C–C Bond Formation by Cross-Coupling☆

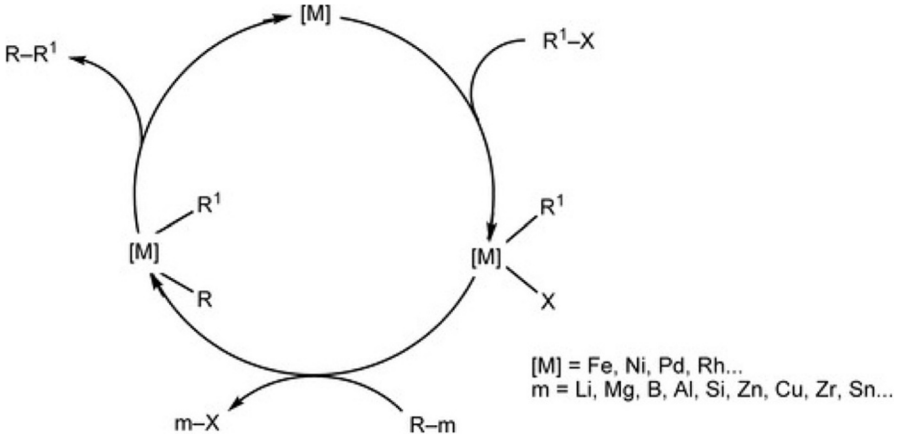
SP Nolan, University of St Andrews, St Andrews, UK
O Navarro, University of Sussex, Brighton, UK

Introduction

Cross-coupling reactions represent a class of synthetic transformations that involve the combination of an organometallic reagent (that has a main group metal atom in most of cases) with an organic electrophile in the presence of groups 8–10 metal catalysts to achieve a C–C, C–H, C–N, C–O, C–S, C–P, or C–M bond formation.[1] Since the initial discoveries in this area in the early 1970s by Kumada, Kochi, Corriu, and Murahashi, many organometallic reagents, such as organoboron, organotin, organosilicon, and organozinc have proved to be useful for cross-coupling reactions. Many different types of electrophiles and metal complexes have been successfully employed in these reactions, resulting in a plethora of synthetic methods for molecular assemblies. For this reason, cross-coupling reactions have been used in numerous organic synthetic applications ranging from polymers and liquid crystals to pharmaceuticals and natural products.

A general catalytic cycle for cross-coupling reactions is depicted in **Scheme 1**. In general, the reaction occurs by a sequence of oxidative addition–transmetallation–reductive elimination. The characteristics of both the transition metal and the main group metal reagent, in addition to effects associated with other reaction conditions, will affect the catalytic performance. The oxidative

☆*Change History:* June 2013. O Navarro updated captions for figures, schemes, tables and references.



Scheme 1 General catalytic cycle for cross-coupling reactions.

addition step is often regarded as the rate-determining step in the catalytic cycle, and the strength of the C–X bond (X = halide or pseudohalide) is determinant. The relative reactivity decreases then in the order I > OTf > Br » Cl.[2]

Improvements in cross-coupling reactions can be associated to two main thrusts: (1) increased activity and stability of catalytic systems; this is related to extensive research on the development of new and more efficient supporting ligands,[3] although, ligandless systems are of great importance also; and (2) the use of new halides, pseudohalides and organometallic nucleophiles. In this chapter, we will focus on the developments in C–C bond formation by cross-coupling reactions related to the development of new and more efficient catalysts. As excellent general reviews have been published covering the literature until the end of 2001, new developments during the period from 2001 to the end of 2004 are mainly discussed here. Some developments prior to 2001 will also be discussed as leading references that contributed to major advances in the area. Each section will include a list of significant reviews.

Cross-Coupling Reactions

Reactions with Organoboron Reagents: The Suzuki–Miyaura Reaction

In 1979 Miyaura, Yamada, and Suzuki reported on the coupling reaction of alkenyl boronates with alkenyl bromides.[4] Nowadays, this reaction is known as the Suzuki–Miyaura reaction.[5] The coupling of organoboron reagents with various organic halides has broadened its scope, becoming arguably the most important transformation leading to the formation of a C–C bond, since organoboron reagents show many advantages,[6] for example: (1) ready availability of reagents by hydroboration and transmetallation, (2) inert to water and related solvents, as well as oxygen, (3) generally thermally stable, (4) tolerant toward various functional groups, (5) low toxicity of starting materials and byproducts. A plethora of new catalysts, reaction conditions, organoboron reagents have been developed by a large number of research groups, and a large number of drugs,[7] polymers,[8] and natural products[9] include a Suzuki–Miyaura cross-coupling step in their synthesis. Some examples are shown in **Figure 1**.

As previously mentioned, the Suzuki–Miyaura reaction is generally thought to occur by a sequence of oxidative addition–transmetallation–reductive elimination. First and last steps are well understood, but the role of the base in the transmetallation step is still unclear. With the information available so far, it seems that three different processes can occur to transfer the organic group from the boron atom (**Scheme 2**).[6b] Although organoboronic acids do not react with R–Pd–X **i** (X = halogen), it is known that ate complexes such as Bu_4BLi,[10] $[R_3BOMe]Na$,[11] and $[ArBF_3]K$[12] readily undergo cross-coupling in the absence of a base, showing how the quaternization of the boron atom with a negatively charged base enhances the nucleophilicity of the organic group on the boron atom. There is no evidence for analogous hydroxyboronate anions,[13] but species such as **ii**, which exist in alkaline solution, could similarly alkylate **i** (path A).

Path B shows the possibility of the *in situ* generation of an (alkoxo)-, (hydroxo)-, (acetyloxo)-, or (acetoxo)palladium(II) complex by exchange between **i** and a base (R^2O), forming an (alkoxo)palladium(II) intermediate **iv** that can undergo transmetallation without the aid of a base.[14] Moreover, the coupling reaction can proceed under neutral conditions for organic electrophiles yielding **iv** (path C).[15,16] Both pathways B and C may involve a rate-determining coordination of the R^2O ligand to the boron atom, as a consequence of the formation of complex **v**, which participates in the formation of **iii** by transfer of the activated organic group from boron to palladium.[16] The high reactivity of the oxo–palladium complexes can be attributed to both the high basicity of the Pd–O species (related Pt complexes are known to be more basic than NaOH)[17] and the oxophilicity of the boron center.

Since it is known that halogens and OTf ligands on **i** are easily displaced by alkoxy, hydroxyl, or acetoxy to provide a basic species **iv**,[12] it seems clear that in alkaline solution both pathways A and B can occur for the cross-coupling reaction, but it is not yet clear which one is predominant.[18] Recent studies suggest that the pathway taken is highly dependent on the organoboron reagent employed.[13]

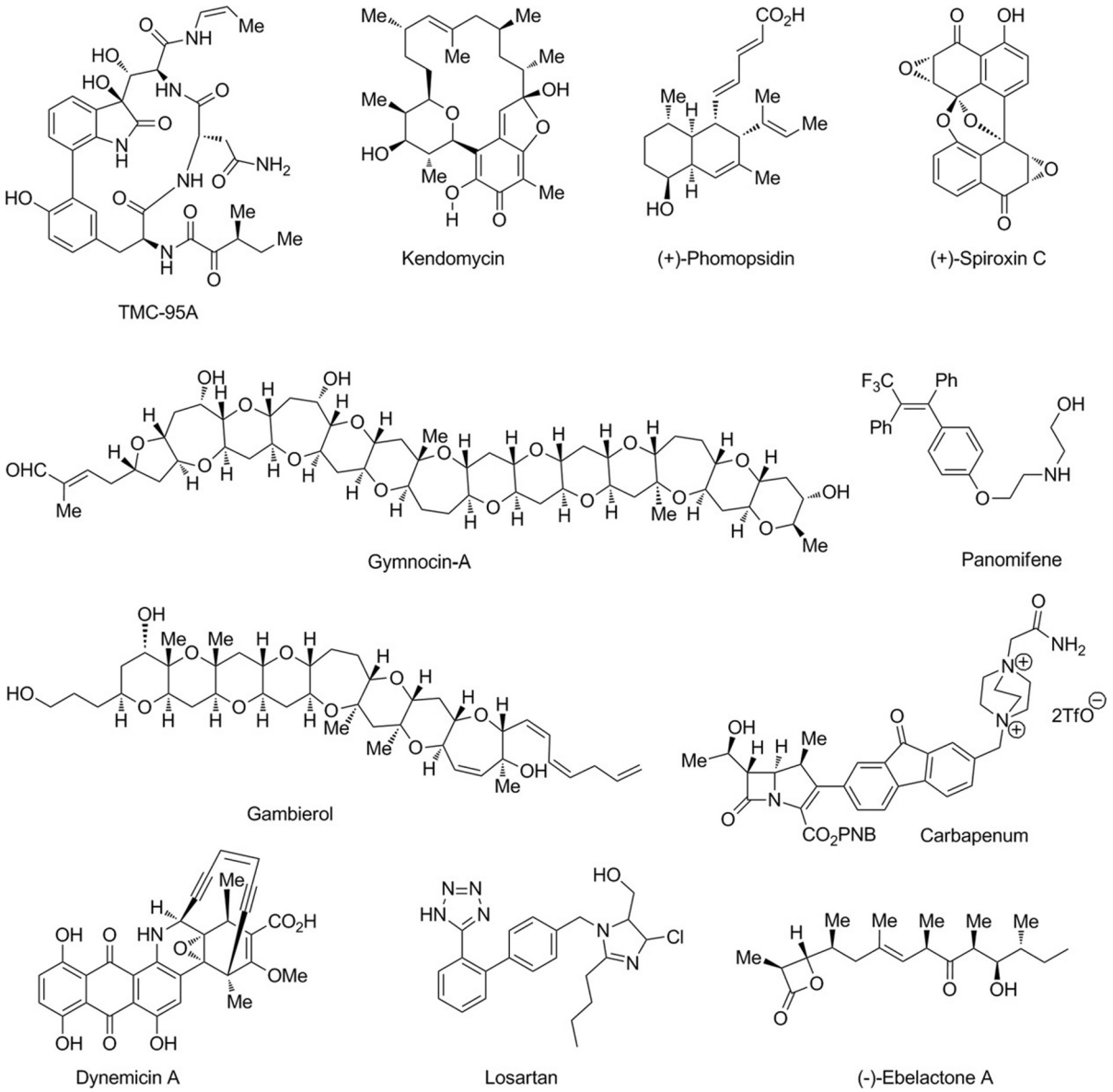
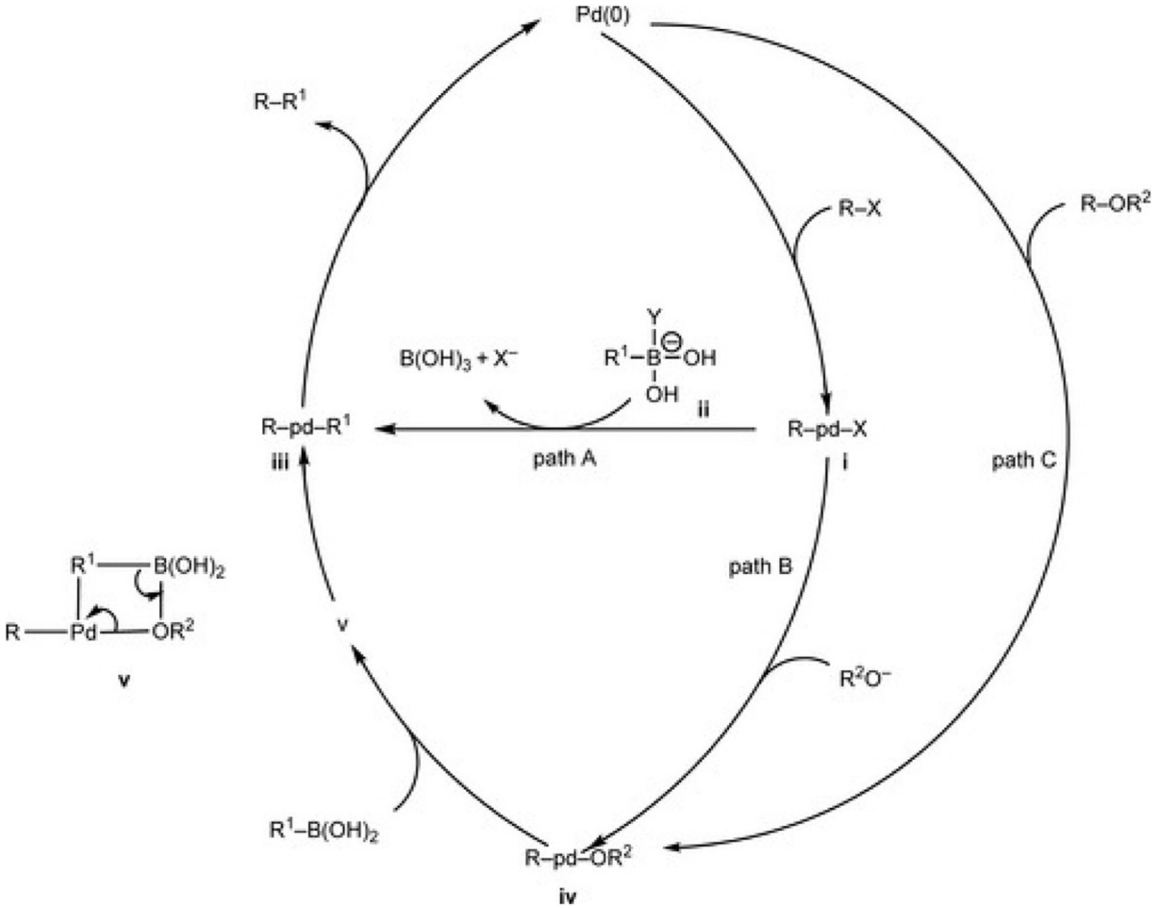


Figure 1 Some compounds with a Suzuki–Miyaura cross-coupling step in their synthesis.

New coupling partners

Historically, one of the most important limitations of the Suzuki–Miyaura reaction was the poor reactivity of organic chlorides, attributed to the strength of the C–Cl bond. Aryl chlorides are very attractive halides due to their low cost and wider diversity of available compounds.[19] Prior to 1998, reports of effective palladium-catalyzed Suzuki reactions of aryl chlorides were limited to activated substrates, and generally employing very high temperatures.[20] In that year, Fu and Buchwald independently reported on catalytic systems that overcame this limitation in good yields.[21,22] Both systems were based in the use of very electron-rich ligands (a trialkylphosphine and an arylalkylphosphine, respectively) that facilitated the cleavage of the C–Cl bond prior to the oxidative addition to the palladium center (Table 1, entries 1 and 2) and stabilize the Pd(0) species in solution to avoid its precipitation.[23] Shortly after that, several research groups described systems that coupled a variety of aryl chlorides, activated and non-activated, making use of electron-rich ligands such as trialkylphosphines,[24] arylalkylphosphines,[25,26] triarylphosphines,[27,28] phosphine oxides,[29] and *N*-heterocyclic carbenes (NHC).[30,31] Some early examples are described in Table 1. NHC ligands have been shown to be better donors than the best donor phosphines,[32] but without the disadvantages most common phosphines display: (1) phosphines often are sensitive to air oxidation and therefore require air-free handling to minimize ligand oxidation, (2) when these ligands are subjected to higher temperatures, significant P–C bond degradation occurs, and then an excess of phosphine is required, and (3) they often react with Pd precursors as $Pd(OAc)_2$ in a redox process leading to the formation of Pd(0) P_n and phosphine oxide.[33] Since their initial use as ligands in homogeneous catalysis,[34] NHCs have been successfully employed as an alternative for tertiary phosphines in a number of cross-coupling reactions.



Scheme 2 Different pathways for the Suzuki–Miyaura catalytic cycle.

Table 1 Suzuki–Miyaura coupling of aryl chlorides

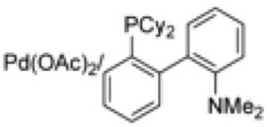
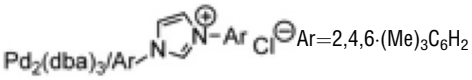
Entry	*Catalyst*	*Conditions*	*Yield (%)*	*References*
1	$Pd_2(dba)_3/PBu^1{}_3$	Cs_3CO_3, dioxane, 80–90 °C	82–90	21
2		CsF, dioxane, RT	92–24	22
3	$Pd(OAc)_2/n$-BuP(1-Ad)$_2$	K_3PO_4, toluene, 100 °C	55–100	24
4		Cs_3CO_3, dioxane, 80 °C	88–99	31

Table 2 Different electrophiles used in Suzuki–Miayura reaction

R_1–X + R_2–"B" → (catalyst, conditions) → R_1–R_2

Entry	*X*	*R_1*	*R_2*
1	F	Aryl	Aryl
2	OTf	Aryl, alkenyl, alkyl	Aryl, alkenyl, alkyl
3	N_2^+ BF_4^-	Aryl	Aryl, alkenyl
4	SO_2Cl	Aryl	Aryl
5	OTs	Aryl, vinyl, alkyl	Aryl, alkyl
6	OMs	Aryl	Aryl
7	$NMe_3^+OTf^-$	Aryl	Aryl

In addition to the already generalized couplings of aryl iodides, bromides, and chlorides, in 2003, the coupling of activated fluorides with boronic acids was reported (Table 2, entry 1).[35] The coupling with pseudohalogens has also attracted considerable attention. Aryl triflates are known as being less reactive than the corresponding iodides and bromides,[36] but have the advantage of being easily synthesized from readily available phenols.[37] Very general methods for the coupling of aryl triflates even at room temperature have been developed (Table 2, entry 2).[38] Other pseudohalides such as aryldiazonium ions (Table 2, entry 3),[39] arylsulfonyl chlorides (Table 2, entry 4),[40] aryl and alkyl tosylates (Table 2, entry 5),[41] aryl mesylates (Table 2, entry 6),[42] and aryltrimethylammonium salts (Table 2, entry 7)[43] have also been employed.

Although boronic acids have been widely accepted as the more convenient transmetallating reagents, other boranes have been used.[3] Reports have appeared regarding the use of alternative types of organoboron reagents: Batey, and more extensively Molander, have reported on the coupling of aryltrifluoroborate salts with aryl bromides,[44] iodides,[45] and triflates.[46] A variety of organoboron intermediates can be converted into the corresponding trifluoroborate salts in a very straightforward manner,[47] having the added advantage of being more air and moisture stable than boronic acids. Already some of them are commercially available. Recently, Buchwald reported on the coupling of aryltrifluoroborate salts with aryl chlorides using very mild reaction conditions.[48]

Palladacycle complexes as catalysts precursors

Of particular interest to large-scale synthetic processes is the development of catalysts that can operate at very low metal loadings. Palladacyclic complexes have played a significant role in this matter.[49] Pioneering work in 1995 was performed by Herrmann and co-workers using the palladacycle complex **1** for the coupling of activated chlorides with catalyst precursor loadings of 0.1 mol%.[50] Some examples in the literature are shown in Figure 2. Good activity is not limited to phosphorus-donor systems **2–4**,[51–53] since N-donor **5** and **6**,[53,54] oxime-containing **7a–f**, **8a** and **8b**,[55] and S-donor **9**[56] palladacycles have also been described with good results. Tertiary phosphine adducts of phosphorus-, imine-, and amine-based palladacycles **10–12**[57,58] show excellent activity at very low catalysts loadings when aryl chlorides, both activated and unactivated, are used as substrates. Silica-supported imine-based palladacycles such as **13** show lower activity in the Suzuki–Miyaura reaction than their homogeneous counterparts.[59] Nolan and co-workers reported on the activity of an NHC-bearing palladacycle **14a** for the Suzuki–Miyaura cross-coupling of sterically hindered unactivated aryl chlorides with sterically hindered boronic acids, allowing for the synthesis in high yields of di- and tri-*ortho*-substituted biaryls at room temperature and in very short reaction times.[60]

Catalytic systems composed of Pd(0) or Pd(II) derivatives and phosphines

As previously mentioned, the use of electron-rich, bulky ligands (phosphines and NHCs) in combination with palladium precursors has made an impact not only on the use of the Suzuki–Miyaura reaction but in all the cross-coupling reactions. Bulky electron-rich phosphines are now by far the most used ligands to stabilize the Pd(0) intermediates, and avoid the precipitation of the metal in homogeneous catalysis[61] Tetra-coordinated palladium–phosphine complexes such as $Pd(PPh_3)_4$ are in equilibrium with their coordinatively unsaturated species, but only the diphosphine palladium(0) or monophosphine palladium(0) species can be involved in the oxidative addition process.[21,62] Thus, bulky, electron-rich phosphines such as P(*o*-tolyl)$_3$ and P(Bu^t)$_3$ provide highly reactive catalysts because of the formation of the coordinatively unsaturated species [Pd–L]. In addition, the electron richness imparted to the palladium by the phosphine assists in the cleavage of the Ar–X bond in the oxidative addition step, while the steric bulk of the ligand promotes the reductive elimination of the desired coupling product. The stoichiometry of phosphine to palladium, the bulkiness and the donating ability of phosphine ligands modulate the reactivity of the catalyst.

A salient example of the optimum combination of steric bulk with strong donating ability was reported in 2000 by Beller and co-workers. The use of the bulky, electron-rich bis(adamantyl)-*n*-butylphosphine in combination with $Pd(OAc)_2$ allowed for the coupling of deactivated aryl chlorides with very high turnover numbers (TONs) (10 000–20 000).[24] Another example of such effects is the use of the air-stable dimer $\{PdBr[P(1\text{-adamantyl})(Bu^t)_2]\}_2$ for the coupling of aryl bromides at room temperature.[63] In 2001, Fu and co-workers disclosed an alternative method to overcome the air-sensitivity limitation of phosphine ligands. They had previously reported on the use of $P(Bu^t)_3/Pd_2(dba)_3$ for the coupling of unactivated chlorides with boronic acids.[64] After this initial report, the air-sensitive and flammable $P(Bu^t)_3$ was converted into the air-stable phosphonium salt $[PH(Bu^t)_3]BF_4$ by simple quaternazition with an appropriate acid.[65] The masked phosphine can be generated by reaction with a Brönsted base. The use the phosphonium salt in

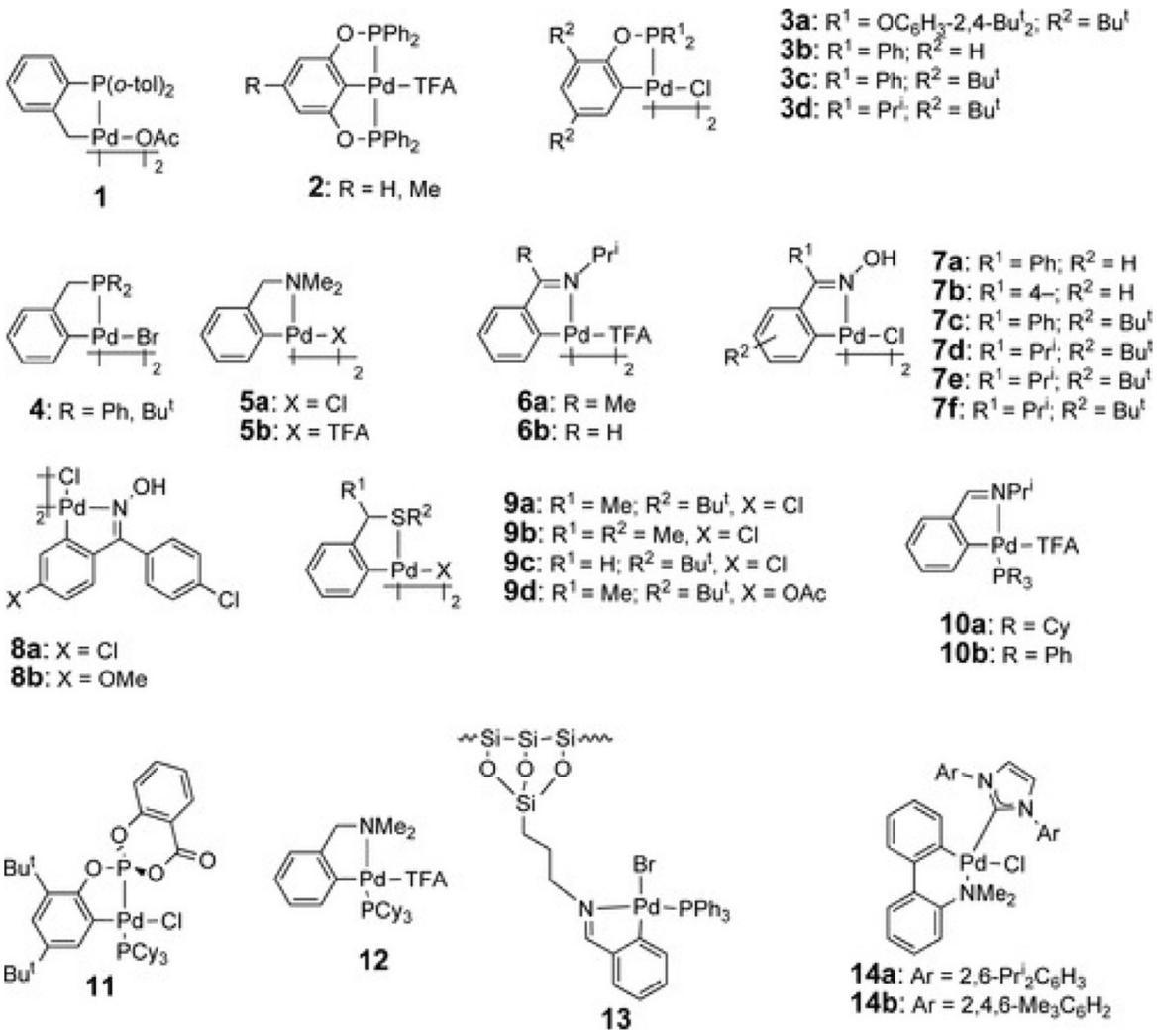


Figure 2 Palladacycle complexes as catalysts precursors in the Stille reaction.

combination with $Pd_2(dba)_3$ and KF as base to perform Suzuki–Miyaura couplings of arylboronic acids with activated chlorides and deactivated aryl bromides and iodides in mild reaction temperatures (20–50 °C) was reported to proceed very effectively. This same salt has been recently used for the palladium-catalyzed preparation of a variety of 2,4,5-trisubstituted 1*H*-imidazoles starting from unprotected 2,4-disubstituted 5-chloro-1*H*-imidazoles.[66] Another example of the use of these phosphonium salts, $[HP(Bu^t)_2Me]BF_4$, was reported for the coupling of alkyl bromides with β-hydrogens and alkyl boronic acids.[67] The combination of steric bulk and strong electron donation can also be obtained with *in situ* systems; the first method for achieving Suzuki–Miyaura cross-coupling of alkyl bromides that contain β-hydrogens made use of a combination of $Pd(OAc)_2$ and the very electron-donating, sterically demanding $P(^tBu)_3$ in a 1:2 ratio. The coupling worked under surprisingly mild conditions (room temperature).[68]

Buchwald and co-workers have described the effectiveness of tertiary phosphines as ligands in a variety of cross-coupling reactions, and provided, simultaneously as Fu,[21] the first examples of Suzuki–Miyaura cross-coupling reactions of unactivated aryl chlorides.[22] The initial system consisted of the combination of ligand **15** and $Pd(OAc)_2$. Alkyl-substituted phosphines such as **16** turned out to be more efficient, and allowed for the reaction to proceed at very low catalyst loadings (0.000 001–0.02 mol% Pd). Even hindered substrates were coupled to generate biaryls with more than one *ortho*-substituent.[69,70] Tetra-*ortho*-substituted biaryls can be synthesized in good yields using the air-stable, commercially available ligand **17**.[71] This ligand has also been employed for the coupling of aryl boronic acids with 6-halonucleosides,[72] haloquinolines,[73] and other substrates.[74]

Ligand **18** (XPhos) displays an optimal performance for the coupling of unactivated aryl tosylates with boronic acids.[75] A 'rational design' of the ligand, involving a fine-tuning of steric and electronic properties, led to phosphine **19**, which was used in combination with $Pd(OAc)_2$ in a 2.5:1 molar ratio, achieved the coupling of very sterically demanding substrates at high temperature in high yields.[76] The system also allows the coupling of *N*-heteroaryl chlorides with arylboronic acids, aryl halides with alkylboron derivates and reactions of aryl chlorides at room temperature.

