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Yasushi Nishihara *Editor*

Applied Cross-Coupling Reactions

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Editor

Applied Cross-Coupling Reactions

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Preface

The cross-coupling reactions, developed for the first time in the 1970s, were acknowledged by the award of the Nobel Prize in Chemistry to three researchers in December, 2010. These cross-coupling reactions have been developed remarkably over the past 40 years vis-à-vis a variety of transition metal catalysts, organometallic reagents, and organic halides. They have enabled the formation of carbon–carbon bonds between unsaturated organic compounds, which is the fundamental framework of organic synthesis. It has become possible to produce extremely complex molecules through the development of the cross-coupling reactions, and as a result, highly selective carbon–carbon-bonding reactions have been achieved.

The large number of publications concerning cross-coupling is continually increasing. The kinds of transition metals used as catalysts, and the organometallic reagents used as coupling partners have also widely expanded in recent years. It has become possible to form a variety of very specific types of carbon–carbon bonds through appropriate selection of the reagents.

Although there are numerous books and reviews on the cross-coupling reactions, until now most of these books have been mainly categorized according to the eponymous (named) reactions. The cross-coupling reactions have had a tremendous impact not only in academic arenas but also in industry. These catalyzed reactions are accomplished using the transition metal complexes with extremely high utility. In this book, from the viewpoint of application, the authors select several representative cross-coupling reactions and classify the types of compounds using the most up-to-date references available. The authors refer to the historical background of the cross-coupling reactions and to the reaction mechanisms. Then the categories of compounds are outlined in order of natural products, pharmaceuticals, liquid crystals, and conjugate polymers. Finally, recent progress is introduced in the form of the new cross-coupling reactions involving aryl chlorides and alkyl halides bearing β-hydrogen as coupling electrophiles.

The authors hope that this book will provide the fundamental basics to both undergraduate and graduate-student readers, but also wish to inspire continued development and innovation of the cross-coupling reactions.

Finally, thanks goes out to Dr. Roderick O'Brien for his helpful input during the preparation of this manuscript and to the editorial team at Springer DE, in particular, Elizabeth Hawkins and Beate Siek for their patience and guidance during the entire projects.

Okayama, Japan, 2012 Yasushi Nishihara

Contents

Part I
Metal-Catalyzed Cross-Coupling Reactions

Chapter 1
A Historic Overview of the Metal-Catalyzed Cross-Coupling Reactions

Yasushi Nishihara

Abstract The main focus of this publication is the innovation of new synthetic reactions that can form various carbon–carbon bonds with high selectivity. The use of transition-metal-catalyzed cross-coupling reactions of organic electrophiles with organometallic nucleophiles started with the discovery of Kumada–Tamao–Corriu coupling in 1972—the reaction of organic halides and organomagnesium compounds under nickel catalysis. Combining fragments with a series of carbon centers into one segment, the transition-metal-catalyzed cross-coupling reactions have long been industrially utilized toward the synthesis of functional materials such as agricultural chemicals, pharmaceuticals, and polymers.

Keywords Cross-coupling · Transition metal catalysts · Organic halides · Organometallic nucleophiles · Carbon-carbon bond formation

1.1 General Introduction

The 2010 Nobel Prize in Chemistry was given to Professor Emeritus Richard F. Heck, Delaware University, USA, Professor Ei-ichi Negishi, Purdue University, USA, and Professor Emeritus Akira Suzuki, Hokkaido University, Japan. These scholars greatly contributed to the creation of palladium-catalyzed cross-coupling

The original version of this chapter was revised: There was a change in the first name of the contributor in Chap. 1. The erratum to this chapter is available at DOI ???10.1007/978-3-642-32368-3_9???

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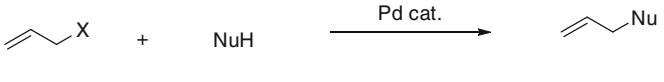
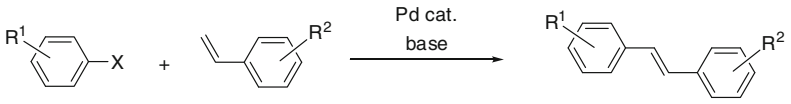
reactions in organic synthesis. The cross-coupling reactions completely changed the concepts for the carbon–carbon bond formation in synthetic organic chemistry and invented a large number of eponymous reactions. This chapter provides an overview of the historical background of cross-coupling reactions.

The palladium-mediated carbon–carbon-bond-forming reactions started with the pioneering work reported by Tsuji in 1965 [1]. A mixture of a $PdCl_2$(cyclo-octadiene) complex and ethyl malonate under basic conditions successfully generated the carbopalladation product at room temperature. This discovery led to the worldwide development of the powerful palladium chemistry. Subsequently, in 1965 Tsuji investigated the reaction of the π-allylpalladium complex with ethyl malonate forming ethyl allyl malonate [2]. In conjunction with a great contribution to this chemistry by Trost who succeeded in 1973 in an asymmetric version of Tsuji's reaction [3], these palladium-catalyzed substitution reactions via the π-allylpalladium complex as a key intermediate have been widely recognized as "Tsuji-Trost" reactions (Eq. 1.1) [4, 5].



X = OAc, Cl, etc (1.1)

Mizoroki [6] and Heck [7] independently investigated the palladium-catalyzed reactions of alkenes with aryl or alkenyl halides in the presence of a base to afford the corresponding coupled products through a substitution of hydrogen in the alkenes (Eq. 1.2). Afterwards, this reaction was aggressively researched by Heck, becoming acknowledged as an excellent carbon–carbon bond-forming class of reactions catalyzed by palladium [8]. In 1995, Herrmann et al. reported that when the palladacycle catalyst, prepared from the commercially available P(*o*-tol)$_3$ ligand and palladium acetate, was used for the Mizoroki-Heck reaction, the turnover numbers reached one million [9]. Recently, remarkable improvements have been realized by using the bulky alkylphosphine and *N*-heterocyclic carbene (NHC) ligands; these ligands enable Mizoroki-Heck reactions of aryl bromides at room temperature. With the use of these bulky ligands, even the inactive aryl chlorides can be utilized when harsh reaction conditions are applied [10–12].



X = halogens, OTf, etc (1.2)

Although these reactions are highly important to understanding the history of the palladium-catalyzed carbon–carbon bond-forming reactions, a large number of reviews covering these reactions have already been published. A list of such reviews and books of the cross-coupling reactions can be found in the appendix. Thus, these early cross-coupling reactions will not be reviewed in depth here.

1.2 The Cross-Coupling Reactions Addressed in this Textbook

This textbook mainly introduces the *cross-coupling reactions,* which are the reactions of organic electrophiles (R^2-X) such as organic halides and pseudohalides (triflates, mesylates, and tosylates) with the organometallic reagents (R^1-m; m = Mg, Li, Cu, Zn, Al, Zr, Sn, B, and Si), catalyzed by complexes of a transition metal (M) such as nickel and palladium, to form the cross-coupled products (R^1-R^2) with newly formed *carbon–carbon bond*s, generating salts (m-X) as by-products [13–15]. A representative reaction is shown in Eq. 1.3.

$$R^1\text{–m} \;+\; R^2\text{-X} \xrightarrow[\text{(addtive)}]{\text{M}} R^1\text{–}R^2 \;+\; \text{m–X} \qquad (1.3)$$

R^1= R^2= alkenyl, aryl, alkyl, etc	m = Mg	Kumada-Tamao-Corriu
X = I, Br, Cl, TfO, etc	m = Li	Murahashi
M = transition metals (Ni, Pd, etc)	m = Al, Zr, Zn	Negishi
	m = Sn	Migita-Kosugi-Stille
	m = B	Suzuki-Miyaura
	m = Si	Hiyama
R^1= alkynyl, m = H, and copper (I) salt		Sonogashira-Hagihara

An advantageous feature of these cross-coupling reactions is substitution with retention of the configuration at the sp^2 carbon, which had not been possible by conventional organic reactions. These reactions can also selectively couple specific points even in complicated molecules with many reactive sites. These innovations have facilitated the synthesis of π-conjugated compounds such as natural products (???Chap. 3???), pharmaceuticals (???Chap. 4???), liquid crystals (???Chap. 5???), and conjugated polymers (???Chap. 6???) as well as luminescence materials and the organic semiconductors.

1.2.1 Kumada–Tamao–Corriu Coupling

Historically, *cross-couplings* started in 1972 (date received, October 28, 1971) from the research of Corriu at Montpellier University, France using Grignard reagents (*m* = MgX) and a catalytic amount of $Ni(acac)_2$ to construct carbon(sp^2)–carbon(sp^2) bonds [16]. This is the first instance of the cross-coupling reactions and is conceptually the same as the research of Kharash [17] and Kochi [18] adding transition-metal salts to Grignard reagents to form the carbon–carbon bonds.

Near the same time, Kumada and Tamao at Kyoto University, Japan reported the reactions of Grignard reagents and aryl or alkenyl halides in the presence of a nickel-dppp (dppp = bis(1,3-diphenylphosphinopropane)) complex as the catalyst

(date received, February 15, 1972) [19], based on the stoichiometric version reported by Yamamoto [20, 21]. In Kumada's paper, the catalytic cycle was proposed for the first time, which consists of three basic reactions identified as: "oxidative addition," "transmetalation," and "reductive elimination." The catalyst cycle indicated by this research completely changed the concept of the carbon–carbon bond-forming reactions.

Kumada discussed, for the first time, the concept of a molecular catalyst by showing a correlation between the nickel–phosphine complexes and the catalytic activity, which greatly depends on the structure of the phosphine ligand. When the dppp ligand was employed on nickel, the highest catalytic activity was observed. It is also noteworthy that when alkyl Grignard reagents bearing β-hydrogens were used as the substrates, carbon–fluorine bond activation in fluorobenzene was attained [22].

Later, an asymmetric version of Kumada–Tamao–Corriu coupling was independently achieved by the Consiglio [23] and Kumada–Tamao [24] groups in 1973 and 1974, respectively. Moreover, the remarkable improvement of enantioselectivity was reported by Hayashi–Tamao–Kumada using asymmetric ferrocene-incorporating ligands in 1976 [25]. Even today, substituted styrene continues to be manufactured by this protocol [26, 27].

One of the drawbacks of the Kumada–Tamao–Corriu coupling reaction is that highly reactive electrophiles such as carbonyl compounds cannot be used due to their high reactivity toward organomagnesium reagents, but these reactions are improved again from the viewpoint of the recent "element strategy" [28–31]. These types of reactions are contemporarily referred to as "Kumada–Tamao–Corriu coupling."

1.2.2 Murahashi Coupling

Although the utility of the palladium catalyst had already been confirmed in the Mizoroki-Heck reaction, the palladium catalyst was not used in the early C–M (M = metal)/C–X (X = halides or pseudohalides) type cross-coupling reactions. Murahashi reported the cross-coupling reactions of organic halides using the palladium catalyst instead of the nickel catalyst for the first time in 1975 [32]. Murahashi and colleagues also described the potential of organolithium compounds for use in the cross-coupling reactions.

It is an advantageous feature that organolithium compounds can be prepared by the treatment of organic halides with lithium metal or by the direct transmetalation of hydrocarbons with BuLi. In addition, the palladium catalyst extended the coverage of the sp^2-carbon-containing nucleophiles of the cross-coupling reactions. As the result, under palladium catalysis, organomagnesium and organolithium reagents generate olefins and biaryls by the reactions of vinyl and aryl halides in high yields [33–35].

Recently, Yoshida et al. investigated the selective Murahashi coupling in a microreactor [36]; a Br–Li exchange of an aryl bromide with BuLi generated an aryllithium compound in situ, which reacted with a different aryl bromide in the microreactor in the presence of the palladium catalyst to give the corresponding asymmetric biaryl as the cross-coupled product within 1 min. This methodology could greatly expand the applicable ranges of the cross-coupling reactions of organolithium compounds.

1.2.3 Sonogashira–Hagihara Coupling

In 1975, Sonogashira and Hagihara reported on the cross-coupling reactions of acetylene gas or the terminal alkynes with aryl or alkenyl halides in the presence of palladium catalysts and copper (I) salts [37]. They demonstrated that the reactions improved the yields of the products under milder conditions by using the copper (I) salts as co-catalysts, although Cassar [38] and Heck [39] have reported on similar reactions that used only the palladium catalysts. In Sonogashira–Hagihara coupling, copper(I) salts and amines are necessary as additives, in addition to the Pd catalyst, to generate alkynylcopper species from terminal alkynes; this is an important intermediate for smooth transmetalation to Pd [40–42]. This reaction has the advantage that the desired products can be obtained in excellent yields under comparatively milder reaction conditions.

The Sonogashira–Hagihara coupling has become arguably the most useful method for preparing natural products, agrochemicals, pharmaceuticals, and conjugated polymers through the coupling of terminal alkynes and sp^2-hybridized carbons (e.g., aryl, heteroaryl, and alkenyl halides). The applications of Sonogashira–Hagihara coupling have been recently reviewed by Chinchilla and Nájera [43–45].

1.2.4 Negishi Coupling

In 1976, Negishi found new cross-coupling reactions other than organomagnesium and organolithium compounds by using various unprecedented metals. Negishi succeeded in a cross-coupling reaction through the combination of the palladium catalyst with organoaluminum reagents [46]. Because alkenylaluminum compounds can be readily synthesized by hydroalumination of alkynes, its combination with the cross-coupling reaction is a very useful process; this was the first example of combining hydrometalation with the cross-coupling reactions [47]. Negishi also thoroughly examined the combination of the transition metal catalysts and the main-group organometallic reagents involving boron [48], zirconium [49, 50], and finally organozinc reagents, which he determined to be the best in combination with the palladium catalysts [51–55].

This reaction, "Negishi coupling," is used in a variety of synthetic organic reactions all over the world. The organozinc compounds can be readily prepared by the treatment of Grignard reagents or organolithium compounds with zinc halides. There is an excellent feature in terms of functional group tolerance because the organozinc compounds do not react with esters, ketones, or nitriles. In addition, the corresponding ketones can be synthesized by the cross-coupling of alkylzinc reagents and alkanoyl halides, which can be synthons of the carbonyl compounds. In particular, the sp^2–sp^2 Negishi coupling has been used for the synthesis of biaryls and conjugate dienes, which are often found in natural products [56–58]

1.2.5 Migita–Kosugi–Stille Coupling

In 1977, the research group of Migita and Kosugi at Gunma University, Japan found that the organotin compounds can be incorporated in the palladium-catalyzed cross-coupling reactions [59]. The late Stille of Colorado State University also independently reported on the cross-coupling of organotin compounds in 1979 [60, 61]. This "Migita–Kosugi–Stille coupling" has the advantage of high functional group compatibility, i.e., the carbonyl group remains intact. Since organotin reagents are comparatively stable and an experimental operation is also often practical, they are widely used for synthesis at the laboratory level. Because organotin compounds are widely used as sterilizers, insecticides, and radical reducing agents, the adverse effects from chronic toxicity of alkylated tin compounds to the human body and the environment might be worrisome.

Despite the challenge that the toxicity of organotin compounds poses to industrial usage, there is still high demand for organotin reagents for Migita–Kosugi–Stille coupling. Owing to the mild and neutral reaction conditions, Migita–Kosugi–Stille has often been used, especially at key stages, in the natural-product synthesis. Close attention must be paid to the presence of organotin contaminants while applying the synthesized natural products to the pharmaceutical industry.

1.2.6 Suzuki–Miyaura Coupling

The most widely exploited cross-coupling reaction protocol, developed by Suzuki and Miyaura at Hokkaido University, Japan in 1979, uses organoboron compounds under palladium catalysis [62, 63]. This coupling reaction is commonly called "Suzuki–Miyaura coupling." Since boron is a non-metallic element (and thus the carbon–boron bond is an almost completely covalent bond) the carbon–boron bond of the organoboronic acids is too inert to undergo protonation with water and the acids. Although the reactivity of organoboron compounds is low, the reactivity can

be improved greatly by adding the bases; this was a breakthrough for the cross-coupling reactions. Pharmaceutical companies all over the world brought to market various organoboron reagents which have the advantage of stability (even to oxygen and moisture), and many industries have been manufacturing these on the scale of tons. Since stereoselective hydroboration of alkynes can be used to prepare various alkenylboron reagents, the syntheses of the stereodefined conjugate olefins have been highly realized. Presently, Suzuki–Miyaura coupling is one of the representative reactions of carbon–carbon bond formation; it is found in virtually every textbook covering the topic [64].

The cross-coupling reactions of arylboronic acids, reported in 1981, further improved Suzuki–Miyaura coupling [65]. Recently, a variety of organoboron reagents, e.g., trifluoroborates [66], trialkoxyborates [67], trihydroxyborates [68], and triolborates [69, 70], as isolable tetracoordinated "-ate" (anionic) complexes have been developed. These boron-containing salts are stable toward air and water and can be used for typical Suzuki–Miyaura coupling.

On the other hand, some recent advances include the preparation of organoboronic acid derivatives which are inert toward cross-coupling, albeit with facile protection-deprotection qualities. Suginome has reported that the boronic acid amide derivatives obtained from 1,8-diaminonaphthalene can be purified by column chromatography [71]. This protecting group can be detached to form the original boronic acids upon treatment with acid. Moreover, Burke has developed the protection method of organoboronic acids using *N*-methyliminodiacetic acid (MIDA) [72]. The synthesized MIDA-masked organoborates are air stable and their reactions can be monitored by TLC. Conveniently, this protecting group can readily be deprotected under basic conditions.

1.2.7 Hiyama Coupling

In 1982, a new carbon–carbon bond-forming reaction was achieved by Kumada, Tamao, and Yoshida, in which organopentafluorosilicates and organic halides were reacted at high temperature with the palladium catalyst [73]. Because saturated hexacoordinated organosilicates are inactive for transmetalation, the removal of one fluoride ion was necessary to generate the more active pentacoordinated silicate, which facilitates transmetalation. Because heating under harsh conditions was necessary, this reaction did not become a widely used protocol. On the other hand, in 1988, Hiyama et al. reported that the tetracoordinated vinyltrimethylsilanes cross-coupled with phenyl and alkenyl iodides in the presence of a fluoride ion and the palladium catalyst [74].

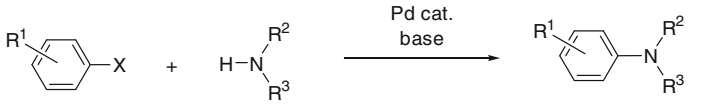
Organosilicon compounds have many advantages: low toxicity, environmental benignness, a natural abundance of silicon (the 2nd Clark's number), low cost, and excellent functional group selectivity. Since the organosilicon compounds are known to be extremely inert, in Hiyama coupling, it is a key issue to activate the organosilicon compounds to achieve smooth transmetalation. Transmetalation

hardly takes place with the trialkylsilyl group, even if activators are added; thus one or more aryl or hydroxy groups are generally introduced as a substituent on silicon. With this strategy, organosilanols (with the hydroxy group on a silicon atom) were reported to be activated by common bases in the Hiyama coupling [75].

Recently, Hiyama et al. prepared the more useful HOMSi reagent by using intramolecular nucleophilic attack of a hydroxy group to activate silicon instead of an added fluoride ion [76, 77]. When this hydroxy group is protected by common protecting groups, the silicon functionality showed no reactivity at all. After an appropriate transformation reaction, deprotection of the hydroxy group enables the smooth cross-coupling. In addition, because the silicon-containing by-products are recovered, overall manipulations are environmentally friendly from the viewpoint of *green chemistry*.

1.3 Perspectives

In addition to the carbon–carbon bond-forming reactions, other cross-couplings forming *carbon–nitrogen bonds* (amination) of aryl halides have been achieved by Hartwig [78, 79] and Buchwald [80, 81] in 1994 (Eq. 1.4). This reaction has rapidly spread all over the world because the triarylamines have received attention as electron transport materials.



(1.4)

Recent advances have been made in the cross-coupling reactions utilizing decarboxylation of carboxylic acids as well as the direct activation of carbon–hydrogen bonds of arenes as nucleophiles in place of organometallic reagents. An array of leaving groups involving triflates, tosylates, and mesylates, has been successfully utilized in addition to the traditional organic halides (???Chap. 7???). Moreover, since 2000, cross-coupling reactions of alkyl electrophiles with β-hydrogens have successfully been conducted (???Chap. 8???).

Through appropriate selection of the transition metal catalysts, vinyl ethers, aryl ethers, thioethers, and cyanides can be used as coupling partners. In addition, efforts to develop the inexpensive and ubiquitous cobalt and iron catalysts (rather than the noble nickel and palladium catalysts) have been underway. However, because radical reactions exclusively take place with these metal catalysts, it remains a future task to determine how the configuration could be controlled during such reactions.

The outstanding feature in the cross-coupling reactions of organic halides with organometallic reagents is that carbon–carbon bonds can be formed on a specific desired position while maintaining the parent molecules' configurations, as shown

in Eq.1.1. The demand for the development of the cross-coupling that can finely control the bond-forming positions and the configuration of the products will continue to grow.

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Chapter 2
Mechanisms and Fundamental Reactions

Masayuki Iwasaki and Yasushi Nishihara

Abstract It is widely accepted that the catalytic cycle of cross-coupling reactions of organometallic reagents with aryl halides catalyzed by transition metals consists of three fundamental processes: oxidative addition, transmetalation, and reductive elimination. Although the details of oxidative addition and reductive elimination have been extensively studied, little research on detailed mechanisms for transmetalation has been exploited until recently. In this chapter, recent examples of the transmetalation process (a transfer of organic groups to palladium) are generally outlined, vis-à-vis the intermediate complexes after transmetalation in Suzuki–Miyaura coupling and the effect of added copper salts in Migita–Kosugi–Stille coupling.

Keywords Reaction mechanism · Transmetalation · Suzuki–Miyaura coupling · Migita–Kosugi–Stille coupling · Copper effect

2.1 Transmetalation in Suzuki–Miyaura Coupling

The cross-coupling reactions of organometallic reagents with organic halides catalyzed by transition metals such as palladium and nickel are extremely useful and reliable methods for the construction of carbon–carbon bonds [1, 2]. The cross-coupling reactions can be applicable to a variety of organometallic compounds from Grignard reagents to organosilicon compounds. In particular, Suzuki–Miyaura coupling (as shown in Eq. 2.1) [3], using organoboron reagents

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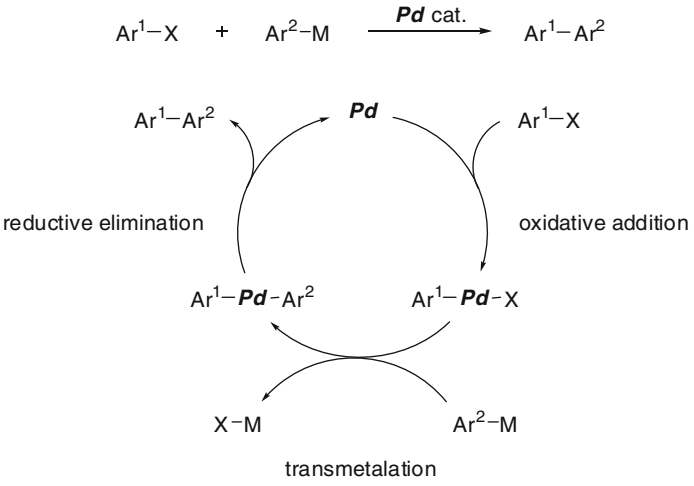
(especially organoboronic acids) with the aid of a base as an activator, is extensively utilized for the synthesis of natural products and biologically active substances. Suzuki–Miyaura coupling is also widely used for the production of functional organic materials with biaryl motifs in a variety of research fields. This versatility is due to: (1) the stability of organoboronic acids to water, air, and heat; (2) the high functional group tolerance of organoboron compounds; and (3) a lower toxicity of the boron-containing by-products produced by the reactions.

$$Ar^1{-}X \quad + \quad Ar^2{-}B(OH)_2 \xrightarrow[\textbf{Base}]{\text{Pd cat.}} Ar^1{-}Ar^2 \tag{2.1}$$

However, unlike the more reactive Grignard and organozinc reagents, the transfer of the organic groups (transmetalation) from boron to the palladium center is limited by the poor nucleophilicity of organoboronic acids. In 1979, Suzuki and Miyaura disclosed that the addition of a base to the reaction system enhances transmetalation between organoboron reagents and palladium to undergo the reaction efficiently [4]. Since that time, Suzuki–Miyaura coupling has been significantly refined and has brought important technical improvements to the field of carbon–carbon bond formation.

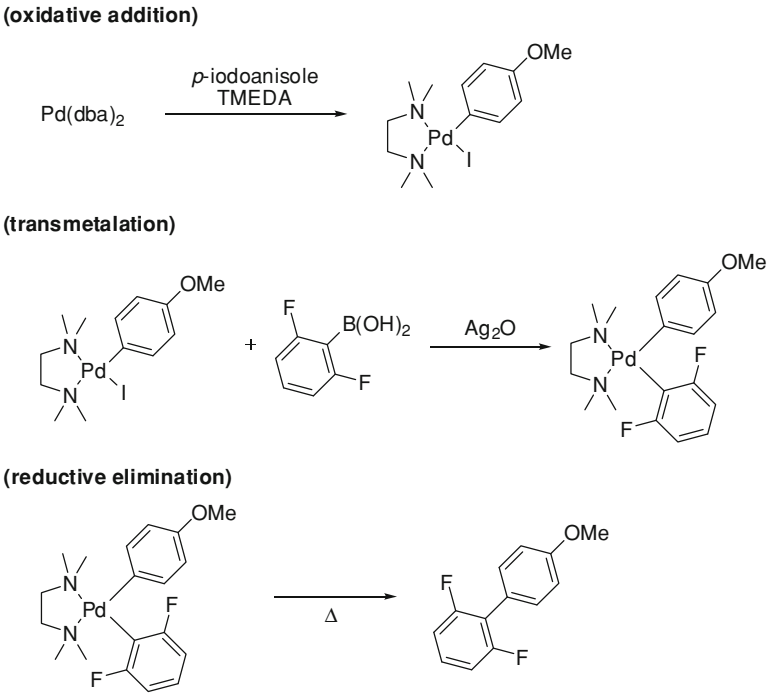
Generally, the cross-coupling reactions are believed to occur through three fundamental steps: oxidative addition, transmetalation, and reductive elimination, in a catalytic cycle as shown in Scheme 2.1. In Suzuki–Miyaura coupling, as well as in other cross-coupling reactions, both the oxidative addition and reductive elimination stages have been well studied; on the other hand, the mechanisms of transmetalation involving an accelerating effect by the addition of bases have scarcely been examined until lately. Recently, many experimental and theoretical aspects of the transmetalation mechanisms in Suzuki–Miyaura coupling have been explored. Herein, the transmetalation step in Suzuki–Miyaura coupling is reviewed from the perspective of a series of cross-coupling reactions, examining the effects of the bases on transmetalation.



Scheme 2.1 A catalytic cycle of the palladium-catalyzed cross-coupling reactions

2.1.1 Stoichiometric Reactions of Suzuki–Miyaura Coupling

To provide mechanistic insight into the transmetalation, each stoichiometric reaction of Suzuki–Miyaura coupling is elucidated, as depicted in Scheme 2.2. Oxidative addition of organic halides to palladium is already known, and the formed halogeno(aryl)palladium(II) complexes can be isolated [5–9], whereas diarylpalladium(II) complexes as intermediates have not been isolated until recently due to spontaneous reductive elimination after transmetalation. Osakada has succeeded in the isolation and structural determination of the diarylpalladium(II) complexes after transmetalation by using arylboronic acids substituted with fluorine in the ortho position, leading to a retardation of the reductive elimination [10–12]. Upon heating of the isolated diarylpalladium(II) complexes, reductive elimination occurs smoothly to afford biaryls as cross-coupled products. These experimental results suggest that the rate-determining step in Suzuki–Miyaura coupling is transmetalation. Moreover, it is noteworthy that in this stoichiometric transmetalation reaction, the reaction does not occur at all when no Ag_2O additive is added.



Scheme 2.2 Three fundamental reactions

2.1.2 Base-Assisted Transmetalation

An accelerating effect on the transmetalation step of Suzuki–Miyaura coupling was observed when the bases were added to the reactions of halogeno(aryl)palladium(II) complexes with trialkylboranes or organoboronic acids. This is not seen in other types of cross-coupling reactions. Organoboronic acids are generally inert toward halogeno(aryl)palladium(II) complexes without any assistance of bases. However, highly nucleophilic organoborates can enhance transmetalation across halogeno(aryl)palladium(II) complexes without bases, and reductive elimination spontaneously follows to form the cross-coupled products, as shown in Eq. 2.2 [13–19].

$$R^1\text{–}X \quad + \quad R^2\text{—}\mathbf{B} \xrightarrow[\textbf{\textit{No Base}}]{\textbf{\textit{Pd}}\ \text{cat.}} R^1\text{–}R^2 \tag{2.2}$$

$[R\text{-}C{\equiv}\ C\text{-}BR_3]Li$	$[R_3B\text{-}OMe]Na$	R_4BLi	$[Ar\text{-}BR_3]Li$
Negishi	*Suzuki* and *Miyaura*	*Suzuki* and *Miyaura*	*Suzuki* and *Miyaura*
(**1982**)	(**1989**)	(**1995**)	(**1995**)
$[Ar\text{-}B(R)(OR)_2]Li$	$[ArBF_3]K$	Ph_4BNa	$[ArB(OH)_3]Na$
Kobayashi	*Genêt*	*Bumagin* (**1999**)	*Cammidge*
(**1996**)	(**1997**)	*Haddach* (**1999**)	(**2006**)

On the other hand, Suzuki and Miyaura have reported that when the oxo complexes such as methoxo-, hydroxo-, and acetoxopalladium complexes (Fig. 2.1) were used as the starting compounds, the transmetalation with boronic acids occurred smoothly even under neutral conditions [20, 21].

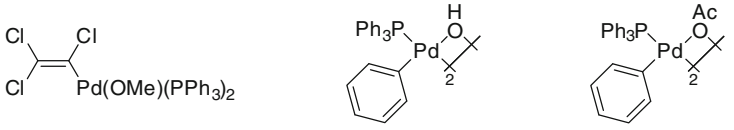


Fig. 2.1 Various oxopalladium complexes

Other examples of Suzuki–Miyaura coupling have been reported under neutral conditions by using the electrophiles shown in Fig. 2.2, because the oxopalladium complexes were immediately obtained by oxidative addition of these reagents [22–27]. In sharp contrast, oxidative addition of Ph_2IX, PhI(OH)OTf, or ArN_2BF_4 generates the cationic palladium species, which also rapidly undergo transmetalation without the addition of bases [28–31].

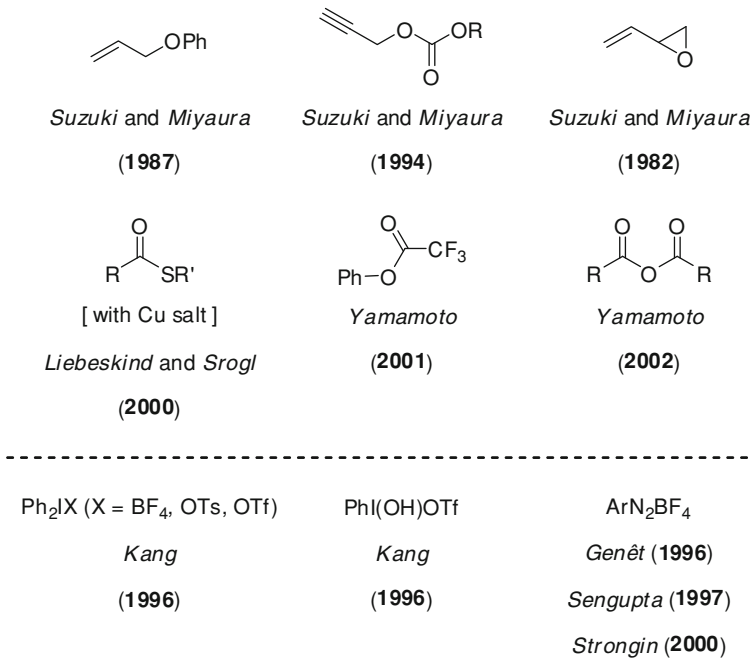
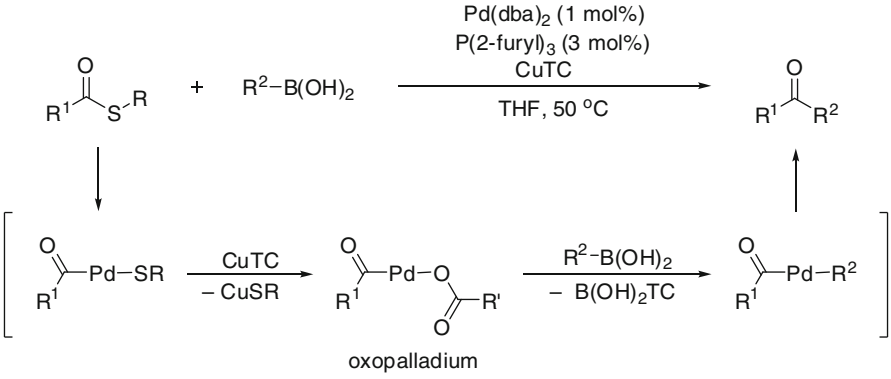


Fig. 2.2 Organic electrophiles directly yielding oxopalladium complexes via oxidative addition

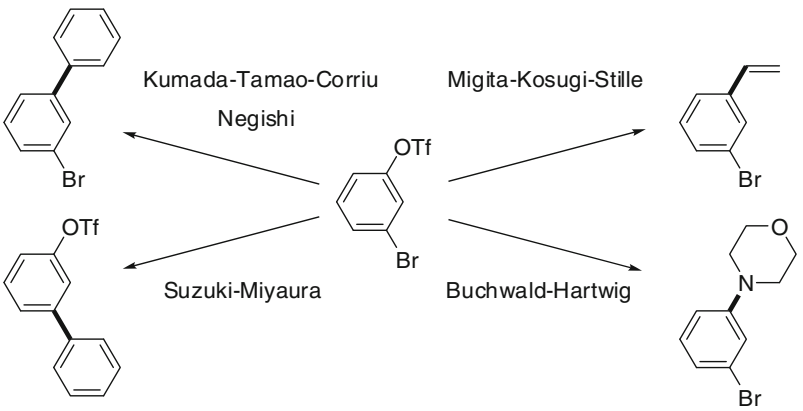
An example of the above-mentioned reactions, the Liebeskind–Srogl coupling, is shown in Scheme 2.3 [22]. The coupling reactions of the arylboronic acids with thioesters afforded the corresponding ketones under the palladium catalysis with the assistance of copper(I) 2-thiophenecarboxylate (CuTC) under neutral conditions. The reaction is thought to occur without the base because thiolatopalladium(II) complexes are converted into the carboxylatopalladium complexes by copper(I) carboxylates [32–42].



Scheme 2.3 Reaction of arylboronic acids with thioesters

2.1.3 The Turnover Limiting Step in Suzuki–Miyaura Coupling

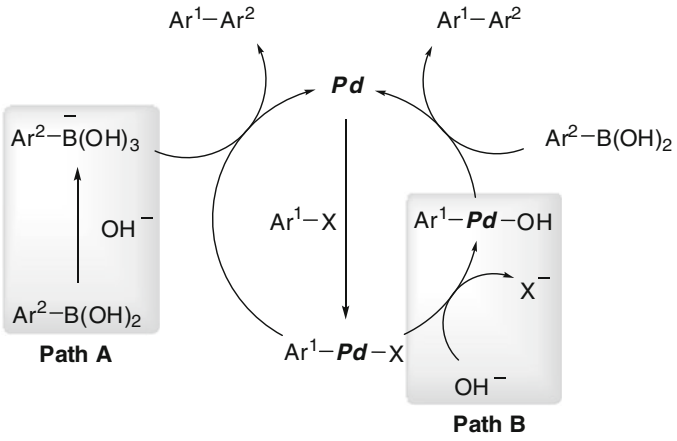
Transmetalation is believed to be the rate-determining step in most Suzuki–Miyaura couplings from the research on substituent effect of organic halides and organoboronic acids [43, 44]. This hypothesis is also supported from theoretical calculations; but, the presumption that transmetalation is the rate-determining step in all Suzuki–Miyaura couplings has become uncertain in recent years owing to the diversity of substrates and reaction conditions. For instance, Buchwald achieved cross-coupling reactions at room temperature by promoting transmetalation with sterically bulky phosphine ligands bearing biaryl backbones [45–47]. Furthermore, Fu reported that the less reactive alkyl chlorides can be used as electrophiles in Suzuki–Miyaura couplings [48]. Fu et al. proposed that the rate-determining step of these reactions is not transmetalation but oxidative addition. However, in most Suzuki–Miyaura couplings, under typical reaction conditions, transmetalation is the rate-controlling reaction in the catalytic cycle. Because a smooth transmetalation is essential for an efficient cross-coupling reaction, future investigation to improve this class of reactions should pay close attention to the transmetalation process. Brown compared the reaction rates by using arenes substituted with both triflates and bromides in a series of cross-coupling reactions. The results disclosed that the bromide chemoselectively reacted in Suzuki–Miyaura coupling, whereas the triflates preferentially reacted in Negishi, Kumada–Tamao–Corriu, and Migita–Kosugi–Stille couplings and Buchwald–Hartwig aminations (Scheme 2.4) [49]. It is clear that these very different results are ascribed to the transmetalation process in each coupling reaction, because the oxidative addition step is reversible [50].



Scheme 2.4 Transformations of 3-bromophenyl triflate

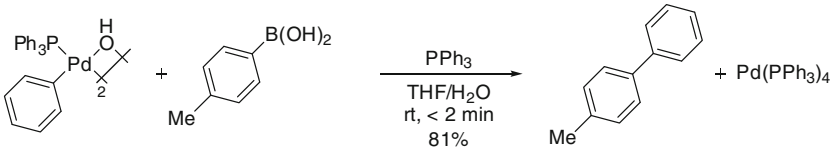
2.1.4 Pathways for Transmetalation

Two possible mechanisms of transmetalation in the base-accelerated Suzuki–Miyaura coupling can be considered. One involves the formation of the nucleophilic borates from the reactions of boronic acids with the added bases, which leads to a nucleophilic attack on the halogenopalladium(II) complexes (Scheme 2.5, Path A); the other contains a nucleophilic attack of the base (a hydroxyl ion) on halogenopalladium(II) complexes to generate the hydroxopalladium(II) intermediate, which further reacts with the neutral organoboron compounds to complete transmetalation (Scheme 2.5, Path B). Although to date there has been no definitive evidence to explain which transmetalation mechanism is correct, recently Hartwig et al. provided insight on the process [51].

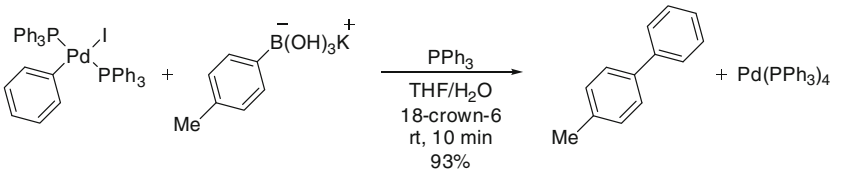


Scheme 2.5 Two possible pathways of transmetalation in Suzuki-Miyaura coupling

First of all, Hartwig examined a series of stoichiometric reactions of isolated arylpalladium(II) complexes with several organoboron reagents; the results indicated that the respective reactions of an arylboronic acid with a hydroxopalladium(II) complex (Eq. 2.3) and of an arylborate with an iodopalladium complex (Eq. 2.4) are much faster than the net catalytic reaction (Eq. 2.5). Therefore, both of the mechanisms (Paths A and B) may be involved in the catalytic cycle of Suzuki–Miyaura coupling.



(2.3)



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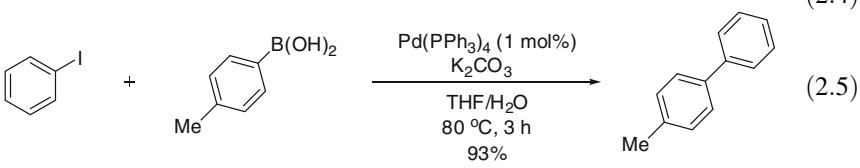
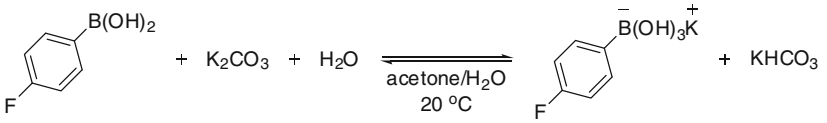


(2.5)

Next, the concentrations of the boronic acid, the borate, the halogenopalladium(II), and the hydroxopalladium complexes were measured by monitoring the ^{31}P and ^{11}B NMR spectra in the reactions. As a result, it was found that the ratio between boronic acid and borate is 1:1 to 1:3 under general conditions, i.e., a slightly basic condition in the organic solvent containing water (Eq. 2.6).

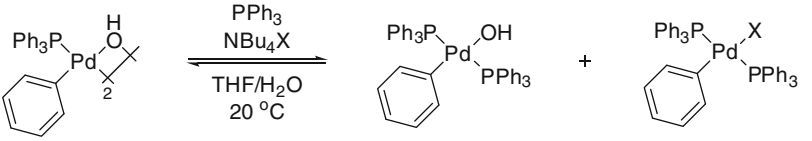


$[Ar\text{-}B(OH)_2]_0 = 0.011$ M

$[K_2CO_3]_0$	$[Ar\text{-}B(OH)_3^-]$
0.15 M	0.043 M
0.10 M	0.040 M
0.03 M	0.030 M

(2.6)

It was also clarified that there was no difference in the ratio between iodopalladium and hydroxopalladium complexes at equilibrium (shown in Eq. 2.7).

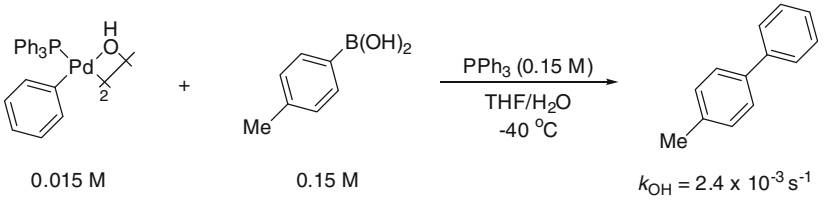


$[(Pd\text{-}OH)_2]_0 = 0.011$ M

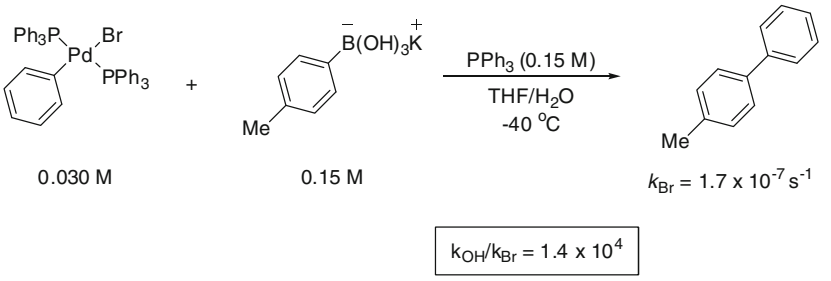
X =	$[(Pd\text{-}OH)_2]$	[Pd-OH]	[Pd-X]
I	0.0049 M	0.0028 M	0.0032 M
Br	0.0043 M	0.0038 M	0.0028 M
Cl	0.0032 M	0.0045 M	0.0031 M

(2.7)

Finally, the reaction rates of a boronic acid with a hydroxopalladium complex and of a borate with a bromopalladium complex were compared. When each reaction was monitored by ^{31}P NMR, a rate constant for the reaction of a boronic acid and a hydroxopalladium complex was found to be 2.4×10^{-3} s^{-1} (Eq. 2.8); whereas that of a bromopalladium complex and a potassium borate was 1.7×10^{-7} s^{-1} (Eq. 2.9), giving rise to significantly different ratios by a factor of 1.4×10^{4}.



(2.8)



(2.9)

These experimental results thus indicate that the transmetalation progresses via Path B in Scheme 2.5. However, it is noteworthy that: (1) this experimental data cannot be applied to all of Suzuki–Miyaura reactions; (2) although weak bases such as carbonates and phosphates are used in most cases of Suzuki–Miyaura reactions, Path B would compete with Path A when stronger bases are employed, leading to the prior generation of the borates; and (3) these data do not reflect any detailed mechanism for a transfer of the organic groups from boron to palladium.

2.1.5 Computational Studies of the Transmetalation Step in Suzuki–Miyaura Coupling

The theoretical calculations for the mechanism of the transmetalation process in Suzuki–Miyaura coupling support the experimental evidence provided by

Hartwig [51]. Maseras has performed the DFT calculations and the energy profiles corresponding to Paths A and B are shown in Figs. 2.3 and 2.4, respectively [52]. The energy profile of the reaction of a bromopalladium complex with vinylborate shown in Fig. 2.3, indicates that transmetalation proceeds exothermically, and the largest activation barrier in this route is rather small at 4.2 kcal/mol. Therefore, this calculation result supports that the bromo(vinyl)palladium complex can react with vinylborate in a catalytic cycle.

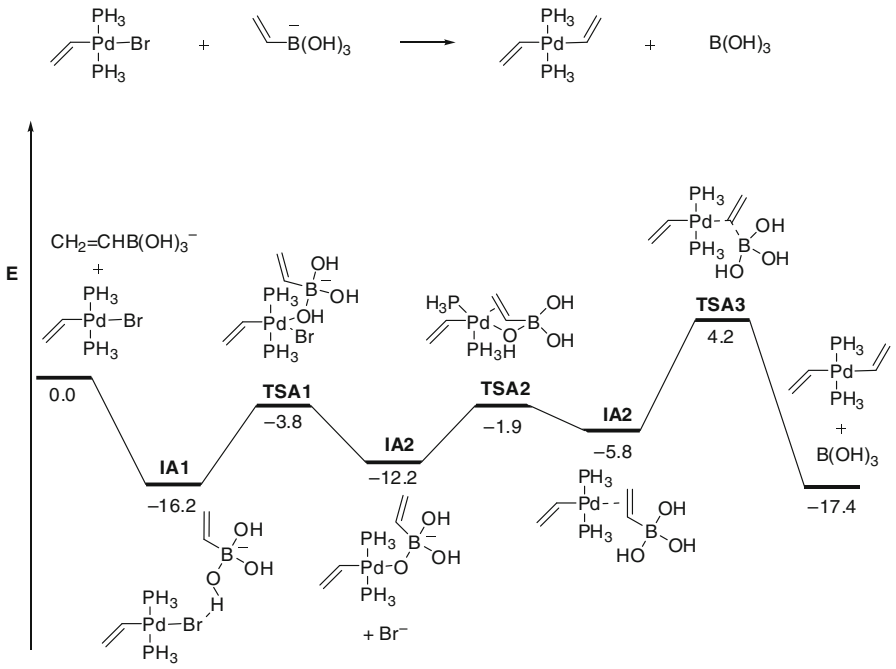


Fig. 2.3 An energy profile for Path A

On the other hand, Fig. 2.4 shows an energy profile for the reaction of vinylboronic acid with a hydroxo(vinyl)palladium(II) complex. This route is also exothermic, and the activation barrier was found to be only 0.6 kcal/mol. Comparison of the respective energy profiles for paths A and B, shown in Figs. 2.3 and 2.4, indicates that the energy of the transmetalation product **TSC3**, divinylpalladium(II) complex in Fig. 2.4, is much smaller. Therefore, path B is favored, which is consistent with the experimental outcomes by Hartwig.

In addition, Maseras calculated the direct reaction of a bromo(vinyl)palladium(II) complex with vinylboronic acid in the absence of the base. The most probable structures in this mechanism are shown in Fig. 2.5. This reaction pathway consists of the following processes: (1) a coordination of the double bond of the boronic acid to the palladium center; (2) a transfer of the bromide from palladium

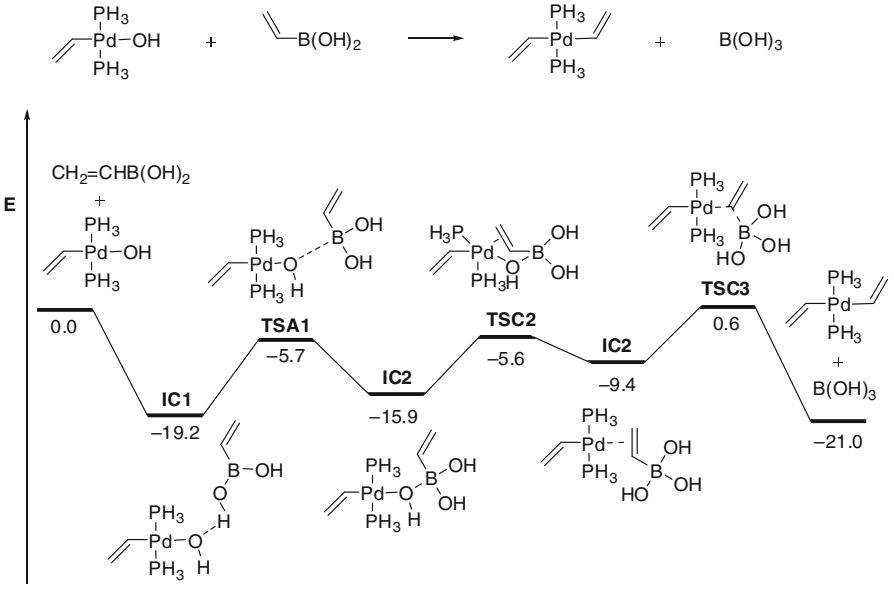


Fig. 2.4 An energy profile for Path B

to boron; and (3) a transfer of the vinyl group from boron to palladium to generate the divinylpalladium complex. Calculated results shown in Fig. 2.5 suggest that this path is endothermic (31.6 kcal) and that there is a large energy barrier (39.3 kcal) from the intermediate **I02** to the transition state **TS02**. This result signifies that the direct transmetalation between the bromopalladium complex and boronic acid in the absence of a base does not occur, which is also supported by experimental data.

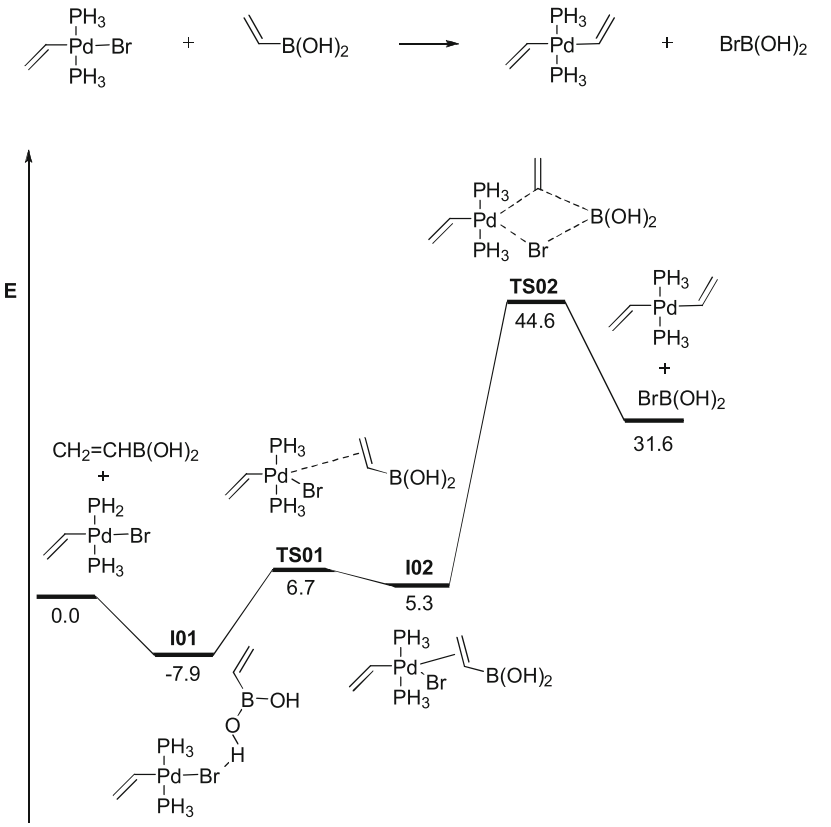
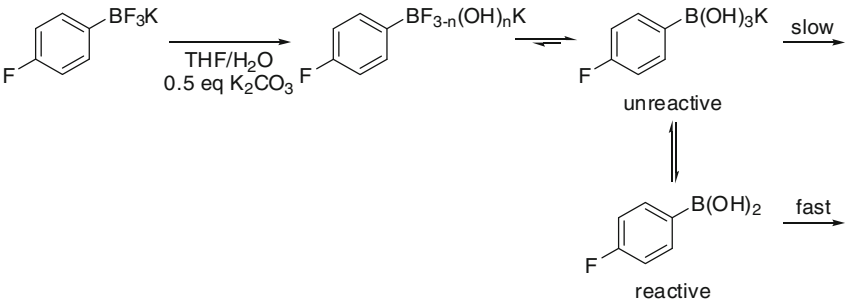


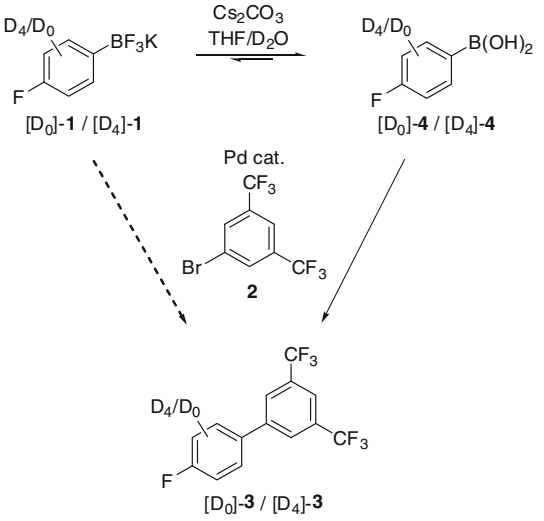
Fig. 2.5 An energy profile for the reaction of a bromo(vinyl)palladium(II) complex with vinylboronic acid

2.1.6 An Interconversion Between Trifluoroborate and Boronic Acid

Very recently, Lloyd-Jones experimentally clarified that in Suzuki–Miyaura coupling of potassium trifluoroborate, hydrolysis of the trifluoroborate takes place to generate the corresponding boronic acid, which further reacts with a hydroxopalladium(II) complex (Scheme 2.6) [53]. This evidence indicates that the transmetalation of potassium trifluoroborate proceeds through Path B shown in Fig. 2.4.



