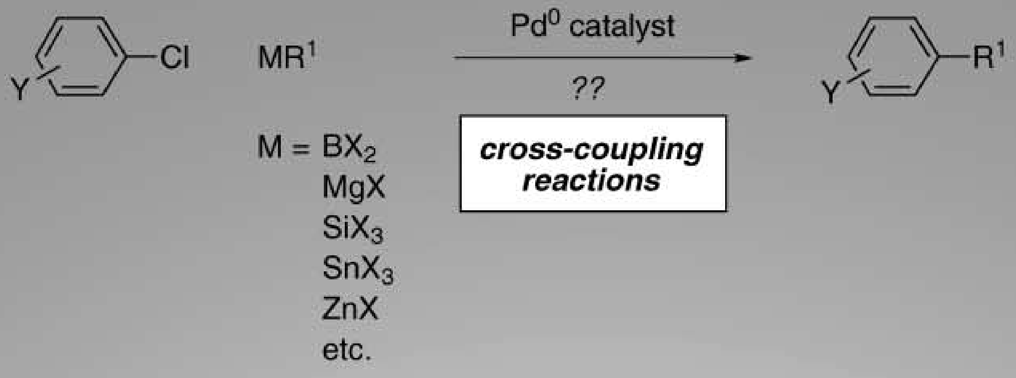
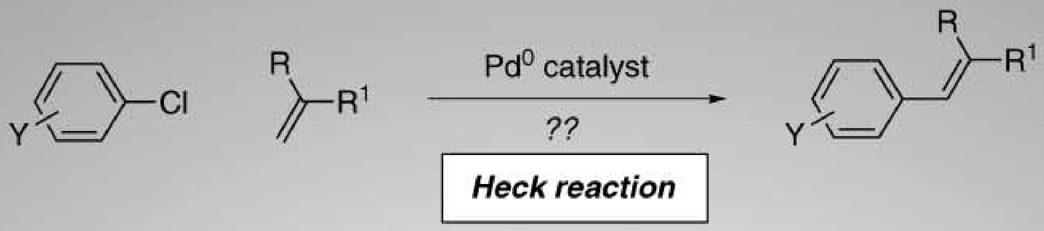
Palladium-Catalyzed Coupling Reactions of Aryl Chlorides



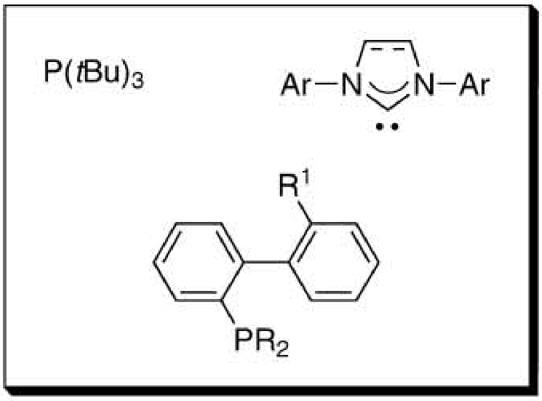


State-of-the-art

1998: *Essentially no general methods*

2002: *Mild and versatile catalysts*

Key: choice of ligand



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Palladium-Catalyzed Coupling Reactions of Aryl Chlorides

Adam F. Littke and Gregory C. Fu*

Collectively, palladium-catalyzed coupling reactions represent some of the most powerful and versatile tools available to synthetic organic chemists. Their widespread popularity stems in part from the fact that they are generally tolerant to a large number of functional groups, which allows them to be employed in a wide range of applications. However, for many years a major limitation of palladium-catalyzed coupling processes has been the poor reactivity of aryl chlorides, which from the standpoints of cost and availability are more attractive substrates than the corresponding bromides, iodides, and triflates. Traditional palladium/triarylphosphane catalysts are only effective for the coupling of certain activated aryl chlorides (for example, heteroaryl chlorides and substrates that bear electron-withdrawing groups), but not for aryl chlorides in general. Since 1998, major advances have been described by a number of research groups addressing this challenge; catalysts based on bulky, electron-rich phosphanes and carbenes have proved to be particularly mild and versatile. This review summarizes both the seminal early work and the exciting recent developments in the area of palladium-catalyzed couplings of aryl chlorides.

Keywords: catalysis · cross-coupling · ligand effects · palladium · synthetic methods

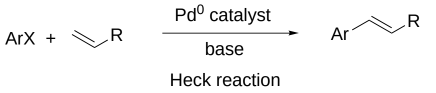
1. Introduction

During the final quarter of the twentieth century, palladium catalysts emerged as extremely powerful tools for the construction of carbon–carbon [Eq. (1) and Eq. (2)], as well as carbon–heteroatom, bonds.[1] Numerous monographs and review articles have documented the increasing frequency with which palladium-catalyzed coupling processes are applied to a wide array of endeavors, which range from synthetic organic chemistry to materials science. Their popularity stems in part from their tolerance of many functional groups, which allows them to be employed in the synthesis of highly complex molecules.[2]

$$RX \quad + \quad MR^1 \xrightarrow[\text{(additive)}]{\text{Pd}^0\text{ catalyst}} RR^1 \qquad (1)$$

R, R^1 = aryl, vinyl
X = Br, I, OTf

M	
B	Suzuki
Sn	Stille
Si	Hiyama
Zn	Negishi
Mg	Kumada
etc.	



(2)

Until recently, nearly all reports of palladium-catalyzed couplings described the use of organic bromides, iodides, and triflates as substrates—organic chlorides were noticeably uncommon partners, despite the fact that, among the halides, chlorides are arguably the most useful single class of substrates, because of their lower cost and the wider diversity of available compounds.[3] Unfortunately, chlorides were generally unreactive under the conditions employed to couple bromides, iodides, and triflates.[4, 5]

The low reactivity of chlorides is usually attributed to the strength of the C–Cl bond (bond dissociation energies for Ph–X: Cl: 96 kcal mol^{-1}; Br: 81 kcal mol^{-1}; I: 65 kcal mol^{-1}),[3] which leads to reluctance by aryl chlorides to oxidatively add to Pd^0 centers, a critical initial step in palladium-catalyzed coupling reactions (Schemes 1 and 2).[6, 7]

Fortunately, remarkable progress has been achieved since 1998 in the development of palladium-based catalysts that can in fact accomplish cross-couplings and Heck reactions of a wide array of chlorides. In this review, we summarize these exciting recent discoveries, as well as some of the seminal studies that laid the groundwork for these advances.[8]

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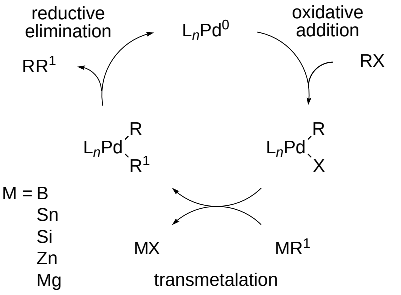
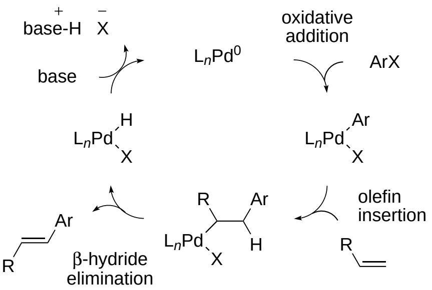


Scheme 1. Generalized mechanism for palladium-catalyzed cross-coupling reactions.



Scheme 2. Mechanism of the Heck reaction.

2. Carbon – Carbon Bond-Forming Reactions

2.1. Cross-Coupling Reactions

The palladium-catalyzed cross-coupling of aryl and vinyl halides/triflates with organometallic reagents serves as a straightforward and powerful method for formation of carbon – carbon bonds (Eq. (1) and Scheme 1). The R^1 group of the organometallic reagent can be any of a variety of saturated or unsaturated groups, for example, alkyl, aryl, vinyl, and alkynyl. Most magnesium, tin, and zinc reagents are sufficiently reactive to undergo transmetalation with palladium without the need for an additive; boron and silicon reagents, on the other hand, are usually reluctant to transmetalate in the absence of an activator. As a consequence, Suzuki and Hiyama cross-couplings are typically carried out in the presence of an additive, the role of which is to form a higher valent, more reactive "ate" complex.

2.1.1. Suzuki Reactions

Among palladium-catalyzed cross-coupling processes, the Suzuki reaction of aryl and vinyl halides/triflates with boronic acids is emerging as a favorite,[9] and it has been applied industrially to the production of compounds such as losartan, a Merck antihypertensive drug.[10] This popularity is attributable to a variety of factors, such as the commercial availability of a large number of boronic acids, as well as their nontoxic nature and stability to heat, air, and moisture. Furthermore, the boron-containing by-product of the Suzuki cross-coupling can readily be separated from the desired compound.

2.1.1.1. Suzuki Reactions of Activated Aryl Chlorides

As for many other palladium-catalyzed coupling processes, certain aryl chlorides, specifically, electron-poor aryl chlorides, which are activated toward oxidative addition, have long been known to serve as suitable substrates for Suzuki reactions. Thus, Suzuki couplings of heteroaryl chlorides such as chloropyridines can often be achieved with traditional triarylphosphane-based palladium catalysts.[11] This reactivity is especially significant because of the abundance of chlorine-containing nitrogen heterocycles (as compared with bromine- or iodine-containing nitrogen heterocycles) that are commercially available.

One of the earliest examples of a Suzuki reaction of a heteroaryl chloride was provided by Gronowitz et al., who

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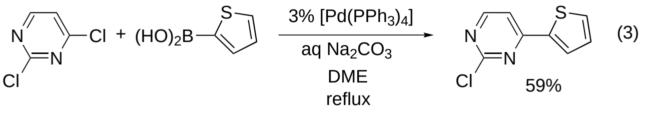
G. C. Fu

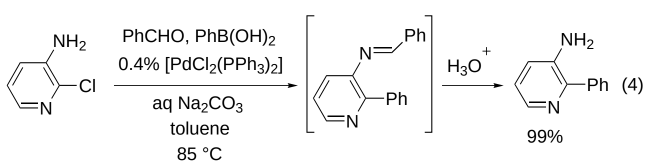

A. F. Littke

Adam F. Littke was born in Toronto, Canada in 1974. He earned his B.Sc. in 1997 from the University of Ottawa, where he worked in the laboratory of Prof. Darrin S. Richeson. In 2002, he received his PhD from the Massachusetts Institute of Technology, where he studied under the direction of Prof. Gregory C. Fu. He initiated the group's program in palladium-catalyzed coupling reactions, and focused his efforts on Suzuki, Stille, and Heck reactions of aryl chlorides. He is currently employed as a process chemist at Bristol – Myers Squibb in New Jersey.

examined the coupling of 2,4-dichloropyrimidine with 2-thienylboronic acid and established that the 4-chloro group is more reactive than the 2-chloro group [Eq. (3)].[12, 13] Subsequently, other chloro-substituted nitrogen heterocycles have been shown to undergo Suzuki coupling in the presence of traditional palladium catalysts including pyridines,[13a–c, 14] pyridine *N*-oxides,[14h] pyrazines,[12d, 13b–d, 15] pyridazines,[12d, 16] triazines,[13e, g, 17] quinolines,[13c, 18] isoquinolines,[13a, 19] quinazolines,[20] cinnolines,[20b] phthalazines,[21] β-carbolines,[22] phenanthrolines,[23] imidazo[1,2-*b*]pyridazines,[24] pyrazolo[1,5-*a*]pyrimidines,[18b] pyrazolopyrimidines,[13e] triazolopyrimidines,[13e] pyrrolopyrimidines,[13e] and purines.[25]

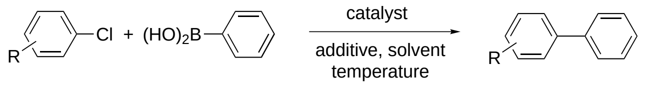


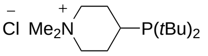
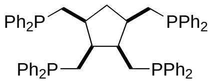
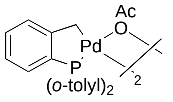
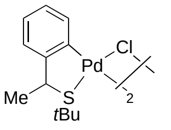
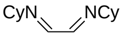
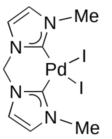
The use of a Suzuki reaction of a heteroaryl chloride to produce 2-phenyl-3-aminopyridine, a key intermediate in the synthesis of 2-phenyl-3-aminopiperidine (an important pharmacophore present in potent non-peptidic NK1 receptor antagonists) has recently been reported. Direct coupling of 2-chloro-3-aminopyridine with phenylboronic acid was unsuccessful; however, a one-pot protection/Suzuki coupling/deprotection sequence furnished the target compound in excellent yield on a greater than 100-gram scale [Eq. (4)].[26]



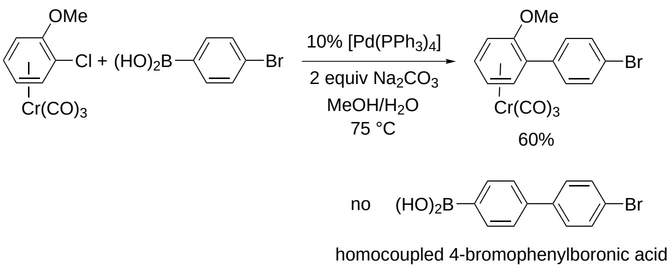
Within the last decade, a number of examples of Suzuki reactions of non-heteroaryl electron-deficient aryl chlorides have been described, and some representative couplings are depicted in Table 1. Equation (5) furnishes a particularly interesting illustration of the activation that can be provided by a powerful electron-withdrawing group. Thus, Uemura et al. have shown that aryl chlorides that are η^6-bound to $Cr(CO)_3$ are remarkably reactive coupling partners in Suzuki reactions.[27, 28] The aryl chloride couples with an aryl boronic acid even in the presence of the electron-donating, deactivating *ortho*-methoxy substituent. Furthermore, no homocou-

Table 1. Suzuki cross-couplings of activated aryl chlorides.



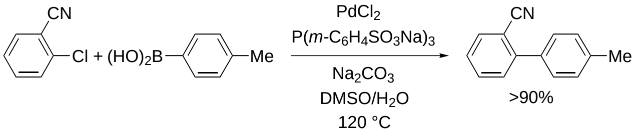
Entry	R	Catalyst	Conditions	Yield [%]
1	4-CN	$Pd(OAc)_2$/ 	Na_2CO_3, H_2O/MeCN, 80 °C	92
2	4-NO_2, CN, 2-CN, 2-Cl-, 3-Cl-pyridine	$PdCl_2 \cdot$ polymer-CH_2PPh_2	aq K_3PO_4, toluene, 80 °C	72–91[a]
3	4-NO_2, COMe, CF_3, CN, CHO, 2-COMe, CF_3, CN, CHO	$[PdCl(allyl)]_2$/ 	K_2CO_3, xylene, 130 °C	13–100
4	4-COMe		K_2CO_3, *o*-xylene, 130 °C	82
5	4-COMe, CN, NO_2		K_3PO_4, DMF, 25, 130 °C	90–95[b]
6	4-COMe, CN, CF_3, 3-CHO, COMe, NO_2, 2-CO_2Me, NO_2, CHO	$Pd(OAc)_2$/dppp or $[PdCl_2(PCy_3)_2]$	CsF, NMP, 100 °C	42–97
7	4-COMe, 3-CF_3, 2-CN	$Pd(OAc)_2$/P(O*i*Pr)$_3$	Na_2CO_3 or NaOH, toluene, 120 °C	78–94
8	4-COMe, CO_2Me	$Pd(OAc)_2$/ 	Cs_2CO_3, dioxane, 100 °C	85–98
9	4-CN, NO_2	$Pd(OAc)_2$	K_3PO_4, DMF, 25, 130 °C	85–100[b]
10	4-CN, COMe, NO_2, CF_3	Pd/C	K_2CO_3, DMA/H_2O, 80 °C	79–95
11	4-COMe		K_2CO_3, toluene, 120 °C	60

[a] 4-Methylphenylboronic acid was used. [b] *n*Bu_4NBr was used as a co-catalyst. Abbreviations: dppp = 1,3-bis(diphenylphosphanyl)propane; NMP = *N*-methylpyrrolidine; DMA = *N*,*N*-dimethylacetamide; DMF = dimethylformamide.

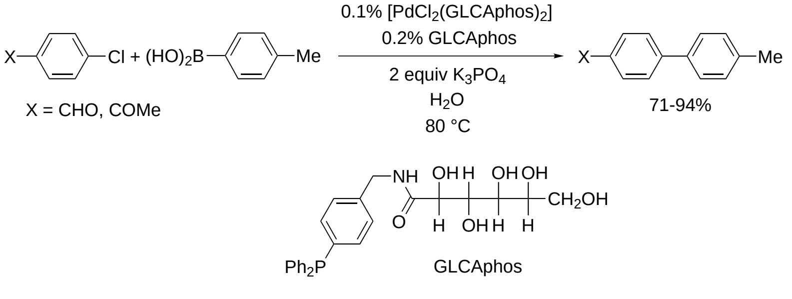

(5)

pled 4-bromophenylboronic acid is observed, thus establishing that highly selective activation of a C–Cl bond occurs in the presence of a typically more reactive C–Br bond.

Conducting reactions in aqueous media can be advantageous, particularly for large-scale industrial applications, as a result of the ease of purification as well as the environmental friendliness and low cost of water.[29] Hoechst has employed the water-soluble triphenylphosphane derivative P(m-$C_6H_4SO_3Na$)$_3$ in the Suzuki cross-coupling of an activated aryl chloride, 2-chlorobenzonitrile for the commercial production (100 tons/year) of 2-cyano-4′-methylbiphenyl,[30] a key intermediate in the synthesis of angiotension II receptor antagonists that are used for the treatment of hypertension [Eq. (6)].[31]


(6)

Another water-soluble triarylphosphane, GLCAphos, derived from D-glucono-1,5-lactone, has been introduced by Miyaura and co-workers.[32] Palladium catalysts based on GLCAphos are effective at low loadings for Suzuki couplings of activated aryl chlorides [Eq. (7)]. More recently, Shaughnessy and Booth have reported that water-soluble alkyl phosphanes are suitable ligands for such processes (Table 1, entry 1).[33]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Inada and Miyaura have established that (polystyrene-CH_2PPh_2) · $PdCl_2$ catalyzes Suzuki reactions of activated aryl chlorides, chloropyridines, and chloroquinolines (Table 1, entry 2).[34] The ligand used for the coupling of 2-chloropyridine with p-tolylboronic acid has been recovered and reused six times, and provided yields ranging from 86–96%. Miyaura and co-workers have also noted that [Pd(PPh_3)$_4$] can be useful for reactions of activated aryl chlorides.[35]

Santelli and co-workers have reported that high turnover numbers (TONs) can be obtained for Suzuki couplings of activated aryl chlorides by using their recently introduced tetrapodal phosphane ligand Tedicyp (Table 1, entry 3).[36] A TON of 6800000 is achieved in the case of highly activated 2-chloro-5-(trifluoromethyl)nitrobenzene; in contrast, a turnover number of just 21 is observed for electron-rich, deactivated 4-chloroanisole. Bidentate ligands such as 1,2-bis(diphenylphosphanyl)ethane (dppe) and 1,4-bis(diphenylphosphanyl)butane (dppb) are considerably less effective. The authors believe that multidentate coordination by Tedicyp imparts increased stability to the palladium catalyst.