Another interesting family of phosphine ligands that has been applied to this coupling reaction is the ferrocenylphosphines. Some air-stable examples are showed in Figure 3. Compound **20** has been used for the coupling of aryl chlorides in combination with a Pd(0) source,[77] while **21** gave excellent results for the coupling of a variety of aryl bromides with aryl and alkylboronic acids.[78] The

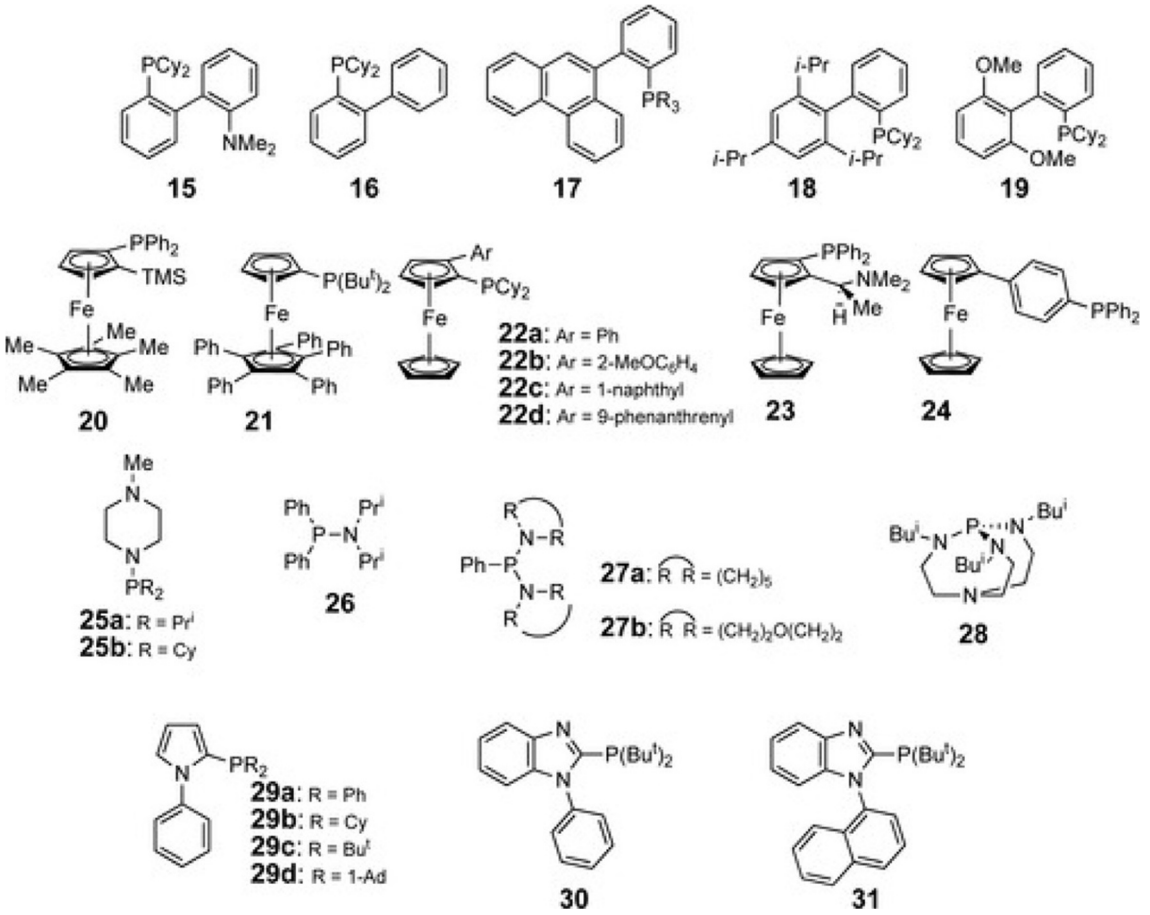


Figure 3 Some phosphines used as ligands in the Suzuki–Miyaura reaction.

series of ligands **22** was employed for the coupling of activated and unactivated aryl chlorides with arylboronic acids in high yields.[79] Chiral binaphthalenes derivatives were prepared in up to 85% ee using the chiral tertiary amine ferrocenylphosphine ligand **23** and $PdCl_2$.[80] More recently, Chan and co-workers have employed ligand **24** in combination with $Pd_2(dba)_3$ for the coupling of unactivated and activated aryl bromides or chlorides with a variety of aryl- and alkylboronic acids at 110 °C with excellent yields.[81]

Electron-rich amine-functionalized phosphines have also been investigated. Woolins et al. have prepared the series of ligands **25** for the coupling of aryl chlorides,[82] while a combination of $Pd(OAc)_2$ and the air-stable monoamine phosphine **26** has been used for the coupling of aryl bromides with arylboronic acids.[83] Better results were observed when ligands **27a** or **27b** were used in this system. The commercially available, very electron-rich ligand **28** has also been successfully employed to catalyze the coupling of a variety of aryl bromides and chlorides with arylboronic acids in excellent yields.[84] Beller and co-workers have shown that monodentate 2-phosphino-1-arylpyrrole ligands **29a–d**, prepared directly from *N*-aryl pyrroles, allowed highly efficient coupling reactions of electron-rich as well as electron-poor aryl chlorides with phenylboronic acid under mild conditions.[85] They have also reported on the synthesis of ligands **30** and **31**, which were used in combination with $Pd(OAc)_2$ for the coupling of aryl and heteroaryl chlorides with phenylboronic acid at 100 °C.[86]

Catalytic systems composed of Pd(0) or Pd(II) and N*-heterocyclic carbenes*

N-heterocyclic carbenes (NHC) have become increasingly popular in the last few years as an attractive alternative to tertiary phosphines in homogeneous catalysis, due to their strong donating ability and thermal stability.[29] Some examples are shown in Figure 4. For the Suzuki–Miyaura reaction, the first example was reported by Herrmann et al. in 1998.[87] Complex **32** was found to efficiently promote the reaction using unactivated aryl bromides or activated aryl chlorides, in the presence of K_2CO_3 in toluene at 120 °C. Soon thereafter, the coupling of unactivated arylchlorides in high yields using ligand **33** and $Pd_2(dba)_3$ was reported by Trudell and Nolan.[31] Ligand **33** was generated *in situ* from the imidazolium chloride **34** by reaction with the base (Cs_2CO_3). Trudell also reported on the use of bisimidazolium salt **35** and $Pd(OAc)_2$ for the coupling of aryl chlorides.[88] Fürstner has reported a very versatile system for the coupling of 9-substituted borabicyclo[3.3.1]nonanes and aryl chlorides using the imidazolium salt **36** in the presence of KOMe.[89] Arentsen et al. recently reported on the use of this imidazolium salt in combination with $Pd(dba)_2$ for the coupling of aryl chlorides or akyl bromides with organoboranes at 40 °C.[90]

In early studies, it was observed that when the NHC was already attached to the metal center, reaction times were shortened since the time for the deprotonation of the salt and coordination to the metal center was no longer required. The use of well-defined

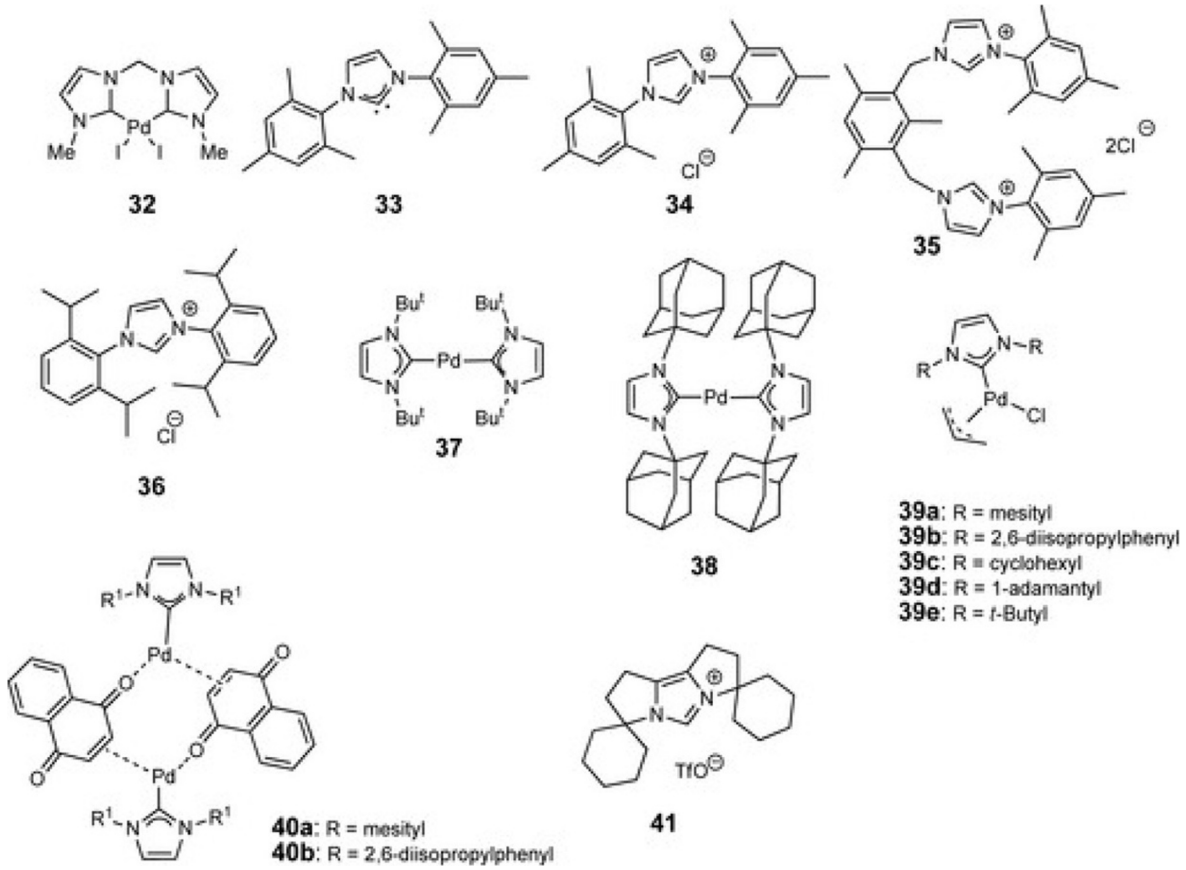


Figure 4 Some NHCs used as ligands in the Suzuki–Miyaura reaction.

systems also allows for a better understanding of the actual amount of stabilized palladium available in the system. Herrmann reported on two similar Pd(0) complexes bearing two carbenes, **37**[91] and **38**.[92] The latter was used in 2002 as the first example of coupling of aryl chlorides (activated and unactivated) with arylboronic acids at room temperature, in high yields, and reaction times between 2 and 24 h in the presence of CsF as base.

Following this concept of well-defined systems, Nolan has reported on the series of air- and moisture-stable NHC-bearing complexes **39**, easily prepared by reaction of $[Pd(allyl)Cl]_2$ with 2 equiv. of the corresponding carbene.[93] The nature of the carbene was determinant in dictating the activity of this pre-catalyst in the Suzuki–Miyaura reaction. Later, the same group reported on the use of the commercially available **39b** for the coupling of aryl halides and with boronic acids in dioxane at 60 °C in the presence of $NaOBu^t$ requiring very short reaction times.

The system was also shown to be compatible with microwave heating.[94] Based on previous findings describing the use of technical grade isopropanol as solvent for this coupling reaction,[60] an investigation on the use of this environmentally friendly solvent employing **39a**, **39b**, **40a**, **40b** and a variety of other NHC- and phosphine-bearing complexes was also reported.[95] In most cases, mild temperature (50 °C) and short reaction times were required for the coupling of 2,6-dimethylphenylchloride with 1-naphthaleneboronic acid leading to high yields of the desired product. In 2003, Glorius and co-workers reported the first system for the coupling of electron-rich aryl chloride for the synthesis of di- and tri-*ortho*-substituted biaryls at room temperature making use of bioxazoline **41** and $Pd(OAc)_2$.[96] The use of this 'flexible' ligand has presumably a beneficial role in the reductive elimination step by increasing the steric pressure on the palladium center. A more extended report in 2004 on this family of ligands included, for the first time, the synthesis of tetra-*ortho*-substituted biaryls with methyl and larger *ortho*-substituents from aryl chlorides using the Suzuki–Miyaura method.[97]

Ligandless systems

The use of expensive catalysts, sometimes difficult to prepare and recover, is a concern, especially when working in large scale. Also, as previously mentioned, the very common use of phosphine-based catalysts oftentimes brings along undesired oxidation side-reactions and formation of difficult-to-remove phosphine oxides.[33] To overcome these problems, ligandless systems are of interest for this and other cross-coupling reactions.

Commercially available $Pd(OAc)_2$ is the palladium source of choice of many of these ligandless systems. $Pd(OAc)_2$ is known to be reduced by arylboronic acids to Pd(0).[98] Monteiro and co-workers reported on a system using $Pd(OAc)_2$ in combination with

the salt additive tetrabutylammonium bromide (TBAB) to promote the coupling of aryl bromides and electron-deficient aryl chlorides with arylboronic acids at room temperature in very high yields.[99] The role of the additive is not clearly understood, but might stabilize anionic Pd species such as [Br–Pd–ligand]$^-$. A similar system was previously used by Guzzi[100] and Rehborn[101] for the coupling of aryl bromides and aryl- and 1-alkenylboronic acids in water. Marco used microwave heating for the coupling of activated aryl iodides, bromides, and chlorides under similar conditions. [102] Later, a transition metal-free system was reported for the coupling of unactivated bromides in the presence of 1 equiv. of TBAB in water, again under microwave irradiation.[103] In 2003, Bedford determined that $Pd(OAc)_2$ in a mixture of TBAB and water efficiently promote the coupling of deactivated aryl chlorides and phenylboronic acid.[104] Potassium aryl- and heteroarylflouroborates also couple with aryl- and heteroarylbromides or triflates in refluxing methanol in the presence of $Pd(OAc)_2$ and K_2CO_3.[105] Another common Pd source is $PdCl_2$; Deng et al. have recently reported on the use of $PdCl_2$ for the coupling of aryl and alkenyl bromides under very mild conditions[106] while Shen et al. have described the use of pyridine as solvent for the coupling of aryl bromides in the presence of this Pd salt.[107]

Systems in aqueous media

The use of water-soluble palladium catalysts has attracted considerable attention, since these could be easily separated from the organic-soluble products and remaining starting materials, once the reaction is complete. The structures of some water-soluble pre-catalysts and ligands are shown in **Figure 5**. By utilizing ligand TPPS **42** in combination with $Pd(OAc)_2$, Genêt et al. were able to couple a wide range of arylboronic acids with aryl bromides.[108] No loss of activity was observed after reutilizing the catalyst three times. Recently, Moore and Shaughnessy were able to perform the coupling of aryl bromides using more sterically demanding modified versions of TPPTS, **43a** and **43b**.[109] Beller and co-workers reported on a very different class of ligands **44a** and **44b** bearing a hydrophilic carbohydrate that, used in combination with $Pd(OAc)_2$ and in the presence of Na_2CO_3, performed the coupling of aryl bromides with phenylboronic acid in ethanol/water/di-*n*-butylether or ethanol/water/toluene mixtures at 78 °C.[110] A similar approach was taken for the synthesis of **45** by Miyaura.[111] Shaughnessy and Booth synthesized the water-soluble alkylphosphine **46** and found it to provide very active palladium catalysts for the reaction of aryl bromides or chlorides with boronic acids.[112] The more sterically demanding ligand **47** was shown to promote the reactions of aryl chlorides with better results than **46**. Nájera and co-workers recently reported on the synthesis of di(2-pyridyl)methylamine–palladium dichloride complexes **48a** and **48b** and their use in the coupling of a variety of electrophiles (aryl bromides or chlorides, allyl chlorides, acetates or carbonates) with alkyl- or arylboronic acids very low catalyst loadings at 100 °C.[113] Palladium–oxime catalysts **8a** and **8b** have also been developed. In conjunction with TBAB, these permit the coupling of aryl chlorides with phenylboronic acid in water.[55]

Supported and heterogeneous systems

Heterogeneous Pd catalysts can activate the C–Cl bond in aryl chlorides for the Suzuki–Miyaura reaction, presumably due to a synergistic anchimeric and electronic effect that occurs between the Pd surface and the aryl chlorides. Pd on carbon has been found to be a very effective pre-catalyst for a variety of substrates even under very mild reaction conditions and aqueous solvent mixtures.[114] In 2001, Kabalka and co-workers described that Pd powder and KF as base were useful to couple aryl iodides with arylboronic acids in methanol.[115] At the conclusion of the reaction, Pd metal could be recovered by simple decantation.

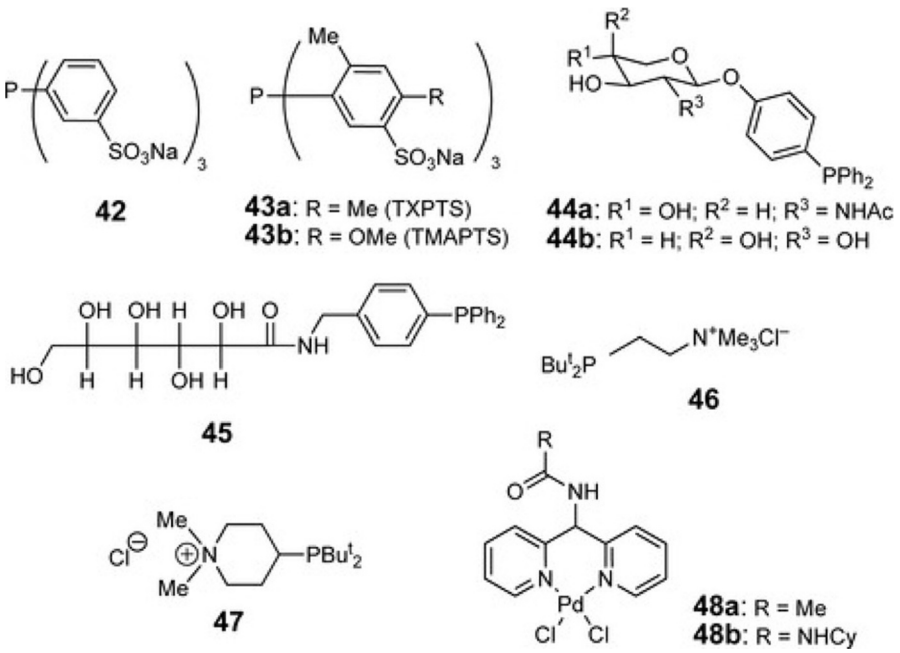


Figure 5 Some water-soluble pre-catalysts and ligands used in the Suzuki–Miyaura reaction.

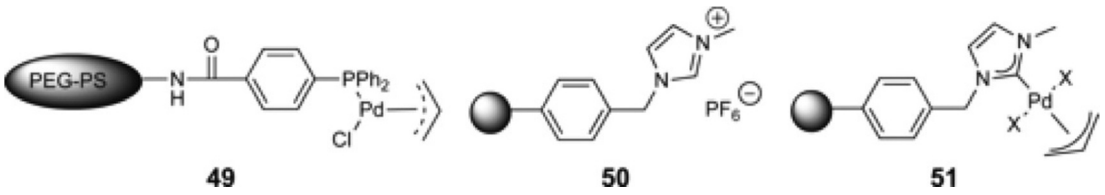


Figure 6 Some supported pre-catalysts and ligands used in the Suzuki–Miyaura reaction.

The use of microwave irradiation accelerates the reaction by decreasing reaction times from hours to minutes.[116] Catalyst loadings as low as 0.005 mol% have been reported when using an air-stable Pd on activated carbon catalyst for the coupling of aryl bromides and boronic acids, with high activity for activated chlorides (TON up to 36 000).[117] In recent years, palladium nanoparticles have also been used as catalysts for Suzuki–Miyaura reactions.[118] The high surface/volume ratio makes them ideal for heterogeneous applications.

Recently, a Pd(0)–Y zeolite system has been reported by Artok and Bulut. In general, aryl bromides coupled with arylboronic acids at room temperature in a DMF/H_2O solvent mixture.[119] The catalyst could be recovered by filtration, but in order to obtain high yields of coupling product the temperature had to be raised to 50 °C. Regeneration of the catalyst by consecutive treatments with O_2 and H_2 was required to obtain high yields after the second use.

Another class of anchored catalysts is linked to the support through the ligand (Figure 6). Poly(ethyleneglycol)–polystyrene resin-supported palladium monophosphine complex **49** was used to catalyze the coupling of allyl acetates and aryl halides with arylboron compounds in aqueous media.[120] An *N*-heterocycle carbene analog, compound **51**, prepared from the reaction of poly(imidazoliummethyl styrene)-sg-PS resin **50** with $Pd(OAc)_2$ in a DMF/H_2O mixture at 50 °C for 2 h is also an efficient system. In DMF/H_2O mixtures 1:1, compound **51** efficiently catalyzed the coupling of aryl iodides with phenylboronic acid. Catalytic activity of the recovered catalyst decreased slightly in its second and third use under the same reaction conditions.