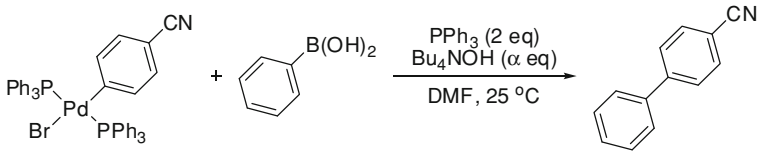
Scheme 2.6 Hydrolysis of potassium trifluoroborate



Scheme 2.7 Competitive reaction between an arylborate and an arylboronic acid

In addition, the mechanism of Suzuki–Miyaura coupling was investigated by using different molar ratios of an arylborate [D_0]-**1** and a deuterated arylboronic acid [D_4]-**4** (Scheme 2.7). When the mixture of a 1:1 ratio of [D_0]-**1** and [D_4]-**4** was used, the formation of the deuterated cross-coupled product [D_4]-**3** had a priority over [D_0]-**3**. Surprisingly, even when a 9:1 mixture of [D_0]-**1** and [D_4]-**4** was used, the deuterated product [D_4]-**3** was obtained preferentially over [D_0]-**3**. These results indicate that trifluoroborates can be a precursor of the corresponding boronic acids in the presence of a base in water.

Amatore and Jutand experimentally proved that the reaction becomes slower as the concentration of the hydroxide ion increases in the reaction of phenylboronic acid with a bromopalladium complex, as shown in Scheme 2.8 [54]. This observation is consistent with the experimental results from Hartwig and Lloyd-Jones, considering that Path B becomes inferior as the concentration of borates increases over boronic acids (under stronger basic conditions).



Scheme 2.8 The reaction of phenylboronic acid with a bromopalladium complex in the presence of the hydroxide ion

Herein the effect of the added bases and possible reaction paths in the Suzuki–Miyaura coupling have been discussed. However, the results of experiments by Hartwig and calculations by Maseras must be interpreted carefully. First, the data shown herein are not applicable to all reaction systems using various transition metals/ligands. Second, under the reaction conditions that use a stronger base, Path A competes with Path B because the concentration of the existing borates increases in the reaction mixture. Overall, these results have greatly contributed to the understanding of the transmetalation process because in most cases Suzuki–Miyaura coupling employs relatively weak bases such as carbonates and phosphates.

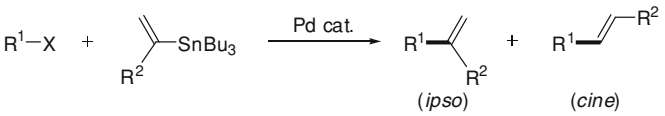
2.2 The "Copper Effect" in Migita–Kosugi–Stille Coupling

The Migita–Kosugi–Stille coupling, the palladium-catalyzed coupling reactions of organotin reagents with organic halides, as well as Suzuki–Miyaura coupling, are very useful carbon–carbon bond-forming reactions (Eq. 2.10) [55–57].

(2.10)

2.2.1 A Cine Substitution Reaction

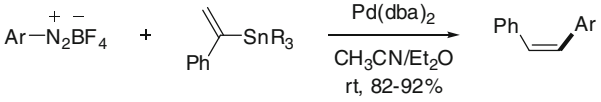
Mechanistic investigation of the Migita–Kosugi–Stille coupling has persisted since its discovery. The traditional cycle of oxidative addition, transmetalation, and reductive elimination, prevalent in transition metal catalyzed carbon–carbon bond-forming reactions, has been widely accepted. When the bulky alkenyltin reagents are employed, a side reaction, the *cine* substitution reaction, is observed due to slow transmetalation (Eq. 2.11) [58].



(2.11)

R^1 = aryl, vinyl; X = Cl, Br, I, OTf, OTs
R^2 = phenyl, alkyl, ester

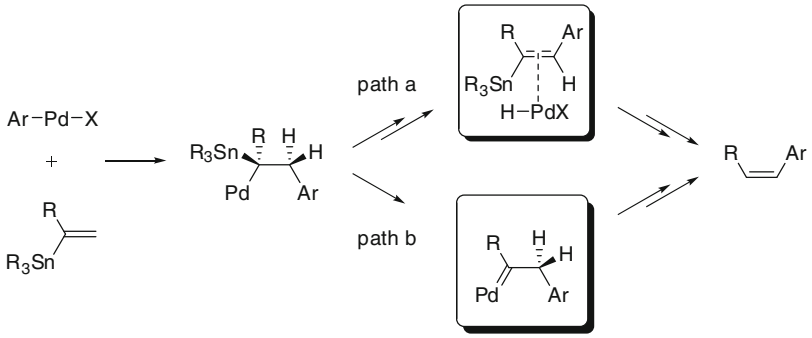
Kikukawa et al. found in 1986 that the reaction of ArN_2BF_4 with trialkyl(α-styryl)stannanes selectively produces the desired stereodefined (*Z*)-stilbene derivatives in high yields, not the α-arylated styrenes (Eq. 2.12) [59]. Due to slow transmetalation, this unexpected *cine* substitution reaction is observed in Migita–Kosugi–Stille coupling by using the bulky organotin reagents. In addition, it is reported that when an excess of diazonium salts are added, isomerization to the Z-stereoisomer becomes more substantial. The hydridopalladium complex plays an important role in this isomerization, which does not occur at all in the absence of the palladium catalyst.



(2.12)

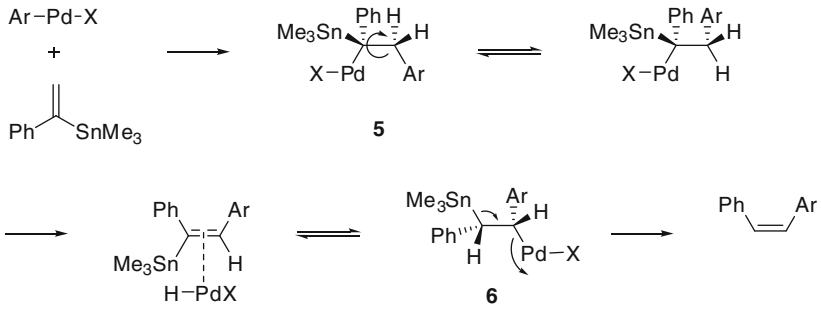
Ar = C_6H_4X, X = H, 4-Me, 4-I, 4-COMe, 4-CO_2Et, 3-NO_2, 4-NO_2
R = Me, Et, *n*-Bu

At present, two different reaction mechanisms giving rise to the *cine* substitution products are postulated, as shown in Scheme 2.9. One is the addition–elimination mechanism (path a) and the other is via the palladium carbene complex (path b). In both mechanisms, the reaction starts from a regioselective addition of the arylpalladium complex to the double bond of the α-substituted alkenylstannane.



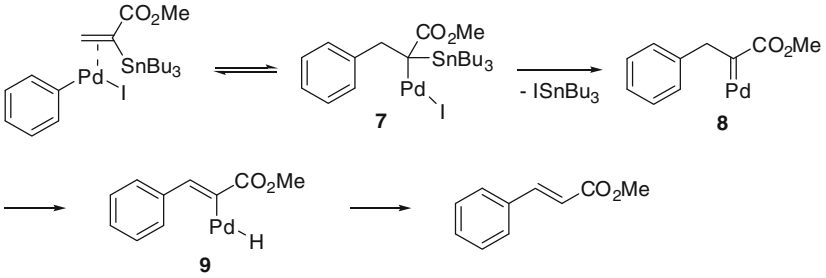
Scheme 2.9 Two reaction pathways of the *cine* substitution reaction

In the addition–elimination mechanism shown in Scheme 2.10, first carbopalladation occurs to the alkenylstannane regioselectively to generate intermediate **5**. The carbon–carbon bond in **5** rotates to give the *syn* configuration, from which *β*-hydrogen elimination takes place. The hydridopalladium complex adds to the generated alkenylstannane at the opposite position to give intermediate **6**. Finally, the Z-alkene is formed by the *anti*-elimination of a trialkylstannyl group and palladium, regenerating the catalyst [59]. However, definitive evidence to support this hypothesis has not been found to date, although many attempts to detect and identify the in situ formed alkenylstannanes have been made.



Scheme 2.10 The addition-elimination mechanism of the *cine* substitution reaction

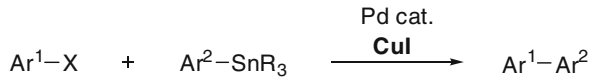
Another considered mechanism is via a palladium carbene complex. The regioselective insertion of an alkenylstannane into a carbon–palladium bond of the arylpalladium complex gives intermediate **7**. Iodostannane is released by α-elimination from the four-centered transitional state to generate the palladium carbene complex **8**. A 1,3-hydrogen shift from complex **8** forming the hydridopalladium complex **9** and the subsequent reductive elimination can afford the *cine* product (Scheme 2.11) [60]. The occurrence of the 1,3-hydrogen shift was confirmed by experiments with deuterated alkenyltin reagents.



Scheme 2.11 Mechanism of the *cine* substitution reaction via a palladium carbene complex

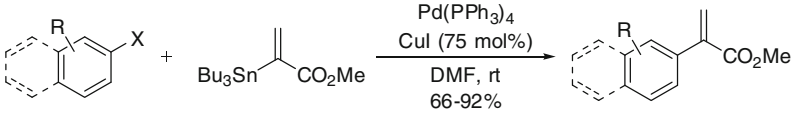
2.2.2 The Copper Effect

Although many reaction condition variables (including electrophiles, solvents, ligands, additives, etc.) were evaluated to avoid the *cine* substitution reaction as a side reaction in Migita–Kosugi–Stille coupling, the improvements of the product yields were not attained. The use of the bulky alkenyltin compounds and the slow transmetalation contribute to the *cine* substitution reactions. Only acceleration of transmetalation, the rate-determining step, can enable the desired reaction. The unambiguous improvement of the *ipso* selectivity and an accelerating effect for transmetalation have been observed by adding copper iodide and other copper(I) salts (Eq. 2.13) [61–73].



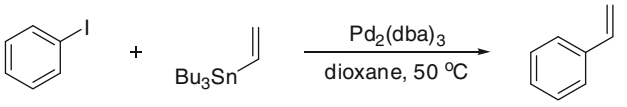
(2.13)

In 1993, for example, Levin reported that the reaction takes place in the *ipso* selective manner in Migita–Kosugi–Stille coupling when the sterically bulky alkenyltin reagents are employed with the copper iodide as a co-catalyst; no formation of the *cine* substitution product was observed (Eq. 2.14) [74].



(2.14)

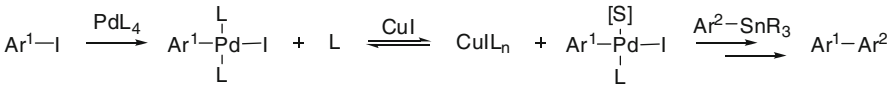
This so-called "copper effect" was researched first by Farina and Liebeskind [75]. They compared the reaction rates of the cross-coupling of vinyltributyltin with iodobenzene in the presence and in the absence of copper iodide. As a result, it has been disclosed that the reaction with the addition of copper iodide ($k_{obs} = 5.90 \times 10^{-3}$ min^{-1}) is about 100 times faster than that without any copper additive ($k_{obs} = 2.66 \times 10^{-5}$ min^{-1}) (Eq. 2.15).



(2.15)

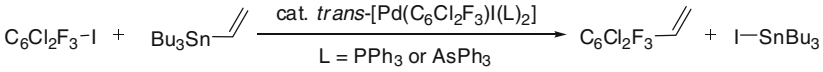
without CuI: $k_{obs} = 2.66 \times 10^{-5}$ min^{-1}
with CuI: $k_{obs} = 5.90 \times 10^{-3}$ min^{-1}

The rate-determining step in Migita–Kosugi–Stille coupling is believed to be the transmetalation process based on recent research [76, 77]. Farina and Liebeskind explained the "copper effect" as follows. The added copper(I) salt traps the triphenylphosphine dissociated from the metal center in oxidative adduct **10** to generate the unsaturated palladium complex **11**, and promotes the transmetalation process (Scheme 2.12). It is noteworthy that the added copper iodide does not promote the dissociation of the ligand from the oxidative adduct **10**, but it traps the ligand dissociated after oxidative addition. Also, the addition of copper salts was reported to prevent the progress of the reverse reaction from **11** to **10**.



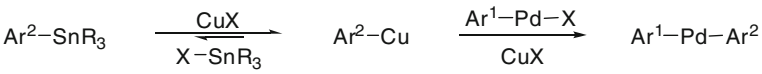
Scheme 2.12 "Copper effect" in Migita-Kosugi-Stille coupling

The soft arsine ligands did not show any accelerating effect, compared with the harder phosphine ligands, as shown in Eq. 2.16. This is because copper iodide has a stronger interaction with phosphine ligands than with arsine ligands [78, 79]. Moreover, when $Pd(AsPh_3)_4$ is used as a catalyst, the association rate of free ligands to the metal center becomes slower than that observed in the case of $Pd(PPh_3)_4$.



(2.16)

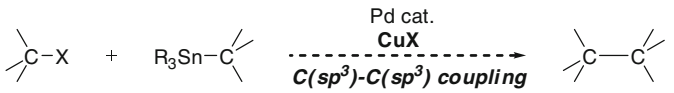
It is known that the organic groups transmetalate from tin to copper in polar solvents (Scheme 2.13) [80]. The generation of tin halides was confirmed by measuring the ^{119}Sn NMR in NMP as the solvent. The newly formed organocopper(I) species showed a higher activity of transmetalation to palladium than the corresponding organotin reagents. Therefore, the generated organocopper reagents take part in transmetalation in Migita–Kosugi–Stille coupling.



Scheme 2.13 Transmetalation from tin to copper

2.2.3 Perspectives

Clearly, there is an accelerating effect in Migita–Kosugi–Stille coupling when copper(I) salts are added. In the future, considering the effect of copper(I) salts, expanded use of Migita–Kosugi–Stille-type carbon(sp^3)–carbon(sp^3) bond-forming reactions is expected. These types of reactions are very challenging because alkyl electrophiles are undesirable for oxidative addition and the synchronal β-hydrogen elimination competitively takes place. However, unprecedented carbon(sp^3)–carbon(sp^3) couplings in the Migita–Kosugi–Stille reaction can be achieved by accelerating transmetalation, the rate-determining step, with the addition of copper(I) salts (Eq. 2.17).



(2.17)

2.3 Summary

This chapter focuses on the transmetalation of Suzuki–Miyaura and Migita–Kosugi–Stille coupling reactions, the various pathways and the mechanisms involved, and the effect of the bases and of copper(I) salts. It has been concluded that the reactions of the arylboronic acids with a hydroxopalladium complex are much faster than that of arylborates with a halogenopalladium(II) complex from experimental and theoretical findings. However, it cannot be asserted that the mechanism in *all* Suzuki–Miyaura reactions has been proven because only the general reaction conditions have been examined at this present stage. In the future, it can be expected that further research on the mechanisms will develop from the studies clarified to date. This will lead to the development of more efficient cross-coupling reactions.

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Part II
Applications of the Cross-Coupling Reactions

Chapter 3
Natural Product Synthesis

Yasuhiro Okuda and Yasushi Nishihara

Abstract The synthetic routes to the natural products are designed with consideration of the structures of the reagents, functional group tolerance, total yields, and the environmental benignness of wastes. In natural product syntheses, the cross-couplings as carbon–carbon bond-forming reactions have been widely utilized for the construction of fragments as the key steps in the total syntheses.

Keywords Natural product · Total synthesis · Selectivity · Convergent synthesis · Hybridization

3.1 Introduction

Natural organic compounds with specific chemical structures and bioactivities have intimate relationships with pharmaceuticals, dyes, spices, etc., and are thus extremely important industrially. Frequently, only a small amount of a natural product can be harvested from its naturally occurring source; in these cases, organic synthesis is necessary if a large amount of the natural product is required. Furthermore, the synthetic route is often simply more cost-effective or practical. Some naturally occurring products with unique physical and chemical properties are preferable for the production of fine chemicals. In fact, the proportion of these products supplied from nature is only about 5 %. This extensive demand implies that partial or total synthesis is necessary and indispensable [1].

Although a variety of organic reactions (e.g., aldol reactions and Grignard reactions) have been conventionally used for carbon–carbon bond formation in natural product syntheses, these reactions are not able to satisfy some demands due

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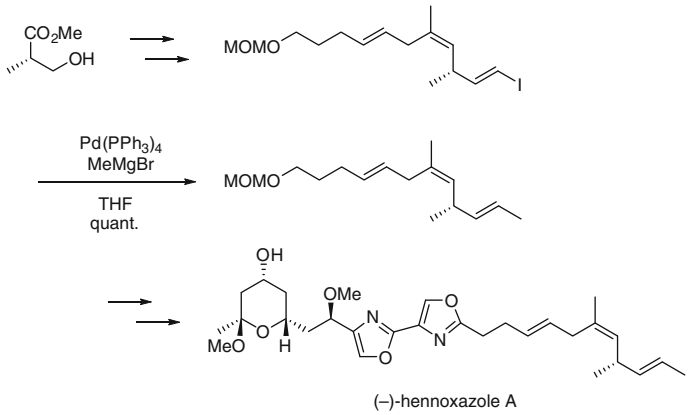
to a low selectivity and due to substrate limitations. However, the cross-coupling reactions are widely accepted as carbon–carbon bond-forming methodologies that can achieve high selectivity and functional group tolerance in the synthesis of natural products with complicated chemical structures [2].

Considering the establishment of convergent synthesis and the easy availability of starting materials in natural product syntheses, the cross-coupling methods introduced in this publication are very powerful strategic tools for carbon–carbon bond formation. However, when the target molecules are synthesized with these cross-coupling reactions, appropriate selection of substrates and reagents is essential. This chapter will review recent examples of how the cross-coupling reactions have been used in practical natural product syntheses.

3.2 Kumada–Tamao–Corriu Coupling (sp^3–sp^2)

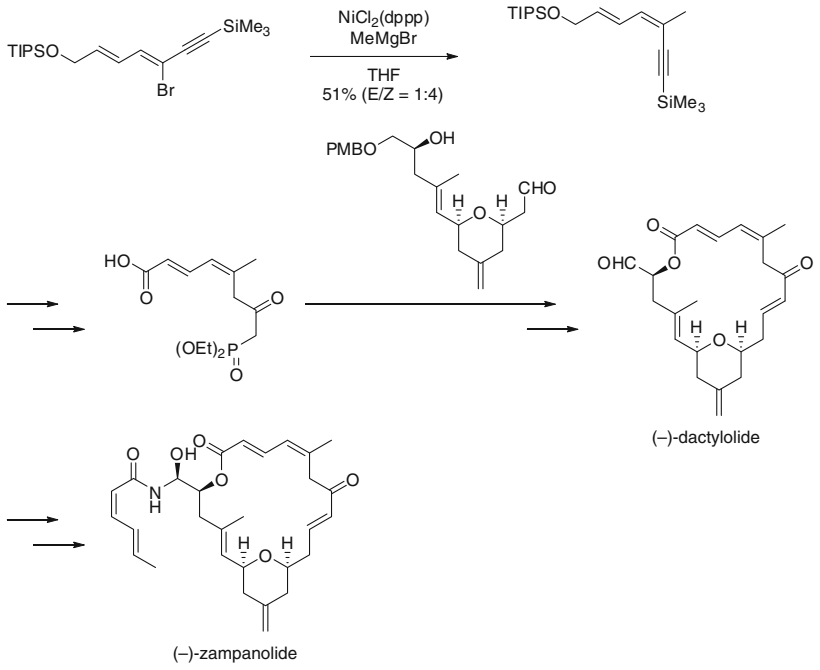
Because the highly reactive Grignard reagents can be employed in Kumada–Tamao–Corriu coupling, these reactions have been applied to natural product syntheses in recent years. Kumada–Tamao–Corriu coupling is advantageous due to the utility of commercially available Grignard reagents. For example, a precursor of (−)-hennoxazole A was synthesized selectively and quantitatively by methylation of the substrate bearing a protected hydroxy group with methylmagnesium bromide under palladium catalysis (Scheme 3.1) [3].



Scheme 3.1 Total synthesis of (–)-hennoxazole A

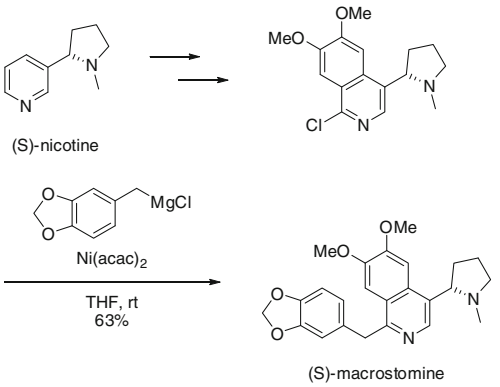
Since Kumada–Tamao–Corriu coupling lacks functional group tolerance, its utilization in the final stages of synthesis of the natural products is rare. However, there is a natural abundance of magnesium with the eighth Clark's number (1.93 wt %), and the preparation of Grignard reagents is relatively easy. Thus, Kumada–Tamao–Corriu coupling can play an important part in synthesis if the substrates are stable enough toward Grignard reagents. Hereafter, more examples of Kumada–Tamao–Corriu coupling as the key step in an overall synthesis will be introduced.

E/Z stereoisomerization is known to be one of the side reactions in the nickel-catalyzed Kumada–Tamao–Corriu coupling of alkenyl halides with Grignard reagents. However, this isomerization has been utilized for the selective synthesis of (−)-zampanolide by manipulating the steric effect of the substituent (Scheme 3.2) [4]. In this method, a selective synthesis of the trisubstituted dienyne as a target product was attained by the introduction of an alkynyl group stereoselectively through Sonogashira–Hagihara coupling and the subsequent isomerization of an olefinic moiety during the Ni-catalyzed Kumada–Tamao–Corriu coupling. Thus, this example shows the advantageous features of the Ni-catalyzed Kumada–Tamao–Corriu coupling—appropriate selection of the substituents and ligands enable control of the stereoselectivity of the products. In this reaction, the undesired side reaction does not take place at all, even under basic conditions, and the cross-coupling of aryl halides with achiral Grignard reagents can be achieved without isomerization.



Scheme 3.2 Total synthesis of (–)-zampanolide using (–)-dactylolide as a precursor with an inversion of the olefin geometry

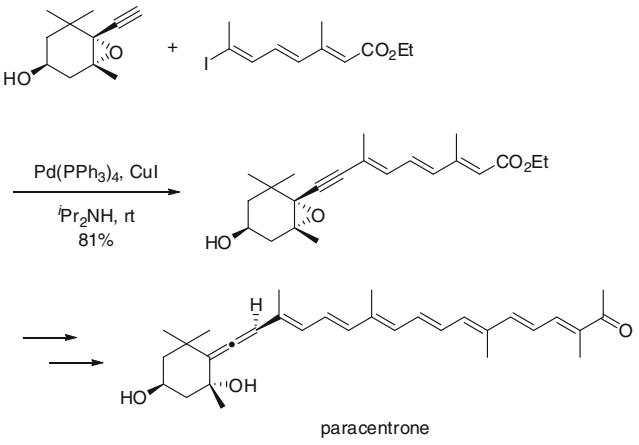
Furthermore, in the next synthetic pathway, the catalyst was carefully selected. $Ni(acac)_2$, which does not contain the phosphine ligands, was used for the enantioselective synthesis of (S)-macrostomine (Scheme 3.3) [5]. This result suggests that Kumada–Tamao–Corriu coupling has the drawbacks of poor selectivity and of substrate limitations. However, this reaction is an economical and preparative approach to natural product syntheses when substrates that are highly reactive toward Grignard reagents are not involved.



Scheme 3.3 Total synthesis of (S)-macrostomine from (S)-nicotine

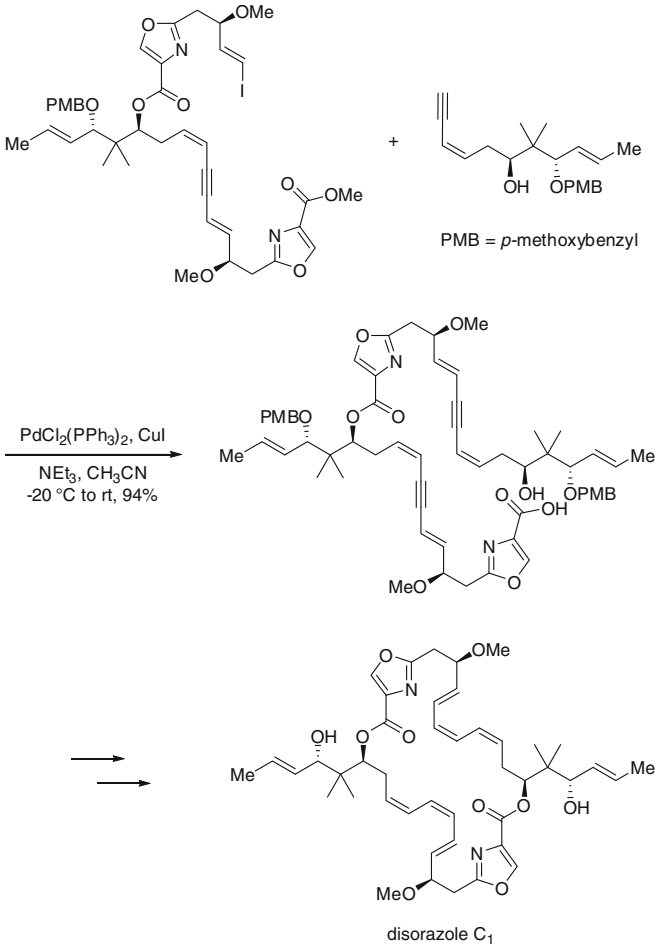
3.3 Sonogashira–Hagihara Coupling (sp–sp^2)

Sonogashira–Hagihara coupling is often employed in the natural product syntheses owing to its ability to construct enyne frameworks through the formation of carbon(sp)–carbon(sp^2) bonds. In general, in the natural product synthesis, the reactive substrates are first masked by a protecting group and economical bases such as triethylamine or diisopropylamine and copper iodide (CuI) are often used as essential reagents. Sonogashira–Hagihara coupling proceeds with high functional group tolerance under mild conditions, and often gives excellent results to afford molecules with complex structures. The total synthesis of paracentrone, shown in Scheme 3.4, is a representative example showing that Sonogashira–Hagihara coupling can be applied to a substrate bearing a reactive epoxide moiety which remains intact during the reaction [6].



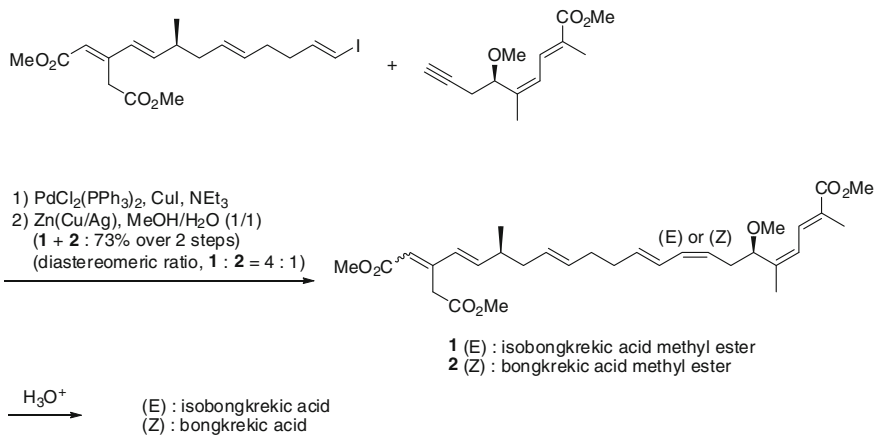
Scheme 3.4 A synthetic route to paracentrone

The air-stable $PdCl_2(PPh_3)_2$ is often used for the palladium catalyst of Sonogashira–Hagihara coupling, instead of a Pd(0) complex, because $PdCl_2(PPh_3)_2$ is reduced promptly during the reaction to form the Pd(0) species. Scheme 3.5 shows the demonstration of $PdCl_2(PPh_3)_2$ as a Pd precursor in the total synthesis of (−)-disorazole C_1 [7].



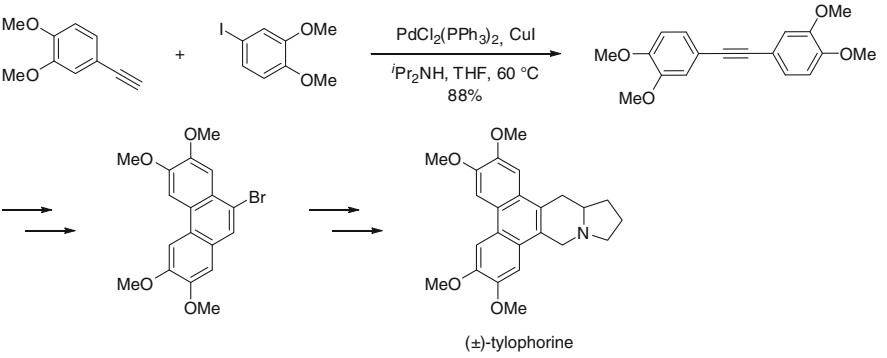
Scheme 3.5 A synthetic route to (–)-disorazole C_1

In the total synthesis of bongkrekic and isobongkrekic acids shown in Scheme 3.6, conjugate enynes were first synthesized by Sonogashira–Hagihara coupling. Then, chemoselective reduction of the alkyne moiety transformed the coupled product into the conjugate diene **1** and **2** [8]. In this reductive reaction, an excess amount of copper/silver activated with zinc was found to be the best synthetic method, since the chemoselectivity was fairly low when the *syn* reduction of the conjugate enyne by Lindlar's catalyst was attempted [9, 10].



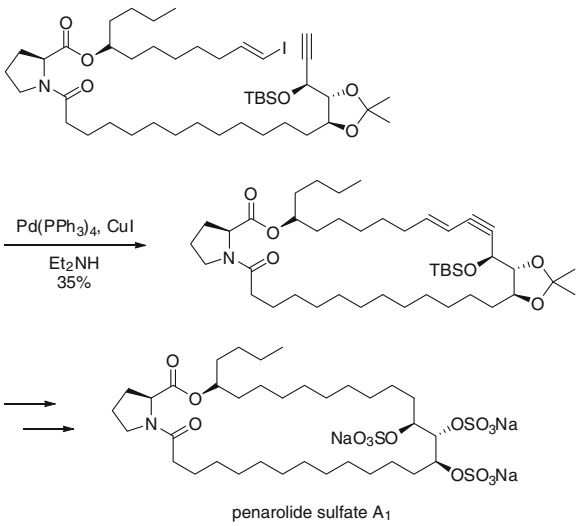
Scheme 3.6 A synthetic route to iso- and bongkrekic acids

Sonogashira–Hagihara coupling of aryl halides/triflates with terminal arylethynes is one of the most useful synthetic methods to afford an array of diarylethynes which are important frameworks applicable to liquid crystals and pharmaceuticals. The total synthesis of (±)-tylophorine shown in Scheme 3.7 is a representative example using diarylethynes as a synthetic intermediate [11].



Scheme 3.7 A synthetic route to (±)-tylophorine

Moreover, an intramolecular Sonogashira–Hagihara coupling enables the construction of large-membered rings; however, the yields of the cross-coupled products are generally very low, as shown in Scheme 3.8 [12]. Therefore, for the construction of large-membered rings, ring-closing metathesis by the Ru or Mo catalysts [13, 14] and macrolactonization [15] is often used rather than intramolecular Sonogashira–Hagihara couplings.



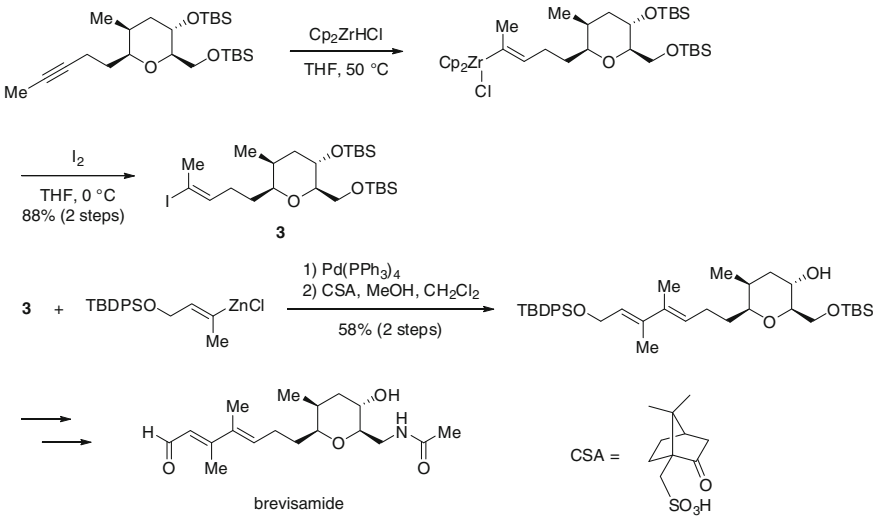
Scheme 3.8 A synthetic route to penarolide sulfate A_1

Additionally, the following are examples of total syntheses utilizing Sonogashira–Hagihara coupling reported after 2000: frondosin B [16], callipeltoside A [17], mucocin [18], borrelidin [19], tetrodotoxin [20], 34-hydroxyasimicin [21], oximidine II [22], (−)-siphonodiol, (−)-tetrahydrosiphonodiol [23], peroxyacarnoates A and D [24], leucascandrolide A [25], macbecin I [26], moracin O, moracin P [27] (+)-neopeltolide [28], furopyrans [29], leiodolide B [30], iso- and bongkrekic acids [31], *cis*- and *trans*- bupleurynol [32], and lukianol A [33].

3.4 Negishi Coupling

3.4.1 sp^2–sp^2 Negishi Coupling

Negishi coupling has also been widely used as a highly selective, efficient cross-coupling reaction in the natural product syntheses. The total synthesis of brevisamide as a natural product can be accomplished using the sp^2–sp^2 Negishi coupling (Scheme 3.9) [34]. Negishi coupling is often used in combination with hydrozirconation of alkynes by a Schwartz reagent, because hydrozirconation of alkynes generates an alkenylzirconium complex in a highly regioselective manner; the iodination and treatment with zinc salts of that complex yield the corresponding alkenyl iodides and alkenylzinc reagents, respectively, in one pot.

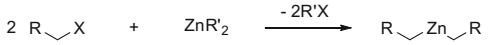


Scheme 3.9 A synthetic route to brevisamide

The sp^2–sp^2 Negishi coupling has been recently reported as applicable to other total syntheses: *cis* and *trans* bupleurynol [32] (−)-motuporin [35], xerulin [36], pitiamide A [37], FR901464 [38, 39], eunicenone A [40], bisabolene [41], xerulinic acid [42], callystatin A [43, 44], anguinomycin C [45], anguinomycin C and D [46], and 6,7-dehydrostipiamide [47].

3.4.2 sp^3–sp^2 Negishi Coupling

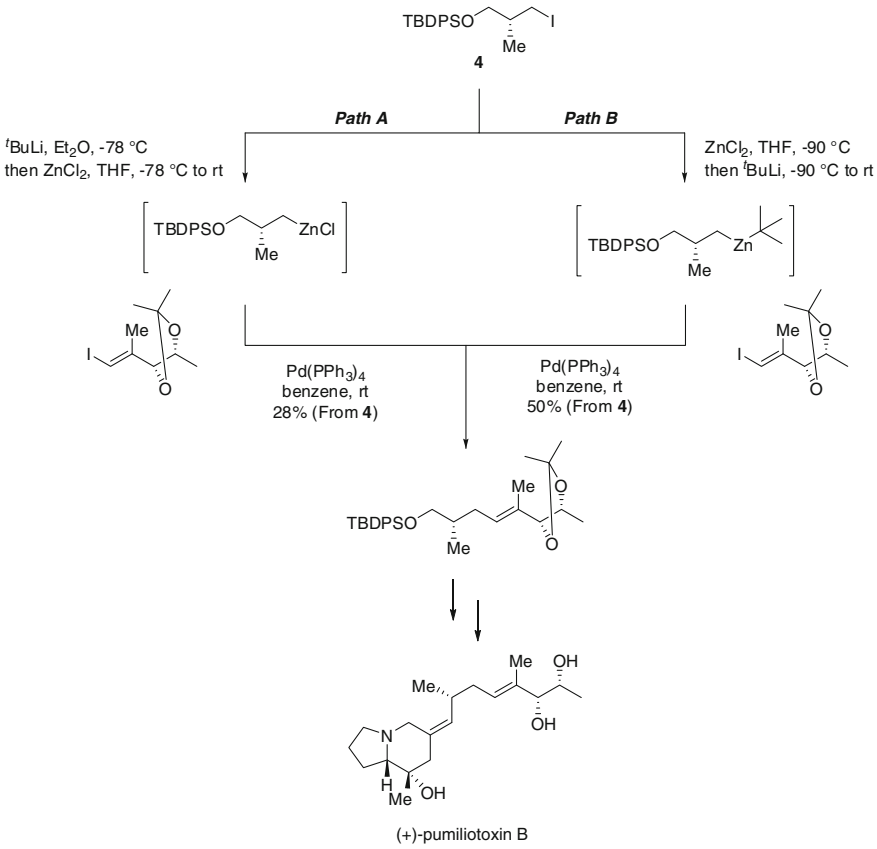
Herein, the natural product syntheses by Negishi cross-coupling of alkenyl or aryl halides (pseudo-halides) (sp^2) with alkylzinc reagents (sp^3) are described. In general, alkyl halides are converted into alkylzinc compounds by halogen–zinc exchange, as shown in Eq.3.1. In addition, a transformation with *tert*-BuLi of alkylzinc halides into dialkylzinc compounds is widely used, because the *tert*-butyl functionality can be used as a dummy group for Negishi coupling, leading to the selective formation of the desired cross-coupled products by carbon(sp^2)–carbon(sp^3) bond formation (See Chap. 8 for the details of carbon(sp^2)–carbon(sp^3) bond formation).



(3.1)

As shown in Scheme 3.10, reactivity between the dialkylzinc compound and alkylzinc chloride was compared to the total synthesis of (+)-pumiliotoxin B [48]. Starting from substrate **4** in Path A, alkylzinc chloride was prepared by halogen–lithium exchange with *tert*-BuLi and the subsequent transmetalation using zinc

chloride. On the other hand, in Path B the dialkylzinc reagent was synthesized from iodine–zinc exchange between substrate **4** and zinc chloride, followed by addition of *tert*-BuLi. As a result, Path B of Negishi coupling with the dialkylzinc reagent was found to give the desired product in better yield (50 vs 28 %).



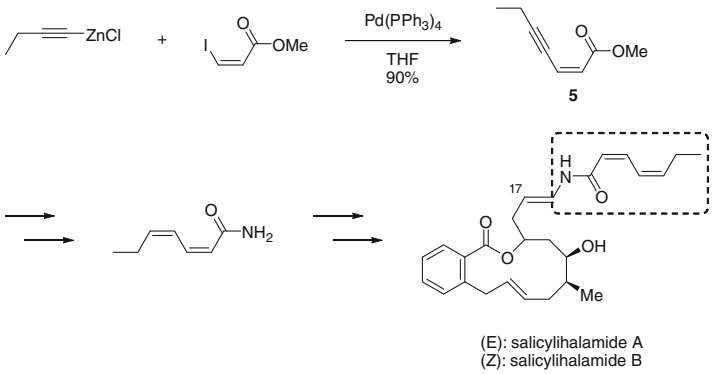
Scheme 3.10 Synthetic strategies of (+)-pumiliotoxin B

In recent years, the sp^3–sp^2 Negishi cross-coupling has been a frequently used synthetic method for multi-substituted aliphatic olefins and the substituted aryl or heteroaryl compounds. Furthermore, the utility of the sp^3–sp^2 Negishi cross-coupling has been recently observed in other total syntheses: borrelidin [19] (−)-callystatin A [43], anguinomycin C [45], anguinomycin C, D [46], (+)-discodermolide [49], dysiherbaine [50], bisabolene [41, 51], (–)-4a, 5-dihydrostreptazolin [52], a core structure of mycolactones [53], coenzyme Q_{10}, (*E*,*Z*,*E*)-geranylgeranoil [54], *trans*-epothilone A [55], oleandolide [56], sphingofungin F [57], ionomycin [58], (–)-longithorone A [59], (−)-delactonmycin [60], capensifuranone [61], (+)-murisolin [62], a side chain of scyphostatin [63],

(+)-scyphostatin [64], (−)-stemoamide [65], dysiherbaine [66], maleic anhydride, maleimide [67], OF4949-III, K-13 [68], harveynone, tricholomenyn A [69], and in the synthesis of important intermediates of ionomycin and borrelidin [70].

3.4.3 sp–sp^2 Negishi Coupling

In Negishi coupling, the coupling partners (alkenyl or aryl halides/triflates and alkynylzinc reagents) are employed to form carbon(sp)–carbon(sp^2) bonds. In the total synthesis of (–)-salicylihalamide shown in Scheme 3.11, Negishi coupling with the combination of the aforementioned substrates afforded the intermediate **5** in 90 % yield while retaining the *Z*-configuration [71].



Scheme 3.11 A synthetic route to salicylihalamide A and B

As shown above, the sp–sp^2 Negishi coupling is highly effective for the construction of the conjugate enyne frameworks. Although conjugate enynes can be synthesized by Sonogashira–Hagihara coupling, the functional group tolerance is dramatically improved with Negishi coupling because the addition of bases is not required. Other natural product syntheses by the sp–sp^2 Negishi coupling are known for the total syntheses of *cis*- and *trans*-bupleurynol [32], xerulin [36], 6,7-dehydrostipiamide [47], and harveynone, tricholomenyn A [69].

3.4.4 Carbometalation and Negishi Coupling Sequences

One of the applied Negishi cross-coupling reactions is the synthesis of a carotenoid having a conjugate polyene structure, e.g., *β*-carotene (Fig. 3.1). Since these compounds possess multi-substituted polyene motifs, a synthetic strategy that selectively introduces the substituents in appropriate positions is necessary.

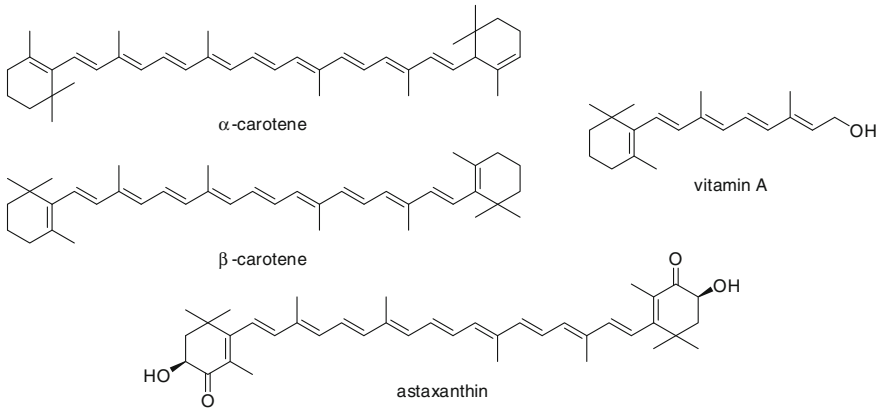
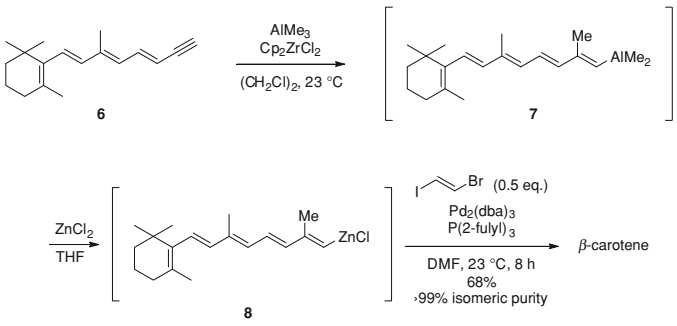


Fig. 3.1 Representative examples of carotenoids

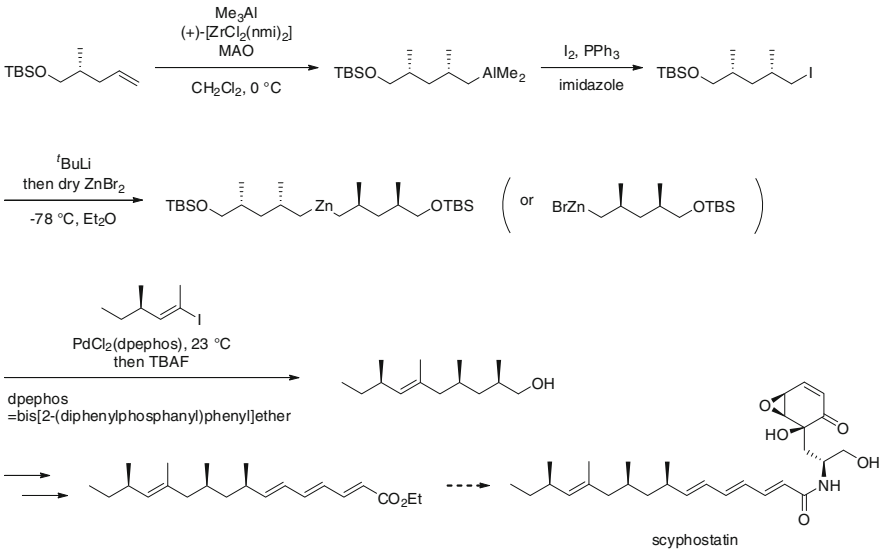
Because these conjugated polyene-type natural products are organic compounds with valuable antioxidant property, efficient and selective innovation for synthetic methods is still actively sought. It is likely that a combination of regioselective carbometalation of alkynes and sequential Negishi coupling could be used for the synthesis of such natural products.

In the syntheses of *β*-carotene and vitamin A, the Zr-catalyzed regio- and stereoselective methylalumination across the terminal alkyne in precursor **6** is the first step [72], as shown in Scheme 3.12. The formed alkenylaluminum compound **7** is transmetalated to zinc to afford the corresponding alkenylzinc compound **8**, which reacts consecutively with a half molar amount of 1-bromo-2-iodoethene leading to the successful total synthesis of *β*-carotene. This method is very advantageous from the viewpoint of the facile formation of the organozinc reagents without the addition of the bases. Using the regioselective alkylmetalation of the alkynes and sequential Negishi coupling, the total syntheses of coenzyme Q_{10}, (*E*,*Z*,*E*)-geranylgeranoil [54], and piericidin A_1 [73] have also been accomplished.



Scheme 3.12 A synthetic route to *β*-carotene

In addition, when the terminal olefins are treated with chiral reagents, regio- and stereoselective carbometalation can be achieved. The synthesis of a side chain in scyphostatin, shown in Scheme 3.13, is an applied example [63]. Moreover, the total synthesis of 6,7-dehydrostipiamide has been attained by regio- and stereoselective methylalumination and the subsequent Negishi coupling [47]. The applied synthetic methods for ionomycin, for the intermediate of borrelidin, and for the total synthesis of doliculide have also been achieved [74].



Scheme 3.13 A synthetic route to the scyphostatin side chain

3.4.5 Utility of Negishi Coupling toward Carbonyl Compound Synthesis

In Negishi coupling, acyl halides can be utilized as electrophiles to synthesize the corresponding ketones. This type of Negishi coupling has been used for the total synthesis of amphidinolide derivatives (Fig. 3.2), as shown in Scheme 3.14 [75].

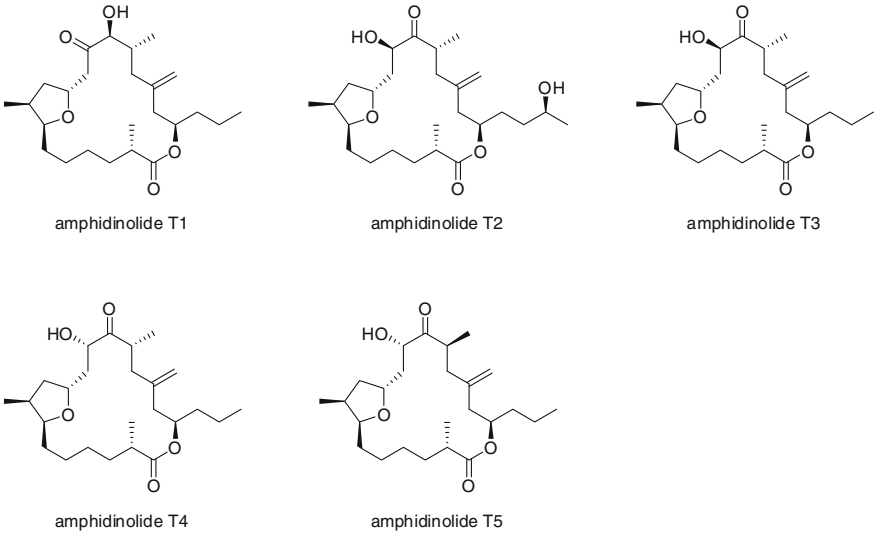
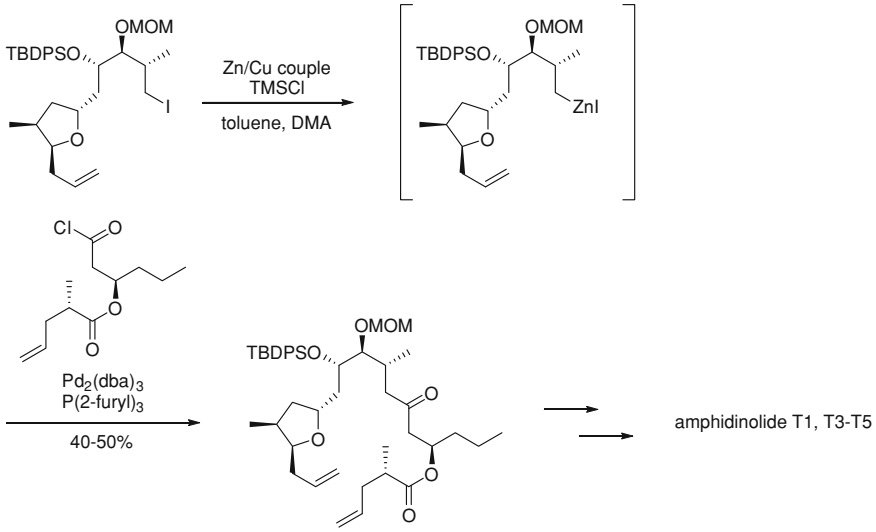


Fig. 3.2 Structures of amphidinolide derivatives



Scheme 3.14 Synthetic route for amphidinolide T1, T3–T5

As mentioned above, because Negishi coupling possesses a large number of advantages (including a wide scope of substrate options, high regio- and stereoselectivities, and preparative reactions under mild conditions), it can be a very powerful tool in the natural product syntheses through its combination with the alkylmetalation of the terminal alkynes and alkenes.

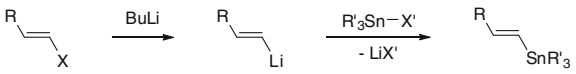
3.5 Migita–Kosugi–Stille Coupling

Although some cross-couplings might not be useful for highly reactive substrates bearing functional groups such as epoxides which are sensitive to both acids and bases, the mild and neutral Migita–Kosugi–Stille coupling has often been used in the key steps of the natural product syntheses. This section introduces representative examples of how Migita–Kosugi–Stille coupling can be used in natural product synthesis.

3.5.1 Synthetic Methods of Organotin Compounds

When Migita–Kosugi–Stille is employed as a coupling reaction, synthesis of organotin compounds is required. Since the preparation of organotin compounds can be achieved by various synthetic methods, the reaction conditions and the reagents used in the natural product synthesis offer many choices for stannation. First, some recently reported stannation reactions used in the natural product synthesis will be introduced.

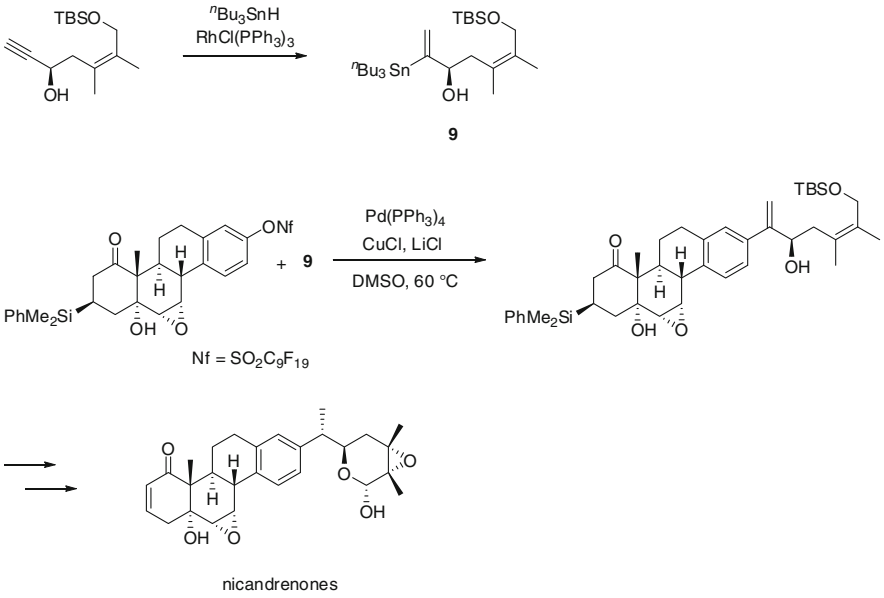
One well-known method for the preparation of organotin is via organolithium reagents; organotin reagents can be prepared by halogen–lithium exchange of alkenyl halides with n-BuLi, followed by treatment of the intermediate organolithium reagents with tin halides, as shown in Scheme 3.15. These organotin reagents can be conveniently synthesized due to the commercial availability of tin chlorides and organolithium compounds, but this synthetic method cannot be used for the substrates that have base-sensitive functional groups.