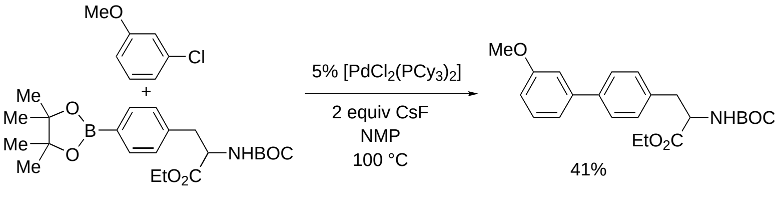
Herrmann et al. introduced phosphorus-based palladacycles[37] to catalyze Suzuki couplings of activated aryl chlorides with catalyst loadings as low as 0.1% Pd (Table 1, entry 4).[38] More recently, metalated benzylphosphane complexes of palladium were shown also to be active in these processes.[39]

Monteiro et al. have established that sulfur-containing palladacycles are effective catalysts for Suzuki reactions of activated aryl chlorides at room temperature (Table 1, entry 5).[40] DMF and K_3PO_4 were the best solvent and base, respectively, among those that were surveyed, and the addition of tetrabutylammonium bromide was found to be beneficial for the reaction rate.[41] Despite the high activity of this catalyst system toward activated aryl chlorides, only poor yields (13–46%; 130°C) were obtained in couplings of electron-neutral and electron-rich aryl chlorides.

Bedford et al. have recently applied "PCP"-pincer complexes to Suzuki cross-couplings of highly activated 4-chloronitrobenzene with phenylboronic acid, and observed turnover numbers as high as 4300. The catalysts are ineffective for reactions of deactivated aryl chlorides.[42]

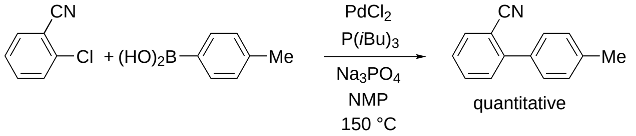
An important observation regarding Suzuki couplings of aryl chlorides was reported in 1997 by Shen, who established that palladium complexes that include a bulky, electron-rich trialkylphosphane (PCy_3, Cy = cyclohexyl) catalyze cross-couplings of activated aryl chlorides at 100°C (Table 1, entry 6).[43] Bidentate 1,3-bis(diphenylphosphanyl)propane (dppp) is also useful in certain cases, whereas dppb, PPh_3, P(2-furyl)$_3$, and $AsPh_3$ are generally ineffective. However, [$PdCl_2$(PPh_3)$_2$] can be employed if the aryl chloride is highly activated (that is, it bears two electron-withdrawing groups).[44] It was speculated that the electron-richness of PCy_3 might facilitate oxidative addition of the Ar–Cl bond to Pd^0 and that the steric demand of PCy_3 might favor ligand dissociation to afford an active monophosphanepalladium catalyst.

Firooznia et al. subsequently applied Pd/PCy_3 to Suzuki cross-couplings of activated aryl chlorides with boronate esters to generate 4-substituted phenylalanines protected with a $tert$-butoxycarbonyl (Boc) group [Eq. (8)].[45] Unfortunately, attempts to extend this chemistry to the synthesis of enantiopure 4-aryl-substituted phenylalanines led to nearly racemic products.[46]



(8)

The high catalytic activity of palladium complexes of bulky, electron-rich trialkylphosphanes in Suzuki couplings of activated aryl chlorides has also been observed by Monteith during the development of a manufacturing route to 2-cyano-4′-methylbiphenyl.[47] Although PCy_3 and $P(iPr)_3$ provided the most active catalysts for this process, their cost was a drawback. Fortunately, $P(iBu)_3$, which is significantly less expensive, is also effective, thereby rendering the route economically viable [Eq. (9), NMP = *N*-methylpyrrolidine].



(9)

Although the success of Pd/trialkylphosphane-based catalysts for Suzuki reactions of activated aryl chlorides has been attributed in part to the electron-richness of the ligands, it is important to note that this feature is not absolutely essential for activity. Thus, Zapf and Beller have shown that Pd/phosphite complexes can catalyze couplings of activated aryl chlorides (Table 1, entry 7).[48] Phosphites are relatively electron-poor phosphorus ligands,[49] yet bulky tris(2,4-di-*tert*-butylphenyl)phosphite and triisopropylphosphite are effective for palladium-catalyzed couplings of activated aryl chlorides with phenylboronic acid. A modest yield (54%) is obtained with chlorobenzene, an unactivated aryl chloride. Less bulky phosphites (for example, triethyl- or triphenylphosphite) are significantly less effective, which is attributed to their greater propensity to hydrolyze under the reaction conditions. It is also possible that more bulky ligands favor the formation of highly reactive palladium complexes with only one ligand.

Until recently, palladium-catalyzed coupling chemistry relied nearly exclusively on phosphorus-based ligands. This has changed rapidly during the past few years (for example, with the development of N-heterocyclic carbenes; see Section 2.1.1.2). In 2001, Nolan and co-workers reported the use of 1,4-diazabutadienes, which are chelating nitrogen-based ligands, in palladium-catalyzed Suzuki reactions (Table 1, entry 8).[50] They determined that an *N*-alkyl substituent furnishes higher reactivity than an *N*-aryl substituent and that couplings of electron-deficient aryl chlorides with phenylboronic acid proceed in good yield at 100 °C with the cyclohexyl-substituted diazabutadiene. Under the same conditions, 4-chlorotoluene and 4-chloroanisole react in poor yield (< 35%), perhaps because the ligand is not sufficiently electron-rich to facilitate oxidative addition of more challenging C–Cl bonds.

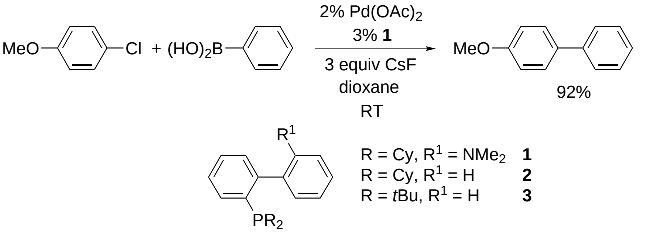
Interestingly, "ligandless" palladium catalysts can effect Suzuki couplings of certain activated aryl chlorides. Thus, Dupont and co-workers have reported that $Pd(OAc)_2/N(nBu)_4Br$ and $[PdCl_2(SEt_2)_2]$ catalyze the reaction of 4-chlorobenzonitrile with phenylboronic acid at 130 °C; in the case of $Pd(OAc)_2/N(nBu)_4Br$, the coupling can be conducted at room temperature, although long reaction times are required (Table 1, entry 9).[51] Unactivated aryl chlorides do not couple under these "ligandless" conditions.[52, 53]

LeBlond et al. have recently described the application of heterogeneous Pd/C to Suzuki reactions of activated aryl chlorides with phenylboronic acid (Table 1, entry 10).[54] Couplings of electron-neutral and electron-rich aryl chlorides proceed in only modest yields (32–54%). The choice of solvent ($DMA/H_2O = 20/1$) is important—more water leads to a significant amount of homocoupling, and less water results in severely retarded reaction rates. Separation of the product from the catalyst can be achieved through simple filtration, which leaves less than 1.0 ppm palladium in the product (< 0.10% loss, based on the initial amount of palladium). Coupling does not occur in the presence of an equivalent of PPh_3, an interesting contrast to the analogous Ni/C-based catalyst for Suzuki reactions of aryl chlorides, for which PPh_3 appears to be required for activity.[55]

2.1.1.2. Suzuki Reactions of Unactivated Aryl Chlorides

Prior to 1998, there were no reports of effective palladium-catalyzed Suzuki reactions of electron-neutral or electron-rich aryl chlorides. Clearly, this represented a serious limitation in the scope of this important process. In 1998, the groups of Buchwald and Fu developed catalyst systems that couple a wide range of aryl chlorides in good yield.

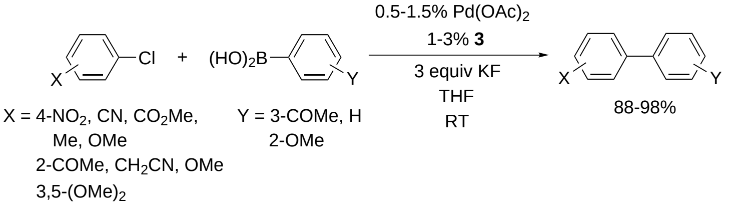
In their study in 1998, Buchwald and co-workers reported that aminophosphane **1** is a very effective ligand for palladium-catalyzed Suzuki reactions of aryl chlorides [Eq. (10)].[56] Remarkably, this catalyst system couples a broad spectrum of aryl chlorides, such as electron-neutral and electron-rich substrates, at room temperature. CsF was the base of choice, although the less expensive K_3PO_4 could be employed at 100 °C.



(10)

R = Cy, $R^1 = NMe_2$ **1**
R = Cy, R^1 = H **2**
R = *t*Bu, R^1 = H **3**

Buchwald and co-workers subsequently determined that biphenyl ligands **2** and **3** can be even more effective than **1** in palladium-catalyzed Suzuki reactions of aryl chlorides, thereby establishing that the amino group of **1** is not essential for high activity.[57] Room-temperature Suzuki couplings of a

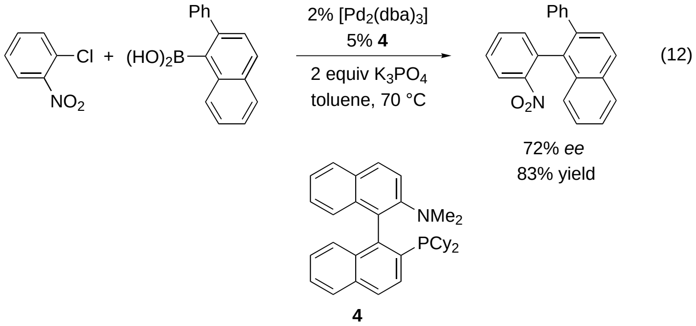


(11)

wide array of partners can be achieved using ligand **3** with 0.5–1.5% Pd and KF as the activator [Eq. (11)].

9-Alkyl-9-BBN derivatives are also suitable substrates for this catalyst system (BBN = 9-borabicyclo[3.3.1]nonane). Ligands **1** and **2** (with K_3PO_4 in toluene) are more effective than **3** for hindered reactants. The air stability and commercial availability of these biphenyl-based ligands make them particularly attractive.[58]

Parrish and Buchwald have developed a polymer-bound dicyclohexylphosphanylbiphenyl ligand that can be employed for Suzuki reactions of electron-neutral and hindered aryl chlorides; the coupling product can be isolated without the need for column chromatography.[59] In addition, binaphthyl derivative **4**, an enantiopure variant of biphenyl ligand **1**, can be applied to the catalytic asymmetric synthesis of axially chiral biaryls, which are present in a number of natural products [Eq. (12); dba = *trans,trans*-dibenzylideneacetone].[60]



(12)

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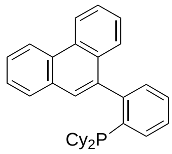
A stabilizing interaction between the *ortho*-aryl group and a palladium d orbital has been suggested as being responsible for the high activity exhibited by catalysts based on biphenyl ligands.[61] An X-ray crystal structure of a palladium complex of phenanthrene derivative **5** is consistent with this hypothesis (Pd/**5**).[62] The first efficient Suzuki couplings to generate tetra-*ortho*-substituted biaryls have been achieved in the presence of $[Pd_2(dba)_3]$/**5** [Eq. (13)].

Observations of Kocovsky et al. are consistent with the idea that an interaction between the *ortho*-aryl group and palladium may be responsible for the unusual reactivity that Buchwald described.[63] Through crystallographic and spectroscopic studies, Kocovsky et al. have established that aminophosphane **6** preferentially serves as a P,C chelate, not a P,N chelate, to palladium (Scheme 3). Interestingly, $Pd(OAc)_2$/**6** catalyzes the Suzuki coupling of 4-chlorobenzaldehyde with phenylboronic acid at room temperature, a surprising level of reactivity for a catalyst based on a triarylphosphane.

In the same year as the original report by Buchwald et al., Littke and Fu also described a versatile method for palladium-catalyzed Suzuki cross-couplings of aryl chlorides in which they used a sterically demanding and electron-rich trialkylphosphane, $P(tBu)_3$ [Eq. (14)].[64] A $P(tBu)_3$:Pd ratio between 1.0–1.5:1 was most effective. Deactivated and hindered aryl chlorides were suitable substrates for this catalyst system. In this initial study, $[Pd_2(dba)_3]$, Cs_2CO_3, and dioxane were employed as the palladium source, activator, and solvent, respectively. A variety of other



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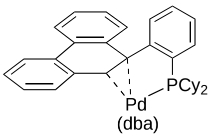
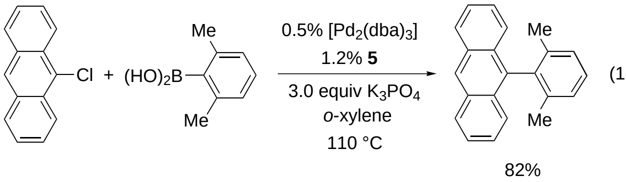


Pd/**5**



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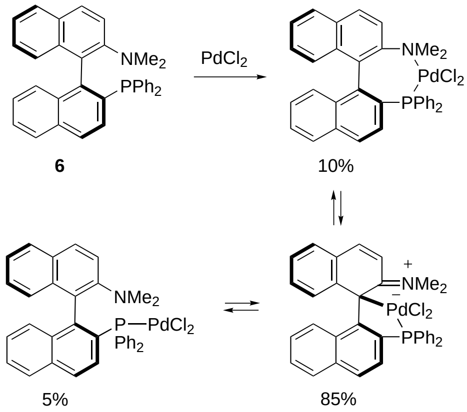
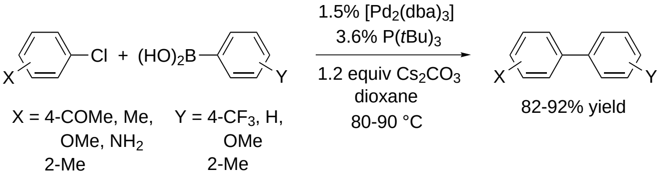


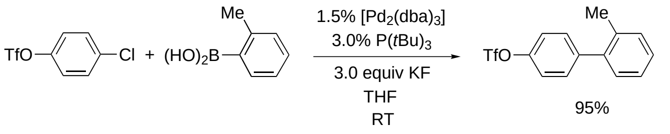
Scheme 3. Pd^{II} complexes of 2-dimethylamino-2′-diphenylphosphanyl-1,1′-binaphthyl.



(14)

commercially available phosphanes were screened, including PPh_3 and 1,1′-binaphthalene-2,2′-diylbis(diphenylphosphane) (binap); however, the only phosphane that showed useful reactivity was sterically demanding and electron-rich PCy_3.

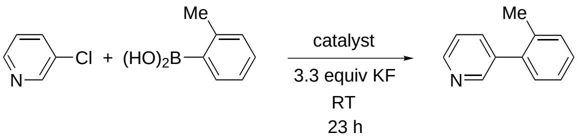
Fu and co-workers subsequently determined that KF is a more effective additive than Cs_2CO_3, which allowed Suzuki cross-couplings of activated aryl chlorides, including heteroaryl chlorides, to proceed at room temperature ($P(tBu)_3$:Pd = 1:1).[65] This Pd/$P(tBu)_3$-based catalyst system exhibits a highly unusual reactivity profile—that is, unprecedented selectivity for the coupling of an aryl chloride in preference to an aryl triflate [Eq. (15)]. Alkyl boronic acids, which are often less reactive in Suzuki reactions than aryl boronic acids, are



(15)

suitable substrates for Pd/P(tBu)$_3$.[66] Turnover numbers as high as 9700 can be achieved with this catalyst system. Since the original report, a number of research groups have applied Pd/P(tBu)$_3$ to Suzuki couplings of a wide range of activated and unactivated aryl and heteroaryl chlorides.[21, 46, 67]

The observation that the use of a 1:1 ratio of P(tBu)$_3$:Pd is important for obtaining high reactivity in room-temperature Suzuki reactions of aryl chlorides prompted a preliminary mechanistic investigation. According to ^{31}P NMR measurements, Pd(PtBu$_3$)$_2$[68] is the only palladium–phosphane complex that is present in an appreciable quantity during the catalytic reaction. Interestingly, though, [Pd(PtBu$_3$)$_2$] is itself a rather ineffective catalyst for room-temperature Suzuki cross-couplings [Eq. (16)]; however, the addition of phosphane-free [Pd$_2$(dba)$_3$], so as to achieve a 1:1 P(tBu)$_3$:Pd ratio, results in a much more active catalyst system [Eq. (16)].



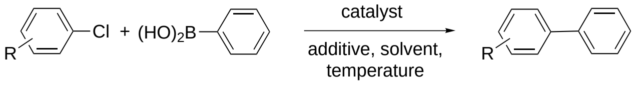
(16)

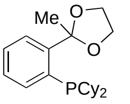
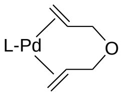
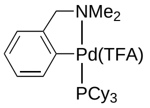
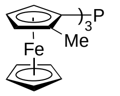
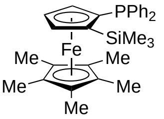
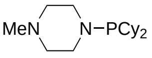
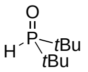
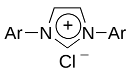
3.0% [Pd{P(tBu)$_3$}$_2$] 7% conversion
1.5% [Pd{P(tBu)$_3$}$_2$]/0.75% [Pd$_2$(dba)$_3$] 91% conversion

These observations suggest that a monophosphane–palladium adduct may play a key role in Pd/P(tBu)$_3$-catalyzed couplings and that phosphane-free palladium complexes that are present in the reaction mixture may serve to increase the concentration of this active species.[69, 70] Thus, P(tBu)$_3$ may be a particularly effective ligand for couplings of aryl chlorides because the steric demand of P(tBu)$_3$ facilitates dissociation to a monophosphane adduct, to which the aryl chloride rapidly oxidatively adds as a result of the electron richness of P(tBu)$_3$.[71, 72]

More recently, a number of research groups have described other ligands that can provide active catalysts for palladium-catalyzed Suzuki couplings of aryl chlorides (Table 2). Like Buchwald et al., Guram and co-workers have determined that dialkylarylphosphanes are effective (Table 2, entry 1).[73] In

Table 2. Suzuki cross-couplings of aryl chlorides.



Entry	R	Catalyst	Conditions	Yield [%]
1	4-CF$_3$, OPh, 3-OMe, 3,5-Me$_2$, 2-CN, Me, COMe	[Pd(dba)$_2$]/ 	CsF in dioxane, toluene, or o-xylene, 80–130 °C	83–97[a]
2	4-Me, OMe, 2-CN, F, Me, 2,6-Me$_2$, 3-Cl-pyridine	Pd(OAc)$_2$/nBuP(1-Ad)$_2$	K$_3$PO$_4$, toluene, 100 °C	55–100
3	4-F, Me, OMe, H, 2-CN	 L = PCy$_3$, (o-biphenyl)PCy$_2$	K$_3$PO$_4$/KF, THF, 100 °C	34–97
4	4-COMe, CHO, NO$_2$, OMe, 2-Me, OMe		Cs$_2$CO$_3$, dioxane, 100 °C	74–100[b]
5	4-NO$_2$, Me, H, 2-Me, OMe	[Pd$_2$(dba)$_3$]/ 	Cs$_2$CO$_3$, dioxane, 60 °C	36–90[c]
6	4-COMe, Me, OMe, 2-CN, Me, 2,6-Me$_2$, 2-Cl-pyridine	[Pd$_2$(dba)$_3$] or Pd(OAc)$_2$/ 	K$_3$PO$_4$ · H$_2$O, toluene, RT–70 °C	82–95[d]
7	4-COMe, CF$_3$, Me, 3-CHO	[Pd$_2$(dba)$_3$]/ 	CsF, toluene, 90 °C	93–100[b]
8	4-H, OMe, 2-OMe	[Pd$_2$(dba)$_3$]/ 	CsF or Cs$_2$CO$_3$, dioxane, 100 °C	83–99[e]
9	4-CO$_2$Me, Me, OMe, 2,5-Me$_2$	[Pd$_2$(dba)$_3$]/  Ar = 2,4,6-(Me)$_3$C$_6$H$_2$	Cs$_2$CO$_3$, dioxane, 80 °C	88–99[f]

[a] 4-CF$_3$-, 4-Me-, and 2-Me-substituted phenylboronic acids were also used. [b] GC conversions. [c] o-Tolylboronic acid was also used. [d] 4-OMe- and 2-Me-substituted phenylboronic acids were also used. [e] 4-Me- and 4-OMe-substituted phenylboronic acids were also used. [f] 4-OMe-, 3-OMe-, and 2-Me-substituted phenylboronic acids were also used. Abbreviations: dba = *trans,trans*-dibenzylideneacetone; Ad = adamantyl.

addition, Beller and co-workers have demonstrated that the new bulky ligand di(1-adamantyl)-*n*-butylphosphane can afford excellent turnover numbers in palladium-catalyzed Suzuki reactions (Table 2, entry 2).[74] This phosphane achieves a TON of 17400 (0.005% Pd, 87% yield) for the coupling of 4-chlorotoluene, compared with a turnover number of 9200 with commercially available $P(tBu)_3$ (0.01% Pd, 92% yield). High TONs (> 10000) can also be obtained with challenging aryl chlorides such as 2-chloro-*m*-xylene and 4-chloroanisole.

