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Cross-Coupling Reactions

A Practical Guide

Volume Editor: Norio Miyaura

With contributions by
S. L. Buchwald, K. Fugami, T. Hiyama, M. Kosugi,
M. Miura, N. Miyaura, A. R. Muci, M. Nomura,
E. Shirakawa, K. Tamao

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Volume Editor

Prof. Norio Miyaura
Division of Molecular Chemistry
Graduate School of Engineering
Hokkaido University
Sapporo 060-8628, Japan
E-mail: miyaura@org-mc.eng.hokudai.ac.jp

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Preface

In 1972, a very powerful catalytic cycle for carbon-carbon bond formation was first discovered by the coupling reaction of Grignard reagents at the sp^2-carbon. Over the past 30 years, the protocol has been substantially improved and expanded to other coupling reactions of Li, B, N, O, Al, Si, P, S, Cu, Mn, Zn, In, Sn, and Hg compounds. These reactions provided an indispensable and simple methodology for preparative organic chemists. Due to the simplicity and reliability in the carbon-carbon, carbon-heteroatom, and carbon-metalloid bond-formations, as well as high efficiency of the catalytic process, the reactions have been widely employed by organic chemists in various fields. Application of the protocol ranges from various syntheses of complex natural products to the preparation of biologically relevant molecules including drugs, and of supramolecules, and to functional materials. The reactions on solid surfaces allow robot synthesis and combinatorial synthesis. Now, many organic chemists do not hesitate to use transition metal complexes for the transformation of organic molecules. Indeed, innumerable organic syntheses have been realized by the catalyzed reactions of transition metal complexes that are not achievable by traditional synthetic methods. Among these, the metal-catalyzed cross-coupling reactions have undoubtedly contributed greatly to the development of such a new area of "metal-catalyzed organic syntheses".

An excellent monograph for the cross-coupling reactions and other metal-catalyzed C-C bond-forming reactions recently appeared in *Metal-catalyzed Cross-coupling Reactions* (Wiley-VCH, 1998). In order to avoid overlapping with previous publications, also in view of space limitation, this book is restricted to the most recent and practical developments in this field. The book covers new advances in the representative coupling reactions of organoboron, -silicon, and -tin compounds, as well as two new areas for carbon-heteroatom bond formation and the carbon-carbon bond formation via direct C-H substitution. The actual practical procedures of the cross-coupling reactions are given, including technical advice on actual applications in organic synthesis. The hope of the authors is that this book will help both expert and novice practitioners to use metal-catalyzed cross-reactions for organic syntheses.

Sapporo, October 2001 Norio Miyaura

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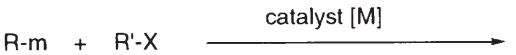
Introduction to Cross-Coupling Reactions

Kohei Tamao[1], Norio Miyaura[2]

[1] Institute for Chemical Research, Kyoto University Uji, Kyoto 611-0011, Japan
E-mail: tamao @sc1.kyoto-u.ac.jp
[2] Division of Molecular Chemistry, Graduate School of Engineering, Hokkaido University, Sapporo 060-8628, Japan
E-mail: miyaura@org-mc.eng.hokudai.ac.jp

1 Historical Perspective

The cross-coupling reaction of organometallic reagents with organic electrophiles in the presence of group 8 – 10 metal catalysts, notably nickel and palladium complexes, is the method of choice for a wide range of C-C, C-H, C-N, C-O, C-S, C-P or C-M bond-forming process [1]. These reactions, now accessible with a variety of organometallic reagents and electrophiles, provide a common class of synthetic transformations, commonly referred to as "cross-coupling reactions" (Eq. 1).



(1)

m= Li (Murahashi)
Mg (Kumada-Tamao, Corriu)
B (Suzuki-Miyaura)
Al (Nozaki-Oshima, Negishi)
Si (Tamao-Kumada, Hiyama-Hatanaka)
Zn (Negishi)
Cu (Normant)
Zr (Negishi)
Sn (Migita-Kosugi, Stille) .....

[M]= Fe, Ni, Cu, Pd, Rh .....

X= I, Br, Cl, OTf .....

The reactions of Li/Mg reagents in the presence of stoichiometric and catalytic amounts of copper halides had been studied extensively during the 1960's to 1970's [2]. The reaction at sp^2- or sp-carbons, however, was very limited until the discovery of the transition metal-catalyzed cross-coupling reaction of Grignard reagents. In 1971, Kochi reported the efficiency of $FeCl_3$ as a catalyst for the coupling of Grignard reagents with 1-alkenyl bromides [3] and Li_2CuCl_4

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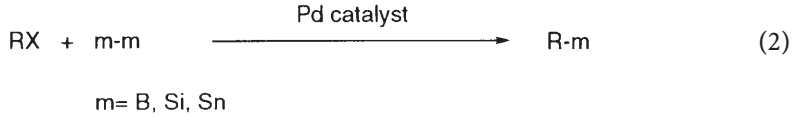
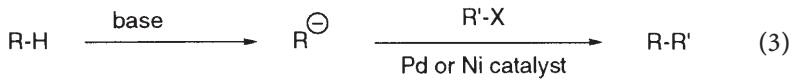
for the sp^3-sp^3 coupling of RMgX and iodoalkanes [4]. In 1972, the nickel-catalyzed reaction of Grignard reagents with 1-alkenyl or aryl bromides and chlorides was independently reported by Kumada and Tamao [5] as well as Corriu and Masse [6]. Although the simple extension of Kharasch-type reaction using phosphine-free metal halides resulted in extensive homocoupling, a selective reaction at the sp^2-carbon was achieved in the presence of a phosphine complex. A mechanistic study by A. Yamamoto also greatly contributed to the design of this powerful catalytic process [7]. There were many independent contributions to the historical evolution of cross-coupling methodology as is the common situation for other important discoveries. However, the mechanistic proposal that the reaction of Grignard reagents with vinyl chlorides proceeds via an oxidative addition-transmetalation-reductive elimination sequence [5a] has substantially stimulated the development of cross coupling methodology. This represented a new strategy for the carbon-carbon bond formation that had great attraction for organic chemists interested in applications of synthetic-organic chemistry.

After those discoveries, many other transition metal complexes and organometallic reagents have proven to be highly useful as catalysts or nucleophiles. Although the reaction of Mg/Li reagents has been studied extensively in earlier examples, the use of such highly reactive reagents is unfortunately complicated and limited by a lack of functional group compatibility or by competitive halogen-metal exchange leading to homocoupling products. The nickel-catalyzed reactions also suffered from stereochemical scrambling of the starting alkenyl halides and metals. Thus, palladium catalysts and less reactive organometallic reagents have proven to be a more attractive combination. Palladium-catalyzed cross-coupling was first demonstrated by Murahashi in the reaction of vinyl halides with aryllithiums [8]. The efficiency of palladium-catalyzed processes was further demonstrated by Negishi [9] in the reactions of 1-alkenylaluminum [10] and -zinc [11], and -zirconium reagents [12] with vinyl and aryl halides. In addition, the reaction between 1-alkenyl halides and 1-alkenylcopper(I) was reported by Normant [13]. Organostannanes were first used by Migita and Kosugi [14], and extensive subsequent works by Stille positioned these as a mainstay of modern synthetic chemistry [15]. Suzuki and Miyaura found that organoboron compounds smoothly undergo cross-coupling reaction in the presence of a base that has been widely embraced by synthetic chemists [16]. The discovery that organopentafluorosilicates could participate in cross-coupling process by Tamao and Kumada [17] was greatly improved by Hiyama and Hatanaka to a practical C-C bond-forming reaction using organosilicon compounds [18]. Cross-coupling procedures that utilize such coupling partners with highly covalent C-M bonds have found many applications in the syntheses of natural products and fine chemicals. This is due to a large extent to the simplicity of their synthesis, isolation and handling, as well as their compatibility with a wide range of functional groups. Additional attributes include safety and applicability in industrial applications. Analogous reactions of other metals will undoubtedly be reported in the future to overcome the limitations of the processes that utilize these metals. Recent advances in coupling reaction of B, Si and Sn compounds are discussed in chapters 2 – 4.



(2)

Organometallic reagents are, in general, available *via* the hydrometalation of alkenes or alkynes or by transmetalation between Li or Mg reagents and other metal halides. The latter method, however, may have limitations associated with the conversion of organic halides to the requisite Li/Mg intermediates. The coupling reaction of organic electrophiles with disilanes [19], distannanes [20] or diborons [21] leading to C-M bonds provides a straightforward method that allows the simple preparations of the organometallic reagents required for many cross-coupling procedures (Eq. 2). The direct borylation of alkanes and arenes *via* the C-H activation has recently been demonstrated and should be an attractive route to these compounds in the future [22]. Further discussion of these reactions can be found in chapters 2.4.



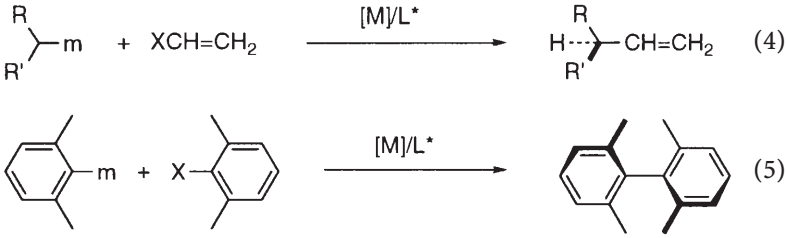
(3)

R-H = R≡C-H (Sonogashira-Hagihara)
$RO_2CCH_2CO_2R$ (Tuji-Trost)
$RCOCH_2R'$ .....
R_2N-H, RO-H (Buchwald, Hartwig)
RS-H (Murahashi)

The direct coupling of organic halides with C-H or heteroatom-H bonds in the presence of a base as well as a palladium catalyst is another useful variant closely related to the present article. Nucleophiles generated *in situ* by mixing a base and an active C-H or heteroatom-H compound directly couple with various organic halides (Eq. 3). The method appears to have a significant advantage in that they can be carried out without preparation of organometallic reagents. In 1975, Cassar [23] and Heck [24] reported a palladium-catalyzed cross-coupling reaction of acetylides, generated *in situ* from terminal alkynes and NaOMe or triethylamine, with aryl halides. In the same year, it was found that the use of copper co-catalyst exhibits a significant accelerating effect in the presence of triethylamine [25]. The procedure, called the Sonogashira or Sonogashira-Hagihara reaction, is now accepted as the most practical method for alkynylation of aryl and 1-alkenyl halides. Although earlier studies mainly focussed on the reactions of terminal alkynes, other coupling reactions of acidic C-H bonds, including allylation of enolate anions (Tsuji-Trost reaction) [1b, 26] and arylation or alkenylation of ketone enolates [27], also have been studied extensively. Very recently, the protocol was further extended to the direct coupling reaction of aromatic C-H bonds [28]. These topics are discussed in chapter 6.

The heteroatom cross-coupling reaction of N-H, O-H, S-H and P-H compounds is a topic of current interest. Alkenyl halides were converted into the

sulfides upon treatment aryl or alkenyl halides with RSLi in the presence of $Pd(PPh_3)_4$ [29]. The cross-coupling reaction of Et_2NSnBu_3 was first studied by Kosugi-Migita [30]. Subsequently, Buchwald [31] and Hartwig [32] found that the corresponding amino nucleophiles could be generated *in situ* from R_2NH and *t*-BuONa. The reaction is attractive as environmentally benign process having the potential to replace, in some instance, the commonly used nitration-reduction method for the synthesis of arylamines. Although the reductive elimination of ethers from Ar-Pd-OR intermediates is significantly slower than that of amines or sulfides, the corresponding reaction of alcohols or phenols is already available [33]. Recent advances in palladium-catalyzed C-N and C-O bond formation are reviewed in chapter 5.



Some of the most powerful applications in the future may involve asymmetric C-C or C-heteroatom bond formation. The first attempts at such a process, the asymmetric coupling of 1-phenylethyl Grignard reagent with vinyl chloride in 1973 by Consiglio and Botteghi, $NiCl_2$/DIOP resulted in the formation of the desired product in 13%ee [34]. Subsequently, Kumada, Tamao and Hayashi found that nickel catalysts with chiral ferrocenylphosphines are highly effective in the kinetic resolution of racemic *sec*-alkylmagnesium or zinc reagents during their coupling reactions with alkenyl or aryl halides (Eq. 4) [35]. The synthesis of axially chiral biaryls is another topic of great interest (Eq. 5). This was studied by Uemura by using chiral haloarene/$Cr(CO)_3$ complexes [36]. Asymmetric biaryl coupling controlled by chiral catalysts was first reported by Tamao [37]. The procedures were later improved to over 90%ee by Hayashi [38] and very recently by Buchwald [39]. This topic has recently been reviewed [40].

2
Catalytic Cycle

The transition metal-catalyzed coupling reaction that forms and cleaves the bonds of two organic molecules occurs by a sequence of oxidative addition-transmetalation (alkylation)-reductive elimination (Fig. 1) [1, 7d, 32d–f, 41].

Group 10 transition metals, particularly nickel and palladium, are highly effective in catalyzing cross-coupling reactions, but other metals undergoing a simultaneous two-electron change via an oxidative addition-reductive elimination couple can participate in the same catalytic cycle. All these steps are well-known processes in homogeneous catalysis [41]; however, a combination of the three processes has provided a very powerful and general catalytic method for

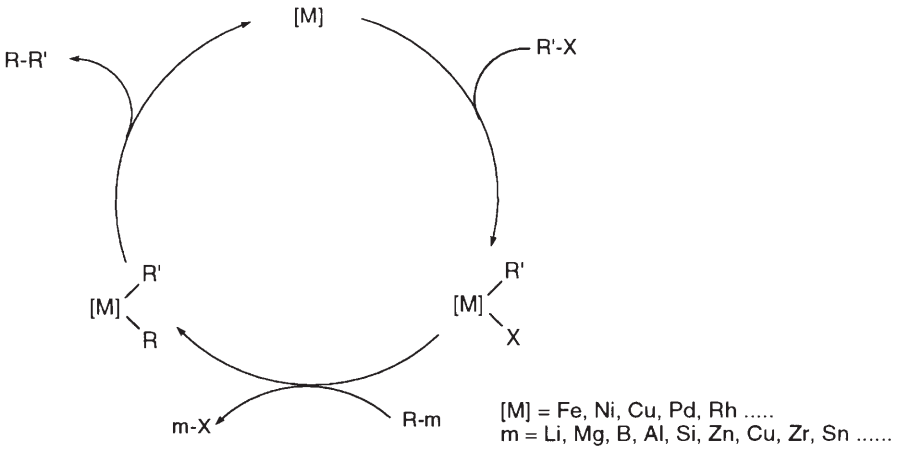


Fig. 1. A General catalytic cycle

C-C, C-H, C-N, C-O, C-S, C-P or C-M bond formation. Among them, transmetalation is the most characteristic of the cross-coupling reaction because this process combines the attributes of transition metals and main group metal reagents. However, the transmetalation is less understood than the other two steps since it is highly dependent on the nature of the organometallic reagents and the reaction conditions, as is discussed in several chapters of this book.

A variety of organometallic reagents and organic electrophiles, including those containing alkyl, allyl, aryl, alkenyl and alkynyl groups, can be employed to assemble carbon-carbon bonds (Fig. 2]. However, there are still limitations in the possible combination of electrophilic and nucleophilic coupling partners. For example, the coupling of two sp^3 centers of unactivated alkyls has been limitted success due to the slow oxidative addition of alkyl halides and β-hydride elimination from organopalladium(II) intermediates [42, 43]. The coupling reaction of Grignard reagents with haloalkanes catalyzed by copper salts is probably the most studied of such processes [4], but the use of organometallic species that are less reactive than Grignard reagents would extend this method of bond formation to more highly functionalized substrates. The low regioselectivity giving a mixture of internal and terminal coupling products on the reac-

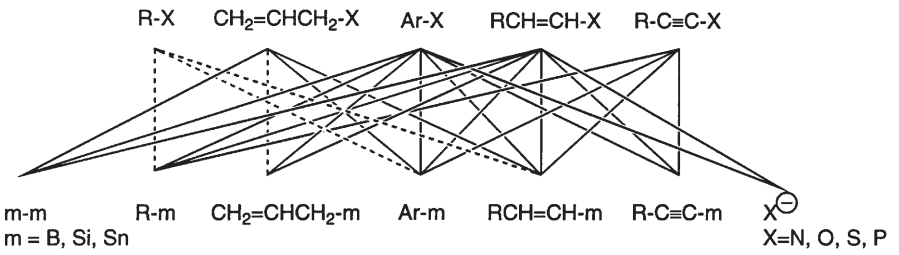


Fig. 2. Scope of reaction

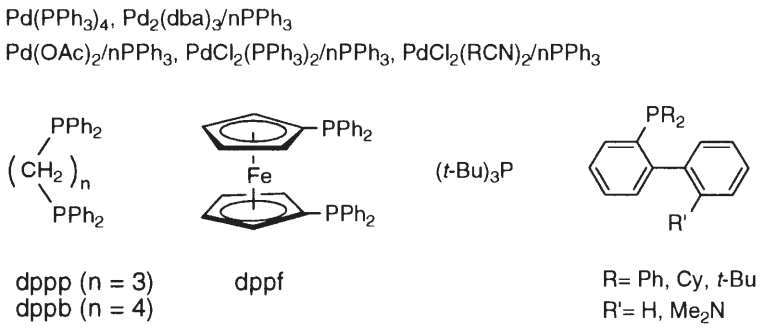


Fig. 3. Ligands and catalysts

tion of allylic electrophiles or nucleophiles [1a, 1b] and the slow reductive elimination from σ-alkyl-π-allyl- or di-π-allylpalladium species [41, 42] also are pending subjects in synthetically useful catalytic transformations.

Various phosphine ligands are effective in stabilizing the Pd(0) or Ni(0) intermediates, but the stoichiometry, size, and electronic effect of the phosphines all contribute to the reactivity of catalysts toward oxidative addition and reductive elimination. In many cases, triphenylphosphine is satisfactory ligand. However, a number of new ligands have been designed and synthesized to attain high catalyst efficiency or selectivity and to expand the scope of the reaction. Bisphosphines having a large P-M-P angle, such as dppp, dppb and dppf, were designed to minimize β-hydride elimination in the sp^3-sp^2 coupling of alkylmetals [5]. Bulkiness of phosphines exhibited a critical role to accelerate reductive elimination of the C-N or C-O bonds in the amination or etherification of aromatic halides [31, 32]. A mono-coordinated palladium intermediate with bulky, electron-donating phosphines, such as $(t\text{-Bu})_3P$, Cy_3P or 2-(di-*t*-butylphosphino)biphenyl, was recognized to be highly reactive for oxidative addition, thus allowing the coupling reactions of chloroarenes with palladium catalysts [45]. Water-soluble ligands have been reported that allowed the C-C bond formation to be carried out in aqueous media [46]. An important issue to facilitate industrial applications of homogeneous catalysis is the need to combine high catalyst efficiency with the ability to recycle the catalyst. As the catalyst efficiency improves and sometimes turnover number of the catalyst (TON) exceeds 10,000. The problems incurred at separation and recycling of the catalyst were solved by using a supported metal catalyst [1c, 1d] or by carrying the reaction in an inmiscible liquid-liquid two-phase system [46].

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Organoboron Compounds

Norio Miyaura

Division of Molecular Chemistry, Graduate School of Engineering, Hokkaido University, Sapporo, 060-8628, Japan
E-mail: miyaura@org-mc.eng.hokudai.ac.jp

Until recently, organoboronic acids had found limited use in organic synthesis due to their low reactivity for ionic reactions. However, it became increasingly clear that they are a valuable reagent capable of undergoing many catalytic carbon-carbon bond formations in organic syntheses including asymmetric synthesis, combinatorial synthesis, and polymer synthesis. A review of the metal-catalyzed cross-coupling reaction of these compounds is presented here with particular emphasis on their application in selective organic syntheses. Representative methods for achieving selective coupling are outlined, along with a survey of a wide range of C-C bond formations.

Keywords. Cross-coupling reaction, Organoboron compounds, Palladium and nickel catalysts, Carbon-carbon bond formation

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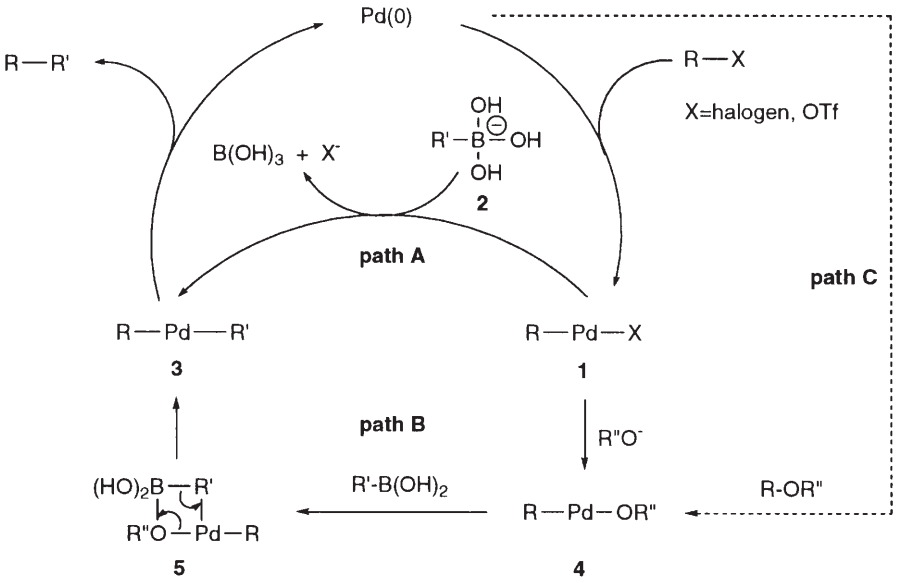
1 Introduction

In 1979, the cross-coupling reaction of organoboron compounds, which involves transmetalation to palladium(II) halides as a key step, was found to proceed smoothly in the presence of an aqueous base. The protocol has been proved to be a quite general reaction for a wide range of selective carbon-carbon bond formations, in addition to previous studies for related coupling reactions of organomagnesiums, -zincs, -stannanes, and -silicones [1]. Now, many organometallic reagents undergo similar cross-coupling reactions, but much attention has recently been focused on the use of organoboronic acids in laboratories and industries since they are convenient reagents, generally thermally stable and inert to water and oxygen, thus allowing handling without special precautions. This review discusses the palladium- or nickel-catalyzed cross-coupling reaction of organoboron compounds with organic halides or triflates, the reaction mechanism, the scope of synthetic applications, and other related catalytic processes with transition-metal complexes. Since the previous reviews covered the references until the end of 1995 [2], new developments which appeared during 1996 to the end of 2000 are discussed in this review, which will, in part, overlap with related articles [3–5].

2 Catalytic Cycle

The cross-coupling reaction of organoboron compounds follows an analogous catalytic cycle to main metal reagents, involving (a) oxidative addition of organic halides or other electrophiles to a palladium(0) complex yielding R-Pd-X (**1**), (b) transmetalation between Pd-X and R′-B, and (c) reductive elimination of R-R′ to regenerate the palladium(0) complex [1]. Although the two steps for oxidative addition and reductive elimination are reasonably well understood, less is known about the transmetalation with the aid of base. Available information indicates that there are three processes, path A-C, for transferring the organic group on the boron atom to R-Pd-X (**1**) (Scheme 1).

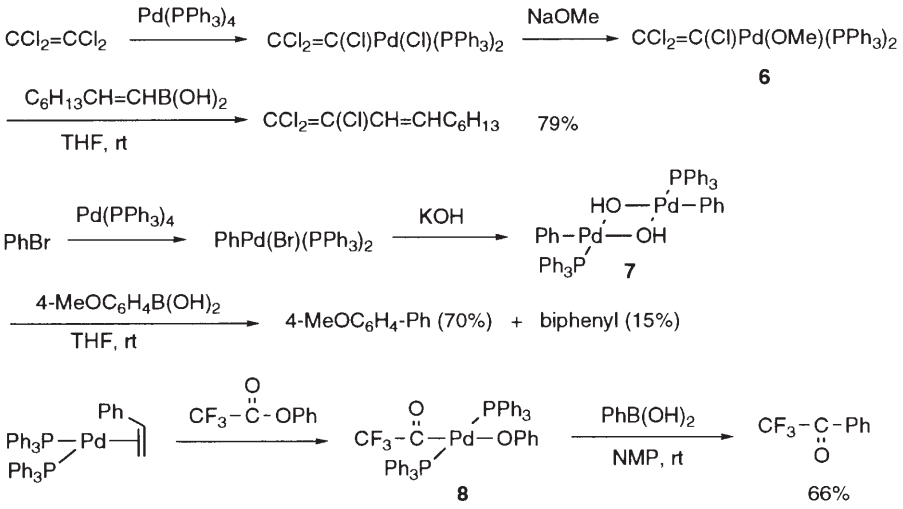
The addition of sodium hydroxide or other bases exerts a remarkable accelerating effect on the transmetalation between R-Pd-X and trialkylboranes or organoboronic acids, which is quite different from the related reactions of other organometallics. Although organoboronic acids do not react with R-Pd-X (X = halogen), the ate-complexes such as Bu_4BLi [2], $[ArB(Bu)_3]Li$ [2], Ph_4BNa [6, 7], $[R_3BOMe]Na$ [8], $[ArB(R)(OR)_2]Li$ [9], and $[ArBF_3]K$ [10, 11] readily undergo the palladium- or nickel-catalyzed coupling reaction in the absence of a base. Thus, the quarternization of the boron atom with a negatively charged base enhances the nucleophilicity of the organic group on the boron atom for alkylation of R-Pd-X (**1**). Although there is no direct evidence for analogous hydroxyboronate anions, $RB(OH)_3^-$ (**2**) [12a], which exists in alkaline solution in equilibrium with a free organoboronic acid, could similarly alkylate R-Pd-X (**1**) (path A). The transmetalation to **1** decreasing in the order of Cl > Br > I [12] is in



Scheme 1. Catalytic cycle for cross-coupling

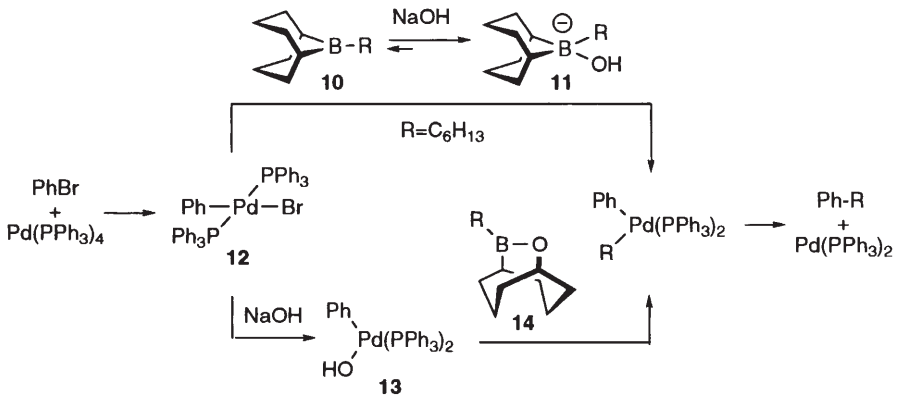
reverse of the oxidative addition of organic halides to palladium(0) complexes and is highly dependent on the added base, as is discussed in the next section.

An alternative process is transmetalation to an (alkoxo)-, (hydroxo)-, (acetoxo)-, or (acetylacetoxo)palladium(II) complex (**4**) *in situ* generated by the ligand exchange between R-Pd-X and a base ($R''O^-$). Such (oxo)palladium(II) complexes smoothly undergo transmetalation with organoboronic acids without the aid of a base (path B). For example, (methoxo)- (**6**) [13], (hydroxo)- (**7**) [14], and (phenoxo)palladium(II) [15] complex (**8**) yield the corresponding coupling products on treatment with an organoboron compounds (Scheme 2). Thus, the coupling reaction often proceeds under neutral conditions for organic electrophiles directly yielding an (oxo)palladium(II) intermediate (**4**) (path C). The cross-coupling reactions of allyl phenoxide [16], propargyl carbonates [17], 1,3-butadiene monoxide [18] and phenyl trifluoroacetates [15] were carried out in the absence of a base. The reaction may involve a rate-determining coordination of the $R''O$ ligand to the boron atom [17]. As a result of complex formation (**5**), the transfer of an activated organic group from boron to palladium then takes place. High reactivity of the oxo-palladium complexes can be attributed to both the high basicity of the Pd-O species and the high oxophilicity of the boron center. The basicity of R-Pd-OH is not known, but the related platinum complexes, such as $PtH(OH)[P(^iPr)_2]$ or *trans*-$Pt(OH)(Ph)(PPh_3)_2$, are reported to be more basic than NaOH [19]. On the other hand, the oxidative addition of Ph_2IX (X=BF_4, OTs, OTf) [20], PhI(OH)OTs [20], or ArN_2BF_4 [21] generating a cationic palladium species directly undergo transmetalation with organoboronic acids, as was reported in a related reaction between $[Pt(MeOH)_2(PPh_3)_2]^{2+}$ and $PhB(OH)_2$ [22].



Scheme 2. Transmetalation to (oxo)palladium(II) complexes

It is known that the halogen or OTf ligand on R-Pd-X (**1**) is readily displaced by an alkoxy, hydroxy, or acetoxy anion to provide a basic R-Pd-OR″ (**4**) complex, as is seen in the syntheses of **6** and **7**. Thus, available information indicates that there are two transmetalation processes (path A and path B) for the cross-coupling reaction in alkaline solution; however, it is not yet obvious in many reactions which process is predominant. It was recently demonstrated that the reaction of 9-alkyl-9-BBN (**10**) proceeded through the former process (path A) and the latter (path B) was predominant in a less acidic 9-oxa-10-borabicyclo[3.3.2]decane (**14**) [23] (Scheme 3). NMR study revealed the exclusive formation of an ate-complex (**11**) between **10** and NaOH whereas the corresponding **14** remained unchanged with an added base. The reactions were zero-order in



Scheme 3. Two transmetalation processes depending on boron reagents

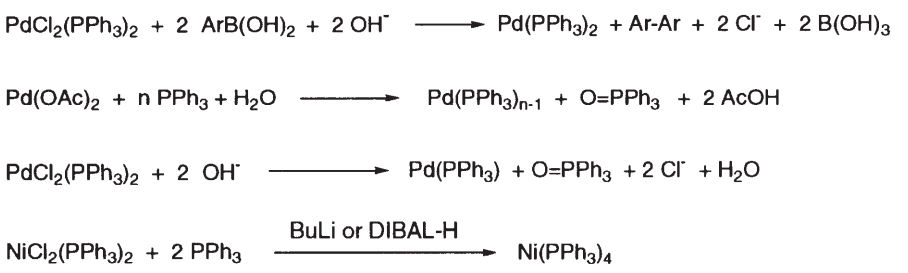
two boranes suggesting no rate-determining role of the transmetalation, whereas the oxidative addition of bromobenzene to palladium(0) leading to **12** or the ligand exchange between **12** and NaOH giving a (hydroxo)palladium species (**13**) determined the reaction rates for **10** and **14**, respectively. The results indicate that transmetalation process and the rate-determining step are highly dependent on organoboron reagents, presumably also organic electrophiles and the functionality therein [12a].

3
Reaction Conditions

3.1
Catalysts, Bases, and Solvents

3.1.1
Catalysts

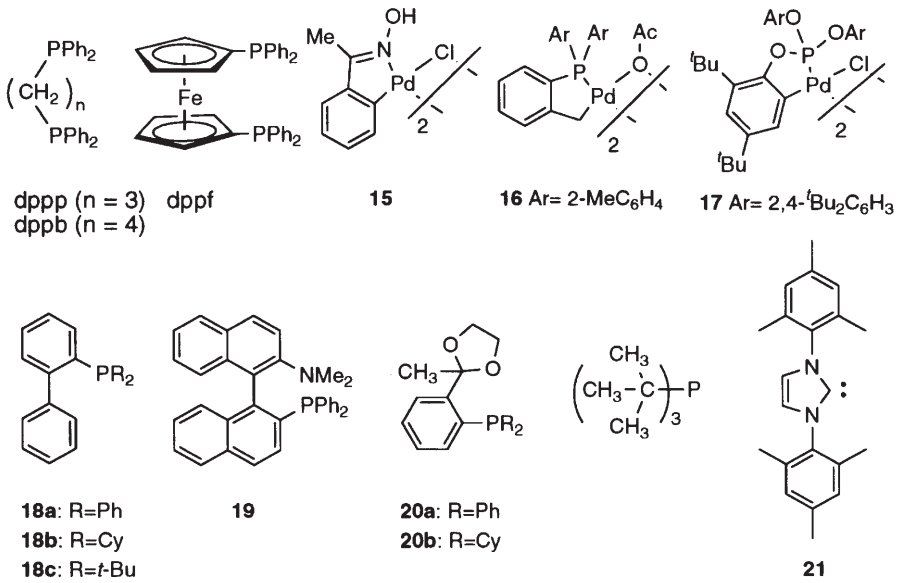
The reaction is feasible with various catalysts, bases, and solvents; however, the combinations will significantly affect the yields and the selectivity of products. $Pd(PPh_3)_4$ is the most common, but $Pd_2(dba)_3$ itself or plus a phosphine ligand are convenient for preparing the desired palladium(0)/phosphine complexes while adjusting the Pd/P ratio. $Pd(OAc)_2$ and $PdCl_2$/phosphines or plus an additional ligand are also good precursors to generate an analogous palladium(0) species because they are easily reduced *in situ* to the corresponding palladium(0) complexes [24] (Scheme 4). The reduction of $Pd(OAc)_2$ with phosphine is instantaneous [25], but $PdCl_2$/phosphines can be aided by the presence of a base [26, 27]. However, the treatment with BuLi or DIBAL-H is recommended for $NiCl_2$/phosphine complexes because their reduction is very slow [28] or leads to nickel hydroxide in the presence of an aqueous base [29].



Scheme 4. In situ reduction of palladium(II) and nickel(II) halides

Various phosphine ligands are effective in stabilizing the palladium(0) species, but the stoichiometry of phosphine to palladium and the bulkiness or donating ability of phosphine ligands change the reactivity of catalysts toward oxidative addition and transmetalation (Scheme 5). $Pd(PPh_3)_4$ and other

Pd/phosphine complexes are in equilibrium with their coordinatively unsaturated species, Among them, either a diphosphine palladium(0) $L_2Pd(0)$ or a monophosphine palladium(0) LPd(0) species could be responsible for the oxidative addition of organic halides [30, 31]. Thus, palladium complexes that having fewer than four phosphines, a weakly coordinating ligand such as $AsPh_3$, or a bulky phosphine, such as P(*o*-tolyl)$_3$ and P(*t*-Bu)$_3$, provide highly reactive catalysts because of the ready formation of the coordinatively unsaturated species. The inhibitory effect of the phosphine ligand can be mainly attributed to its large steric hindrance during oxidative addition and transmetalation. Another role of the ligand is electron donation to the palladium(0) metal center, which was amply demonstrated in the coupling reaction of chloroarenes. Although triarylphosphines are an efficient ligand for organic iodides, bromides, and triflates, their reaction with chlorides is very slow [32]. Bulky and highly donating ligands overcome this limitation; for example, P(*t*-Bu)$_3$ [31] and 2-(di-*t*-butylphosphino)biphenyl (**18c**) [33] provided highly active catalysts for chloroarenes even at room temperature. The high reactivity of these catalysts is attributable to a strong electron-donating ability to the metal center and the ready dissociation of the ligand to generate a coordinatively unsaturated species. However, it was also noted that less bulky phosphines, such as P(Cy)$_3$ [31], (dicyclohexylphosphino)arylphosphines (**18b** and **20b**) [33, 34], **19** [35] and N-heterocyclic carbene (**21**) [36, 37], are more practical ligands yielding stable catalysts at higher temperature. On the other hand, the biaryl coupling of activated chloroarenes possessing an electron-withdrawing group [38], chloropyridines [39, 40, 41] and chloroquinolines [42] is well catalyzed by triphenylphosphine/palladium or bisphosphime/palladium complexes. Palladacycles



Scheme 5. Ligands for palladium catalysts

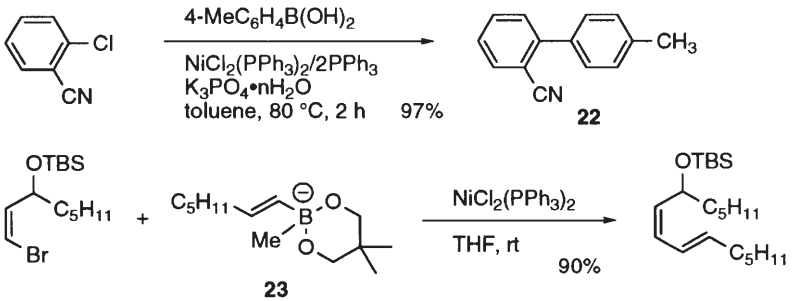
(**15** [43], **16** [44] and **17** [45]) exhibited exceptionally high catalyst-efficiency in the biaryl coupling of arylboronic acids. The highest turnover number of catalyst (TON) achieved for 4-bromoacetophenone was 74,000 with **16** and 1,000,000 with **17**.

*Biaryl coupling by ligand **18c*** [33]: A flask was charged with $Pd(OAc)_2$ (0.01 mmol), **18c** (0.02 mmol), arylboronic acid (1.5 mmol), and KF (3 mmol). The flask was evacuated and backfilled with argon, and THF (1 ml) and chloroarene (1 mmol) were then added. The mixture was stirred at room temperature until the starting chloroarene was completely consumed (2 – 24 h). The reaction with phenylboronic acid: 4-chloroanisole (6 h, 93%), 2-chloroanisole (24 h, 96%), 4-chlorotoluene (6 h, 95%), methyl 4-chlorobenzoate (2 h, 91%), 3-chloropyridine (9 h, 94%).

*Biaryl coupling by ligand **21*** [36]: A Schlenk tube charged with $Pd_2(dba)_3$ (0.015 mmol) and **21** (0.03 mmol) and Cs_2CO_3 (2 mmol) was flushed with argon. 1,4-Dioxane (3 ml), chloroarene (1 mmol) and arylboronic acid (1.5 mmol) were added, and the mixture was then stirred for 1.5 – 2 h at 80 °C.

The nickel catalyst has an advantage over the palladium/phosphine complexes because of their high catalyst activity for chloroarenes [28, 46] and mesylates [47] [Scheme 6]. Preliminary study for the reaction of chloroarenes had been carried out in dioxane in the presence of $NiCl_2$(dppf) and $K_3PO_4 \cdot nH_2O$ [28, 46], but $NiCl_2/PPh_3$ complexes are desirable in large-scale preparation in industry. The triphenylphosphine complex achieved higher catalyst efficiency than that of dppf when using toluene as the solvent [29]. The reduced nickel catalyst supported on charcoal [48] and $NiCl_2$(bipyridine) [49] also had been studied as the catalyst for analogous biaryl coupling. The nickel(II) complexes catalyze the reaction of ate-complexes of aryl- or 1-alkenylboronates (e.g., **23**) [50] under very mild conditions. The vinyl-vinyl or aryl-aryl coupling of iodo- or bromoalkenes [50, 51], allyl acetates [52], and aryl mesylates [53] proceeded smoothly at room temperature in the presence of $NiCl_2(PPh_3)_2$.

*Synthesis of **22*** [29]: $NiCl_2(PPh_3)_2$ (0.03 mmol), PPh_3 (0.06 mmol), 4-tolylboronic acid (1.3 mmol), and $K_3PO_4 \cdot nH_2O$ (2.6 mmol) were added to a flask flushed with argon. Toluene (2 ml) and 2-chlorobenzonitrile (1.0 mmol) were then added. The resulting mixture was stirred at 80 °C for 2 h. Chromatography over silica gel gave **22** (97%).

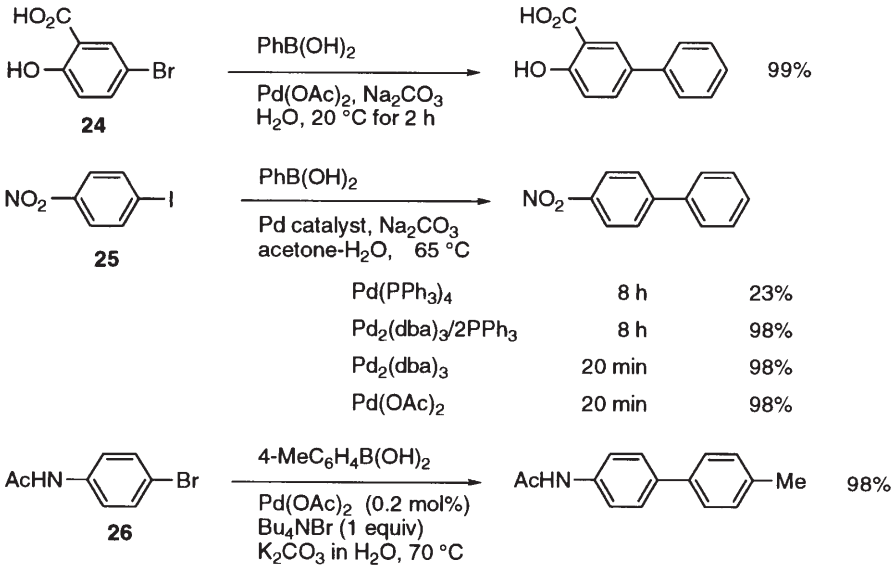


Scheme 6. Nickel-catalyzed cross-coupling reaction

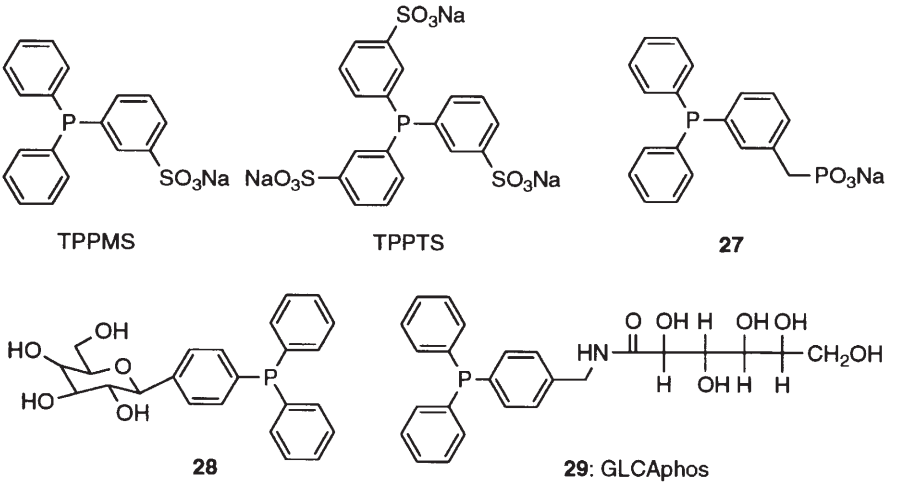
A free-phosphine palladium generated *in situ* from $Pd(OAc)_2$ is an excellent catalyst for biaryl coupling in water or in aqueous organic solvents (Scheme 7). The advantage of such ligandless catalyst is that it eliminates phosphine-related side reactions such as aryl-aryl exchange and phosphonium salt formation (see, section 3–2), and achieves high catalyst efficiency allowing for shorter reaction times and high turnover of the catalyst. The catalyst completed the reaction of water-soluble bromoarenes (**24**) within 2 h at room temperature [54]. On the other hand, $Pd(OAc)_2$, $[(\eta^3\text{-}C_3H_5)PdCl]_2$, or $Pd_2(dba)_3$ in aqueous acetone was recognized to be the best combination for water-insoluble bromo- and iodoarenes (**25**). Ligandless palladiums significantly shortened the reaction time than that of phosphine complexes [55]. Addition of 1 equivalent of Bu_4NBr to the bromides (**26**) allowed the quantitative reaction in a single water phase with 0.2 mol% of $Pd(OAc)_2$ [56, 57]. The role of Bu_4NBr is not known, but it will act for generating or stabilizing a fine metallic palladium. A novel solventless biaryl coupling of arylboronic acids was recently carried out in a solid-phase of KF/γ-alumina in the presence of palladium black [58].

Biaryl coupling of ***26*** [57]: *p*-Tolylboronic acid (2.2 mmol), **26** (2 mmol), $Pd(OAc)_2$ (0.2 mol%), Na_2CO_3 (5 mmol) and Bu_4NBr (2 mmol) were added to a flask and flushed with argon. Water (2.2 ml) was then added and the resulting suspension was stirred for 2 h at 70 °C. The product was extracted with EtOAc, dried (Na_2SO_4), and chromatographed on silica gel to give the biaryl (98%).

Although the ligandless catalysts often achieve significantly fast coupling in aqueous media, complete conversion can not be always possible, especially for the slow reactions of electron-rich and sterically hindered haloarenes. The addition of more than two phosphines is generally recommended to avoid the pre-



Scheme 7. Ligandless palladium catalysts



Scheme 8. Water-soluble ligands

cipitation of palladium-black by stabilizing the resting state of the palladium species. Various water-soluble phosphines are now available for the catalyzed reactions in aqueous media (Scheme 8).

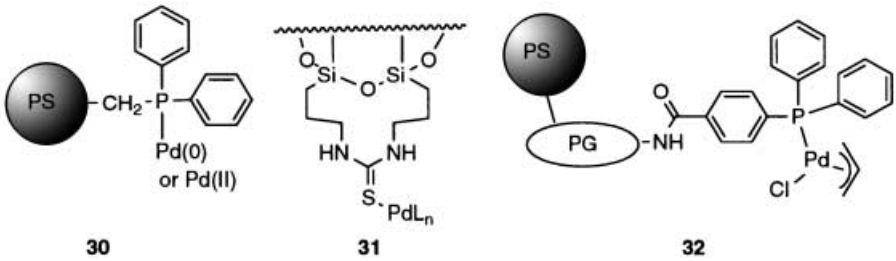
Sulfonated phosphines such as TPPMS and TPPTS are a traditional ligand for homogeneous palladium or rhodium catalysts in aqueous media, which are now utilized in several industrial processes [59]. Hoechst succeeded in replacing a previous five-step synthesis of 2-cyano-4′-methylbiphenyl to the one-step process using a cross-coupling reaction of *p*-tolylboronic acid with 2-chlorobenzonitrile in aqueous media in the presence of a Pd/TPPTS catalyst (50 – 100 tons/year) [59, 60]. The reaction in aqueous media offers advantages in large-scale industrial processes because of the simplicity of catalyst-product separation, economy, and safety in using water as the solvent [61]. The glycosides of triphenylphosphine **28** [62] and **29** (GLCAphos) [63] are a new ligand which achieved higher turnover numbers of the catalyst (7100 – 9000) than TPPTS in a two-phase basic aqueous-organic or in a single basic aqueous media. Due to the electron-withdrawing property of the SO_3Na group ($\sigma_m = 0.30$), the relative efficiency is in the order of the electron-donating ability of phosphines (**28** ~ **29** > TPPMS > TPPTS). Water-insoluble solid and liquid haloarenes as well as water-soluble haloarenes were promoted the reaction to completion at 80 °C in a single aqueous media [63].

Biaryl coupling by TPPMS [61]: To an aqueous solution of Na_2PdCl_4 (0.242 mmol) was added a solution of TPPMS (0.863 mmol) in ethanol (5 ml). After being stirred for 5 min, the mixture was then treated with activated zinc powder (0.09 g) for 1 h. The mixture was filtered through Celite, concentrated *in vacuo*, and layered with *t*-BuOH to give air-sensitive yellow crystals of $Pd[PPh_2(TPPMS]_3(H_2O)_4$ in a yield of 94%. A solution of *p*-tolylboronic acid (1 mmol) in EtOH (5 ml) was added to a solution of $4\text{-}BrC_6H_4SO_3Na$ (1.25 mmol), Na_2CO_3 (2 mmol), and the above catalyst (0.06 mmol) in water (5 ml). The mix-

ture was stirred for 7 h at 80 °C. The solid precipitated was filtered, washed with water, benzene, and ether, to give the analytically pure biaryl. The filtrate from the initial filtration was concentrated *in vacuo* and refiltered to give a second crop of the biaryl (78 %).

Biaryl coupling by ligand ***29*** [63]: $Pd(OAc)_2$ (0.001 mmol), GLCAphos **29** (0.004 mmol) and arylboronic acid (1.3 mmol) were added. The flask was flushed with argon and then charged with degassed H_2O (2 ml), K_3PO_4 (2 M solution, 2 mmol), and aryl halides (1.0 mmol). After being stirred for 16 h at 80 °C, chromatography on silica gel gave biaryl.

The basic problems of homogeneous catalysts incurred at separation and recycling of the catalyst can be solved by using a supported metal catalyst or by carrying the reaction in a liquid-liquid two-phase system, particularly for industrial applications [1, 59]. The cross-coupling reaction of organoboronic acids proceeds smoothly even in a multi-phase system consisting of a solid catalyst, an organic solvent, and an aqueous base (Scheme 9). Palladium supported on charcoal (Pd/C)[64] or clay [65] and a reduced nickel on charcoal ($Ni(NO_3)_2$/C/BuLi) [48] have been used for the biaryl-coupling of arylboronic acids. A palladium-phosphine complex supported on polystyrene resin (**30**) catalyzed the reaction of vinyl- and arylboronic acids with organic halides or triflates in a two-phase system of using toluene and aqueous base [41, 66, 67]. Deloxan consists of a cross-linked macroporous polysiloxane backbone (**31**) and is a commercially available resin which catalyzed the biaryl coupling in refluxing aqueous isopropanol [68]. A palladium supported on amphiphilic resin (**32**) was used for the coupling reaction of arylboronic acids with haloarenes or allyl acetates [69]. By combining a highly unsaturated palladium complex and an amphiphilic poly(ethylene glycol) graft resin, the reaction was carried out at room temperature in a single water media. Unlike $Pd(PPh_3)_4$, these supported catalysts are stable to air, easily separated from the reaction mixture, and can be reused with no significant decrease in activity.



Scheme 9. Polymer-supported catalysts

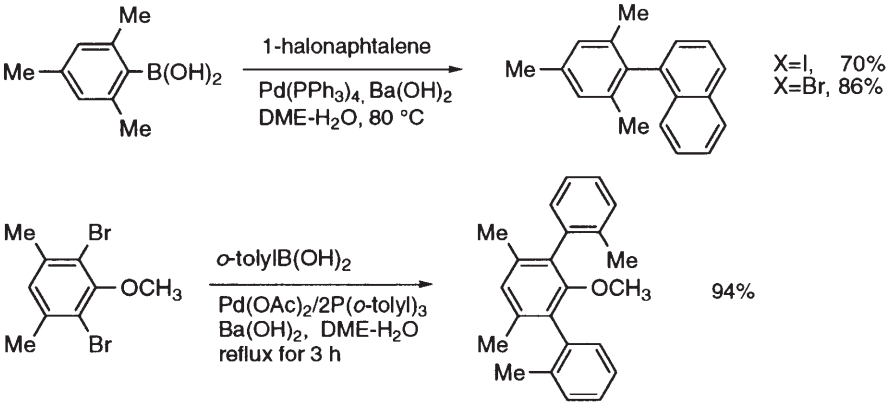
3.1.2
Bases and Solvents

The cross-coupling reaction of organoboronic acids, in general, require the presence of a negatively charged base, such as sodium or potassium carbonate, phosphate, and hydroxide (1.5 ~ 2 equivalents), which is used as aqueous solution, or

as suspension in toluene, dioxane, DME or DMF. A combination of a base and a phase transfer catalyst such as Bu_4NX is also used successfully.

Aqueous Na_2CO_3 is a mild base effective for the biaryl-coupling reaction of arylboronic acids. However, the slow reaction of mesitylboronic acid with iodobenzene revealed the following order of reactivity; TlOH > Tl_2CO_3 ~ $Ba(OH)_2$ > NaOH > K_3PO_4 > Na_2CO_3 > $NaHCO_3$ [70, 71]. Among them, $Ba(OH)_2$ was recognized to be the best base for the synthesis of sterically crowded 2,6,2′-trisubstituted biaryls from *ortho*-disubstituted haloarenes or arylboronic acids [70, 72–74] (Scheme 10). Since the transmetalation involves nucleophilic substitution of Pd-X (path A or B in Scheme 1), a strong base is recommended when several *ortho* substituents are in the halides or the boronic acids. The substitution of metal halides with thallium, barium, or silver nucleophiles is significantly faster than that of sodium or potassium due to the irreversible formation of highly insoluble metal salts.

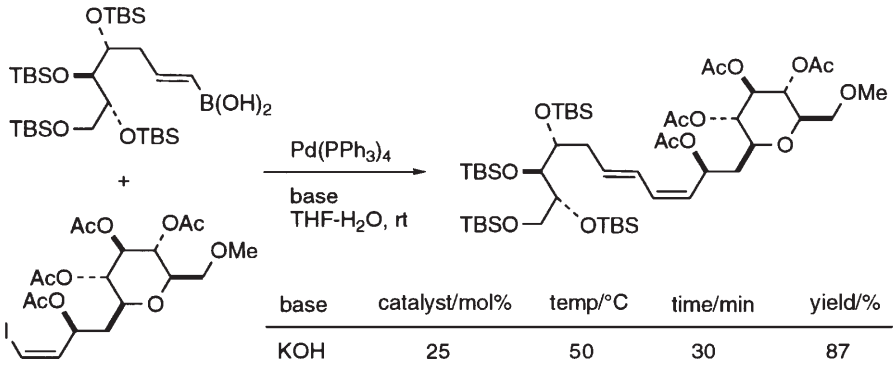
Biaryl coupling induced by Ba(OH)$_2$ [70]: A flask was charged with $Pd(PPh_3)_4$ (0.02 mmol), mesitylboronic acid (1.1 mmol), and $Ba(OH)_2 \cdot 8H_2O$ (1.5 mmol), and flushed with nitrogen. DME (6 ml), H_2O (1 ml) and 1-bromonaphthalene (1 mmol) were added. The resulting mixture was then stirred overnight at 80 °C. Chromatography over silica gel gave the biaryl (86%).



Scheme 10. $Ba(OH)_2$ for the synthesis of sterically hindered biaryls

The cross-coupling reaction of 1-alkenylboronic acids with 1-halo-1-alkenes requires a relatively stronger base than that of arylboronic acids [13], in the order of K_3PO_4 < NaOH < Ag_2O < TlOH [75] (Scheme 11). Aqueous TlOH solution exhibited an exceptionally large accelerating effect, completing the reaction within 1 h at room temperature. These significantly mild conditions modified by Kishi have been successfully applied to the syntheses of palytoxine [75] and other various natural products including a stereodefined conjugate dienes or trienes [76–78].

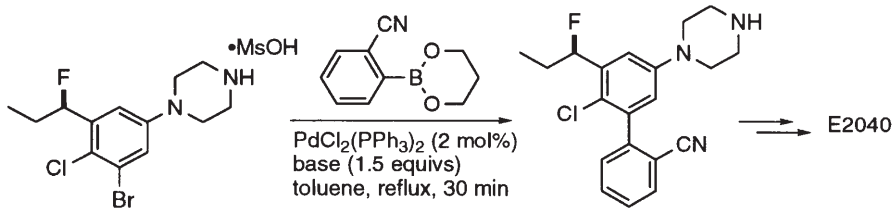
The difficulties encountered during the reaction in basic solutions are saponification of the esters, racemization of optically active compounds, Aldol



base	catalyst/mol%	temp/°C	time/min	yield/%
KOH	25	50	30	87
KOH	25	rt	120	86
Ag_2O	25	rt	5	92
TlOH	3	rt	30	94

Scheme 11. Effect of bases on vinyl-vinyl coupling

condensation of carbonyl compounds or hydrolytic B-C bond cleavage. These difficulties associated with bases can be overcome by the heterogeneous use of the bases. Esters can remain intact in two-phase systems using an aqueous NaOH and toluene [79], or a solid $K_3PO_4 \cdot nH_2O$, or Cs_2CO_3 suspended in DMF, dioxane or toluene [8]. For example, the synthesis of arylalanine suffered from base-induced racemization, but the optically pure compound was finally obtained when anhydrous K_2CO_3 was suspended in toluene [80]. However, the presence of some water or the use of hydrated inorganic bases is preferable since the reaction is greatly accelerated in the presence of some water [81]. The cross-coupling reaction of 2-cyanophenylboronate suffered from incomplete conversion of the haloarene due to fast hydrolytic B-C bond cleavage, but it finally furnished an antagonist of D3/D2/5-HT2 (E2040) within 30 min on addition of an 8 equivalents of water to $K_3PO_4 \cdot 2H_2O$ [82] (Scheme 12). Such large acceler-

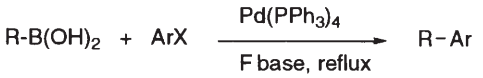


base	conversion/%
K_3PO_4•$2H_2O$	63
K_3PO_4•$2H_2O$ + $2H_2O$	96
K_3PO_4•$2H_2O$ + $8H_2O$	100

Scheme 12. Effect of H_2O on reaction rates

ating effect of water is observed commonly in other coupling reactions of organoboron compounds.

Fluoride salts such as CsF and Bu_4NF (2–3 equivs) are a mild base accelerating the coupling reaction of such substrates sensitive to bases [83] (Scheme 13). Although the reaction is slow for sterically crowded halides or boronic acids, a wide range of functional groups is tolerated.

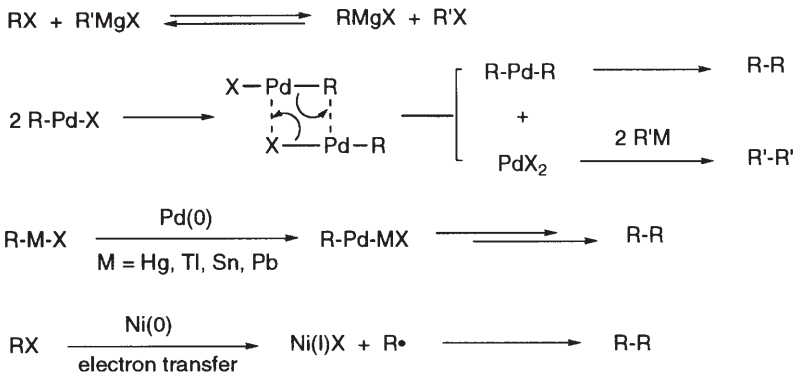


$RB(OH)_2$	ArX	fluoride	solvent	time/h	yields/%
$PhB(OH)_2$	*p*-$BrC_6H_4CH_2CO_2Me$	CsF	DME	2	100
	p-$BrC_6H_4CH_2CO_2Me$	KF	DME/MeOH	8	91
$C_6H_{13}CH{=}CHB(OH)_2$	*p*-$BrC_6H_4CH_2CO_2Me$	CsF	DME	18	81
$CF_2{=}C(Bu)B(OR)_2$	*p*-IC_6H_4OMe	Bu_4NF	THF	12	71

Scheme 13. Fluoride bases for cross-coupling

3.2 Side Reactions

The side reactions giving undesirable homocoupling products are summarized [Scheme 14]. The Grignard reagent has suffered from the homocoupling resulting from the metal-halogen exchange reaction. The metathesis of R-M-X to R_2M and MX_2 (M = Ni, Pd) yields both dimers of electrophiles and organometallics [84a]. The oxidative addition of the metal-carbon bonds to the low-valent transition metals is another route leading to the dimer of organometallics [84b]. The homocoupling of electrophiles derives from the oxidative addition involving an electron transfer mechanism [85]. Although there are several probable process-

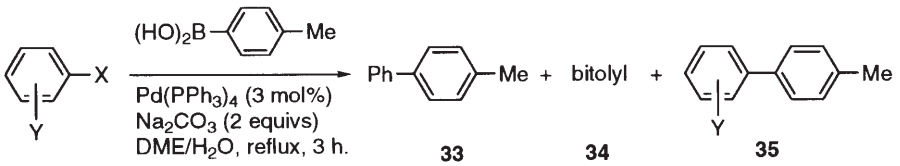


Scheme 14. Homocouplings in Pd- and Ni-catalyzed reaction

es leading to homocoupling products, these reactions will not disturb the coupling reaction of organoboronic acids with palladium or nickel catalysts.

3.2.1
Participation of Phosphine-Bound Aryls

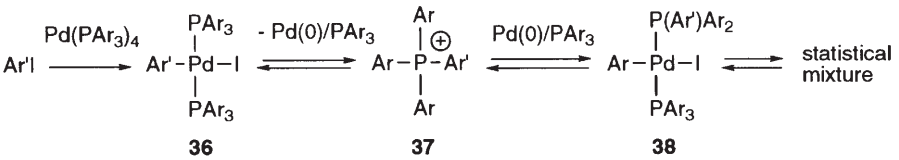
Triarylphosphines are an excellent ligand to stabilize the palladium species; however, there is an undesirable side reaction of the aryl-aryl interchange between palladium- and phosphine-bound aryls leading to the coupling product of phosphine-bound aryls [86, 87]. The phenyl-coupling product (**33**) derived from triphenylphosphine was serious in electron-rich haloarenes, while it was obtained in very small amounts in electron-deficient haloarenes [88] (Scheme 15). On the other hand, the presence of an *ortho*-substituent effected to reduce such side-reaction. It is also interesting to note that bromoarenes always afforded better selectivity than the corresponding iodides, though iodoarenes had been widely used due to their high reactivity to a palladium(0) complex. Thus, the phosphine-bound aryls can participate in the cross-coupling reaction of electron-rich haloarenes having no steric hindrance of *ortho* substituent.



haloarene ArX	Hammett σ	distribution of biaryls/% 33	34	35
p-$MeCOC_6H_4Br$	+ 0.847	< 1	1	98
m-$MeOC_6H_4Br$	+ 0.115	4	1	95
p-MeC_6H_4I	- 0.170	29	0	71
p-$MeOC_6H_4I$	- 0.268	49	3	48
p-$MeOC_6H_4Br$	- 0.268	33	1	66
o-$MeOC_6H_4Br$		0	2	98

Scheme 15. Participation of triphenylphosphine (**33**)

The aryl-aryl interchange is highly sensitive to electronic and steric effects of a phosphine ligand and haloarenes [89–91] (Scheme 16). An electron-donating group in either phosphine or haloarenes increased the aryl-aryl interchange whereas both withdrawing groups and steric hindrance of *ortho*-substituent reversely slowed down the equilibration. Since the interchange between **36** and **38** proceeds through phosphonium salt formation (**37**) [92, 93], it is retarded by steric hindrance and is accelerated by electron-rich aryls stabilizing **37**. The results indicate the superiority of sterically bulky and low donating phosphines for the ligand of a palladium catalyst, but donating phosphines having large

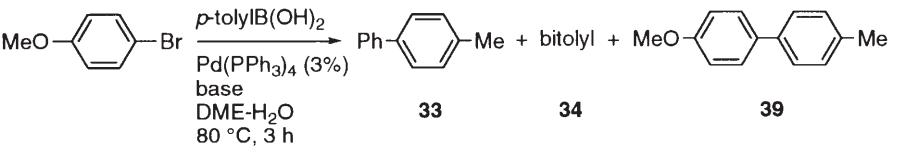


entry	Ar	Ar'	interchange/% (**38**)
1	4-$MeOC_6H_4$	C_6H_5	28
2	C_6H_5	4-$MeOC_6H_4$	99
3	C_6H_5	2-$MeOC_6H_4$	11
4	C_6H_5	4-MeC_6H_4	64
5	C_6H_5	2-MeC_6H_4	0
6	C_6H_5	4-$CF_3C_6H_4$	0
7	4-$CF_3C_6H_4$	C_6H_5	trace

Scheme 16. Aryl-Aryl interchange (**36** to **38**) at 50 °C for 1 h

steric hindrance are generally recommended because of fast oxidative addition of organic halides to the coordinatively unsaturated and electron-rich complexes. P(*o*-tolyl)$_3$ [89], P(*t*-Bu)$_3$ [31], (di-*t*-butylphosphino)- and (dicyclohexylphosphino)arenes (**18**–**21**) [33, 34, 36] have been successfully used, avoiding the participation of phosphine-bound aryls. The dppf complexes are better catalysts than that of triphenylphosphine to suppress such side reaction. The advantages of ligandless palladiums such as $Pd(OAc)_2$ are discussed in Scheme 7.

The aryl exchange occurs before transmetalation; thus, the slow transmetalation due to steric and electronic reasons results in increasing the participation of phosphine-bound aryls. The transmetalation is slowed down in electron-rich haloarenes, but strong bases will sufficiently accelerate transmetalation relative to aryl-aryl interchange. The phenyl coupling product **33** significantly decreased indeed in the order of basic strength: $Na_2CO_3 > K_3PO_4 > NaOH$ [88] (Scheme 17).



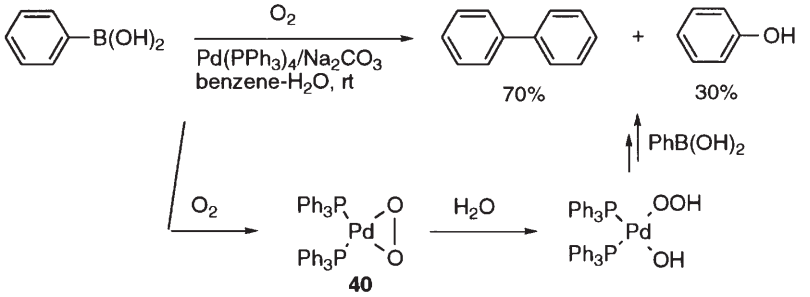
base (equivs)	conversion /%	distribution/%		
		33	**34**	**39**
Na_2CO_3 (2)	100	33	1	66
K_3PO_4 (2)	88	4	2	94
NaOH (2)	82	1	7	92

Scheme 17. Effect of bases on selectivity

Since the rate of transmetalation to **36** is in the order of Cl > Br > I [12], the choice of haloarene also served to minimize such side-reaction.

3.2.2
Oxygen-Induced Homocoupling

The side reactions shown in Scheme 14 may provide a very minor amount of homocoupling products. However, a large amount of homocoupling of arylboronic acids has been often reported in literature. In the experimental operation, careful consideration must be given to oxygen [Scheme 18]. When the reaction mixture was exposed to air, arylboronic acid readily yielded a homocoupling biaryl [88]. The reaction was slow under neutral conditions, but it was very fast in the presence of an aqueous base: yields of biphenyl, 31% (30 min), 54% (60 min), and 70% (180 min). It is also probable that such dimerization takes place during the workup operation in air when there is unreacted arylboronic acid. A catalytic cycle proceeding through a peroxopalladium(II) complex(**40**) was reasonably presumed [94].



Scheme 18. Oxygen-induced homocoupling of organoboronic acids

3.2.3
Dehalogenation, Deamination and Dehydrogenation

The coupling reaction is often accompanied with dehalogenation of organic halides (RX to RH) [95], particularly when alcohols were used as the solvent. Such products can be derived from β-hydride elimination from Ar-Pd-OCH_2R giving Ar-Pd-H and RCH=O [13] or the reduction of Ar-Pd-OH with Ph_3P affording Ar-Pd-H and Ph_3P=O [26]. The deamination (RNH_2 to RH) was unexpectedly resulted in the cross-coupling reaction of arylboronic acid with 2,6-dibromoaniline [96]. Since various transition metals catalyze the aromatization of cyclic alkenes and dienes, the cross-coupling reaction of 2,5-dihydropyrole triflate with arylboronic acids afforded pyrrole derivatives via *in situ* dehydrogenation [97].

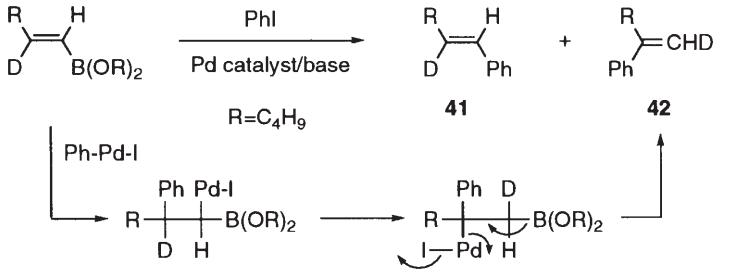
3.2.4
Protodeboronation

Even if there is no great steric hindrance, the reaction under aqueous conditions gives undesirable results due to competitive hydrolytic B-C bond cleavage

($RB(OH)_2$ to RH) which is accelerated by the presence of bases, adjacent heteroatoms and *ortho*-substituents. 2-Pyridyl-, 2,6-dimethoxy-, and 2-formyl benzeneboronic acids, and 1-trimethylsilyl-1-alkenylboranes are sensitive to such hydrolytic B-C bond cleavage [98, 99].

3.2.5
Head to Tail Coupling

The coupling reaction of 1-alkenylboronic esters results in the formation of a head-to-tail coupling product (**42**) when a ligandless palladium catalyst and a weak base such as triethylamine are used [100] (Scheme 19). The formation of such abnormal coupling product can be best understood by the mechanism of the Heck reaction for vinylic metal compounds, that has been observed in the cross-coupling reaction of weakly nucleophilic organometallics, such as 1-alkenylmercurials [101], -silanes [102], and -tin [103] compounds. A deuterium labeling study proved the addition-elimination mechanism where a β-hydrogen transfers to the terminal carbon [100].



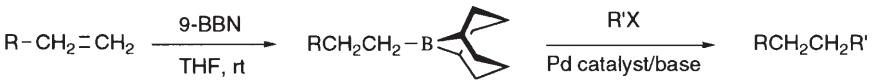
catalyst	base	solvent	time/h	yield/%	**41/42**
$Pd(PPh_3)_4$	NaOH	benzene	2	99	(100/0)
$Pd(OAc)_2$	NaOH	DMF	6	86	(56/44)
$Pd(OAc)_2$	Et_3N	DMF	20	94	(4/96)

Scheme 19. Head-to-tail cross-coupling

4
Representative Procedures and Applications

4.1
Alkylboron Compounds

Trialkylboranes including 9-alkyl-9-BBN and alkyl(disiamyl)borane readily undergo the cross-coupling with 1-alkenyl or aryl halides or triflates [8] (Scheme 20). The reaction is limitedly used for primary alkylboranes; thus, hydroboration of terminal alkenes with 9-BBN or $HB(Sia)_2$ is the most convenient to furnish the desired boron reagents. Trialkylboranes thus obtained are

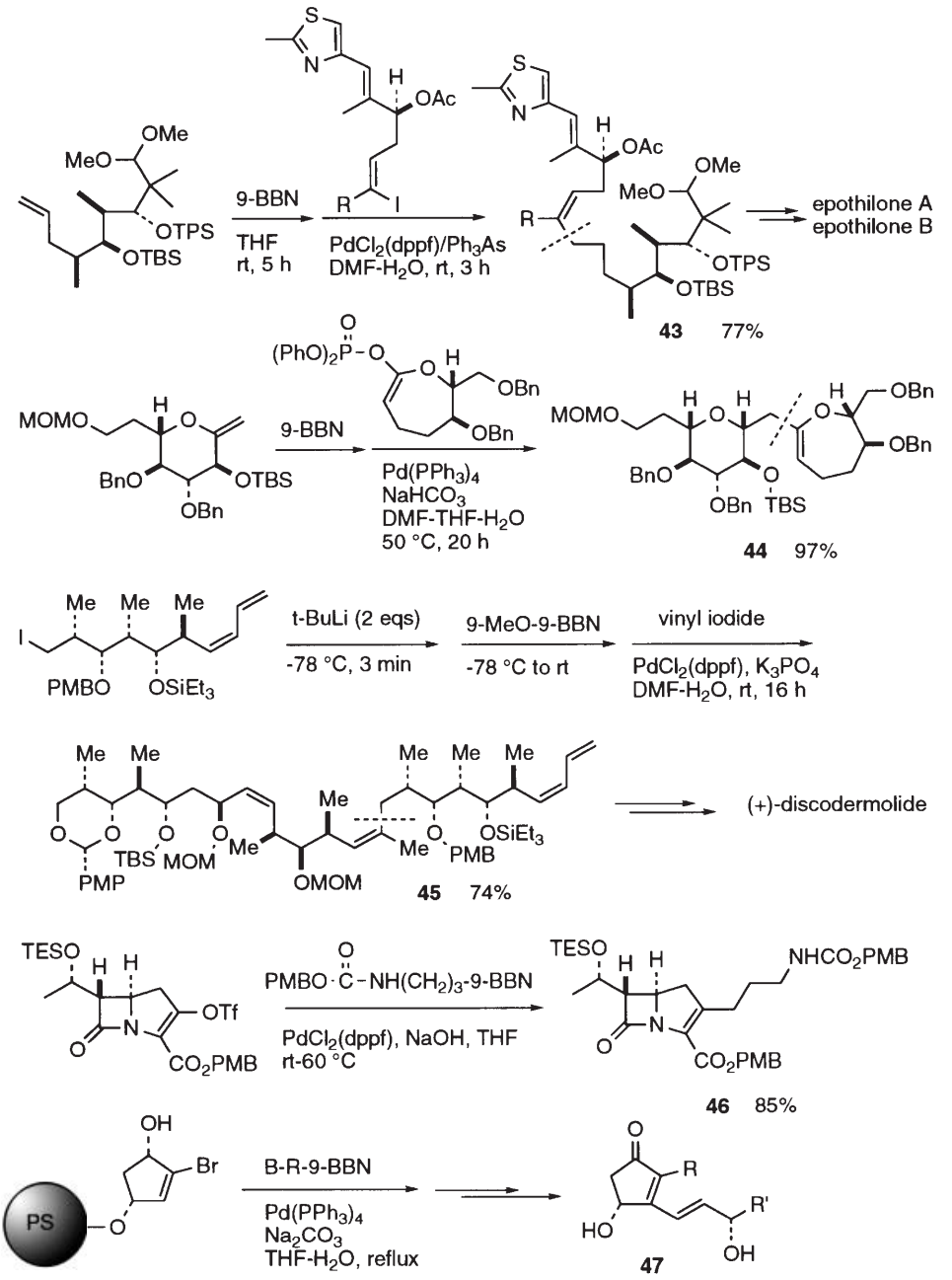


R'-X	catalyst	base/solvent	temp/°C	ref.
vinyl, aryl I, Br, OTf	$PdCl_2$(dppf)	K_3PO_4•nH_2O/DMF	rt-50	[8][104][105][106]
vinyl, aryl I, Br	$PdCl_2$(dppf)	NaOH/THF-H_2O	rt-reflux	[8][107][108]
vinyl, aryl I, Br	$PdCl_2$(dppf)	NaOMe/THF	rt-reflux	[8][109][110]
vinyl, aryl I	$PdCl_2$(dppf)/$AsPh_3$	Cs_2CO_3/DMF-H_2O	rt	[81][111][112]
aryl Br	$Pd(PPh_3)_4$	NaOH/toluene-H_2O	80	[113]
vinyl OTf	$PdCl_2$(dppf)/$AsPh_3$	Cs_2CO_3/KBr/DMF-H_2O	rt	[114]
aryl OTf	$PdCl_2$(dppf)	NaOMe/KBr/THF	reflux	[105][115]
vinyl OP(O)$(OPh)_2$	$Pd(PPh_3)_4$	$NaHCO_3$/DMF-H_2O	50	[116]

Scheme 20. Reaction conditions for alkyl-vinyl and alkyl-aryl coupling

highly sensitive to air, but they can be used directly for the next coupling reaction without isolation. The coupling reaction of organic iodides proceeds at room temperature in the presence of $PdCl_2$(dppf) [8] or $PdCl_2$(dppf)/2Ph_3As [81]. Since the presence of water greatly accelerates the reaction, the use of aqueous bases or hydrated inorganic bases such as $K_3PO_4 \cdot nH_2O$ is recommended [81]. On the other hand, solid sodium methoxide added to 9-alkyl-9-BBN dissolves in THF by forming the corresponding ate-complex, which allows the room temperature coupling under non-aqueous conditions [8]. Treatment of 9-methoxy-9-BBN with primary-alkyllithiums is an alternative of *in situ* synthesizing analogous boron ate-complexes [104]. The reactions of aryl and 1-alkenyl triflates are carried out in the presence of KBr (1 equiv) to prevent decomposition of the catalyst [105].

The connection of two building blocks *via* the hydroboration/cross-coupling sequence has found a wide range of applications in the synthesis of natural products and functional molecules (Scheme 21). Bacterial metabolites, epothilone A and B, are powerful cytotoxic agents which function through stabilization of cellular microtubules. Hydroboration of the terminal alkene followed by cross-coupling with iodoalkene furnished the desired cis-alkene (**43**) [111, 117]. A general method for convergent assembly of polyethers (**44**) was developed based on the analogous cross-coupling protocol. The triflates had been used for six-membered ketene acetals [114], but the phosphates were recently recognized to be the better substrate for the seven, eight, and nine-sized ketene acetals because they are more stable in alkaline solution [116]. The B-alkyl-9-BBN required for the synthesis of (+)-discodermolide (**45**) was not available by hydroboration of the terminal alkene due to difficulty in introducing a chiral center at the β-carbon [104]. The metalation of the corresponding iodide with *t*-BuLi was followed by addition of B-methoxy-9-BBN to provide a convenient one-pot procedures for forming the C-B bond. Clinically useful 2-alkylcarbapenems (**46**) were synthesized *via* coupling reaction of triflate



Scheme 21. Cross-coupling reaction of B-alkyl-9-BBN derivatives

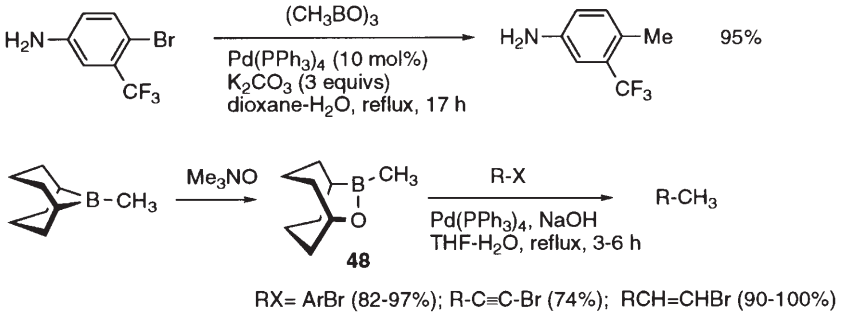
[118]. Protection of allylic amines with a *t*-butoxycarbonyl (Boc), benzyloxycarbonyl (Cbz), or *p*-methoxybenzyloxycarbonyl (PMB) group furnished the desired 9-BBN derivative for the coupling reaction [106, 107, 119]. The alkyl-vinyl and alkyl-aryl coupling reactions readily proceed on the solid-phase which was demonstrated in the preparation of members of several structurally distinct PG classes (**47**) [120].