Scheme 3.15 Preparation of organostannanes from organolithium reagents

On the other hand, tin-containing functional groups can be introduced into unsaturated organic molecules in a highly regioselective fashion through hydrostannation and carbostannation reactions catalyzed by the transition metal

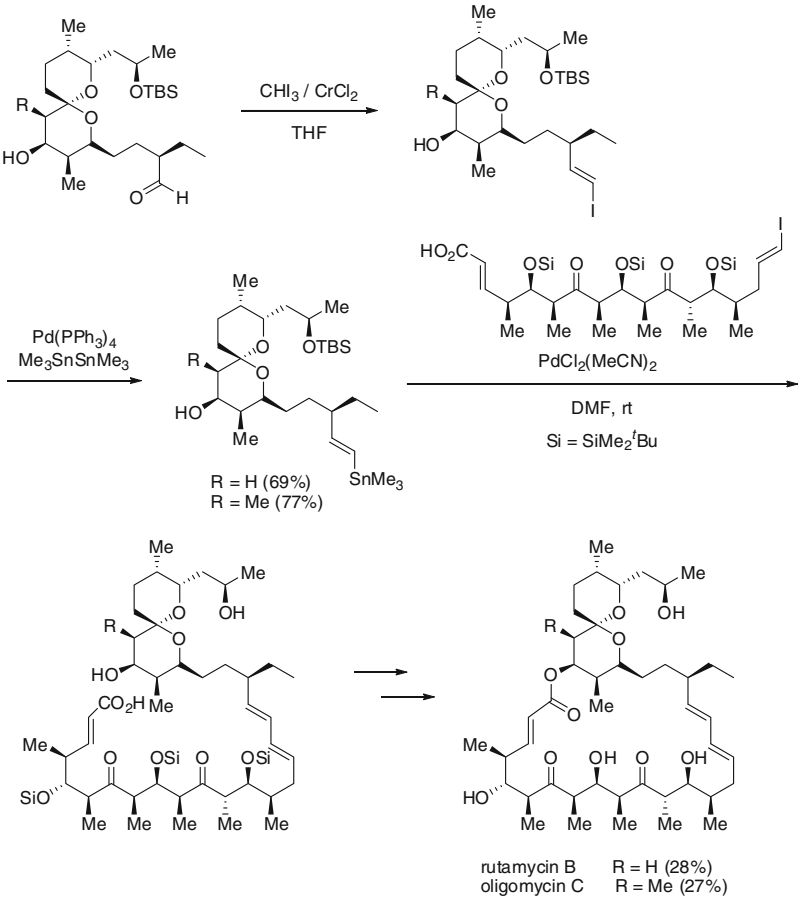
complexes. A synthetic example of a precursor of nicandrenones by the Rh-catalyzed regioselective hydrostannation and the subsequent Migita–Kosugi–Stille coupling is shown in Scheme 3.16 [76].



Scheme 3.16 A synthetic route to nicandrenones

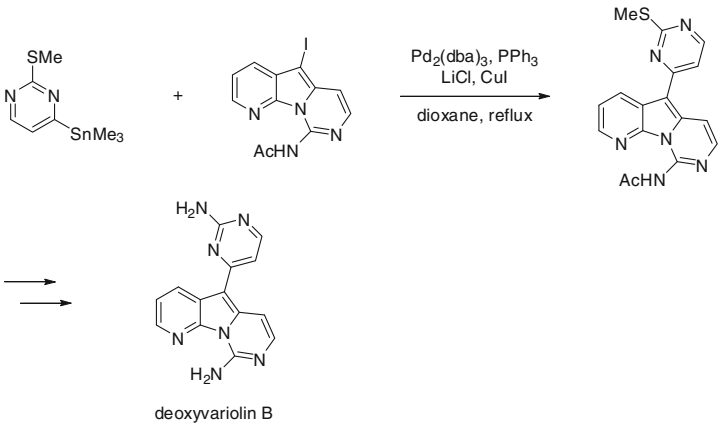
3.5.2 sp^2–sp^2 Migita–Kosugi–Stille Coupling

Migita–Kosugi–Stille coupling is often used at the key stage when the convergently synthesized fragments are bonded in natural product syntheses. Most of the reactions involve sp^2–sp^2 coupling to give the conjugate dienes and polyenes. The total syntheses of rutamycin B and oligomycin C are shown in Scheme 3.17 [77].



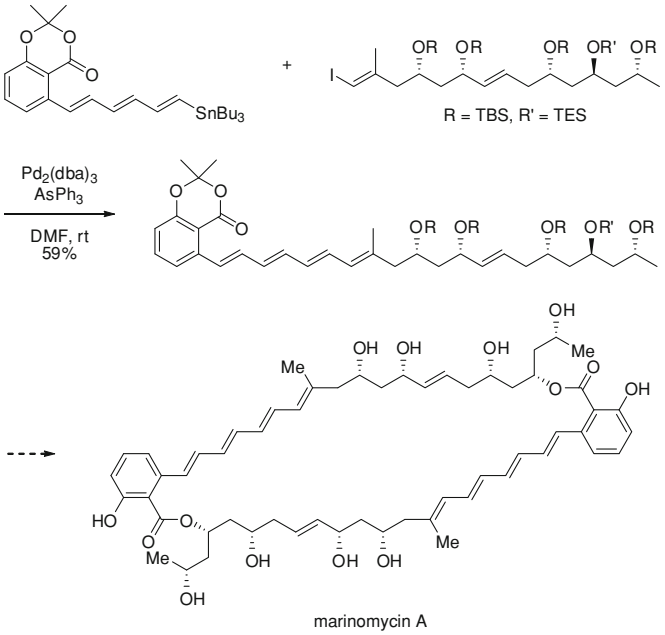
Scheme 3.17 A synthetic route to rutamycin B and oligomycin C

In Migita–Kosugi–Stille coupling, LiCl and CuI are added to promote transmetalation (see, Chap. 2). In regard to the effect of these additives, it is assumed that the added copper salt can trap the excess phosphine ligands retarding transmetalation. The more nucleophilic organocopper species, generated via transmetalation from tin to copper, accelerate the transmetalation [78]. The total synthesis of deoxyvariolin B can be achieved by applying these reaction conditions (Scheme 3.18) [79, 80].



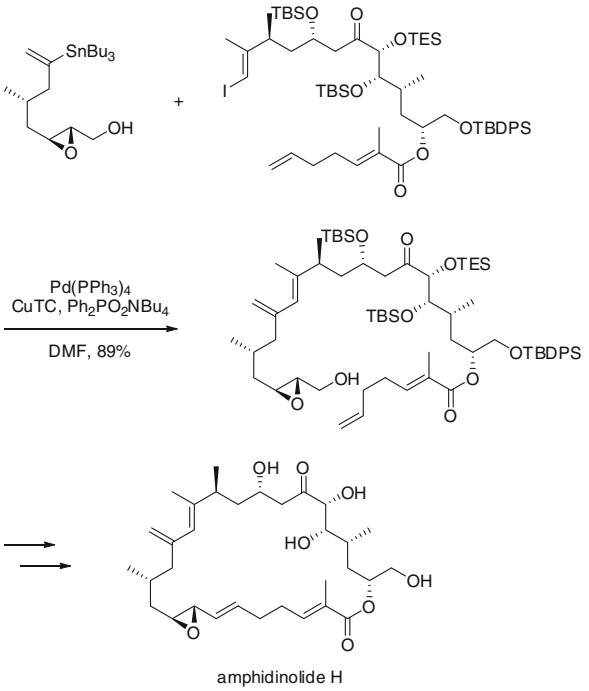
Scheme 3.18 A synthetic route to deoxyvariolin B

In some cases $AsPh_3$, which has a moderate electron-donating ability, gives better results for the construction of sp^2–sp^2 carbon–carbon bonds in Migita–Kosugi–Stille coupling. For instance, such a ligand is used in the total synthesis of marinomycin A (Scheme 3.19) [81, 82].



Scheme 3.19 A synthetic route to a monomer of marinomycin A

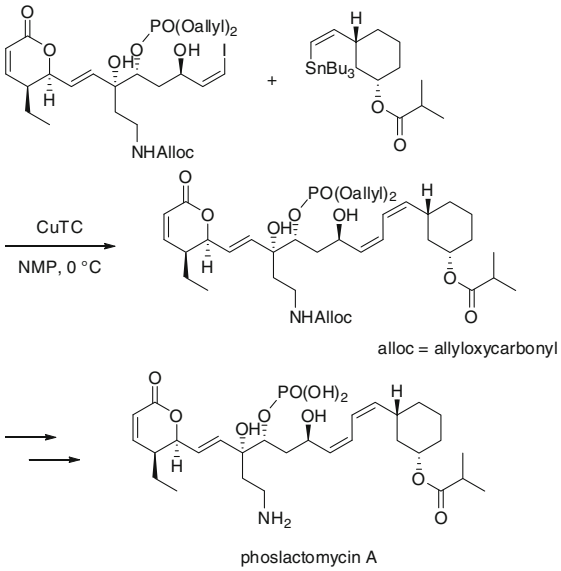
As mentioned above, the mild Migita–Kosugi–Stille coupling enables application to the substrates that are unstable under acidic and basic condition. Hence, this reaction is useful for the total synthesis of amphidinolide H, which bears an epoxide functionality (Scheme 3.20) [83]. A stoichiometric amount of copper(I)-thiophene-2-carboxylate (CuTC) can enhance Migita–Kosugi–Stille coupling as an activator [84].



Scheme 3.20 A synthetic route to amphidinolide H

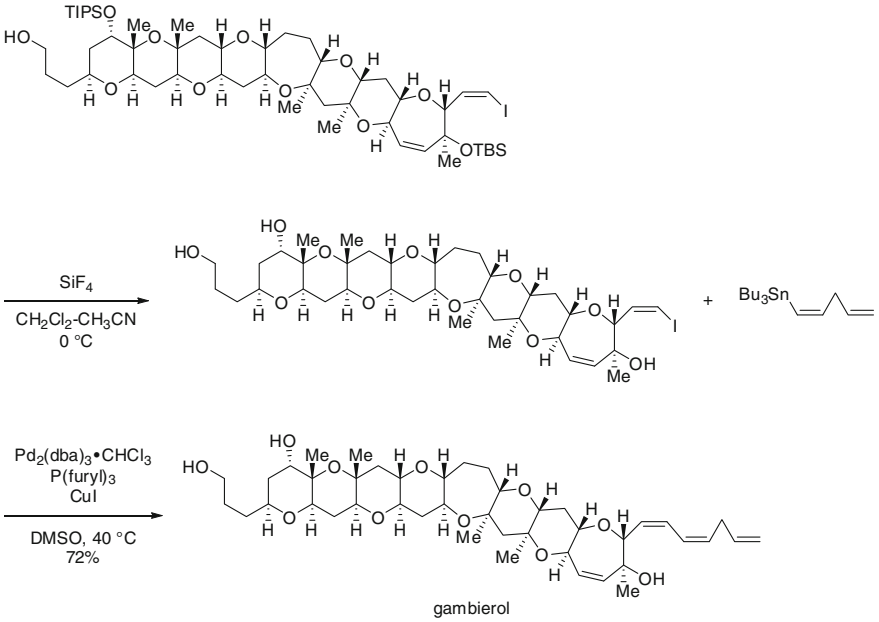
Migita–Kosugi–Stille coupling, using a stoichiometric amount of CuTC, can be used in the total synthesis of phoslactomycin A, while avoiding the side reaction of allylphosphate with the Pd catalyst (Scheme 3.21) [85]. Other stoichiometric

reactions mediated by a copper compound have been reported for the total synthesis of dictyostatin [86], formamicin [87], and amphidinolide A [88].



Scheme 3.21 A synthetic route to phoslactomycin A

The total synthesis of gambierol, shown in Scheme 3.22, is another example of a synthetic strategy utilizing Migita–Kosugi–Stille coupling [89–92]. An important aspect of this synthesis is that a silyl protecting group was removed *before* the cross-coupling. This underscores the fact that Migita–Kosugi–Stille coupling will not take place if the reaction site of the cross-coupling is sterically hindered by the presence of a bulky TBS group. Deprotection of the silyl group counteracts the steric congestion to smoothly accelerate the cross-coupling.

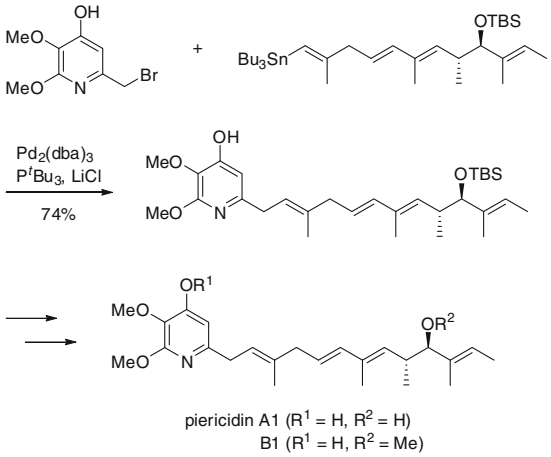


Scheme 3.22 A synthetic route to gambierol

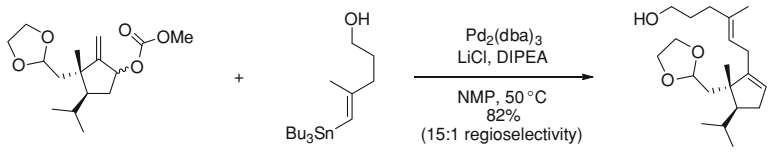
The following are known examples of the utility of the sp^2–sp^2 Migita–Kosugi–Stille coupling reactions for the natural product syntheses: paracentrone [6], iso- and bongkrekic acids [8], leiodolide B [30], (−)-callystatin A [43], sanglifehrin A [93–95], a biaryl moiety of TMC-95 [96], (−)-reveromycin B [97], manzamine A [98], quadrigemine C, psycholeine [99], pentacyclic skeletons [100], SNF4435 C, SNF4435 D [101], (−)-crispatene [102], (–)-SNF4435 C, (+)-SNF4435 D [103], 28-^{19}F-amphotericin B methyl ester [104], FR252921, pseudotrienic acid B [105, 106], (−)-spirangien A and its methyl ester [107], amphidinolide H1 [108], (+)-crocacin C [109], amphidinolides B1, B4, G1, H1 [110], (±)-havellockate [111], (±)-goniomitine [112], amphidinolide A [113], CD-D' rings in angelmicin B (hibarimicin B) [114], and brevenal [115, 116].

3.5.3 Other Migita–Kosugi–Stille Couplings

In addition to the sp^2–sp^2 coupling, sp^2–sp^3 Migita–Kosugi–Stille coupling is also utilized for natural product syntheses. The total syntheses of piericidin A1 and B1 [117] and (±)-neodolabellane-type diterpenoids [118] are shown in Schemes 3.23 and 3.24, respectively.



Scheme 3.23 A synthetic route to piericidin A1 and B1



Scheme 3.24 A synthetic route to (±)-neodolabellane-type diterpenoids

Because stable π-benzyl- and π -allylpalladium complexes are generated, these sp^2–sp^3 Migita–Kosugi–Stille couplings can be utilized with a low risk of β-hydrogen elimination. The sp^3 organotin reagents have rarely been utilized in Migita–Kosugi–Stille coupling because they cause β-hydrogen elimination (See also Chap. 8).

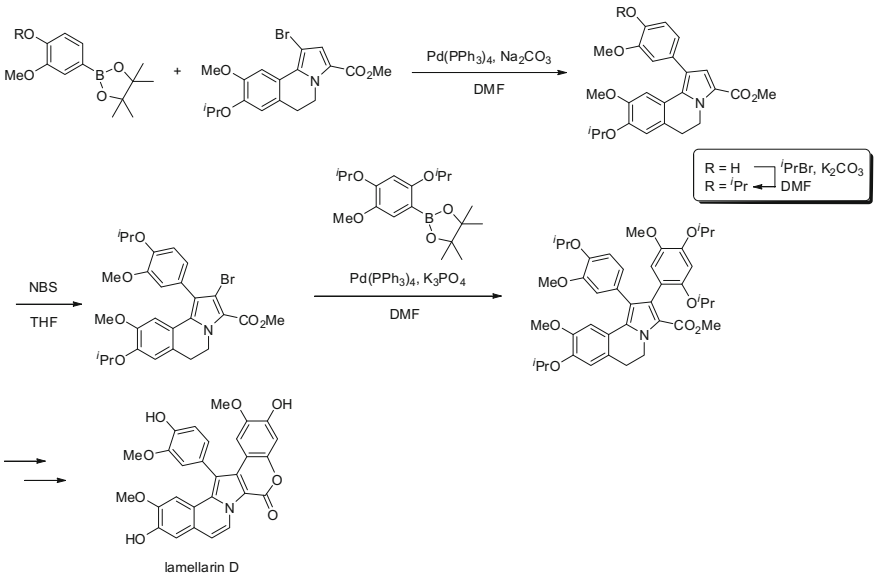
In addition, using the sp^3–sp^2 Migita–Kosugi–Stille coupling, the total syntheses of amphidinolide A [113], azaspiracid-1 [119, 120], tardioxopiperazine A, isoechinulin A, and variecolorin C [121] have been reported.

3.6 Suzuki–Miyaura Coupling

Suzuki–Miyaura coupling is extremely advantageous because the organoboron compounds have low toxicity and have stability toward water and air; this cross-coupling has been used extensively in natural product syntheses. However, Suzuki–Miyaura coupling requires the use of bases, thus functional groups that are unstable under basic conditions are incompatible. Herein, the applications of Suzuki–Miyaura coupling to natural product syntheses are described.

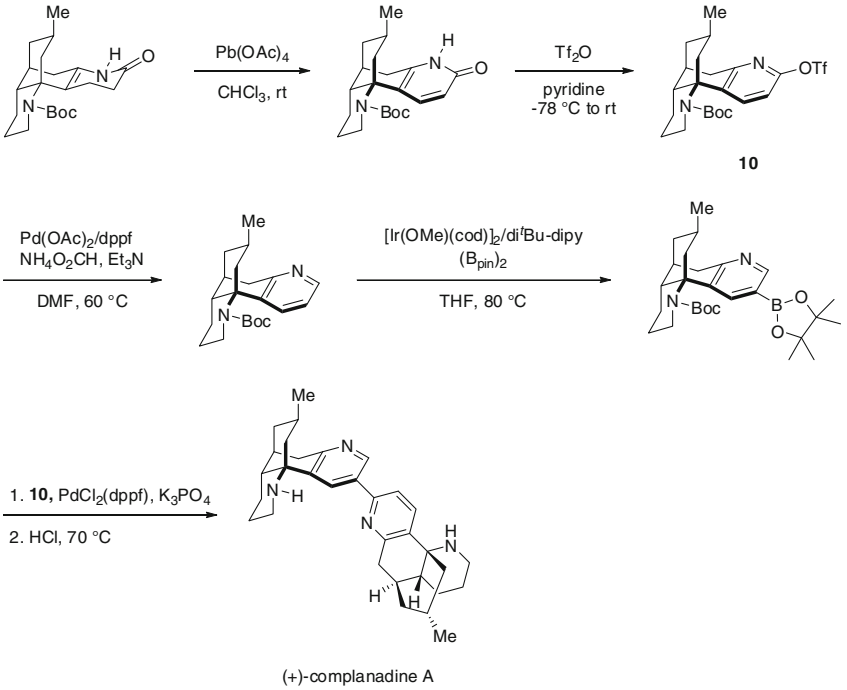
3.6.1 sp^2–sp^2 Suzuki–Miyaura Coupling

Construction of biaryl and conjugate diene motifs using the sp^2–sp^2 Suzuki–Miyaura coupling is particularly important in the natural product syntheses. Some examples include: 5,6-DiHETE methyl esters [122], (−)-chlorothricolide [123], and rutamycin B [124]. Although Negishi and Migita–Kosugi–Stille couplings can be used for sp^2–sp^2 carbon–carbon bond formation, Suzuki–Miyaura coupling is more widely utilized owing to its versatility of ligands and its various types of boron-containing reagents. The total synthesis of lamellarin D shown in Scheme 3.25 is one such example employing pinacolborane as the boron moiety [125].



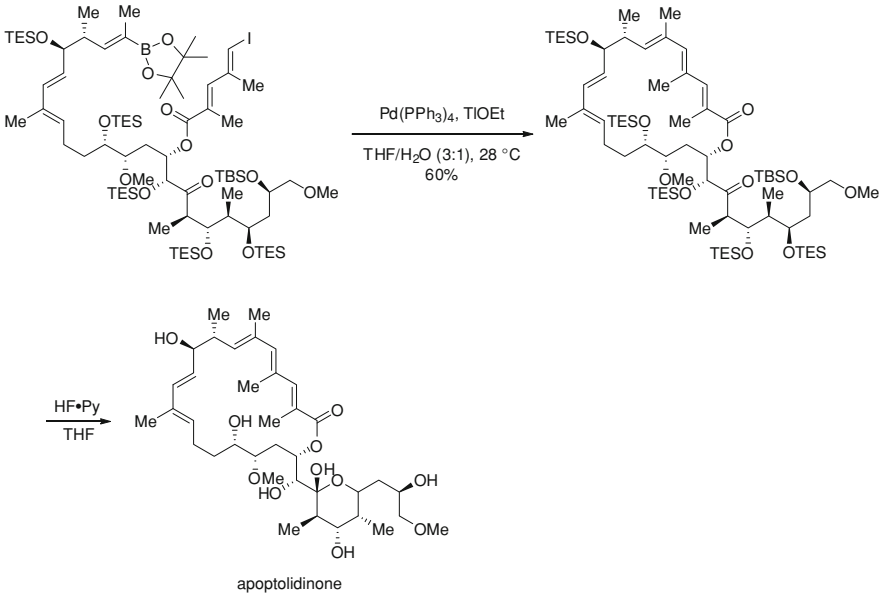
Scheme 3.25 A synthetic route to lamellarin D

$Pd(PPh_3)_4$ is generally the most frequently used Pd(0) complex in Suzuki–Miyaura coupling, but $PdCl_2$(dppf) also shows high catalytic activity in the synthesis of (+)-complanadine A (Scheme 3.26) [126].



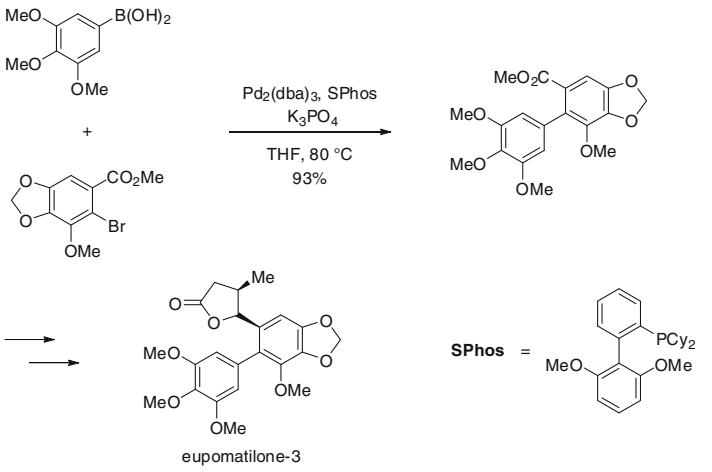
Scheme 3.26 A synthetic route to (+)-complanadine A

In general, as the substrate becomes larger, the achievement of cross-coupling becomes more difficult due to poor access to the reaction sites. However, Kishi reported in 1989 that the reactivity of a congested substrate was drastically improved by the use of thallium hydroxide as the base in the total synthesis of palytoxin [127]. More recently, TlOEt and Tl_2CO_3 have been utilized as a precursor of thallium hydroxide because thallium hydroxide is difficult to handle due to its instability to light and air [128]. The example of the synthesis of apoptolidinone via Suzuki–Miyaura coupling with TlOEt as the base is shown in Scheme 3.27 [129].



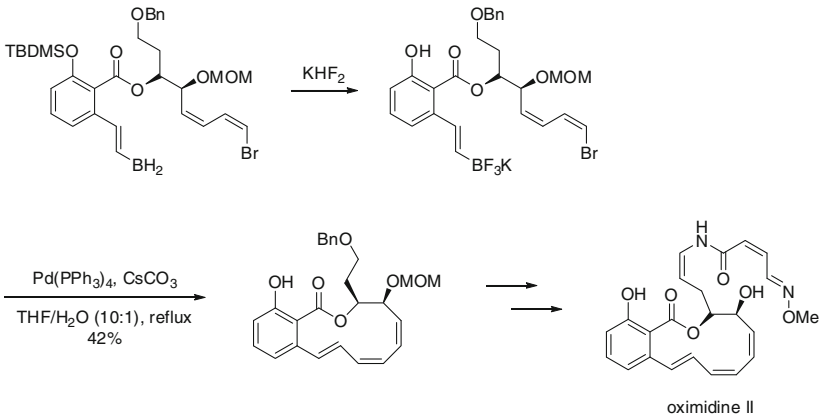
Scheme 3.27 A synthetic route to apoptolidinone

Buchwald reported that the bulky phosphine ligands with a biaryl backbone such as SPhos have a high activity in Suzuki–Miyaura coupling [130]. In the total synthesis of eupomatilones, as little as 0.005 mol % of the Pd catalyst can afford the cross-coupled products in 93 % yield (Scheme 3.28) [131, 132].



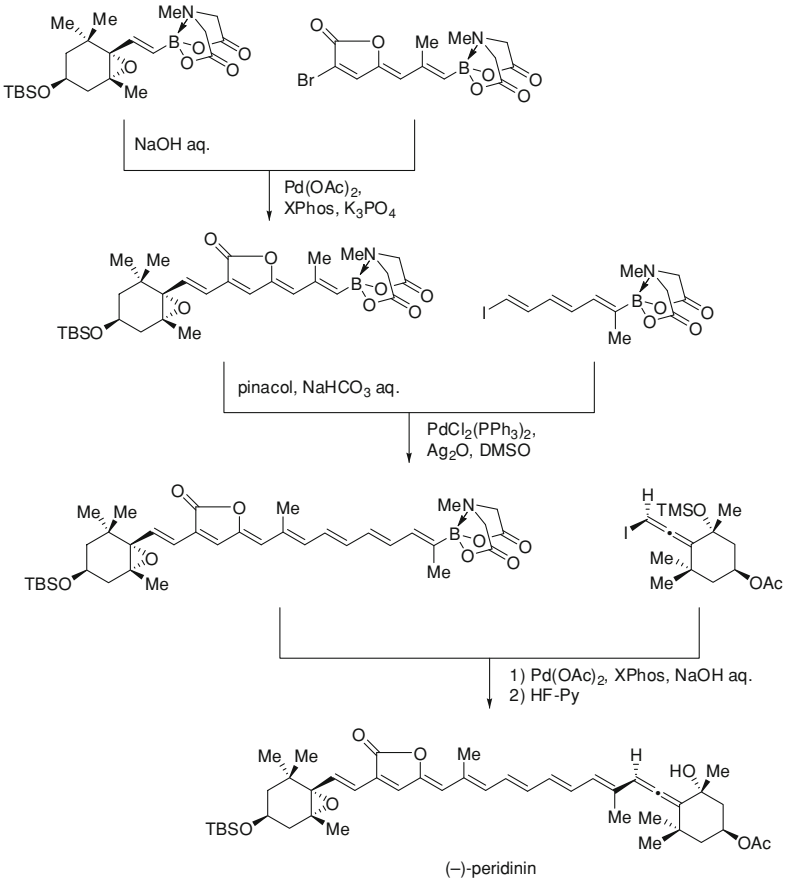
Scheme 3.28 A synthetic route to eupomatilones

Furthermore, Suzuki–Miyaura coupling is practical because it offers a superior selection of bases and ligands. As the result of recent research utilizing the benefits of organoboronic acids, many progressive synthetic routes have been established. Herein, some examples of modified organoboron compounds used in natural product syntheses are introduced. As shown in Scheme 3.29, the total synthesis of oximidine II [22] is an example of the application of organotrifluoroborates [133] to the natural product synthesis. The construction of an unsaturated 12-membered ring with a large strain was achieved.



Scheme 3.29 A synthesis route to oximidine II

In addition, Suzuki–Miyaura couplings using *N*-methyliminodiacetic acid (MIDA) have been invented [134]. (–)-Peridinin has been synthesized by repeated reactions with MIDA-containing organoborates (Scheme 3.30) [135].



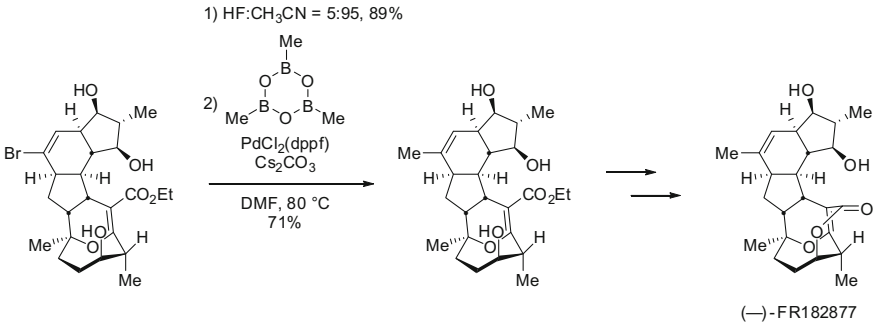
Scheme 3.30 A synthesis route to (–)-peridinin

Thus, the sp^2–sp^2 Suzuki–Miyaura coupling has achieved selective and efficient carbon–carbon bond formation in natural product syntheses through the use of a wide variety of substrates. The following examples of natural product syntheses using sp^2–sp^2 Suzuki–Miyaura coupling have been recently reported: iso- and bongkrekic acids [8, 31], furopyrans [29], lukianol A [33], maleic anhydride, maleimide [67], (+)-crocacin C [109], CD-D′ rings in angelmicin B (hibarimicin B) [114], (+)-fostriecin [136], dragmacidin D [137], (−)-FR182877 [138, 139], nakadomarin A [140], styelsamine C [141], (±)-spiroxin C [142], diazonamide A [143], quinine, quinidine [144], lamellarin G trimethyl ether [145], (+)-dragmacidin F [146], eupomatilone diastereomers [147], biphenomycin B [148], (−)-

spirofungin A, (+)-spirofungin B [149], pulvinic acids [150], N-shifted and ring-expanded buflavine [151, 152], (±)-hasubanonine [153], altenuene, isoaltenuene [154], C-15 vindoline analogs [155], (−)-erythramine and 3-*epi*-(+)-erythramine [156], biaryl hybrids of allocolchicine and steganacin [157], ratanhine [158], palmerolide A [159], eupomatilones [160], butylcycloheptylprodigiosin [161], isotetronic acids [162], 1/2 of amphotericin B macrolide [163], GEX1A [164], (±)-cyclocolorenone, (±)-α-gurjunene [165], withasomnines [166], the vacidin A (*E*,*E*,*E*,*Z*,*E*,*E*)-heptaene framework [167], fortuneanoside E [168], (–)-exiguolide [169], dunnianol [170], and hirtellanine A [171].

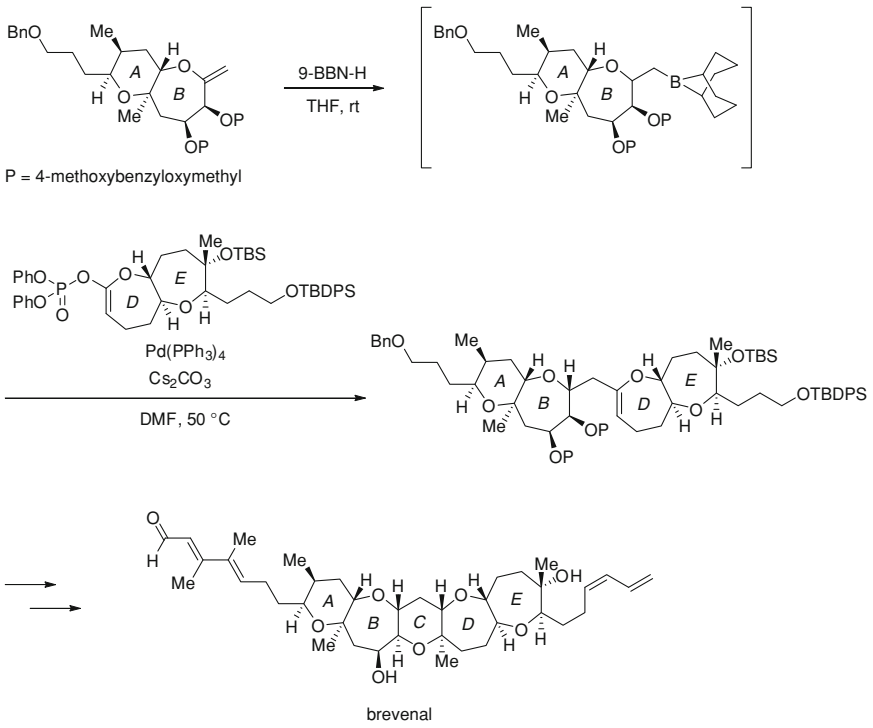
3.6.2 sp^3–sp^2 Suzuki–Miyaura Coupling

Suzuki–Miyaura coupling has also been used to construct sp^3–sp^2 carbon–carbon bonds (See also Chap. 8). One such example is the methylation using trimethylboroxine, which is a dehydrated trimer of methylboronic acid, toward aryl or alkenyl halides [172]. The total synthesis of (−)-FR182877 using the sp^3–sp^2 Suzuki–Miyaura coupling is shown in Scheme 3.31 [138].



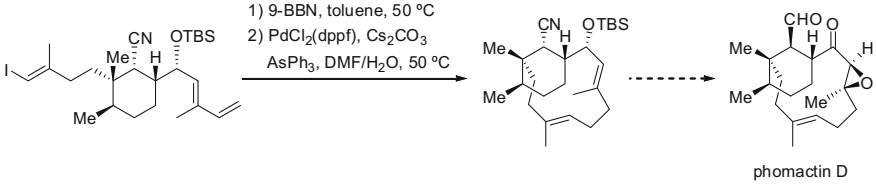
Scheme 3.31 A synthetic route to (–)-FR182877

In most cases, the sp^3–sp^2 Suzuki–Miyaura coupling employs a typical hydroboration of the terminal olefin by 9-BBN and the subsequent B-alkyl Suzuki–Miyaura coupling. Since hydroboration using a bulky 9-BBN takes place in a highly regioselective fashion [173], B-alkyl Suzuki–Miyaura coupling has been widely utilized for the connection of fragments in the natural product syntheses, e.g., the total synthesis of brevenal (Scheme 3.32) [115, 116, 174].



Scheme 3.32 A synthetic route to brevenal

In addition, the B-alkyl Suzuki–Miyaura coupling can be applied to the intramolecular cyclization in the total synthesis of phomactin D; compared with other sp^3–sp^2 cross-coupling reactions, the organoboron compounds have low toxicity and are highly stable (Scheme 3.33) [175].



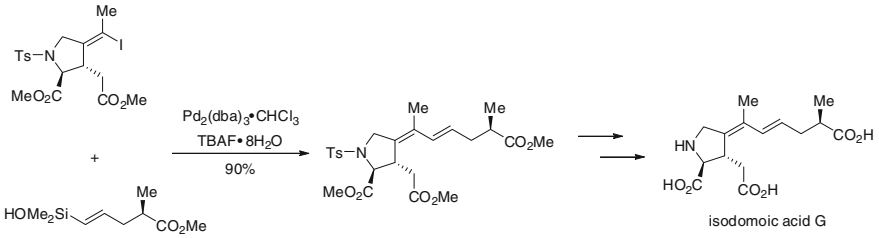
Scheme 3.33 A synthetic route to phomactin D

Other synthetic examples using the sp^3–sp^2 Suzuki–Miyaura coupling include the total synthesis of: anguinomycin C [45], anguinomycin C and D [46], transepothilone A [55], oleandolide [56], salicylihalamide [71], CP-225,917, CP-263,114 [176], epothilone A [55, 177], 12,13-desoxyepothilone F [178], FGH ring fragments of gambierol [179], sphingofungin E [180], GHIJKLM ring fragments in ciguatoxin (CTX1B) [181], ABCD ring fragments of ciguatoxin (CTX3C) and

ciguatoxin (51-hydroxyCTX3C) [182], (−)-ebelactone A [183], gymnocin-A [184–187], (+)-phomactin [188], the C6–C21 segment of amphidinolide E [189], (±)-geigerin [190], (+)-oocydin A [191], 4-hydroxydictyolactone [192], jatrophane diterpenes [193], (+)-brefeldin C, (+)-nor-Me brefeldin A, (+)-4-*epi*-nor-Me brefeldin A [194], ABC ring fragments of brevesin [195], and (−)-brevisin [196].

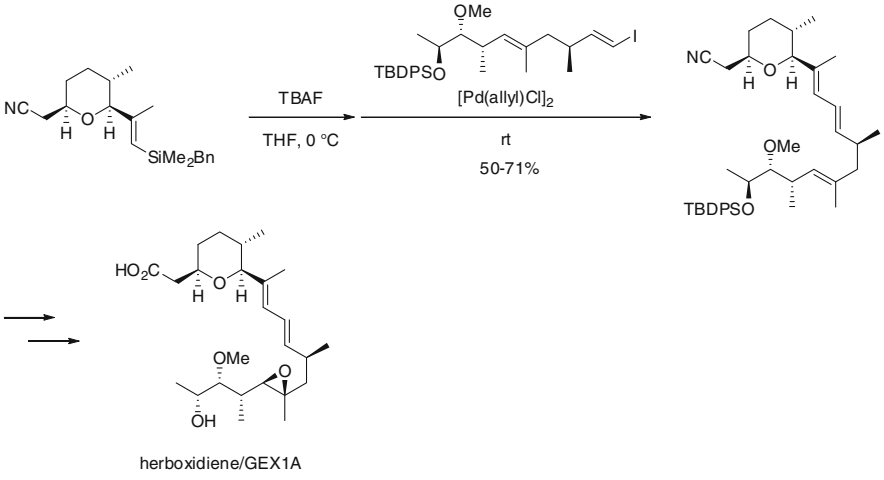
3.7 Hiyama Coupling (sp^2–sp^2)

Finally, recent examples utilizing the sp^2–sp^2 Hiyama coupling in the natural product syntheses will be briefly introduced. As shown in Scheme 3.34, silanol (the substrate bearing a hydroxyl group on silicon) is activated by TBAF to react with an alkenyl iodide in the total synthesis of isodomoic acid G [197].



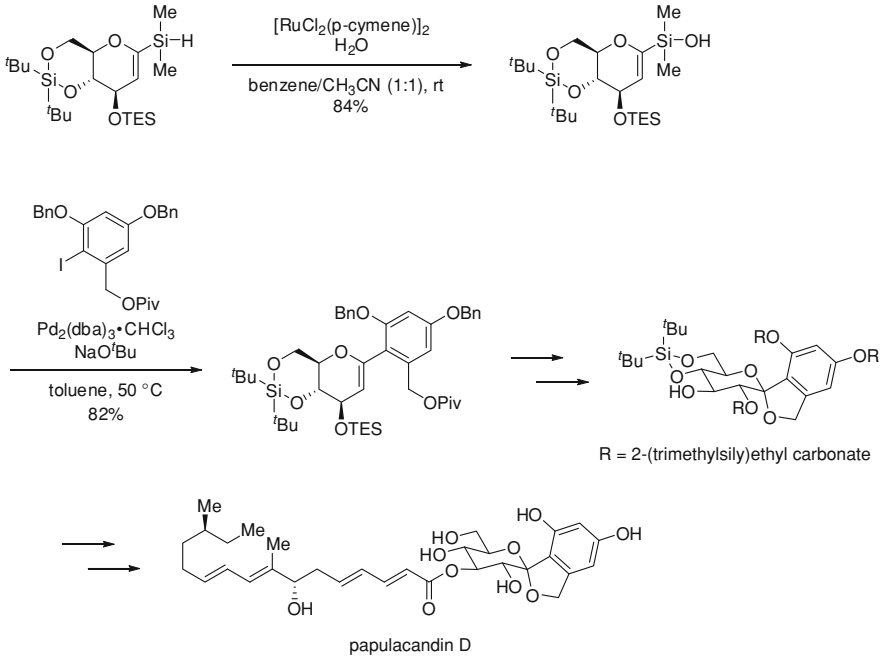
Scheme 3.34 A synthetic route to isodomoic acid G

Another alkenylsilane substituted with a benzyldimethylsilyl group was successfully subjected to Hiyama coupling for the synthesis of a precursor of herboxidiene/GEX 1A (Scheme 3.35) [198]. It should be noted that in this synthetic example, during the Hiyama coupling, the alcohol was protected by a silyl protecting group.



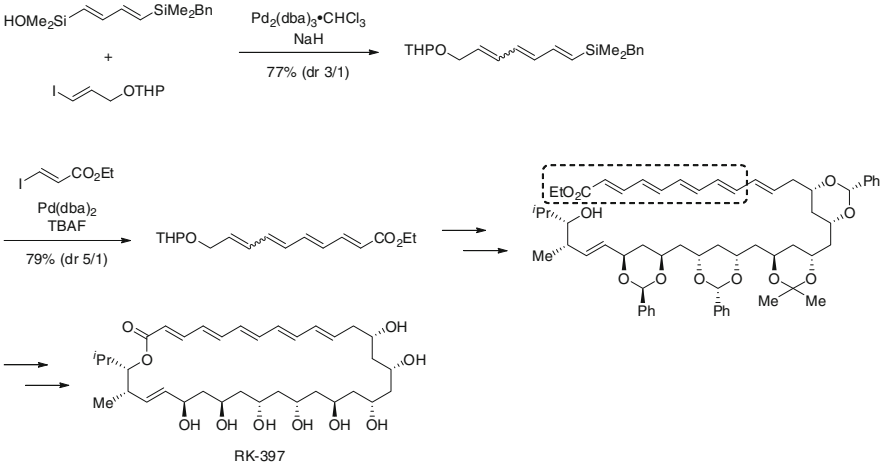
Scheme 3.35 A synthetic route to herboxidiene/GEX 1A

In the total synthesis of papulacandin D, after a hydrosilane was converted into a silanol using the Ru catalyst, Hiyama cross-coupling of silanol was applied (Scheme 3.36) [199].



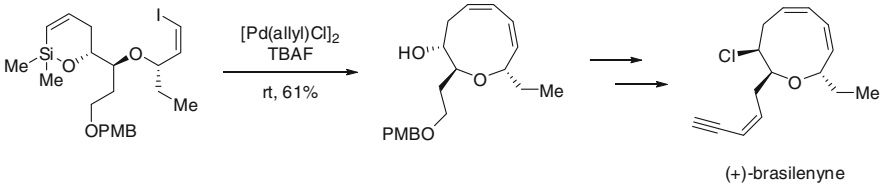
Scheme 3.36 A synthetic route to papulacandin D

In addition, a conjugate diene bearing two different silicon functional groups was subjected to the successive Hiyama coupling, achieving the total synthesis of RK-397, as shown in Scheme 3.37 [200].



Scheme 3.37 A synthetic route to RK-397

Moreover, the total synthesis of a highly strained 9-membered compound, (+)-brasilenyne, has been achieved through intramolecular Hiyama coupling (Scheme 3.38) [201, 202].



Scheme 3.38 A synthetic route to (+)-brasilenyne

Thus, Hiyama coupling has a large number of advantages from the viewpoints of high stability, low toxicity, and natural abundance of the organosilicon

compounds. Thus, Hiyama coupling can be a powerful tool in the natural product syntheses. However, Hiyama coupling has not been advanced much, because the silyl functionalities require the introduction of hydroxyl or fluoride substituents to be activated, which limits the selection of substrates.

3.8 Summary

The cross-coupling reactions have facilitated the synthesis of complex organic compounds with high selectivity and reactivity in the natural product syntheses. In addition, recent advancement of technologies for cross-couplings includes: the expansion of organometallic reagents, increased reactivity and safety by the improvement of catalysts, and the reduction of chemical wastes. This remarkable progress has made the cross-coupling reactions increasingly easy to utilize. Complicated natural product syntheses that have not yet been achieved will likely be artificially synthesized by using the cross-coupling reactions in the future. More technological development is expected toward clarification and application of the biologically active compounds.

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Chapter 4
Pharmaceuticals

Jiao Jiao and Yasushi Nishihara

Abstract This chapter describes the design and development of biologically active compounds using cross-coupling reactions as key steps. These biologically active compounds are of both academic and industrial importance. Drug candidates can be prepared from easily available substrates in a few steps through cross-coupling—underscoring the versatility, effectiveness, functional group tolerance, and mild reaction conditions of the cross-coupling methods. Due to these advantages, palladium-catalyzed cross-coupling reactions are being utilized in the industrial production of pharmaceuticals.

Keywords Pharmaceutical · Large-scale synthesis · Functional group tolerance

4.1 Introduction

Owing to many pioneering chemists' unremitting efforts, recent innovations have replaced earlier protocols to achieve milder, broader, and more efficient catalytic methods for carbon–carbon bond formations [1–11]. The cross-coupling protocols are appropriately considered to be the cornerstones for the synthesis of pharmaceuticals. These reactions provide new entries into pharmaceutical ingredients of continuously increasing complexity. Transition-metal catalysts such as Ni, Cu, Rh, and Ru have been substantially developed in the synthesis of drugs or their precursors [12–16]; however, Pd catalysis, with its high activity and mild reaction conditions, has considerable potential in large-scale applications for pharmaceuticals.

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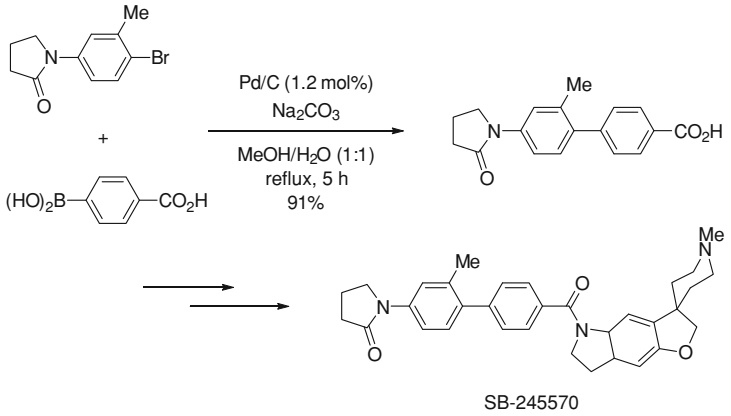
DOI: 10.1007/978-3-642-32368-3_4,

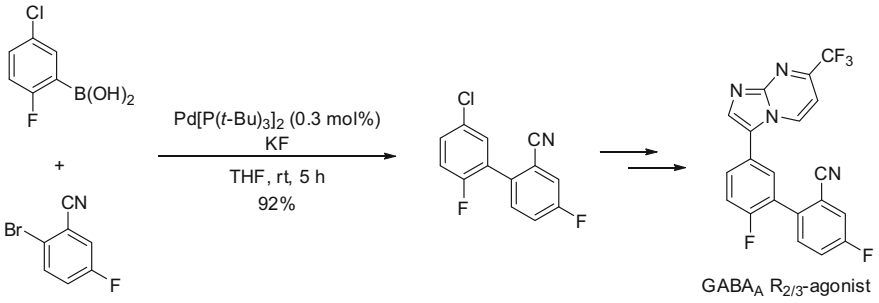
4.2 Suzuki–Miyaura Coupling

The most representative coupling for the synthesis of pharmaceuticals is the Suzuki–Miyaura coupling, which has been widely studied in the past decade. One of the earliest examples of industrial-scale Suzuki–Miyaura coupling in pharmaceuticals was reported in 1999 [17], which described the synthetic pathway of SB-245570, a candidate for the treatment of depression (Scheme 4.1). This synthesis was efficient and inexpensive. The Pd/C-catalyzed Suzuki–Miyaura coupling provided access to the desired product, and reaction in MeOH/H_2O gave an improved product yield with a residual Pd level of <6 ppm.



Scheme 4.1 A synthetic route to SB-245570

Cameron et al. published the preparation of a $GABA_A$ $R_{2/3}$ agonist for the treatment of generalized anxiety disorder (Scheme 4.2) [18]. The biaryl system was assembled from the palladium-catalyzed Suzuki–Miyaura coupling of an aryl bromide with an arylboronic acid. The arylboronic acid was prepared via *ortho*-lithiation of 4-chlorofluorobenzene with lithium 2,2,6,6-tetramethylpiperidine, followed by a B[O(*i*-Pr)]$_3$ quench and acidic workup [19, 20].



Scheme 4.2 A synthetic route to a $GABA_A$ $R_{2/3}$-agonist

3-Amino-2-phenylpiperidines are important pharmacophores because of their role as potent, non-peptidic NK1 receptor antagonists such as CP-99,994 and GR203040 (Fig. 4.1).

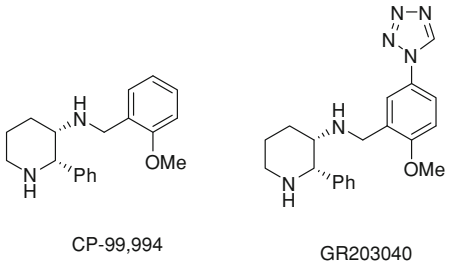
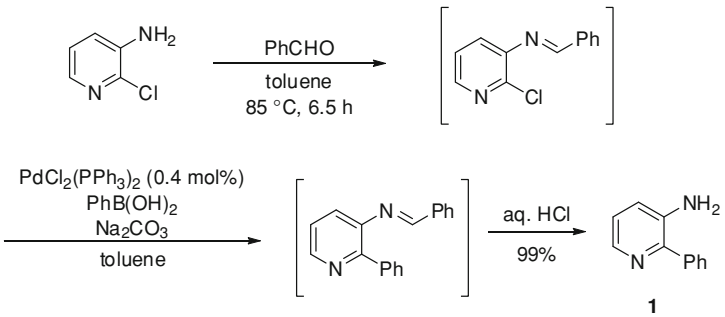


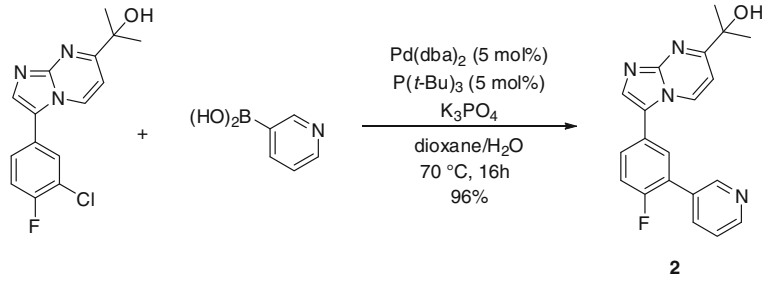
Fig. 4.1 3-Amino-2-phenylpiperidine derivatives

Caron and co-workers have reported Suzuki–Miyaura coupling to prepare 3-amino-2-phenylpyridine, a key intermediate in the preparation of 3-amino-2-phenylpiperidine [21]. The in situ protection of 3-amino-2-chloropyridine with benzaldehyde, followed by Suzuki–Miyaura coupling with phenylboronic acid and the subsequent acidic hydrolysis provides 3-amino-2-phenylpyridine (**1**) in a single, high-yielding step from inexpensive and commercially available starting materials (Scheme 4.3).



Scheme 4.3 Synthesis of 3-amino-2-phenylpyridine (**1**)

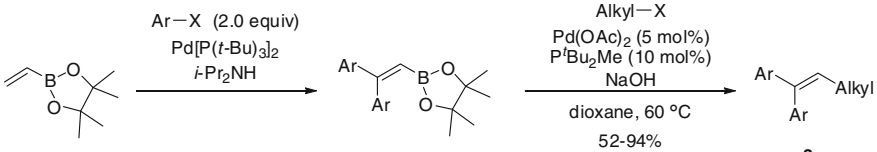
Jensen has described the synthesis of a $GABA_A$ $R_{2,3}$-selective allosteric modulator **2**, a potential treatment for central nervous system conditions, in high yield by Suzuki–Miyaura coupling of imidazopyrimidine with 3-pyridylboronic acid (Scheme 4.4) [22]. This synthetic method highlights the versatility of Pd-catalyzed Suzuki–Miyaura coupling.



2

Scheme 4.4 Synthesis of a $GABA_A$ $R_{2,3}$-selective allosteric modulator **2**

Itami and Yoshida have described a sequence of double Mizoroki–Heck reactions of the vinylboronate pinacol ester with aryl halides, followed by Suzuki–Miyaura coupling of the generated β,β-diarylvinylboronates with alkyl halides (Scheme 4.5) [23], to very efficiently produce pharmaceutically important 1,1-diaryl-1-alkenes **3** (Fig. 4.2). In the Pd-catalyzed Suzuki–Miyaura coupling step, the use of bulky electron-rich ligands such as P^tBu_2Me and PCy^t_2Bu was found to be very effective.