Non-palladium-based systems

Along with palladium, several metal-based catalysts have been used for the Suzuki–Miyaura reaction. Zhou and Fu have reported on the use of $Ni(COD)_2$ and bathophenanthroline for the coupling of unactivated secondary bromides and arylboronic acids in the presence of KO^tBu.[121] Unactivated alkyl iodides couple with aryl- or alkenylboronic acids under the same conditions. The same Ni precursor was used by Yu and Hu in combination with PCy_3 for the coupling of aryl and alkenyl arenesulfonates and arylboronic acids at room temperature.[122,123] Monteiro and co-workers have made use of $NiCl_2(PCy_3)_2$ to report the first Ni-based system for the coupling of aryl tosylates and arylboronic acids.[41f] Chang has recently reported on a heterogeneous system consisting of Ru/Al_2O_3 and NaOH in a solvent mixture DME/H_2O for the coupling of aryl iodides and arylboronate esters at 60 °C.[124] Paetzold has described the catalytic cross-coupling of aromatic carboxylic anhydrides or acid chlorides with triarylboroxines under decarbonylation, giving rise to the unsymmetrical biaryls rather than the expected diaryl ketones. This new system, which requires temperatures of 160 °C, is catalyzed by a combination $[Rh(ethylene)_2Cl]_2$/KF, and can be applied to aromatic, heteroaromatic, and vinylic carboxylic anhydrides.[125] You and co-workers have recently reported on the platinum-catalyzed Suzuki–Miyaura coupling of aryl iodides and arylboronic acids using $Pt(PPh_3)_4$ and Cs_2CO_3 in DMF at 120 °C.[126]

Reactions with Organostannane Reagents: The Migita–Kosugi–Stille Reaction

The palladium-catalyzed cross-coupling of organostannanes, discovered by the Kosugi–Migita[127] and Stille[128] groups, is a very versatile and general carbon–carbon bond-forming reaction,[129] a special feature of which is its high chemoselectivity due to the relative inertness of the C–Sn bond. This is evidenced by the drastic reaction conditions, sometimes required for the cross-coupling. The growing availability of organostannanes and their stability to moisture and air have contributed to the widespread use of this coupling reaction. On the other hand, a disadvantage of this reaction is the toxicity of organotin reagents, which makes the coupling less attractive for large-scale processes. Tin reagents containing more alkyl groups and smaller alkyl chains show an increased toxicity.[130] This drawback is limited, owing to some recent results showing that tin derivatives of lower toxicity can be used.[131] The tolerance of the Stille reaction toward most functional groups makes it particularly effective for the synthesis of complex and functionalized molecules,[132,133] macrocycles,[134] and polymers.[135] Some examples of compounds that include a Stille cross-coupling step in their synthesis are shown in Figure 7. Excellent publications are also available in the literature addressing mechanistic issues of this reaction.[136]

New coupling partners

In 1999, the first general method for Stille cross-couplings of aryl chlorides was reported by Fu and co-workers.[137] The reactions were catalyzed by a combination $Pd_2(dba)_3/P(^tBu)_3$ in the presence of TBAF and CsF, at 100 °C in dioxane. Phenyliodoinium dipoles have been described as suitable electrophiles for the coupling with aryltrimethylstannanes[138] and alkylstannanes.[139] Heterobenzylic sulfonium salts have also been used.[140] Recently, Dubbaka and Vogel have reported on the coupling of sulfonyl chlorides and organostannanes in good yields.[141] A combination of $Pd_2(dba)_3$, tri-(2-furyl)phosphine, and $CuBr \cdot Me_2S$ was used

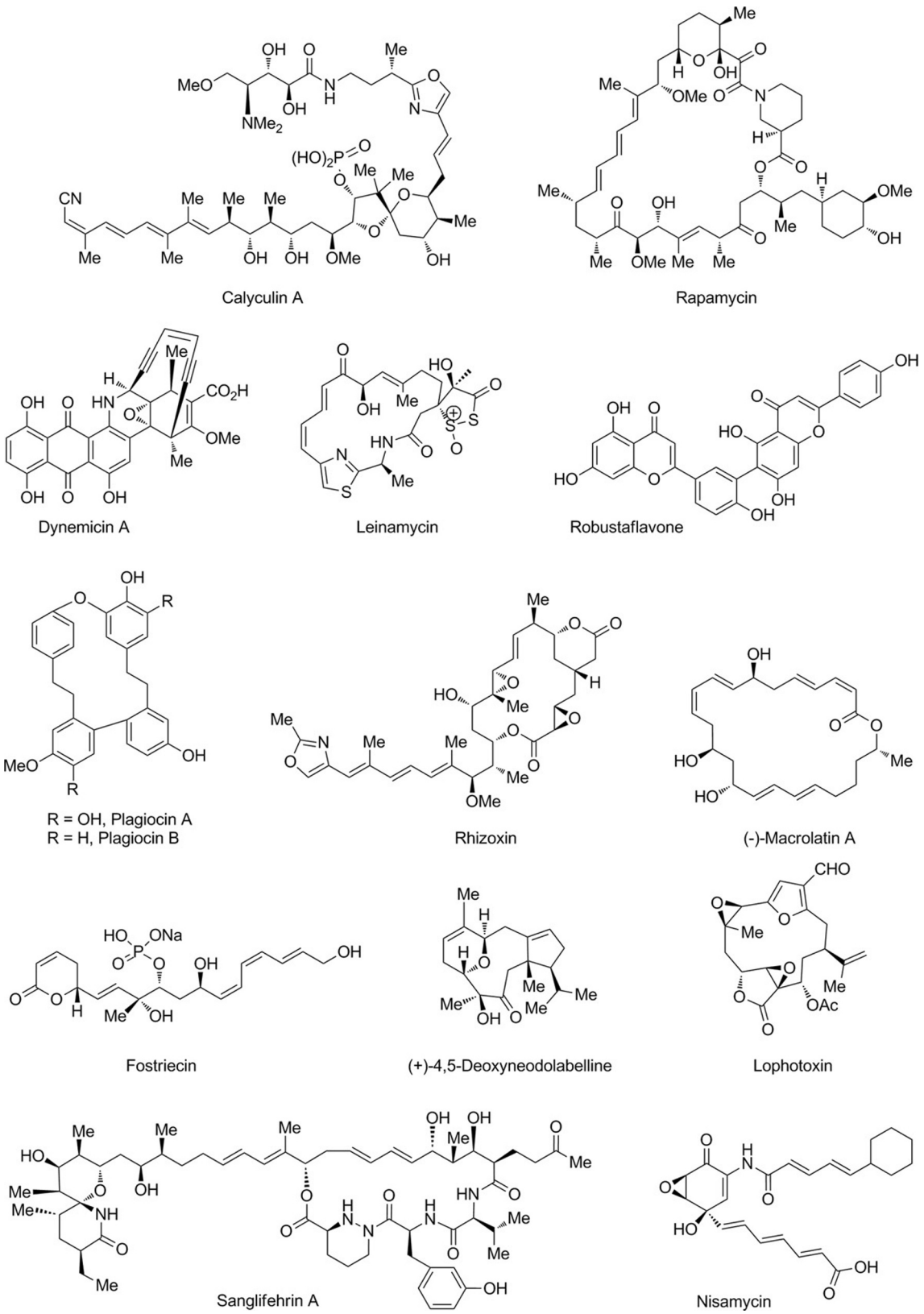


Figure 7 Some compounds that include a Stille cross-coupling step in their synthesis.

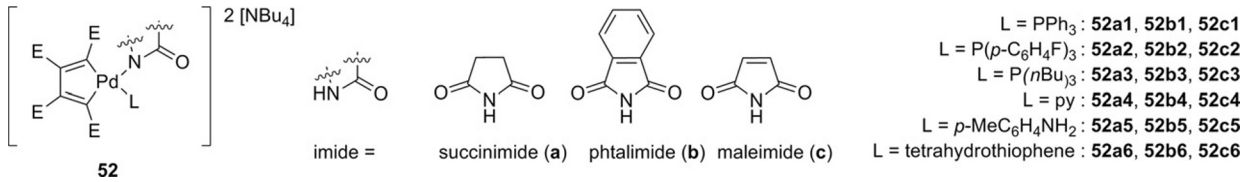
in refluxing tetrahydrofuran (THF) or toluene to carry out the reaction. In a one-step synthesis, Duchêne and co-workers have been able to prepare α-pirones from acyl chlorides with a Stille coupling,[142] while Guillaumet and co-workers recently reported on the coupling of vinyl- and arylstannanes with electron-deficient methylthioether heteroaromatics.[143] This reaction was carried out with $Pd(PPh_3)_4$ in the presence of $CuBr \cdot Me_2S$. New organostannanes have been employed by Rodríguez and co-workers in the *in situ* preparation and activation of monooganostannanes and their coupling with alkenyl or alkyl triflates in the presence of TBAF as a fluoride source to generate the 'hypervalent' organostannanes species that undergo the transmetallation.[144] By using a combination of $Pd_2(dba)_3$, PPh_3, and TBAF, Kosugi and co-workers were able to couple compounds of the general formula $ArSnBu_2Cl$ with aryl halides.[145] Osío Barcina and co-workers have recently reported on the coupling of hypervalent reagents with formula $(n\text{-}Bu_4N)^+(R^1{}_3SnF_2)^-$ (R^1 = aryl, benzyl) with vinyl and aryl triflates.[146] The hypervalent reagents are easily prepared by reaction of $R^1{}_3SnF$ and TBAF. Very recently, Kim and Yu reported on the Stille coupling of electron-deficient aryl fluorides with a variety of organostannanes in the presence of $Pd(PPh_3)_4$ in DMF at 65 °C with yields in the range 28–65%.[35]

Palladacycle complexes as catalysts precursors

In 1996, Louie and Hartwig demonstrated that palladacycle **1** (Figure 2) could also be used in the Stille coupling of aryl bromide substrates.[147] A turnover of 1650 could be achieved in the reaction of 4-bromoacetophenone and $PhSnMe_3$. Complex **1** turned out to be very active for solid-phase Stille reaction of aryl bromides with polystyrene-bond stannyl components.[148] Bedford reported in 2002 that a combination of palladacycle **3a** and PCy_3 in the presence of K_3PO_4 in dioxane allowed for the coupling of unactivated aryl chlorides and aryl and vinyl stannanes at 100 °C in very high yields. Interestingly, the same results were obtained when the Pd source employed was $Pd(OAc)_2$ in the same ratios Pd:P.[149] Recently, Taylor and co-workers have reported on the synthesis of a series of palladacyclopentadiene complexes **52** (Figure 8) with mono- and didentate imidato ligands.[150] A screening for the coupling of benzyl bromide and (*Z*)-vinnylstannyl carboxylate at 60 °C showed that the tetrahydrothiophene ligand was the best for all of the imidate complexes, indicating that ligand dissociation is probably crucial for the reaction to proceed.

Catalytic systems composed of Pd(0) or Pd(II) and phosphines

A variety of palladium(0) or palladium(II)/phosphine systems have been used as catalyst precursors (Figure 9). Triphenylphosphine was usually the ligand of choice until Farina showed in 1991 that the use tri-(2-furyl)phosphine enhanced reaction rates.[151] The positive effects of additives such as copper salts[152] and diethylamine[153] have been described. In 1997, Shirakawa and Hiyama reported on the use of the iminophosphine **53** in combination with $[Pd(allyl)Cl]_2$ in THF at room temperature for the coupling of aryl halides and alkynylstannanes.[154] Mechanistic studies showed that the reaction of an alkynylstannane proceeds through an unprecedent catalytic cycle, which involves an oxidative addition of the organostannanes to the Pd(0)–iminophosphine complex.



52

Figure 8 Palladacyclopentadiene complexes with mono- and didentate imidato ligands.

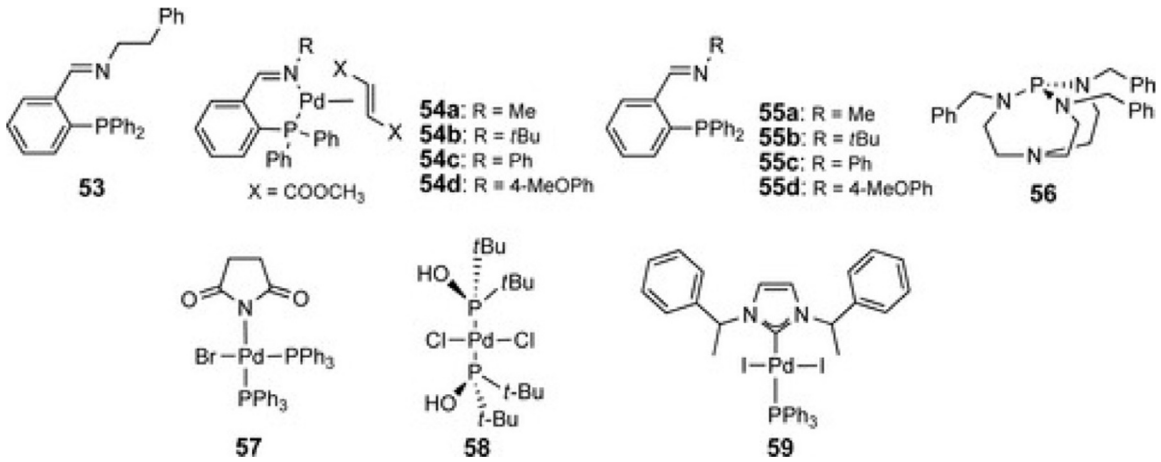


Figure 9 Palladium/phosphine systems used as catalyst precursors in Stille coupling.

Maleczka and co-workers have performed very extensive work on systems catalytic in the organnostannane reagent.[155] In 2002, Scrivanti and co-workers reported on the synthesis of iminophosphine–palladium(0) complexes **54a–d** as catalysts for the Stille reaction of iodobenzene with tributylvinylstannane or tributylphenylethynylstannane.[156] In most cases, the addition of 1 equiv. of the corresponding free ligand **55a–d** to the reaction mixture increased the reaction rate. Interestingly, very similar results were obtained when combinations of $Pd(OAc)_2$ and free ligand were used. In 2004, Verkade and co-workers reported on a system for the coupling of activated and unactivated aryl chlorides and aryl and vinylstannanes: a combination $Pd_2(dba)_3$/**28** or **56** in the presence of CsF of Me_4NF in dioxane at 100–110 °C.[157]

Cheng and co-workers reported on an efficient method for the coupling allenylstannanes with aryl or alkenyl iodides for the preparation of various monosubstituted arylallenes, disubstituted allenes, and alkenylallenes.[158] The reactions were carried out in the presence of $Pd(PPh_3)_4$ and LiCl using DMF as solvent at very mild temperatures (25–50 °C). The same year, Larebours and Wolf described the use of complex **58** for the coupling of aryl bromides and chlorides and phenyltrimethylstannane in water at 135–140 °C in the presence of Cy_2NMe.[159]

One of the major breakthroughs in the Stille reaction was reported by Fu and co-workers in 2002. They used $Pd/P(^tBu)_3$ in a 1:2 ratio as a very reactive catalyst for Stille reactions of aryl bromides and chlorides.[160] An unprecedented array of aryl chlorides could be cross-coupled with a range of organotin reagents, including $SnBu_4$. Tetra-*ortho*-substituted biaryls could be synthesized using this system, and aryl chlorides could be coupled in the presence of aryl triflates. When the commercially available $Pd(P(^tBu)_3)_2$ was used, excellent yields were obtained. $Pd/P(^tBu)_3$ also functions as an active catalyst for Stille reactions of aryl bromides with vinyl-, alkynyl-, and arylstannanes, furnishing the first general method at room temperature for these cross-couplings. Later, these researchers established that, in the presence of $PCy(pyrrolidinyl)_2$ (pyrrolidinyl = 1-pyrrolidinyl), Stille cross-couplings of alkyl bromides and iodides not only with vinyl stannanes, but also with aryl stannanes could be accomplished.[161] Changing the phosphine to $P(^tBu)_2Me$ or to the corresponding phosphonium salt, the Stille cross-soupling of alkenyltin reagents and functionalized alkyl bromides possessing β-hydrogens at room temperature was also possible.[162]

In 2003, Fairlamb and co-workers reported on the synthesis of complex **57** as a novel catalyst for Stille reactions.[163] The complex is prepared in one step from $Pd_2dba_3 \cdot CHCl_3$, PPh_3, and *N*-bromosuccinimide, and catalyzes the coupling of allylic and benzylic bromides with a variety of organostannanes in toluene at 60 °C.

Catalytic systems composed of Pd(0) or Pd(II) and N*-heterocyclic carbenes*

In 2001, Nolan described the palladium/imidazoilium salt-catalyzed coupling of aryl halides with hypervalent organostannanes.[164] The imidazolium salt **36** in combination with $Pd(OAc)_2$ and TBAF was found to be most effective for the cross-coupling of aryl bromides and electron-deficient aryl chlorides with aryl and vinyl stannanes. The same year, Herrmann and co-workers prepared a series of mixed palladium(II) complexes bearing *N*-heterocyclic carbenes and alkyl or arylphosphines.[165] Complex **59** was identified as the most active catalyst for the coupling of aryl bromides, but failed in the case of aryl chlorides.

Other systems

Triphenylarsine is commonly used as a replacement for phosphines.[118] In 1995, Roth and Farina described the coupling reaction of aryl and vinyl iodides, triflates, and bromides with organostannanes using Pd on carbon in the presence of CuI and triphenylarsine.[166] Recently, Handy and Scott reported on the Stille coupling of aryl iodides and bromides with a variety of organostannanes.[167] The reaction was carried out in 1-butyl-3-methylimidazolium tetrafluoroborate, at room temperature, in an ionic liquid, in the presence of $PdCl_2(PhCN)_2$, CuI, and $AsPh_3$ at 80 °C. The facile recycling of solvent and catalyst system allowed for its use, at least five times with little loss of activity.

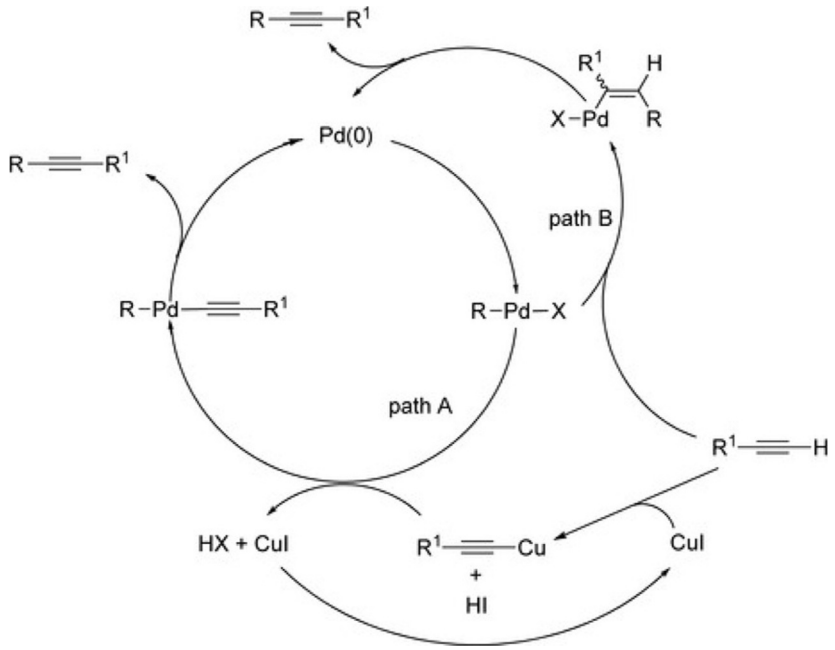
Reactions of Terminal Alkynes

In 1968, Stephen and Castro reported on the direct introduction of sp^2-carbon to alkynes by the reaction of Cu acetylides with aryl and alkenyl halides to arylalkynes and alkenylalynes.[168] Cassar[169] and Heck,[170] and later Sonogashira[171] found that the coupling of terminal alkynes with halides can proceed smoothly by using Pd catalysts. Sonogashira and Hagihara found that the addition of CuI as co-catalyst gave better results; this is the basis for what now is known as the Sonogashira reaction.[1,172] The reaction follows the general **Scheme 1**; the transmetallating species, Cu–acetylide, is formed from the *in situ* reaction of CuI and the 1-alkyne (**Scheme 3**, path A). Alternatively, a less likely Cu-free mechanism can also be involved. In this case, carbopalladation (or insertion) of a triple bond with R–Pd–X generates an alkenylpalladium intermediate that undergoes dehydropalladation (path B).

Trialkylsilanes are commonly used as protecting groups for terminal alkynes. The low polarization of the C–Si bond makes them stable to classical Sonogashira reaction conditions. An added advantage is that many alkynylsilanes are commercially available, for example, trimethylilylacetylene (TMSA), triethylsilylacetylene (TESA) and triisopropylsilylacetylene (TIPSA).[1c] Once the coupling reaction with a haloarene is complete, the trialkylsilyl group can easily be removed *in situ* with aqueous or methanolic KOH or K_2CO_3,[173] affording a new enlarged terminal alkyne that can be coupled again if necessary. Alkynylsilanes can also be used for direct cross-coupling with haloarenes (see Alkynylsilicon reagents).

The Sonogashira coupling reaction

The Sonogashira reaction has become the most widely used of the palladium-catalyzed alkynylation methods due to its generality and reliability, particularly in the context of total synthesis. Some recent examples are shown in **Figure 10**.[174]



Scheme 3 Catalytic cycle for the Sonogashira reaction.

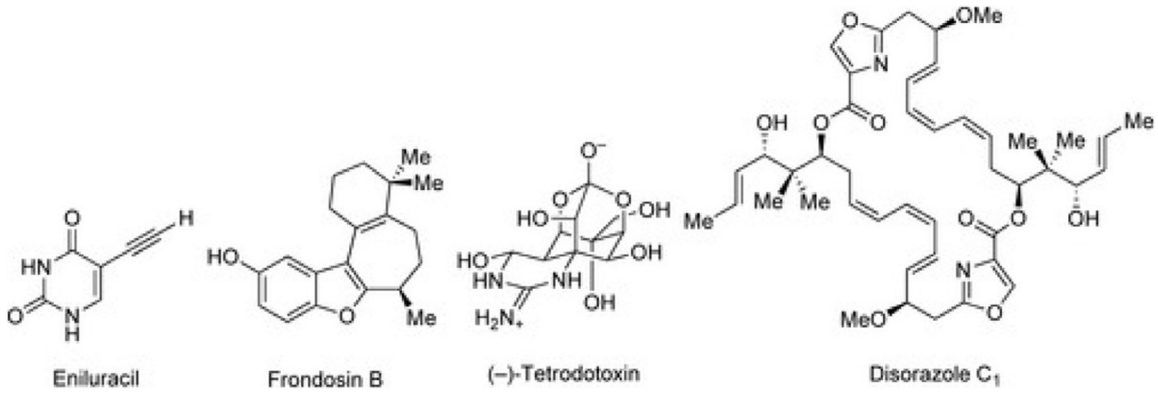


Figure 10 Some compounds that include a Sonogashira coupling step in their synthesis.

Palladacycle complexes and systems composed of Pd(0) or Pd(II) derivatives and N-heterocyclic carbenes as catalysts precursors

Herrmann reported using 0.1 mol% of palladacycle **60** (Figure 11) for the coupling of aryl bromides and terminal acetylenes at 90 °C with no added CuI.[175] The Nájera group reported on two different systems for the Sonogashira reaction. The first system consisted in the use of the oxime palladacycles **7a–f** at elevated temperatures, without the aid of CuI or an amine base, for the coupling of aryl iodides and bromides.[176] They also reported on the use of complex **48b** in aqueous media for the coupling of aryl iodides and bromides and terminal acetylenes in excellent yields.[113a]

Regarding the use of *N*-heterocyclic carbenes, complex **32** was used by Herrmann and co-workers for the coupling of activated aryl bromides with phenylacetylene in the presence of Et_3N at 90 °C.[87] Cavell and McGuiness made use of complexes **61** and **62** for the coupling of activated aryl bromides under the same conditions.[177] Complex **61** performed better than the biscarbene **62**, presumably due to a less crowded environment around the palladium center. Complex **63** was designed by Crabtree and co-workers, and tested in combination with CuI for the coupling of aryl iodides and bromides. Iodobenzene coupled in very high yield and short reaction time, while the activated bromide 4-bromoacetophenone did not lead to any coupling product.[178] An additional example of the use of NHC-bearing complexes for the Sonogashira reaction is complex **64**, which allowed for the coupling of deactivated bromides with a variety of terminal acetylenes in the presence of CuI and PPh_3 in DMF at 80 °C.[179] The reactions could be carried out at room temperature, when coupling activated and unactivated aryl iodides. Andrus and co-workers recently reported on the coupling of unactivated aryl iodides and bromides with a variety of terminal acetylenes using a combination of phenantryl ligand **65** and $Pd(PPh_3)_2Cl_2$, in the presence of K^tOBu in refluxing THF in good yields (Figure 11).[180]

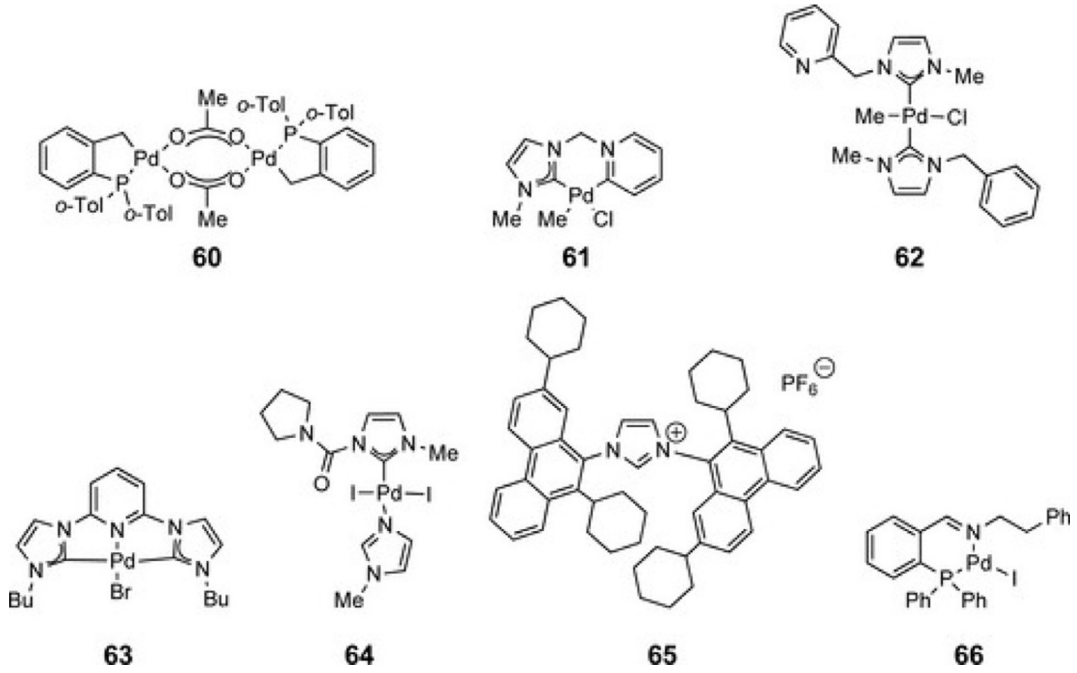


Figure 11 Palladacycle complexes and Pd/ *N*-heterocyclic carbene systems as catalysts precursors.

