Cross coupling reactions catalyzed by (NHC)Pd(II) complexes

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Abstract: This review is focused on new developments reported during the last 3 years concerning the catalytic performances of in situ formed or preformed NHC–Pd(II) complexes (NHC: *N*-heterocyclic carbene) for cross-coupling reactions such as Heck–Mizoraki (often shortened to the Heck reaction), Kumada, Negishi, Suzuki–Miyaura (often shortened to the Suzuki reaction), Sonogashira and Hiyama couplings, and the Buchwald–Hartwig aminations, which are extremely powerful in the formation of C–C and C–heteroatom bonds. Due to the great number of publications and limited space here, we made a special attempt to compile the relevant data in tables, which we hope will serve as a guide for chemists interested in these reactions. The syntheses of the precatalysts and the generally accepted reaction mechanisms are also briefly described.

Key words: *N*-heterocyclic carbene, palladium, cross-coupling reaction

1. Introduction

The awarding of the 2010 Nobel Prize jointly to Heck, Suzuki, and Negishi clearly reflects the importance of palladium-catalyzed cross-coupling reactions in chemistry.[1] They provide chemists with a very versatile tool for the construction of carbon–carbon and carbon–heteroatom bonds in the synthesis of pharmaceuticals, agrochemicals, and organic electronic materials.[2,3] Although in the early 1900s Ullmann reported copper catalyzed C–C and C–N bond forming reactions in which a stoichiometric amount of copper is required,[4] prior to the advent of TM catalysts, cross-coupling reactions were limited to a few examples involving main group organometallics (M = Mg, Li, Na, and K). These nucleophiles react with unhindered alkyl (sp^3) elecrophiles. In contrast, unsaturated carbons (sp^2–sp^2 or sp^2–sp bonds) were very limited. Until 1972, only simple metal salts had been employed as catalysts to solve these problems. For example, in the coupling of iodobenzene with alkenes, both $PdCl_2$ (1 mol%) and $Pd(OAc)_2$ (1 mol%) were used by Mizoroki[5] and Heck,[6] respectively (Eq. (1)).

$$\text{(1)}$$
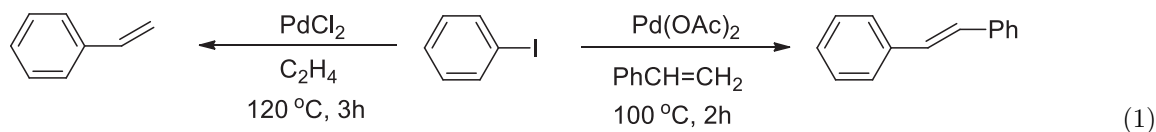
The first cross coupling involving an aryl and vinyl Grignard reagent was reported independently by

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Kumada and Corriu in 1972 by the use of nickel/phosphane-containing catalysts.[7,8] The discovery of beneficial effects of using phosphane ligands {as in $[Pd(PPh_3)_4]$, $[Pd(OAc)_2(PPh_3)_2]$, and $[PdCl_2(PPh_3)_2]$} by four independent groups in 1975 had a striking impact on the progress of homogeneous catalysis.[9−12] Subsequently, many additional coupling approaches have been developed. Negishi and Suzuki reported their respective ideas in 1976 and 1979 for the use of organozinc[13] and organoboron[14] reagents as organometallic components. During the following four decades, the development on palladium catalyzed cross-coupling reactions has progressed enormously. Researchers have increasingly aimed for more challenging substrates, with lower catalyst loading and greater selectivity, under increasingly mild conditions or with greener solvents like water.

With the exception of Kumada coupling, carbon–carbon coupling reactions have the ability to permit a number of functional groups such as ketone, aldehyde, amino, cyano, carbonyl, hydroxyl, ester, or nitro groups, thus avoiding the need for protection and deprotection of functional groups during organic transformations. The catalytic system used for an efficient coupling reaction consists of a palladium source, ligand(s), base, and solvent. Generally, phosphane ligands are employed in these reactions, since they play a crucial role in stabilization and in situ generation of Pd(0) species from Pd(II) complexes. Moreover, a major restriction on palladium catalyzed coupling processes has been the poor reactivity of cheaper and more readily available aryl bromides and chlorides in comparison with more active aryl iodides. Therefore, the search for efficient catalysts for the cross couplings of deactivated aryl bromides and, eventually, activated aryl chlorides is under way.

Efforts to find more stable and effective catalysts have often focused on ligands that are bulky and strong donors, as these ligands tend to bind the palladium tightly and thus prevent catalyst deactivation via ligand loss. Because of the high cost, toxicity, and thermal instability of phosphane complexes, various phosphane-free catalytic systems have been introduced as less complicated and environmentally more desirable alternatives to the original Pd–phosphane catalysts. With these facts in mind, during the last two decades N-heterocyclic carbenes (NHCs) have generated great attention. Several authorities up to 2013 have reviewed the above-mentioned advances from different aspects.[15−24]

1.1. NHC ligands

Earlier, NHCs were considered simple phosphane mimics. However, NHCs have stronger σ-donor and exhibit poor π-acceptor properties than tertiary phosphanes, which explains the fact that the metal–carbene bond is stronger and shorter than the M–PR$_3$ bonds. As a consequence, NHCs display higher thermal stability than phosphane complexes. Moreover, NHC complexes exhibit higher stability towards oxygen and moisture. The excess ligand requirement in catalytic systems, due to the tendency for the phosphanes to oxidize in air, is reduced.

The location of the nitrogen atoms in the ring is decisive on the electronic property of the NHCs and the nitrogen atoms stabilize the carbene via overlap between the lone pairs on the nitrogen atoms and the free orbital of the carbene. The increase in electron density on the metal caused by the NHC ligand will labilize the M–L bond *trans* to M–NHC, facilitating dissociation of the L ligand, which is needed for catalysis. The experimental evidence that NHC–metal catalysts exceed their phosphane-based counterparts in both activity and scope is increasing. This is attributed to the combination of strong σ-donor, poor π-acceptor, and steric properties of NHCs.

NHCs are defined as singlet carbenes in which the divalent carbenic center is coupled directly with at least one N atom within the heterocycle. The most common NHCs are imidazole-2-ylidenes, containing 5-membered heterocyclic ring. Examples of the most frequently used NHC ligands in homogeneous catalysis are shown in Figure 1.
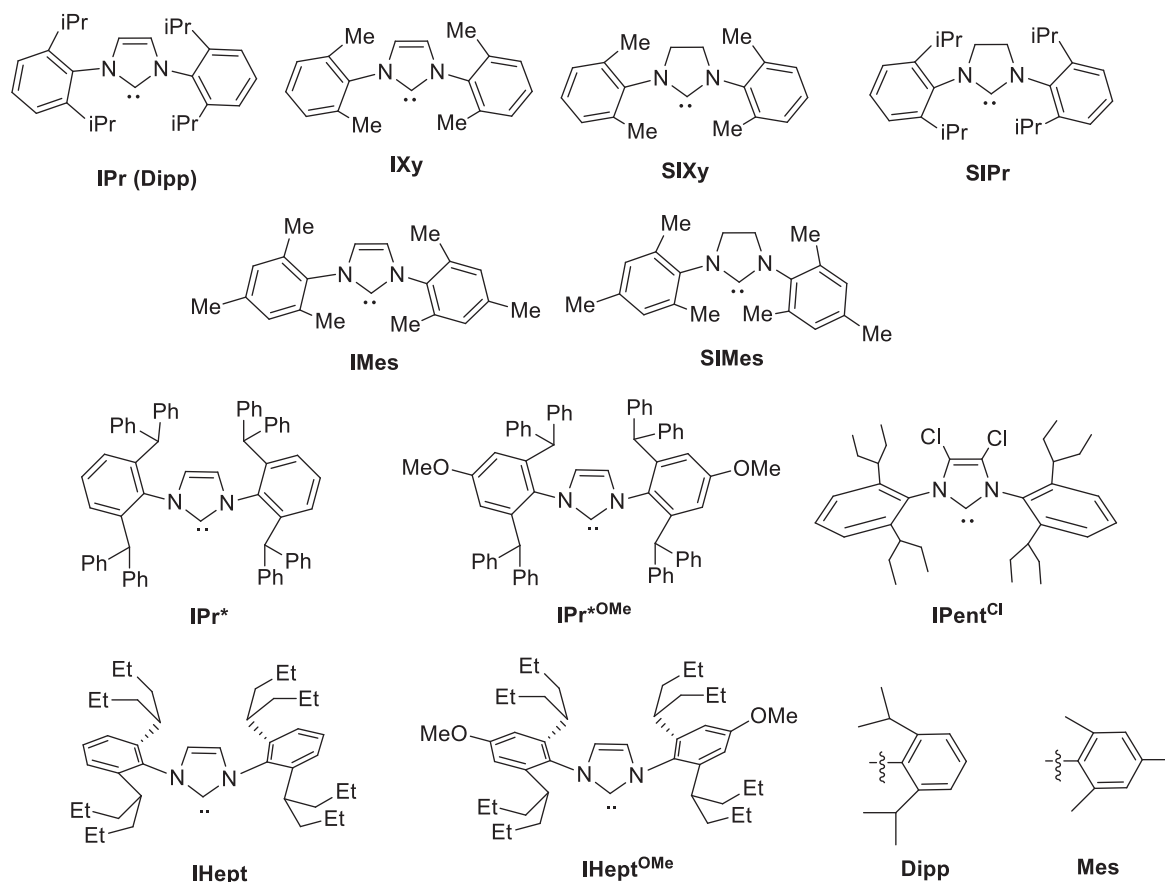
Figure 1.

NHC ligands have been studied extensively recently and are still of considerable interest due to their unique electronic properties and the ability to form shell-shaped ligands by appropriate N-substituents, which renders them useful alternatives to tertiary phosphane ligands. Their metal complexes are generally air and moisture stable, and they can be employed as catalysts for a variety coupling reactions. More recently, donor functionalized and NHC-pincer complexes have begun to attract much attention, as it was found that steric hindrance is an important factor for chemo- and stereoselectivity. The increased steric demand aids the reductive elimination step during catalysis and complexes of higher steric encumbrance may allow the synthesis and stabilization of low coordination complexes to facilitate oxidative addition.

Several methods for the synthesis of stable carbenes have been developed. For example, 1,1-elimination of HX from imidazolines generates the corresponding nucleophilic NHC. However, they are generally prepared by deprotonation of azol(in)ium salts. The most common coordination mode established for azole-based NHC ligands involves C-2 attachment. Moreover, NHC complexations through C-4/C-5 coordination for C-2 alkylated or nonalkylated NHCs are also known. The latter, stronger σ-donor than C-2 NHCs, are named abnormal NHCs (abbreviated as aNHC) and 1,2,3-triazol-5-ylidene (tzNHC) complexes are intensively studied, due to the ready availability of the precursor salt. A great range of N-substituents has been reported for NHC ligands, including bulky alkyl and aryl groups. There is also increasing interest to modify the 5-membered N,N-heterocycle to introduce more carbon or heteroatoms to tune the donating abilities of 5-NHCs. The extra carbon of the ring leads to the emergence of the "ring expanded NHCs, 6-NHC or 7-NHC" and N,S-NHCs, respectively.[25] For more comprehensive discussions of the synthesis and properties of stable carbenes, the reader is referred to the

reviews by Herrmann et al.[26] and Bertrand et al.[27] The most commonly used NHC ligands, with abbreviations, are given in Figure 1. These ligands and their easy conversions to other organic and organometallic derivatives are summarized in Scheme 1.
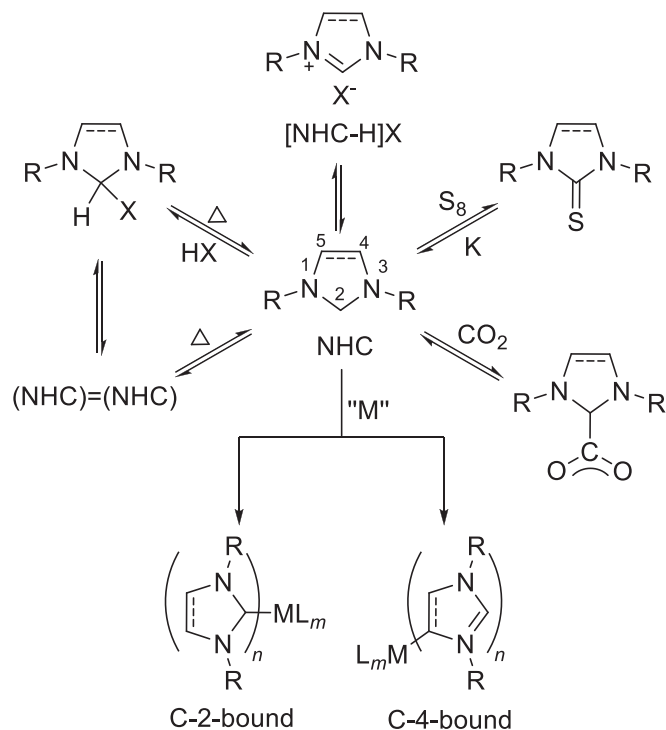
Scheme 1. Generation and reactivity of free (imidazole(in)-2-ylidene (NHC) with various electrophiles.
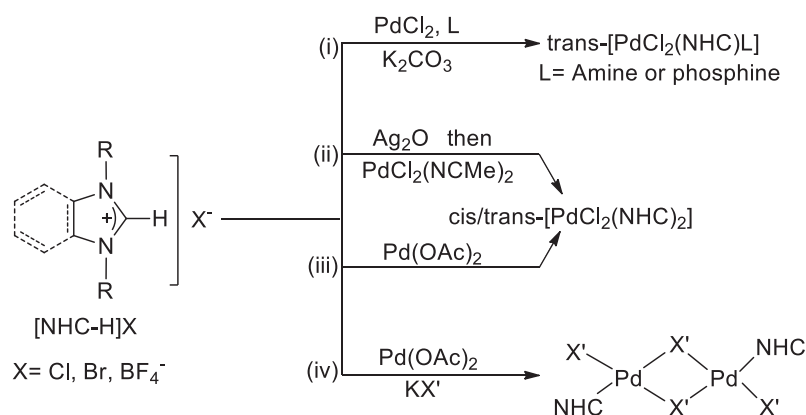
1.2. Synthesis of NHC–Pd(II) complexes

The synthesis of carbene transition metal complexes has been the focus of considerable attention due to their stability towards moisture, air, and heat and useful catalytic properties. Indeed, they display catalytic behavior superior to that of the corresponding phosphane complexes.

NHCs tend to form stable complexes with almost all of the transition metals; among them octahedral complexes with d^6 metals and square planar complexes with d^8 metals are widespread and in those complexes the NHC ligand is preferably coordinated *trans* to a π-acceptor ligand, as the *trans* effect of the strongly σ-donating NHC ligand is large.

NHC complexes may be generated using various methods[28−33] starting mostly from metals complexated to weakly coordination ligands such as alkenes, CO, and PR_3 or halide complexes.

The first reports of NHC complexes were published in the early 1970s by Wanzlick, Öfele, and Lappert.[34−36] However, their promising applications were not explored until the discovery of an isolable NHC in 1991 by Arduengo et al.[37] The first applications of Ru(II) and Pd(II) complexes as catalysts revived interest, and since then the number of reports published has increased exponentially. The formation of NHC–Pd(II) complexes can be carried out in two subsequent steps: deprotonation and complexation. Nonbulky imidazolinium and benzimidazolium yield the electron-rich olefin or the Wanzlick dimer, NHC = NHC, which have been used as precursor for the preparation of metal complexes. Since the NHC dimers and free NHCs are sensitive to air and moisture, they are isolated only for special studies. Instead they are converted directly to the desired com-

plexes. The majority of synthetic routes to mono- or bis NHC–Pd(II) complexes directly employ ([NHC–H]X) precursors and metal salts. Their preparation is achieved in two ways: (i) Use of an external base such as NaH, KOBu^t KN(SiMe$_3$)$_2$, NaHCO$_3$, or Ag$_2$O that deprotonates the salt at the 2-position to yield the corresponding NHC. In the presence of metal precursors, the free NHCs replace the ligands like alkenes, nitriles, CO, PR$_3$, and halides. (ii) The reaction of the azoliums with a metal salt bearing basic ligans like OAc$^-$ and acac$^-$ is a very common method. The application of these procedures to the commercially available PdCl$_2$ or Pd(OAc)$_2$, depending on the stoichiometry, produces high yields of mono-, bis-, or bimetallic (NHC)–Pd(II) complexes (Scheme 2, routes i–iv). (iii) Frequently, an NHC–Ag complex, synthesized by reacting Ag$_2$O with the azolium chloride, could be employed as transfer reagents. In the transmetalation reaction silver is replaced by Pd^{II}, which forms a more stable bond with the NHC and the precipitation of the silver salt is a driving force (route ii).

Scheme 2. General methodologies for the synthesis of mono-, bis-, and bimetallic NHC–Pd(II) complexes, used as catalyst in the cross-coupling reactions. Here [NHC-H]X is a convenient representation of imidazolium, imidazolinium (or dihydroimidazolium), and benzimidazolium salt in which the proton at the 2-position undergoes deprotonation with various bases.

Palladium–NHC complexes have frequently been reported to show high catalytic activity in C–C bond formation reactions. On the other hand, there is increasing interest in the chemistry of functionalized NHC carbenes in which a donating group is attached to a strongly bonded imidazolyl ring. In this context, a variety of heteroatom-functionalized carbene ligands containing phosphine, pyridine amido, ester, keto, or ether and oxazoline donor functions have been synthesized and, in some cases, used as the catalyst for a number of catalytic transformations. The combination of a strongly bonded carbene moiety with the appropriate donor function should allow for potential hemilability.
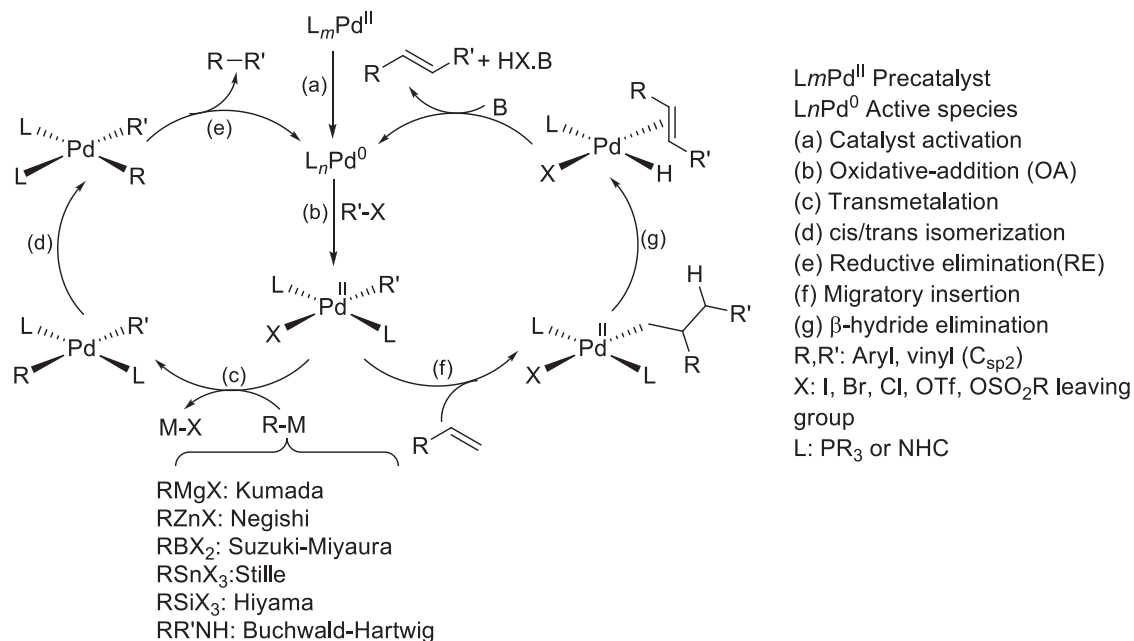
2. Cross-coupling reactions: R-X + R'-M → R-R' + MX

In the cross couplings, two different partners take part: a nucleophile, generally an aryl halide (R-X, also vinyl, allyl, or benzy halide are possible) and an electrophile, usually main group organometallics, R'-M, to yield unsymmetrical R-R'. In contrast, homocoupling reactions, like Ullmann reactions, involve two identical partners to give R-R or R'-R'. Depending on the nucleophilic partner used (an olefin or an organometallic compound), the couplings can be divided in two subclasses. Here M represents Mg (Kumada), Zn (Negishi), B (Suzuki), Sn (Stille), Si (Hiyama).