3

Ar = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-FC_6H_4, 1-naphthyl.
Alkyl = $^nC_4H_8Ph$, $^nC_6H_{12}OH$, $^nC_6H_{12}OPiv$, $C_2H_4SiMe_3$, $^nC_6H_{12}CN$, $^nC_6H_{12}$-$OSiEt_3$, C_3H_6Ph, $^nC_4H_8NPhth$, 1-hexen-6-yl

Scheme 4.5 Synthesis of 1,1-diaryl-1-alkenes **3**

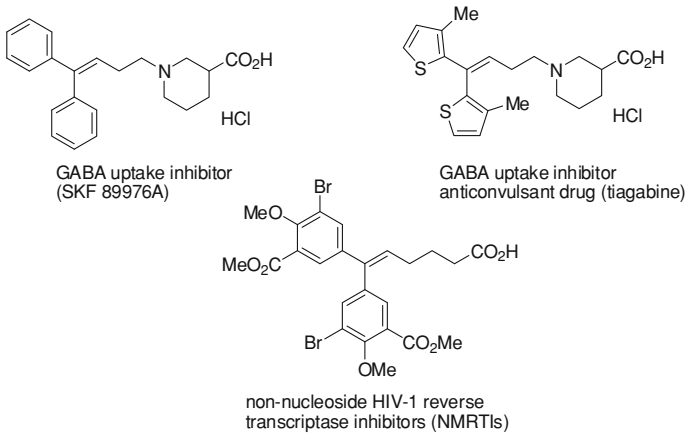
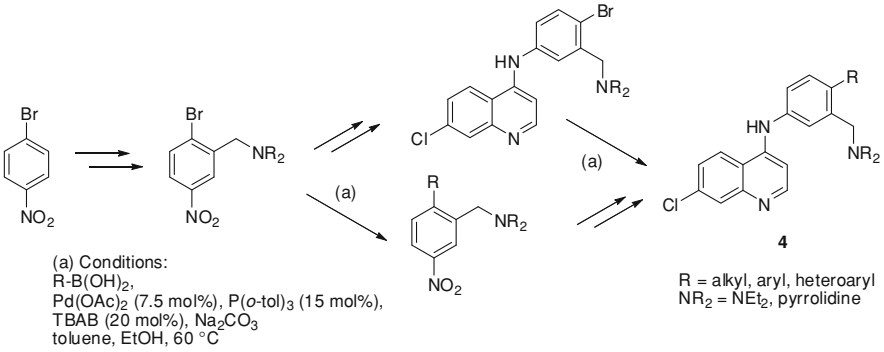


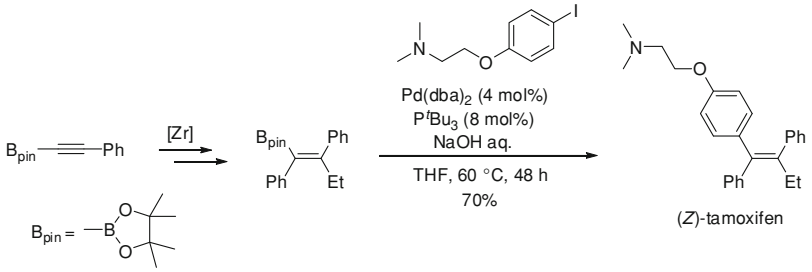
Fig. 4.2 Examples of pharmaceutically important 1,1-diaryl-1-alkenes

A versatile methodology for the synthesis of 4-aminoquinoline derivatives **4** (antimalarial drugs) using $C(sp^2)$-$C(sp^2)$ Suzuki–Miyaura cross-coupling reactions as key steps is presented in Scheme 4.6 [24]. These methodologies provided the novel synthesis of a variety of aryl- and alkyl-substituted 4-aminoquinoline analogs by a general protocol, which allowed the convenient introduction of diversity using Suzuki–Miyaura couplings between aryl bromides and commercially available arylboronic acids.



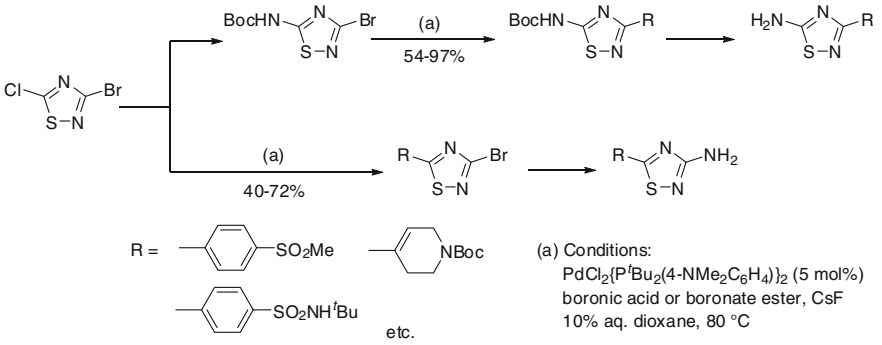
Scheme 4.6 Synthesis of 4-aminoquinoline derivatives **4**

A versatile and direct synthesis of multi-substituted olefins has been developed by the regioselective formation of zirconacyclopentenes, followed by Pd-catalyzed cross-coupling and sequential Suzuki–Miyaura coupling with various aryl iodides (Scheme 4.7) [25]. (*Z*)-Tamoxifen, a widely used treatment for all stages of breast cancer, can be successfully synthesized via this methodology with high regio- and stereoselectivities (>99 %).



Scheme 4.7 Synthesis of (Z)-tamoxifen

Wehn has demonstrated a novel approach to the synthesis of the substituted 5-amino- and 3-amino-1,2,4-thiadiazoles beginning from a common precursor (Scheme 4.8). Derivatization by palladium-catalyzed Suzuki–Miyaura coupling enables an efficient supply of analogs around this pharmaceutically relevant core (Fig. 4.3) [26].



Scheme 4.8 Synthesis of the substituted 5-amino- and 3-amino-1,2,4-thiadiazoles

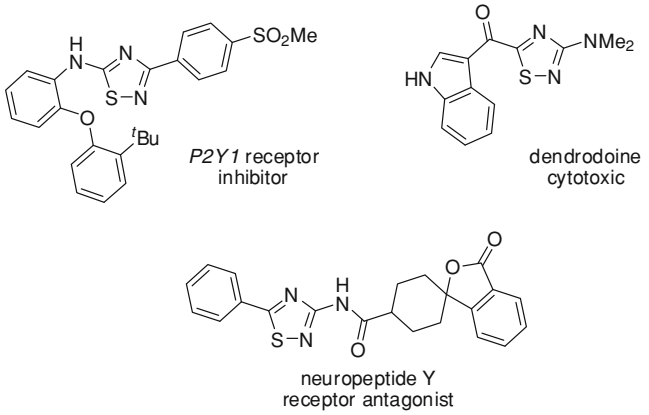
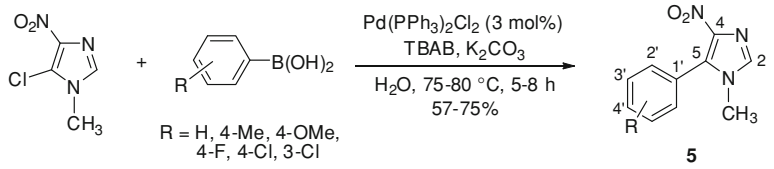


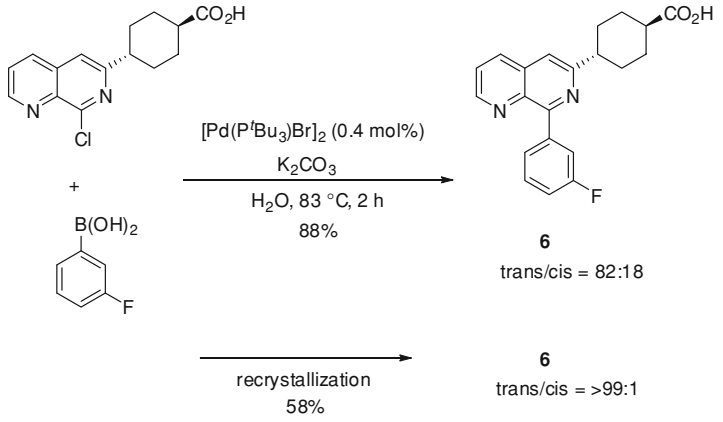
Fig. 4.3 Representative amino-1,2,3-thiadiazoles in natural products and potential pharmaceuticals

Saadeh has reported a one-pot synthesis of several 5-aryl-1-methyl-4-nitroimidazoles **5**, which exhibit potent lethality against Entamoeba histolytica and Giardia intestinalis, through Suzuki–Miyaura coupling between 5-chloro-1-methyl-4-nitroimidazole and a variety of arylboronic acids (Scheme 4.9) [27].



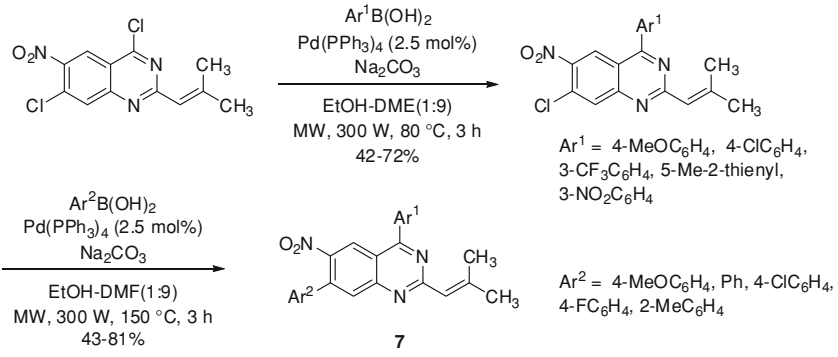
Scheme 4.9 A one-pot synthesis of 5-aryl-1-methyl-4-nitroimidazoles **5**

Jiang and Prasad have used this methodology in the synthesis of a phosphodiesterase-4 inhibitor **6** for the treatment of chronic obstructive pulmonary disease and asthma (Scheme 4.10) [28]. The desired drug substance **6** was obtained in 58 % yield. After recrystallization using 10 % water in acetonitrile, less than 1 % of the *cis*-isomer remained. The remaining 1 % of undesired *cis*-isomer was largely isomerized to the *trans*-isomer using phosphorus oxychloride at 110 °C.



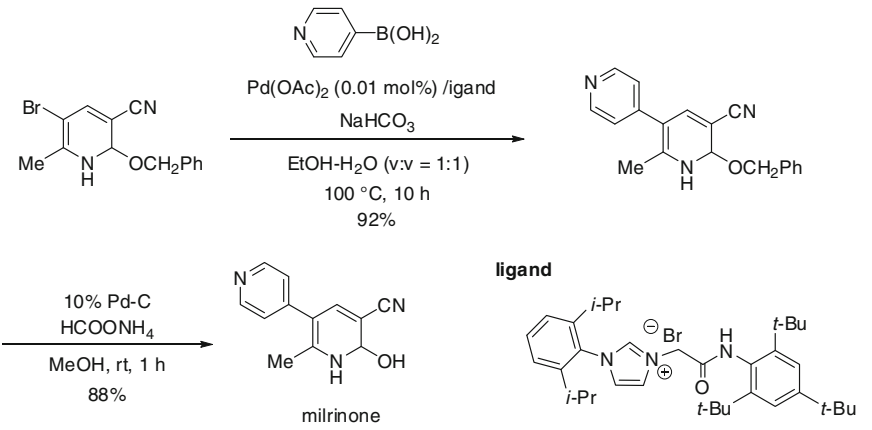
Scheme 4.10 Synthesis of a phosphodiesterase-4 inhibitor **6**

Vanelle has reported a synthetic pathway for diarylquinazolines **7**, which display significant pharmaceutical potential, starting from 4,7-dichloro 2-(2-methylprop-1-enyl)-6-nitroquinazoline and using microwave-promoted chemoselective Suzuki–Miyaura cross-coupling reactions (Scheme 4.11) [29].



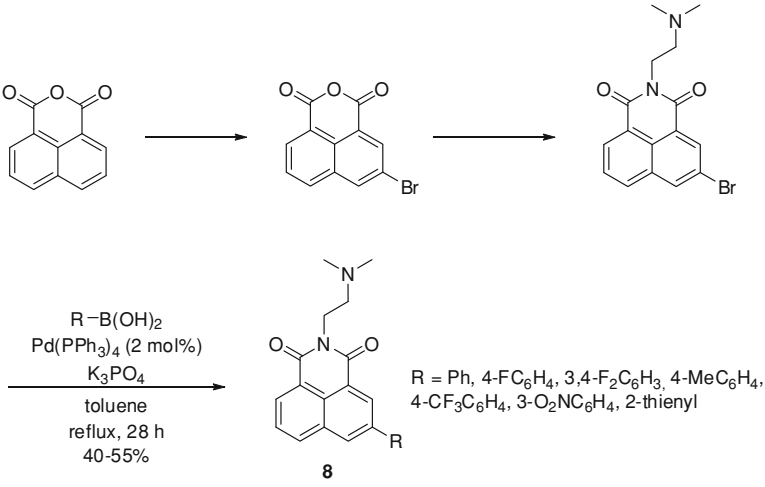
Scheme 4.11 A synthetic route to diarylquinazolines **7**

Very recently, Lee investigated a new catalytic system based on the palladium-amido-*N*-heterocyclic carbenes for Suzuki–Miyaura coupling reactions of heteroaryl bromides and chlorides with 4-pyridylboronic acids to produce a precursor of milrinone (Scheme 4.12) [30].



Scheme 4.12 A synthetic route to a precursor of milrinone

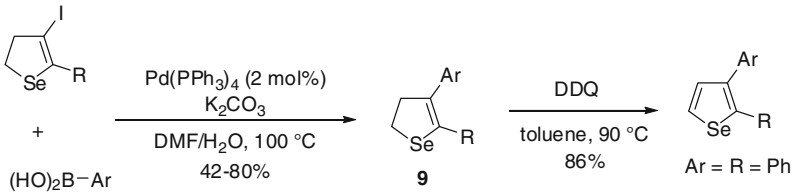
Also, Qian recently designed and synthesized a series of 5 non-amino aromatic-substituted naphthalimides **8** from naphthalic anhydride by three steps, including bromination, amination, and $Pd(PPh_3)_4$-catalyzed Suzuki–Miyaura coupling (Scheme 4.13) [31]. Compared with the current state-of-the-art antitumor agent, amonafide, these new naphthalimide derivatives not only exhibited better antitumor activity against HeLa and P388D1 cancer cell lines in vitro, but they also may have fewer side effects.



Scheme 4.13 A synthetic route to substituted naphthalimides **8**

Zeni has reported the palladium-catalyzed Suzuki–Miyaura coupling reactions of a variety of arylboronic acids with 4-iodo-2,3-dihydroselenophene derivatives

to afford 4,5-diaryl-2,3-dihydroselenophenes **9** (Scheme 4.14) [32]. The subsequent dehydrogenation of these 4,5-diaryl-2,3-dihydroselenophenes **9** were activated by DDQ, and the corresponding 2,3-diarylselenophenes were obtained in good yields. The 2,3-diarylselenophenes were found to be effective in counteracting lipid and protein oxidation as well as scavenging 2,2′-azino-bis(3-ethylbenzothiazoline-6-sulphonic acid (ABTS) radicals. These findings indicate that 2,3-diarylselenophenes are prototypes for future drug development programs to treat disorders involving reactive oxygen species.

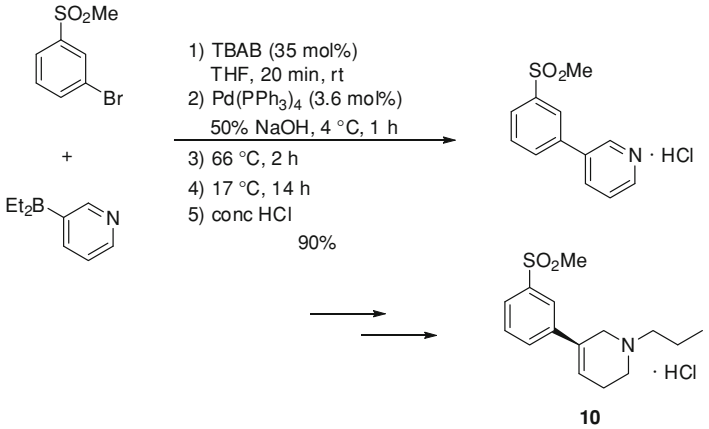


R = Ph, 4-MeC_6H_4, 4-ClC_6H_4, 4-$MeOC_6H_4$, *sec*-Bu, SCH_3, $CH(OH)C_5H_{11}$, H

Ar = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 2-MeC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 3-$F_3CC_6H_4$, 3-$O_2NC_6H_4$, 3-$MeCOC_6H_4$

Scheme 4.14 4,5-Diaryl-2,3-dihydroselenophenes **9**

Boranes and boronic esters can also be efficiently employed, rather than the boronic acids, as the coupling partners with aryl or alkyl halides [33–38]. Lipton has reported the large-scale synthesis of **10**, a potential central nervous system drug candidate. The key step was the Suzuki–Miyaura coupling reaction of methyl-3-bromophenylsulfone and diethyl-3-pyridylborane (Scheme 4.15) [39].

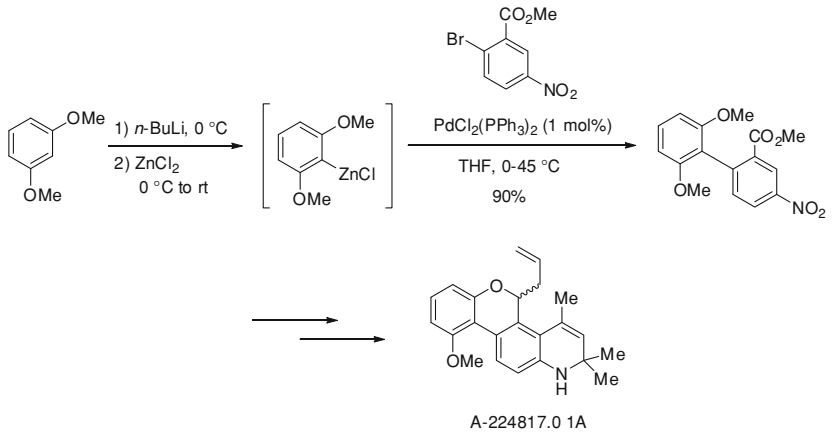


Scheme 4.15 Suzuki-Miyaura coupling reaction of methyl-3-bromophenylsulfone and diethyl-3-pyridylborane

4.3 Negishi Coupling

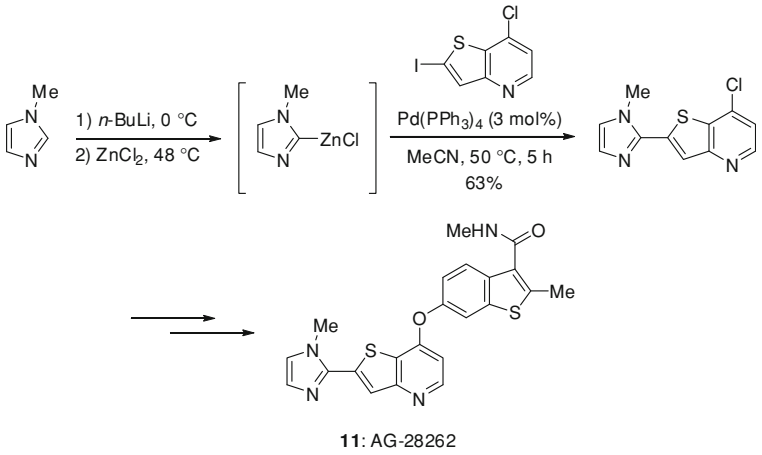
Negishi coupling, another widely applied synthetic pathway for building carbon–carbon bonds in pharmaceuticals, has also undergone extensive advancements in the past decade [40–42]. Chemists such as Knochel [43] and Uchiyama [44, 45] have developed milder reaction conditions for the preparation of organozinc reagents bearing sensitive functional groups such as alcohols and aldehydes. These new methods should find broad applications in the synthesis of complex molecules.

Ku and coworkers incorporated Negishi coupling in the scalable synthesis of A-224817.0 1A, a non-steroidal ligand for the glucocorticoid receptor, which can be used for the treatment of inflammatory diseases and with fewer side effects than the preceding therapeutic agents. The synthesis was accomplished in a few steps, starting from 1,3-dimethoxybenzene. The biaryl intermediate was prepared by an optimized high-yield and high-throughput Negishi protocol (Scheme 4.16) [46].



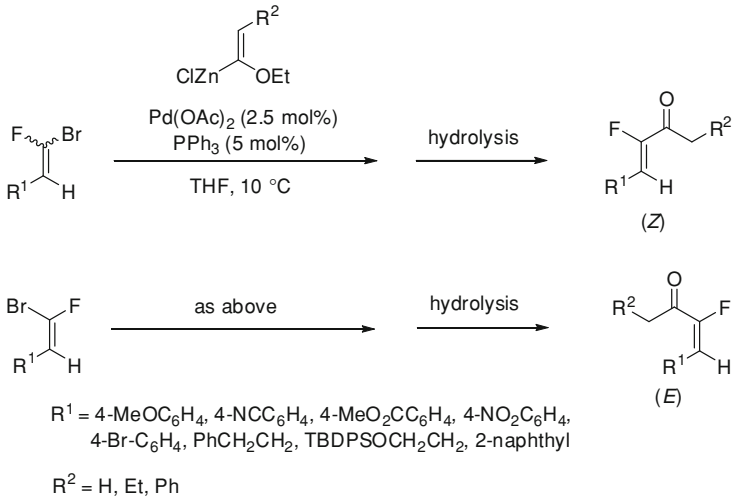
Scheme 4.16 A synthetic route to A-224817.0 1A

Scott has described the synthesis of AG-28262 **11**, a promising VEGFR kinase inhibitor (Scheme 4.17) [47]. The precursor of this molecule was achieved via Pd-catalyzed Negishi coupling. This procedure was repeated for a total of seven batches; the crude product was purified to provide a total of 1.5 kg of **11** with >95 % purity in a 63 % overall yield.



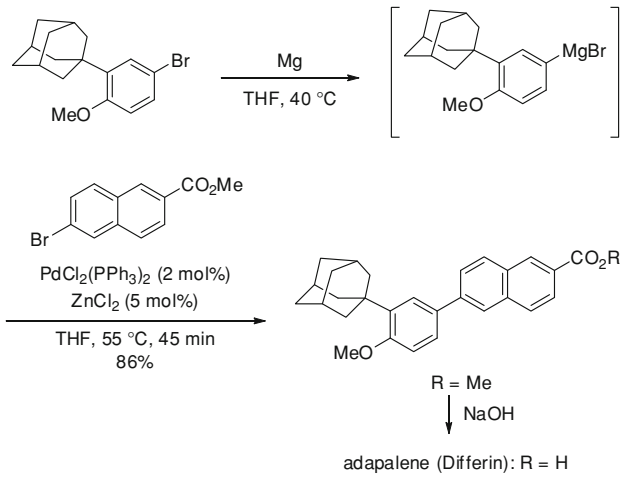
Scheme 4.17 A synthetic route to AG-28262

Pannecoucke has developed a highly stereo-specific synthesis of (*E*)- or (*Z*)-α-fluoro-α,β-unsaturated ketones via a kinetically controlled Negishi coupling, providing easy and general access to valuable fluorinated intermediates for pharmaceuticals and peptide mimics (Scheme 4.18) [48].



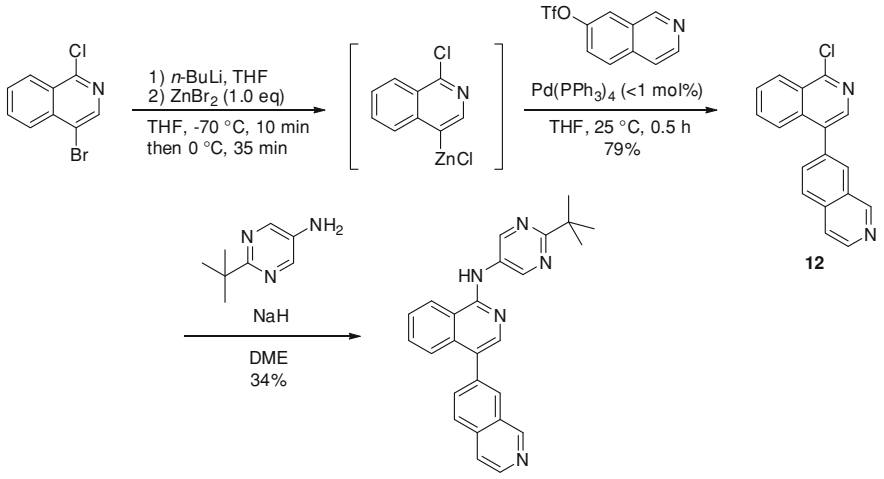
Scheme 4.18 Synthesis of (*E*)- or (*Z*)-α-fluoro-α,β-unsaturated ketones

Liu and Xiang assembled adapalene (Differin®), a synthetic retinoid for the topical treatment of acne, psoriasis, and photoaging, via the $ZnCl_2$-mediated Negishi coupling of a Grignard reagent and an aryl bromide (Scheme 4.19) [49].



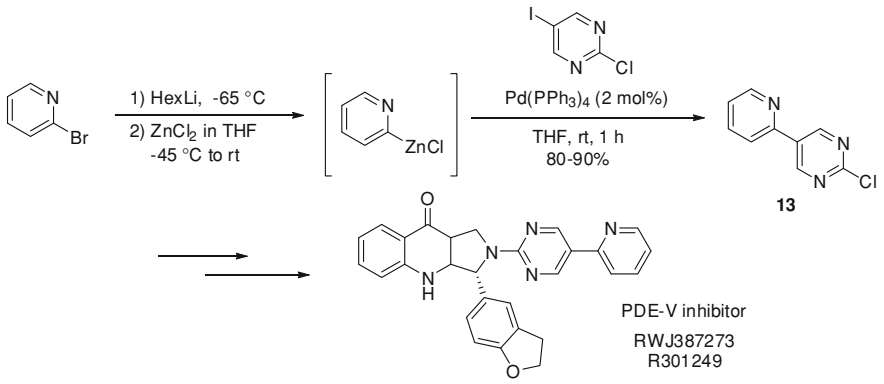
Scheme 4.19 A synthetic route to adapalene (Differin®)

A scalable synthetic route to [4,7′]bis-isoquinolinyl-1-yl-(2-*tert*-butyl-pyrimidine-5-yl)amine, an inhibitor of B-Raf kinase, was described by Bänziger and Yusuff (Scheme 4.20) [50]. The key step in this synthesis is the Pd-catalyzed Negishi coupling of 4-bromo-1-chloroisoquinoline with trifluoromethanesulfonic acid isoquinoline-7-yl ester to yield the molecule **12**. This cross-coupled intermediate was transformed to the desired drug by an amination reaction with 2-*tert*-butyl-5-aminopyrimidine in the presence of NaH. Special care had to be taken to ensure complete removal of traces of Zn and Pd from the final drug substance.



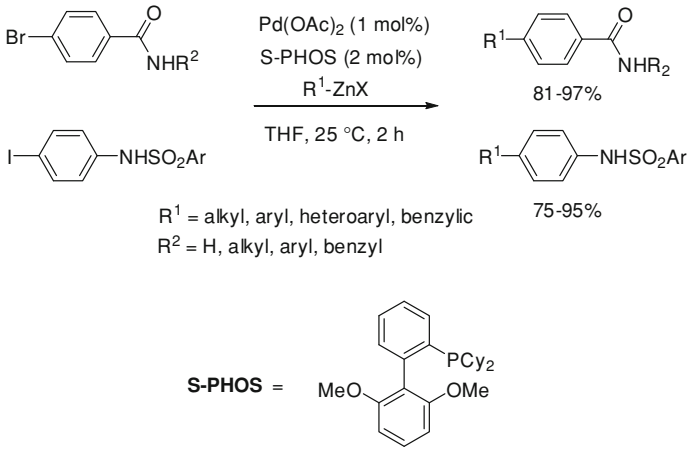
Scheme 4.20 A synthetic route to [4,7’]bis-isoquinolinyl-1-yl- (2-*tert*-butyl-pyrimidine-5-yl)amine

Pérez-Balado has developed a practical and scalable synthesis of 2-chloro-5-(pyridin-2-yl)pyrimidine **13**, an intermediate to a selective PDE-V inhibitor (Scheme 4.21) [51]. Negishi cross-coupling between the in situ prepared 2-pyridylzinc chloride and 5-iodo-2-chloropyrimidine, catalyzed by $Pd(PPh_3)_4$, can afford the product **13** in one step.



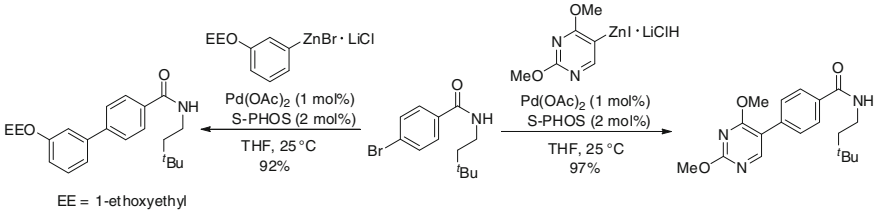
Scheme 4.21 Synthesis of 2-chloro-5-(pyridin-2-yl)pyrimidine **13**

Knochel has demonstrated that the acidic hydrogens of amines, alcohols, and phenols are compatible with Negishi cross-coupling conditions and do not require the use of protecting groups (Scheme 4.22) [52]. The reaction conditions use Buchwald's S-PHOS, which allows general Pd-catalyzed Negishi cross-coupling of functionalized alkyl, aryl, heteroaryl, and benzylic zinc reagents with aryl halides bearing amide or sulfonamide functionalities in spite of their acidic hydrogens.



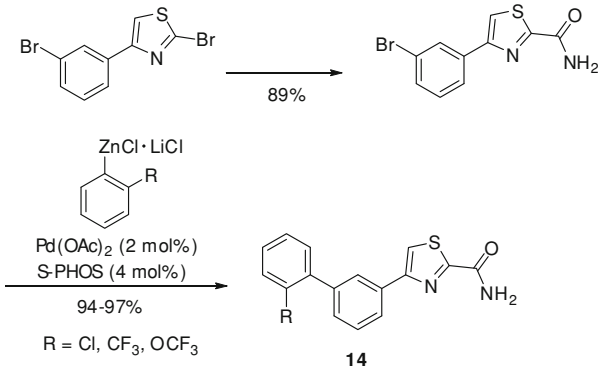
Scheme 4.22 Negishi cross-coupling compatible with acidic hydrogens

Furthermore, many antiarrhythmic agents (Bristol–Myers Squibb) have been prepared by Knochel et al. in 92–97 % yields by the direct Negishi coupling of aromatic and heteroaromatic zinc reagents under standard conditions (Scheme 4.23).



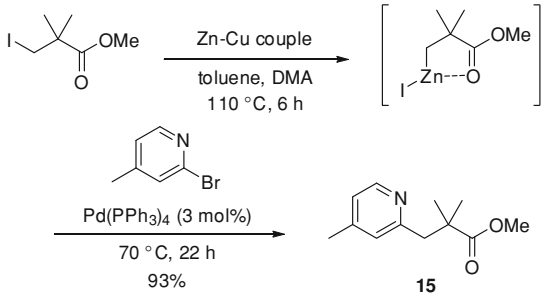
Scheme 4.23 A synthetic route to antiarrhythmic agents (Bristol–Myers Squibb)

In addition, sodium channel blockers **14** (Merck) were synthesized from the corresponding primary amide and zinc reagents in 94–97 % yield (Scheme 4.24).



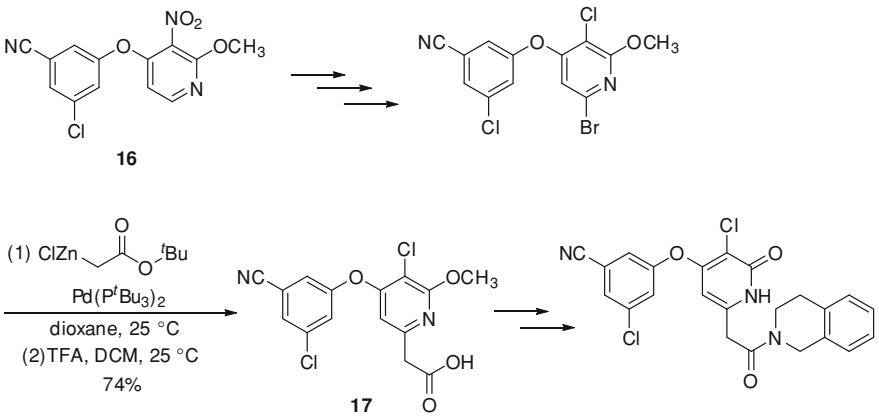
Scheme 4.24 A synthetic route to sodium channel blockers **14**

Kwak has developed an efficient and convenient Negishi coupling protocol for the preparation of 3-aryl-2,2-dimethylpropanoates **15**, providing easy access to key pharmaceutical intermediates that would otherwise require multi-step syntheses using conventional enolate chemistry (Scheme 4.25) [53].



Scheme 4.25 A synthetic route to 3-aryl-2,2-dimethylpropanoates **15**

Kennedy-Smith and Sweeney have reported the synthesis of non-nucleoside reverse transcriptase inhibitors (NNRTIs), which are important components of antiretroviral therapy for the treatment of HIV infection [54]. A pyridone compound, which was found to strongly inhibit the polymerase activity of wild-type HIV reverse transcriptase, was successfully synthesized from compound **16** (Scheme 4.26). Negishi coupling was involved as one of the key steps to install the acetic acid functionality, giving rise to intermediate **17**.

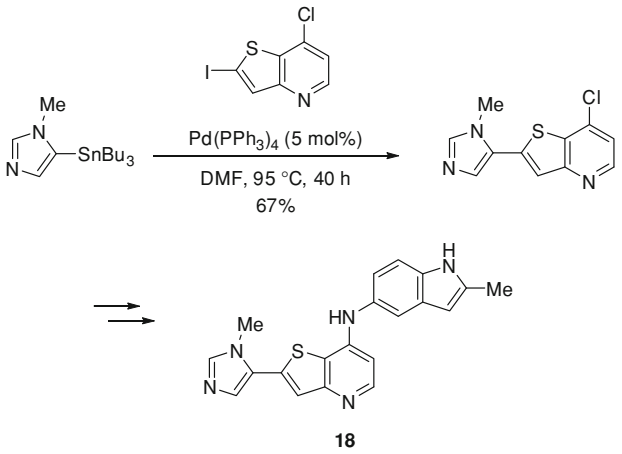


Scheme 4.26 A synthetic route to an HIV reverse transcriptase

4.4 Migita-Kosugi-Stille Coupling

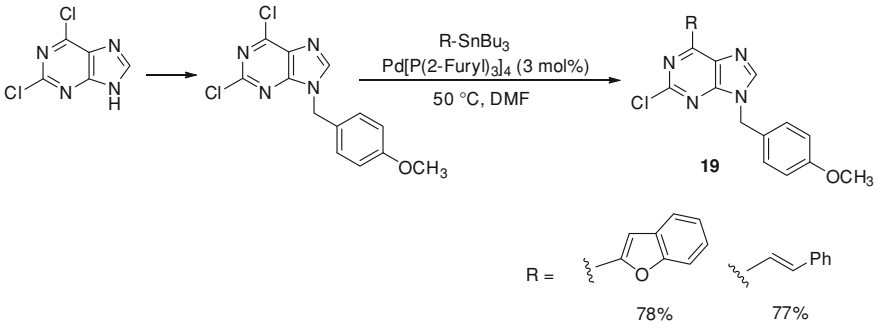
The Migita-Kosugi-Stille Coupling has not been widely used in the large-scale manufacturing of pharmaceuticals. This is mainly due to the toxicity of the organotin reagents and the difficulty of purging tin-containing by-products from drug intermediates and active pharmaceutical ingredients. Despite these issues, many organotin reagents used for Migita-Kosugi-Stille Coupling are widely available, stable to air and moisture, and compatible with a variety of functional groups.

Ragan has incorporated the Migita-Kosugi-Stille Coupling of imidazolylstannane and iodothienopyridine into the synthesis of a VEGFR kinase inhibitor **18**, a compound with promising antitumor activity (Scheme 4.27) [55]. An exhaustive survey of coupling reactions revealed this Migita–Kosugi–Stille approach to be the only robust and scalable method for the coupling of the imidazole and thienopyridine rings.



Scheme 4.27 A synthetic route to a VEGFR kinase inhibitor **18**

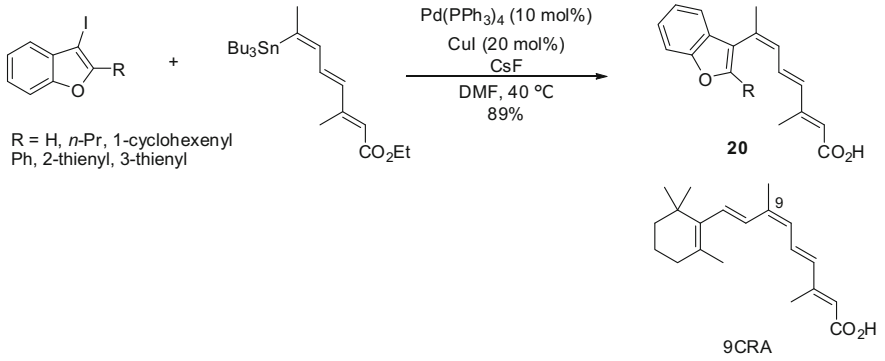
Gundersen has reported the synthesis of 6-benzofuryl- and styrylpurines **19**, in which Migita-Kosugi-Stille coupling was involved as a synthetic strategy to achieve the target molecules with regioselectivity (Scheme 4.28) [56]. Several of these compounds displayed profound antimycobacterial activity with low toxicity toward mammalian cells.



Scheme 4.28 Synthesis of 6-benzofuryl- and styrylpurines **19**

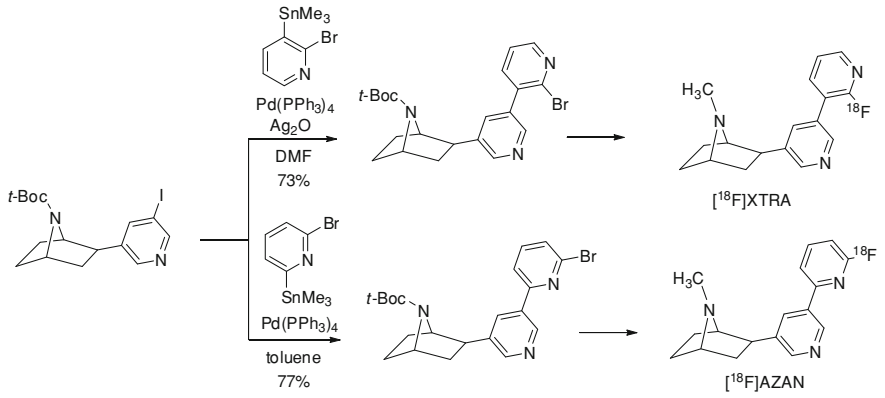
Wada developed cesium-fluoride-promoted Migita-Kosugi-Stille Coupling reactions of vinyl triflates with an alkenylstannane bearing an electron-withdrawing group. These methodologies were then adopted for the preparation of the 9Z-retinoic acid (9CRA) analogs (known metabolites of vitamin A and ligands of the retinoid X receptor) having a 2-substituted benzo[b]furan [57]. Treatment of 2-substituted 3-iodobenzofurans (derived from 2-alkynyl-1-(1-ethoxyethoxy)benzenes) with the alkenylstannane in the presence of cesium fluoride, copper iodide,

and with $Pd(PPh_3)_4$ as the catalyst, afforded the coupled products **20** in good yield without isomerization of the double bonds (Scheme 4.29).



Scheme 4.29 Synthesis of the 9Z-retinoic acid (9CRA) analogs **20**

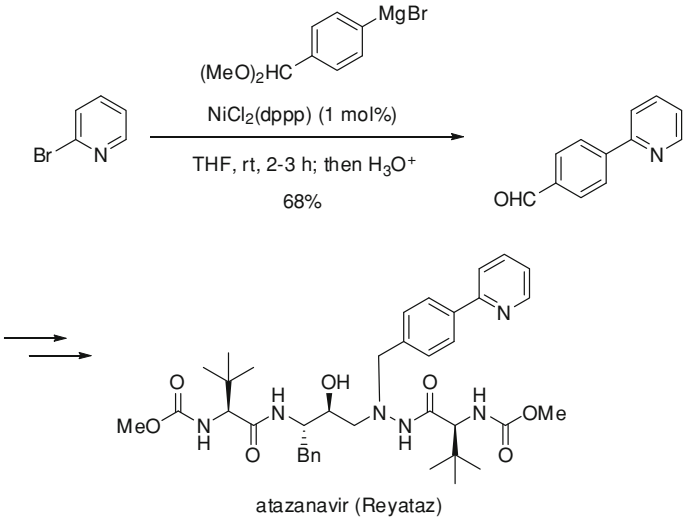
Gao has recently described an improved synthesis of precursors for the positron emission tomography (PET) radioligands [^{18}F]XTRA and [^{18}F]AZAN, involving a key Migita-Kosugi-Stille Coupling step, followed by deprotection of a Boc group and *N*-methylation sequences (Scheme 4.30) [58].



Scheme 4.30 Synthesis of precursors for [^{18}F]XTRA and [^{18}F]AZAN

4.5 Kumada-Tamao-Corriu Coupling

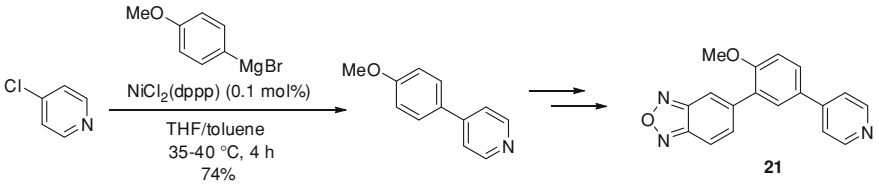
Because of the high reactivity of Grignard reagents relative to other organometallic species, the scope of Kumada-Tamao-Corriu Coupling for the large-scale synthesis of pharmaceuticals has been limited. Long has reported the coupling reaction of 2-bromopyridine and arylmagnesium bromide to prepare a biaryl



Scheme 4.31 A synthetic route to the HIV protease inhibitor atazanavir (Reyataz®)

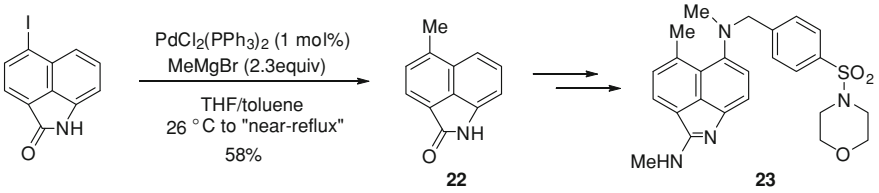
compound, an intermediate in the synthetic route to the HIV protease inhibitor atazanavir (Reyataz®), as shown in Scheme 4.31 [59].

Manley has employed Kumada-Tamao-Corriu Coupling of 4-chloropyridine and arylmagnesium bromide to prepare a biaryl compound, followed by further reactions to prepare compound **21**, an inhibitor of the phosphodiesterase-4D isoenzyme that could potentially be used in the treatment of asthma (Scheme 4.32) [60].



Scheme 4.32 A synthetic route to an inhibitor **21** of the phosphodiesterase 4D isoenzyme

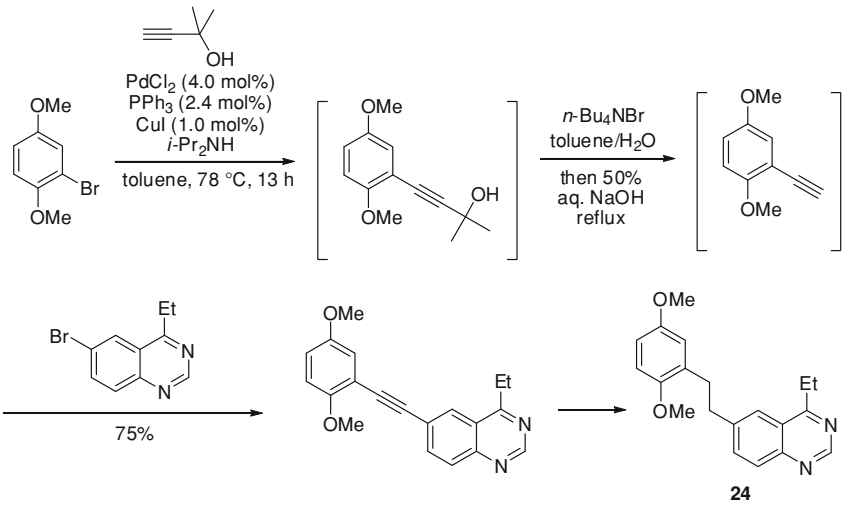
Marzoni and Varney applied the methylation of an aryl iodide under Kumada-Tamao-Corriu Coupling conditions for their improved synthesis of compound **22**. This is an intermediate to a thymidylate synthase inhibitor **23** which has potential for the treatment of cancer (Scheme 4.33) [61].



Scheme 4.33 Synthesis of an intermediate to a thymidylate synthase inhibitor **22**

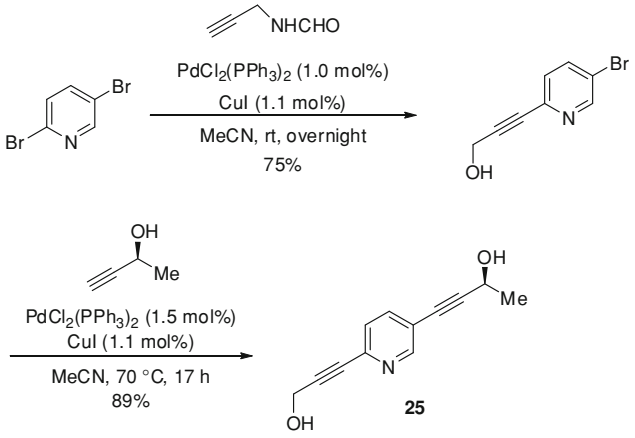
4.6 Sonogashira–Hagihara Coupling

Prasad has developed an elegant process for the one-pot coupling of an aryl bromide and a heteroaryl bromide via stepwise Sonogashira-Hagihara reactions with an acetylene linker masked as 2-methyl-3-butyn-2-ol for the synthesis of an antimitotic agent **24** (Scheme 4.34) [62].



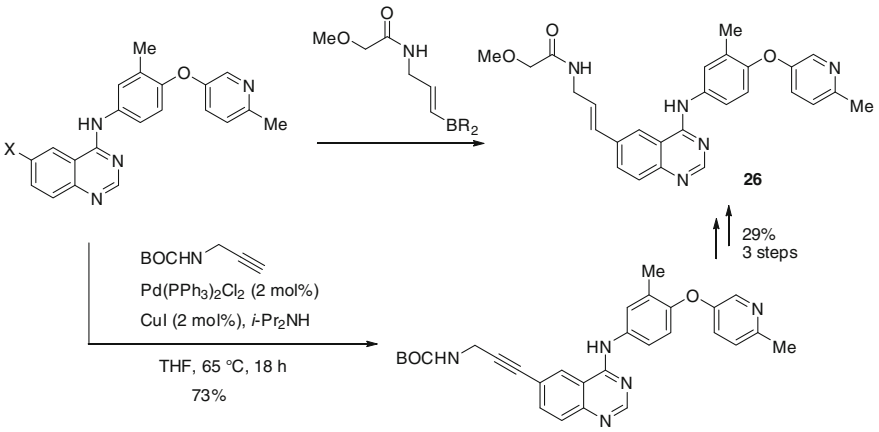
Scheme 4.34 A synthetic route to an antimitotic agent **24**

Hartner developed a series of Sonogashira–Hagihara coupling reactions, in which various alkynes were coupled with 2,5-dibromopyridine at both bromo positions, for the preparation of key intermediates to $\alpha_V\beta_3$ antagonists **25** (Scheme 4.35) [63]. These are potential agents for the treatment for osteoporosis.



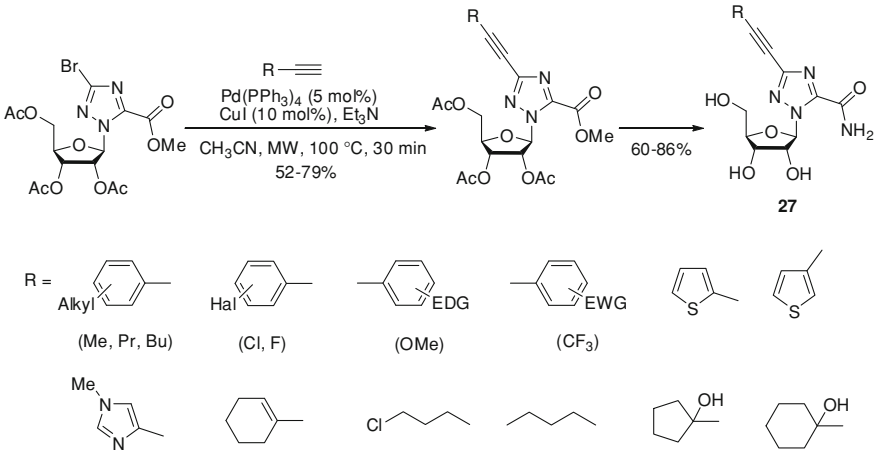
Scheme 4.35 A synthetic route to $\alpha V\beta_3$ antagonists 25

Ripin has described the synthesis of the anti-cancer agent (CP-724, 714) **26** on a multi-kilogram-scale using several different synthetic routes (Scheme 4.36) [64]. Applications of the Sonogashira–Hagihara and Mizoroki–Heck couplings to this synthesis have been investigated, seeking a safe, environmentally benign, and robust process for the production of this drug candidate.



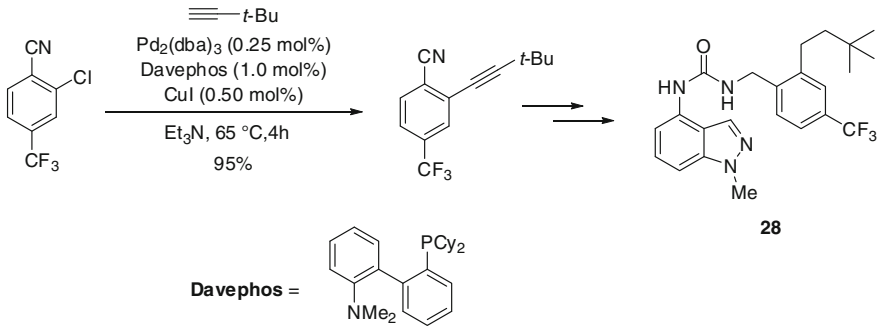
Scheme 4.36 Synthesis of the anti-cancer agent (CP-724,714) **26**

Peng has developed the synthesis of a series of 3-arylethynyltriazolyl ribonucleosides **27** via a microwave-assisted Sonogashira–Hagihara coupling reaction (Scheme 4.37); these products show promise vis-à-vis anti-cancer activity on the drug-resistant pancreatic cancer cell line MiaPaCa-2. The Sonogashira–Hagihara coupling reactions between the 3-bromo-triazole nucleoside and various alkynes were followed by ammonolysis to give the deprotected nucleosides **27** [65].



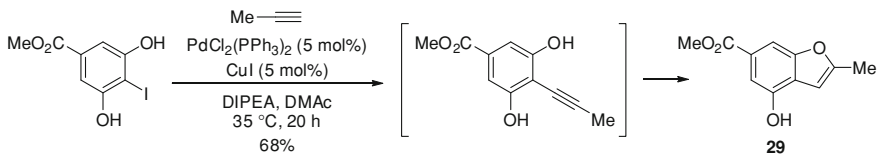
Scheme 4.37 Synthesis of a series of 3-arylethynyltriazolyl ribonucleosides **27**

Yu and coworkers commenced a synthetic route to the TRPV1 receptor antagonist **28** with Sonogashira–Hagihara coupling of an aryl chloride and *tert*-butylacetylene (Scheme 4.38) [66]. In general, aryl chlorides exhibit poor reactivity in the Pd-catalyzed Sonogashira–Hagihara coupling reactions (See Chap. 7); however, an aryl chloride activated by the electron-withdrawing trifluoromethyl and nitrile groups smoothly couples with very low catalyst loading, using the sterically hindered and electron-rich DavePhos as the ligand [67].



Scheme 4.38 A synthetic route to the TRPV1 receptor antagonist **28**

Berliner has developed a Sonogashira–Hagihara reaction of propyne gas and iodoresorcinol for the synthesis of 4-hydroxy-2-methylbenzofuran **29**, a core intermediate to several compounds of pharmaceutical interest (Scheme 4.39) [68].



Scheme 4.39 Synthesis of 4-hydroxy-2-methylbenzofuran **29**;

4.7 Summary

Palladium-catalyzed cross-coupling is clearly a powerful tool to synthesize pharmaceuticals not only for academic research but also for industrial applications. This chapter has demonstrated the versatility of these reactions. In the design and synthesis of biologically active molecules, serious consideration must be given to important factors such as: reactivity of functional groups, stereo- and regioselectivity, toxicity of potential residual contaminants, and efficiency of yield. These are all aspects in which the aforementioned cross-coupling models provide

exceptional and innovative opportunities for the modern process chemist. In addition, considering the myriad of advancements seen in the past decade, many new discoveries should soon offer even more practical and reliable methods of cross-coupling for the large-scale manufacturing of pharmaceuticals.

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Chapter 5
Liquid Crystals

Ning-Hui Chang, Megumi Kinoshita and Yasushi Nishihara

Abstract Liquid crystalline molecules are extensively used for technological applications such as liquid crystal displays, and there is a great deal of research underway in various fields exploring other uses. The carbon–carbon bond-forming cross-coupling reactions can provide innovative synthetic methods for new liquid crystalline molecules with novel physical properties. Moreover, the organic molecules synthesized with the cross-coupling reactions may be used in new areas such as organic electroluminescence (EL) and thin film transistors (TFT).

Keywords Liquid crystals · Nematic phases · Smectic phases · Organic devices · Endotherms · Calamitic

5.1 Introduction

In 1888, Reinitzer discovered that cholesteryl benzoate had two melting points: it first melted into a turbid *liquid with crystalline properties*, and then at higher temperatures, it became clear [1]. Since then, a myriad of materials with liquid crystalline properties have been used in a wide variety of applications, including optical devices [2–7]. Research on liquid crystals is diverse, covering several

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scientific fields, such as chemistry, physics, and engineering. In the development of novel organic functional materials, liquid crystals often demonstrate substantial potential [8, 9].