Catalytic systems composed of Pd(0) or Pd(II) and phosphines

The most common utilized ligands for the Sonogashira reaction are phosphines, especially PPh_3. For example, Draper and Bailey reported on the use of $Pd(PPh_3)_2Cl_2$ for the coupling of aryl iodides and phenylacetylene at room temperature in the presence of CuI and Et_3N using THF as solvent.[181] The same catalyst was used by Novák and Kotschy for the first cross-coupling reactions on chlorotetrazines to furnish a variety of alkynyl tetrazines in good to moderate yield.[182]

Due to their success in other coupling reactions, electron-rich and/or phosphines have been applied with great success. Buchwald and Fu reported on the use of $P(^tBu)_3$ in combination with $Pd(PhCN)_2Cl_2$ and CuI for the coupling of electron-rich aryl bromides and phenyl and alkylacetylenes using $^iPr_2$–NH in dioxane at room temperature,[183] and Herrmann used the same phosphine, this time simply with $Pd_2(dba)_3$, in Et_3N at room temperature, for the coupling of aryl bromides.[184] Recently, Plenio and co-workers have used the phosphonium salt $(1\text{-Ad})_2PBn \cdot HBr$ in toluene at 120 °C in the presence of Na_2CO_3 and CuI, with Na_2PdCl_4 as the palladium source.[185] Netherton and Fu also used a phosphonium salt in combination with CuI, $[PH(^tBu)_3]BF_4$, for the coupling of 4-bromoanisole and phenylacetylene in nearly quantitative yield at room temperature.[65]

Acetylene surrogates

Acetylides of other main group metals such as B (Suzuki–Miyaura coupling), Mg (Kumada–Corriu coupling), Si (Hiyama coupling), Sn (Kosugi–Migita–Stille coupling), and Zn (Negishi coupling) have been found to be suitable partners. In-,[186] Ag-,[187] Al-,[188] and Ge-[189] containing acetylides have also been investigated for potential cross-coupling capabilities. The coupling of these species with halides proceeds without Cu. As in most of the literature regarding the reactions of terminal alkynes, these couplings will be discussed in this section since the same products are obtained by this method and the Sonogashira reaction.

Alkynylsilicon reagents

As previously mentioned, organosilicon reagents have been used extensively for the protection of terminal acetylenes, due to their stability to classical Sonogashira reaction conditions. On the other hand, in the presence of fluoride ions, pentacoordinate silicate intermediates are formed, which undergo transmetallation in the presence of palladium catalysts (see section '**Reactions with Organosilicon Reagents: The Hiyama Reaction**'). More recently, it has been found that alkynylsilanes cross-couple with organohalides in the presence of catalytic amounts of CuCl and $Pd(PPh_3)_4$ in DMF through an organocopper intermediate as in the Sonogashira reaction. This modification is known as the 'sila-Sonogashira–Hagihara' coupling, and it has been used for the coupling of aryl[190] and alkynyl[191] triflates at 80 °C in modest yields. Activated chlorides can be coupled, also in modest yields, by increasing the temperature to 120 °C and using $Pd(dppb)Cl_2$ as palladium source. Under similar conditions but in the absence of palladium catalyst, the couplings of arylchloroethynes,[192] acyl chlorides,[193] and alkenyl halides[194] with alkynylsilanes have also been reported.

Nolan and co-workers reported on the coupling of arylbromides with TMS acetylenes making use of the imidazolium salt **34** in combination with $Pd(OAc)_2$ and CuI.[195] Slightly lower yields were obtained in the absence of the copper salt. Ag_2O and AgI,

instead of copper salts, have also been used with $Pd(PPh_3)_4$ for the coupling of aryl iodides with bis(TMS)alkynes[196] and the coupling of vinyltriflates with a variety of alkynylsilanes,[197] respectively.

Alkynyltin reagents

Preparation of alkynyltin reagents is typically achieved by lithiation of the corresponding terminal acetylene or by formation of the alkynylmagnesium reagent, followed by transmetallation with trialkyltin chloride.[198] The process can be performed to generate the tin species *in situ*, prior to the coupling with the organic electrophile. Alternatively, these can be prepared by reaction of the acetylene with $RSnNR^1{}_2$.[199]

Some of the most common catalysts for this coupling are $Pd(PPh_3)_4$ and $Pd(PPh_3)_2Cl_2$. The first one has been used for the coupling of alkenyl,[200,201] aryl,[202] and heteroaryl[203] iodides and alkenyl[204] and aryl triflates[205,206] with alkenyltin reagents under mild reaction conditions (50–80 °C) leading to high yields, while $Pd(PPh_3)_2Cl_2$ has been used for the coupling of alkenyl[207,208] and aryl[209] iodides at room temperature. Other palladium reagents have been used in this reaction: $Pd(MeCN)_2Cl_2$,[210,211] $Pd(PhCN)_2Cl_2$,[212] $Pd_2(dba)_3$,[213] $PdBn(PPh_3)_2Cl$,[214] and iminophosphino catalyst **66**.[215]

Alkynylmagnesium reagents

In addition to their use as precursors for alkynylboron, tin or zinc compounds, alkynylmagnesium reagents show a moderate reactivity toward the coupling with haloarenes and haloalkenes.[216] They are often commercially available, or easy to prepare. Their main drawback is their low chemoselectivity and high nucleophilicity, which implies incompatibilities with functional groups such as nitro and carbonyl.

Aryl and heteroaryl iodides coupling with alkynylmagnesium reagents can be performed in the presence of $Pd(PPh_3)_4$, in THF, at room temperature,[217] while the coupling of aryl triflates has been reported to proceed smoothly using $Pd(alaphos)Cl_2$ as catalyst, in combination with LiBr in Et_2O in toluene achieving high yields at mild temperature (30 °C) (where alaphos = (2-dimethylamino)propyldiphenylphosphine).[218] With the same system, the coupling of aryl iodides can be performed with no LiBr added. Very recently, Luh and co-workers reported on a system that uses a combination of $Pd_2(dba)_3$ and PPh_3 for the coupling reactions of unactivated alkylbromides and iodides with an alkynylmagnesium reagent in THF at 65 °C.[219]

An example of a non-palladium-based system was reported by Madec et al. They made use of $Ni(PPh_3)_2Cl_2$ for the coupling of vinylcarbamates and alkynylmagnesium reagents in benzene at higher temperatures (70 °C), and obtained good yields of product.[220]

Alkynylboron reagents

In 1995 Soderquist[221] and Fürstner[222] independently reported that alkynylborates **67**, prepared *in situ* from 9-OMe-9-BBN and alkynylmetals, effectively cross-couple with aryl and alkyl bromides using a Pd catalyst under base-free conditions at 60 °C. Soderquist and co-workers also reported on the synthesis of alkynylborinates **68**, which are easier to isolate (**Figure 12**).[223]

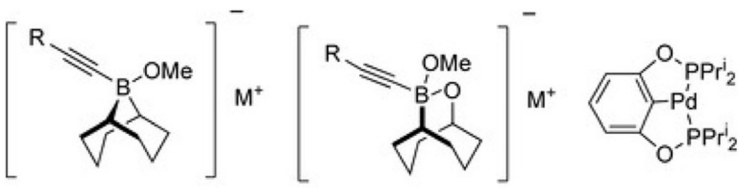
Lithium alkynyl(trialkoxy)borates have also been found suitable partners for this reaction, and have been successfully coupled with aryl bromides,[224,225] iodides,[226] and allyl carbonates.[227] Molander recently reported on the coupling of alkynyltrifluoroborates with aryl bromides, triflates, and chlorides in moderate yields using $Pd(dppf)Cl_2$ as catalyst and Cs_2CO_3 as base, in THF or water at 60 °C.[228]

Alkynylzinc reagents

In the late 1970s, Negishi and co-workers found that alkynylzincs gave superior yields and increased reaction rates over other alkynylmetals in cross-coupling reactions with organic electrophiles,[229] making this cross-coupling commonly referred to as the Negishi coupling (see Pd- or Ni-catalyzed Reactions with Organozinc Reagents: The Negishi Coupling). This protocol should be considered especially in cases involving electron-withdrawing groups conjugated to the alkyne, where it has been proved superior to the Sonogashira protocol.[230] The alkynylzinc reagent can also be prepared *in situ* form terminal alkynes by addition of $ZnCl_2$ as a co-catalyst.[231]

Alkenyl iodides can be coupled with organozinc reagents in moderate to good yields at room temperature using $Pd(MeCN)_2Cl_2$,[232] $Pd(PPh_3)_4$,[233] or a combination of $Pd(dba)_2$ and P(2-furyl)$_3$.[234] Alkenyl bromides can be coupled in very good yields using $Pd(DPEphos)Cl_2$ in THF at 0 °C,[235] and alkenyl triflates using $Pd(PPh_3)_4$ at room temperature.[236] This last example also included the coupling of heteroaryl and alkynyl iodides with alkynylzinc reagents.

Aryl iodides also couple with organozinc reagents at room temperature in the presence of $Pd(PPh_3)_4$ in THF.[212] An increase in temperature is required when multiple electron-donating groups are present.[237] Acyl chlorides also couple at room temperature



67 **68** **69**

Figure 12 Alkynylboron reagents **67** and **68** and pincer palladacycle **69**.

using the same catalyst/solvent system.[238] As an example of an *in situ* system, Eberhard and co-workers were able to couple a variety of aryl chlorides with phenylacetylene using pincer palladacycle **69** (Figure 12) in the presence of ZnCl and Cs_2CO_3 at 160 °C, in 19–91% yield.[239] Very recently, Saá and co-workers reported on the synthesis of ynamines in high yields by Negishi coupling of terminal alkynyl amides with heteroaryl iodides in the presence of $Pd_2(dba)_3$ and PPh_3.[240]

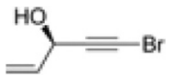
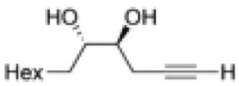
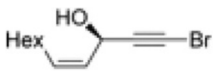
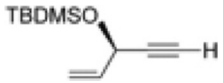
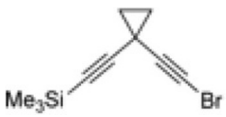
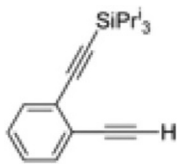
The Cadiot–Chodkiewicz reaction

Haloalkynes can cross-couple with alkynylcopper species to give unsymmetrical 1,3-butadiynes, with or without the need of Pd complexes. This cross-coupling takes place in a pyridine solution at room temperature, being analogous to the Stephen–Castro coupling.[241] The reaction between a terminal alkyne and a haloalkyne using a catalytic amount of Cu(I) salt in an amine base is known as the Cadiot–Chodkiewicz reaction.[242] Slow addition of the halide is often required to minimize homocoupling as a side-reaction, and usually $NH_2OH \cdot HCl$ is added as a reducing agent. A list of recent examples in the literature is shown in Table 3.[243–248] The amount of homocoupling byproducts can be reduced by introducing a palladium co-catalysts such as $Pd(OAc)_2$,[249] $Pd(PPh_3)_2Cl_2$,[250] or $Pd(PPh_3)_4$,[251] and carrying out the reactions under anaerobic conditions.

Reactions with Organomagnesium Reagents: The Kumada–Tamao–Corriu Reaction

The first organomagnesium reagents were prepared over 100 years ago by Grignard, and still occupy an important place in organic chemistry.[252] Kumada[253] and Corriu[254] independently reported on their application in nickel-catalyzed cross-coupling reactions with aryl and alkenyl halides. Thus, this coupling reaction is nowadays recognized as the Kumada–Tamao–Corriu reaction.[1,255]

Table 3 Recent examples of Cadiot–Chodkiewicz reactions in the literature

Haloalkyne	*Terminal alkyne*	*Conditions*	*References*
		$CuCl, EtNH_2, NH_2OH{\cdot}HCl, BuNH_2, H_2O$	
		$CuCl, EtNH_2, NH_2OH{\cdot}HCl, BuNH_2, H_2O$	243
		$CuCl, EtNH_2, NH_2OH{\cdot}HCl, BuNH_2, H_2O$	
		$CuCl, EtNH_2, NH_2OH \cdot HCl, MeOH$	244
		$CuCl, EtNH_2, NH_2OH \cdot HCl, H_2O, MeOH$	244
		(i) MeLi, THF, CuCl, –78 °C (ii) pyridine	246
		(i) BuLi, THF, –78 °C (ii) CuBr, pyridine	247
		(i) BuLi, THF, –78 °C (ii) CuBr, $PrNH_2$	248

As previously mentioned, organoboron, tin, and zinc reagents are usually prepared from organolithium or organomagnesium reagents. Therefore, the direct couplings of these reagents are more atom economical and convenient. However, the limited access to functionalized organomagnesium reagents considerably lowered the interest and development of this reaction, since no method was available for preparing polyfunctional organomagnesium reagents. The halogen–magnesium exchange reaction,[256] developed in the 1930s, has recently resurfaced as a general method for preparing a wide range of functionalized organomagnesium compounds.[257] Also, work in the late 1990s proved the compatibility of the C–Mg bond with a number of sensitive electrophilic functional groups.[258] Because of these two factors, an impressive amount of very significant contributions have appeared in the last 5 years with very exciting improvements in the Kumada–Tamao–Corriu cross-coupling reaction.

Nickel-based systems

In 2000, Hermann and co-workers reported on the nickel-catalyzed cross-coupling of unactivated aryl chlorides with aryl Grignard reagents at room temperature in excellent yields.[259] The system consisted in the use of $Ni(acac)_2$ in combination with either $P(^tBu)_3$, **34**, or **36** in a 1:1 ratio of Ni to ligand in THF. Li and Marshall showed that air-stable phosphine sulfonides or oxides in combination with $Ni(COD)_2$ were suitable ligands to catalyze the cross-coupling of unactivated aryl chlorides with aryl Grignards.[260]

By using a variety of chiral ligands **70**–**72** (Figure 13), Hayashi and co-workers reported on the asymmetric cross-coupling of dinaphtothiophene with a variety of Grignard reagents to give axially chiral 1,1′-binaphthyls.[261] These reactions were carried out at room temperature using $Ni(COD)_2$ as the nickel source, with 54–97% yield and 14–95% ee. They later reported on the asymmetric synthesis of axially chiral biaryls with the same system, but this time using dibenzothiophenes as the starting materials.[262]

Grignard reagent **73** (Figure 13) in ca. 90% ee was coupled with vinyl bromide using either Ni(0) or Pd(0) catalysts in THF at −78 °C to give the corresponding product with full retention of configuration (ee = 88–89%).[263] The use of Fe- or $Co(acac)_3$ leads to considerable racemization. Also, Ni complexes allowed for higher yields than when their Pd congeners were used.

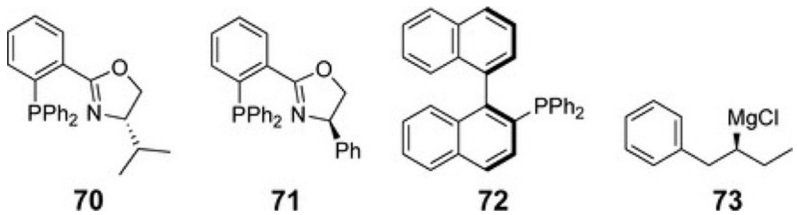
Alkyl bromides and tosylates can be efficiently coupled with a variety of R–MgBr (R = primary or secondary alkyl, aryl) in the presence of $NiCl_2$ and 1,3-butadiene as additive instead of a phosphine ligand.[264] Alkyl fluorides can couple with the same types of Grignard reagents in similar conditions, even when using $CuCl_2$ as catalyst.[265] It was shown later that the selection of the additive is critical, since the use of *N*,*N*-bis(penta-2,4-dienyl)benzylamine as additive allowed for a drastic reduction in catalyst loading for the coupling of *n*-nonylfluoride and *n*-PrMgBr.[266]

Dankwardt and Miller reported on the coupling of modified alkyl and alkenyl Grignard reagents with aryl and heteroaryl nitriles for the preparation of styrene and alkyl arene derivatives. The reactions were carried out using $NiCl_2(PMe_3)_2$ in refluxing THF.[267] Alkyl tosylates have also been reported to couple with aryl Grignards in the presence of $Ni(dppf)Cl_2$ in refluxing THF leading to moderate to good yields (43–85%).[268] Dankwardt also described the use of $NiCl_2(PCy)_2$ for the coupling of aromatic alkyl ethers with aryl organomagnesium reagents.[269] The reaction supported functionalities such as alcohols, amines, enamines, and *N*-heterocycles in the aromatic ether substrate. It was also found that alkyl and alkenyl Grignard reagents were not suitable partners for this system.

Iron-based systems

The use of iron salts as catalysts for cross-coupling reactions was already reported by Kochi and co-workers in 1971,[270] although little attention was given to this possibility in the following decades. A renewed interest has risen in the last 5 years in the use of cheap, stable, commercially available, and toxicologically benign iron salts in the Kumada–Tamao–Corriu reaction. In 1998, Cahiez showed that organomagnesium reagents readily reacted with alkenyl iodides, bromides, or chlorides in the presence of $Fe(acac)_3$ and NMP at −5 to 0 °C, with high stereo- and chemoselectivity and group tolerance.[271] The method is of special interest when functionalized arylmagnesium reagents are used, since Ni(0)- or Pd(0)-catalyzed reactions require temperatures above 20 °C, resulting in the destruction of sensitive functions either in the substrates or the product.[272]

Recently, Alami, and Figadère reported on the iron(III)-catalyzed cross-coupling of chloroenynes with alkyl Grignards to synthesize a variety of substituted quinolines, using very mild conditions, using $Fe(acac)_3$.[273] The same system was later used for the cross-coupling reaction of 1,1-dichloro-1-alkenes with Grignard reagents,[274] leading mainly to the dicoupled products in good to excellent yields. $Fe(acac)_3$ was also used by Nagano and Hayashi for the coupling of aryl organomagnesium reagents with primary and secondary alkyl bromides possessing β-hydrogens in refluxing diethyl ether.[275] Nakamura and co-workers reported on the $FeCl_3$-catalyzed coupling of primary and secondary alkyl halides with the same Grignard reagents in THF, using *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (tmeda) as additive, leading to excellent yields.[276]



70 71 72 73

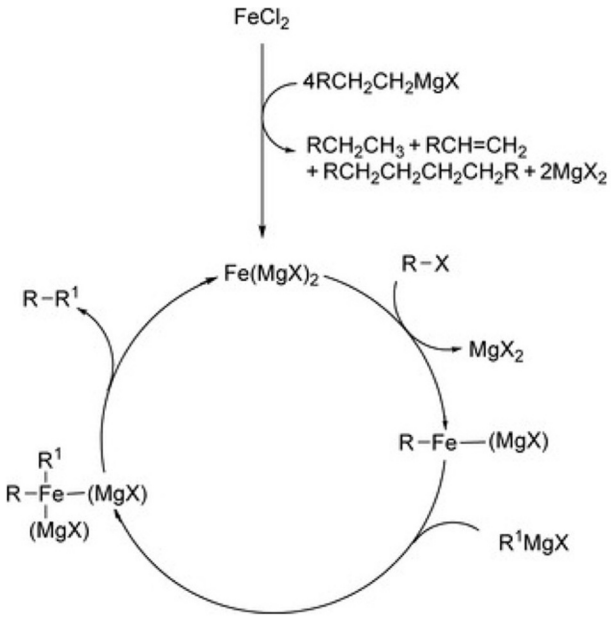
Figure 13 Chiral ligands (**70**-**72**) and reagent (**73**) used in Kumada reactions.

Fürstner has most recently contributed to the development of iron-catalyzed Kumada–Tamao–Corriu reactions. A series of key articles have appeared addressing different aspects of the reaction: mechanism, scope, and applications. In 2002, taking recent advances in the field of 'inorganic Grignard reagents' into consideration,[277] Fürstner suggested the catalytic cycle depicted in Scheme 4 (spatial distribution of the ligands is arbitrary for sake of clarity).[278] The mechanism depicts the reaction of $FeCl_2$ with 4 equiv. of RMgX to produce a new species of formal composition [$Fe(MgX_2)$], which implies that the reduction process generates Fe(II) centers, very nucleophilic, that insert into the aryl halide to initiate the cycle. The reactions carried out for the coupling of aryl chlorides, tosylates, and triflates showed to be virtually independent of the chosen iron salt, and the authors decided to use $Fe(acac)_3$ for sake of convenience. On the other hand, the system was found to be highly dependant on the nature of the nucleophile; secondary alkyl Grignards reacted better with Fe(salen)Cl complex **74** (Figure 14). In all cases, the couplings were performed in THF/*N*-methylpyrrolidone (NMP) mixtures, and the products were obtained in very good yields. A more extended report was published shortly after remarking on the compatibility of a large variety of functional groups.[279] Enol triflates, acid chlorides, and dichloroarenes are also suitable partners for the reaction.[280] This catalytic system was used in the total synthesis of the natural product latrunculin B[281] and the inmunosuppresive agent FTY720 (Figure 15).[282]

Following these results with the salen complex, Bedford reported on the synthesis of a series of Fe(III)-salen-type complexes and the use of one of them, **75** (Figure 14), for the coupling of aryl Grignard reagents with primary and secondary alkyl halides, in Et_2O at 45 °C.[283] Fürstner subsequently reported on the use of the tetrakis(ethylene)ferrate complex $[Li(tmeda)]_2[Fe(C_2H_4)_4]$ to effectively catalyze the cross-coupling of alkyl halides with a variety of aryl Grignard reagents in THF at −20 °C in excellent yields.[284]

Palladium-based systems

In 1999, Huang and Nolan reported the first example of cross-coupling of unactivated aryl chlorides, bromides, and iodides with aryl Grignard reagents in excellent yields. The reactions were mediated by a combination of $Pd_2(dba)_3$ and imidazolium salt **36** in a 1 : 4 ratio, in a THF/dioxane mixture at 80 °C.[285] Li reported on the use of a combination of $Pd_2(dba)_3$ and phosphine oxide $P(^tBu)_2O$, generated *in situ* from the reaction of $P(Bu^t)_2Cl$ and H_2O, for the coupling of unactivated aryl chlorides with



Scheme 4 Catalytic cycle for the iron-catalyzed Kumada reaction suggested by Fürstner.

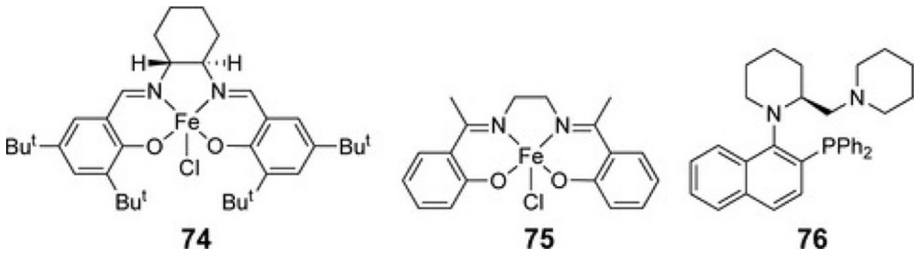


Figure 14 Fe(salen)-type complexes (**74**,**75**) and chiral ligand **76**.

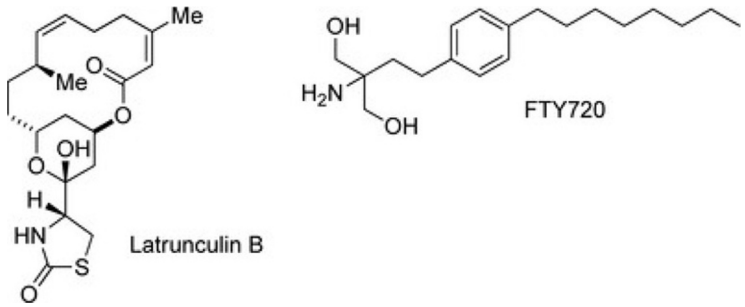
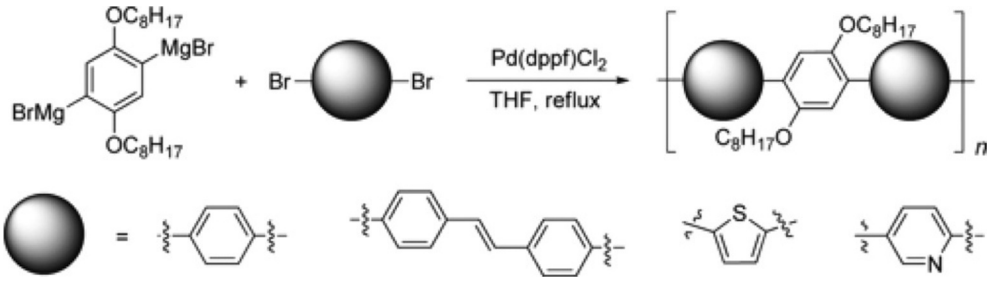


Figure 15 Latrunculin B and the inmunosuppresive agent FTY720.



Scheme 5 $Pd(dppf)Cl_2$ catalyzed synthesis of polyconjugated polymers.

o-tolylmagnesium bromide at room temperature.[29] For the first time, lithium triarylmagnesates were coupled with heteroaryl bromides by Dumouchel et al. in the synthesis of 2-, 3-, and 4-quinolines, using $Pd(dba)_2$ and dppf in THF at room temperature.[286]

Beller and co-workers developed a novel method for the palladium-catalyzed cross-coupling of alkyl chlorides and aryl Grignard reagents with good functional group tolerance.[287] The system consisted of a combination of $Pd(OAc)_2$ and PCy_3 in a THF/NMP mixture; the reactions were carried out at room temperature in very good yields. They also reported the first Kumada reaction of alkyl chlorides catalyzed by a well-defined NHC-bearing complex, **40a**.[288] The reactions were carried out using the same conditions as the previous example.

Sato and co-workers described the site-selective coupling of 1,4-diiodo-1,3-alkadienes with Grignard reagents for the synthesis of fulvenes, catalyzed by $Pd(PPh_3)_4$.[289] The couplings proceeded selectively at the least hindered vinylic carbon. Asymmetric couplings in good yields and ee were reported by Horibe et al. for the reactions of 1-phenylethylmagnesium chloride and (*E*)-β-bromostyrene derivatives using the axially chiral ligand **76** and $Pd_2(dba)_3 \cdot CHCl_3$.[290] Chemoselective reaction of the vinyl bromide instead of the aryl bromide, when both are present in the substrate, was also described. Naso and co-workers recently made use of the Kumada–Tamao–Corriu reaction as a general route to polymers.[291] By using a variety of dibrominated halides and bis-organomagnesium reagents in the presence of $Pd(dppf)Cl_2$ in refluxing THF, they were able to synthesize a series of polyconjugated polymers (Scheme 5).