2.1. General mechanism for cross-coupling reactions

Mechanistic data about a particular metal-catalyzed reaction may be crucial because it can be used to develop very efficient catalysts. In that respect, there is one generalized cycle for the palladium catalyzed cross couplings, which is subject to minor variations depending on the reaction type. On the other hand, palladium is able to vary its oxidation state and coordination number and enters the cycle in an oxidation state of zero.

There are three basic steps in palladium-catalyzed coupling reactions: (i) oxidative addition of R-X to $L_m Pd(0)$, (ii) transmetalation (substitution), (iii) reductive elimination of R-R'. The cycle starts with oxidative addition of the C-X bond of organohalide (R-X) to the $L_m Pd(0)$ to form a Pd(II) complex, where L represents a neutral two-electron ligand such as PR_3 or NR_3 or an NHC, and the efficiency of the system has been achieved by changing the ligands around palladium. The first step is considered to be the rate-determining step and the couplings can be categorized into two subclasses based on the second step. Transmetalation with the main group organometallic reagent then follows, where the R group of the reagent replaces the halide anion on the palladium complex. With the help of the base, reductive elimination then gives the final coupled product, regenerates the catalyst, and the catalytic cycle can begin again. Before the third step, isomerization is necessary to bring the organic ligands next to each other into mutually cis positions (Scheme 3). Pd^{2+} is readily reduced to $L_m Pd(0)$ by ROH, NR_3, CO, alkenes, phosphanes, and main group organometallics. The Heck reaction does not involve a transmetalation step. Instead, a migratory insertion takes place (the coordinated alkene inserts into the Pd-R bond) and with the nucleophilic partners two different intermediates ($\|$-Pd-R and R-Pd-R') form.

Scheme 3. General catalytic cycles for Pd-catalyzed cross-coupling reactions.

β-Hydride elimination is a typical reaction for σ-bound alkyl complexes with hydrogens in the β position. It is usually not a desired reaction in catalysis, except for example in the coupling of aryl halides with olefins (Heck coupling). In other reactions such as the Negishi coupling of alkyl organozincs and alkyl bromides, it severely limits the development of efficient catalysts. The low reactivity of unactivated aryl chlorides, which are the most widely available and cheapest coupling partners of aryl halides, is attributed to the bond dissociation energy of the C–halide bonds. Comparison of these bonds (95×4.18 kJ mol^{-1} for C–Cl) (79×4.18 kJ

mol^{-1} for C–Br) or $(64 \times 4.18$ kJ $mol^{-1})$ indicates a good agreement with the difficulty for an aryl halide to add oxidatively to a less-electron-rich $LmPd(0)$ species. The steric hindrance of the ligand eases the reductive elimination and also stabilizes the coordinatively unsaturated $LmPd(0)$. The simplified and generally accepted catalytic cycle of a transition metal mediated reaction is outlined in Scheme 3.

It is the ligand, however, that aids the metal in its coordination properties and, thus, determines the catalytic efficiency of the complex. Through ligand variation, a high specificity of the metal center towards the incoming reaction partners can be tailored. Furthermore, the ligand should be able to stabilize the different coordination states and activate the zerovalent metal center towards the oxidative addition of the electrophile. Therefore, control of product selectivity can be achieved by careful selection of the ligand.

2.2. Heck reaction

The Heck reaction, one of the simplest and oldest methods of synthesizing various substituted olefins, is a cross-coupling reaction of an aryl halide with an alkene using palladium as a catalyst and a base. Like the other couplings, the cycle begins by the oxidative addition of the aryl halide to the palladium, which is followed by coordination and migratory insertion of the olefin to the palladium. Bond rotation then places the two groups *trans* to each other to relieve the steric strain. Subsequent β-hydride elimination results in a *trans* final product.[6,38]

The regioselectivity of the product is influenced by the olefin substitution: electron-withdrawing on the olefin prefers linear products. Mono- or 1,1-disubstituted alkenes are more reactive and as the substitution number in the alkene increases the reactivity decreases. There are only a few examples of trisubstituted alkenes that undergo cross coupling. Aprotic solvents, such as dimethylformamide (DMF), dimethyl sulfoxide (DMSO), or acetonitrile, are most frequently used. Tertiary amines or a sodium/potassium acetate, carbonate, or bicarbonate salt are used as a base. The first NHC–Pd catalyzed reaction, able to couple aryl bromides and aryl chlorides to alkenes in high yields, was applied by Herrmann et al. in 1995.[39] Since that report, increasing attention has been focused on their performances and influencing parameters. Palladium NHC complexes, used in Heck coupling reactions, are compiled in Figure 2.

The NHC–Pd complex **C1** was an efficient precatalyst for the monoarylation of terminal alkenes using K_3PO_4 as base in DMA. Both electron-rich and electron-deficient aryl iodides and bromides could be coupled with styrene or ethyl acrylate in good yield (Table 1, entries 1–7). This methodology has also been extended to the synthesis of unsymmetrical diarylated alkenes and the double arylation products were observed in good to excellent yields. The catalyst was not effective for aryl chloride.[40]

1,6-Hexylene-bridged NHC–Pd complex **C2** was tested as a catalyst for Heck couplings of aryl bromides with styrene, run in 1,4-dioxane as solvent and K_2CO_3 as the base in the presence of 10 mol% TBAB with a catalyst loading of 0.5 mol% complex in air. The *trans* isomer appeared to be the dominant conformation (Table 1, entries 8–11).[41] The complex **C2** also showed high activity in the Suzuki reactions in water (Table 8, entries 1–5).

Lin et al. focused on the catalytic performance of complexes **C3** and **C4** in Heck reactions of aryl chlorides with styrene.[42] The catalyst system is capable of delivering excellent *trans* product yield with aryl chlorides, which are known to be less reactive (Table 1, entries 12–15). Benzimidazole-derived complexes (**C4a–c**) exhibited better catalytic activity than imidazole-based complexes (**C3a–c**). Formation of palladium nanoparticles in the reaction mixture was confirmed by dynamic light scattering and transmission electron microscopy studies and a mercury poisoning experiment.
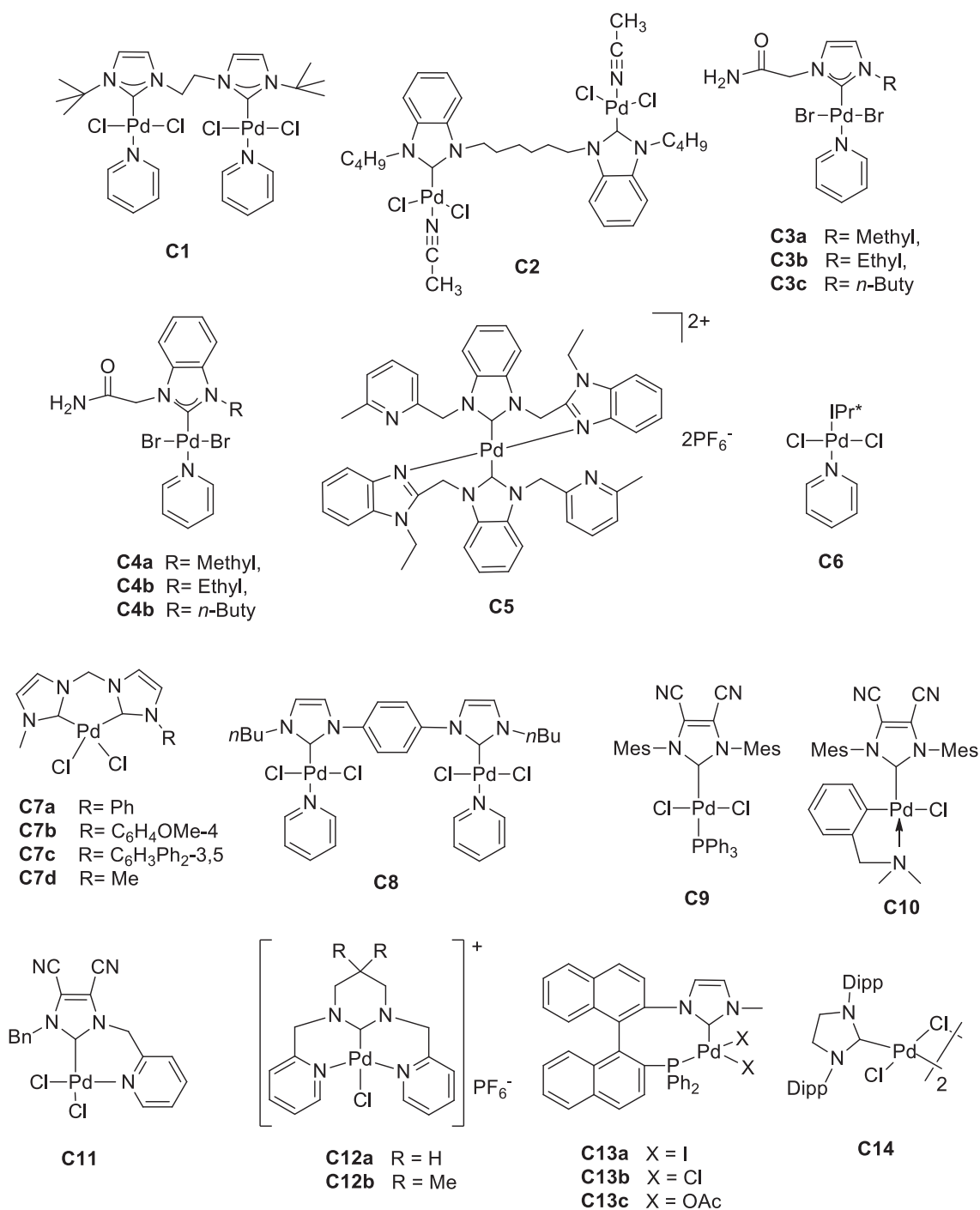
C1

C2

C3a R= Methyl,
C3b R= Ethyl,
C3c R= n-Buty

C4a R= Methyl,
C4b R= Ethyl,
C4b R= n-Buty

C5

C6

C7a R= Ph
C7b R= C$_6$H$_4$OMe-4
C7c R= C$_6$H$_3$Ph$_2$-3,5
C7d R= Me

C8

C9

C10

C11

C12a R = H
C12b R = Me

C13a X = I
C13b X = Cl
C13c X = OAc

C14

Figure 2.

The complexes **C5**, bearing benzimidazole and pyridine groups have been proved to be a highly efficient catalyst for the coupling reaction of aryl halides with various substituted acrylates under mild conditions in excellent yields (Table 1, entries 16–22).[43] Electron-deficient aryl bromides gave a slightly higher yield than electron-rich ones under the optimized conditions.

Table 1. Heck coupling reactions carried out using Pd–NHC catalysts.
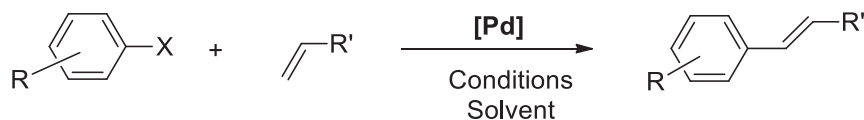
Entry	Catalyst	X	R	R'	Solvent	Conditions	Yield [%]	Ref.
1	**C1**	Br	H	Ph	DMA	1 mol% [Pd], K_3PO_4, TBAB, 110 °C, 5 h	84^b	40
2	**C1**	Br	4-OMe	Ph	DMA	1 mol% [Pd], K_3PO_4, TBAB, 110 °C, 5 h	95^b	40
3	**C1**	Br	4-COMe	Ph	DMA	1 mol% [Pd], K_3PO_4, TBAB, 110 °C, 5 h	82^b	40
4	**C1**	Br	4-F	Ph	DMA	1 mol% [Pd], K_3PO_4, TBAB, 110 °C, 5 h	86^b	40
5	**C1**	Br	4-OMe	CO_2Et	DMA	1 mol% [Pd], NaOAc, TBAB, 120 °C, 18 h	86^b	40
6	**C1**	I	4-Me	Ph	DMA	1 mol% [Pd], K_3PO_4, TBAB, 110 °C, 5 h	82^b	40
7	**C1**	Br	$4-C_{10}H_7$	Ph	DMA	1 mol% [Pd], K_3PO_4, TBAB, 110 °C, 5 h	97^b	40
8	**C2**	Br	H	Ph	Dioxane	0.5 mol% [Pd], K_2CO_3, TBAB, 110 °C, 12 h	81^b	41
9	**C2**	Br	4-OMe	Ph	Dioxane	0.5 mol% [Pd], K_2CO_3, TBAB, 110 °C, 8 h	92^b	41
10	**C2**	Br	4-Me	Ph	Dioxane	0.5 mol% [Pd], K_2CO_3, TBAB, 110 °C, 18 h	83^b	41
11	**C2**	Br	4-COMe	Ph	Dioxane	0.5 mol% [Pd], K_2CO_3, TBAB, 110 °C, 18 h	93^b	41
12	**C3a–c**	Cl	4-COMe	Ph	DMF	1 mol% [Pd], K_2CO_3, TBAB, 140 °C, 15 h	$90–97^b$	42
13	**C3a–c**	Cl	$4-NO_2$	Ph	DMF	1 mol% [Pd], K_2CO_3, TBAB, 140 °C, 15 h	$92–97^b$	42
14	**C4a–c**	Cl	$4-NO_2$	Ph	DMF	1 mol% [Pd], K_2CO_3, TBAB, 140 °C, 15 h	$> 99^b$	42
15	**C4a–c**	Cl	4-COMe	Ph	DMF	1 mol% [Pd], K_2CO_3, TBAB, 140 °C, 15 h	99^b	42
16	**C5**	Br	H	CO_2Et	DMF	1 mol% [Pd], K_2CO_3, 100 °C, 24 h	90^b	43
17	**C5**	Br	4-OMe	CO_2Et	DMF	1 mol% [Pd], K_2CO_3, 100 °C, 24 h	95^b	43
18	**C5**	Br	4-COMe	CO_2Me	DMF	1 mol% [Pd], K_2CO_3, 100 °C, 24 h	96^b	43
19	**C5**	Br	4-CHO	CO_2Et	DMF	1 mol% [Pd], K_2CO_3, 100 °C, 24 h	96^b	43
20	**C5**	Br	4-COMe	CO_2Et	DMF	1 mol% [Pd], K_2CO_3, 100 °C, 24 h	98^b	43
21	**C5**	Br	4-CHO	CO_2Et	DMF	1 mol% [Pd], K_2CO_3, 100 °C, 24 h	96^b	43
22	**C5**	Br	2-COMe	CO_2Et	DMF	1 mol% [Pd], K_2CO_3, 100 °C, 24 h	95^b	43
23	**C6**	Br	H	Ph	Dioxane	1 mol% [Pd], TEA, 110 °C, 8 h	75^b	44
24	**C6**	Br	4-Cl	4-ClPh	Dioxane	1 mol% [Pd], TEA, 110 °C, 7 h	80^b	44
25	**C6**	Br	4-Cl	4-FPh	Dioxane	1 mol% [Pd], TEA, 110 °C, 7 h	85^b	44
26	**C7a–d**	I	H	Ph	DMA	0.2 mol% [Pd], NEt_3, 110 °C, 24 h	$64–99^a$	45
27	**C8**	Br	H	Ph	DMAc	1 mol% [Pd], NEt_3, 100 °C, 8 h	98^a	46
28	**C8**	Br	4-OMe	Ph	DMAc	1 mol% [Pd], NEt_3, 100 °C, 8 h	87^a	46
29	**C8**	Br	4-F	Ph	DMAc	1 mol% [Pd], NEt_3, 100 °C, 8 h	99^a	46
30	**C9–C11**	Br	H	CO_2^nBu	DMF	0.1 mol% [Pd], K_2CO_3, TBAB 140 °C, 16 h	$98–100^a$	47
31	**C9–C11**	Br	4-COMe	CO_2^nBu	DMF	0.1 mol% [Pd], K_2CO_3, TBAB 140 °C, 16 h	$89–98^a$	47
32	**C9–C10**	Br	4-Me	CO_2^nBu	DMF	0.1 mol% [Pd], K_2CO_3, TBAB 140 °C, 16 h	$81–98^a$	47
33	**C12a–b**	Br	H	Ph	DMA	0.0125 mol% [Pd], NEt_3, 135 °C, 12 h	$86–88^b$	48
34	**C12a–b**	Br	4-Me	Ph	DMA	0.0125 mol% [Pd], NEt_3, 135 °C, 12 h	$75–78^b$	48
35	**C12a–b**	Br	H	CO_2Me	DMA	0.0125 mol% [Pd], NEt_3, 135 °C, 12 h	$93–95^b$	48
36	**C12a–b**	Br	4-Me	CO_2^nBu	DMA	0.0125 mol% [Pd], NEt_3, 135 °C, 12 h	$90–93^b$	48
37	**C12a–b**	Br	$4-C_{10}H_7$	CO_2^nMe	DMA	0.0125 mol% [Pd], NEt_3, 135 °C, 12 h	$84–87^b$	48
38	**C13a–c**	Br	4-Me	CO_2^nBu	DMAc	2 mol% [Pd], K_2CO_3, TBAB, 150 °C, 18 h	$76–89^b$	49
39	**C13a–c**	Br	4-F	CO_2^nBu	DMAc	2 mol% [Pd], K_2CO_3, TBAB, 150 °C, 18 h	$63–86^b$	49
40	**C14**	Br	4-OMe	Ph	DMF	100 ppm [Pd], $KHCO_3$, 140 °C, 20 h	91^b	50
41	**C14**	Br	4-Me	Ph	DMF	100 ppm [Pd], $KHCO_3$, 120 °C, 20 h	94^b	50
42	**C14**	Br	4-COMe	Ph	DMF	100 ppm [Pd], $KHCO_3$, 140 °C, 20 h	96^b	50
43	**C14**	Br	4-CHO	Ph	DMF	100 ppm [Pd], $KHCO_3$, 120 °C, 20 h	99^b	50
44	**C14**	Br	$4-C_{10}H_7$	Ph	DMF	100 ppm [Pd], $KHCO_3$, 120 °C, 20 h	96^b	50

[a]GC yield. [b]Yield of isolated product.