With current technology, liquid crystalline compounds can be widely applied to a uniform and large display and can electrically control optical anisotropy, owing to their characteristic physical properties. Most liquid crystalline compounds used for displays must show the nematic phases. In order to apply the liquid crystals to optoelectronic materials, the temperature range showing the liquid crystal phases should encompass ambient temperatures.

In general, liquid crystals have several common characteristics. They are polarizable molecules having a rigid core unit (rod-like or disc-like) with an extended π-electron system and one or more flexible ends. There are two important types of the most frequently utilized liquid crystalline materials with high dielectric anisotropy: analogs of 4-pentyl-4′-cyanobiphenyl (5CB) and analogs of fluorinated tolane (FT) liquid crystals, shown in Fig. 5.1. These mesogenic rigid biphenyl and diarylethene cores along with polar electron-withdrawing groups (a cyano or a fluoride group) at the edges offer the anisotropy necessary for the composition of the liquid crystal phase, whereas the alkyl chains contribute to a decrease in melting point [10]. Recent developments in this field have included the use of naphthalene and stilbene derivatives, in addition to the traditional phenylene groups, to produce the required motifs to control transition temperatures and solubility which are influenced by the various substituents.

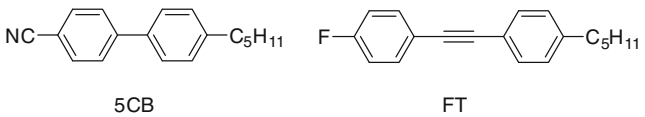


Fig. 5.1 Chemical structure of 5CB and FT

The transition metal-catalyzed cross-coupling reactions in synthetic organic chemistry can construct sp^2-sp^2 or sp^2-sp carbon–carbon bonds for a variety of reactions in which two organic fragments are coupled with the aid of a catalyst. Because of the tremendous importance of the motifs of unsymmetrical biphenyls and diarylethenes, a series of catalytic reactions for synthesizing these types of molecules from two coupling partners in the cross-coupling reactions has been developed over the last three decades.

In sharp contrast to the rod-shaped (calamitic) liquid crystalline molecules, discotic liquid crystalline molecules consist of a tabular frame as the rigid molecular core, which is surrounded by long, flexible alkyl or alkoxy chains (Fig. 5.2). The planarity, symmetry, and attractive interactions in the direction perpendicular to the plane of the molecules are essential properties for a liquid crystalline molecule.

The discotic liquid crystals have been shown to have a high mobility of charge because of the strong intermolecular interaction of the π-electrons. The discotic liquid crystals are able to improve display fineness by using their polymers as a film for the liquid crystal displays. Recently, discotic nematic liquid crystals have received significant attention because they can improve the viewing angle and the contrast ratio of the twisted nematic (TN) liquid crystal displays [11, 12].

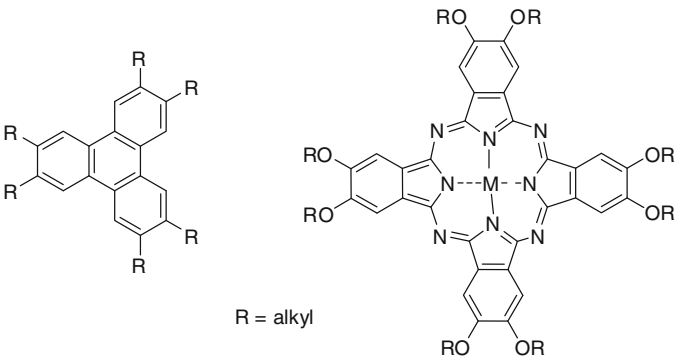
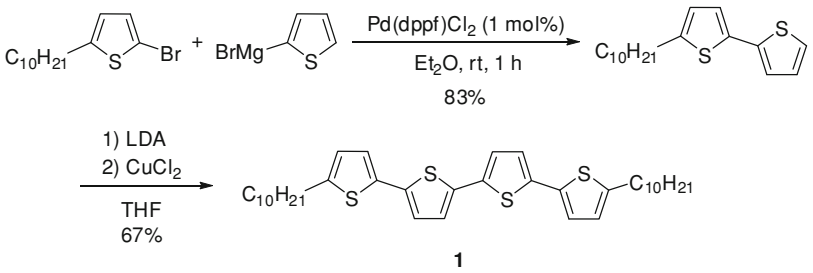


Fig. 5.2 Representative examples of discotic liquid crystals

Recent research clarified that the high conductivity of liquid crystalline materials is caused by electrons and holes, with characteristics applicable to organic semiconductors [13]. Therefore, the liquid crystal materials can be expected to be applied to electronic devices such as organic EL and TFT. Since a variety of liquid crystals are presently utilized in an assortment of organic functional materials, the development of practicable synthetic methods is highly desirable. In this chapter, a brief introduction of the applied cross-coupling reactions in the field of liquid crystals will be provided.

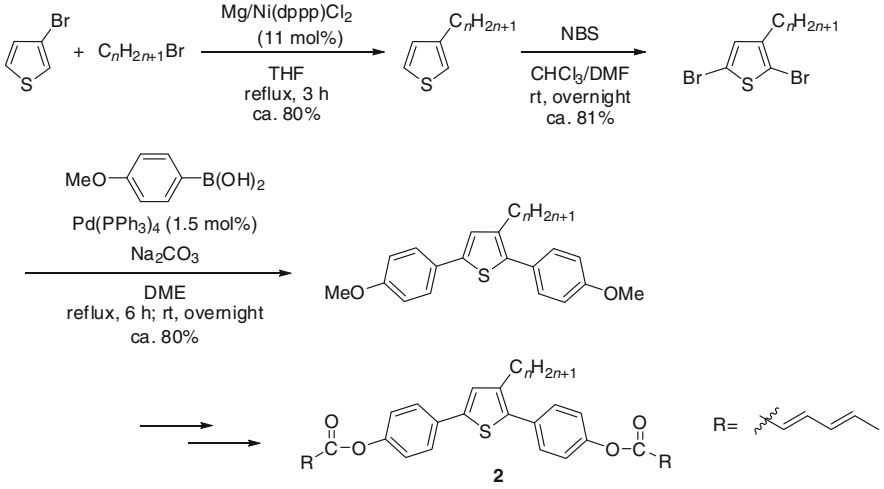
5.2 Kumada-Tamao-Corriu Coupling

Kumada-Tamao-Corriu coupling is a longstanding methodology for the synthesis of oligothiophenes **1** that do not bear electrophilic functional groups, as shown in Scheme 5.1 [14]. Because the obtained products show smectic liquid crystal phases in the range of 98–168 °C, these compounds could be expected to be useful in field-effect transistors (FETs).



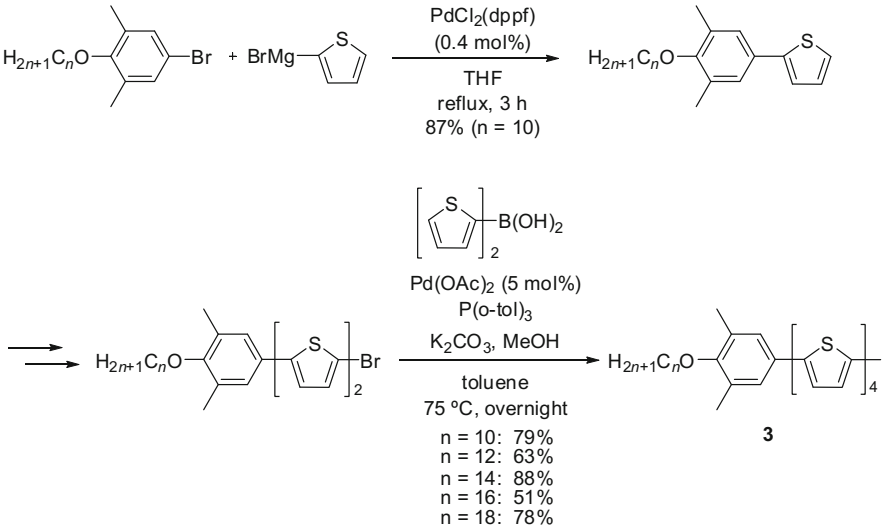
Scheme 5.1 Synthesis of oligothiophenes **1** by Kumada-Tamao-Corriu coupling

Cheng has synthesized 2,5-diarylated thiophene derivatives with liquid crystalline properties by using a combination of Kumada-Tamao-Corriu and Suzuki–Miyaura couplings (Scheme 5.2) [15]. The synthesized compounds **2** showed nematic phases below 71 ($n = 6$) and 60 °C ($n = 12$); however, the liquid crystal phase was not apparent in the case of $n = 16$. It is suspected that the obtained compounds form monotropic liquid crystals as a result of their bent structures.



Scheme 5.2 Synthesized 2,5-diarylated thiophene derivatives

Recently, Tao et al. have reported the synthesis of liquid crystalline compounds **3** with oligothiophene backbones also through the combination of Kumada-Tamao-Corriu and Suzuki–Miyaura cross-coupling reactions (Scheme 5.3) [16]. These oligothiophenes were found to behave as enantiotropic liquid crystals and have the smectic E and nematic phases. In particular, the compound ($n = 10$) was confirmed to have characteristics of a typical *p*-type organic semiconductor.

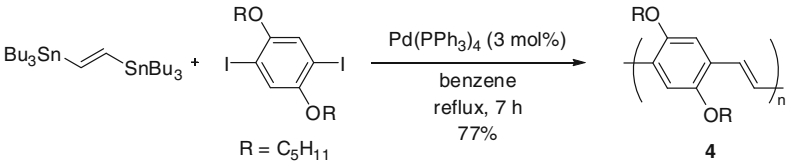


Scheme 5.3 Synthesis of liquid crystalline compounds **3**

Herein, the Kumada-Tamao-Corriu coupling synthetic protocols of liquid crystals with a thiophene ring in the polymer main chains have been introduced. However, the number of these synthetic examples for liquid crystalline compounds is relatively small because Kumada-Tamao-Corriu coupling lacks functional group tolerance.

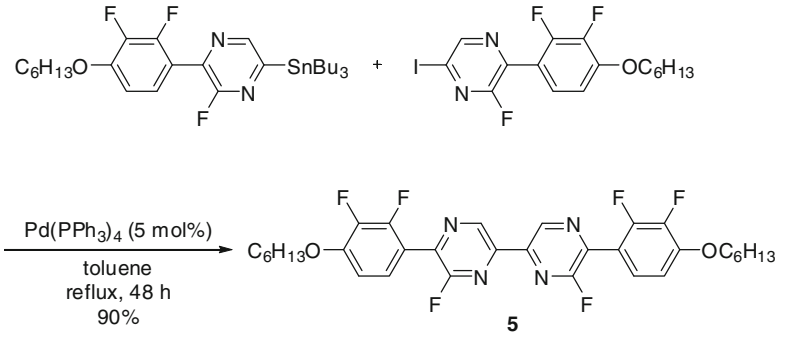
5.3 Migita-Kosugi-Stille Coupling

Naso has synthesized the liquid crystalline conductive polymers **4** with the bifunctional Migita-Kosugi-Stille coupling reactions of bis(tributylstannyl)ethene and diiodoarenes (Eq. 5.1) [17]. It was also clarified that these polymers showed the smectic phases in the temperature range of 110–210 °C.



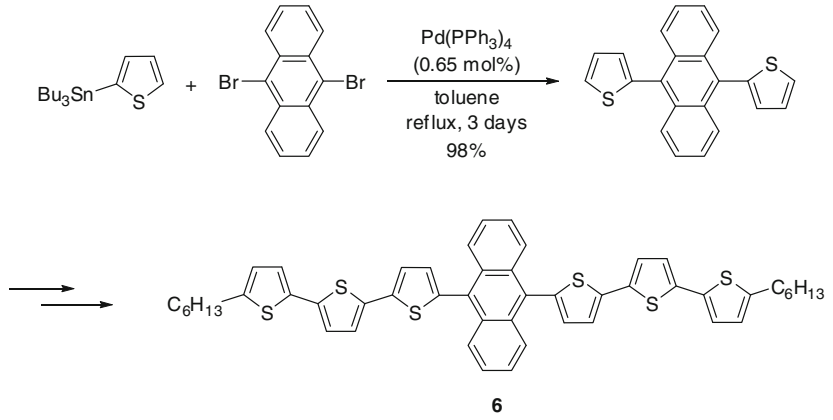
(5.1)

Fluoropyrazines were subjected to Migita-Kosugi-Stille coupling to synthesize a cylinder-shaped liquid crystal **5** (Eq. 5.2) [18]. This compound showed the smectic C phases at 145–164 °C and the nematic phases at 164–196 °C, respectively.



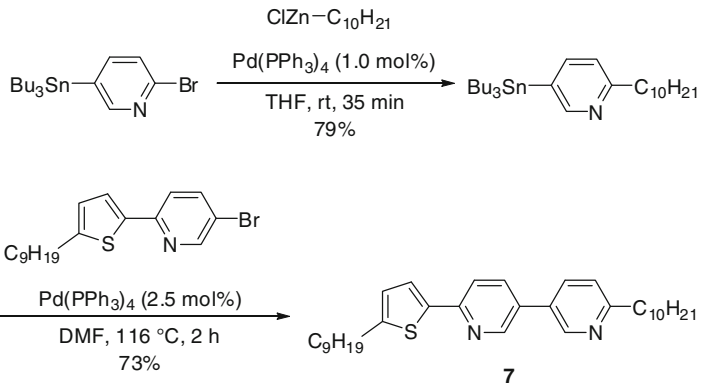
(5.2)

Yoon has reported that the hexyl end-capped bis-terthienylanthracene oligomer **6**, with an anthracene core, showed a higher thermal stability compared to the corresponding oligothiophenes (Scheme 5.4) [19]. Oligomer **6** showed a liquid crystalline mesophase at 166 °C in the heating process. The thermal analyses as well as the electrochemical measurement indicated that these designed materials showed better thermal and oxidation stability than the corresponding oligothiophenes without the anthracene core.



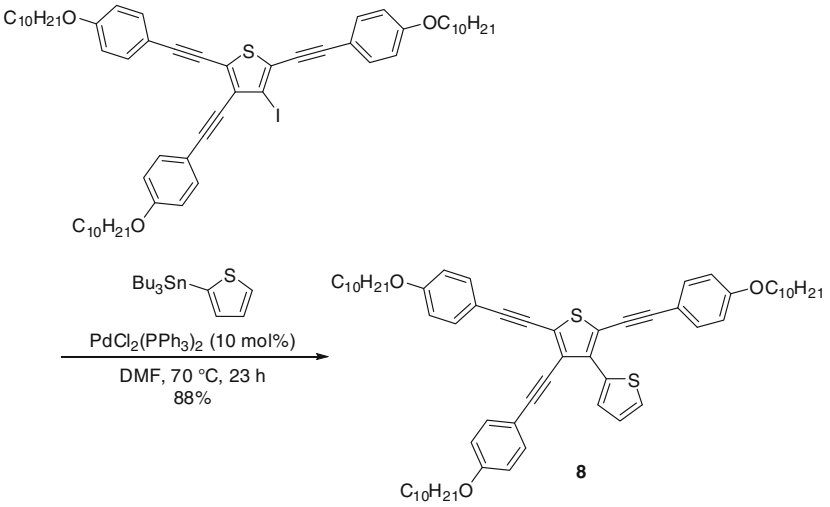
Scheme 5.4 Synthesis of oligomer **6** with an anthracene core

The liquid crystalline molecule **7**, having the 3,3′-bipyridine skeleton shown in Scheme 5.5, has been synthesized via successive Negishi and Migita-Kosugi-Stille couplings [20]. This reaction was the first successful example for synthesizing a new type of liquid crystal bearing both thiophene and pyridine rings, simultaneously. Negishi coupling was performed on a substrate having the tin-containing functional group on the pyridine ring.



Scheme 5.5 Synthesis of liquid crystalline compound **7**

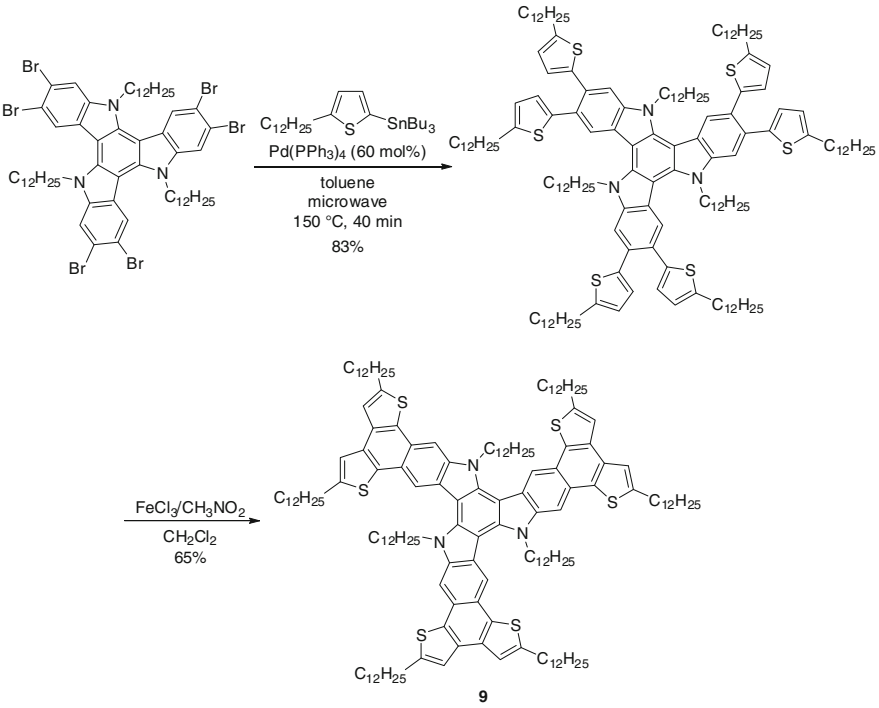
Next, some examples for the synthesis of discotic liquid crystals by Migita-Kosugi-Stille coupling are described. Hsu has synthesized the centered thiophene core substituted by several alkynyl groups (Eq. 5.3) [21]. The obtained compound **8** exhibited a monotropic nematic liquid crystalline phase. The mesomorphic properties of **8** indicate that molecular dipole, molecular shape, and molecular symmetry, are all important factors. Manipulations of the dipoles as well as the overall molecular shapes (with a variety of substituents) have provided a better understanding of the structure–property correlations.



(5.3)

In 2009 a new type of discotic liquid crystal was synthesized by the introduction of thiophene units via Migita-Kosugi-Stille coupling and subsequent oxidative coupling to form triazatruxene **9**, as shown in Scheme 5.6 [22]. The

synthesized compound **9** showed the enantiotropic liquid crystalline phase at room temperature and a single mesophase structure over a wide temperature range (including room temperature). Owing to this stability and the facile synthesis, the application of these derivatives to electronic devices is expected.

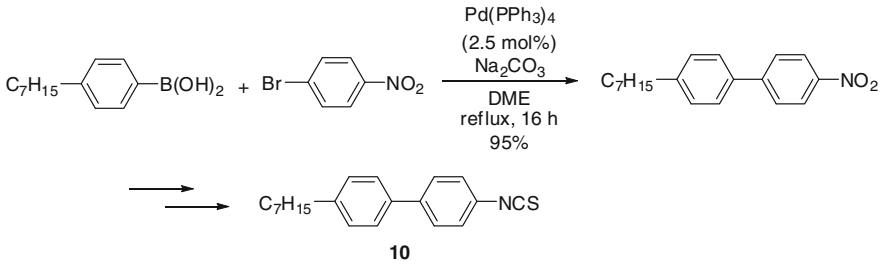


Scheme 5.6 Synthesis of liquid crystalline triazatruxene **9**

5.4 Suzuki–Miyaura Coupling

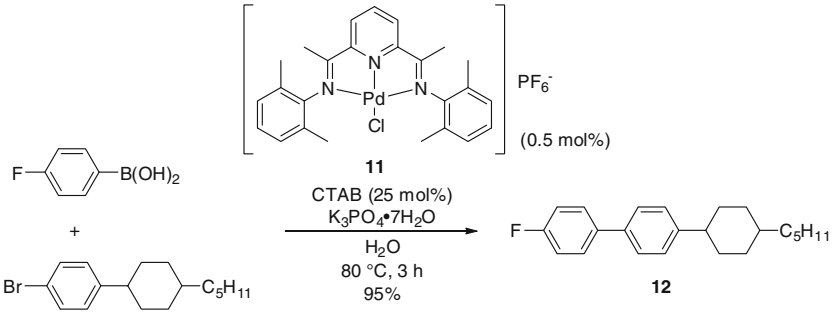
Suzuki–Miyaura coupling is the typical method used to synthesize the liquid crystalline molecules with biphenyl core units. Suzuki–Miyaura coupling, followed by functionalization of a nitro group, produces the desired isothiocyanato-substituted product **10** (Scheme 5.7). In conjunction with the biphenyl core, the

introduction of the NCS terminal group would be expected to provide materials of high optical anisotropy. In fact, mesogenic and optical properties of compound **10** have been confirmed [23].



Scheme 5.7 Synthesis of liquid crystalline isothiocyanato-substituted biphenyl **10**

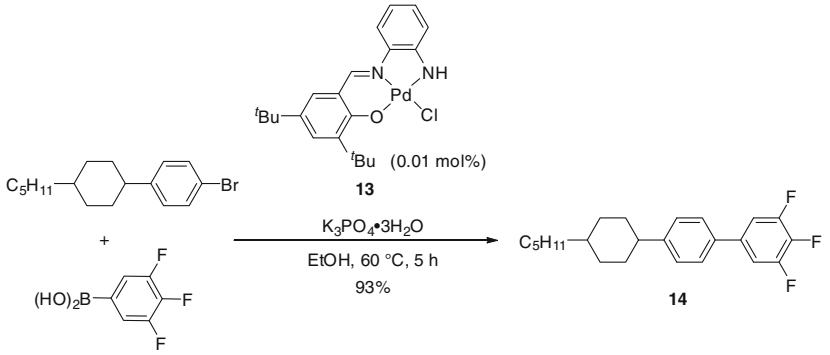
The synthesis of a fluorinated biphenyl bearing a long alkyl chain was successfully achieved using the palladium(II) complex **11** ligated by a tridentate ligand in the presence of surfactants bearing long alkyl chains (Eq. 5.4) [24]. This approach can provide a practical procedure for the synthesis of fluorinated liquid crystals with industrial applications, such as compound **12**.



CTAB = hexadecyltrimethylammonium bromide

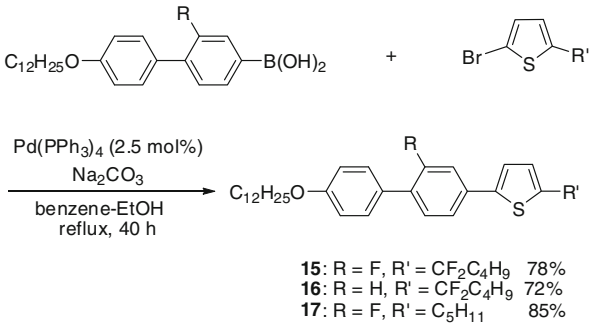
(5.4)

The half-salen palladium(II) complex **13** has proven to be a highly efficient catalyst (if activated) for Suzuki–Miyaura coupling reactions of arylboronic acids with aryl bromides and even aryl chlorides to afford biphenyls (Eq. 5.5) [25]. This method provides a highly efficient synthetic method to prepare biphenyl liquid crystalline compounds such as **14**.



(5.5)

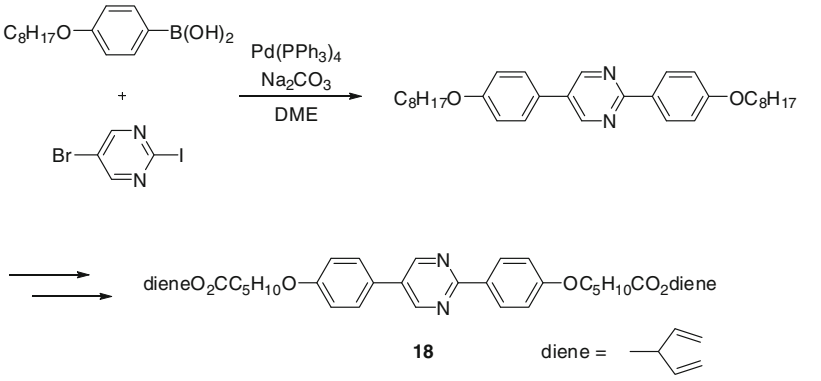
Seed has synthesized liquid crystals containing the 2-biphenylated thiophene rods (Eq. 5.6) [26]. Compounds **15** and **17** bear fluoride substituents on the benzene ring which lowers their melting points compared to the corresponding parent compounds. A high thermal stability in the smectic C and nematic phases was observed in compound **17**. On the other hand, compounds **15** and **16** have difluoroalkyl groups, and they showed high melting points.



(5.6)

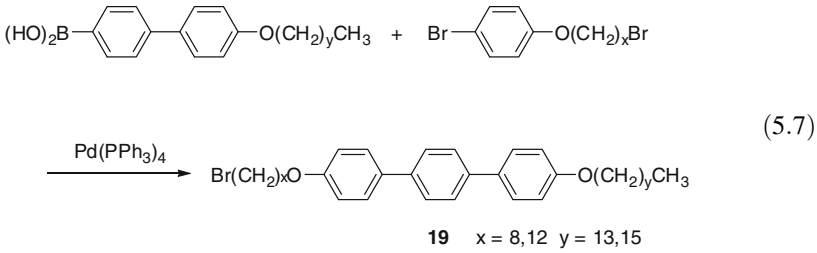
Using Suzuki–Miyaura coupling, Kelly synthesized the pyrimidine-containing liquid crystals substituted by two alkoxylphenyl groups in the 2,5-positions (Scheme 5.8) [27]. Moreover, it was found that the introduction of a diene moiety

into the formed compound **18** enables photochemical polymerization, leading to applications for organic light-emitting diodes (OLEDs) with high electron mobility.



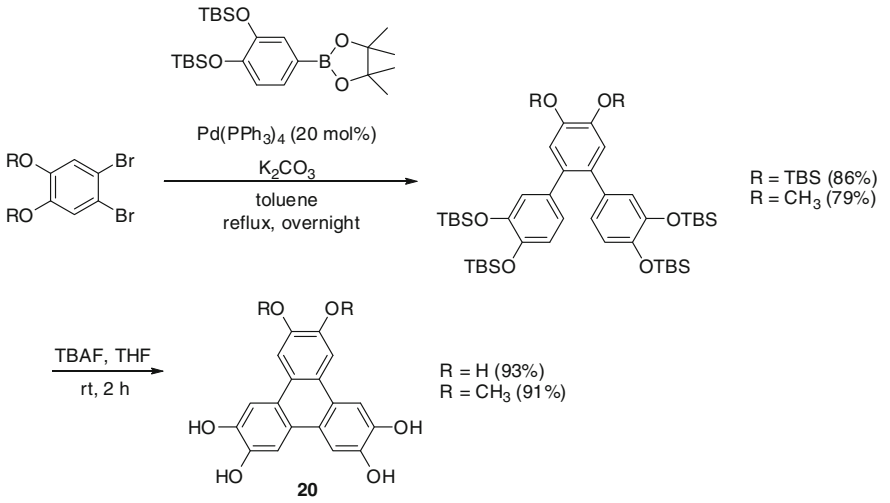
Scheme 5.8 Synthesis of liquid crystalline compound **18**

Terphenyls **19** have been synthesized via Suzuki–Miyaura coupling reactions using aryl bromides with a bromoalkoxy groups in the 4-position of the benzene ring. (Eq. 5.7) [28]. These compounds are found to be thermotropic liquid crystals, and show the smectic phases in the range of 110–180 °C.



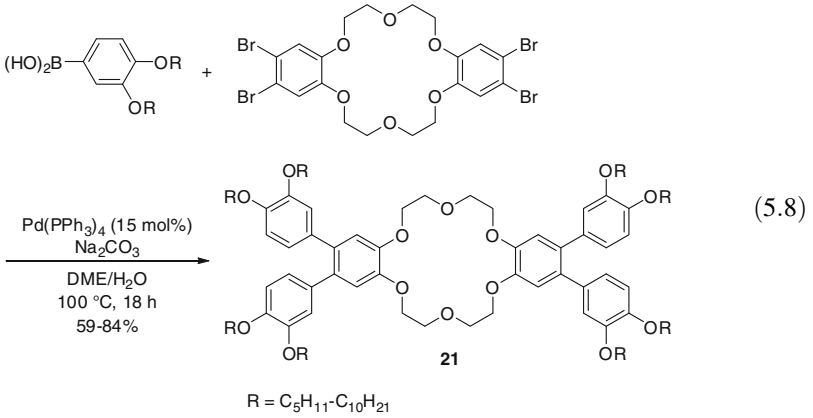
(5.7)

Suzuki–Miyaura coupling has also been utilized for the synthesis of discotic liquid crystals. The triphenylenes **20** offer a broad scope of investigation into unsymmetrically-substituted systems because of their inherent liquid crystalline character (Scheme 5.9) [29].



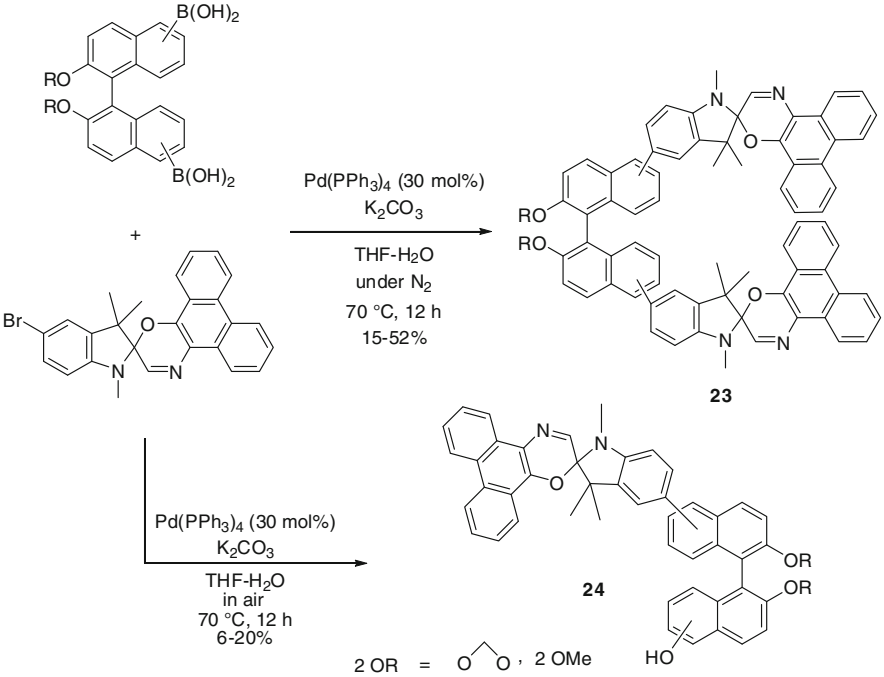
Scheme 5.9 Synthesis of liquid crystalline triphenylenes **20**

The synthesis of columnar liquid crystals with a central crown ether unit has been reported (Eq. 5.8) [30]. In compounds **21** with alkyl chain lengths of C5 to C8, monotropic nature was observed; the liquid crystalline phases were observed only during rising temperatures, whereas liquid crystalline phases were observed in both directions in the case of compounds with C9 and C10 alkyl chains. Interestingly, when a potassium ion was captured by the crown ether core, the stability of the complex was improved and the phase transition temperatures of the original compounds were changed, and there was an elevation of the clearing point.



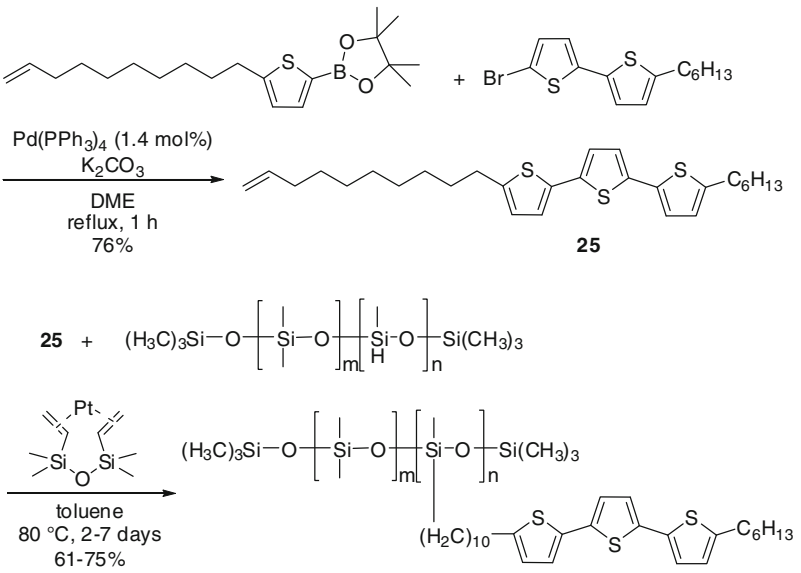
(5.8)

Suzuki–Miyaura couplings of diboronic acid with brominated spirooxazine under a nitrogen atmosphere and under aerobic conditions, gave the dispirooxazine-substituted binaphthyl product **23** and the monospirooxazine-substituted binaphthyl derivative **24**, respectively (Scheme 5.10) [31]. These chiral spirooxazines were found to impart their chirality to an achiral liquid crystal host at low doping levels, to form a self-organized photoresponsive helical superstructure.



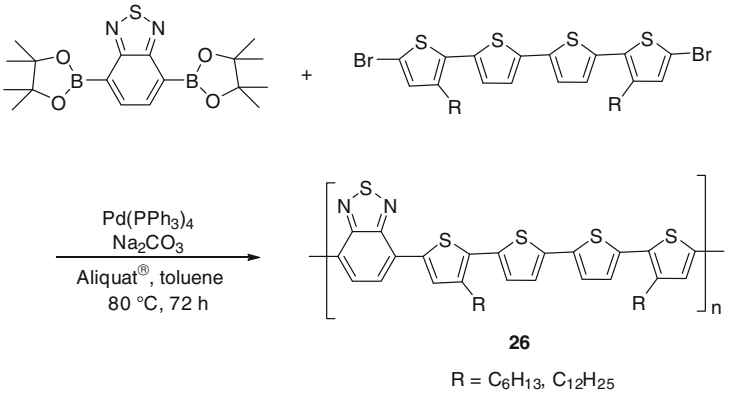
Scheme 5.10 Synthesis of the dispirooxazine-substituted binaphthyl product **23** and the monospirooxazine-substituted binaphthyl derivative **24**

The liquid crystalline terthiophene **25** has been synthesized and used in mesogenic pendant groups (Scheme 5.11) [32]. This terthiophene moiety was introduced in the side chain of siloxane polymers at the terminal olefinic part by the platinum-catalyzed hydrosilation.



Scheme 5.11 Synthesis of liquid crystalline terthiophene **25**

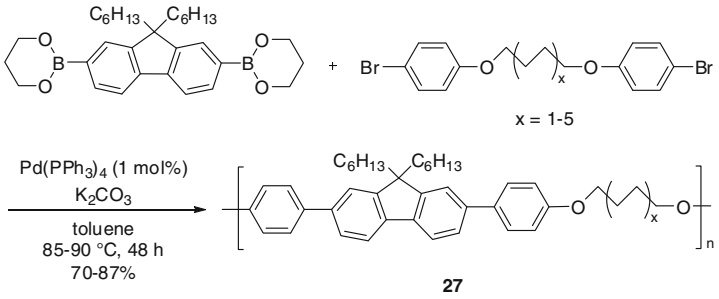
Lee has developed a new strategy for improving the device performances of polymer photovoltaic cells by using Suzuki–Miyaura coupling with bifunctional boronic acids and aromatic bromides, as shown in Eq. 5.9 [33]. These polymers **26** showed liquid crystalline characteristics with two endotherms, at 62 and 230 °C. The various examples of Suzuki–Miyaura coupling reactions for polymer syntheses are independently described in Chap. 6.



(5.9)

Chen and Liu reported a similar manner of synthesis of the rod–coil type liquid crystalline polymers **27** with fluorene motifs (Eq. 5.10) [34]. The thermal stability of these polymers decreased with an increase in the length of the coil segments. The polymer ($x = 1$) displayed a characteristic strip liquid crystalline texture.

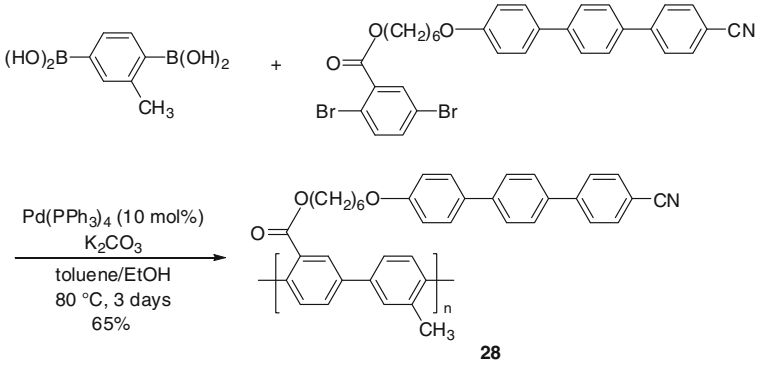
A change in the coil segments remarkably affected the thermal behavior and morphology of these rod–coil polymers.



(5.10)

27

Very recently, synthesis of liquid crystals with optical luminescence was reported through the copolymerization of bifunctional arylboronic acids and bromides (Eq. 5.11) [35]. By incorporating a rigid biphenyl core in the polymer main chains, these polymers **28** showed a high thermal stability and an elevated phase transition temperature (compared with the corresponding homopolymer), and the smectic phases enantiotropically appeared over a wide temperature range.

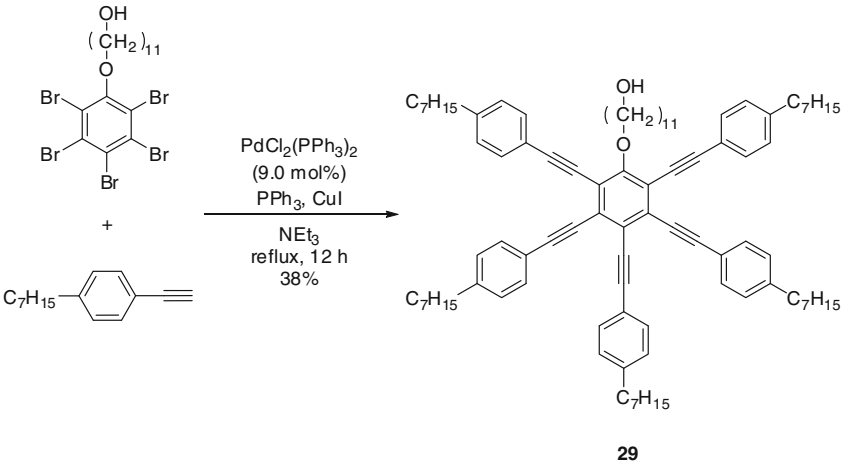


(5.11)

28

5.5 Sonogashira-Hagihara Coupling

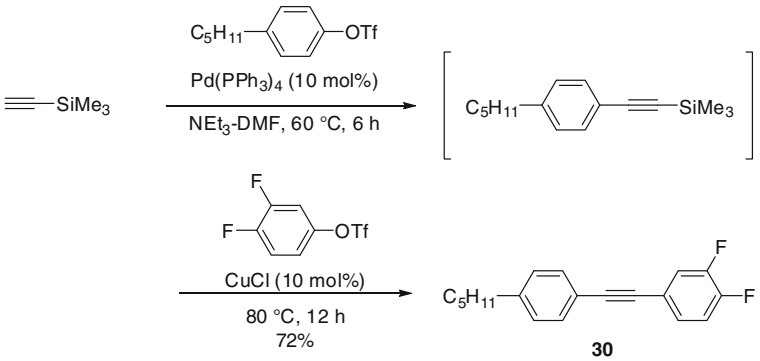
Sonogashira-Hagihara coupling is a very powerful tool for synthesizing compounds with alkynyl moieties via sp^2-sp carbon–carbon bond-forming reactions. Accordingly, the disc-shaped mesogen **29** has been prepared by the palladium-catalyzed Sonogashira-Hagihara coupling of a pentabromophenol derivative and the five-fold appropriate terminal alkynes as outlined in Eq. 5.12 [36].



29

(5.12)

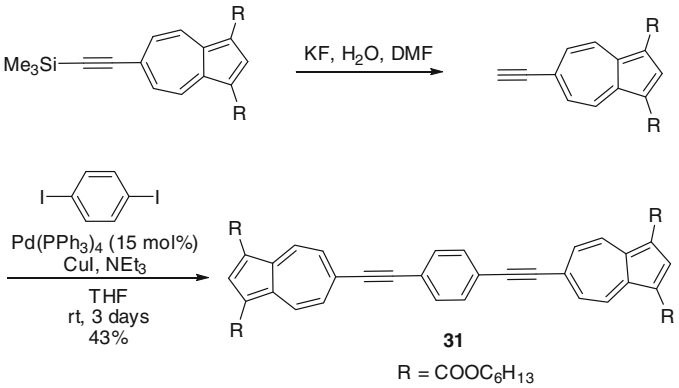
In 2000, the liquid crystalline compound **30**, having an unsymmetrical diarylethene motif, was synthesized through a reaction of the starting (trimethylsilyl)ethyne with two different aryl triflates in one pot (Scheme 5.12) [37]. This unprecedented protocol for the synthesis of unsymmetrical diarylethenes provided a preparative method by the direct activation of the carbon–silicon bond of the in situ-formed alkynylsilane by the addition of copper(I) chloride.



30

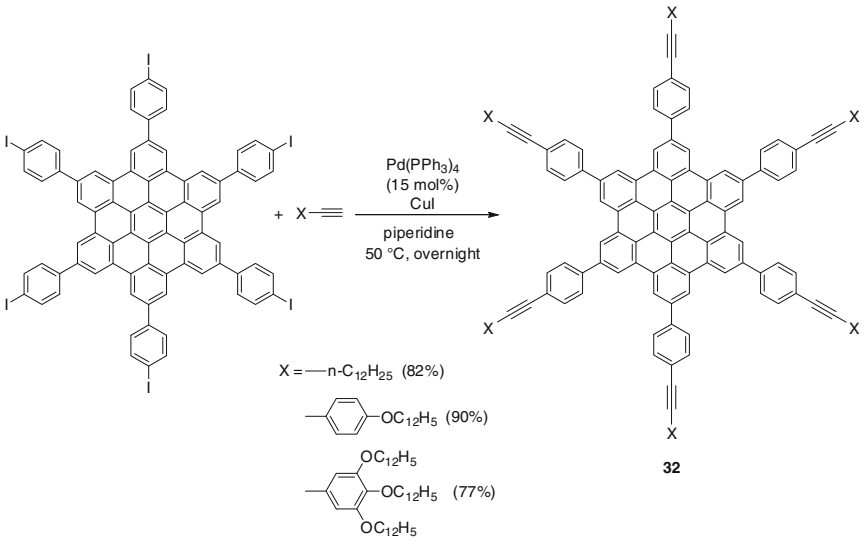
Scheme 5.12 Synthesis of liquid crystalline unsymmetrical diarylethyne **30**

Scheme 5.13 shows the first synthetic example in the chemistry of azulenes of a liquid crystalline compound **31** which exhibits both multiple melting points and columnar mesomorphism [38].



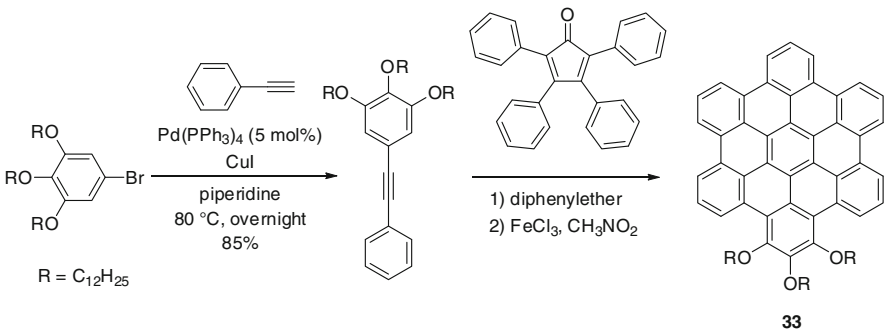
Scheme 5.13 Synthesis of liquid crystalline compound **31**

Wu has reported the multistep synthesis of hexakis(4-iodophenyl)-*peri*-hexabenzocoronene, for use as a novel mesogenic building block. Wu achieved a series of highly ordered columnar liquid crystalline molecules **32**, synthesized via Sonogashira-Hagihara coupling, despite poor solubility in the common organic solvents (Eq. 5.13) [39].



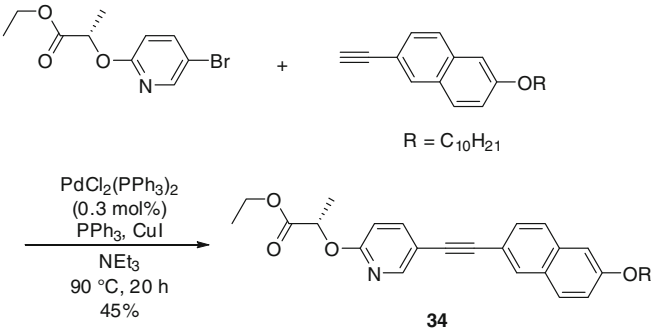
(5.13)

The facile preparation and characterization of the first "unwrapped" hexa-*peri*-hexabenzocoronene derivative **33** is presented in Scheme 5.14. This molecule forms a stable columnar liquid crystal mesophase with a practically accessible isotropization temperature [40].



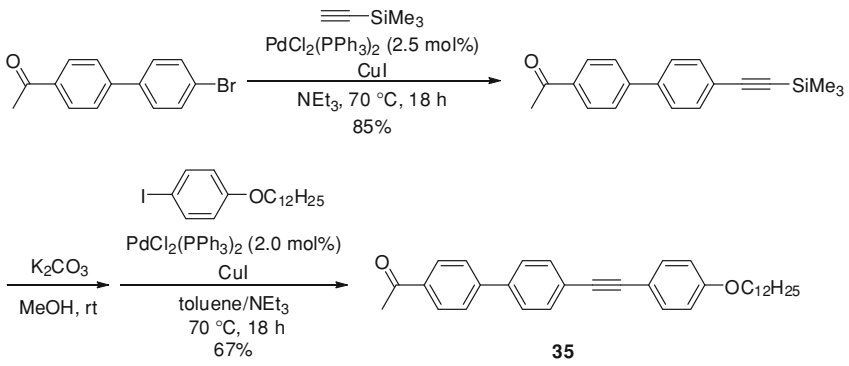
Scheme 5.14 Synthesis of hexa-peri-hexabenzocoronene derivative **33**

In order to explore the potential of the 2,5-pyridine derivatives as liquid crystal templates or dopants for liquid crystal mixtures, Merlo synthesized the chiral compound **34** by Sonogashira-Hagihara coupling (Eq. 5.14) [41]. Compound **34** has a chiral lactate tail; the differential scanning calorimetry (DSC) analysis revealed that this compound is stable under heating. The melting point and enthalpy values were collected from second heating scans. Their values were found to be 32 °C and 5.7 kcal·mol^{-1}, respectively.



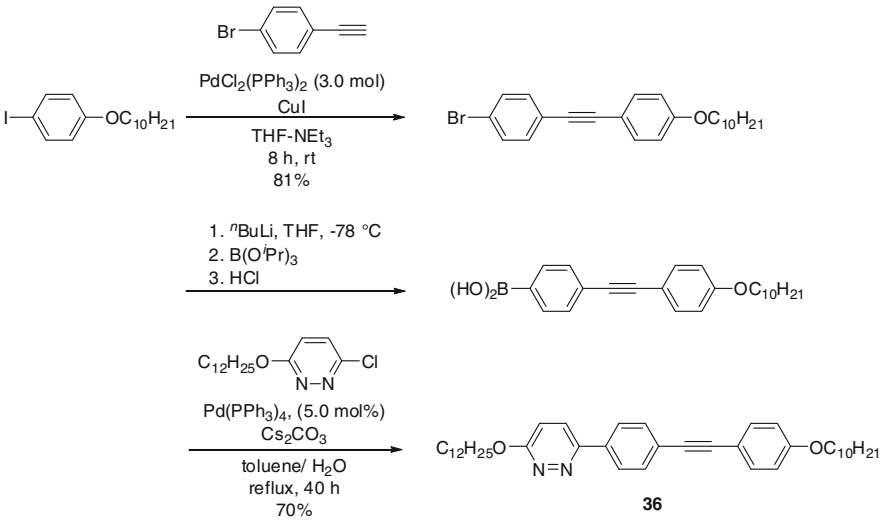
(5.14)

A standard Sonogashira-Hagihara coupling protocol has been applied to the preparation of a phenylacetylene **35**, incorporating terminal biphenyl substituents. Study of the mesomorphic properties of the target compounds revealed that the calamitic diarylethene **35** forms smectic liquid crystals (Scheme 5.15) [42].



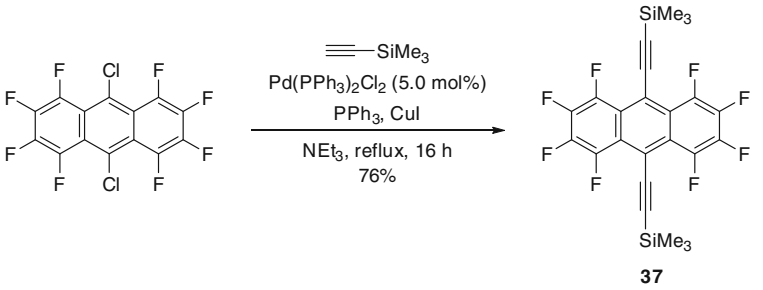
Scheme 5.15 Synthesis of liquid crystalline compound **35**

An unsymmetrical diarylethene with a pyridazine unit has been synthesized via Sonogashira-Hagihara and Suzuki–Miyaura cross-coupling sequences (Scheme 5.16) [43]. This compound **36** presented unique liquid crystal properties when investigated through DSC and polarized light microscopy.



Scheme 5.16 Synthesis of liquid crystalline compound **36**

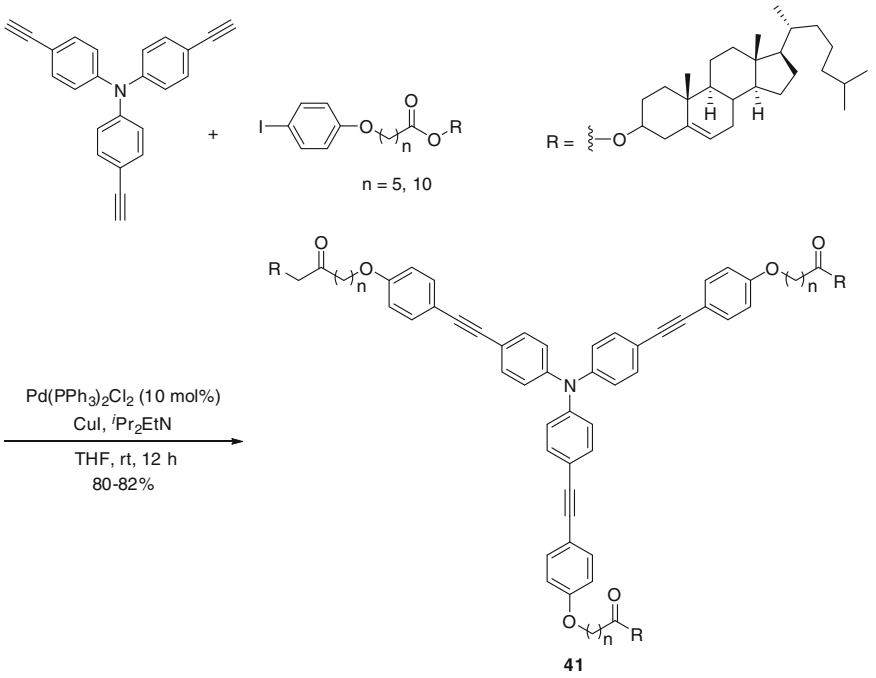
X-ray crystallographic analysis of 9,10-dialkylated anthracene **37** revealed that its solid-state structure mimics columnar liquid crystals with a π-π stacking distance of 3.39 Å between the octafluoroanthracene cores (Eq. 5.15) [44].



(5.15)

37

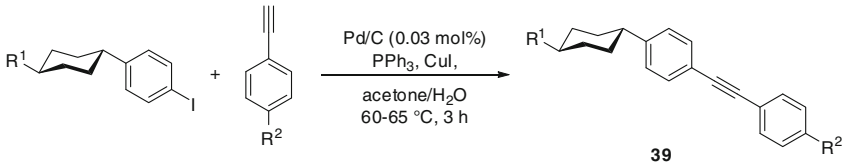
A series of highly π-conjugated unsymmetrical liquid crystals **38**, based on the 3,5-(disubstituted)-1,2,4-oxadiazole core, were successfully synthesized by convergent Sonogashira-Hagihara coupling (Scheme 5.17) [45].