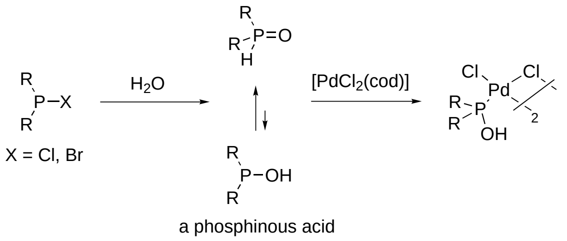
Since monophosphane–palladium adducts have been implicated as the active catalyst in many of the systems described above, Beller and co-workers have investigated the relative reactivity of several discrete $[PdL_1(diene)]$ complexes (Table 2, entry 3).[75, 76] As expected, a complex derived from PPh_3 does not catalyze couplings of unactivated aryl chlorides, which indicates that generation of a $[PdL_1]$ complex is not a sufficient condition for achieving this process. On the other hand, the corresponding electron-rich PCy_3-based catalyst is effective for Suzuki reactions of both electron-neutral and electron-rich aryl chlorides; furthermore, this preformed catalyst is significantly more reactive than a mixture of $[Pd_2(dba)_3]$ or $Pd(OAc)_2$ with PCy_3. The complex derived from the (*o*-biphenyl)PCy_2 ligand of Buchwald et al. was also studied, and, among the three ligands examined, it furnished the highest turnover numbers.

In related work, Bedford and Cazin demonstrated that a Pd/PCy_3 complex that bears an orthometalated nitrogen-donor ligand is effective for Suzuki cross-couplings of electron-rich aryl chlorides with loadings down to 0.01% Pd (Table 2, entry 4).[77] The active catalyst is believed to be a low-coordinate Pd^0/PCy_3 species that is generated by loss of the orthometalated nitrogen donor ligand. The cross-couplings can be conducted under air.

As described earlier, it was established in 1999 that a triarylphosphane can serve as a useful ligand for a room-temperature palladium-catalyzed Suzuki coupling of 4-chlorobenzaldehyde. Until recently, though, triarylphosphanes had not proved to be effective for reactions of unactivated aryl chlorides. However, in 2001, Pickett and Richards demonstrated that Pd/tris(2-methylferrocenyl)phosphane can achieve Suzuki cross-couplings of this family of substrates in modest to good yield (Table 2, entry 5).[78] During the same year, Fu and co-workers reported that a diphenylferrocenylphosphane ligand provides a versatile method for palladium-catalyzed Suzuki reactions of aryl chlorides: Activated substrates couple at room temperature and unactivated aryl chlorides react at 70 °C (Table 2, entry 6).[79] Since PPh_3 is ineffective under these conditions, the unusual reactivity of the diphenylferrocenylphosphane ligand can be attributed to the greater electron-donating ability[80] and the increased bulk of the ferrocenyl group, relative to a phenyl substituent. With regard to the influence of the steric demand of the ligand, it was noted that removal of the trimethylsilyl group or replacement of C_5Me_5 with C_5H_5 results in a considerably less-effective ligand.

Woolins and co-workers have determined that *N*-dicyclohexylphosphanyl-*N*′-methylpiperazine is useful for the palladium-catalyzed coupling of 4-chlorotoluene with phenylboronic acid at 90 °C (Table 2, entry 7).[81] The analogous *N*-diisopropylphosphanyl-substituted ligand furnishes a less-reactive catalyst.

Phosphinous acids are a promising new class of phosphorus ligands for Suzuki cross-couplings of unactivated aryl chlorides. Hydrolysis of diorganophosphorus halides generates phosphane oxides and their less-stable phosphinous acid tautomers [Eq. (17); cod = cycloocta-1,5-diene]. Binding of a phosphinous acid to palladium can provide a P-bound adduct, which may be deprotonated to yield an electron-rich, anionic palladium–phosphane complex suitable as a catalyst for coupling processes. Li has recently demonstrated the viability of this strategy, in which he established that $[Pd_2(dba)_3]/(tBu)_2P(O)H$, as well as $[Pd_2(dba)_3]/(tBu)_2PCl/H_2O$, effect Suzuki reactions of hindered and electron-rich aryl chlorides (Table 2, entry 8).[82]

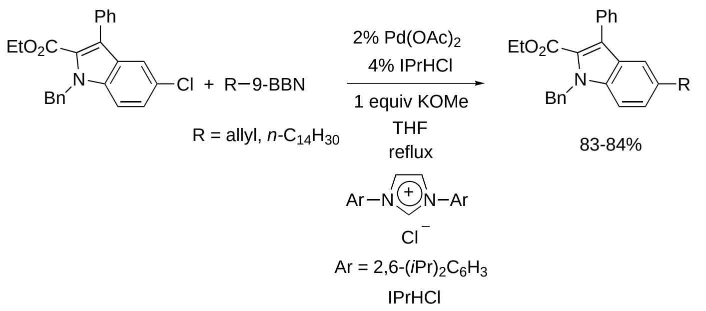


(17)

All of the catalysts for Suzuki couplings of unactivated aryl chlorides that have been discussed above have been based on phosphorus ligands. Carbon-based ligands, specifically, nucleophilic N-heterocyclic carbenes, are also effective for such processes.[83] Herrmann et al. were the first to apply this family of ligands to palladium-catalyzed coupling reactions, and showed that a first-generation catalyst can achieve the cross-coupling of an activated aryl chloride with phenylboronic acid (Table 1, entry 11).[84] It was subsequently determined that mixed PCy_3/carbene complexes can couple unactivated aryl chlorides at elevated temperature.[85]

Palladium adducts of 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene (IMes)[86] have been reported to be active catalysts for the Suzuki cross-couplings of a wide variety of aryl chlorides with aryl boronic acids (Table 2, entry 9).[87] Handling the air- and moisture-sensitive carbene can be avoided through the use of the easier-to-handle, commercially available, chloride salt (IMesHCl), which can be deprotonated in situ to generate the carbene ligand. Herrmann and co-workers independently explored the catalytic activity of Pd/IMes in Suzuki reactions of aryl chlorides.[88] They observed that the preformed bis(carbene) complex $[Pd(IMes)_2]$ is ineffective as a catalyst, in analogy with the observations for $[Pd(PtBu_3)_2]$ by Fu and co-workers [Eq. (16)].[89, 90]

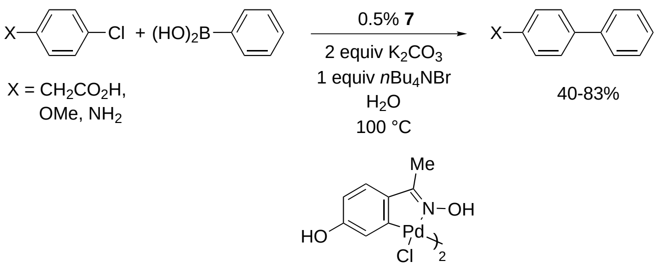
Furstner and Leitner have significantly expanded the scope of Pd/carbene-catalyzed Suzuki reactions of aryl chlorides by employing 9-alkyl-9-BBN derivatives as coupling partners [Eq. (18)].[91] Interestingly, the most effective ligand for these processes is not IMes, but is instead the more bulky 2,6-diisopropylphenyl-substituted carbene, IPr (from commer-



(18)

cially available IPrHCl). Use of the preformed carbene, rather than in situ generation from the chloride salt, leads to significantly worse results. Alkenyl- and alkynyl-9-BBN derivatives are also suitable partners in these cross-couplings. In the course of the synthesis of a large, highly diverse library of heterocycles, Schultz and co-workers recently employed Pd/IPr as a catalyst for Suzuki reactions of a wide array of solid-supported heteroaryl chlorides and aryl boronic acids.[92]

Air- and water-stable oxime palladacycles such as **7** represent another class of non-phosphorus-based ligands that show promise in Suzuki couplings of unactivated aryl chlorides. Thus, Botella and Nájera have reported that **7** catalyzes cross-couplings of a range of aryl and heteroaryl chlorides, including electron-rich substrates, in water in variable yield [Eq. (19)].[93]



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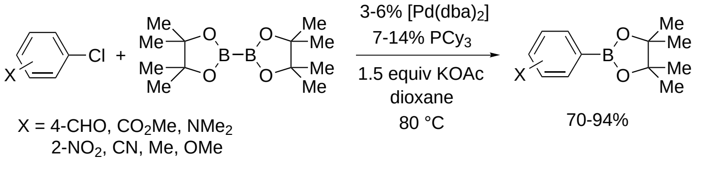
(19)

Related to the Suzuki reaction is the cross-coupling of aryl halides and triflates with tetraalkoxydiboron reagents, an efficient and versatile method for the synthesis of aryl boronates from electrophilic arenes.[94] This process is particularly useful for substrates that contain functional groups that are not compatible with traditional routes to aryl boronic acids/esters, which involve Grignard or organolithium reagents.

Miyaura and co-workers have recently disclosed that $[Pd(dba)_2]/PCy_3$ is an effective catalyst for the borylation of aryl chlorides using 4,4,5,5-tetramethyl[1,3,2]-dioxaborolane [Eq. (20)].[95] A broad spectrum of functional groups are tolerated. Highly electron-rich chlorides (for example, 4-chlorodimethylaniline) are suitable substrates, as are heteroaryl chlorides such as 3-chloropyridine and 2-chlorobenzo[*b*]furan. PCy_3 is more efficient than $P(tBu)_3$, dialkylarylphosphanes, and triarylphosphanes. Furstner and Seidel subsequently reported that carbene ligand IPr can be employed in palladium-catalyzed couplings of electron-deficient aryl chlorides with 4,4,5,5-tetramethyl[1,3,2]-dioxaborolane.[96] However, reactions of unactivated aryl chlorides result in competitive reduction of the C−Cl bond.



(20)

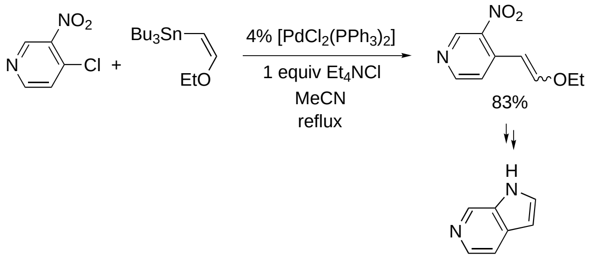
2.1.2. Stille Reactions

The palladium-catalyzed Stille cross-coupling of aryl and vinyl halides/triflates with organostannanes is a powerful and widely used method for formation of carbon–carbon bonds.[97,98] Stille reactions have proved to be an especially popular tool in complex natural product synthesis, as a result in part of the air- and moisture-stability of organotin reagents and the excellent functional-group compatibility of the process. Thus, the Stille cross-coupling has played a pivotal role in a number of total syntheses, such as those of rapamycin[99] and dynemicin.[100,101]

2.1.2.1. Stille Reactions of Activated Aryl Chlorides

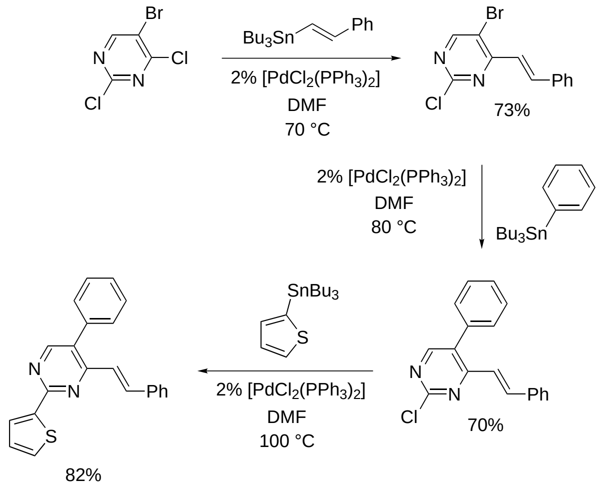
Stille cross-couplings of heteroaryl chlorides, mainly nitrogen-containing heterocycles, have a rich history. As for Suzuki reactions of this class of substrates (Section 2.1.1.1), many of these processes have employed traditional Pd/triarylphosphane-based catalysts.

A wide array of chloropyridines participate in Stille couplings.[14b–d, f, g, i, 102] In one of the earliest examples, Yamanaka and co-workers demonstrated that 2- and 4-chloro-3-nitropyridines react with (*Z*)-1-ethoxy-2-tributylstannylethylene in good yield; the products can be converted to 1*H*-pyrrolopyridines [Eq. (21)].[103]



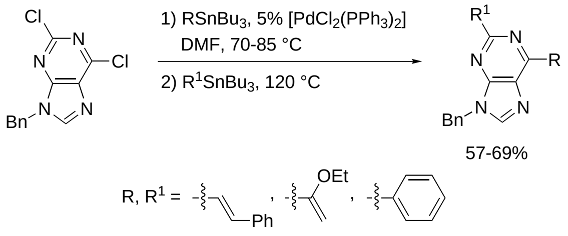
(21)

Stille cross-couplings of chloro-substituted pyridazines,[16c] pyrimidines,[104] pyrazines,[105] thiadiazoles,[106] and triazines[107] have also been reported. For halopyrimidines, the 4-position is the most activated, followed by the 2-position, and then the 5-position. Therefore, selective coupling can be achieved of the 4-position of 2,4-[108] and 4,5-dichloropyrimidines[109] as well as the 2-position of 2,5-dichloropyrimidines.[108a] Interestingly, a 4-chloro group can react in preference to a 5-bromo group, thus allowing the stepwise functionalization of 2,4-dichloro-5-bromopyrimidine (Scheme 4).[108a]



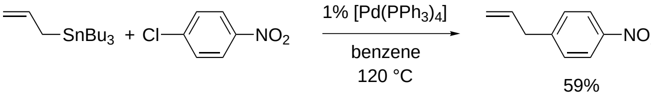
Scheme 4. Stepwise coupling of 2,4-dichloro-5-bromopyrimidine.

Fused heterocycles, such as chloro-substituted quinolines,[18, 110] isoquinolines,[19b, 110d] quinolones,[111] 1,8-naphthyridines,[112] quinazolines,[113] quinoxalines,[114] benzothiazoles,[115] purines,[25d, 116] diazaoxindoles,[117] β-carbolines,[22a, 118] phenanthrolines,[23] and benzo[*c*][2,7]naphthyridines[119] also undergo Stille cross-coupling. Good selectivity for coupling 6,8-dichlorosubstituted purines at the more activated 6-position is observed with a variety of stannanes, although small amounts of disubstituted purines (namely, reaction at both the 6- and the 8-positions) are obtained.[120] Similarly, in the presence of $[PdCl_2(PPh_3)_2]$ or $[Pd\{P(2\text{-furyl})_3\}_4]$, the 6-position of 2,6-dichlorosubstituted purines cross-couples in preference to the 2-position; in contrast to 6,8-dichloro-substituted purines, no disubstituted purines are observed if the temperature and the reaction time are carefully controlled.[121] This high selectivity allows the one-pot Stille cross-coupling of 2,6-dichloropurines with two different organostannanes [Eq. (22)].



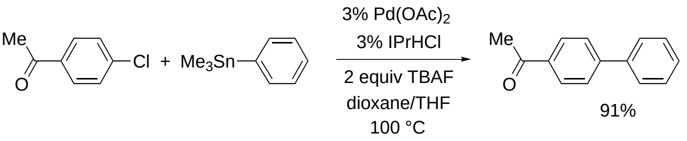
(22)

In contrast to Suzuki reactions (Section 2.1.1), there are relatively few examples of palladium-catalyzed Stille couplings of non-heteroaryl chlorides, even activated ones. The first example of such a process was provided by Migita and coworkers, who established that $[Pd(PPh_3)_4]$ catalyzes the cross-coupling of allyltributyltin with the highly activated 1-chloro-4-nitrobenzene in moderate yield [Eq. (23)].[122] As for the Suzuki reaction [Eq. (5)], tricarbonyl(η^6-chloroarene)chromium complexes are suitable substrates for palladium-catalyzed Stille couplings;[27b, 123] the reaction proceeds at room temperature with $AsPh_3$ as the ligand.[27c]



(23)

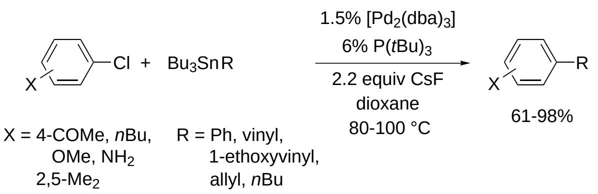
In 2001, Grasa and Nolan reported that Pd/N-heterocyclic carbene complexes, in combination with a fluoride additive, catalyze the Stille cross-coupling of electron-deficient aryl chlorides [Eq. (24); TBAF = tetrabutylammonium fluoride].[124] The fluoride ion presumably accelerates transmetalation through formation of a more reactive hypervalent tin species (see Section 2.1.2.2), as well as deprotonates the imidazolium salt to generate the free carbene ligand in situ. 2,6-Diisopropylphenyl-substituted carbene IPr and 1-adamantyl-substituted carbene IAd were found to be superior to other carbenes, including mesityl-substituted IMes. Poor to moderate yields (15–54%) were obtained for reactions of unactivated aryl chlorides.



(24)

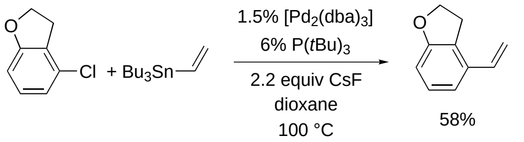
2.1.2.2. Stille Reactions of Unactivated Aryl Chlorides

Currently, the only general method for achieving Stille cross-couplings of unactivated aryl chlorides is the Pd/$P(tBu)_3$/CsF system described by Littke and Fu.[125] This catalyst works well for electron-deficient, electron-rich, and hindered aryl chlorides [Eq. (25)]. A variety of groups can be transferred from tin, including typically unreactive alkyl substituents. The coupling proceeds much more slowly in the absence of fluoride ions. The fluoride ions appear to play at least two useful roles in this chemistry—they activate the organotin reagent for transmetalation, and produce insoluble Bu_3SnF, which is straightforward to separate from the product (difficulty in eliminating tin impurities is commonly encountered during purifications of Stille reactions[126]). Zhu et al. have recently applied this method to the generation of 4-vinyl-2,3-dihydrobenzofuran, an intermediate in the synthesis of melatonergic agents [Eq. (26)].[127]



(25)

It was subsequently demonstrated that commercially available $[Pd\{P(tBu)_3\}_2]$ can be employed as a catalyst for Stille couplings of aryl chlorides.[128] This method is effective even for very hindered substrates, as evidenced by the synthesis of a tetra-*ortho*-substituted biaryl, an extremely challenging family of targets for cross-coupling methods [Eq. (27)].[129] Fu and



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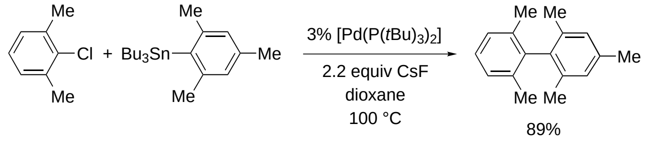
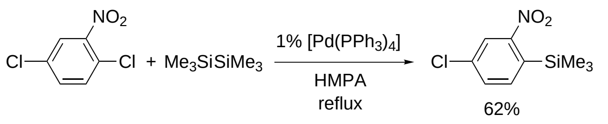


(27)

co-workers also reported that $[Pd\{P(tBu)_3\}_2]$ accomplishes the selective coupling of an aryl chloride in the presence of a triflate and that reactions with certain activated aryl chlorides can be carried out at room temperature. A turnover number as high as 920 was achieved for the Stille cross-coupling of an unactivated aryl chloride.