The complex **C6** efficiently catalyzed the Heck reaction with low catalyst loading (1.0 mol%).[44] The catalytic reactions proceed under aerobic conditions and a variety of aryl bromides and terminal alkenes have been examined for their generality (Table 1, entries 23–25). The complexes **C7a–d**, with a bidentate bis-NHC ligand having methyl and aryl substituents, showed catalytic activity in the Heck reaction of iodobenzene with styrene in DMA (Table 1, entry 26).[45] In all cases, the reactions afforded two products, *trans*-stilbene and geminal olefin, in a ratios of about 90:10.

Wang et al. reported the synthesis of dipalladium di-NHC complexes bridged with a rigid phenylene spacer (**C8**) and their use as catalysts for the Heck reaction.[46] The choice of solvents also has a great effect on the reaction. With DMAC as solvent, the yield and regioselectivity were both good. The arylation of styrene with different substituted bromobenzenes catalyzed by **C8** was also tested (Table 1, entries 27–29). The results show that the reactions with *p*-methoxybromobenzene and *p*-bromoflourobenzene gave high yields and good selectivity.

Baier et al. prepared stable precatalysts with π-acceptor carbenes. The new precatalysts showed high activity in the Heck reactions, giving good-to-excellent product yields with 0.1 mol% precatalyst.[47] The nanoparticle nature of the catalytically active species of **C9**, **C10**, and **C11** was confirmed by poisoning experiments with mercury and transmission electron microscopy. Precatalyst **C10** showed the best overall catalytic performance (Table 1, entries 30–32).

Yang et al. reported the synthesis, characterization, and catalytic activity of picolyl functionalized pincer six-membered NHC palladium complexes based on tetrahydropyrimidin-2-ylidenes.[48] **C12** showed high catalytic activity toward the Heck reaction of aryl bromides with acrylate/styrene, using Et_3N as base and DMA as solvent (Table 1, entries 33–37).

The complexes **C13a–c**, connected with different kinds of coordination anions, were applied in Heck reactions.[49] The acetate-coordinated NHC–palladium complex (**C13c**) exhibited better catalytic activity to afford the products in excellent yield under mild conditions. **C13a–c** also showed high activity in Suzuki reactions (Table 1, entries 38 and 39).

The commercially available complex $[Pd(\mu\text{-Cl})Cl(SIPr)]_2$ (**C14**) has been shown to be an excellent precatalyst for the Heck reaction involving aryl and heterocyclic bromides at catalyst loadings (20–200 ppm) (Table 1, entries 40–44).[50]

2.3. Kumada coupling

Kumada cross coupling is the reaction of an organohalide with an organomagnesium compound to give the coupled product using a palladium or nickel catalyst. The reaction is notable for being among the first reported catalytic cross-coupling methods. Despite the subsequent development of alternative reactions, the Kumada coupling continues to enjoy many large-scale applications in the pharmaceutical and electronic material industries.[7,8]

In contrast to the Suzuki or Negishi reactions, the Grignard reagent is directly employed as nucleophilic partner in Kumada coupling, (Scheme 5, route i). Thus, the synthetic procedure is shortened because the arylboronic acids used in Suzuki coupling are synthesized from their Grignard precursors (Scheme 5, ii and iii). The zinc reagent used in Negishi coupling is also prepared via a Grignard reagent.

Although alkyl Grignard reagents do not suffer from β-hydride elimination, Kumada couplings have limited functional group tolerance, which can be problematic in large-scale syntheses. For example, Grignard
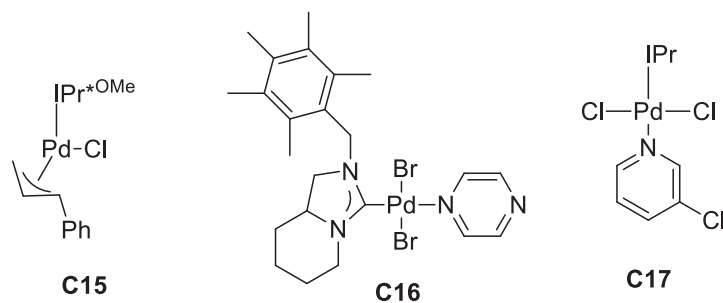
reagents are sensitive to protonolysis of alcohols. NHC–Pd complexes used in Kumada coupling reactions are given in Figure 3.
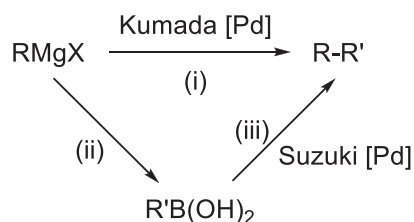
Scheme 4. Comparison of Kumada (i) and Suzuki procedures (ii and iii). i: X-Ar', ii B(OR)$_3$ then H$^+_{(aq)}$, iii X-Ar'.
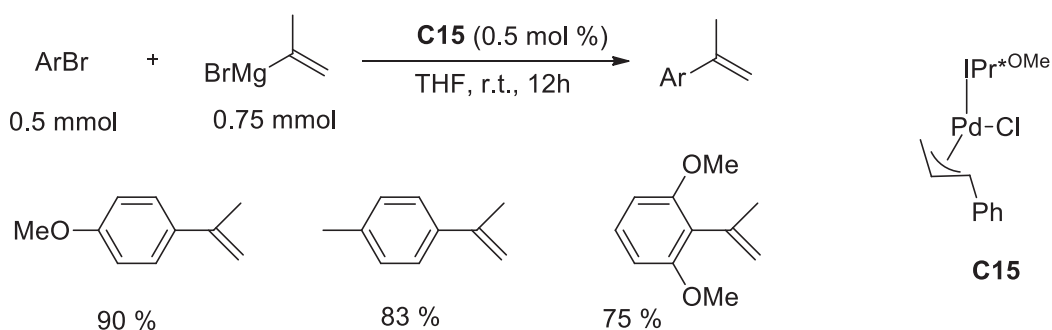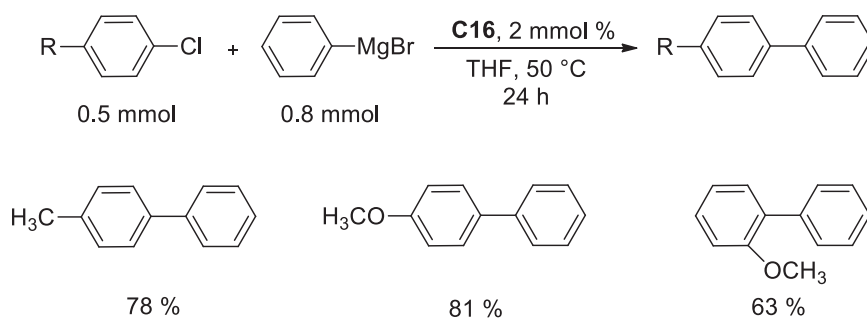

Scheme 5. Kumada reaction catalyzed by **C15**.

Figure 3.

The efficiency of NHC–Pd catalysts is directly related to the properties of the NHCs: the strong σ-donor character facilitates the oxidative addition of aryl halides, while their steric bulk enables stabilization of a low-valent active intermediate and favors reductive elimination. **C15** was used as catalyst for Kumada–Corriu coupling reactions of isopropenylmagnesium with aryl bromides.[51]

Compound **C15** was catalytically active towards the Kumada coupling reaction in toluene and generated the corresponding products in moderate to good yields within 12 h at room temperature, with only 0.5 mol% of catalyst. Under these conditions, isopropenylmagnesium bromide was successfully coupled to 4-bromoanisole and 4-bromotoluene (Scheme 5). The reaction between the bis-ortho-substituted aryl bromide and vinylmagnesium bromide was also achieved in a good yield. The complexes with pyrazine, **C16**, was used as catalyst for Kumada–Corriu coupling reactions of penylmagnesium with aryl chlorides at 50 °C in high yields (Scheme 6).[52]

Scheme 6. Kumada reaction catalyzed by the Pd complexes **C16**.

Recently, Larrosa et al. have reported the first general, (IPent)-PdCl$_2$(PEPPSI) (PEPPSI: pyridine-enhanced precatalyst preparation, stabilization and inhibition) mediated catalyst system for the exhaustive cross coupling on poly-chloroarenes under a deficit of the nucleophilic coupling partner applicable to a wide range of substrates.[53] The optimized reaction conditions for the reaction of dichloroarenes (1.0 equiv.) with ArMgBr (1.0 equiv.) involved the use of 2 mol% **C17** as a catalyst in THF at 50 °C (Table 2). A number of substituted dichloroarenes were tested and both electron-withdrawing and electron-donating groups showed excellent compatibility with the reaction. On the other hand, examination of a series of regioisomers of dichloroanisole demonstrated that the relative position of the substituents has an appreciable effect on the reaction selectivity; for example, when the MeO substituent was placed ortho to only one of the C–Cl bonds, di-selectivity was significantly reduced or even reversed. Moreover, the di-selectivity of p-dichlorobenzene is not restricted to the Kumada coupling: the reaction yielded 3:97 and 11:89 selectivity with PhB(OH)$_2$ and PhZnCl, respectively.

Table 2. Cross-coupling of poly-chloroarenes mediated by PEPPSI–IPent (**C17**).
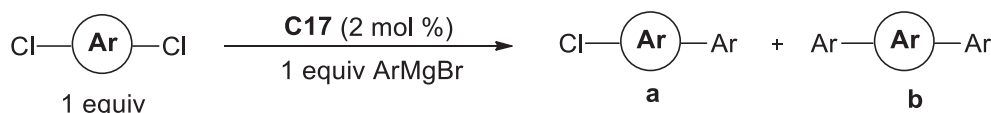
Entry	Ar	Solvent	Conditions	Yield^a [%] a:b	Ref.
1	1,4-Cl$_2$Ph	THF	2 mol% [Pd], 50 °C, 3 h	6:94	53
2	1,3-Cl$_2$Ph	THF	2 mol% [Pd], 50 °C, 3 h	13:87	53
3	1,2-Cl$_2$Ph	THF	2 mol% [Pd], 50 °C, 3 h	16:84	53
4	1,3-Cl$_2$_5-F-Ph	THF	2 mol% [Pd], 50 °C, 3 h	3:97	53
5	1,3-Cl$_2$-5-CF$_3$-Ph	THF	2 mol% [Pd], 50 °C, 3 h	5:95	53
6	1,3-Cl$_2$_5-Me-Ph	THF	2 mol% [Pd], 50 °C, 3 h	2:98	53
7	1,3-Cl$_2$-5-OMe-Ph	THF	2 mol% [Pd], 50 °C, 3 h	< 1 :> 99	53
8	1,2-Cl$_2$-5-OMe-Ph	THF	2 mol% [Pd], 50 °C, 3 h	12:88	53
9	1,4-Cl$_2$-2-OMe-Ph	THF	2 mol% [Pd], 50 °C, 3 h	21:79	53
10	1,3,5-Cl$_3$-Ph	THF	2 mol% [Pd], 50 °C, 3 h	7:93	53
11	1,2,4,5-Cl$_4$-Ph	THF	2 mol% [Pd], 50 °C, 3 h	23:77	53

^{a}Ratio a:b was determned by ^{1}H NMR and GCMS.

2.4. Negishi cross coupling

Grignard reagents used in the Kumada coupling experience competitive reactivities of functional groups. This issue was approached by Negishi et al., and organozinc reagents were found to be the most efficient among

the transmetalation reagents to give the coupled product using a palladium catalyst.[54] Similar to the Kumada coupling, the palladium catalyzed mechanism begins with oxidative addition of the organohalide to the Pd(0) to form a Pd(II) complex. Transmetalation with the organozinc then follows where the R' group of the organozinc reagent replaces the halide anion on the palladium complex and makes a zinc(II) halide salt. Reductive elimination then gives the final coupled product, regenerates the catalyst, and the catalytic cycle can begin again. Palladium NHC complexes, used in the Negishi coupling reaction, have been compiled in Figure 4.
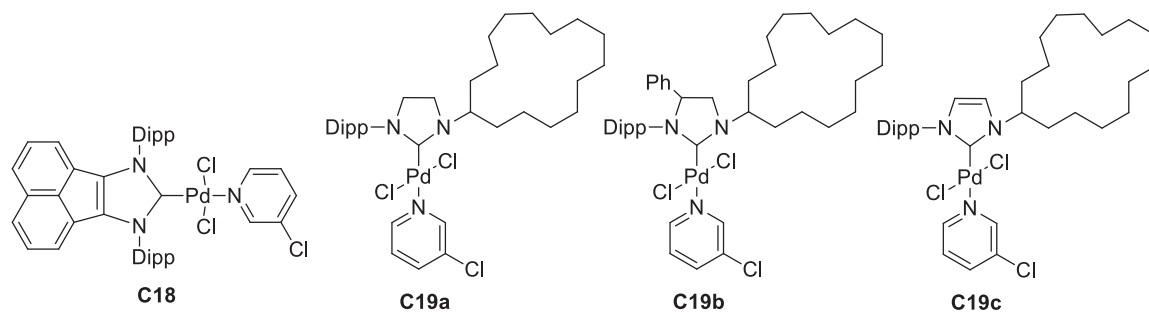

Figure 4.

NHCs derived from π-extended arylimidazolium salts exhibited stronger σ-donor and weaker π-acceptor properties, which can further increase the electron density of the metal center and result in better catalytic activity than their imidazolium analogues.[55] The complex **C18** with bulkier isopropyl groups revealed a higher catalytic activity (Table 3, entries 1–18). The relative position of substituents hardly hampered the process, and all resulted in similarly excellent isolated yields. Electron-poor substituents were much more favorable than electron-rich ones.

Hashmi et al. prepared a series of new (PEPPSI)-type complexes by modular and convergent template synthesis strategy and tested them in Negishi cross-coupling reactions by using one or two substituents in ortho position. A sterically demanding arylzinc reagent, which was generated in situ by transmetalation of mesitylmagnesium bromide to zinc chloride, was effectively coupled with different aryl chlorides and bromides. The saturated complexes **C19a** and **C19b** were better than corresponding unsaturated analogue **C19c** (Table 3, entries 19–21).[56]

2.5. Suzuki cross coupling

Suzuki cross coupling involves the reaction of an organohalide with an organoborane, which is an electrophile, to give the coupled product using a palladium catalyst and base. A molecule of the base (like OH^-, OR^-, and F^-) then replaces the halide on the palladium complex, while another adds to the organoborane to form a borate that makes its R group more nucleophilic.[57]

Some of the challenges associated with cross-coupling reactions have focused on the use of "unreactive" aryl chlorides as coupling partners in view of their attractive cost and readily available diversity. Efforts aimed at developing catalytic systems that perform at mild reaction temperatures in short times using low catalyst loadings are an ongoing effort. Another challenge is to achieve cross coupling under optimum conditions for highly hindered biaryls, such as poly-ortho-substituted biaryls. Significant progress has been achieved in these areas. Palladium NHC complexes used in Suzuki coupling reactions are presented in Figure 5.

Table 3. Negishi coupling reactions carried out using Pd–NHC catalysts.
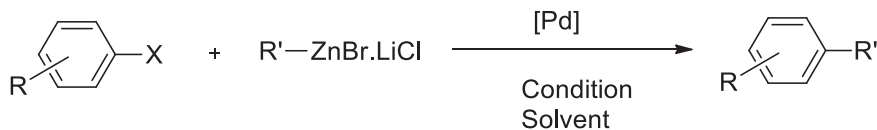
Entry	Catalyst	X	R	R'	Solvent	Conditions	Yield [%]	Ref.
1	**C18**	Br	4-CN	Cp	Dioxane	0.25 mol% [Pd], r.t., 0.5 h	> 99[a]	55
2	**C18**	Cl	4-CN	Cp	Dioxane	0.25 mol% [Pd], r.t., 0.5 h	> 99[a]	55
3	**C18**	Cl	4-CN	Me	Dioxane	0.25 mol% [Pd], r.t., 0.5 h	> 99[a]	55
4	**C18**	Cl	4-CN	n-Oct	Dioxane	0.25 mol% [Pd], r.t., 0.5 h	> 99[a]	55
5	**C18**	Cl	4-CN	Bn	Dioxane	0.25 mol% [Pd], r.t., 0.5 h	99[a]	55
6	**C18**	Cl	4-CN	Cy	Dioxane	0.25 mol% [Pd], r.t., 0.5 h	99[a]	55
7	**C18**	Cl	4-CN	Ph	Dioxane	0.25 mol% [Pd], 80 °C, 24 h	94[a]	55
8	**C18**	Cl	4-CN	Mes	Dioxane	0.25 mol% [Pd], 80 °C, 24 h	96[a]	55
9	**C18**	Br	2-CN	Cp	Dioxane	0.25 mol% [Pd], r.t., 0.5 h	> 99[a]	55
10	**C18**	Cl	4-CN	Cp	Dioxane	0.25 mol% [Pd], r.t., 0.5 h	> 99[a]	55
11	**C18**	Cl	4-F	Cp	Dioxane	0.25 mol% [Pd], r.t., 0.5 h	99[a]	55
12	**C18**	Br	4-COOEt	Cp	Dioxane	0.25 mol% [Pd], r.t., 0.5 h	99[a]	55
13	**C18**	Cl	4-CHO	Cp	Dioxane	0.25 mol% [Pd], r.t., 0.5 h	> 99[a]	55
14	**C18**	Br	2-Ph	Cp	Dioxane	0.25 mol% [Pd], r.t., 0.5 h	99[a]	55
15	**C18**	Br	4-Me	Cp	Dioxane	1 mol% [Pd], 0.6 mmol NMI, 80 °C, 24 h	93[a]	55
16	**C18**	Br	2-Me	Cp	Dioxane	1 mol% [Pd], 0.6 mmol NMI, 80 °C, 24 h	> 99[a]	55
17	**C18**	Br	2,6-Me$_2$	Cp	Dioxane	1 mol% [Pd], 0.6 mmol NMI, 80 °C, 24 h	> 99[a]	55
18	**C18**	Br	C$_{10}$H$_7$	Cp	Dioxane	0.25 mol% [Pd], r.t., 0.5 h	99[a]	55
19	**C19a–c**	Br	H	Mes	NMP	2 mol% [Pd], 70 °C, 17 h	59–93[b]	56
20	**C19a–c**	Cl	H	Mes	NMP	2 mol% [Pd], 70 °C, 17 h	30–58[b]	56
21	**C19a–c**	Br	C$_{10}$H$_7$	Mes	NMP	2 mol% [Pd], 70 °C, 17 h	83–96[b]	56

[a]Yield of isolated product. [b]GC yield.