Other systems

In 2001, Knochel and co-workers described the $CuCN \cdot 2LiCl$-mediated cross-coupling of functionalized arylmagnesium reagents with functionalized alkyl and benzylic halides.[292] Stoichiometric amounts of the copper reagent, in combination with 1.9 equiv. of $P(OMe)_3$, were required, although the reactions could be carried out with catalytic (20 mol%) amounts of copper, but in lower yields. Later, they reported on the $CoCl_2$-catalyzed cross-coupling involving a variety of arylmagnesium halides and heterocyclic chlorides, in diethyl ether and at −40 °C, achieving the desired coupling products in good yields.[293] The use of $CoBr_2$ or CoI_2 reduced the reaction times, but led to lower yields. Oshima and co-workers reported that $Co(dppp)Cl_2$ effectively catalyzes the cross-coupling reaction of primary, secondary, and teriary alkyl halides with allylic Grignard reagents in THF at room temperature.[294] A more detailed study was reported shortly after which included benzylic Grignard reagents.[295]

Reactions with Organosilicon Reagents: The Hiyama Reaction

In contrast to other organometallic compounds, organisilicon reagents are inert to normal palladium-catalyzed conditions, because of the low polarization of the carbon–silicon bond. Tetracoordinate organosilanes are not capable of transferring even one of their groups to palladium, as is possible with tetracoordinate organostannanes, although Si and Sn do not differ much in their location in the periodic table and possess similar electronegativities (1.96 for Sn, 1.90 for Si).[296] The low nucleophilic character of organosilicon compounds is important when considering tolerance toward a wide variety of functional groups.

One of the first indications that higher valent silanes could be useful donors in palladium-catalyzed cross-coupling reactions was reported by Kumada and Tamao, when they observed that the dipotassium salt of pentafluorosilicate **70** could transfer its vinylphenyl group for the palladium-catalyzed coupling with iodobenzene at high temperature (Scheme 6).[297]

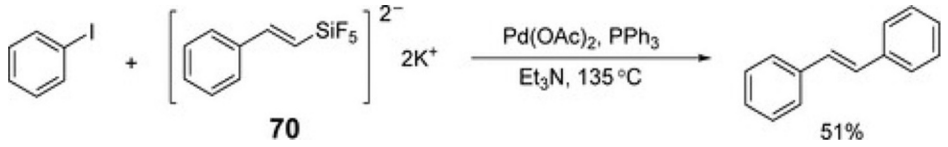
The coupling of organosilicon compounds with organic electrophiles was not disclosed until 1988 by Hatanaka and Hiyama,[298] when they demonstrated that through the addition of an appropriate silicophilic nucleophile, those desired pentacoordinate species can be generated *in situ* and transfer an unsaturated group. Nucleophilic fluoride sources were found to be the additive of choice, typically TASF, TBAF, and, in some cases, KF and CsF. These are the fundamental concepts of what is nowadays called the Hiyama reaction.[1,299] The use of fluoride activation has some drawbacks such as the cost and corrosiveness of the fluoride ion sources and their incompatibility with common protective groups. Several fluoride-free systems have been reported that employ either other activators or other organosilicon reagents. Very recently, Denmark and co-workers have done very extensive work in this area describing mechanistic details of the fluoride-promoted and the fluoride-free cross-coupling reactions of organosilicon reagents with aryl and alkenyl iodides.[300,301]

Coupling of arylsilanes

In 1996, Hiyama and co-workers reported on the cross-coupling of activated aryl chlorides with aryl- and alkenylchlorosilanes **71** (Figure 16).[302] The high temperatures required to activate the aryl chlorides did not affect the organosilanes; an added advantage that can be attributed to their relative inertness. The system could be catalyzed by a variety of phosphine-bearing palladium complexes in the presence of either KF or TBAF as promoters.

Mowery and DeShong reported on the use of siloxanes **72** (Figure 16) as versatile transmetallation agents for $Pd(dba)_3$-catalyzed couplings with aryl halides and allylic alcohol derivates, in the presence of TBAF and at high temperature (95 °C).[303] They later used aryl silatrane **73** (Figure 16) as a suitable partner for the fluoride-promoted cross-coupling with aryl triflates,[304] since attempts to couple siloxanes with triflates had led to hydrolysis of the aryl triflate. The system was palladium based, in the presence of a phosphine ligand and TBAF. Interestingly, the coupling with iodides and bromides led to lower yields than the analogous siloxane.

In 2000, Lee and Nolan described the use of the imidazolium salt **36** in combination with $Pd(dba)_2$ and TBAF for the coupling of aryl chlorides and bromides with phenyl or vinyltrimethoxysilane, using a solvent mixture 1,4-dioxane/THF at 80 °C, leading to good yields.[305] Lee and Fu recently reported the first method for achieving Hiyama couplings of unactivated alkyl bromides and iodides at room temperature.[306] The system worked with a combination of $PdBr_2$, $P(^tBu_2)Me$, and TBAF in THF. Fu and co-workers also reported the first metal-catalyzed cross-coupling of organosilicon reagents with secondary alkyl bromides and iodides.[307] In this case, the catalyst of choice was $NiBr_2 \cdot$diglyme, using bathophenantroline as ligand and in the presence of CsF as fluoride promoter. The system also allowed for the coupling with primary alkyl halides in good yields.



Scheme 6 Early example of the cross-coupling with an organosilicon reagent.

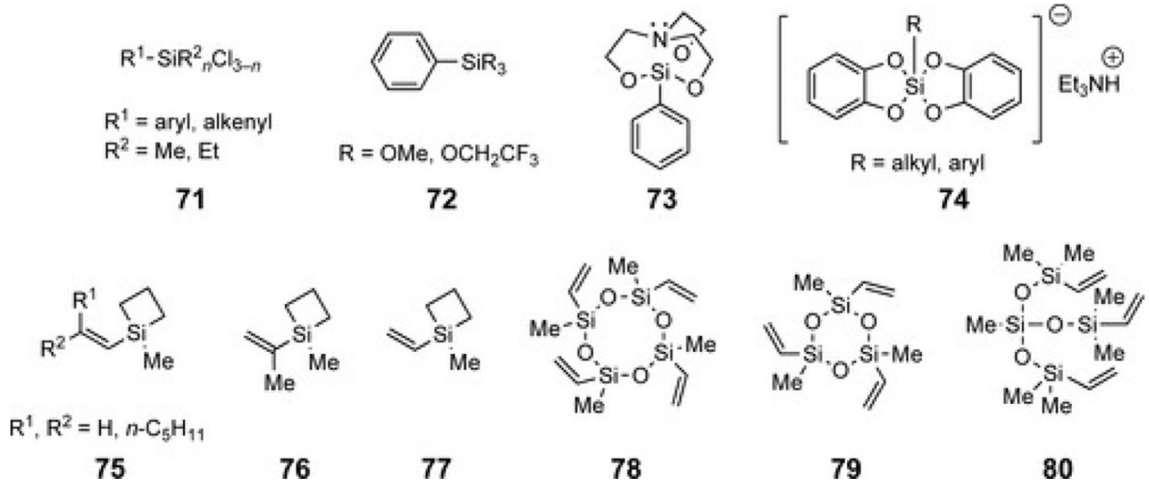


Figure 16 Silanes, siloxanes, silatranes, silicates, silacyclobutanes and polysiloxanes.

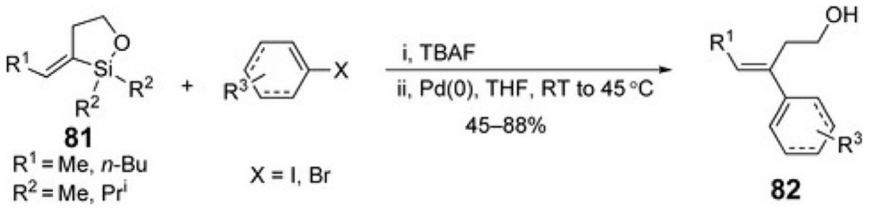
Following work by Hosomi and co-workers on the use of pentavalent bis(catechol)silicates **74** for Hiyama cross-couplings with electro-deficient aryl iodides, bromides, and triflates,[308] Seganish and DeShong reported on the palladium-catalyzed cross-coupling of a series of aryl bis(catechol)silicates with a large variety of electron-rich and electro-poor aryl iodides and triflates.[309] The reactions were carried out either in refluxing THF or refluxing dioxane.

Coupling of alkenylsilanes

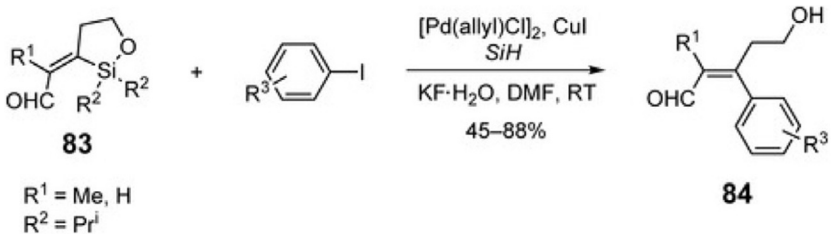
Based on previous studies that demonstrated the ability of silacyclobutanes to access a hypercoordinate state in the presence of Lewis bases,[310] Denmark and Choi investigated the coupling of alkenylsilacyclobutanes **75** with aryl and alkenyl iodides.[311] The reactions were carried out in the presence of $Pd(dba)_2$ and TBAF, at room temperature in THF, with excellent yields. They later reported on the use of 1-methyl-1-vinyl **76** and 1-methyl-1(prop-2-enyl)silacyclobutane **77** as new class of alkene donors for the coupling with aryl and alkenyl iodides.[312] The compatibility with a variety of functionalities revealed these organosilicon compounds as very useful vinylation reagents. Vinylpolysiloxanes **78–80** (Figure 16) were found to be very useful precursors for this reaction as well.[313] Compound **78** was selected, on the basis of cost and efficiency of vinyl transfer, for coupling with a variety of aryl iodides in the presence of $Pd(dba)_2$ and TBAF, at room temperature in THF, a selection that led to product formation in good yields.

Alkylidenesilacyclopentanes **81**, formed by intramolecular hydrosilylation of homopropargyl alcohols, are proved to be efficient partners for the coupling with aryl or alkenyl iodides or bromides (Scheme 7).[314] The couplings led to a series of trisubstituted homoallylic alcohols **82** in high stereoselectivities in moderate to good yields. When substrates of the type **83** are used, α,β-unsaturated aldehyde coupling products **84** can be obtained in high yields, although the coupling conditions must be reoptimized, as shown in Scheme 8 and the use of a hydrosilane SiH is required to initiate the catalytic cycle.[315] In a similar fashion, cycloalkenylsiloxanes ethers **85**, formed by ring-closing metathesis of alkenyldimethylsilylethers of ω-unsaturated alcohols, can couple with various aryl and alkenyl halides in the presence of $Pd(dba)_2$ and TBAF, at room temperature in THF, to yield highly substituted unsaturated alcohols (Scheme 9).[316]

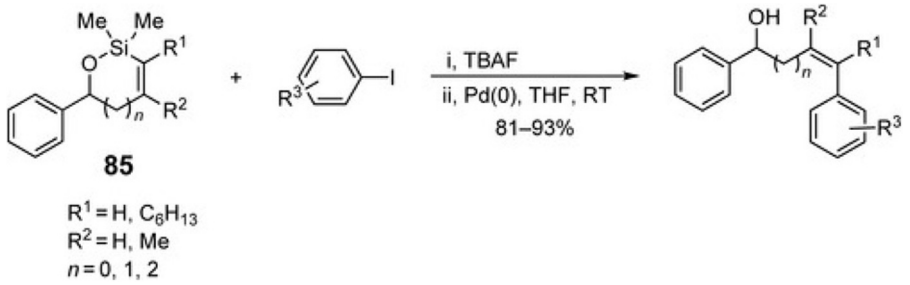
A route to synthesize medium-sized rings with an internal 1,3-*cis*-*cis*-diene unit was also developed by Denmark in good yields and high stereospecificity.[317] Silylation of the alcohols **86** followed by ring-closing metathesis leads to substrates **87**, that undergoes an intramolecular cross-coupling reaction in the presence of $[Pd(allyl)Cl]_2$ and TBAF at room temperature. Medium-sized ring



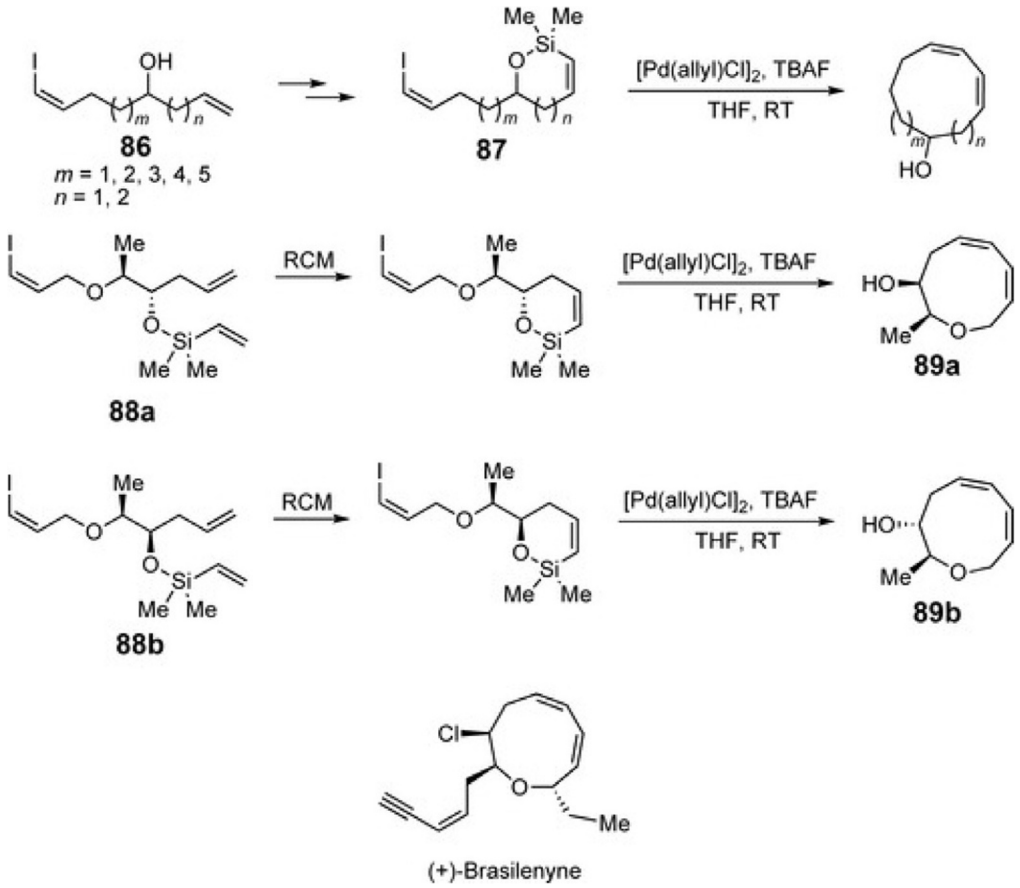
Scheme 7 Cross-couplings with alkylidenesilacyclopentanes.



Scheme 8 Cross-couplings with modified alkylidenesilacyclopentanes.



Scheme 9 Cross-couplings with cycloalkenylsiloxanes ethers.



Scheme 10 Synthesis of medium-sized ether rings with an internal 1,3-*cis*-*cis*-diene unit.

ethers **89a** and **89b** can also be prepared, using this approach, in good yields. No difference in rate or efficiency was observed for the intramolecular reaction of diasteroisomers **88a** and **88b** (Scheme 10). The system was later applied to the total synthesis of the natural product (+)-brasilenyne.[318]

Yoshida and co-workers have reported on the use of alkenyldimethyl(2-pyridil)silanes as versatile platforms for olefin synthesis.[319] The combination of Mizoroki–Heck-type coupling[320] and Hiyama cross-coupling provided a diverse range of stereodefined polysubstituted olefins.

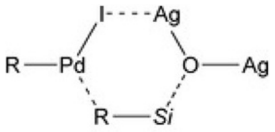
Fluoride-free systems

Hiyama and co-workers reported on the NaOH-promoted cross-coupling reactions of aryl and alkenylchlorosilanes with organic halides (activated aryl and alkenyl bromides, iodides, and chlorides) in very good yields.[321] The reaction appeared to be very sensitive to variation of the base with LiOH, KOH, and Na_2CO_3, affording only traces of desired coupling products. The coupling reactions took place in the presence of an excess of NaOH (6 equiv. per equivalent of silane) and catalytic amounts of $Pd(OAc)_2$ and PPh_3. Phosphine-bearing palladium complexes such as $Pd(dcpe)Cl_2$ and $Pd(P^iPr_3)_2Cl_2$ also were quite effective in the coupling of alkenylchlorosilanes with aryl chlorides.

Mowery and DeShong used the commercially available hypervalent silicate complex TBAT as a phenylating agent for the cross-coupling reaction with allylic esters.[322] They later reported on the use of the same organosilane for the coupling with aryl iodides and triflates and electron-deficient aryl bromides.[323] The reactions were catalyzed by either $Pd(dba)_2$ or $[Pd(allyl)Cl]_2$ without the need of added phosphine ligands.

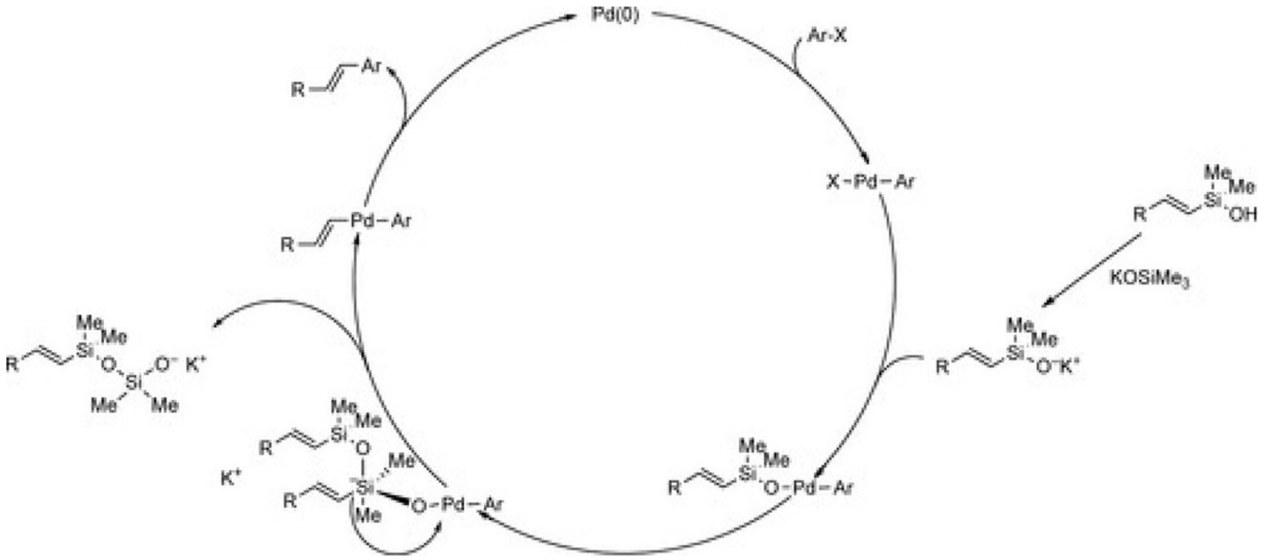
Silver(I) oxide has been used as promoter for the cross-coupling reactions of aryl- and alkenylsilanols, aryl- and alkenylsilanediols, and arylsilanetriols with aryl iodides.[324] Silanediols and silanetriols were, in general, more reactive than silanols. XRD analyses revealed that Ag_2O was transformed into AgI during the reaction, so the authors suggested the species **90** (Figure 17) as intermediate of the reaction after the oxidative addition of the aryl iodide to the palladium center. Yoshida and co-workers also used Ag_2O as additive for the cross-coupling of benzyl(2-pyridyl)silanes with aryl iodides, to synthesize a variety of diarylmethanes in moderate yields (34–71%).[325]

The scope of the use of the inexpensive, commercially available $KOSiMe_3$ as base was examined by Denmark and Sweis.[326] High yields and high stereospecificities were obtained for the coupling of a variety of alkenyldimethylsilanols and aryl iodides, in DME at



90

Figure 17 Potential intermediate in the Ag_2O-catalyzed cross-coupling of silanols.



Scheme 11 Proposed catalytic cycle for the the coupling of alkenyldimethylsilanols and aryl iodides in the presence of $KOSiMe_3$.

room temperature, in very short reaction times. TBS-protected alcohols are not affected by the presence of this base. The authors proposed the formation of a silicon–oxygen–palladium linkage as a pre-association step prior to the transmetallation (Scheme 11).

Later, Denmark and Ober reported on the use of Cs_2CO_3 in combination with water for the palladium-catalyzed cross-coupling of aryl iodides and bromides with aryl silanols.[327] Although the system was not very general, since ligands, ratios, and solvents varied depending on the substrate, good yields were obtained in most cases.

Pd- or Ni-catalyzed Reactions with Organozinc Reagents: The Negishi Coupling

The cross-coupling of organozinc reagents with electrophilic halides proceeds generally with high yields and tolerates a wide range of functionalities, since organozinc reagents are inert to ketones, amino, esters, and cyano groups. The most convenient way to prepare organozinc reagents is *in situ* from organomagnesium, lithium, or aluminum reagents and $ZnCl_2$.[328] The cross-coupling reactions can be catalyzed by palladium, nickel (Negishi coupling),[1] or copper. Organozinc reagents are an excellent choice for the introduction of alkyl substituents with β-hydrogens in a substrate, since the couplings can proceed smoothly without β-elimination. Also, several reports on microwave-assisted Negishi cross-coupling have appeared in the literature.[1i,329] Some recent examples of compounds that include a Negishi cross-coupling step in their synthesis are shown in Figure 18.[330]

Arylzinc reagents

In 2001, Dai and Fu reported the first general method for the Negishi cross-coupling of sterically demanding vinyl and aryl chlorides with a wide range of aryl and alkylzinc reagents, using the commercially available $Pd(P(^tBu)_3)_2$ in THF/NMP mixtures at 100 °C.[331] High TONs could be obtained for the synthesis of hindered biaryls. Very recently, Milne and Buchwald used phosphine ligand **91** (Figure 19) in combination with $Pd_2(dba)_3$ to prepare tri- and tetra-*ortho*-substituted biaryls.[332] Excellent yields were obtained even at low catalyst loadings (0.1–1 mol% Pd), with a good tolerance for group functionalities.

Yang and co-workers investigated the cross-coupling of 4-tosylcoumarins and arylzinc reagents for combinatorial purposes, using $Pd(PPh_3)_4$ as catalyst in mild reaction conditions and high yields.[333] The same catalyst was used by Wei for the coupling of phenyl-, ethyl- or dibenzylzinc bromide with a variety of 4-phenylsulfinyl-2-iodo-2(*E*)-alkenols in high yields,[334] and by Bäckvall and co-workers for the cross-coupling reaction of a zinc-metallated ferrocenyl *p*-tolyl sulfoxide and highly substituted aryl

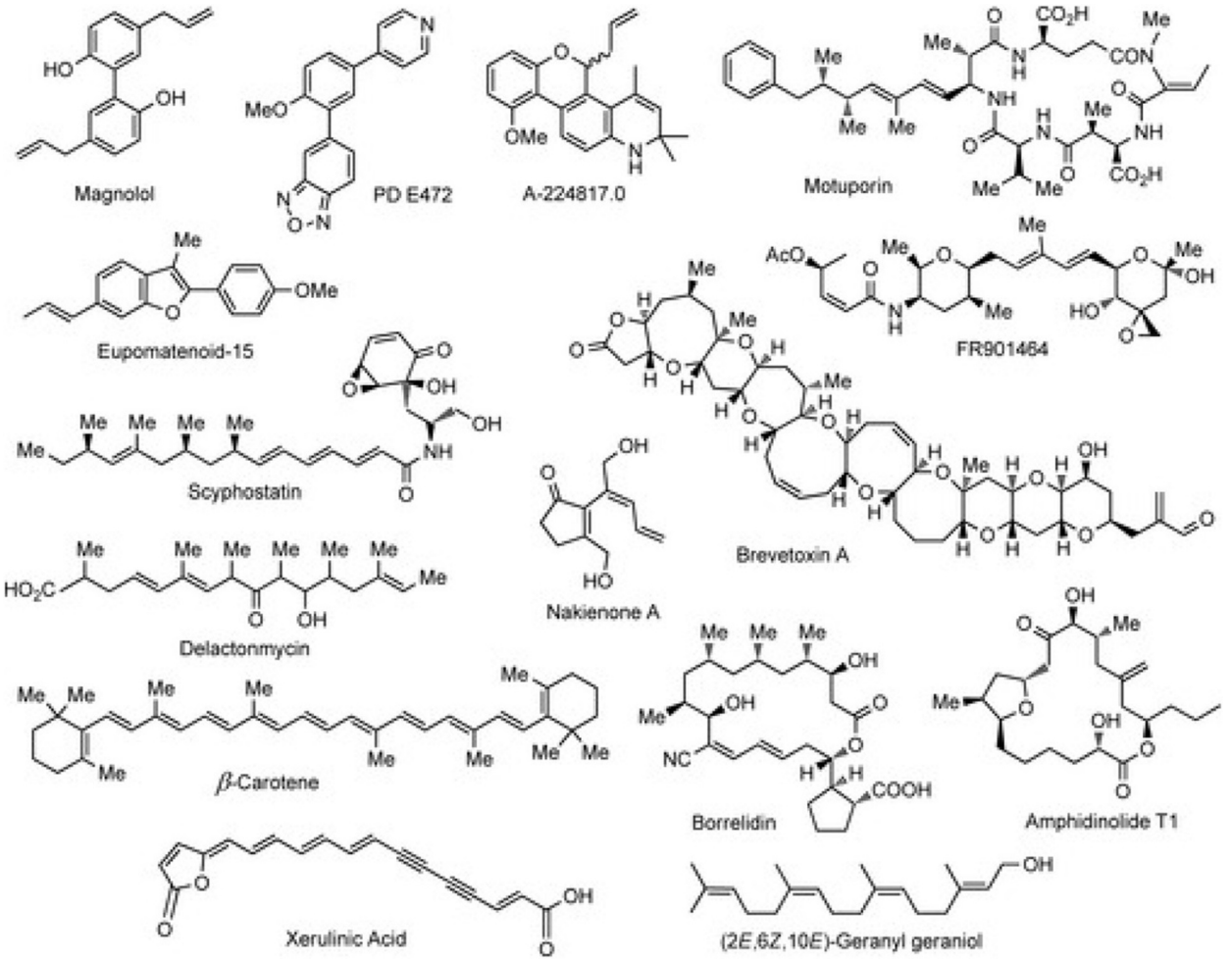


Figure 18 Some compounds that include a Negishi cross-coupling step in their synthesis.