The above hydroboration-cross coupling strategy has been used extensively in the synthesis of biologically active compounds, which includes a novel class of glycomimetic compounds, aza-C-disaccharides [121], sphingofungin F which acts as serinepalmitoyl transferase inhibitors [112], a rare family of C_{15} *Lupine* alkaloid, aloperine [122], 5-alkylresorcinols with DNA-cleaving properties [109], a fungal metabolite caloporoside [115], (+)-aspicilin [123], and an inhibitor of VCAN-1, (+)-halichlorine [124].

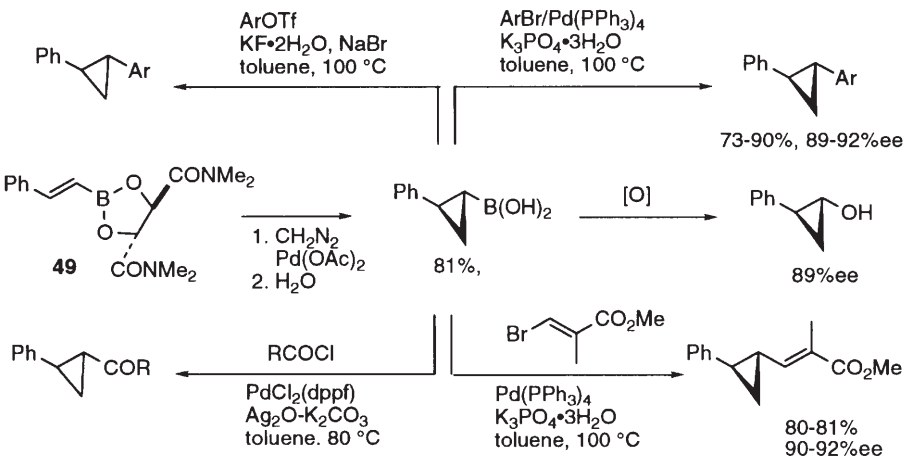
*Synthesis of **43*** [111]: To a solution of alkene (1.55 mmol) in THF (3 ml) was added 9-BBN (0.5 M in THF, 1.7 mmol) and the mixture was stirred for 4 h. In a separate flask, iodoalkene (1.92 mmol) was dissolved in DMF (5 ml). Cs_2CO_3 (3.54 mmol) was then added with vigorous stirring followed by sequential addition of $PdCl_2$(dppf) (0.198 mmol), Ph_3As (0.2 mmol), H_2O (0.42 ml), and finally the above borane solution. After being stirred for 2 h, the product was separated by chromatography over silica gel (77 %).

*Synthesis of **45*** [104]: To a solution of iodoakane (0.35 mmol) in Et_2O (5 ml) was added *t*-BuLi (1.7 M in pentane, 0.75 mmol) at –78 °C. After 3 min, 9-MeO-9-BBN (1 M in hexane, 0.82 mmol) was added followed by THF (5 ml). After being stirred for 10 min, the mixture was allowed to warm to room temperature over 1.25 h. Aqueous K_3PO_4 (3 M, 0.8 mmol), iodoakene (0.16 mmol) in DMF (5 ml) and finally $PdCl_2$(dppf) 0.016 mmol) were added. The resultant dark solution was stirred for 16 h.

Although the reaction of alkylboronic acids is significantly slower than that of trialkylboranes, methylboroxine $(MeBO)_3$ or methylboronic acid exceptionally alkylates bromo- and chloroarenes [125, 126]. Methylation of electron-poor bromoarenes was efficient, whereas prolonged reaction time was required for more electron-rich substrates. The reaction times can be shortened by use of the polar solvent DMF at 115 °C. B-Methyl-9-BBN and its oxy-derivative (**48**) [127] undergo methylation of aryl and vinyl halides under more mild conditions (Scheme 22).



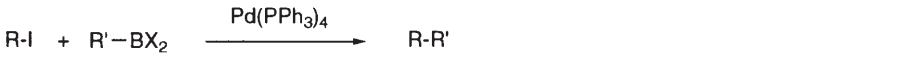
Scheme 22. Reagents for methylation



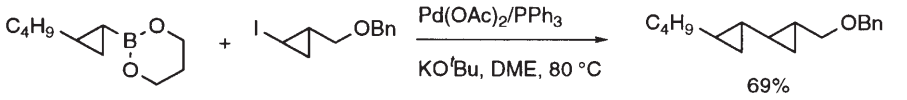
Scheme 23. Cross-coupling reaction of cyclopropylboronic acids

The cyclopropane ring is present in many natural products, and is increasingly being incorporated into pharmaceutically interesting mimetics of natural materials. The cross-coupling reaction of cyclopropylboronic acids or esters provides such compounds including chiral derivatives (Scheme 23). Alkylboronic acids do not undergo the cross-coupling reaction, but cyclopropylboronic acids exceptionally alkylate aryl and vinyl halides or triflates [128, 129], and acyl chlorides [130] without loss of stereochemistry. The chiral boronic acids have been synthesized by cyclopropanation of alkenylboronic tartrates with CH_2N_2 and $Pd(OAc)_2$. Tetramethyltartric acid diamide (**49**) was recently recognized a better chiral auxiliary than diisopropyl tartrate (ca, 90%ee) [128].

The sp^3-sp^3 bond formation between alkyl derivatives has been much less successful among the possible combinations of different-type nucleophiles and electrophiles (Scheme 24). The difficulties arise from the slow oxidative addition



R-I	R'-BX_2	base	solvent	yield/%
Me-I	B-$(MeO_2C(CH_2)_{10})$-9-BBN	$K_3PO_4•nH_2O$	dioxane	71
$C_{10}H_{21}$-I	B-(C_4H_9)-9-BBN	$K_3PO_4•nH_2O$	dioxane	50
$ClC_4F_8CH_2CH_2$-I	$PhCH=CHB(OH)_2$	$NaHCO_3$	DME-H_2O	80
$C_6F_{13}CH_2CH_2$-I	$PhB(OH)_2$	$NaHCO_3$	DME-H_2O	70



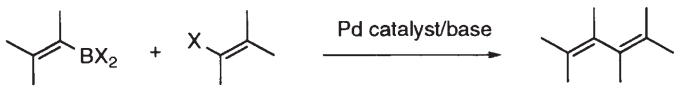
Scheme 24. Alkyl-alkyl cross-coupling

of alkyl halides (RCH_2CH_2X) to a palladium(0) complex with accompanying side-reaction yielding $RCH{=}CH_2$ and RCH_2CH_3, and the susceptibility of the alkylpalladium(II) species to β-hydride elimination. In spite of these difficulties, primary iodoalkanes coupled with alkyl-, aryl-, and 1-alkenylboron compounds in moderate yields [131]. A more selective sp^3-sp^3 coupling was recently achieved in the synthesis of symmetrical or unsymmetrical contiguous cyclopropanes [132]. The process can be feasible because of sp^2-bond character of the cyclopropane ring and slow β-hydride elimination from the (cyclopropyl)palladium(II) intermediates. A relatively strong base such as ^{t}BuOK exhibited a large accelerating effect.

4.2 1-Alkenylboron Compounds

The cross-coupling reaction of 1-alkenylboron compounds with 1-alkenyl halides requires a relatively strong base in the presence of a palladium/phosphine catalyst (Scheme 25). The relative rate can be in the order of their basic strength and counter cations forming insoluble metal salts (TlOH > NaOH > K_3PO_4 > Na_2CO_3) [13, 75]. Aqueous NaOH or KOH has been used for 1-alkenylboronic acids or esters in a refluxing THF-H_2O, DME-H_2O, or benzene-H_2O. In spite of its toxicity, TlOH is excellent of base completing the vinyl-vinyl coupling within a few hours at room temperature.

Typical procedure for TlOH-induced cross-coupling [78]: To a solution of vinylboronic acid (0.154 mmol) in THF (4.8 ml) was added 10% aqueous TlOH (0.4 mmol) solution. This was stirred for 5 min, and a solution of vinyl iodide (0.055 mmol) followed by $Pd(PPh_3)_4$ (0.011 mmol) in THF (0.3 ml) were added and the mixture was then stirred at room temperature.



R^1-X	BX_2	catalyst	base/solvent	temp/°C	ref.
vinyl Br	$B(OH)_2$	$Pd(PPh_3)_4$	NaOEt/benzene-EtOH	reflux	[13][133]
vinyl I	$B(Sia)_2$	$Pd(PPh_3)_4$	LiOH/THF-H_2O	reflux	[134][135]
vinyl I, Br	$B(OR)_2$	$Pd(PPh_3)_4$	NaOH/THF or DME -H_2O	reflux	[136--138]
vinyl I	$B(OH)_2$	$Pd(PPh_3)_4$	TlOH/THF-H_2O	rt	[75][139--141]
vinyl I, Br	$B(OR)_2$	$Pd(PPh_3)_4$	NaOH/benzene-H_2O	70	[13][142][143]
vinyl OTf	$B(OR)_2$	$Pd(PPh_3)_4$	K_3PO_4•nH_2O/dioxane	80	[105]
vinyl OTf	$B(OR)_2$	$PdCl_2(PPh_3)_2$	Na_2CO_3/THF-H_2O	40	[144]

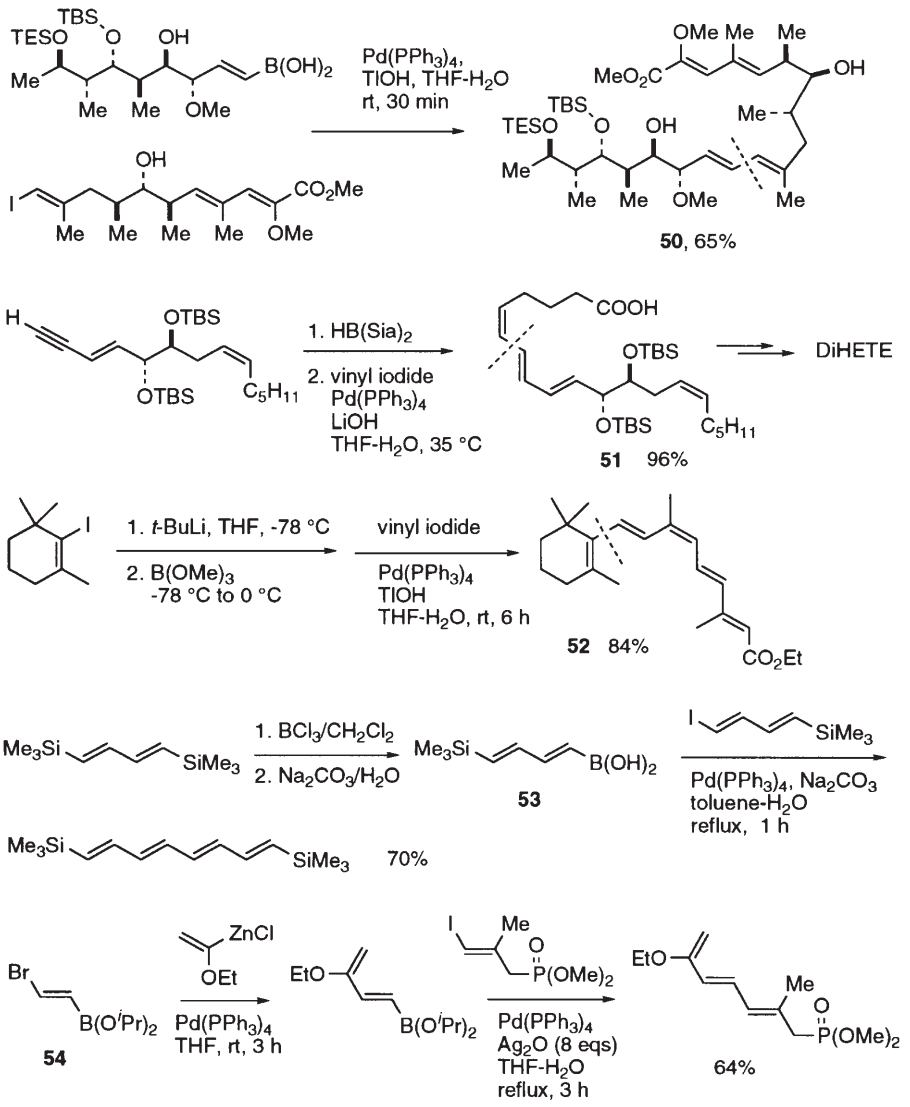
Sia=C(Me)HC(Me)$_2$H; $(OR)_2$=$(OH)_2$ or catecholate

Scheme 25. Reaction conditions for vinyl-vinyl coupling

The vinyl-vinyl cross-coupling affords stereodefined dienes, trienes, and further conjugated polyenes without isomerization of the C-C double bonds [Scheme 26]. Hydroboration of terminal alkynes with catecholborane followed by hydrolysis provides various 1-alkenylboronic acids. The boronic acids thus obtained couple with iodoalkenes at room temperature when a thallium base is used in the presence of $Pd(PPh_3)_4$. Mild conditions for thermally unstable polyenes allowed various syntheses of natural products, such as (–)-bafilomycin A (**50**) [145]. Disiamylborane is a chemo- and regioselective hydroboration reagent strongly directing the addition of boron at the terminal carbon for conjugate enynes. Its utility was demonstrated in the synthesis of DiHETE (**51**) [135]. Aqueous LiOH was recognized to be the best base that avoids the hydrolytic B-C bond cleavage during the cross-coupling. Cyclic 1-alkenylboronic acids are available *via* transmetalation between alkenyllithiums and trialkylborates. The one-pot two-step procedures without isolating the vinylboron intermediates afforded 9-*cis*-retinoic acid (**52**) [139]. The synthesis suffered from isomerization or decomposition of a tetraenyl fragment, but a thallium base again achieved the stereoselective coupling. The transmetalation of vinylsilanes to BCl_3 in CH_2Cl_2 at 0 °C is another method for synthesizing conjugate vinylboronic acids (**53**) [143a]. The series of (*E*)-vinylsilanes were prepared by the nickel-catalyzed cross-coupling reaction of Grignard reagents with (*E*)-$BrCH{=}CHSiMe_3$ and treated with BCl_3 for the synthesis of vinylboronic acids [143b]. Haloboranes add to terminal alkynes in a *cis* anti-Markovnikov manner, but addition of BBr_3 to acetylene exceptionally yields a *trans*-β-bromoethenylboronate (**54**) [146]. The palladium-catalyzed coupling of vinylzinc with **54** was followed by second coupling with iodoalkene to furnish the triene which was required for the synthesis of a tetraene unit of (+)-calyculin A or B [147].

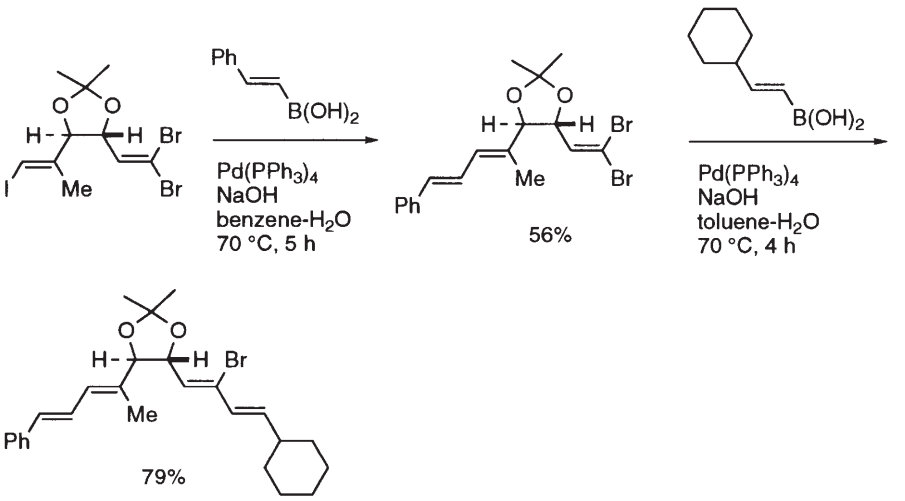
Since a variety of 1-alkenylboron compounds including (*E*)- and (*Z*)-isomers are now available, the above vinyl-vinyl coupling reaction has been applied for the synthesis of biologically active natural products, including a macrolide antibiotic rutamycin B [78], a metabolite of arachidonic acid, (12R)-HETE [77], an antiproliferative agent, (+)-curacin A [136], an aglycon of chlorothricin, (–)-chlorothricolide [76, 140], a small family of C_{15} lupinine alkaloids, (+)-aloperine [148], and restrictinols which exhibit antifungal activity [149].

The order of reactivity of halides and triflates is I > Br > OTf $\gg$ Cl for palladium(0)/triarylphosphine complexes [105] and Cl > OTf for $Pd_2(dba)_3$/2P(*t*-Bu)$_3$ [31]. Thus, a sequential cross-coupling of dihaloalkenes or dihaloarenes provides unsymmetrical double coupling products when two leaving groups with different reactivity are selected. Iodo- and bromoalkenes were well differentiated by $Pd(PPh_3)_4$, thus allowing a stepwise double coupling of two different alkenylboronic acids [142] (Scheme 27). The second coupling of 1,1-dibromoalkene selectively occurred at the less-hindered *trans*-C-Br bond [133, 141, 142, 150] because the oxidative addition is highly susceptible to the β-substituent *cis* to the carbon-halogen bond. The reaction provided a simple strategy for the sterodirected synthesis of polyunsaturated butenolides such as peridinin. The stepwise double coupling to C-Br and C-B bond of **54** is an alternative method for the synthesis of polyenes [151].



Scheme 26. Synthesis of vinylboron compounds and their cross-coupling

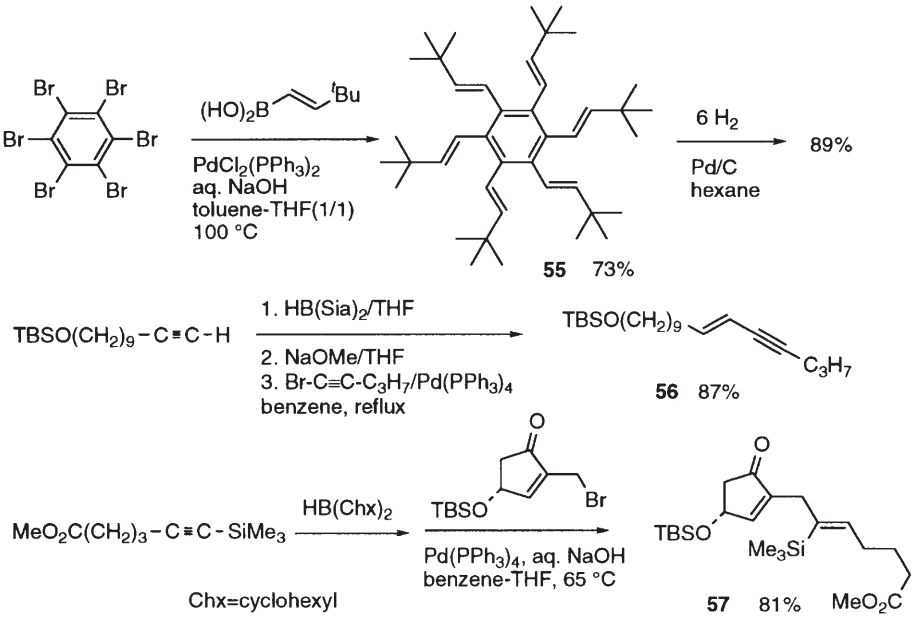
1-Alkenylboron compounds couple with the representative organic halides or triflates (Scheme 28). Hexaalkylbenzene was synthesized by sixfold alkenylation (**55**) of hexabromobenzene followed by catalytic hydrogenation of the double bonds [152]. The reaction of 1-alkenylborane with 1-bromo-1-alkyne stereoselectively provided (*E*)-enyne (**56**) which was then converted into (*E,Z*)-hexadeca-10,12-dienal, a sex pheromone of the melonworm [153]. Due to the difficulty of purification of a geometrical mixture, the stereoselective synthesis is critical for such dienes or trienes. The PGE_1 derivatives (**57**) were synthesized



Scheme 27. Sequential double coupling for synthesis of polyenes

by the analogous hydroboration-cross coupling sequence [79]. The base-labile *β*-silyloxy group and ester group remained intact in the two-phase system using benzene and aqueous NaOH.

Synthesis of 57 [79]: Cyclohexene (2 mmol) was added to BH_3 in THF (1 M, 1 mmol) at 0 °C. After being stirred for 1.5 h at 0 °C, the trimethylsilylalkyne (1 mmol) in THF was added and the solution was stirred for 1 h at ambient tem-

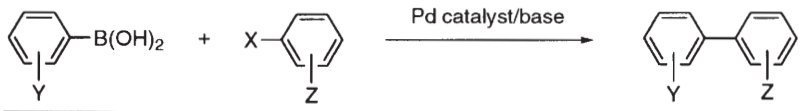


Scheme 28. Vinyl-aryl, vinyl-alkynyl and vinyl-allyl coupling

perature. In a separate flask charged with 2-bromomethyl-2-cyclopentenone (0.327 mmol) and benzene (3.3 ml) were added $Pd(PPh_3)_4$ (0.0164 mmol), the above alkenylborane solution, and 3 M NaOH (0.656 mmol) and the mixture was then stirred for 1 h at 65 °C. Chromatography on silica gel gave an oil (81%).

4.3 Arylboron Compounds

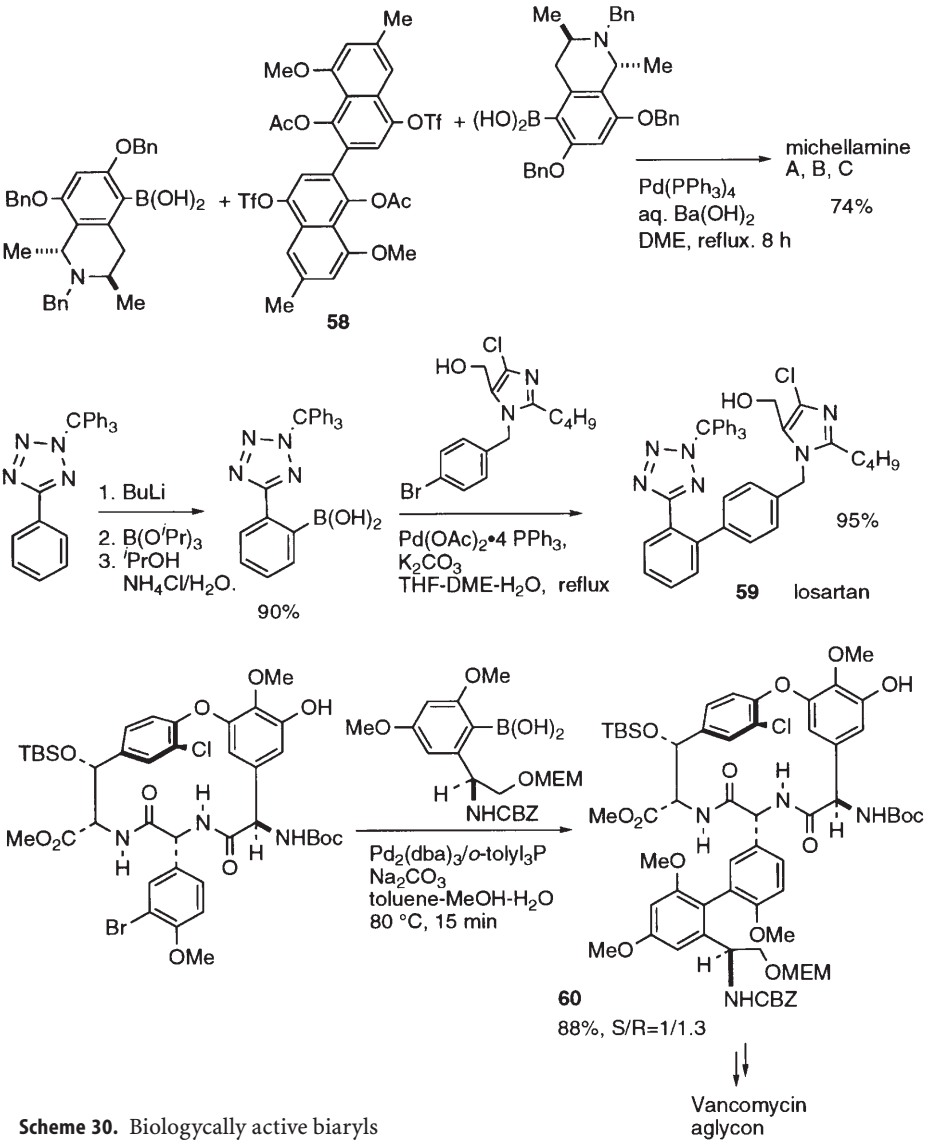
Various combinations of catalysts, bases, and solvents allow the biaryl coupling of arylboronic acids with aryl halides and triflates if there are no side-reactions such as the hydrolytic B-C bond cleavage or the participation of phosphine-bound aryls [4] (Scheme 29). The representative conditions are summarized in the scheme and the effects of catalysts and bases on yields and side reactions are discussed in sections 3.1 and 3.2.



X=	catalyst	base/solvent	temp/°C	ref.
I, Br	$Pd(PPh_3)_4$	$NaHCO_3$ or Na_2CO_3/DME-H_2O	reflux	[154--156]
I, Br, OTf	$Pd(PPh_3)_4$	K_3PO_4•nH_2O/dioxane or DMF	80	[70][105][157][158]
I, Br	$Pd(PPh_3)_4$	CsF/DME	reflux	[83][159]
I, Br	$Pd(PPh_3)_4$	Na_2CO_3/MeOH-H_2O	reflux	[160][161]
I, Br, OTf	$Pd(PPh_3)_4$	Na_2CO_3 or K_3PO_4/toluene-H_2O	80-100	[162--165]
I, Br, OTf	$Pd(PPh_3)_4$	$Ba(OH)_2$/DME-H_2O	reflux	[70][73]
Br	$Pd(OAc)_2$	K_2CO_3/Bu_4NBr/H_2O	70	[55][57]
I	$Pd(OAc)_2$	K_2CO_3 or Cs_2CO_3/acetone-H_2O	reflux	[56][166]
Cl	$Pd_2(dba)_3$/*t*-Bu_3P	Cs_2CO_3/dioxane	rt	[31]
Cl	$Pd_2(dba)_3$/**18b**	K_3PO_4/toluene	80-100	[32][33]
Cl	$Pd_2(dba)_3$/**18c**	KF/THF	rt	[33]
Cl	$Pd_2(dba)_3$/**20b**	CsF or K_3PO_4/toluene or dioxane	100	[34]
Cl	$Pd_2(dba)_3$/**21**	Cs_2CO_3/dioxane	80	[36]
Cl	$NiCl_2$(dppf)	K_3PO_4•nH_2O/dioxane	80	[28][46]
Cl	$NiCl_2(PPh_3)_2$	K_3PO_4•nH_2O/toluene	80	[29]
N_2BF_4	$Pd(OAc)_2$	MeOH-H_2O	reflux	[11][21]

Scheme 29. Reaction conditions for aryl-aryl coupling

The mixed Ullman reaction in which two haloarenes couple in the presence of copper powder is still commonplace in industrial process, but the catalyzed cross-coupling reactions appear to be more productive and provide reliable results in synthesis of unsymmetrical biaryls (Scheme 30). The isomeric michel-



Scheme 30. Biologycally active biaryls

lamines A, B and C demonstrate activity against human immunodeficiency virus (HIV)-1 and HIV-2 strains. Michellamines A and B, both having identical tetrahydroisoquinoline structures and different configurations at the biaryl axes, were synthesized by a simultaneous double-coupling of the di-triflate (**58**) [74, 167]. A highly hindered biaryl-coupling leading to a mixture of two atropodiastereoisomers was achieved by the barium base. A sequence of the direct *ortho*-metalation to give arylboronic acid and its cross-coupling reaction was reported by Merck in USA, as a one-pot, two-step procedure for the angiotensin

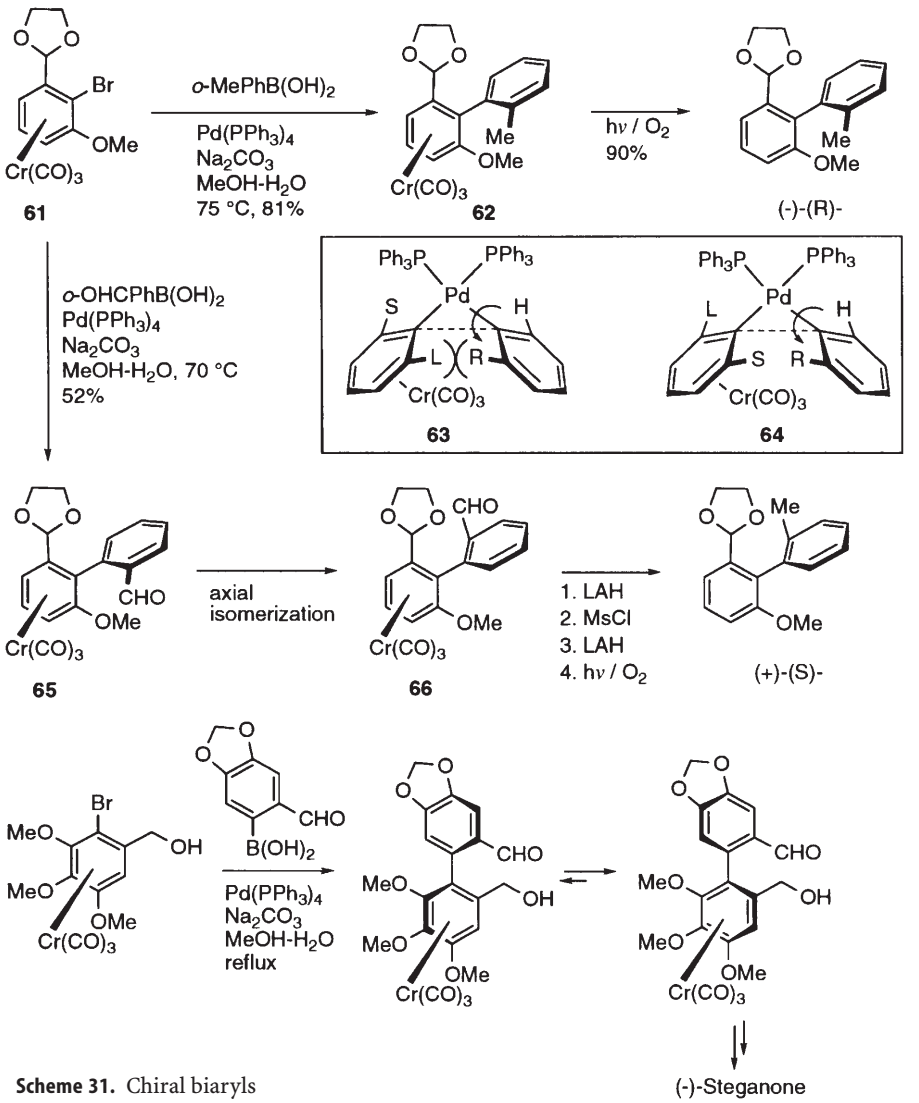
II receptor antagonist (losartan, **59**) which plays a critical role in the regulation of blood pressure [168]. A highly efficient, convergent approach overcomes many of the drawbacks associated with previously reported syntheses, thus providing a method for large-scale preparation (ca. 1000 kg/year). The biaryl coupling furnished the AB biaryl ring of vancomycin aglycon with a mixture of two atropisomers (**60**, S/R = 1/1.3) which was then thermally equilibrated to the natural isomer [169]. The palladium/triphenylphosphine or dppf complex was unsuccessful, but the preparation of a highly unsaturated palladium catalyst from $Pd_2(dba)_3$ and P(*o*-tolyl)$_3$ achieved a significantly fast reaction for a sterically crowded combination.

The biaryls are useful in rational designing functional molecules and materials. The large steric hindrance and the semirigid structure with restrict rotation provided various functional biaryls, such as arylporphyrins [162, 170], molecular-scale motors rotate by chemical power or light [73, 163], a photoswitchable electron transfer aromatic compounds for the design of molecular photonic devices [171, 172], a stable thioaminyl radicals [173], phenylnitroxide-substituted Zn(II) porphyrins [174], and polycyclic aromatic compounds [175–177].

Biaryls with axial chirality are of potential importance not only as chiral ligands for asymmetric reactions but also as synthetic intermediates of biologically active natural compounds. Arene-$Cr(CO)_3$ complex (**61**) exists in two enantiomeric forms based on planar chilarity. The biaryl coupling of **61** gave both optically pure atropisomers starting from a single chromium complex [161] (Scheme 31). The coupling reaction of *o*-tolylboronic acid diastereoselectively produced a kinetic controlled product (**62**) in which the 2-methyl group was in *syn*-orientation to the $Cr(CO)_3$ fragment. The selective formation of **62** proceeds through a transition state (**64**), where the R substituent rotates toward the $Cr(CO)_3$ moiety avoiding a large nonbonding interaction between R and PPh_3 during the C-C bond formation. On the other hand, a less hindered 2-formylphenyl group allowed the axial isomerization of the (R,R)-chromium complex (**65**) to the thermodynamically more stable (R,S)-isomer (**66**). The utility of the strategy was demonstrated in the synthesis of (–)-steganone [160]. Aqueous methanol was recognized to be the best solvent for *o*-formylarylboronic acids because analogous reactions in other solvents resulted in low yields due to hydrolytic protodeboronation.

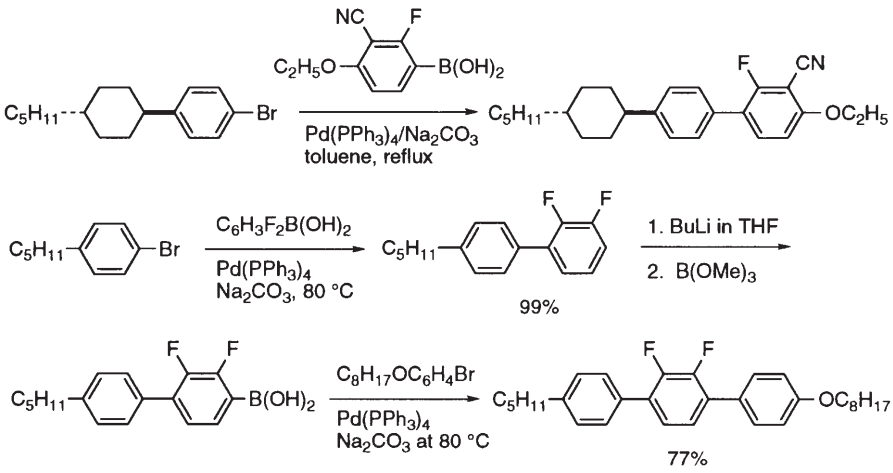
The log, lath-like molecular structure of most liquid crystalline compounds makes the cross-coupling protocol very important in syntheses [178, 179]. The method based on arylboronic acids simplifies the procedure for liquid crystal materials of more complex substitution patterns [64, 180, 181] (Scheme 32). The synthesis of arylboronic acids via *ortho*-metalation of fluoroarenes and the successive cross-coupling reaction readily extended the aryl units. The Pd/C-catalyzed reaction was also reported as an economical alternative [64]. Several liquid crystals having a biaryl unit are now an industrial process of Merck in Germany (ca. 3 tons/year) [182].

The synthesis of teraryls, quateraryls, and further higher-order polyaryls, and the ever-increasing complexity in the more functionalized materials requires simple and practical methods for synthesizing building blocks (Scheme 33). The transmetalation between an aryllithium, -magnesium, or other metal (Al, Si, Zn)



Scheme 31. Chiral biaryls

and a trialkylborate or boron trihalide is the most common for the synthesis of arylboronic acids [183]. Many (bromoaryl)boronic acids and arene diboronic acids have been synthesized from aryllithiums *in situ* generated by halogen-metal exchange (**67** [172]) or *ortho*-metalation directed by a heteroatom (**68** [184, 185]). The transmetalation between arylsilanes and BBr_3 or BCl_3 is also convenient (**69** to **73**) [186, 187]. The boronic acids, in general, present a host of difficulties with regard to their analysis and isolation. The principal difficulty is their spontaneous condensation to the boroxines [$(ArBO)_3$] to varying degrees. Thus, NMR spectroscopy exhibits two pairs of signals corresponding to a free boronic acid and a boroxine. The boronic acid itself can not be chromato-



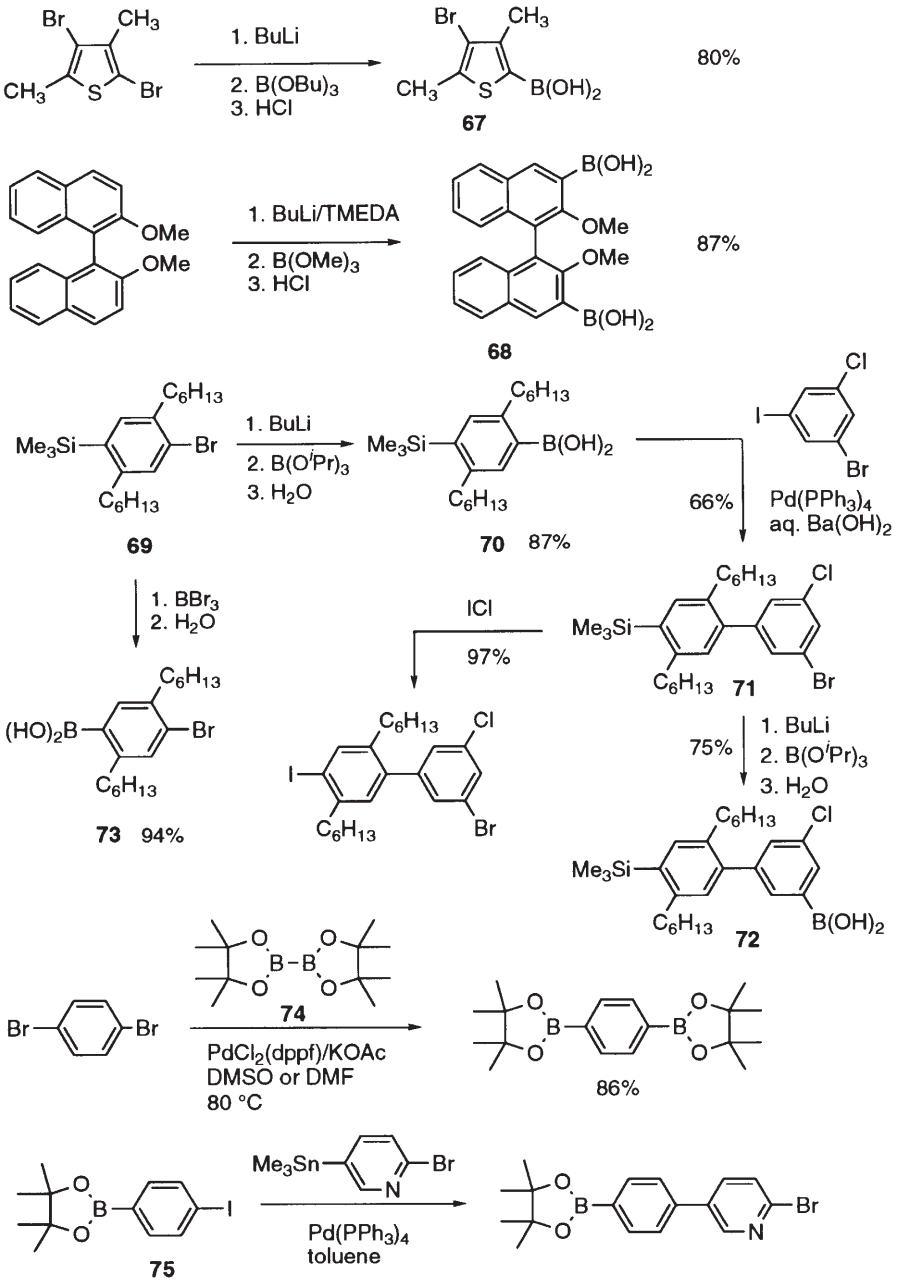
Scheme 32. Liquid crystals

graphed, but dehydration to the corresponding boroxine allows the separation through silica gel.

The cross-coupling protocol provides another valuable method for homologation of arylboronic esters or direct borylation of haloarenes [181]. The reaction of **70** with 5-bromo-3-chloroiodobenzene selectively occurred at the C-I bond thus providing a biaryl unit (**71**) for the synthesis of diarylboronic acid (**72**) [186, 188, 189]. The coupling reaction of bis(pinacolato)diboron (**74**) is an alternative of the lithium/boron transmetalation and is available for various functional groups sensitive to organolithiums [5]. Diborylation of dibromobenzene and selective monoborylation of 4-bromoiodobenzene gave the desired pinacol esters quantitatively [190, 191]. The arylation or alkylation of (*p*-iodophenyl)boronate (**75**) with arylstannanes [188, 192] or alkylzinc halides [193] selectively occurred at the C-I bond without affecting the boryl group.

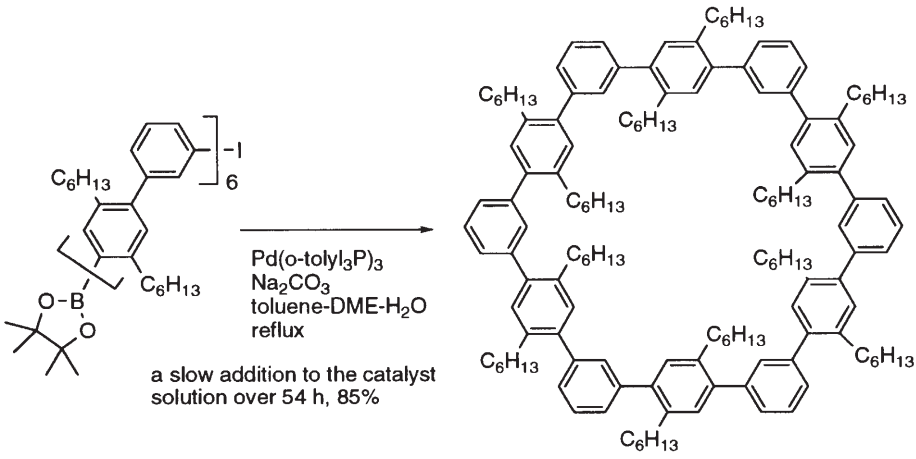
*Synthesis of **68*** [184]: To a solution of TMEDA (54 mmol) in ether (300 ml) was added BuLi (1.6 M in hexane, 56 mmol). After being stirred for 30 min at room temperature, solid 2,2′-dimethoxy-1,1′-dinaphthyl (19 mmol) was added in one portion, and the mixture was then stirred for 3 h. Finally, $B(OEt)_3$ (117 mmol) was added at –78 °C over a period of 10 min. The solution was allowed to warm to room temperature and was stirred overnight. The mixture was cooled to 0 °C, 1 M HCl (100 ml) was then added. The organic phase was separated, washed with twice with 1 M HCl, brine, and dried over Na_2SO_4. Crystallization from toluene gave **68** (6.53 g, 87%).

*Synthesis of **73*** [186]: To a solution of 1-bromo-2,5-dihexyl-4-trimethylsilylbenzene (2.52 mmol) in CH_2Cl_2 (20 ml) was added a solution of BBr_3 (3.77 mmol) in CH_2Cl_2 (12 ml), and the mixture was then stirred for 3 h. Water (10 ml) was added and the layers were separated. The aqueous layer was washed twice with CH_2Cl_2, and the combined organic phase was dried over $MgSO_4$. Chromatographic separation on silica gel with (1) hexane and (2) CH_2Cl_2 gave the boronic acid (94%). mp 85.5 °C, R_f = 0.27 (hexane/ethyl acetate = 3/1).



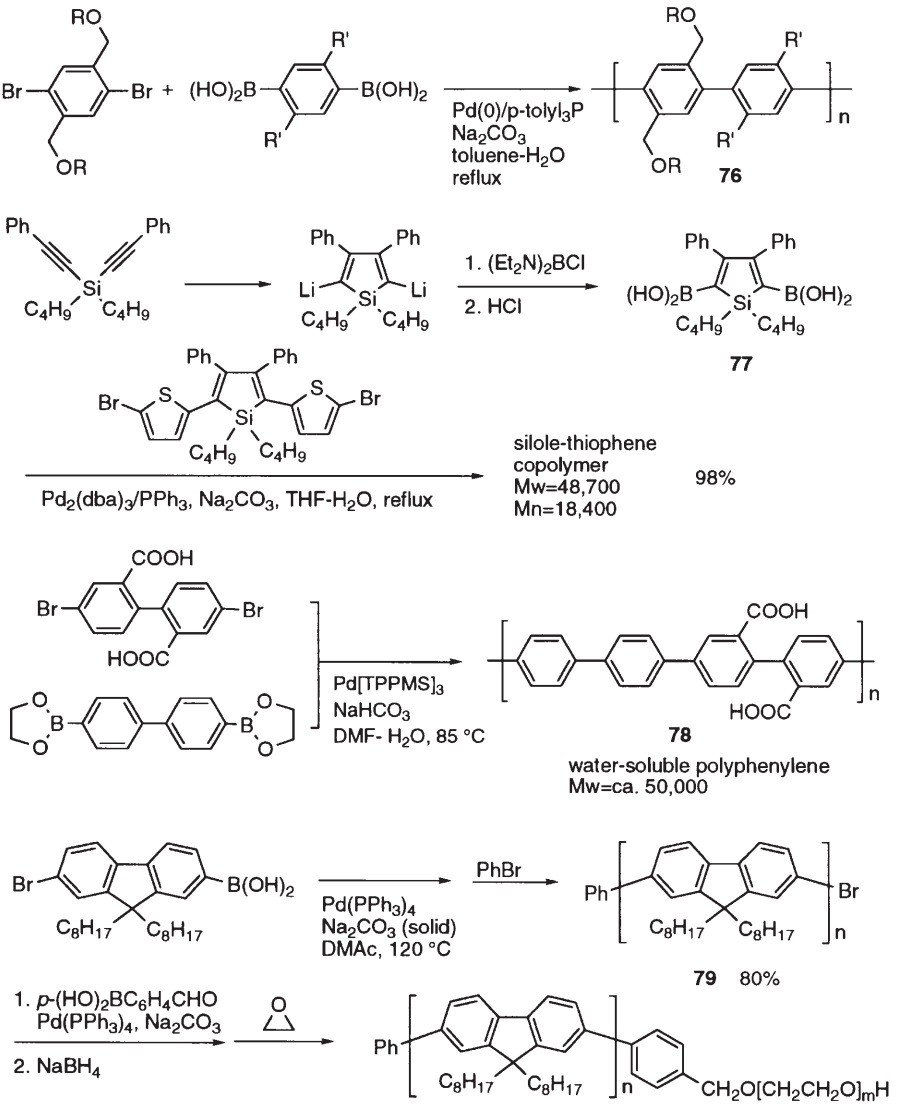
Scheme 33. Building blocks for synthesis of polyphenyles

Cyclic oligophenylenes with conformationally rigid structures have attracted the interest of chemists for issues including aromaticity, host-guest chemistry and molecular construction of macrocyclic compounds. The synthesis of macrocyclic oligophenylene was achieved by the high-dilution technique adding pinacol (ω-iododododecaphenyl)boronate to the catalyst solution by using a syringe pump [194] (Scheme 34).



Scheme 34. Macrocyclic polyphenylenes

The synthesis of poly(*p*-phenylene) *via* the homocoupling of *p*-bromophenylboronic acids was first reported by Max Planck Institute [195]. After this discovery, various new poly(*p*-phenylenes) have been designed and synthesized based on the cross-coupling reaction of arylboronic acids (Scheme 35). The reaction between dihaloarenes and arene diboronic acids or esters yields high molecular weight polymers having a regular repeated structure (**76**) [196]. Due to the insolubility of polyphenylenes in organic solvents, the polymers possessing long alkyl side-chains (R′ = C_6–C_{12}) have been synthesized so that the polymer surface are easily modified to the desired functional groups (RO), as is shown in the next scheme. The narrow band gap of silole-thiophene copolymers has been theoretically predicted, but their synthesis has been hampered by the limited availability of suitable precursors. The silole-2,5-diboronic acid (**77**) was recently synthesized by a one-pot procedure starting from the intramolecular reductive cyclization of bis(alkynyl)silane [197]. The polymerization achieved a quantitative formation of the copolymer which exhibits a band gap with good linear correlation to the silole/thiophene ratio. A water-soluble complex prepared from $PdCl_2$ and TPPMS catalyzed the polymerization in aqueous media to provide a rigid-chain polyelectrolyte (**78**) soluble in aqueous Na_2CO_3 [198]. Poly(fluorene)s and derivatives are attractive as active components in light-emitting diodes (LEDs) or solid-sate light-emitting cells (LECs) due to their stability and high fluorescence quantum yields in the solid sate [199, 200]. Both the synthesis of the polymer (**79**) and its end-functionalization were carried out by the coupling reaction of arylboronic acids.



Scheme 35. Polyphenylenes

The biaryl coupling protocol is a versatile tool for synthesizing a wide range of functional materials based on a poly(phenylene) backbone (Scheme 36). The polymeric chiral catalysts have practical advantages due to the possibility to carry out reactions in flow reactors or in flow membrane reactors for large-scale production. Although such catalysts have been prepared by anchoring a chiral metal complex to an achiral polymer backbone, they are usually less efficient than their monomeric version. The rigid and sterically regular chiral polymers

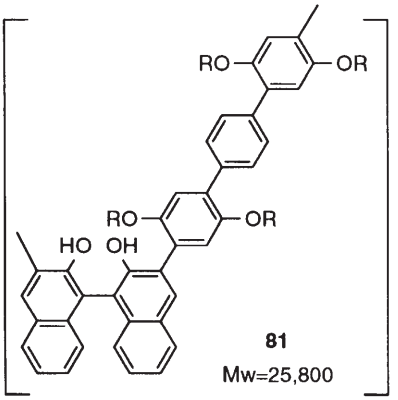
including BINOL (**81**)[201 – 205] or BINAP (**82**) [206] ligand preserved the high selectivity of monomer catalysts. The synthesis of various poly(*p*-phenylene)s has been studied extensively for its possible electronic and photonic applications, but they have 23° twist between the consecutive aryl units due to *ortho* hydrogen interactions. Thus, polymerization by the biaryl-coupling strategy was followed by cyclization to give planar polyaromatic materials which keep the aryl units planar while maximizing the extended π-conjugation through the poly(*p*-phenylene) backbone, e. g., graphite ribbon (**83**) [207].

Functionalization of the polyphenylene surface also produced a wide range of functional materials. Poly(phenylene-dithiophene) having a calixarene-based ion receptor (**84**) is an ionophoric polymer material that displayed exceptional selectivity for the Na^+ ion [208]. The poly(*p*-phenylene)s substituted with oligo(oxymethylene) side chains (**85**) and blends of these novel polymers with lithium salts were studied as the solid polymer electrolytes of lithium secondary batteries [209]. Octapoly(*p*-phenylene) having polyhydroxy groups (**86**) functions as the artificial ion channel which specially recognized (bio)membranes [210]. Analogous polyphenylenes anchoring crown ethers (**87**) were designed as the bilayer membranes with negative membrane potential [211]. The synthesis and physical properties of polyphenyles anchoring dendrimers also have been studied extensively [164, 212, 213].

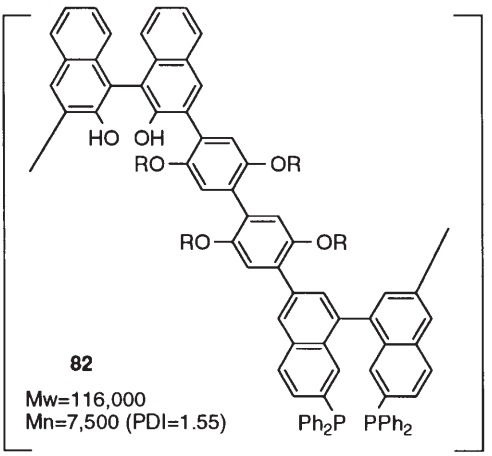
The ready availability of *ortho*-functionalized arylboronic acids by a metalation-boronation sequence provides a synthetic link to the cross-coupling protocol, which has been amply demonstrated in the syntheses of polycyclic heteroaromatics. The synthesis of arylboronic acids having an *ortho*-CON^iPr_2, -$OCONEt_2$, -NH^tBoc, or -CHO, their cross-coupling, and cyclization between two *ortho*-functionalities have been extensively studied [4, 214, 215]. For example, the coupling reaction of **88** provided a short-step synthesis of the ABC rings of (+)-dynemicin A [216] (Scheme 37). The introduction of aryl moieties at the 2 position of carbapenum (**89**) was first demonstrated by the Stille coupling, but the procedure is being reinvestigated by arylboronic acids to avoid contamination of toxic stannyl compounds [217]. The carbapenum triflate is thermally unstable, but phosphine-free palladium was recognized as an excellent catalyst for carrying out the reaction at low temperature.

Synthesis of ***88*** [216]: A solution of *t*-BuLi in pentane (1.7 M, 340 mmol) was added to a solution of *t*-butyl 4-methoxycarbanilate (136 mmol) in ether (500 ml) at – 20 °C. After being stirred for 5 h at – 20 °C, $(MeO)_3B$ (408 mmol) was added. The resulting viscous solution was swirled manually for 5 min, then allowed to warm to 23 °C, and to stand for 12 h. The solution was partitioned between saturated aqueous NH_4Cl (500 ml) and ethyl acetate (500 ml). The aqueous layer was extracted further with ethyl acetate (2 × 500 ml) and the combined organic layers were dried over $MgSO_4$. The product was purified by flash chromatography (2.5 % MeOH in CH_2Cl_2 → 10 % MeOH in CH_2Cl_2) to provide the boronic acid (19.9 g, 55 %). $R_f = 0.43$ (10 % MeOH in CH_2Cl_2).

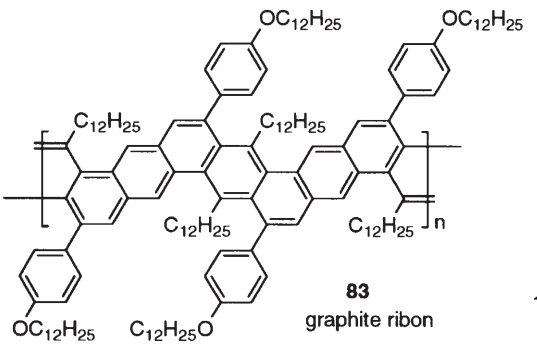
There are very few reports on the aryl-allyl or aryl-benzyl coupling reaction, but these combinations are very popular in other organometallics (Scheme 38). Arylation of allyl acetates or carbonates was catalyzed by $NiCl_2(PPh_3)_2$ or $NiCl_2$(dppf) with net inversion of the stereochemistry of the C-O bond for



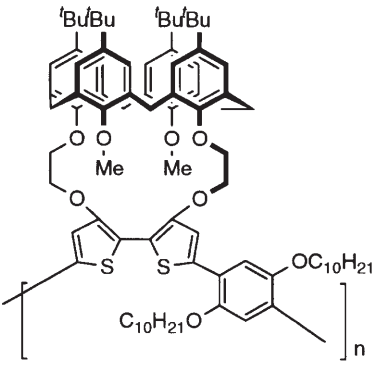
81
Mw=25,800



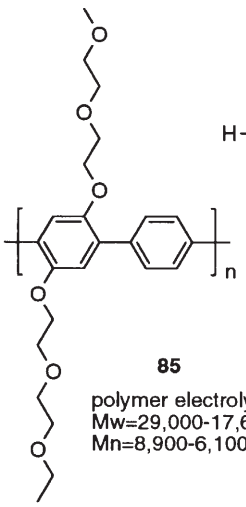
82
Mw=116,000
Mn=7,500 (PDI=1.55)



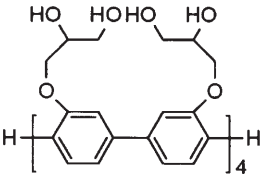
83
graphite ribon



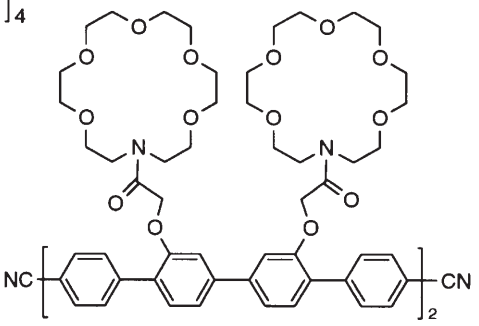
84
ionophoric conjugate polymer
Mn=4,500, PDI=1.55



85
polymer electrolyts
Mw=29,000-17,600
Mn=8,900-6,100

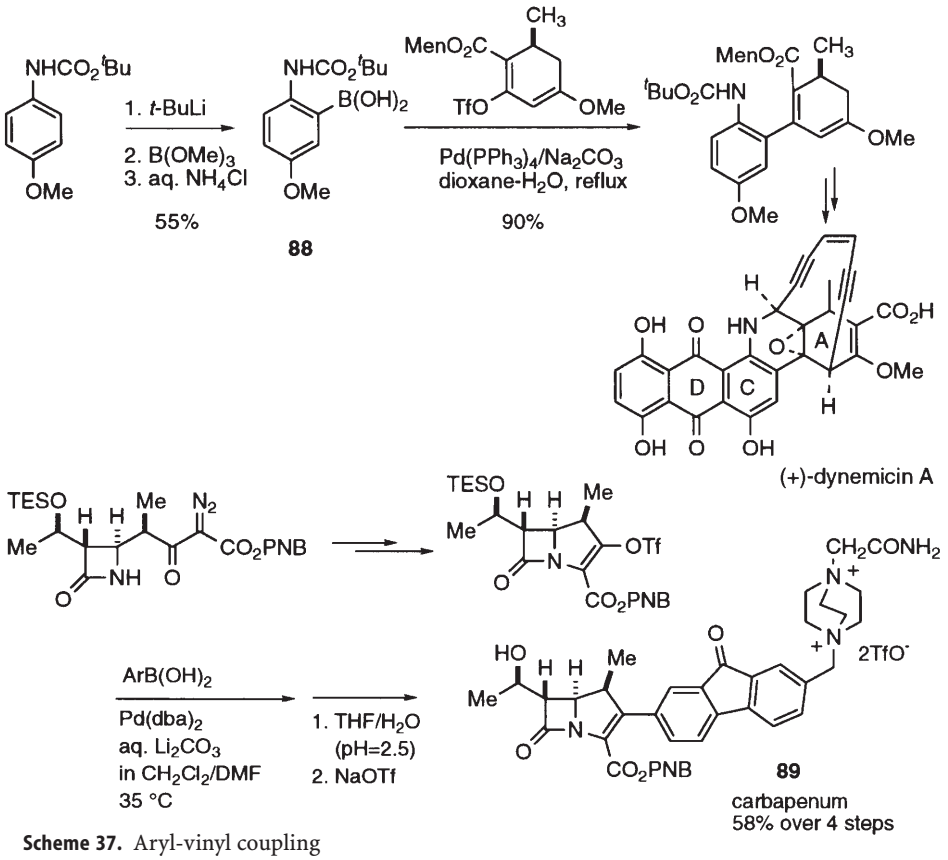


86
Biomimetic
ion channels

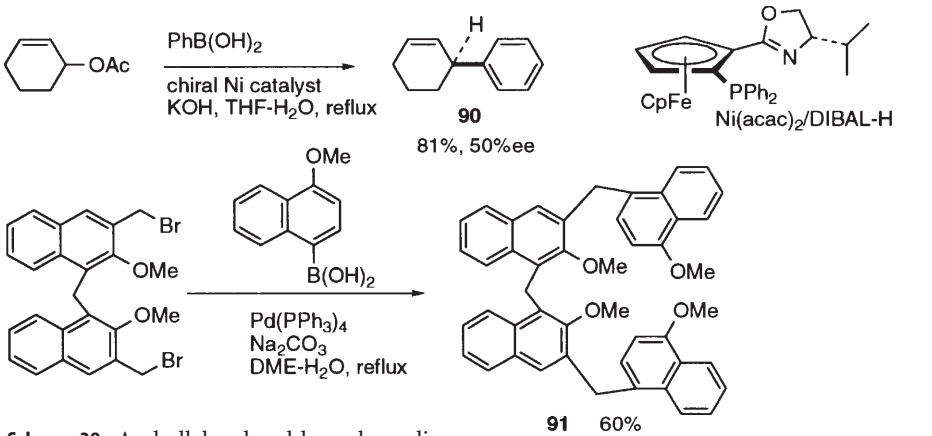


87
Bilayer membranes

Scheme 36. Polyphenylenes for functional materials



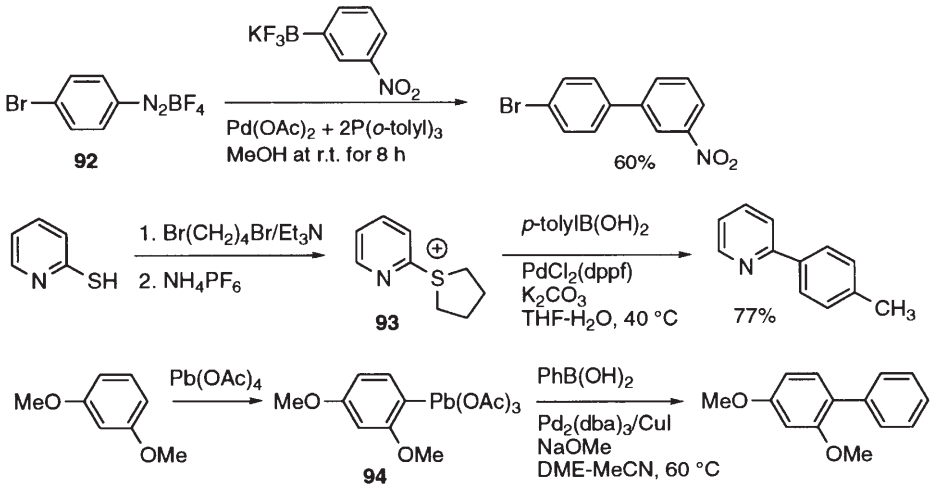
Scheme 37. Aryl-vinyl coupling



Scheme 38. Aryl-allyl and aryl-benzyl coupling

2-cyclohexenyl carbonates [52]. A chiral nickel catalyst generated *in situ* from $Ni(acac)_2$ and an oxazolinylferrocenyl ligand afforded optically active 3-arylcyclohexenes (**90**) up to 50%ee [218]. The aryl-benzyl coupling reaction provides a simple method for the synthesis of mixed calix[4]arenes (**91**) [219].

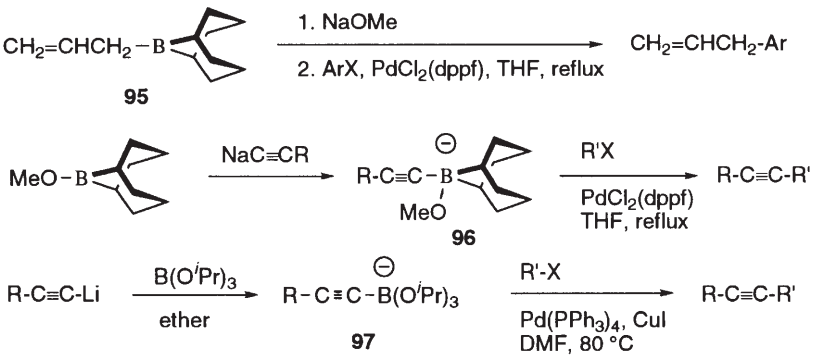
Various aryl electrophiles are now available for the biaryl coupling reaction of arylboronic acids [Scheme 39]. Arenediazonium salts ArN_2BF_4 (**92**) synthesized from aromatic amines undergo oxidative addition under very mild conditions. For example, the coupling reaction with trifluoroborates $[ArBF_3]K$ was conducted at room temperature [10]. Ligandless palladium such as $Pd(OAc)_2$ or its combination with bulky phosphine (e.g., *o*-$tolyl_3P$) was recommended because such substrates yielding a cationic palladium species are very labile to produce phosphonium salts of the ligand [11, 21]. Sulfonium salts (**93**) possess unique attributes that set them apart from other cross-coupling reagents. The palladium-catalyzed C-S bond cleavage of aryl-, benzyl and vinyl sulfonium salts led to the cross-coupling reaction of organoboronic acids or organotin compounds [220]. Aryllead(IV) (**94**) [221] or arylthallium(IV) [222] compounds synthesized by metalation of arenes couple with arylboronic acids since the C-Pb and C-Tl bond oxidatively add to palladium(0) complexes. The process has not yet been examined, but a related reaction of RHgCl with platinum(0) complex involves the formation of R-Pt-HgCl which is led to R-Pt-Cl *via* reductive elimination of mercury(0) from the bimetallic adduct [223].



Scheme 39. Metalation-cross coupling sequence

4.4
Allyl- and 1-Alkynylboron Compounds

Less is known about the reaction of allylboron compounds; however, allylation will occur smoothly in the presence of a base and a palladium catalyst (Scheme 40). The reaction of tri(crotyl)borane with iodobenzene in THF in the presence



Scheme 40. Coupling reactions of allyl and 1-alkynylboron compounds

of aqueous NaOH and $Pd(PPh_3)_4$ gave a mixture of 3-phenyl-1-butene (74%) and 1-phenyl-2-butene (13%) [88]. Analogous reaction of an ate-complex between B-allyl-9-BBN (**95**) and NaOMe afforded allylarenes in high yields within 0.5–1 h [110]. The reaction was considerably faster than the addition of **95** to aromatic ketones, but aldehydes were not tolerated. Analogously, alkynyl(methoxy)-borates (**96**) prepared *in situ* from an alkynyllithium or sodium and 9-methoxy-9-BBN coupled with 1-alkenyl and aryl halides [224]. Addition of NaC≡CH to $(MeO)_3B$ (1.5 equivs) in THF led to a mixture of borate complexes by ligand scrambling, but the subsequent coupling with haloarenes afforded ethynylarenes in good yields in the presence of $PdCl_2(dppf)$ [224c]. Addition of triisopropylborate to lithium acetylide yielded a stable ate-complex (**97**) which readily alkylated aryl and alkenyl halides [225].

Cross-coupling reaction of ***97*** [225]: Alkynyllithium prepared from 1-alkyne and BuLi was treated with $(^iPrO)_3B$ to give a white precipitate of **97** which was then filtered and dried *in vacuo*. $Pd(PPh_3)_4$ (0.011 mmol), CuI (0.011 mmol), **97** (0.42 mmol) and DMF (1 ml) were added to a flask which was then flushed with nitrogen. A halide (0.21 mmol) in DMF (1 ml) was added, and the resulting solution was then stirred for 5–48 h at 80 °C.

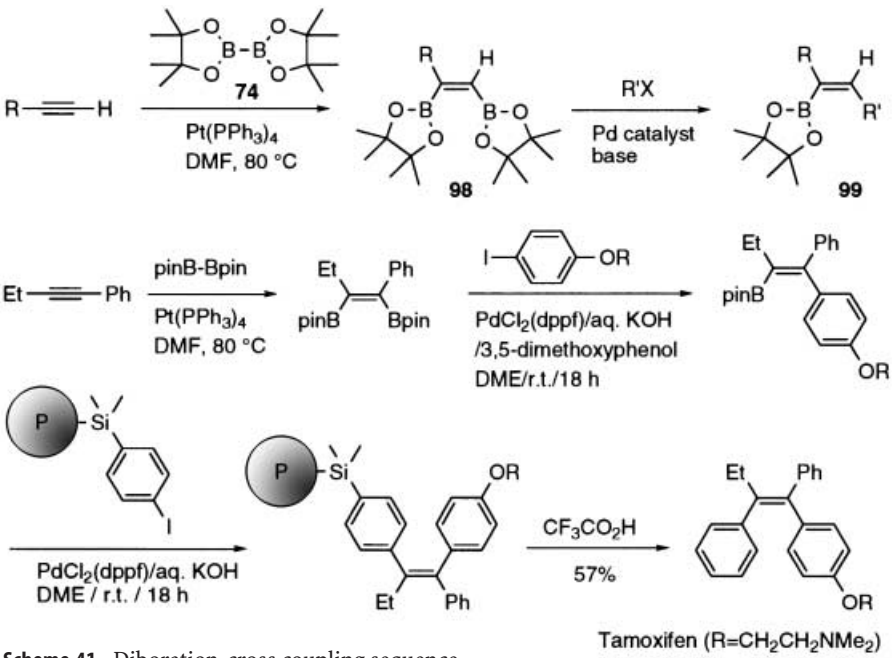
4.5 Diborons

This section briefly summarizes the representative reactions since the metal-catalyzed reactions of diborons were reviewed elsewhere [5]. Various B-B compounds are now available for the metal-catalyzed diboration of alkenes and alkynes (Scheme 41). The addition of bis(pinacolato)diboron [226] to alkynes was catalyzed by a platinum(0) complex such as $Pt(PPh_3)_4$, $Pt(C_2H_4)(PPh_3)_2$ or $Pt(CO)_2(PPh_3)_2$ (3 mol%) yielding *cis*-1,2-diborylalkenes (**98**) in high yields [227]. There were no large differences in the yields between internal and terminal alkynes, and the reaction was available with various functional groups. The addition proceeds through (a) oxidative addition of the B-B bond to Pt(0) giving a *cis*-B-Pt-B complex, (b) migratory insertion of alkene or alkyne into the B-Pt bond, and finally (c) reductive elimination of **98** [228, 229]. The trans-

formation of 1,2-bis(boryl)-1-alkenes *via* a cross-coupling reaction provided a method for regio- and stereoselective synthesis of 1-alkenylboranes (**99**) because they have potential reactivity difference between two C-B bonds [230]. Although the reaction was often accompanied with a double-coupling product at both C-B bonds (5–10%), high terminal-selectivity of over 99% was readily achieved in the coupling reaction with aryl, 1-alkenyl, benzyl, and cinnamyl halides. The utility of the stepwise, double-coupling procedure was demonstrated in the parallel synthesis of Tamoxifen derivatives on solid support [231].

*Syntheses of **98** and **99*** [227, 230]: A 25-mL flask was charged with $Pt(PPh_3)_4$ (0.03 mmol) and diboron **74** (1.0 mmol), and then flushed with nitrogen. DMF (6 mL) and 1-hexyne (1.1 mmol) were added successively. After being stirred for 24 h at 80 °C, the reaction mixture was diluted with benzene (30 mL), repeatedly washed with cold water to remove DMF (5 times), and finally dried over $MgSO_4$. Kugelrohr distillation (0.15 mmHg) gave **98** ($R=C_4H_9$). To a separate flask charged with $Pd(PPh_3)_4$ (0.015 mmol) were added DME (3 ml), (*E*)-*β*-bromostyrene (0.5 mmol), **98** ($R=C_4H_9$, 0.55 mmol), and aqueous KOH (4 M, 1 mmol), and the mixture was then stirred for 16 h at 70 °C. Chromatography over silica gel gave **99** ($R=C_4H_9$, $R'=CH=CHPh$)(72%).

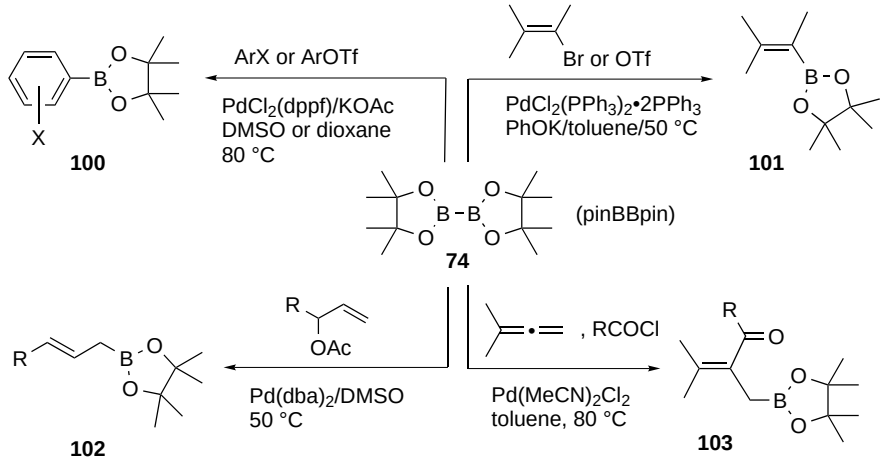
The traditional synthesis of organoboron compounds from organic halides is based on the reaction of trialkyl borates with Grignard or lithium reagents. However, the cross-coupling reaction of diboron solves the difficulties associated with the use of Mg/Li compounds. The cross-coupling reaction of diborons



Scheme 41. Diboration-cross coupling sequence

with organic halides and triflates directly yielded organoboronic esters (Scheme 42). The use of $PdCl_2$(dppf) and KOAc in DMSO or DMF was found to be the best conditions for aryl iodides and bromides (**100**) [190, 232–237]. The coupling with aryl triflates was best carried out in dioxane in the presence of an additional dppf ligand [191]. Analogous synthesis of arylboronic esters from ArN_2BF_3 and **74** was recently reported [238]. The synthesis of 1-alkenylboronic acids from 1-alkenylmagnesiums or -lithiums suffers from difficulty in retaining the stereochemistry of halides, but the direct borylation of 1-alkenyl halides or triflates with diboron stereoselectively yielded cyclic and acyclic (*E*)- or (*Z*)-alkenylboronic esters (**101**) [239]. The cross-coupling reaction of diboron **74** with allyl acetates or chlorides regio- and stereoselectively yielded allylboronic esters (**102**) [240, 241]. The reaction of allyl acetates occurred without the assistance of a base, but the presence of AcOK was critical for allyl chlorides. The coupling at the less hindered terminal carbon and the formation of thermally stable (*E*)-allylboronates were observed for various allyl electrophiles. A three components coupling reaction of acyl chlorides, allene and diboron achieved a regio- and stereoselective acylboration of allenes (**103**). The aroyl and boryl groups were added to the central and to the unsubstituted terminal carbons, respectively [242].

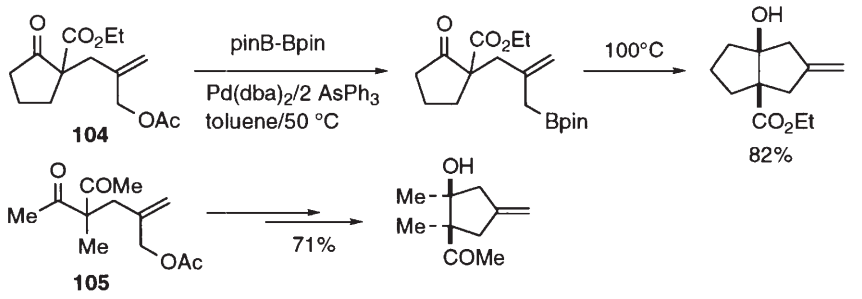
*Synthesis of **100*** [190, 191]: A flask charged with $PdCl_2$(dppf) (0.03 mmol), KOAc (3 mmol), bis(pinacolato)diboron (1.1 mmol) was flushed with nitrogen. DMSO (6 ml) and haloarene (1 mmol) were added, and the mixture was stirred for 1–24 h at 80 °C. The product was extracted with benzene, washed with water, and dried over $MgSO_4$. Kugelrohr distillation gave the arylboronate. The coupling with aryl triflates was carried out under the following reaction conditions. The flask was charged with $PdCl_2$(dppf) (0.03 mmol), dppf (0.03 mmol), KOAc (3 mmol) and bis(pinacolato)diboron (1.1 mmol), and flushed with nitrogen. Dioxane (6 ml) and aryl triflate (1.0 mmol) were added, and the resulting mixture was then stirred at 80 °C for 6–24 h.