The use of [PdCl$_2$(IPent)(3-ClPy)] as catalyst for the synthesis of poly-ortho-substituted biaryls gave better yields than less hindered [PdCl$_2$(Mes)(3-ClPy)] or [PdCl$_2$(IPr)(3-ClPy)] under mild conditions. The success of the catalyst was attributed to the "the flexible steric" bulk of the IPent ligand. Calculations revealed that increasing the steric bulk does not alter the oxidative addition; however, reductive elimination is affected.[19]

In 2011 Dorta's group described naphthyl derived side chains and an allyl group, which were very successful for tetra-substituted biaryls.[58] The BASF group patented an isonitryl NHC–Pd(II) complex, which was very successful.[59] Albrecht et al. and Huang et al. obtained very good yields with 1,2,3-triazol-5ylidene.[60,61]

Trimetallic complexes based on a rigid, a triphenylene core, **C20**, **C21**, and the related monometallic complex **C22**, have been tested in the Suzuki coupling between arylboronic acids and aryl bromides (Table 4, entries 5 and 6).[62] **C20** displayed the best catalytic activity for all the substrates used. Palladium complexes with a pyracene-linked bis-imidazolylidene group (**C23**, **C24**) and their monometallic counterparts (**C25**) have also been studied in the Suzuki coupling of aryl halides and aryl boronic acids.[63] The results showed that the presence of a second metal in dimetallic complexes induces some benefits in the catalytic behavior of the complexes (Table 4, entries 7 and 8).
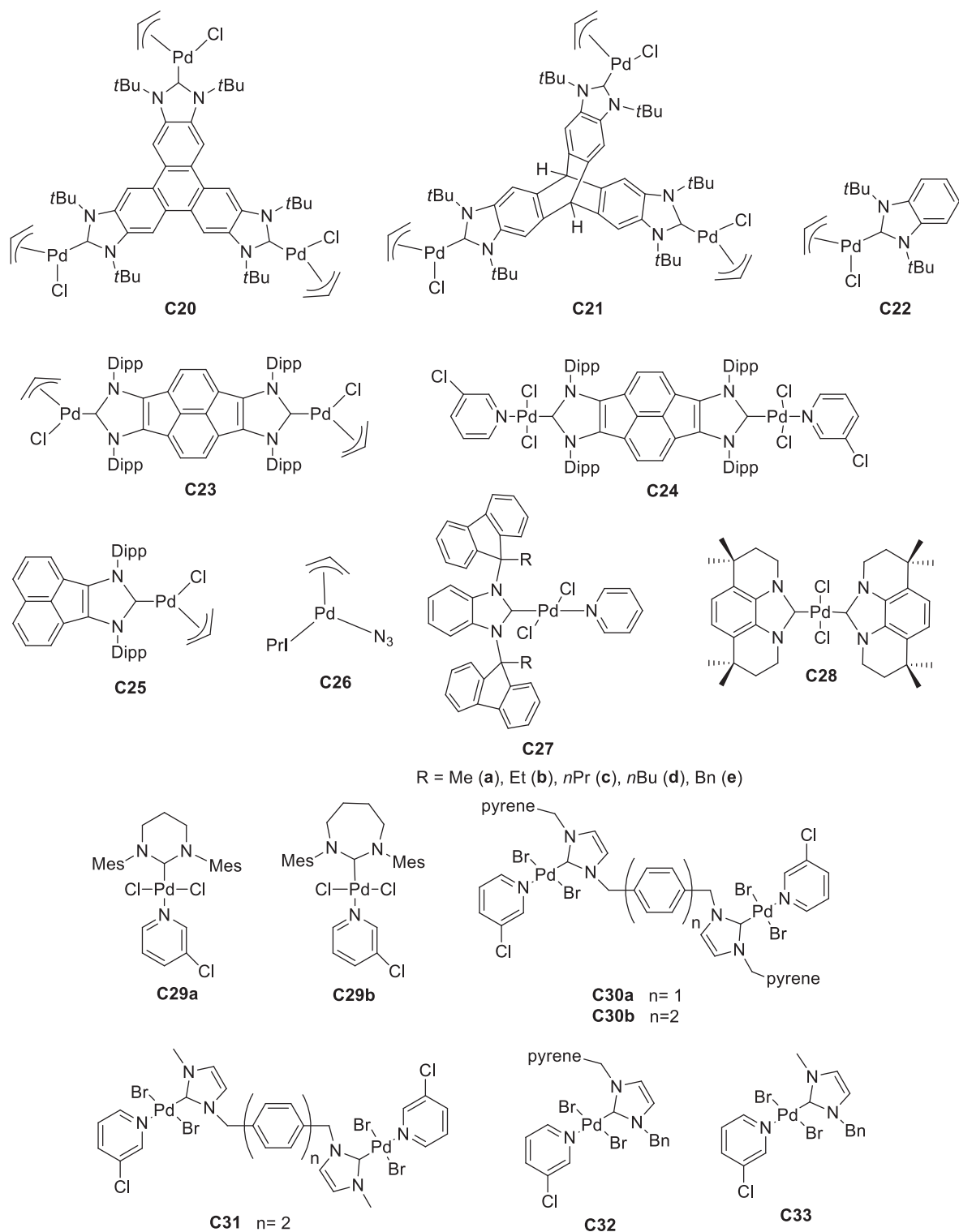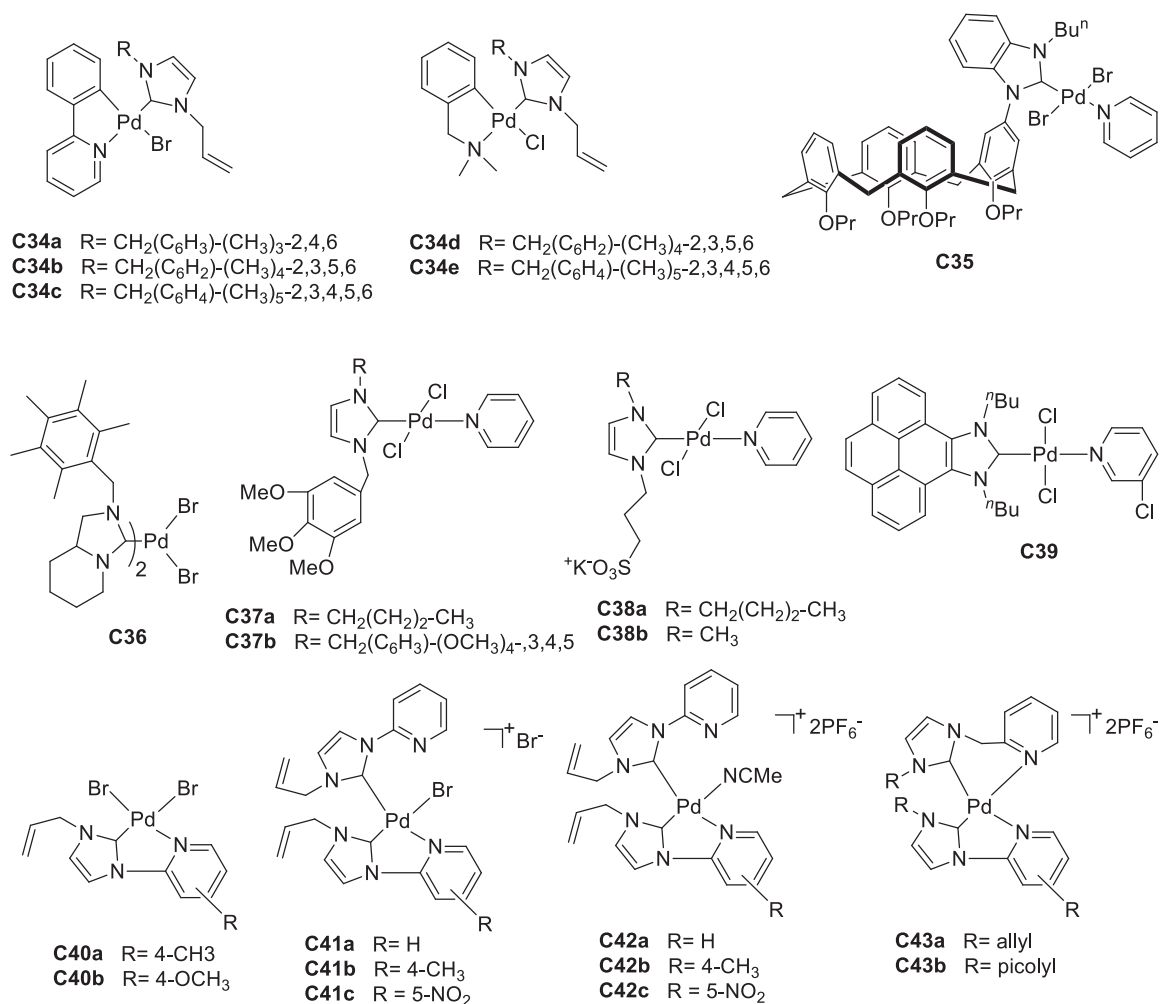
Figure 5.

C34a R= CH$_2$(C$_6$H$_3$)-(CH$_3$)$_3$-2,4,6
C34b R= CH$_2$(C$_6$H$_2$)-(CH$_3$)$_4$-2,3,5,6
C34c R= CH$_2$(C$_6$H$_4$)-(CH$_3$)$_5$-2,3,4,5,6

C34d R= CH$_2$(C$_6$H$_2$)-(CH$_3$)$_4$-2,3,5,6
C34e R= CH$_2$(C$_6$H$_4$)-(CH$_3$)$_5$-2,3,4,5,6

C35

C36

C37a R= CH$_2$(CH$_2$)$_2$-CH$_3$
C37b R= CH$_2$(C$_6$H$_3$)-(OCH$_3$)$_4$-,3,4,5

C38a R= CH$_2$(CH$_2$)$_2$-CH$_3$
C38b R= CH$_3$

C39

C40a R= 4-CH3
C40b R= 4-OCH$_3$

C41a R= H
C41b R= 4-CH$_3$
C41c R = 5-NO$_2$

C42a R= H
C42b R= 4-CH$_3$
C42c R = 5-NO$_2$

C43a R= allyl
C43b R= picolyl

Figure 5. Continued.

Kim et al. prepared a series of (π-allyl)Pd–NHC pseudohalogen complexes, [(π-allyl)Pd(X)(NHC)], and examined their catalytic activity in Suzuki–Miyaura cross-coupling reactions with arylboronic acids.[64] The (π-allyl)PdN$_3$NHC pseudohalogen complexes (**C26**) exhibited higher catalytic efficiency than the corresponding chlorides (Table 4, entries 9–12).

The palladium complexes **27a**–**e**, containing 9-fluorenylidene moiety, were shown to display activities superior or equal to those obtained with the fastest Pd–NHC in the Suzuki cross-coupling catalysts with aryl chloride (Table 4, entry 13).[65] The utility of **C28**, based on a tetracyclic scaffold, in the Suzuki cross-coupling reaction is demonstrated with a low catalyst loading at room temperature (Table 4, entries 14–18).[66] The reaction times were reduced dramatically under microwave conditions.

The six- and seven-membered Pd–PEPPSI-type complexes **C29a** and C**29b** have been employed in Suzuki coupling of aryl bromide and chloride substrates (Table 4, entries 19–22).[67] A series of dimetallic complexes (**C30** and **C31**), bridged by bis-imidazolylidenes, with different spacers (phenylene and biphenylene) and the related monometallic complexes (**C32** and **C33**) were screened in the Suzuki coupling between aryl halides and arylboronic acids. In general, the dimetallic complexes display better activities than the monometallic analogues (Table 4, entries 23–26).[68]

Table 4. Suzuki coupling reactions carried out using Pd–NHC catalysts.
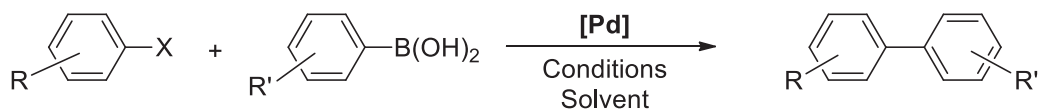
Entry	Catalyst	X	R	R'	Solvent	Conditions	Yield [%]	Ref.
1	**C13a–b**	Br	4-F	H	^{i}PrOH	1 mol% [Pd], ^{t}BuOK, 60 °C, 18 h	74–86^b	49
2	**C13c**	Br	4-F	H	^{i}PrOH	1 mol% [Pd], ^{t}BuOK, 25 °C, 18 h	91^b	49
3	**C13a–b**	Br	4-Me	H	^{i}PrOH	1 mol% [Pd], ^{t}BuOK, 60 °C, 18 h	83–91^b	49
4	**C13c**	Br	4-Me	H	^{i}PrOH	1 mol% [Pd], ^{t}BuOK, 25 °C, 18 h	96^b	49
5	**C20–C22**	Br	H	4-OMe	Dioxane	2 mol% [Pd], Cs$_2$CO$_3$, 80 °C, 2 h	55–81^a	62
6	**C20–C22**	Br	4-Me	H	Dioxane	2 mol% [Pd], Cs$_2$CO$_3$, 80 °C, 2 h	55–71^a	62
7	**C23–C25**	Br	4-COMe	4-Me	Dioxane	2 mol% [Pd], Cs$_2$CO$_3$, 80 °C, 2 h	92–98^a	63
8	**C23–C25**	Br	4-COMe	H	Dioxane	2 mol% [Pd], Cs$_2$CO$_3$, 80 °C, 2 h	72–96^a	63
9	**C26**	Cl	4-COMe	4-Me	MeOH	1 mol% [Pd], Cs$_2$CO$_3$, 80 °C, 60 min	98^b	64
10	**C26**	Cl	4-COMe	H	MeOH	1 mol% [Pd], Cs$_2$CO$_3$, 80 °C, 0.5 h	99^b	64
11	**C26**	Cl	4-C$_{10}$H$_7$	4-OMe	MeOH	1 mol% [Pd], Cs$_2$CO$_3$, 80 °C, 0.5 h	99^b	64
12	**C26**	Cl	4-CN	H	MeOH	1 mol% [Pd], Cs$_2$CO$_3$, 80 °C, 90 min	99^b	64
13	**C27a–e**	Cl	4-Me	H	Dioxane	1 mol% [Pd], Cs$_2$CO$_3$, 80 °C, 1 h	19–40^c	65
14	**C28**	Br	4-OMe	H	DMF	0.5 mol% [Pd], K$_3$PO$_4$, r.t., 16 h	85^c	66
15	**C28**	Br	4-OMe	4-C$_{10}$H$_7$	DMF	0.5 mol% [Pd], K$_3$PO$_4$, 80 °C, mw, 15 min	84^c	66
16	**C28**	Br	4-COMe	4-OMe	DMF	0.5 mol% [Pd], K$_3$PO$_4$, r.t., 2 h	90^c	66
17	**C28**	Cl	H	H	DMF	0.5 mol% [Pd], K$_3$PO$_4$, r.t., 2 h	75^c	66
18	**C28**	Cl	H	H	DMF	0.5 mol% [Pd], K$_3$PO$_4$, 80 °C, mw, 5 min	88^c	66
19	**C29a–b**	Br	H	H	^{i}PrOH	1 mol% [Pd], ^{t}BuOK, 80 °C, r.t., 1 h	79–94^d	67
20	**C29a–b**	Cl	H	H	^{i}PrOH	1 mol% [Pd], ^{t}BuOK, 80 °C, r.t., 7 h	84–100	67
21	**C29a–b**	Br	4-Me	H	^{i}PrOH	1 mol% [Pd], ^{t}BuOK, 80 °C, r.t., 1 h	81–95^d	67
22	**C29a–b**	Cl	4-OMe	H	^{i}PrOH	1 mol% [Pd], ^{t}BuOK, 80 °C, r.t., 7 h	94–95^d	67
23	**C30a**	Br	4-COMe	4-Me	Toluene	2 mol% [Pd], Cs$_2$CO$_3$, 80 °C, 2 h	90^a	68
24	**C30a**	Br	4-COMe	4-OMe	Toluene	2 mol% [Pd], Cs$_2$CO$_3$, 80 °C, 2 h	90^a	68
25	**C30–C33**	Br	4-Me	H	Toluene	2 mol% [Pd], Cs$_2$CO$_3$, 80 °C, 2 h	55–69^a	68
26	**C30–C33**	Br	4-OMe	H	Toluene	2 mol% [Pd], Cs$_2$CO$_3$, 80 °C, 2 h	35–78^a	68
27	**C34a–e**	Br	H	H	^{i}PrOH	1 mol% [Pd], Cs$_2$CO$_3$, 80 °C, 4 h	20–26^a	69
28	**C34a–e**	Br	4-COMe	H	^{i}PrOH	1 mol% [Pd], Cs$_2$CO$_3$, 80 °C, 4 h	10–53^a	69
29	**C35**	Br	4-COMe	4-OMe	Dioxane	0.08 mol% [Pd], K$_3$PO$_4$, 100 °C, 24 h	> 90^c	70
30	**C35**	Br	4-CF$_3$	4-OMe	Dioxane	0.08 mol% [Pd], K$_3$PO$_4$, 100 °C, 24 h	99^c	70
31	**C35**	Br	F	4-OMe	Dioxane	0.08 mol% [Pd], K$_3$PO$_4$, 100 °C, 24 h	90^c	70
32	**C35**	Br	4-CN	4-OMe	Dioxane	0.08 mol% [Pd], K$_3$PO$_4$, 100 °C, 24 h	99^c	70
33	**C36a–c**	Cl	H	H	^{i}PrOH	1 mol% [Pd], KOH, 80 °C, 6 h	73–87^a	52
34	**C16, C36**	Cl	4-OMe	H	^{i}PrOH	1 mol% [Pd], KOH, 80 °C, 6 h	75–93^a	52
35	**C16, C36**	Cl	2-OMe	H	^{i}PrOH	1 mol% [Pd], KOH, 80 °C, 6 h	71–78^a	52
36	**C37a–b**	I	4-OMe	H	Glycerol	1 mol% [Pd], K$_2$CO$_3$, 40 °C, with 40% amplitude, 30 min	85–86^{a,b}	71
37	**C37a**	I	4-OMe	4-C$_{10}$H$_7$	Glycerol	1 mol% [Pd], K$_2$CO$_3$, 40 °C, with 40% amplitude, 30 min	87^{a,b}	71
38	**C38a**	Br	4-C$_{10}$H$_7$	4-Me	Glycerol	1 mol% [Pd], K$_2$CO$_3$, 40 °C, with 40% amplitude, 30 min	90^{a,b}	71
39	**C38b**	I	4-NO$_2$	H	Glycerol	1 mol% [Pd], K$_2$CO$_3$, 40 °C, with 40% amplitude, 30 min	89^{a,b}	71
40	**C39**	Br	H	H	Dioxane	2 mol% [Pd], Cs$_2$CO$_3$, 80 °C, 2 h	79^a	72
41	**C39**	Br	4-COMe	H	Dioxane	2 mol% [Pd], Cs$_2$CO$_3$, 80 °C, 2 h	84^a	72
42	**C39**	Cl	4-COMe	H	Dioxane	2 mol% [Pd], Cs$_2$CO$_3$, 120 °C, 2 h	73^a	72
43	**C40a–b**	Br	H	H	Dioxane	1 mol% [Pd], Cs$_2$CO$_3$, 80 °C, 2 h	56–68^a	73
44	**C41a–c**	Br	H	H	Dioxane	1 mol% [Pd], Cs$_2$CO$_3$, 80 °C, 2 h	78–86^a	73
45	**C42a–c**	Br	H	H	Dioxane	1 mol% [Pd], Cs$_2$CO$_3$, 80 °C, 2 h	81–86^a	73
46	**C43a–b**	Br	H	H	Dioxane	1 mol% [Pd], Cs$_2$CO$_3$, 80 °C, 2 h	92–99^a	73

^{a}GC yield. ^{b}Yield of isolated product. ^{c}Yield determined by NMR spectroscopy. ^{d}GCMS yield.