2.1.3. Hiyama Reactions

The palladium-catalyzed cross-coupling of organosilanes with aryl/vinyl halides and triflates, commonly referred to as the Hiyama reaction, is an attractive alternative to the Stille coupling, because organosilicon compounds are nontoxic.[130] The first examples of aryl chlorides participating in this type of process were provided by Matsumoto et al., who observed that $[Pd(PPh_3)_4]$ catalyzes the cross-coupling of nitro-substituted aryl chlorides with hexamethyldisilane to furnish arylsilanes;[131] a high level of selectivity for substitution at the *ortho*-position can be obtained in the case of 2,5-dichloronitrobenzene [Eq. (28); HMPA = hexamethyl phosphoramide].[132, 133]



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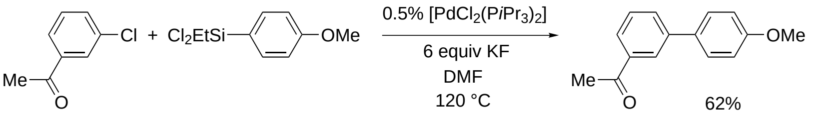
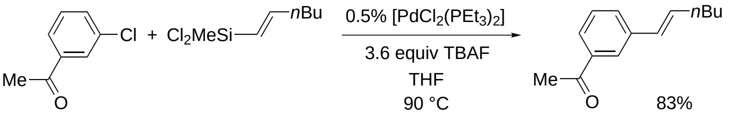
In 1996 Hatanaka and co-workers considerably expanded the scope of this process by using $[PdCl_2(PiPr_3)_2]$ as the catalyst in the presence of KF, and established that a wide variety of electron-deficient aryl chlorides cross-couple with aryl chlorosilanes [Eq. (29)].[134] The bulky, electron-rich bidentate ligand 1,2-bis(dicyclohexylphosphanyl)ethane is also effective in certain instances, whereas PPh_3-based catalysts are ineffective. Unactivated aryl chlorides do not couple in satisfactory yields under these conditions.



(29)

Hatanaka and co-workers have demonstrated that alkenylchlorosilanes also participate in Hiyama cross-couplings with activated aryl chlorides in the presence of $[PdCl_2(PEt_3)_2]$ as the catalyst and TBAF as the fluoride source [Eq. (30)]. They subsequently determined that inexpensive NaOH is a superior promotor to fluoride salts, although a large excess is required (ca. 6 equiv; Table 3, entry 1).[135]



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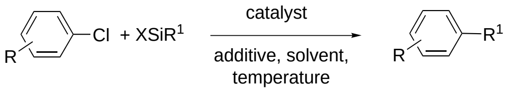
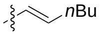
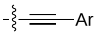
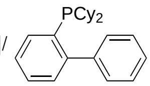
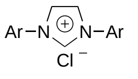
Tricarbonyl(η^6-chloroarene)chromium complexes also undergo Hiyama coupling with organofluorosilanes in the presence of TBAF. A wide variety of organic groups, such as aryl, 2-thienyl, alkenyl, and alkynyl, can be transferred.[136]

Mori and co-workers have reported that electron-poor aryl chlorides can be cross-coupled with alkynyltrimethylsilanes

Table 3. Hiyama cross-couplings of aryl chlorides.



Entry	R	R1	Catalyst	Conditions	Yield [%]
1	4-CF3, 3-COMe, Me, 2-Cl-pyridine		$[PdCl_2(PiPr_3)_2]$	NaOH, benzene, 80 °C	65–95[a]
2	4-COMe, H		$[PdCl_2(dppb)]$	cat. CuCl, DMF, 120 °C	42–86[b,c]
3	4-COMe, Me, OMe	Ph	$[Pd_2(dba)_3]$/ 	TBAF, DMF, 85 °C	47–71[d]
4	4-COMe, CN, 2-chloropyridine	Ph	$Pd(OAc)_2$/  Ar = 2,6-(iPr)2C6H3	TBAF, dioxane/THF, 80 °C	81–100[d,e]

[a] X = $MeCl_2$. [b] X = Me_3. [c] Ar = 4-$MeOC_6H_4$, 4-NCC_6H_4, C_6H_5. [d] X = $(OMe)_3$. [e] 100% conversion when R^1 = vinyl and R = 4-COMe. Abbrevia-

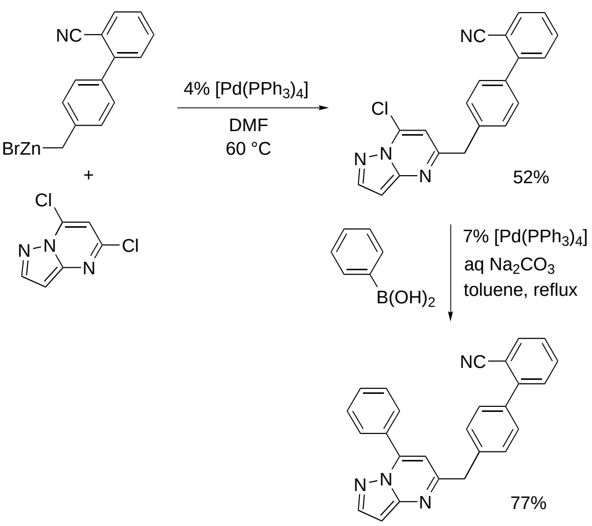
using $[PdCl_2(dppb)]/CuCl$ as the catalyst (Table 3, entry 2).[137] However, under these conditions, unactivated chlorobenzene couples in a modest 43 % yield. In this reaction, transmetalation from silicon to copper may be occurring to generate an alkynylcopper species, which then transfers the alkynyl group to palladium. This method is noteworthy in that no fluoride or hydroxide ions are required, which may be especially beneficial for alkynylations of base-sensitive substrates (see Section 2.1.7, Sonogashira reactions).

Siloxanes serve as useful partners in Hiyama cross-couplings of aryl chlorides. Mowery and DeShong have demonstrated that palladium-catalyzed reactions of phenyltrimethylsiloxane with a range of substrates, including challenging electron-neutral and electron-rich aryl chlorides, can be achieved in the presence of 2-(dicyclohexylphosphanyl)biphenyl ligand (Table 3, entry 3).[138] In addition, Lee and Nolan have determined that the use of N-heterocyclic carbenes allows for couplings of phenyl- and vinyltrimethylsiloxane with activated aryl chlorides (Table 3, entry 4).[139]

2.1.4. Negishi Reactions

The palladium-catalyzed Negishi cross-coupling—the reaction of aryl and vinyl halides/triflates with organozinc reagents—represents a powerful tool for the formation of carbon–carbon bonds because of the ready availability and high functional-group compatibility of organozinc compounds.[140] As with Suzuki and Stille couplings, there are quite a few examples of heteroaryl chlorides, mainly nitrogen-containing species, which participate in the Negishi reaction. Thus, chloropyridines,[141] pyrazines,[15a, 142] pyrimidines,[143] and triazines[144] are suitable substrates, as are fused heterocycles such as chloroquinolines,[18b, 110d, 145] quinazolines,[113] and purines.[25d, 116b]

One particular example of such a cross-coupling was provided by Shiota and Yamamori during the course of a synthesis of a family of angiotension II receptor antagonists. Their strategy relied upon a regioselective Negishi coupling of 5,7-dichloropyrazolo[1,5-*a*]pyrimidine, which proceeds as desired when the reaction is performed in DMF (Scheme 5; 7 % of the unwanted isomer is produced);[18b] in contrast, no selectivity is observed in THF. A second palladium-catalyzed cross-coupling (Suzuki reaction) then furnishes the target compound in good yield. Interestingly, direct nucleophilic substitution of the starting dichloride by the benzylzinc reagent in the presence of LiCl, but in the absence of a palladium catalyst, leads to preferential reaction of the other Ar–Cl bond.

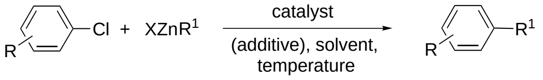


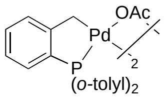
Scheme 5. Selective Negishi cross-coupling of a heteroaryl dichloride.

Miller and Farrell have described a Pd/dppf-based catalyst for the cross-coupling of activated aryl chlorides with aryl zinc reagents (Table 4, entry 1).[146] They found that other phosphanes, such as PPh_3, $P(o\mathrm{Tol})_3$, and binap, are inferior to dppf. These cross-couplings can also be carried out with a Grignard reagent and a catalytic amount of a zinc salt such as $ZnCl_2$ (Table 4, entry 2).[147, 148]

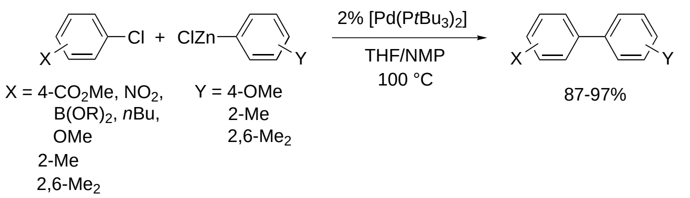
The first example of a palladium-catalyzed Negishi coupling of an unactivated aryl chloride (chlorobenzene) was reported by Herrmann et al., in which they used a palladacycle as the catalyst (Table 4, entry 3).[37a] The scope of this method for this family of substrates was not discussed. The first general protocol for accomplishing Negishi couplings of unactivated and electron-rich aryl chlorides was provided by Dai and Fu in 2001, in which commercially available $[Pd\{P(t\mathrm{Bu})_3\}_2]$ was used as the catalyst [Eq. (31)].[149] Functionalities such as nitro and ester groups are tolerated, and chlorothiophenes and chloropyridines are suitable substrates. Hindered compounds can be cross-coupled effectively, thus allowing the synthesis of a tetra-*ortho*-substituted biaryl. In addition, turnover numbers as high as 3000 can be achieved. Finally, primary and secondary alkyl zinc reagents can be

Table 4. Negishi cross-couplings of aryl chlorides.



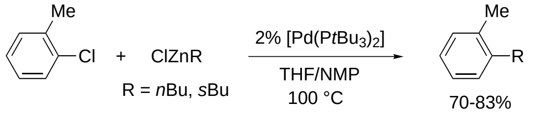
Entry	R	R1	Catalyst	Conditions	Yield [%]
1	4-CO_2Me, CN, 2-CN	*p*Tol, Ph	$[PdCl_2(dppf)]$	THF, reflux	75–82[a]
2	4-CN	Ph[b]	$[PdCl_2(dppf)]$	cat. $ZnCl_2$, THF, 55–60 °C	88
3	4-NO_2, H	Ph		THF, 90 °C	76–88[c]

[a] X = Cl or Ph. [b] PhMgCl was used instead of $XZnR^1$. [c] X = Br. Abbreviations: dppf = bis(diphenylphosphanyl)ferrocene; *p*Tol = *para*-tolyl.



(31)

employed; the coupling of *s*BuZnCl with 2-chlorotoluene generates predominantly the desired compound 2-*s*-butyltoluene along with 8% of the isomerized product 2-*n*-butyltoluene. [Eq. (32)].



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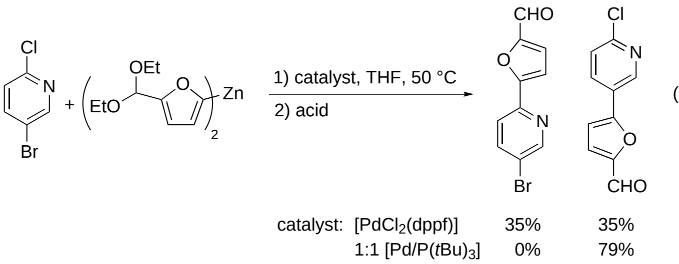
Gauthier et al. have recently applied Pd/P(*t*Bu)$_3$ to Negishi couplings of 2- and 3-chloropyridines with di(2-furyl)zinc reagents.[150] The use of a 1:1 ratio of Pd:P(*t*Bu)$_3$ furnishes significantly better results than a 1:2 ratio. [PdCl$_2$(dppf)] is an equally effective catalyst for reactions that involve 2-chloropyridine derivatives. Interestingly, the Negishi coupling of 5-bromo-2-chloropyridine by [PdCl$_2$(dppf)] affords a 1:1 mixture of products as a result of reaction of the chloride and the bromide, whereas exclusive coupling of the bromide is observed with Pd/P(*t*Bu)$_3$ [Eq. (33)].



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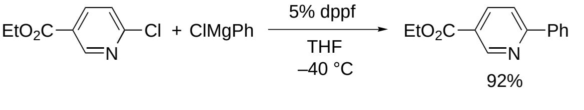
2.1.5. Kumada Reactions

The palladium-catalyzed coupling of Grignard reagents with aryl/vinyl halides and triflates is most commonly called the Kumada reaction.[151, 152] This process is of great significance among cross-couplings because of its relatively early discovery, but its utility is somewhat limited, compared to the reactions described above, as a consequence of the incompatibility of Grignard reagents with many functional groups.

A few palladium-catalyzed Kumada cross-couplings of heteroaryl chlorides have been reported.[153] Knochel and co-workers have recently determined that certain 2-chloropyridine derivatives react with functionalized aryl Grignard reagents under very mild conditions [Eq. (34)].[154] The use of the low temperature means that the presence of normally incompatible esters is tolerated. The facility of this process at low temperature suggests that an addition–elimination mechanism is operative (Scheme 6). Nucleophilic addition of a palladium "ate" complex, formed from the reaction of PdL$_n$ and PhMgCl, to the highly electrophilic 2-chloropyridine yields a stabilized magnesium amide which, after loss of MgCl$_2$ and reductive elimination, furnishes the coupled product. The corresponding 3-halopyridine derivatives are considerably less reactive under these conditions.



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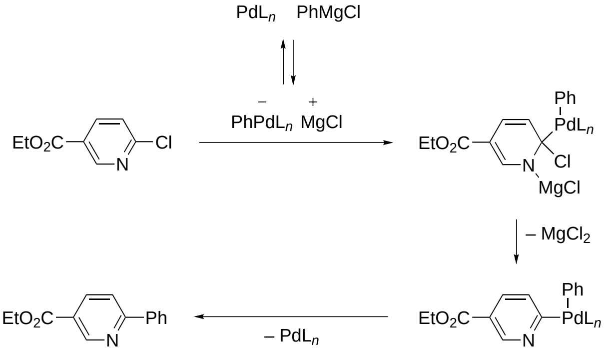
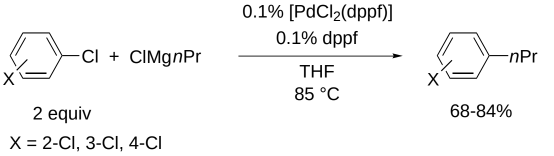


Scheme 6. Possible mechanism for the Pd^0-catalyzed Kumada coupling of a 2-chloropyridine with PhMgCl.

Katayama and Umeno described the first examples of palladium-catalyzed Kumada cross-couplings of (activated) non-heteroaryl chlorides. Thus, selective monocoupling of dichlorobenzenes with aryl and alkyl Grignard reagents can be achieved with [PdCl$_2$(dppf)] as the catalyst [Eq. (35)]; in all cases, less than 5% of the dialkylated product is observed.[155] Uemura et al. have noted that tricarbonyl(η^6-chloroarene)chromium complexes participate in Kumada couplings, although dehalogenation is a significant side reaction.[27a]



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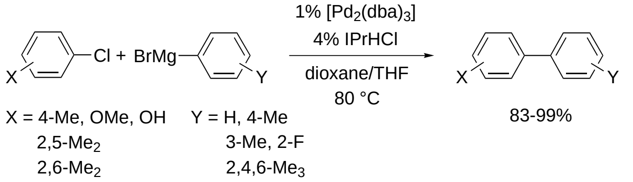
The first report of a palladium-catalyzed Kumada cross-coupling of an unactivated aryl chloride was provided by Herrmann et al., who showed that palladacycles accomplish the coupling of chlorobenzene with MeMgBr and PhMgCl.[37a] Electron-rich aryl chlorides have been shown to react with aryl magnesium bromides in the presence of [Pd$_2$(dba)$_3$] and carbene salt IPrHCl; a slight excess of Grignard reagent is used to deprotonate the salt and generate the free carbene ligand in situ [Eq. (36)].[156] Hindered substrates such as 2-chloro-*m*-xylene can be coupled efficiently. However, the utility of this Kumada cross-coupling process is limited by its relatively low functional-group tolerance; for example, the



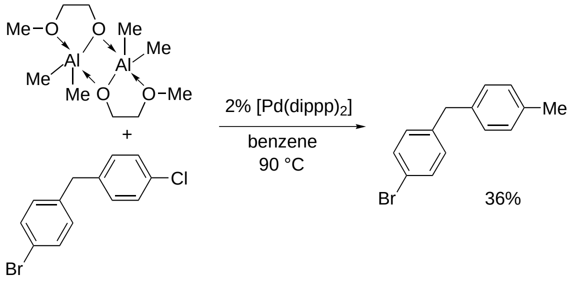
(36)

reaction of methyl 4-chlorobenzoate results in the formation of significant amounts of side products.

2.1.6. *Related Cross-Coupling Reactions*

Palladium-catalyzed cross-couplings of aryl chlorides with organometallic species other than B-, Sn-, Si-, Zn-, and Mg-based compounds are relatively uncommon, with most of the reports involving heteroaryl chlorides.[157] For example, Undheim and co-workers have demonstrated that alkenylzirconocenes, readily available through hydrozirconation of terminal alkynes, selectively couple at the 4-, rather than the 2-position of 2,4-dichloropyrimidine and 2,4-dichloroquinazoline.[158] Furthermore, palladium-catalyzed methylations and ethylations with $AlMe_3$ and $AlEt_3$ have been described for chloropyrazines,[15a, 159] pyrazine *N*-oxides,[160] quinazolines,[161] purines,[25b, 162] and β-carbolines.[22b, 163, 164]

Blum et al. have recently shown that aryl chlorides can be methylated by hypervalent aluminum and gallium complexes.[165] [Pd(PPh$_3$)$_4$] is an acceptable catalyst for highly activated nitro-substituted aryl chlorides, but the palladium complex of a bulky, electron-rich, chelating ligand such as 1,3-bis(diisopropylphosphanyl)propane (dippp) is required for electron-neutral substrates. Surprisingly, this catalyst is ineffective for couplings of typically more reactive aryl bromides, thereby allowing the selective reaction of a chloride in preference to a bromide, albeit in quite modest yield [Eq. (37)].



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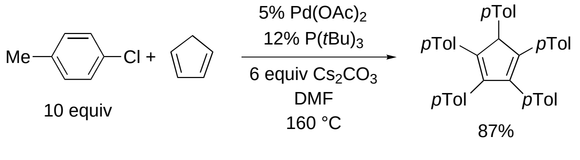
A very interesting palladium-catalyzed pentaarylation of cyclopentadienes has been reported by Dyker et al. in which they used P(*t*Bu)$_3$ as a ligand [Eq. (38)].[166] The authors suggest that the coupling proceeds by transmetalation of the cyclopentadienyl anion with [ArClPd{P(*t*Bu)$_3$}$_n$], which is the product of oxidative addition of an aryl chloride to palladium.



