catalyst systems. J Organomet Chem 687:403–409
15. Tamura M, Kochi JK (1971) Vinylation of Grignard reagents. Catalysis by iron. J Am Chem Soc 93:1487–1489
16. Fürstner A, Leitner A (2002) Iron-catalyzed cross-coupling reactions of alkyl-Grignard reagents with aryl chlorides, tosylates, and triflates. Angew Chem Int Ed 41:609–612
17. Martin R, Fürstner A (2004) Cross-coupling of alkyl halides with aryl Grignard reagents catalyzed by a low-valent iron complex. Angew Chem Int Ed 43:3955–3957
18. Nagano T, Hayashi T (2004) Iron-catalyzed Grignard cross-coupling with alkyl halides possessing β-hydrogens. Org Lett 6:1297–1299
19. Nakamura M, Matsuo K, Ito S, Nakamura E (2004) Iron-catalyzed cross-coupling of primary and secondary alkyl halides with aryl Grignard reagents. J Am Chem Soc 126:3686–3687
20. Bedford RB, Bruce DW, Frost RM, Goodby JW, Hird M (2004) Iron(III) salen-type catalysts for the cross-coupling of aryl Grignards with alkyl halides bearing β-hydrogens. Chem Commun, 2822–2823
21. Bedford RB, Bruce DW, Frost RM, Hird M (2005) Simple iron-amine catalysts for the cross-coupling of aryl Grignards with alkyl halides bearing β-hydrogens. Chem Commun, 4161–4163
22. Bedford RB, Betham M, Bruce DW, Danopoulos AA, Frost RM, Hird M (2006) Iron-phosphine, -phosphite, -arsine, and -carbene catalysts for the coupling of primary and secondary alkyl halides with aryl Grignard reagents. J Org Chem 71:1104–1110
23. Cahiez G, Habiak V, Duplais C, Moyeux A (2007) Iron-catalyzed alkylations of aromatic Grignard reagents. Angew Chem Int Ed 46:4364–4366
24. Chowdhury RR, Crane AK, Fowler C, Kwong P, Kozak CM (2008) Iron(III) amine-bis(phenolate) complexes as catalysts for the coupling of alkyl halides with aryl Grignard reagents. Chem Commun, 94–96
25. Ohmiya H, Yorimitsu H, Oshima K (2006) Cobalt(diamine)-catalyzed cross-coupling reaction of alkyl halides with arylmagnesium reagents: stereoselective constructions of arylated asymmetric carbons and application to total synthesis of AH13205. J Am Chem Soc 128:1886–1889

26. Ohmiya H, Wakabayashi K, Yorimitsu H, Oshima K (2006) Cobalt-catalyzed cross-coupling reactions of alkyl halides with aryl Grignard reagents and their application to sequential radical cyclization/cross-coupling reactions. Tetrahedron 62:2207–2213
27. Yasuda S, Yorimitsu H, Oshima K (2008) Vanadium-catalyzed cross-coupling reactions of alkyl halides with aryl Grignard reagents. Bull Chem Soc Jpn 81:287–290
28. Tucker CE, Knochel P (1993) Cross-coupling between functionalized alkylcopper reagents and functionalized alkyl halides. J Org Chem 58:4781–4782
29. Devasagayaraj A, Stüdemann T, Knochel P (1995) A new nickel-catalyzed cross-coupling reaction between sp^3 carbon centers. Angew Chem Int Ed Engl 34:2723–2725
30. Giovannini R, Stüdemann T, Dussin G, Knochel P (1998) An efficient nickel-catalyzed cross-coupling between sp^3 carbon centers. Angew Chem Int Ed 37:2387–2390
31. Giovannini R, Knochel P (1998) Ni(II)-catalyzed cross-coupling between polyfunctional arylzinc derivatives and primary alkyl iodides. J Am Chem Soc 120:11186–11187
32. Giovannini R, Stüdemann T, Devasagayaraj A, Dussin G, Knochel P (1999) New efficient nickel-catalyzed cross-coupling reaction between two Csp^3 centers. J Org Chem 64:3544–3553
33. Zhou J, Fu GC (2003) Palladium-catalyzed Negishi cross-coupling reactions of unactivated alkyl iodides, bromides, chlorides, and tosylates. J Am Chem Soc 125:12527–12530
34. Zhou J, Fu GC (2003) Cross-couplings of unactivated secondary alkyl halides: room-temperature nickel-catalyzed Negishi reactions of alkyl bromides and iodides. J Am Chem Soc 125:14726–14727