The complexes **C34a–e** with N-allyl functionalized NHC ligands were employed in the Suzuki reaction.[69] It was shown that the imidazol-2-ylidenes in combination with cyclic palladium complexes form a less effective catalytic system (Table 4, entries 27 and 28). The catalytic activity of calix[4]arene-supported NHC–palladium complexes (**C35**) was investigated at low catalyst loadings (Table 4, entries 29–32).[70]

A series of complexes with pyrazine (**C36a**) or pyridine (**C36b**) and NHC (**C36c**) were studied in the Suzuki coupling reaction of aryl chlorides and phenyl boronic acid in IPA under air atmosphere with low catalyst loading (1%) (Table 4, entries 33–35).[52] The complexes with 3,4,5-trimethoxybenzyl (**C37a–b**) and sulfonate N-substituents (**C38a–b**) were used as precatalysts in the Suzuki coupling of various aryl halides/boron sources in glycerol under pulsed-ultrasound (P-US) activation.[71] High yields were obtained under mild reaction conditions, without formation of undesired by-products (Table 4, entries 36–39). TEM and XPS were used to characterize the nanoparticles and to investigate the fate of the catalysts.

The catalytic activities of the complexes **C39** were evaluated in the Suzuki coupling in 1,4-dioxane, in the presence of Cs_2CO_3 and using a 2 mol% catalyst loading at 80 °C (Table 4, entries 40–42).[72] For the coupling of aryl chlorides, longer reaction times or higher temperatures were needed. Pyridyl- and picolyl-substituted imidazol-2-ylidene palladium(II) complexes, neutral $Pd(NHC)X_2$ (**C40**), cationic $[Pd(NHC)_2X]X$ (**C41** and **C42**), and dicationic $[Pd(NHC)_2]X_2$ (**C43**) have been employed in a model Suzuki cross-coupling reaction to yield a sterically congested tetra-orthosubstituted biaryl product, with comparable activity to Pd–PEPPSI–IPr catalyst (Table 4, entries 43–46).[73]

3. Sonogashira cross coupling

The Sonogashira cross-coupling reaction involves the reaction of an organohalide with a terminal alkyne to give the coupled product using a palladium catalyst, a copper co-catalyst, and base.[74] The cycle begins with oxidative addition of the organohalide to the Pd(0) to form a Pd(II) complex. Transmetalation with the organocopper reagent, formed from the terminal alkyne and the copper catalyst, then follows. The alkynyl anion replaces the halide on the palladium complex and regenerates the copper halide catalyst. The possibilities of applying NHC ligands in Sonogashira coupling were also explored by various groups (Figure 6).

Complex **C6** efficiently catalyzed Sonogashira reactions of aryl bromides, aryl tosylates, and terminal alkynes under CuI-free condition with low catalyst loading (1.0 mol%) in the presence of air (Table 5, entries 1–7).[44] Complex **C44** proved to be an efficient catalyst for Sonogashira reaction of aryl bromides and some activated aryl chlorides under copper- and amine-free conditions (Table 5, entries 8–13).[75]

L-phenylalanine based **C45** catalyzed the cross-coupling reaction of phenylacetylene with more reactive aryl iodides, with less reactive aryl bromides in the absence of copper co-catalysis, and the catalyst was not effective for aryl chloride (Table 5, entries 14–19).[76]

The complexes **C46a–d** of imidazo[1,2-a]pyridine derived abnormal *N*-heterocyclic carbene ligands with varying electron donating capacities at a distant phenyl group have been examined in the Cu- and amine-free Sonogashira coupling of aryl halides with terminal alkynes (Table 5, entries 20–23). Among the complexes, the bromo derivative (**C46c**) was the most active. The aryl chlorides did not yield any product under these reaction conditions.[77]

Benzimidazole-derived ligand (bimy) with a potentially "mesoionic and remote" character, **C47**, proved to be a suitable catalyst precursor and led to quantitative yields for activated aryl bromides (Table 5, entries

24 and 25), and was superior to its structurally related analogues bearing an aryl, $[Pd(Ph)(PPh_3)_2Br]$, or a normal NHC complex, $[Pd(PPh_3)_2(Bim)Br]$.[78]
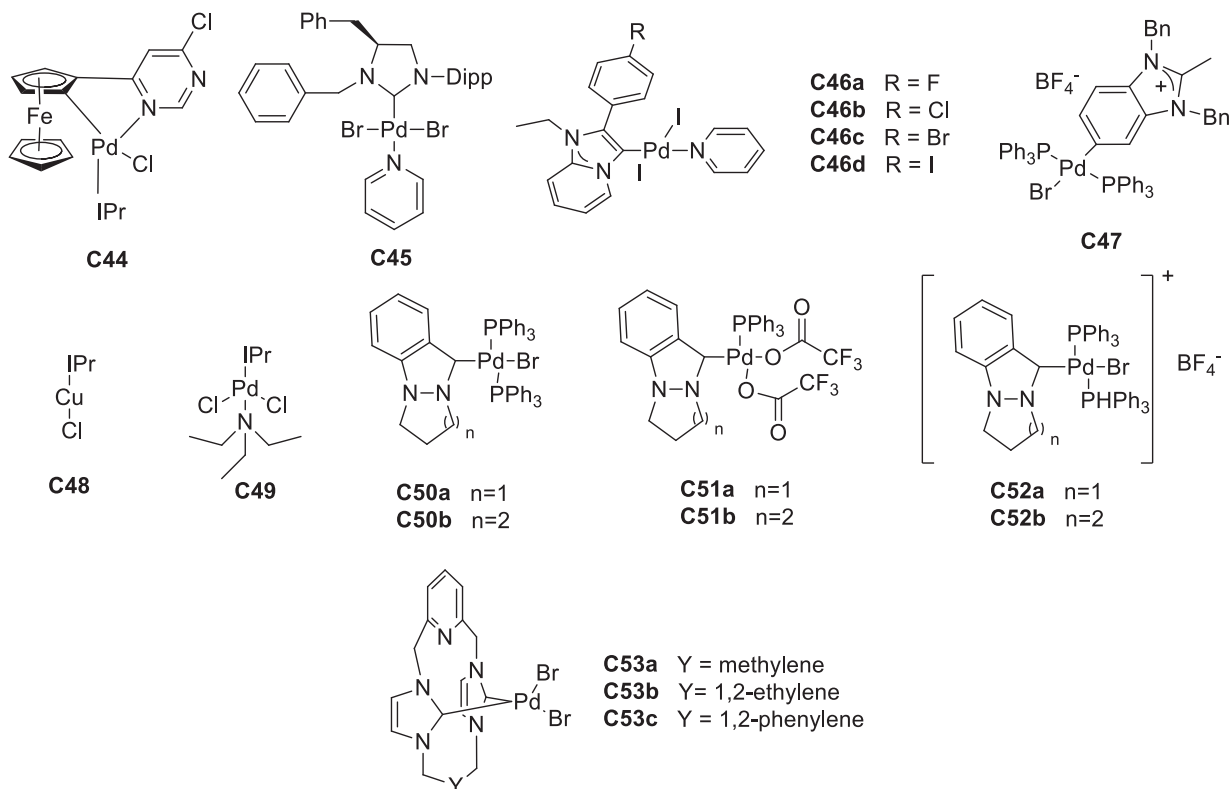

Figure 6.

For Sonogashira coupling of arylacetylenes and aryl bromides **C48** and **C49** were used, without the need for anhydrous conditions or inert atmosphere (Table 5, entries 26–29).[79] Palladium(II) complexes bearing 2,3-dihydro-1H-pyrazolo[1,2-a]indazolin-3-ylidene (indy-5, **C50a**, **C51a**, **C52a**) or 6,7,8,9-tetrahydropyridazino[1,2-a]indazolin-3-ylidene (indy-6, **C50b**, **5C1b**, **C52b**) ligands proved to be efficient (Table 5, entries 30–32).[80]

Macrocyclic di-NHC ligands bearing 2,6-lutidinyl bridges exert a positive effect on the catalytic efficiency of the complexes in standard Sonogashira reactions.[81] Catalytic activity of these complexes $PdBr_2(L^{propyl})$ (**C53a**), $PdBr_2(L^{xylyl})$ (**C53b**), and $PdBr_2(L^{butyl})$ (**C53c**) was studied in copper- and amine-free Sonogashira reactions (Table 5, entries 33–37).

3.1. Stille cross coupling

The Kosugi–Migita–Stille coupling (shortened to Stille cross coupling) reaction involves the reaction of an organohalide with an organostannane compound to give the coupled product using a palladium catalyst.[82,83] The mechanism begins with oxidative addition of the organohalide to the Pd(0) to form a Pd(II) complex. Transmetalation with the organostannane then follows where the R group of the organostannane reagent replaces the halide anion on the palladium complex. Reductive elimination then gives the final coupled product and regenerates the palladium catalyst.

Table 5. Sonogashira coupling reactions carried out using Pd–NHC catalysts.

$$R \text{---}\equiv \quad + \quad Ar\text{-}X \quad \xrightarrow[\text{Condition Solvent}]{[Pd]} \quad R\text{---}\equiv\text{---}Ar$$
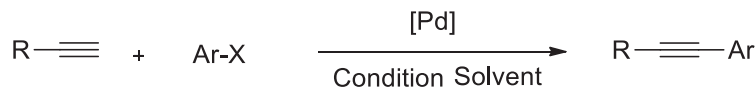
Entry	Catalyst	X	R	Ar	Solvent	Conditions	Yield [%]	Ref.
1	**C6**	Br	Ph	4-CNPh	DMSO	1 mol% [Pd], NEt$_3$, 80 °C, 0.7 h	89[a]	36
2	**C6**	OTs	Ph	4-NO$_2$Ph	DMSO	1 mol% [Pd], NEt$_3$, 85 °C, 4 h	86[a]	36
3	**C6**	Br	Ph	2-C$_4$H$_3$S	DMSO	1 mol% [Pd], NEt$_3$, 80 °C, 1.5 h	85[a]	36
4	**C6**	Br	Ph	Ph	DMSO	1 mol% [Pd], NEt$_3$, 80 °C, 1 h	86[a]	36
5	**C6**	OTs	Ph	Ph	DMSO	1 mol% [Pd], NEt$_3$, 85 °C, 5 h	82[a]	36
6	**C6**	Br	4-MePh	2-C$_4$H$_3$S	DMSO	1 mol% [Pd], NEt$_3$, 85 °C, 2 h	76[a]	36
7	**C6**	Br	4-MePh	4-CNPh	DMSO	1 mol% [Pd], NEt$_3$, 80 °C, 1.5 h	83[a]	36
8	**C44**	Br	Ph	C$_{10}$H$_7$	DMA	1 mol% [Pd], CsOAc, 120 °C, 12 h	96[a]	66
9	**C44**	Br	Ph	4-MePh	DMA	1 mol% [Pd], CsOAc, 120 °C, 12 h	94[a]	66
10	**C44**	Br	Ph	4-OMePh	DMA	1 mol% [Pd], CsOAc, 120 °C, 12 h	92[a]	66
11	**C44**	Br	Ph	4-NO$_2$Ph	DMA	0.5 mol% [Pd], CsOAc, 120 °C, 12 h	95[a]	66
12	**C44**	Br	Ph	4-CNPh	DMA	0.1 mol% [Pd], CsOAc, 120 °C, 12 h	91[a]	66
13	**C44**	Br	Ph	2-C$_4$H$_3$S	DMA	1 mol% [Pd], CsOAc, 120 °C, 12 h	80[a]	66
14	**C45**	Br	Ph	4-NO$_2$Ph	DMSO	1 mol% [Pd], K$_2$CO$_3$, 100 °C, 1 h	84[a]	67
15	**C45**	Br	nBu	4-NO$_2$Ph	DMSO	1 mol% [Pd], K$_2$CO$_3$, 100 °C, 1 h	91[a]	67
16	**C45**	Br	Ph	4-CF$_3$Ph	DMSO	1 mol% [Pd], K$_2$CO$_3$, 100 °C, 1 h	78[a]	67
17	**C45**	Br	nBu	4-CF$_3$Ph	DMSO	1 mol% [Pd], K$_2$CO$_3$, 100 °C, 1 h	90[a]	67
18	**C45**	Br	nBu	4-FPh	DMSO	1 mol% [Pd], K$_2$CO$_3$, 100 °C, 1 h	91[a]	67
19	**C45**	Br	nBu	4-NO$_2$Ph	DMSO	1 mol% [Pd], K$_2$CO$_3$, 100 °C, 1 h	88[a]	67
20	**C46a–d**	I	Ph	4-MePh	DMF/H$_2$O	4 mol% [Pd], Cs$_2$CO$_3$, 90 °C, 3 h	40–76[b]	68
21	**C46a–d**	I	Ph	4-OMePh	DMF/H$_2$O	4 mol% [Pd], Cs$_2$CO$_3$, 90 °C, 3 h	50–80[b]	68
22	**C46a–d**	I	Ph	4-MeOCPh	DMF/H$_2$O	4 mol% [Pd], Cs$_2$CO$_3$, 90 °C, 3 h	99[b]	68
23	**C46a–d**	Br	Ph	4-CNPh	DMF/H$_2$O	4 mol% [Pd], Cs$_2$CO$_3$, 90 °C, 3 h	81–91[b]	68
24	**C47**	Br	Ph	4-CHOPh	DMF	1 mol% [Pd], 5 mol% CuI, NEt$_3$, 80 °C, 1 h	> 99[c]	69
25	**C47**	Br	Ph	4-MeOCPh	DMF	1 mol% [Pd], 5 mol% CuI, NEt$_3$, 80 °C, 3 h	> 99[c]	69
26	**C48+C49**	Br	Ph	C$_{10}$H$_7$	DMSO	0.05 mol% [Pd], 0.01 mol% [Cu], K$_2$CO$_3$, 120 °C, 24 h	95[c]	70
27	**C48+C49**	Br	Ph	4-MeOCPh	DMSO	0.005 mol% [Pd], 0.01 mol% [Cu], K$_2$CO$_3$, 120 °C, 3 h	93[c]	70
28	**C48+C49**	Br	Ph	2-C$_5$H$_4$N	DMSO	1 mol% [Pd], 0.01 mol% [Cu], K$_2$CO$_3$, 120 °C, 3 h	93[c]	70
29	**C48+C49**	Br	4-OMePh	2-C$_5$H$_4$N	DMSO	1 mol% [Pd], 0.01 mol% [Cu], K$_2$CO$_3$, 120 °C, 3 h	94[c]	70
30	**C50a–b**	Br	Ph	4-MeOCPh	DMF	1 mol% [Pd], 5 mol% CuI, NEt$_3$, 80 °C, 3 h	84–93[c]	71
31	**C51a–b**	Br	Ph	4-MeOCPh	DMF	1 mol% [Pd], 5 mol% CuI, NEt$_3$, 80 °C, 3 h	82–96[c]	71
32	**C52a–b**	Br	Ph	4-MeOCPh	DMF	1 mol% [Pd], 5 mol% CuI, NEt$_3$, 80 °C, 3 h	> 99[c]	71
33	**C53a**	Br	Ph	4-MeOCPh	DMF/H$_2$O	1 mol% [Pd], K$_2$CO$_3$, 100 °C, 17 h	80[c]	72
34	**C53a**	Br	Ph	4-MeOCPh	DMF/H$_2$O	1 mol% [Pd], K$_2$CO$_3$, 100 °C, 17 h	71[c]	72
35	**C53a–c**	Br	Ph	4-MeOCPh	DMF/H$_2$O	1 mol% [Pd], K$_2$CO$_3$, 100 °C, 2 h	70–85[c]	72
36	**C53a**	Br	Ph	4-MeOCPh	DMF/H$_2$O	1 mol% [Pd], K$_2$CO$_3$, 100 °C, 17 h	90[c]	72
37	**C53a–b**	Br	Ph	4-MeOCPh	DMF/H$_2$O	1 mol% [Pd], K$_2$CO$_3$, 80 °C, 22 h	71–99[c]	72

[a]Yield of isolated product. [b]GC yield. [c] Yield determined by NMR spectroscopy.

Stille coupling is one of the most versatile methods for preparing highly functional semiconducting polymers via step-growth polycondensation of monomers. Surprisingly, exploration of chain-growth polymerization with tin-based transmetalating agents remains limited. In 2015, a commercially available (IPr)-PdCl$_2$(3-Cl-Py) was used to induce Stille coupling of the monomer, 2-bromo-3-hexyl-5-trimethylstannaylthiophen, SnHTBr (Scheme 7). The resultant high-molecular-weight poly(3-hexylthiophene) (P3HT) was regioregular and the chain length could be controlled by varying the catalyst concentration.[84]

**Scheme 7.** Synthesis of poly(3-hexylthiophene) using a Pd–NHC catalyst.

3.2. Hiyama coupling

Organosilanes are readily available compounds that upon activation (as in organoboron compounds) with a base like fluoride and a palladium catalyst can react with organohalides to form biaryls in a chemo- and regioselective manner. The activation step takes place in situ or at the same time as the catalytic cycle in the reaction.

Among the organometallic coupling reagents used in cross-coupling reactions, the organoboranes, organostannanes, and organosilanes are the most commonly employed partners because of excellent yields, high stereoselectivities, and wide functional group tolerances. However, the toxicity of tin reagents in Stille couplings, difficulties in the preparation and purification of organoboranes, low chemoselectivity of Grignard and organocopper reagents, and moisture sensitivity of organozinc reagents are the main disadvantages. On the other hand, organosilanes are easily prepared, environmentally benign, and stable agents under many reaction conditions.