Scheme 42. Cross-coupling reactions of diboron

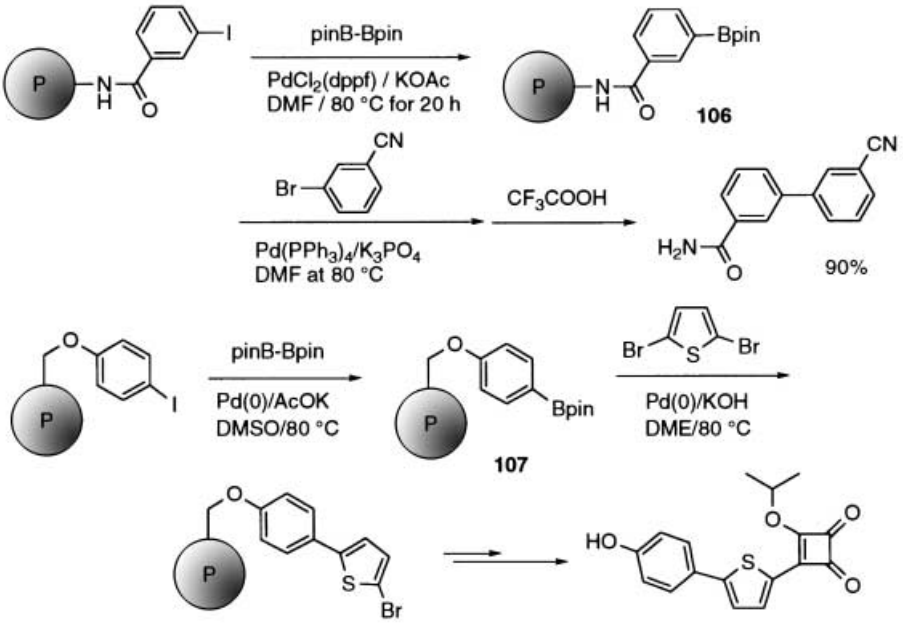
Intramolecular addition of allylmetal reagents to carbonyl substrates is a powerful tool for the synthesis of cyclic homoallyl alcohols with high regio- and stereoselectivity. However, the corresponding reaction of allylboranes has not been well developed mainly due to the lack of a general method for the synthesis of allylboronates having a carbonyl group. The palladium(0)-catalyzed crosscoupling reaction of diboron provides an efficient and convenient access to variously functionalized allyboronates under neutral conditions [241] [Scheme 43]. A variety of 5–5, 6–5, and 7–5 *cis*-fused exomethylene cyclopentanols were synthesized from β-ketoesters or β-diketones (**104**, **105**) *via* a cross-coupling/ intramolecular allylboration sequence. The observed diastereoselectivity suggested that the allylboration proceeded through a chair-like, six-membered transition state, analogously to the corresponding intermolecular version.

Reaction of ***104*** [241]: A dry 25-ml flask was charged with $Pd(dba)_2$ (0.03 mmol), $AsPh_3$ (0.06 mmol), and toluene (6 ml) under nitrogen. After being stirred at room temperature for 30 min, diboron **74** (1.1 mmol) and **104** (1.0 mmol) were successively added. The mixture was heated at 50 °C for 16 h and then at 100 °C for 24 h. The resulting mixture was treated with saturated NH_4Cl solution (10 ml) at room temperature for 1 h, extracted with ether, and dried over $MgSO_4$. An analytically pure product was isolated by chromatography over silica gel (82%).



Scheme 43. Cross-coupling-intramolecular allylboration sequence

The direct preparation of arylboronic esters from aryl halides or triflates now allows a one-pot, two-step procedure for the synthesis of unsymmetrical biaryls. The synthesis of biaryls was readily carried out in the same flask when the first coupling of aryl halide with diboron was followed by the next reaction with another halide or triflate [240]. The protocol offered a direct and efficient method for the synthesis of the boronic ester in the solid-phase that hitherto met with little success using classical methodology (Scheme 44). The solid-phase boronate (**106**, **107**) [243] was quantitatively obtained by treating a polymer-bound haloarene with the diboron. The subsequent coupling with haloarenes furnished various biaryls. The robot synthesis or the parallel synthesis on the surface of resin is the topic of further accounts of the research.

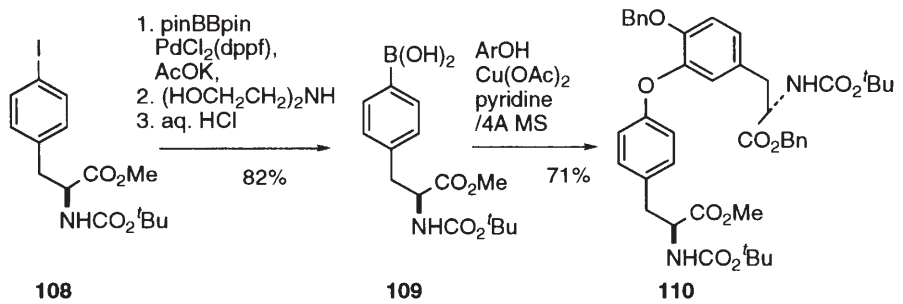


Scheme 44. Solid-phase one-pot synthesis of biaryls

4.6 Arylation of N-H and O-H Compounds

The arylation of N-H and O-H containing compounds, such as amines, amidos, imines, and phenols, with arylboronic acids is promoted by copper(II) acetate (1 equivalent) and tertiary amine (2–5 equivalents) at room temperature [244–248]. The mild reaction conditions at room temperature permit the synthesis of phenolic amino acids without racemization, methodology that has been applied to an efficient synthesis of (S,S)-isodityrosine from two natural amino acids [248] (Scheme 45).

*Synthesis of **110*** [248]: To a solution of a phenol synthesized from tyrosine (ArOH) (0.062 mmol) in CH_2Cl_2 (2.5 ml) were added **109** (0.062 mmol), $Cu(OAc)_2$



Scheme 45. O-arylation with arylboronic acids

(0.062 mmol), pyridine (0.314 mmol), 4 A molecular sieves, and the mixture was stirred for 18 h at room temperature. Chromatography over silica gel gave **110** (60%).

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Organosilicon Compounds

Tamejiro Hiyama [1] · Eiji Shirakawa [2]

[1] Department of Material Chemistry, Graduate School of Engineering, Kyoto University, Sakyo-ku, Kyoto 606-8501, Japan
E-mail: thiyama@npc05.kuic.kyoto-u.ac.jp
[2] Japan Advanced Institute of Science and Technology, Asahidai, Tatsunokuchi, Ishikawa 923-1292, Japan
E-mail: shira@jaist.ac.jp

Oraganosilicon compounds react with a wide variety of organic electrophiles in the presence of a palladium catalyst and a Lewis base activator such as a fluoride or hydroxy ion to give the corresponding coupled products. The reaction is applicable to synthesis of diynes, enynes, arylacetylenes, alkenylarenes, biaryls, allylarenes and alkylarenes in addition to 1,3-, 1,4- and 1,5-dienes with tolerance for various functional groups.

Keywords. Palladium catalyst, Organosilicate, Fluoride ion, Functional group tolerance

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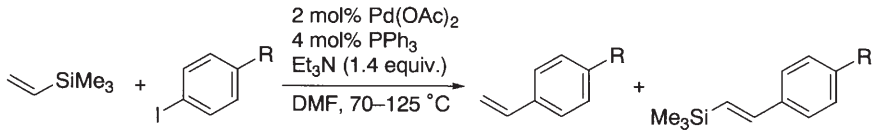
Abbreviations

dba	dibenzylideneacetone
DMF	*N,N*-dimethylformamide
DMI	*N,N*-dimethylimidazolidinone
dppb	1,4-bis(diphenylphosphino)butane
dppe	1,2-bis(diphenylphosphino)ethane
dppp	1,3-bis(diphenylphosphino)propane
ee	enantiomeric excess
HMPA	hexamethylphosphoric triamide
r.t.	room temperature
TASF	tris(diethylamino)sulfonium difluoro(trimethyl)silicate
TBAF	tetrabutylammonium fluoride
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran
tol	tolyl

1 Introduction [1–3]

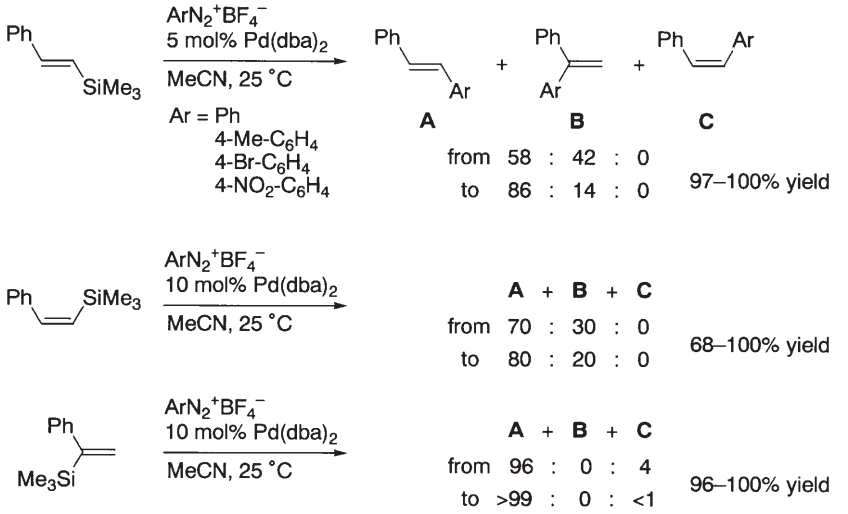
Organosilicon compounds are weak nucleophiles compared with other organometallic compounds because the carbon–silicon bond in organosilicon compounds is only weakly polarized. This character is advantageous for organic synthesis in view of tolerance toward a wide variety of functional groups, since appropriate methods to activate either organosilicon compounds or electrophilic substrates are available. For example, the reaction of allyl- or alkenylsilanes with aldehydes or acyl halides is accelerated considerably in the presence of a Lewis acid and is widely used as a chemoselective reaction. The situation holds true to the transition metal-catalyzed cross-coupling reaction of organosilicon compounds used in combination with a Lewis base activator. The resulting pentacoordinate silicates are sufficiently nucleophilic to react with palladium(II) complexes chemoselectively as disclosed in 1988 [4]. In this section, the history of the cross-coupling reaction of organosilicon compounds up to 1988 will be presented briefly.

There are scattering examples that neutral organosilanes R-$SiMe_3$ undergo a desilylative coupling reaction with aryl halides in the presence of a palladium catalyst. Hallberg and his co-workers disclosed that trimethyl(vinyl)silane reacts with an arylpalladium(II) complex to afford coupled products accompanied by aryl-substituted alkenylsilanes formed through the Heck type reaction



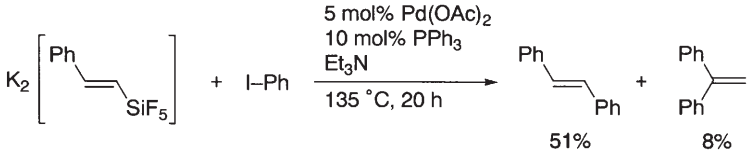
(1)

(Eq. 1) [5]. On the other hand, Kikukawa and his co-workers found that the reaction of trimethyl(α- or β-styryl)silane with arenediazonium tetrafluoroborates gave regioisomeric mixtures of coupling products [6–8]. The catalytic cycle of the reaction is considered to involve carbopalladation toward the C–C double bond of an alkenylsilane by an arylpalladium intermediate followed by tetrafluoroborate-assisted elimination of the silyl group and regeneration of a palladium(0) species (Scheme 1).



Scheme 1

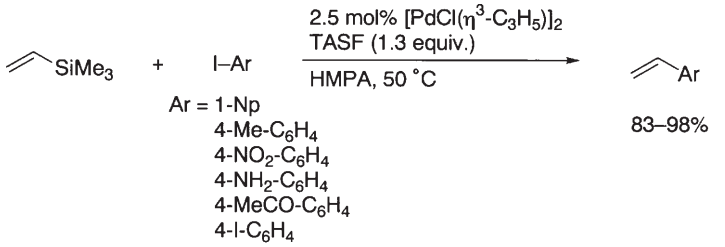
On the other hand, Kumada and Tamao disclosed that an organo(pentafluoro)silicate underwent desilylative coupling with iodobenzene in the presence of a palladium catalyst under rather drastic reaction conditions (Eq. 2) [9]. Although the nucleophilicity at the carbon atom having a silicate group is apparently enhanced, a *cine*-coupling product in addition to an *ipso*-coupling product is produced.



(2)

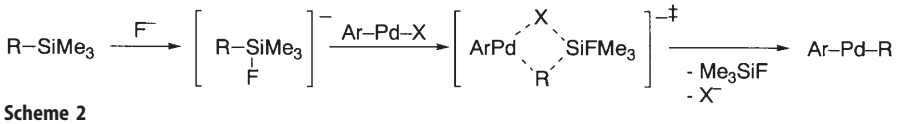
From a standpoint of organic synthesis, the coupling through carbopalladation of C=C bonds of alkenylsilanes is less attractive, because the reaction generally affords mixtures of regioisomers and the substrates are limited strictly to alkenylsilanes. Hiyama and Hatanaka overcame these drawbacks by using fluoride salts to *in situ* activate organosilicon compounds. Thus, alkenyl(trimethyl)silanes coupled with aryl or alkenyl halides in the presence of a palladium catalyst and fluoride ion source $(Et_2N)_3S^+(Me_3SiF_2)^-$, abbreviated as TASF (Eq. 3) [4].

Upon activation by a fluoride ion, the nucleophilicity of alkenylsilanes becomes adequate to complete transmetalation. This cross-coupling reaction is tolerant of a wide variety of functional groups such as ester, ketone, aldehyde and alcohol. Furthermore, mild reaction conditions prevent degradation and/or isomerization of products even in the reaction of substrates having a complicated structure. The strategy that uses a Lewis base activator had opened up the door of the cross-coupling reaction of organosilicon compounds including not only alkenylsilanes but also alkynyl-, aryl-, allyl- and alkylsilanes.



(3)

The following mechanism is suggested for the cross-coupling of alkenylsilanes. Nucleophilic attack of a fluoride ion to the silicon atom of alkenylsilanes is first assumed to afford a pentacoordinate silicate and enhance both nucleophilicity of the silicon-substituted carbon and Lewis acidity of silicon to assist transmetalation effectively through a four-centered transition state (Scheme 2). Lewis acidity on silicon is critical as evidenced by the fact that hexacoordinate pentafluorosilicates that are fully coordinated and thus should have sufficient nucleophilicity are much less effective for the cross-coupling reaction (Eq. 2, *vide supra*).



Scheme 2

2 Various Carbon–Carbon Coupling Reactions

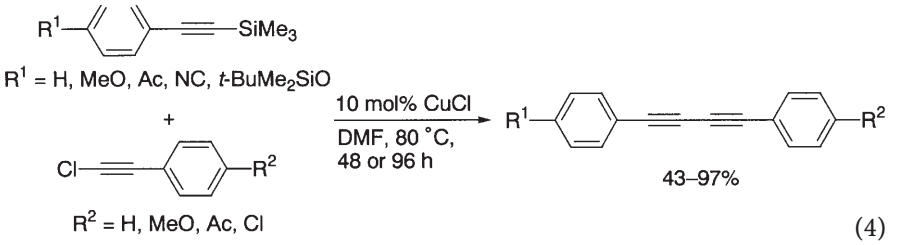
Except for the coupling between *sp* and sp^3 carbons that are easily accomplished by the nucleophilic substitution reaction of alkynylmetals with alkyl halides in the absence of a catalyst, all of the possible Carbon–Carbon coupling patterns are attained by the cross-coupling reaction of organosilicon compounds. This section reviews the transition metal-catalyzed Carbon–Carbon bond formation using organosilicon compounds in the order of *sp*-*sp*, *sp*-sp^2, sp^2-sp^2, sp^2-sp^3 and sp^3-sp^3 coupling, giving rise to a variety of carbon frameworks such as diynes, enynes, arylacetylenes, alkenylarenes, biaryls, allylarenes, and alkylarenes in addition to 1,3-, 1,4- and 1,5-dienes. The coupling reaction carried out in the

presence of carbon monoxide gives ketones. This three component coupling also is described.

2.1 Coupling between *sp* Carbon Centers

2.1.1 *Diyne*

Arylethynyl(trimethyl)silanes react with arylethynyl chlorides in the presence of copper(I) catalyst under neutral conditions without any base to give unsymmetrical diynes (Eq. 4) [10]. The reaction is thought to proceed via transmetalation of an alkynylsilane with a copper(I) complex.



(4)

Experimental Procedure for 1-(4-methoxyphenyl)-4-phenyl-1,3-butadiyne (Eq. 4)

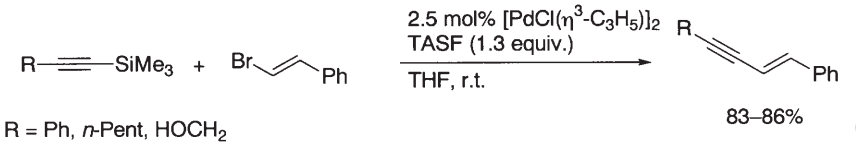
To a solution of copper chloride (2.4 mg, 0.024 mmol) in DMF (1.5 ml) was added 1-chloro-2-phenylacetylene (50 mg, 0.37 mmol) at r.t. To the mixture was added trimethyl(4-methoxyphenylethynyl)silane (50 mg, 0.25 mmol). The reaction mixture was stirred for 48 h at 80 °C, quenched with 3 M HCl, and extracted with diethyl ether (25 ml × 2). The combined ethereal layer was washed with aqueous $NaHCO_3$ solution, then with brine and dried over $MgSO_4$. Filtration and evaporation provided a brown oil. Purification by column chromatography (SiO_2, hexane:dichloromethane = 10:1) gave 1-(4-methoxyphenyl)-4-phenyl-1,3-butadiyne (36 mg, 65% yield) as a colorless solid.

2.2 Coupling between *sp* and sp^2 Carbon Centers

2.2.1 *Enyne*

Alkynyl(trimethyl)silanes smoothly couple with alkenyl halides at room temperature in the presence of a palladium catalyst and TASF (Eq. 5) [4]. The difference in reactivity between alkynylstannanes and -silanes were utilized in a palladium-catalyzed three component cross-coupling reaction. Thus, the palladium-catalyzed sequential reaction of tributylstannyl(trimethylsilyl)ethyne

first with an alkenyl iodide and then with another alkenyl iodide in the presence of newly added TASF afforded conjugated dienynes (Eq. 6) [11].



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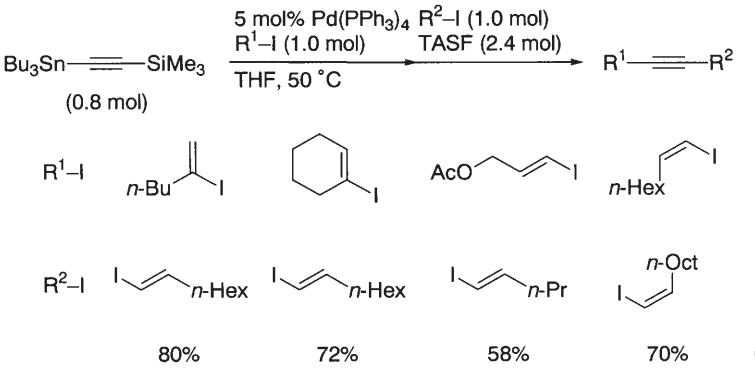


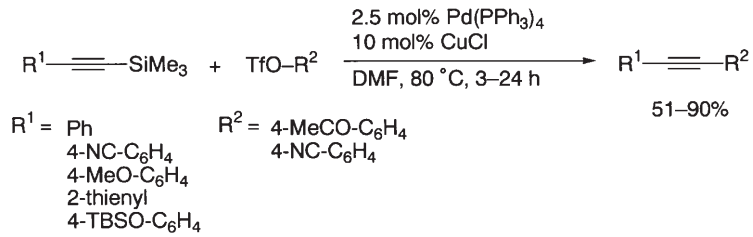
(6)

Experimental Procedure for 1,4-diphenyl-3-buten-1-yne (Eq. 5)

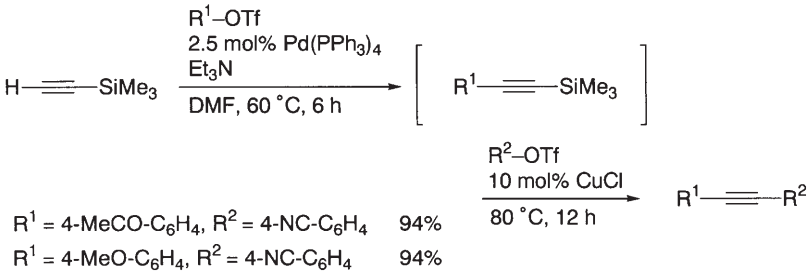
A THF solution of TASF (1.0 M solution, 0.40 ml, 0.40 mmol) was added to trimethyl(phenylethynyl)silane (40 mg, 0.40 mmol) and $(\eta^3\text{-}C_3H_5PdCl)_2$ (2.7 mg, 0.0075 mmol) dissolved in THF (0.3 ml) at 0 °C under an argon atmosphere. (*E*)-1-Bromo-2-phenylethene was injected to the resulting solution, and the mixture was stirred at r.t. After completion of the reaction, the bulk of the solvent was removed by passing through a silica gel column with pentane as an eluent. Evaporation of pentane under reduced pressure gave pure 1,4-diphenyl-3-buten-1-yne (83 % yield).

2.2.2 *Arylacetylene*

A catalytic amount of CuCl was found to activate alkynyl(trimethyl)silanes in the palladium-catalyzed coupling reaction with aryl triflates (Eq. 7) [12]. The catalytic cycle is considered to involve the transfer of an alkynyl group from an alkynylsilane to Cu(I) and then to palladium(II). A sequential palladium-catalyzed reaction of trimethylsilylacetylene gives unsymmetrical diarylacetylenes (Eq. 8).



(7)



(8)

Experimental Procedure for 4-(phenylethynyl)acetophenone (Eq. 7)

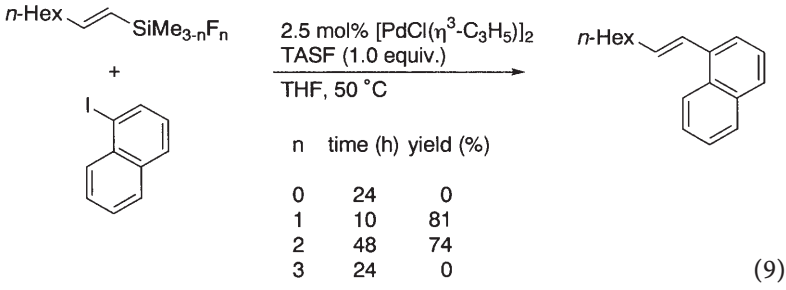
To a solution of CuCl (10 mg, 0.1 mmol) and $Pd(PPh_3)_4$ (58 mg, 0.05 mmol) in DMF (25 ml) were added trimethyl(phenylethynyl)silane (0.98 ml, 6.0 mmol) and 4-(trifluoromethanesulfonyloxy)acetophenone (0.95 ml, 5.0 mmol) at r.t. The reaction mixture was stirred for 24 h at 80 °C, quenched with 3 M HCl and extracted with diethyl ether. The ethereal layer was washed with aqueous $NaHCO_3$ solution and then with brine and dried over $MgSO_4$. Filtration and evaporation provided a brown oil (GC yield 97%). Purification by column chromatography (SiO_2, hexane:diethyl ether = 1:1) followed by bulb-to-bulb distillation (200 to 210 °C/5 mmHg) gave 4-(phenylethynyl)acetophenone (0.98 g, 89% yield) as a colorless solid.

2.3 Coupling between sp^2 Carbon Centers

2.3.1 *Alkenylarene*

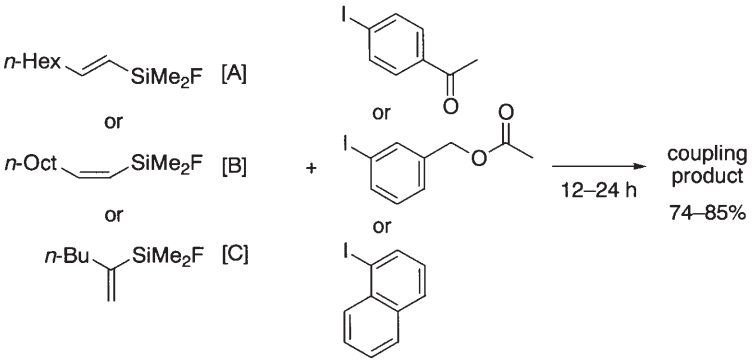
Although trimethyl(vinyl)silane undergoes the coupling reaction with aryl halides in the presence of TASF and a palladium catalyst as described in Section 1 (Eq. 3), those having an aliphatic substituent on vinyl fail to couple with aryl iodides under similar conditions, probably because they are not capable of affording pentacoordinate silicates efficiently owing to the electron-donating nature of the substituent. To assist the formation of the pentacoordinated intermediates, the methyl on silicon was replaced by fluorine [13]. The cou-

pling reaction of (*E*)-1-fluoro(methyl)silyl-1-octene with 1-iodonaphthalene in Eq. 9 clearly suggests that one or two fluorine atom(s) on silicon is definitely effective. Inertness of (*E*)-1-trifluorosilyl-1-octene is attributed to the formation of an unreactive hexacoordinated silicate. These findings led to the successful coupling reaction of various alkenylsilanes with aryl iodides with complete retention of configuration of both the coupling partners (Eq. 10).



n	time (h)	yield (%)
0	24	0
1	10	81
2	48	74
3	24	0

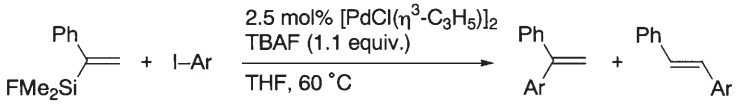
(9)



[A] 2.5 mol% $[PdCl(\eta^3\text{-}C_3H_5)]_2$, TASF (1.5 equiv.), THF, 60 °C.
[B] 5 mol% $Pd(PPh_3)_4$, TASF (1.5 equiv.), THF, 60 °C.
[C] 2.5 mol% $[PdCl(\eta^3\text{-}C_3H_5)]_2$, TBAF (1.5 equiv.), THF, 60 °C. (10)

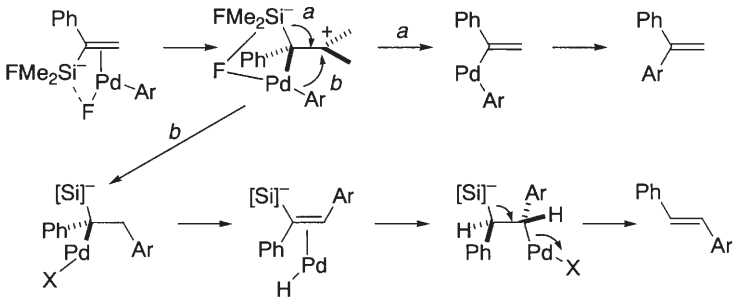
The cross-coupling reaction of alkenyl(fluoro)silanes with aryl halides sometimes produces, in addition to the desired *ipso*-coupled products, small amounts of *cine*-coupled products [14]. The *cine*-coupling is often striking in the reaction with organotin compounds. The isomer ratio of products produced by the reaction of 1-fluoro(dimethyl)silyl-1-phenylethene with aryl iodides is found to depend on the electronic nature of a substituent on aryl iodides (Eq. 11): an electron-withdrawing group like trifluoromethyl and acetyl favors the formation of the *ipso*-coupled product. To explain the substituent effect, the mechanism depicted in Scheme 3 is proposed for the transmetalation of alkenylsilanes with palladium(II) complexes. It is considered that an electron-donating substituent on Ar enhances

the nucleophilicity of the aryl group to promote intramolecular nucleophilic attack of Ar to the cationic β-carbon (path b), leading to the *cine*-coupled product.



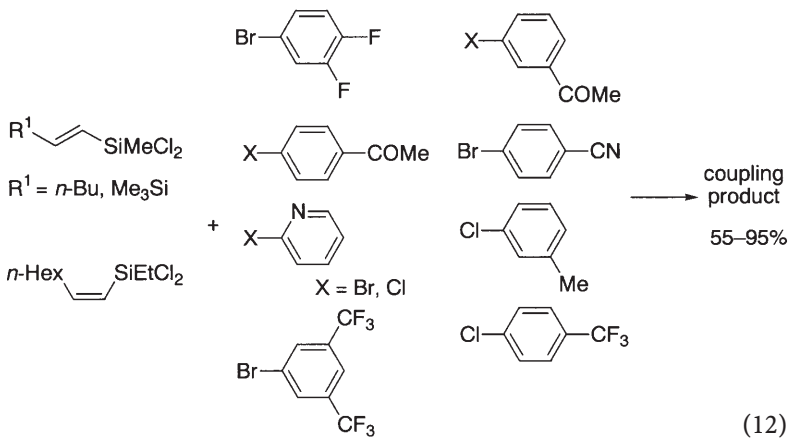
Ar = 4-CF_3-C_6H_4	24 h	72%	93	: 7
4-MeCO-C_6H_4	20 h	73%	88	: 12
4-F-C_6H_4	4 h	80%	79	: 21
Ph	4 h	69%	75	: 25
4-Me-C_6H_4	14 h	84%	59	: 41
4-EtO-C_6H_4	20 h	63%	60	: 40

(11)



Scheme 3

The fluoride ion activator can be replaced by a hydroxide ion, and the fluoride ligand on silicon by chlorine [15]. Thus, the palladium-catalyzed coupling of alkenylchlorosilanes with aryl halides was accomplished in the presence of NaOH under mild conditions (Eq. 12). It is worthy to note that the system can be

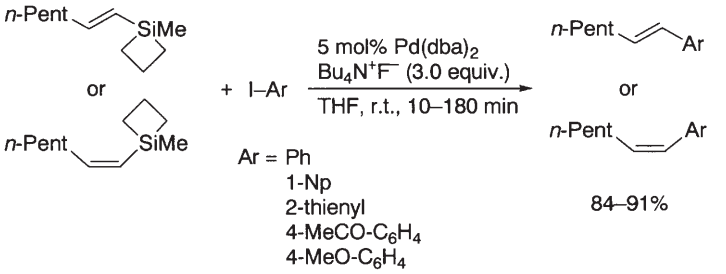


(12)

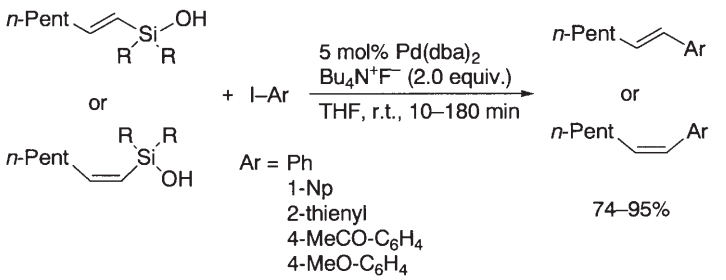
[A] 2.5 mol% $Pd(OAc)_2$, NaOH (6.0 equiv.), THF, 60 °C, 5–36 h (for aryl bromides).
[B] 2.5 mol% $PdCl_2(i\text{-}Pr_3P)_2$, NaOH (6.0 equiv.), THF, 80 °C, 12 h (for aryl chlorides).

applied to aryl chlorides, which are much less reactive than the corresponding bromides and iodides, when a palladium complex containing a triisopropylphosphine or tricyclohexylphophine ligand. Aryl triflates in addition to alkenyl triflates also are effective coupling partners not only for alkenylsilanes but also for allyl-, aryl-, alkyl- and alkynylsilanes [16].

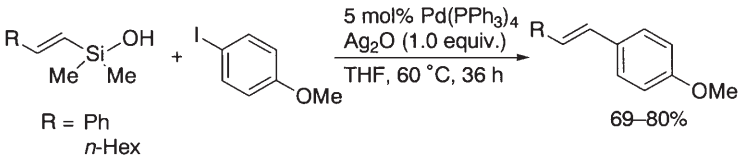
Denmark and his co-workers recently reported a series of the palladium-catalyzed coupling reactions of alkenylsilicon compounds with aryl iodides. Thus, (*E*)- or (*Z*)-alkenylsilacyclobutanes, which are readily prepared by the reaction of the corresponding alkenylaluminum compounds with chlorosilacylobutanes or the reduction of alkynylsilacyclobutanes, respectively, were found to be active nucleophiles to react with aryl iodides in 10 min at room temperature in most cases (Eq. 13) [17]. Later, it was clarified that silacyclobutanes were first converted into alkenyl(propyl)silanols by hydrolysis under the reaction conditions [18], and these were shown to be truly active species. Alkenylsilanols actually react with aryl iodides under the similar conditions (Eq. 14) [19, 20]. Independent study by Hiyama and Mori revealed that silver(I) oxide also is an excellent activator for the palladium-catalyzed coupling of alkenylsilanols with an aryl iodide (Eq. 15) [21]. Very recently Denmark



(13)



(14)



(15)

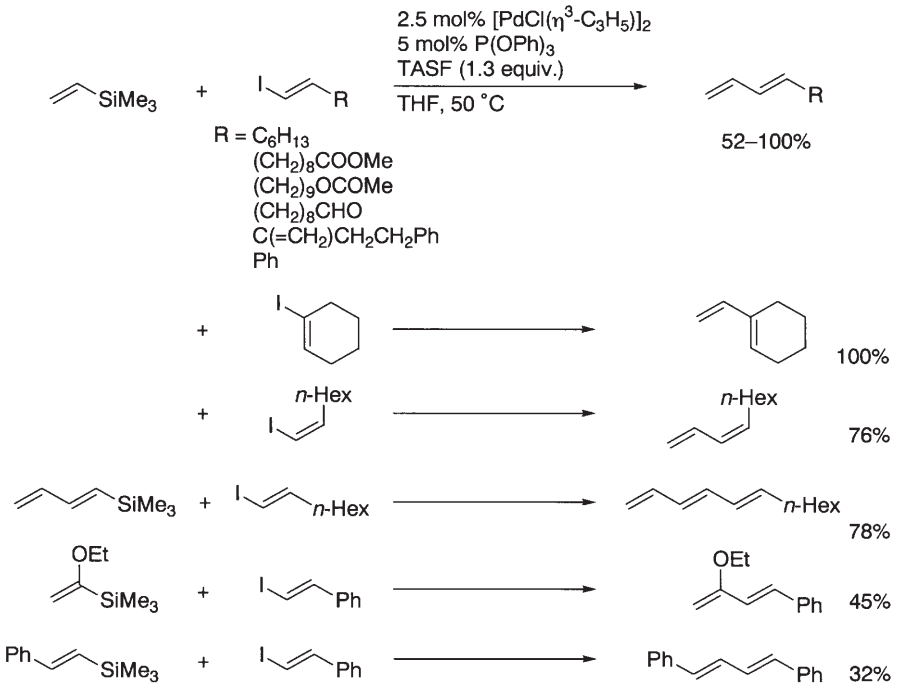
reported that 5-alkylidene-2-oxasilacyclopentanes also participate in the cross-coupling reaction with aryl or alkenyl halides in the presence of TBAF and a palladium(0) catalyst [22].

Experimental Procedure for 1-vinylnaphthalene (Eq. 3)

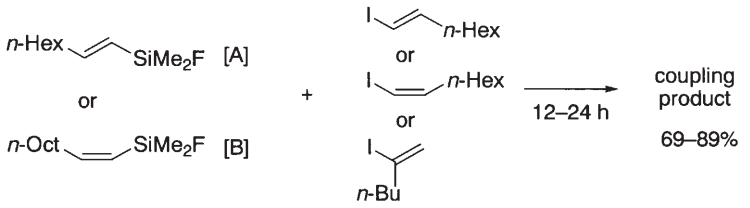
A THF solution of TASF (1.0 M solution, 0.40 ml, 0.40 mmol) was added to trimethyl(vinyl)silane (40 mg, 0.40 mmol) and (η^3-$C_3H_5PdCl)_2$ (2.7 mg, 0.0075 mmol) dissolved in HMPA (0.3 ml) at 0 °C under an argon atmosphere. 1-Iodonaphthalene (76 mg, 0.30 mmol) was injected to the resulting solution, and the mixture was stirred at 50 °C for 2 h. After completion of the reaction, the bulk of the solvent was removed by passing through a silica gel column with pentane as the eluent. Evaporation of pentane under reduced pressure gave pure 1-vinylnaphthalene (42 mg, 98% yield).

2.3.2 *1,3-Diene*

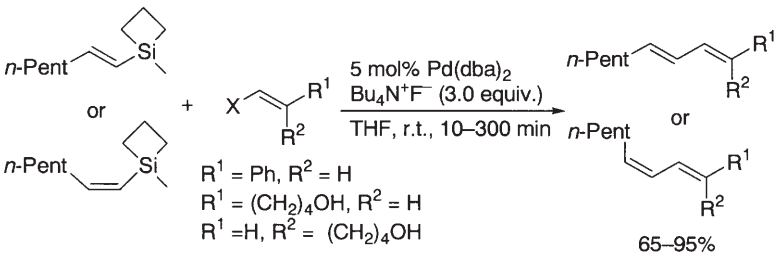
Since alkenyl halides behave in a manner similar to aryl halides in the cross-coupling reactions, 1,3-dienes can be obtained using alkenyl halides in lieu of aryl halides (Scheme 4 [4], Eq. 16 [13], Eq. 17 [17], Eq. 18 [19]).



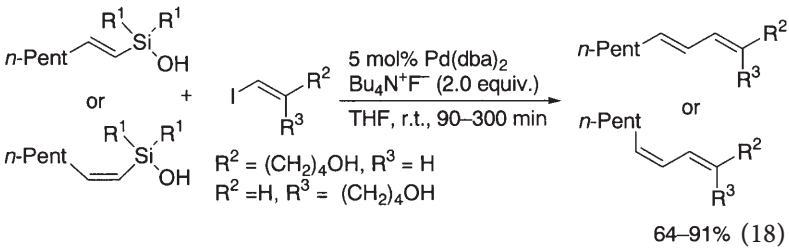
Scheme 4



[A] 2.5 mol% $[PdCl(\eta^3\text{-}C_3H_5)]_2$, TASF (1.5 equiv.), THF, 60 °C.
[B] 5 mol% $Pd(PPh_3)_4$, TASF (1.5 equiv.), THF, 60 °C. (16)



R^1 = Ph, R^2 = H
R^1 = $(CH_2)_4OH$, R^2 = H
R^1 =H, R^2 = $(CH_2)_4OH$
X = I, Br (17)



R^2 = $(CH_2)_4OH$, R^3 = H
R^2 =H, R^3 = $(CH_2)_4OH$ (18)

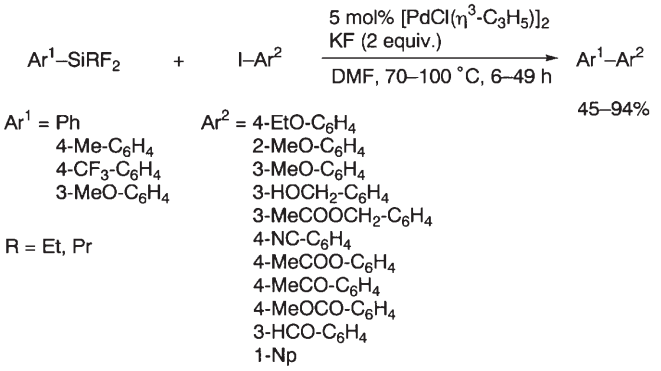
Experimental Procedure for (7E,9E)-hexadecadiene (Eq. 16)

To a THF (1.5 ml) solution of (*E*)-iodo-1-octene (48 mg, 0.20 mmol) and (η^3-$C_3H_5PdCl)_2$ (2.1 mg, 0.057 mmol) were added (*E*)-1-(dimethylfluorosilyl)-1-octene (47 mg, 0.25 mmol) and then a THF solution of TASF (0.71 M, 0.36 ml, 0.25 mmol) under an argon atmosphere, and the mixture was heated at 60 °C for 16 h. Concentration under reduced pressure followed by purification by column chromatography (SiO_2, hexane) afforded (7*E*,9*E*)-hexadecadiene (37 mg, 83% yield).

2.3.3 *Biaryl*

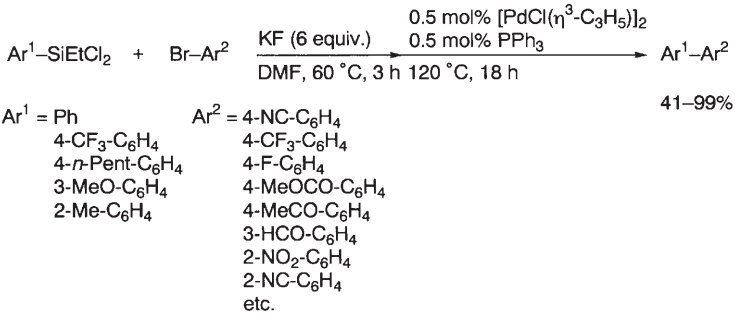
The coupling reaction of arylsilanes with aryl iodides is also mediated by a palladium catalyst and a fluoride ion [23, 24]. Optimized reaction conditions are as

follows: (1) two fluorine atoms on silicon are required, (2) an ethyl or propyl group is preferred as a dummy alkyl ligand, because a methyl group competitively participates in the cross-coupling reaction, and (3) TBAF, a highly effective fluoride ion source, is preferably replaced by inexpensive KF. Various unsymmetrical biaryls are synthesized under the conditions (Eq. 19).



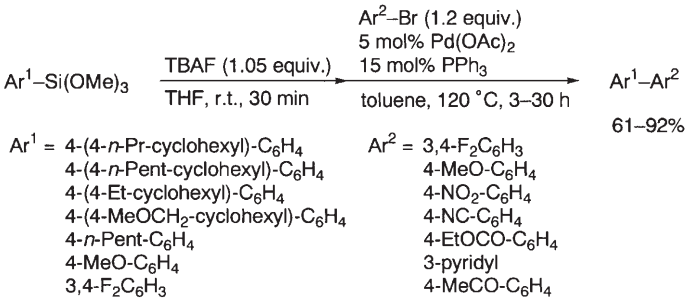
(19)

Aryl(chloro)silanes, upon pretreatment with KF, smoothly undergo the palladium-catalyzed coupling with aryl bromides and iodides to give various biaryls. For this procedure, $Pd(OAc)_2$ (0.5 mol%)/P(*o*-tol)$_3$ (0.5 mol%) is convenient (Eq. 20).

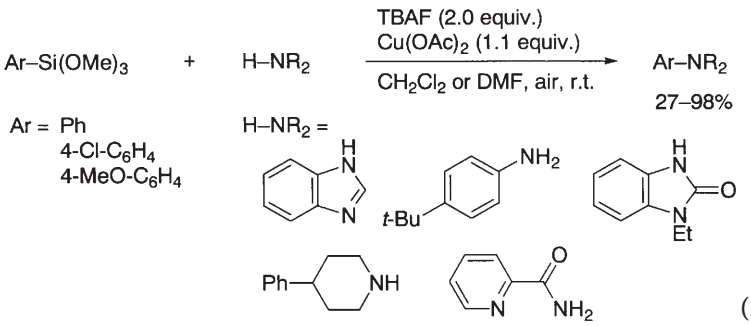


(20)

Recently, Shibata and his co-workers found that aryl(trimethoxy)silanes were also applicable to the palladium-catalyzed cross-coupling reaction with aryl bromides (Eq. 21) [25]. Similar procedure using phenyl-, vinyl- and allyl(trialkoxy)silanes was also reported by DeShong and his co-workers [26, 27]. The coupling of phenyl(trialkoxy)silane with aryl halides including chlorides was found to be catalyzed effectively by a palladium–diaminocarbene complex [28]. The reaction of aryl(trimethoxy)silane is reported very recently to react with amines in the presence of TBAF, $Cu(OAc)_2$ and pyridine under mild conditions to give *N*-arylated products (Eq. 22) [29]. The key step of the reaction is thought to be transmetalation of a pentacoordinate silicate with a copper(II) complex having an amide ligand.

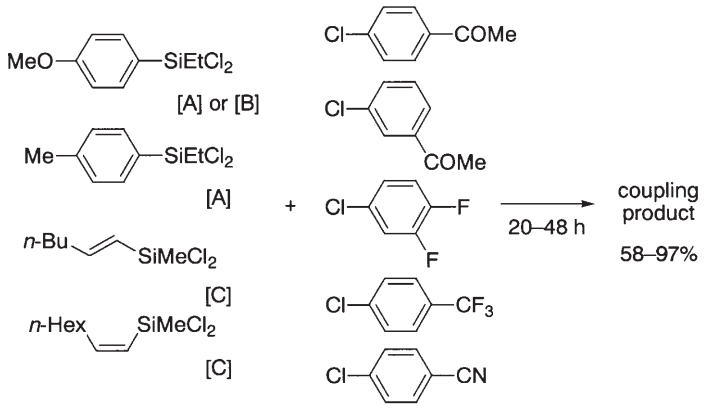


(21)



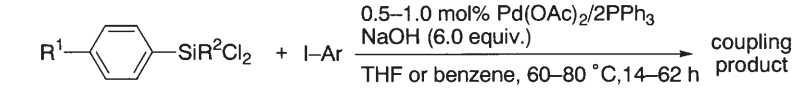
(22)

Aryl chlorides that are usually unreactive in the palladium-catalyzed cross-coupling reaction are applicable to the reaction with aryl- and alkenylchlorosilanes using a fluoride ion reagent and a catalytic amount of $(i\text{-}Pr_3P)_2PdCl_2$, $(Cy_2PCH_2CH_2PCy_2)PdCl_2$ or $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (Eq. 23) [30]. Sodium hydroxide as a Lewis base activator can be utilized as is the case with the coupling of alkenylsilanes with aryl halides (Eq. 24) [15]. The protocols for silacyclobutanes (Eq. 25) [31] and silanols (Eq. 26) [21] are also effective for the aryl-aryl coupling.

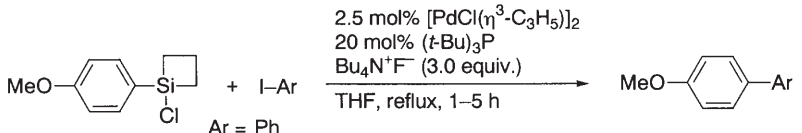


(23)

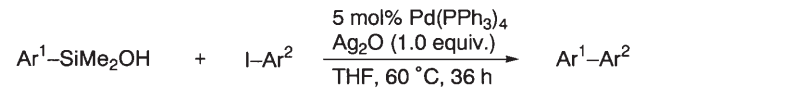
[A] 0.5 mol% $PdCl_2(i\text{-}Pr_3P)_2$, KF (6 equiv.), DMF, 120 °C.
[B] 2.0 mol% $PdCl_2(Cy_2PCH_2CH_2PCy_2)$, KF (10 equiv.), DMF, 120 °C.
[C] 0.5 mol% $[PdCl(\eta^3\text{-}C_3H_5)]_2$, TBAF (3.6 equiv.), THF, 90 °C in a sealed tube.



R^1 = H, MeO, Me, *trans*-4-*n*-Pr-cyclohexyl
R^2 = Et, Me
Ar = 3,4-$F_2C_6H_3$, 4-MeCO-C_6H_4, 2-pyridyl, 3,5-$(CF_3)_2$-C_6H_3 (24)



Ar = Ph, 4-EtOCO-C_6H_4, 4-MeCO-C_6H_4, 4-NO_2-C_6H_4, 4-NC-C_6H_4, 4-Me-C_6H_4, 1-Np, 3-Me-C_6H_4, 3-NO_2-C_6H_4, 2-Me-C_6H_4, 2-NO_2-C_6H_4, 3-pyridyl (25)



Ar^1 = 4-MeO-C_6H_4, 4-CF_3-C_6H_4, 2-Me-C_6H_4
Ar^2 = Ph, 4-Me-C_6H_4, 2-Me-C_6H_4, 4-MeCO-C_6H_4, 4-CF_3-C_6H_4, 4-NO_2-C_6H_4, 4-TfO-C_6H_4 (26)

Experimental Procedure for 4-fluoro-4′-methoxybiphenyl (Eq. 20)

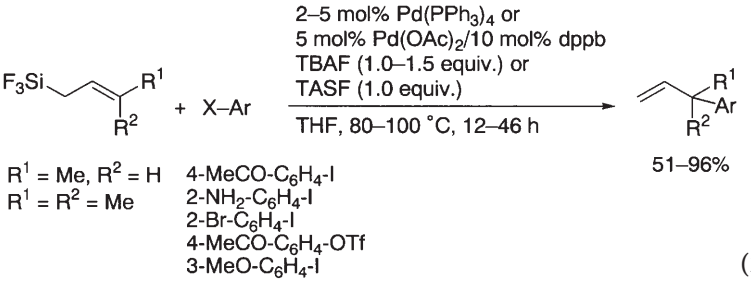
To a suspension of KF (spray dried, 2.1 g, 36 mmol) in DMF (7.0 ml) was added 1.7 g (7.2 mmol) of (dichloro)(ethyl)(4-methoxyphenyl)silane and 4-trifluoro-1-bromobenzene (1.05 g, 6.0 mmol) at 0 °C under an argon atmosphere. The resulting reaction mixture was then stirred at 60 °C for 3 h. The mixture was allowed to cool to r.t., and a solution of palladium acetate (6.7 mg, 0.030 mmol) and triphenylphosphine (7.8 mg, 0.030 mmol) in DMF was added. The reaction mixture was heated at 120 °C for 18 h and then cooled to r.t., poured into a saturated aqueous NaCl solution, and extracted with ethyl acetate (20 ml × 3). The combined organic extracts were dried over $MgSO_4$. Concentration under

reduced pressure afforded a crude product, which was purified by column chromatography (SiO_2, hexane:ethyl acetate = 10:1) to give 4-fluoro-4′-methoxybiphenyl (1.11 g, 91% yield).

2.4 Coupling between sp^2 and sp^3 Carbon Centers

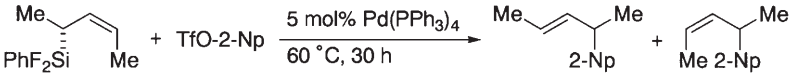
2.4.1 *Allylarene*

Allyltrifluorosilanes undergo the cross-coupling reaction with aryl halides exclusively at the γ-carbon to give allylated products (Eq. 27) [32]. The γ-selectivity is noteworthy, because the cross-coupling reaction using other allylmetals usually takes place *via* α-attack.



(27)

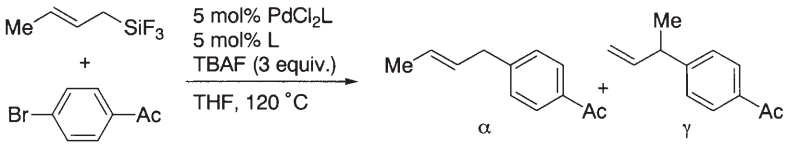
The reaction of optically active allyl(difluoro)phenylsilanes with aryl triflates affords optically active allylarenes with high stereoselectivities, wherein the absolute configuration of the newly generated chiral carbon can be controlled by proper choice of a fluoride reagent and a polar solvent (Eq. 28) [33].



	Stereoselectivity (config. of (*E*)-isomer)	*E*/*Z*	yield (%)
TASF (4 equiv.), DMF	99% (*S*)	8.6	70
CsF (4 equiv.), THF	74% (*R*)	42	50

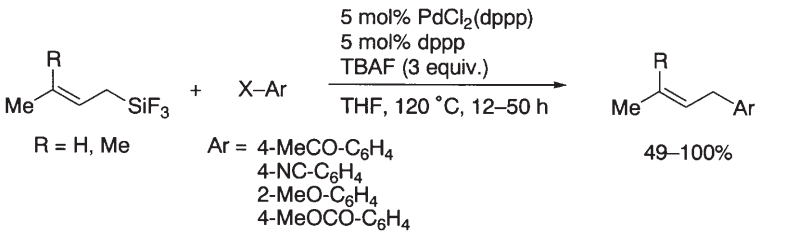
(28)

Bisphosphine ligands having an appropriate bite angle, however, change the regioselectivity of allylsilane-coupling from γ- to α-carbon (Eq. 29) [34]. A dppe or dppp ligand is assumed to retard the reductive elimination, inducing isomerization of a secondary γ (σ)-allyl(aryl)Pd(II) complex to the corresponding primary α-allyl complex. The α-selective reaction is applied to various aryl bromides or triflates (Eq. 30).



L	time (h)	yield (%)	α : γ	*E* : *Z* in α
$Ph_2PCH_2PPh_2$	23	85	55 : 45	4.6 : 1
$Ph_2P(CH_2)_2PPh_2$	18	86	97 : 1	8.1 : 1
$Ph_2P(CH_2)_3PPh_2$	15	92	99 : 1	7.2 : 1
$Ph_2P(CH_2)_4PPh_2$	6	57	16 : 84	4.3 : 1
$Ph_2P(CH_2)_5PPh_2$	41	77	6 : 94	4.8 : 1
Ph_3P	12	97	0 : 100	—

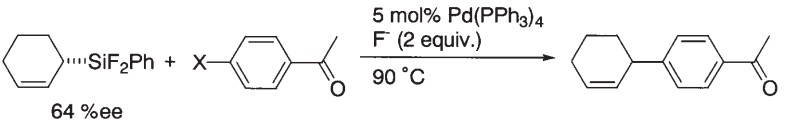
(29)



(30)

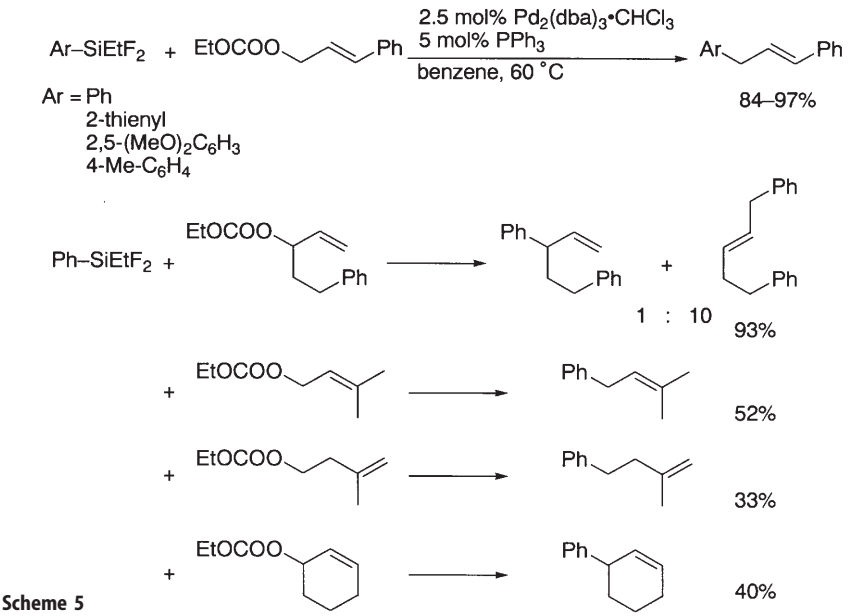
The kind of a fluoride ion activator and the leaving group in electrophiles affects the stereochemistry in the cross-coupling reaction of allylsilanes as exemplified with 2-cyclohexenyl(difluoro)phenylsilane (Eq. 31) [35].

Allyl carbonates (Scheme 5) and diene monoxides (Eq. 32) were also employed in the palladium-catalyzed coupling reaction of arylsilanes [36, 37]. The reaction does not require activation by a fluoride ion or an additional base like a hydroxide ion.

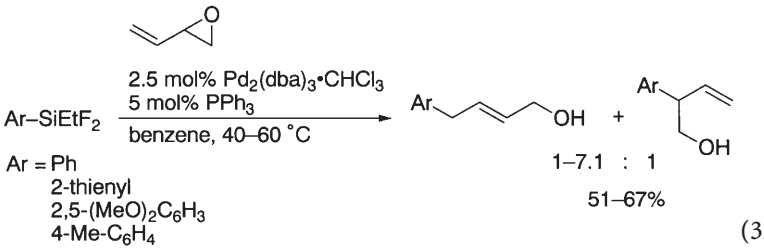


X	F^-	solvent	time (h)	yield (%)	%ee (config.)	chirality transfer (%)
I	TBAF	THF	3	84	52 (*S*)	81 (*ret*)
I	CsF	THF	108	39	22 (*S*)	34 (*ret*)
OTf	TBAF	THF	51	90	5 (*S*)	8 (*ret*)
OTf	CsF	CH_2Cl_2	21	17	24 (*R*)	38 (*inv*)

(31)



Scheme 5



(32)

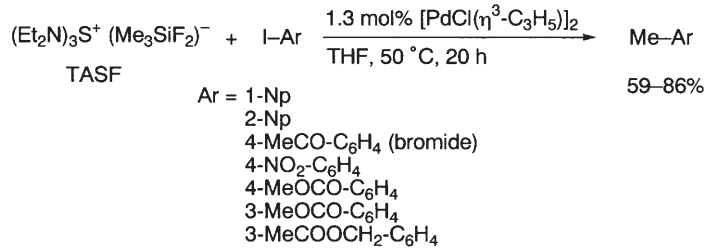
Experimental Procedure for 3-(4-acetylphenyl)–1-butene (Eq. 27)

A THF solution of TBAF (1.0 M, 3.0 ml, 3.0 mmol) was added to 4-iodoacetophenone (0.49 g, 2.0 mmol), (*E*)-crotyl(trifluoro)silane (0.42 g, 3.0 mmol), and $Pd(PPh_3)_4$ (62 mg, 0.05 mmol) dissolved in THF (10 ml) at r.t. under an argon atmosphere. The reaction mixture was then heated at 80 °C for 19 h. Concentration and purification by column chromatography (SiO_2, hexane:ethyl acetate = 10:1) gave 3-(4-acetylphenyl)-1-butene (0.34 g, 95% yield).

2.4.2 *Alkylarene*

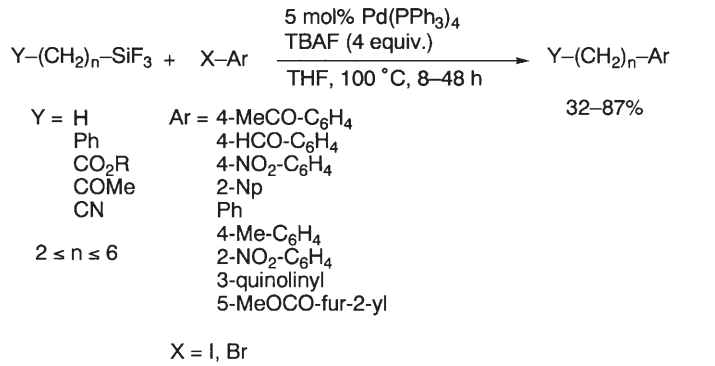
As we have seen, pentacoordinate silicate TASF is one of the best activators for organosilicon compounds in the palladium-catalyzed cross-coupling

reaction, but can participate in the coupling reaction with aryl halides in the absence of other organosilanes and gives methylated arenes (Eq. 33) [38]. Recently, DeShong and his co-workers also reported that tetrabutylammonium triphenyldifluorosilicate, another pentacoordinated silicate, is applicable to phenylation of allyl benzoates [39] or aryl halides [40] using a palladium catalyst.



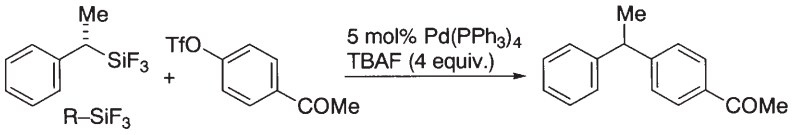
(33)

Alkyl(trifluoro)silanes are also applicable to the cross-coupling reaction with aryl halides (Eq. 34) [41,42]. TBAF in excess is required for giving products in acceptable yields, as the coproduced SiF_4 is readily converted into $(SiF_5)^-$ or $(SiF_6)^{2-}$.



(34)

The cross-coupling reaction of an optically active alkylsilane gives us valuable information on the stereochemistry in transmetalation [43]. The reaction of (*S*)-1-phenyl-1-(trifluorosilyl)ethane (34%ee) with 4-acetylphenyl triflate in the presence of 5 mol% of $Pd(PPh_3)_4$ and TBAF (2 equiv.) at 50 °C gives (*S*)-1-phenyl-1-(4-acetylphenyl)ethane of 34%ee with nearly complete retention of configuration. At higher temperatures, ee of the product decreases linearly, and above 75 °C inversion of configuration predominates (Eq. 35). Similar temperature dependency is observed also in the reaction of 3-formylphenyl triflate. The stereochemistry is affected also by the solvent polarity. The reaction using (*S*)-1-phenyl-1-(trifluorosilyl)ethane of 38%ee at 60 °C proceeded with retention (23%ee, *S*) in THF, but with inversion (8%ee, *R*) in HMPA–THF



from (*S*)-R–SiF_3 of 34 %ee

temp. (°C)	50	60	70	80	90	100	in THF
%ee (config.)	33 (*S*)	23 (*S*)	10 (*S*)	7 (*R*)	18 (*R*)	20 (*R*)	

from (*S*)-R–SiF_3 of 38 %ee

solvent	THF	DMF–THF (1 : 10)	DMSO–THF (1 : 10)	HMPA–THF (1 : 10)	at 60 °C
%ee (config.)	23 (*S*)	16 (*S*)	16 (*S*)	8 (*R*)	(35)

(1:10). Higher temperatures and polar solvents are considered to switch the reaction mechanism of transmetalation from a four-centered transition state (S_E2 (cyclic)) to a back-side attack of the palladium(II) complex (S_E2 (open)) (Fig. 1).

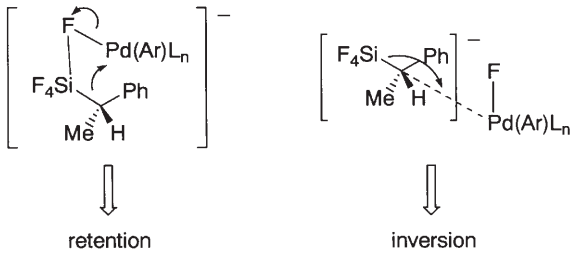


Fig. 1

Experimental Procedure for 4-hexylacetophenone (Eq. 34)

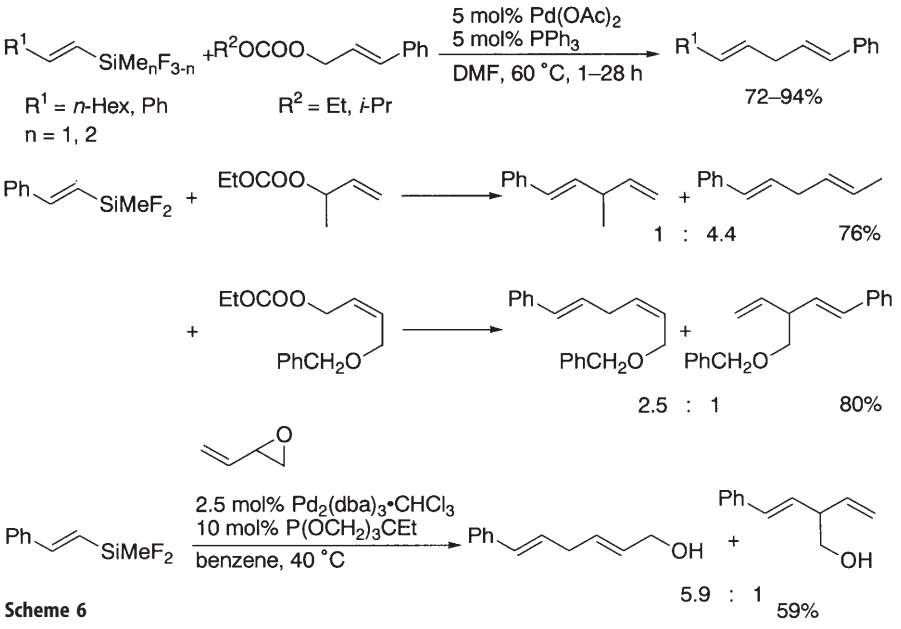
To a solution of $Pd(PPh_3)_4$ (12 mg, 0.010 mmol) and 4-bromoacetophenone (40 mg, 0.20 mmol) in THF (1 ml) placed in a screwed sealed glass tube were added sequentially hexyl(trifluoro)silane (68 mg, 0.40 mmol) and TBAF (1 M THF solution, 0.80 ml, 0.80 mmol) at r.t. The mixture was stirred for 30 min at r.t. and heated at 100 °C for 22 h. The reaction mixture was concentrated in vacuo, and the viscous residue was purified briefly by column chromatography (silica gel, CH_2Cl_2) to remove the Pd catalyst and tetrabutylammonium salt. The residue was further purified by flash column chromatography on silica gel to afford 3-(4-acetylphenyl)-1-butene (65% yield).

2.4.3
1,4-Diene

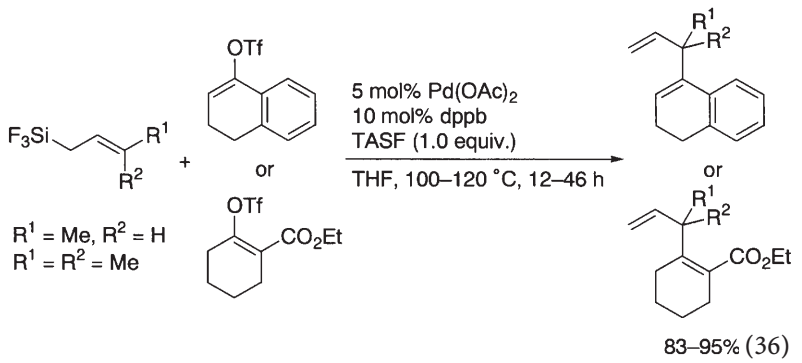
Preparation of 1,4-dienes can be affected by the palladium-catalyzed cross-coupling of alkenylsilanes with allyl carbonates or 1,3-butadiene monoxides (Scheme 6) [36,37] or alternatively by the reaction of allylsilanes with alkenyl triflates (Eq. 36) [32].

Experimental Procedure for 1,5-diphenyl-1,4-pentadiene (Scheme 6)

A mixture of $Pd(OAc)_2$ (2.0 mmol) and PPh_3 (2.0 mmol) in DMF (1 ml) was stirred for 10–30 min at r.t. in a screw capped glass tube. Ethyl (*E*)-3-phenyl-2-propenyl



Scheme 6

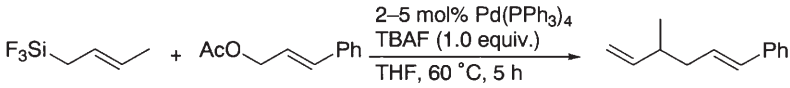


carbonate (0.40 mmol) and difluoro(methyl)[(*E*)-2-phenylethenyl]silane (0.80 mmol) were added to the mixture, and the whole reaction mixture was stirred at 60 °C for 2 h. The solvent was removed under vacuum, and the residue was purified briefly by column chromatography (SiO_2, hexane:ethyl acetate = 10:1) to remove the palladium catalyst. The product was further purified by flash column chromatography on silica gel to give 1,5-diphenyl-1,4-pentadiene (91% yield).

2.5
Coupling between sp^3 Carbon Centers

1,5-Diene

The reaction of an allylsilane with an allyl acetate in the presence of TBAF and a palladium catalyst is reported to give a 1,5-diene (Eq. 37) [32].



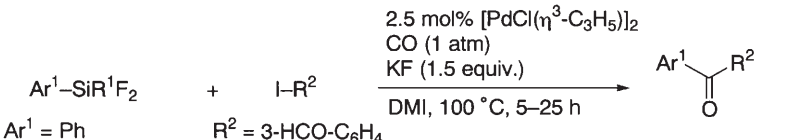
54% (37)

Experimental Procedure for 4-methyl-1-phenyl-1,5-hexadiene (Eq. 37)

4-Methyl-1-phenyl-1,5-hexadiene was obtained in a similar manner as 3-(4-acetylphenyl)-1-butene depicted in **2.4.1**.

2.6
Carbonylative Coupling

Under an atmospheric pressure of carbon monoxide, aryl- and alkenylsilanes undergo a carbonylative coupling reaction with aryl and alkenyl halides [44, 45]. The optimized conditions for arylsilanes involve the use of *N*,*N*-dimethyl-2-imidazolidinone (DMI) as a solvent and KF as a fluoride ion source (Eq. 38), whereas alkenylsilanes prefer THF and TBAF (Eq. 39).

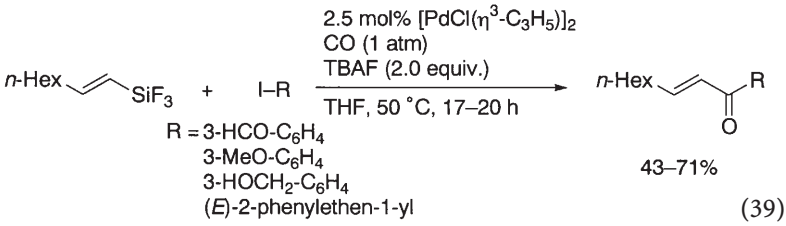


Ar^1 = Ph, 3-MeO-C_6H_4, 4-CF_3-C_6H_4, 4-Me-C_6H_4, 2-thienyl

R^1 = Et, *n*-Pr

R^2 = 3-HCO-C_6H_4, 1-Np, 4-MeCO-C_6H_4, 4-NC-C_6H_4, 4-MeOCO-C_6H_4, 3-quinolinyl, (*E*)-1-octen-1-yl

38–80% (38)



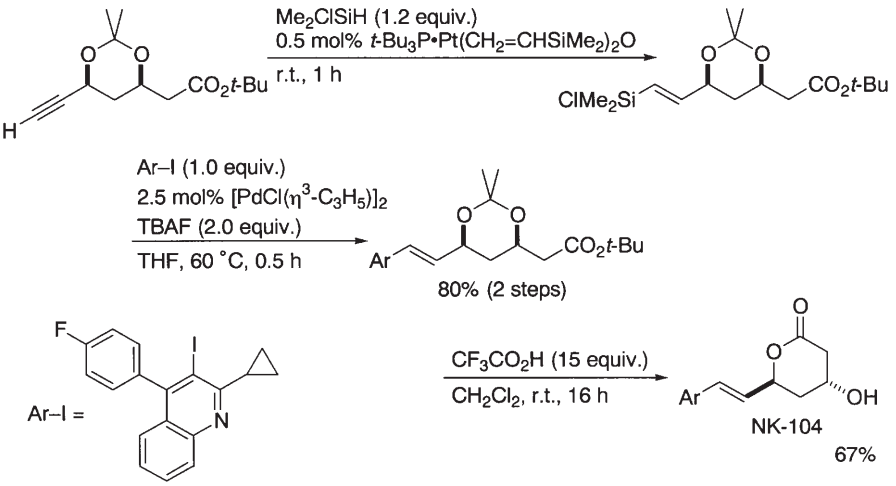
(39)

Experimental Procedure for 4-acetylphenyl 4-methylphenyl ketone (Eq. 38)

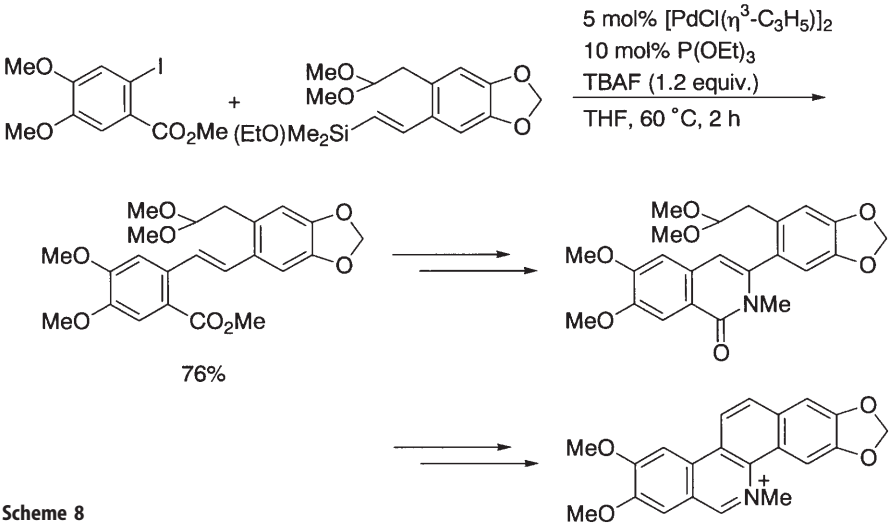
To a suspension of KF (0.19 g, 2.0 mmol) in DMI (10 ml) was added difluoro(ethyl)(4-methylphenyl)silane (0.56 g, 3.0 mmol) under 1 atm of carbon monoxide (balloon). After stirring at room temperature for 10 min, the reaction mixture was heated at 100 °C for 3 h. Bulk of the solvent and the catalyst were removed by passing the mixture through a silica gel column with ethyl acetate–hexane = 1:10 as an eluent solvent. Evaporation of the solvent under reduced pressure afforded 4-acetylphenyl 4-methylphenyl ketone (0.43 g, 91% yield) as a colorless solid.

3 Synthetic Applications

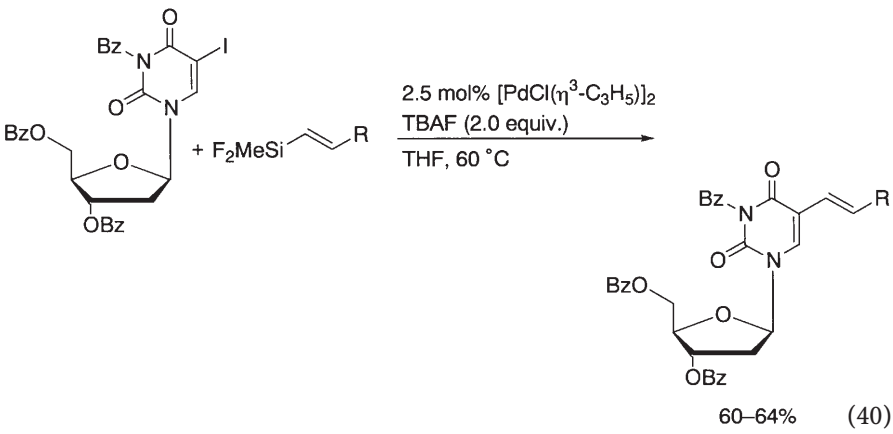
The palladium-catalyzed cross-coupling reaction of organosilicon compounds is applied to the synthesis of biologically active compounds. Some examples are described in the following schemes: artificial HMG-CoA reductase inhibitor, NK-104 (Scheme 7) [46–48], a precursor of a DNA topoisomerase inhibitor (Scheme 8) [49] and nucleosides (Eq. 40) [50].



Scheme 7



Scheme 8



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Organotin Compounds

Keigo Fugami · Masanori Kosugi

Department of Chemistry, Faculty of Engineering, Gunma University, 1-5-1 Tenjin-cho, Kiryu, Gunma 376-8515, Japan
E-mail: kosugi@chem.gunma-u.ac.jp

Palladium-catalyzed cross-coupling reaction between organotin compounds and various electrophiles provides a vast range of carbon skeletons.

Keywords. Organotin compounds, Palladium catalyst, Cross-coupling reaction, Carbonylative coupling

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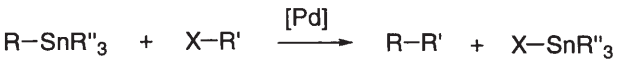
Abbreviations

BHT 4-methyl-2,6-bis(1,1-dimethylethyl)phenol [bis-*t*-butyl-*p*-hydroxytoluene]
dba 1,5-diphenyl-1,4-pentadien-3-one [dibenzylideneacetone]
dppb 1,4-bis(diphenylphosphino)butane
Nf 1,1,2,2,3,3,4,4,4-nonafluorobutanesulfonyl [nonaflyl]
NMP *N*-methylpyrolidin-2-one
TLC (silica gel) thin layer chromatography

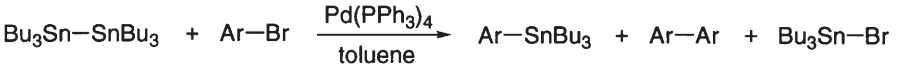
1 Brief History

A number of publications unambiguously indicate that organotin-mediated cross coupling is a quite powerful tool in organic synthesis (Scheme 1). Organotin reagents tolerate a wide variety of functional groups that many other reactive organometallics do not. Such functionalities on the electrophiles can also survive the cross-coupling reaction. In consequence, there have been developed a number of routes to prepare such reagents and this protocol has widely been applied to syntheses of a vast number of densely functionalized substances such as biologically intriguing compounds and other functional molecules. Since most of organotin reagents are neither sensitive to moisture nor oxygen, they can be easily isolated and stored. Thus organic chemists can easily handle them only with a special care of their toxicity.



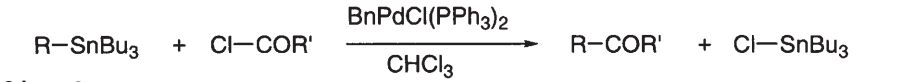
Scheme 1

The palladium-catalyzed reaction of organotin compounds was first published by Eaborn's group in 1976 [1]. It was initially taken as a variation of the Kharasch type reaction, namely, a radical reaction (Scheme 2).



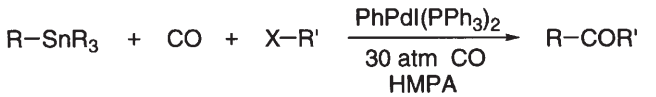
Scheme 2

In 1977, three reports appeared from Kosugi and Migita's group, that are concerned with transition-metal-catalyzed carbon-carbon bond-forming reactions, i.e., rhodium-catalyzed reaction of acid chlorides with allyl or benzyltributyltin [2], palladium-catalyzed reaction of acid chlorides with other organotins [3], and then palladium-catalyzed reaction of aryl halides with allyltributyltin [4]. The first Stille's paper that appeared in 1978 was on a ketone synthesis utilizing acid chlorides and organotin compounds catalyzed by $BnPdCl(PPh_3)_2$ in HMPA [5, 6]. The reaction conditions became milder and the yields higher. Subsequently he switched the solvent to chloroform to avoid the strongly carcinogenic HMPA (Scheme 3) [7].



Scheme 3

In 1979 the reaction of benzyl and aryl halides was reported with mechanistic discussions [8, 9]. The first palladium-catalyzed carbonylative coupling of organic halides with organotin compounds was reported by Tanaka in the same year (Scheme 4) [10, 11].