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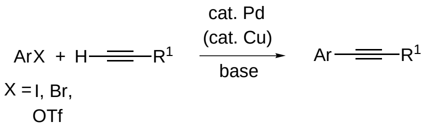
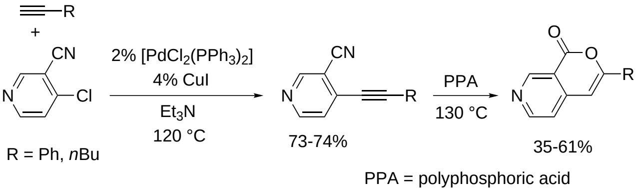
2.1.7. *Sonogashira Reactions*

The palladium-catalyzed coupling of terminal alkynes with aryl/vinyl halides and triflates, usually in the presence of a copper co-catalyst, is commonly known as the Sonogashira reaction [Eq. (39)].[167] Despite its utility and the effort that has been dedicated to expanding its scope, a general protocol for employing unactivated aryl chlorides in this process has not yet been developed. On the other hand, there have been numerous reports of couplings of activated aryl chlorides, particularly nitrogen-containing heteroaryl chlorides, which afford alkynylated N-heteroaromatic compounds that can cyclize to form a variety of interesting fused heterocycles.[168]



(39)

An array of naphthyridinones[169] and pyranopyridinones[170] can be obtained by Sonogashira coupling of cyano-substituted 2-, 3-, or 4-chloropyridines, followed by cyclization [Eq. (40)]. Indoles may be synthesized from cyano-substituted 2-chloropyridines utilizing a Hofmann rearrangement as a key step [Eq. (41)].[171, 172]



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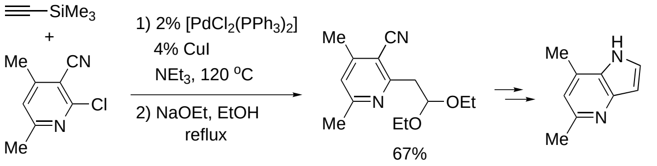
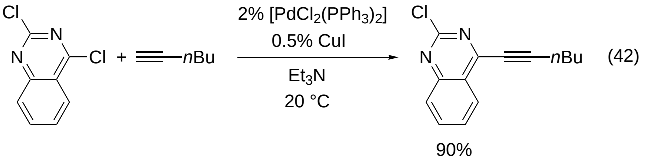


(41)

Other chloro-substituted six-membered heterocycles, such as pyridazines,[172a, 173] pyrimidines,[158, 172a, c, 174] pyrazines,[172a, b, 173d, 175] and triazines,[176] are also suitable substrates for Sonogashira couplings. Furthermore, fused heteroaromatics, for example, chloroquinolines,[18a, 172a, 173c, 175c] isoquinolines,[172a, 173c, 177] quinazolines,[178] quinoxalines,[179] pterins,[175d, 180] purines,[181] naphthyridines,[182] and phenanthrolines,[182] are useful coupling partners. In the case of 2,4-dichlorosubstituted quinazolines, selective Sonogashira coupling at the 4-position can be achieved at 20 °C; introduction of a second alkynyl group requires heating to 65 °C [Eq. (42)].[158]



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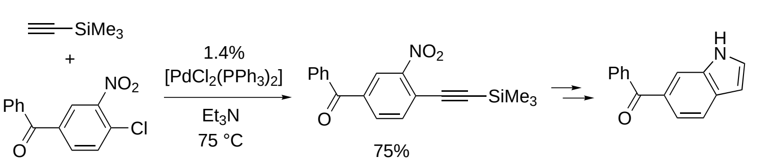
The first example of a Sonogashira reaction of an aryl chloride, activated 4-chlorobenzonitrile, was provided by Cassar, using $[Pd(PPh_3)_4]$ as the catalyst and a somewhat unusual base, NaOMe, in DMF at 80°C (coupling with phenylacetylene; 64% yield).[183] Several additional reports of Sonogashira reactions of electron-deficient aryl chlorides have subsequently appeared.[144, 184, 185] One interesting example involves substituted *o*-nitrochlorobenzenes, which can be converted into indoles through a four-step process that begins with a Sonogashira coupling with trimethylsilylacetylene [Eq. (43)].[186] This method is noteworthy because indoles that bear an electron-withdrawing group at the 6-position can be difficult to synthesize.



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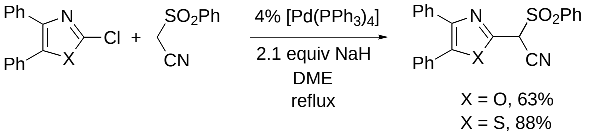
2.1.8. α-Arylation Reactions of Enolates and Other Stabilized Carbanions

The palladium-catalyzed α-arylation of enolates and other stabilized carbanions has been extensively investigated during the past several years.[187] Initial efforts focused largely on couplings of aryl bromides, but more recently a number of catalysts have been developed that permit the use of aryl chlorides as substrates.

The first example of a palladium-catalyzed arylation of a stabilized carbanion by a heteroaryl or aryl chloride was provided by Yamanaka and co-workers, who showed that diphenyl-substituted 2-chlorooxazoles and thiazoles can be coupled with phenylsulfonylacetonitrile in the presence of NaH [Eq. (44)].[188] The analogous 2-chloro-1-methylimidazole is unreactive under these conditions.



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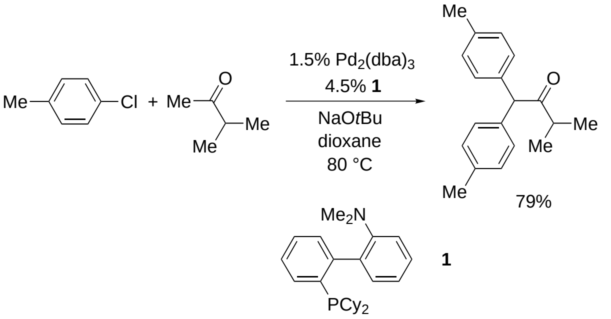
The palladium-catalyzed α-arylation of a ketone with an aryl chloride was first reported by Buchwald and co-workers in which they used biphenyl ligand **1** [Eq. (45)].[56] While Pd/binap is selective for monoarylation of methyl ketones by aryl bromides, Pd/**1** favors diarylation of methyl ketones by aryl chlorides.



(45)

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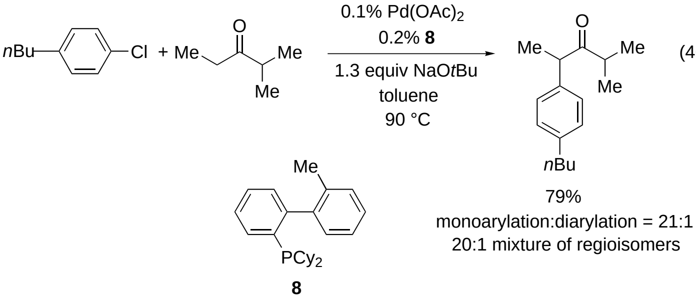
In a subsequent study, Buchwald and co-workers surveyed an array of dialkylarylphosphanes, and determined that phosphane **8**, now commercially available, is unusually effective in palladium-catalyzed α-arylations of ketones. With this ligand, electron-poor, electron-neutral, electron-rich, and hindered aryl chlorides can efficiently be coupled with a wide range of ketones. Furthermore, a low catalyst loading (0.1–1.0% Pd) can be employed.[189] Ligand **8** provides high selectivity for monoarylation over diarylation and for arylation at a methylene, rather than a methine, position [Eq. (46)].

Buchwald and co-workers have also established that NaO*t*Bu can be replaced with K_3PO_4, which significantly enhances the functional-group compatibility of the α-arylation process involving substrates that contain base-sensitive functional groups [Eq. (47)]. One unsolved challenge, however, is the regioselective arylation of ketones such as 2-hexanone that require differentiation between a methyl and a methylene group.



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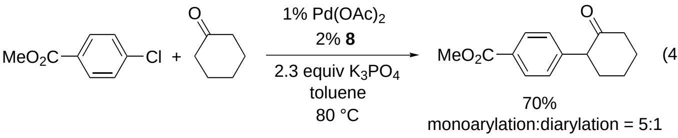
8

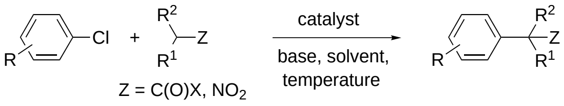


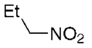
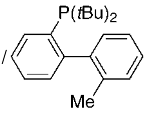
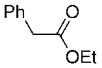
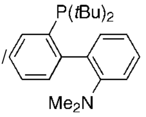
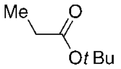
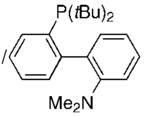
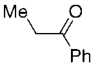
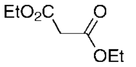
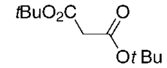
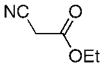
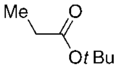
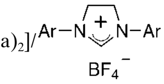
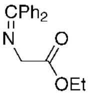
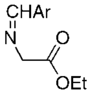
(47)

α-Arylation with aryl chlorides can be expanded to other stabilized carbanions, including the conjugate base of nitroalkanes (Table 5, entry 1)[190] and esters (entries 2 and 3).[191] When an ester is the substrate, $LiN(SiMe_3)_2$ must be used for deprotonation to selectively obtain monoarylated, rather than diarylated, product.

Kawatsura and Hartwig have investigated the palladium-catalyzed α-arylation of ketones with aryl chlorides, in which

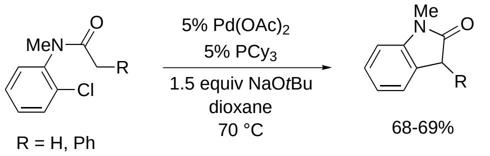
Table 5. α-Arylations of Enolates and Other Stabilized Carbanions.



Entry	R	Carbonyl or nitro compound	Catalyst	Conditions	Yield [%]
1	4-CO_2Me, 3-OMe, CO_2Me		$[Pd_2(dba)_3]$/ 	Cs_2CO_3, DME, 55–60 °C	65–86
2	4-Me, OMe		$[Pd_2(dba)_3]$/ 	$LiN(SiMe_3)_2$, toluene, 80 °C	82–87
3	4-OMe, OPh		$[Pd_2(dba)_3]$/ 	$LiN(SiMe_3)_2$, toluene, 80 °C	54–56
4	4-COPh, H, OMe, 2-Me		$Pd(OAc)_2$ or $[Pd(dba)_2]/PCy_3$, $P(tBu)_3$, or DtBPF	NaOtBu, THF, 50–70 °C	80–95
5	4-CF_3, H, OMe, 2-OMe, 2,5-Me_2		$[Pd(dba)_2]/Ph_5FcP(tBu)_2$	K_3PO_4, toluene, 100 °C	81–89
6	4-CF_3, H, OMe, 2,5-Me_2		$[Pd(dba)_2]/P(tBu)_3$ or $[PdCl(allyl)]_2/P(tBu)_3$	NaOtBu, dioxane, 100 °C	84–90
7	4-H, F, OMe, 2,5-Me_2		$[PdCl(allyl)]_2/P(tBu)_3$	Na_3PO_4, toluene, 100 °C	82–90
8	4-H		$[Pd(dba)_2]$/ 	$NaN(SiMe_3)_2$, toluene, RT	71[a]
9	4-CN, CF_3, F, H, OMe, 2-Me, 3-Cl-pyridine		$[Pd(dba)_2]/P(tBu)_3$	K_3PO_4, toluene, 120 °C	80–85
10	4-CF_3, H		$[Pd(dba)_2]/P(tBu)_3$	K_3PO_4, toluene, 120 °C	67[b]

they focused initially on a potentially bidentate ligand, 1,1′-bis(di-*tert*-butylphosphanyl)ferrocene (D*t*BPF). Since ^{31}P NMR studies of independently synthesized [ArPdL(enolate)] complexes revealed that only one phosphorus atom of D*t*BPF is bound to the palladium center, the use of monodentate $P(tBu)_3$ and PCy_3 (Cy = cyclohexyl) was also explored. In fact, all three ligands have proved to be effective for coupling a variety of aryl chlorides with ketones (Table 5, entry 4).[192] Arylations of malonates can also be achieved. Pentaphenylferrocenylphosphane $Ph_5FcP(tBu)_2$ is the ligand of choice for diethyl malonate (Table 5, entry 5), while $P(tBu)_3$ is the ligand of choice for di-*tert*-butyl malonate (entry 6).[193] A range of aryl chlorides serve as suitable coupling partners, with exceptions being chloropyridines and cyano-substituted substrates.

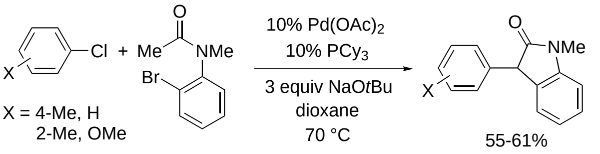
Amides also undergo palladium-catalyzed α-arylation. An intramolecular process can furnish biologically interesting oxindoles; PCy_3, as well as carbene ligands SIPr and IPr,[194] are the most effective of the ligands that have been screened [Eq. (48)].[195] A combined, one-pot intra- and intermolecular



(48)

amide arylation can provide 3-aryloxindoles from readily available 2-bromoanilides and aryl chlorides, including hindered and electron-rich compounds [Eq. (49)].

Hartwig and co-workers have also determined that palladium-catalyzed couplings of ethyl cyanoacetate with aryl



(49)

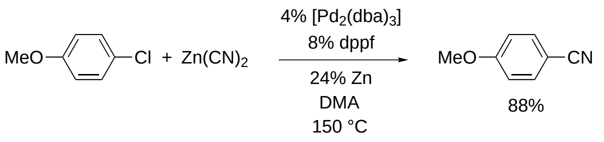
chlorides can be accomplished (Table 5, entry 7).[193, 196] Both electron-rich and hindered chlorides can be employed in the presence of Pd/P(tBu)$_3$, although the presence of certain electron-withdrawing groups, such as esters, ketones, and nitriles, is not well-tolerated. This catalyst system emerged from a high-throughput screen that was based on a fluorescence resonance energy transfer assay.[197] A wide range of ligands (>100), palladium sources, and bases was explored.

Like Buchwald and co-workers, Hartwig and co-workers have described a method for the α-arylation of esters—with a Pd/carbene catalyst, the coupling of chlorobenzene with *tert*-butyl propionate proceeds at room temperature (Table 5, entry 8).[198] In addition, alkylidene glycinates may be arylated with a wide range of chlorides, thereby providing facile access to α-aryl-α-amino acid derivatives (Table 5, entries 9–10).

2.1.9. Cyanation Reactions

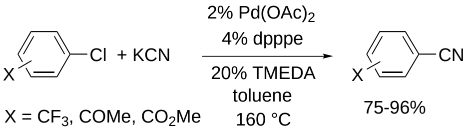
Although there are a number of methods for achieving the synthesis of aryl cyanides (for example, Rosenmund–von Braun reaction and Sandmeyer-based routes), milder and less expensive routes are nevertheless desirable.[199] Metal-catalyzed cyanation of aryl chlorides has the potential to furnish a solution to this challenge, and useful progress has been made. For example, palladium-catalyzed cyanations of activated heteroaryl chlorides, such as pyrazines[200] and 2- and 6-chloropurines,[201] have been described. Furthermore, Andersson and Langstrom reported in 1994 that the coupling of unactivated chlorobenzene can be accomplished by [Pd(PPh$_3$)$_4$] at 90 °C, albeit in modest yield (45 %).[202]

In 2000, Jin and Confalone established that Pd/dppf catalyzes the cyanation of an electronically and sterically diverse array of aryl chlorides with Zn(CN)$_2$ used as the cyanide source [Eq. (50)].[203] The yields for the couplings are uniformly excellent (≥85 %), although the reaction temperatures are somewhat high (120–150 °C).



(50)

More recently, Beller and co-workers reported the palladium-catalyzed cyanation of chloroquinolines and activated aryl chlorides using KCN as the source of cyanide, 1,5-bis(diphenylphosphanyl)pentane (dpppe) as the ligand, and tetramethylethylenediamine (tmeda) as an additive [Eq. (51)].[204] Among the monodentate and bidentate phosphanes that were screened, dpppe, which can form an eight-membered chelate, was found to clearly be the most effective.

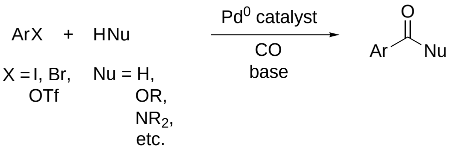


(51)

2.1.10. Related Processes

2.1.10.1. Carbonylation Reactions

The palladium-catalyzed carbonylation of aryl halides and triflates furnishes a powerful method for synthesizing an array of carbonyl compounds, such as aldehydes, esters, and amides (Eq. (52) and Scheme 7).[205] From a historical perspective, some of the earliest studies of the activation of aryl chlorides focused on carbonylation processes.



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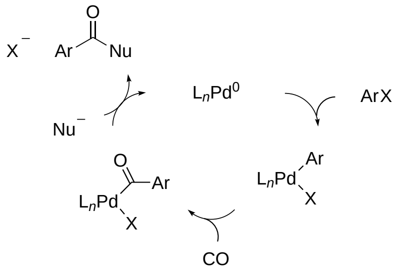
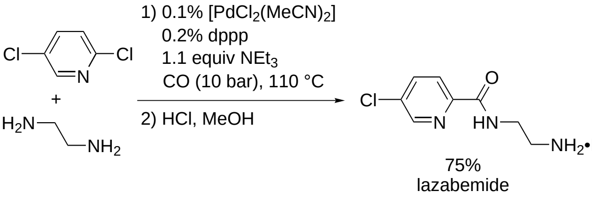


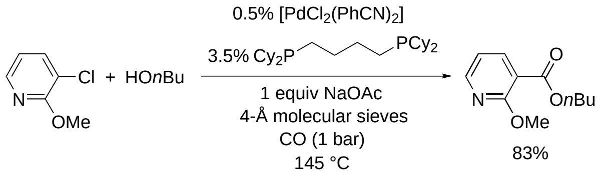
Scheme 7. Generalized mechanism for palladium-catalyzed carbonylation reactions.

The palladium-catalyzed carbonylation of chloropyridines and other nitrogen-containing heterocycles is of particular interest to industrial chemists because the products are valuable intermediates for the production of a variety of herbicides and pharmaceuticals.[206] The Hoffmann–La Roche one-step synthesis of lazabemide, a monoamine oxidase B inhibitor, exploits a highly selective monoamidocarbonylation of 2,5-dichloropyridine [Eq. (53)]; the previous syntheses of lazabemide had required four to eight steps.[207, 208]



(53)

There are quite a few examples of carbonylations of other heteroaryl chlorides, for example, chloropyrazines,[208b, 209] pyrimidines,[210] quinolines,[18a, 208f] chlorothiophenes,[208c] naphthyridines,[211] and phenanthrolines.[211] A thorough study by Beller et al. revealed that bidentate phosphanes, including dppf, are very effective for palladium-catalyzed alkoxycarbonylations of 2-chloropyridines, 2- and 4-chloroquinolines, pyrazines, pyrimidines, and pyridazines; a turnover number of 13000 was achieved for a carbonylation of 2-chloropyridine using dppb as the ligand.[212] For less reactive 3-chloropyridines, more bulky and electron-rich 1,4-bis(dicyclohexylphosphanyl)butane was found to be most useful [Eq. (54)].

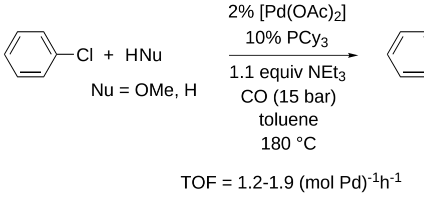


(54)

Monodentate ligands were found to be less effective for these carbonylation processes, perhaps because bidentate ligands disfavor formation of an unproductive dimer after the substrate oxidatively adds to palladium(0). Consistent with this hypothesis, the oxidative-addition dimer that is generated upon reaction of [Pd(PPh$_3$)$_4$] with 2-chloropyridine does not undergo carbonylation when treated with CO at elevated temperature.