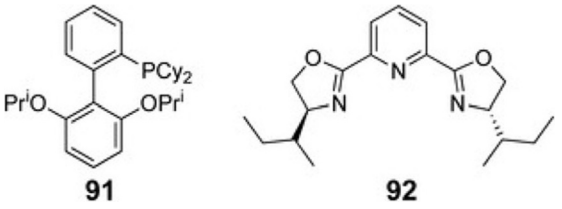


Figure 19 Ligands for the coupling of organozing reagents.

bromides, to synthesize a series of ligands to be used in asymmetric oxidation reaction.[335] A similar system was described by Pedersen and Johannsen involving aryl iodides.[336]

A method for the synthesis of symmetrical and unsymmetrical ketones in good yields from the cross-coupling of organozinc reagents and anhydrides or mixed anhydrides, generated *in situ* from the corresponding carboxylic acids or their sodium salts and ethyl chloroformate, was developed by Wang and Zhang.[337] The reactions were catalyzed by $Pd(PPh_3)_4$ and carried out in refluxing THF.

Aryl and alkyl organozincate reagents, generated *in situ* by reaction of Grignard reagents and sub-stoichiometric amounts of $ZnCl_2$, cross-couple smoothly in refluxing THF with functionalized aryl and alkenyl as well as primary and secondary alkyl chlorides in the presence of $Pd(dppf)Cl_2$.[338]

Knochel and co-workers prepared a series of nitro-containing biphenyls in moderate to good yields by Negishi cross-coupling of various aryl iodides and nitro-substituted arylzinc reagents.[339] Heteroarylzinc chlorides can couple with vinylic and aryltellurides (R–TeBu) with in the presence of $PdCl_2$ and CuI, in THF and at room temperature, in high yields and with high stereoselectivities.[340]

Alkenyl- and alkylzinc reagents

In 1997, Dunn and Jackson reported on a new approach to the synthesis of di- and tripeptides with unnatural amino acids by converting di- and tripeptides into organozinc reagents and coupling them with aryl iodides or acyl chlorides in the presence of $Pd_2(dba)_3$ and either PPh_3 or P(*o*-tol)$_3$ under mild reaction conditions, with no loss of optical purity.[341] The synthesis of β- and γ-amino acids in an analogous fashion was reported shortly after (**Scheme 12**).[342]

Knochel and co-workers developed the Ni(acac)$_3$-catalyzed cross-coupling reaction between polyfunctional primary iodoalkanes and a variety of primary diorganozinc compounds in the presence of *m*-trifluoromethylstyrene as a promoter.[343] The addition of this unsaturated promoter is required in order to coordinate to the nickel center and remove electron density from the metal atom, to facilitate the reductive elimination step.[344] The scope of the reaction is extended, when Ni(acac)$_2$ is used in the presence of Bu_4NI and fluorostyrene (**Scheme 13**).[345] With these modifications, primary and secondary alkylzinc iodides cross-couple with a variety of primary alkyl iodides or bromides in good yields. Dialkylzincs, more reactive, can couple in the absence of Bu_4NI. The same concept was used by Kambe and co-workers for the coupling of alkyl bromides and tosylates with aryl and alkyl organozinc reagents in the presence of $NiCl_2$ and N,N-bis(penta-2,4-dienyl)benzylamine.[266]

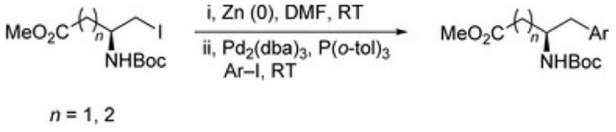
Fu and co-workers reported that unactivated secondary alkyl halides can be coupled in good yields with alkylzinc reagents at room temperature in dimethylacetamide (DMA) in the presence of Ni(COD)$_2$ and ligand **92** (**Figure 19**).[346] They later reported a general method for the cross-coupling of a range of β-hydrogen-containing primary alkyl iodides, bromides, chlorides, and tosylates with a large variety of alkyl-, alkenyl- and arylzinc halides.[347] The system consisted of a combination of $Pd_2(dba)_3$, P(Cyp)$_3$/NMI in THF/NMP, allowed for the couplings to be performed at 80 °C, but required 14 h.

Herbert made use of either Pd(dppe)Cl_2 or Pd(dppf)Cl_2 for the the cross-coupling of activated and unactivated aryl bromides with dimethylzinc in refluxing dioxane, in short reaction times and high yields.[348]

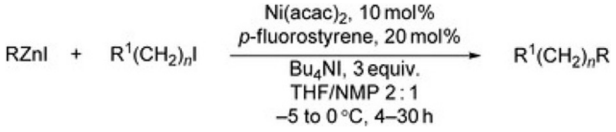
Very recently, Negishi and co-workers have reported two related systems for the synthesis of stereodefined conjugated dienes: a cross-coupling reaction of (*Z*)-2-bromo-1,3-dienes with organozinc reagents, catalyzed by a variety of phosphine-bearing palladium complexes, that proceeds with clean stereoinversion of the Br-bearing CC bond,[349] and a stereoselective synthesis of (1*E*)-2-methyl-1,3-dienes by the palladium-catalyzed *trans*-selective cross-coupling of 1,1-dibromo-1-alkenes with alkenyl- and phenylzinc reagents, with full retention of configuration, using a combination of $Pd_2(dba)_3$ with either **36** or P(Bu^t)$_3$ (**Scheme 14**).[350]

Closing Remarks

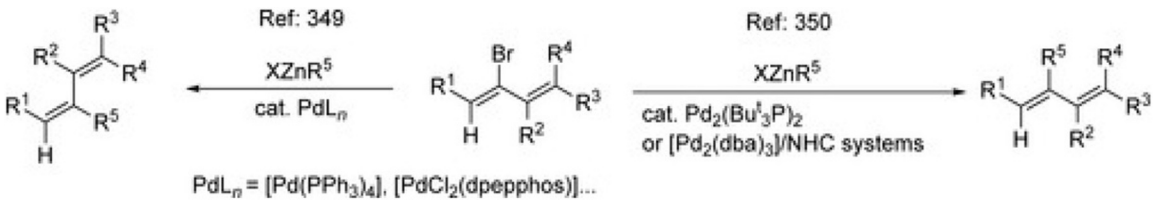
It should be fairly evident that more than 10 years of metal-catalyzed cross-coupling chemistry cannot be summarized in the limited number of pages allocated to this review. The amount of activity and literature in this area is still rapidly growing! One would be hard pressed to open any chemistry journal and not find at least one cross-coupling reaction, used in one form or other. We have attempted to include the most recent reviews and references.



Scheme 12 Synthesis of β- and γ-amino acids using organozinc reagents prepared in situ.



Scheme 13 Ni(acac)$_2$-catalyzed cross-coupling reaction between primary iodoalkanes and primary and secondary diorganozinc compounds.



Scheme 14 Synthesis of (*Z*)-2-bromo-1,3-dienes and (1*E*)-2-methyl-1,3-dienes.

Obviously, we owe much to the pioneers of this area and it is a testimony of the importance of their work to find cross-coupling affecting so many areas of chemistry. Much progress has been made in the last decade, and at the look of things much will emerge in the very near future to solidify the crucial importance of metal-mediated cross-coupling in modern synthetic chemistry.

References

1. For general reviews, see: (a)Tsuji, J. *Transition Metal Reagents and Catalysts*; Wiley: Bath, 2000 pp. 56–76; (b) In *Metal-Catalyzed Cross-Coupling Reactions*; Diedrich, F.; Stang, P. J., Eds.; 3rd ed.; Wiley-VCH: Weinheim, 2004 (c) In *Transition Metals for Organic Chemistry*; Beller, M.; Bolm, C., Eds.; *Transition Metals for Organic Chemistry*; Vol. 1; Wiley-VCH: Weinheim, 1998 pp 158–193; (d) Hassan, J.; Sévignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359–1469; (e) Tsuji, J. *Palladium Reagents and Catalysts*. Wiley: Chichester, 2004 (f) In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; Wiley-Interscience: New York, 2002 (g) Special issue on *30 Years of the Cross-coupling Reaction*Tamao, K.; Hiyama, T.; Negishi, E. *J. Organomet. Chem.* **2002**, *653*, 1–303; (h) For a review on microwave-assisted organic chemistry including C–C bond formations, see: Kappe, C. O. *Angew. Chem. Int. Ed.* **2004**, *43*, 6250–6284.
2. Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457–2483.
3. Miura, M. *Angew. Chem. Int. Ed.* **2004**, *43*, 201–2203.
4. Miyaura, N.; Yamada, K.; Suzuki, A. *Tetrahedron Lett.* **1979**, *36*, 3437–3439.
5. (a) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147–168; (b) Miyaura, N. *Top. Curr. Chem.* **2002**, *219*, 11–59; (c) Kotha, S.; Lahiri, K.; Kashinath, D. *Tetrahedron* **2002**, *58*, 9633–9695; (d) Chemler, S. R.; Trauner, D.; Danishefsky, S. J. *Angew. Chem. Int. Ed.* **2001**, *40*, 4544–4568; (e) For a recent review covering until March 2004Bellina, F.; Carpita, A.; Rossi, R. *Synthesis* **2004**, *15*, 2419–2440.
6. Suzuki, A. *J. Organomet. Chem.* **2002**, *653*, 83–90.
7. Konno, T.; Daitoh, T.; Noiri, A.; Chae, J.; Ishihara, T.; Yamanaka, H. *Org. Lett.* **2004**, *6*, 933–936.
8. (a) Yamamoto, T.; Kobayashi, K.; Yasuda, T.; Zhou, Z.-H.; Yamaguchi, I.; Ishikawa, T.; Koshihara, S. *Polym. Bull.* **2004**, *52*, 315–319; (b) Bo, Z.; Qiu, J.; Li, J.; Schlueter, A. D. *Org. Lett.* **2004**, *6*, 667–669; (c) Beinhoff, M.; Karakaya, B.; Schluter, A. D. *Synthesis* **2003**, 79–90; (d) Yamaguchi, S.; Goto, T.; Tamao, K. *Angew. Chem. Int. Ed.* **2000**, *39*, 1695–1697.
9. (a) Lin, S.; Yang, Z.-Q.; Kwok, B. H. B.; Koldobskiy, M.; Crews, C. M.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2004**, *126*, 6347–6355; (b) Yuan, Y.; Men, H.; Lee, C. *J. Am. Chem. Soc.* **2004**, *126*, 14720–14721; (c) Suzuki, T.; Usui, K.; Miyake, Y.; Namikoshi, M.; Nakada, M. *Org. Lett.* **2004**, *6*, 553–556; (d) Tsukano, C.; Sasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 14294–14295; (e) Miyashita, K.; Sakai, T.; Imanishi, T. *Org. Lett.* **2003**, *5*, 2683–2686; (f) Fuwa, H.; Kainuma, N.; Tachibana, K.; Sasaki, M. *J. Am. Chem. Soc.* **2002**, *124*, 14983–14992; (g) Mandal, A. K. *Org. Lett.* **2002**, *4*, 2043–2045; (h) Sasaki, M.; Fuwa, H. *Synlett* **2004**, 1851–1874.
10. Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457–2483.
11. Miyaura, N.; Ishiyama, T.; Sasaki, H.; Ishikawa, M.; Satoh, M.; Suzuki, A. *J. Am. Chem. Soc.* **1989**, *111*, 314–321.
12. (a) Darses, S.; Genet, J. P.; Brayer, J. L.; Demoute, J. P. *Tetrahedron Lett.* **1997**, *38*, 4393–4396; (b) Darses, S.; Michaud, G.; Genet, J. P. *Eur. J. Org. Chem.* **1999**, *8*, 1875–1883.
13. Smith, G. B.; Dezeny, G. C.; Hughes, D. L.; King, A. O.; Verhoeven, T. R. *J. Org. Chem.* **1994**, *59*, 8151–8156.
14. Miyaura, N.; Yamada, K.; Suginome, H.; Suzuki, A. *J. Am. Chem. Soc.* **1985**, *107*, 972–980.
15. Miyaura, N.; Tanabe, Y.; Suginome, H.; Suzuki, A. *J. Organomet. Chem.* **1982**, *233*, C13–C16.
16. Moriya, T.; Miyaura, N.; Suzuki, A. *Synlett* **1994**, 149–151.
17. Otsuka, S. *J. Organomet. Chem.* **1980**, *200*, 191–205.
18. Matos, K.; Soderquist, K. A. *J. Org. Chem.* **1998**, *63*, 461–470.
19. Grushin, V. V.; Alper, H. In *Activation of Unreactive Bonds an Organic Synthesis*; Murai, S., Ed.; Springer: Berlin, 1999; pp 193–226.
20. For a review in palladium-catalyzed coupling reactions of aryl chlorides:Littke, A. F.; Fu, G. C. *Angew. Chem. Int. Ed.* **2002**, *41*, 4176–4211.
21. Littke, A. F.; Fu, G. C. *Angew. Chem. Int. Ed.* **1998**, *37*, 3387–3388.
22. Old, D. W.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 9722–9723.
23. (a) Wolfe, J. P.; Wagaw, S.; Macroux, J.-F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805–818; (b) Hartwig, J. F. *Acc. Chem. Res.* **1998**, *31*, 852–860.
24. Zapf, A.; Ehrentraut, A.; Beller, M. *Angew. Chem. Int. Ed.* **2000**, *39*, 4153–4155.
25. Andreu, M. G.; Zapf, A.; Beller, M. *Chem. Commun.* **2001**, 2475–2476.
26. Bei, X.; Turner, H. W.; Weinberg, W. H.; Guram, A. S.; Petersen, J. L. *J. Org. Chem.* **1999**, *64*, 6797–6803.
27. Liu, S.-Y.; Choi, M. J.; Fu, G. C. *Chem. Commun.* **2001**, 2408–2409.
28. Pickett, T. E.; Richards, C. J. *Tetrahedron Lett.* **2001**, *42*, 3767–3769.
29. Li, G. Y. *Angew. Chem. Int. Ed.* **2001**, *40*, 1513–1516.
30. Literature on NHC: (a)Arduengo, A. J., III; Rasika Dias, H. V.; Harlow, R. L.; Kine, M. *J. Am. Chem. Soc.* **1992**, *114*, 5530–5534; (b) Regitz, M. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 725–728; (c) Arduengo, A. J., III; Krafczyc, R. *Chem. Z.* **1998**, *32*, 6–14; For reviews on NHC in cross-coupling reactions, see: (d)Herrmann, W. A.; Öfele, K.; Preising, D. V.; Schneider, S. K. *J. Organomet. Chem.* **2003**, *687*, 229–248; (e) Herrmann, W. A. *Angew. Chem. Int. Ed. Engl.* **2002**, *41*, 1290–1309; (f) Hillier, A.; Grasa, G. A.; Viciu, M. S.; Lee, H. M.; Yang, C.; Nolan, S. P. *J. Organomet. Chem.* **2002**, *653*, 69–82; (g) Kissling, R. M.; Viciu, M. S.; Grasa, G. A.; Germaneau, R. F.; Güveli, T.; Pasareanu, M.-C.; Navarro-Fernandez, O.; Nolan, S. P. *ACS Symp. Series* **2003**, *856*, 323–341.
31. Zhang, C.; Huang, J.; Trudell, M. L.; Nolan, S. P. *J. Org. Chem.* **1999**, *64*, 3804–3805.
32. Jafarpour, L.; Nolan, S. P. *Adv. Organomet. Chem.* **2001**, *46*, 181–222, ($P(Bu^t)_3$ was not included in this study).
33. Collman, J. P.; Hedegus, L. S.; Norton, J. R.; Finke, R. G. *Principles and Applications of Organotransition Metal Chemistry*, 2nd ed.; University Science: Mill Valley, 1987.
34. Herrmann, W. A.; Elison, M.; Fischer, J.; Köcher, C.; Artus, G. R. J. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2371–2374.
35. (a) Yu, S.; Kim, Y. M. *J. Am. Chem. Soc.* **2003**, *125*, 1696–1697; (b) Widdowson, D. A.; Wilhem, R. *Chem. Commun.* **2003**, 578–579.
36. Oh-e, T.; Miyaura, N.; Suzuki, A. *J. Org. Chem.* **1993**, *58*, 2201–2208.
37. Echavarren, A. M.; Stille, J. K. *J. Am. Chem. Soc.* **1987**, *109*, 5478–5486.
38. (a) Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020–4028; (b) Brenstrum, T.; Gerristma, D. A.; Adjabeng, G. M.; Frampton, C. S.; Britten, J.; Robertson, A. J.; McNulty, J.; Capretta, A. *J. Org. Chem.* **2004**, *69*, 7635–7639; (c) Grasa, G. A.; Viciu, M. S.; Huang, J.; Zhang, C.; Trudell, M. L.; Nolan, S. P. *Organometallics* **2002**, *21*, 2866–2873; (d) Takagi, J.; Takahashi, T. I.; Miyaura, N. *J. Am. Chem. Soc.* **2002**, *124*, 8001–8006.
39. (a) Sengupta, S.; Bhattacharyya, S. *J. Org. Chem.* **1997**, *62*, 3405–3406; (b) Andrus, M. B.; Song, C. *Org. Lett.* **2001**, *3*, 3761–3764.
40. Dubbaka, S. R.; Vogel, P. *Org. Lett.* **2004**, *6*, 95–98.
41. (a) Nguyen, H. N.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 11818–11819; (b) Huffman, M. A.; Yasuda, N. *Synlett* **1999**, 471–473; (c) Lakshman, M. K.; Thomson, P. F.; Nuqui, M. A.; Hilmer, J. H.; Sevova, N.; Boggess, B. *Org. Lett.* **2002**, *4*, 1479–1482; (d) Wu, J.; Zhu, Q.; Wang, L.; Fathi, R.; Yang, Z. *J. Org. Chem.* **2003**, *68*, 670–673; (e) Netherton, M. R.; Fu, G. C. *Angew. Chem. Int. Ed.* **2002**, *41*, 3910–3912; (f) Nickel-catalyzed Suzuki–Miyaura coupling of ArOTsZim, D.; Lando, V. R.; Dupont, J.; Monteiro, A. L. *Org. Lett.* **2001**, *3*, 3049–3051.
42. (a) Percec, V.; Bae, J.-Y.; Hill, D. H. *J. Org. Chem.* **1995**, *60*, 1060–1065; (b) With lithium arylboratesKobayashi, Y.; Mizojiri, R. *Tetrahedron Lett.* **1996**, *37*, 8531–8534.
43. Blakey, S. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2003**, *125*, 6046–6047.