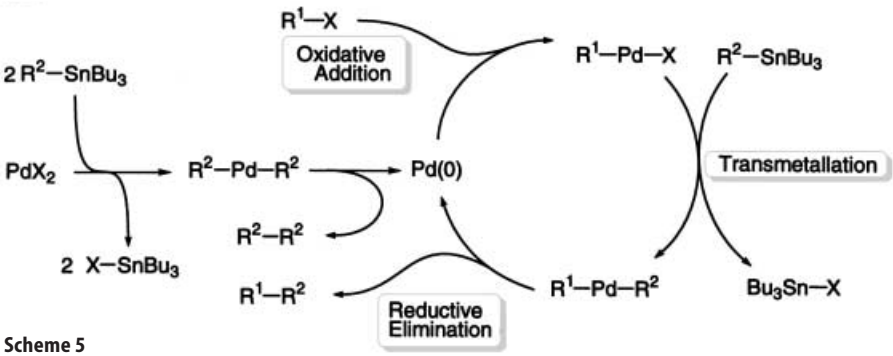
Scheme 4

Aldehyde synthesis by means of the palladium-catalyzed reduction of acid chloride using tributyltin hydride was published by Guibe et al. in 1980 [12]. The first report from Beletskaya's group also appeared in 1980 [13]. She introduced "ligandless palladium catalyst" and has developed a wide variety of reactions with it. Her first review on this topic appeared in 1983 [14]. The scope of the reaction was widened by Stille's employment of vinyl triflates instead of halides as organic electrophiles in 1984 [15]. His famous review was published in 1986 [16]. Mitchell's review is also noteworthy [17]. Since then it has been recognized that organotin protocol is useful for organic synthesis as the Stille reaction. The monograph "Tin in Organic Synthesis" was published in 1987 [18]. The next Mitchell's review covered literature from 1985 to 1990 [19]. A number of synthetic applications were introduced in it. From the late 1980s, striking advances have been brought about by Farina who developed new ligands for palladium such as tris(2-furyl)phosphine or triphenylarsine and introduced copper(I)

salts as additives to make the reaction conditions milder and the yields higher [20–23]. Recent progress up to 1996 was surveyed by Mitchell in the monograph "Metal-catalyzed Cross-coupling Reactions" in 1998 [24]. A comprehensive survey of this protocol was given in "Organic Reactions" vol. 50 by Farina, Krishnamurthy, and Scott in 1997 [25]. The present review describes some useful methods of preparation and use of organotin reagents toward organic synthesis [26–31].

2
Catalyst System and Guiding Mechanism

Mechanism was first discussed of the reaction with benzylic and aryl halides in 1979 [8, 9]. As shown in other protocols, the three-step catalytic cycle is widely accepted, that is, oxidative addition, transmetallation, and reductive elimination (Scheme 5).



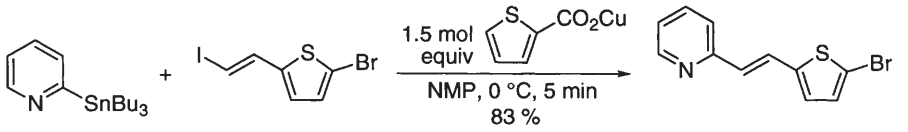
Scheme 5

The reaction is supposed to start with oxidative addition of an electrophilic component to Pd(0) species. Shirakawa and Hiyama demonstrated the possibility of oxidative addition of carbon-tin bond to palladium(0) to drive the catalytic cycle [32], that was suggested without evidence by Stille [33].

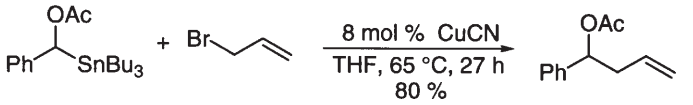
Pd(0) catalysts such as $Pd(PPh_3)_4$ and $Pd(dba)_2$ with or without an added ligand are often used. Although Pd(II) catalyst precursors such as $PdCl_2(PPh_3)_2$, $BnPdCl(PPh_3)_2$, $PdCl_2(MeCN)_2$, $Pd(OAc)_2$, etc. are favored in some cases, they are assumed to be reduced to Pd(0) species either by the stannane or an added phosphine ligand prior to the main catalytic process.

The reaction rates and/or yields sometimes vary with the choice of Pd(0) or Pd(II). Although the reason is not simple, it seems that the stoichiometric ratio between palladium and ligand is important in most of such cases. In the early stage of Stille's investigation, he reported that an excess of phosphine retards the oxidative-addition step that is often the rate-determining step [5]. The transmetallation step is also the rate-determining step in many cases, however, detailed mechanism is still not clear [21, 34]. Detailed studies on the transmetallation step has been underway [35–38]. Those would provide useful informations for determining the best conditions for specific cases. Recent development

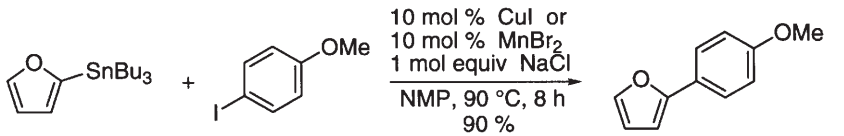
in this area includes application of other metals than palladium, such as copper (Scheme 6) [43], (Scheme 7) [40–46, 48], nickel [47, 49], and manganese (Scheme 8) [44], to this protocol. Palladium-charcoal has also been found to catalyze the reaction [50, 51].



Scheme 6



Scheme 7



Scheme 8

3 Experimental Aspects

3.1 Overview

Choice of conditions seems hard to predict for any specific class of substrates or reagents. Thus one had better surveying the most suitable conditions by try and error when trying any new reaction components. Some of rather general informations are described here.

Addition of ligand, cocatalyst, and other additives sometimes alters the results dramatically. Although the most commonly employed ligand used to be triphenylphosphine, the use of tris(2-furyl)phosphine [20, 21, 52, 53] or triphenylarsine [21, 22, 54] brings about large rate acceleration in many cases. Addition of copper(I) cocatalyst is also quite effective [54–62]. Palladium-catalysts without phosphine ligand [14] mostly show quite high initial reaction rate [63–66] but their lifetimes are often too short to get to completion [53, 67]. It is suggested that copper(I) cocatalyst accelerates the reaction by either capturing excess ligand [55–57, 68] or transmetallation from tin to copper and copper to

palladium [50, 69]. The way of contribution depends on the choice of the reaction medium [23, 70]. Copper(II) oxide is also reported to enhance the efficiency of the reaction probably by another way [71 – 75].

As an electrophile, organic bromide, iodide, and triflate are the most commonly employed. Carboxylate and chloride can also be good leaving groups in allylic and acyl electrophiles. Hyper-valent iodine derivatives generally react at rt (Sect. 4.10). Employment of triflate as a leaving group enabled carbonyl compounds and phenols [30, 76] to be taken into consideration as precursors of the electrophilic as well as organotin reaction components. It also made stereo- and regioselective access to a variety of alkenyl reaction components much easier. It should be noted that reaction with aryl triflates mostly requires addition of lithium chloride or another suitable salt [77]. Alkenyl triflates also need lithium chloride to react in THF [15, 78], while they do not in NMP [21]. The reactivity of triflates is usually competitive with that of the corresponding bromides. Chemoselectivity versus bromide may be altered by changing catalyst [77] or other conditions [54]. Although not so widely used so far, successful ractions with aromatic diazonium salts made it possible to obtain the electrophiles from anilines [79].

It is unavoidable to generate a stoichiometric amount of triorganotin-based waste, that often disturb isolation of the desired product because of low polarity and good solubility in many organic solvents, in most of cases. Development of process to separate such a waste from the product is therefore one of the central issues in this protocol. Treatment of the reaction mixture with aqueous KF solution to precipitate polymeric trialkyltin fluoride is the most widely used procedure [22, 23, 80]. Partition between acetonitrile and pentane can effectively remove the tin waste and unreacted nonpolar organotin reagent if the desired product is polar enough [53]. Use of combinatorial technique may be one of recent solutions (see Sects. 4.7.2 and 4.7.3). Conventional and widely used procedures are nicely summarized in the review by Farina et al. [25, 78, 81 – 83].

Major side reactions include homocoupling [22, 50, 54, 69, 84 – 100] of the reaction component. Homocoupling competes with the desired cross coupling especially when it is slow [67]. Careful purge of oxygen [22, 67], slow addition of the tin reagent [44], addition of lithium chloride [69, 101, 102], BHT [54, 103 – 105], and/or a combination of $AsPh_3$ and lithium- or zinc chloride [22] may improve the desired process. It should be noted that the above modifications do not necessarily improve the results because there are too many factors to establish a generally applicable manuduction, so far [9, 67, 78, 106]. Introduction of an organic moiety from phosphine ligand also cause contamination [107 – 112]. Performing the reaction at as low temperature as possible or the use of "ligandless" palladium [14, 113, 114] or other metal catalysts that do not need phosphine ligand (Scheme 6) [43, 45], (Scheme 7) [40], (Scheme 8) [44] is recommended to avoid it. When the reaction of aryltrialkyltin is slow, alkyl transfer sometimes competes [22, 77] or predominates [58]. The selectivity could be improved by adjusting conditions [22, 58].

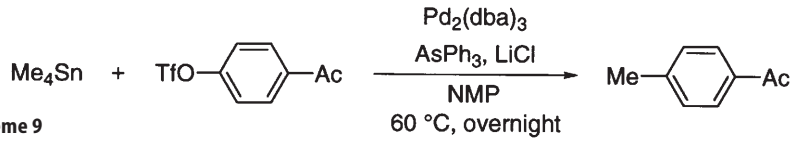
Alkenyl double-bond migration [7] and geometrical isomerization [77] are sometimes observed when alkenyl reaction components are used, especially for allylic and (*Z*)-alkenyl components under harsh conditions (Sects. 4.2 and 4.8).

Addition of BHT and employment of milder conditions achieved by either selection of more reactive leaving group or effective additives may improve the selectivity.

Some typical experimental procedures are described in Sect. 3.2.

More specific topics are presented in the following sections.

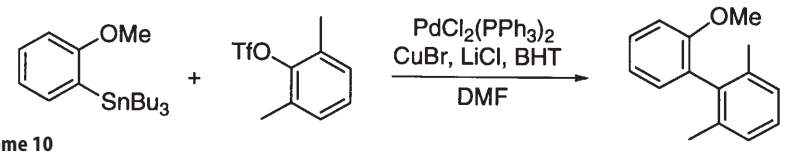
3.2 Typical Experimental Procedures



Scheme 9

4-Methylacetophenone [$AsPh_3$ for the cross coupling between aryl triflate and tetramethyltin] [21].

4-Acetylphenyl trifluoromethanesulfonate (239.3 mg, 0.892 mmol) was dissolved in NMP (5 cm^3) and treated with anhydrous lithium chloride (113.5 mg, 3 equiv), triphenylarsine (21.8 mg, 0.08 equiv), and $Pd_2(dba)_3$ (8.2 mg, 0.02 equiv of Pd). After 10 min at rt, tetramethyltin (0.15 cm^3, 1.083 mmol) was added and the mixture was heated at 60 °C overnight. Monitoring was carried out by HPLC (C-18, 70% MeOH, 30% H_2O). Saturated potassium fluoride solution was added to the resulting reaction mixture. Hexane extraction followed by evaporation of the dried organic phase and chromatography over silica gel gave 96 mg (80%) of the title compound.

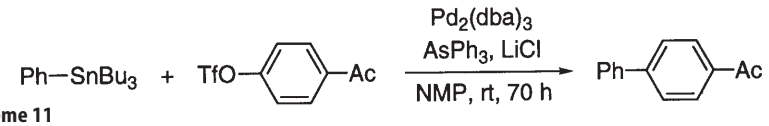


Scheme 10

2′-Methoxy-2,6-dimethylbiphenyl [BHT, LiCl, and CuBr as additives for a hindered aryl triflate and aryltin] [54].

A round-bottom flask was charged with a mixture of 2,6-dimethylphenyl trifluoromethanesulfonate (127.1 mg, 0.5 mmol), anhydrous lithium chloride (4 mmol), copper(I) bromide (0.2 mmol), and dichlorobis(triphenylphosphine)-palladium(II) (10–20 mol %) suspended in DMF (2.5 cm^3). 2-Methoxyphenyltributyltin (1–1.5 mmol) was added to the mixture in two portions, i.e., at the beginning of the reaction and at half completion. A crystal of 2,6-bis(1,1-dimethylethyl)-4-methylphenol (BHT) was added as an inhibitor of radical processes, and the mixture was then heated to reflux, under argon, during 8–24 h. Water and Et_2O (25 cm^3) was added, and the organic phase was washed subsequently with hydrochloric acid solution (1.5 mol dm^{-3}, 6 × 20 cm^3), a saturated solution of potassium fluoride (5 × 20 cm^3), and finally dried over anhydrous sodium sulfate. Evaporation to dryness furnished a residue and that was suspended in ethyl acetate and the insoluble material was filtered off. The filtrate was

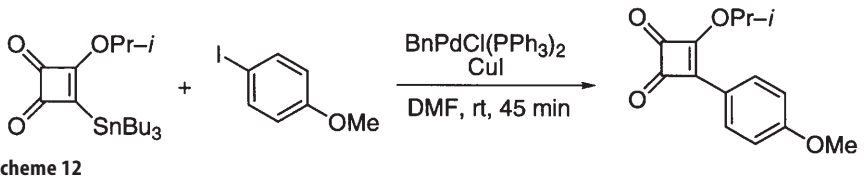
evaporated, and the resulting crude product was purified by column chromatography on silica gel (hexane-ethyl acetate). Final bulb-to-bulb distillation usually furnished the title compound (99.8 mg, 94%) as oil: bp 95–100 °C/16 Pa.



Scheme 11

4-Phenylacetophenone [$AsPh_3$ is superior to PPh_3 and P(2-furyl)$_3$ for the reaction between aryltin and organic triflates] [22].

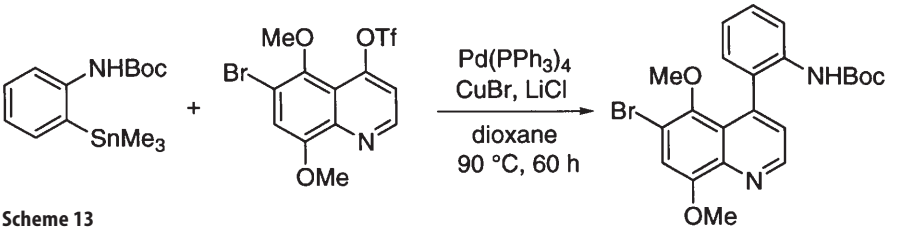
4-Acetylphenyl trifluoromethanesulfonate (308.4 mg, 1.15 mmol), triphenylarsine (28.2 mg, 0.0920 mmol), $Pd_2(dba)_3$ (10.5 mg, 0.0230 mmol Pd), and lithium chloride (146 mg, 3.44 mmol) were placed in a dry flask and stirred in anhydrous degassed NMP (5 cm^3) for 10 min. Phenyltributyltin (0.450 cm^3, 1.38 mmol) was then added neat by syringe, and the solution was stirred at rt for 70 h. Addition of aqueous potassium fluoride solution (1 mol dm^{-3}, 2 cm^3), with stirring for 30 min, and dilution with ethyl acetate was followed by filtration. The filtrate was extensively washed with water, dried, and evaporated. Flash chromatography (silica, 10% ethyl acetate in hexane) gave 4-phenylacetophenone as a white solid (185 mg, 82%).



Scheme 12

4-(1-Methylethoxy)-3-(4-methoxyphenyl)cyclobut-3-ene-1,2-dione [CuI to improve the reaction between an alkenyltin and an iodoarene] [57].

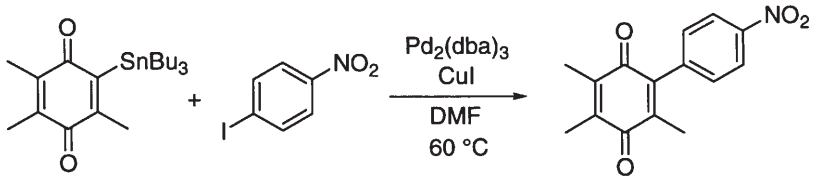
4-(1-Methylethoxy)-3-(tributylstannyl)cyclobut-3-ene-1,2-dione (0.345 g, 0.80 mmol) and 4-iodoanisole (0.208 g, 0.89 mmol) were dissolved in 1.0 cm^3 of DMF (sparged with nitrogen) under nitrogen at rt. Benzylchlorobis(triphenylphosphine)palladium (II) (0.037 g, 6 mol %) and copper(I) iodide (0.014 g, 9 mol %), purified according to the procedure of Kauffman [115], were added, and the reaction was stirred at rt and monitored by TLC (SiO_2, 15% Et_2O in hexanes, the tin reagent $R_f = 0.37$, the product $R_f = 0.08$) for disappearance of the tin reagent (~45 min). The reaction was diluted with 15 cm^3 of Et_2O and washed with saturated aqueous NH_4Cl (1 × 15 cm^3) and 10% aqueous KF (3 × 15 cm^3), and the resulting organic layer was filtered through a plug of SiO_2 (1.3 cm × 7.6 cm) with Et_2O. Removal of solvent left an orange solid that was purified by radial chromatography on a 2 mm SiO_2 rotor with 20% Et_2O in hexanes, yielding 0.156 g (79%) of the title compound: mp 99–101 ° C (CH_2Cl_2/hexane).



Scheme 13

6-Bromo-4-[2-[(1,1-dimethylethoxycarbonyl)amino]phenyl]-5,8-dimethoxyquinoline [CuBr to accelerate a chemoselective reaction between an aryltin and a heteroaryl triflate] [58].

A mixture of 6-bromo-4-(trifluoromethanesulfonyloxy)-5,8-dimethoxyquinoline (1.35 g, 3.25 mmol), trimethyl[2-[(1,1-dimethylethoxycarbonyl)amino]phenyl]tin (1.68 g, 4.70 mmol), lithium chloride (330 mg, 7.80 mmol), copper(I) bromide (25 mg, 0.17 mmol), and tetrakis(triphenylphosphine)palladium (0) (180 mg, 0.16 mmol) in dioxane (60 cm^3) was heated at 90 °C for 60 h. After being cooled to rt, the mixture was partitioned between EtOAc and a 5% aqueous ethylenediamine solution to remove any copper species, completely. After the usual work up, the residue was chromatographed (1.5:1 hexanes – EtOAc) to yield the title compound as a white solid (952 mg, 64%, several other fractions contained the title compound contaminated with 6-bromo-5,8-dimethoxy-4-methylquinoline): mp 166–168 °C.

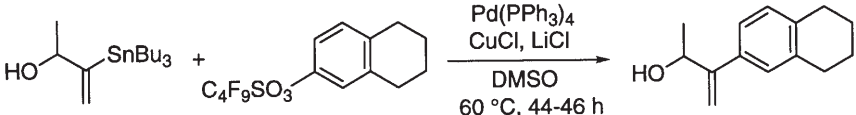


Scheme 14

2,3,5-Trimethyl-6-(4-nitrophenyl)-1,4-benzoquinone [Ligandless palladium under open air in the presence of CuI to facilitate the coupling between a stannylquinone and an aryl iodide] [67].

In a 10 cm^3 round-bottomed flask open to the air was dissolved $Pd_2(dba)_3$ (10 mg, 0.011 mmol, 2.3 mol %) in DMF (1 cm^3) and the mixture was stirred for 1 min. Then, 1-iodo-4-nitrobenzene (0.23 g, 0.92 mmol, 2 equiv) in DMF (2 cm^3) was added and the solution was warmed to 60 °C for 2 min. 2,3,5-Trimethyl-6-(tributylstannyl)-1,4-benzoquinone (0.20 g, 0.48 mmol) was added in DMF (2 cm^3) followed immediately by copper(I) iodide (43 mg, 0.23 mmol, 47 mol %). When the starting material was consumed as judged by TLC (10% Et_2O in hexanes, 30 min to 1 h), the mixture was cooled to rt, diluted with Et_2O (30 cm^3), washed with 10% aqueous potassium fluoride solution (2 × 30 cm^3), dried over anhydrous magnesium sulfate, passed through a silica gel plug, and concentrated in vacuo. The resulting yellow solid was purified by gravity chromatography (two sequential columns: SiO_2, 20% Et_2O in hexanes then SiO_2, 10%

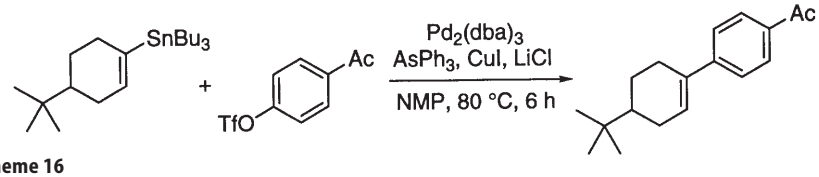
hexanes in CH_2Cl_2) to give 0.10 g (77%) of a yellow solid. Recrystallization from acetone/methanol/water gave large bright yellow crystals: mp 138.8–139.4 °C.



Scheme 15

3-(5,6,7,8-Tetrahydronaphthalen-2-yl)-3-buten-2-ol [Coupling between an alkenyltin and an aryl perfluorobutanesulfonate using copper(I) and lithium chloride] [69].

A Schlenck tube (25 cm^3, ChemGlass-air free) was charged with lithium chloride (64 mg, 1.5 mmol) and flame dried under high vacuum. Upon cooling, $Pd(PPh_3)_4$ (29 mg, 0.025 mmol) and CuCl (124 mg, 1.25 mmol) were added, and the mixture was degassed four times under high vacuum with an argon purge. DMSO (2.0 cm^3) was introduced with concomitant stirring, followed by the addition of 5,6,7,8-tetrahydronaphthalen-2-yl 1,1,1,2,2,3,3,4,4-nonafluorobutanesulfonate (108 mg, 0.25 mmol) and 3-(tributylstannyl)-3-buetn-2-ol (108 mg, 0.30 mmol). The resulting mixture was rigorously degassed four times by the freeze-thaw process (–78 to 25 °C under argon). The reaction mixture was stirred at rt for 1 h, then heated to 60 °C for 44–46 h. Following completion of the coupling as monitored by TLC, the reaction mixture was cooled, diluted with Et_2O (30 cm^3), and washed with a mixture of brine (40 cm^3) and 5% aqueous NH_4OH (8 cm^3). The aqueous layer was further extracted with Et_2O (2 × 15 cm^3), and the combined organic layers were washed with water (2 × 40 cm^3) then brine (2 × 40 cm^3), dried over anhydrous sodium sulfate, and concentrated to a residue that was purified by flash chromatography (1:15 ethyl acetate/hexanes eluent) gave 3-(5,6,7,8-tetrahydronaphthalen-2-yl)-3-buten-2-ol (47 mg, 94%) as a colorless oil.

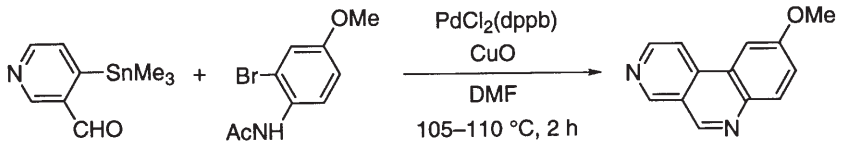


Scheme 16

4-[(1,1-Dimethylethyl)cyclohexen-1-yl]acetophenone [A combination of $AsPh_3$ and CuI greatly suppress alkyl transfer to allow selective alkenyl transfer from tin] [23].

In a two-necked 25 cm^3 round-bottomed flask were placed [4-(1,1-dimethylethyl)cyclohexen-1-yl]tributyltin (167 mg, 0.391 mmol), 4-acetylphenyl trifluoromethanesulfonate (102 mg, 0.380 mmol), triphenylarsine (9.3 mg, 0.031 mmol), $Pd_2(dba)_3$ (4.5 mg, 0.0049 mmol), lithium chloride (48 mg, 1.1 mmol), and copper(I) iodide (3.64 mg, 0.0191 mmol), dry degassed NMP (2 cm^3) was then added, and the solution was stirred at rt for 15 min. Then it was placed in an oil bath at 80 °C for 6 h. After cooling, the mixture was treated

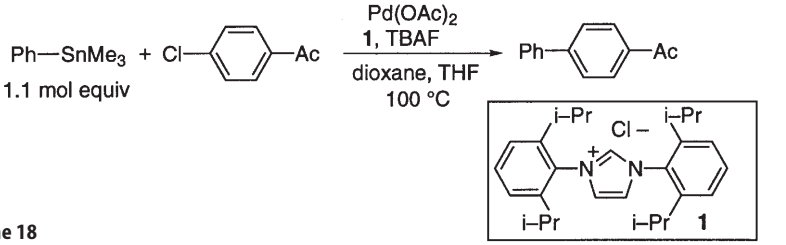
with aqueous potassium fluoride (1 mol dm^{-3}, 5 cm^3) for 30 min and filtered with thorough rinsing with ethyl acetate, and the organics were further washed with water and brine and dried with anhydrous sodium sulfate. Silica gel column chromatography of the crude product (10% ethyl acetate in hexane) gave 4-[(1,1-dimethylethyl)cyclohexen-1-yl]acetophenone (82 mg, 84%): mp 96–97 °C (MeOH).



Scheme 17

9-Methoxybenzo[c]-2,7-naphthyridine [CuO was used as an additive for the reaction between a heteroaryltin and aryl bromide] [72].

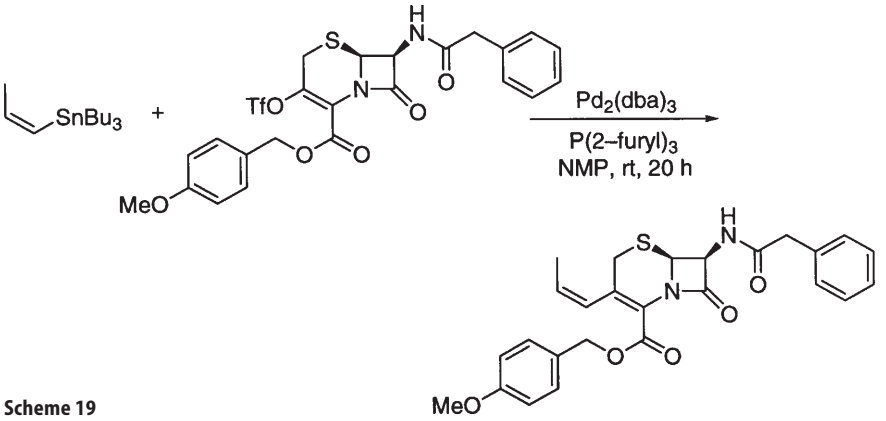
A mixture of 2-bromo-4-methoxyacetanilide (244 mg, 1.0 mmol), dichloro[1,4-bis(diphenylphosphino)butane]palladium(II) (30 mg, 0.05 mmol), and copper(II) oxide (80 mg, 1.0 mmol) in DMF (4 cm^3) was stirred at 105–110 °C. After 1 min 4-trimethylstannyl-3-pyridinecarbaldehyde (405 mg, 1.5 mmol) dissolved in DMF (1 cm^3) was added. After the halide was consumed (2 h), the reaction mixture was allowed to attain rt, the precipitate was filtered off and the filtrate was concentrated under reduced pressure. The residue was subjected to HPLC-chromatography using chloroform/2-propanol (95:5) as eluent. This gave 191 mg (91%) of the title compound: mp 145–146 °C.



Scheme 18

4-Acetylbiphenyl [A bulky carbene ligand to employ a non-activated aryl chloride in the present protocol] [116].

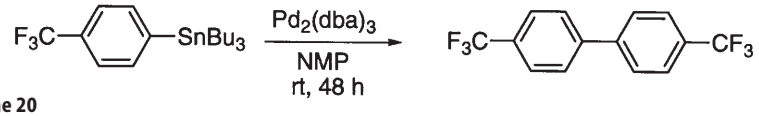
Under an atmosphere of argon 1,4-dioxane (1 cm^3), 4-chloroacetophenone (155 mg, 1 mmol), trimethylphenyltin (289 mg, 1.2 mmol) and TBAF (1 mol dm^{-3} in THF, 2.0 cm^3, 2.0 mmol) were added in turn to a screw-capped vial with a septum charged with $Pd(OAc)_2$ (7 mg, 0.03 mmol), the ligand precursor **1** (13 mg, 0.03 mmol), and a magnetic stirring bar. The vial was placed in an oil bath and stirred at 80 °C for 1 h. The reaction was monitorred by GC. The mixture was then allowed to cool at room temperature. The product was extracted with diethyl ether and washed with brine. The organic extracts were dried over $MgSO_4$, concentrated in vacuo, and then purified by flash chromatography to afford the title compound (179 mg, 91%).



Scheme 19

4-Methoxybenzyl (6*S*,7*S*)-(*Z*)-8-oxo-7-phenylacetylamino-3-propenyl-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate [Removal of organotin waste from the desired product by partition in synthesizing a sufficiently polar compound] [53].

4-Methoxybenzyl (6*S*,7*S*)-8-oxo-7-phenylacetylamino-3-(trifluoromethanesulfonyloxy)–5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate (5.860 g, 9.990 mmol) was dissolved in dry NMP (20 cm^3), the solution was degassed with argon, and zinc chloride (2.720 g, 19.96 mmol) was added, followed by tris(2-furyl)phosphine (92 mg, 0.40 mmol) and $Pd_2(dba)_3$ (90.8 mg, 0.198 mmol Pd). The solution was stirred for 10 min, and then (*Z*)-1-propenyltributyltin (98.5 % *Z*, 3.640 g, 10.99 mmol) was added neat by syringe, rinsing with dry NMP (2 cm^3). The reaction mixture was stirred at rt for 20 h, diluted with ethyl acetate (100 cm^3), washed three times with water and once with brine, and dried over anhydrous sodium sulfate. Filtration and concentration gave a crude product that was redissolved in acetonitrile (100 cm^3) and washed three times with pentane (100 cm^3 each), in order to remove the tin-containing coproducts. Evaporation gave oil that was recrystallized from warm methanol to provide the title compound (3.910 g, 82 %) as tan crystals: mp 133 – 134 °C. The amount of *E* isomer present was estimated at 2 % by NMR integration, by comparison with the NMR spectrum of an authentic sample, prepared according to the literature [117].

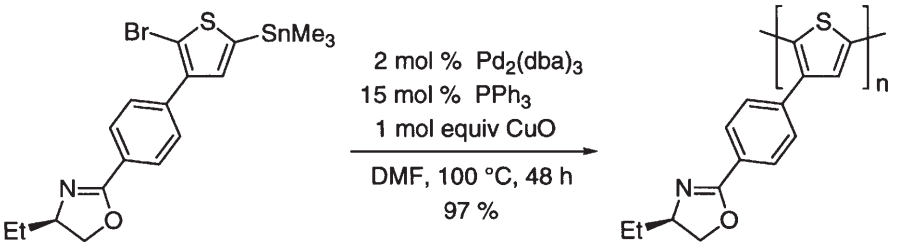


Scheme 20

4,4′-Bis(trifluoromethyl)biphenyl [Homocoupling observed when the reaction system is not degassed] [22].

[4-(Trifluoromethyl)phenyl]tributyltin (117.3 mg, 0.269 mmol) in dry non-degassed NMP (5 cm^3) was treated with $Pd_2(dba)_3$ (3.7 mg, 0.0081 mmol Pd) at rt for 48 h. Addition of aqueous potassium fluoride (1 mol dm^{-3}) with stirring for 30 min, dilution with ethyl acetate, and filtration were followed by evapora-

tion of the filtrate and purification by flash chromatography over silica gel with hexane as eluent to furnish 27 mg (69 %) of 4,4′-bis(trifluoromethyl)biphenyl as a white solid: mp 90 – 92 °C.



Scheme 21

Poly[(*R*)-2-bromo-5-(tributylstannyl)-3-[4-(4-ethyl-2-oxazolin-2-yl)-phenyl]thiophene [Polymerization of (*R*)-2-bromo-5-(tributylstannyl)-3-[4-(4-ethyl-2-oxazolin-2-yl)phenyl]thiophene (EOPT-Br,Sn) with $Pd_2(dba)_3$ as a catalyst, the CuO-modified Stille-McCullough method] [74].

Polymerization of EOPT-Br,Sn was carried out according to the reported method by McCullough et al. [118] with a modification. To a solution of EOPT-Br,Sn (3.49 g, 6.99 mmol) in DMF (35 cm^3) was added CuO (0.555 g, 6.98 mmol), PPh_3 (0.373 g, 1.42 mmol), and $Pd_2(dba)_3$ (0.159 g, 0.174 mmol) under nitrogen and the mixture was stirred at 100 °C for 48 h. After the solvent was almost removed under reduced pressure, the resulting purple-colored polymer was precipitated into a large amount of methanol, collected by centrifugation, washed with methanol and THF, and dried in vacuo at rt overnight. The polymer was then dissolved in chloroform and precipitated into a large amount of hexane, collected by centrifugation, and dried in vacuo at rt overnight (1.73 g, 97 %).

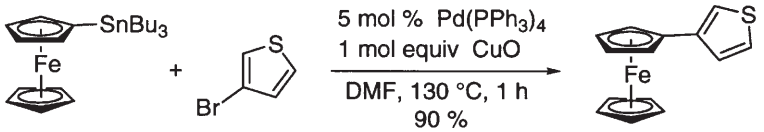
4
Preparation of the Tin Reagents and Scope of the Protocol

4.1
Aryltins

4.1.1
Reaction

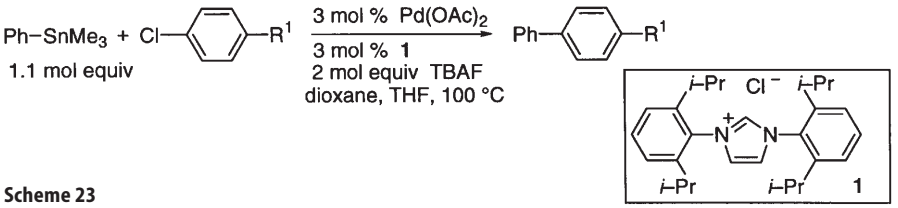
Aryltins can be used as powerful arylating agents to arylate a variety of organic halides, sulfonates, diazonium and iodonium salts, phosphates, etc. Some carboxylic esters can also be arylated. The most widely used tin reagents in this class are aryltrialkyltins. Although tetraaryltins can also be used, it is rather desirable to use trialkyltin reagents, especially when aryl moieties are precious, because only one among four organic moieties attached to tin can be practically used (cf. Sect 4.7.1.1 – 4.7.1.4). On the aryl ring of aryltrialkyltins can be introduced both electron-releasing and electron-withdrawing substituents. Steric effects can be important, however. The presence of an alkyl group ortho to tin often retards the cou-

pling and alkyl-group transfer may compete in this case. This problem can sometimes be overcome by adding Cu(I) salts [22]. Ferrocenyltin reagents can also take part in the protocol just as aryl counterparts do (Scheme 22) [75].



Scheme 22

Acid chlorides are suitable electrophiles. As aromatic and 1-alkenyl halides, bromides and iodides are generally good substrates. Until quite recently, the use of the corresponding chlorides, which are cheaper and often more readily accessible, had been limited to that bearing a strongly electron-withdrawing substituent at a proper position. The use of nickel catalyst [47], bulky phosphine [119], and heterocyclic carbene ligand (Scheme 23, Table 1) [116] enabled aryl chlorides to take part in the reaction.

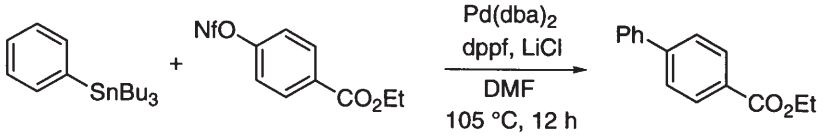


Scheme 23

Table 1. Arylation with aryl chlorides using carbene ligand

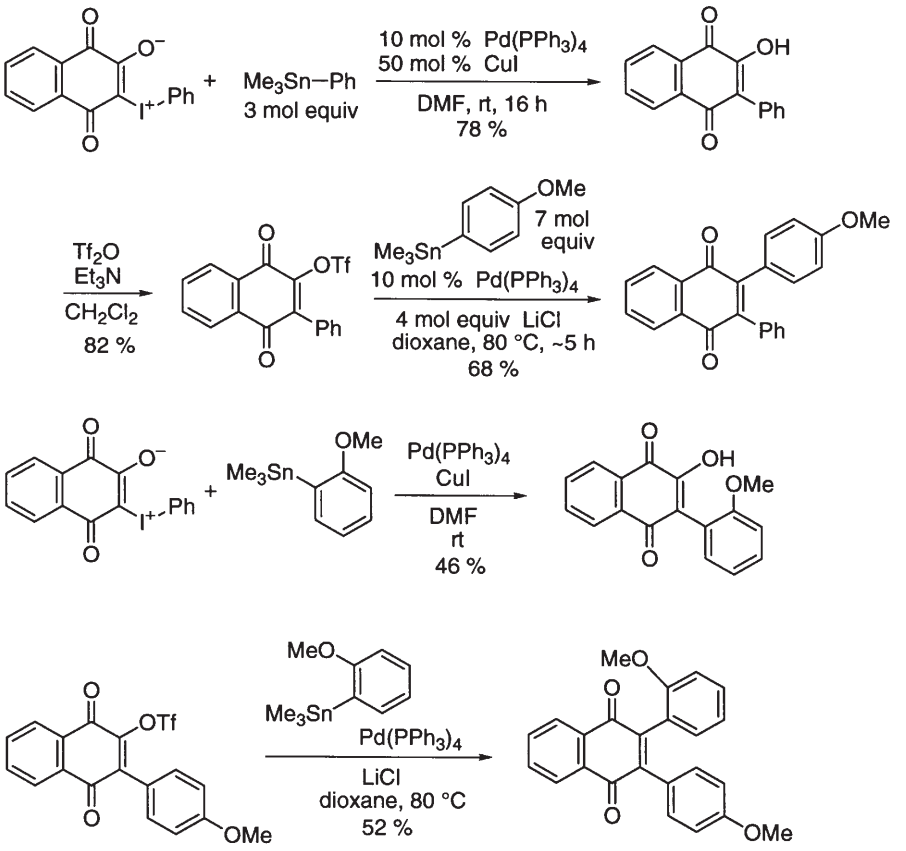
Entry	R^1	Time	Yield
1	MeCO	1	91
2	Me	24	54
3	MeO	48	35

Among organic sulfonates, triflates are the most frequently used, by far. The use of aryl triflates is sometimes troublesome, however, because they are prone to O-SO_2 bond cleavage. In such cases, it is advantageous to use the corresponding nonafluorobutanesulfonate that is easily prepared using commercially available nonafluorobutanesulfonyl fluoride and survives silica gel column chromatography (Scheme 24) [69, 120].



Scheme 24

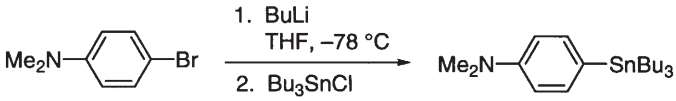
An impressive use of an iodonium salt for chemoselective tandem unsymmetrical diarylation is shown in Scheme 25 [121].



Scheme 25

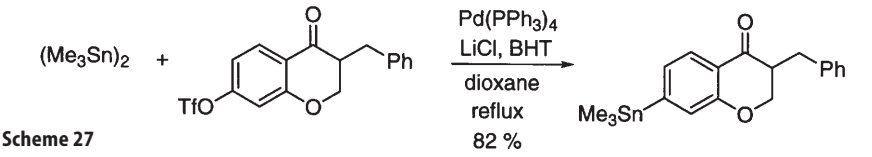
4.1.2 *Preparation*

The simplest and economically favorable way to an aryltributyl- and -trimethyltin is the reaction between an appropriate Grignard reagent and tributyl- or trimethyltin chloride. A symmetrical tetraaryltin is obtained by the treatment of tin(IV) chloride with an excess of the corresponding arylmetal. These procedures can be applied to the preparation of many kinds of organotin reagents [122]. Other than aryl Grignard reagents, aryllithiums are quite widely used. Direct lithiation of an arene is advantageous in view of substrate availability, permitted that regioselective lithiation is possible. Halogen-lithium exchange allows a more regiocontrolled introduction of a tin moiety when the corresponding bromides or iodides are available (Scheme 26) [123].

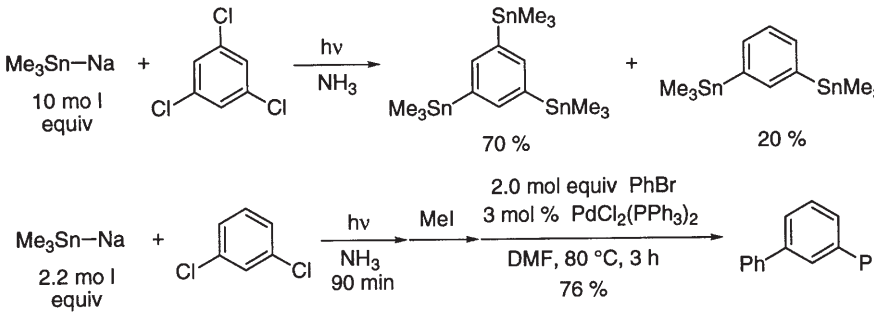


Scheme 26

Palladium-catalyzed cross coupling between aryl halide or triflate and ditin is useful for preparation of aryltins with functionalities sensitive toward highly nucleophilic or basic organometallics [124–126] (Scheme 27) [127, 128]. The reaction between aryl chlorides and stannylmetal reagents can also be a useful route to aryltin reagents. Reaction of trimethylstannylsodium with an aryl bromide can be performed under mild conditions, without destruction of other electrophilic substituents, to yield aryltrimethyltin reagents [129, 130]. Polychlorobenzene is transformed into the corresponding polystannylarenes in good yields under photostimulated conditions (Scheme 28) [131]. The process can be one-pot from the chloride to the cross-coupling product [131].



Scheme 27



Scheme 28

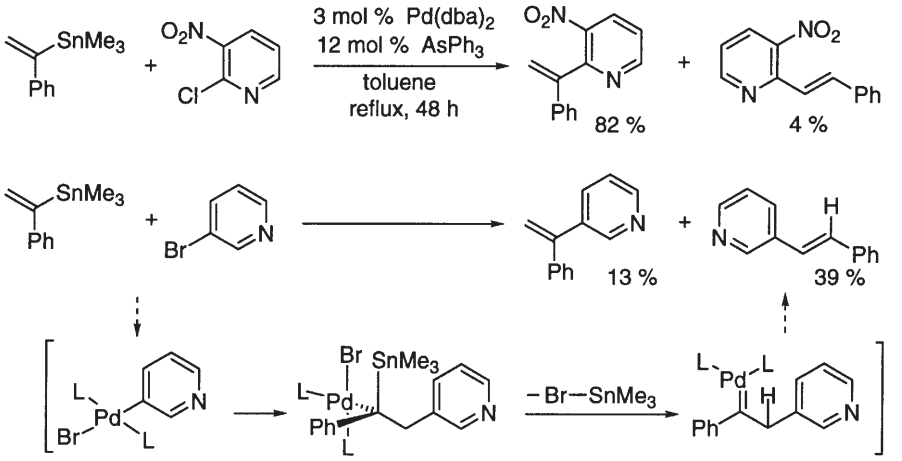
A Diels-Alder reaction between methyl tributylstannylpropiolate and substituted butadienes gives good yields of the 1,4-cyclohexadiene, which can be dehydrogenated to the aryltin reagent [132].

4.2 Alkenyltins

4.2.1 *Reaction*

The coupling of alkenyltrialkyltins is a general and a synthetically useful reaction. Most studies are on easily available 1,2-disubstituted substrates which couple efficiently with good stereospecificity except for some of *Z* substrates.

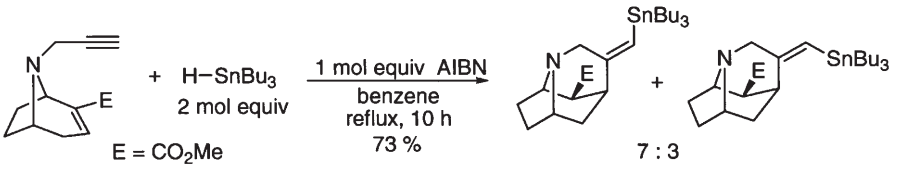
Again steric hindrance makes the reaction with electrophiles slower or difficult. Also in this case, the addition of Cu(I) salts is effective [16]. In the reactions with 1-substituted 1-stannylethene, *cine*-substitution is sometimes observed especially in the reaction of tins with electron-rich alkenes [69, 133–138]. This might be attributed to a participation of a Pd(0)-carbene species generated via α-elimination of regioisomeric Heck intermediate [136, 139]. *Cine*-substitution is scarce when the electrophile is electron deficient (Scheme 29) [136, 137]. Levin reported that *ipso*-selectivity in vinylation of α-stannylacrylate was restored by the addition of CuI [140].



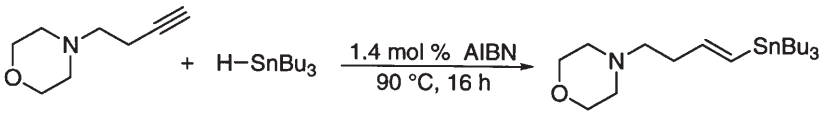
Scheme 29

4.2.2
Preparation

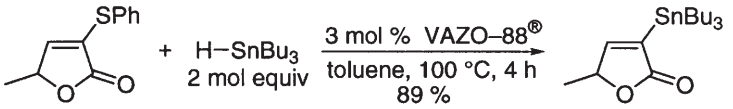
Hydrostannylation of 1-alkynes along radical pathway provides the corresponding 1-stannyl-1-alkenes. Although the reaction is generally regioselective, a mixture of stereoisomers is usually provided [141, 145, 146]. Intermediary alkenyl radical can be trapped by another double bond in the molecule, regioselectively (Scheme 30) [141]. Scheme 31 depicts an example that gives (*E*)-1-alkenyltin quite selectively [142]. Radical substitution of alkenyl sulfide provides regiodefined preparation. It is not affected by a conjugated carbonyl group that directs the position of radical addition when the thiyl group is absent (Scheme 32) [143].



Scheme 30

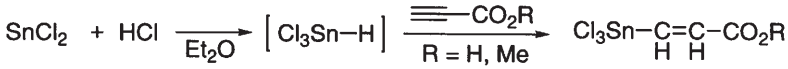


Scheme 31



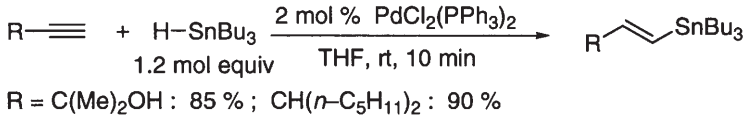
Scheme 32

Addition of in situ generated trichlorostannane to propiolic acid derivatives furnishes the corresponding β-trichlorostannylacrylic acid derivatives (Scheme 33) [144]. The procedure provides an access to trialkyltin free alkenyltin reagents.

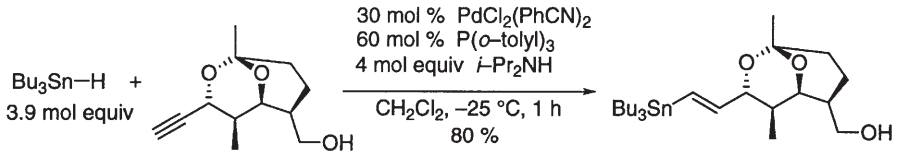


Scheme 33

Palladium-catalyzed hydrostannylation is stereoselective, giving *syn*-adduct. Regioselectivity is not always perfect, however. Exclusive formation of (*E*)-1-stannylalkene is obtained only when 1-alkyne with a bulky substituent is employed (Scheme 34) [147–150]. Nicolaou also reported a stereo- and regioselective hydrostannylation (Scheme 35) [151]. Use of a combination of tributyltin chloride and poly(methylhydro)siloxane in the presence of TBAF is also an impressive method in this class [152].



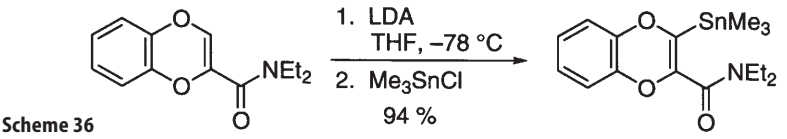
Scheme 34



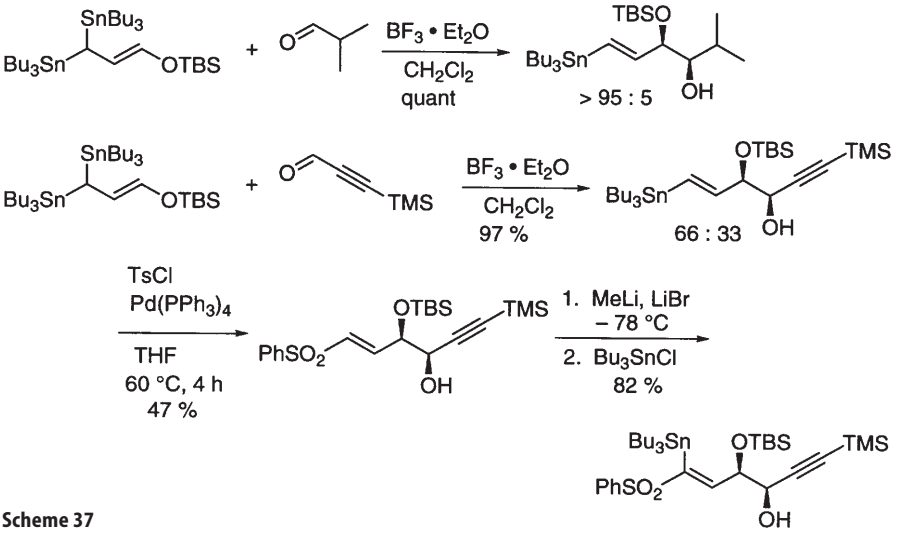
Scheme 35

Regio- and stereoselective stannylcupration of terminal alkynes provides the corresponding (*E*)-1-stannylalkenes, exclusively [62, 150, 153 – 167]. Methylation of the intermediary alkenylcopper species provides the corresponding trisubstituted alkenyltin reagent, stereoselectively [168]. Carbostannylation of alkynes offers another sophisticated possibility [32, 169 – 179]. Hetero-atom assisted lithiation and subsequent stannylation of alkene also provides the corresponding alkenyltins (Scheme 36) [180].

The use of 3,3-tributylstannyl-1-siloxy-1-propene leads to stereodefined preparation of a variety of polyfunctionalized 1-alkenyltin reagents, of which some examples are depicted in Scheme 37 [181-183].

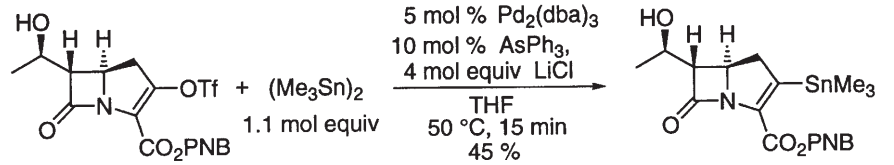


Scheme 36

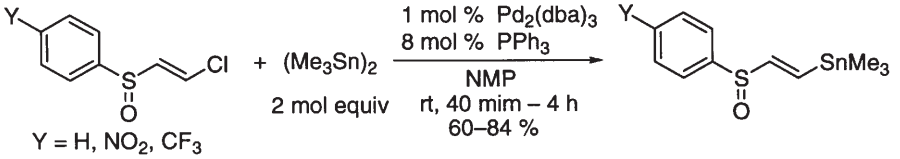


Scheme 37

Palladium-catalyzed cross coupling between alkenyl halides or triflates (Scheme 38) [184] and ditin affords the corresponding alkenyltin stereospecifically with retention of configuration (Scheme 39) [185].

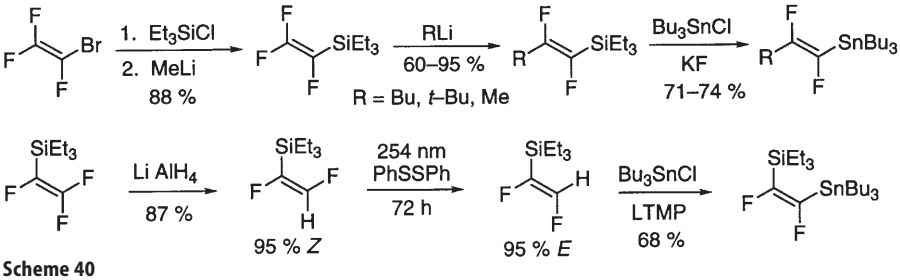


Scheme 38



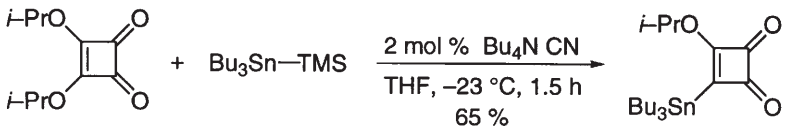
Scheme 39

Both isomers of 1,2-difluoroalkenyltins were stereoselectively prepared as in Scheme 40 [186–188].

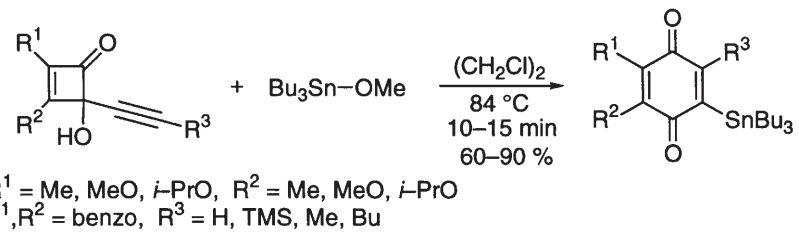


Scheme 40

Cyclobutenyltin was synthesized using an interesting variation (Scheme 41) [57, 189]. A cyclobutenol-thermal rearrangement can be used to prepare stannylbenzoquinone derivatives (Scheme 42) [67].



Scheme 41

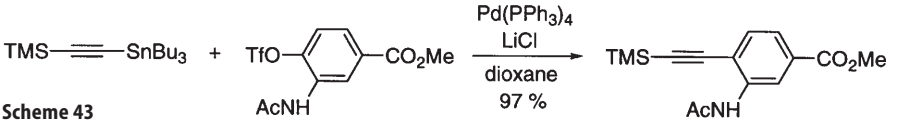


Scheme 42

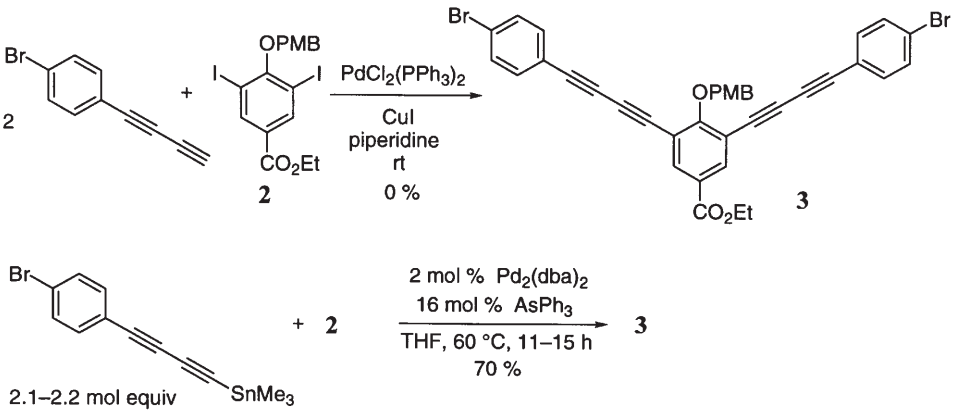
4.3 Alkynyltins

4.3.1 *Reaction*

These tins are the most reactive class of organotin reagents to couple with a variety of electrophiles, smoothly [16, 19, 101, 190–194]. In order to substitute an alkynyl group for a halide on an aromatic ring, Sonogashira coupling is straightforward and more convenient, if it works [195, 196]. Nevertheless, alkynyltin or other alkynylmetal reagens are quite often used. There are recently reported unexpectedly many examples that employ alkynyltin reagents in stead of Sonogashira protocol (Scheme 43) [197]. It would indicate that Sonogashira coupling does not always provide sufficient results. For example, the attempted alkynylation of diiodoarene **2** failed to result in the recovery of the iodide and decomposition of the diyne (Scheme 44) [198]. On the other hand, iodide-selective substitution could be performed with bromides retained by using the corresponding alkynyltin reagent.



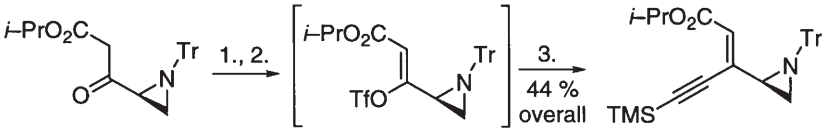
Scheme 43



Scheme 44

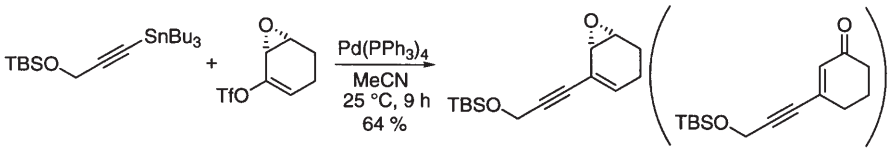
Although cross coupling of alkynyltins is usually slower than that with many other alkynylmetals such as zinc and magnesium, as Negishi's recent campaign shows [199–201], it seems to be still advantageous in view of reagent storage, tolerance of a wide range of functionalities, easy handling, convenient procedures for preparations, good reproducibilities in preparation and reaction of the reagents, and mild conditions permitted by a proper selection of the reaction partner, catalyst, additive, and solvent [196].

An example that used this protocol the substrate of which contains a sensitive functionality is depicted in Scheme 45 [202]. 1,3-Diene monoepoxide is easily attacked by a palladium(0) complex to form the corresponding π-allylpalladium species. Thus such a process could be banished from the desired selective transformation as depicted in Scheme 46 by the employment of the alkynyltin reagent with an aid of triphenylarsine ligand [203]. Organotin protocol is also convenient for introduction of a small alkynyl moiety such as C_2 or C_3 or preparation of symmetrical diarylethynes (Scheme 47) [204]. Shirakawa et al. reported recently that iminophosphine **4** is much more effective ligand for palladium than tris(2-furyl)phosphine in this reaction (Scheme 48) [32, 205].

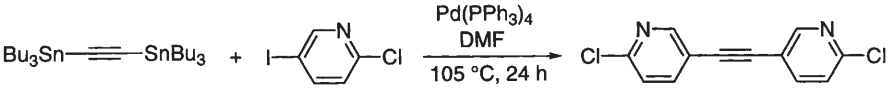


1. 2.5 mol equiv *i*-Pr_2NH, THF, –78 °C, 15 min
2. 2.5 mol equiv Tf_2O, THF, –78 °C, 2 h
3. [NMP, 2 mol % $Pd_2(dba)_3$•$CHCl_3$, 8 mol % $AsPh_3$], [2 mol equiv TMS–C≡C–$SnBu_3$, 1.2 mol equiv $ZnCl_2$, Et_2O], rt, 7 d

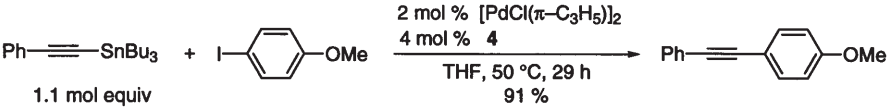
Scheme 45

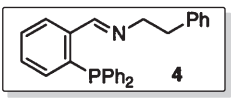


Scheme 46



Scheme 47

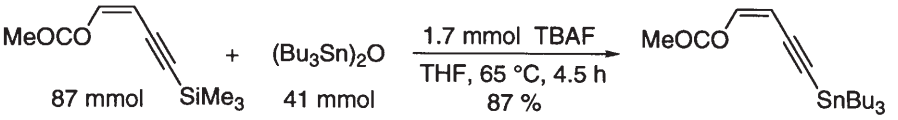




Scheme 48

4.3.2
Preparation

One of the mildest ways is direct conversion from the corresponding 1-trimethylsilylalkyne that employs bis(tributyltin) oxide instead of tributyltin chloride that requires more basic or nucleophilic metal acetylide (Scheme 49) [206–208].



Scheme 49

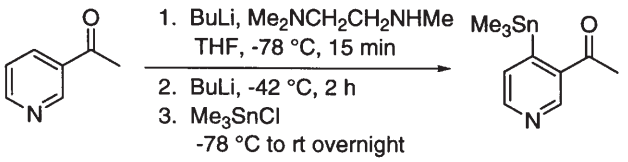
4.4
Heteroaryltins

4.4.1
Reaction

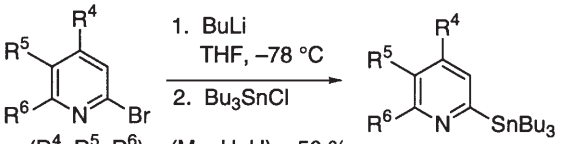
There are a number of examples using heteroaryltrialkyltins such as pyridyl-, furyl-, thienyl-, pyrrolyl-, thiazolyl-, etc [16, 25]. Tin reagents in this category are important for synthesis of biologically active compounds and functional polymers [209, 210] (see Sect 4.9). Heteroaryltin trichlorides also react with water-soluble electrophiles in aqueous media as described in Sect. 4.7.1.2 [211, 212].

4.4.2
Preparation

Though Grignard-based method appears economically preferable if possible, lithium-based procedures are much more widely employed, probably because it is free from trouble caused by Lewis acid-base interaction that is sometimes encountered with the corresponding Grignard route. Choice of the lithiation



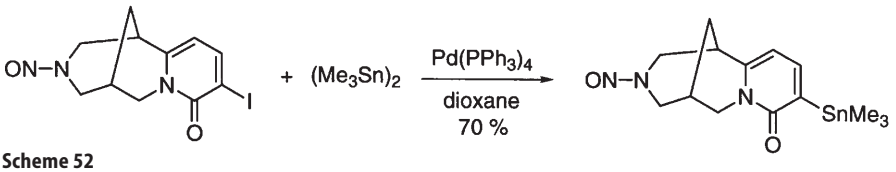
Scheme 50



Scheme 51

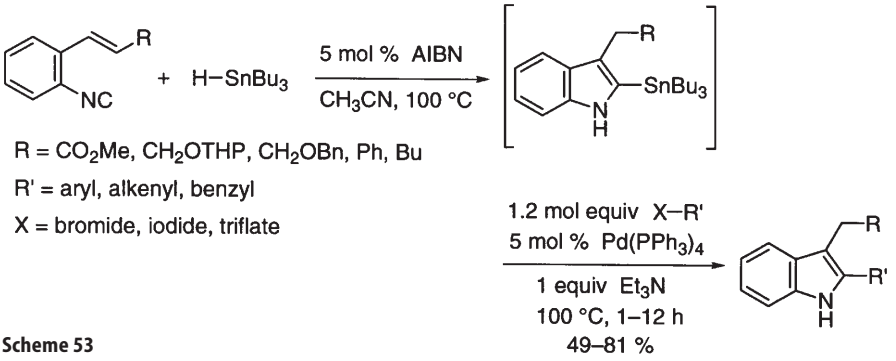
method can be decided analogously to that mentioned in Sect. 4.1.2. Following schemes show some of the recent examples [72, 213–217].

Treatment of halides and triflates with ditin and palladium catalyst is quite useful, especially for the preparation of the corresponding tin reagents with sensitive functionalities (Scheme 52) [16, 218].



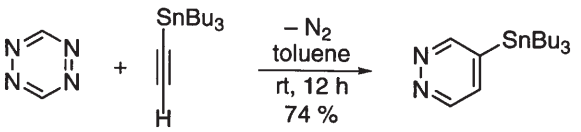
Scheme 52

An impressive procedure for 2-stannylindole is depicted in Scheme 53 [219]. Since the product is prone to proto-destannylation, in situ generated indolyltin reagent is directly used for the cross-coupling reaction. Thus the overall schemes provides a direct synthesis of 2,3-disubstituted indoles from 2-alkenylphenylisonitrile [51, 220, 221].



Scheme 53

Like in the case of an aryltin reagent, an interesting example using Diels-Alder reaction has been reported (Scheme 54) [222].

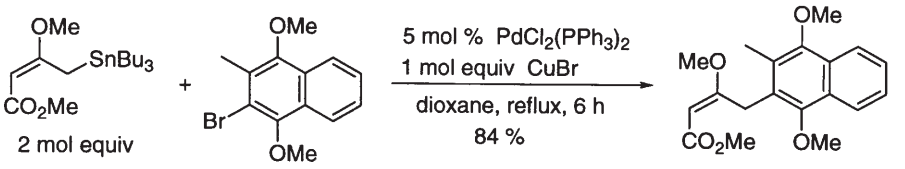


Scheme 54

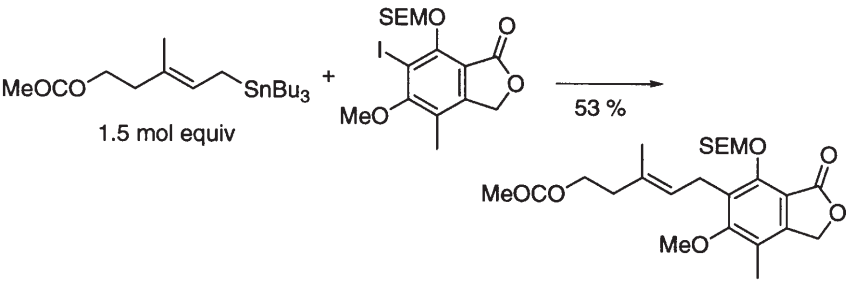
4.5
Allylic Tins

4.5.1
Reaction

Simple allyltrialkyltins may couple with acid chlorides or aryl halides or triflates to give the allylation product in good yield (Scheme 55) [223], (Scheme 56) [224]. Subsequent works revealed, however, that the reaction takes place at either α or γ position, depending on the structure of tins and the conditions used [25]. At present the regiochemistry of the coupling is still unpredictable [77]. Moreover, allylic double bond tends to move into conjugation, when acyl halides and aryl triflates are used as electrophiles [7, 225, 226]. This can sometimes be suppressed by lowering the reaction temperatures [21].



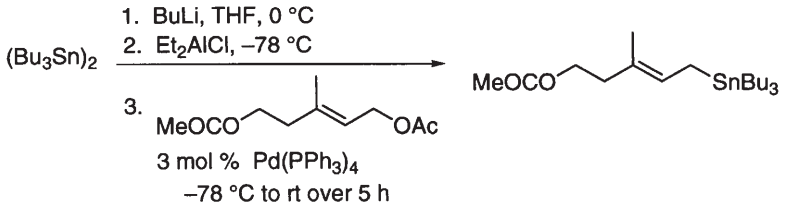
Scheme 55



Scheme 56 30 mol % $Pd(dba)_2$, 90 mol % $AsPh_3$, NMP, 100 °C, 4 h

4.5.2
Preparation

Palladium-catalyzed allylic substitution of acetate by stannylaluminum developed by Trost is compatible with ester group (Scheme 57) [224, 227].

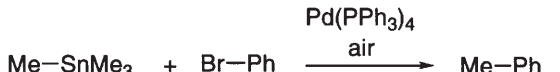


Scheme 57

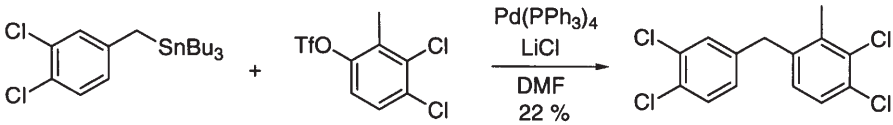
4.6
Alkyltins

4.6.1
Reaction

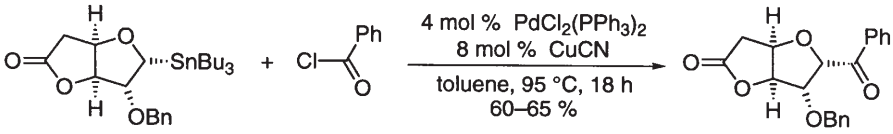
The transfer of alkyl groups from tin is much slower than that of other groups. The use of tetraalkyltins is usually essential in order to transfer an alkyl group from tin selectively. Choice of ligand and solvent is quite important to obtain cross-coupling products in good yields. In general, only one group among four can be transferred from the tins, because halogen substituted tin is less reactive [6, 9, 14]. As expected from the structural analogies with an allylic group as an α-substituted alkyl group bearing π- or unshared electrons, benzyl [228], hydroxymethyl, alkoxymethyl [229, 230], cyanomethyl, ethoxycarbonylmethyl, and acetonyl groups can be selectively transferred from the corresponding trialkyltins [16, 231–234].



Scheme 58



Scheme 59



Scheme 60

4.6.2
Preparation

Palladium-catalyzed hydrostannylation of appropriate enyne provides cyclic organotin compound [235].

4.7
Miscellaneous Organotin Reagents

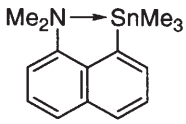
4.7.1
Hyper-Valent Organotin Reagents

Activation of alkyl groups on tin is one of the subjects which are paid attention. There are a number of reports that demonstrate that highly coordinated alkyltin

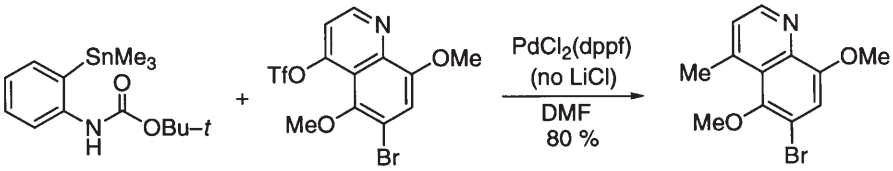
reagents more readily liberate such an organic group. More recently, there have been developed a number of examples that utilyze organic groups on tin that possess deactivating groups, i.e., heteroatom.

4.7.1.1 Vedejs Reagent and Related Reagents

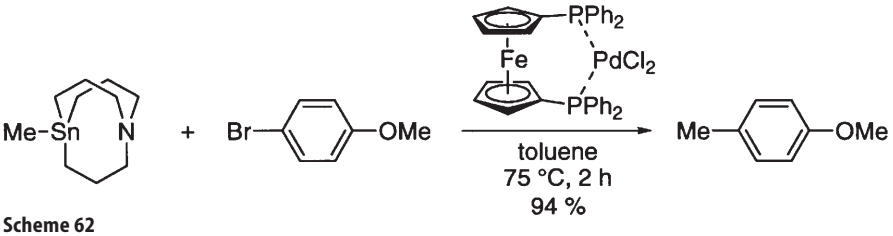
Aryltin with such an intramolecular coordination as shown in Structure 1 tends to supply a methyl group in preference to the aryl group [236, 237]. Echavarren has reported "the first" selective alkyl transfer from trialkylaryltin (Scheme 61) [58]. Hyper-valent organotin reagents are usually more reactive than the corresponding organotrialkyltins. They therefore enables cross-coupling reactions under milder conditions (Scheme 62) [237]. Above observations form a striking contrast to the Farina's in which alkyl transfer competes with aryl transfer when aryltin with ortho substituents that are potentially coordinating to tin but no rate acceleration in the alkyl transfer process was observed (Scheme 63) [22]. Magnitude of the effect may deeply depend on the reaction conditions, especially on solvents and additives.



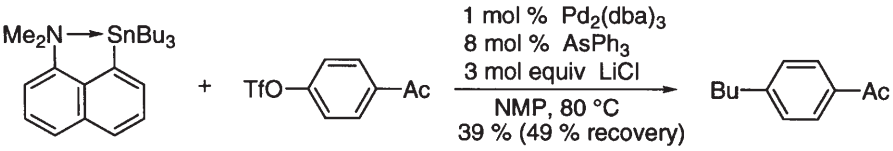
Structure 1



Scheme 61

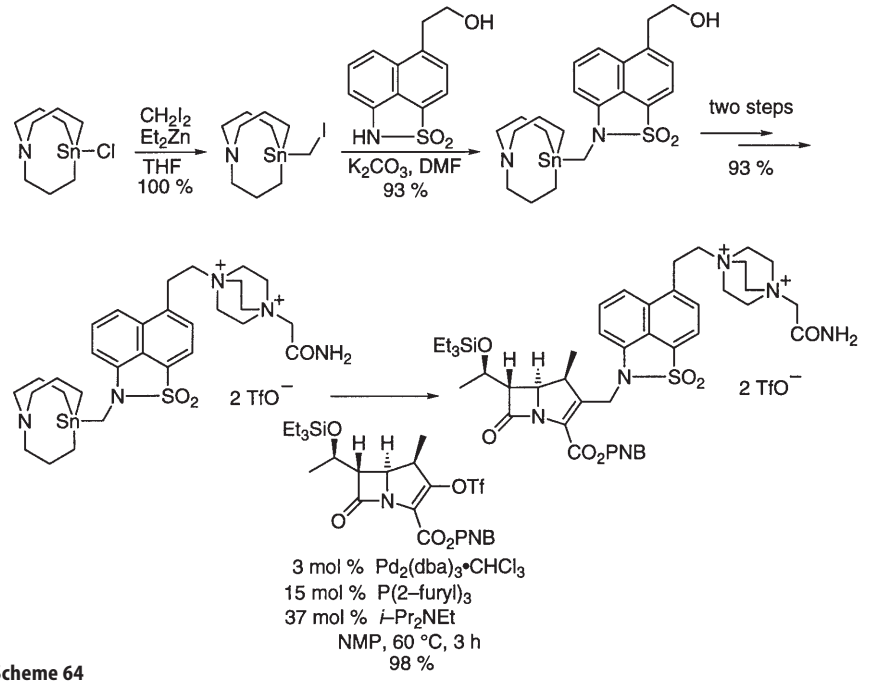


Scheme 62



Scheme 63

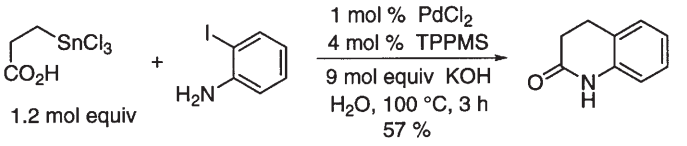
The following example realized synthesis of an anti-Methicillin-resistant *Staphylococcus aureus* carbapenem that can otherwise hardly obtained, so far (Scheme 64) [238].



Scheme 64

4.7.1.2 Organotin Trichlorides in Alkaline Solution

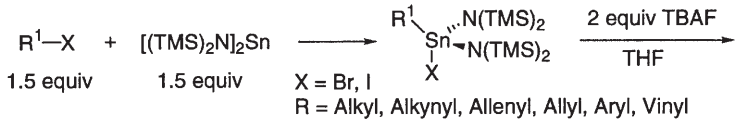
Although organotin reagents can carry four organic moieties, at once, only one of them can take part in the cross-coupling reaction, probably due to the deactivating nature of halogen in the haloorganotin reagents [16]. Thus organotin reagents furnished with three alkyl groups as dummy substituents are used in most of cases. On the other hand, various organotin trichlorides undergo palladium-catalyzed cross-coupling reactions quite efficiently in alkaline aqueous media [211, 212, 239]. In these systems, the reaction proceeds presumably via an in situ generated hyper-valent species. In some cases, coexistence of a water-soluble phosphine ligand [240–243] is quite effective [211, 212, 244]. Even sp^3-carbon group can be involved (Scheme 65) [212].



Scheme 65

4.7.1.3
Fouquet Reagent

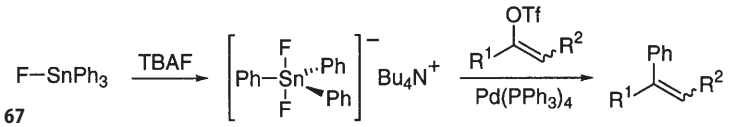
Lappert's stannylene reacts with a variety of organic bromides and iodides to form the corresponding monoorganotins. Addition of TBAF generates **5** that undergo palladium-catalyzed cross-coupling reaction (Scheme 66) [245–247]. The reaction is performed in a one-pot process from Lappert's stannylene. The reaction of the tin reagent and alkenyl and aryl triflates does not require the addition of LiCl. The halide ion that is released along generation of the monoorganotin species might play a role of chloride ion of the corresponding reaction that needs LiCl.



Scheme 66

4.7.1.4
Other Examples of Fluoride Ion-Mediated Generation of Hyper-Valent Reagents

Other hyper-coordinated-alkyltin reagents are also generated by the addition of fluoride ion to triphenyltin fluoride (Schemes 67) [248].



Scheme 67

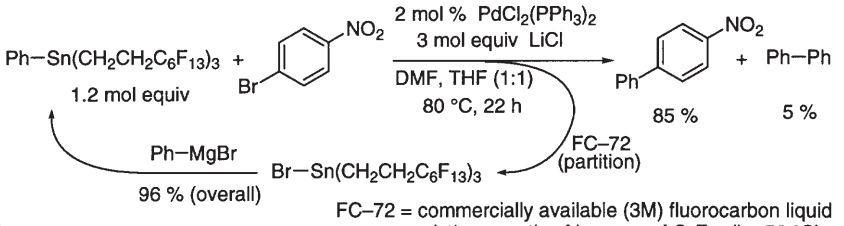
Generation of a hyper-valent organotin reagent was recently evidenced by a ^{19}F NMR study in DMSO-d_6 [116, 249]. The reaction of ordinary organotrialkyltins are also accelerated by addition of TBAF [116, 250]. Addition of fluoride ion to tetraaryl- and alkenyltin species enables utilization of all four organic moieties carried on tetraorganotin reagents [251, 252]. Up to two organic groups of tetrabutyl- and tetrabenzyltin can take part in the cross coupling in the presence of an appropriate fluoride ion [252].

4.7.2
Fluorous Tin Reagents

In this protocol, product isolation is often a serious problem. Elimination of the triorganotin byproduct is a central issue, because it is toxic, remains in the organic layer in time of partition, and hardly separable by either chromato-

graphy or distillation in many cases [148, 253–256]. Combinatorial approach may provide promissing solutions.