However, the Hiyama coupling reaction generally requires a more catalytic amount of Pd when compared

Table 6. Hiyama coupling reactions carried out using Pd–NHC catalysts.
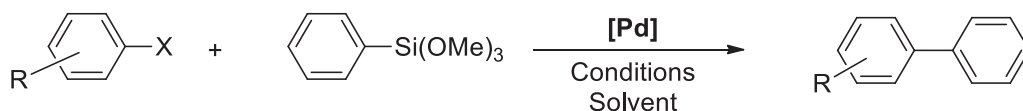
Entry	Catalyst	X	R	Solvent	Conditions	Yield [%]	Ref.
1	**C54**	Cl	4-NO$_2$	Toluene	1 mol% [Pd], TBAF, 120 °C, 3 h	88[a]	86
2	**C54**	Cl	4-CN	Toluene	1 mol% [Pd], TBAF, 120 °C, 3 h	89[a]	86
3	**C54**	Cl	4-CO$_2$Me	Toluene	1 mol% [Pd], TBAF, 120 °C, 3 h	88[a]	86
4	**C54**	Cl	4-OMe	Toluene	0.5 mol% [Pd], TBAF, 120 °C, 5 h	88[a]	86
5	**C54**	Cl	2-C$_5$H$_4$N	Toluene	1 mol% [Pd], TBAF, 120 °C, 3 h	90[a]	86
6	**C55**	Cl	4-NO$_2$	Toluene	0.5 mol% [Pd], TBAF, 120 °C, 5 h	90[a]	87
7	**C55**	Cl	4-COMe	Toluene	0.5 mol% [Pd], TBAF, 120 °C, 5 h	88[a]	87
8	**C55**	Cl	4-CN	Toluene	0.5 mol% [Pd], TBAF, 120 °C, 5 h	90[a]	87
9	**C55**	Cl	2-C$_5$H$_4$N	Toluene	0.5 mol% [Pd], TBAF, 120 °C, 5 h	80[a]	87
10	**C56a–f**	Cl	H	Toluene	1 mol% [Pd], TBAF, 120 °C, mw, 0.5 h	65–73[a]	88
11	**C56a–f**	Cl	4-NO$_2$	Toluene	1 mol% [Pd], TBAF, 120 °C, mw, 0.5 h	83–92[a]	88
12	**C56a–f**	Cl	4-COMe	Toluene	1 mol% [Pd], TBAF, 120 °C, mw, 0.5 h	67–84[a]	88
13	**C56a–f**	Cl	4-Me	Toluene	1 mol% [Pd], TBAF, 120 °C, mw, 0.5 h	55–63[a]	88
14	**C56a–f**	Cl	4-CN	Toluene	1 mol% [Pd], TBAF, 120 °C, mw, 0.5 h	62–90[a]	88
15	**C57a–d**	Cl	4-NO$_2$	Toluene	0.5 mol% [Pd], TBAF, 110 °C, 6 h	87–94[a]	89
16	**C57a–d**	Cl	4-OMe	Toluene	0.5 mol% [Pd], TBAF, 110 °C, 6 h	87–94[a]	89
17	**C57a–d**	Cl	2-C$_5$H$_4$N	Toluene	0.5 mol% [Pd], TBAF, 110 °C, 6 h	80–86[a]	89
18	**C58a–d**	Cl	4-NO$_2$	Toluene	0.5 mol% [Pd], TBAF, 110 °C, 6 h	85–93[a]	89
19	**C58a–d**	Cl	4-OMe	Toluene	0.5 mol% [Pd], TBAF, 110 °C, 6 h	85–93[a]	89
20	**C58a–d**	Cl	3-OMe	Toluene	0.5 mol% [Pd], TBAF, 110 °C, 6 h	82–86[a]	89

[a]Yield of isolated product.

to other types of cross couplings.[85] Hiyama coupling is limited by the need for fluoride to activate the organosilicon reagent because the fluoride cleaves any silicon protecting groups (e.g., silyl ethers), which are frequently employed in organic synthesis. The fluoride ion is also a strong base, and so base-sensitive protecting groups, acidic protons, and functional groups may be affected by the addition of this activator. To address this issue, many groups have looked into the use of other basic additives for activation, or use of a different organosilane reagent all together, leading to the modification of the original Hiyama coupling. Modifications using organochlorosilanes and alkoxysilanes have been reported with the use of milder bases like NaOH, K_3PO_4, and water.

Mechanistic studies suggest that the presence of pentavalent silicon is not needed, but the formation of the silonate is needed to activate addition of the organosilane to the palladium center, because this reaction has first order dependence on silonate concentration.[85] It seems that the rate-determining step in this catalytic cycle is the Pd–O bond formation, in which increased silonate concentrations increase the rate of this reaction. Monoligated palladium NHC complexes applied to the Hiyama coupling reaction are shown in Figure 7.
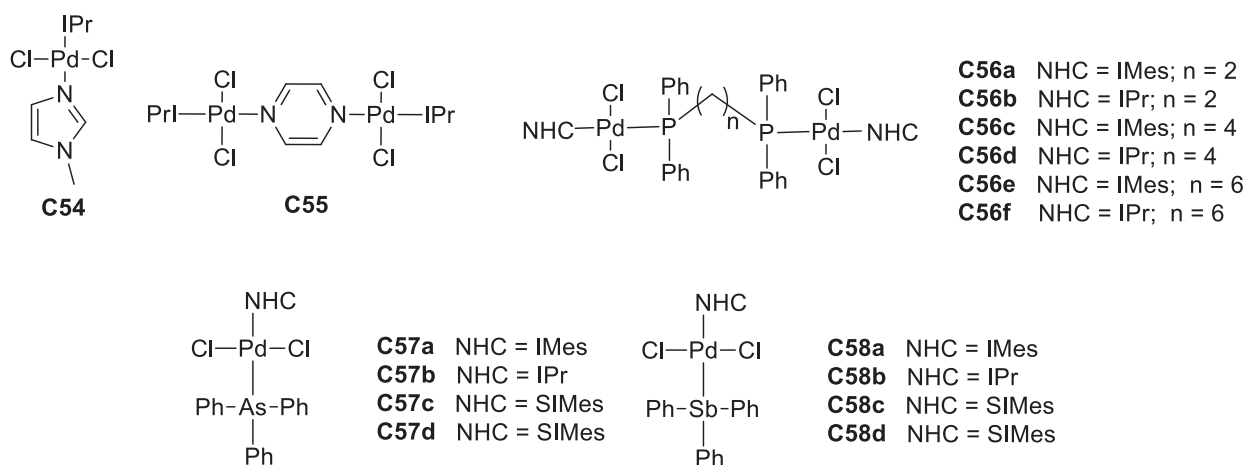

Figure 7.

A well-defined NHC–Pd(II)–Im complex, **C54**, was found to be an efficient catalyst in the reaction of aryl chlorides with aryltrimethoxysilanes.[86] The addition of TBAF.3H$_2$O was necessary and no reaction occurred in the absence of TBAF.3H$_2$O (Table 6, entries 1–5). Substituents on the aryl chlorides have some effects on the reactions. For example, 2-chloropyridine was found to be a good reaction partner to give the corresponding product in 90% yield. When 0.5 mol% of **C55** was employed in the Hiyama reaction, both electron-rich and electron-deficient aryl (or heteroaryl) chlorides gave moderate to good yields of the corresponding biphenyl products (Table 6, entries 6–9).[87] Dinuclear NHC–palladium complexes with bridging diphosphine ligands **C56a–f** were studied in the Hiyama coupling reaction of trimethoxyphenylsilane with a range of aryl chlorides under microwave irradiation conditions (Table 6, entries 10–14).[88] Complexes bearing As (**C57**) and Sb (**C58**) donors-stabilized *N*-heterocyclic carbene palladium complexes catalyzed the Hiyama coupling reaction in dried toluene in the presence of TBAF (Table 6, entries 15–20).[89]

3.3. Chiral catalysis

The possibilities of applying NHC ligands in asymmetric catalysis were also explored by various groups. Chiral palladium complexes catalyzed Suzuki couplings of aryl bromides and chlorides in good yields.[24] A number

of chiral mono and bis palladium NHC complexes have been demonstrated to have reactivity in the Suzuki coupling reaction (Figure 8). Zhang et al. prepared a series of chiral bis N-heterocyclic carbene complexes (**C59a**–**h**). These complexes were able to catalyze the asymmetric Suzuki coupling of boronic acids with aryl halides in good yield and moderate enantioselectivities (up to 64% ee). A strong steric effect of the aromatic substituents on the enantiocontrol of the reaction was observed.[90]
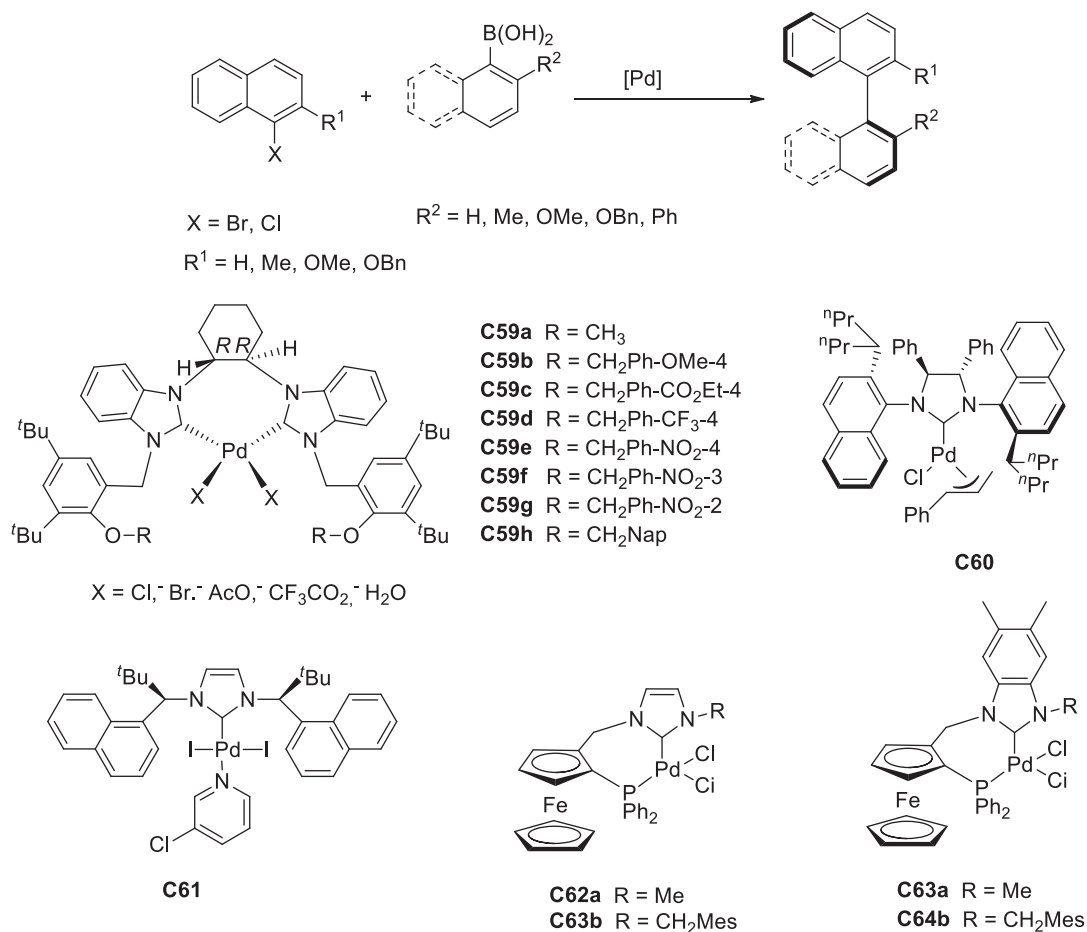

Figure 8.

Chiral monodentate NHC complex **C60** has also been found in these reactions. Chiral NHC complexes with naphthyl side chains were synthesized by Dorta et al. Complex **C60** revealed high yield (up to 94%) and moderate enantioselectivities (up to 60% ee).[91] PEPSI complex **C61** showed good catalytic activity and moderate to good enantioselectivities in asymmetric Suzuki coupling (80% ee).[92] Enantiomeric excesses, up to 46%, have been obtained in the palladium-catalyzed asymmetric Suzuki–Miyaura reaction using very bulky (benz)imidazole-2-ylidene ligands (**C62** and **C63**).[93]

3.4. Biphasic catalysis

In order to reduce the generation of hazardous substances, variation in the coupling reactions has been developed using green solvents, particularly water. Biphasic catalysis is normally based on the conversion of known reactions from a one-phase homogeneous system (solvent phase) to a two-phase homogeneous system

(water/solvent/reagents phases). The catalyst dissolved in the water phase could be collected by decantation, extraction, or distillation.[20,22,94]

In such systems the advantages of homogeneous and heterogeneous catalysis can be combined. Changing from volatile organic solvents to water has enormous economic potential, avoids health risks, and eases the separation of products from the catalyst. In these processes the water solubility of the catalyst was increased via ligands with hydrophilic functionalities like $-SO_3^-$, $-COO^-$, $-OH$, or NR_4^+. Although several NHC–Pd catalysts are produced on an industrial scale, no industrial application of a water soluble NHC–Pd complex has been reported.[15] Palladium NHC complexes used in biphasic Heck and Suzuki coupling reactions are given in Figures 9–11.
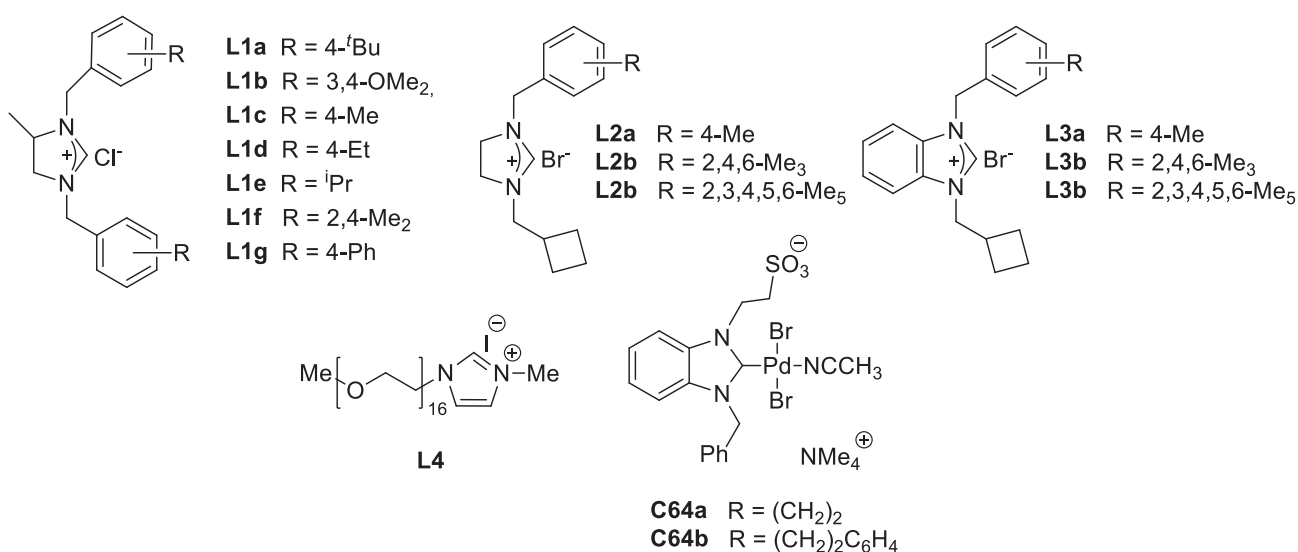

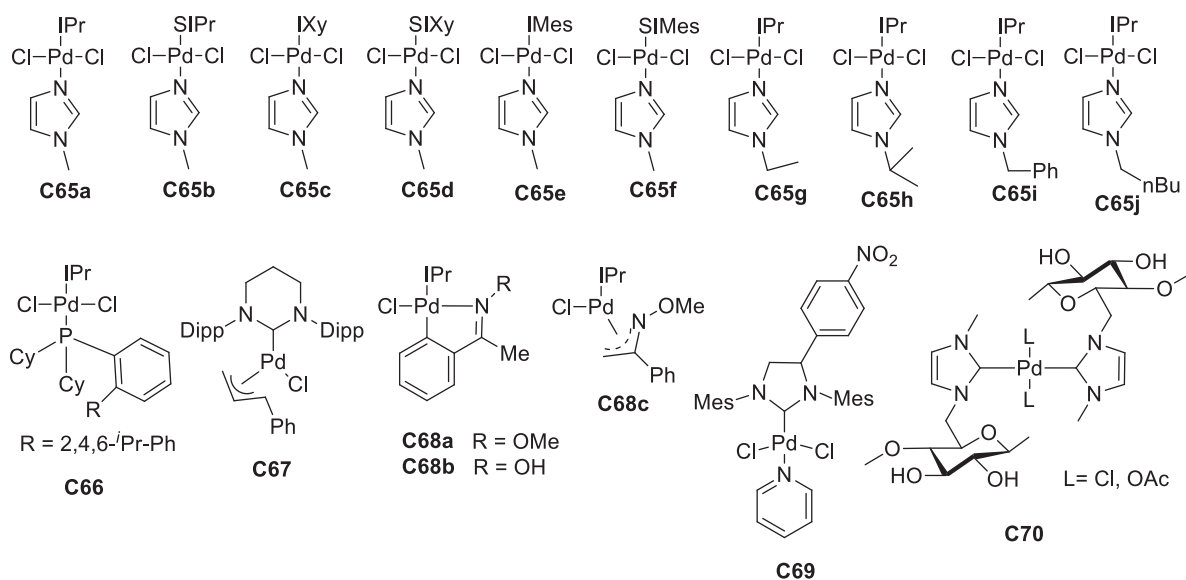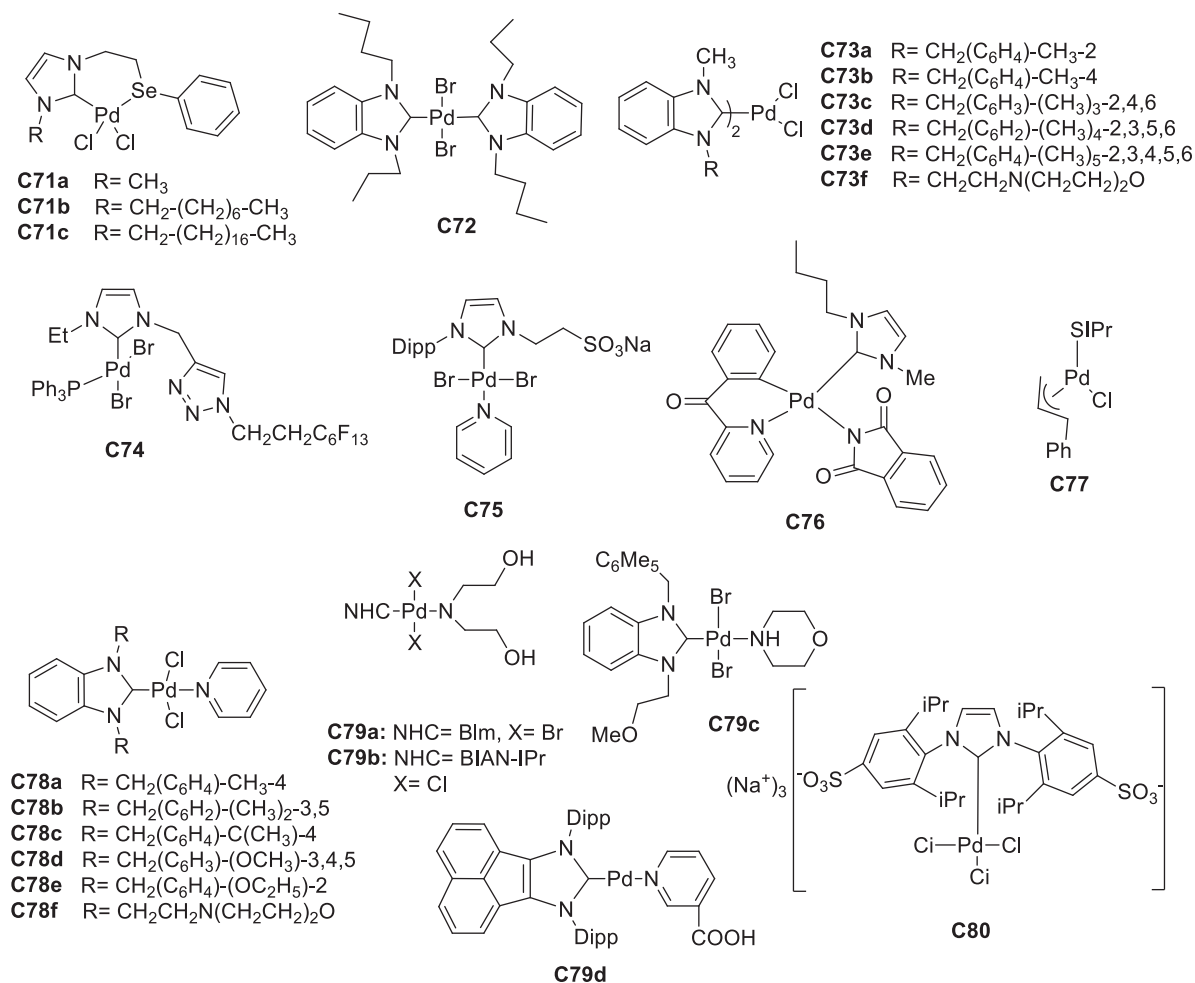**L1a** R = 4-^{t}Bu
L1b R = 3,4-OMe$_2$,
L1c R = 4-Me
L1d R = 4-Et
L1e R = ^{i}Pr
L1f R = 2,4-Me$_2$
L1g R = 4-Ph