44. Biolatto, B.; Molander, G. A. *Org. Lett.* **2002**, *4*, 1867–1870.
45. Batey, R. A.; Quach, T. D. *Tetrahedron Lett.* **2001**, *42*, 9099–9103.
46. Ito, T.; Molander, G. A. *Org. Lett.* **2001**, *3*, 393–396.
47. Vedejs, E.; Fields, S. C.; Hayashi, R.; Hitchock, S. R.; Powell, D. R.; Schrimpf, M. R. *J. Am. Chem. Soc.* **1999**, *121*, 2460–2470.
48. Barder, T. E.; Buchwald, S. L. *Org. Lett.* **2004**, *6*, 2649–2652.
49. (a) Bedford, R.; Cazin, C. S. J.; Hursthose, M. B.; Light, M. E.; Scordia, V. J. M. *Dalton Trans.* **2004**, 3864–3868; (b) For an excellent review in palladacyclic complexes in C–C bond-forming reactionsBedford, R. B. *Chem. Commun.* **2003**, 1787–1796.
50. Beller, M.; Fischer, H.; Herrmann, W. A.; Öfele, K.; Brossmer, C. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1848–1849.
51. (a) Bedford, R. B.; Draper, S. M.; Scully, P. N.; Weilch, S. L. *New J. Chem.* **2000**, *24*, 745–747; (b) Albisson, D. A.; Bedford, R. B.; Lawrence, S. E.; Scully, P. N. *Chem. Commun.* **1998**, 2095–2096; (c) Bedford, R. B.; Welch, S. L. *Chem. Commun.* **2001**, 129–130; (d) Bedford, R. B.; Hazelwood, S. L.; Limmert, M. E.; Albisson, D. A.; Draper, S. M.; Scully, P. N.; Coles, S. J.; Hursthouse, M. B. *Chem. Eur. J.* **2003**, *9*, 3216–3227; (e) Bedford, R. B.; Hazelwood, S. L.; Horton, P. N.; Hursthouse, M. B. *Dalton Trans.* **2003**, 4164–4174.
52. Gibson, S.; Foster, D. F.; Eastman, G. R.; Tooze, R. P.; Cole-Hamilton, D. J. *Chem. Commun.* **2001**, 779–780.
53. (a) Albisson, D. A.; Bedford, R. B.; Scully, P. N. *Tetrahedron Lett.* **1998**, *39*, 9793–9796; (b) Iyer, S.; Ramesh, C. *Tetrahedron Lett.* **2000**, *41*, 8981–8984; (c) Beletskaya, I. P.; Kashin, A. N.; Karslted, N. B.; Mitin, A. V.; Cheprakov, A. V.; Kazankov, G. M. *J. Organomet. Chem.* **2001**, *622*, 89–96; (d) Yang, F.; Zhang, Y.; Zheng, R.; Tie, J.; He, M. *J. Organomet. Chem.* **2002**, *651*, 146–148.
54. Weissman, H.; Milstein, D. *Chem. Commun.* **1999**, 1901–1902.
55. (a) Alonso, D. A.; Nájera, C.; Pacheco, M. C. *J. Org. Chem.* **2002**, *67*, 5588–5594; (b) Botella, L.; Nájera, C. *Angew. Chem. Int. Ed.* **2002**, *41*, 179–181; (c) Botella, L.; Nájera, C. *J. Organomet. Chem.* **2002**, *663*, 46–57; (d) Alonso, D. A.; Botella, L.; Nájera, C.; Pacheco, M. C. *Synthesis* **2004**, 1713–1718.
56. Zim, D.; Gruber, A. S.; Ebeling, G.; Dupont, J.; Monteiro, A. L. *Org. Lett.* **2000**, *2*, 2881–2884.
57. (a) Bedford, R. B.; Cazin, C. S. J. *Chem. Commun.* **2001**, 1540–1541; (b) Bedford, R. B.; Cazin, C. S. J.; Coles, S. J.; Gelbrich, T.; Horton, P. N.; Hurtshouse, M. B.; Light, M. E. *Organometallics* **2003**, *22*, 987–999.
58. (a) Bedford, R. B.; Cazin, C. S. J.; Hazelwood, S. L. *Angew. Chem. Int. Ed.* **2002**, *41*, 4120–4122; (b) Bedford, R. B.; Cazin, C. S. J.; Hazelwood, S. L. *Chem. Commun.* **2002**, 2608–2609; (c) Bedford, R. B.; Hazelwood, S. L.; Limmert, M. E. *Chem. Commun.* **2002**, 2610–2611.
59. Bedford, R. B.; Cazin, C. S. J.; Hurtshouse, M. B.; Light, M. E.; Pike, K. J.; Wimperis, S. *J. Organomet. Chem.* **2001**, *633*, 173–181.
60. Navarro, O.; Kelly, R. A., III; Nolan, S. P. *J. Am. Chem. Soc.* **2003**, *125*, 16194–16195.
61. (a) Parshall, G. W.; Ittel, S. *Homogeneous Catalysis*; Wiley: New York, 1992; (b) In *Homogeneous Catalysis with Metal Phosphine Complexes*; Pignolet, L. H., Ed.; Plenum: New York, 1983.
62. Krause, J.; Cestaric, G.; Haack, K. J.; Seegovel, K.; Strom, W.; Porschke, K. R. *J. Am. Chem. Soc.* **1999**, *121*, 9807–9823.
63. Stambuli, J. P.; Kuwano, R.; Hartwig, J. F. *Angew. Chem. Int. Ed.* **2002**, *41*, 4746–4748.
64. Littke, A. F.; Fu, G. C. *Angew. Chem. Int. Ed.* **1998**, *37*, 3387–3388.
65. Netherton, M. R.; Fu, G. C. *Org. Lett.* **2001**, *3*, 4263–4266.
66. Zhong, Y.-L.; Lee, J.; Reamer, R. A.; Askin, D. *Org. Lett.* **2004**, *6*, 929–932.
67. Kirchoff, J. H.; Netherton, M. R.; Hills, I. D.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 13662–13663.
68. Netherton, M. R.; Dai, C.; Neuschütz, K.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 10099–10100.
69. Wolfe, J. P.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **1999**, *38*, 2413–2416.
70. Wolfe, J. P.; Singer, R. A.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9550–9561.
71. Yin, J.; Rainka, M. P.; Zhang, X.-X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 1162–1163.
72. Lakshman, M. K.; Hilmer, J. H.; Martin, J. Q.; Keeler, J. C.; Dinh, Y. Q. V.; Ngassa, F. N.; Russon, L. M. *J. Am. Chem. Soc.* **2001**, *123*, 7779–7787.
73. Tagata, T.; Nishida, M. *J. Org. Chem.* **2003**, *68*, 9412–9415.
74. (a) Lakshman, M. K.; Thompson, P. F.; Nuqui, M. A.; Hilmer, J. H.; Sevova, N.; Bogges, B. *Org. Lett.* **2002**, *4*, 1479–1482; (b) Kotharé, M. A.; Ohkanda, J.; Lockman, J. W.; Qian, Y.; Blaskovich, M. A.; Sebti, S. M.; Hamilton, A. D. *Tetrahedron* **2000**, *56*, 9833–9841.
75. Nguyen, H. N.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 11818–11819.
76. Walker, S. D.; Barder, T. E.; Martinelli, J. R.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2004**, *43*, 1871–1876.
77. Liu, S.-Y.; Choi, M. J.; Fu, G. C. *Chem. Commun.* **2001**, 2408–2409.
78. Kataoka, N.; Shelby, Q.; Stambuli, J. P.; Hartwig, J. F. *J. Org. Chem.* **2002**, *67*, 5553–5566.
79. Jensen, J. F.; Johannsen, M. *Org. Lett.* **2003**, *5*, 3025–3028.
80. Cammidge, A. N.; Crépy, K. V. L. *Chem. Commun.* **2000**, 1723–1724.
81. Kwong, F. Y.; Chan, K. S.; Yeung, C. H.; Chan, A. S. C. *Chem. Commun.* **2004**, 2336–2337.
82. Clarke, M. L.; Cole-Hamilton, D. J.; Woolins, J. D. *J. Chem. Soc. Dalton Trans.* **2001**, 2721–2723.
83. Cheng, J.; Wang, F.; Xu, J.-H.; Pan, Y.; Zhang, Z. *Tetrahedron Lett.* **2003**, *44*, 7095–7098.
84. Urgaonkar, S.; Nagarajan, M.; Verkade, J. G. *Tetrahedron Lett.* **2002**, *43*, 8921–8924.
85. Zapf, A.; Jackstell, R.; Rataboul, F.; Riermeier, T.; Monsees, A.; Fuhrmann, C.; Shaikh, N.; Dingerdissenb, U.; Beller, M. *Chem. Commun.* **2004**, 38–39.
86. Harkal, S.; Rataboul, F.; Zapf, A.; Fuhrmann, C.; Riermeier, T.; Monsees, A.; Beller, M. *Adv. Synth. Cat.* **2004**, *346*, 1742–1748.
87. Herrmann, W. A.; Reisinger, C.-P.; Spiegler, M. *J. Organomet. Chem.* **1998**, *557*, 93–96.
88. Zhang, C.; Trudell, M. L. *Tetrahedron Lett.* **2000**, *41*, 595–598.
89. Fürstner, A.; Leitner, A. *Synlett* **2001**, 290–292.
90. Arentsen, K.; Caddick, S.; Cloke, F. G. N.; Herring, A. P.; Hitchcock, P. B. *Tetrahedron Lett.* **2004**, *45*, 3511–3515.
91. Böhm, V. P. W.; Gstöttmayr, C. W. K.; Weskamp, T.; Herrmann, W. A. *J. Organomet. Chem.* **2000**, *595*, 186–190.
92. Gstöttmayr, C. W. K.; Böhm, V. P. W.; Herdtweck, E.; Grosche, M.; Herrmann, W. A. *Angew. Chem. Int. Ed.* **2002**, *41*, 1363–1365.
93. (a) Viciu, M. S.; Germaneau, R. F.; Navarro-Fernandez, O.; Stevens, E. D.; Nolan, S. P. *Organometallics* **2002**, *21*, 5470–5472; (b) Viciu, M. S.; Navarro, O.; Germaneau, R. F.; Kelly, R. A., III; Sommer, W.; Marion, N.; Stevens, E. D.; Cavallo, L.; Nolan, S. P. *Organometallics* **2004**, *23*, 1629–1635.
94. Navarro, O.; Kaur, H.; Mahjoor, P.; Nolan, S. P. *J. Org. Chem.* **2004**, *69*, 3173–3180.
95. Navarro, O.; Oonishi, Y.; Kelly, R. A.; Stevens, E. D.; Briel, O.; Nolan, S. P. *J. Organomet. Chem.* **2004**, *689*, 3722–3727.
96. Altenhoff, G.; Goddard, R.; Lehmann, C. W.; Glorius, F. *Angew. Chem. Int. Ed.* **2003**, *42*, 3690–3693.
97. Altenhoff, G.; Goddard, R.; Lehmann, C. W.; Glorius, F. *J. Am. Chem. Soc.* **2004**, *126*, 15195–15201.
98. (a) Moreno-Mañas, M.; Pérez, M.; Pleixats, R. *J. Org. Chem.* **1996**, *61*, 2346–2351; (b) Smith, K. A.; Campi, E. M.; Jackson, W. R.; Marcuccio, S.; Naeslund, C. G. M.; Deacon, G. B. *Synlett* **1997**, 131–132.
99. Zim, D.; Monteiro, A. L.; Dupont, J. *Tetrahedron Lett.* **2000**, *41*, 8199–8202.
100. Badone, D.; Baroni, M.; Cardamone, R.; Ielmini, A.; Guzzi, U. *J. Org. Chem.* **1997**, *62*, 7170–7173.
101. Bussolari, J. C.; Rehborn, D. C. *Org. Lett.* **1999**, *1*, 965–967.
102. Leadbeater, N. E.; Marco, M. *Org. Lett.* **2002**, *4*, 2973–2976.
103. Leadbeater, N. E.; Marco, M. *Angew. Chem. Int. Ed.* **2003**, *42*, 1407–1409.

104. Bedford, R. B.; Blake, M. E.; Butts, C. P.; Holder, D. *Chem. Commun.* **2003**, 466–467.
105. Molander, G. A.; Biolatto, B. *Org. Lett.* **2002**, *4*, 1867–1870.
106. Deng, Y.; Gong, L.; Mi, A.; Liu, H.; Jang, Y. *Synthesis* **2003**, 337–339.
107. Tao, X.; Zhao, Y.; Shen, D. *Synlett* **2004**, 359–361.
108. Dupuis, C.; Adiey, K.; Charruault, L.; Michelet, V.; Savignac, M.; Genêt, J. P. *Tetrahedron Lett.* **2001**, *42*, 6523–6526.
109. Moore, L. R.; Shaughnessy, K. H. *Org. Lett.* **2004**, *6*, 225–228.
110. Beller, M.; Krauter, J. G. E.; Zapf, A. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 772–774.
111. Ueda, M.; Nishimura, M.; Miyaura, N. *Synlett* **2000**, 856–858.
112. Shaughnessy, K. H.; Booth, R. S. *Org. Lett.* **2001**, *3*, 2757–2759.
113. (a) Nájera, C.; Gil-Moltó, J.; Karlström, S. *Adv. Synth. Cat.* **2004**, *346*, 1798–1811; (b) Nájera, C.; Gil-Moltó, J.; Karlström, S.; Falvello, L. R. *Org. Lett.* **2003**, *5*, 1451–1454.
114. (a) Walsh, C. J.; Mandal, B. K. *Chem. Mater.* **2001**, *13*, 2472–2475; (b) McClure, M. S.; Roschangar, F.; Hodson, S. J.; Millar, A.; Osterhout, M. H. *Synthesis* **2001**, 1681–1685; (c) LeBlond, C. R.; Andrews, A. T.; Sun, Y.; Sowa, J. R., Jr. *Org. Lett.* **2001**, *3*, 1555–1557; (d) Guolin, Z. *J. Chem. Res.* **2004**, 593–595.
115. Kabalka, G. W.; Namboodiri, V.; Wang, L. *Chem. Commun.* **2001**, 775.
116. Kabalka, G. W.; Wang, L.; Pagni, R. M.; Hair, C. M.; Namboodiri, V. *Synthesis* **2003**, 217–222.
117. Heidenreich, R. G.; Köhler, K.; Krauter, J. G. E.; Piestch, J. *Synlett* **2002**, 1118–1122.
118. (a) Kim, S.-W.; Kim, M.; Lee, W. Y.; Hyeon, T. *J. Am. Chem. Soc.* **2002**, *124*, 7642–7643; (b) Liu, Y.; Khemtong, C.; Hu, J. *Chem. Commun.* **2004**, 398–399; (c) Lu, F.; Ruiz, J.; Astruc, D. *Tetrahedron Lett.* **2004**, *45*, 9443–9445.
119. Artok, L.; Bulut, H. *Tetrahedron Lett.* **2004**, *45*, 3881–3884.
120. Uozumi, Y.; Danjo, H.; Hayashi, T. *J. Org. Chem.* **1999**, *64*, 3384–3388.
121. Zhou, J.; Fu, G. C. *J. Am. Chem. Soc.* **2004**, *126*, 1340–1341.
122. Tang, Z.-Y.; Hu, Q.-S. *J. Am. Chem. Soc.* **2004**, *126*, 3058–3059.
123. Tang, Z.-Y.; Hu, Q.-S. *Adv. Synth. Cat.* **2004**, *346*, 1635–1637.
124. Na, Y.; Park, S.; Han, S. B.; Han, H.; Ko, S.; Chang, S. *J. Am. Chem. Soc.* **2004**, *126*, 250–258.
125. Gooßen, L. J.; Paetzold, J. *Adv. Synth. Cat.* **2004**, *345*, 1665–1668.
126. Oh, C. H.; Lim, Y. M.; You, C. H. *Tetrahedron Lett.* **2002**, *43*, 4645–4647.
127. (a) Kosugi, M.; Sasazawa, K.; Shimizu, Y.; Migita, T. *Chem. Lett.* **1977**, 301–302; (b) Kosugi, M.; Shimizu, Y.; Migita, T. *Chem. Lett.* **1977**, 1423–1424.
128. Milstein, D.; Stille, J. K. *J. Am. Chem. Soc.* **1978**, *100*, 3636–3638.
129. (a) Stille, J. K. *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 508–524; (b) Farina, V. In Abel, E. W.; Stone, F. G. A.; Wilkinson, G., Eds.; *Comprehensive Organometallic Chemistry II*; Elsevier: Oxford, 1995; vol. 12; (c) Farina, V.; Krishnamurthy, V.; Scott, W. J. *The Stille Reaction*. Wiley: New York, 1998; (d) Kugami, K.; Kosugi, M. *Top. Curr. Chem.* **2002**, *219*, 87–130.
130. Pereyre, M.; Quintard, J.-P.; Rahm, A. *Tin in Organic Synthesis*; Butterworths: London, 1987.
131. Ruel, G.; Dumartin, G.; Delmond, B.; Lalère, B.; Donard, O. F. X.; Pereyre, M. *Appl. Org. Chem.* **1995**, *9*, 591–595.
132. (a) Nicolau, K. C.; Sorensen, E. J. *Classics in Total Synthesis*. VCH: Weinheim, 1996; (b) Nicolau, K. C.; Snyder, S. A. *Classics in Total Synthesis II*. Wiley-VCH: Weinheim, 2003; (c) Pattenden, G.; Sinclair, D. J. *J. Organomet. Chem.* **2002**, *653*, 261–268.
133. (a) Shair, M. D.; Yoon, T. Y.; Mosny, K. K.; Chou, T. C.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1996**, *118*, 9509–9525; (b) Nicolau, K. C.; Piscopio, A. D.; Bertinato, P.; Chakraborty, T. K.; Minowa, N.; Koide, K. *Chem. Eur. J.* **1995**, *1*, 318–323; (c) Wang, J.; Wei, B.; Huang, D.; Hu, Y.; Bai, L. *Synth. Commun.* **2001**, *31*, 3337–3343; (d) Tanimoto, N.; Gerritz, S. W.; Sawabe, A.; Noda, T.; Filla, S. A.; Masamune, S. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 673–675; (e) Smith, A. B., III; Ott, G. R. *J. Am. Chem. Soc.* **1998**, *120*, 3935–3948; (f) Wipf, P.; Coish, P. D. G. *J. Org. Chem.* **1999**, *64*, 5053–5061; (g) Miyashita, K.; Ikejiri, M.; Kawasaki, H.; Maemura, S.; Imanishi, T. *J. Am. Chem. Soc.* **2003**, *125*, 8238–8243; (h) Williams, D. R.; Heidebrecht, R. W., Jr. *J. Am. Chem. Soc.* **2003**, *125*, 1843–1850; (i) Zembower, D. E.; Zhang, H. *J. Org. Chem.* **1998**, *63*, 9300–9305; (j) Alcaraz, L.; Macdonald, G.; Ragot, J.; Lewis, N. J.; Taylor, R. J. K. *Tetrahedron* **1999**, *55*, 3707–3716; (k) Paquette, L. A.; Duan, M.; Konetzi, I.; Kempmann, C. *J. Am. Chem. Soc.* **2002**, *124*, 4257–4270; (l) Trost, B. M.; Dirat, O.; Gunzner, J. L. *Angew. Chem. Int. Ed.* **2002**, *41*, 841–843; (m) Brückner, R.; Sorg, A. *Angew. Chem. Int. Ed.* **2004**, *43*, 4523–4526.
134. Duncton, M. A. J.; Pattenden, G. J. *J. Chem. Soc. Perkin Trans. I* **1999**, 1235–1246.
135. Zhenan, B.; Chan, W. K.; Yu, L. *J. Am. Chem. Soc.* **1995**, *117*, 12426–12435.
136. (a) Espinet, P.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2004**, *43*, 4704–4734; (b) Casado, A. L.; Espinet, P.; Gallego, A. M.; Martinez-Ilardua, J. M. *Chem. Commun.* **2001**, 339–340; (c) Casado, A. L.; Espinet, P. *J. Am. Chem. Soc.* **1998**, *120*, 8978–8985; (d) Casado, A. L.; Espinet, P.; Gallego, A. M. *J. Am. Chem. Soc.* **2000**, *122*, 11771–11782; (e) Napolitano, E.; Farina, V.; Persico, M. *Organometallics* **2003**, *22*, 4030–4037; (f) Itami, K.; Kamei, T.; Yoshida, J. *J. Am. Chem. Soc.* **2001**, *123*, 8773–8779; (g) Amatore, C.; Bahsoun, A. A.; Jutand, A.; Meyer, G.; Ntepe, A. N.; Ricard, L. *J. Am. Chem. Soc.* **2003**, *125*, 4212–4222.
137. Littke, A. F.; Fu, G. C. *Angew. Chem. Int. Ed.* **1999**, *38*, 2411–2413.
138. Stagliano, K. W.; Malinakova, H. C. *Tetrahedron Lett.* **1997**, *38*, 6617–6620.
139. Kobayashi, K.; Uneda, T.; Kawakita, M.; Morikawa, O.; Konishi, H. *Tetrahedron Lett.* **1997**, *38*, 837–840.
140. Zhang, S.; Marshall, D.; Liebeskind, L. S. *J. Org. Chem.* **1999**, *64*, 2796–2804.
141. Dubbaka, S. R.; Vogel, P. *J. Am. Chem. Soc.* **2003**, *125*, 15292–15293.
142. Thibonnet, J.; Abarbri, M.; Parrain, J.-L.; Duchêne, A. *J. Org. Chem.* **2002**, *67*, 3941–3944.
143. Alphonse, F.-A.; Suzenet, F.; Kerommes, A.; Lebret, A.; Guillaumet, G. *Org. Lett.* **2003**, *5*, 803–805.
144. (a) Fouquet, E.; Pereyre, M.; Rodriguez, A. L. *J. Org. Chem.* **1997**, *62*, 5242–5243; (b) Fouquet, E.; Rodriguez, A. L. *Synlett* **1998**, 1323–1324.
145. Fugami, K.; Ohnuma, S. Y.; Kameyama, M.; Saotome, T.; Kosugi, M. *Synlett* **1999**, 63–64.
146. García Martínez, A.; Osío Barcina, J.; Colorado Heras, M. J.; de Fresno Cerezo, Á. *Organometallics* **2001**, *20*, 1020–1023.
147. Loiue, J.; Hartwig, J. F. *Angew. Chem. Int. Ed.* **1996**, *35*, 2359–2361.
148. Brody, M. S.; Finn, M. G. *Tetrahedron Lett.* **1999**, *40*, 415–418.
149. Bedford, R. B.; Cazin, C. S. J.; Hazelwood, S. L. *Chem. Commun.* **2002**, 2608–2609.
150. Serrano, J. L.; Fairlamb, I. J. S.; Sánchez, G.; García, L.; Pérez, J.; Vives, J.; López, G.; Crawforth, C. M.; Taylor, R. J. K. *Eur. J. Inorg. Chem.* **2004**, 2706–2715.
151. Farina, V.; Krishnan, B. *J. Am. Chem. Soc.* **1991**, *113*, 9585–9595.
152. (a) Han, X.; Stolz, B. M.; Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 7600–7605; (b) Mee, S. P. H.; Lee, V.; Baldwin, J. E. *Angew. Chem. Int. Ed.* **2004**, *43*, 1132–1136; (c) Mazzola, R. D., Jr.; Giese, S.; Benson, C. L.; West, F. G. *J. Org. Chem.* **2004**, *69*, 220–223.
153. Barros, M. T.; Maycock, C. D.; Madureira, M. I.; Ventura, M. R. *Chem. Commun.* **2001**, 1662–1663.
154. Shirakawa, E.; Hiyama, T. *J. Organomet. Chem.* **1999**, *575*, 169–178.
155. (a) Maleczka, R. E., Jr.; Gallagher, W. P.; Terstiege, I. *J. Am. Chem. Soc.* **2000**, *122*, 384–385; (b) Gallagher, W. P.; Terstiege, I.; Maleczka, R. E., Jr. *J. Am. Chem. Soc.* **2001**, *123*, 3194–3204; (c) Maleczka, R. E., Jr.; Gallagher, W. P. *Org. Lett.* **2001**, *3*, 4173–4176.
156. Scrivanti, A.; Matteoli, U.; Beghetto, V.; Antonaroli, S.; Crociani, B. *Tetrahedron* **2002**, *58*, 6881–6886.
157. Su, W.; Urgaonkar, S.; Verkade, J. G. *Org. Lett.* **2004**, *6*, 1421–1424.
158. Huang, C.-W.; Shanmugasundaram, M.; Chang, H.-M.; Cheng, C.-H. *Tetrahedron* **2003**, *59*, 3635–3641.
159. Wolf, C.; Lerebours, R. *J. Org. Chem.* **2001**, *68*, 7551–7554.

160. Littke, A. F.; Schwarz, L.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 6343–6348.
161. Tang, H.; Menzel, K.; Fu, G. C. *Angew. Chem. Int. Ed.* **2003**, *42*, 5079–5082.
162. Menzel, K.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 3718–3719.
163. Crawforth, C. M.; Burling, S.; Fairlamb, I. J. S.; Taylor, R. J. K.; Whitwood, A. C. *Chem. Commun.* **2003**, 2194–2195.
164. Grasa, G. A.; Nolan, S. P. *Org. Lett.* **2000**, *3*, 119–122.
165. Herrmann, W. A.; Bohm, V. P. W.; Gstottmayr, C. W. K.; Grosche, M.; Reisinger, C.-P.; Weskamp, T. *J. Organomet. Chem.* **2001**, *617*, 616–628.
166. Roth, G. P.; Farina, V. *Tetrahedron Lett.* **1995**, *36*, 2191–2194.
167. Handy, S. T.; Zhang, X. *Org. Lett.* **2001**, *3*, 233–236.
168. Stephen, R. D.; Castro, C. E. *J. Org. Chem.* **1963**, *28*, 3313–3315.
169. Cassar, L. *J. Organomet. Chem.* **1975**, *93*, 253–257.
170. Dieck, H. A.; Heck, R. F. *J. Organomet. Chem.* **1975**, *93*, 259–263.
171. (a) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467–4470; (b) Takahashi, S.; Kuroyama, Y.; Sonogashira, K.; Hagihara, N. *Synthesis* **1980**, 627–630.
172. For an excellent comprehensive review on Pd-catalyzed alkynylation: Negishi, E.; Anastasia, L. *Chem. Rev.* **2003**, *103*, 1979–2017.
173. Shultz, D. A.; Gwaltney, K. P.; Lee, H. *J. Org. Chem.* **1998**, *63*, 4034–4038.
174. (a) Cooke, J. W. B.; Bright, R.; Coleman, M. J.; Jenkins, K. P. *Org. Process Res. Dev.* **2001**, *5*, 383–386; (b) Inoue, M.; Carson, M. W.; Frontier, A. J.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2001**, *123*, 1878–1879; (c) Ohyabu, N.; Nishikawa, T.; Isobe, M. *J. Am. Chem. Soc.* **2003**, *125*, 8798–8805; (d) Wipf, P.; Graham, T. H. *J. Am. Chem. Soc.* **2004**, *126*, 15346–15347.
175. (a) Herrmann, W. A.; Reisinger, C.-P.; Öfele, K.; Broßmer, C.; Beller, M.; Fischer, H. *J. Mol. Cat. A* **1996**, *108*, 51–56; (b) Herrmann, W. A.; Böhm, V. P. W.; Reisinger, C.-P. *J. Organomet. Chem.* **1999**, *576*, 23–41.
176. Alonso, D. A.; Nájera, C.; Pacheco, M. C. *Org. Lett.* **2000**, *2*, 1823–1826.
177. McGuiness, D. S.; Cavell, K. J. *Organometallics* **2000**, *19*, 741–748.
178. Loch, J. A.; Albrecht, M.; Peris, E.; Matas, L.; Faller, J. W.; Crabtree, R. H. *Organometallics* **2002**, *21*, 700–706.
179. Batey, R. A.; Shen, M.; Lough, A. J. *Org. Lett.* **2002**, *4*, 1411–1414.
180. Ma, Y.; Song, C.; Jiang, W.; Wu, Q.; Wang, Y.; Liu, X.; Andrus, M. B. *Org. Lett.* **2003**, *5*, 3317–3319.
181. Draper, T. L.; Bailey, T. R. *J. Org. Chem.* **1995**, *60*, 748–750.
182. Novák, Z.; Kotschy, A. *Org. Lett.* **2003**, *5*, 3495–3497.
183. Hundertmark, T.; Littke, A. F.; Buchwald, S. L.; Fu, G. C. *Org. Lett.* **2000**, *2*, 1729–1731.
184. Böhm, V. P. W.; Herrmann, W. A. *Eur. J. Org. Chem.* **2000**, 3679–3681.
185. Köllhofer, A.; Pullman, T.; Plenio, H. *Angew. Chem. Int. Ed.* **2003**, *42*, 1056–1058.
186. (a) Pérez, I.; Sestelo, J. P.; Sarandeses, L. A. *J. Am. Chem. Soc.* **2001**, *123*, 4155–4160; (b) Pérez, I.; Sestelo, J. P.; Sarandeses, L. A. *Org. Lett.* **1999**, *1*, 1267–1269.
187. Dillinger, S.; Bertus, P.; Pale, P. *Org. Lett.* **2001**, *3*, 1661–1664.
188. Gelman, D.; Tsvelikhovsky, D.; Molander, G. A.; Blum, J. *J. Org. Chem.* **2002**, *67*, 6287–6290.
189. (a) Kosugi, M.; Tanji, T.; Tanaka, Y.; Yoshida, A.; Fugami, K.; Kameyama, M.; Migita, T. *J. Organomet. Chem.* **1996**, *508*, 255–257; (b) Faller, J. W.; Kultyshev, R. G. *Organometallics* **2002**, *21*, 5911–5918.
190. (a) Nishihara, Y.; Ikegashira, K.; Hirabayashi, K.; Ando, J.; Mori, A.; Hiyama, T. *J. Org. Chem.* **2000**, *65*, 1780–1787; (b) Nishihara, Y.; Ando, J.; Mori, A.; Hiyama, T. *Macromolecules* **2000**, *33*, 2779–2781.
191. Nishihara, Y.; Ikegashira, K.; Mori, A.; Hiyama, T. *Chem. Lett.* **1997**, 1233–1234.
192. Nishihara, Y.; Ikegashira, K.; Mori, A.; Hiyama, T. *Tetrahedron Lett.* **1998**, *39*, 4075–4078.
193. Ito, H.; Arimoto, K.; Sensui, H.; Hosomi, A. *Tetrahedron Lett.* **1997**, *38*, 3977–3980.
194. Marshall, J. A.; Chobanian, H. R.; Yanik, M. M. *Org. Lett.* **2001**, *3*, 4107–4110.
195. Yang, C.; Nolan, S. P. *Organometallics* **2002**, *21*, 1020–1022.
196. (a) Mori, A.; Kondo, T.; Kato, T.; Nishihara, Y. *Chem. Lett.* **2001**, 286–287; (b) Chang, S.; Yang, S. H.; Lee, P. H. *Tetrahedron Lett.* **2001**, *42*, 4833–4835.
197. Halbes, U.; Bertus, P.; Pale, P. *Tetrahedron Lett.* **2001**, *42*, 8641–8644.
198. Brandsma, L. *Preparative Acetylenic Chemistry*; 2nd ed.; Elsevier: Amsterdam, 1988.
199. Stille, J. K.; Simpson, J. H. *J. Am. Chem. Soc.* **1987**, *109*, 2138–2152.
200. Xiang, J. S.; Mahadevan, A.; Fuchs, P. L. *J. Am. Chem. Soc.* **1996**, *118*, 4284–4290.
201. Le Ménez, P.; Fargeas, V.; Berque, I.; Poisson, J.; Ardisson, J. *J. Org. Chem.* **1995**, *60*, 3593–3599.
202. Antonelli, E.; Rosi, P.; Lo Sterzo, C.; Viola, E. *J. Organomet. Chem.* **1999**, *578*, 210–222.
203. Ye, X.-S.; Wong, H. N. C. *J. Org. Chem.* **1997**, *62*, 1940–1954.
204. Ogawa, Y.; Maruno, M.; Wakamatsu, T. *Synlett* **1995**, 871–872.
205. Falck-Pedersen, M. L.; Undheim, K. *Acta Chem. Scand.* **1998**, *41*, 1711–1715.
206. Gilbert, A. M.; Wulff, W. D. *J. Am. Chem. Soc.* **1994**, *116*, 7449–7450.
207. Mukai, C.; Miyakoshi, N.; Hanaoka, M. *J. Org. Chem.* **2001**, *66*, 5875–6880.
208. Graham, A. E.; Mckerrecher, D.; Davies, D. H.; Taylor, R. J. K. *Tetrahedron Lett.* **1996**, *37*, 7445–7448.
209. Sakamoto, T.; Yasuhara, A.; Kondo, Y.; Yamanaka, H. *Chem. Pharm. Bull.* **1994**, *42*, 2032–2035.
210. Prié, G.; Abarbri, J.; Thibonnet, J.; Parrain, J.-L.; Duchêne, A. *New J. Chem.* **2003**, *27*, 432–441.
211. Wang, J.; Wei, B.; Huang, D.; Hu, Y.; Bai, L. *Synth. Commun.* **2001**, *31*, 3337–3343.
212. Minakawa, N.; Sasabuchi, Y.; Kiyosue, A.; Kojina, N.; Matsuda, A. *Chem. Pharm. Bull.* **1996**, *44*, 288–295.
213. Faust, R.; Göbelt, B. *Tetrahedron Lett.* **1997**, *38*, 8017–8020.
214. Ryan, J. H.; Stang, P. J. *J. Org. Chem.* **1996**, *61*, 6162–6165.
215. Shirakawa, E.; Yoshida, H.; Takaya, H. *Tetrahedron Lett.* **1997**, *38*, 3752–3759.
216. Dang, H. P.; Linstrumelle, G. *Tetrahedron* **1978**, *19*, 191–194.
217. (a) Negishi, E.; Kotora, M.; Xu, C. *J. Org. Chem.* **1997**, *62*, 8957–8960; (b) Negishi, E.; Xu, C.; Tan, Z.; Kotora, M. *Heterocycles* **1997**, *46*, 209–214.
218. (a) Kamikawa, T.; Hayashi, T. *J. Org. Chem.* **1998**, *63*, 8922–8925; (b) Kamikawa, T.; Hayashi, T. *Synlett* **1997**, 163–164; (c) Kamikawa, T.; Uozumi, Y.; Hayashi, T. *Tetrahedron Lett.* **1996**, *37*, 3161–3164.
219. Yang, L.-M.; Huang, L.-F.; Luh, T.-Y. *Org. Lett.* **2004**, *6*, 1461–1463.
220. Madec, D.; Pujol, S.; Henryon, V.; Férézou, J. P. *Synlett* **1995**, 435–438.
221. Soderquist, J. A.; Matos, K.; Rane, A.; Ramos, J. *Tetrahedron Lett.* **1995**, *36*, 2401–2402.
222. Fürstner, A.; Seidel, G. *Tetrahedron* **1995**, *51*, 11165–11176.
223. Soderquist, J. A.; Rane, A.; Matos, K.; Ramos, J. *Tetrahedron Lett.* **1995**, *36*, 6847–6850.
224. Fürstner, A.; Nikolakis, K. *Liebigs Ann.* **1996**, 2107–2113.
225. Castanet, A.-S.; Colobert, F.; Schlama, T. *Org. Lett.* **2000**, *2*, 3559–3561.
226. Oh, C. H.; Jung, S. H. *Tetrahedron Lett.* **2000**, *41*, 8513–8516.