The use of tris[(perfluorohexyl)ethyl]phenyltin reagents in place of trialkyltin counterpart makes product separation from the tin waste simpler [257–259]. After the cross-coupling reaction in DMF-THF, partitioning between CH_2Cl_2 and commercially available perfluorohexanes provides the desired coupling product from the organic phase and tris[(perfluorohexyl)ethyl]tin chloride in more than 90% yield from the fluorous phase, which can be directly treated with a Grignard reagent after evaporation of the fluorous solvent to prepare the organotin reagent for reuse (Scheme 68). The reaction under irradiation by a microwave oven undergoes rapidly [93, 260].

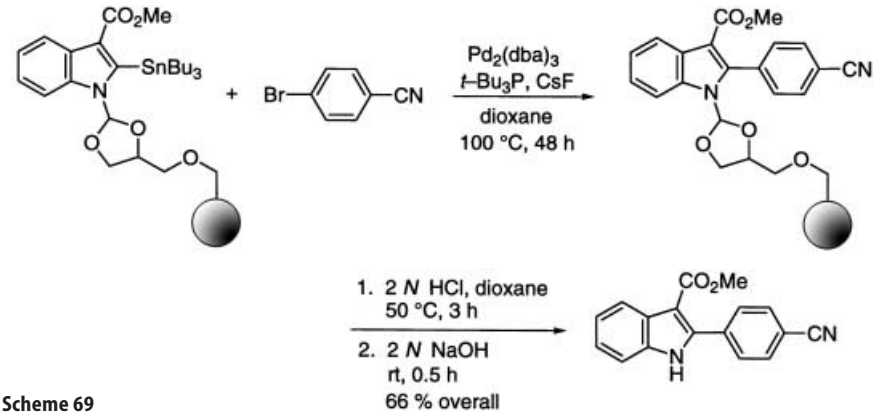


Scheme 68

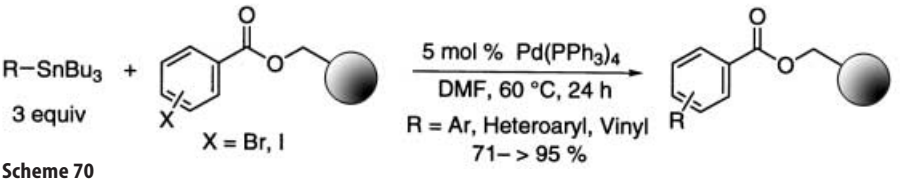
4.7.3
The Use of Polymer-Supported Reaction Components [261, 262]

4.7.3.1
Polymer-Supported Reagents and Substrates

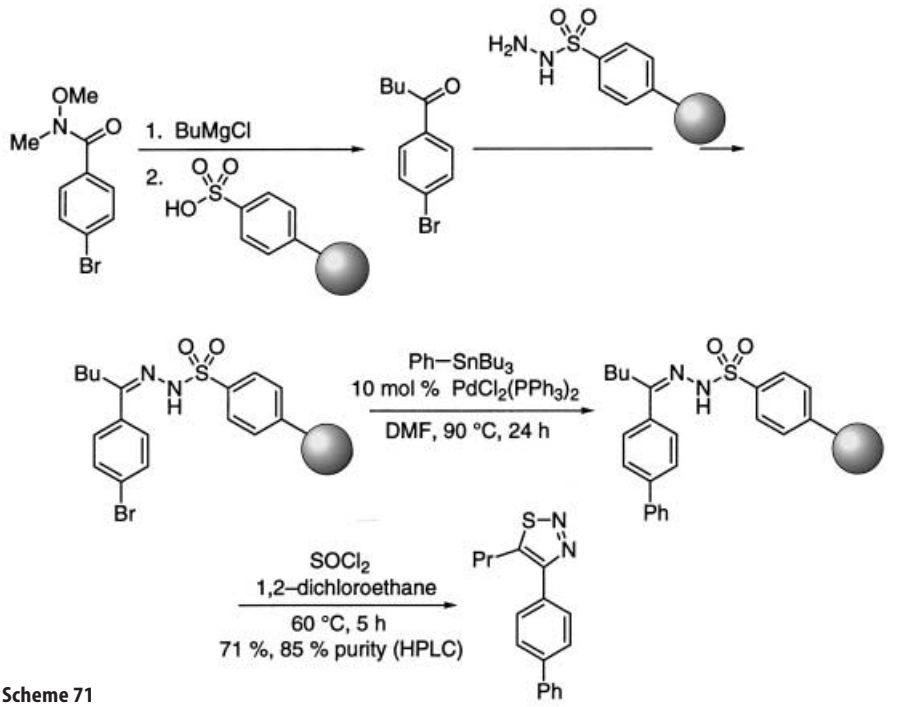
Some interesting procedures are being developed to make the present protocol more useful as a synthetic tool. Directing to the combinatorial synthesis, solid-phase syntheses have currently been under development using polymer-supported stannanes (Scheme 69) [263–268] or electrophiles (Scheme 70, Scheme 71) [149, 269–272]. In the latter case, unreacted organotin reagent as



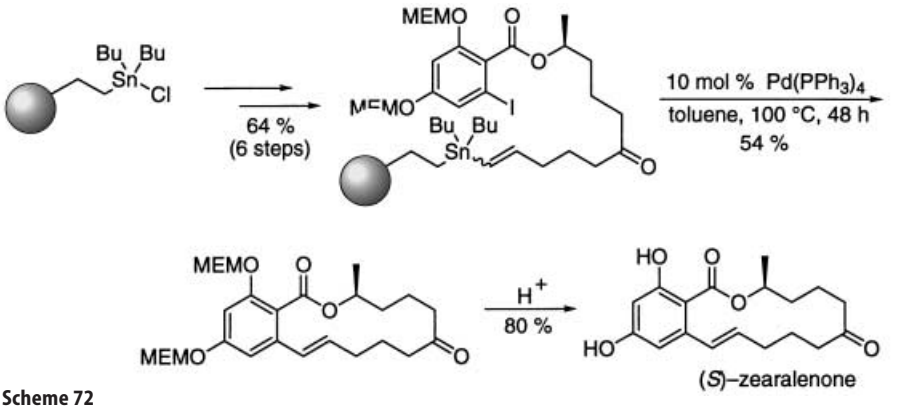
Scheme 69



Scheme 70



Scheme 71

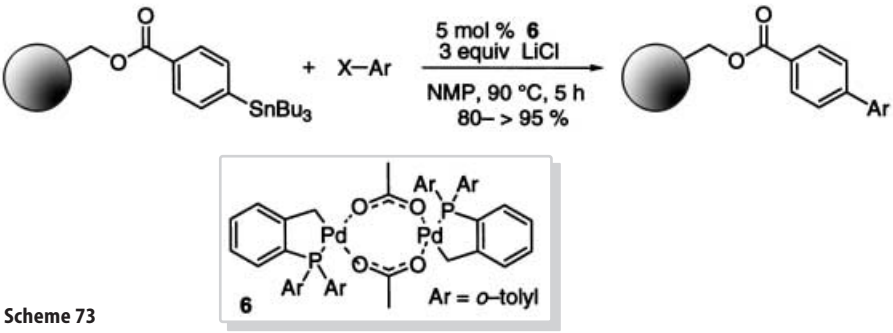


Scheme 72

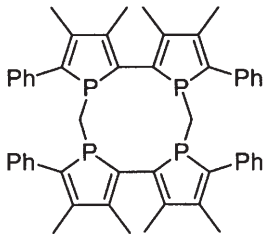
well as the organotin byproduct can be washed away prior to the detouchment of the product from the polymer support. A solution-phase combinatorial procedure is also developed for a rapid construction of a large compound library [273]. In these cases, trialkyltin halide is liberated along the reactions. On the other hand, Nicolaou developed another version in which stannyl group remains on the polystyrene-support that can be recovered for reuse (Scheme 72) [274].

4.7.3.2
Convenient Catalysts for Combinatorial Chemistry

There was recently developed polymer-supported palladium catalyst that can be used in aqueous medium and can be recovered for reuse simply by filtration [275]. To avoid precipitation of insoluble palladium black on the polymer support, a quite stable palladium complex **6** is proposed (Scheme 73) [276, 277]. Mathey reported that their complex with tetraphosphole-based macrocyclic ligand is even more stable and good for reuse (Structure 2) [278].



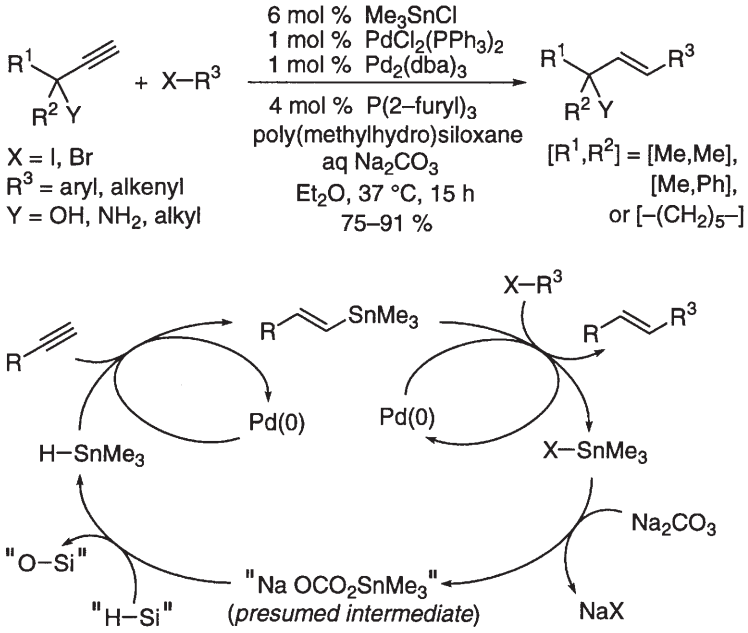
Scheme 73



Structure 2

4.7.4
Organotin-Cross Coupling with a Catalytic Amount of Tin Reagent

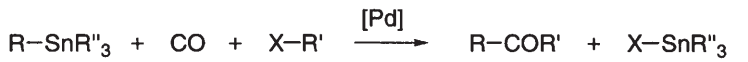
Regeneration of tin hydride from the corresponding halide in situ by poly(methylhydro)siloxane enables alkenyl-alkenyl- or alkenyl-aryl coupling by the use of only catalytic amount of tin (Scheme 74) [279–287].



Scheme 74

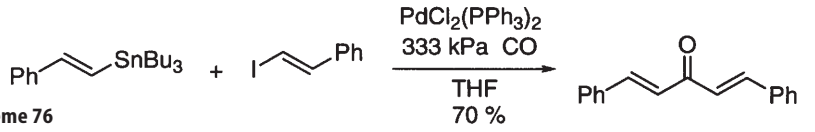
4.8 Carbonylative Coupling

For the ketone synthesis via the present protocol, acid chlorides are useful precursors, in deed. Nevertheless, carbonylative cross coupling with organic halides is strategically the most simple and direct way to this purpose. The palladium-catalyzed carbonylative cross-coupling reaction with various organic halides has been extensively investigated, because of its merits from synthetic as well as phenomenal point of view. Acid chlorides are not always readily available, and their preparation is not always compatible with many sensitive functionalities. Therefore the development of this type of reaction widens the scope of the ketone synthesis in the present protocol because of the ready availability and storability of organic halides and pseudohalides.



Scheme 75

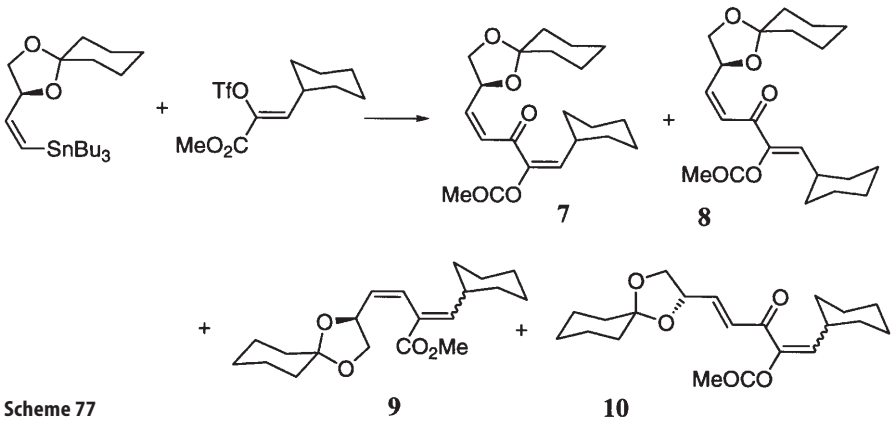
A guiding mechanism for this reaction is analogous to the direct coupling as shown in Scheme 5, except CO insertion that takes place probably between the oxidative-addtion step and the transmetallation step. The reaction of alkenyl iodides with alkenyltins takes place under neutral and mild conditions (40–50°, under 1–3 atm CO in THF) (Scheme 76) [288].



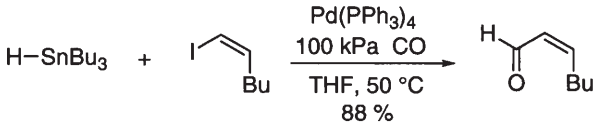
Scheme 76

The major side reaction is the direct coupling without CO insertion, that can be suppressed by employing higher CO pressures. Table 2 shows an example that fine tuning of the conditions enables complete uptake of CO (Scheme 77) [289]. A problem to be solved is *Z*/*E* isomerization of alkenyl groups from both of the reaction components, especially when *Z*-alkenyl derivatives are used (Schemes 77, 78) [65].

Aryl iodides and bromides also readily take part in this reaction, while chlorides usually do not. In this case, the side reaction mentioned above is also obvious, especially when the aromatic ring possesses an electron-withdrawing group. The reac-



Scheme 77



Scheme 78

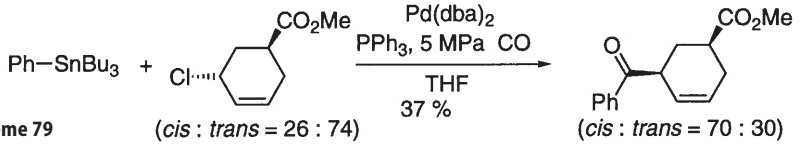
(*Z* : *E* of the crude product = 85 : 15)

Table 2. Stereospecific carbonylative cross coupling of a (*Z*)-alkenyltin

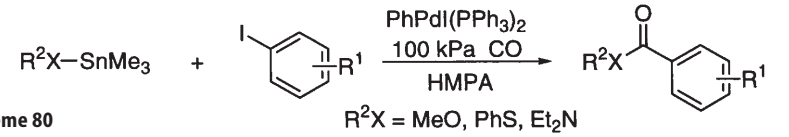
Entry	cat (mol %)	Ligand	Additives (mol equiv)	Temp	Time	**7**	**8**	**9**	**10**
1	$Pd(PPh_3)_4$ (7)	none	CuI (0.14), LiCl (3)	60 °C	3.5 h	13	24	14	18
2	$Pd_2(dba)_3$ (5)	$AsPh_3$	CuI (0.20), LiCl (3)	rt	55 min	40	40	–	–
3	$Pd_2(dba)_3$ (5)	$AsPh_3$	CuI (0.20), $ZnCl_2$ (3)	rt	–[a]	–	–	–	–
4	$Pd_2(dba)_3$ (5)	P(2-furyl)$_3$	CuI (0.20), LiCl (3)	rt	5 h	(50	50)[b]	–	–

[a] Palladium black precipitated immediately after addition of substrates.
[b] Yields were not determined because of no obvious improvement.

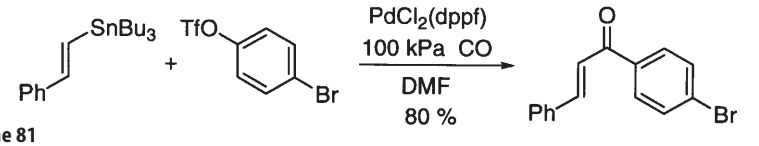
tion is also tolerant of allyl- and benzyl chlorides, giving the corresponding ketones with inversion of configuration (Scheme 79) [64]. A variety of heterostannanes such as alkoxy, thioalkoxy, and aminostannanes, can be used in this type of reactions to yield the corresponding carboxylic acid derivatives (Scheme 80) [290]. Alkenyl- and aryl triflates widen availability of the electrophilic reaction components (Schemes 81 and 82) [27, 225].



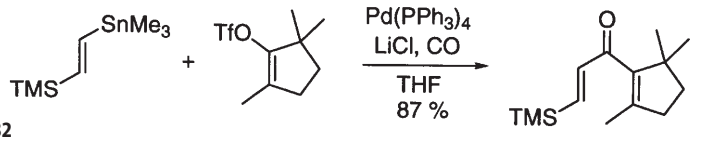
Scheme 79



Scheme 80



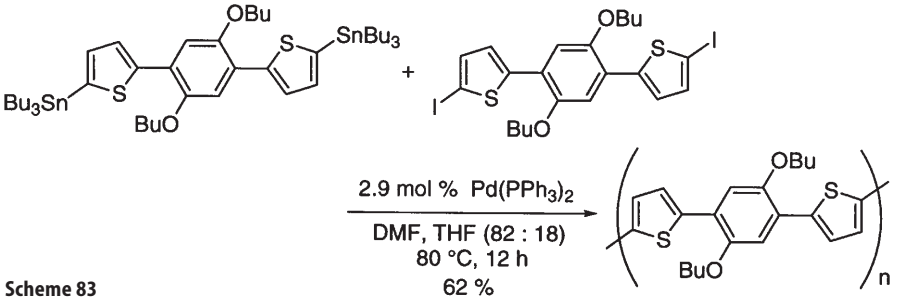
Scheme 81



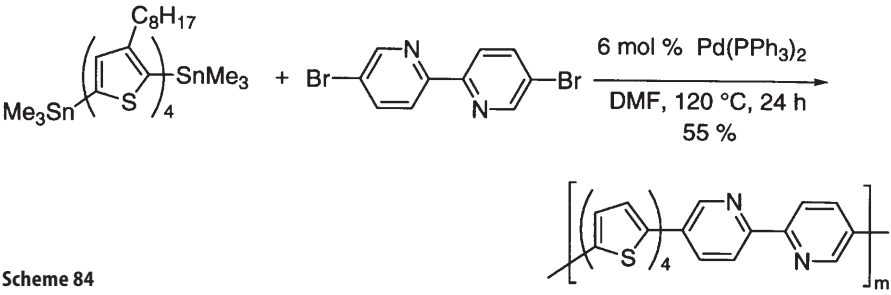
Scheme 82

4.9 Polymer Synthesis

The use of this protocol in polymer synthesis [46, 73, 74, 213, 291–304] is one of the recent topics (Scheme 83) [305]. The most extensively investigated application is toward functional materials (Scheme 84) [306].



Scheme 83

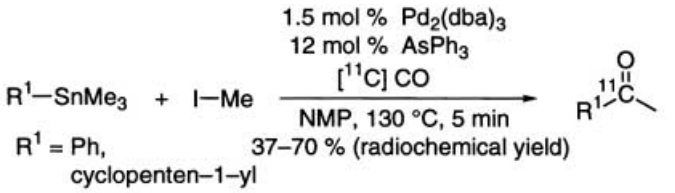


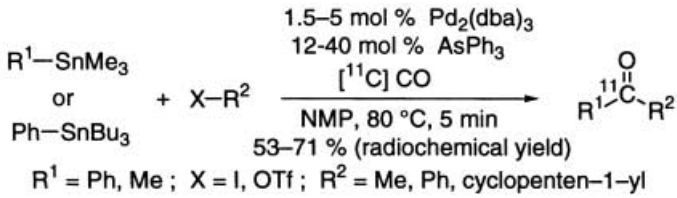
Scheme 84

4.10 Application to Rapid Syntheses

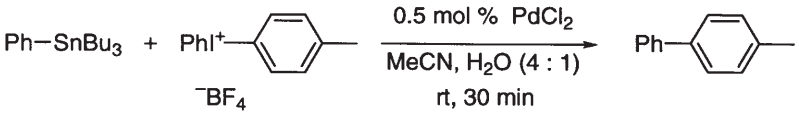
Careful tuning of conditions can also make it possible to apply this protocol to a rapid synthesis [307–309]. Such a procedure is useful for preparation of short-living species such as that containing unstable isotopes [218]. Aryl and methyl iodides are successfully employed (Scheme 85) [310, 311]. Iodonium salts can be more useful if available because they usually react at rt (Scheme 86) [312]. The problem in the use of aryl(phenyl)iodonium is chemoselectivity (Scheme 87) [313].

Supercritical carbon dioxide can be a solvent for rapid cross-coupling reaction [314]. Fluorinated palladium sources are reported to be surperior to non-fluorinated ones in such a reaction medium (Scheme 88) [315, 316].

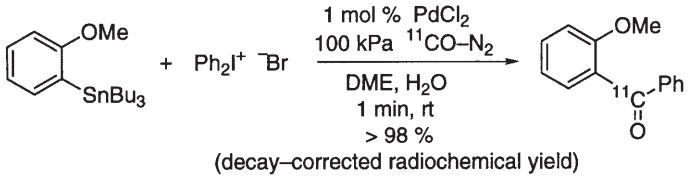


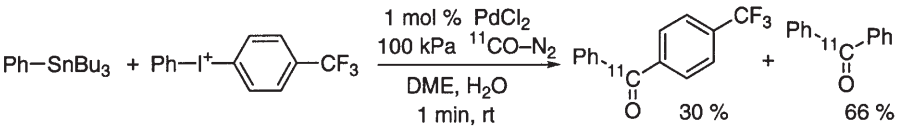


Scheme 85

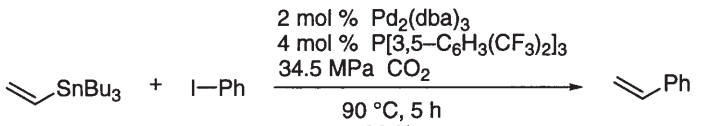


Scheme 86





Scheme 87



Scheme 88

5 Conclusion

The Stille protocol is now well established, and finds many uses in preparative chemistry. Especially, application to the synthesis of bioactive substances and functional materials is noteworthy. The choice of catalyst and solvent, however, is still remained veiled. If the reaction to be attempted is not well documented, one should first try to find the most suitable reaction conditions. Organotin compounds can be extremely toxic, and tributyltin compounds are recently suspected to be endocrine disrupters. The presence of even traces of organotin contaminants in organic products must be avoided, as far as possible. In spite of these problems, the Stille protocol will continue to be a favorite method for carbon-carbon-bond formation, owing to the mildness of the reaction conditions and the functional tolerability of both substrates and reagents.

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Practical Palladium Catalysts for C-N and C-O Bond Formation

Alex R. Muci · Stephen L. Buchwald

Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139, USA
E-mail: armuci@mit.edu and sbuchwal@mit.edu

The development of new palladium catalysts for the arylation of amines and alcohols with aryl halides and sulfonates is reviewed. Initial systems as well as mechanistic issues are discussed briefly, while subsequent generations of catalysts are described in greater detail. For these later generations of catalysts, substrate scope and limitations are also discussed. The review is organized by substrate class. Modifications and improvements in technical aspects of reaction development are described where appropriate. In addition, applications of this technology toward natural product synthesis, new synthetic methodology, and medicinal chemistry are chronicled. This review is organized in a manner that is designed to be useful to the synthetic organic chemist.

Keywords. Amination, Arylation, Catalyst, Ligand, Palladium

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Abbreviations

Ac	acetyl
Ar	aryl
Bn	benzyl
Boc	*tert*-butoxycarbonyl
Bu	*n*-butyl
t-Bu	*tert*-butyl
cat	catalyst, catalytic
conc	concentrated
Cy	cyclohexyl
Dba	dibenzylideneacetone
de	diastereomeric excess
DME	1,2-dimethoxyethane
DPPP	1,3-bis(diphenylphosphino) propane
ee	enantiomeric excess
equiv	equivalent(s)
Et	ethyl
h	hour(s)
LHMDS	lithium hexamethyl disilazide
Me	methyl
mol	mole(s)
Nf	nonafluorobutylsulfonyl
Ph	phenyl
PMB	4-methoxybenzyl
i-Pr	*iso*-propyl
RT	room temperature
TBS	*tert*-butyldimethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetyl

THF	tetrahydrofuran
TMS	trimethylsilyl
o-tol	2-methylphenyl
p-tol	4-methylphenyl
Troc	triphenylmethoxycarbonyl
Ts	tosyl, 4-toluenesulfonyl

1 Introduction

Arylamines and aryl ethers are ubiquitous in numerous fields of chemistry. Arylamines are commonly encountered in natural products [1] pharmaceuticals [2] xerographic and photographic materials [3] as well as conducting polymers [4]. Similarly, aryl ethers are commonly found in natural products [1] and biologically active compounds [2] as well as polymeric materials [5]. Traditionally, the preparation of alkylarylamines has been carried out by the reductive amination of aniline derivatives or arene nitration/reduction protocols [6, 7]. These methods, although often effective, suffer from a relatively limited substrate generality and functional group tolerance. Additionally, these synthetic strategies often require multiple steps or the use of expensive reagents in stoichiometric amounts. The preparation of aryl ethers has most often been achieved via the Ullman ether synthesis [8]. Though useful, the Ullman reaction suffers from a limited substrate scope; the reaction typically works best for the coupling of electron-deficient and sterically unhindered aryl halides.

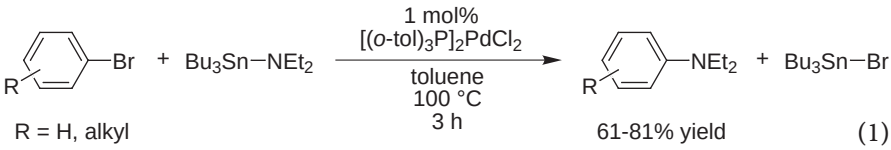
Thus, the transition metal catalyzed arylation reactions of amines and alcohols would constitute powerful tools for synthetic chemists. We have been developing practical procedures for the palladium-catalyzed arylation of amines and alcohols with aryl halides or sulfonates. During the course of our investigations [9] as well as those of John Hartwig and co-workers [10] the substrate scope of these transformations has been incrementally expanded. With each cycle of this catalyst improvement process, advances in mechanistic understanding and ligand design have also been made.

This review covers the literature through December, 2000 and is designed to be of greatest use to the synthetic organic chemist. Thus, the mechanistic studies will be not be covered in detail, and it is left to the reader to refer to the literature describing such studies [11]. In addition, the reader is encouraged to consult previous reviews on amine and alcohol arylation [9, 10, 12]. Procedures detailing other transition metal catalysts (e. g., Ni and Cu) effective in amine and alcohol aryl couplings have also been reported, but because of space limitations, are beyond the scope of this review [13]. Experimental procedures were chosen based on the general utility of the procedure as well as the commerical availability of the catalyst precursors.

2
Palladium-Catalyzed Amine Arylation

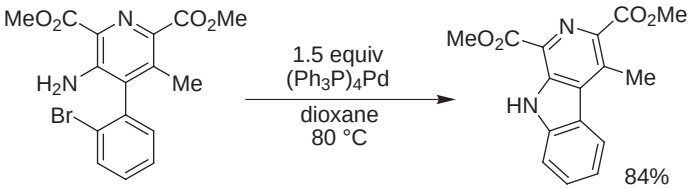
2.1
Initial Systems

The first palladium-catalyzed formation of aryl C-N bonds was reported in 1983 by Migita and co-workers, Eq. (1) [14]. The reaction of electronically neutral aryl bromides and aminotin compounds in the presence of catalytic $[(o\text{-tol})_3P]_2PdCl_2$ resulted in the efficient preparation of the corresponding aniline in moderate to good yield. This seminal discovery was limited by the necessity to use the thermally and moisture sensitive tributyltin amides, however.



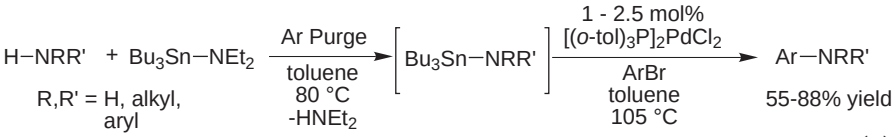
(1)

Additionally, Boger and Panek reported an intramolecular amine arylation mediated by stoichiometric quantities of Pd (0), Eq. (2) [15]. Efforts to render this transformation catalytic in palladium were fruitless, however. The resulting heterocycle was utilized in the total synthesis of lavendamycin.



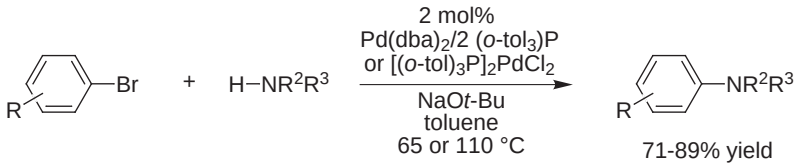
(2)

In 1994, Buchwald and Guram reported a new catalytic procedure based on Migita's amination procedure where the tin amide could be generated *in situ* by an amine exchange reaction, Eq. (3) [16]. Thus, by pre-mixing *N*,*N*-diethylaminostannane with the reacting amine followed by removal of the volatile diethyl amine by argon purge, they were able to cleanly produce the desired aminotin compound. This intermediate was found to undergo coupling with several aryl bromides in moderate to good yields, although this procedure still necessitated the use of stoichiometric tributyltin compounds.



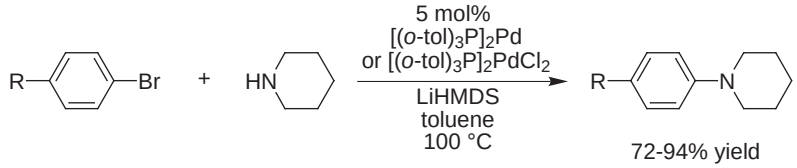
(3)

The limitations associated with the use of tin compounds in this chemistry was overcome by the Buchwald and Hartwig groups concurrently in 1995. By using NaO*t*-Bu as base, the Buchwald, Guram, and Rennels were able to effect catalytic C-N bond formation, Eq. (4) [17]. Thus, the sodium amide generated *in situ* by deprotonation of the reacting amine could be used instead of the corresponding aminotin species. They reported that the isolated complex $[(o\text{-tol})_3P]_2PdCl_2$ or a catalyst generated by mixing Pd_2dba_3 and two equivalents of $(o\text{-tol})_3P$ achieved the C-N bond formation with comparable efficiency.



(4)

Similarly, Hartwig and Louie reported that LiHMDS was also a useful base for such transformations, Eq. (5) [18]. They also reported two different complexes as catalysts; $[(o\text{-tol})_3P]_2PdCl_2$ and $[(o\text{-tol})_3P]_2Pd$ effectively catalyzed the amine arylation reaction.

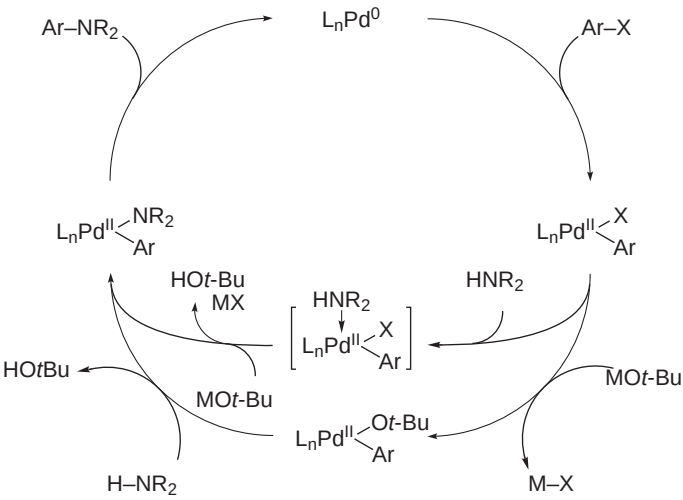


(5)

Although both of these reports greatly expanded the scope and utility of the amine arylation reaction, these catalytic systems enjoyed a relatively narrow substrate scope compared to subsequent generations of catalysts developed both by the Buchwald and Hartwig groups. Through iterative cycles of ligand design, methodological studies, and mechanistic investigations, highly active and broadly useful catalyst systems have been developed.

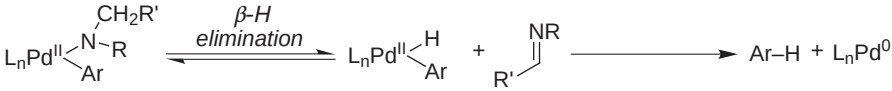
The generally accepted mechanism for the amine arylation is shown in Scheme 1. The catalytic cycle begins with the oxidative addition of the aryl halide (or sulfonate) by Pd (0). The palladium (II) aryl amide can be formed either by direct displacement of the halide (or sulfonate) by the amide or via the intermediacy of a palladium (II) alkoxide [19]. Reductive elimination of the C-N bond results in the formation of the desired arylamine and regeneration of the Pd (0) catalyst [11e, 20].

In the coupling of more challenging substrates, reduction of the aryl halide is frequently observed [21]. Specifically, in the reaction of electron-rich aryl halides or sulfonates, reduced arene is a major by-product. Presumably, this side-product arises when the palladium amide can undergo β-hydride elimination to generate an imine and a palladium (II) aryl hydride (Scheme 2). Subse-



Scheme 1

quent reductive elimination yields the reduced arene and regenerates the Pd (0) catalyst. Thus, one of the major challenges confronted in the development of more efficient amine arylation catalysts was to shut down this unwanted side reaction.



Scheme 2

2.2
N-Arylation of Secondary Amines

2.2.1
Reaction of Cyclic Secondary Amines with Aryl Bromides

The initial catalyst systems described above were effective with aryl bromides and a relatively narrow array of amines, although these procedures found utility in the preparation of diaminofluorenes [22], poly(aryleneamines) [23], certain *N*-aryl-aza-crown ethers [24], *N*-arylpiperazines [25], and diaminobenzenes [26] (Fig. 1). These original methods often proved reasonably effective in the coupling of cyclic amines. Presumably, cyclic amines are less challenging substrates for the palladium-catalyzed coupling because the cyclic palladium (II) amide intermediates are less prone to β-H elimination compared to their acyclic counterparts.

Although the arylation reaction could be effected with $(o\text{-tol})_3P$ as ligand, Buchwald and co-workers investigated the use of BINAP (**1**) and other diphosphine ligands in the C-N bond forming reaction. (±)-BINAP often provided better yields of the desired product with both cyclic and acyclic amines, and lower

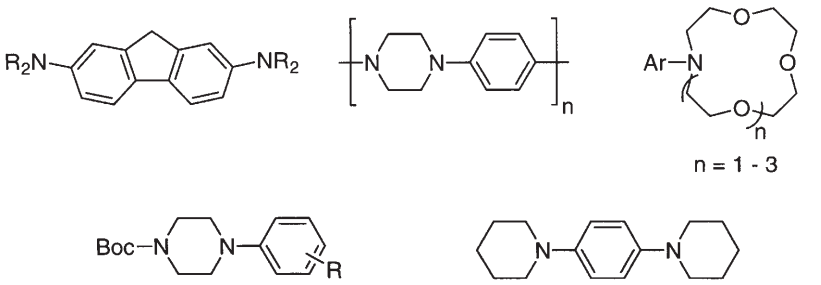
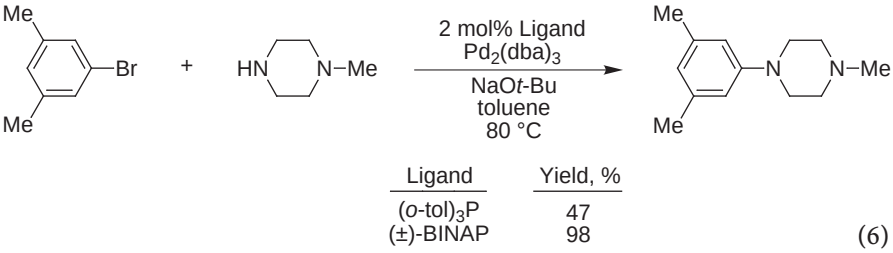


Fig. 1. Compounds prepared by the $[(o\text{-tol})_3P]_2PdCl_2$-catalyzed amine arylation

amounts or aryl bromide reduction were observed [27, 28]. While the coupling of *N*-methylpiperazine with 3,5-dimethylbromobenzene proceeded in 47% isolated yield when the $(o\text{-tol})_3P$–based protocol was used, the (±)-BINAP-derived catalyst effected the reaction in 98% yield, Eq. (6). In fact, a 94% yield of the desired product was obtained when the (±)-BINAP/Pd-catalyst was used in only 0.05 mol% in the absence of solvent. Substantial improvements in yield in the coupling of acyclic secondary amines were also observed with the BINAP system as well as well as a DPPF (**2**)-based catalyst reported by Hartwig [29]. Like the $(o\text{-tol})_3P$/Pd system, NaO*t*-Bu is most often used as base, however, recently a Novartis group has reported that alkoxide bases containing β-hydrides such as NaOMe or NaO*i*-Pr can also be used [30]. Additionally, milder bases such as Cs_2CO_3 and K_3PO_4 are often compatible with these methods.



Ligand	Yield, %
$(o\text{-tol})_3P$	47
(±)-BINAP	98

(6)

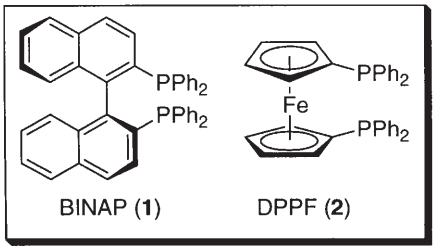
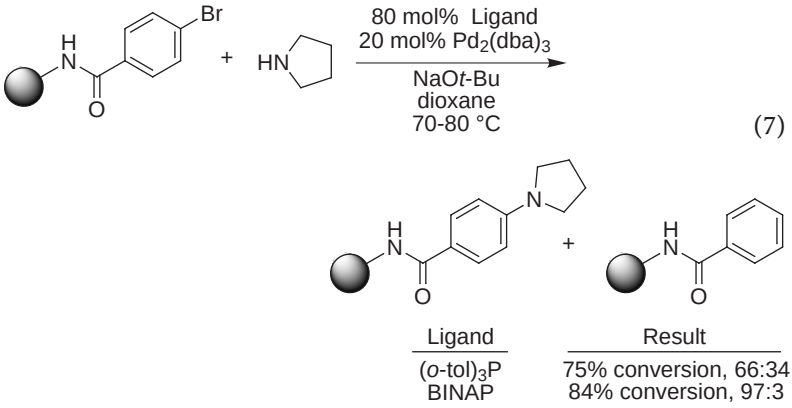


Fig. 2

General Procedure for the Palladium-Catalyzed Arylation of Amines with Aryl Bromides using BINAP/Pd: (Excerpted with permission from [27]. © 2000 American Chemical Society) An oven-dried Schlenk flask was charged with

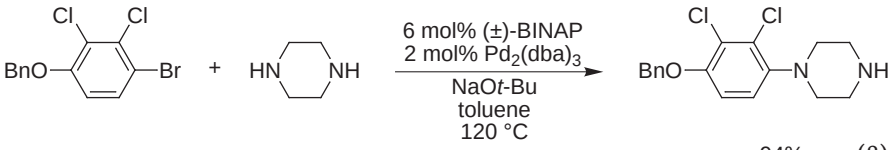
sodium *tert*-butoxide (134.5 mg, 1.4 mmol), $Pd_2(dba)_3$ (2.3–9.2 mg, 0.0025–0.01 mmol), and BINAP (4.7–18.7 mg, 0.0075–0.03 mmol). The Schlenk flask was fitted with a septum and attached to a Schlenk line. After the air atmosphere was replaced with argon, toluene (2–9 ml), aryl bromide (1.0 mmol), and amine (1.2 mmol) were added by syringe. After the septum was replaced with a teflon valve, the reaction was sealed and heated to 80 °C with stirring until starting material was consumed as judged by GC analysis. The reaction mixture was cooled to room temperature, diluted with ether (15 ml), filtered, and concentrated. The crude reaction mixture was then purified further by flash chromatography on silica gel.

Numerous groups have used the BINAP/Pd- and DPPF/Pd-based reaction protocols for the arylation of cyclic secondary amines. Independently, Ward and Farina [31] as well as Willoughby and Chapman [32] disclosed that the palladium-catalyzed arylation reaction could be effected on resin-bound amines, Eq. (7). Both groups reported that while the (*o*-tol)$_3$P-based catalysts were often inferior to the BINAP-based system, using DPPF as ligand often resulted in comparable yields and reaction rates. They also observed that BINAP-derived catalysts usually yielded smaller amounts of reduced arene by-products.



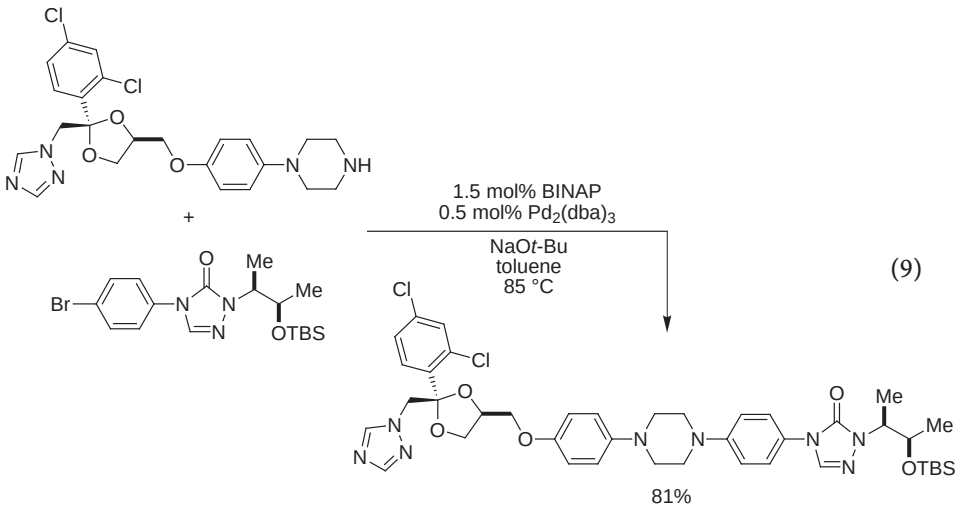
(7)

Morita and co-workers have utilized the BINAP/Pd-catalyst system to prepare arylpiperazines which are metabolites of Aripiprazole, an anti-psychotic agent, Eq. (8) [33].



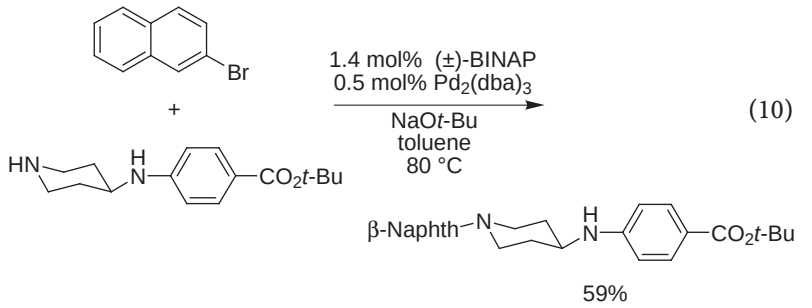
94% (8)

Tanoury, Senanayake, and co-workers utilized the BINAP/Pd-based catalyst in the synthesis of hydroxitraconazole, an antifungal agent [34]. The key C-N bond formation reaction provided the TBS-protected compound in 81% yield, Eq. (9).



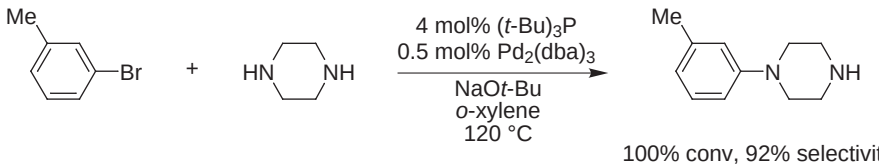
(9)

Similarly, Kung and co-workers utilized the (±)-BINAP/Pd-catalyst to prepare various aryl analogues of a novel quinazoline antibacterial agent [35]. For example, the coupling below proceeded in 59% isolated yield with 1 mol% palladium, Eq. (10). The moderate yield was likely due to cleavage of the *tert*-butyl ester.



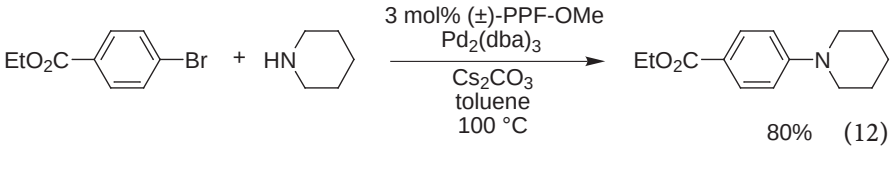
(10)

Other ligands are useful in the C-N bond coupling of aryl bromides and cyclic amines. In 1998, Nishiyama and co-workers at Tosoh corporation reported that tri-*tert*-butylphosphine is an effective supporting ligand for the palladium-catalyzed arylation of piperazine [36]. The $(t\text{-Bu})_3$P/Pd-catalyst provided the product with 1 mol% Pd in high selectivity, Eq. (11).



(11)

The Buchwald group subsequently disclosed that sterically hindered ferrocene-based monophosphines such as PPF-OMe (**3**), were useful ligands that extended the substrate scope of the amine arylation reaction, particularly with acyclic secondary amines [37, 38, 39]. In addition, during the development of catalysts derived from **3,** it was discovered that Cs_2CO_3 could be used as base in the amine arylation, resulting in greater functional group tolerance. Esters, enolizable ketones and nitroalkane functional groups were now compatible with the C-N bond forming reaction, Eq. (12) [40]. Cesium carbonate was also an effective base when used with the (±)-BINAP/Pd-based catalyst, Eq. (13) [27a]. Recently, Torisawa and co-workers have reported that the use of catalytic amounts of 18-crown-6 (10 mol%) improved the yield in certain arylation reactions where Cs_2CO_3 was used as base [41].



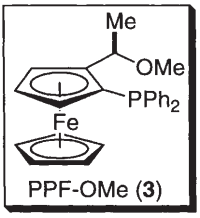
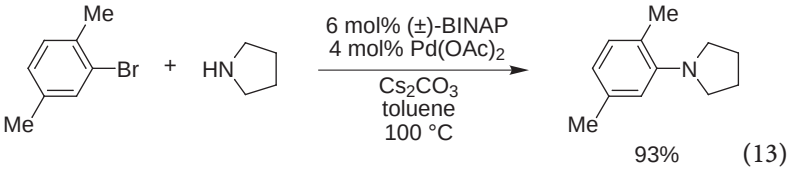
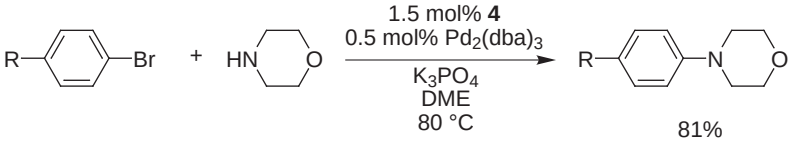


Fig. 3



The catalyst derived from aminophosphine **4** enjoys very high reactivity and a similar substrate scope as ligand **3**. In addition, mild bases could be employed in the arylation of dialkylamines [42, 43, 44]. With the catalyst derived from $Pd_2(dba)_3$ and **4**, 4-bromomethylbenzoate reacted cleanly with morpholine in the presence of K_3PO_4, Eq. (14). With stronger bases such as NaO*t*-Bu, ester



R	Yield, %
-CO_2Me	81
-COMe	82

(14)

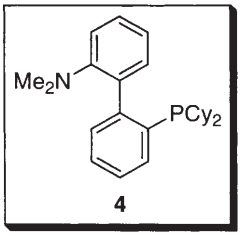
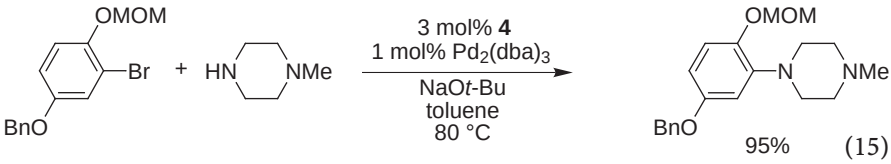


Fig. 4

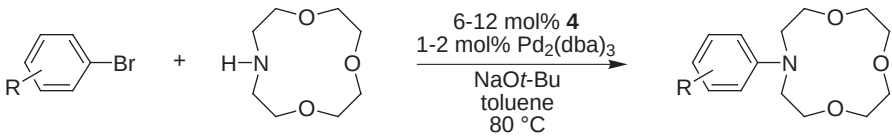
cleavage by-products are observed. 4-Bromoacetophenone was coupled with morpholine in high yield and without unwanted aldol side-reactions.

Schmalz and co-workers utilized the **4**/Pd-catalyzed arylation to prepare several novel chiral bidentate ligands [45]. For example, the arylation of *N*-methylpiperazine below proceeded in 95% yield to furnish the desired ligand building block, Eq. (15).



95% (15)

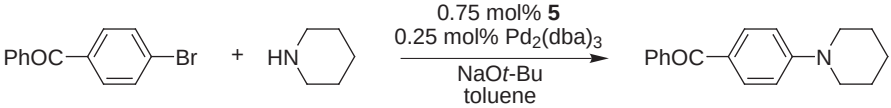
Zhang and Buchwald have recently reported that the **4**/Pd-catalyst is particularly effective in the arylation of aza-crown ethers [46]. These reactions proceed in high yield when with *meta*- or *para*-substituents on the aryl bromide; *ortho*-substituted aryl bromides react in moderate yield, Eq. (16).



R	Yield, %
p-*t*-Bu	87
o-Me	41

(16)

Guram has reported similar P,N- and P,O-chelating ligands useful in the amine arylation reaction [47]. For example, the coupling of piperidine with 4-bromobenzophenone proceeds in 98% yield with as little as 0.5 mol% of the palladium catalyst resulting from ligand **5**, Eq. (17).



98% (17)

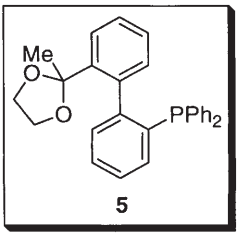
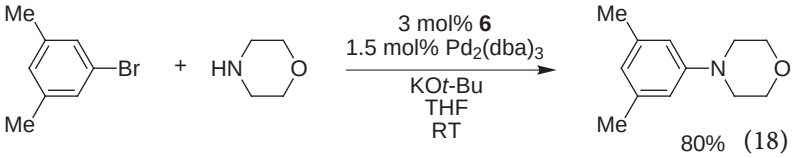


Fig. 5

In 1999, Wolfe and Buchwald reported the synthesis of hindered, electron-rich phosphine **6** and its use in the amine arylation reaction. Use of this new ligand resulted in a catalyst capable of effecting the room temperature reaction between cyclic amines and aryl bromides [42a, 44, 48, 49]. The catalyst derived from $Pd_2(dba)_3$ and **6** couples 3,5-dimethybromobenzene with morpholine in 80% yield while stirring for 20 hours at room temperature, Eq. (18). This new highly active catalyst efficiently arylates a variety of amines with aryl bromides as well as chlorides at room temperature.



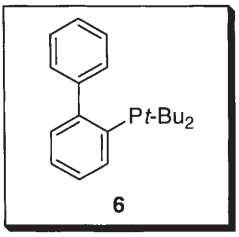
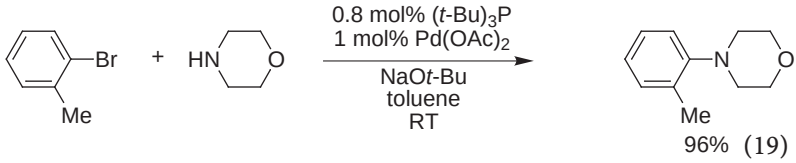
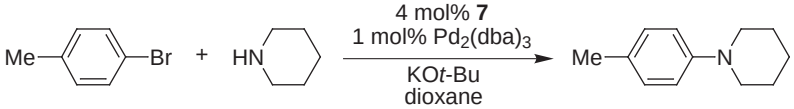


Fig. 6

Concurrently with this contribution from Buchwald and co-workers, the Hartwig group reported that the $P(t\text{-Bu})_3P$/Pd-catalyst system first reported by Koie and co-workers [36] is sufficiently active to couple aryl bromides with secondary amines at room temperature [50]. For example, 2-bromotoluene is efficiently aminated with morpholine at in 96% yield, Eq. (19). This catalyst is capable of the room temperature coupling of acyclic secondary amines and aryl bromides as well as the coupling of aryl chlorides at elevated temperatures.



Recently, heterocyclic carbene ligands, first investigated by Arduengo [51] have been utilized as ligands for palladium in the arylation reaction. Nolan reported the use of ligands derived from heterocycles such as **7** in the arylation of piperdine using 4-bromotoluene. The reaction proceeds in 83 % yield at room temperature, Eq. (20) [52].



83% (20)

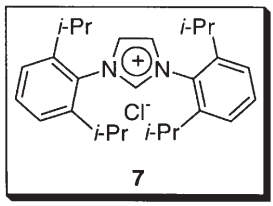
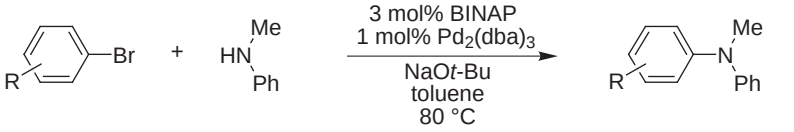


Fig. 7

2.2.2
Reaction of Acyclic Secondary Amines with Aryl Bromides

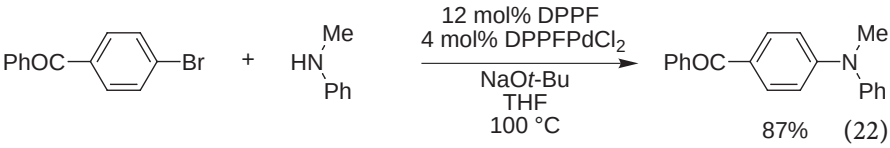
Acyclic secondary amines often are more challenging substrates for the palladium-catalyzed amine arylation due to their greater propensity for β-hydride elimination, and a screening of different ligands in the reaction of acyclic secondary amines revealed a stronger dependence of the reaction efficiency on the ligand relative to their cyclic counterparts. Early on, the Buchwald group discovered that the use of (±)-BINAP as a ligand in these reactions resulted in the clean coupling of *N*-methylaniline with aryl halides that possess electron-donating groups or moderate steric hindrance, Eq. (21) [27, 28].



R	Ligand	Yield, %
3,5-Me_2	P(*o*-tol)$_3$	5
3,5-Me_2	BINAP	79
2-NMe_2	P(*o*-tol)$_3$	0
2-NMe_2	BINAP	65

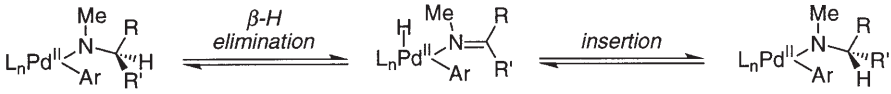
(21)

Hartwig and co-workers simultaneously described an improved procedure employing DPPFPdCl_2, and added DPPF, as catalyst, Eq. (22) [29]. Considerable improvements in yield were observed using this DPPF/Pd catalyst to couple primary as well as acyclic secondary amines compared to (*o*-tol)$_3$P-based systems.



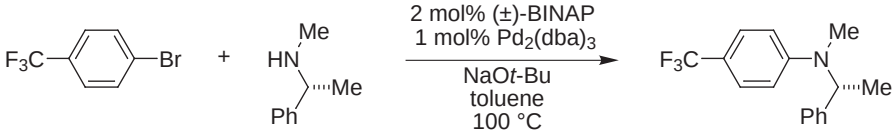
87% (22)

Presumably, the use of a bidentate ligand such as (±)-BINAP or DPPF results in the occupation of a vacant coordination site, preventing β-hydride elimination of the Pd (II) amide intermediate [53]. Dissociation of the imine and C-H bond reductive elimination results in formation of the reduced aryl bromide. If this β-hydride elimination is rapid relative to reductive elimination and reversible, then significant erosion of the enantiomeric excess of optically active α-substituted amines may be observed during the reaction (Scheme 3).



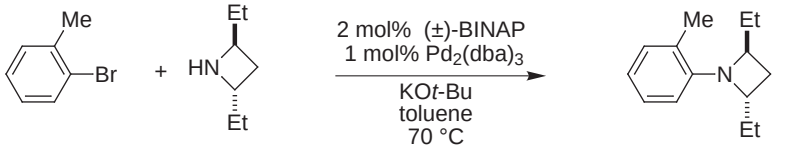
Scheme 3

Buchwald and co-workers investigated this β-hydride elimination/reinsertion phenomenon in the coupling of optically active amines. They observed significant epimerization of the α-stereocenter during the coupling of (*R*)-*N*-methyl-α-methylbenzylamine and 4-bromo-α,α,α-trifluorotoluene when the $(o\text{-tol})_3$P-derived catalyst was used. In contrast, the use of (±)-BINAP/Pd-based system resulted in retention of the integrity of the α-stereocenter, Eq. (23) [54]. It should be noted that the chirality of the ligand is inconsequential to the reaction since racemic BINAP was used in these studies. The Buchwald group reported that use of the Pd/DPPF-based catalysts prevents the epimerization of the α-stereocenter as well.



(23)

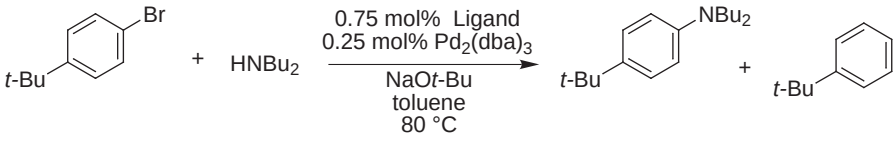
This observation was exploited by Marinetti in the *N*-arylation of chiral azetidines [55]. For example, 2,4-diethylazetidine was coupled with *ortho*-bromotoluene in high yield using the (±)-BINAP-based protocol, Eq. (24). No stereoisomerization of the amine was observed during the arylation reaction. Other groups have utilized the BINAP/Pd-system to couple α-chiral primary amines.



85% (24)

Despite the significant improvements in substrate scope that were enjoyed in the development of these new bisphosphine-based protocols, significant aryl bromide reduction side products were observed with other secondary amines. Specifically, the coupling of certain acyclic secondary amines was often accompanied by a large amount of aryl bromide reduction. While *N*-methylarylamines were good substrates for this reaction, substituents larger than methyl were not well tolerated and significant amounts of aryl bromide reduction was observed. Additionally, large amounts of arene side products were observed when electron rich aryl bromides were used. Thus, it was necessary to design new catalyst systems to broaden the scope of the amine arylation reaction.

The use of ferrocene-based ligands such as **3** and PPFA (**8**) result in the formation of catalysts that extended the scope of the arylation reaction to more difficult transformations [37, 38, 56]. For example, di-*n*-butylamine could now be effectively coupled with electronically neutral as well as electron-deficient aryl bromides. Reaction of 4-*tert*-butylbromobenzene with di-*n*-butylamine with the (±)-BINAP/Pd- or DPPF/Pd-based catalysts resulted in significant amounts of *tert*-butylbenzene formation, however the use of ligands **3** and **8** resulted in formation of the desired product in excellent yield, Eq. (25).



Ligand	Ratio	Yield, % (GC)
(±)-BINAP (**1**)	1.0:5.2	8
DPPF (**2**)	1.0:4.9	9
(±)-PPFOMe (**3**)	39:1.0	97
(±)-PPFA (**8**)	12.5:1.0	92

(25)

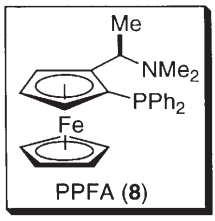
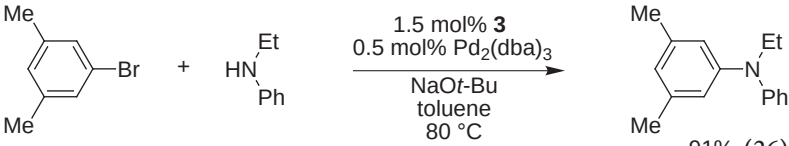


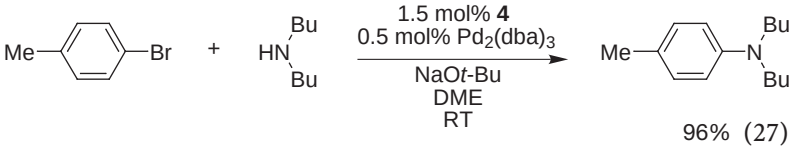
Fig. 8

The use of PPF-OMe (**3**) also allowed the coupling of secondary alkylarylamines that possess alkyl groups other than methyl. The reaction of *N*-ethylaniline and 5-bromo-*meta*-xylene proceeds in excellent yield with no reduced arene formation, Eq. (26). It should be noted that the **3**/Pd-catalyst system tolerates the use of Cs_2CO_3 as base.



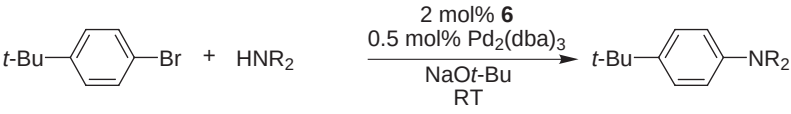
91% (26)

Commercially available aminophosphine **4** provided even better yields in the coupling of acyclic secondary amines [42]. The resulting catalyst was found to be so active that the reaction could often be conducted at room temperature. For example, Di-*n*-butylamine was efficiently reacted with 4-bromotoluene in 96% isolated yield at room temperature, Eq. (27). In addition, electron-rich, electronically neutral, and electron-deficient aryl bromides were effectively utilized with this new system. The **4**/Pd-based catalysts also mediate the coupling of *N*-alkylanilines that bear electron-donating substituents on the amine partner. A Xantphos/Pd-catalyst is effective in the coupling of electron-poor alkylarylamines with electron-poor aryl bromides.



96% (27)

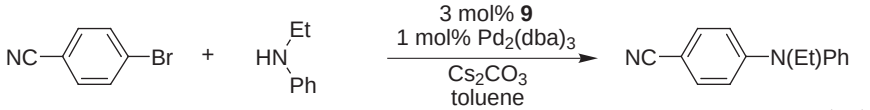
As was the case with ligand **4**, 2-biphenyldi-*tert*-butylphosphine (**6**) effects the amination of acyclic secondary amines at room temperature [42a, 48]. The catalyst derived from this commercially available ligand and $Pd_2(dba)_3$ promotes the coupling of 4-bromo-*tert*-butylbenzene and di-*n*-butylamine or *N*-methylaniline in excellent yields at room temperature, Eq. (28).



Amine	Solvent	Yield, %
H-NBu_2	toluene	92
H-N(Me)Ph	DME	83

(28)

The use of Xantphos (**9**), first reported by Van Leeuwen [57], as supporting ligand allows for the efficient coupling of alkylarylamines and aryl bromides [58]. For example, the reaction of 4-bromobenzonitrile and *N*-ethylaniline proceeds in 85% isolated yield, Eq. (29). This ligand is particularly effective in the coupling of electron-deficient alkylarylamines and electron-deficient aryl bromides.



85% (29)

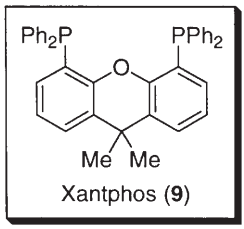
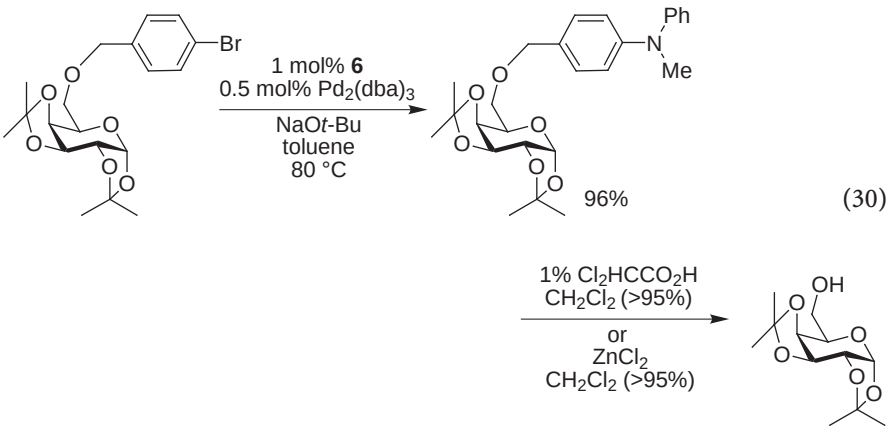


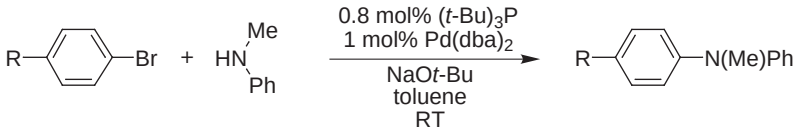
Fig. 9

Seeberger and Buchwald have reported the use of the **6**/Pd-catalyzed amine arylation reaction as a method for protecting group activation [59]. The 4-bromobenzyl protecting group may be easily aminated to furnish the corresponding 4-aminobenzyl ether derivative, Eq. (30). The resulting electron-rich benzyl ether can be easily deprotected by use of a Brønsted or Lewis acid under very mild conditions. Notably, this strategy can be further elaborated by the selective reaction of 4-chloro- and 4-iodobenzyl protecting groups as well.



(30)

Hartwig's group disclosed that $(t\text{-Bu})_3$P/Pd-based catalysts were sufficiently active such that the coupling of secondary amines and aryl bromides may be performed at room temperature, Eq. (31) [50]. This system tolerates electron-withdrawing, electronically neutral, as well as electron-donating substituents on the aryl bromide.

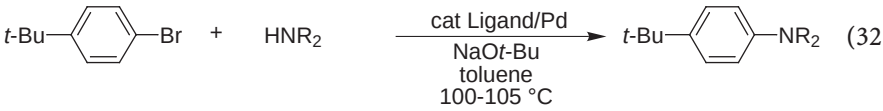


R	Yield, %
CN	95
OMe	99

(31)

Other groups have described systems that catalyze the arylation of acyclic secondary amines using aryl bromides, Eq. (32). Uemura reported the use of

chromium arene based ligands such as **10** in the Pd-catalyzed C-N bond forming reaction [60]. Similar to PPFA (**8**), ligand **10** effects the coupling of numerous aryl bromides with *N*-ethylaniline. The catalyst derived from $Pd_2(dba)_3$ and phosphinoether **5** promotes the amination of acyclic secondary amines and aryl bromides as well [47]. Related ligands were found useful in the coupling of aryl chlorides. Hayashi has reported the use of DPBP (**11**) in the amine arylation reaction [61]. It is expected that **11** would behave similarly to BINAP in these transformations, since it possesses similar electronic properties and bite angle.



(32)

Amine	Ligand (mol%)	Pd Source (mol %)	Yield, %
H-NEt_2	**10** (3)	$Pd(dba)_2$ (1)	90
H-N(Et)Ph	**10** (3)	$Pd(dba)_2$ (1)	90
H-N(Me)Bn	**5** (6)	$Pd_2(dba)_3$ (2)	83
H-$N(Oct)_2$	**5** (6)	$Pd_2(dba)_3$ (2)	93
H-(Me)Bn	**11** (7.5)	$Pd_2(dba)_3$ (2.5)	97

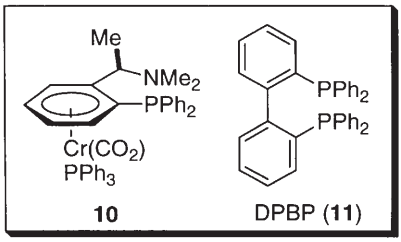
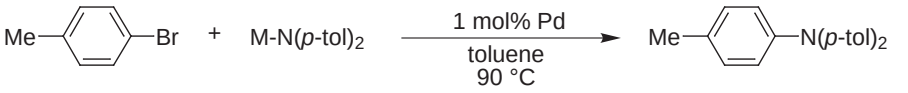


Fig. 10

Heterogeneous catalysts have also been reported to effect the arylation of secondary amines using aryl bromides. Buchmeister reported the preparation of a polymer-bound catalyst, which effects the arylation reaction at elevated temperatures. No attempts to recycle the catalyst were reported, however [62]. Djakovitch and co-workers reported the use of Pd particles immobilized on metal oxides or Pd-loaded zeolites as a catalyst [63]. The yields and selectivities for the reaction were diminished compared to homogeneous systems previously described.

2.2.3
Reaction of Diarylamines with Aryl Bromides

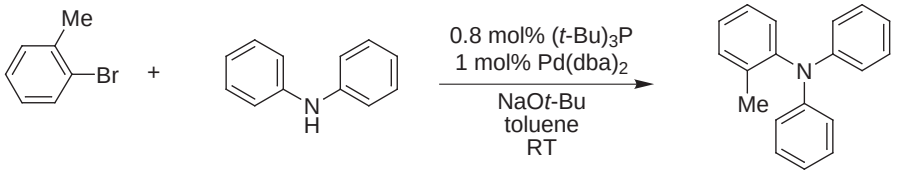
Hartwig first reported the arylation of diarylamines using both (*o*-tol)$_3$P/Pd- and DPPF/Pd-catalysts, Eq. (33) [29, 64]. The Yale group utilized the (*o*-tol)$_3$P/Pd- and DPPF/Pd-based protocols for the preparation of triarylamine-containing dendrimers and cyclophanes, respectively.



M	Reaction Conditions	Yield, %
Li	$[(o\text{-tol})_3P]_2Pd$	99
H	$[(o\text{-tol})_3P]_2Pd$, Base = NaO*t*-Bu	92
H	$Pd(dba)_2$, DPPF, Base = NaO*t*-Bu	89

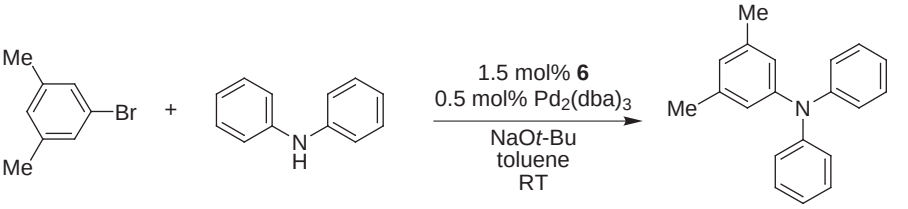
(33)

Nishiyama, and co-workers first reported that the catalyst derived from $Pd(OAc)_2$ and $(t\text{-Bu})_3P$ effects the C-N bond formation to produce triarylamines in excellent yield [65]. This system also is useful in the coupling of diarylamines and aryl chlorides. Hartwig and co-workers found this protocol optimal for the preparation of triarylamines. The $(t\text{-Bu})_3P$/Pd-catalyst was sufficiently active such that the coupling of diarylamines and aryl bromides can be performed at room temperature, Eq. (34) [50]. The $(t\text{-Bu})_3P$/Pd-system has been used to produce new triarylamine-based polymers [64a–d].



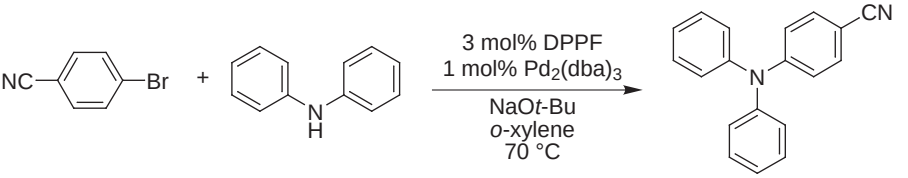
97% (34)

The highly active **6**/Pd-catalyst is capable of effecting C-N bond formation between and aryl bromide and a diarlyamine at room temperature [42a, 48]. Using, NaO*t*-Bu as base, the reaction below proceeded in 89% yield over 23 h, Eq. (35).



89% (35)

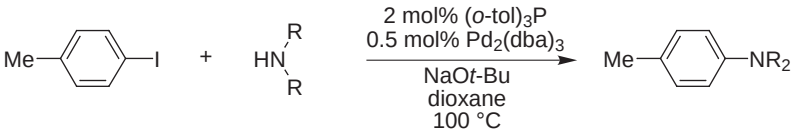
Recently, Stupp and co-workers, as well as others, have utilized the DPPF or $t\text{-Bu}_3P$/Pd-catalyst to prepare substituted triarylamines in high yield, Eq. (36) [66]. The product below was used to prepare 4-diphenylaminostysene, which was incorporated into an optoelectronic polymer.



83% (36)

2.2.4
Reaction of Secondary Amines with Aryl Iodides

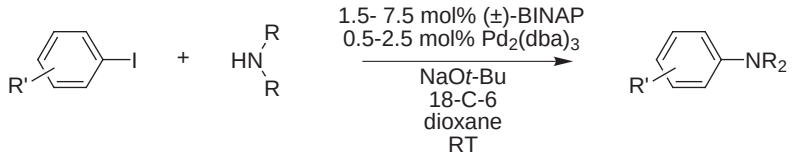
In 1996, Wolfe and Buchwald reported that the (*o*-tol)$_3$P/Pd catalyst system effectively couples secondary amines with aryl iodides, Eq. (37) [67]. This protocol allowed for the successful reaction of both cyclic and acyclic secondary amines; the use of dioxane as solvent was key to the success of these reactions. Similarly, Zhao and co-workers reported the coupling of aryl iodides and piperazines mediated by the (*o*-tol)$_3$P/Pd catalyst [25b].



Amine	Yield, %
H-N(Me)Bn	78
H-N(Bu)$_2$	68
H-N(Me)Ph	74
morpholine	73

(37)

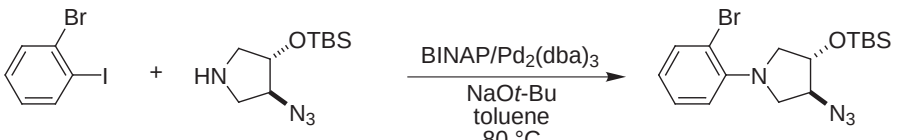
The room-temperature reaction of secondary amines and aryl iodides can be efficiently catalyzed by the (±)-BINAP/Pd system, Eq. (38) [68]. In order to achieve complete conversion, it was necessary to utilize stoichiometric 18-crown-6 as an additive. However, role of the crown ether is not entirely clear. Notably, aryl iodides react exclusively under these conditions while aryl bromides are left unchanged.



R'	Amine	Yield, %
p-*t*-Bu	H-N(Me)Ph	90
p-*t*-Bu	morpholine	71
o-Br	morpholine	78

(38)

The difference in reactivity between the aryl iodide and bromide was exploited by Sulikowski in the synthesis of a mytomycin skeleton [69]. The desired arylamine was prepared in 66% yield with exclusive reaction at the iodide, Eq. (39).



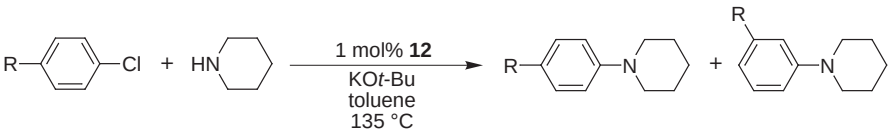
66% (39)

Nishiyama, Yamamoto, and Koie also reported that the $(t\text{-Bu})_3$P/Pd-based catalyst is effective in the C-N bond forming reaction between an aryl iodide as well as an aryl bromide and piperazine [36].

2.2.5
Reaction of Cyclic Secondary Amines with Aryl Chlorides

The use of aryl chlorides in the palladium catalyzed C-N bond forming reaction is highly desirable since aryl chlorides are often less expensive the analogous bromides and because there are a greater number of aryl chlorides which are commercially available. However, the use of aryl chlorides as reactants in numerous palladium-catalyzed processes has until recently been an elusive goal.

The first palladium-catalyzed coupling between a secondary amine and an aryl chloride was described by Beller, Hermann and co-workers in 1997 [70]. Use of palladacycle **12** as catalyst resulted in C-N bond formation in good yield for several secondary amines and electron-deficient aryl chlorides, Eq. (40). In these transformations, varying amounts of the regioisomeric product was observed, indicative that to some degree the reaction proceeds via a benzyne intermediate.



R	Yield, %	Ratio
CF_3	74	7:1
COPh	40	>50:1

(40)

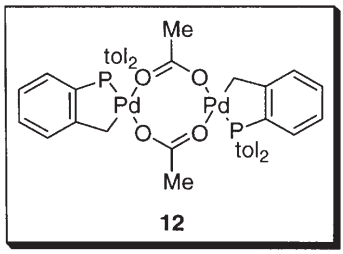
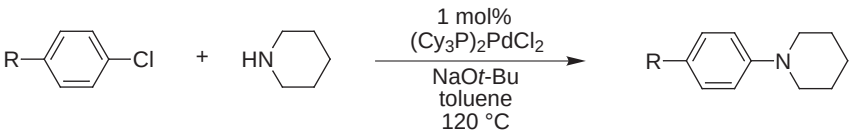


Fig. 11

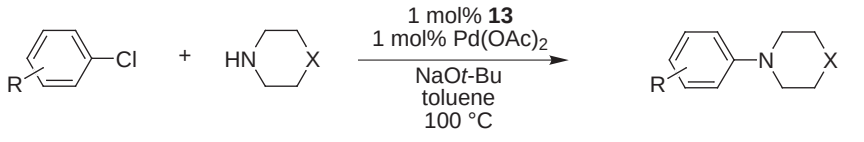
Reddy and Tanaka reported that $(Cy_3P)_2PdCl_2$ catalyzes the coupling of secondary amines with aryl chlorides, Eq. (41) [71]. With this catalyst system based on the use of sterically hindered, electron-rich trialkylphosphines, electron-poor and electronically neutral aryl halides were reacted at elevated temperatures. Similarly, Nishiyama, Yamamoto and Koie reported the formation of an arylpiperazine from chlorobenzene using a $(t\text{-Bu})_3$P/Pd catalyst [36].