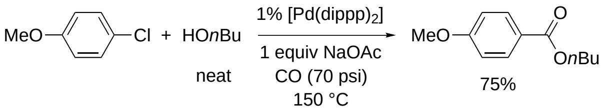
In 1989, the research groups of Milstein and Osborn independently provided the first examples of palladium-catalyzed carbonylations of unactivated aryl chlorides.[213] These landmark studies furnished early evidence that bulky, electron-rich phosphanes can be unusually effective in activating carbon–chlorine bonds.

Osborn and co-workers demonstrated that Pd/PCy$_3$ and Pd/P(*i*Pr)$_3$ are active catalysts for both alkoxycarbonylation and hydrocarbonylation (formylation) of chlorobenzene [Eq. (55)].[214] Perhaps not surprisingly, less electron-rich and less bulky phosphanes such as PPh$_3$ are ineffective. Interestingly, the more electron-rich and more bulky P(*t*Bu)$_3$ is also ineffective, which indicates that the electronic and steric properties of the ligand define a window of reactivity.



(55)

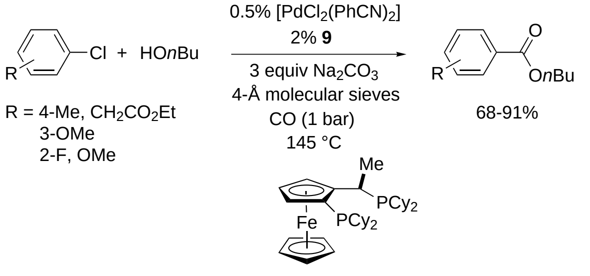
At the same time, Milstein and co-workers established that a palladium complex bearing sterically demanding, electron-rich, chelating 1,3-bis(diisopropylphosphanyl)propane (dippp) achieves the amidocarbonylation, alkoxycarbonylation,[215] and formylation[216] of aryl chlorides, including deactivated substrates [Eq. (56)]. The catalyst with a dippp ligand was much more effective than catalysts with the other monodentate and bidentate ligands screened. Milstein and co-workers believe that the distinguishing features of dippp are its capacity to chelate to form a six-membered ring, its bulk, and its basicity.



(56)

Subsequently, additional homogeneous[208c, 217] and heterogeneous[218] methods for the carbonylation of aryl chlorides have been developed. One example of an application of such processes comes from polymer chemistry, where poly(imideamides)[219] and poly(amides)[220] have been synthesized by palladium-catalyzed amidocarbonylation of aryl chlorides with aromatic amines.

Beller and co-workers has very recently employed commercially available 1-[2-(dicyclohexylphosphanyl)ferrocenyl]ethyldicyclohexylphosphane (**9**) in carbonylations of aryl chlorides [Eq. (57)].[221] In contrast to other catalysts, which generally require considerable CO pressure, this reaction proceeds at 1 bar.



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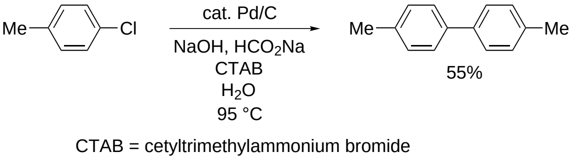
2.1.10.2. Homocoupling Reactions

The palladium-catalyzed homocoupling of aryl halides can offer a mild alternative to the classical Ullmann coupling, which employs a stoichiometric amount of copper and very high temperature.[222] A very early example of this type of reaction was reported by Bamfield and Quan, who discovered that heterogeneous Pd/C catalyzes the homocoupling of unactivated aryl chlorides and of chloropyridines to produce symmetrical biaryls in moderate yield [Eq. (58)].[223] Alkaline sodium formate is employed as the reducing agent and cetyltrimethylammonium bromide (CTAB) is used as a surfactant.



(58)

Sasson and co-workers subsequently investigated Pd/C-catalyzed homocouplings of aryl chlorides in detail. They determined that not only formate salts,[224] but also hydrogen gas[225] and zinc,[226] may serve as the reductant. There have been several reports of homocouplings of aryl chlorides catalyzed by homogeneous complexes, but they are very limited in scope.[227]

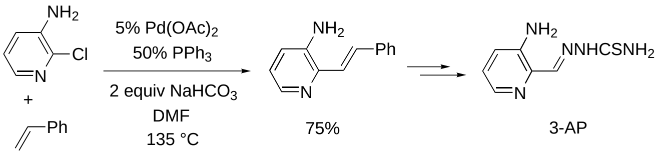
2.2. Heck Reactions

The palladium-catalyzed coupling of aryl/vinyl halides and triflates with olefins, usually referred to as the Heck reaction [Eq. (2)], is arguably one of the most important carbon–carbon bond-forming processes in synthetic organic chemistry (Scheme 2).[228, 229] It is mechanistically distinct from the cross-coupling reactions described above, although the first step, oxidative addition of the halide or triflate to Pd^0, is the same (Scheme 1).

2.2.1. Heck Reactions of Activated Aryl Chlorides

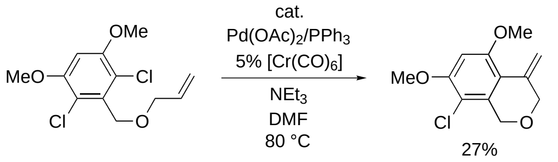
Heck couplings of 2-halopyridines are sometimes problematic as a result of the formation of an unreactive dimer from the oxidative addition adduct.[153a, 230] Nevertheless, several successful Heck reactions of 2-chloropyridines have been described,[102e, 231] as well as couplings of other heteroaryl chlorides, such as pyrazines,[175a, 232] chloroquinolines,[110d, 233] quinoxalines,[234] and pterins.[235]

The synthesis of the antitumor agent 3-aminopyridine-2-carboxaldehyde thiosemicarbazone (3-AP) furnishes an interesting example of a Heck reaction of a 2-chloropyridine [Eq. (59)].[14g] The initial routes to 3-AP focused on Stille and Suzuki cross-couplings of 2-chloro-3-nitropyridine with vinyltributyltin and methylboronic acid, respectively, followed by a $SnCl_2$-mediated reduction of the nitro group. Work-up and purification problems associated with the reduction step prohibited large-scale production of 3-AP, so direct Suzuki and Stille reactions of 2-chloro-3-aminopyridine were investigated; unfortunately, neither process provides the desired product in satisfactory yield. Fortunately, however, the Heck coupling of 2-chloro-3-aminopyridine with styrene can be achieved and affords the target stilbene derivative, which can be converted in several steps into 3-AP.



(59)

The earliest examples of Heck reactions of activated nonheteroaryl chlorides were described by Spencer, who established that $Pd(OAc)_2/PPh_3$ catalyzes couplings of electron-deficient aryl chlorides with electron-deficient alkenes at 150 °C in poor to modest yield (21–51 %).[236] As for many of the cross-couplings that were discussed in Section 2.1, it is possible to activate the C–Cl bond for Heck reactions through η^6-complexation of the aryl chloride to tricarbonylchromium complexes.[123a, 213d, 213e] In one particularly interesting report, the Heck coupling of an aryl chloride with only a catalytic amount of chromium has been achieved, albeit in low yield [Eq. (60)].[237] During this process, the starting material presumably binds to chromium and undergoes a Heck reaction; the chromium-complexed product thus generated then releases the tricarbonyl chromium, which can then bind to additional starting material to continue the catalytic cycle.



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Herrmann et al. were the first to demonstrate that palladacycles can catalyze Heck couplings of activated aryl chlorides (Table 6, entry 1).[238] To obtain high conversions, $n\mathrm{Bu_4NBr}$ was employed as a co-catalyst. These conditions were not effective for electron-neutral or electron-rich aryl chlorides. Subsequently, both nitrogen- (Table 6, entry 2)[239, 240] and sulfur-containing palladacycles[241] have also been shown to be reasonably efficient catalysts for Heck reactions of activated aryl chlorides.

Herrmann et al. pioneered not only the use of palladacycles, but also of palladium carbenes as catalysts for Heck couplings of activated aryl chlorides (Table 6, entry 3).[242] Recently, additional palladium–carbene adducts have been shown to be active, but, as with the original catalyst, only electron-poor chlorides are suitable substrates, and elevated temperatures are required (Table 6, entries 4–6).[243–246]

Beller and Zapf have established that Pd/phosphite mixtures catalyze Heck couplings of activated aryl chlorides; both trialkyl- and triarylphosphites are effective (Table 6, entry 7).[247] In addition, Li et al. have demonstrated that commercially available, air-stable Pd^{II} complexes that bear phosphinous acid ligands are useful for the Heck reaction of an electron-poor aryl chloride (Table 6, entry 8).[248]

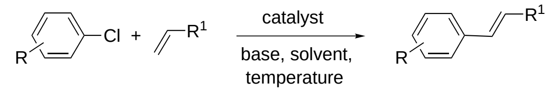
A wide-ranging study of palladium-catalyzed Heck couplings of activated aryl chlorides in the presence of a variety of phosphorus ligands has recently been described by Zapf and Beller. With $n\mathrm{Bu_4NBr}$ as a co-catalyst, even simple phosphanes can provide turnover numbers approaching 1000 at 160 °C (Table 6, entry 9).[249] Unfortunately, electron-neutral and electron-rich aryl chlorides did not furnish appreciable amounts of product under any of the broad array of conditions that were screened.

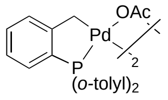
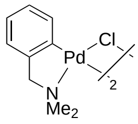
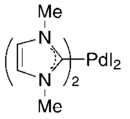
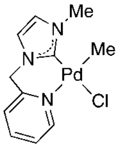
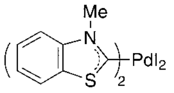
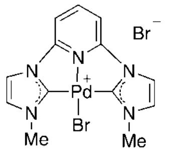
Dupont and co-workers have reported that the phosphane-free catalyst system $[\mathrm{PdCl_2(SEt_2)_2}]/n\mathrm{Bu_4NBr}$, which was found to be effective for Suzuki reactions of activated aryl chlorides (see Section 2.1.1.1), can also be applied to Heck couplings of this family of substrates with styrene and *n*-butyl acrylate. This method can be conducted in air with little loss in efficiency.[250] An example of a Heck reaction of an activated aryl chloride by a heterogeneous catalyst has been provided by Djakovitch et al., who showed that a palladium complex entrapped in a zeolite cage can achieve the coupling of 4-chloroacetophenone with styrene.[251]

2.2.2. Heck Reactions of Unactivated Aryl Chlorides

Davison et al. were the first to describe significant success in a Heck coupling of an unactivated aryl chloride: The palladium-catalyzed Heck reaction of electron-neutral chlorobenzene with styrene proceeds in modest yield in the presence

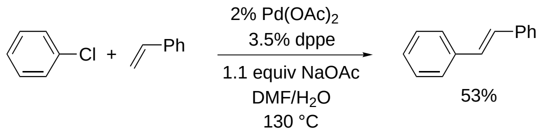
Table 6. Heck cross-couplings of activated aryl chlorides.



Entry	R	R^1	Catalyst	Conditions	Yield [%]
1	4-CHO, CN, COMe	Ph, CO_2nBu		NaOAc, DMA, 130 °C	32–81[a]
2	4-NO_2	Ph, CO_2Et		K_2CO_3, NMP, 150 °C	51–71
3	4-CHO, NO_2	CO_2nBu		NaOAc, DMA, 130 °C	99[a]
4	4-CHO	CO_2nBu		NaOAc, DMA, 120 °C	75[b,c]
5	4-NO_2	CO_2nBu		$NaHCO_3$, $n$$Bu_4$NBr, 130 °C	95
6	4-CHO	Ph		NaOAc, DMA, reflux	75[a]
7	4-CF_3, 3-CF_3	Ph, $CONMe_2$	$Pd(OAc)_2/P(OR)_3$	Na_2CO_3, DMA, 160 °C	15–89[a,d]
8	4-COMe	CO_2tBu	$[PdCl_2\{P(t\mathrm{Bu})_2OH\}_2]$	NaOAc, DMF, 135 °C	66[a]
9	4-COMe	Ph	$Pd(OAc)_2/P(n\mathrm{Bu})_3$	Na_2CO_3, DMA, 160 °C	85[a]

[a] $n$$Bu_4$NBr was used as a co-catalyst. [b] $n$$Pr_4$NBr was used as a co-catalyst. [c] GC conversions. [d] R = 2,4-(tBu)$_2$$C_6H_3$ or Et.

of bidentate 1,2-bis(diphenylphosphanyl)ethane (dppe) [Eq. (61)].[252] A lower yield (45%) is obtained if PPh_3 is employed instead of dppe.



(61)

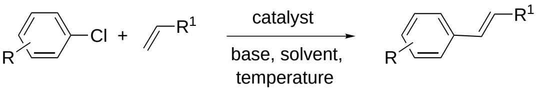
Milstein and co-workers subsequently revealed several important findings regarding Heck reactions of aryl chlorides. They determined that use of a bulky, electron-rich, chelating phosphane ligand (1,4-bis(diisopropylphosphanyl)butane; dippb) furnishes a palladium catalyst that can efficiently couple electron-poor and electron-neutral aryl chlorides (Table 7, entry 1).[253] Unfortunately, the catalyst affords low yields for reactions of electron-rich chlorides. Remarkably, other bulky, electron-rich chelating phosphanes, such as dippp and dippe, as well as monodentate phosphanes such as P(iPr)$_3$, provide essentially inactive catalysts. Milstein and co-workers attribute this difference in reactivity to:

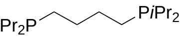
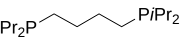
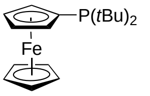
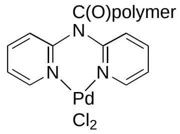
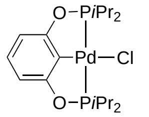
1) Easier dissociation of one of the phosphane groups in the case of dippb (versus dippp and dippe), which allows olefin coordination;
2) Faster oxidative addition of the aryl chloride to PdL_1 (L = dippb) than to L_2Pd (L = monophosphane);
3) More rapid olefin insertion (versus monodentate phosphanes), as a result of chelation by dippb.[254]

Heck reactions of unactivated aryl chlorides with styrene can be performed in the presence of Pd/dippp under reducing, nonbasic conditions to preferentially generate *cis*-stilbenes (Table 7, entry 2).[255] Coupling of electron-rich 4-chloroanisole proceeds in a respectable yield of 49%, although dehalogenation is a significant side reaction.

Herrmann et al. used palladium complexes and simple triarylphosphanes (for example, PPh_3) and obtained modest success (up to 48% yield) in effecting Heck reactions of 4-chloroanisole with n-butyl acrylate, although quite high temperatures were required (160 °C) and side products arising from P–C bond cleavage were observed.[256] Palladium-supported on MgO[257] and nanostructured palladium clusters stabilized with propylene carbonate also exhibit some activity in Heck couplings of chlorobenzene and styrene.[258]

Table 7. Heck couplings of aryl chlorides.



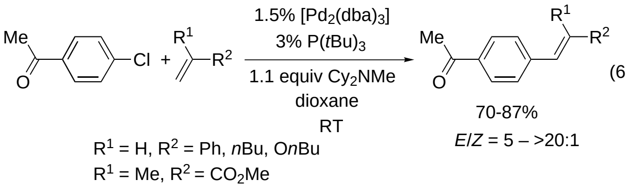
Entry	R	R1	Catalyst	Conditions	Yield [%]
1	4-NO$_2$, CHO, H, CH$_3$	Ph	Pd(OAc)$_2$/ 	NaOAc, DMF, 150 °C	55–95
2	4-COMe, H, OMe, 3-OMe	Ph	Pd(OAc)$_2$/ 	Zn, DMF, 140 °C	49–88
3	4-CHO, H	Ph	[PdCl$_2$(MeCN)$_2$]/PPh$_4$Cl	NaOAc, NMP, 150 °C	96–98[a,b]
4	4-COMe, H, OMe, 2-Me	Ph, CO$_2$Me	[Pd$_2$(dba)$_3$]/P(*t*Bu)$_3$	Cs$_2$CO$_3$, dioxane, 100–120 °C	70–84
5	4-CO$_2$Me, Me, OMe	CO$_2$*n*Bu	[Pd(dba)$_2$]/P(*t*Bu)$_3$ or 	NaOAc, DMF, 110 °C	48–97
6	4-COMe, H	Ph		Na$_2$CO$_3$/K$_2$CO$_3$, DMA, 140 °C	89–95[c]
7	4-CHO, COMe, H, OMe, 2-Me	Ph		CsOAc, dioxane, 120, 180 °C	81–99
8	4-H, Me, OMe, 2-Me	Ph, CO$_2$C$_8$H$_{17}$	[Pd(dba)$_2$]/*n*BuP(1-Ad)$_2$	K$_3$PO$_4$, dioxane, 120 °C	33–98

[a] GC conversions. [b] *N*,*N*-Dimethylglycine was used as an additive. [c] *n*Bu$_4$NBr was used as a co-catalyst.

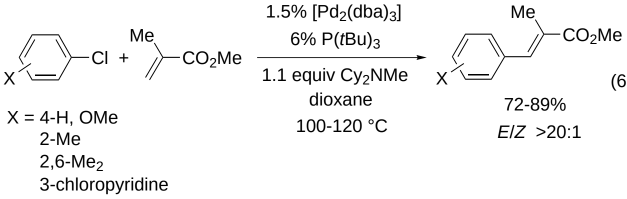
An important contribution in the development of Heck chemistry of unactivated aryl chlorides was described by Reetz et al. in 1998. In this study, they noted that simple Pd^{II} complexes such as [PdCl$_2$(MeCN)$_2$] and Pd(OAc)$_2$ exhibit high activities in Heck couplings of electron-neutral aryl chlorides with styrene in the presence of tetraphenylphosphonium salts (Table 7, entry 3).[259] The addition of *N*,*N*-dimethylglycine improves the regioselectivity of the reaction. Turnover numbers as high as 130 and 950 can be obtained for chlorobenzene and 4-chlorobenzaldehyde, respectively.

The most versatile method that has been reported to date for Heck couplings of unactivated aryl chlorides employs Pd/P(*t*Bu)$_3$ as the catalyst. In 1999, Littke and Fu reported a first-generation system based on this combination. In the presence of Cs$_2$CO$_3$, this catalyst couples both electron-rich and hindered aryl chlorides with styrene and methyl acrylate (Table 7, entry 4).[260] Although the reaction temperature was still high (100–120 °C), it was lower than for other catalysts that had been described at that time. Interestingly, P(*t*Bu)$_3$ was the only effective ligand among the commercially available phosphanes that were screened, which included PCy$_3$[261] and tris(2,4,6-trimethoxyphenyl)phosphane,[262] both of which are also quite bulky and electron-rich.[263]

A significant improvement in the scope and the mildness of this catalyst system was realized by replacing Cs$_2$CO$_3$ with Cy$_2$NMe.[264, 265] Heck couplings of activated aryl chlorides can be accomplished at room temperature with this new method [Eq. (62)]. Importantly, the scope of the reaction with respect to the olefin partner is considerably widened—a range of monosubstituted and disubstituted olefins are arylated with high *E*/*Z* stereoselectivity; essentially all previous studies of Heck couplings of aryl chlorides had focused exclusively on styrene and acrylic acid derivatives, which are particularly reactive coupling partners. The catalyst is effective for electron-rich, hindered, and heteroaryl aryl chlorides [Eq. (63)]. In addition, a high turnover number (~300) can be achieved in the relatively challenging coupling of chlorobenzene with methyl methacrylate. Commercially available [Pd{P(*t*Bu)$_3$}$_2$], sometimes in combination with [Pd$_2$(dba)$_3$], can be employed for many of these reactions.