41

Scheme 5.17 Synthesis of liquid crystalline compound **38**

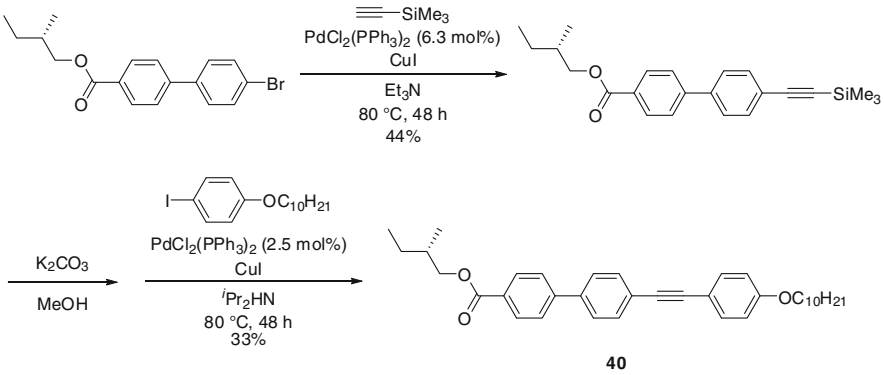
A practical synthesis of liquid crystals **39** based on *trans*-cyclohexyltolans by Sonogashira-Hagihara coupling has been described (Eq. 5.16) [46]. The liquid crystals can be obtained in high yields as a solid with excellent purity by simple filtration. The filtrate can be reused several times, while still retaining a high catalytic activity of the palladium.



R^1 = n-C_5H_{11}, R^2 = OMe, 89%
R^1 = n-C_3H_7, R^2 = Me, 85%

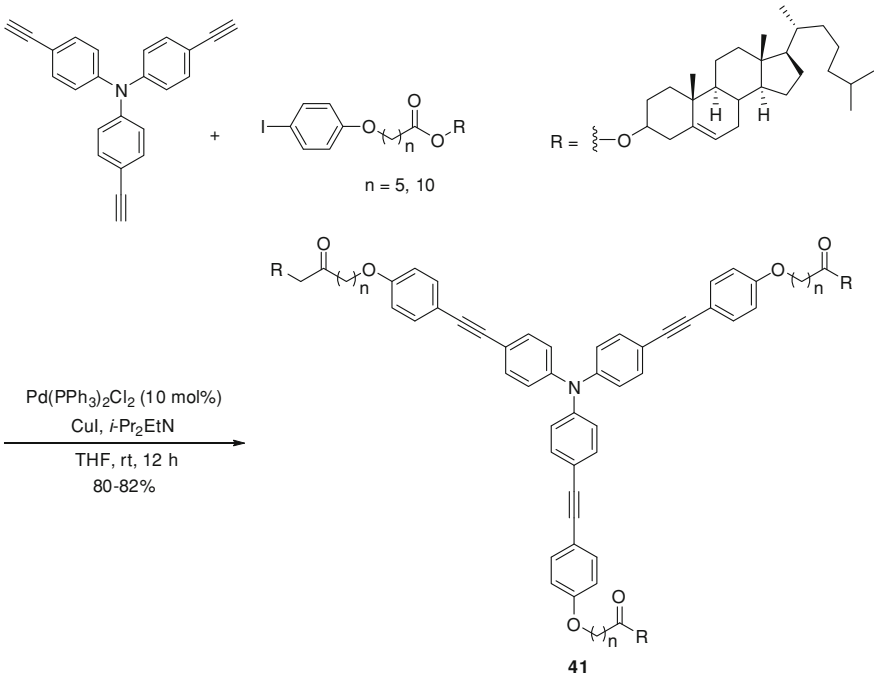
(5.16)

Sonogashira-Hagihara coupling has afforded the rod-like, unsymmetrical tolanes **40**; these were extended biphenyl mesogens substituted with different chiral alkoxy chains. Depending on the position of the chiral center and the polar nature of the target molecules (as determined by the electron-withdrawing end-groups), different types of smectic liquid crystals were obtained (Scheme 5.18) [47].



Scheme 5.18 Synthesis of liquid crystalline compound **40**

Roy has succeeded in designing and synthesizing a new class of disc-like mesogens **41**, containing both cholesteryl and triphenylamine moieties, via Sonogashira-Hagihara coupling as a key step (Eq. 5.17) [48].



(5.17)

5.6 Summary

In this chapter, representative examples for the synthesis of liquid crystals via cross coupling have been introduced. The cross-coupling reactions are presently one of the most widely accepted methods for forming the carbon–carbon bonds in the synthesis of liquid crystals. Liquid crystalline compounds generally consist of a flexible side chain as well as a rigid core; Suzuki–Miyaura and Sonogashira-Hagihara coupling reactions are very useful for the construction of such motifs. In addition, various liquid crystalline compounds have been synthesized using Kumada-Tamao-Corriu and Migita-Kosugi-Stille couplings. Future novel molecules produced through these cross-coupling methods are likely to find applications in innovative technology such as organic LED and TFT.

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Chapter 6
Conjugated Polymers

Daisuke Ogawa and Yasushi Nishihara

Abstract The synthesis of π-conjugated polymers by cross-coupling-based polymerization is a practical method that has been widely employed. The obtained polymers have received considerable attention owing to their interesting properties that have applications as electrochemically conductive materials.

Keywords Conjugated polymers · Cross-coupling polymerization · Photoluminescence · Electroluminescence · Light-emitting diodes (LEDs)

6.1 Introduction

Over the past 30 years, π-conjugated polymers have received much attention because they possess high conductivity and have unique electrochemical qualities [1–5]. The properties of these polymers are influenced by the type of conjugated system, the maximum effective conjugation length, stereoregularity, regioregularity, and the character of substituents in the polymers. In general, optical and electric characteristics of these polymers are remarkably improved by incorporating the heteroaromatic rings in the polymer main chains.

Oxidative polymerization has been widely utilized for synthesizing a variety of π-conjugated polymers involving heteroaromatic rings. For instance, polypyrroles that bear the nitrogen-containing heteroaromatic rings have been obtained by electrochemical oxidative reactions of the corresponding monomers [6]. However,

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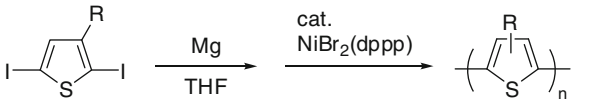
the electrochemical polymerization methods have some drawbacks: the polymerization is adversely affected by the bulkiness of the substituents of the monomers, and thus structurally irregular polymers having cross-linked bonds are generated. To solve these problems, the transition-metal-catalyzed cross-coupling reactions have been applied to the polymer syntheses, and π-conjugated polymers with a variety of structures have been synthesized with regioregularity [7–9].

This chapter introduces recent research topics, focusing on the synthesis of π-conjugated polymers that have aromatic and heteroaromatic rings. Particular attention is given to the use of transition metal catalysts and organometallic reagents in the synthesis of π-conjugated polymers; representative examples are outlined.

6.2 Kumada-Tamao-Corriu Coupling

Kumada-Tamao-Corriu coupling has been used to synthesize π-conjugated polymers for decades. The polythiophenes have been paid particular attention among the conjugated polymers because they show a relatively small bandgap, excellent stability, and easy processability. The pioneering research in synthesizing insoluble polythiophenes by using transition metal catalysts and magnesium reagents was reported by Yamamoto in the 1980s [10–12].

Increasing the solubility of polythiophenes in common organic solvents, Elsenbaumer el al. facilitated the synthesis of the poly(3-alkylthiophene) in 1986 [13]. In this reaction, the alkyl-substituted 2,5-diiodothiophenes in the 3-position were converted to Grignard reagents, and the subsequent Kumada-Tamao-Corriu coupling reactions by the nickel catalyst gave the desired polythiophenes. These polymers become highly soluble in various organic solvents through the introduction of the alkyl group in the 3-position, and they showed high conductibility by doping with additives such as $NOSbF_6$, $FeCl_3$, and I_2. Although this polymerization by Kumada-Tamao-Corriu coupling is highly preparative, regioregularity of the polymers cannot be controlled (Scheme 6.1).

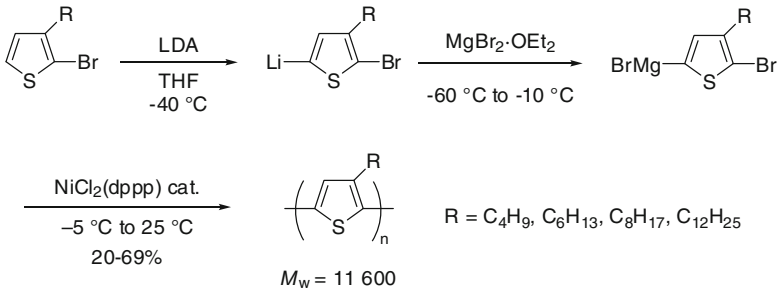


R = C_2H_5, C_4H_9, C_8H_{17} M_n = 3 000-8 000

Scheme 6.1 Synthesis of the regiorandom poly(3-alkylthiophene)

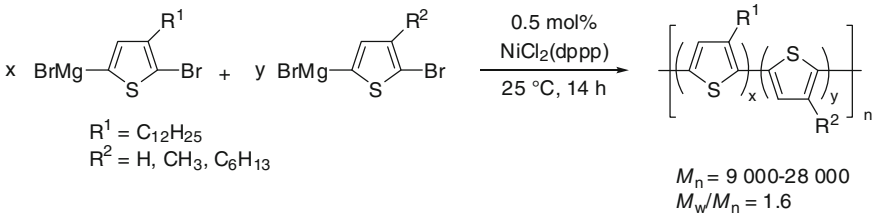
In 1992, McCullough found an innovative synthetic strategy for poly(3-alkylthiophene) with regioregularity [14, 15]. In this protocol, the corresponding organomagnesium reagent was prepared by the selective lithiation at the 5-position of 2-bromo-3-alkylthiophene with lithium diisopropylamide (LDA), followed by

treatment with magnesium bromide. The generated Grignard reagent was subjected to Kumada-Tamao-Corriu coupling by using $NiCl_2$(dppp) as the catalyst to afford the corresponding polythiophenes with more than 90 % regioregularity (Scheme 6.2). This synthetic method was applied to the synthesis of polythiophenes having the ether group in the 3-position, and regioregular polythiophenes were obtained [16].



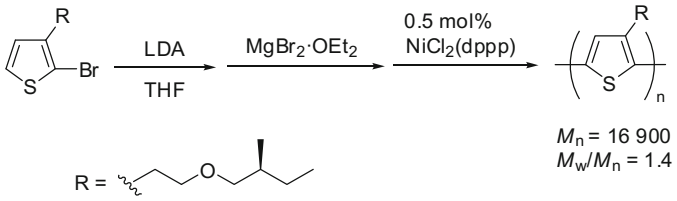
Scheme 6.2 Synthesis of the regioregular poly(3-alkylthiophene)

In addition to the regioregularly coupled polythiophenes, random copolymers have been similarly synthesized by the use of two different monomers bearing alkyl groups (Scheme 6.3) [17]. The physical properties of these head-to-tail (HT) random copolymers can be tuned by altering the ratio of the ingredients, leading to increases or decreases in conjugation. Altering the alkyl chains impacts the conductivity and performance of polymers; design and control of consistency in the formation of the copolymers is important.



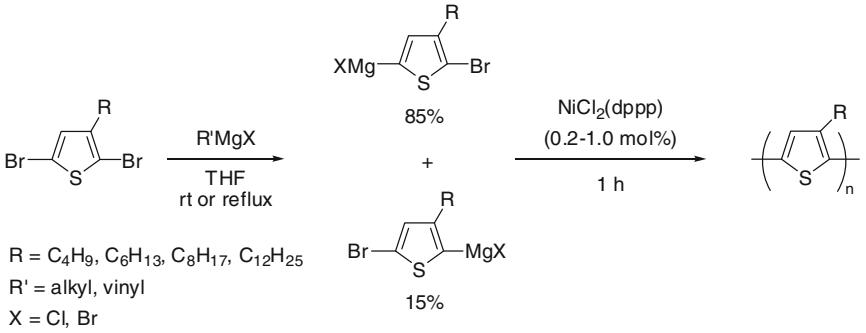
Scheme 6.3 Synthesis of random copolymers of 3-alkylthiophene

Based on the synthetic protocols of McCullough, polythiophenes with optical activity were sequentially obtained by using the chiral 2-bromo 3-[2-(S-methylbutoxy)ethyl]thiophene as the starting material (Scheme 6.4) [18, 19]. This polymer showed the complete disappearance of optical activity in the π-π^* transition band at its melting point of 160 °C. However, a reversible thermochromism was observed, and the optical activity was recovered in the absorption band by slow cooling of the polymer films.



Scheme 6.4 Synthesis of optically active poly(3-alkylthiophene)

McCullough has also synthesized regioregular poly(3-alkylthiophene)s by the magnesium-halogen exchange reactions, a method known as Grignard metathesis (GRIM), in which 2,5-dibromo-3-alkylthiophene was treated with alkyl or vinyl Grignard reagents. This resulted in two metalated regioisomers, 2-bromo-3-alkyl-5-bromomagnesiothiophene and 2-bromomagnesio-3-alkyl-5-bromothiophene, in a ratio of 85:15 (Scheme 6.5). It is noteworthy that this ratio has no dependence on reaction temperature, reaction time, or even the amount of Grignard reagents. Poly(3-alkylthiophene)s with more than 95 % of regioregularity were obtained by adding a catalytic amount of $NiCl_2$(dppp) to this isomeric mixture. This high regioregularity was explained by kinetic and thermodynamic effects generated from steric or electronic factors in the catalyzed reaction [20, 21]. In addition, McCullough has demonstrated that the in situ end-group functionalization of the regioregular poly(3-alkylthiophene)s is viable and facile by using the GRIM method [22, 23].



Scheme 6.5 Synthesis of poly(3-alkylthiophene)

As depicted in Fig. 6.1, the synthesis of polythiophene **1** has been reported with anthraquinone as a redox active pendant functional group in the side chain [24]. Cyclic voltammetric studies of the polymer-coated electrodes showed that the

observed response was coverage dependent. On the other hand, a polythiophene bearing a mercapto group **2** [25] was used in the thin film technology of soft lithography.

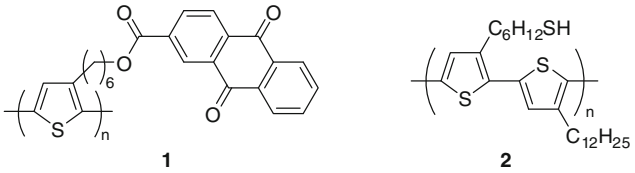
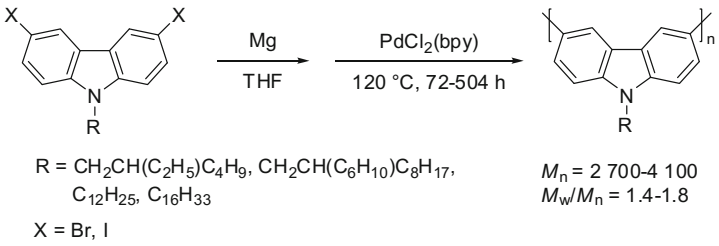


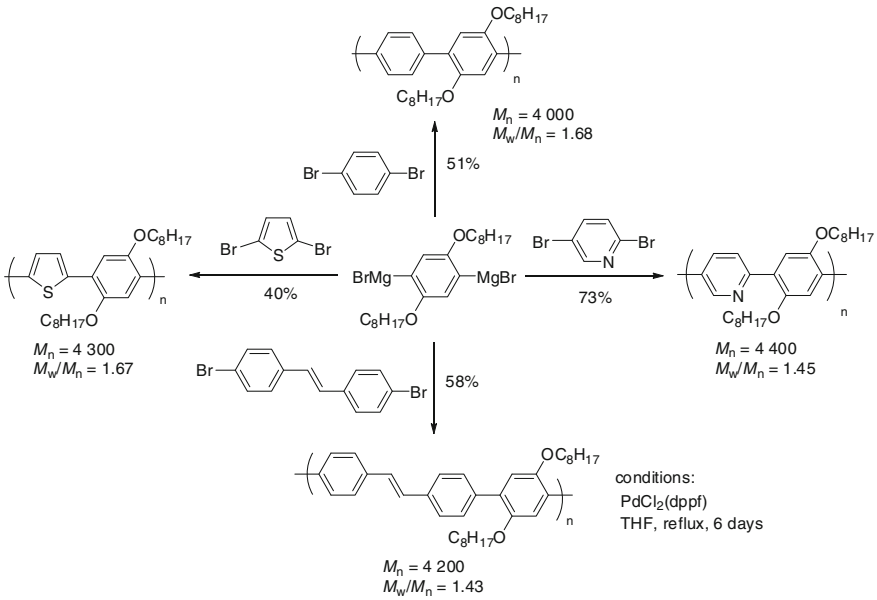
Fig. 6.1 Polythiophenes with a variety of functional groups

The palladium-catalyzed polycondensation, in the synthesis of the nitrogen-containing heterocyclic poly(9-alkylcarbazole-3,6-diyl), was achieved by Kumada-Tamao-Corriu coupling (Scheme 6.6) [26]. The steric effects of the alkyl groups on the carbazole rings dramatically affected the polymerization.



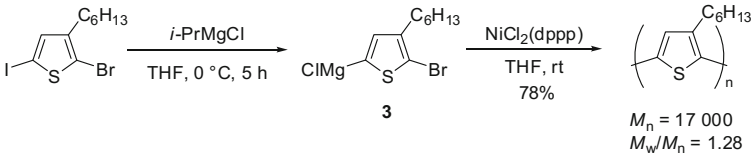
Scheme 6.6 Synthesis of poly(9-alkylcarbazole-3,6-diyl)

Naso et al. have synthesized various copolymers in moderate to good yields by the palladium-catalyzed Kumada-Tamao-Corriu coupling reactions between bifunctional organomagnesium reagents and various aromatic dibromides (Scheme 6.7). Molecular weights and molecular weight distributions of the obtained polymers were measured by size exclusion chromatography (SEC) and matrix-assisted laser desorption ionization time-of-flight (MALDI-TOF) mass spectroscopy. The number-average molecular weights (M_n) were 4,000–8,000; and the ratio of weight-average molecular weights (M_w) to number-average molecular weights (M_w/M_n) were 1.44–1.67 [27, 28].



Scheme 6.7 Copolymerization of bifunctional organomagnesium reagents

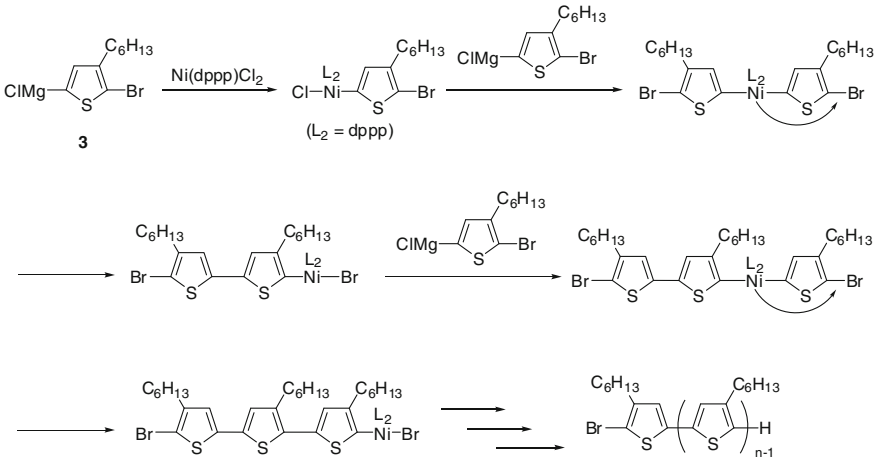
In 2004, Yokozawa et al. reacted 2-bromo-3-hexyl-5-iodothiophene with i-propylmagnesium chloride and polymerized the resulting 2-bromo-5-chloromagnesio-3-hexylthiophene (**3**) via nickel catalysis with good regioselectivity (Scheme 6.8) [29, 30]. This polymerization was found to proceed by chain-growth polymerization; thus, HT-poly(3-hexylthiophene) (HT-P3HT) was obtained with narrow molecular weight distributions. It was found that the molecular weights of HT-P3HT could be controlled by changing the ratio of monomer to the Ni catalyst.



Scheme 6.8 Synthesis of the regioregular poly(3-alkylthiophene) by chain-growth polymerization

Later, Yokozawa clarified the mechanism of the chain-growth polymerization of 2-bromo-5-chloromagnesio-3-hexylthiophene (**3**) catalyzed by $NiCl_2$(dppp). Measurements from MALDI-TOF mass spectroscopy indicated that HT-P3HT had a hydrogen atom at one end of the polymer and a bromine atom at the other end. One

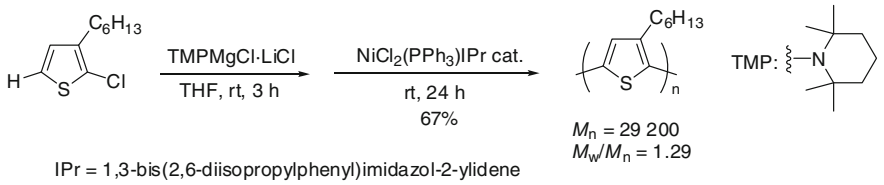
polymer chain was found to be formed by one Ni catalyst. The degree of polymerization and absolute molecular weights of the synthesized polymers was estimated from the ^{1}H NMR spectra. In addition, the reaction of Grignard reagents with 50 mol % of $NiCl_2$(dppp) disclosed that the bithiophene-bonded nickel complex is an important intermediate, generated by reductive elimination forming bithiophene and by oxidative addition of the C–Br bond in the bithiophene (Scheme 6.9). Based on this observation, this chain-growth polymerization has been referred to as "catalyst-transfer polycondensation," in which the Ni catalyst intramolecularly (step-by-step) shifts along the C–Br bond at the polymer's end [31].



Scheme 6.9 A mechanism of the chain-growth polymerization

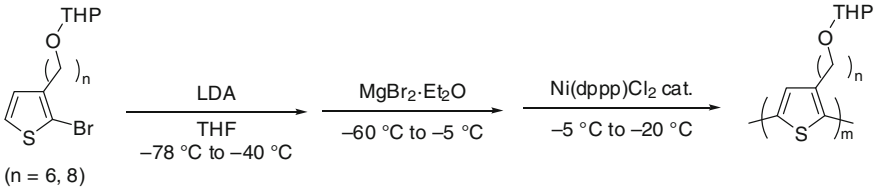
Yokozawa has also found that this chain-growth polymerization is highly dependent on the ligands of the Ni catalyst; polymers with narrow polydispersities can be attained when the dppe ligand is employed at 0 °C [32]. McCullough has also independently explained the mechanism of the chain-growth polymerization catalyzed by $NiCl_2$(dppp) [33, 34].

Very recently, Mori et al. carried out the nickel-catalyzed polymerization of 2-chloro-3-hexylthiophene with a stoichiometric amount of a magnesium amide, TMPMgCl·LiCl via C–H functionalization (Scheme 6.10). The process could also be accomplished with the combination of Grignard reagents and a catalytic amount of a secondary amine in place of TMPMgCl·LiCl. They also demonstrated that when bromothiophene was used as a monomer, the highly active $NiCl_2$(dppe) did not allow control of molecular weights. However, when the nickel catalyst was incorporated with an *N*-heterocyclic carbene ligand, control of molecular weights as well as molecular weight distributions was possible [35–37].



Scheme 6.10 The nickel-catalyzed polymerization of 2-chloro-3-hexylthiophene via C-H functionalization

Even more recently, Holdcroft synthesized polythiophenes having a tetrahydropyranyl (THP) group in the 3-position, giving rise to high solubility (Scheme 6.11) [38].

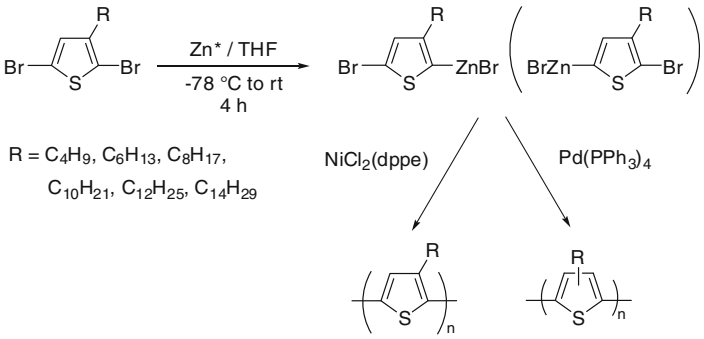


Scheme 6.11 Synthesis of polythiophenes having a tetrahydropyranyl (THP) group

Recent research suggests that π-conjugated polymers have potential applications in solar cells, and the introduction of the 3,4-ethylenedioxythiophene (EDOT) unit into the polymer chain increased absorption over the solar spectrum.

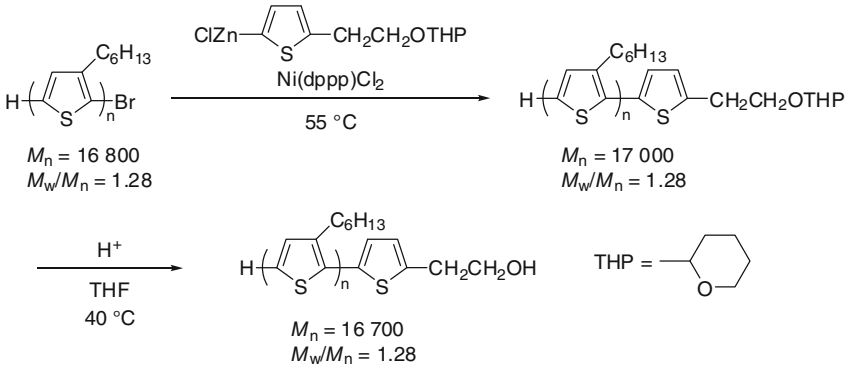
6.3 Negishi Coupling

In the early 1990s, Rieke polymerized the zincated 3-alkylthiophene (prepared from 2,5-dibromothiophene and highly active zinc) to give poly(3-alkylthiophene)s by Negishi coupling [39–41]. Interestingly, when $NiCl_2$(dppe) was used as the catalyst, poly(alkylthiophene)s with regioregularity as high as 98.5 % were obtained; whereas the $Pd(PPh_3)_4$ catalyst produced poly(alkylthiophene) without regioregularity (50:50) (Scheme 6.12).



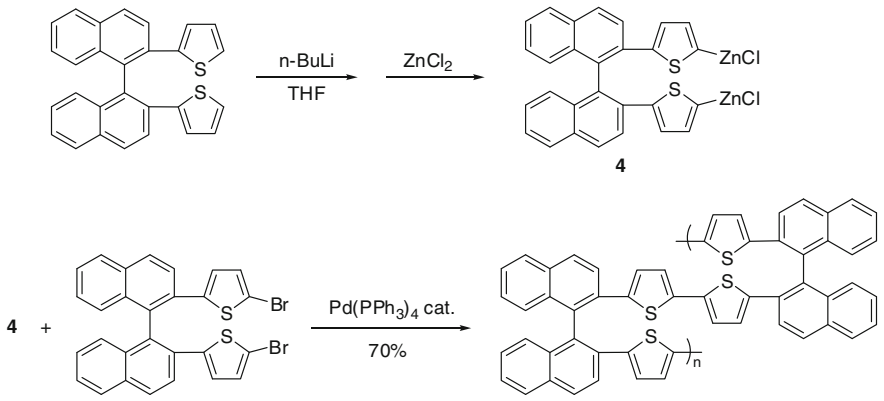
Scheme 6.12 Synthesis of poly(3-alkylthiophene)s by Negishi coupling

McCullough has also reported the synthesis of the regioregular poly(3-alkylthiophene)s by polymerization of 2-thienylzinc reagents [42–44]. In addition, the nickel-catalyzed Negishi coupling reactions of the synthesized polythiophenes with the functionalized 2-thienylzinc reagent further enabled the end functionalization (Scheme 6.13) [36].



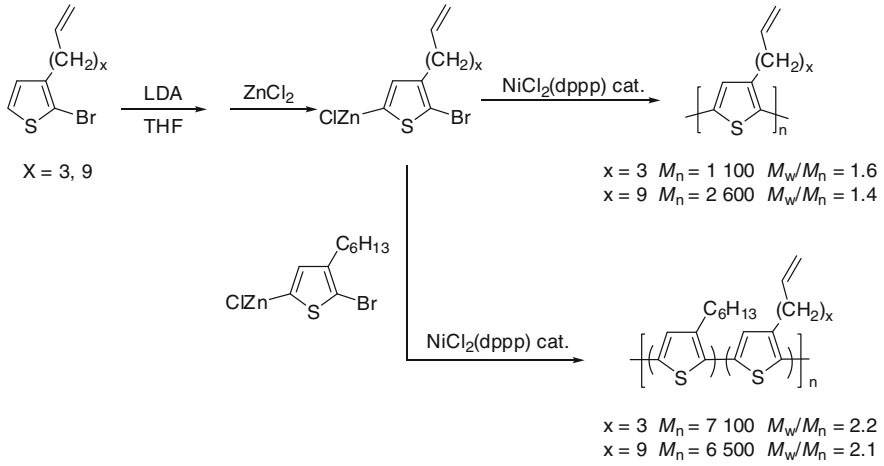
Scheme 6.13 Reactions of polythiophenes with 2-thienylzinc reagent

In 2003, Li et al. reported the synthesis of highly conductive binaphthylene-thiophene copolymers via the palladium-catalyzed Negishi coupling of a doubly zincated compound **4** in 70 % yield (Scheme 6.14) [45]. This polymer could be doped by both chemical and electrochemical methods; the chemical doping by $NOPF_6$ and the electrochemical doping increased their conductivities up to 3×10^{-5} and 2.2×10^{-5} S/cm, respectively.



Scheme 6.14 Synthesis of binaphthylene-thiophene copolymers

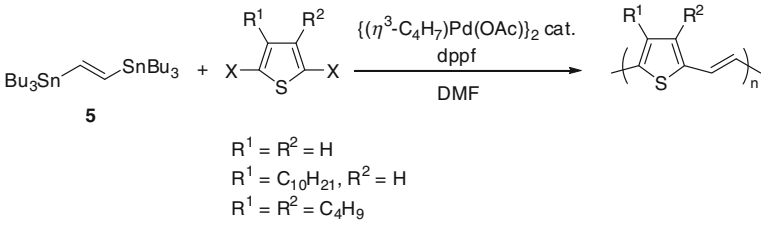
Recently, Stefan has synthesized polythiophenes bearing a terminal olefin moiety in the 3-position (Scheme 6.15) [46]. It is expected that the terminal olefin side chains can be transformed into various functional groups by preparative chemical modifications, leading to the synthesis of new types of polymers that can fine tune their optoelectronic characteristics.



Scheme 6.15 Synthesis of polythiophenes bearing a terminal olefin moiety

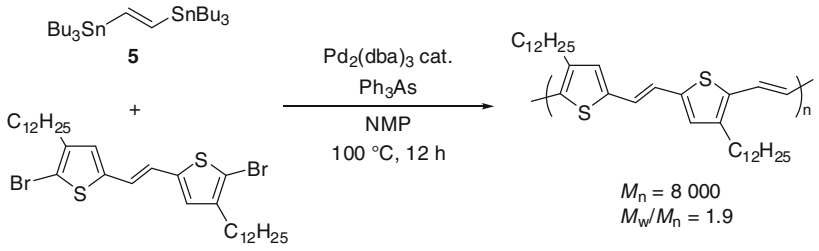
6.4 Migita-Kosugi-Stille Coupling

In 1991, Musco reported a preparative protocol to synthesize poly(thiophene-2,5-diylvinylene) by the Migita-Kosugi-Stille-coupling-based polymerization of dihalogenated thiophene and bis(tributylstannyl)ethene (**5**) under palladium catalysis (Eq. 6.1) [47]. Doping and undoping cycles of the polymer resulted in a decrease of the intensity of the band due to the π-π^* transition together with a shift toward higher energy. Conductivity measurements in iodine-doped powders after compression showed values close to 10^{-2} S/cm.



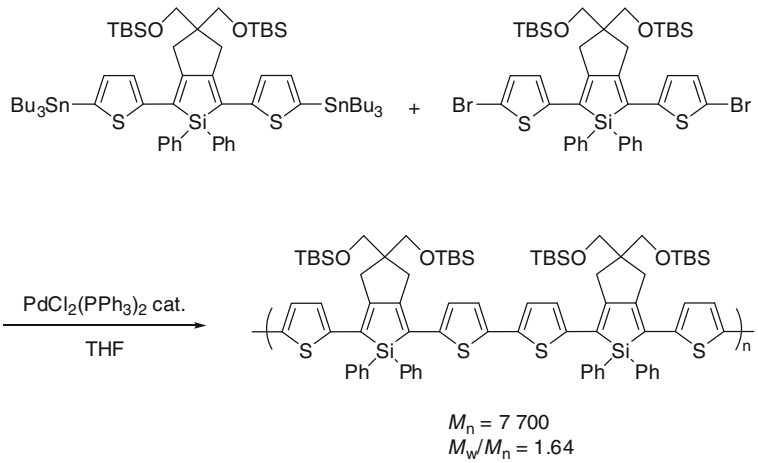
(6.1)

Employing the aforementioned coupling protocol, the use of the previously prepared 5,5′-dibromo-2,2′-dithienylethene as the starting material allowed for control of regioregularity (Eq. 6.2) [48]. It is expected that these synthesized regioregular polymers could lead to very interesting new materials for transistors and other important conjugated polymer applications.



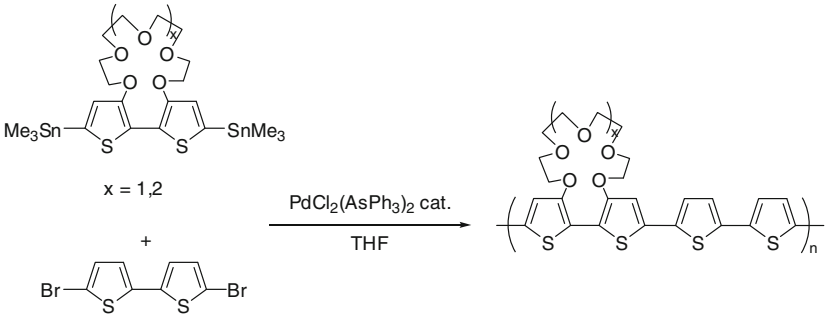
(6.2)

The Migita-Kosugi-Stille coupling reactions have been applied to the synthesis of a thiophene-silole copolymer (Eq. 6.3) [49]. This polymer shows characteristic absorption at 594 and 615 nm, and the absorption of long wavelengths is ascribed to the intramolecular electron-transfer from the thiophene ring to the silole ring.



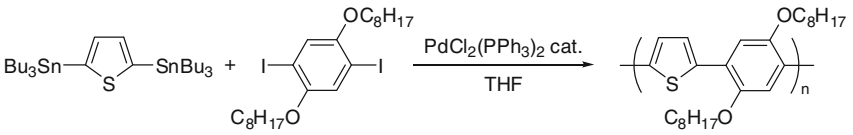
(6.3)

Polythiophenes bearing the crown ethers have been synthesized by Migita-Kosugi-Stille coupling. The capture of various alkali metal ions (Li^+, Na^+, and K^+) in solution by the crown ether fragments in these polymers showed an ionochromic response (Eq. 6.4) [50].

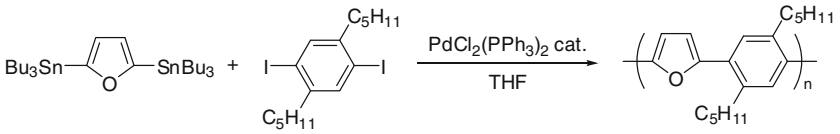


(6.4)

The thiophene-dialkoxyphenylene and furan-dialkylphenylene alternating copolymers have been similarly synthesized, and their photogenic properties were evaluated (Eqs. 6.5 and 6.6) [51, 52]. These polymers showed desirable photogenic properties; their UV–vis, electronic luminescence, photoluminescence, and electric field characteristics have been researched, aiming at applications in LED devices.

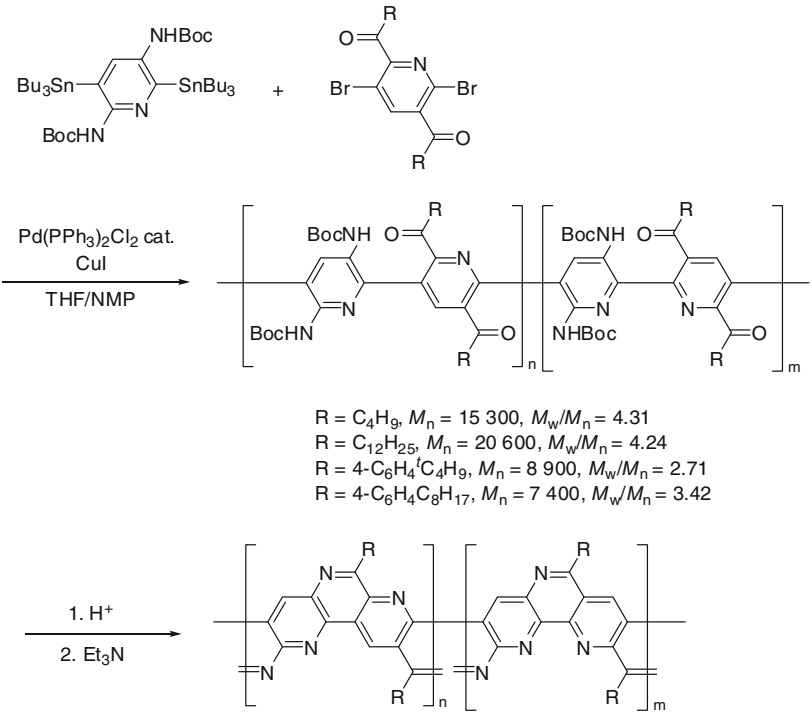


(6.5)



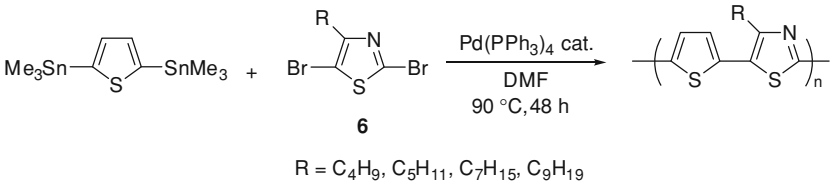
(6.6)

The Migita-Kosugi-Stille coupling reactions of dibromopyridine with distannylpyridine in the Pd/Cu co-catalyst system afforded the functionalized polypyridines with alternating copolymers bearing two separate substituents (Scheme 6.16) [53]. Since these polymers were facially bridged with imine, they became planar after deprotection of the Boc group. Thus, electron-deficient ladder-type polymers were efficiently synthesized. The resulting planarity of the polymers shortened their band gaps.



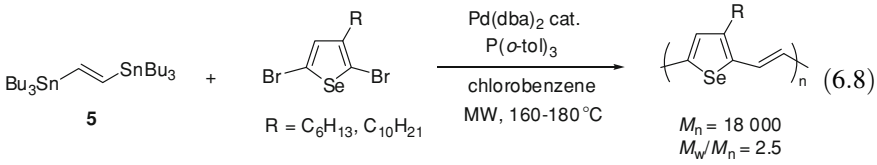
Scheme 6.16 Synthesis of the functionalized polypyridines and ladder-type polymers

The palladium-catalyzed polycondensation of the electron-donating 2,5-dibromo-4-alkylthiazole (**6**) with the electron-withdrawing 2,5-bis(trimethylstannyl) thiophene produced charge-transfer-type alternating copolymers with high regioregularity (Eq. 6.7) [54]. The XRD measurement revealed that the polymer chains have an intermolecular interaction with one another causing a stacking structure. Because steric adaptability may increase further by regioregularity of alkylthiazole and because of the charge transfer characteristics between the thiazole ring and the thiophene ring, this stacking structure is facially formed.



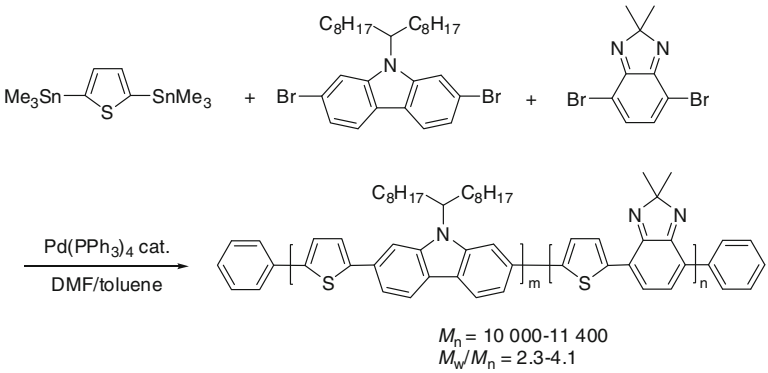
(6.7)

Heeny et al. have synthesized poly(3-alkyl-2,5-selenylenevinylene)s by the microwave-assisted Migita-Kosugi-Stille coupling reaction of 2,5-dibromo-3-alkylselenophene with (*E*)-1,2-bis(tributylstannyl)ethene (**5**) (Eq. 6.8) [55]. The polymers substituted with a decyl group showed excellent solubility in common organic solvents, and the ^{1}H NMR measurements indicated that regioregularity of the side chains reached more than 90 %. This polymer showed the wavelength of maximum absorption (λ_{max}) at 621 nm in solution.



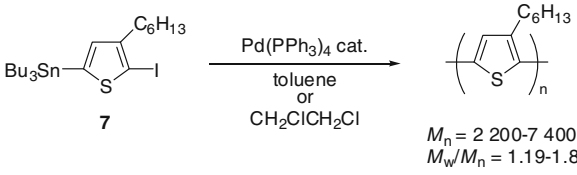
(6.8)

Song has synthesized random copolymers by the Migita-Kosugi-Stille coupling of 2,5-bis(trimethylstannyl)thiophene with electron-rich carbazoles or electronic-poor benzimidazoles (Eq. 6.9) [56].



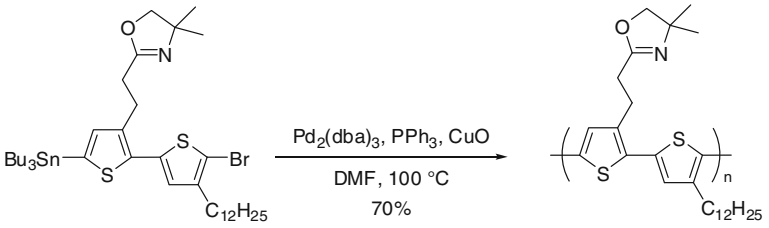
(6.9)

As the ratios of head-to-tail regioregularity of the adjacent thiophene rings in poly(3-alkylthiophene)s increased, the planarity of the polymer chains improved. As the result, larger maximum effective conjugation lengths of the polymer backbones and lower band gaps were observed. In order to attain lower band gaps and higher conductivity, Migita-Kosugi-Stille coupling of the monomer 2-iodo-3-hexyl-5-tributylstannylthiophene (**7**) was used to produce highly regioregular (>96 %) poly(3-hexylthiophene)s (Eq. 6.10) [57].



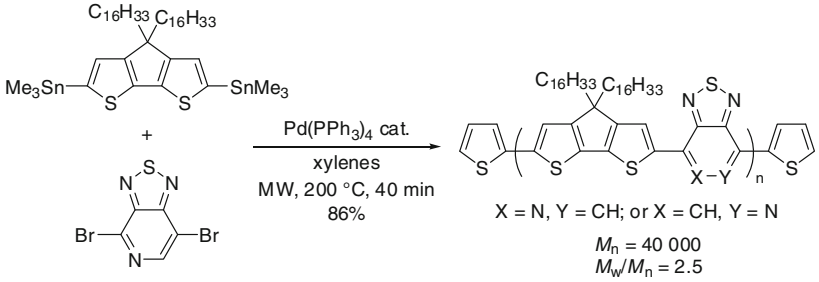
(6.10)

Analogously, the synthesis of regioregular polythiophenes was achieved by Migita-Kosugi-Stille coupling of bithiophene with bromide and stannyl groups in the 5 and 5′-positions, respectively [58]. Also, regioregular polythiophenes bearing an oxazoline moiety were obtained in a high yield by the palladium-catalyzed Migita-Kosugi-Stille coupling using CuO as a co-catalyst (Eq. 6.11) [59]. The oxazoline moiety was found to be either easily hydrolyzed under acidic conditions or the polymers were found to change color, depending on the size of the cation. In addition, regioregular polythiophenes substituted with phosphonic acid were synthesized in a similar manner [60].



(6.11)

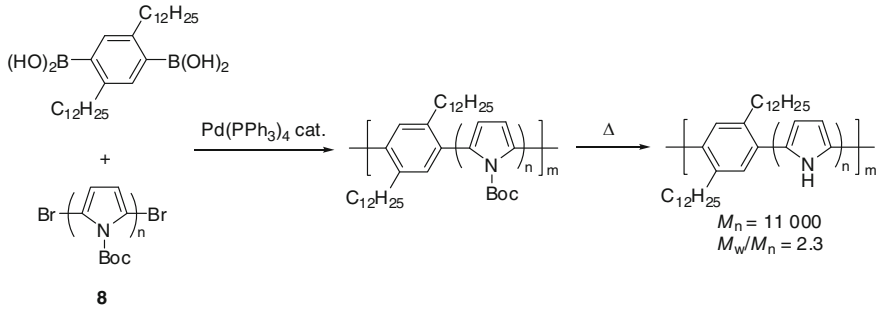
Bazan has synthesized the conjugated polymers of pyridal[2,1,3]thiadiazole (PT) with regioregularity (Eq. 6.12) [61]. This polymerization protocol produced polymers with two different regioregular structures: one is all the PTs aligning in the same direction, and the other is the structure aligning to the alternate direction for each repeating unit. Surprisingly, regiorandom polymers showed hole mobility of only 0.005 $cm^2\ V^{-1}\ s^{-1}$, whereas the mobility of regioregular polymers was 0.6 $cm^2\ V^{-1}\ s^{-1}$, which is $\sim$2 orders of magnitude larger.



(6.12)

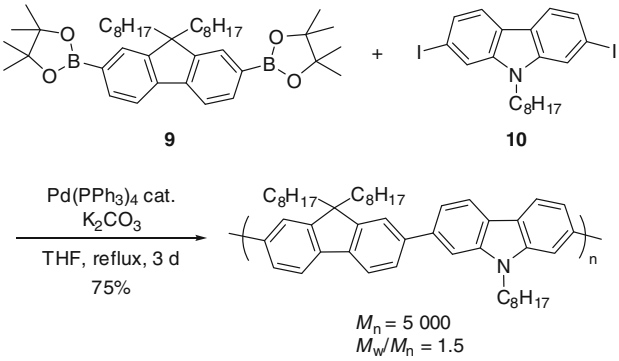
6.5 Suzuki–Miyaura Coupling

Schluter has synthesized the alternating copolymers that have phenylene and pyrrole rings from the benzenediboronic acid derivatives and the *N*-Boc-protected (Boc = *tert*-butoxycarbonyl) dibromopyrrolic monomers **8** via Suzuki–Miyaura coupling reactions (Scheme 6.17) [62]. The Boc protecting group does not retard the polymerization and is removable after polymerization.



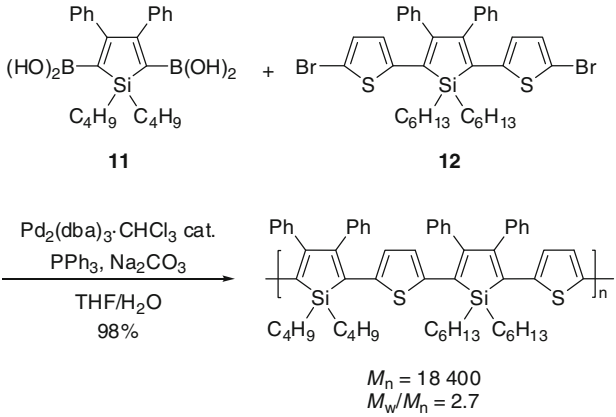
Scheme 6.17 Synthesis of the alternating copolymers of p-phenylene with 2,5-pyrrole

Similarly, a conjugated copolymer was obtained from 2,7-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-9,9-dioctylfluorene (**9**) and *N*-octyl-2,7-diiodocarbazole (**10**) (Eq. 6.13) [63]. The application of these conjugated polymers to various optoelectronic devices is expected.



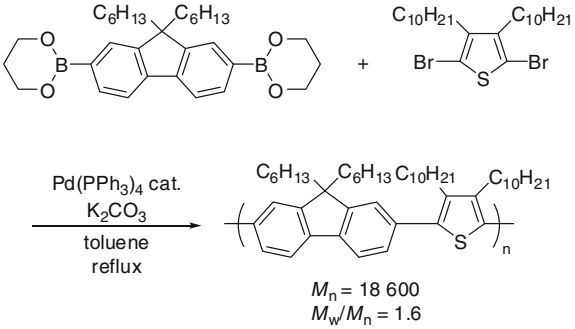
(6.13)

The silole-thiophene alternating copolymers have been synthesized by Suzuki–Miyaura coupling of silole-2,5-diboronic acid (**11**) with 2,5-bis(5-bromo-2-thienyl)silole (**12**) (Eq. 6.14) [64]. In addition, the silole-phenylene, silole-pyridine, and silole-thiazole alternating copolymers have also been synthesized in similar manners [65]. The silole-based π-electron systems were found to show a unique photophysical property originating from characteristic electronic structures of the silole ring, and it is expected to be utilized as emissive materials for organic electroluminescent devices.



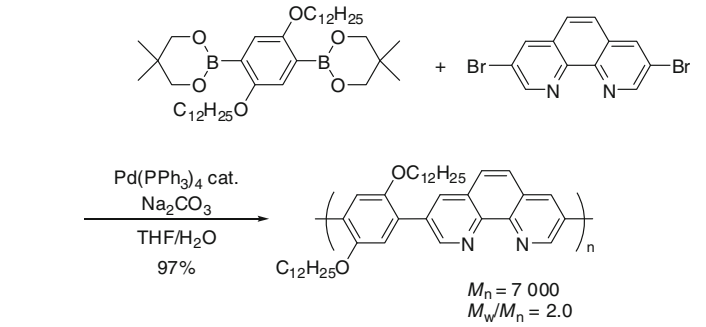
(6.14)

Fluorene/thiophene alternating copolymers were also obtained by Suzuki–Miyaura coupling (Eq. 6.15) [66]. This polymer was reported to have a blue-light-emitting quality, to dissolve in common organic solvents, and to show high thermal stability at glass transition temperatures. Optical, electrochemical, and thermal properties can be freely tuned by changing the substituents of the side chains on the aromatic rings.

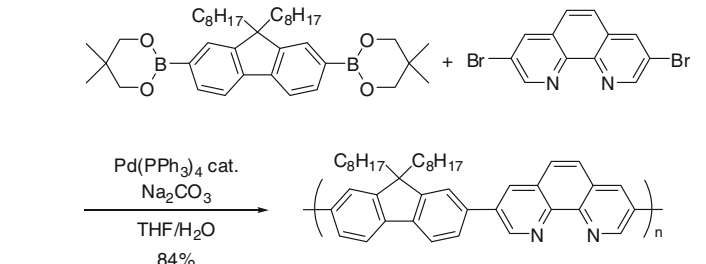


(6.15)

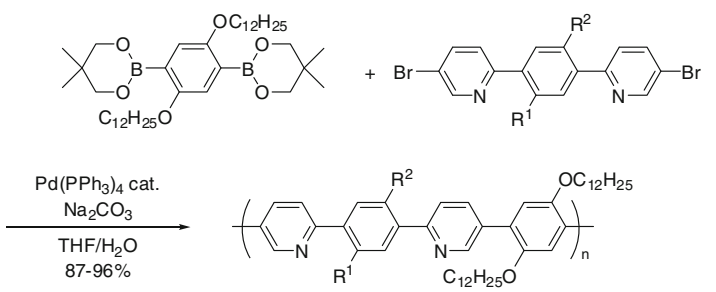
A series of alternating copolymers of 1,10-phenanthroline/1,4-didodecyloxybenzene, 1,10-phenanthroline/9,9-dioctylfluorene, and pyridine/1,4-dialkoxybenzene have been synthesized by the palladium-catalyzed Suzuki–Miyaura coupling reactions in excellent yields (Eqs. 6.16–6.18) [67]. These polymers were reported to show high thermal stability.


OC12H25
C12H25O
Br
Br
Pd(PPh3)4 cat.
Na2CO3
THF/H2O
97%
OC12H25
C12H25O
n
Mn = 7 000
Mw/Mn = 2.0

(6.16)

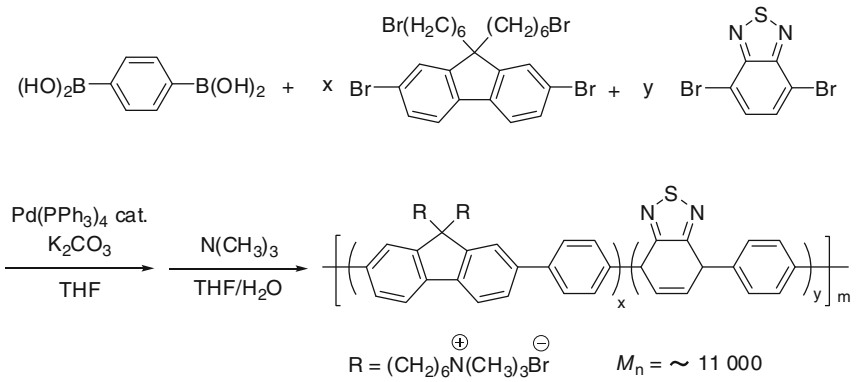

C8H17
C8H17
Br
Br
Pd(PPh3)4 cat.
Na2CO3
THF/H2O
84%
C8H17
C8H17
n
Mn = 6 700
Mw/Mn = 1.8

(6.17)


OC12H25
C12H25O
Br
Br
R2
R1
Pd(PPh3)4 cat.
Na2CO3
THF/H2O
87-96%
R2
OC12H25
R1
C12H25O
n
R1 = H, OCH3, OH
R2 = H, OC12H25, OCH3
Mn = 5 400-8 800
Mw/Mn = 1.2-1.9

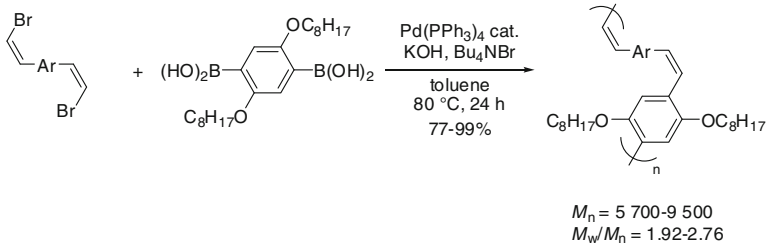
(6.18)

The polymerization of p-phenylenebisboronic acid with a mixture of 4,7-dibromo-2,1,3-benzothiadiazole and 2,7-dibromofluorene derivatives was conducted by Suzuki–Miyaura coupling to give the corresponding copolymers (Scheme 6.18) [68]. These polymers could be converted into water-soluble polycationic conjugated copolymers whose emission color was changed by their conformation and aggregation.