R	Yield, % (GC)
CN	65
Me	56

(41)

In 1998, Hamann and Hartwig reported that electron-rich, ferrocene-based diphosphines such as **13** allowed for the coupling of cyclic amines with aryl chlorides [72, 73]. The known ligand **13** proved to be most generally useful for this transformation, Eq. (42). The **13**/Pd-catalyzed arylation reaction was performed with cyclic amines as well primary amines, however, no reactions with acyclic secondary amines were reported.



R	X	Yield, %
m-OMe	CH_2	81
p-Me	O	85

(42)

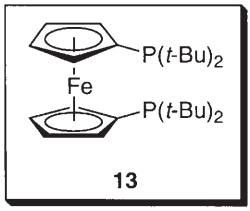
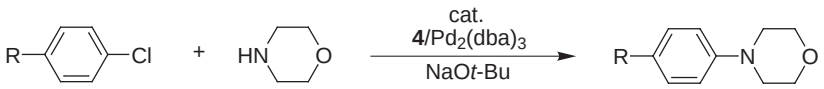


Fig. 12

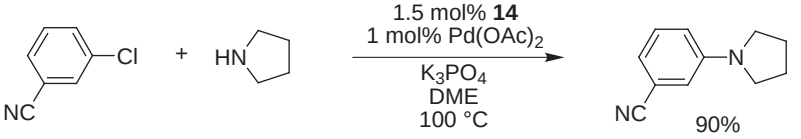
Almost concurrently with this report by Hartwig, Old, Wolfe, and Buchwald reported that catalysts derived from aminophosphine **4** are capable of effecting C-N bond formation with aryl chlorides cyclic amines [42]. This catalyst system effects the amination of aryl chlorides bearing electron-withdrawing, electronically neutral, and electron-donating groups. For the first time, the coupling of an activated aryl chloride, 4-cyanochlorobenzene, with morpholine could be performed at room temperature, Eq. (43). The reaction of a deactivated aryl chloride such as 4-chloroanisole and morpholine also proceeded in excellent yield in the presence of the **4**/Pd catalyst, although heating the reaction to 80 °C was necessary.



(43)

R	mol% $Pd_2(dba)_3$	mol% **4**	Reaction Conds.	Yield, %
-CN	2.5	7.5	DME, RT	96
-OMe	0.5	1.5	toluene, 80 °C	91

Dicyclohexyl-*o*-biphenylphosphine (**14**) is an excellent supporting ligand for the Pd-catalyzed C-N bond forming reaction, particularly when the coupling involves a functionalized aryl chloride, Eq. (44) [42a, 44, 74].



(44)

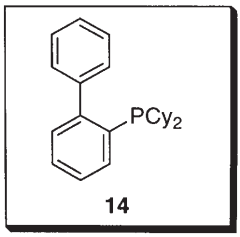
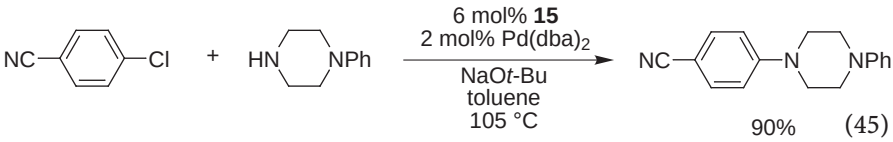


Fig. 13

Guram and co-workers at Symyx prepared phosphinoether ligand **15** that allows the efficient coupling of aryl chlorides with cyclic amines [47, 75]. For example, *N*-phenylpiperazine is reacted with 4-chlorobenzonitrile in the presence of **15**/Pd(dba)$_2$ in high yield, Eq. (45).



(45)

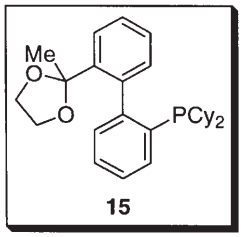
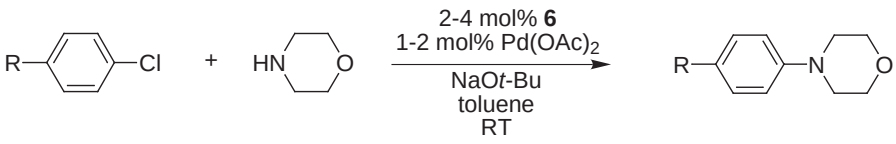


Fig. 14

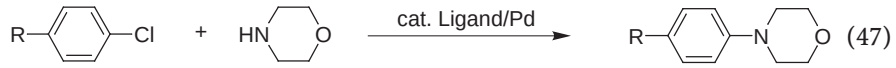
As was observed in the reactions of aryl bromides, the catalyst derived from commercially available ligand **6** displayed very high reactivity; as a result, it was now possible to couple a large variety of aryl chlorides with cyclic amines at room temperature [42a, 48]. Morpholine was reacted with both electron-rich and electron-deficient aryl chlorides in excellent yield, Eq. (46). Mild bases such as Cs_2CO_3 and K_3PO_4 can be used with this system, although elevated temperatures are necessary. This new catalyst system enjoys greater substrate scope in the arylation of acyclic secondary amines, and primary amines with aryl chlorides.



R	Yield, %
OMe	90
CN	86

(46)

Nolan's heterocyclic carbene-based system (7 + KO*t*-Bu/$Pd_2(dba)_3$) was effective in the coupling of secondary amines with aryl chlorides at elevated temperatures, Eq. (47) [52]. This protocol could be used for the room-temperature amination of aryl bromides as well. Hartwig reported that the saturated heterocyclic carbene ligand prepared by deprotonation of **16** forms a catalyst that is considerably more reactive than the system reported by Nolan. The resulting complex formed was capable of coupling aryl chlorides with cyclic amines at room temperature [76].



(47)

R	L (mol%)	Pd Source (mol%)	Reaction Conds.	Yield, %
Me	**7** (4)	$Pd_2(dba)_3$ (1)	KO*t*-Bu, dioxane, 100 °C	82
OMe	**7** (4)	$Pd_2(dba)_3$ (1)	KO*t*-Bu, dioxane, 100 °C	80
Me	**16** (1)	$Pd(dba)_2$ (1)	NaO*t*-Bu, DME, RT	99
OMe	**16** (1)	$Pd(dba)_2$ (1)	NaO*t*-Bu, DME, RT	96

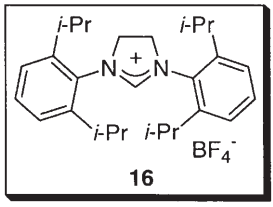
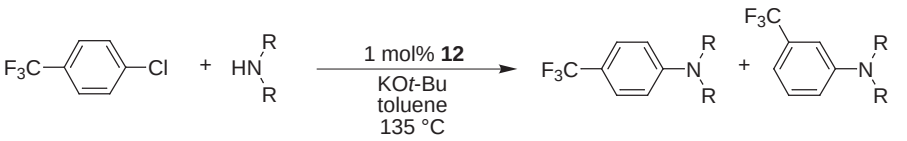


Fig. 15

2.2.6
Reaction of Acyclic Secondary Amines with Aryl Chlorides

As was the case with aryl bromides, the reaction of acyclic secondary amines with aryl chlorides is more challenging than their cyclic counterparts due to competitive formation of the reduced arene by-products.

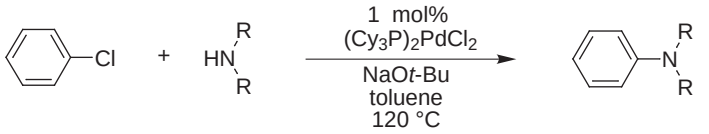
Beller's palladacycle (**12**) catalyzes the arylation of *N*-methylaniline and di-*n*-butylamine with an activated aryl chloride, Eq. (48) [70]. As was observed in the reactions of cyclic amines, significant amounts of the regioisomeric product was formed, indicative of reaction through a benzyne intermediate.



Amine	Yield, %	Ratio
H-N(Me)Ph	60	10:1
H-NBu$_2$	60	20:1

(48)

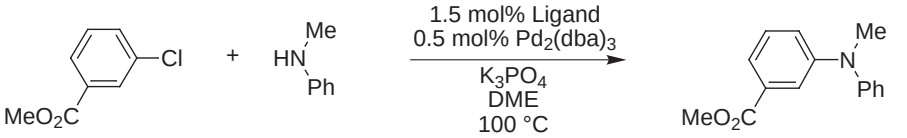
Reddy and Tanaka's procedure provides moderate to good yields in the arylation of cyclic amines as well as *N*-methylaniline, low yields were observed when dialkylamines were used, Eq. (49) [71].



Amine	Yield, %
H-N(Me)Ph	60
H-NHex$_2$	20

(49)

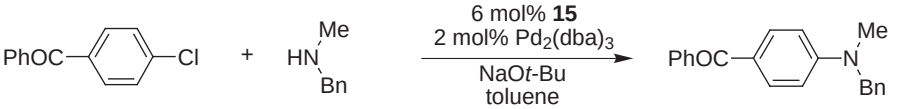
The **4**/Pd-based catalyst is effective in the arylation of acyclic secondary amines with functionalized aryl chlorides at elevated temperatures, Eq. (50) [42]. Similarly, ligand **14** is useful in these transformations. Strong bases such as NaO*t*-Bu and milder bases such as K_3PO_4 have found utility with both **4**- and **14**-based catalysts.



Ligand	Yield, %
4	83
14	88

(50)

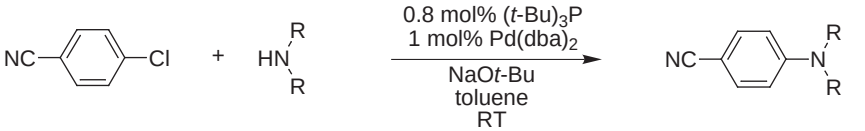
Guram's phosphinoether **15** mediates the coupling of acyclic secondary amines and aryl chlorides, Eq. (51) [47, 75].



96% (51)

Yamamoto, Nishiyama, and Koie first reported that the (*t*-Bu)$_3$P/Pd-catalyst is effective in coupling chlorobenzene and diphenylamine at elevated tempera-

tures (130 °C) [65]. Hartwig subsequently demonstrated, however, that this catalyst system enjoyed considerable substrate scope and in the case of activated aryl chlorides, the reaction could be performed at room temperature, Eq. (52) [50].

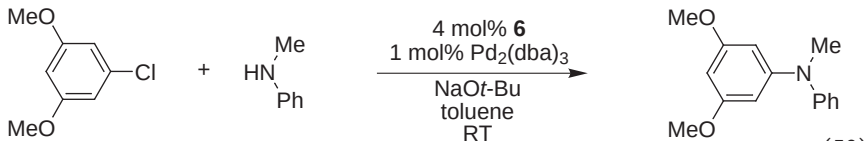


Amine	Yield, %
H-N(Me)Ph	90
H-NPh$_2$	89

(52)

Representative for the Palladium-Catalyzed Arylation of Amines with Aryl Chlorides using (t-Bu)$_3$P/Pd: (Reproduced with permission from [50]. © 1999 American Chemical Society) In a dry box, aryl halide, amine, Pd(dba)$_2$, (t-Bu)$_3$P, and sodium *tert*-butoxide were weighed directly into a screw cap vial. A stir bar was added followed by 1.0 – 2.0 ml of toluene to give a purple mixture. The vial was removed from the dry box, and the mixture was stirred at room temperature. After 5.5 h, the reaction mixture was adsorbed onto silica gel and chromatographed with 50 % toluene/hexanes to give 242 mg (90 %) of *N*-(4-cyanophenyl)diphenylamine as a white solid.

The catalyst derived from phosphine **6** and palladium is among the most active catalysts for the arylation of acyclic secondary amines with aryl chlorides [42a, 48]. The **6**/Pd-system is able to effect C-N bond formation at room temperature in many cases, Eq. (53).

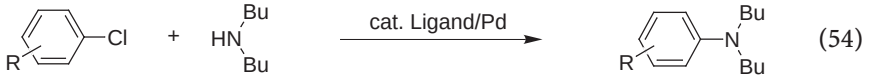


97% (53)

General Procedure for the Room-Temperature Palladium-Catalyzed Arylation of Amines with Aryl Chlorides using 6/Pd: (Excerpted with permission from [50]. © 2000 American Chemical Society) An oven-dried resealable Schlenk flask was evacuated and backfilled with argon. The flask was evacuated and backfilled with argon and then capped with a rubber septum. The flask was charged with Pd(OAc)$_2$ (2.2 mg, 0.01 mmol, 1 mol%), **6** (6.0 mg, 0.02 mmol, 2 mol%), and sodium *tert*-butoxide (135 mg, 1.4 mmol). Toluene (0.5 ml), the aryl chloride (1.0 mmol), the amine (1.2 mmol), and additional toluene (0.5 ml) were added through the septum (aryl halides or amines that were solids at room temperature were added as solids following the addition of NaO*t*-Bu). The septum was replaced with a Teflon screwcap, the flask was sealed, and the mixture was stirred at room temperature until the starting aryl chloride had been completely consumed as judged by GC analysis. During the course of the reaction, the mixture was observed to form a gel (at around 50 % conversion) and then

liquify again as the reaction proceeded to completion. Following complete consumption of the aryl chloride starting material, the mixture was diluted with ether (20 ml), filtered through Celite, and concentrated in vacuo. The crude material was purified by flash chromatography on silica gel.

Nolan reported that the use of the carbene ligand derived from the deprotonation of **7** results in the formation of an efficient catalyst for the reaction of aryl chlorides and acyclic secondary amines [52]. For example, di-*n*-butylamine efficiently reacts with 4-chloroanisole at 100 °C in the presence of this catalyst, Eq. (54). Hartwig disclosed that the saturated carbene ligand derived from the deprotonation of **16** yields a considerably more reactive catalyst which is capable of coupling acyclic secondary amines and aryl chlorides at room temperature [76].



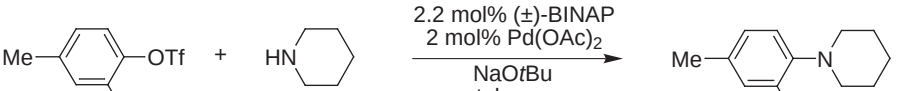
(54)

R	L (mol%)	Pd Source (mol%)	Reaction Conds.	Yield, %
p-OMe	**7** (4)	$Pd_2(dba)_3$ (1)	KO*t*-Bu, dioxane, 100 °C	98
o-Me	**16** (1)	$Pd(dba)_2$ (1)	NaO*t*-Bu, DME, RT	97
p-CN	**16** (1)	$Pd(dba)_2$ (1)	NaO*t*-Bu, DME, RT	97

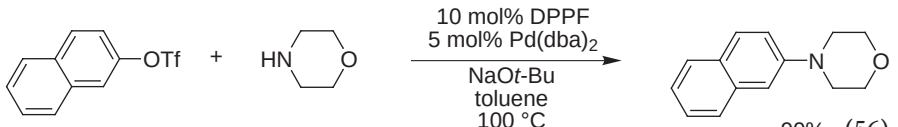
2.2.7
Reaction of Cyclic Amines with Aryl Sulfonates

The use of aryl triflates or other sulfonates in the amine arylation reaction is highly desirable from a synthetic standpoint since a large variety of phenols are easily accessed and derivatized. Aryl and vinyl triflates have enjoyed great utility in other Pd-catalyzed transformations such as the Stille [77] and Suzuki [78] couplings, and the Heck [79] reaction.

In 1997, the Buchwald and Hartwig groups reported the efficient couplings of aryl triflates with cyclic amines [80, 81]. In general, both groups obtained moderate to good yields of the desired products when electronically neutral or electron-rich aryl triflates were used (Eqs. 55, 56). Yields were lower in the reactions of electron-deficient aryl triflates due to competitive triflate cleavage under the reaction conditions. Hartwig first showed that slow addition of the aryl triflate could minimize this unwanted side reaction.



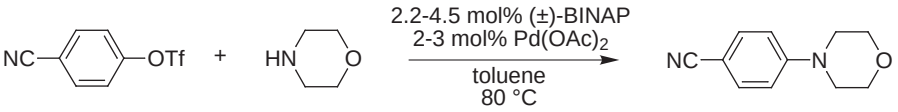
76% (55)



90% (56)

Later that year, the Åhman and Buchwald reported an improved procedure for the reaction of triflates and cyclic secondary amines [82]. The use of Cs_2CO_3 as base allowed numerous electron-deficient aryl triflates to be coupled in high yield. The reaction between the 4-cyano-substituted aryl triflate and morpholine in the presence of (±)-BINAP/Pd provided the desired arylamine in 28% yield, Eq. (57). However, when the triflate was added over the course of 30 minutes, the desired product was isolated in 60% yield. The use of Cs_2CO_3 as base improved the yield of arylamine to 84%. The use of a mild base also allowed for the use of functionalized aryl triflates in the C-N bond forming reaction.

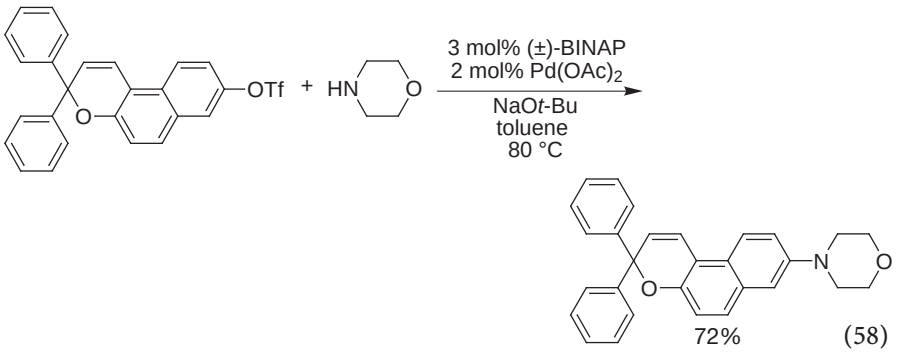
General Procedure for the Palladium-Catalyzed Arylation of Amines with Aryl Triflates using a BINAP/Pd-Catalyst and Cs_2CO_3 as Base: (Excerpted with permission from [82]. © 1997 Pergamon Press). An oven-dried Schlenk tube was charged with cesium carbonate which had been finely ground with a mortar and pestle. The tube was then charged with $Pd_2(dba)_3$ (4.6 – 9.2 mg, 0.005 – 0.01 mmol) and BINAP (9.3 – 18.7 mg, 0.015 – 0.03 mmol). The Schlenk flask was fitted with a septum and attached to a Schlenk line. After the air atmosphere was replaced with argon, toluene (2 ml), aryl bromide (1.0 mmol), and amine (1.2 mmol) were added by syringe. After the septum was replaced with a teflon valve, the reaction was sealed and heated to 100 °C with stirring until starting material was consumed as judged by GC analysis. The reaction mixture was cooled to room temperature, diluted with ether (20 ml), filtered, and concentrated. The crude reaction mixture was then purified further by flash chromatography on silica gel.



Rxn. Conditions	Yield, %
NaO*t*-Bu	28
NaO*t*-Bu, slow addition	60
Cs_2CO_3	84

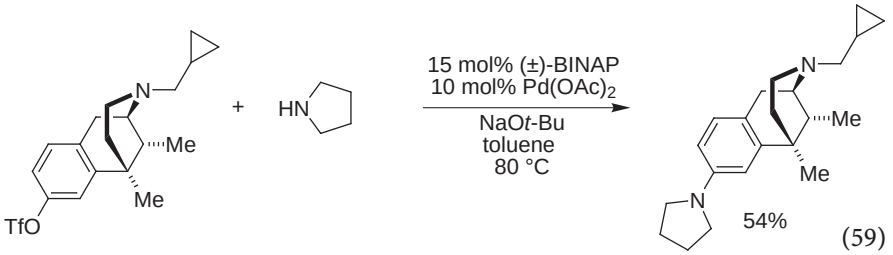
(57)

Other groups have utilized the (±)-BINAP/Pd-catalyst to prepare several interesting products by the amination of aryl triflate precursors. For example, the 3*H*-naphth[2,1-*b*]pyran triflate below was coupled in 72% yield, providing a photochromic material, Eq. (58) [83]



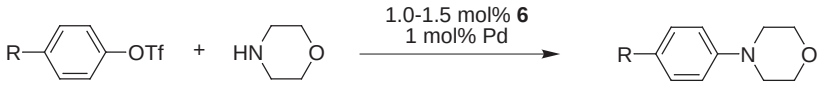
(58)

Wentland and co-workers reported that amine-substituted analogues of the analgesic cyclozine could be easily prepared by the Pd-catalyzed C-N bond forming reaction [84]. For example, the pyrrolide-substituted compound was prepared by using the (±)-BINAP/Pd-catalyst in 54% yield, Eq. (59). Several cyclic, acyclic secondary, and primary amines were coupled with this triflate utilizing both (±)-BINAP and DPPF as supporting ligands.



(59)

The **6**/Pd-system is the most efficient catalyst for the coupling of cyclic amines and aryl triflates [42a]. In the case of electron-rich or electronically neutral aryl triflates, the reaction can be performed at room temperature with NaO*t*-Bu as base, Eq. (60). In reactions of electron-deficient aryl triflates, use of K_3PO_4 as base and running the reaction at 80 °C results in clean C-N bond formation.

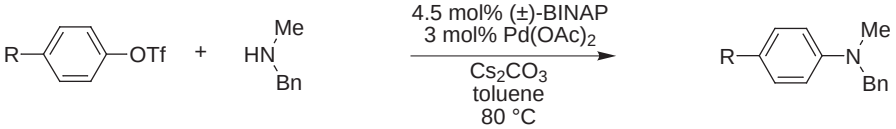


R	Reaction Conds.	Yield, %
t-Bu	$Pd(OAc)_2$, NaO*t*-Bu, Toluene, RT	79
OMe	$Pd(OAc)_2$, NaO*t*-Bu, Toluene, RT	81
NO_2	$Pd_2(dba)_3$, K_3PO_4, DME, 80 °C	76

(60)

2.2.8
Reaction of Secondary Acyclic Amines with Aryl Sulfonates

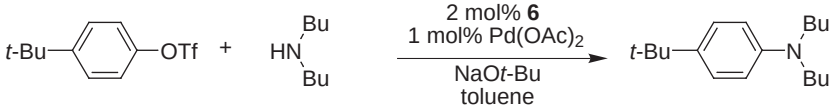
Using the conditions described above for the reaction between cyclic amines and electron-rich or electronically neutral aryl triflates, acyclic secondary amines can also be effectively coupled, Eq. (72) [80, 81]. As was observed with cyclic amines, the use of electron-deficient aryl triflates results in lower yields due to triflate cleavage. The use of a mild base such as Cs_2CO_3 allowed for the coupling of electron-deficient aryl triflates and acyclic secondary amines [82]. This protocol, which employed a (±)-BINAP/$Pd(OAc)_2$ catalyst, furnished the desired coupled products with good to excellent yield, Eq. (61).



R	Yield, %
CN	78
CO_2Me	85

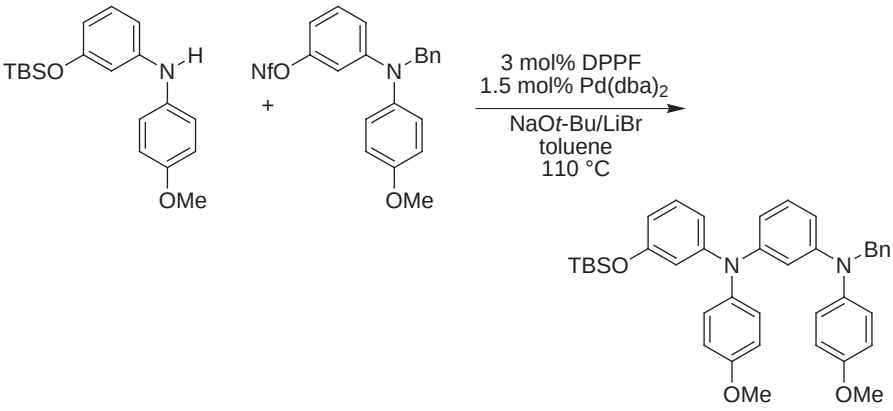
(61)

The **6**/Pd-catalyst system is very effective at the arylating acyclic secondary amines with aryl triflates in moderate to good yield, Eq. (62) [42a].



73% (62)

Hartwig has reported a DPPF/Pd-catalyzed C-N coupling reaction between a diarylamine and an aryl nonaflate, Eq. (63) [64b]. The coupling below proceeded in 95–100% yield (NMR) and was used in a strategy to prepare oligo(*m*-aniline) compounds.

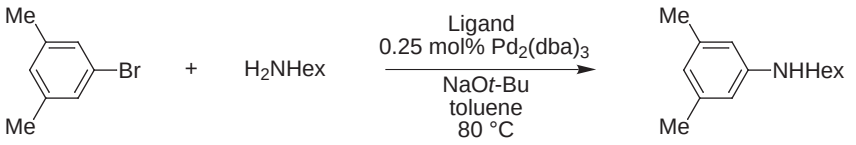


95-100% (NMR) (63)

2.3 N-Arylation of Primary Amines

2.3.1 *Reaction of Primary Aliphatic Amines with Aryl Bromides*

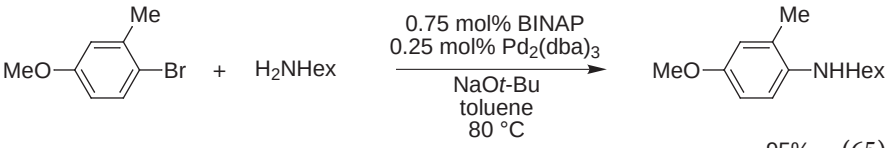
The coupling of aryl bromides with primary aliphatic amines often suffered from the formation of reduced arene by-products similar to the reactions with secondary amines. For example, the use of (±)-BINAP as a ligand greatly improved the yield in the coupling of 5-bromo-*meta*-xylene and *n*-hexylamine, Eq. (64) [27].



Ligand	Yield, %
(*o*-tol)$_3$P (1 mol%)	35
BINAP (0.75 mol%)	88

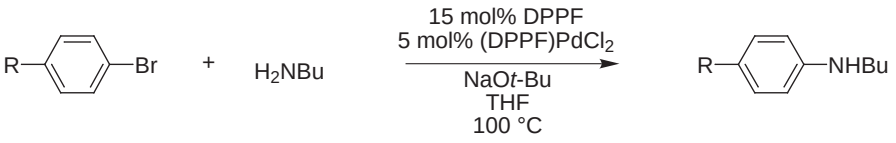
(64)

In addition, electron-rich aryl bromides were better tolerated with the BINAP/Pd-system, Eq. (65). Although NaO*t*-Bu is typically used as base, Prashad and co-workers recently reported that NaOMe and NaO*i*-Pr may also be used as well [30].



95% (65)

Simultaneously with the report by Buchwald, Hartwig demonstrated that the DPPF/Pd-catalyst efficiently couples primary amines and electron-deficient and electronically neutral aryl bromides [29]. For example, the couplings of *n*-butylamine with aryl bromides possessing nitrile and ketone functional groups proceed with excellent yields, Eq. (66).

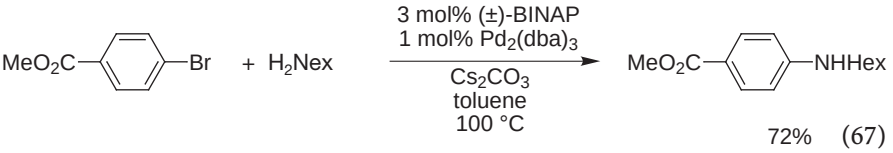


R	Yield, %
COPh	96
CN	93

(66)

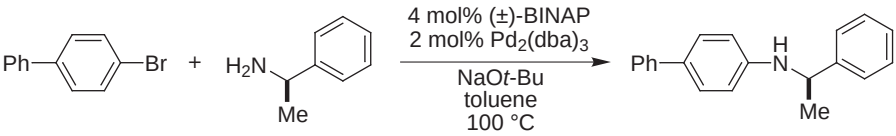
Representative Procedure for the Palladium-Catalyzed Arylation of Amines with Aryl Bromides using DPPF/Pd: (Excerpted with permission from [29]. © 1996 American Chemical Society) In an inert atmosphere dry box, $DPPFPdCl_2$ and 3.0 equiv. of DPPF/Pd were added to a solution of 20 equiv of bromobenzophenone and 25 equiv of sodium *tert*-butoxide in 8 ml of anhydrous THF. The reaction tube was sealed with a cap containing a PTFE septum and removed from the dry box. Butylamine (25 equiv) was added to the reaction mixture by syringe, and the mixture was heated to 100 °C for 3 h. The reaction was cooled to room temperature, the volatile materials were removed by rotary evaporation, and the product was isolated by either sublimation or silica-gel chromatography (20:1 hexane/EtOAc or 10:1 hexane/Et_2O followed by 4:1 hexane:Et_2O).

Weak bases such as Cs_2CO_3 and K_3PO_4 have been utilized in the BINAP/Pd-catalyzed reaction between aryl bromides and primary amines [27a, 40]. For example, the coupling of 4-bromomethylbenzoate with *n*-hexylamine can be performed in 72% yield without cleavage of the ester, Eq. (67).



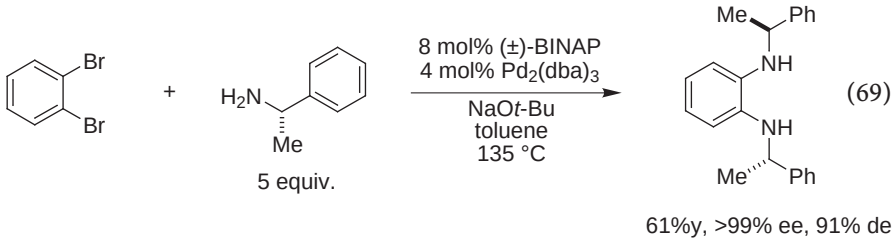
72% (67)

The efficacy of BINAP to shut down β-hydride elimination was demonstrated in the arylation of enantiomerically enriched primary amines as well [53, 54]. For example, the arylation of α–methylbenzylamine with 4-bromobiphenyl proceeded with preservation of optical activity when (±)-BINAP was used as the ligand, Eq. (68). In contrast, the use of $(o\text{-tol})_3P$ as ligand resulted in a significant erosion of enantiomeric excess (70 % ee).



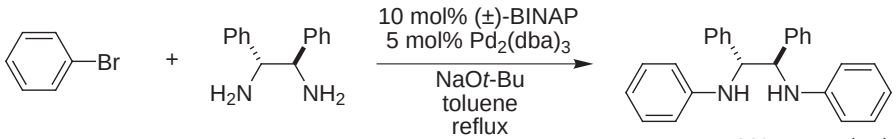
(68)

The efficacy of the BINAP/Pd-system to mediate C-N bond formation without stereochemical erosion has been taken advantage of by several groups. Diver and co-workers described the double amination or *ortho*-dibromobenzene with (*S*)-α-methylbenzylamine to yield the desired C_2-symmetric diamine in 61 % yield, > 99 % ee, and 91 % de, Eq. (69) [85]. Schmalz reported a similar coupling reaction to prepare new ligands for asymmetric catalysis [45].



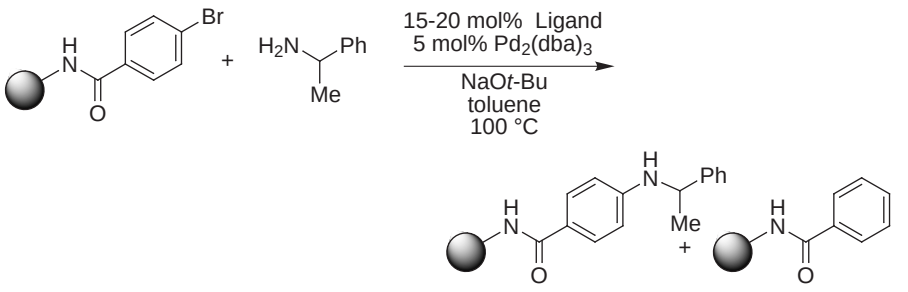
(69)

Mangeny doubly arylated (*R*,*R*)-1,2-diphenylethylenediamine with several aryl bromides to yield the desired chiral ligands in good to excellent yields [86]. For example, the reaction of bromobenzene mediated by the (±)-BINAP/Pd-catalyst furnished the desired compound in 89 % yield, Eq. (70).



(70)

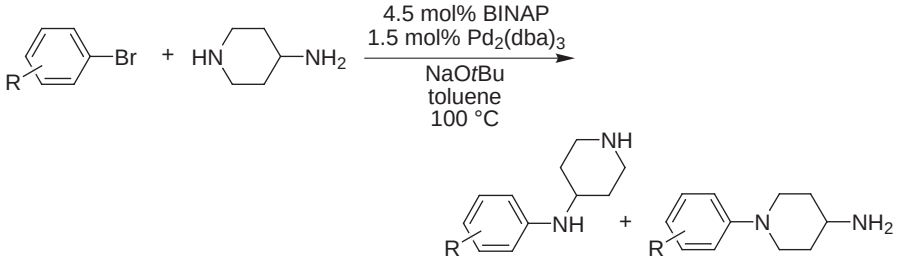
The coupling of primary amines with resin-bound aryl bromides was effected cleanly with both the (±)-BINAP/Pd- and DPPF/Pd-catalyst systems. Groups at Boehringer-Ingelheim and Merck have reported that BINAP/Pd- and DPPF/Pd-based protocols allow for efficient C-N bond formation, while use of $(o\text{-tol})_3P$/Pd-catalysis results in significant aryl bromide reduction, Eq. (71) [31, 32].



Ligand	Ratio
(*o*-tol)$_3$P	65:35
BINAP	100:0
DPPF	100:0

(71)

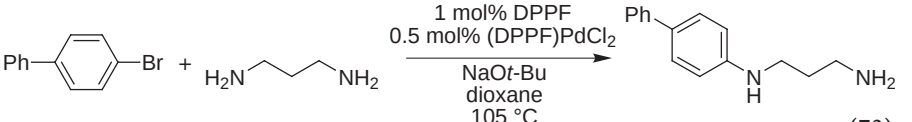
During their studies on the synthesis of norastemizol, Senanayake, Tanoury and co-workers reported that high levels of regioselectivity were observed in the amine arylation such that primary amines reacted in preference to secondary ones [87]. For example, the coupling of 4-aminopiperidine in the presence of the BINAP/Pd-catalyst resulted in reaction at the primary amine functional group, Eq. (72) [34].



R	Yield, %	Ratio
o-CN	87	59:1
p-CN	84	27:1

(72)

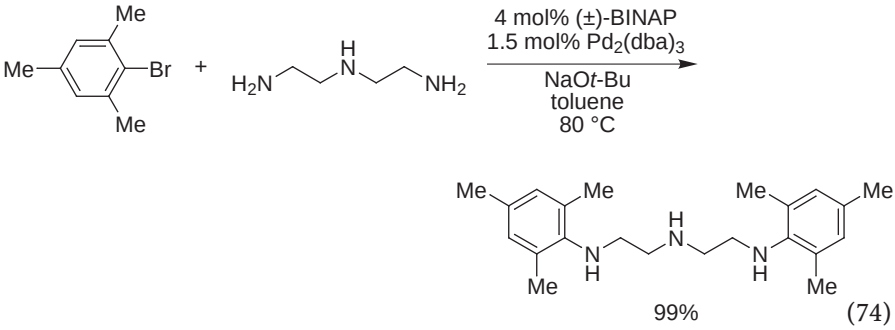
Beletskaya was able to prepare monoarylated propylenediamine derivatives by using an excess of the starting diamine and a DPPF/Pd-catalyst; the reaction below proceeded in 75% isolated yield, Eq. (73) [88].



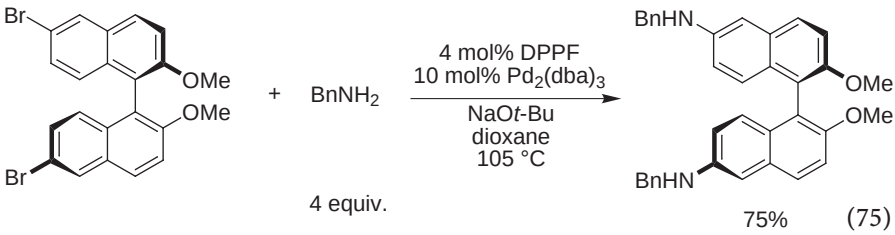
75% (73)

Similarly, Schrock utilized the (±)-BINAP/Pd-system to doubly arylate diethylene triamine to afford the ligand shown below in quantitative yield,

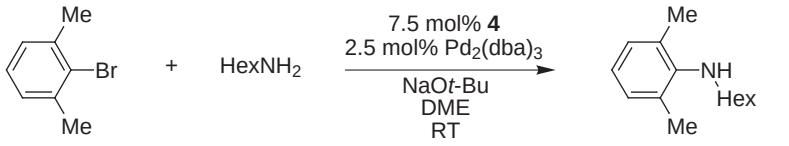
Eq. (74) [89]. Notably, the arylation is observed exclusively at the primary amino group. The MIT group prepared several polyamine-based ligands in this fashion.



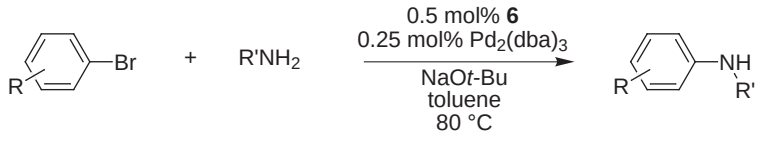
Lim and Lee coupled the binaphthol derivative below with benzylamine to yield the desired product in 75% yield, Eq. (75) [90]. Subsequent removal of the benzyl protecting groups was effected by hydrogenation, thus demonstrating that benzylamine may be used as an ammonia equivalent.



Aminophosphine **4** is an excellent supporting ligand in the room-temperature reaction of aryl bromides and primary amines [42]. The **4**/Pd-catalyst is capable of coupling a hindered aryl bromide such as 2-bromo-*meta*-xylene with *n*-butylamine in excellent yield, Eq. (76).



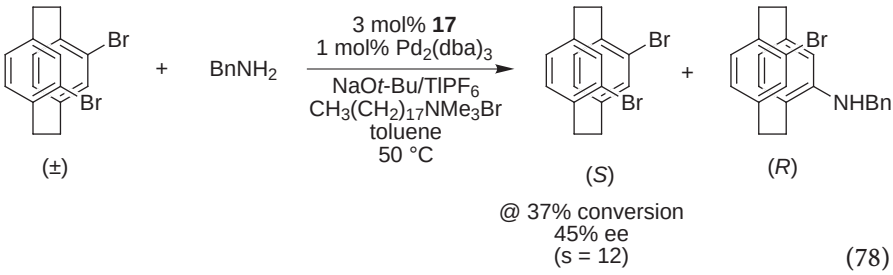
The catalyst derived from hindered phosphine **6** also is effective in the arylation of primary aliphatic amines with aryl bromides, Eq. (77). Although this system is capable of mediating such a reaction at room temperature, with more hindered substrates, heating is required [42a, 48].



R	R'	Yield, %
3,5-Me_2	Bn	86
2,6-Me_2	$CH_2CH{=}CH_2$	92

(77)

A Merck group reported an interesting kinetic resolution of a racemic dibromocyclophane via Pd-catalyzed amination [91]. While BINAP was a poor ligand for the reaction in terms of selectivity, the C_2-symmetric cyclophane-derived PHANEPHOS (**17**) proved to be optimal. Reaction of the cyclophane derivative with benzylamine afforded the unreacted dibromide in 45% ee after 37% conversion, corresponding to a selectivity factor of 12, Eq. (78).



(78)

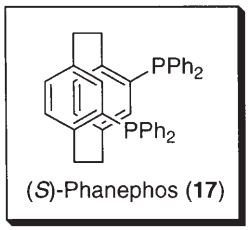
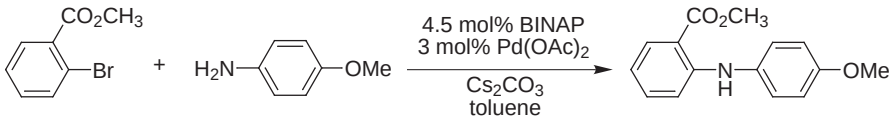


Fig. 16

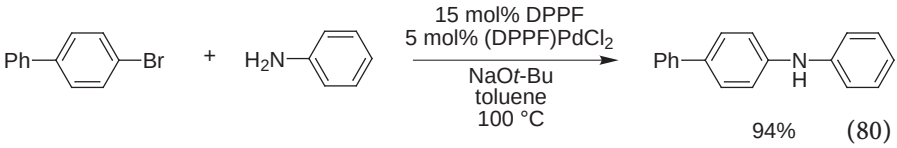
2.3.2
Reaction of Primary Aromatic Amines with Aryl Bromides

Buchwald's original BINAP/Pd-catalyst effectively couples aryl bromides with aniline derivatives, and either alkoxide bases [30] such as NaO*t*-Bu or mild bases such as Cs_2CO_3 may be used, Eq. (79) [27, 37]. Similarly, Hayashi et al. have reported the use of DPBP (**11**) in the coupling of an aryl bromide and aniline.



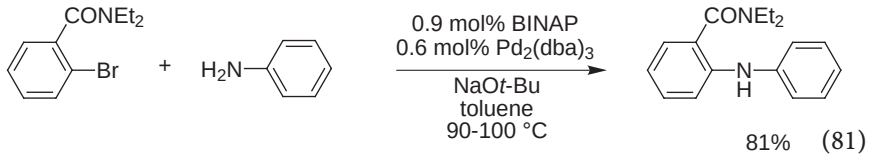
(79)

Hartwig's DPPF/Pd-based system is able to effect similar C-N bond formation reactions between aryl bromides and aniline derivatives, Eq. (80) [29].

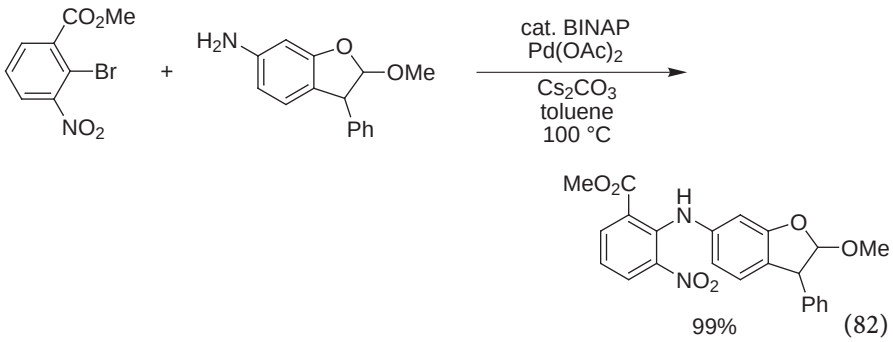


(80)

The BINAP/Pd- and DPPF/Pd-catalyst systems have been used by numerous groups to react aryl bromides with arylamines. Ward and Farina as well as Willoughby and Chapman performed the arylation reaction with arylamines and resin-bound aryl bromides [31, 32]. Snieckus reported the use of the Pd-catalyzed C-N bond forming reaction to prepare several acridone derivatives, Eq. (81) [92]. Kamikawa et al. prepared phenazine derivatives via an initial C-N bond coupling and subsequent cyclization, Eq. (82) [93].

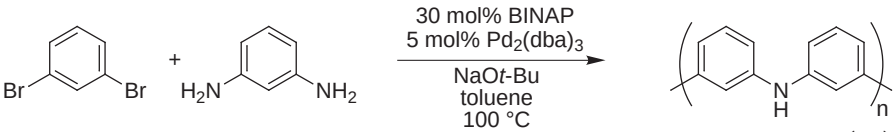


(81)

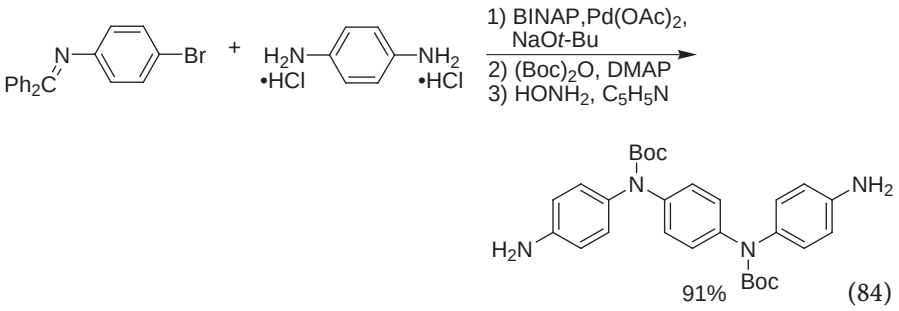


(82)

In 1997, Kanbara reported the preparation of poly(imino-1,3-phenylene) using Pd and several different supporting ligands. BINAP/Pd-catalysts provided the desired polymer in 86% yield, Eq. (83) [94]. Similarly, Singer, Sadighi, and Buchwald described the preparation well defined end-functionalized oligoanilines using the BINAP based-system [95]. The general strategy is outlined in Eq. (84); the double coupling reaction proceeded in 91% isolated yield. More reactive catalyst systems were later developed and used to prepare high molecular weight polyaniline.

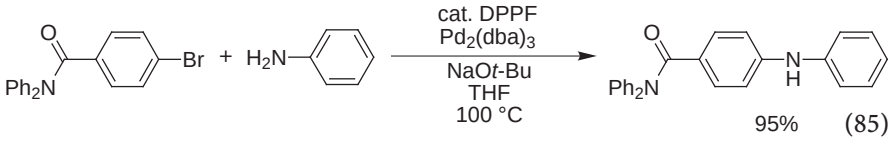


(83)



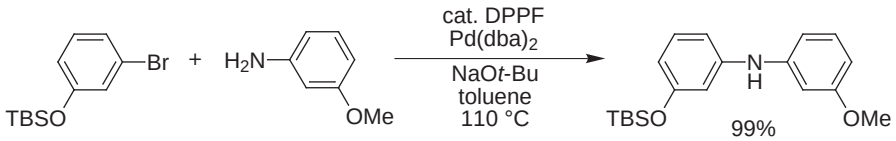
(84)

Frost and Medonça utilized an iterative amine arylation strategy to prepare benzamide-based peptidomimetics [96]. The researcher reported the DPPF/Pd-catalyzed coupling with several primary amines, including aniline, Eq. (85). Acylation of the resulting diarylamine with 4-bromobenzoylchloride furnished the substrate for the subsequent amination reaction. Schmalz reported a similar coupling to prepare new ligand precursors [45].



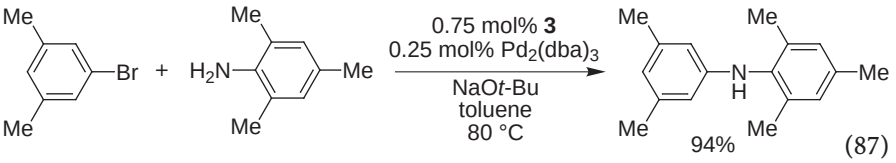
(85)

Louie and Hartwig described an application of the DPPF/Pd-catalyst toward the synthesis of oligo(*m*-anilines). The diarylamine monomer was prepared using this protocol in quantitative yield, Eq. (86) [64b]. Goodson and Hartwig have extended the method to synthesize other monomers for the preparation of poly(*N*-arylanilines) [54c].



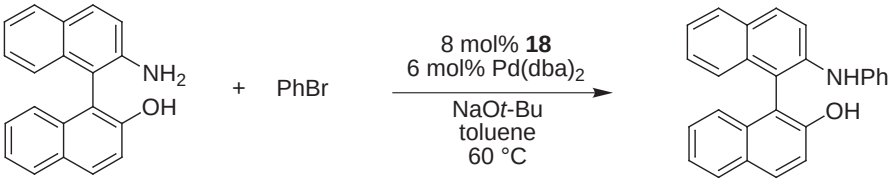
(86)

Phosphinoether PPF-OMe (**3**) is an effective supporting ligand in the palladium-catalyzed coupling of aryl bromides and arylamines [37]. For example, reaction of the hindered aniline below proceeded in 94% yield with as little as 0.5 mol% Pd, Eq. (87).



(87)

Kocovsky and co-workers reported the arylation of aminobinol mediated by a catalyst prepared from bulky aminophosphine **18** and $Pd(dba)_2$ [97]. Complete conversion was observed in less than 5 minutes at 60 °C using the **18**/Pd-system, Eq. (88); the BINAP/Pd-catalyst required 2 h for complete consumption of substrate under the same conditions.



100% conversion (88)

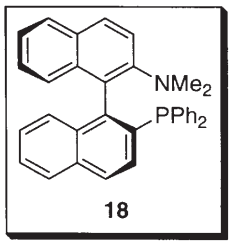
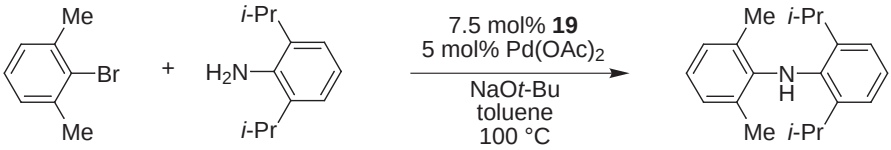


Fig. 17

DPEphos (**19**)/Pd-catalysts are effective in the coupling of arylamines and aryl bromides, particularly with sterically hindered coupling partners [57, 98]. For example, the coupling below proceeded in 90% yield when a **19**/$Pd(OAc)_2$-catalyst was used, Eq. (89).



90% (89)

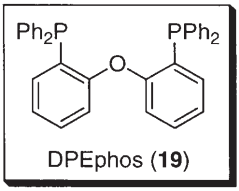
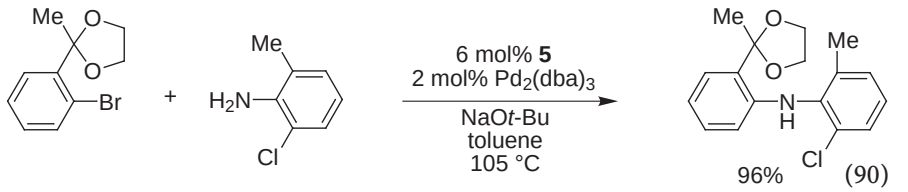


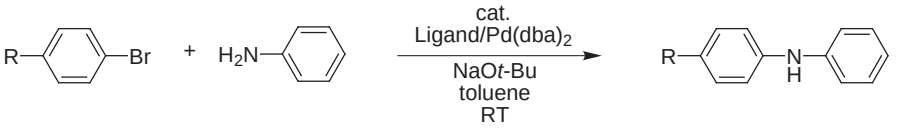
Fig. 18

Guram's phosphine **5** and $Pd_2(dba)_3$ efficiently mediate the arylation of aniline derivatives at elevated temperatures as well, Eq. (90) [47].



(90)

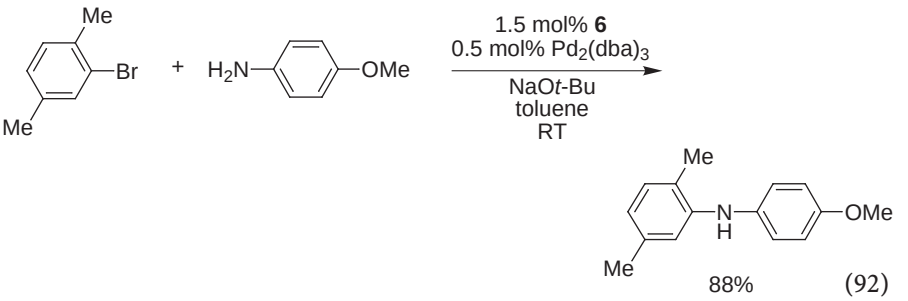
Hartwig reported that ferrocene-based diphosphine **13** catalyzes the arylation of aniline at room temperature, Eq. (91) [72]. Additionally, the $(t\text{-Bu})_3$P/Pd-based system effects the room-temperature condensation of anilines and aryl bromides. However, the $(t\text{-Bu})_3$P/Pd-catalyst is considerably more active [50]. While the reaction with 4-bromotoluene and aniline proceeded in 20 h using 5 mol% **15**/Pd(dba)$_2$, the reaction between bromobenzene and aniline was complete in 1 h using only 1 mol% of the $(t\text{-Bu})_3$P-derived catalyst.



R	Reaction Conditions	Yield, %
Me	5 mol % **15**, 5 mol% Pd(dba)$_2$	94
H	0.8 mol % $(t\text{-Bu})_3$P, 2 mol% Pd(dba)$_2$	87

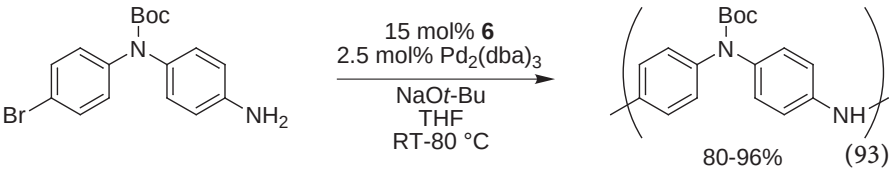
(91)

The **6**/Pd-catalyst is also capable of coupling aryl bromides and arylamines at room temperature and tolerates electron-donating groups and *ortho* substitution on the aryl bromide, Eq. (92) [42a]. Although the transformation can be performed at ambient temperature, the scope of the reaction is much greater at 80–100 °C. In addition, at elevated temperatures, bases such as Cs_2CO_3 and K_3PO_4 may be used.

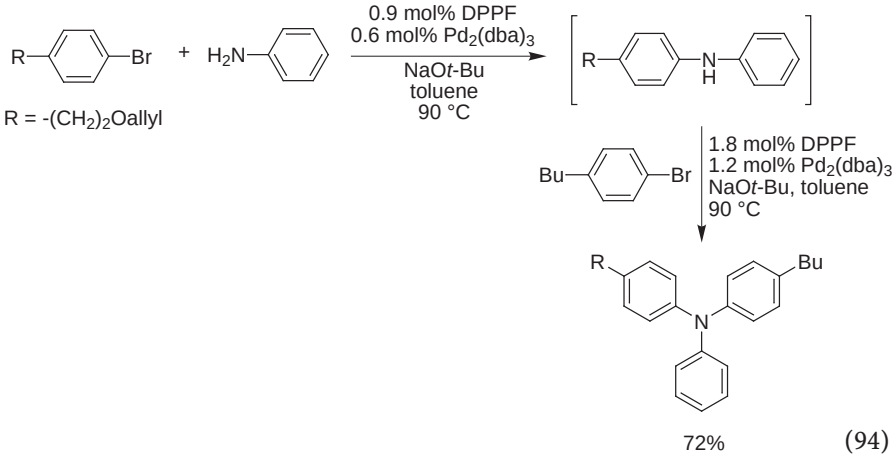


(92)

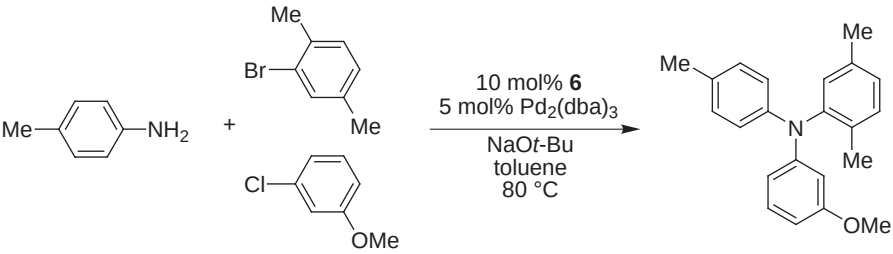
The high reactivity of the **6**/Pd-catalyst was exploited in the preparation of high molecular weight polyaniline, Eq. (93) [99]. After thermolytic deprotection of the Boc protecting groups and air oxidation, emeraldine, the conductive form of polyaniline was obtained.



The arylation of aniline derivatives can be executed such that triarylamine products can be obtained from a one-pot procedure. Marder and co-workers coupled aniline with the first equivalent of aryl bromide using the DPPF/Pd-based catalyst at 90 °C, Eq. (94) [100]. After the reaction was judged complete by TLC, the second aryl bromide was added to the reaction, along with an addition amount of base and catalyst. The resulting mixture was heated to 90 °C. After chromatography, the unsymmetrical triarylamine was obtained in 72 % yield.

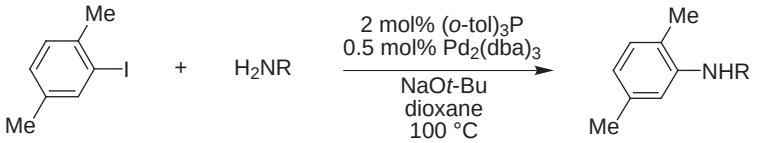


Harris and Buchwald took advantage of the differential reactivity between aryl chlorides and aryl bromides in the Pd-catalyzed C-N bond coupling to design a simple one-pot procedure for the preparation of unsymmetrical triarylamines, Eq. (95) [101]. Reaction of the aniline with an aryl bromide and an aryl chloride in the presence of the **6**/Pd-catalyst resulted in clean production of the desired triarylamine. After complete consumption of the aryl bromide to furnish the corresponding diarylamine, the aryl chloride then reacted to yield the desired unsymmetrical product.



2.3.3
Reaction of Primary Amines with Aryl Iodides

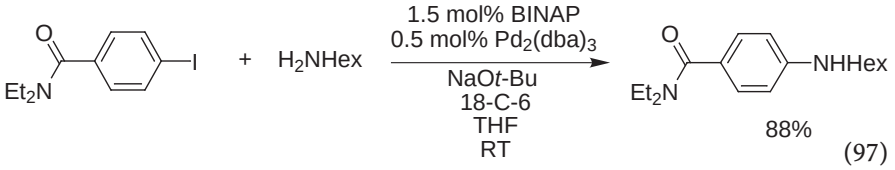
Wolfe and Buchwald first reported the palladium-catalyzed arylation of primary amines with aryl iodides in 1996 [67]. The (*o*-tol)$_3$P/Pd-system effected the reaction in moderate yields. Both aliphatic and arylamines were coupled in moderate yield, Eq. (96).



R	Yield, %
Hex	69
Ph	64

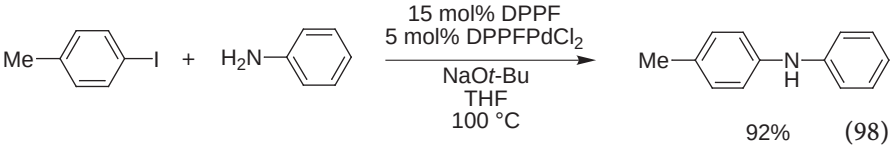
(96)

Subsequently, Wolfe and Buchwald reported a significant improvement in the coupling of aryl iodides and primary amines [68]. The addition of 18-crown-6 to the reaction resulted in a significant improvement in this catalyst system. In addition, BINAP was used as the supporting ligand instead of (*o*-tol)$_3$P. While the coupling of 4-iodo-*N*,*N*-diethylbenzamide and *n*-hexylamine proceeded in only 19% yield using the original procedure, the room-temperature/BINAP/18-crown-6 procedure resulted in an 88% isolated yield of the desired product, Eq. (97).



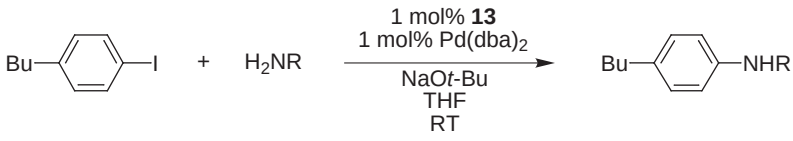
(97)

Hartwig reported the arylation of anilines with aryl iodides using a DPPF/Pd-catalyst, Eq. (98) [29]. This system provided the desired diarylamines in good to excellent yield.



(98)

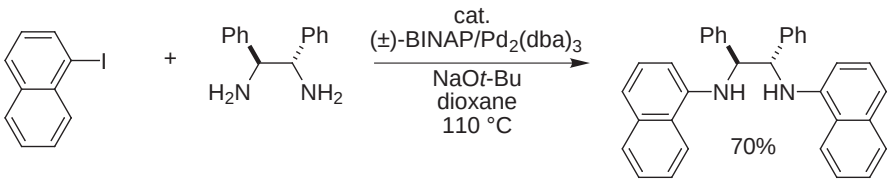
The catalyst derived from **13** and Pd(dba)$_2$ is effective in the arylation of primary amines with aryl iodides as well [72]. The **13**/Pd-system is sufficiently reactive to accomplish this transformation at room temperature, Eq. (99). While aliphatic amines are coupled in moderate yield, the arylation of aniline derivatives proceeds quite efficiently.



R	Yield, %
Bu	47
Ph	95

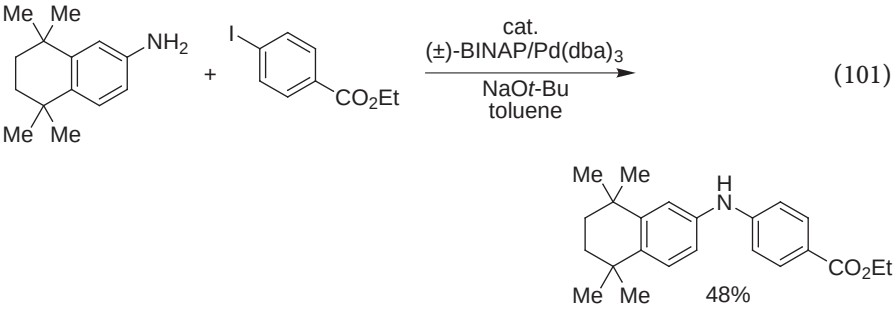
(99)

Denmark utilized the BINAP/Pd-catalyst to doubly arylate 1,2-diphenylethylenediamine with 2-iodonaphthalene, Eq. (100) [102]. The reaction below proceeded in 70% yield, and no epimerization due to β-hydride elimination/reinsertion was observed. The resulting diamine was used to prepare a chiral HMPA derivative.



(100)

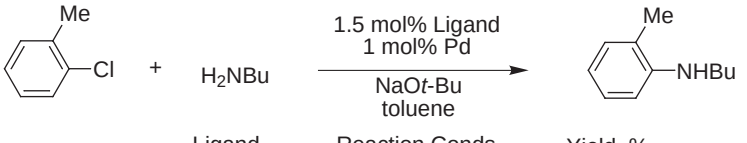
Kagechika et al. reported the preparation of a retinoic nuclear receptor ligand utilizing the BINAP/Pd-catalyzed C-N bond forming reaction [103]. The aniline derivative below was coupled with 4-iodoethylbenzoate in 48% yield, Eq. (101).



(101)

2.3.4
Reaction of Primary Aliphatic Amines with Aryl Chlorides

Hartwig and co-workers reported that several ferrocene-based diphosphines are useful in the arylation of primary amines with aryl chlorides [72]. Known ligands **20** [104] and **21** [105] are particularly effective in the coupling of chloroarenes and primary aliphatic amines, Eq. (102).



Ligand	Reaction Conds.	Yield, %
13	$Pd(dba)_2$, 110 °C	57
20	$Pd(OAc)_2$, 85 °C	89
21	$Pd(OAc)_2$, 85 °C	94

(102)

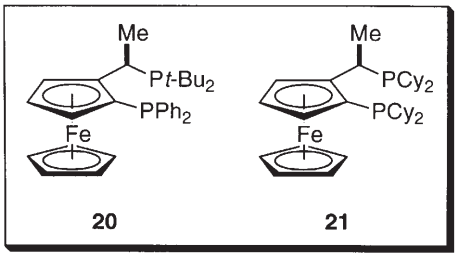
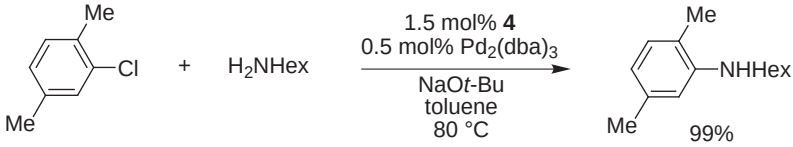


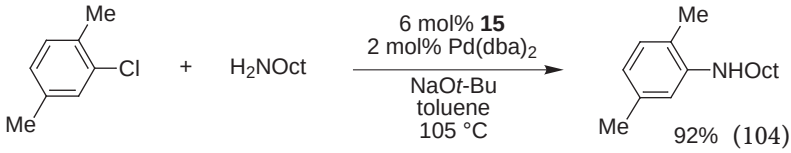
Fig. 19

Concurrently with this report from Hartwig, Buchwald and co-workers reported that the system based on commercially available ligand **4** is an excellent catalyst for the coupling of aryl chlorides and primary aliphatic amines, Eq. (103) [42].



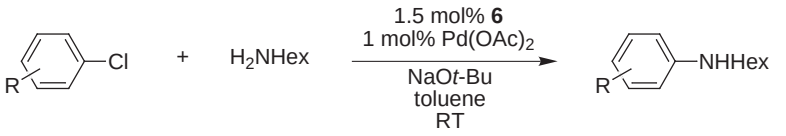
(103)

Phosphine **15**, developed by the Symyx group, can also mediate the C-N bond formation between an aryl chloride and a primary amine, Eq. (104) [47, 75].



(104)

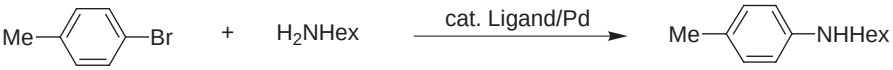
The catalyst formed from **6** and palladium acetate mediates the reaction between a large number primary amines and aryl chlorides as room temperature, Eq. (105) [42a, 48]. This catalyst enjoys an even wider substrate scope, however, when the transformation is performed at elevated temperatures. Additionally, elevated temperatures allow for the use of mild bases in the C-N bond forming reaction.



R	Yield, %
2,5-Me_2	98
o-OMe	99

(105)

Heterocyclic carbene ligands have also proven effective in the coupling of aryl chlorides and primary amines. While Nolan reported that the ligand based on **7** effects the desired reaction at elevated temperatures [52], Hartwig reported that the saturated ligand catalyzes the reaction at room temperature, Eq. (106) [76].

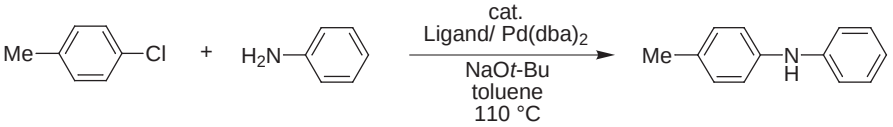


L (mol%)	Pd Source (mol%)	Reaction Conds.	Yield, %
7 (4)	$Pd_2(dba)_3$ (1)	KO*t*-Bu, dioxane, 100 °C	86
16 (2)	$Pd(dba)_2$ (2)	NaO*t*-Bu, DME, RT	40

(106)

2.3.5
Reaction of Primary Arylamines with Aryl Chlorides

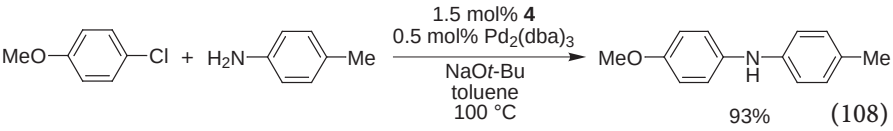
Hartwig reported that the ferrocene-derived phosphines **13**, **20**, and **21** are all effective as supporting ligands in the Pd-catalyzed reaction of aniline derivatives and aryl chlorides, Eq. (107) [72]. These bulky, electron-rich ligands allow for the desired C-N formation to be performed with as little as 1 mol% Pd.



Ligand (mol%)	mol% Pd	Yield, %
13 (4.5)	3	93
20 (1.5)	1	99
21 (3.0)	2	96

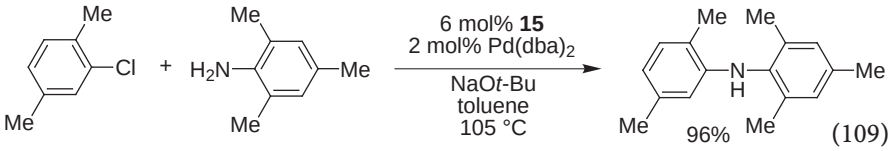
(107)

The catalyst derived from commercially available aminophosphine **4** is also mediates the desired reaction between chloroarenes and aniline derivatives, Eq. (108). Although the **4**/Pd-system is effective for many applications, the **14**/Pd-catalyst enjoys a similar substrate scope in the cross coupling reaction [42].



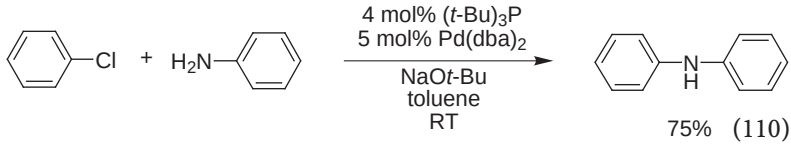
93% (108)

Guram's phosphine **15** proved to be an excellent supporting ligand for Pd in the coupling of arylamines and aryl chlorides [47, 75]. Reaction of the hindered aniline below with a **15**/Pd-catalyst provided the desired product in excellent yield, Eq. (109).



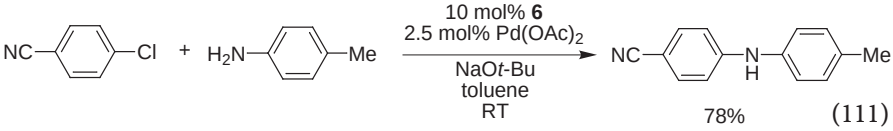
(109)

Hartwig reported that tri-*tert*-butylphosphine/Pd-catalysts mediate the coupling of aniline derivatives and aryl chlorides at room temperature, Eq. (110) [50]. Electron-deficient, electronically neutral, and electron-rich aryl chlorides were tolerated in the coupling reaction.



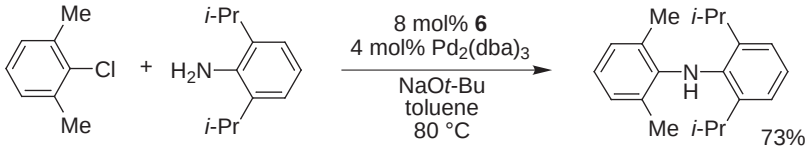
(110)

Bulky phosphine **6** also effects the desired cross coupling at room temperature for a wide variety of aryl bromides and arylamines, and at elevated temperatures, the substrate scope is greatly enhanced [42a,48].



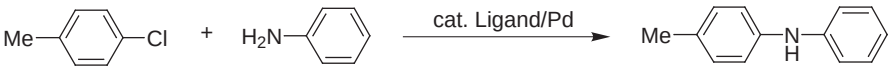
(111)

The high reactivity of the of the **6**/Pd-system is exemplified by the transformation depicted in Eq. 122. Despite the extreme steric demand of these two substrates, the desired product was obtained in 73 % yield [42a].



(112)

As was observed with primary aliphatic amines, the carbene-derived catalysts are able to effect the coupling of aniline derivatives with chloroarenes. The saturated carbene-based system reported by Hartwig provided the desired C-N bond formation product at room temperature, while the system described by Nolan required elevated temperatures [52, 76].

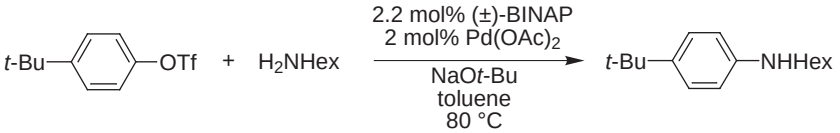


L (mol%)	Pd Source (mol%)	Reaction Conds.	Yield, %
7 (4)	$Pd_2(dba)_3$ (1)	KO*t*-Bu, dioxane, 100 °C	96
16 (2)	$Pd(dba)_2$ (2)	NaO*t*-Bu, DME, RT	82

(113)

2.3.6
Reaction of Primary Aliphatic Amines with Aryl Sulfonates

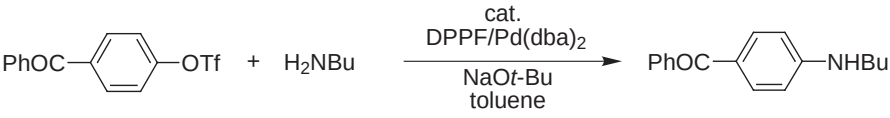
Wolfe and Buchwald reported that the arylation of aliphatic amines with aryl triflates could be effected with the BINAP/Pd-catalyst [80]. Triflate cleavage was a common side reaction, thus, slow addition of the aryl triflate often resulted in improved yields of the desired compound.



Reaction Conds.	Yield, %
Standard Conditions	55
Slow Addition of Triflate	65

(114)

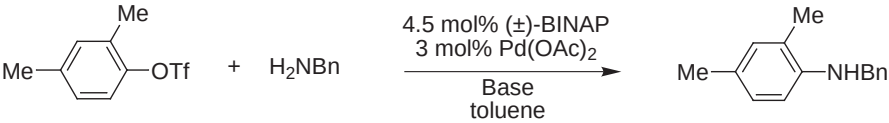
Simultaneously, Hartwig reported that the DPPF-based system also mediates the desired C-N bond formation [81]. The Yale group observed that slow addition of the aryl triflate often improved yield of the desired product, Eq. (115).



Reaction Conds.	Yield, %
Standard Conditions, 5 mol% Pd, 100 °C	57
Slow Addition of Triflate, 1.5 mol% Pd, 85 °C	63

(115)

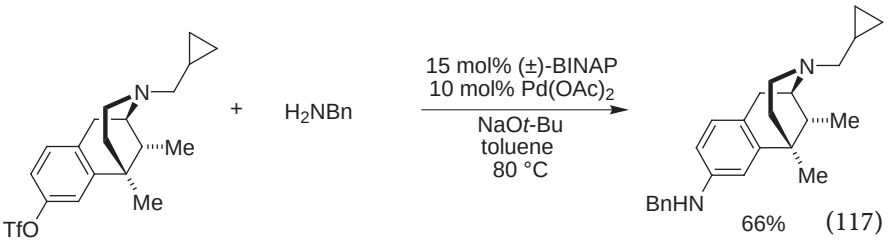
Wolfe and Buchwald susbsequently reported that by use of a milder base such as Cs_2CO_3 resulted in significant improvements in yield, particularly in the cases with electron-poor aryl triflates [82].



Base	Yield, %
NaO*t*-Bu	72
Cs_2CO_3	90

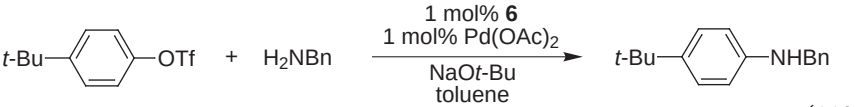
(116)

Wentland et al. utilized the BINAP/Pd-protocol to derivatize the opioid cyclazocine with several amines. For example, the desired aminated alkaloid was obtained in 66 % yield, Eq. (117) [84].



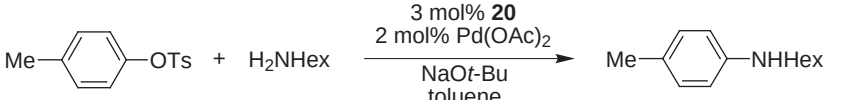
66% (117)

Catalysts based on bulky phosphine **6** effect the arylation of primary aliphatic amines with aryl triflates at room temperature, Eq. (118) [42a]. Substantial improvement in scope is observed when the reactions are performed at elevated temperatures with mild bases such as K_3PO_4; triflate cleavage is often less problematic under these conditions.



81% (118)

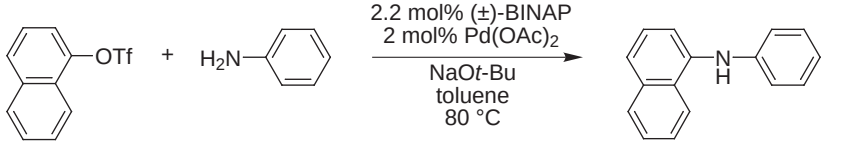
Hartwig reported the first amination of an aryl tosylate with an aliphatic amine. Utilizing electron-rich ferrocene-based ligand **20**, the coupling with hexylamine shown below proceeded in 83 % isolated yield, Eq. (119) [72].



83% (119)

2.3.7
Reaction of Primary Arylamines with Aryl Sulfonates

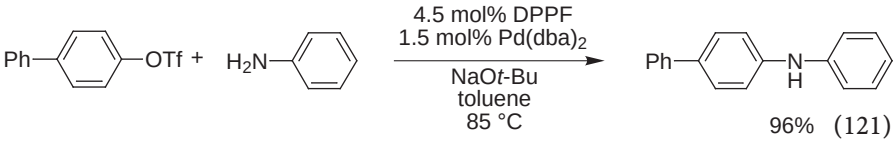
As was observed with aliphatic amines, slow addition of the aryl triflate to the aniline in the presence of the BINAP/Pd-catalyst often improved the yield of the desired product, Eq. (120) [80].