227. Chen, H.; Deng, M.-Z. *J. Organomet. Chem.* **2000**, *603*, 189–193.
228. Molander, G. A.; Katona, B. W.; Machrouhi, F. *J. Org. Chem.* **2002**, *67*, 8416–8423.
229. Negishi, E. *Aspects Mech. Organomet. Chem.* **1978**, 285–317.
230. Negishi, E. In *Organozinc Reagents: A Practical Approach*; Knochel, P.; Jones, P., Eds.; Oxford University Press: Oxford, 1999; pp 213–243.
231. Crisp, G. T.; Turner, P. D.; Stephens, K. A. *J. Organomet. Chem.* **1998**, *570*, 219–224.
232. Abarbri, M.; Parrain, J.-L.; Cintrat, J.-C.; Duchêne, A. *Synthesis* **1996**, 82–86.
233. Negishi, E.; Liu, F.; Choueiry, D.; Mohamud, M. M.; Silveira, A., Jr.; Reeves, M. *J. Org. Chem.* **1996**, *61*, 8325–8328.
234. Negishi, E.-i.; Tan, Z.; Liou, S.-Y.; Liao, B. *Tetrahedron* **2000**, *56*, 10197–10207.
235. Shi, J.; Zeng, X.; Negishi, E.-i. *Org. Lett.* **2003**, *51*, 825–1828.
236. Negishi, E.; Qian, M.; Zeng, F.; Anastasia, L.; Babinski, D. *Org. Lett.* **2003**, *5*, 1597–1600.
237. Tietze, L. F.; Görlitzer, J. *Synthesis* **1997**, 877–885.
238. Liu, F.; Negishi, E. *J. Org. Chem.* **1997**, *62*, 8591–8594.
239. Eberhard, M. R.; Wang, Z.; Jensen, C. M. *Chem. Commun.* **2002**, 818–819.
240. Rodríguez, D.; Castedo, L.; Saá, C. *Synlett* **2004**, 783–786.
241. (a) Rubin, Y.; Parker, T. C.; Khan, S. I.; Holliman, C. L.; McElvany, S. W. *J. Am. Chem. Soc.* **1996**, *118*, 5308–5309; (b) Bartik, B.; Dembinski, R.; Bartik, T.; Arif, A. M.; Gladysz, J. A. *New J. Chem.* **1997**, *21*, 739–750.
242. (a) Chodkiewicz, W.; Cadiot, P. *Compt. Rend. Hebd. Seances Acad. Sci.* **1955**, *241*, 1055–1057; (b) Chodkiewicz, W. *Ann. Chim. Paris* **1957**, *2*, 819–869; (c) Cadiot, P.; Chodkiewicz, W. In *Chemistry of Acetylenes*; Viehe, H. G., Ed.; Marcel Dekker: New York, 1969; p 697, 647.
243. Marino, J. P.; Nguyen, H. N. *J. Org. Chem.* **2002**, *67*, 6841–6844.
244. Yun, H.; Danishefsky, S. J. *J. Org. Chem.* **2003**, *68*, 4519–4522.
245. Zheng, G.; Lu, W.; Cai, J. *J. Nat. Prod.* **1999**, *62*, 626–628.
246. De Meijere, A.; Kozhushkov, S. I. *Chem. Eur. J.* **2002**, *8*, 3195–3203.
247. Bell, M. L.; Chiechi, R. C.; Johnson, C. A.; Kimball, D. B.; Matzger, A. J.; Wan, W. B.; Weakly, T. J. R.; Haley, M. M. *Tetrahedron* **2001**, *57*, 3507–3520.
248. Steffen, W.; Laskoski, M.; Collins, C.; Collins, G.; Bunz, U. H. F. *J. Organomet. Chem.* **2001**, *630*, 132–138.
249. Amatore, C.; Blart, E.; Genêt, J. P.; Jutand, A.; Lemaire-Audoire, S.; Savignac, M. *J. Org. Chem.* **1995**, *60*, 6829–6839.
250. Alami, M.; Ferri, F. *Tetrahedron Lett.* **1996**, *37*, 2763–2766.
251. Alzeer, J.; Vasella, A. *Helv. Chim. Acta* **1995**, *78*, 177–193.
252. Grignard, V. *Compt. Rend. Acad. Sci. Paris* **1900**, *130*, 1322–1324.
253. Tamao, K.; Sumitami, K.; Kumada, M. *J. Am. Chem. Soc.* **1972**, *94*, 4374–4376.
254. Corriu, R. J. P.; Masse, J. P. *J. Chem. Soc. Chem. Commun.* **1972**, 144–145.
255. Tamao, K. *J. Organomet. Chem.* **2002**, *653*, 23–26.
256. Prévost, C. *Bull. Soc. Chim.* **1931**, *49*, 1372–1381.
257. Knochel, P.; Dohle, W.; Gommermann, N.; Kneisel, F. F.; Fopp, F.; Korn, T.; Sapountzis, I.; Vu, V. A. *Angew. Chem. Int. Ed.* **2003**, *42*, 4302–4320.
258. Boudier, A.; Bromm, L. O.; Lotz, M.; Knochel, P. *Angew. Chem. Int. Ed.* **2000**, *39*, 4414–4425.
259. Böhm, V. P. W.; Weskanmp, T.; Gstöttmayr, C. W. K.; Herrmann, W. A. *Angew. Chem. Int. Ed.* **2000**, *39*, 1602–1604.
260. Li, G. Y.; Marshall, W. J. *Organometallics* **2002**, *21*, 590–591.
261. Shimada, T.; Cho, Y.-H.; Hayashi, T. *J. Am. Chem. Soc.* **2002**, *124*, 13396–13397.
262. Cho, Y.-H.; Kina, A.; Shimada, T.; Hayashi, T. *J. Org. Chem.* **2004**, *69*, 3811–3823.
263. Hölzer, B.; Hoffmann, R. W. *Chem. Commun.* **2003**, 732–733.
264. Terao, J.; Watanabe, H.; Ikuni, A.; Kuniyasu, H.; Kambe, N. *J. Am. Chem. Soc.* **2002**, *124*, 4222–4223.
265. Terao, J.; Ikumi, A.; Kuniyasu, H.; Kambe, N. *J. Am. Chem. Soc.* **2003**, *125*, 5646–5647.
266. Terao, J.; Todo, H.; Watanabe, H.; Ikuni, A.; Kambe, N. *Angew. Chem. Int. Ed.* **2004**, *43*, 6180–6182.
267. Miller, J. A.; Dankwardt, J. W. *Tetrahedron Lett.* **2003**, *44*, 1907–1910.
268. Cho, C.-H.; Yun, H.-S.; Park, K. J. *J. Org. Chem.* **2003**, *68*, 3017–3025.
269. Dankwardt, J. W. *Angew. Chem. Int. Ed.* **2004**, *43*, 2428–2432.
270. Tamura, M.; Kochi, J. K. *J. Am. Chem. Soc.* **1971**, *93*, 1487–1489.
271. Cahiez, G.; Avedissian, H. *Synthesis* **1998**, 1199–1205.
272. Dohle, W.; Kopp, F.; Cahiez, G.; Knochel, P. *Synlett* **2001**, 1901–1904.
273. Seck, M.; Franck, X.; Hocquemiller, R.; Figadère, B.; Peyrat, J.-F.; Provot, O.; Brion, J.-D.; Alami, M. *Tetrahedron Lett.* **2004**, *451*, 881–1884.
274. Dos Santos, M.; Franck, X.; Hocquemiller, R.; Figadère, B.; Peyrat, J.-F.; Provot, O.; Brion, J.-D.; Alami, M. *Synlett* **2004**, 2697–2700.
275. Nagano, T.; Hayashi, T. *Org. Lett.* **2004**, *6*, 1297–1299.
276. Nakamura, M.; Matsuo, K.; Ito, S.; Nakamura, E. *J. Am. Chem. Soc.* **2004**, *126*, 3686–3687.
277. (a) Aleandri, L. E.; Bogdanović, B. In *Active Metals: Preparation, Characterization, Applications*; Fürstner, A., Ed.; VCH: Weinheim, 1996; pp 299–338; (b) Aleandri, L. E.; Bogdanović, B.; Bons, P.; Dürr, C.; Gaidies, A.; Hartwig, T.; Huckett, S. C.; Lagarden, M.; Wilczok, U.; Brand, R. A. *Chem. Mater.* **1995**, *7*, 1153–1170.
278. Fürstner, A.; Leitner, A. *Angew. Chem. Int. Ed.* **2002**, *41*, 609–612.
279. Fürstner, A.; Leitner, A.; Méndez, M.; Krause, H. *J. Am. Chem. Soc.* **2002**, *124*, 13856–13863.
280. Scheiper, B.; Bonnekessel, M.; Krause, H.; Fürstner, A. *J. Org. Chem.* **2004**, *69*, 3943–3949.
281. Fürstner, A.; De Souza, D.; Parra-Rapado, L.; Jensen, J. T. *Angew. Chem. Int. Ed.* **2003**, *42*, 5358–5360.
282. Seidel, G.; Laurich, D.; Fürstner, A. *J. Org. Chem.* **2004**, *69*, 3950–3952.
283. Bedford, R. B.; Bruce, D. W.; Frost, R. M.; Goodby, J. W.; Hird, M. *Chem. Commun.* **2004**, 2822–2823.
284. Martin, R.; Fürstner, A. *Angew. Chem. Int. Ed.* **2004**, *43*, 3955–3957.
285. Huang, J.; Nolan, S. P. *J. Am. Chem. Soc.* **1999**, *121*, 9899, 9890.
286. Dumouchel, S.; Mongin, F.; Trécourt, F.; Quéguiner, G. *Tetrahedron Lett.* **2003**, *44*, 3877–3880.
287. Frisch, A. C.; Shaikh, N.; Zapf, A.; Beller, M. *Angew. Chem. Int. Ed.* **2002**, *41*, 4056–4059.
288. Frisch, A. C.; Rataboul, F.; Zapf, A.; Beller, M. *J. Organomet. Chem.* **2003**, *687*, 403–409.
289. Uemura, M.; Takayama, Y.; Sato, F. *Org. Lett.* **2004**, *6*, 5001–5004.
290. Horibe, H.; Fukuda, I.; Kondo, K.; Okuno, H.; Murakami, Y.; Aoyama, T. *Tetrahedron* **2004**, *60*, 10701–10709.
291. Baduri, F.; Colangiuli, D.; Farinola, G. M.; Naso, F. *Eur. J. Org. Chem.* **2002**, 2785–2791.
292. Dohle, W.; Lindsay, D. M.; Knochel, P. *Org. Lett.* **2001**, *3*, 2871–2873.
293. Korn, T. J.; Cahiez, G.; Knochel, P. *Synlett* **2003**, 1892–1894.
294. Tsuji, T.; Yorimitsu, H.; Oshima, K. *Angew. Chem. Int. Ed.* **2002**, *41*, 4137–4139.
295. Ohmiya, H.; Tsuji, T.; Yorimitsu, H.; Oshima, K. *Chem. Eur. J.* **2004**, *10*, 5640–5648.
296. Pauling, L. C. *The Nature of the Chemical Bond*, 3rd ed.; Cornell University Press: Ithaca, 1960.

297. Yoshida, J.; Tamao, K.; Yamamoto, H.; Kakui, T.; Uchida, T.; Kumada, M. *Organometallics* **1982**, *1*, 542–549.
298. Hatanaka, Y.; Hiyama, T. *J. Org. Chem.* **1988**, *53*, 918.
299. (a) Hiyama, T.; Shirakawa, E. *Top. Curr. Chem.* **2002**, *219*, 61–85; (b) Dennmark, S. E.; Sweis, R. F. *Acc. Res. Chem.* **2002**, *35*, 835–846; (c) Dennmark, S. E.; Sweis, R. F. *Chem. Pharm. Bull.* **2002**, *50*, 1531–1541; (d) Hiyama, T. *J. Organomet. Chem.* **2002**, *653*, 58–61; (e) Spivey, A. C.; Gripton, C. J. G.; Hannah, J. P. *Curr. Org. Synt.* **2004**, *1*, 211–226; (f) Hiyama, T.; Hatanaka, Y. *Pure Appl. Chem.* **1994**, *66*, 1471–1478; (g) Horn, K. A. *Chem. Rev.* **1995**, *95*, 1317–1350.
300. Denmark, S. E.; Sweis, R. F.; Wehrli, D. *J. Am. Chem. Soc.* **2004**, *126*, 4865–4875.
301. Denmark, S. E.; Sweis, R. F. *J. Am. Chem. Soc.* **2004**, *126*, 4876–4882.
302. Gouda, K.; Hagiwara, E.; Hatanaka, Y.; Hiyama, T. *J. Org. Chem.* **1996**, *61*, 7232–7233.
303. Mowery, M. E.; DeShong, P. *J. Org. Chem.* **1999**, *64*, 1684–1688.
304. Riggleman, S.; DeShong, P. *J. Org. Chem.* **2003**, *68*, 8106–8109.
305. Lee, H. M.; Nolan, S. P. *Org. Lett.* **2000**, *2*, 2053–2055.
306. Lee, J.-Y.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 5616–5617.
307. Powell, D. A.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *126*, 7788–7789.
308. Hojo, M.; Murakami, C.; Aihara, H.; Komori, E.; Kohra, S.; Tominaga, Y.; Hosomi, A. *Bull. Soc. Chim. Fr.* **1995**, *132*, 499–508.
309. Seganish, W. M.; DeShong, P. *J. Org. Chem.* **2004**, *69*, 1137–1143.
310. (a) Denmark, S. E.; Griedel, B. D.; Coe, D. M.; Schnute, M. E. *J. Am. Chem. Soc.* **1994**, *116*, 7026–7043; (b) Denmark, S. E.; Griedel, B. D. *J. Org. Chem.* **1994**, *59*, 5136–5138.
311. Denmark, S. C.; Choi, J. Y. *J. Am. Chem. Soc.* **1999**, *121*, 5821–5822.
312. Denmark, S. E.; Wang, Z. *Synthesis* **2000**, *7*, 999–1003.
313. Denmark, S. E.; Wang, Z. *J. Organomet. Chem.* **2001**, *624*, 372–375.
314. (a) Denmark, S. E.; Pan, W. *Org. Lett.* **2001**, *3*, 61–64; (b) Denmark, S. E.; Pan, W. *Org. Lett.* **2003**, *5*, 1119–1122.
315. Denmark, S. E.; Kobayashi, T. *J. Org. Chem.* **2003**, *68*, 5153–5159.
316. Denmark, S. E.; Yang, S.-M. *Org. Lett.* **2001**, *3*, 1749–1752.
317. Denmark, S. E.; Yang, S.-M. *J. Am. Chem. Soc.* **2002**, *124*, 2102–2103.
318. Denmark, S. E.; Yang, S.-M. *J. Am. Chem. Soc.* **2004**, *126*, 12432–12440.
319. (a) Itami, K.; Nokami, T.; Yoshida, J.-I. *J. Am. Chem. Soc.* **2001**, *123*, 5600–5601; (b) Itami, K.; Nokami, T.; Ishimura, Y.; Mitsudo, K.; Kamei, T.; Yoshida, J. *J. Am. Chem. Soc.* **2001**, *123*, 11577–11585; (c) Itami, K.; Mitsudo, K.; Nokami, T.; Kamei, T.; Koike, T.; Yoshida, J. *J. Organomet. Chem.* **2002**, *653*, 105–113.
320. Heck, R. F. In Trost, B. M., Ed.; *Comprehensive Organic Synthesis;* Vol. 4 Pergamon: New York, 1991; Chapter 4.3.
321. Hagiwara, E.; Gouda, K.; Hatanaka, Y.; Hiyama, T. *Tetrahedron Lett.* **1997**, *38*, 439–442.
322. Brescia, M.-R.; DeShong, P. *J. Org. Chem.* **1998**, *63*, 3156–3157.
323. Mowery, M. E.; DeShong, P. *J. Org. Chem.* **1999**, *64*, 3266–3270.
324. Hirabayashi, K.; Mori, A.; Kawashima, J.; Suguro, M.; Nishihara, Y.; Hiyama, T. *J. Org. Chem.* **2000**, *65*, 5342–5349.
325. Itami, K.; Mineno, M.; Kamei, T.; Yoshida, J. *Org. Lett.* **2002**, *4*, 3635–3638.
326. Denmark, S. E.; Sweis, R. F. *J. Am. Chem. Soc.* **2001**, *123*, 6439–6440.
327. Denmark, A. E.; Ober, M. H. *Org. Lett.* **2003**, *5*, 1357–1360.
328. Knochel, P.; Jones, P., Eds.; *Organozinc Reagents*; Oxford University Press: Oxford, 1999.
329. (a) Mutele, I.; Suna, E. *Tetrahedron Lett.* **2004**, *45*, 3909–3912; (b) Walla, P.; Kappe, C. O. *Chem. Commun.* **2004**, 564–565; (c) Krascsenicsová, K.; Walla, P.; Kasák, P.; Uray, G.; Kappe, C. O.; Putala, M. *Chem. Commun.* **2004**, 2606–2607.
330. (a) Ku, Y.-Y.; Grieme, T.; Raje, P.; Sharma, P.; Morton, H. E.; Rozema, M.; King, S. A. *J. Org. Chem.* **2003**, *68*, 3238–3240; (b) Hu, T.; Panek, J. S. *J. Am. Chem. Soc.* **2002**, *124*, 11368–11378; (c) Duffey, M. O.; LeTiran, A.; Morken, J. P. *J. Am. Chem. Soc.* **2003**, *125*, 1458–1459; (d) Inoue, M.; Yokota, W.; Murugesh, M. G.; Izuhara, T.; Katoh, T. *Angew. Chem. Int. Ed.* **2004**, *43*, 4207–4209; (e) Sorg, A.; Brückner, R. *Angew. Chem. Int. Ed.* **2003**, *43*, 4523–4526; (f) Aïsa, C.; Riveiros, R.; Ragot, J.; Fürstner, A. *J. Am. Chem. Soc.* **2003**, *125*, 15512–15520; (g) Corrêa, I. R.; Pilli, R. A. *Angew. Chem. Int. Ed.* **2003**, *42*, 3017–3020; (h) Agharahimi, M. R.; LeBel, T. *J. Org. Chem.* **1995**, *60*, 1856–1863; (i) Bach, T.; Bartels, M. *Synlett* **2001**, 1284–1286; (j) Manley, P. W.; Acemoglu, M.; Marterer, W.; Pachinger, W. *Org. Process Res. Dev.* **2003**, *7*, 436–445; (k) Zeng, F.; Negishi, E. *Org. Lett.* **2001**, *3*, 719–722; (l) Thompson, C. F.; Jamison, T. F.; Jacobson, E. N. *J. Am. Chem. Soc.* **2001**, *123*, 9974–9983; (m) Pour, M.; Negishi, E. *Tetrahedron Lett.* **1997**, *38*, 525–528; (n) Negishi, E.; Liou, S.-Y.; Xu, C.; Huo, S. *Org. Lett.* **2002**, *4*, 261–264; (o) Matsuo, G.; Kawamura, K.; Hori, N.; Matsukura, H.; Nakata, T. *J. Am. Chem. Soc.* **2004**, *126*, 14374–14376.
331. Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 2719–2724.
332. Milne, J. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2004**, *126*, 13028–13032.
333. Wu, J.; Liao, Y.; Yang, Z. *J. Org. Chem.* **2001**, *66*, 3642–3645.
334. Ma, S.; Ren, H.; Wei, Q. *J. Am. Chem. Soc.* **2003**, *125*, 4817–4830.
335. Cotton, H. K.; Huerta, F. F.; Bäckvall, J.-E. *Eur. J. Org. Chem.* **2003**, 2756–2763.
336. Pedersen, H. L.; Johannsen, M. *J. Org. Chem.* **2002**, *67*, 7982–7994.
337. Wang, D.; Zhang, Z. *Org. Lett.* **2003**, *5*, 4645–4648.
338. Peyrat, J.-F.; Thomas, E.; L'Hermite, N.; Alami, M.; Brion, J.-D. *Tetrahedron Lett.* **2003**, *44*, 6703–6707.
339. Sapountzis, I.; Dube, H.; Knochel, P. *Adv. Synth. Cat.* **2004**, *346*, 709–712.
340. Zeni, G.; Alves, D.; Braga, A. L.; Stefani, H. A.; Nogueira, C. W. *Tetrahedron Lett.* **2003**, *45*, 4823–4826.
341. Dunn, M. J.; Jackson, R. F. W. *Tetrahedron* **1997**, 13905–13914.
342. Dexter, C. S.; Jackson, R. F. W.; Elliot, J. *J. Org. Chem.* **1999**, *64*, 7579–7585.
343. Giovannini, R.; Stüdemann, T.; Dussin, G.; Knochel, P. *Angew. Chem. Int. Ed.* **1998**, *37*, 2387–2390.
344. Devasagayaraj, A.; Stüdemann, T.; Knochel, P. *Angew. Chem. Int. Ed.* **1995**, *34*, 2723–2725.
345. Jensen, A. E.; Knochel, P. *J. Org. Chem.* **2002**, *67*, 79–85.
346. Zhou, J.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 14726–14727.
347. Zhou, J.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 12527–12530.
348. Herbert, J. M. *Tetrahedron Lett.* **2004**, 817–819.
349. Zeng, X.; Hu, Q.; Qian, M.; Negishi, E. *J. Am. Chem. Soc.* **2003**, *125*, 13636–13637.
350. Zeng, X.; Qian, M.; Hu, Q.; Negishi, E.-I. *Angew. Chem. Int. Ed.* **2004**, *43*, 2259–2263.