35. Organ MG, Avola S, Dubovyk I, Hadei N, Kantchev EAB, O'Brien CJ, Valente C (2006) A user-friendly, all-purpose Pd-NHC(NHC = *N*-heterocyclic carbene) precatalyst for the Negishi reaction: a step towards a universal cross-coupling catalyst. Chem Eur J 12:4749–4755
36. Krasovskiy A, Duplais C, Lipshutz BH (2009) Zn-mediated, Pd-catalyzed cross-couplings in water at room temperature without prior formation of organozinc reagents. J Am Chem Soc 131:15592–15593
37. Nakamura M, Ito S, Matsuo K, Nakamura E (2005) Iron-catalyzed chemoselective cross-coupling of primary and secondary alkyl halides with arylzinc reagents. Synlett, 1794–1798
38. Ejiri S, Odo S, Takahashi H, Nishimura Y, Gotoh K, Nishihara Y, Takagi K (2010) Negishi alkyl–aryl cross-coupling catalyzed by Rh: efficiency of novel tripodal 3-diphenylphosphino-2-(diphenylphosphino)methyl-2-methylpropyl acetate ligand. Org Lett 12:1692–1695
39. Shimizu R, Fuchikami T (1996) Palladium catalyzed coupling reactions of β-perfluoroalkyl-substituted alkyl halides with organostannanes. Tetrahedron Lett 37:8405–8408
40. Shimizu R, Fuchikami T (2001) Effect of fluorine substituents on functionalizations of alkyl halides with organostannanes. Tetrahedron Lett 42:6891–6894
41. Tang H, Menzel K, Fu GC (2003) Ligands for palladium-catalyzed cross-couplings of alkyl halides: use of an alkyldiaminophosphane expands the scope of the Stille reaction. Angew Chem Int Ed 42:5079–5082
42. Hosoya T, Sumi K, Doi H, Wakao M, Suzuki M (2006) Rapid methylation on carbon frameworks useful for the synthesis of $^{11}CH_3$-incorporated PET tracers: Pd(0)-mediated rapid coupling of methyliodide with an alkenyltributylstannane leading to a 1-methylalkene. Org Biomol Chem, 410–415
43. Ishiyama T, Abe S, Miyaura N, Suzuki A (1992) Palladium-catalyzed alkyl-Alkyl cross-coupling reaction of 9-alkyl-9-BBN derivatives with iodoalkanes possessing β-hydrogens. Chem Lett, 691–694
44. Charette AB, Giroux A (1996) Palladium-catalyzed Suzuki-type cross-couplings of iodocyclopropanes with boronic acid: synthesis of trans-1,2-dicycopropyl alkenes. J Org Chem 61:8718–8719
45. Netherton MR, Dai C, Neuschütz K, Fu GC (2001) Room-temperature alkyl–alkyl Suzuki cross-coupling of alkyl bromides that possess β hydrogens. J Am Chem Soc 123:10099–10100

46. Kirchhoff JH, Dai C, Fu GC (2002) A method for palladium-catalyzed crosscouplings of simple alkyl chlorides: Suzuki reactions catalyzed by $[Pd_2(dba)_3]/PCy_3$. Angew Chem Int Ed 41:1945–1947
47. Netherton MR, Fu GC (2002) Suzuki cross-couplings of alkyl tosylates that possess β hydrogen atoms: synthetic and mechanistic studies. Angew Chem Int Ed 41:3910–3912
48. Kirchhoff JH, Netherton MR, Hills ID, Fu GC (2002) Boronic acids: new coupling partners in room-temperature Suzuki reactions of alkyl bromides. Crystallographic characterization of an oxidative-addition adduct generated under remarkably mild conditions. J Am Chem Soc 124:13662–13663
49. Arentsen K, Caddick S, Cloke FGN, Herring AP, Hitchcock PB (2004) Suzuki–Miyaura cross-coupling of aryl and alkyl halides using palladium/imidazolium salt protocols. Tetrahedron Lett 45:3511–3515
50. Hills ID, Netherton MR, Fu GC (2003) Toward an improved understanding of the unusual reactivity of Pd^0/trialkylphosphane catalysts in cross-coupling of alkyl electrophiles: quantifying the factors that determine the rate of oxidative addition. Angew Chem Int Ed 42:5749–5752
51. Terao J, Kambe N (2006) Transition metal-catalyzed C–C bond formation reactions using alkyl halides. Bull Chem Soc Jpn 79:663–672