Reaction Conds.	Yield, %
Standard Conditions	61
Slow Addition of Triflate	68

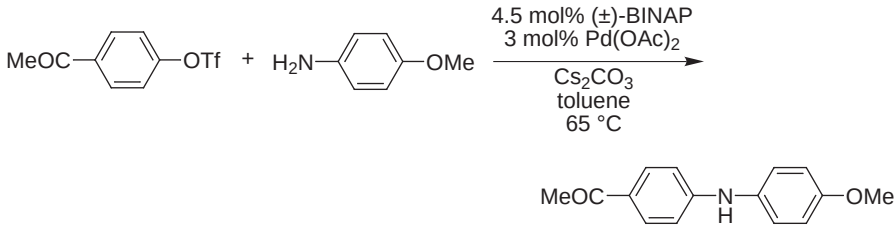
(120)

With the DPPF-based system, better yields of the C-N bond formation products were often obtained in the reaction of aryl triflats and anilines compared to the BINAP-catalysts, Eq. (121), however, triflate cleavage was still a significant side reaction when electron-poor aryl triflates were used [81].



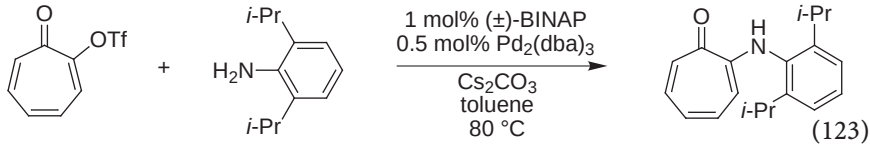
96% (121)

The Buchwald group revealed that the use of mild bases such as Cs_2CO_3 and K_3PO_4 helps minimize the amount of triflate cleavage [82], thus improving the yield of the arylation product, Eq. (122). In addition, functionality that is sensitive to NaO*t*-Bu is better tolerated when bases such as Cs_2CO_3 are used.



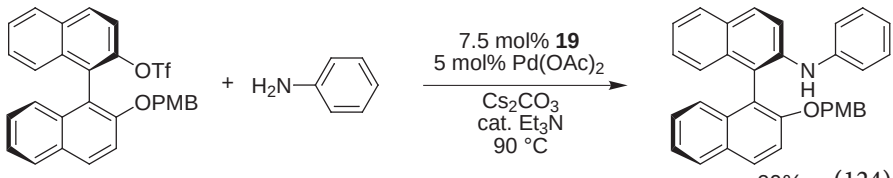
90% (122)

Hicks and Brookhart reported the amination of a tropolone triflate using the BINAP/Pd-catalyst as a strategy to prepare new ligand precursors [106]. For example, the coupling the sterically hindered 2,5-di*iso*-propylaniline proceeded in 86% isolated yield, Eq. (123).



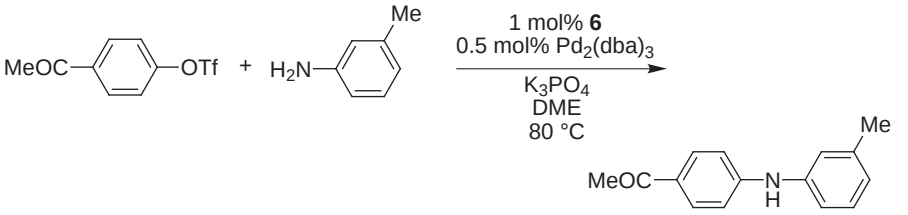
(123)

Singer and Buchwald found that the catalyst derived from DPEphos (**19**) was optimal for the arylation of the triflate derived from BINOL shown below, Eq. (124) [107]. Several useful chiral ligand building blocks were prepared in good to excellent yield.



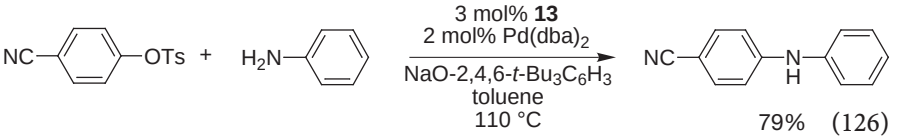
90% (124)

Bulky phosphine **6** affords an extremely active catalyst which is capable of effecting the C-N bond formation reaction between aryl triflates and aniline derivatives at room temperature [42a]. However, better yields, less triflate cleavage, and a wider substrate scope are observed when the reactions are performed with K_3PO_4 at elevated temperatures, Eq. (125).



91% (125)

Hartwig reported the first arylation of aniline using an aryl tosylate. The reaction was catalyzed by a **13**/Pd-catalyst, Eq. (126). Using a bulky base and elevated temperatures, the desired product was obtained in 78% yield [72].

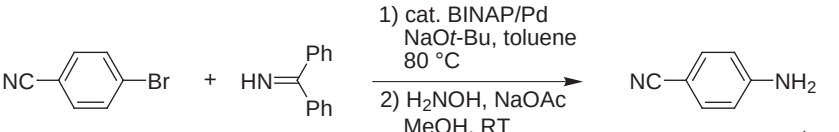


79% (126)

2.4 Arylation of Ammonia Equivalents

Since the use of ammonia in the palladium-catalyzed C-N bond formation reaction is not possible, it was desirable from a synthetic standpoint to develop a practical protocol for the installation of an ammonia equivalent. In 1997, Buchwald et al. reported that commercially available benzophenone imine is useful for such a purpose [108]. This reactant may be coupled with a large variety of aryl halides and triflates to furnish the desired product in good yields. The benzophenone moiety has the advantage that it can be removed via several different methods, allowing the synthetic chemist flexibility in the protecting group removal strategy. Imine removal may be effected by a transamination protocol (with excess hydroxylamine), by hydrogenolysis in the presence of a palladium catalyst, or by acidic hydrolysis.

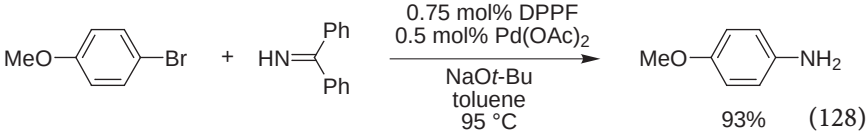
The reaction of benzophenone imine and an aryl bromide usually proceeds in excellent yield. For example, the transformation below is accomplished in 97% yield over both the coupling and deprotection steps, Eq. (127). Good yields are often observed with aryl iodides and triflates with the BINAP/Pd-catalyst as well.



97% (127)

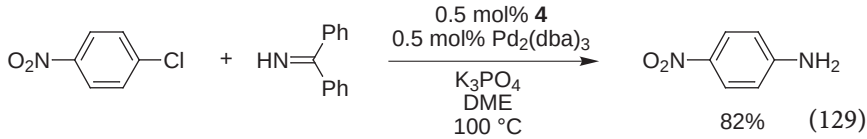
Representative Procedure for the Use of Benzophenone Imine as an Ammonia Equivalent: (Excerpted with permission from [108]. © 1996 Pergamon Press) A Schlenk tube was charged with sodium *tert*-butoxide (1.4 mmol), $Pd_2(dba)_3$ (0.00125 mmol), and BINAP (0.00375 mmol). The Schlenk tube was fitted with a septum and attached to a Schlenk line. After the air atmosphere was replaced with argon, toluene (4 ml), 4-*tert*-butylbromobenzene (1.0 mmol), and benzophenone imine (1.2 mmol) were added by syringe. After the septum was replaced with a teflon valve, the reaction was sealed and heated to 80 °C with stirring until starting material was consumed as judged by GC analysis. The reaction mixture was cooled to room temperature, diluted with ether (40 ml), filtered, and concentrated. The crude reaction mixture was then recrystallized from MeOH to furnish the desired product in 90 % yield.

The DPPF-catalyst system is also useful in the arylation of the benzophenone-based ammonia equivalent [109]. The coupling of 4-bromoanisole and benzophenone imine proceeded in excellent yield with only 0.5 mol% palladium, Eq. (128).



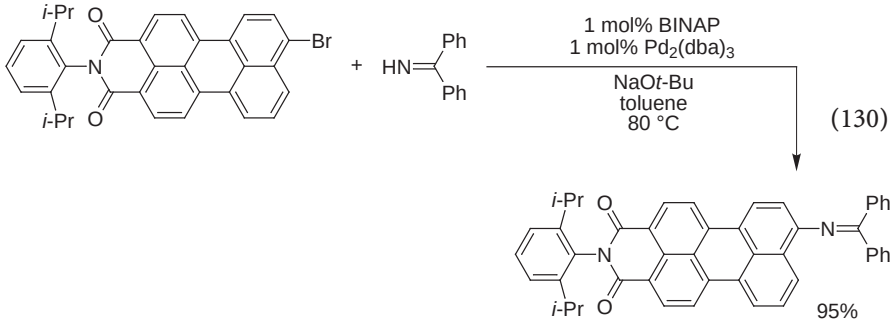
(128)

Aminophosphine **4** has been reported to effect the coupling of benzophenone imine and an electron-poor aryl chloride, Eq. (129) [42a]. Hartwig also reported that the system derived from heterocycle **17** is sufficiently reactive to effect a similar transformation [76].



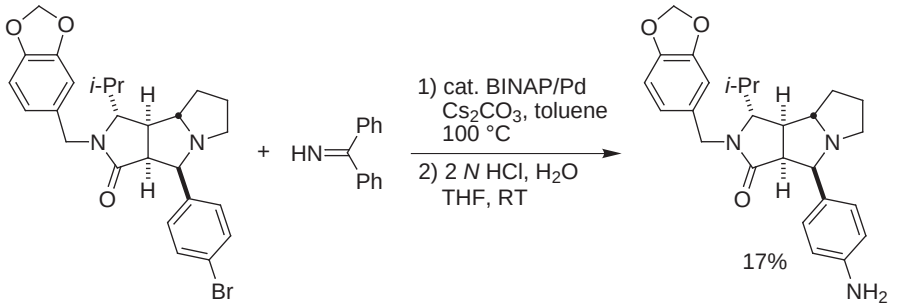
(129)

Several groups have utilized benzophenone imine as an ammonia equivalent in the palladium-catalyzed cross coupling. For example, Müllen and co-workers prepared a new thermotropic dye via the BINAP/Pd-coupling of the corresponding bromide, Eq. (130) [110]. Similarly, Basu reported the amination of a mixture of bromopyrene derivatives [111].



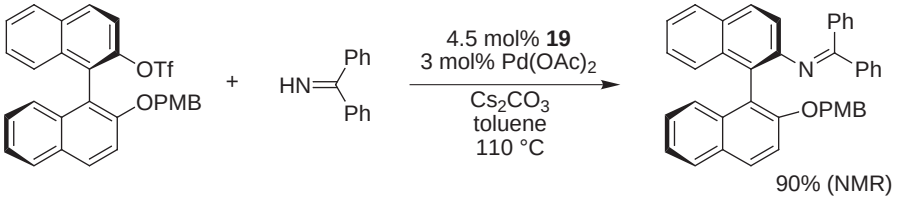
(130)

Diederich et al. prepared the highly functionalized thrombin inhibitor below using the Pd-catalyzed reaction [112]. The desired product was obtained in 17% yield over two steps.



(131)

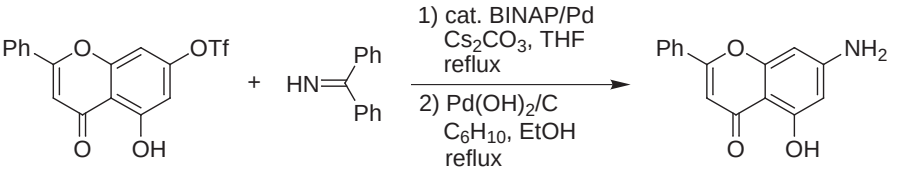
Aryl triflates are also good substrates for the benzophenone imine coupling reaction. For example, Singer and Buchwald prepared the desired amino-BINOL precursor in 87% yield after acidic hydrolysis; the amination itself proceeded in 90% NMR yield when DPEphos (**19**) was used as the supporting ligand, Eq. (132) [107].



90% (NMR)

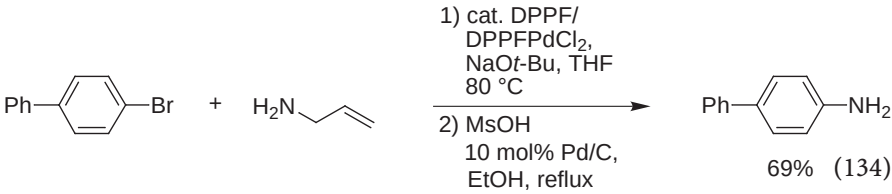
(132)

Similarly, Lemière utilized the Pd/BINAP-protocol to prepare the amino-flavone below in 50% yield over two steps from the corresponding triflate, Eq. (133) [113].



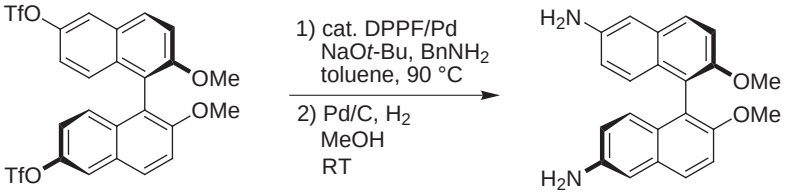
50% (133)

Putnam reported that allylamines may also be used as ammonia equivalents in the Pd-catalyzed coupling reaction [114]. The desired C-N formation was effected with the DPPF/Pd-catalyst; subsequent cleavage of the allyl group was achieved by treatment with methanesulfonic acid in the presence of a Pd/C catalyst, Eq. (134).



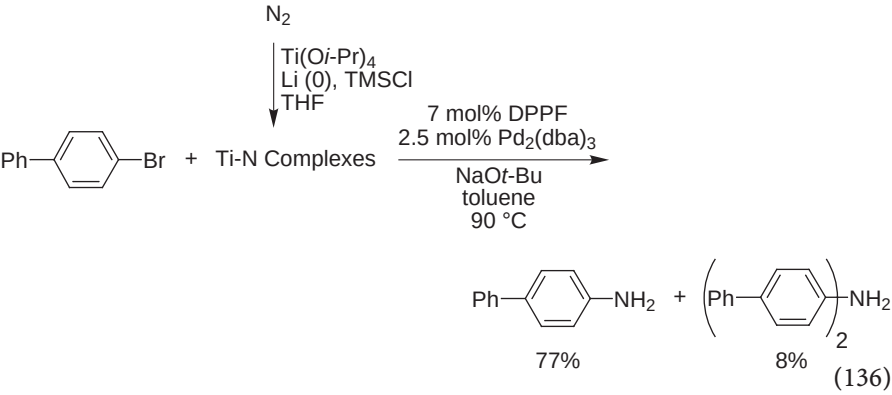
69% (134)

Lee described a strategy where benzylamine could be used as an ammonia equivalent as well [90]. The double reaction of the ditriflate below, followed by hydrogenolysis, furnished the desired ligand precursor in 69% yield over two steps, Eq. (135). The diamine product was also produced by double amination of the corresponding dibromide.



69% (135)

Mori reported that Ti-N complexes obtained from N_2 fixation could be utilized to prepare aniline derivatives via the Pd-catalyzed cross-coupling [115]. The complexes obtained from the reaction of dinitrogen with a mixture of lithium metal, $Ti(O\textit{i}\text{-}Pr)_4$, and TMSCl served as an effective ammonia equivalent to produce the desired aniline derivative after workup, Eq. (136). Thus, with this system, the removal of any nitrogen protecting group was obviated.

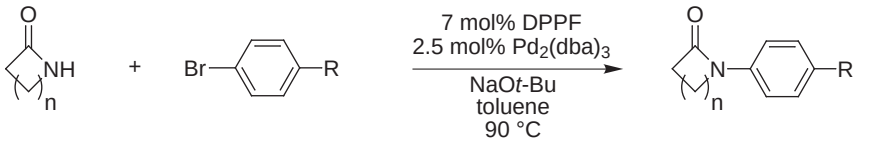


77% 8% (136)

2.5
Arylation of Amides and Carbamates

The coupling of amides and aryl halides or sulfonates is a highly desirable transformation since amides are ubiquitous in biologically active compounds. The arylation of amides however, is considerably different from the analogous reactions of amines since their pKas, and thus their relative reactivities, are considerably different.

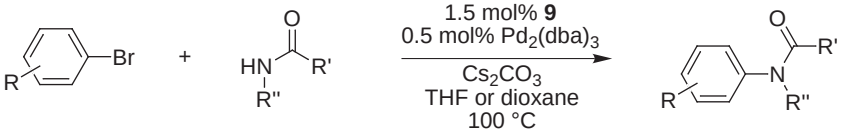
Shakespeare reported the first Pd-catalyzed arylation of an amide [116]. Specifically, he investigated the coupling of lactams and aryl bromides using a DPPF/Pd-protocol, Eq. (137). Significant generality was observed in the coupling of 2-pyrrolidone, however, with both larger and smaller ring sizes, good yields were only observed with electron-poor aryl bromides.



n	R	Yield, %
1	H	20
1	CF_3	52
2	H	82
2	CF_3	90
3	COPh	89

(137)

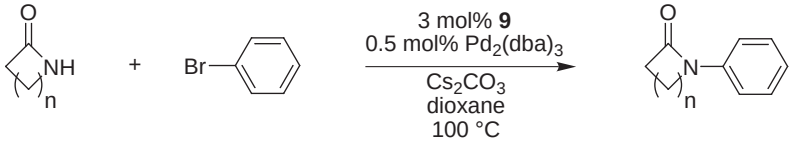
Yin and Buchwald reported that the catalyst based on Xantphos (**9**) as a supporting ligand is an effective and general system for the arylation of amides [117]. Using Cs_2CO_3 as base, aryl bromides possessing electron-withdrawing and electronically neutral groups were effectively coupled, Eq. (138). Both primary and secondary amides cleanly afforded the desired products.



R	R'	R''	Yield, %
p-CN	Ph	H	93
p-CN	Me	Me	97
o-CO_2Me	Ph	H	91
m-CO_2Me	Ph	H	90

(138)

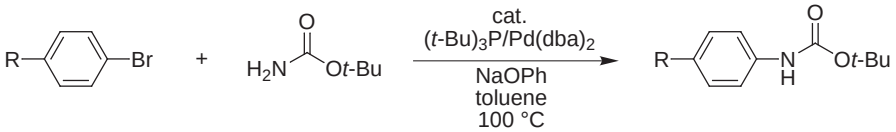
Lactams were also excellent substrates in the arylation reaction using **9**/Pd-catalysts. Notably, the coupling of a β-lactam (n = 1) and bromobenzene afforded the desired product in 93% yield, Eq. (139) [117].



n	Yield, %
1	93
2	96
3	92
4	90

(139)

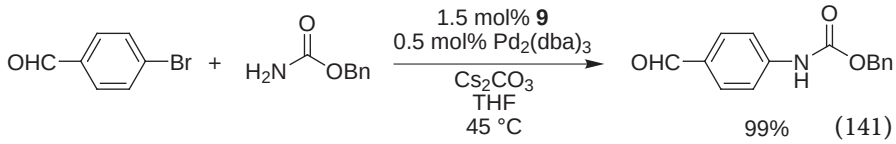
Hartwig reported the first arylation of carbamates utilizing a (*t*-Bu)$_3$P/Pd-catalyst [50]. Aryl bromides bearing electron-withdrawing groups are excellent substrates for the reaction, however, increasing electron density on the aryl bromide results in moderate yields of the desired amide, Eq. (140).



R	Reaction Conds.	Yield, %
Me	5 mol% (*t*-Bu)$_3$P, 2.5 mol% Pd(dba)$_2$	80
CN	5 mol% (*t*-Bu)$_3$P, 2.5 mol% Pd(dba)$_2$	83
OMe	8 mol% (*t*-Bu)$_3$P, 4 mol% Pd(dba)$_2$	62

(140)

The Xantphos (**9**)/Pd-system also mediates the coupling of aryl bromides and carbamates [117]. The coupling of benzyl carbamate below proceeds in quantitative yield when Cs_2CO_3 is used as base, Eq. (141).

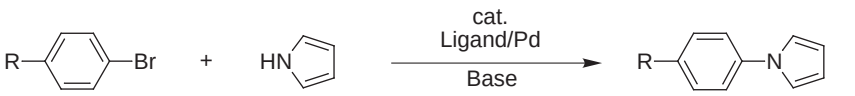


(141)

2.6 Arylation of Nitrogen-Containing Heterocycles

Nitrogen-containing heterocycles are interesting substrates for the amine arylation reaction since many pharmaceuticals possess such functionality. The arylation of such a species is not always straightforward, however, since their pKas are considerably different from simple amines. In addition, some heterocycles, such as indoles, are able to go unwanted side reactions.

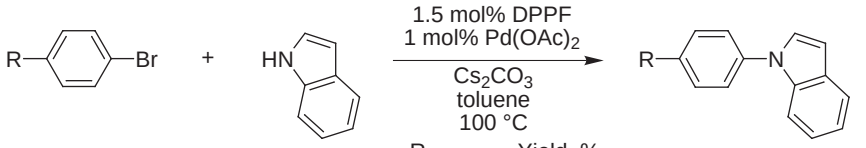
Hartwig first reported the use of the pyrrole in the arylation reaction. Use of a DPPF/Pd-catalyst afforded the desired products in moderate to good yield [109]. Subsequently, the Yale group disclosed that a (*t*-Bu)$_3$P/Pd-catalyst is able to effect the reaction in comparable yields with lower catalyst loadings [50]. Similarly, the Tosoh group reported that Rb_2CO_3 is a more efficient base using the (*t*-Bu)$_3$P/Pd-catalyst under their conditions [118].



R	Reaction Conds.	Yield, %
t-Bu	6 mol% DPPF, 5 mol% $Pd(OAc)_2$, NaO*t*-Bu, 120 °C	87
H	3 mol% $(t\text{-Bu})_3P$, 3 mol% $Pd(dba)_2$, Cs_2CO_3, 100 °C	77
Me	3 mol% $(t\text{-Bu})_3P$, 1 mol% $Pd(OAc)_2$, Rb_2CO_3, 120 °C	70

(142)

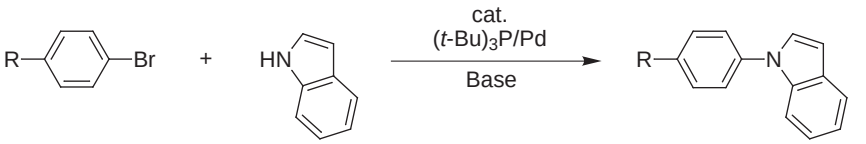
In 1998, Hartwig also described the arylation of indoles using Pd catalysis [109]. With the DPPF/Pd-system, good to excellent yields of the desired product was obtained with electron-deficient aryl bromides.



R	Yield, %
CN	98
Ph	72

(143)

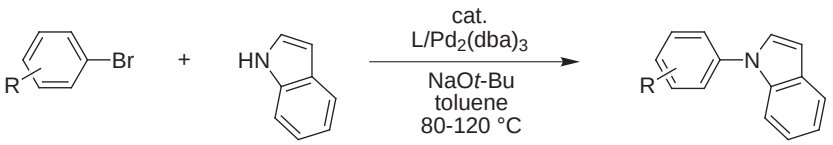
The use of $(t\text{-Bu})_3P$/Pd-catalysts in the arylation of indoles has been reported by both the Hartwig and Watanabe groups [50,118]. Moderate to good yields are observed in the coupling reactions, however, side products resulting from *C*-arylation at the 3-position are commonly isolated as well. Similarly, both groups reported the arylation of carbazoles as well.



R	Reaction Conds.	Yield, %
OMe	3 mol% L, 3 mol% $Pd(dba)_2$, Cs_2CO_3, 100 °C	77
H	3 mol% L, 1 mol% $Pd(OAc)_2$, Rb_2CO_3, 120 °C	70

(144)

Old, Harris, and Buchwald investigated the arylation of indoles and found a very strong dependence of the reaction efficiency on the supporting ligand used [119]. Specifically, it was observed that *C*-arylation was problematic when aryl bromides possessing electron-donating groups or *ortho*-substituents were subjected to the Pd-catalyzed coupling. For example, while aminophosphine **4** was useful in the reaction of 4-bromotoluene, related ligand **22** proved optimal in the coupling of electron-rich aryl bromides such as 4-bromoanisole. Binaphthyl-derived ligand **23** is useful in the coupling of *ortho*-substituted aryl bromides, Eq. (145).



R	Reaction Conds.	Yield, %
p-Me	3.75 mol% **4**, 1.25 mol% $Pd_2(dba)_3$	88
p-OMe	1.5 mol% **22**, 0.5 mol% $Pd_2(dba)_3$	84
3,5-Me_2	7.5 mol% **23**, 2.5 mol% $Pd_2(dba)_3$	87

(145)

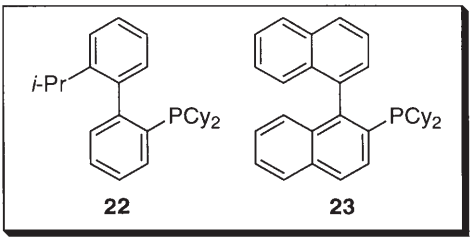
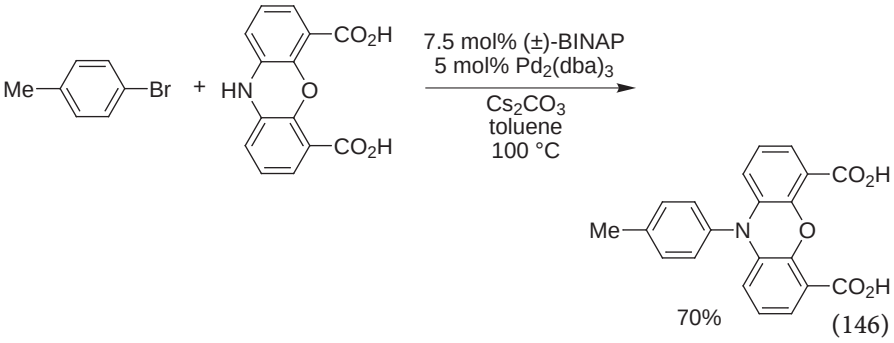


Fig. 20

General Procedure for the N-Arylation of Indoles: (Excerpted with permission from [119]. © 2000 American Chemical Society) A Schlenk tube was charged with sodium *tert*-butoxide (1.4 mmol), $Pd_2(dba)_3$ (0.005 mmol), and **4** (0.015 mmol). The Schlenk tube was fitted with a septum and attached to a Schlenk line. After the air atmosphere was replaced with argon, toluene (2 ml), aryl bromide (1.0 mmol), and the indole (1.2 mmol) were added. After the septum was replaced with a teflon valve, the reaction was sealed and heated to 80 – 100 °C with stirring until starting material was consumed as judged by GC analysis. The reaction mixture was cooled to room temperature, diluted with ether (20 ml), filtered, and concentrated. The crude reaction mixture was then purified by flash chromatography on silica gel.

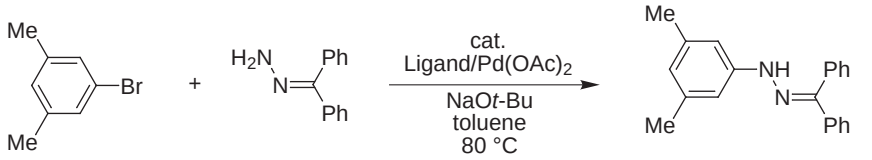
Kelly reported the preparation of several transthyretin amyloid fibril inhibitors using the BINAP/Pd-catalyzed coupling [120]. For example, the coupling below furnished the desired phenoxazine derivative in 70 % isolated yield, Eq. (146).



(146)

2.7
Arylation of Other Nitrogen Substrates

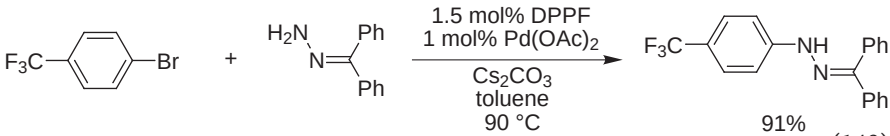
In 1998, the Buchwald group reported the arylation of benzophenone hydrazone with several aryl bromides [121]. The desired reaction could be effected with the BINAP/Pd-catalyst, however, the Xantphos/Pd-system proved particularly well-suited for this transformation, Eq. (147).



Catalyst (mol%)	Yield, %
(*S*)-BINAP/Pd(OAc)$_2$ (1)	87
9/Pd(OAc)$_2$ (0.1)	98

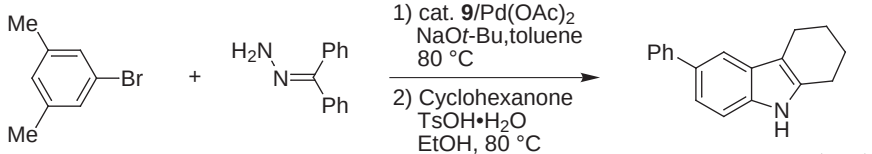
(147)

Concurrently with the report by Buchwald, Hartwig described a similar reaction using the DPPF/Pd-based protocol [122]. The C-N bond coupling proceeded in good to excellent yield with 1 mol% Pd, Eq. (148).



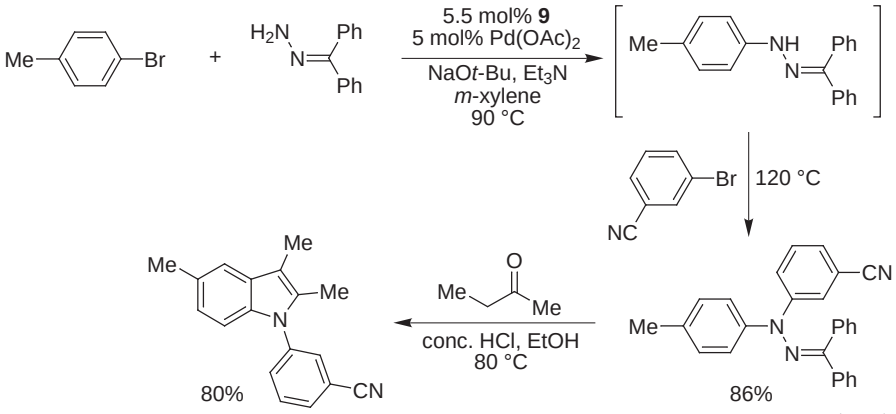
91% (148)

The Buchwald group exploited the Pd-catalyzed hydrazone synthesis for the efficient preparation of indoles. While removal of the benzophenone moiety and isolation of the free hydrazine did not proceed cleanly, the MIT workers found that Fischer indole synthesis could be effected by *in situ* exchange of the ketone group. The desired indoles could thus be isolated in good to excellent yield over two steps, Eq. (149) [121].



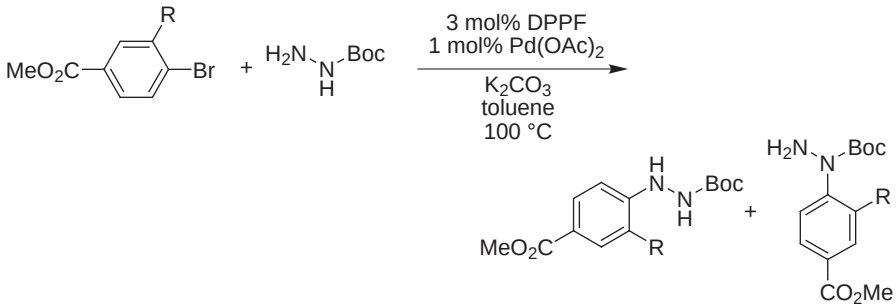
92% (149)

N-Arylindoles could be prepared via a one-pot sequential arylation of benzophenone hydrazone. For example, after the first C-N bond coupling with the less reactive aryl bromide was performed with the **9**/Pd-catalyst; after complete reaction, the second aryl bromide was then introduced to the reaction mixture, Eq. (150) [121]. The doubly arylated product could be cyclized to yield the desired *N*-arylindole in moderate to good yield.



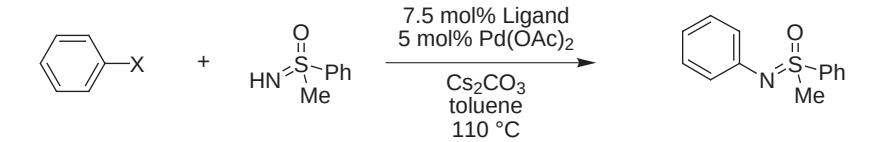
(150)

Skerjl reported that *tert*-butylcarbazate could be regioselectively arylated with the DPPF/Pd-catalyst [123]. When aryl bromides possessing *ortho*-substituents were used, reaction at the less hindered nitrogen was observed, Eq. (151). However, in the absence of *ortho* substitution, the arylation proceeded on the Boc-protected nitrogen.



(151)

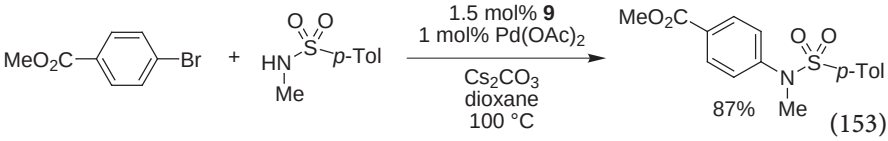
Bolm and co-workers have described the arylation of sulfoximes with aryl bromides, iodides, triflates, and nonaflates [124]. The BINAP/Pd-catalyzed transformation proceeds in moderate to excellent yields, Eq. (152). The resulting *N*-arylsulfoximines were used to prepare new chiral ligands. Harmata and Pavri have used similar transformations to prepare several benzothiazines [125].



X	Ligand	Yield, %
Br	tolBINAP	83
OTf	BINAP	51

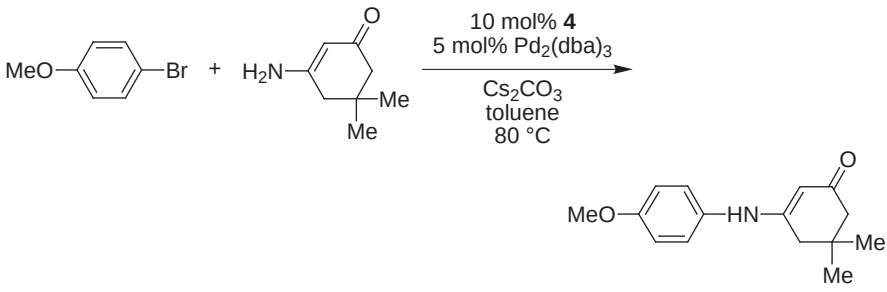
(152)

Yin and Buchwald found that Xantphos (**9**) was the most effective supporting ligand for the arylation of sulfonamides, Eq. (153). Primary and secondary sulfonamides were efficiently reacted under these conditions [117].



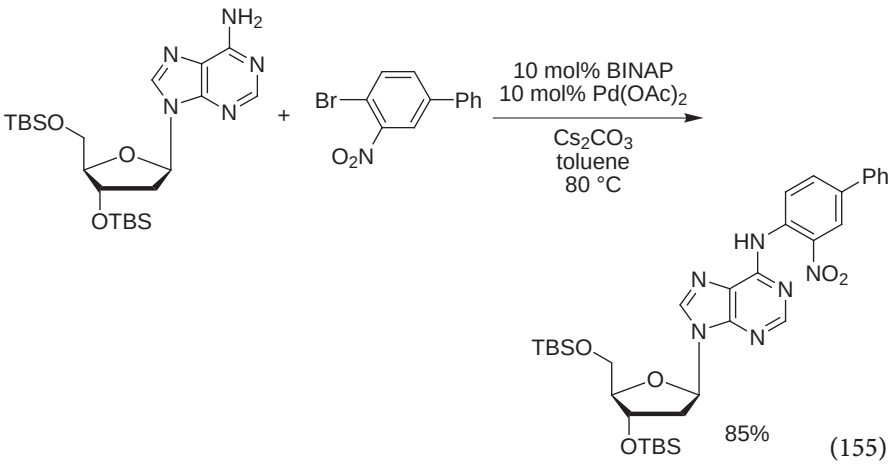
(153)

Several aryl bromides were coupled with the vinylogous amide below in moderate to excellent yields by Edmonson et al., Eq. (154) [126]. The Merck investigators also reported that this C-N bond forming reaction could be exploited to prepare quinoline and indole derivatives.



(154)

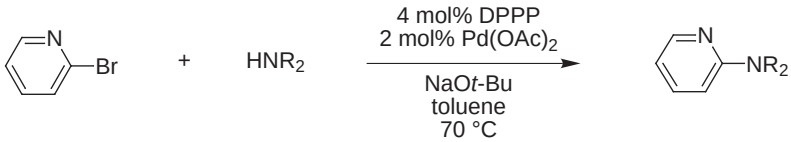
Johnson described the preparation of several 2′-deoxyadenosine and guanosine amine adducts that have been implicated in carcinogenesis via the Pd-catalyzed coupling [127]. The TBS-protected purine derivatives were reacted with several aryl bromides and triflates in good yield using a BINAP/Pd-catalyst and Cs_2CO_3 as base, Eq. (155).



(155)

2.8
Heteroaryl Halides in the Pd-Catalyzed Amine Arylation

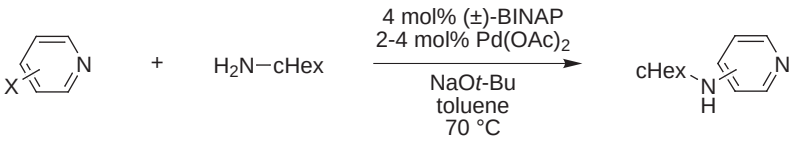
The use of heteroaryl halides in the Pd-catalyzed C-N coupling would be useful to the pharmaceutical chemist since heterocycles are commonly found in biologically active agents. Wagaw and Buchwald first investigated the amination of halopyridines and found that the original $(o\text{-tol})_3P$/Pd-protocols were ineffective [128]. By using bis(1,3-diphenylphosphino)propane (dppp) as a supporting ligand, however, the coupling of bromopyridine with several amines could be effected in good yield, Eq. (156).



Amine	Yield, %
H-N(Me)Bn	85
Morpholine	87

(156)

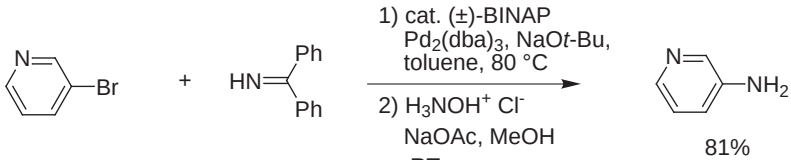
BINAP also proved useful in the C-N bond coupling reactions involving halopyridines [128]. For example, the coupling of primary amines with chloro- and bromopyridines could be performed with the (±)-BINAP/Pd-catalyst in good yield, Eq. (157).



X	Yield, %
2-Cl	73
3-Br	82

(157)

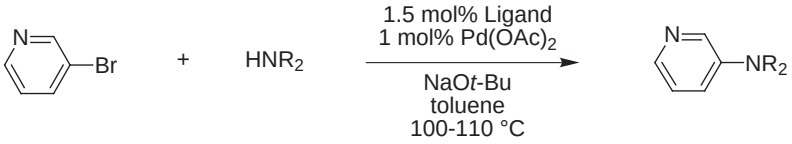
Benzophenone imine may be used as an ammonia equivalent with halopyridines as well. The coupling of the bromopyridine below, followed by deprotection via transamination with hydroxylamine, proceeded in 81% yield over the two steps, Eq. (158) [128]. Analogously, Puttman found that allylamine could also be used as an ammonia equivalent in the C-N coupling reactions of halopyridines [114].



81%

(158)

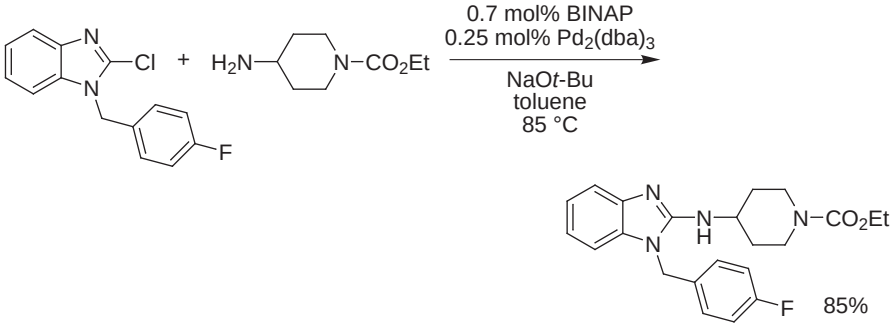
Sterically hindered monophosphines may also be used as supporting ligands in the amination of halopyridines. Commercially available ligands **4** and **6** allow for the desired reaction to proceed in good to excellent yield, Eq. (159) [42].



Amine	Ligand	Yield, %
H-N(Me)Ph	**4**	94
H_2NBn	**6**	86

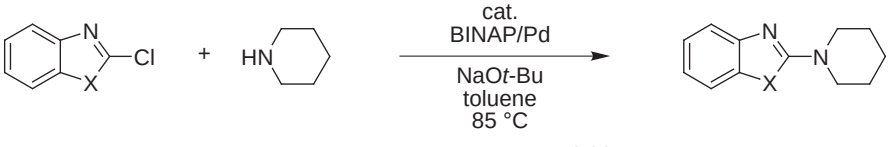
(159)

Other heteroaryl halides may be used in the Pd-catalyzed cross coupling reaction. Senanayake and co-workers reported the reaction of a chlorobenzimidazole and a primary amine to synthesize the antihistamine norastemizol [34, 87]. The key Pd-catalyzed coupling reaction proceeded in 85% isolated yield using 0.5 mol% Pd, Eq. (160). During these investigations, the Sepracor group also noted that primary amines reacted preferentially over secondary amines.



(160)

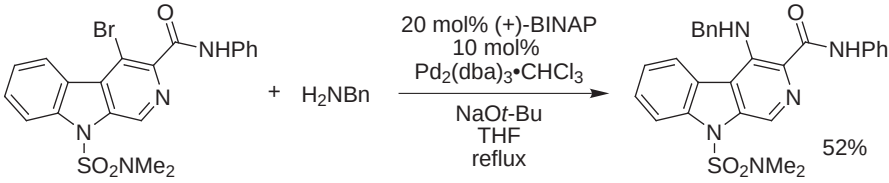
Senanayake also demonstrated that the amination reaction could be effected with several related heteroaryl chlorides [34, 87]. The coupling of piperidine with several heteroarene substrates proceeded in good yield, Eq. (161).



X	Yield, %
O	66
S	78
$NCH_2(4\text{-}F\text{-}C_6H_4)$	71

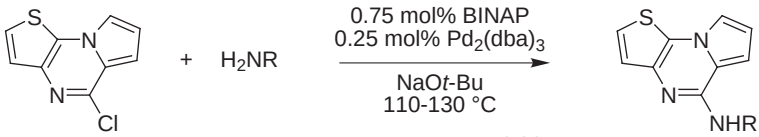
(161)

In 1998, Dodd reported the amination of the β-carboline-carboxylic amide below using the BINAP/Pd-protocol, Eq. (162) [129]. The desired product was obtained in 52 % yield.



(162)

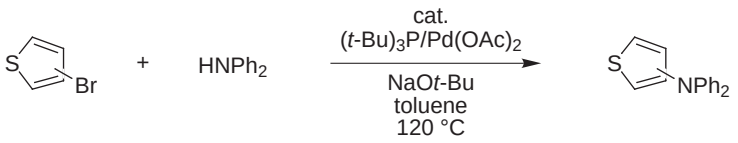
Rouden described the amination of the heteroaryl chloride below with several primary amines using the BINAP/Pd-catalyst, Eq. (163) [130]. The resulting products were new ligands for serotoninergic receptors.



R	Yield, %
n-Hexyl	94
tert-Butyl	65

(163)

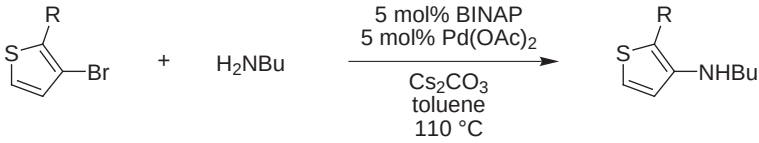
The Tosoh group described the first amination of bromothiophenes with a (t-Bu)$_3$P/Pd-based system [131]. The reactions between several bromothiophenes and diphenylamine proceeded with moderate yields, Eq. (164).



Substitution	Yield, %
3	69
2	36

(164)

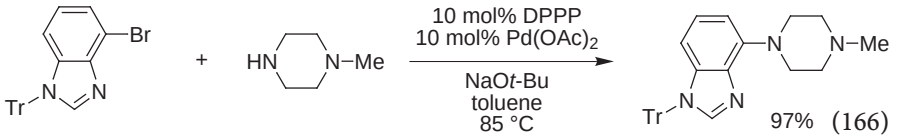
Luker et al. subsequently investigated the use of electron-deficient thiophenes in the C-N bond forming reaction [132]. Using a BINAP/Pd-catalyst, the Nottingham group reported that the desired transformations proceed in good to excellent yield with several primary and secondary amines, Eq. (165).



R	Yield, %
CO_2Me	94
CN	89

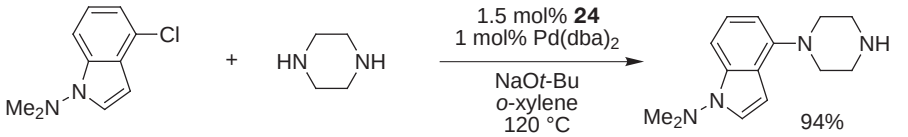
(165)

López-Rodriguez and co-workers prepared a number of serotonin 5-HT_{1A} receptor ligands using palladium catalysis [133]. The Spanish group used both DPPP- and BINAP-based systems to couple bromine-substituted benzimidazoles with piperazines. For example, the reaction of the protected heterocycle below with *N*-methylpiperazine proceeds in excellent yield, Eq. (166).



(166)

Watanabe's group at Tosoh Corporation reported the coupling of a chlorine-substituted indole and piperazine using a **24**/Pd-based catalyst, Eq. (167) [134]. The indole substrate, which was prepare via a novel palladium-catalyzed cyclization, was aminated in 94% yield.



(167)

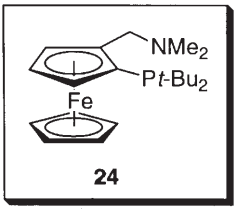
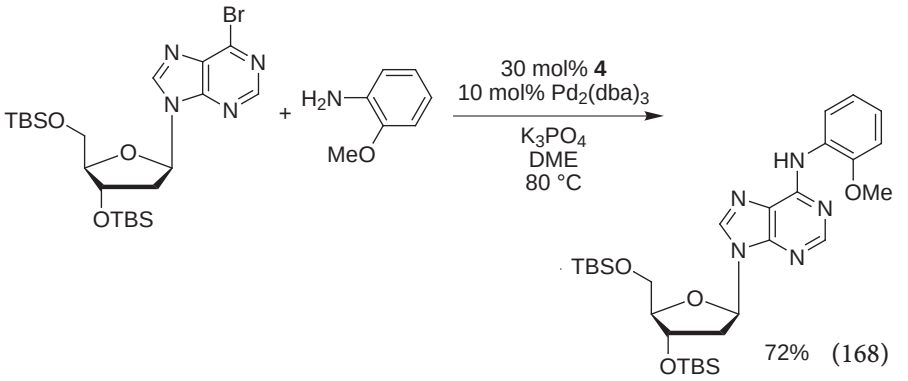


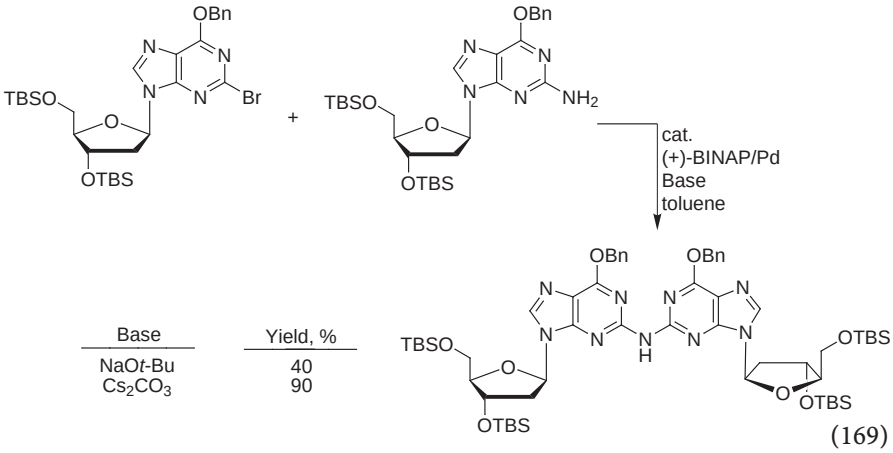
Fig. 21

Several 2′-deoxyadenosine-amine adducts that have been implicated in carcinogenesis were prepared via the Pd-catalyzed amine arylation reaction as reported by Lakshman and co-coworkers [135]. For example, the coupling of the protected 6-bromoadenosine derivative below was achieved in good yield using the **4**/Pd-catalyst, Eq. (168).



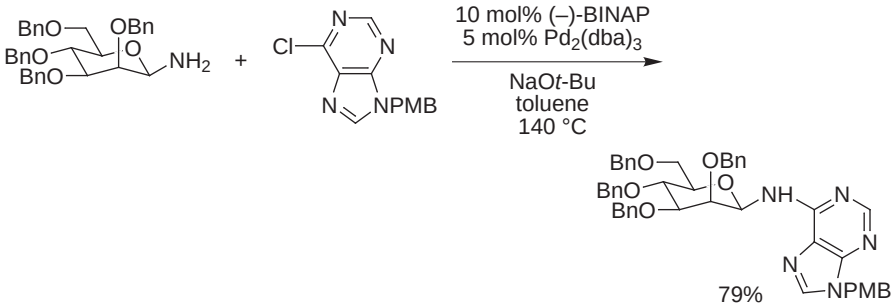
(168)

Crosslinked nucleosides have been similarly prepared by two different groups. While Sigurdsson and Hopkins performed the dimerization below with the BINAP/Pd-catalyst, in the presence of NaO*t*-Bu to isolate the desired product in 40% yield, Johnson found that when Cs_2CO_3 was used as base, the dimer was obtained in 90% yield, Eq. (169) [136].



(169)

Glycosylamines have been coupled to 6-halopurines using the BINAP/Pd-system. Chida and co-workers performed these reaction as a model study towards the synthesis of spicamycin and septacidin antitumor agents [137]. The coupling of the mannose derivative below was achieved at elevated temperatures in a sealed tube to furnish the desired C-N bond formation product in 79% yield, Eq. (170).



(170)

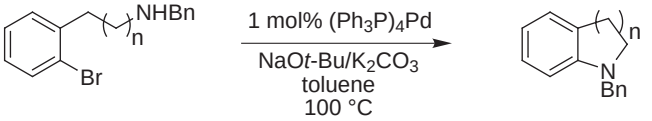
2.9
Intramolecular Arylation of Amines and Amides

2.9.1
Intramolecular Arylation of Amines

More than 15 years ago, Boger reported an intramolecular amine arylation using stoichiometric quantities of palladium. In 1997, the Buchwald group investigated catalytic variants of the cyclization [138]. Initial studies involved the *in situ*

generation of the aminostannane previously described for intermolecular reactions, however, tin-free methods were soon discovered.

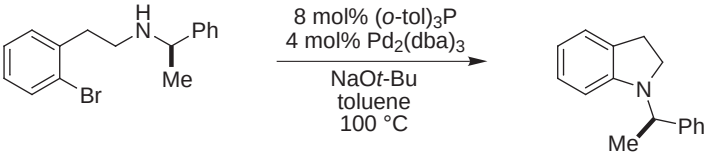
The intramolecular C-N bond forming reactions proved to be more straightforward than their intermolecular counterparts [138]. The desired couplings often could be achieved using $(Ph_3P)_4Pd$ as catalyst to form 5-, 6-, and 7-membered nitrogen heterocycles, Eq. (171).



n	Yield, %
1	87
2	72
3	61

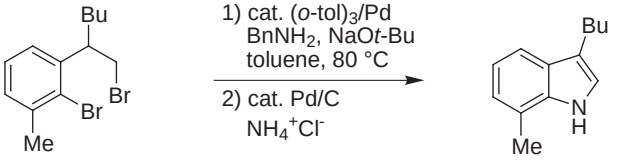
(171)

Unlike the intermolecular variants, the intramolecular amine arylation of α-chiral substrates proceeded without racemization when the reaction was performed with the $(o\text{-tol})_3P$/Pd-catalyst, Eq. (172) [54].



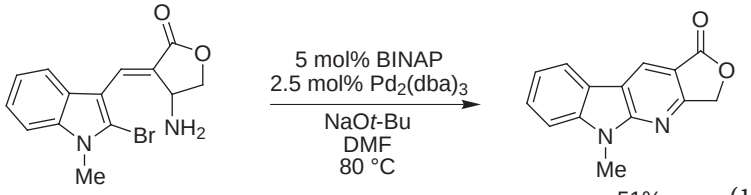
96% ee — 80% y, 96% ee (172)

An alternative indole synthesis was reported by the Buchwald group where initial displacement of the primary bromide by benzylamine is followed by a Pd-catalyzed cyclization, Eq. (173) [139]. After deprotection, the desired indole was obtained in 54% yield over two steps.



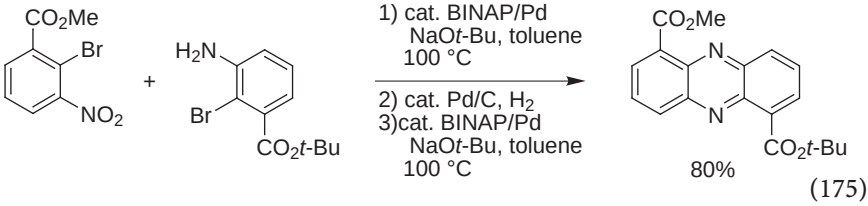
54% (173)

Dodd and Abouabdellah performed the cyclization below with a BINAP/Pd-catalyst to furnish, after air oxidation, the pyrido[2,3-b]indole in 51% yield, Eq. (174) [140].



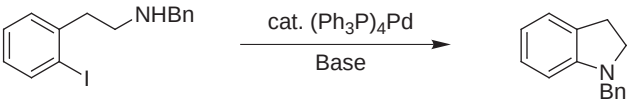
51% (174)

Kamikawa used two different Pd-catalyzed C-N bond-forming reactions for the convergent preparation of several phenazines [93]. After intermolecular coupling was achieved, the nitro group was reduced. Subsequent Pd-catalyzed cyclization afforded the desired product in 80% yield over three steps, Eq. (175).



(175)

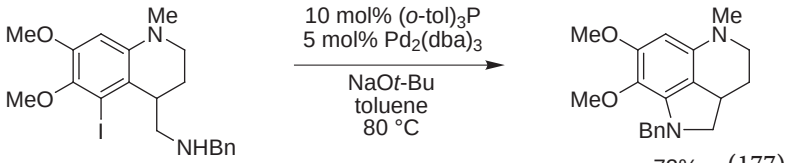
Aryl iodides could also be used in the intramolecular C-N bond coupling. Notably, cyclization could be achieved using triethylamine as base and solvent at room temperature in good yield with the iodide substrate, Eq. (176) [138].



Reaction Conds.	Yield, %
1 mol% cat., NaO*t*-Bu/K_2CO_3, toluene, 65 °C	96
5 mol% cat., Et_3N, RT	87

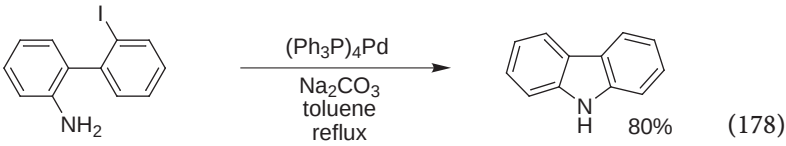
(176)

Exploiting the utility of this type of cylization, Peat and Buchwald described the formal synthesis of several alkaloids. Reaction of the aminoiodide below proceeded in 72% yield, Eq. (177) [141].



72% (177)

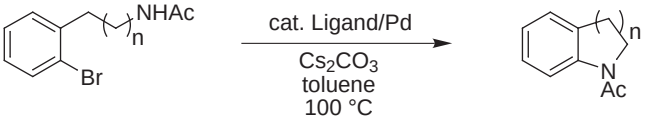
The cyclization below proceeded in 80% yield using stoichiometric quantities of palladium, similar to the report by Boger, Eq. (178) [15, 142]. Wood reported that efforts to render this reaction catalytic in Pd (5 mol%) resulted in only 60% conversion after 5 days.



(178)

2.9.2
Intramolecular Arylation of Amides

Initial studies on the intramolecular arylation of amides revealed that tri(2-furyl)-phosphine was an effective supporting ligand for the cyclization of substrates that furnish five-membered rings, Eq. (179) [138]. The analogous reaction to prepare the six-membered ring product was considerably less efficient, however, providing the quinoline derivative in 44% yield. Subsequent studies by Yang and Buchwald found that several different catalyst systems were more efficient than the original one reported [143]. Specifically, the catalyst derived from MOP (**25**) and $Pd(OAc)_2$ proved particularly effective and formed the same six-membered ring in 87% yield using only 3.3 mol% Pd. Cyclization to the seven-membered ring could best be effected using Xantphos (**9**) as ligand.



n	Reaction Conds.	Yield, %
1	20 mol% (2-furyl)$_3$P, 10% $Pd_2(dba)_3$	99
2	20 mol% (2-furyl)$_3$P, 10% $Pd_2(dba)_3$	44
2	5 mol% **25**, 3.3 mol% $Pd(OAc)_2$	87
3	5 mol% **9**, 3.3 mol% $Pd(OAc)_2$	90

(179)

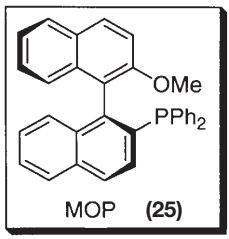
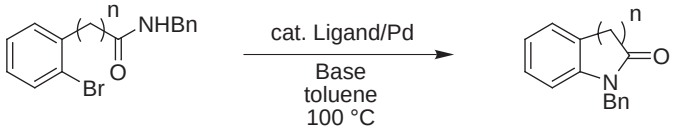


Fig. 22

The synthesis of lactams could also be performed by the (*o*-tol)$_3$P/Pd-system, however, high catalyst loadings were required, Eq. (180) [138]. Yang and

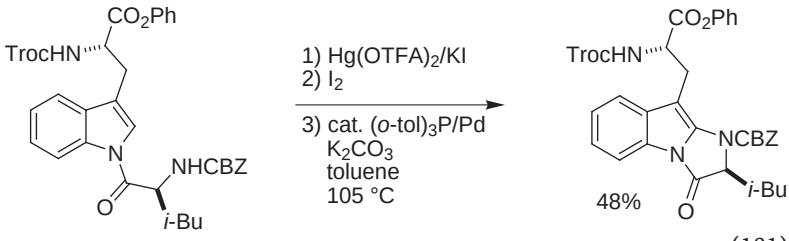


(180)

n	Reaction conds.	Yield, %
1	20 mol% (*o*-tol)$_3$P, 10% $Pd_2(dba)_3$, K_2CO_3	59
2	20 mol% (*o*-tol)$_3$P, 10% $Pd_2(dba)_3$, K_2CO_3	82
1	5 mol% **25**, 3.3 mol% $Pd(OAc)_2$, Cs_2CO_3	82
2	5 mol% **25**, 3.3 mol% $Pd(OAc)_2$, Cs_2CO_3	94
3	5 mol% **25**, 3.3 mol% $Pd(OAc)_2$, Cs_2CO_3	88

Buchwald later showed that the same reaction could be more efficiently accomplished using a MOP (**25**)/Pd-catalyst [143]. In addition, the **25**/Pd-protocol allowed for the analogous cyclizations to be conducted with carbamate substrates.

Snider and co-workers executed a palladium-catalyzed carbamate cyclization as a key step in the synthesis of (–)-asperlicin [144]. The dipeptide below was converted to the desired intermediate in 48% yield over 3 steps without epimerization of the two stereocenters, Eq. (181).



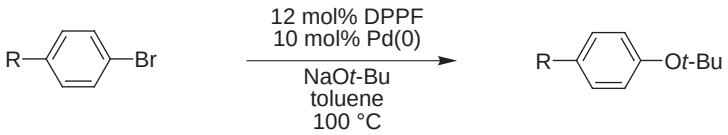
(181)

3
Palladium-Catalyzed Alcohol Arylation

3.1
Reaction of Aliphatic Alcohols

The arylation of aliphatic alcohols is particularly challenging because the competitive β-hydride elimination side reaction that was problematic in the amine arylation is even more prevalent in the analogous C-O bond forming reactions. Thus, the coupling of tertiary alcohols such as *tert*-butanol and aryl halides has seen considerable success, while general methods for the arylation of primary and secondary alcohols have been more elusive.

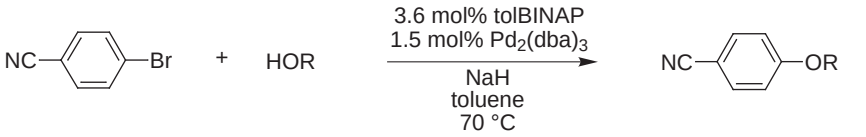
Hartwig first reported the arylation of *tert*-butanol in 1996 [145]. Using a DPPF/Pd-catalyst and NaO*t*-Bu as the *tert*-butoxy source, several electron-deficient aryl bromides were coupled in moderate yield, Eq. (182).



R	Yield, %
CHO	66
CN	58
COPh	69

(182)

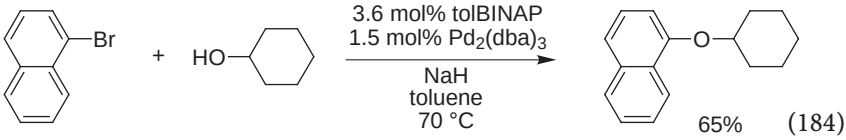
The reaction between aryl bromides and aliphatic alcohols bearing α-hydrogens was first described by Buchwald et al. using a tolBINAP/Pd-system [146]. Several primary and secondary alcohols were coupled with electron-deficient aryl bromides in moderate to good yield, Eq. (183).



R	Yield, %
Bn	71
Me	81

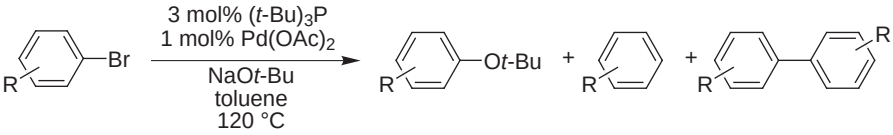
(183)

In limited cases, electronically neutral aryl bromides also served as good substrates in the Pd-catalyzed C-O bond formation with the tolBINAP/Pd-system. For example, 1-bromonaphthalene was coupled with cyclohexanol in 65% yield, Eq. (184).



(184)

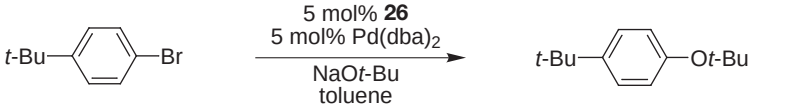
The Tosoh group reported that a $(t\text{-Bu})_3$P/Pd-catalyst allowed the preparation of *tert*-butyl ethers from the corresponding aryl bromides and NaO*t*-Bu [147]. Electron-withdrawing as well as electron-donating substituents were tolerated on the aryl bromide, although increased electron density on the aryl bromide results in greater amounts of reduced arene and biaryl side products, Eq. (185).



R	Ratio	Yield, %
4-CHO	99.5:0.5:0	91
4-*t*-Bu	94:4:2	85
3-OMe	70:26:4	82

(185)

Di-*tert*-butylferrocenylphosphine (**26**) is an excellent supporting ligand for the coupling of NaO*t*-Bu and aryl bromides (eq 186) [148]. During kinetic studies of this reaction, Hartwig and co-workers noted that a portion of the aryl halide was consumed prior to formation of the aryl ether product [149]. It was subsequently determined that ligand **26** was being arylated during the course of the reaction to yield a much more active catalyst system. Pentaphenylated ligand **27** could in fact be prepared from **26** and chlorobenzene via palladium catalysis in 85% yield.



(186)

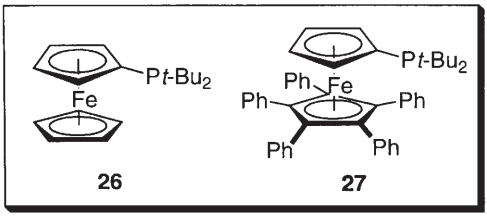
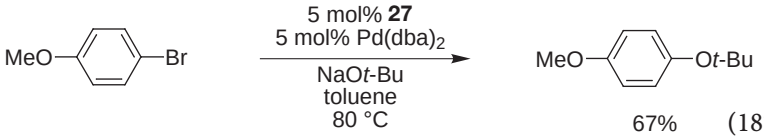


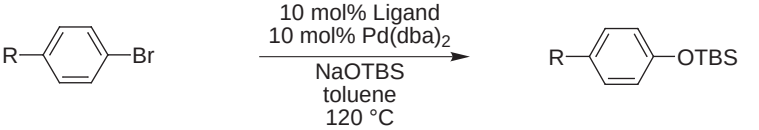
Fig. 23

The **27**/Pd-catalyst is considerably more reactive that the **26**-based system. The new, more reactive catalyst was reported to allow the coupling of electron-rich aryl bromides with NaO*t*-Bu in moderate yields, Eq. (187) [149].



(187)

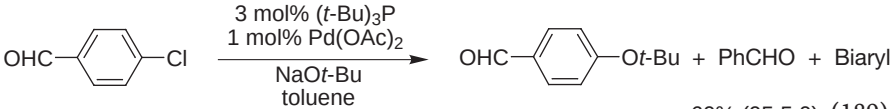
Mann and Hartwig have also investigated the use of sodium *tert*-butyldimethylsilanoate (NaOTBS) in the C-O bond forming reaction with aryl bromides [150]. The efficacy of DPPF- and tolBINAP-based catalysts, as well as nickel-based systems, were compared, Eq. (188).



Ligand	GC Yield, %
DPPF	49
tolBINAP	75

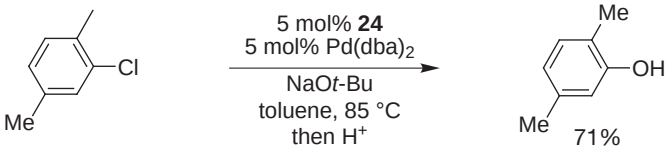
(188)

Watanabe et al. have reported that electron-deficient aryl chlorides may be coupled with NaO*t*-Bu in the presence of the (*t*-Bu)$_3$P/Pd-catalyst, Eq. (189) [147].



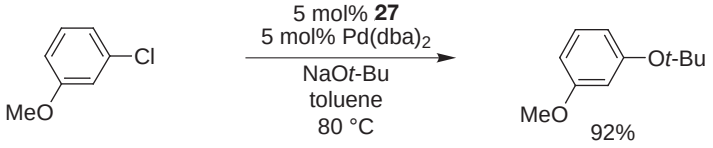
(189)

Ferrocene-based phosphine **24** is also an effective supporting ligand for the Pd-catalyzed condensation of chloroarenes and sodium *tert*-butoxide [148]. The coupling of 2-chloro-*para*-xylene, followed by acid mediated cleavage of the *tert*-butyl group, yielded the desired phenol in 71% yield, Eq. (190).



(190)

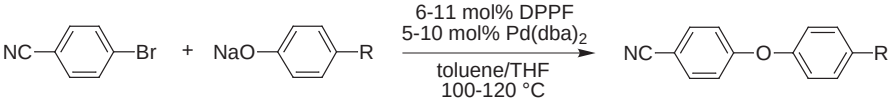
Pentaphenylated ligand **27** forms a catalyst that is considerably more reactive than **26**. This system mediates the efficient coupling of electron-rich aryl chlorides with NaO*t*-Bu; *meta*-chloroanisole was reacted in 92% yield, Eq. (191) [149].



(191)

3.2 Reaction of Phenol Derivatives

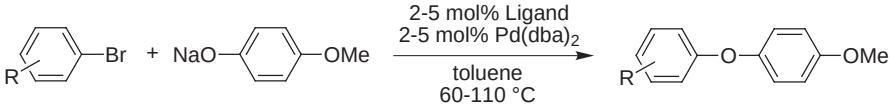
Methods for the arylation of phenols have been more successful than analogous reactions of aliphatic alcohols since the Pd (II) phenoxide intermediate is unable to undergo unwanted β-hydride elimination. Hartwig and co-workers first reported the use of a DPPF/Pd-catalyst to prepare diaryl ethers in 1997 [151]. The system was particularly effective with electron-deficient aryl bromides and electron-rich phenols, Eq. (192).



R	Yield, %
OMe	92
H	51

(192)

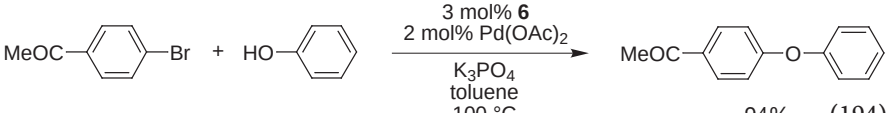
The use of ferrocene-based ligands **26** and **27** also effected the Pd-catalyzed formation of diaryl ethers, Eq. (193) [148, 149]. The **27**/Pd-catalyst is more reactive and mediates the transformation in better yield and at lower temperatures.



Ligand	R	Yield, %
26	2-Me	85
27	2-Me	99
26	4-*t*-Bu	74

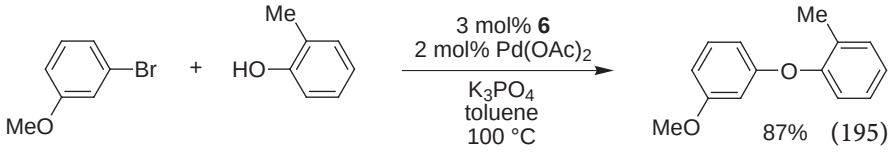
(193)

Buchwald and co-workers disclosed that the palladium-catalyzed diaryl ether formation can be performed with a **6**/Pd-based system [152]. These reactions are accomplished using a mild base such as K_3PO_4, and with electron-poor aryl bromides, the reactions proceed in good to excellent yield, Eq. (194).



94% (194)

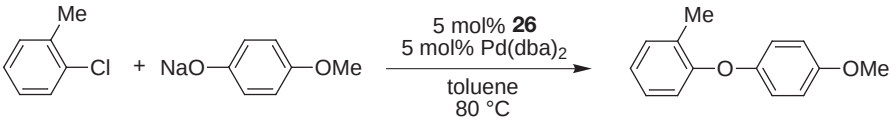
In some cases, the **6**/Pd-catalyst is capable of mediating the coupling of electron-rich aryl bromides and phenols as well [152]. For example, the reaction of 3-bromoanisole shown below proceeded in 87% yield, Eq. (195). With more challenging electron-rich substrates, other bulky ligands are better suited.



87% (195)

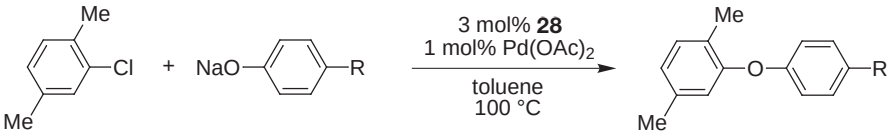
General Procedure for the Preparation of Diaryl Ethers using 6/Pd: (Excerpted with permission from [152]. © 1999 American Chemical Society). An oven-dried resealable Schlenk tube was fitted with a rubber septum and was cooled to room temperature under an argon purge. The septum was removed, and the tube was charged with palladium acetate (4.5 mg, 0.02 mmol, 2.0 mol%), ligand **6** (13.6 mg, 0.03 mmol, 3.0 mol%) potassium phosphate (424 mg, 2.0 mmol), the phenol (1.2 mmol) and the aryl halide (1.0 mmol). The tube was capped with a septum and purged with argon, and then toluene (3 ml) ws added through the septum. The tube was sealed with a Teflon screwcap, and the reaction mixture was stirred at 100 °C for 14–26 h. The reaction was then allowed to cool to room temperature and was then diluted with ether (40 ml), filtered and concentrated. The crude material was purified by flash chromatography on silica gel.

The catalyst based on ligand **26** has also been reported to mediate the formation of diaryl ethers from aryl chlorides. The reaction below proceeded in 82% yield, Eq. (196) [148].



82% (196)

The Buchwald group has reported that hindered binaphthyl-derived phosphine **28** is an effective supporting ligand for the coupling of aryl chlorides and phenols [152]. This catalyst system provided the desired ethers in good to excellent yield, Eq. (197).



R	Yield, %
OMe	79
H	92

(197)

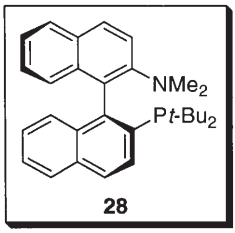
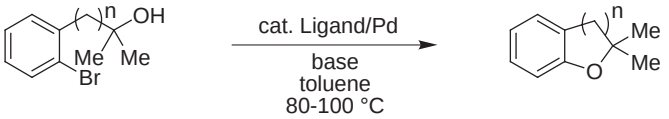


Fig. 24

3.3 Intramolecular Arylation of Alcohols

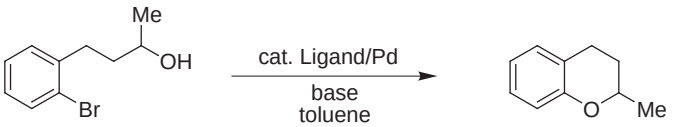
Similar to the development of the palladium-catalyzed C-N bond forming reactions, investigations into the intramolecular alcohol arylation were first conducted. The Buchwald group first reported the intramolecular variant of this reaction in 1996 utilizing both tolBINAP- and DPPF-based catalysts [153]. Five- and six- and seven-membered rings were formed in the cyclizations in moderate to excellent yield, Eq. (198). Yields were greatly diminished when the alcohol substrates contained hydrogens α- to the oxygen due to competitive β-hydride elimination of the palladium (II) alkoxide intermediate. Similarly, Hartwig subsequently reported that the **26**/Pd-catalyst could effect the cyclization below [148].



(198)

n	Reaction Conds.	Yield, %
1	6 mol% tolBINAP, 5 mol% $Pd(OAc)_2$, K_2CO_3	89
1	2 mol% **26**, 2 mol% $Pd(dba)_2$, NaO*t*-Bu	78
2	3.6 mol% DPPF, 3 mol% $Pd(OAc)_2$, NaO*t*-Bu	69
3	3.6 mol% DPPF, 3 mol% $Pd(OAc)_2$, NaO*t*-Bu	64

Recently, Buchwald and co-workers reported improved procedures for intramolecular Pd-catalyzed C-O bond forming reactions with primary and secondary alcohol-containing substrates based on hindered ligands **6, 29**, and **30** [154]. While the DPPF/Pd-system accomplished the cyclization below in only 32% yield, the catalyst based on commercially available phosphine **6** furnished the heterocycle in 83% yield, Eq. (199). Hindered ligand **29** also provided the desired product in good yield.



(199)

Reaction Conds.	Yield, %
10 mol% DPPF, 5 mol% $Pd(OAc)_2$, NaO*t*-Bu	32
5 mol% **27**, 5 mol% $Pd(dba)_2$, NaO*t*-Bu	64
3.5 mol% **6**, 3 mol% $Pd(OAc)_2$, Cs_2CO_3	83
3.5 mol% **29**, 3 mol% $Pd(OAc)_2$, Cs_2CO_3	79

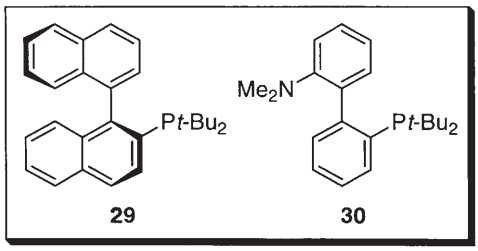
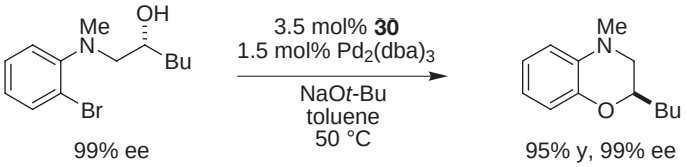


Fig. 25

The **29** and **30**/Pd-catalysts allowed for the efficient cyclization of substrates bearing primary and secondary alcohol substituents [154]. Reaction of both aryl chlorides and bromides was possible, providing five-, six- and seven-membered heterocycles in moderate to good yield. Additionally, enantiomerically enriched heterocycles could be prepared without epimerization of the carbinol-bearing stereocenter, Eq. (200).



(200)

4 Conclusions

Palladium-catalyzed C-N bond and C-O bond forming reactions are useful methods for organic synthesis. The iterative development of new catalyst systems has revealed profound ligand effects, both electronic and steric, on the selectivity and efficiency of these transformations. Mechanistic studies have been instrumental to the progress of both our research program as well as that of the Hartwig group. Based on empirical observations, it seems that designing a "silver bullet" ligand that effects all desired cross couplings is unlikely. Thus, our group, and others, have sought to develop a toolbox of ligands that allow the synthetic chemist to effect the desired transformation as efficiently and practically as possible. Continued efforts will improve the scope of these methods and the mechanistic understanding of these processes.

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Direct Arylation via Cleavage of Activated and Unactivated C-H Bonds

Masahiro Miura · Masakatsu Nomura

Department of Applied Chemistry, Faculty of Engineering, Osaka University, Suita, Osaka 565–0871, Japan
E-mail: miura@chem.eng.osaka-u.ac.jp

Palladium catalyzed direct coupling of aryl halides not only with various carbon nucleophiles having acidic C-H bonds, but also with aromatic and heteroaromatic compounds accompanied by cleavage of their unactivated C-H bonds, has been significantly developed in recent years. In this review the progress of these reactions as effective methods for preparing aromatic fine compounds is summarized. A brief description of related direct coupling of arenes with unsaturated compounds is also given.