(62)



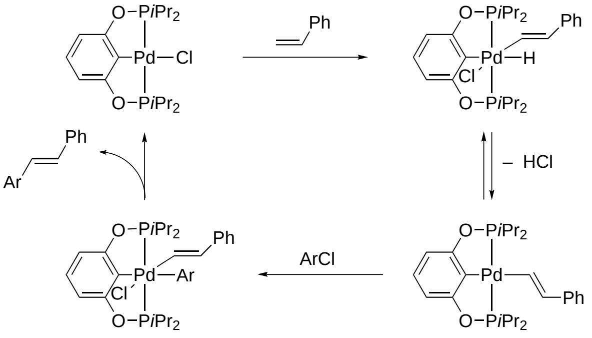
(63)

The unusually high reactivity of Pd/P(tBu)$_3$ in Heck reactions of aryl chlorides was discovered independently by Hartwig and co-workers through a fluorescence-based assay in which over 40 phosphane ligands were screened for activity. Only two, P(tBu)$_3$ and di(*tert*-butyl)phosphanylferrocene, were effective for Heck couplings of unactivated aryl chlorides (Table 7, entry 5).[266]

In 1999, Buchmeiser and Wurst described a heterogeneous catalyst for Heck reactions of aryl chlorides based on a polymer-bound dichloropalladium(di(pyrid-2-yl)amide) that was prepared by ring-opening metathesis (Table 7, entry 6).[267] The use of this air- and moisture-stable catalyst can, with the addition of nBu$_4$NBr, enable turnover numbers as high as 23600 to be achieved for the coupling of chlorobenzene with styrene.

Nonaqueous ionic liquids have been reported by Herrmann and Bohm to be excellent media for conducting palladacycle-catalyzed Heck reactions of unactivated aryl chlorides.[268] Phosphane- and phosphite-based palladacycles, as well as carbene-derived catalysts, show improved activity for couplings of chlorobenzene in molten nBu$_4$NBr, relative to DMF, which is a traditional solvent for the Heck reaction.[269] Even catalysts such as [Pd(PPh$_3$)$_4$] and PdCl$_2$ exhibit some reactivity under these conditions. However, only [Pd$_2$(dba)$_3$]/P(tBu)$_3$ displays high activity for Heck couplings of electron-rich aryl chlorides.

Jensen and co-workers have determined that a phosphite PCP-pincer complex, which can be prepared in two steps,[270] is an effective catalyst for Heck reactions of a range of aryl chlorides, including hindered and electron-rich substrates (Table 7, entry 7).[271] A disadvantage of this system is that a very high temperature (180 °C, 24 hours) or a prolonged reaction time (120 °C, 5 days) is required. Interestingly, under identical conditions, the more electron-rich phosphane PCP-pincer complex[272] is almost inactive. The Heck-type reactions catalyzed by the phosphite PCP-pincer complex may proceed through Pd^{II} and Pd^{IV} intermediates (Scheme 8). Thus, oxidative addition of a vinyl C–H bond is followed by reductive elimination of H–Cl, oxidative addition of Ar–Cl, and finally reductive elimination of the coupled product. The markedly lower reactivity of the more electron-rich phosphane PCP-pincer complex may be attributed to slower reductive elimination of HCl, which is believed to be the turnover-limiting step of the catalytic cycle.

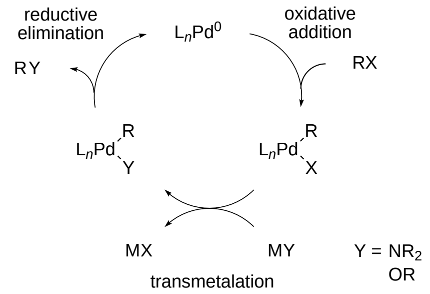


Scheme 8. Proposed mechanism for Heck-type reactions catalyzed by a phosphite PCP-pincer complex.

Beller and co-workers have established that di(1-adamantyl)-n-butylphosphane is a highly effective ligand for Heck couplings of unactivated aryl chlorides, although hindered aryl chlorides furnish modest yields (Table 7, entry 8).[273] An array of bulky, electron-rich dialkylaryl- and trialkyphosphanes were screened for the palladium-catalyzed coupling of 4-chlorotoluene and styrene, and it was determined that di(1-adamantyl)-n-butylphosphane and P(tBu)$_3$ afford the highest yields and turnover numbers.

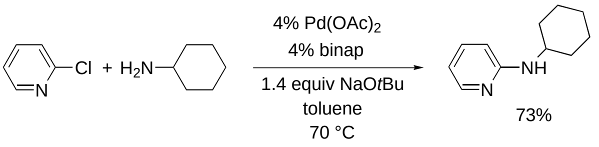
3. Carbon – Nitrogen Bond-Forming Reactions

As a result of the pioneering efforts of Buchwald and co-workers[274] and Hartwig et al.,[69b, 275] metal-catalyzed C(aryl)–N bond formation has recently emerged as an extremely powerful tool for the synthesis of aniline derivatives, which are important to a diverse array of fields, such as pharmaceuticals, agrochemicals, and photography.[276, 277] A simplified overview of the mechanism of the Buchwald–Hartwig reaction, as well as a related C–O bond-forming process (Section 4), is provided in Scheme 9. The pathway is analogous to that of the C–C bond-forming reactions described above (Scheme 1), except that the transmetalating agent is a metal amide or a metal alkoxide.



Scheme 9. Simplified mechanism for palladium-catalyzed C–N and C–O bond formation.

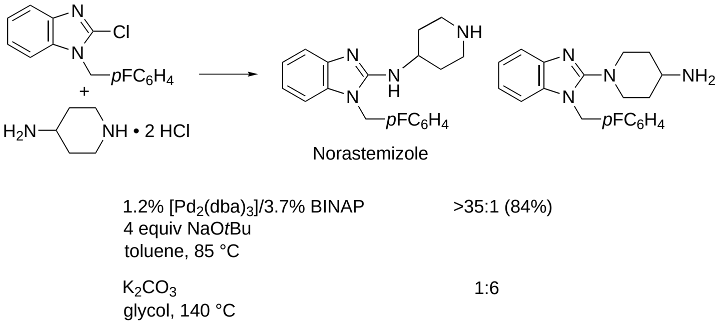
Although initial studies by the research groups of Buchwald and Hartwig focused on traditional coupling partners such as aryl bromides, later reports by these and other groups have described mild and general protocols for the palladium-catalyzed amination of aryl chlorides. In 1996, Wagaw and Buchwald furnished the first example of a reaction of a heteroaryl chloride, the Pd(OAc)$_2$/binap-catalyzed amination of 2-chloropyridine with cyclohexylamine [Eq. (64)].[278]



(64)

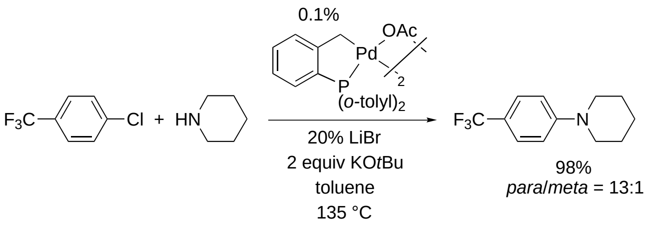
Subsequently, palladium-catalyzed aminations of chloroquinolines,[279] heteroarylimidoyl chlorides,[280] chloropurines,[281] chlorothiophenes,[282] chlorobenzothiazoles,[283] chlorobenzooxazoles,[283] and other chloropyridines[279, 284] have been achieved, generally with either Pd/binap or Pd/dppf as the catalyst. For dichloro-substituted pyridines, Pd/binap/K_2CO_3 can effect highly selective aminations of the 2-chloro group, in preference to the 3-, 5-, and 6-chloro, group.[285]

Senanayake and co-workers have devised a practical synthesis of the nonsedating antihistamine norastemizole that relies upon the amination of 4-fluorobenzyl-2-chlorobenzimidazole [Eq. (65)].[286] This work furnishes the first example of a selective palladium-catalyzed coupling of a primary amine in the presence of a secondary amine. This selectivity is not limited to 4-aminopiperidine, but can be extended to acyclic diamines and triamines. In contrast, thermal amination leads to preferential reaction of the secondary amine with 6:1 selectivity.



(65)

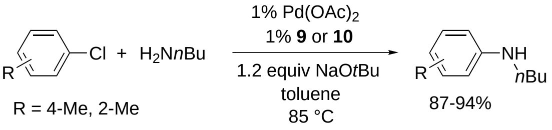
The first report of a palladium-catalyzed amination of an activated, but non-heteroaryl, chloride was provided by Beller et al. in which they used a palladacycle complex [Eq. (66)].[287] A small amount of the *meta*-substituted product is obtained, which suggests that at least some benzyne is generated under these conditions (in the absence of a catalyst, a 1:1 mixture of *para* and *meta* isomers is observed).[288] The choice of base is crucial—KO*t*Bu is far superior to NaO*t*Bu, which is more commonly used in palladium-catalyzed aminations.



(66)

In 1997, Reddy and Tanaka described the first examples of palladium-catalyzed aminations of unactivated aryl chlorides using $[PdCl_2(PCy_3)_2]$ as the catalyst (Table 8, entry 1).[289] $[PdCl_2(PiPr_3)_2]$ is also effective, but binap-,[290] dppf-, and P(*o*tol)$_3$-based catalysts provide less than 10% of the desired product. $[PdCl_2(PCy_3)_2]$-catalyzed aminations of *ortho*-substituted aryl chlorides proceed in poor yield. Reactions of cyclic secondary amines furnish the highest yields, and secondary anilines afford modest to good yields. On the other hand, acyclic secondary amines are not suitable substrates for this method, because of their propensity to undergo β-hydride elimination, which results in imine formation and hydrodehalogenation of the aryl chloride. Thus, PCy_3 appears to be effective at achieving oxidative addition of the aryl chloride to palladium, but it is not always ideal for subsequent steps in the catalytic cycle, such as promoting reductive elimination over β-hydride elimination.

Hindered, chelating ferrocenyldialkylphosphanes, in particular 1,1′-bis(di-*tert*-butylphosphanyl)ferrocene (D*t*BPF), are useful in palladium-catalyzed aminations of aryl chlorides (Table 8, entry 2).[291] The high reactivity furnished by this ligand may be a result both of its electron-richness, which promotes the oxidative addition of unactivated aryl chlorides to Pd^0, and its steric demand and chelating nature, which favor reductive elimination over β-hydride elimination. Thus, Pd/D*t*BPF efficiently couples aniline and secondary cyclic amines with electron-neutral aryl chlorides. Ferrocenyl ligands **9** and **10** are very effective for arylations of primary alkylamines [Eq. (67)].



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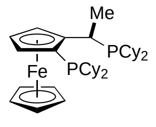

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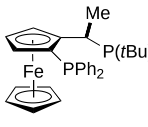
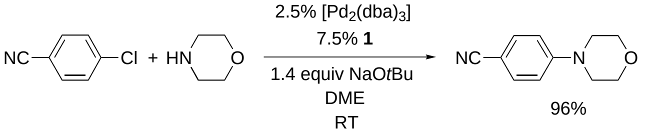


10

Buchwald and co-workers have demonstrated that the dialkylarylphosphane ligands that are so efficient for Suzuki couplings of aryl chlorides [Eqs. (10) and (11)] are also useful for aminations of this family of substrates. Thus, Pd/**1** provided the first example of a room-temperature reaction of an aryl chloride (4-chlorobenzonitrile) [Eq. (68)].[56] This catalyst couples a wide array of chlorides, including electron-rich ones, with secondary and primary alkyl amines and anilines. Subsequent studies revealed that di(*tert*-butyl)phosphanyl-substituted biphenyl ligand **3** is considerably more effective in achieving room-temperature aminations, and effects coupling of even hindered and electron-rich aryl chlorides [Eq. (69)].[57a]



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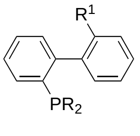
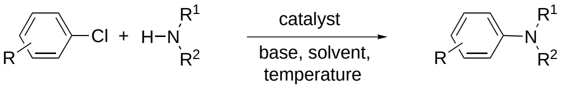
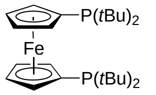
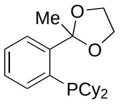
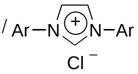
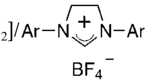
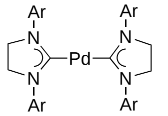


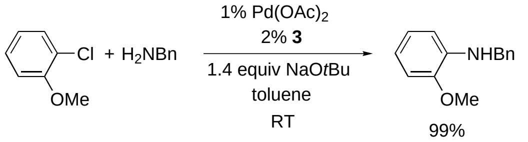
R = Cy, R^1 = NMe$_2$ **1**
R = Cy, R^1 = H **2**
R = *t*Bu, R^1 = H **3**

Table 8. Carbon – nitrogen bond-forming reactions of aryl chlorides.



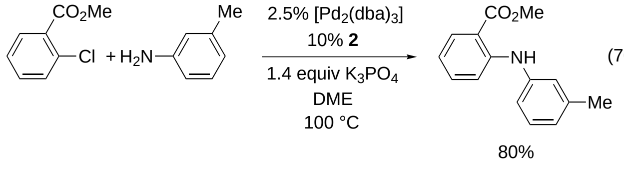
Entry	R	Amine	Catalyst	Conditions	Yield [%]
1	4-CN, H, CH_3	2° cyclic; 2° aryl	$[PdCl_2(PCy_3)_2]$	NaO*t*Bu, toluene, 120 °C	56 – 88
2	4-Me, 3-OMe, 2-Me	2° cyclic; 1° alkyl; 1° aryl	Pd/ 	NaO*t*Bu, toluene, 100 – 110 °C	57 – 93[a]
3	4-CN, H, Me, OMe	2° alkyl; 2° aryl; 1° aryl	$[Pd(dba)_2]/P(tBu)_3$	NaO*t*Bu, toluene, RT-70 °C	75 – 97
4	$4\text{-}CO_2Me$, H, F, Me, OMe, 2-Cl-pyridine	$LiN(SiMe_3)_2$	$[Pd(dba)_2]/P(tBu)_3$	toluene, RT-90 °C	62 – 99[b]
5	4-COPh, CF_3, CN, 3,5-Me_2, 2,5-Me_2, 2-OMe	2° cyclic; 2° alkyl; 1° alkyl; 1° aryl	$[Pd(dba)_2]$/ 	NaO*t*Bu, toluene, 105 °C	83 – 97
6	4-Me	1° aryl	$[PdCl_2(P(tBu)_2OH)_2]$	NaO*t*Bu, dioxane, 110 °C	97
7	4-Me, OMe, 2,5-Me_2	2° cyclic; 2° alkyl; 2° aryl; 1° alkyl; 1° aryl	$[Pd_2(dba)_3]$/ 	KO*t*Bu, dioxane, 100 °C	59 – 99 %[c]
8	4-CN, Me, OMe, 2-Me, 2-Cl-pyridine, 3-Cl-pyridine	2° cyclic; 2° alkyl; 2° aryl; 1° aryl	$[Pd(dba)_2]$/ 	NaO*t*Bu, DME, RT	82 – 99[c]
9	4-Me	2° cyclic; 2° alkyl; 2° aryl; 1° alkyl; 1° aryl		KO*t*Bu, dioxane, 100 °C	81 – 99[c,d]

[a] Both $[Pd(dba)_2]$ and $Pd(OAc)_2$ were used as the Pd sources. [b] The isolated product was the desilylated aniline. [c] Ar = 2,6-$(iPr)_2C_6H_3$. [d] The $[Pd(carbene)P(oTol)_3]$ complex was also an efficient catalyst.



(69)

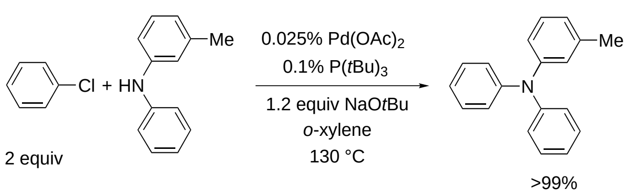
The scope of aminations catalyzed by Pd/**3** is enhanced at 80 – 110 °C; primary and secondary anilines, primary amines, diarylamines, benzophenone imine, and benzophenone hydrazone can all be coupled with aryl chlorides, including very hindered chlorides and chloropyridines.[292] Catalyst loadings as low as 0.05 % Pd can be employed for certain substrate combinations. Aminations of aryl chlorides that contain sensitive functional groups can be achieved by using a weaker base (K_3PO_4) and phosphanes **1** or **2** [Eq. (70)].



(70)

Since the initial work of Buchwald and co-workers, there have been numerous applications of these versatile dialkylphosphanylbiphenyl ligands to aminations of aryl chlorides, for example, to the *N*-arylation of indoles[293] and vinylogous amides,[294] as well as to the activation of halobenzyl ether protecting groups for oligosaccharide synthesis[295] and the "one-pot" synthesis of unsymmetrical triarylamines.[296, 297] Polymer-supported versions of these ligands can be used.[298] Primary anilines can be synthesized from aryl and heteroaryl chlorides by employing lithium hexamethyldisilazide (LiHMDS) or Ph_3SiNH_2 as ammonia equivalents and Pd/**2** as the catalyst; in addition, symmetrical di- and triarylamines may be obtained through Pd/**3**-catalyzed arylations of $LiNH_2$.[299]

In 1998, a group at the Tosoh Corporation reported that $P(tBu)_3$ is an effective ligand for palladium-catalyzed aminations of aryl chlorides. Chlorobenzene can be coupled with piperazine[300] and *N*-(3-methyphenyl)aniline[301] in good yield; in the latter case, just 0.025 % Pd is required [Eq. (71)]. The scope of Pd/$P(tBu)_3$-catalyzed aminations of aryl chlorides is quite broad. Unactivated chlorides can be coupled with secondary amines at 70 °C, and activated aryl chlorides and even chlorobenzene can be aminated at room

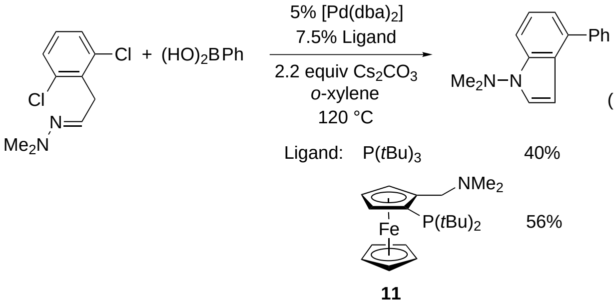


(71)

temperature (Table 8, entry 3).[302] As was observed for Suzuki reactions [Eq. (16)], a low P(*t*Bu)$_3$:Pd ratio (0.8:1) can provide an improved reaction rate. Pd/P(*t*Bu)$_3$ catalyzes the coupling of aryl chlorides with a range of nitrogen-containing substrates, including indoles[303] and *tert*-butyl carbamate,[304] which leads to Boc-protected anilines. LiHMDS can be arylated to afford primary anilines, after treatment of the coupling products with HCl (Table 8, entry 4).[305] Aryl chlorides that bear ortho substituents are not suitable substrates.

Alcazar-Ramon and Hartwig have pursued mechanistic studies of Pd/P(*t*Bu)$_3$-catalyzed aminations of aryl chlorides in the presence of alkoxide bases, and have proposed that two distinct pathways can be followed.[306] One mechanism involves turnover-limiting oxidative addition to the monophosphane–palladium complex that is formed upon ligand dissociation from the resting state complex [Pd{P(*t*Bu)$_3$}$_2$]. The second mechanism involves oxidative addition to an anionic adduct of the alkoxide and palladium, namely, [Pd(alkoxide){P(*t*Bu)$_3$}]$^-$.[307] For aminations that employ P(*t*Bu)$_3$:Pd (1:1) and NaO*t*Bu, the reaction rate is first-order in base, which Hartwig and co-workers cite as evidence for the predominance of the second pathway. In contrast, a zero-order dependence on base is observed when the more hindered NaOCEt$_3$ is used, which suggests that the first pathway is being followed. A zero-order dependence on base is observed for both NaO*t*Bu and NaOCEt$_3$ for Pd/binap-catalyzed aminations.[308]

Watanabe et al. have established that both P(*t*Bu)$_3$ and P,N ligand **11**, available in one step from commercially available dimethylaminomethylferrocene, can be used to synthesize 1-aminoindole derivatives by intramolecular aminations of *N*,*N*-disubstituted *o*-chloroacetaldehyde hydrazones.[67a] Two palladium-catalyzed bond-forming reactions can be achieved in one pot to generate functionalized 1-aminoindoles by use of dichloroarylacetaldehyde hydrazones in the presence of an amine, an azole, or an arylboronic acid [Eq. (72)]. For the illustrated transformation, the Suzuki coupling proceeds more quickly than the amination/cyclization.[309]



(72)

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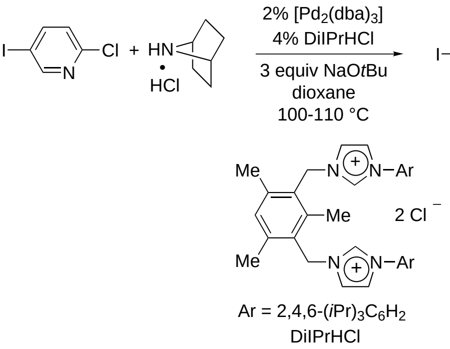
The dialkylarylphosphane prepared by Guram and co-workers is a suitable ligand for palladium-catalyzed aminations of sterically and electronically diverse aryl chlorides. Unhindered chlorides couple well with secondary amines, whereas *ortho*-substituted aryl chlorides are aminated cleanly by primary amines (Table 8, entry 5).[310] Studies of closely related ligands indicate that the oxygen atom(s) of the phosphane are important for its effectiveness.