L2a R = 4-Me
L2b R = 2,4,6-Me$_3$
L2b R = 2,3,4,5,6-Me$_5$

L3a R = 4-Me
L3b R = 2,4,6-Me$_3$
L3b R = 2,3,4,5,6-Me$_5$

L4

C64a R = (CH$_2$)$_2$
C64b R = (CH$_2$)$_2$C$_6$H$_4$

Figure 9.

C65a **C65b** **C65c** **C65d** **C65e** **C65f** **C65g** **C65h** **C65i** **C65j**

R = 2,4,6-^{i}Pr-Ph

C66

C67

C68a R = OMe
C68b R = OH

C68c

C69

C70 L= Cl, OAc

Figure 10.

C71a R= CH$_3$
C71b R= CH$_2$-(CH$_2$)$_6$-CH$_3$
C71c R= CH$_2$-(CH$_2$)$_{16}$-CH$_3$

C72

C73a R= CH$_2$(C$_6$H$_4$)-CH$_3$-2
C73b R= CH$_2$(C$_6$H$_4$)-CH$_3$-4
C73c R= CH$_2$(C$_6$H$_3$)-(CH$_3$)$_3$-2,4,6
C73d R= CH$_2$(C$_6$H$_2$)-(CH$_3$)$_4$-2,3,5,6
C73e R= CH$_2$(C$_6$H$_4$)-(CH$_3$)$_5$-2,3,4,5,6
C73f R= CH$_2$CH$_2$N(CH$_2$CH$_2$)$_2$O

C74

C75

C76

C77

C78a R= CH$_2$(C$_6$H$_4$)-CH$_3$-4
C78b R= CH$_2$(C$_6$H$_2$)-(CH$_3$)$_2$-3,5
C78c R= CH$_2$(C$_6$H$_4$)-C(CH$_3$)-4
C78d R= CH$_2$(C$_6$H$_3$)-(OCH$_3$)-3,4,5
C78e R= CH$_2$(C$_6$H$_4$)-(OC$_2$H$_5$)-2
C78f R= CH$_2$CH$_2$N(CH$_2$CH$_2$)$_2$O

C79a: NHC= Blm, X= Br
C79b: NHC= BIAN-IPr
       X= Cl

C79c

C79d

C80

Figure 10. Condution.

L5a R= H, X= Cl
L5b R= CH$_3$, X= Br
L5c R= NO$_2$, X= Cl
L5d R= Cl, X= Cl
L5e R= Br, X= Br

L6

L7a

L7b n= 7
L7c n= 15

Figure 11.

The use of palladium complexes generated in situ from palladium acetate, and 1,3-dialky-4-methylimidazolinium salts (**L1**–**g**) was investigated as catalysts for the Heck coupling reactions of styrene with aryl bro-

mides in water/DMF and demonstrated good catalytic activity (Table 7, entries 1–4).[95] This catalytic system provides good conditions for the coupling of aryl bromides without additives such as tetrabutylammonium bromide in air. The in situ formed catalytic system derived from the cyclobutylmethyl functionalized imidazolinium/benzimidazolium salts (**L2**–**L3**), and Pd(OAc)$_2$ was used in the Heck reaction between aryl halides and styrene with KOH in water (Table 7, entries 5–11).[96] The carbene ligand **L2a** is much more active than those carbene ligands.

Table 7. Heck coupling reactions carried out using Pd–NHC catalysts in biphasic system.
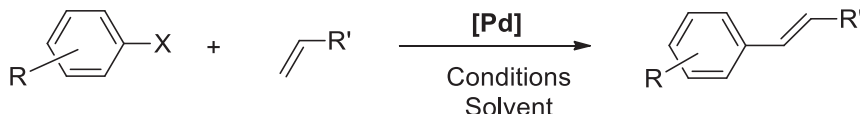
Entry	Catalyst	X	R	R'	Solvent	Conditions	Yield [%]	Ref.
1	**L1/Pd(OAc)$_2$**	Br	H	Ph	DMF/H$_2$O	1 mol% [Pd], 2 mol **L1**%, K$_2$CO$_3$, 80 °C, 2 h	85–95^a	95
2	**L1/Pd(OAc)$_2$**	Br	4-COMe	Ph	DMF/H$_2$O	1 mol% [Pd], 2 mol **L1**%, K$_2$CO$_3$, 80 °C, 2 h	94–99^a	95
3	**L1/Pd(OAc)$_2$**	Br	4-Me	Ph	DMF/H$_2$O	1 mol% [Pd], 2 mol **L1**%, K$_2$CO$_3$, 80 °C, 2 h	81–88^a	95
4	**L1/Pd(OAc)$_2$**	Br	4-CHO	Ph	DMF/H$_2$O	1 mol% [Pd], 2 mol **L1**%, K$_2$CO$_3$, 80 °C, 2 h	85–91^a	95
5	**L2/Pd(OAc)$_2$**	Br	4-OMe	Ph	H$_2$O	1 mol% [Pd], 2 mol **L2**%, K$_2$CO$_3$, 80 °C, 10 h	72–92^a	96
6	**L2/Pd(OAc)$_2$**	Br	4-Me	Ph	H$_2$O	1 mol% [Pd], 2 mol **L2**%, K$_2$CO$_3$, 80 °C, 10 h	83–89^a	96
7	**L2/Pd(OAc)$_2$**	Br	4-CHO	Ph	H$_2$O	1 mol% [Pd], 2 mol **L2**%, K$_2$CO$_3$, 80 °C, 5 h	81–92^a	96
8	**L3/Pd(OAc)$_2$**	Br	4-COMe	Ph	H$_2$O	1 mol% [Pd], 2 mol **L3**%, K$_2$CO$_3$, 80 °C, 3 h	47–68^a	96
9	**L3/Pd(OAc)$_2$**	Br	4-OMe	Ph	H$_2$O	1 mol% [Pd], 2 mol L3%, K$_2$CO$_3$, 80 °C, 10 h	42–55^a	96
10	**L3/Pd(OAc)$_2$**	Br	4-Me	Ph	H$_2$O	1 mol% [Pd], 2 mol **L3**%, K$_2$CO$_3$, 80 °C, 10 h	51–83^a	96
11	**L3/Pd(OAc)$_2$**	Br	4-CHO	Ph	H$_2$O	1 mol% [Pd], 2 mol **L3**%, K$_2$CO$_3$, 80 °C, 5 h	35–51^a	96
12	**L4/Pd(OAc)$_2$**	Br	H	Ph	H$_2$O	0.5 mol% [Pd], 2 mol **L4**%, K$_2$CO$_3$, 100 °C, 3 h	93^d	97
13	**L4/Pd(OAc)$_2$**	I	H	Ph	H$_2$O	0.5 mol% [Pd], 2 mol **L4**%, K$_2$CO$_3$, 100 °C, 1 h	95^d	97
14	**L4/Pd(OAc)$_2$**	Cl	4-COMe	Ph	H$_2$O	0.5 mol% [Pd], 2 mol **L4**%, K$_2$CO$_3$, 100 °C, 6 h	90^d	97
15	**L4/Pd(OAc)$_2$**	Br	4-OMe	Ph	H$_2$O	0.5 mol% [Pd], 2 mol **L4**%, K$_2$CO$_3$, 100 °C, 3 h	94^d	97
16	**L4/Pd(OAc)$_2$**	Cl	4-Me	Ph	H$_2$O	0.5 mol% [Pd], 2 mol **L4**%, K$_2$CO$_3$, 100 °C, 3 h	96^d	97
17	**L4/Pd(OAc)$_2$**	Cl	4-NO$_2$	Ph	H$_2$O	0.5 mol% [Pd], 2 mol **L4**%, K$_2$CO$_3$, 100 °C, 6 h	91^d	97
18	**C64a–b**	Br	4-CHO	CO$_2^n$Bu	H$_2$O	1 mol% [Pd], K$_2$CO$_3$, 160 °C, mw, 24 h	92^c	98
19	**C64b**	Br	4-CHO	CO$_2^n$Bu	H$_2$O	0.5 mol% [Pd], K$_2$CO$_3$, 160 °C, mw, 2 h	99^c	98
20	**C64b**	Br	4-CHO	CO$_2^n$Bu	H$_2$O	0.1 mol% [Pd], K$_2$CO$_3$, 160 °C, mw, 24 h	> 99^c	98

^{a}GC yield. ^{b}Yield of isolated product. ^{c}Yield determined by NMR spectroscopy. ^{d}GCMS yield.

The in situ-generated Pd(OAc)$_2$/**L4** (1:5) complex represented an efficient and reusable catalyst system for Heck coupling reactions (Table 7, entries 12–17). The catalytic system could be reused several times with

Table 8. Suzuki coupling reactions carried out using Pd–NHC catalysts in biphasic system.
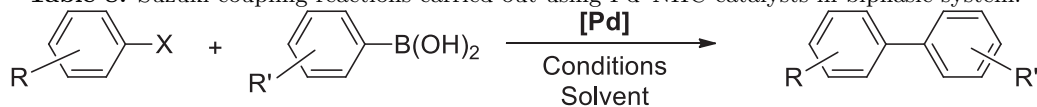
Entry	Catalyst	X	R	R'	Solvent	Conditions	Yield [%]	Ref.
1	C2	Cl	H	H	H_2O	0.2 mol% [Pd], K_3PO_4, TBAB, 40 °C, 17 h	88[b]	33
2	C2	Br	4-OMe	H	H_2O	0.2 mol% [Pd], K_3PO_4, TBAB, 40 °C, 17 h	88[b]	33
4	C2	Br	4-OMe	4-OMe	H_2O	0.2 mol% [Pd], K_3PO_4, TBAB, 40 °C, 12 h	89[b]	33
5	C2	Br	4-OMe	$4-C_{10}H_7$	H_2O	0.2 mol% [Pd], K_3PO_4, TBAB, 40 °C, 26 h	80[b]	33
6	C65a–j	Cl	4-OMe	H	THF/H_2O	1 mol% [Pd], K_3PO_4, r.t., 24 h	48–91[b]	99
7	C66	Cl	4-Me	H	$^iPrOH/H_2O$	0.06 mol% [Pd], NaOH, 100 °C, 14h	91[b]	100
8	C66	Cl	4-OMe	H	$^iPrOH/H_2O$	0.06 mol% [Pd], NaOH, 100 °C, 14h	83[b]	100
9	C66	Cl	$4-C_{10}H_7$	H	$^iPrOH/H_2O$	0.06 mol% [Pd], NaOH, 100 °C, 14h	98[b]	100
10	C68a–b	Cl	4-Me	H	$^iPrOH/H_2O$	0.05 mol% [Pd], KOH, 80 °C, 2 h	85–87[a]	102
11	C68a–b	Cl	4-CHO	H	$^iPrOH/H_2O$	0.05 mol% [Pd], KOH, 80 °C, 2 h	95–98[a]	102
12	C68a–b	Cl	2-Me	$3,5-Me_2$	$^iPrOH/H_2O$	0.05 mol% [Pd], KOH, 80 °C, 2 h	96–99[a]	102
13	C68a–b	Cl	$2,6-Me_2$	$4-^tBu$	$^iPrOH/H_2O$	0.05 mol% [Pd], KOH, 80 °C, 2 h	90–99[a]	102
14	C68a–b	Cl	$4-C_{10}H_7$	$4-C_{10}H_7$	$^iPrOH/H_2O$	0.05 mol% [Pd], KOH, 80 °C, 2 h	93–96[a]	102
15	C69	Cl	H	H	$^iPrOH/H_2O$	0.02 mol% [Pd], K_2CO_3, r.t., 6 h	98[b]	103
16	C69	Cl	4-OMe	H	$^iPrOH/H_2O$	0.02 mol% [Pd], K_2CO_3, r.t., 6 h	96[b]	103
17	C69	Cl	$4-C_{10}H_7$	$4-C_{10}H_7$	$^iPrOH/H_2O$	0.02 mol% [Pd], K_2CO_3, r.t., 6 h	94[b]	103
18	C69	Cl	4-OMe	$4-C_{10}H_7$	$^iPrOH/H_2O$	0.02 mol% [Pd], K_2CO_3, r.t., 6 h	96[b]	103
19	C70	Br	4-CN	$4-CF_3$	DMF/H_2O	0.75 mol% [Pd], K_2CO_3, 80 °C, 1.5 h	80[b]	104
20	C70	Br	4-CN	H	DMF/H_2O	0.75 mol% [Pd], K_2CO_3, 80 °C, 2 h	99[b]	104
21	C70	Br	4-OMe	4-F	DMF/H_2O	0.75 mol% [Pd], K_2CO_3, 80 °C, 5 h	91[b]	104
22	C71a–c	Br	4-OMe	H	DMF/H_2O	1 mol% [Pd], K_2CO_3, 80 °C, 24 h	24–72[c]	105
23	C71a–c	Br	COOH	H	DMF/H_2O	1 mol% [Pd], K_2CO_3, 80 °C, 2 h	75–95[c]	105
24	C71a–c	Br	4-COMe	H	DMF/H_2O	0.01 mol% [Pd], K_2CO_3, 80 °C, 2 h	70–96[c]	105
25	C72	Br	4-OMe	H	$Acetone/H_2O$	1 mol% [Pd], K_2CO_3, r.t., 60 min	98[b]	106
26	C72	I	4-Me	H	$Acetone/H_2O$	1 mol% [Pd], K_2CO_3, r.t., 45 min	97[b]	106
27	C72	Br	4-CN	4-CHO	$Acetone/H_2O$	1 mol% [Pd], K_2CO_3, r.t., 60 min	98[b]	106
28	C73a–f	Cl	H	H	DMF/H_2O	1 mol% [Pd], $KOBu^t$, 50 °C, 3 h	54–88[c]	107
29	C73a–f	Cl	4-OMe	H	DMF/H_2O	1 mol% [Pd], $KOBu^t$, 50 °C, 3 h	54–90[c]	107
30	C73a–f	Cl	4-CHO	H	DMF/H_2O	1 mol% [Pd], $KOBu^t$, 50 °C, 3 h	54–88[c]	107
31	C74	Br	4-COMe	4-OMe	DMF/H_2O	36 ppm [Pd], K_3PO_4, 100 °C, 210 min	80[b]	108
32	C74	Br	$4-NO_2$	4-OMe	DMF/H_2O	500 ppm [Pd], K_3PO_4, 100 °C, 150 min	89[b]	108
33	C75	Br	4-COMe	H	H_2O	0.1 mol% [Pd], KOH, r.t., 24 h	> 99[c,e]	109
34	C75	Br	4-COMe	H	H_2O	0.1 mol% [Pd], KOH, r.t., 24 h	94[c,f]	109
35	C75	Br	4-OMe	H	H_2O	0.1 mol% [Pd], KOH, r.t., 36 h	97[c]	109
36	C75	Br	4-OMe	$4-CF_3$	H_2O	0.1 mol% [Pd], KOH, r.t., 24 h	89[c]	109
37	C76	Br	$C_{14}H_9$	4-Oph	$PhMe/H_2O$	0.01 mol% [Pd], Na_2CO_3, 80 °C, 12 h	96[b]	110
38	C76	Br	$C_{14}H_9$	4-Me	$PhMe/H_2O$	0.01 mol% [Pd], Na_2CO_3, 80 °C, 12 h	94[b]	110
39	C76	Br	$C_{14}H_9$	4-F	$PhMe/H_2O$	0.01 mol% [Pd], Na_2CO_3, 80 °C, 12 h	88[b]	110
40	C77	Cl	4-Me	H	$EtOH/H_2O$	0.5 mol% [Pd], K_2CO_3, 80 °C, 16 h	88[b]	111
41	C77	Cl	4-CN	H	$EtOH/H_2O$	0.5 mol% [Pd], K_2CO_3, 80 °C, 4 h	78[b]	111
42	C77	Cl	$4-SO_2Me$	4-Me	$EtOH/H_2O$	0.5 mol% [Pd], K_2CO_3, 80 °C, 4 h	86[b]	111
43	C77	Cl	4-OMe	2-Me	$EtOH/H_2O$	0.5 mol% [Pd], K_2CO_3, 80 °C, 16 h	91[b]	111
44	C78a–f	Cl	4-OMe	H	DMF/H_2O	1 mol% [Pd], K_2CO_3, 80 °C, 3 h	56–83[c]	113
45	C78a–f	Cl	4-Me	H	DMF/H_2O	1 mol% [Pd], K_2CO_3, 80 °C, 3 h	55–72[c]	113
46	C78a–f	Cl	4-CHO	H	DMF/H_2O	1 mol% [Pd], K_2CO_3, 80 °C, 3 h	82–99[c]	113
47	C78a–f	Cl	4-COMe	H	DMF/H_2O	1 mol% [Pd], K_2CO_3, 80 °C, 3 h	81–96[c]	113
48	C79a–d	Cl	4-CHO	H	H_2O	1 mol% [Pd], $HN(CH_2CH_2OH)_2$, 100 °C, 4 h	34–100[a]	114
49	C79a–d	Cl	4-COMe	H	H_2O	1 mol% [Pd], $HN(CH_2CH_2OH)_2$, 100 °C, 4 h	91–100[a]	114
50	C79a	Cl	4-CN	H	H_2O	1 mol% [Pd], KOH, 100 °C, 4 h	80[a]	114
51	C79a,b,d	Cl	$4-NO_2$	H	H_2O	1 mol% [Pd], $HN(CH_2CH_2OH)_2$, 100 °C, 4 h	91–100[a]	114
52	C80	Cl	4-Me	H	$^iPrOH/H_2O$	0.1 mol% [Pd], NaOH, 60 °C, 6 h	98[c]	115
53	C80	Cl	4-OMe	2-Me	$^iPrOH/H_2O$	0.1 mol% [Pd], NaOH, 60 °C, 24 h	99[c]	115
54	C80	Cl	$2,6-Me_2$	2-Me	$^iPrOH/H_2O$	0.1 mol% [Pd], NaOH, 60 °C, 24 h	95[c]	115
55	C80	Cl	4-COOH	H	H_2O	0.1 mol% [Pd], NaOH, 60 °C, 6 h	95[b]	115

[a]GC yield. [b]Yield of isolated product. [c]Yield determined by NMR spectroscopy. [d]GCMS yield. [e]1st cycle. [d]4th cycle

only a slight decrease in its activity.[97] Sulfonate functionalized complexes **C64a–b** are soluble in H_2O, and so their catalytic activities were tested in aqueous Heck reactions (Table 7, entries 18–20).[98]

Complexes **C65a–j** were investigated for the coupling between 4-methoxyphenyl chloride and phenylboronic acid, and the effects of the NHCs and Im moieties were fully discussed.[99] The sterically hindered IPr-based complex showed the highest catalytic activity (Table 8, entry 6).