52. Zhou J, Fu GC (2004) Suzuki cross-couplings of unactivated secondary alkyl bromides and iodides. J Am Chem Soc 126:1340–1341
53. Duncton MAJ, Estiarte MA, Tan D, Kaub C, O'Mahony DJR, Johnson RJ, Cox M, Edwards WT, Wan M, Kincaid J, Kelly MG (2008) Preparation of aryloxetanes and arylazetidines by use of an alkyl-aryl Suzuki coupling. Org Lett 10:3259–3262
54. González-Bobes F, Fu GC (2006) Amino alcohols as ligands for nickel-catalyzed Suzuki reactions of unactivated alkyl halides, including secondary alkyl chlorides, with arylboronic acids. J Am Chem Soc 128:5360–5361
55. Saito B, Fu GC (2007) Alkyl–alkyl Suzuki cross-couplings of unactivated secondary alkyl halides at room temperature. J Am Chem Soc 129:9602–9603
56. Rodríguez N, de Arellano CR, Asensio G, Medio-Simón M (2007) Palladium-catalyzed Suzuki–Miyaura reaction involving a secondary sp^3 carbon: studies of stereochemistry and scope of the reaction. Chem Eur J 13:4223–4229
57. Saito B, Fu GC (2008) Enantioselective alkyl–alkyl Suzuki cross-couplings of unactivated homobenzylic halides. J Am Chem Soc 130:6694–6695
58. Lu Z, Fu GC (2010) Alkyl–alkyl Suzuki cross-coupling of unactivated secondary alkyl chlorides. Angew Chem Int Ed 49:6676–6678
59. Lundin PM, Fu GC (2010) Asymmetric Suzuki cross-couplings of activated secondary alkyl electrophiles: arylations of racemic α-chloroamides. J Am Chem Soc 132:11027–11029
60. Owston NA, Fu GC (2010) Asymmetric alkyl–alkyl cross-coupling of unactivated secondary alkyl electrophiles: stereoconvergent Suzuki reactions of racemic acylated halohydrins. J Am Chem Soc 132:11908–11909
61. Lu Z, Wisily A, Fu GC (2011) Stereoconvergent amine-directed alkyl–alkyl Suzuki reactions of unactivated secondary alkyl chlorides. J Am Chem Soc 133:8154–8155
62. He A, Falk JR (2010) Stereospecific Suzuki cross-coupling of alkyl α-cyanohydrin triflates. J Am Chem Soc 132:2524–2525
63. Hatakeyama T, Hashimoto T, Kondo Y, Fujiwara Y, Seike H, Takaya H, Tamada Y, Ono T, Nakamura M (2010) Iron-catalyzed Suzuki–Miyaura coupling of alkyl halides. J Am Chem Soc 132:10674–10676
64. Nishihara Y, Okada Y, Jiao J, Suetsugu M, Lan M-T, Kinoshita M, Iwasaki M, Takagi K (2011) Highly regio- and stereoselective synthesis of multialkylated olefins through carbozirconation of alkynylboronates and sequential Negishi and Suzuki–Miyaura coupling reactions. Angew Chem Int Ed 50:8660–8664
65. Lee J-Y, Fu GC (2003) Room-temperature Hiyama cross-couplings of arylsilanes with alkyl bromides and iodides. J Am Chem Soc 125:5616–5617

66. Powell DA, Fu GC (2004) Nickel-catalyzed cross-couplings of organosilicon reagents with unactivated secondary alkyl bromides. J Am Chem Soc 126:7788–7789
67. Strotman NA, Sommer S, Fu GC (2007) Hiyama reactions of activated and unactivated secondary alkyl halides catalyzed by a nickel/norephedrine complex. Angew Chem Int Ed 46:3556–3558
68. Dai X, Strotman NA, Fu GC (2008) Catalytic asymmetric Hiyama cross-couplings of racemic α-bromo ester. J Am Chem Soc 130:3302–3303
69. Eckhardt M, Fu GC (2003) The first applications of carbene ligands in cross-couplings of alkyl electrophilics: Sonogashira reactions of unactivated alkyl bromides and iodides. J Am Chem Soc 125:13642–13643
70. Altenhoff G, Wurtz S, Glorius F (2006) The first palladium-catalyzed Sonogashira coupling of unactivated secondary alkyl bromides. Tetrahedron Lett 47:2925–2928
71. Vechorkin O, Barmaz D, Proust V, Hu X (2009) Ni-catalyzed Sonogashira coupling of nonactivated alkyl halides: orthogonal functionalization of alkyl iodides, bromides, and chlorides. J Am Chem Soc 131:12078–12079