Keywords. Aryl halides, Arylation, Palladium catalysts, Carbonyl compounds, Aromatic compounds

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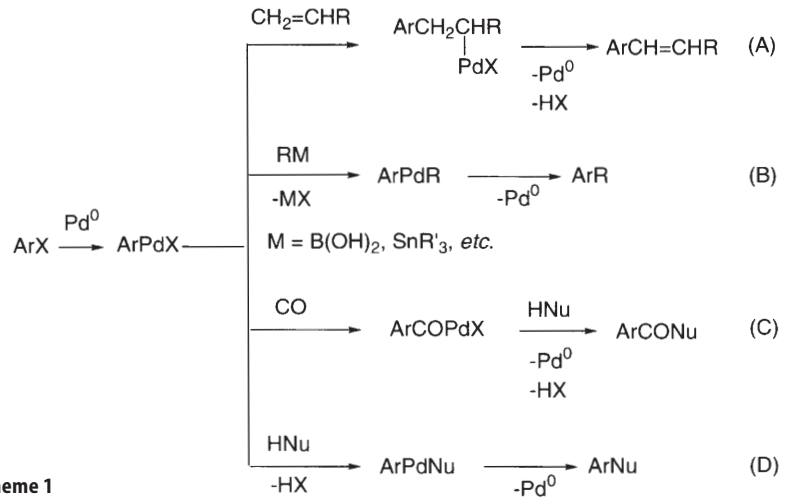
List of Abbreviations

BINAP	2,2′-bis(diphenylphosphino)-1,1′-binaphthyl
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
dppe	1,2-bis(diphenylphosphino)ethane
D^{t}BPF	bis(di-*tert*-butylphosphino)ferrocene
DTPF	1,1′-bis(di-*o*-tolylphosphino)ferrocene
KHMDS	potassium hexamethyldisilazide
NaHMDS	sodium hexamethyldisilazide
PNP	*cis*,*exo*-2-phenylnorbornylpalladium chloride
Xantphos	9,9-dimethyl-4,6-bis(dimethylphosphino)xanthene

1 Introduction

The palladium catalyzed substitution reactions of aryl halides and their synthetic equivalents such as aryl triflates are now recognized to be highly useful for the preparation of various aromatic fine compounds [1, 2]. For making carbon-carbon bonds, Mizoroki-Heck reaction with alkenes and Suzuki-Miyaura and Kosugi-Migita-Stille reactions with organoboron compounds and organostannanes, respectively, are often employed. The carbonylation of aryl halides with carbon monoxide in the presence of nucleophiles is also an important reaction for preparing aromatic carbonyl compounds. These reactions involve arylpalladium(II) species as common intermediates (Scheme 1, mechanisms A – C). Insertion of alkenes or carbon monoxide into the aryl-palladium bond (A and C, respectively) and transmetalation with organometallic reagents (B) lead to the corresponding products.



Scheme 1

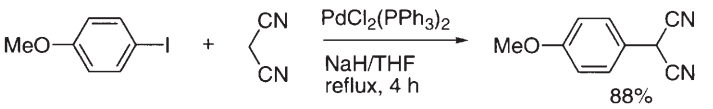
On the other hand, the direct coupling of aryl halides with carbanionic species generated from substrates having relatively acidic hydrogens such as active methylene compounds and ketones can occur (Scheme 1, mechanism D), as in the well-known Tsuji-Trost reaction using allylic compounds including allyl esters and carbonates in place of aryl halides [1]. Aryl halides are also capable of coupling directly with aromatic and heteroaromatic compounds as formal carbon nucleophiles via cleavage of their unactivated C-H bonds. These reactions appear to have a synthetically significant advantage, being able to be carried out without stoichiometric metalation of the substrates. Consequently, the methods have been extensively studied in recent years. In this review the progress is summarized. In addition, the development of related direct coupling between arenes and unsaturated compounds via palladium catalysis is briefly described. It is noted that much effort has simultaneously been made on the palladium catalyzed reactions of aryl halides with nitrogen and oxygen nucleophiles and the outcome has been reviewed elsewhere [3–6].

2
Arylation of Carbon Nucleophiles

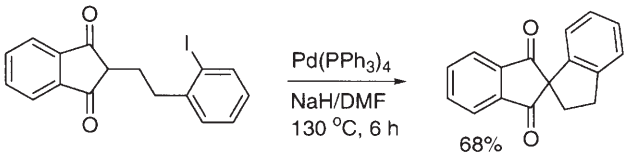
Among common carbon-carbon bond formation reactions involving carbanionic species, the nucleophilic substitution of alkyl halides with active methylene compounds in the presence of a base, e.g., malonic and acetoacetic ester syntheses, is one of the most well documented important methods in organic synthesis. Ketone enolates and protected ones such as vinyl silyl ethers are also versatile nucleophiles for the reaction with various electrophiles including alkyl halides. On the other hand, for the reaction of aryl halides with such nucleophiles to proceed, photostimulation or addition of transition metal catalysts or promoters is usually required, unless the halides are activated by strong electron-withdrawing substituents [7]. Of the metal species, palladium has proved to be especially useful, while copper may also be used in some reactions [8]. Thus, aryl halides can react with a variety of substrates having acidic C-H bonds under palladium catalysis.

2.1
Active Methylene Compounds

In 1984, Takahashi and coworkers reported that aryl iodides efficiently couple with malononitrile in the presence of $PdCl_2(PPh_3)_2$ using NaH as base (Eq. 1) [9, 10]. The reaction is considered to proceed by mechanism D in Scheme 1. Cyanoacetate esters could be employed in place of malononitrile [11], but the use of other active methylene compounds having no cyano group such as malonate esters was not successful under similar conditions. It was, however, found that various carbanion centers bearing two electron-withdrawing groups can be involved in the intramolecular version (Eq. 2) [12, 13].

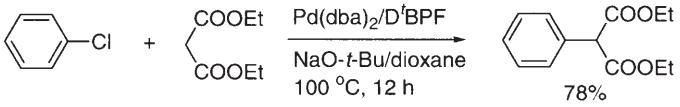


(1)

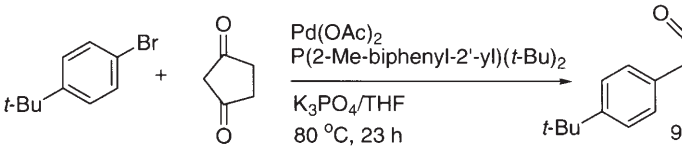


(2)

Recently, the limitations for the intermolecular coupling have been significantly mitigated. Kawatsura and Hartwig [14] and Buchwald et al. [15] have demonstrated that aryl bromides and even aryl chlorides react with malonates (Eq. 3) and 1,3-diketones (Eq. 4) by using sterically bulky and electron-rich phosphines, such as P(*t*-Bu)$_3$, D^{t}BPF, and 2-(di-*tert*-butylphosphino)-2′-methylbiphenyl, as ligands.



(3)



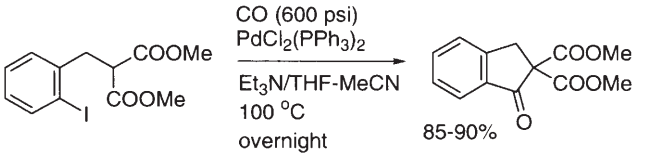
(4)

A typical procedure for Eq. (4) [15] is as follows. An oven-dried, resealable Schlenk tube containing a stirbar is capped with a rubber septum, evacuated, and cooled under argon. The tube is then charged with $Pd(OAc)_2$ (2.3 mg, 0.01 mmol), the ligand (6.9 mg, 0.022 mmol), the 1,3-diketone (1.2 mmol), and K_3PO_4 (490 mg, 2.3 mmol). The septum is replaced, and the tube is again evacuated and backfilled with argon. Solvent (3 ml) and the aryl bromide (1.0 mmol) are sequentially injected, and the septum is replaced with a Teflon screw cap under a flow of argon. The tube was sealed, and the mixture is stirred and heated for the time specified. The mixture is then diluted with MeOH and filtered. The filtrate is concentrated and chromatographed.

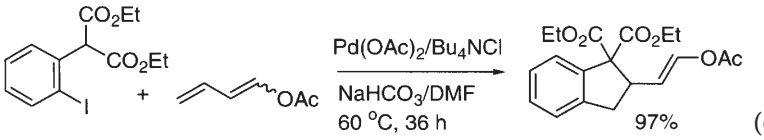
Bulky ligands as above have also proved to be effective in other palladium-catalyzed reactions of aryl halides, e.g., amination [16–19], Suzuki-Miyaura reaction [20–22], Mizoroki-Heck reaction [23, 24], Migita-Kosugi-Stille reaction [25], and aryloxylation and alkoxylation [26–28] as well as the reaction with various carbon nucleophiles as described below. The ligands are considered to enhance both the initial oxidative addition of aryl halides and the reductive elimination of products [29, 30]. The effectiveness of the commercially available simple ligand, P(*t*-Bu)$_3$, was first described for the amination by Nishiyama et al. [16].

A number of related reactions, which occur by different mechanisms, have been reported. The intramolecular reaction of halo-malonates under carbon monoxide gives cyclic ketones (Eq. 5) [31, 32]. This proceeds by mechanism C. Halo-malonates also couple with unsaturated compounds such as 1,3-dienes

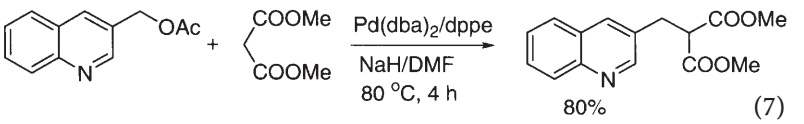
(Eq. 6) and allenes to give annulated products [33, 34]. Naphthylmethyl and quinoylmethyl acetates react with malonates (Eq. 7) [35, 36]. The reactions in Eqs. 6 and 7 involve π-allylpalladium type intermediates.



(5)



(6)



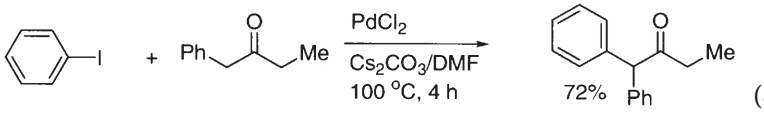
(7)

It is noted that the coupling of aryl halides, especially iodides, with a number of active methylene and methine compounds are promoted effectively by a stoichiometric amount of copper(I) halides [8, 37, 38]. The reaction using cyanoacetate esters and 1,3-diketones can catalytically proceed [39–41].

2.2
Ketones, Aldehydes, Esters, and Amides

Relatively less acidic ketones compared to 1,3-dicarbonyl compounds are also suitable substrates for the palladium catalyzed coupling. α-Aryl ketones are obtained as products. In the early examples, masked ketone enolates such as silyl enol ethers [42] and enol acetates [43–45] were used in the presence of a tin source. These reactions involve tin enolates or acylmethyltins as intermediates and thus proceed by transmetalation (mechanism B in Scheme 1).

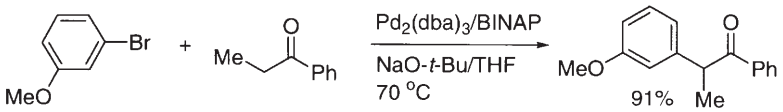
Several papers describing the direct intermolecular α-arylation of ketones proceed by mechanism D were published in 1997 [46–48]. Only a single example had been disclosed in a patent by the year [49]. The authors found that aryl iodides react with benzyl ketones in the presence of $PdCl_2$ using Cs_2CO_3 as base (Eq. 8) [46, 50]. Bromobenzenes can also be used for this reaction when a phosphine ligand is added.



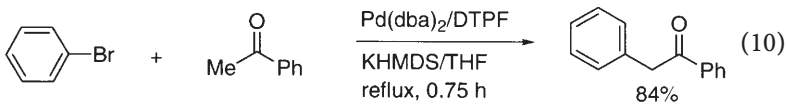
(8)

A typical procedure for Eq. (8) [50] is as follows. In a 100-ml two-necked flask is placed Cs_2CO_3 (1.2 mmol), which is then dried at 150 °C in vacuo for 2 h. (The use of this drying procedure is recommended, when the hygroscopic base is employed). Then $PdCl_2$ (0.05 mmol), the aryl iodide (1.2 mmol), the ketone (1 mmol), and DMF (5 ml) are added. The resulting mixture is stirred at 100 °C for 4 h under nitrogen (with a balloon). After cooling, the reaction mixture is extracted with diethyl ether and dried over sodium sulfate. The product is isolated by column chromatography on silica gel using hexane-ethyl acetate (98:2, v/v).

Palucki and Buchwald [47] and Hamann and Hartwig [48] groups reported that the reactions of aryl bromides with mainly alkyl aryl ketones to give aryl benzyl ketones (Eqs. 9 and 10). Combinations of Pd-dba complexes, bidentate ligands such as BINAP and DTPF, and relatively bulky strong bases such as NaO-*t*-Bu and KHMDS are suitable for the reactions. Only small or negligible amounts of diarylated products are formed even in the reactions using aryl methyl ketones, giving aryl benzyl ketones selectively. This is probably due to steric reasons (cf. Eq. 8).

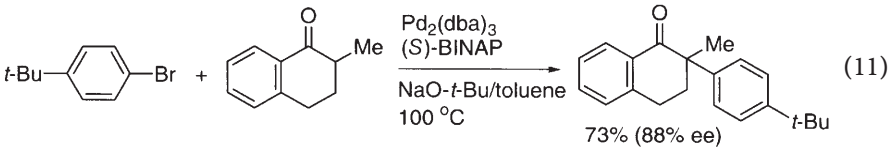


(9)



(10)

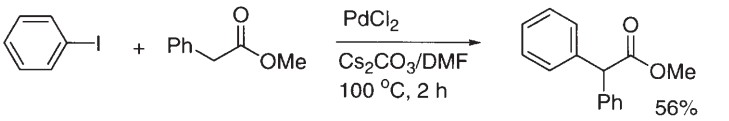
More recently, it has been shown that various bulky monodentate and bidentate phosphines, including P(*t*-Bu)$_3$, 2-(di-*tert*-butylphosphino)biphenyl, and Xantphos as well as BINAP and DTPF work as efficient ligands for the arylation of ketones, as well as that of 1,3-dicarbonyl compounds as described in Sect. 2.1 [14, 15]. The identity of bases is also an important factor to obtain high yields. NaO-*t*-Bu, K_3PO_4, K_2CO_3, Cs_2CO_3, NaHMDS, and KHMDS are those of choice. Consequently, even aryl chlorides can be used as arylating reagents in a number of cases and a variety of ketones can be employed. By using a chiral ligand such as (*S*)-BINAP, the asymmetric arylation of some cyclic ketones can be performed with good enantiomeric excesses (Eq. 11) [51].



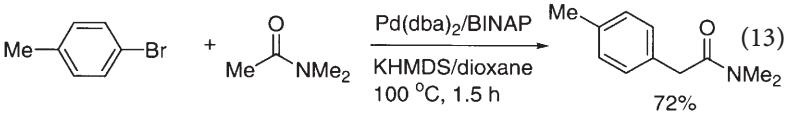
(11)

Some esters (Eq. 12) [50] and amides (Eq. 13) [52] have also been shown to undergo direct α-arylation. Hallberg et al. reported the arylation of 1,2-cyclohexanedione that seems to occur in a different mechanism, possibly via car-

bopalladation (mechanism A) (Eq. 14) [53]. 4-Halophenyl alkyl ketones undergo condensation polymerization to form polyketones that can be readily converted to poly(phenylenevinylene) and its derivatives (Eq. 15) [54].



(12)



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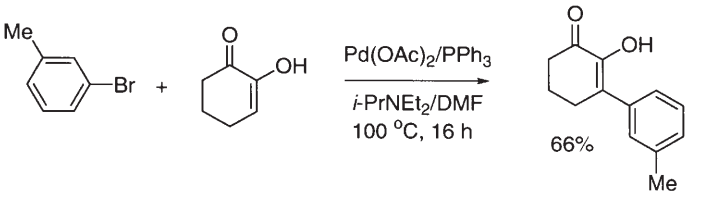
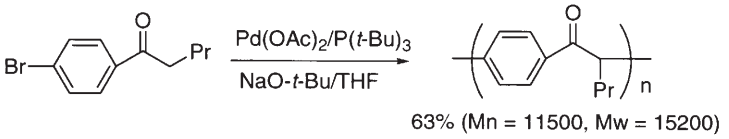
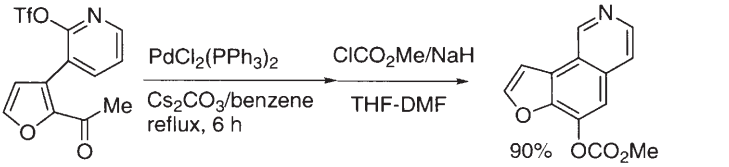


(14)

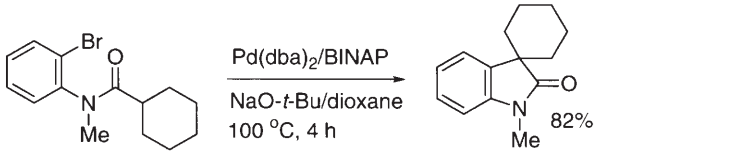


(15)

Muratake et al. reported the intramolecular α-arylation of ketones [55, 56]. Thus, polycyclic compounds are readily obtained from aromatic keto-bromides and keto-triflates (Eq. 16). Bromo-amides can give the corresponding cyclization products (Eq. 17) [52]. Related intramolecular vinylation reactions to give aliphatic polycyclic compounds have also been reported (Eq. 18) [57, 58]. The intramolecular cyclization of aromatic halo-ketones under carbon monoxide, which proceeds by mechanism C, gives the corresponding α-acylated products (Eq. 19) [32].



(16)



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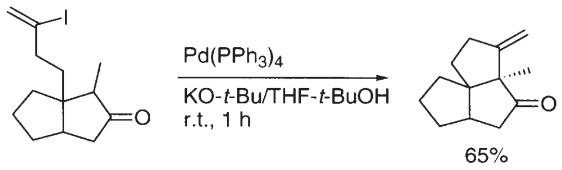

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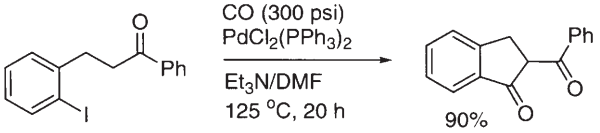
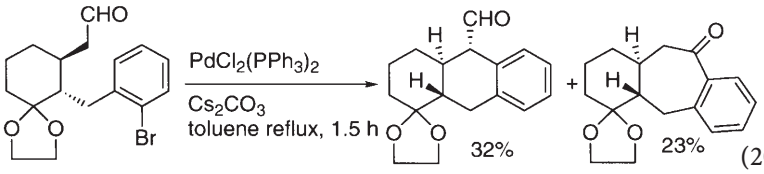


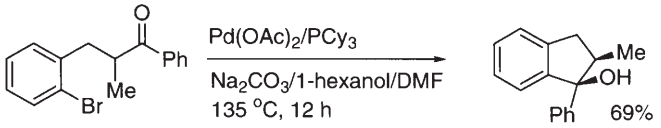
(19)

Since simple aliphatic aldehydes readily undergo aldol condensation under basic conditions, their intermolecular α-arylation is not successful. However, the intramolecular reaction is possible (Eq. 20) [59]. It is interesting that an unusual cyclization product via cleavage of the aldehyde C-H bond is observed in addition to the normal α-arylation product. Other examples of this kind of arylation are described in Sect. 3.3.



(20)

In contrast to the above intramolecular reactions, Yamamoto and coworkers have demonstrated that aromatic halo-ketones having an alkyl substituent at their α-position are transformed to cyclized products at the carbonyl carbon (Eq. 21) [60]. This suggests that a new mechanism, nucleophilic addition of the arylpalladium moiety in the key intermediate to the carbonyl group (Scheme 2), can occur. Addition of an alcohol such as 1-hexanol is essential for the reaction. A possible role of it might be to facilitate the reduction of Pd(II) to Pd(0).



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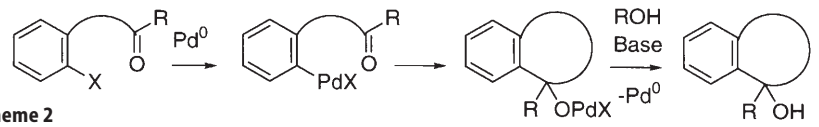
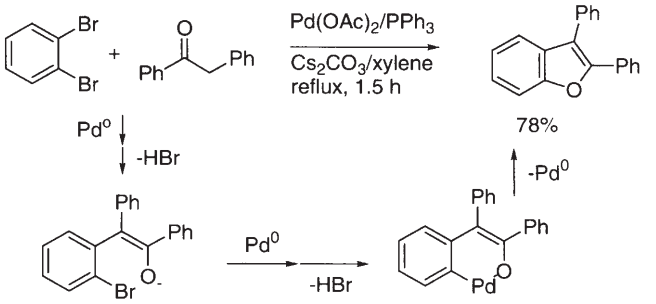


Scheme 2

Treatment of *ortho*-functionalized halobenzenes with ketones gives cyclized products even in the intermolecular cases. The reaction of *o*-dibromobenzene

with benzyl phenyl ketones affords 2,3-diphenylbenzofurans, forming C-C and C-O bonds (Eq. 22) [61]. This reaction seems to occur by initial α-arylation followed by the coupling of the second bromide moiety with the enol oxygen. In contrast, treatment of the dibromide with dibenzyl ketone gives 1,3-diphenyl-2-indanone, forming two C-C bonds (Eq. 23).



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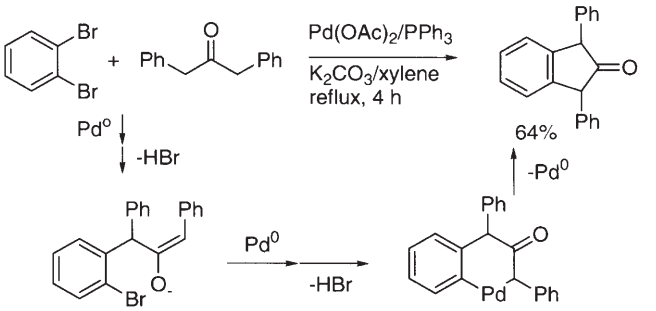
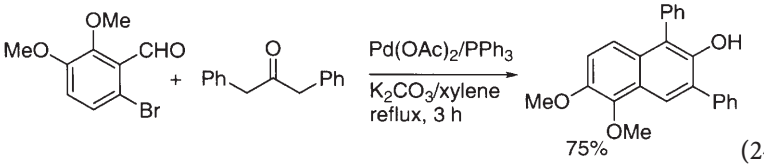


(23)

This suggests that in the case that both intramolecular C- and O-arylations are of geometrically equal possibility, the former preferentially takes place. The reaction of *o*-bromobenzaldehydes with dibenzylketones gives 1,3-diaryl-2-naphthols that may be useful materials as bulky O-ligands (Eq. 24) [62]. This cyclization involves palladium-catalyzed α-arylation and base-promoted dehydrative condensation. Treatment of *o*-iodoanilines with ketones produces indole derivatives (Eq. 25) [63]. In this case, dehydrative condensation between the amino group and the carbonyl group occurs initially and the subsequent carbopalladation (mechanism A) leads to the products.



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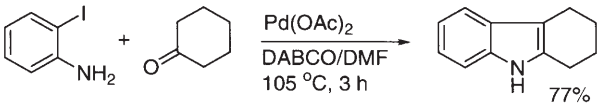
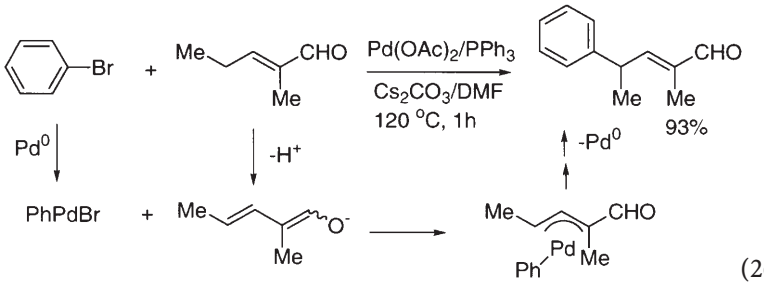


(25)

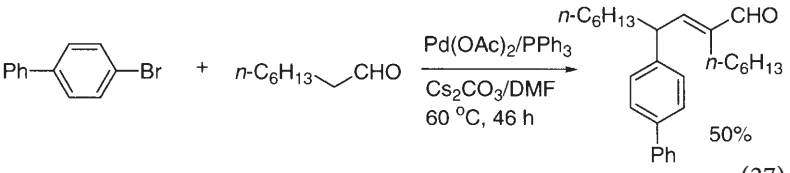
2.3
α,β-Unsaturated Carbonyl Compounds

As described above, the intermolecular α-arylation of simple aliphatic aldehydes is not successful. However, the authors have found that their aldol products, 2-substituted (*E*)-2-alkenals, are arylated efficiently and selectively at their γ-position (Eq. 26) [64].



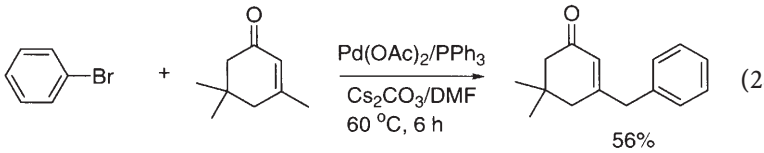
(26)

The use of a relatively soluble base such as Cs_2CO_3 allows good product yield. No products are formed via carbopalladation. Therefore the reaction is considered to occur on a dienolate anion generated from the enal to give an aryl(π-allyl)palladium intermediate. The regioselectivity seems to be determined in the reductive elimination of the product. Treatment of aliphatic aldehydes with aryl bromides brings about aldol condensation followed by γ-arylation to afford 2:1 coupling products (Eq. 27). Note that γ-arylation products are also produced in the arylation of a tin-masked dienolate [65, 66].



(27)

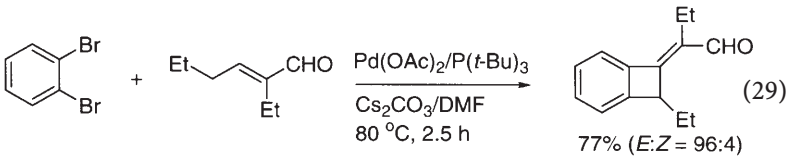
A number of cyclic enones also undergo γ-arylation. In the reaction of isophorone, for example, there are two possible γ-sites. Of these, the 3-methyl group is exclusively attacked (Eq. 28) [64].



(28)

Enals and enones as well as ketones react with *ortho*-functionalized bromobenzenes to give the corresponding cyclized products (cf. Eqs. 22 – 24). The reaction of *o*-dibromobenzenes with alkenals gives benzocyclobutane derivatives (Eq. 29) [61]. 1-Naphthol derivatives are produced by using *o*-bromobenzalde-

hydes (Eq. 30) [62]. From the reaction of cyclic enones with *o*-dibromobenzenes are obtained tricyclic compounds (Eq. 31). Each of these reactions involves γ-arylation as the key step.



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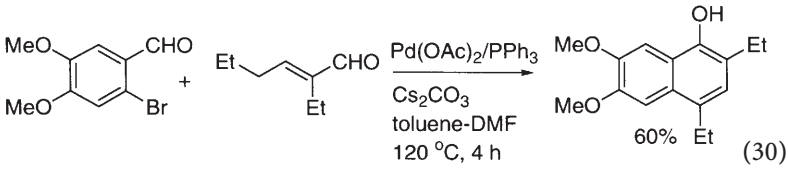

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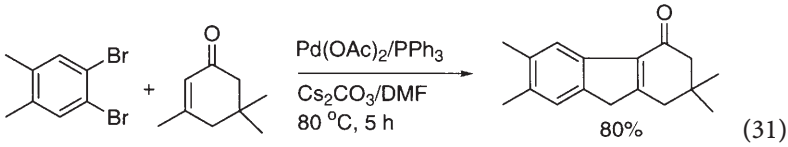
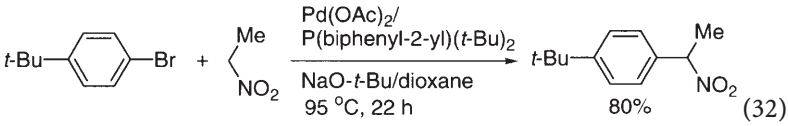


(31)

2.4 Nitro Compounds

Aliphatic nitro compounds can be arylated using appropriate catalyst systems. For example, the reaction of nitroethane using a bulky phosphine affords the corresponding monoarylated product with good selectivity and yield (Eq. 32) [15]. The intramolecular version of α-arylation of nitro compounds has also been reported (Eq. 33) [59].



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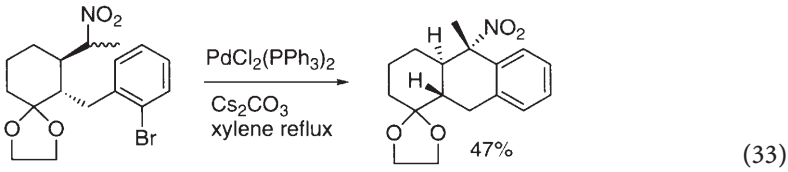
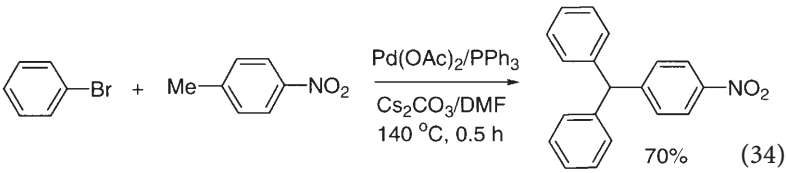


(33)

Interestingly, aromatic nitro compounds, especially 4-alkylnitrobenzenes, are readily arylated at their side chains [67]. Simple substrates such as 4-nitrotoluene tend to undergo diarylation (Eq. 34). In contrast, only monoarylated products are obtained when a neighboring substituent exists in either the halides or the nitro compounds (Eqs. 35 and 36), probably due to steric reasons.

In the reaction of 3,4-dimethylnitrobenzene, only the 4-methyl group is arylated. In expectation, 3-methylnitrobenzene, whose methyl hydrogen is less acidic, does not undergo arylation. This suggests that the reaction of 4-alkylnitrobenzenes seems to involve benzylic anions as principal intermediates. Treatment of 2-nitrotoluene with bromobenzene gives an unexpected coupling product, 2-benzoylaniline.



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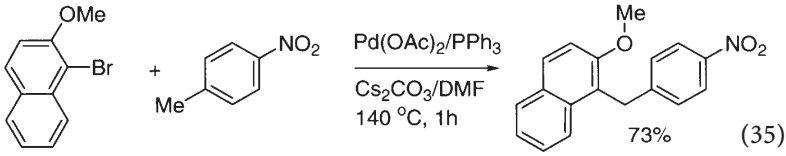

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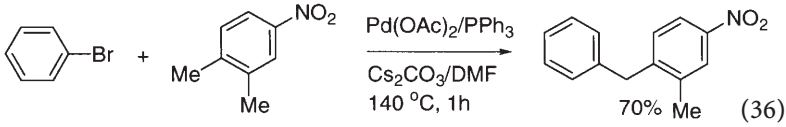
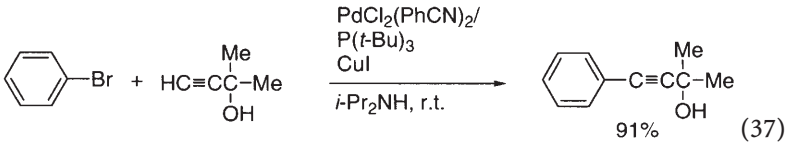


(36)

2.5
Terminal Alkynes

The first examples of palladium catalyzed direct coupling of aryl halides with terminal alkynes, whose acetylenic hydrogen has substantial acidity, were reported by three groups in 1975 [68–70]. The reaction using aryl halides and vinyl halides are highly useful for the preparation of aromatic alkynes and enynes, respectively. Of the original methods, that using copper(I) species as cocatalyst (Sonogashira-Hagihara reaction) can be carried out under relatively mild conditions with good efficiency, and hence has been most often employed. The coupling with terminal alkynes as well as with alkynylmetals has been reviewed [71]. A recent paper has described that a bulky electron-rich ligand such as P(*t*-Bu)$_3$ considerably enhances the reaction (Eq. 37) [72], as observed in other palladium-catalyzed reactions described above.



(37)

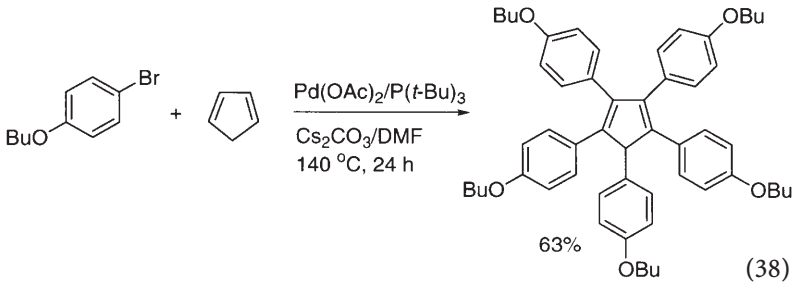
It is worth noting that the reaction using aryl iodides can proceed catalytically using only less expensive copper(I) species, while somewhat harsh conditions are required [73].

2.6
Cyanides

The palladium-catalyzed reaction of aryl halides with cyanides to give cyanobenzenes takes place under relatively mild conditions compared to the conventional method using a stoichiometric amount of CuCN [74]. Thus, palladium catalysis has been often employed. Recently, a number of effective methods for the cyanation have been reported. The reaction of aryl iodides with NaCN under two-phase conditions [75] and those of aryl triflates [76, 77] and aryl chlorides [78] with $Zn(CN)_2$ occur with good efficiency, while these are considered to proceed via mechanism B.

2.7
Cyclopentadienes

Cyclopentadiene, whose deprotonation in the presence of a base gives relatively stable cyclopentadienyl anion, has also been found to be a suitable substrate for palladium catalyzed arylation [79]. Metallocenes, typically zirconocene dichloride, are also arylated [79, 80]. By using excess aryl bromides, they are completely arylated to produce structurally interesting pentaarylcyclopentadienes (Eqs. 38 and39).



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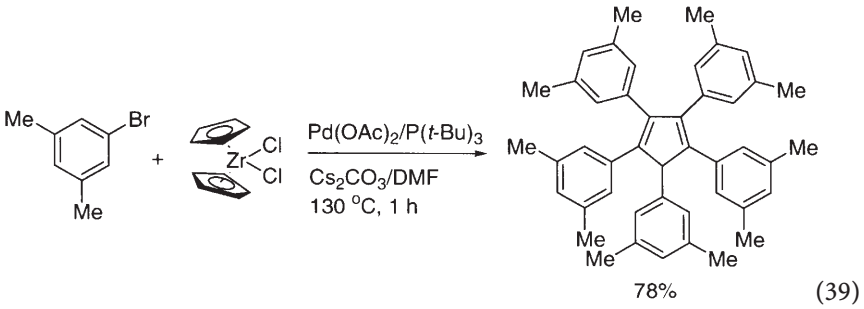


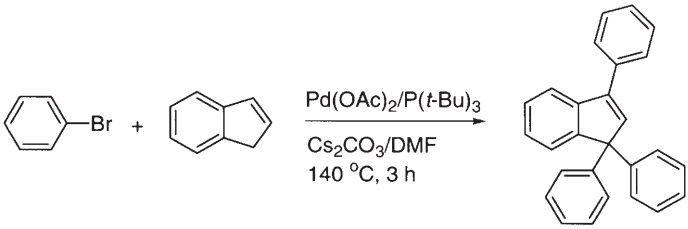
(39)

Note that the products are useful building blocks for the construction of certain functional systems including electroluminescent devices [81, 82]. The arylation proceeds via partially arylated cyclopentadienes in a stepwise manner. Thus, by the reaction of di- and triarylated cyclopentadienes, the corresponding

pentaaryl compounds having different aryl groups can be obtained. In the case using metallocenes, the initial arylation may involve transmetalation. It should be noted that P(*t*-Bu)$_3$ as ligand significantly enhances these arylation reactions as for the reactions using other carbon nucleophiles described above. Another important merit using the phosphine is that, while PPh_3 causes the contamination of phenyl groups in the products [83–85], the scrambling can be avoided.

A typical procedure for Eq. (38) [79] is as follows. A mixture of cyclopentadiene (1 mmol), the aryl bromide (6 mmol), Cs_2CO_3 (6 mmol), $Pd(OAc)_2$ (0.05 mmol), P(*t*-Bu)$_3$ (0.12 mmol) in DMF (10 ml) is heated in a screw-capped tube for 24 h at 140 °C under nitrogen (the phosphine ligand is added after the solvent; the oil bath is preheated to the reaction temperature before the tube is dipped in). After cooling to room temperature, CH_2Cl_2 (50 ml) and *p*-TsOH (12 mmol) are added under stirring and after 10 min the mixture is filtered through silica gel (5 g) with CH_2Cl_2 (25 ml) as eluent. The solvent is evaporated, the residue dried in vacuo at 50 °C, and finally fractionated by flash chromatography on silica gel using hexane-ether (98:2, v/v) as eluent.

Indene as a fused cyclopentadiene is arylated to give 1,1,3-triarylindenes (Eq. 40), while the reaction of 2-phenylindene gives 1,3-diaryl-2-phenylindenes. The third arylation in the latter reaction seems to be inhibited by steric factors. This is consistent with the lack of hexaarylated products in the reaction of cyclopentadiene.



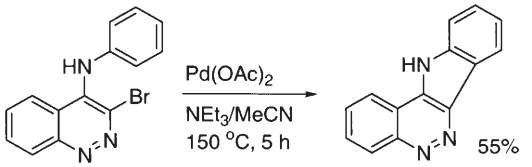
(40)

3 Arylative Coupling via Cleavage of Aromatic and Formyl C-H Bonds

Biaryl structures are found in a wide range of important compounds, including natural products and organic functional materials [86, 87]. One of the most common and useful methods for preparing biaryls is the palladium catalyzed coupling of aryl halides with arylmetals (mechanism B). On the other hand, aryl halides have been known to be capable of directly coupling with aromatic compounds as formal nucleophiles under palladium catalysis. While the intramolecular cases are particularly effective, appropriately functionalized aromatic compounds such as phenols and aromatic carbonyl compounds as well as aromatic heterocycles have been found to undergo intermolecular arylation on their aromatic rings. Related arylation reactions with aldehydes via cleavage of their formyl C-H bonds are also known as described below.

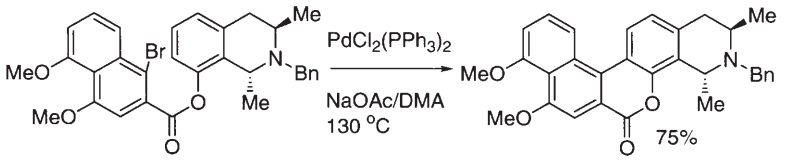
3.1
Intramolecular Coupling with Aromatic Compounds

In 1982, Ames and coworkers reported the cyclization of bromocinnolines as one of the first examples of the intramolecular aryl-aryl coupling (Eq. 41) [88–90].



(41)

This method has been applied to the synthesis of various polycyclic aromatic compounds [91]. Among the interesting applications are lactone formation in the preparation of natural products having biaryl skeletons (Eq. 42) [87] and double cyclization leading to spirocyclic compounds (Eq. 43) [92] and a fullerene fragment (Eq. 44) [93].



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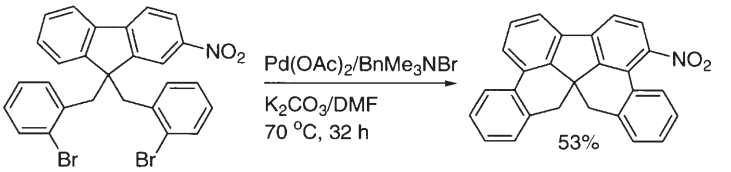

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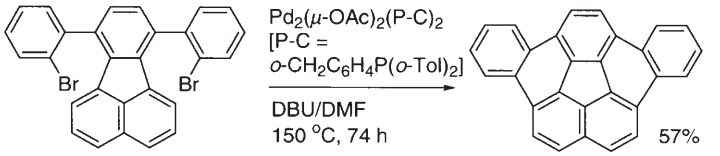
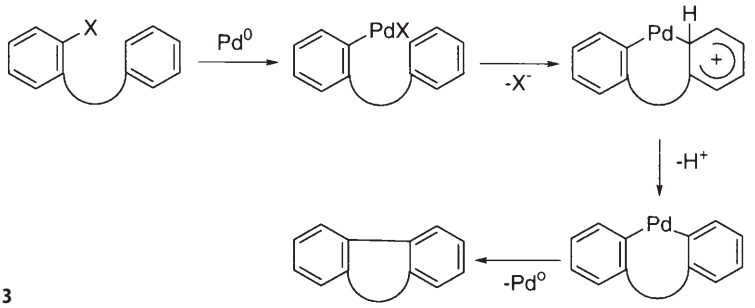


(44)

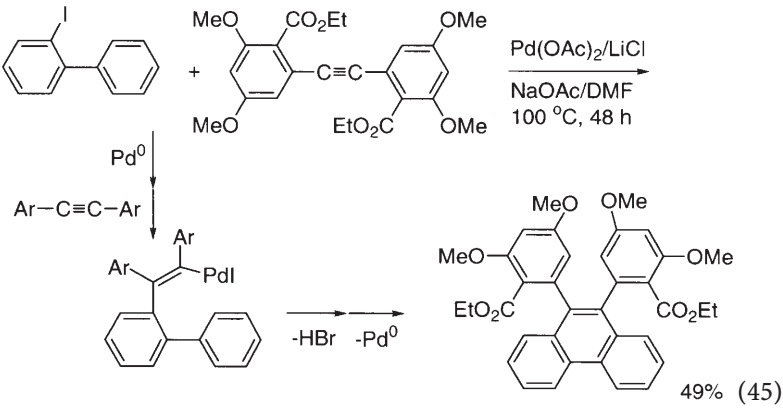
It is often considered that such a cyclizative coupling involves intramolecular electrophilic attack of arylpalladium(II) moiety on another aromatic ring in the key intermediate (Scheme 3) [91, 94, 95].

However, the reaction of substrates having a strong electron-withdrawing substituent such as nitro group can occur effectively (e.g., Eq. 43) [91, 92]. Thus, another mechanism involving intramolecular aromatic C-H activation would also participate in the reaction. Other possibilities including carbopalladation have also been considered [91]. Therefore, it is likely that the mechanism is not unity and several pathways occur depending on the employed substrates, catalysts, and reaction conditions.



Scheme 3

The intramolecular reaction can be extended to the cross-annulation reaction of aryl halides with unsaturated compounds [31, 33]. For example, 2-halobiphenyls react with alkynes to give phenanthrene derivatives [96, 97]. By using the method, the analogs of hypericin known as antiviral agent (Eq. 45) [98] and indolocarbazoles (Eq. 46) [99] have been prepared. In these reactions, vinylpalladium intermediates are involved.



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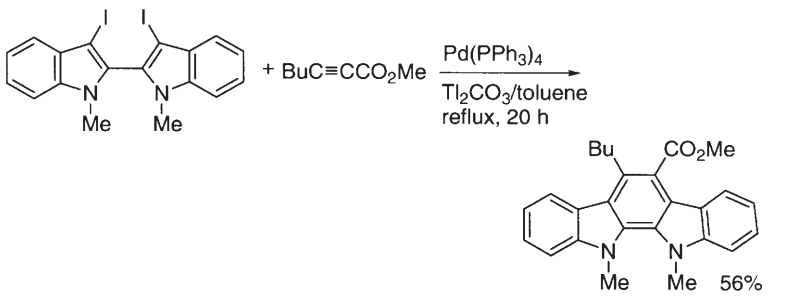
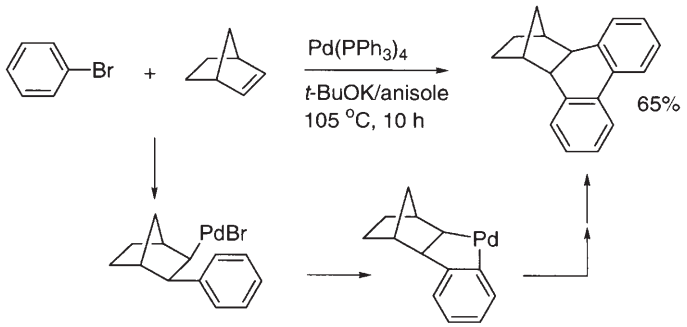


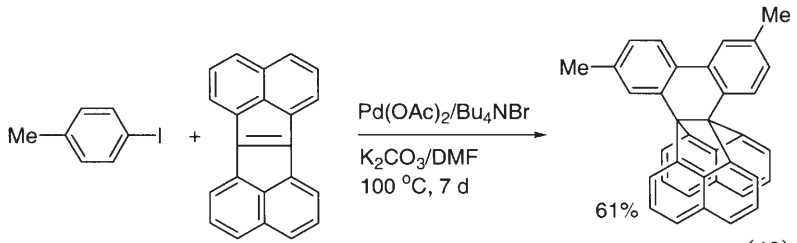
(46)

It is of particular interest that phenanthrene derivatives can also be obtained by the reaction of halobenzenes with alkenes or alkynes. Bromobenzenes react with norbornene to give 2:1 coupling products (Eq. 47) [100].



(47)

From the reaction of iodobenzenes with acenaphth[1,2-*a*]acenaphthylene are formed propellane type products (Eq. 48) [101, 102]. The reaction with diarylacetylenes affords 9,10-diarylphenanthrenes (Eq. 49) [103, 104].



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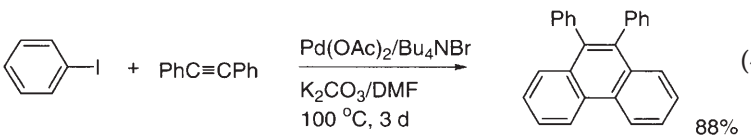
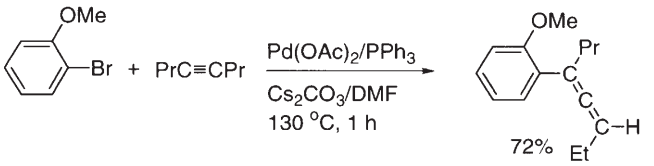


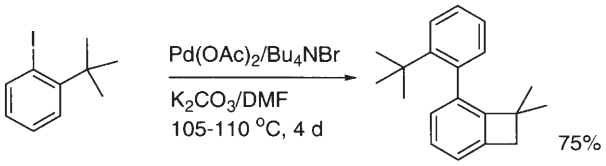
(49)

These reactions are considered to involve insertion of the unsaturated compounds to arylpalladium species followed by the formation of palladacycle intermediates. Oxidative addition of another halide molecule to them leads to the products. In the reaction with norbornene [105–108] and diphenylacetylene [109], the corresponding 3:1 and 4:1 products and 3:1 product, respectively, are also formed under somewhat different conditions. The mechanisms to account for the formation of these unusual products involving multiple C-H cleavage steps have been proposed. It is noted that, in contrast to Eq. (49), treatment of aryl bromides with aliphatic internal alkynes gives allene derivatives (Eq. 50) [110].



(50)

A number of di- or trimerization reactions of aryl and vinyl halides, which are mechanistically related to those in Eqs. 47 – 49, have been reported. Interestingly, in the reaction of *o*-*tert*-butyl- and *o*-methoxyiodobenzenes, the aliphatic C-H bonds in the *ortho*-substituents are intramolecularly activated to give di- and trimerized products, respectively, with good yields (Eqs. 51 and 52) [111 – 114]. These reactions can also be applied to the cross-coupling of different halides. Dimerization of vinyl halides has also been reported [115, 116].



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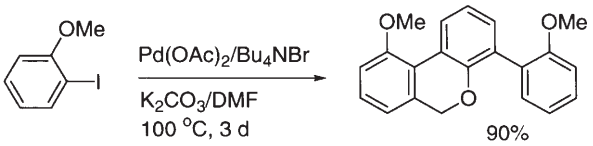
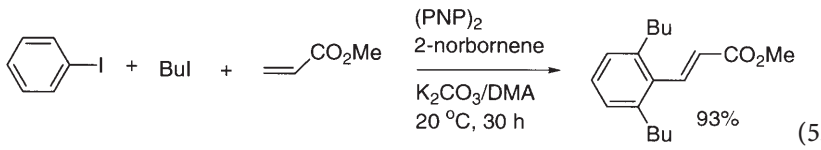
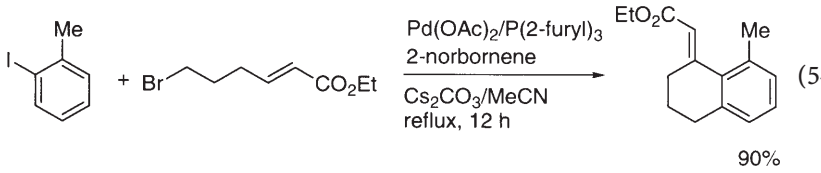


(52)

There is an intriguing application of the reaction in Eq. (47) using norbornene. Catellani et al. reported that the sequential vinylative 2,6-dialkylation of aryl iodides occurs by single treatment with alkyl iodides and other alkenes such as acrylic esters in the presence of norbornene (Eq. 53) [117, 118]. The fact that the insertion of norbornene to arylpalladium species and the successive cyclopalladation are reversible is the key for the unique reaction to occur. Thus, the strained alkene is not involved in the product, but acts as the template for the activation of *ortho* C-H bonds which leads to a 2,6-dialkylphenylpalladium intermediate. The subsequent vinylation takes place as in a usual Mizoroki-Heck reaction to give the final products. Using appropriate haloalkenes gives cyclized products (Eq. 54) [119]. The use of arylboronic acids in place of alkenes brings about Suzuki-Miyaura reaction in the last step to give dialkylated biaryls (Eq. 55) [120].



(53)



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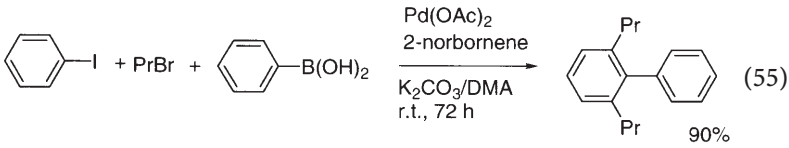


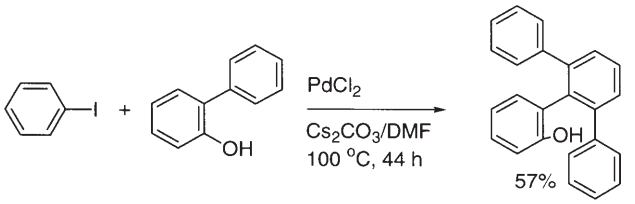
(55)

A typical procedure for Eq. (53) [117] is as follows. Under nitrogen the palladium complex (PNP dimer) (0.017 mmol) and K_2CO_3 (0.5 mmol) are placed in a Schlenk-type flask. A solution containing iodobenzene (0.35 mmol), *n*-butyl iodide (1.4 mmol), norbornene (0.32 mmol), and methyl acrylate (0.52 mmol) in DMA is then added. After the mixture has been stirred at 20 °C for 30 h, 5 % H_2SO_4 is added, and the organic part is extracted with CH_2Cl_2, and dried. Concentration to dryness gives almost pure product. Flash chromatography on silica with hexane/ethyl acetate (9:1) as eluent affords pure methyl 2,6-di-*n*-butylcinnamate in 93 % yield on the arene (including the phenyl group contained in the catalyst).

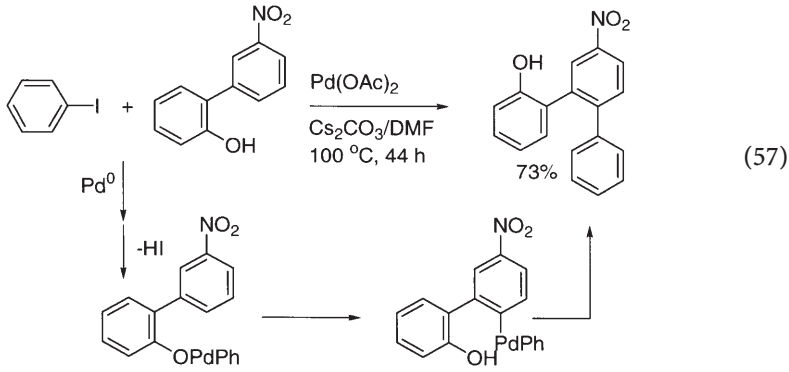
3.2
Intermolecular Coupling with Aromatic Compounds

3.2.1
Phenols

Biphenyl-2-ols undergo not only monoarylation but also diarylation on treatment with iodobenzenes to give the corresponding products coupled regioselectively at the 2′-positions (Eq. 56) [46, 50]. Thus, sterically crowded 1,2,3-triphenylbenzene derivatives are obtained by single treatment. While 4′-substituted biphenyl-2-ols are also diarylated, 3′-substituted ones give only monoarylated products due to steric reasons (Eq. 57). The reaction of biphenyl-2-ols seems to involve coordina-

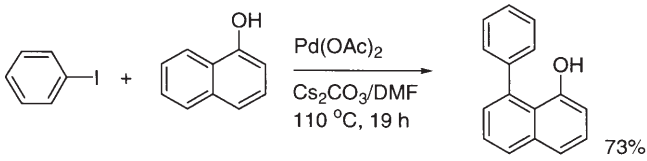


(56)



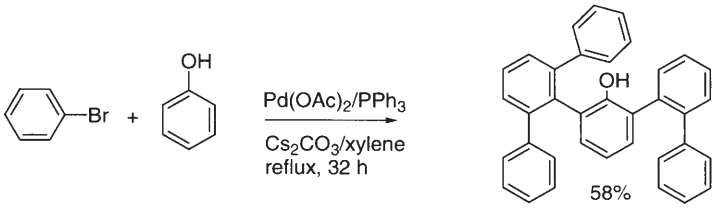
(57)

tion of the phenolate oxygen to intermediary arylpalladium species followed by C-H cleavage at the spatially neighboring positions as the key steps. Since the arylation proceeds even when the 3′-substituent is strongly electron-withdrawing or -donating, the mechanism of the C-H cleavage may not be unity as described in Sect. 3.1. 1-Naphthols are arylated at their 8-position (Eq. 58).



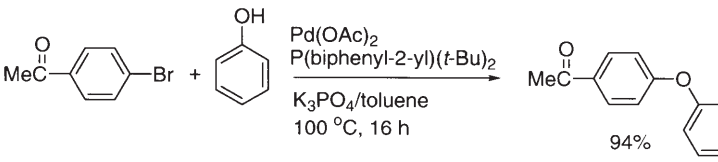
(58)

Interestingly, phenol itself and 4-substituted phenols are multiply arylated around the oxygen up to five times in the presence of excess aryl bromides to selectively give 2-biphenyl-6-terphenylphenols (Eq. 59) [121].

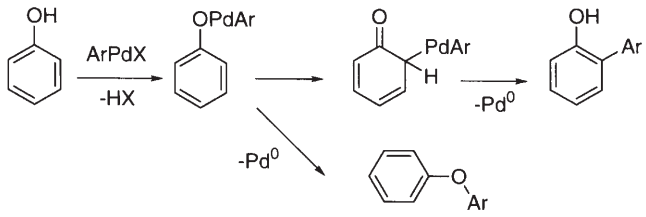


(59)

The reaction is considered to involve two mechanistic patterns; i. e., the reactions of arylpalladium intermediates with (a) phenolates at the *ortho*-positions, this being similar to the α-arylation of ketones (see Sect. 2.2 and Scheme 4), and with (b) thus formed biphenyl-2-ols as in Eq. (56). While the latter proceeds in both DMF and xylene, the use of the less polar solvent is essential for the former to occur effectively. However, the intramolecular cyclization of halophenyl-linked phenols is known to occur in DMA [122]. It is worth noting that *O*-arylation of phenols to give diaryl ethers occurs when bulky phosphine ligands are used (Eq. 60) [26–28]. This may imply that in the aryl(aryloxy)palladium intermediates, reductive elimination to give the ethers is enhanced by the ligands (Scheme 4).

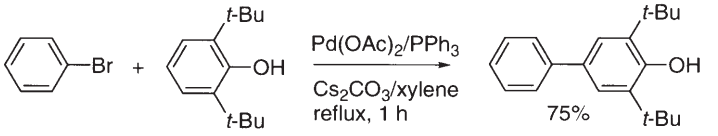


(60)

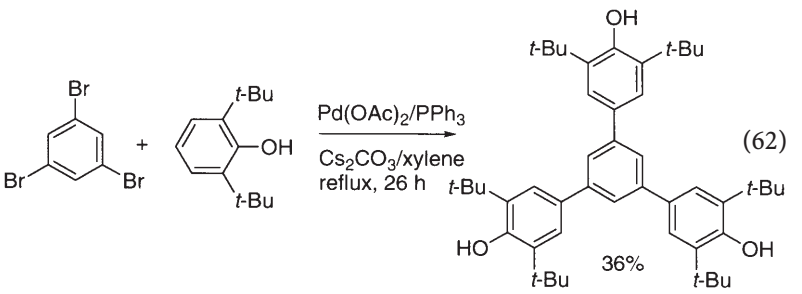


Scheme 4

In contrast to the above reactions, 2,6-di-*tert*-butylphenol undergoes arylation at the *p*-position (Eq. 61) [123]. This is attributable to the fact that not only the bulkiness of the *tert*-butyl groups makes the coordination of the phenolic oxygen to arylpalladium species impossible, but also their electron-donating ability enables electrophilic attack of the complex at the *p*-position. The reaction can be carried out using aryl bromides having various substituents and the *tert*-butyl groups in the products can be easily removed in the presence of acids [124]. Thus, the reaction appears to be useful as a general synthetic method for 1,1′-biphenyl-4-ols that are valuable building blocks of liquid crystalline materials [125]. By using 1,3,5-tribromobenzene a 1,3,5-tri(4-hydroxyphenyl)benzene derivative (Eq. 62) [126] is obtained that can give a relatively stable radical [127, 128].



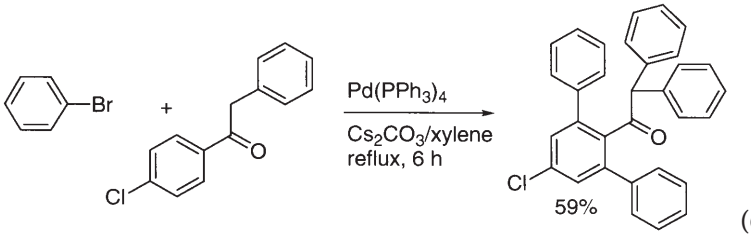
(61)



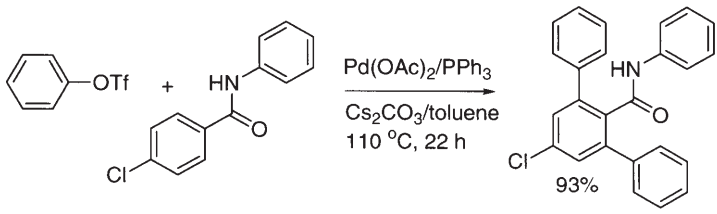
(62)

3.2.2
Aromatic Carbonyl Compounds

Acetophenones and benzyl phenyl ketones are arylated not only on the α-position, but also on the two *ortho*-positions using excess aryl bromides (Eq. 63) [129]. The reaction proceeds via α-arylation (see Sect. 2.2) followed by aromatic arylation. The latter seems to occur via coordination of the enolate oxygen to arylpalladium species, as in the reaction of 2-phenylphenols and 1-naphthols (Eqs. 56 – 58). Benzanilides are similarly diarylated on the benzoyl moiety using aryl bromides or triflates (Eq. 64) [130]. *N*-Arylation [131] is not observed under the given conditions.



(63)

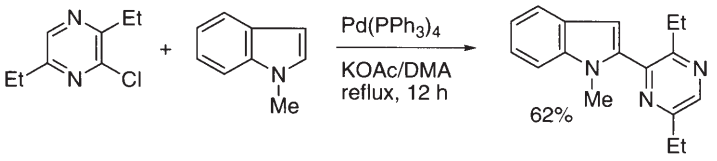


(64)

A typical procedure for Eq. (64) [121] is as follows. A mixture of benzanilide (1 mmol), phenyl triflate (4 mmol), $Pd(OAc)_2$ (0.05 mmol), PPh_3 (0.3 mmol), Cs_2CO_3 (4 mmol), and toluene (8 ml) is stirred under nitrogen (with a balloon) at 110 °C for 24 h. After cooling, the reaction mixture is poured into dilute HCl, extracted with ethyl acetate, and dried over sodium sulfate. Evaporation of the solvent followed by washing the residual solid well with hexane gives the product.

3.2.3
Aromatic Heterocycles

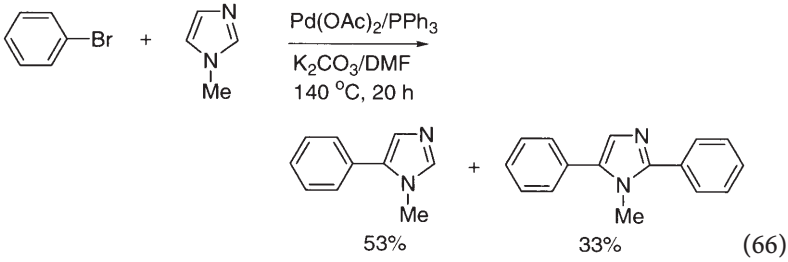
In 1989, Ohta and coworkers reported that 2-chloro-3,6-dialkylpyradines directly and regioselectively react with *N*-substituted indoles at the 2- or 3-position depending on the *N*-substituents (Eq. 65) [132].



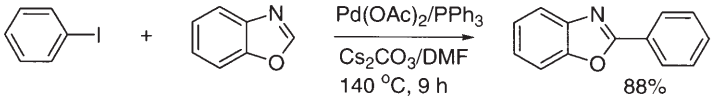
(65)

This may imply that the intermolecular coupling of various aryl halides with other heteroaromatic compounds may proceed. Indeed, it is now known that not only the special heteroaromatic halides but also usual aryl halides can react with a variety of five-membered aromatic heterocycles, including furans, thiophenes, and azole compounds such as *N*-substituted imidazoles, oxazoles, and thiazoles [133–137]. The arylation of azoles can be carried out using iodobenzoate immobilized on an insoluble polymer support [138]. Related intermolecular reactions of indole [139] and imidazole [140] derivatives have also been reported.

It was found that the identity of bases employed is a significant factor determining the reaction efficiency as in other reactions. When alkali metal carbonates are used, solubilities of both the bases and alkali metal halides as by-products affect the reaction [135]. The relatively soluble base, Cs_2CO_3, is effective for the reactions using aryl iodides and K_2CO_3 is as effective as Cs_2CO_3 for those using aryl bromides. As represented by the arylation of 1-methylimidazole (Eq. 66), the reaction of azole compounds preferentially occurs at the most electron-rich 5-position. Thus, the coupling seems to involve electrophilic attack of arylpalladium species on the azole. However, the electron-poor 2-position can also be arylated (Eqs. 66 and 67), indicating that another mechanism intervenes as discussed in Sect. 3.1.

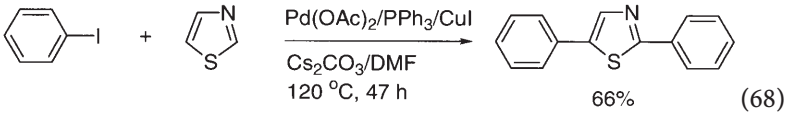


(66)

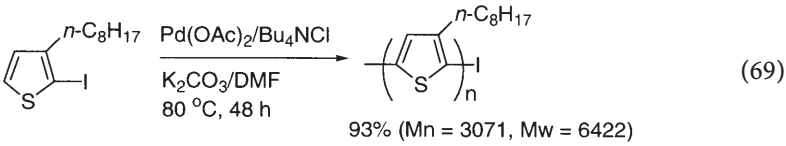


(67)

The reaction of sulfur-containing heterocyclic compounds such as thiophenes and thiazoles (Eq. 68) is specifically enhanced by addition of CuI, while the role is not yet definitive [135]. The use of a bulky phosphine ligand such as P(*t*-Bu)$_3$ also promotes the arylation [141]. 2-Iodothiophenes are polymerized to produce polythiophenes (Eq. 69) [142].



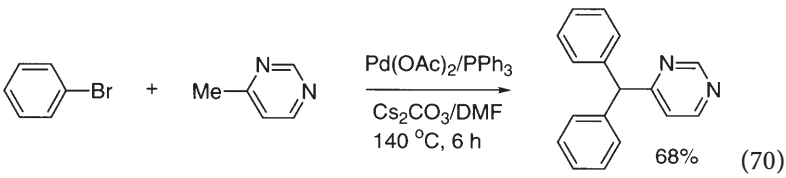
(68)



(69)

A typical procedure for Eq. (68) [135] is as follows. In a 100-ml two-necked flask is placed Cs_2CO_3 (2 mmol), which is then dried. Then thiazole (1 mmol), iodobenzene (2 mmol), $Pd(OAc)_2$ (0.1 mmol), PPh_3 (0.2 mmol), CuI (2 mmol), and DMF (5 ml) are added and the resulting mixture is stirred under nitrogen (with a balloon) at 120 °C for 47 h. After cooling, the mixture is poured into an aqueous solution of ethylenediamine (ca. 4%, 50 ml), extracted with CH_2Cl_2, and dried over sodium sulfate. The diarylated product is isolated by column chromatography on silica gel using hexane-ethyl acetate (2:1, v/v) as eluent.

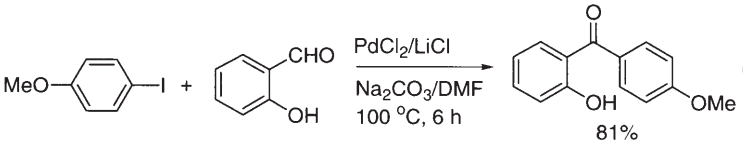
4-Methylpyrimidine undergoes arylation not on the nuclei, but on the substituent (Eq. 70) [67]. This may be attributed to the fact that the nuclei is less susceptible toward electrophiles and the methyl hydrogen is relatively acidic.



(70)

3.3 Aldehydes

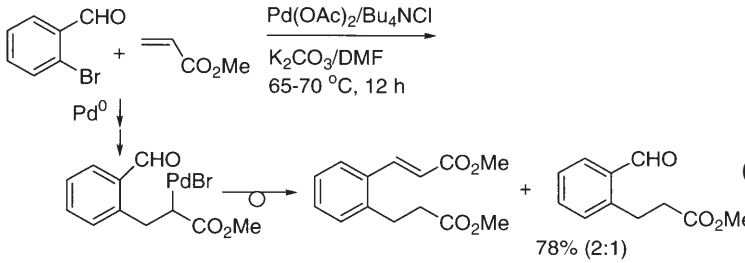
Some arylative coupling reactions involving cleavage of aldehyde C-H bonds have been reported. The authors found that treatment of salicylaldehydes with aryl iodides gives benzophenone derivatives (Eq. 71) [143].



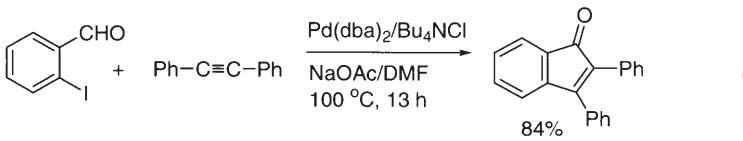
(71)

This reaction seems to involve coordination of the phenolate oxygen to aryl-palladium intermediate and the successive cyclopalladation as the key steps. This is similar to the arylation of biphenyl-2-ols in Eqs. (56) and (57). A similar intramolecular reaction of haloaryl-linked aldehydes to give cyclic ketones is found in Eq. (20). This occurs along with α-arylation.

o-Bromobenzaldehydes react with alkenes (Eq. 72) [144] and alkynes (Eq. 73) [145, 146] accompanied by C-H cleavage of the formyl group. The reactions are considered to involve alkyl- and vinylpalladium intermediates, respectively, which attack the formyl function. Disubstituted arenes accompanied by decarbonylation and indenones by usual dehydrohalogenation, respectively, are formed as the products.

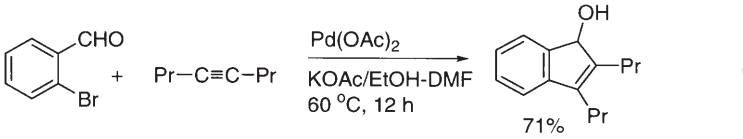


(72)



(73)

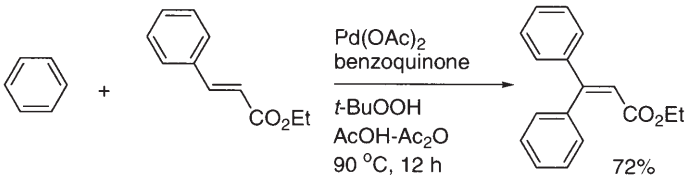
In contrast to the reaction in Eq. (73), treatment of *o*-bromobenzaldehydes as well as *o*-bromophenyl ketones with alkynes in the presence of ethanol gives cyclized products at the carbonyl carbon, i. e., indenols (Eq. 74) [147, 148]. This reaction resembles that in Eq. (21).



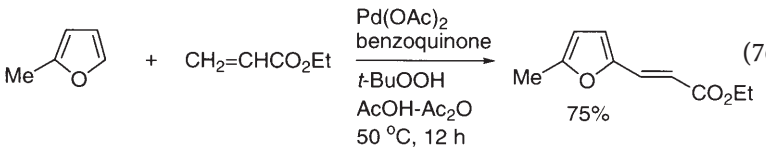
(74)

4
Direct Coupling of Arenes with Unsaturated Compounds

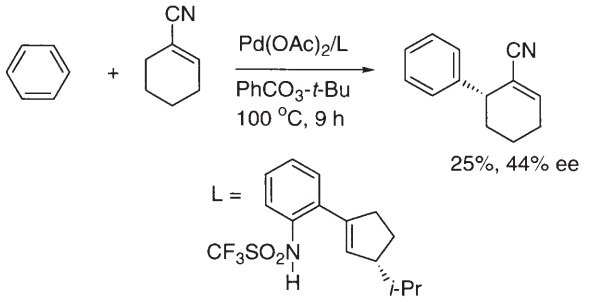
Aromatic compounds can react with Pd(II) species, typically $Pd(OAc)_2$, via cleavage of their C-H bonds to give arylpalladium(II) species. Therefore, the arylation of alkenes can be performed directly using arenes and aromatic heterocycles (Fujiwara-Moritani reaction) [149, 150]. In this arylation, halogenation of arenes can be omitted, but an oxidizing reagent for the reoxidation of Pd(0) to Pd(II) should be added for making the reaction catalytic. Thus, much effort has been made to find effective reoxidizing systems. Recently, the use of *tert*-BuOOH together with a catalytic amount of benzoquinone has been reported to be significantly effective (Eqs. 75 and 76) [151]. The first example of asymmetric version of Fujiwara-Moritani reaction using chiral oxazoline ligands in the presence of $PhCO_3$-*t*-Bu has also been described (Eq. 77) [152].



(75)



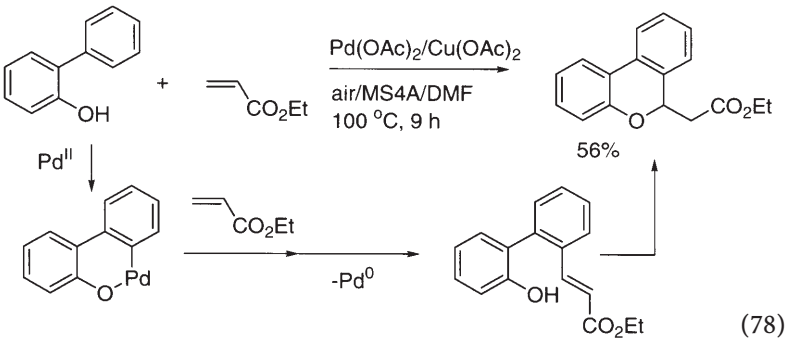
(76)



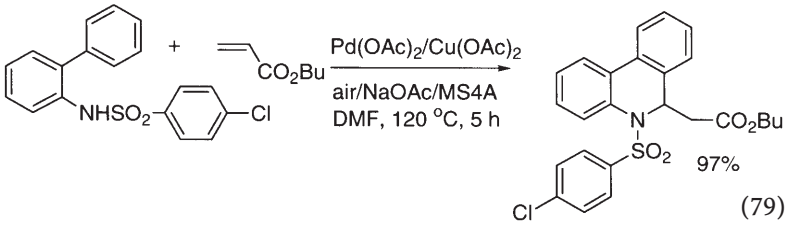
(77)

It is well known that aromatic compounds having an appropriate functional group readily and regioselectively undergo palladation with Pd(II) species on their *ortho*-position to form intramolecularly chelated arylpalladium complexes [1]. They can also react with various reagents including alkenes and alkynes. However, no effective catalytic version has been reported until recently. One of the possible reasons for this is due to the fact that the functional groups can give stable chelating complexes are susceptible toward oxidizing reagents. On the other hand, the authors found that some functional groups having acidic hydro-

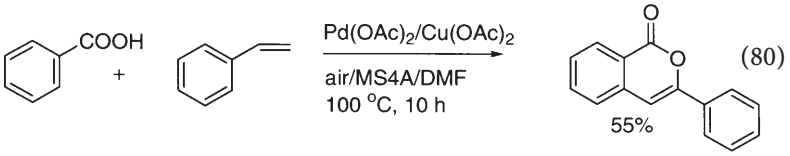
gen including phenolic hydroxyl, sulfonylamino, and carboxyl groups are suitable substituents to realize the direct catalytic coupling with alkenes. Thus, biphenyl-2-ols efficiently react with alkenes such as acrylate esters in the presence of $Cu(OAc)_2$-air as reoxidizing system, giving the corresponding products via vinylation followed by nucleophilic cyclization (Eq. 78) [153]. Similarly, 2-sulfonylaminobiphenyls react with alkenes (Eq. 79) [154]. The reaction of aromatic acids with styrene also affords cyclized products (Eq. 80).



(78)



(79)



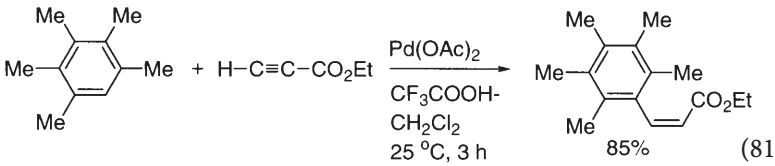
(80)

A typical procedure for Eq. (78) [153] is as follows. In a 100-ml two-necked flask with a reflux condenser, a balloon, and a rubber cap are placed $Pd(OAc)_2$ (0.05 mmol), $Cu(OAc)_2 \cdot H_2O$ (0.05 mmol), and molecular sieves 4 A (400 mg). After the apparatus is evacuated by pumping, nitrogen (750 ml) is introduced. Then the phenol (1 mmol), the alkene (3 mmol), DMF (5 ml), and air (150 ml) are injected into the flask, and the resulting mixture is stirred at 100 °C for 9 h. After cooling, the mixture is extracted with diethyl ether and dried over sodium sulfate. The coupling product is isolated by column chromatography on silica gel using hexane-ethyl acetate (99.5:0.5, v/v) as eluent.

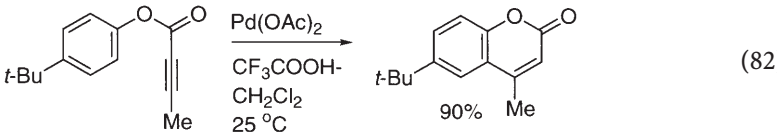
In these reactions, coordination of the functional groups to Pd(II) species in the medium with liberation of proton appears to be the key, as in the arylation of phenolic compounds and aryl ketones (see Sects. 3.2.1 and 3.2.2). It should be

noted that related coupling reactions of aromatic compounds having carbonyl- and nitrogen-containing functional groups with unsaturated compounds especially by using ruthenium and rhodium catalysts, which involve pre-coordination of the functional groups followed by *ortho*-C-H activation, have been developed significantly [155–157].

Arenes, especially electron-rich ones, have been found to react with alkynes in the presence of Pd(II) or Pt(II) species in a mixed solvent containing CF_3COOH (Eq. 81) [158–160]. The intramolecular reaction is also possible (Eq. 82). The mechanism proposed for the reaction involves aromatic palladation to form arylpalladium species as in Fujiwara-Moritani reaction, insertion of an alkyne, and protonolysis of the resulted vinylpalladium intermediate.



(81)



(82)

5 Conclusion

It has been proved that aryl halides react directly with a variety of carbon nucleophiles including active methylene compounds, ketones, aldehydes, esters, amides, α,β-unsaturated carbonyl compounds, nitro compounds, terminal alkynes, cyanide, and cyclopentadienes, irrespective of the fact that the acidities of these substrates are diverse [161]. The halides have also been found to be capable of coupling with various aromatic and heteroaromatic compounds and aldehydes via cleavage of their sp^2 C-H bonds. Substantial progress has been made in the coupling of arenes and unsaturated compounds. These direct methods, not requiring stoichiometric metalation or halogenation, appear to be useful and economical for preparing a broad range of aromatic fine compounds, while there are still limitations which should be mitigated.

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