Li has demonstrated that Pd/phosphinous acid complexes can catalyze the amination of electron-neutral aryl chlorides in moderate to excellent yield. With respect to the amine component, only ArNH$_2$ and secondary cyclic amines have been shown to be efficient coupling partners. The catalyst can be generated in situ from a phosphane oxide and [Pd$_2$(dba)$_3$],[82] or commercially available Pd^{II}/phosphinous acid complexes may be used (Table 8, entry 6).[248]

The amination of aryl chlorides can also be achieved with Pd/carbene catalysts. Nolan and co-workers screened a variety of salts of N-heterocyclic carbene ligands, and found diisopropylaryl-substituted IPr, which is effective for Kumada reactions of unactivated aryl chlorides, to be the most efficient. Both primary and secondary amines can be coupled with electron-neutral and electron-rich aryl chlorides in good yield (Table 8, entry 7).[311] The scope of Pd/IPr-catalyzed aminations was subsequently expanded to include reactions of chloropyridines and of benzophenone imine.[312]

Cheng and Trudell established that related Pd/bis(carbene) complexes catalyze the amination of 2-chloro-5-iodopyridine by 7-azabicyclo[2.2.1]heptane. Interestingly, the chloride reacts preferentially [Eq. (73)]; the product arising from coupling of the iodide is isolated in just 5 % yield.[313]

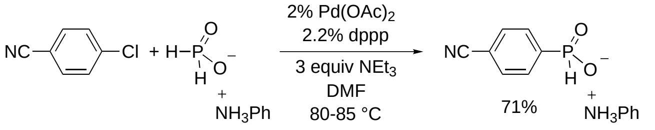


(73)

The saturated analogue of IPr, which can be generated from dihydroimidazolium salt SIPrHBF$_4$,[86b, c, 314, 315] was later reported to provide a more active catalyst than IPr itself for aminations of aryl chlorides (Table 8, entry 8).[316] It is possible to accomplish room-temperature couplings of unactivated and deactivated aryl chlorides and of chloropyridines with a variety of unhindered secondary amines by using the more electron-rich SIPr as the ligand. The catalyst is not effective, however, for reactions of primary alkyl amines, for which rates are slower and substantial amounts of hydrodehalogenated arene are formed. At elevated temperature, a high turnover number can be achieved (for example, nearly 5000 for the coupling of 4-chlorotoluene and morpholine after 7 hours at 100 °C).

Caddick and co-workers have demonstrated that discrete, two-coordinate bis(SIPr) and SIPr/P(*o*tol)$_3$ complexes of palladium are active catalysts for couplings of electron-neutral 4-chlorotoluene with a variety of amines, including primary amines (Table 8, entry 9).[317] In contrast to the SIPr-based catalyst system, which was generated in situ, these preformed palladium complexes of SIPr are not effective coupling catalysts at room temperature.[318]

Related to C–N bond construction are C–P bond-forming processes. Although there are quite a few examples of such reactions catalyzed by palladium,[319] the only one that involves an aryl chloride is the cross-coupling of activated 4-chlorobenzonitrile with anilinium hypophosphite in the presence of Pd/dppp [Eq. (74)].[320] [Pd(PPh$_3$)$_4$], the catalyst of choice for the corresponding reactions of aryl bromides, iodides, and triflates, furnishes no coupling product when 4-chlorobenzonitrile is the substrate.



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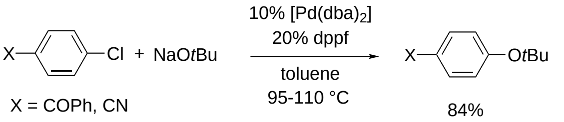
4. Carbon – Oxygen Bond-Forming Reactions

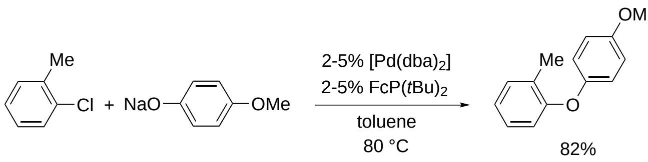
Diaryl and aryl alkyl ethers are important to a range of fields, including pharmaceutical and natural products chemistry.[277a, 321] Compared to palladium-catalyzed formation of C(aryl)–N bonds, the formation of C(aryl)–O bonds is much less well-developed. Nevertheless, during the past few years, important progress has been described, largely by the Buchwald and the Hartwig research groups, and a number of these advances have involved coupling reactions of aryl chlorides.

The first report of palladium-catalyzed C–O bond formation with an aryl chloride was provided by Mann and Hartwig, who determined that Pd/dppf effects coupling of electron-deficient aryl chlorides with NaO*t*Bu to generate *tert*-butyl aryl ethers, which can serve as useful protected versions of phenols [Eq. (75)].[322] Of course, the uncatalyzed reaction of alkoxides with aryl halides by nucleophilic aromatic substitution is well-established, with highly electron-poor aryl fluorides generally being the most reactive substrates.[323] The control experiments by Mann and Hartwig revealed that, under the conditions used, C–O bond formation does not proceed in the absence of the palladium catalyst.



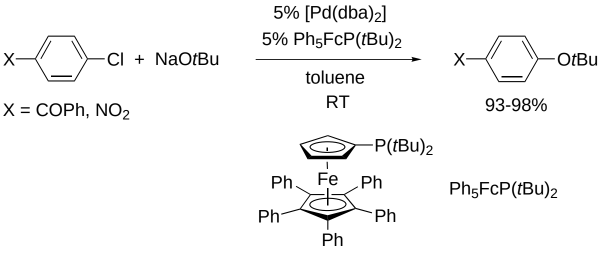
(75)

Since electron-neutral and electron-rich aryl chlorides are not suitable substrates for C–O bond formation through nucleophilic aromatic substitution, the development of a method for coupling these compounds using palladium catalysts would be a worthwhile achievement. In 1999, Hartwig and co-workers described the first system for accomplishing C–O bond formation with electron-neutral aryl chlorides by employing either P(*t*Bu)$_3$ or di(*tert*-butyl)phosphanylferrocene (FcP(*t*Bu)$_2$) as the ligand [Eq. (76)];[324] under these conditions, binap, dppf, and P(*o*tol)$_3$ are ineffective. Both NaO*t*Bu and electron-rich sodium phenoxides are useful coupling partners, but aryl chlorides that lack an *ortho* substituent are not. The beneficial effect of an *ortho* substituent may be the result of steric acceleration of turnover-limiting reductive elimination. In 1999, Watanabe et al. also reported that Pd/P(*t*Bu)$_3$ can catalyze the coupling of electron-neutral aryl chlorides with NaO*t*Bu.[325]



(76)

In a subsequent study, it was revealed that, under the reaction conditions described above, FcP(*t*Bu)$_2$ undergoes pentaarylation to generate Ph$_5$FcP(*t*Bu)$_2$,[166] which provides a more active palladium catalyst than that furnished by FcP(*t*Bu)$_2$ itself.[326] The first room-temperature C–O bond-forming reactions of aryl chlorides, albeit activated ones, were achieved with [Pd(dba)$_2$]/Ph$_5$FcP(*t*Bu)$_2$ [Eq. (77)].

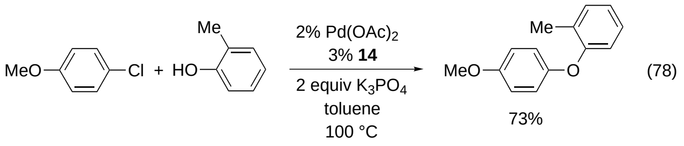


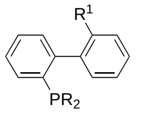
(77)

A significant expansion in the scope of palladium-catalyzed C–O bond-forming reactions of aryl chlorides was reported by Buchwald and co-workers, in which they used bulky, electron-rich dialkylarylphosphanes **3**, **12**, **14**, and **16**.[327] Electron-deficient chlorides couple smoothly with phenols using commercially available **3** as the ligand, whereas more challenging reactions of electron-neutral and electron-rich aryl chlorides require the use of **12**, **14**, and **16**. The first example of a coupling of a highly electron-rich chloride was achieved using ligand **14** [Eq. (78)]. This method has recently been applied to the solid-phase synthesis of a diverse library of heterocycles.[92]

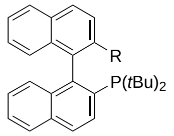
Parrish and Buchwald determined that, with the aid of ligands **1** and **13**, it is also possible to efficiently couple NaO*t*Bu with a wide range of aryl chlorides—electron-neutral, electron-rich, and hindered—to form aryl *tert*-butyl ethers.[328] It is believed that bulky ligands are necessary for these coupling processes to destabilize the [Pd(OAr^1)ArL$_n$] intermediate by forcing the Ar and OAr^1 groups closer together. This process facilitates reductive elimination, which is postulated to be the turnover-limiting step of the catalytic cycle.[329]

A significant limitation of most methods for palladium-catalyzed C–O bond formation is their inability to effectively couple alcohols that contain β-hydrogen atoms, that is,



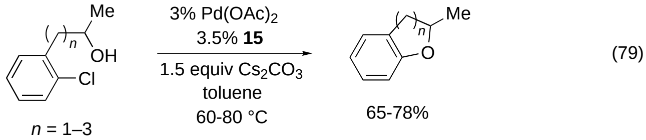


R = Cy, R^1 = NMe_2 **1**
R = *t*Bu, R^1 = H **3**
R = *t*Bu, R^1 = Ph **12**
R = *t*Bu, R^1 = Me **13**
R =1-adamantyl, R^1 = H **14**

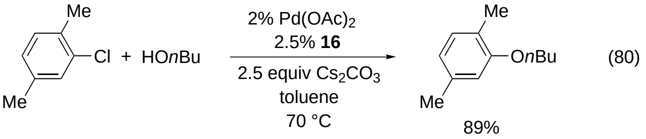


R = H **15**
R = NMe_2 **16**

primary and secondary alcohols. This limitation is attributed to the propensity of $[PdAr(OR)L_n]$ to undergo β-hydride elimination from the OR group, rather than reductive elimination to generate ArOR. However, both primary and secondary alcohols can be employed in intramolecular C–O bond-forming reactions of aryl chlorides by utilizing commercially available phosphane **15** [Eq. (79)].[330] This method achieves the synthesis of five-, six-, and seven-membered oxygen heterocycles in good yield. Enantioenriched secondary alcohols cyclize with only small losses in enantiomeric purity (1–10% *ee*).[330b]

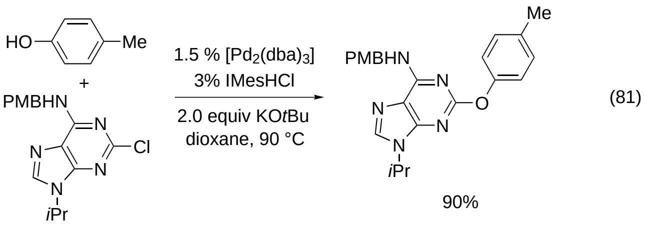


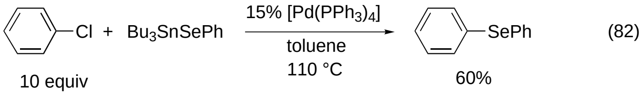
Ligand **16** (and sometimes **15**) is effective for palladium-catalyzed intermolecular C–O bond-forming reactions of primary alcohols.[331] Electron-neutral aryl chlorides with at least one *ortho* substituent, electron-deficient chlorides, and 2-chloropyridine are suitable substrates [Eq. (80)].



To date, there have been only two reports of the use of a non-phosphane-based ligand system for a C–O bond-forming reaction of an aryl chloride. Thus, Schultz and co-workers have demonstrated that couplings of 2-chloropurine derivatives with phenols proceed in high yields with Pd/IMes as the catalyst [Eq. (81); PMB = *para*-methoxybenzyl].[89, 92]

In a related reaction (C–Se bond formation), Nishiyama et al. have observed that $[Pd(PPh_3)_4]$ catalyzes the coupling of chlorobenzene with $SnBu_3SePh$ to generate diphenylselenide [Eq. (82)].[332]

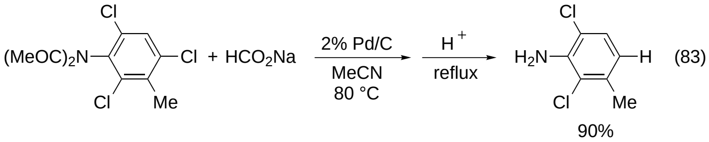




5. Hydrodechlorination Reactions

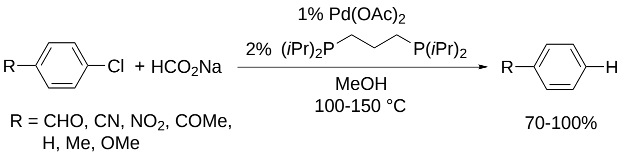
The dechlorination of aryl chlorides is an important process not only for synthetic organic chemistry,[333] but also for environmental chemistry, since the dechlorination of polychlorinated biphenyls (PCBs) and related chlorinated aromatics provides a mechanism for the detoxification of these persistent pollutants.[334] The heterogeneous palladium-catalyzed dechlorination of aryl and heteroaryl chlorides has been applied extensively for many years.[335] Most commonly, palladium on carbon is employed in the presence of a reducing agent such as hydrogen,[336] triethylsilane,[337] sodium hypophosphite,[338] 1,4-cyclohexadiene,[336c] formic acid,[339] and formate salts.[340]

One interesting application of heterogeneous palladium-catalyzed dechlorination is the synthesis of 2,6-dichloroanilines by selective reduction of the *para* chlorine atom of a 2,4,6-trichloro precursor [Eq. (83)].[341] This can be a useful strategy, since these dichloroanilines cannot be directly accessed by electrophilic aromatic halogenation of the aniline.



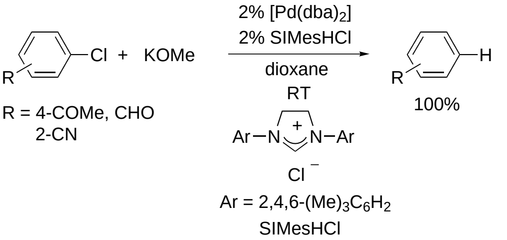
In contrast to the numerous reports of dechlorination by heterogeneous palladium catalysts, there are comparatively few studies that employ homogenous complexes. Chlorobenzene can be reduced to benzene in 76% yield at 140 °C with catalytic $PdCl_2$ and indoline as the hydrogen donor; Rh-, Ru-, Re-, Fe-, Ni-, Co-, Ir-, and Pt-based complexes are less effective.[342, 343] $[Pd(PPh_3)_4]$ has also been applied as a catalyst for the reduction of aryl chlorides,[344] but most of the investigations have focused on activated substrates.[345] On the other hand, palladium complexes of the bulky, electron-rich, chelating ligand dippp may be employed for dechlorinations of an electronically diverse set of functionalized aryl chlorides [Eq. (84)].[346]

Pd/carbene-based catalysts can accomplish dechlorination under milder conditions. Saturated mesityl-substituted carbene SIMes was found to be particularly effective among a



(84)

number of carbenes and phosphanes that were screened [Eq. (85)].[347] Electron-deficient aryl chlorides are sufficiently reactive to undergo reduction at room temperature, whereas unactivated substrates and chloropyridines are dechlorinated at 100 °C.



(85)

6. Conclusions

A remarkable amount of progress has been reported during the last few years toward solving the long-standing challenge of bringing readily available and inexpensive aryl chlorides into the family of generally useful substrates for palladium-catalyzed coupling reactions. Thus, through the appropriate choice of ligand—bulky, electron-rich phosphanes and carbenes have thus far proved to be the most versatile—a number of surprisingly mild and general catalyst systems have been developed. Although the traditional view has been that oxidative addition is the problematic step in the catalytic cycle for reactions of aryl chlorides, facilitating this step is simply a necessary, not a sufficient, condition for achieving effective catalysis. Thus, the ligands that have been developed also have steric and electronic properties that are appropriate for subsequent steps in the catalytic cycle.

In view of these recent advances one can anticipate a marked increase in the use of palladium-catalyzed coupling reactions, particularly in industry, where the relatively low cost of aryl chlorides makes these new developments especially attractive. Importantly, many of the key ligands are now commercially available.

Despite the impressive progress, a number of challenges remain. Clearly, the price advantage of aryl chlorides over other coupling partners only holds if comparable turnover numbers can be attained and if the catalysts are of similar cost. In many of the pioneering studies that have been described above, relatively high catalyst loadings have been employed (>1 %). For industrial applications in particular, it will be important to establish that higher turnover numbers and turnover frequencies can indeed be achieved. Furthermore, it is desirable to develop effective supported variants of these new catalysts, since this can provide a significant practical benefit in industry. Finally, there is clearly still room for improvement in terms of both scope and mildness for nearly all of the methods that have been discusssed. In view of the ever-increasing level of activity in this rapidly developing area, one can reasonably expect that solutions to these challenges will quickly emerge in the near future.

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[3] For a discussion, see a) V. V. Grushin, H. Alper in *Activation of Unreactive Bonds and Organic Synthesis*, (Ed.: S. Murai), Springer, Berlin, **1999**, pp. 193–226; b) V. V. Grushin, H. Alper, *Chem. Rev.* **1994**, *94*, 1047–1062.

[4] For an example in which an aryl chloride was converted into an aryl iodide (33 % yield) to enable a palladium-catalyzed Suzuki coupling to take place, see J. M. Lovell, J. A. Joule, *Synth. Commun.* **1997**, *27*, 1209–1215.

[5] Nickel-based complexes can show higher reactivity toward aryl chlorides than palladium-based complexes, and they will certainly play an important role in efforts to utilize these substrates in coupling processes. At the same time, nickel can suffer from disadvantages relative to palladium, including lower tolerance of functional groups (L. Brandsma, S. F. Vasilevsky, H. D. Verkruijsse, *Application of Transition Metal Catalysts in Organic Synthesis*, Springer, New York, **1998**, pp. 150, 228–229), lower selectivity (H. Geissler in *Transition Metals for Organic Synthesis*, *Vol. 1* (Eds.: M. Beller, C. Bolm), Wiley-VCH, New York, **1998**, p. 177), and higher toxicity (F. W. Sunderman, Jr. in *Handbook on Toxicity of Inorganic Compounds* (Eds.: H. G. Seiler, H. Sigel), Marcel Dekker, New York, **1988**, chap. 37; C. W. Bradford, B. J. Chase in *Handbook on Toxicity of Inorganic Compounds* (Eds.: H. G. Seiler, H. Sigel), Marcel Dekker, New York, **1988**, chap. 43; B. L. Carson, *Toxicology and Biological Monitoring of Metals in Humans*, Lewis Publishers, Chelsea, MI, **1986**).

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