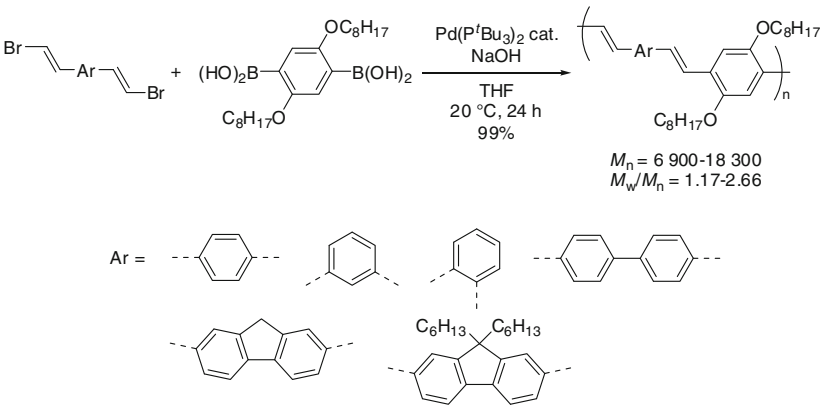


Scheme 6.18 Synthesis of the copolymers of p-phenylene with 4,7-benzothiadiazole and 2,7-fluorene

Ozawa et al. have succeeded in the stereoselective synthesis of (*Z*)-poly(arylenevinylene)s by Suzuki–Miyaura coupling-based polycondensation under the palladium catalysis (Eq. 6.19) [69]. When Bu_4NBr was added as the phase-transfer catalyst, the number-average molecular weights reached 5,700–9,500 and the stereoregularity of vinylene linkages in the polymer backbone was more than 95 %. Analogously, the polymers with the (*E*)-configurations were stereoselectively obtained by Suzuki–Miyaura coupling of (*E*)-styryl bromides and areneboronic acids (Eq. 6.20) [70].

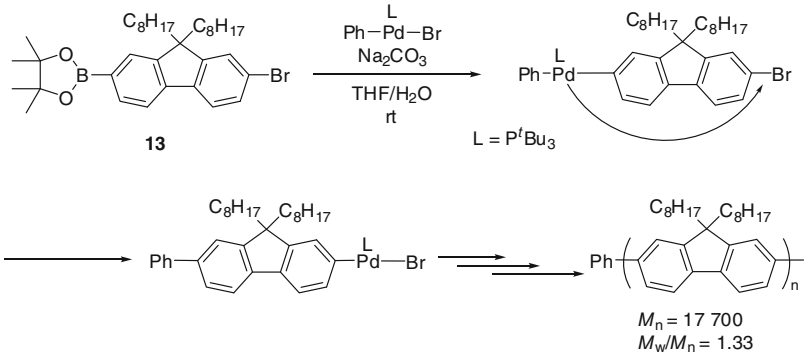


(6.19)



(6.20)

Yokozawa et al. have developed a process for the polycondensation of 2-(7-bromo-9,9-dioctyl-9*H*-fluoren-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**13**) by the Suzuki–Miyaura coupling, employing Pd(Ph)Br(P^tBu_3) as the catalyst (Scheme 6.19) [71]. The polymerization took place smoothly at room temperature, and well-defined polyfluorenes with narrow polydispersity and controlled molecular weight were obtained. It was clarified that the obtained polymers possess the phenyl end groups by the measurements of MALDI-TOF mass spectroscopy. The relationship of conversion-M_n and feed ratio-M_n is linear, indicating that this polycondensation proceeds by chain-growth polymerization caused by an initiator unit derived from the catalyst.

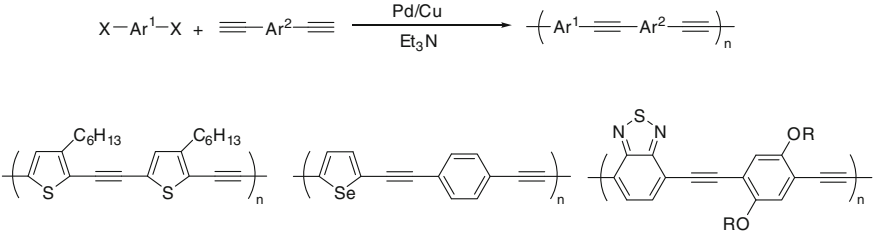


Scheme 6.19 Polycondensation of **13** by Suzuki-Miyaura coupling

In addition, Yokozawa has reported polymerization by the catalyst transfer-type Suzuki-Miyaura coupling of 2,5-bis(hexyloxy)-4-iodophenylboronic acid, catalyzed by Pd(Ph)Br(P^tBu_3) [72]. This polymerization enabled the synthesis of poly(*p*-phenylene) with a narrow molecular weight distribution.

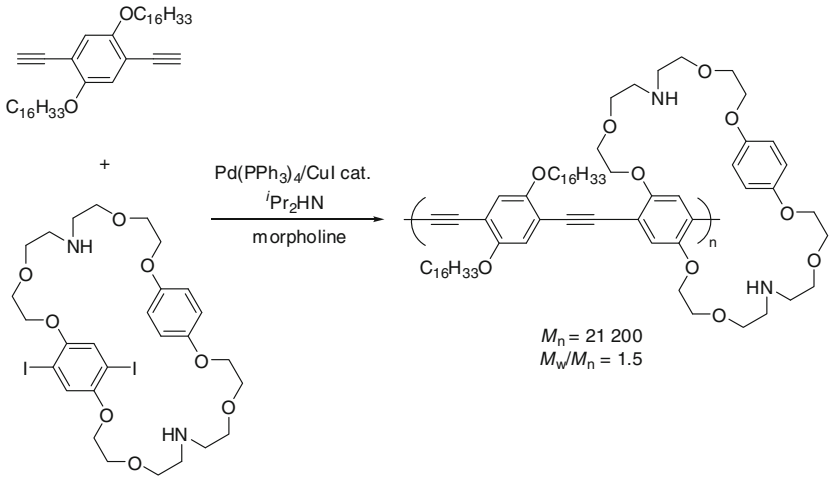
6.6 Sonogashira–Hagihara Coupling

Since the palladium/copper co-catalyzed Sonogashira–Hagihara coupling can form carbon(sp^2)–carbon(sp) bonds, this polymerization methodology is extremely important for the synthesis of conjugated polymers that have a triple bond in the polymer main chain. The synthesis of the conjugated polymers via the Sonogashira–Hagihara coupling of dihaloheteroaryl compounds and diethynylarenes have been reported by using triethylamine, which has the dual role of solvent and base (Eq. 6.21) [73, 74].



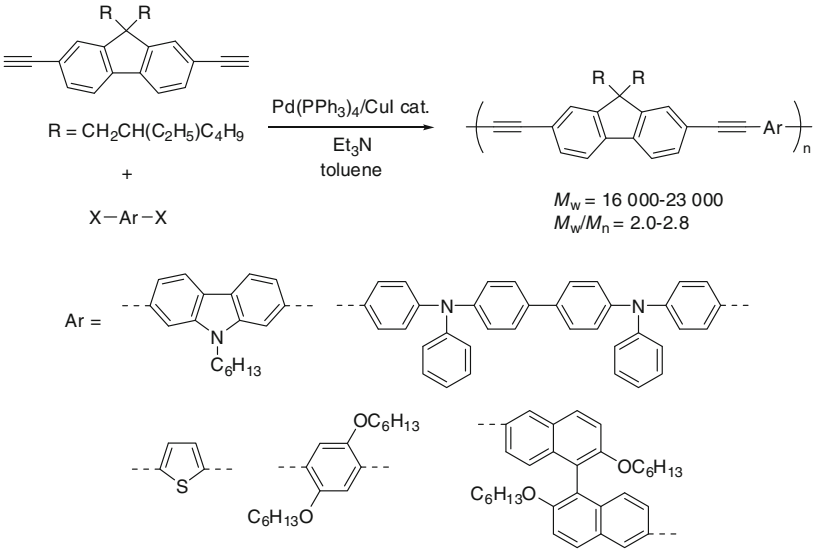
(6.21)

Swager et al. have synthesized the poly(*p*-phenyleneethynylene) containing cyclophane through Sonogashira–Hagihara coupling in a palladium/copper co-catalyst system (Eq. 6.22) [75]. This polymer shows unusual solid-state aggregation behavior, giving rise to highly emissive materials.



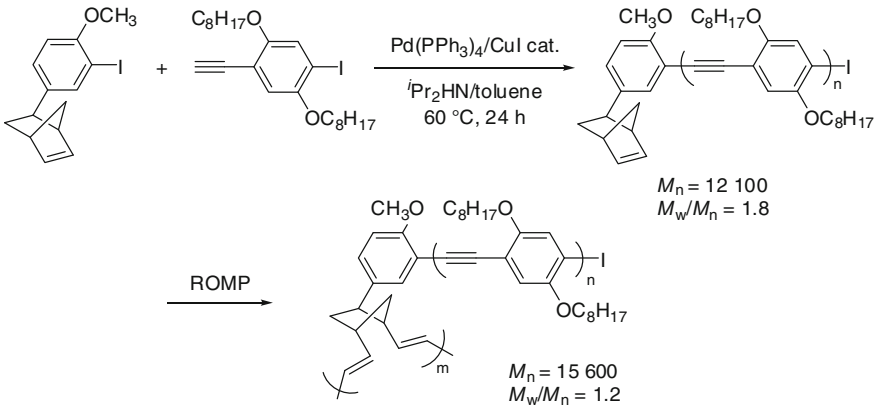
(6.22)

Liu et al. have synthesized poly(aryleneethynylene)s (PAE) that show electroluminescence (EL) via the palladium-catalyzed Sonogashira–Hagihara coupling of fluorene bearing sterically bulky alkyl substituents and aromatic rings such as carbazoles and thiophene that have holetransport units (Eq. 6.23) [76]. The luminescent property of the PAE-type polymers can be improved by introducing the holetransport units into the polymer main chain. Even a slight change of the structure in the main chain can readily control the electronic structures and the EL characteristics of polymers.



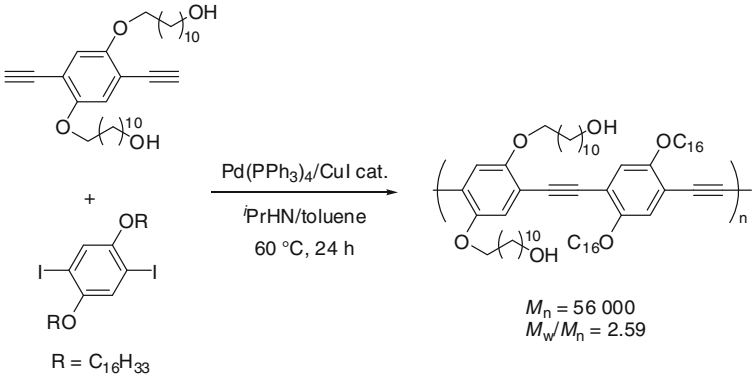
(6.23)

The synthesis of the poly(*p*-phenyleneethynylene) (PPE) brushes by Sonogashira-Hagihara coupling was reported by Swager (Scheme 6.20) [77]. First, the end-functionalized polymers were synthesized in the presence of iodoarenes incorporating the norbornene moiety. The sequential ruthenium-catalyzed ring-opening metathesis polymerization (ROMP) on oxidized silicon surfaces led to the formation of high-density PPE brushes.



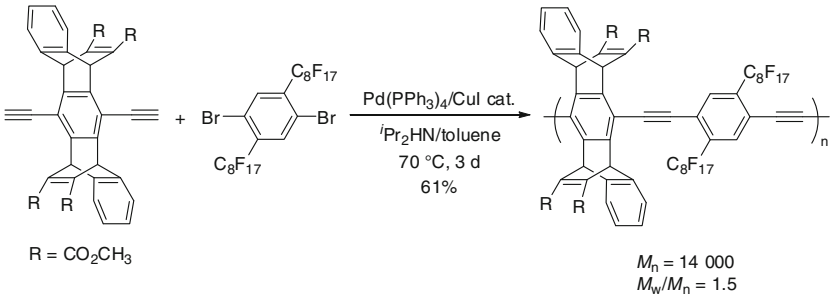
Scheme 6.20 Synthesis of the poly(*p*-phenyleneethynylene) (PPE)

In addition, poly(*p*-phenyleneethynylene)s have received attention as polarized photoluminescent materials due to the intrinsic anisotropy of their one-dimensional electronic structure and their ability to be processed in uniaxially oriented blends by various techniques (Eq. 6.24) [78].



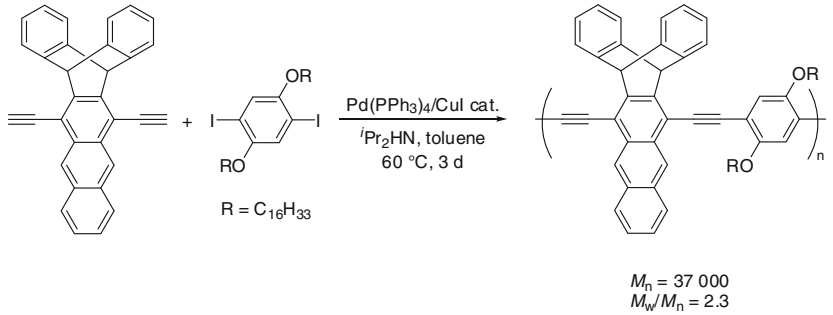
(6.24)

Swager has also facilitated the synthesis of poly(phenyleneethynylene)s with fused pendant [2.2.2] ring structures having alkene bridges substituted with two ester groups. These polymers were obtained by Sonogashira-Hagihara coupling and showed broad and red-shifted emission spectra in the solid state (Eq. 6.25) [79].



(6.25)

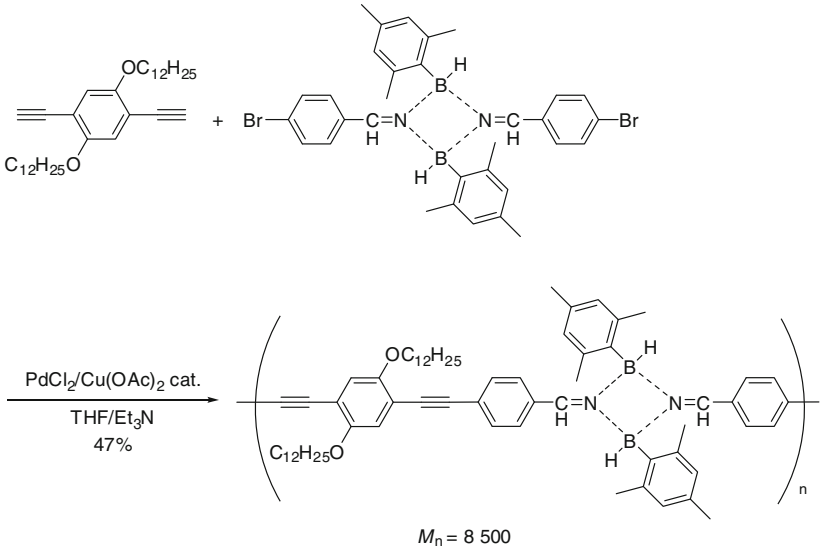
Conjugated polymers with an anthryl group in the core have been synthesized by the palladium/copper co-catalyzed Sonogashira-Hagihara coupling (Eq. 6.26) [80]. These polymers are known to react selectively with dienophiles; Diels–Alder reactions promptly progress across the less bulky dienophiles like *N*-alkylated maleimide derivatives. Compared with their parent polymers, polymers generated by cycloaddition showed a remarkable increase of quantum yields as well as dramatic hypsochromic shifts of their emission and absorption maxima by up to 80 nm.



(6.26)

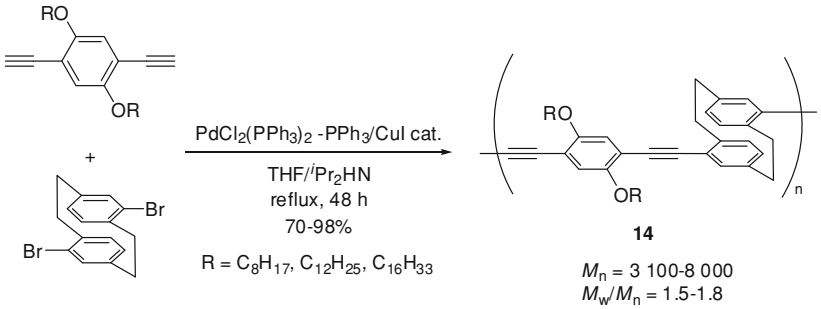
Chujo et al. have synthesized the donor–acceptor-type, conjugated poly (cyclodiborazane)s by Sonogashira–Hagihara coupling of 2,5-didodecyloxy-1,4-diethynylbenzene and bifunctional aryl bromides bearing cyclodiborazane (Eq. 6.27) [81]. The number-average molecular weights of these polymers were determined to be 8,500 by the GPC measurements. The UV–vis spectra in chloroform showed an absorption maximum at 414 nm. This originates from the

expanded π-conjugation enhanced by the empty p-orbital of the boron atom and the intramolecular charge transfer structure. This polymer intensely emits blue-green light upon irradiation at 414 nm, and thus it has garnered attention for use as an emission polymer.



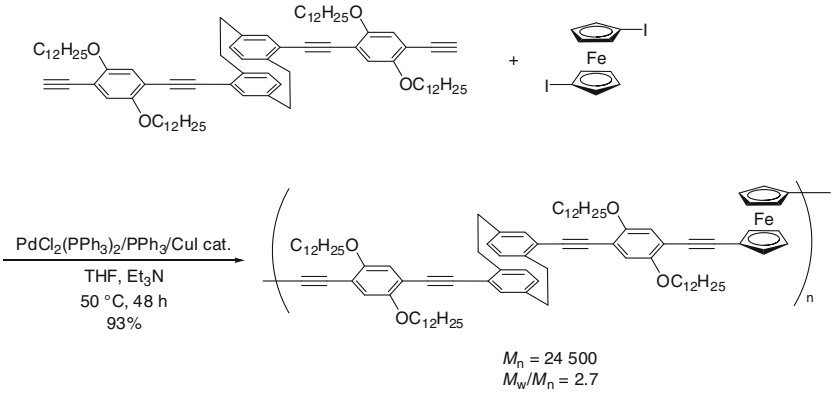
(6.27)

In addition, Chujo has succeeded in synthesizing the conjugated polymers bearing [2.2]paracyclophane skeletons in the main chain by Sonogashira-Hagihara coupling (Eq. 6.28) [82]. A deep orange fluorescent solution was obtained from the reaction of *p*-dibromo[2.2]paracyclophane with 2,5-dialkoxy-substituted diethynylbenzene. The GPC measurements revealed that the number-average molecular weights (M_n) of the polymers was 8000 (R = n-dodecyl). Whereas in the reactions of *p*-dibromo[2.2]paracyclophane with diethynylbenzene (R = H) or dimethoxydiethynylbenzene (R = Me), only low-molecular weights were detected because of the low solubilities of the polymers **14**. In the UV–vis spectra, the maximum absorption was approximately 310-380 nm in chloroform, where a red shift of absorption was observed because the extended π-conjugation via through-space caused by the two-faced benzene rings of [2.2]paracyclophane.



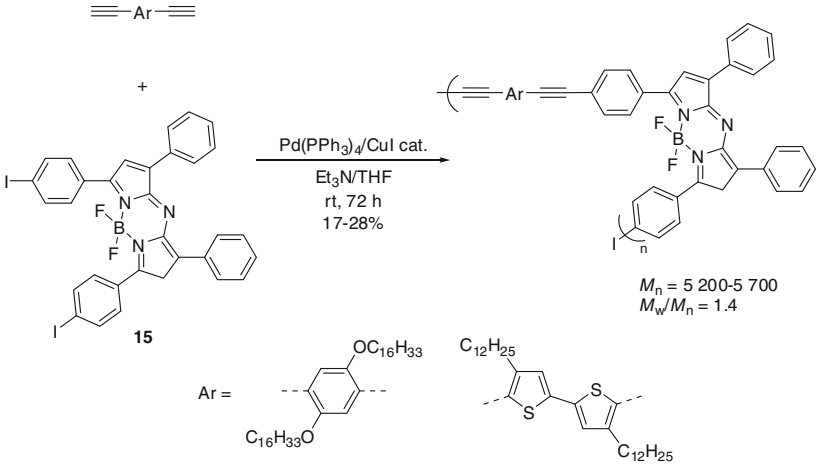
(6.28)

Subsequently, the synthesis of analogous polymers was achieved through Sonogashira–Hagihara coupling in which a ferrocene unit was introduced into the main chain of these polymers (Eq. 6.29) [83]. Comparison revealed that a [2.2]paracyclophane unit was found to be more effective than a ferrocene unit for the delocalization of π-electrons. The polymer that bears both [2.2]paracyclophane and ferrocene units exhibited a broad and reversible oxidation potential with an E_{pa} value of 0.62 V in the measurements of cyclic voltammetry. When the polymers were doped by iodine under standard conditions, the conductivity can reach a maximum of up to 1.6×10^{-4} S/cm.



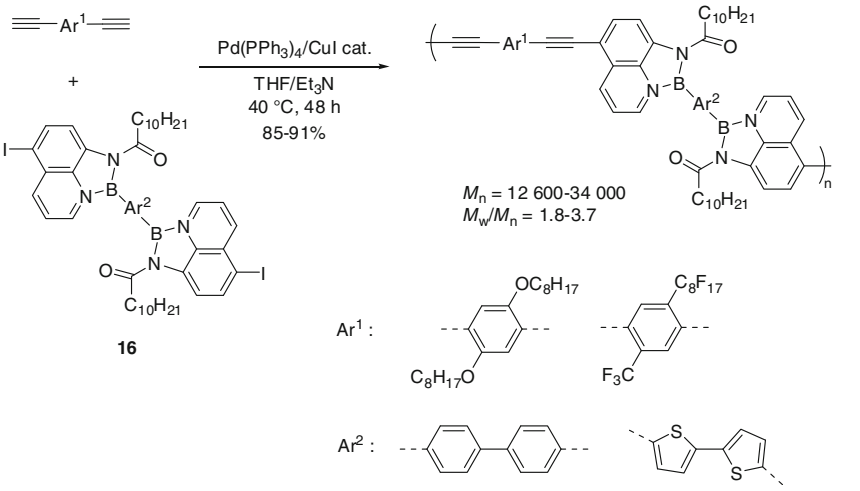
(6.29)

Chujo has synthesized polymers that have the near-infrared (NIR) photoluminescence characteristics via the Sonogashira–Hagihara coupling of diiodobenzene-functionalized aza-borondipyrromethene **15** with 1,4-diethynyl-2,5-dihexadecyloxybenzene or 3,3′-didodecyl-2,2′-diethynyl-5,5′-bithiophene. (Eq. 6.30) [84]. Their polymers exhibited a significant red shift in the UV–vis absorption and photoluminescence spectra because of the effectively extended π-conjugation, and they showed near-infrared (NIR) light with narrow emission bands at 713–777 nm on excitation at each absorption maximum.



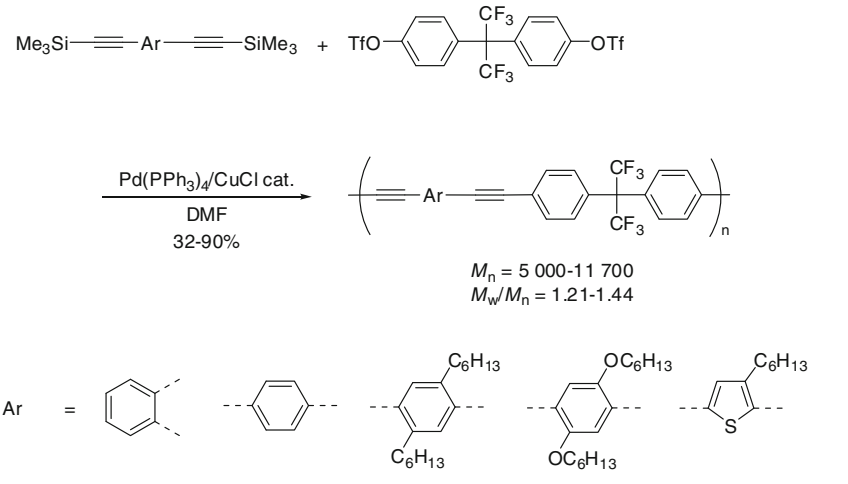
(6.30)

Subsequently, Chujo analogously synthesized polymers that have high luminescence through the polymerization of organoboron aminoquinolate-based monomers **16**, originating from the Sonogashira-Hagihara coupling (Eq. 6.31) [85]. The color and the emission intensity of these polymers could be finely tuned by the Ar^1 and Ar^2 units in the monomers, respectively. The absorption and emission bands in the region above 400 nm are strongly influenced by the two quinoline rings and the diethynylbenzene moieties. The polymers with a biphenyl group as the Ar_2 unit showed high fluorescence absolute quantum yields, whereas no emission was observed with the perfluoroalkylated benzene or bithiophene moieties.



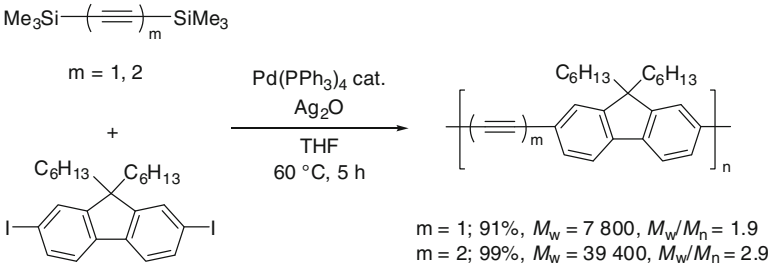
(6.31)

Polycondensation based on Sonogashira-Hagihara methods has been applied to the coupling of alkynylsilanes and aryl triflates as the bifunctional monomers; polymers with M_n of 11,700 were synthesized (Eq. 6.32) [86]. These polymers are expected to become new functional materials because they show the characteristic UV–vis and fluorescence spectra as well as thermal stability.



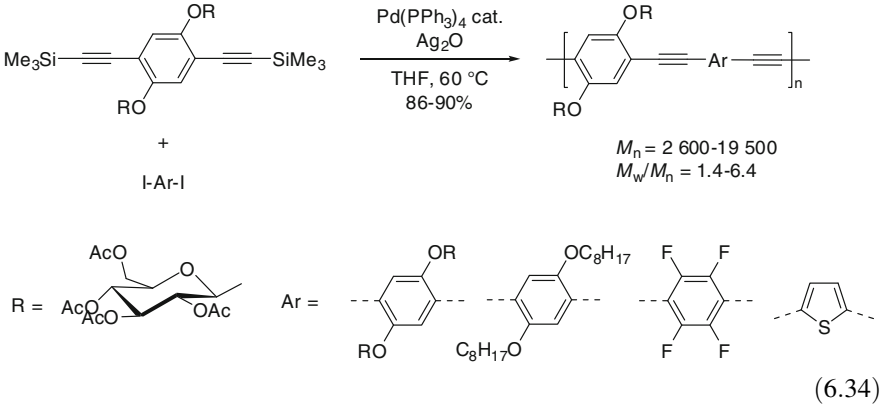
(6.32)

Mori et al. have conducted the polymerization by sila-Sonogashira-Hagihara coupling of bis(trimethylsilylethyne) (m = 1) or 1,4-bis(trimethylsilylbutadiyne) (m = 2) with diiodoarene bearing the fluorene unit, mediated by $Pd(PPh_3)_4$ and silver(I) oxide as an activator, to afford poly(aryleneethynylene)s in excellent yields (Eq. 6.33) [87]. This method would be a valuable alternative to the parent Sonogashira-Hagihara coupling, which has to employ the gaseous acetylene and 1,3-butadiyne.



(6.33)

This reaction was applied sequentially by Naso, and a series of poly(aryleneethynylene)s containing the acetylated glucopyranosyl group has been synthesized (Eq. 6.34) [88]. This synthetic method has several advantageous features. The versatility afforded by the possibility of placing the sugar moiety on either the disilyl derivative or the aromatic diiodides leads to high yields in products.

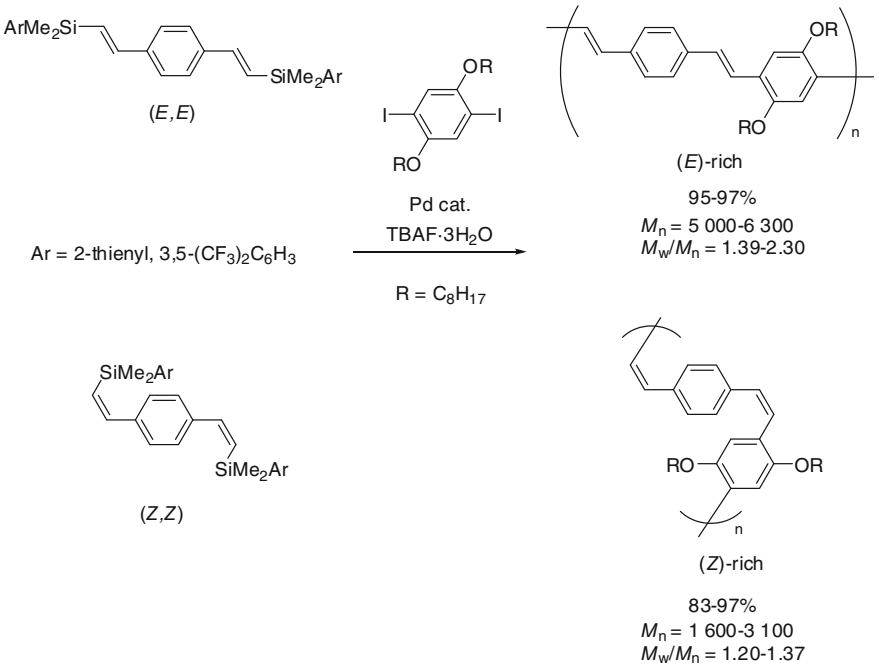


(6.34)

6.7 Hiyama Coupling

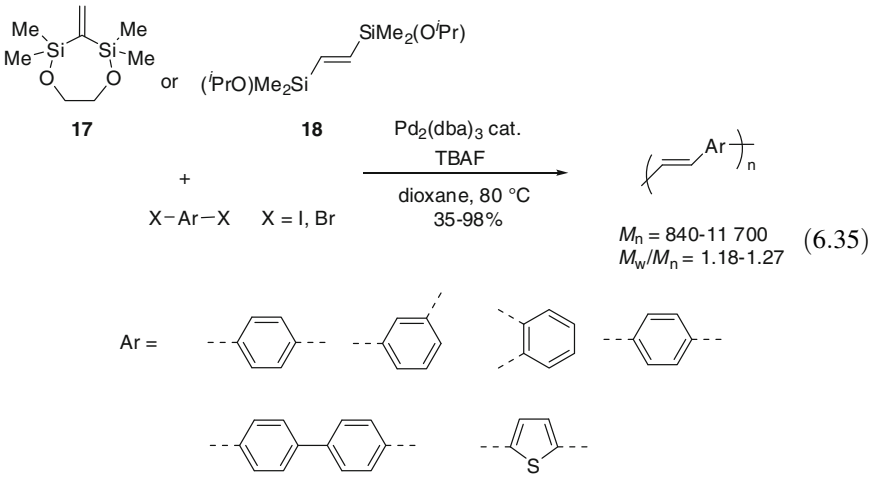
Ozawa has investigated the palladium-catalyzed polycondensation based on Hiyama coupling of the bifunctional (*E*)- or (*Z*)-alkenylsilanes synthesized by the ruthenium-catalyzed stereodefined hydrosilylation of 1,4-diethynylbenzene

(Scheme 6.21) [89]. During the polymerization of (*E*)-alkenylsilanes, the stereochemistry was retained ($E/Z => 99: < 1$) to form the poly(arylenevinylene); whereas the cross-coupling polymerization of the (*Z*)-monomer gave rise to a mixture of stereoisomers (Z/E = 45:55–34:66) [90, 91].



Scheme 6.21 Synthesis of poly(arylenevinylene)s by Hiyama coupling

Marciniec has carried out the palladium-catalyzed Hiyama coupling of dihaloarenes with cyclic 1,1-bis(silyl)ethene (**17**) or (*E*)-1,2-bis(isopropoxydimethylsilyl)ethene (**18**), affording the corresponding (*E*)-poly(arylenevinylene)s stereoselectively (Eq. 6.35) [92]. This polymerization utilized Hiyama coupling to form a carbon–carbon bond by the conversion of a carbon–silicon bond. The favorable features of this new catalytic approach to stereodefined poly(arylenevinylene)s involve: the facile availability of organosilicon starting compounds, the simplicity of the experimental technique, and the alternative use of inexpensive aryl bromides in place of aryl diiodides.



6.8 Summary

In this chapter, recently investigated representative synthetic examples of the conjugated polymers using the cross-coupling reactions were summarized. Synthesis of a variety of conjugated polymers, which could not be obtained by electrochemical polymerization, became possible by utilizing the transition metal-catalyzed cross-coupling reactions. In particular, polymers containing the heteroaromatic rings such as thiophene are expected to function as optoelectronic materials with unique chemical and physical properties. The role of the cross-coupling reactions will continue to expand in the synthesis of these conjugated polymers in conjunction with the development and expansion of industrial applications for optoelectronics.

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Part III
Recent Advances in Cross-Coupling Reactions

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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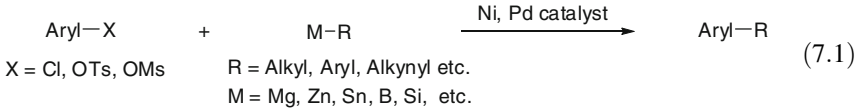
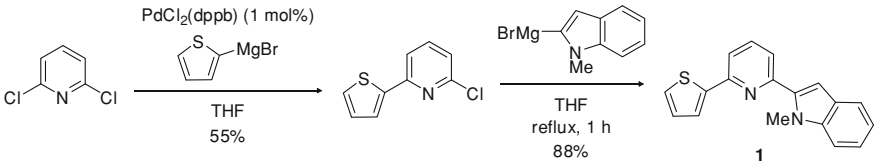
occur under standard conditions. However, around 2000 it began to be reported that the appropriate combination of certain ligands with the transition metal catalysts enables cross-coupling reactions of aryl chlorides, tosylates, and mesylates as coupling partners [5–7]. This chapter outlines the examples 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.



(7.1)

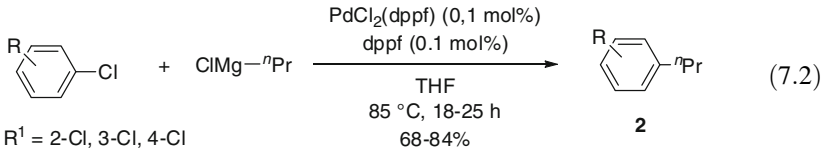
7.2 Kumada–Tamao−Corriu Coupling

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

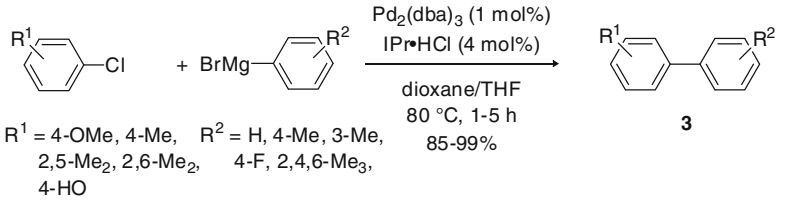
Later, Umeno and Katayama succeeded in the first cross-coupling reactions of alkyl Grignard reagents with aryl chlorides, rather than heteroaryl chlorides. The reactions of dichloroarenes with alkyl Grignard reagents afforded the corresponding monoalkylated products **2**. The double alkylated products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



(7.2)

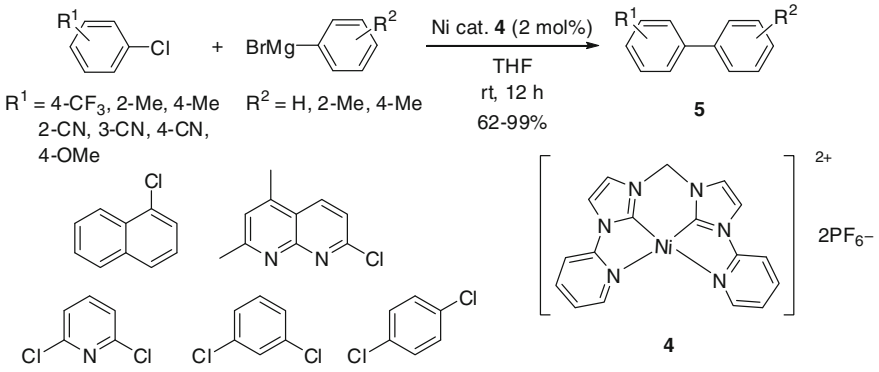
In 1999, Nolan et al. reported that Kumada–Tamao–Corriu coupling reactions, catalyzed by the palladium complexes having the *N*-heterocyclic carbene (NHC) ligands, took place across aryl chlorides bearing electron-donating groups to afford the

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.



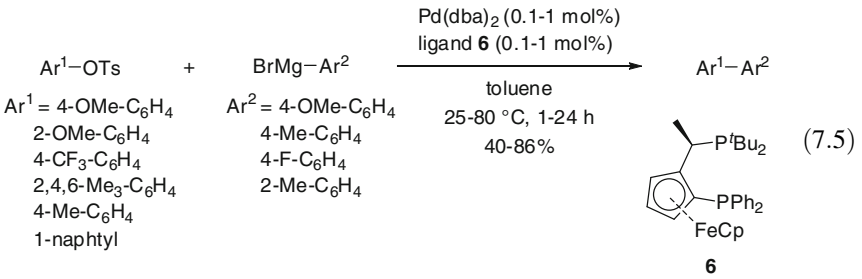
(7.3)

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].

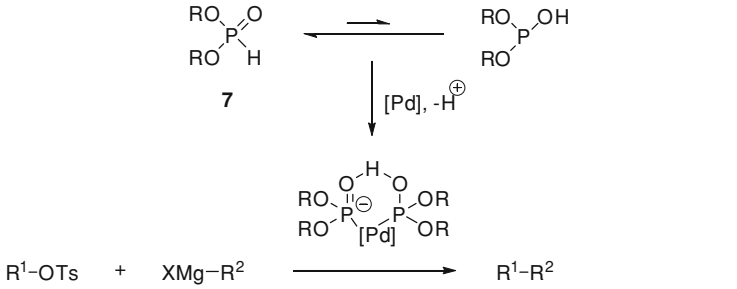


(7.4)

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.



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].



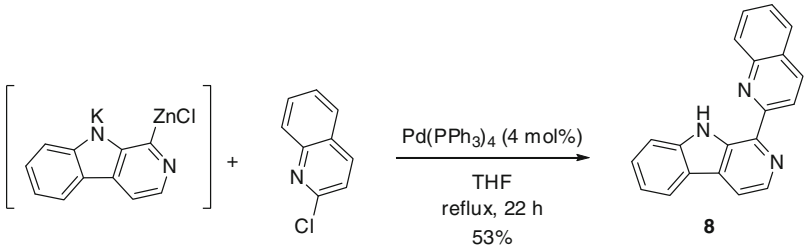
Scheme 7.2 Kumada-Tamao-Corriu coupling of aryl tosylates using the air-stable phosphonate ligands

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

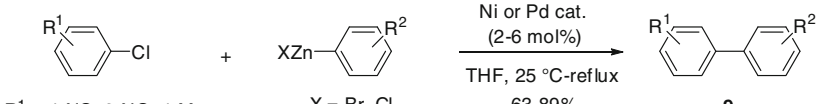
Negishi coupling reactions of organozinc compounds with aryl chlorides have been actively researched as well. In the 1980s, the studies started with the reactions of a variety of activated heteroaryl chlorides such as pyridines [23].

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**.

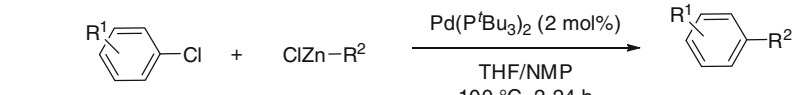


R^1 = 4-NC, 2-NC, 4-Me
4-MeO_2C, 4-EtO_2C

X = Br, Cl
R^2 = H, 4-Me

(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].

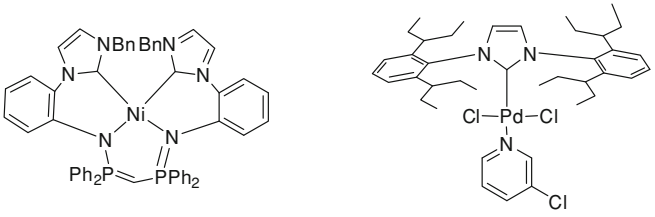


R^1 = 4-CO_2Me, 4-NO_2
2-Me, 4-OMe
4-$B(OR)_2$, 2,6-Me_2

R^2 = 4-OMe-C_6H_4
2-Me-C_6H_4
2,6-Me_2-C_6H_4
^{s}Bu, ^{n}Bu

(7.8)

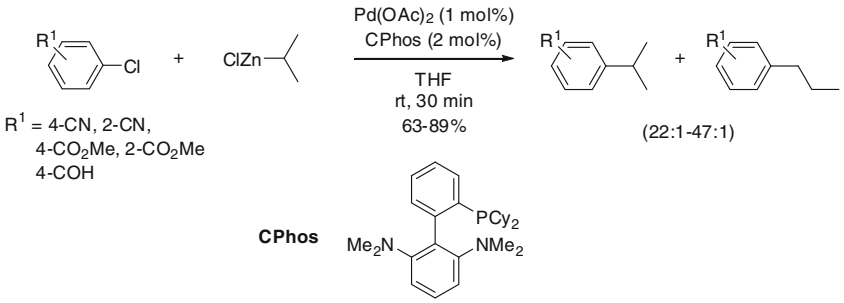
The analogous Negishi coupling reactions were found to take place, not only with the palladium catalysts [27–29], but also with the nickel catalysts [30]. For instance, Wang synthesized the NHC-ligated nickel complex **11** and applied this to Negishi coupling reactions with a variety of aryl chlorides [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

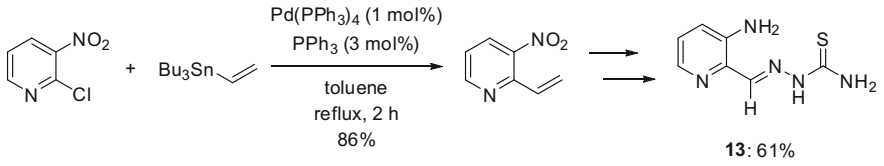
In contrast to the large number of Negishi coupling reactions of arylzinc reagents and aryl chlorides reported, in 2009 Buchwald succeeded in Negishi coupling reactions of secondary alkylzinc compounds and a variety of aryl chlorides by using CPhos as the ligand of the palladium catalyst (Eq. 7.9) [35].



(7.9)

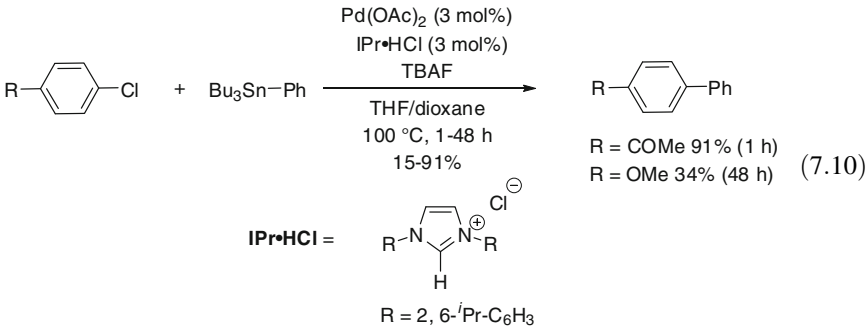
7.4 Migita–Kosugi–Stille Coupling

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].



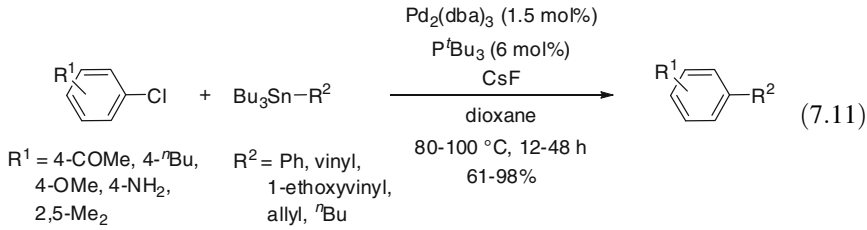
Scheme 7.3 Vinylation reactions of chloropyridine by Migita-Kosugi-Stille coupling

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)

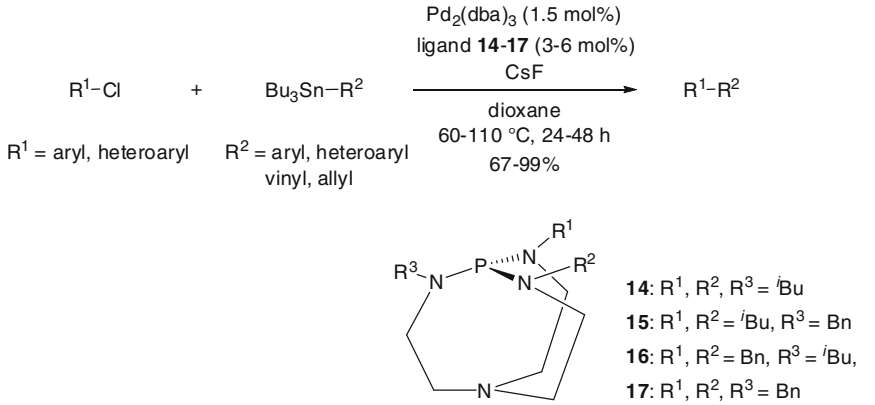
In 1999, Fu and Littke succeeded in the Migita–Kosugi–Stille coupling of aryl chlorides bearing electronic-rich substituents under palladium catalysis by using an electron-donating and bulky tri-*tert*-butylphosphine as the ligand. In addition, it was disclosed that not only aryltin compounds but also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



(7.11)

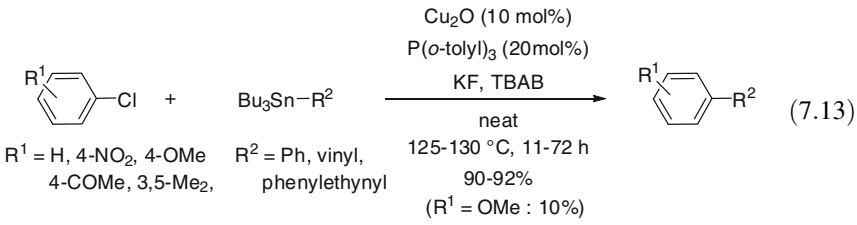
In 2004 Verkade et al. reported active catalyst systems to accelerate the coupling reactions of more inert aryl chlorides [40]. The electronic density on the phosphorus atom of the proazaphosphatrane ligands **14**–**17** (as shown in Eq. 7.12) is rather large because: (1) the three nitrogen atoms around 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.



(7.12)

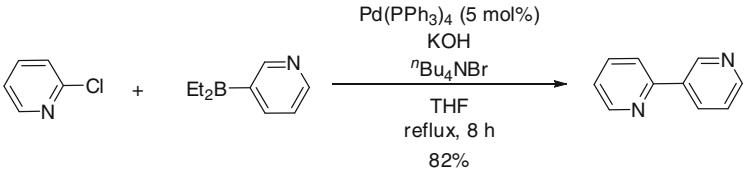
Although the use of palladium as a catalyst is frequent in the cross-coupling reactions of aryl chlorides [41–43], in 2006 Zhang reported that copper(I) oxide can catalyze the coupling reactions of aryl chlorides and aryltin compounds through the assistance of appropriate activators (Eq. 7.13) [44].



(7.13)

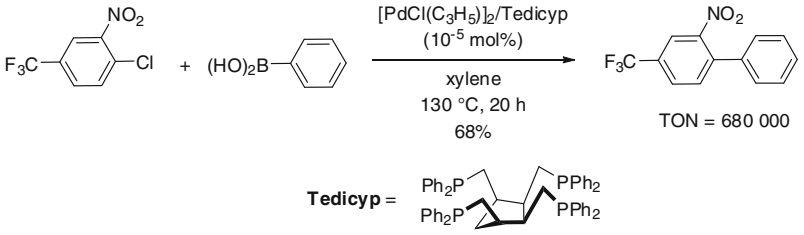
7.5 Suzuki–Miyaura Coupling

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.



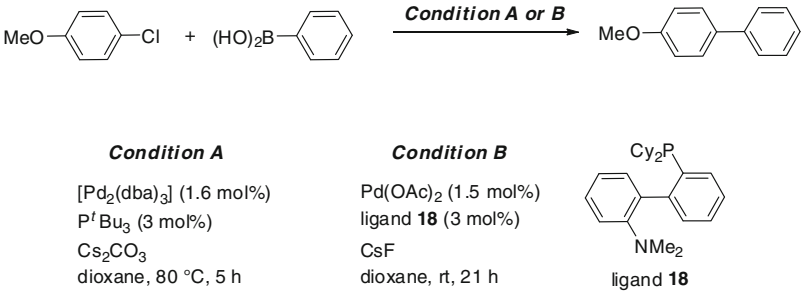
(7.14)

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].

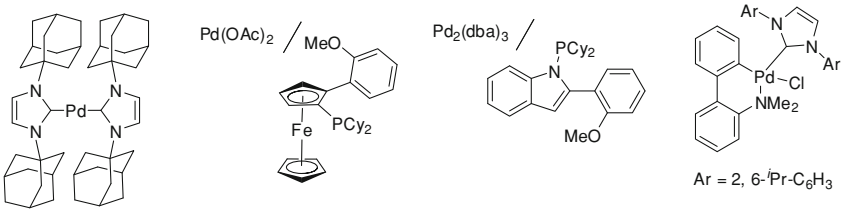
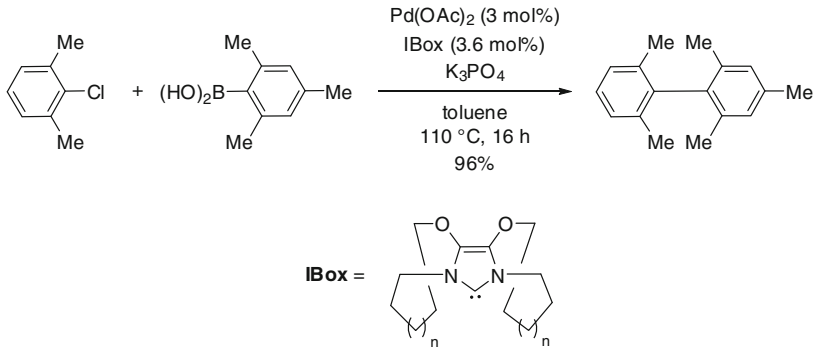


Fig. 7.2 Various palladium catalysts effective for Suzuki–Miyaura couplings of aryl chlorides

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].

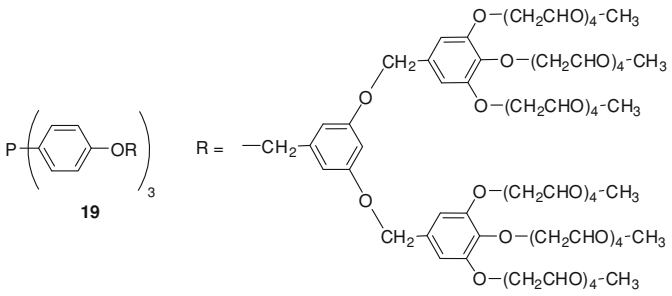
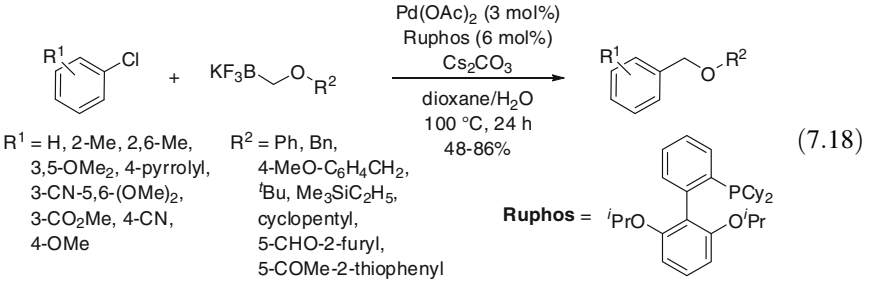


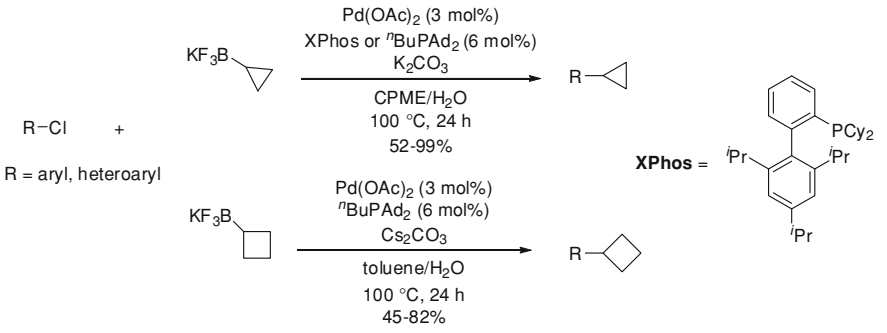
Fig. 7.3 Active ligand containing the TEG moieties

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].

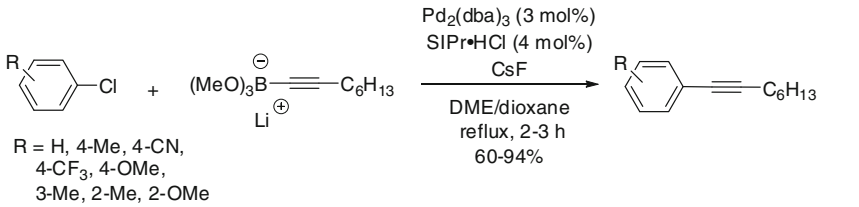


(7.18)

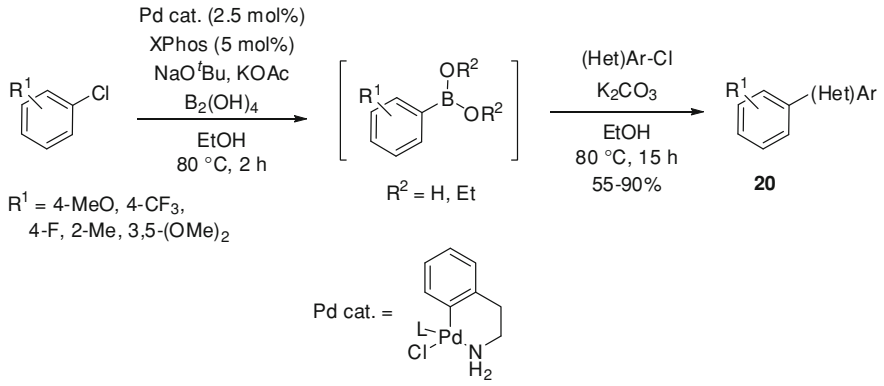


Scheme 7.4 Suzuki-Miyaura coupling of aryl chlorides with cyclopropyl- and cyclobutyltrifluoroborates

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].



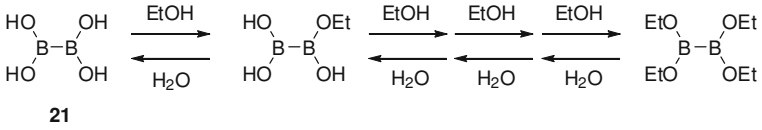
(7.19)



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

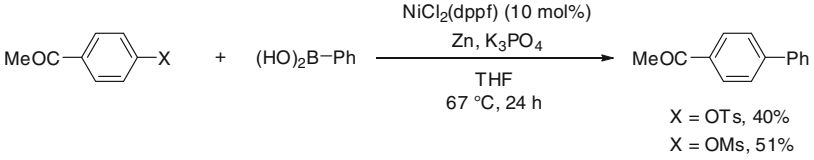
In 2010, Dreher synthesized the corresponding biaryls **20** from the subsequent Suzuki–Miyaura cross-coupling reactions of tetrahydroxydiborane with two different aryl chlorides in one pot (Scheme 7.5) [84].

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.



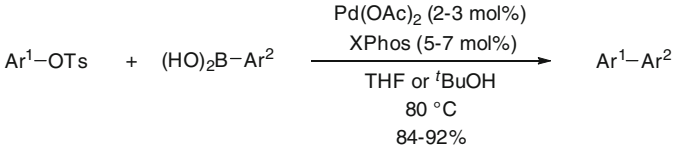
Scheme 7.6 The equilibrium between tetrahydroxydiborane (**21**) and tetraethoxydiborane

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.



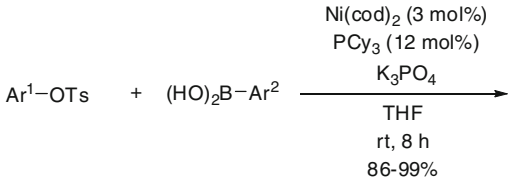
(7.20)

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].



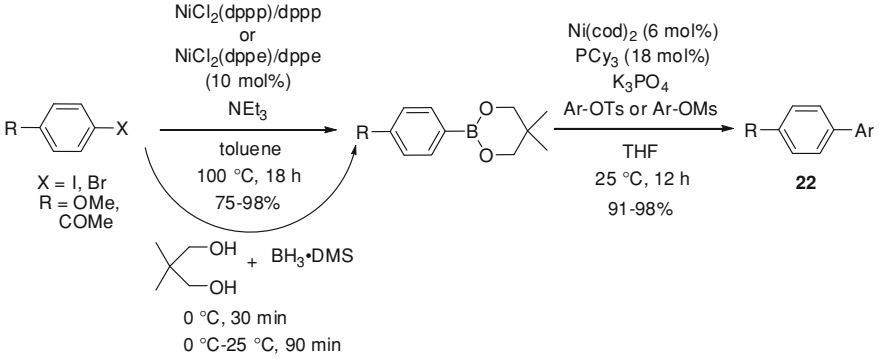
(7.21)

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].



(7.22)

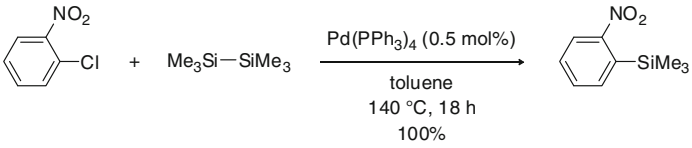
Furthermore, it has been reported that the preparation of the corresponding arylboronic acids from aryl halides, followed by the coupling reactions with aryl tosylates or mesylates can obtain the target biaryl compounds **22** (Scheme 7.7) [100].



Scheme 7.7 Suzuki-Miyaura coupling with aryl tosylates or mesylates

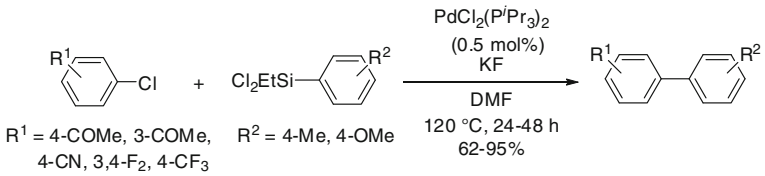
7.6 Hiyama Coupling

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-dichloronitorobenzene as the coupling partner [102].



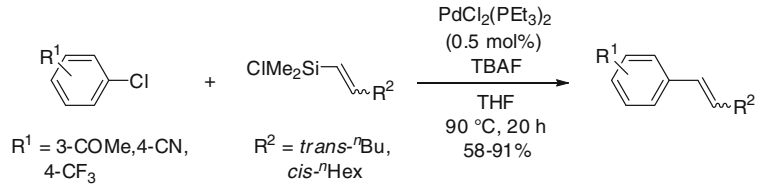
(7.23)

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].



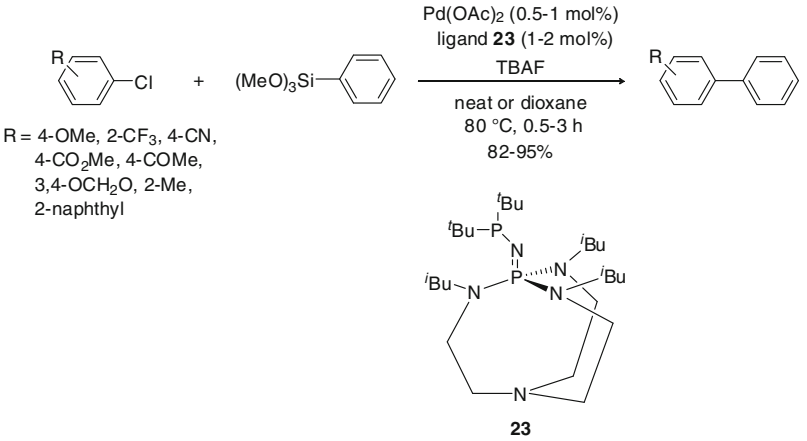
(7.24)

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.



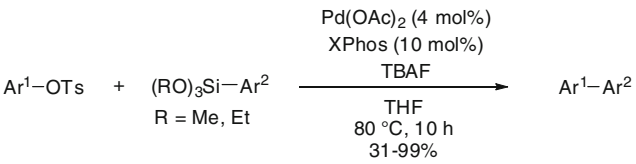
(7.25)

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].

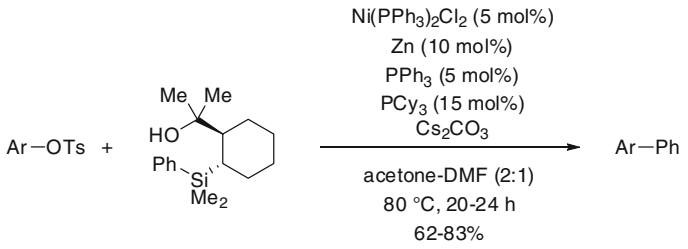


(7.27)

Ar^1 = 4-^{t}BuC$_6$H$_4$, 4-PhC$_6$H$_4$, 4-EtO$_2$CC$_6$H$_4$, 4-NCC$_6$H$_4$, 4-MeC$_6$H$_4$, 4-CF$_3$C$_6$H$_4$, 2-MeC$_6$H$_4$, 3-pyridinyl, 1-naphthyl, 2-naphthyl,

Ar^2 = Ph, 4-MeOC$_6$H$_4$, 2-MeC$_6$H$_4$, 2-thiophenyl

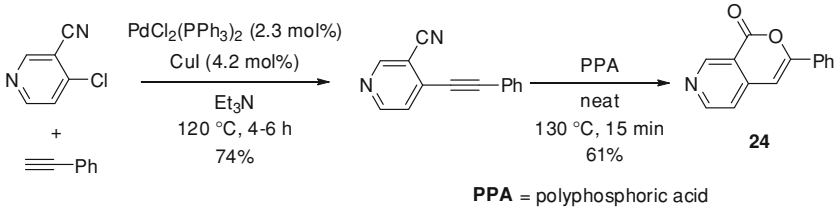
Only one example of a nickel version of coupling reactions of aryl tosylates was reported; Hiyama et al. very recently accomplished this by using the mixed system of two different phosphine ligands (Eq. 7.28) [112]. Importantly, an aryl mesylate also participated in the coupling reaction to give the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



(7.28)

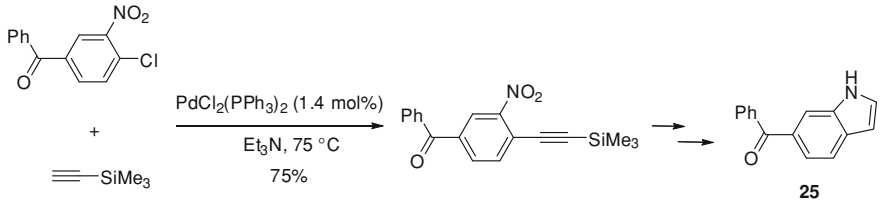
7.7 Sonogashira–Hagihara Coupling

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**).



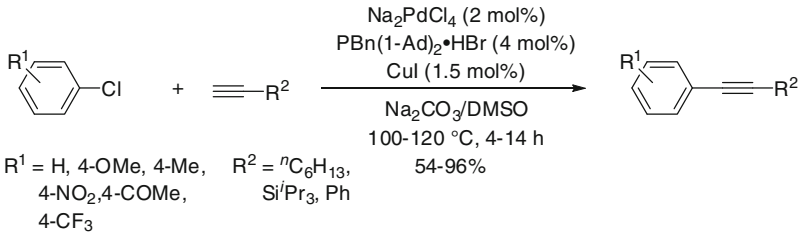
Scheme 7.8 Sonogashira-Hagihara coupling with aryl chlorides

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].



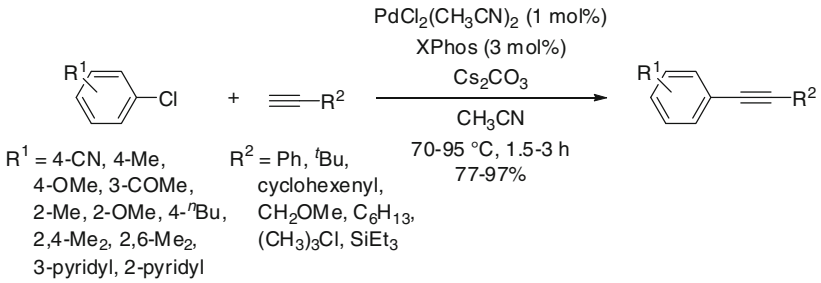
Scheme 7.9 Synthesis of arylethynes from aryl chlorides having a nitro group in the 2-position

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)

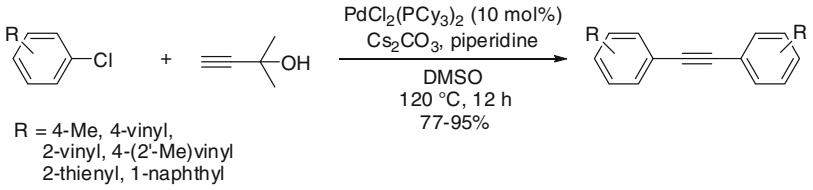
In the same year, Buchwald reported that Sonogashira–Hagihara coupling reactions of a variety of aryl chlorides smoothly proceeded in the presence of the palladium catalysts ligated by XPhos (see Scheme 7.4) (Eq. 7.30) [117]. This reaction overcame the prior limitations of substrates. In the past, coupling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



(7.30)

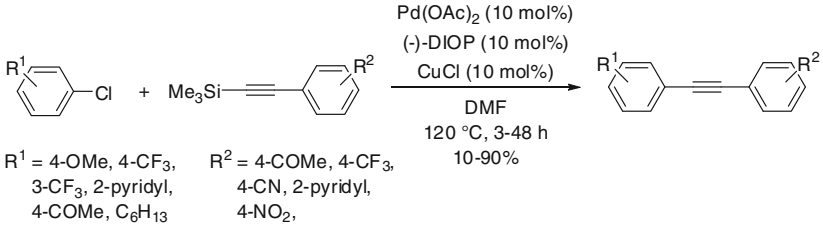
In 2007, Hua et al. reported the reactions of aryl chlorides affording the symmetrical diarylethynes in one pot (Eq. 7.31) [118]. In this reaction, the same aryl groups can be introduced to both ends of the ethyne by using 1,1-

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].



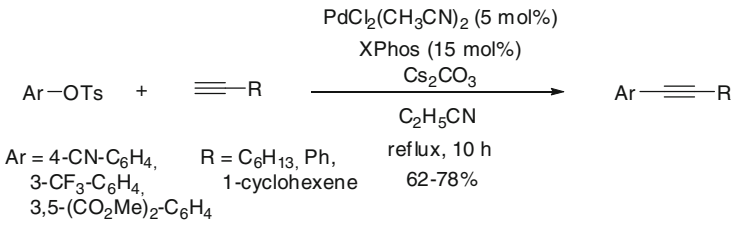
(7.31)

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].



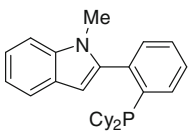
(7.32)

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.

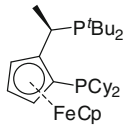


(7.33)

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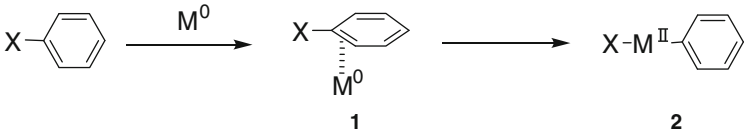
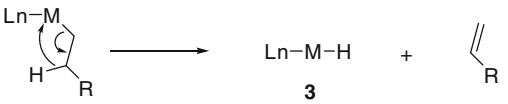
various inert carbon electrophiles such as organic chlorides, as well as mesylates and tosylates converted from a hydroxyl group, have become available as coupling partners in this catalyst system.

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.



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

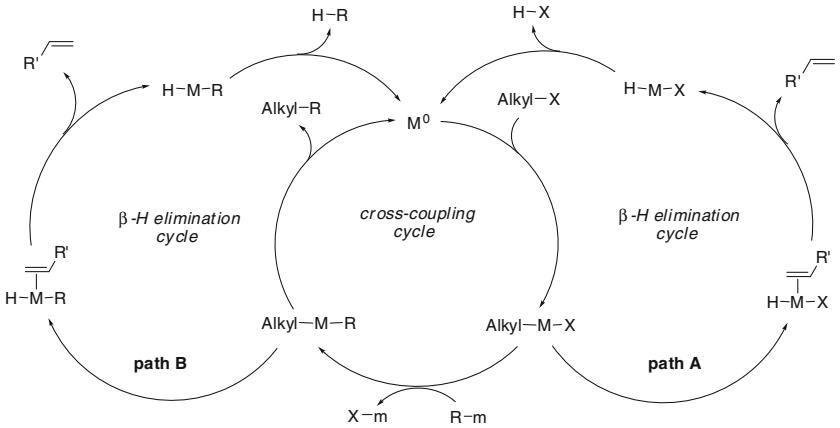
In sharp contrast to the molecules bearing π-bonds, the alkyl electrophiles bearing the β-hydrogens have scarcely been used as carbon electrophiles in the catalytic cross-coupling reactions. The main reasons for the poor success of cross-coupling reactions of the alkyl halides are as follows: (1) the 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).



(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.



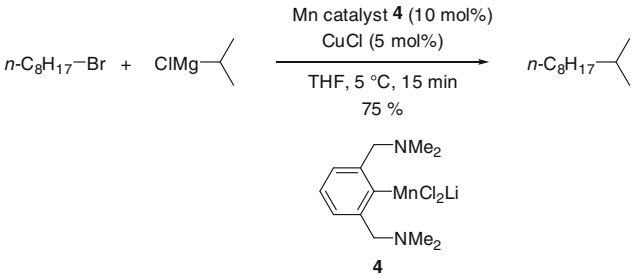
Scheme 8.2 Catalytic cycles involving alkyl electrophiles

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

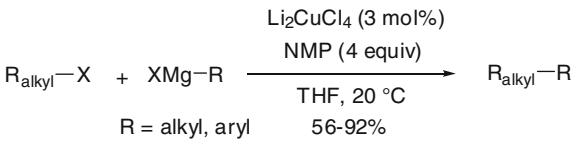
The first Kumada–Tamao–Corriu coupling of alkyl halides was the reaction with Grignard reagents catalyzed by silver, reported by Kochi and Tamura in the early 1970s [1–3]. Although a few similar reactions catalyzed by transition metals such as copper and nickel had been reported over the ensuing 20 years,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



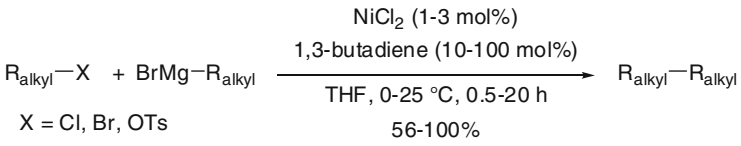
(8.2)

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.



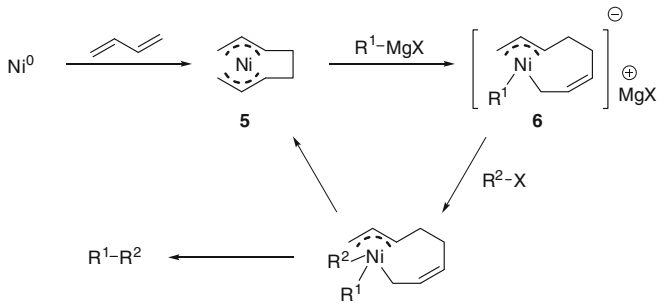
(8.3)

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.



(8.4)

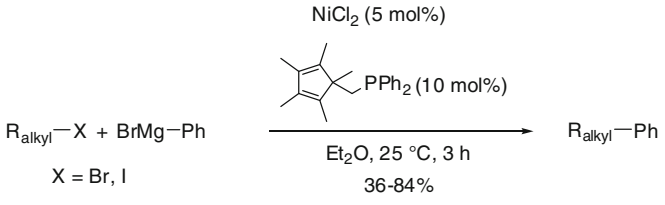
Moreover, Terao and Kambe showed that the 1,3-butadiene ligand stabilized the active species and promoted reductive elimination. The proposed reaction mechanisms are shown in Scheme 8.3. First, $NiCl_2$ is reduced by R^1MgX, and then two molar equivalents of 1,3-butadiene react with the generated Ni(0) 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



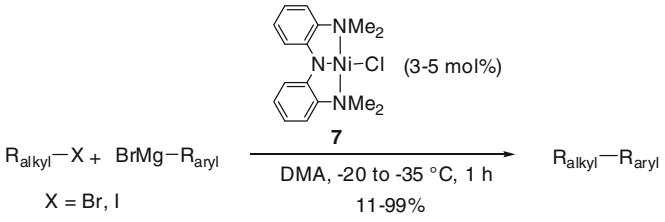
Scheme 8.3 Ni-catalyzed alkyl-alkyl coupling by using 1,3-butadiene ligand

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].

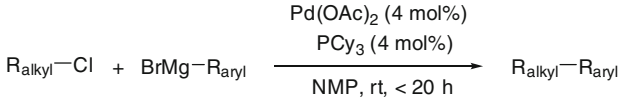


(8.5)



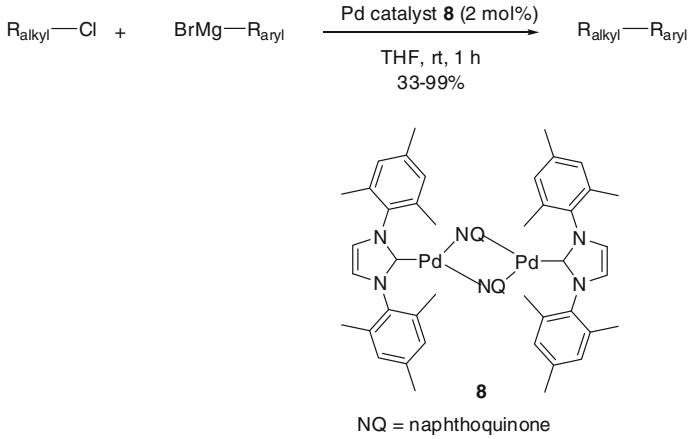
(8.6)

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].



(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].



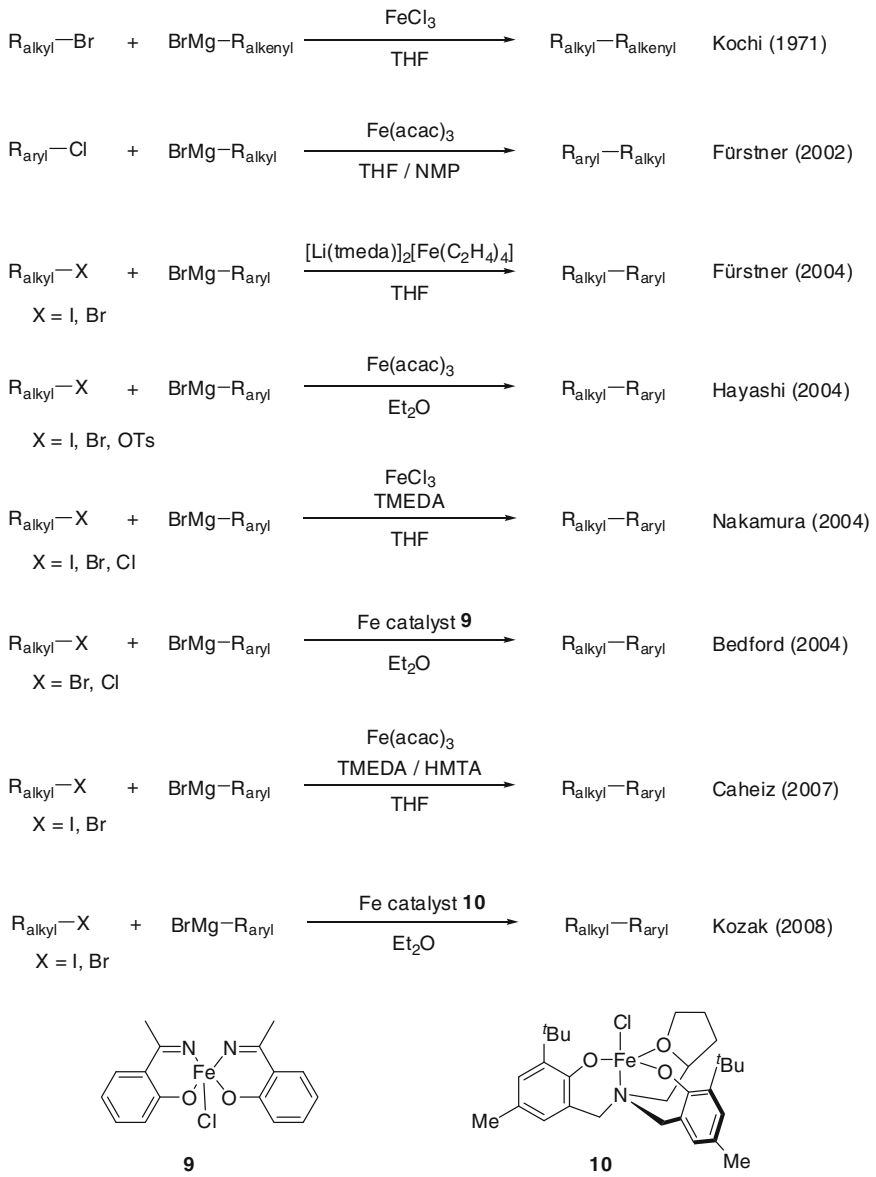
(8.8)

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].

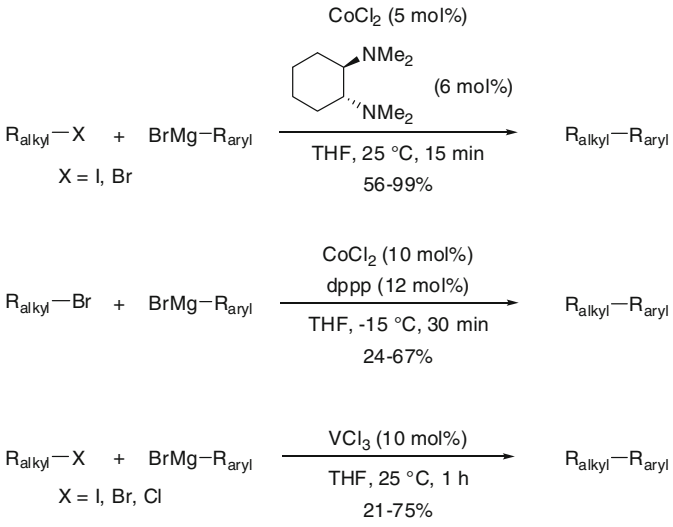
As described herein, it seems that the catalysts for Kumada–Tamao–Corriu coupling reactions of the alkyl electrophiles are no longer limited to palladium and nickel. In the iron-catalyzed reactions the anionic iron complex is postulated to be the active species, while in the reactions catalyzed by cobalt 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

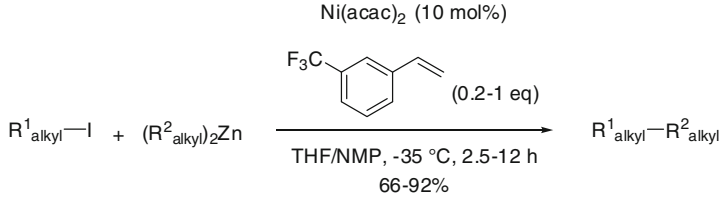
Tucker and Knochel reported the first account of Negishi coupling using alkyl halides in 1993; this work dealt with the reactions of alkyl iodides and dialkyl zinc reagents, mediated by a stoichiometric amount of $[Cu(CN)Me_2(MgCl_2)]$ [28]. Two



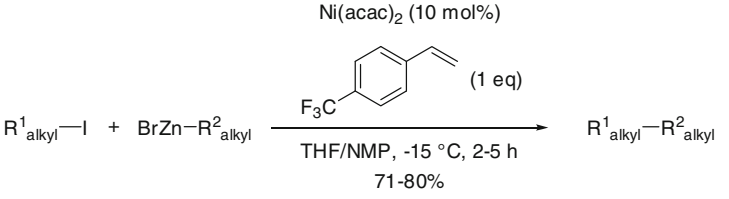
Scheme 8.5 Co- and V-catalyzed Kumada-Tamao-Corriu coupling of alkyl electrophiles

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].



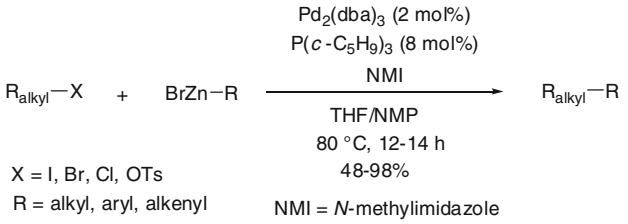
(8.9)



(8.10)

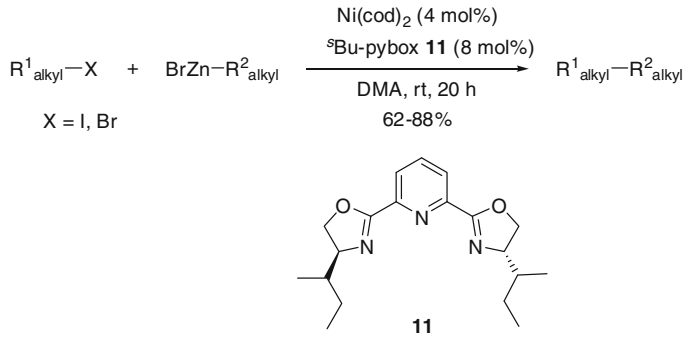
In 2003, Zhou and Fu reported Negishi coupling reactions with alkyl electrophiles by using a palladium catalyst ligated with tricyclopentylphosphine (Eq. 8.11) [33]. The reaction efficiently took place with unactivated primary alkyl

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.



(8.11)

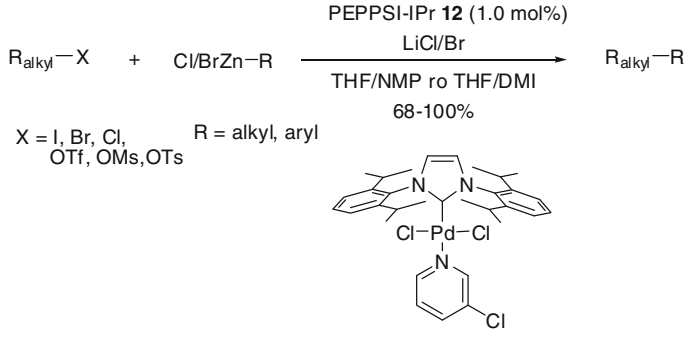
In addition, Fu has also succeeded in an extension of these reactions to include the cross-coupling reactions of secondary alkyl bromides and iodides (Eq. 8.12) [34]. These newer reactions smoothly proceed at room temperature with the aid of the nickel catalyst bearing the bis(oxazolinyl)pyridine (pybox)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



11

(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].



12

(8.13)

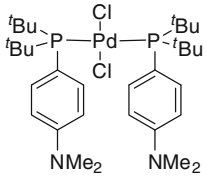
Lipshutz reported reactions of alkyl halides at room temperature in water using the organozinc reagents generated in situ from zinc-diamine complexes and the commercially available amphiphile polyoxyethanyl α-tocopheryl sebacate (PTS); these reactions were catalyzed by palladium complex **13** having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

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

65-92%

PTS = polyoxyethanyl α-tocopheryl sebacate

(8.14)



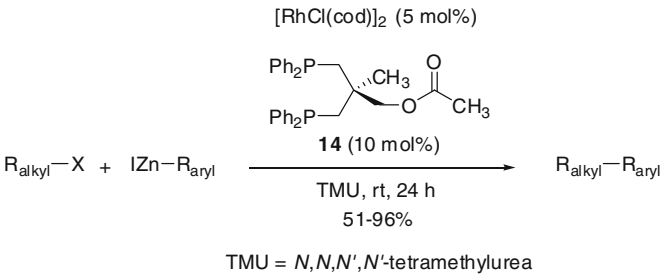
13

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].

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

72-98%

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].

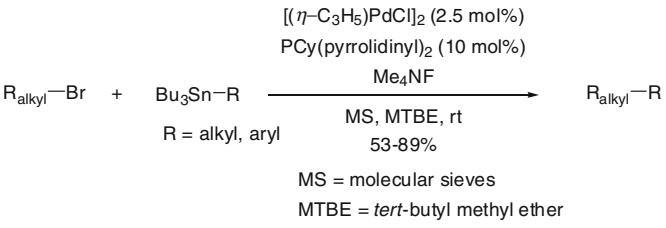


(8.16)

8.4 Migita–Kosugi–Stille Coupling

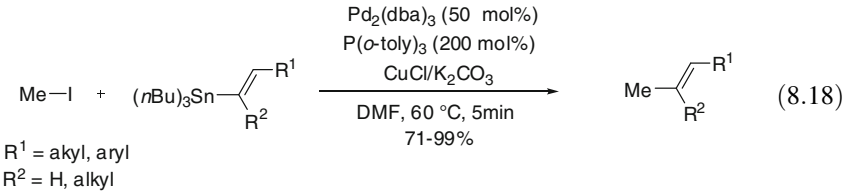
Migita–Kosugi–Stille coupling reactions of alkyl halide electrophiles were reported by Fuchikami in 1996, using $PdCl_2(PPh_3)_2$ as the catalyst [39]. In these reactions, alkyl iodides substituted with an electron-deficient fluorine atom in the β-position reacted with organotin compounds. However, the 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)

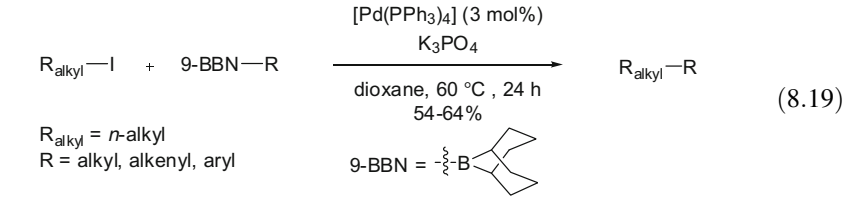
In 2006, the palladium-catalyzed methylation of alkenyl stannanes was carried out by incorporating a short-lived ^{11}C-labeled methyl group into biologically significant methylated alkenes with the aim of synthesizing a positron emission tomography (PET) tracer (Eq. 8.18) [42]



(8.18)

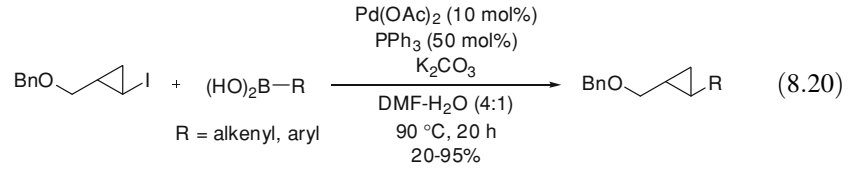
8.5 Suzuki–Miyaura Coupling

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.



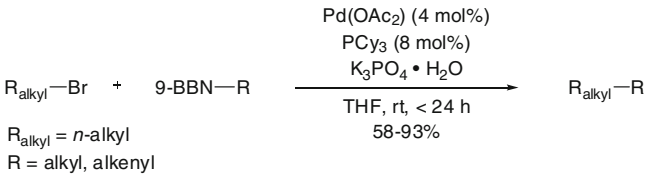
(8.19)

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.



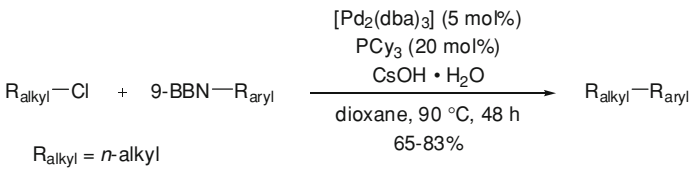
(8.20)

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.



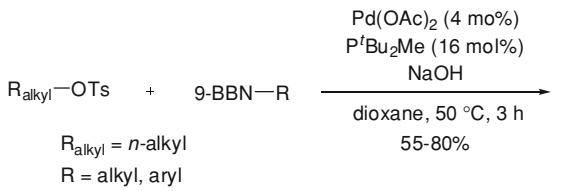
(8.21)

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.

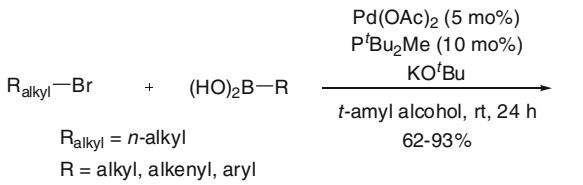


(8.22)

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.

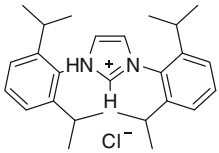


(8.23)



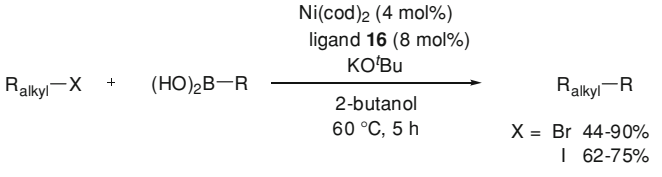
(8.24)

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



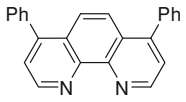
In 2004, Caddick and Cloke reported the alkyl–alkyl-type Suzuki–Miyaura coupling reactions of primary alkyl bromides with alkyl boron compounds by using the palladium catalyst with *N*-heterocyclic carbene ligand **15** (Fig. 8.1) [49]. However, yields of the coupled products were below 60% and not satisfactory.

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].



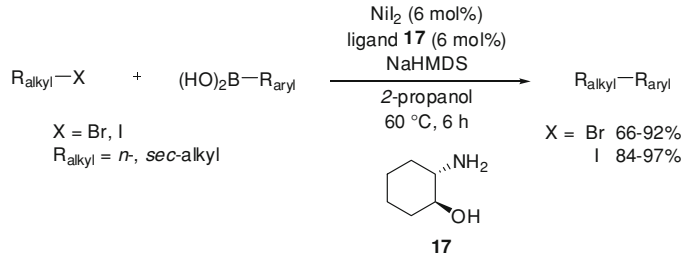
(8.25)

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

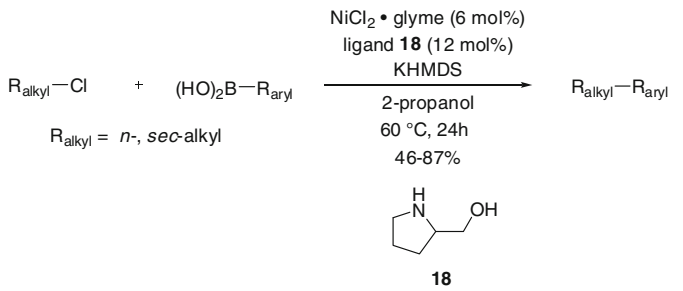


16

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 $Ni(cod)_2$.

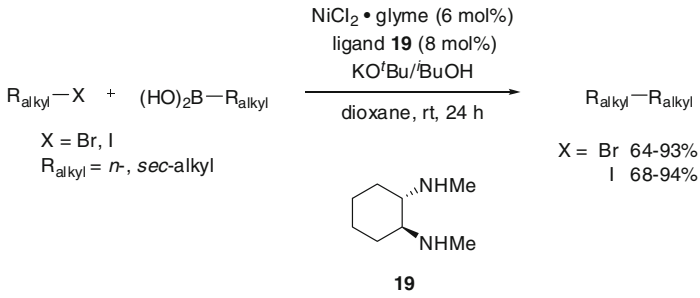


(8.26)



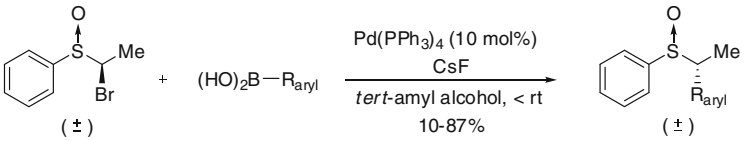
(8.27)

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.).



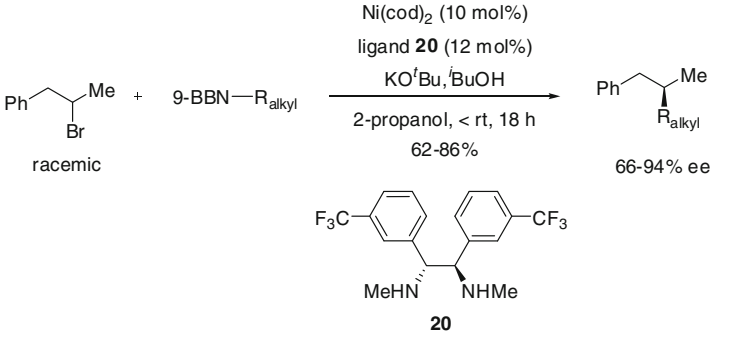
(8.28)

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 aryl-sulfoxides 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.



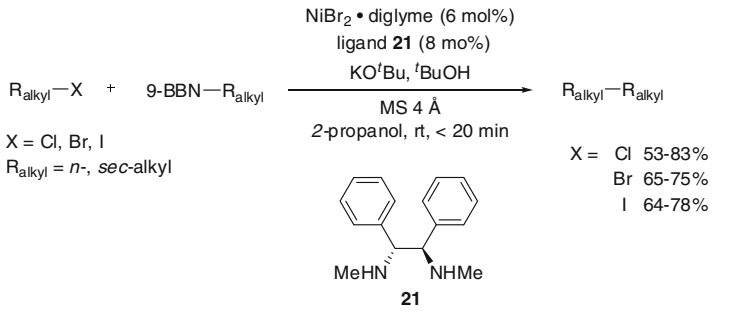
(8.29)

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.



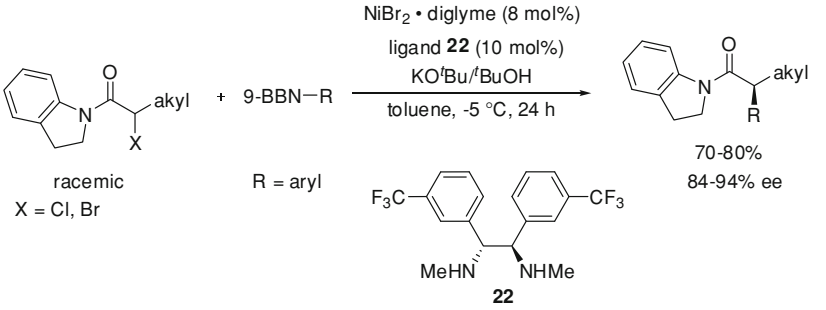
(8.30)

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.



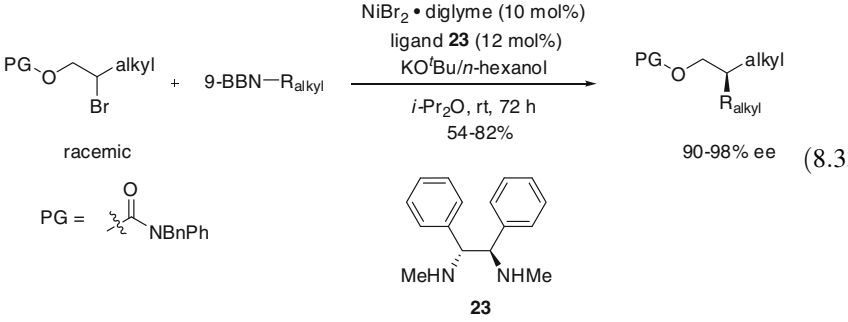
(8.31)

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)

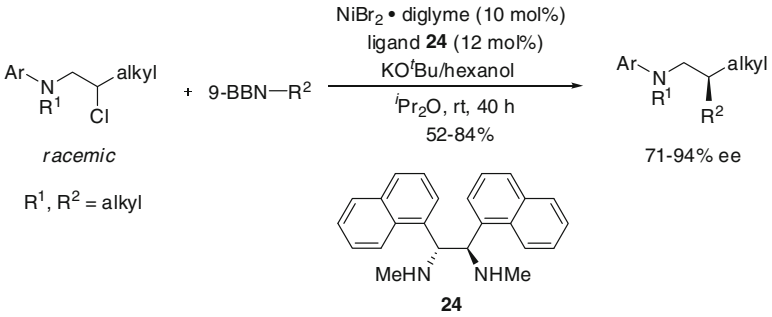
Subsequently, Fu reported the enantioselective alkyl–alkyl-type Suzuki–Miyaura coupling reactions of inert secondary alkyl chlorides with alkylboron compounds (Eq. 8.33) [60]. In this reaction, the chiral coupled products were synthesized from the racemic acylated halohydrins and alkylboron compounds,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



(8.33)

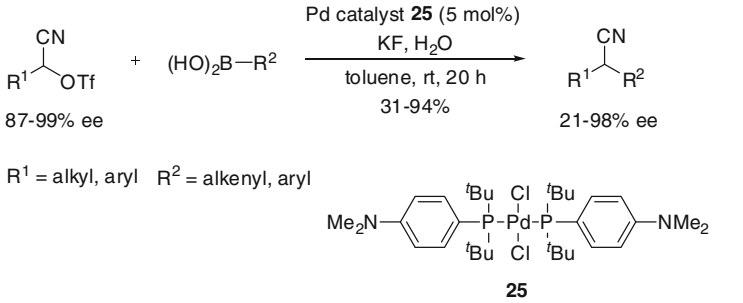
Very recently, Fu et al. reported the stereoconvergent alkyl–alkyl-type Suzuki–Miyaura coupling reactions of inert secondary alkyl chlorides substituted with amines (Eq. 8.34) [61]. Detailed mechanistic studies indicated that the primary site of coordination of the arylamine substrates to the nickel 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.



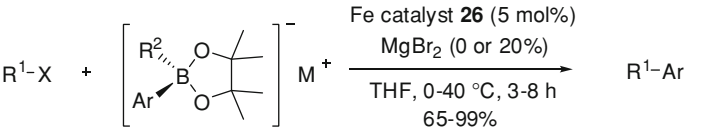
(8.34)

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].

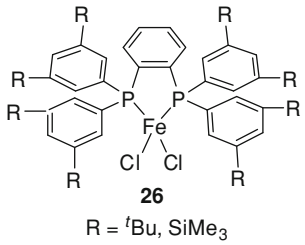


(8.35)

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.



X = Cl, Br, I M = Li or MgBr
R^1 = *n*-, *sec*-alkyl R^2 = Et, Bu, ^{t}Bu

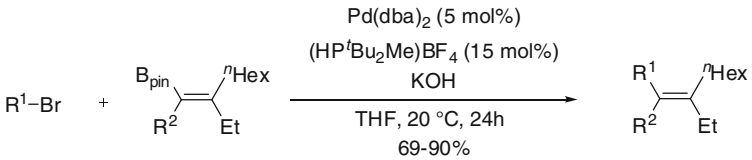


26

R = ^{t}Bu, $SiMe_3$

(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.



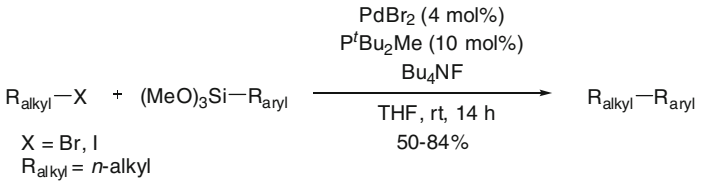
R^1, R^2 = *n*-alkyl

(8.37)

8.6 Hiyama Coupling

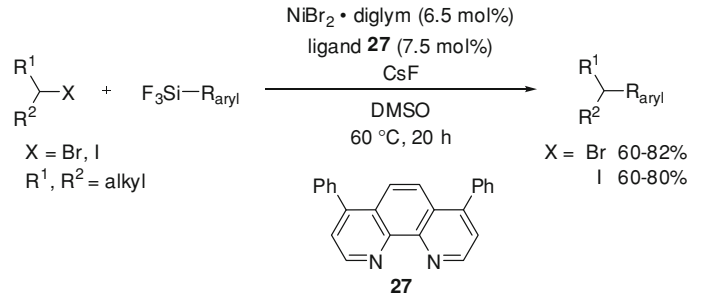
The synthetic examples of Hiyama coupling reactions of alkyl halides as the coupling partners are comparatively few, but have gradually increased in number in recent years. For instance, in 2003 Fu et al. reported Hiyama coupling reactions of inert primary alkyl halides with aryl silicon compounds, utilizing palladium with the P^{t}Bu$_2$Me 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.



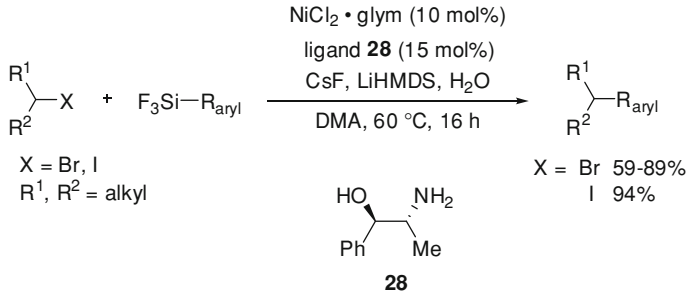
(8.38)

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.



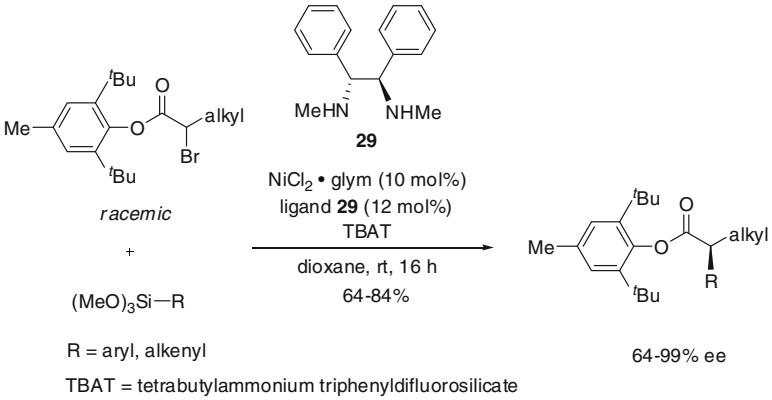
(8.39)

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)

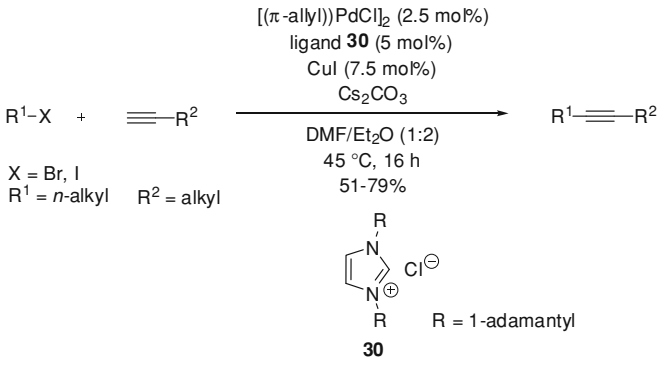
In 2008, Fu et al. reported the nickel-catalyzed asymmetric Hiyama coupling reactions of the racemic secondary α-bromoesters, employing diamine ligands **29** to give the corresponding chiral secondary esters with high enantioselectivity (Eq. 8.41) [68]. Anhydrated tetrabutylammonium triphenyldifluorosilicate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



(8.41)

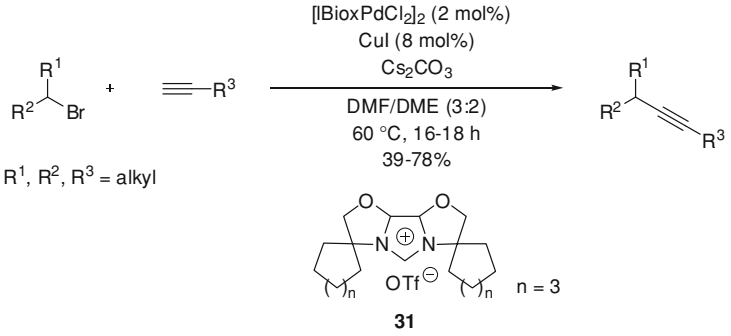
8.7 Sonogashira–Hagihara Coupling

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.



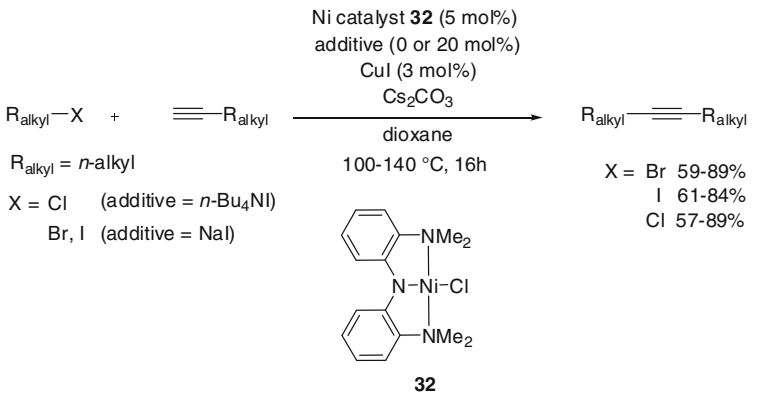
(8.42)

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.



(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.

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Erratum to: A Historic Overview of the Metal-Catalyzed Cross-Coupling Reactions

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The subjected book was inadvertently published with an incorrect first name of the contributor in Chap. 1 as Yaushi Nishihara, whereas the correct first name is Yasushi Nishihara. The chapter has been updated.

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Appendix
Reviews and Books of Cross-Coupling Reactions

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Index

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