Mixed PR_3/NHC Pd complexes **C66** were applied in Suzuki coupling of aryl chlorides with very low catalyst loadings in an aqueous medium (water/isopropanol 9:1) (Table 8, entries 7–9).[100] Complex **C67** was used successfully for the coupling of arylboronic acids with heteroaryl bromides and chlorides.[101]

Monoligated imine-Pd-NHC complexes (**C68a–c**) with very high activity for the coupling of aryl chlorides and aryl boronic acids have been well explored. The use of ^{i}PrOH–H_2O as the solvent and KOH as the base at 80 °C proved to be an efficient and mild condition for the synthesis of biphenyls in excellent yields with only 0.05 mol% catalyst loadings, even at the condition of 0.005 mol% catalyst loadings, especially with catalyst **C68c** (Table 8, entries 10–14).[102]

The cross coupling of a broad variety of aryl chlorides and arylboronic acids using a palladium catalyst (**C69**) bearing a functionalized NHC ligand run under air in aqueous media at room temperature with low loadings of the catalyst was reported (Table 8, entries 15–18).[103] A cellulose-supported N-methylimidazole-palladium catalyst (**C70**) was used for coupling of aryl halides and phenylboronic acids to create the corresponding coupling products in good to excellent yields.[104] Moreover, the catalyst is easily recovered using only a few cycles of simple filtration. Nanopalladium sites on the surface of the cellulose support were very well distributed, as demonstrated by TEM images (Table 8, entries 19–21).

C71a–c have been found to be efficient catalysts for Suzuki coupling reactions (yield up to 96% in 2 h at 80 °C).[105] Nanoparticles (NPs) formed at the beginning of these reactions appear to be important for catalytic coupling, probably as dispensers of Pd(0), and contain Pd and Se. The catalytic activity of **C71c**, with the longest alkyl chain, has been found to be higher relative to those of **C71a** and **C71b** (Table 8, entries 22–24).

Benzimidazole-based Pd-N-heterocyclic carbene complex (**C72**) catalyzed the Suzuki cross-coupling reaction in a wide variety of substrates, including the heteroaromatic system under ambient conditions.[106] The catalyst is also effective for the multi-Suzuki cross-coupling reaction (Table 8, entries 25–27). The sterically hindered NHC complexes (**C73a–f**) smoothly catalyzed the reactions of electron-rich and electron-poor aryl chlorides under mild reaction conditions in aqueous DMF (Table 8, entries 28–30).[107] Functionalizable N-heterocyclic carbene-triazole palladium complex (**C74**) was active in the Suzuki cross-coupling reaction (Table 8, entries 31 and 32).[108] Sulfonated water-soluble PEPPSI–Pd–NHC-type complexes, **C75**, bearing one dipp substituent on one N atom of the imidazole ring, displayed good recyclability and performed couplings of aryl chlorides and bromides at room temperature (Table 8, entries 33–36).[109]

The cyclometalated complex **C76** was shown to catalyze the coupling of 9-bromophenanthrene with a wide scope of aryl boronic acids, irrespective of their electronic properties and at a very low catalyst concentration (Table 8, entries 37–39).[110] Commercially available Pd–NHC complex (**C77**) acts as precatalyst under very mild conditions using a mixture of ethanol/water as solvent at low catalyst loading (Table 8, entries 40–43).[111] Stereospecific and regioselective cross coupling of 2-arylaziridines with arylboronic acids by [(SIPr)Pd(cinnamyl)Cl], **C77**, was very recently described to obtain configurationally defined arylphenethylamine derivatives.[112]

NHC–$PdCl_2$ (pyridine) complexes (**C78a–f**) for the coupling of various aryl chlorides under mild condi-

tions in aqueous DMF with low catalyst loadings (0.01 mol%) resulted in high yields (Table 8, entries 44–47).[113] The complexes **C79** were applied in the reaction of phenylboronic acid with aryl halides in neat water, the complexes **79b** and **79d** displayed the highest catalytic activity at 100 °C (Table 8, entries 48–51), and the catalytic system could be reused several times with only a slight decrease in its activity.[114] Water-soluble Pd(II)–NHC complex, **C80**, where NHC is a dianionic sulfonated and sterically hindered catalyst, was used for the Suzuki coupling of aryl chlorides and boronic acids in mixtures ^{i}PrOH/water or water (Table 8, entries 52–55).[115]

Microwave-promoted catalytic activity **L5a–e** for the Suzuki cross-coupling reaction were determined using in situ formed palladium(0) nanoparticles (PdNPs) from a catalytic system consisting of Pd(OAc)$_2$/K$_2$CO$_3$ in DMF/H$_2$O.[116] Suzuki reactions with aryl iodides and aryl bromides were found to be nearly quantitative (Table 9, entries 1–5). Chiral 1-(acetylated glucopyranosyl)-3-substituted-imidazolium salt (**L6**) was remarkably efficient in a Pd-catalyzed reaction of functionalized aryl boronic acids with aryl halides using environmentally friendly conditions (Table 9, entries 6–16).[117]

Phosphine-chelated palladium catalyst precursors with a poly(ethylene glycol) (PEG) chain (**L7a–c**) were highly efficient for coupling of aryl bromides with phenylboronic acid at the palladium loading of 0.1 mol% in both organic and aqueous solvents (Table 9, entries 17–22).[118]

The catalytic system consisting of 0.1 mol% palladium acetate and **L8** in 1:5 ratio allowed the effective coupling of a range of aryl bromides and chlorides with trimethoxy(phenyl)silane. The Hiyama reactions were carried out in NaOH solution (50% H$_2$O w/w) at 120 °C under microwave irradiation over 60 min (Table 10, entries, 1–11).[119]

3.5. Immobilization

The first principle of green chemistry is prevention of waste. Thus, the prevention of waste can be achieved if most of the reagents and the solvent are recyclable. For example, catalysts and reagents that are bound to a solid phase can be filtered off, and can be regenerated and reused in a subsequent run.

Catalysts suitable for cross-coupling processes based on supported N-heterocyclic carbene (NHC) complexes of palladium are separable after their simple manipulations, reusable, and resistant to metal leaching.[23] These catalysts are well defined, and after their use they are easily separated from the products without degradation. They can be reused and do not contaminate the product with leached palladium under mild conditions or even in aqueous media. The types of catalyst supports can be classified into solid and liquid organic materials, such as organic polymers, ionic liquids, and carbon nanotubes, and into inorganic materials, like mesoporous materials, inorganic polymers and silica, alumina, and inorganic oxides. The physical properties of the support are very important for application and separation. A selected number of supported palladium–NHC complexes used in Heck, Suzuki, and Sonogashira coupling reactions are shown in Figures 12–14.

The catalytic activity of **C81** was tested for a Heck reaction of aryl halides with styrene and n-butyl acrylate using NMP as the solvent and K$_2$CO$_3$ as the base and 0.5 mol% of catalyst at 120 °C (Table 11, entries 1–9). Recovery and reusability of the supported catalyst (**C76**) were investigated using iodobenzene and n-butyl acrylate as model substrates.[120] This catalyst was used in 12 subsequent reactions and the catalyst retained its activity in these repeating cycles (Table 11, entry 5). The XRD technique, TEM image, and AFM histogram were used to ascertain the presence of Pd(0). Simple filtration of the catalyst, excellent dispersity of Pd particles, short reaction times, and high yields were advantages of this catalytic system.

Table 9. Suzuki coupling reactions carried out using in situ formed Pd–NHC catalysts.

$$R{-}\!\!\bigcirc\!\!{-}X \ + \ \bigcirc\!\!{-}B(OH)_2 \ \xrightarrow[\text{Solvent}]{[Pd] \atop \text{Conditions}} \ R{-}\!\!\bigcirc\!\!{-}\bigcirc\!\!{-}R'$$

Entry	Catalyst	X	R	R'	Solvent	Conditions	Yield [%]	Ref.
1	L5/Pd(OAc)₂	I	4-Me	H	DMF/H₂O	1 mol% [Pd], 2 mol **L5**%, K₂CO₃, 120 °C, 10 min	96–99^d	116
2	L5/Pd(OAc)₂	Cl	4-Me	H	DMF/H₂O	1 mol% [Pd], 2 mol **L5**%, K₂CO₃, 120 °C, 10 min	71–84^d	116
3	L5/Pd(OAc)₂	I	4-OMe	H	DMF/H₂O	1 mol% [Pd], 2 mol **L5**%, K₂CO₃, 120 °C, 10 min	96–99^d	116
4	L5/Pd(OAc)₂	Cl	4-OMe	H	DMF/H₂O	1 mol% [Pd], 2 mol **L5**%, K₂CO₃, 120 °C, 10 min	68–79^d	116
5	L5/Pd(OAc)₂	Cl	4-CHO	H	DMF/H₂O	1 mol% [Pd], 2 mol **L5**%, K₂CO₃, 120 °C, 10 min	73–85^d	116
6	L6/Pd(OAc)₂	I	H	H	EtOH	0.1 mol% [Pd], 2 mol **L6**%, NaOH, reflux, 3 h	99^b	117
7	L6/Pd(OAc)₂	Br	H	H	EtOH	0.1 mol% [Pd], 2 mol **L6**%, NaOH, reflux, 0.2 h	99^b	117
8	L6/Pd(OAc)₂	I	4-Me	H	EtOH	0.1 mol% [Pd], 2 mol **L6**%, NaOH, reflux, 0.2 h	99^b	117
9	L6/Pd(OAc)₂	Br	4-Me	H	EtOH	0.1 mol% [Pd], 2 mol **L6**%, NaOH, reflux, 3 h	99^b	117
10	L6/Pd(OAc)₂	Br	4-OMe	H	EtOH	0.1 mol% [Pd], 2 mol **L6**%, NaOH, reflux, 3 h	99^b	117
11	L6/Pd(OAc)₂	Br	4-COMe	H	EtOH	0.1 mol% [Pd], 2 mol **L6**%, NaOH, reflux, 3 h	99^b	117
12	L6/Pd(OAc)₂	Cl	4-CF₃	H	EtOH	0.1 mol% [Pd], 2 mol **L6**%, NaOH, reflux, 12 h	92^b	117
13	L6/Pd(OAc)₂	Br	4-Me	4-Me	EtOH	0.1 mol% [Pd], 2 mol **L6**%, NaOH, reflux, 3 h	96^b	117
14	L6/Pd(OAc)₂	Br	4-Me	3,5-Me₂	EtOH	0.1 mol% [Pd], 2 mol **L6**%, NaOH, reflux, 3 h	93^b	117
15	L6/Pd(Oac)₂	Br	4-Me	3,4,5-F₃	EtOH	0.1 mol% [Pd], 2 mol **L6**%, NaOH, reflux, 3 h	99^b	117
16	L6/Pd(OAc)₂	Br	4-COMe	4-CF₃	EtOH	0.1 mol% [Pd], 2 mol **L6**%, NaOH, reflux, 3 h	98^b	117
17	L7b–c/Pd(OAc)₂	Br	4-Me	H	H₂O, PEG	0.005 mol [Pd], 0.0055 mol **L7**%, K₂CO₃, 110 °C, 3 h	92–95^b	118
18	L7a–c/Pd(OAc)₂	Br	4-Me	H	Dioxane	0.1 mol% [Pd], 1 mol **L7**%, K₂CO₃, 110 °C, 3 h	93–95^b	118
19	L7c/Pd(OAc)₂	Br	4-Me	H	H₂O, PEG	0.005 mol [Pd], 0.0055 mol **L7**%, K₂CO₃, 110 °C, 3 h	92^b	118
20	L7a–c/Pd(OAc)₂	Br	4-OMe	H	Dioxane	0.1 mol% [Pd], 1 mol **L7**%, K₂CO₃, 110 °C, 3 h	85–95^b	118
21	L7c/Pd(OAc)₂	Br	4-OMe	H	H₂O, PEG	0.005 mol [Pd], 0.0055 mol **L7**%, K₂CO₃, 110 °C, 3 h	94^b	118
22	L7c/Pd(OAc)₂	Br	4-COMe	H	H₂O, PEG	0.005 mol [Pd], 0.0055 mol **L7**%, K₂CO₃, 110 °C, 3 h	95^b	118

^{a}GC yield. ^{b}Yield of isolated product. ^{c}Yield determined by NMR spectroscopy. ^{d}GCMS yield.

Table 10. Hiyama coupling reactions carried out using $Pd(OAc)_2$ / L8 catalysts.
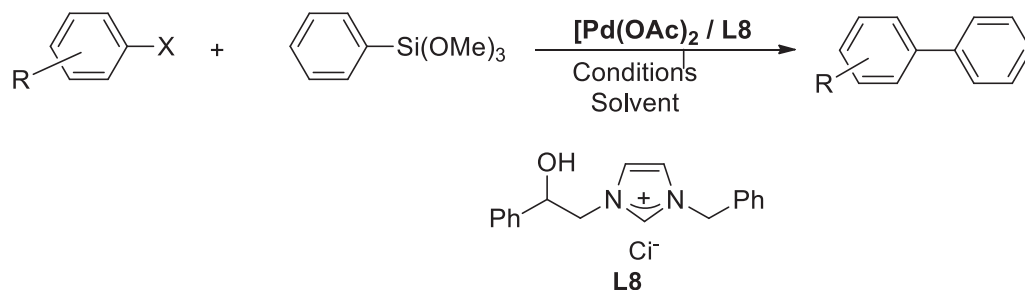
Entry	X	R	Solvent	Conditions	Yield [%]	Ref.
1	Cl	4-COMe	Aq. NaOH	0.1 mol% [Pd], 0.2 mol L8%, NaOH, 120 °C, mw, 60 min	77^a	119
2	Cl	4-COMe	Aq. NaOH	0.1 mol% [Pd], 0.4 mol L8%, NaOH, 120 °C, mw, 60 min	93^a	119
3	Br	$4\text{-}C_5H_4N$	Aq. NaOH	0.1 mol% [Pd], 0.2 mol L8%, NaOH, 120 °C, mw, 60 min	48^a	119
4	Br	$4\text{-}C_5H_4N$	Aq. NaOH	0.1 mol% [Pd], 0.5 mol L8%, NaOH, 120 °C, mw, 60 min	63^a	119
5	Br	$4\text{-}C_4H_3S$	Aq. NaOH	0.1 mol% [Pd], 0.5 mol L8%, NaOH, 120 °C, mw, 60 min	63^a	119
6	Br	4-OH	Aq. NaOH	0.1 mol% [Pd], 0.2 mol L8%, NaOH, 120 °C, mw, 60 min	86^a	119
7	Br	4-OH	Aq. NaOH	0.1 mol% [Pd], 0.5 mol L8%, NaOH, 120 °C, mw, 60 min	89^a	119
8	Br	4-COOH	Aq. NaOH	0.1 mol% [Pd], 0.2 mol L8%, NaOH, 120 °C, mw, 60 min	67^a	119
9	Br	4-COOH	Aq. NaOH	0.1 mol% [Pd], 0.5 mol L8%, NaOH, 120 °C, mw, 60 min	81^a	119
10	Cl	$4\text{-}CF_3$	Aq. NaOH	0.1 mol% [Pd], 0.2 mol L8%, NaOH, 120 °C, mw, 60 min	90^a	119
11	Cl	$4\text{-}CF_3$	Aq. NaOH	0.1 mol% [Pd], 0.5 mol L8%, NaOH, 120 °C, mw, 60 min	92^a	119

^{a}Yield of isolated product.
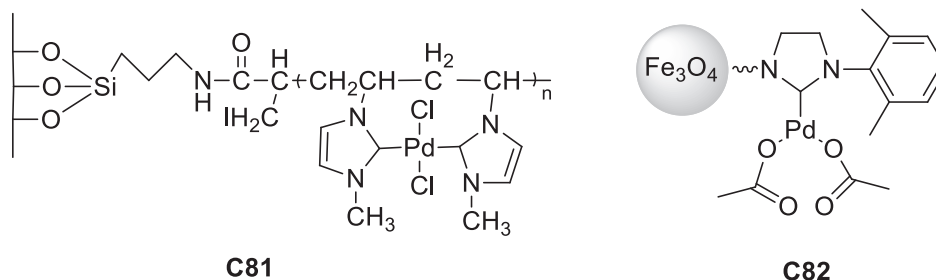
Figure 12.

The "grafting from" immobilization of imidazolinium salts on magnetic nanoparticles, its complexation with palladium ions (**C82**), and application in the Heck reaction were presented by Wilczewska et al. (Table 11, entries 10–16). The separation and purification of products were easily carried out by an external magnetic field. The catalyst could be easily removed from the reaction mixture and reused five times without loss of their activity (Table 11, entry 13).[121]
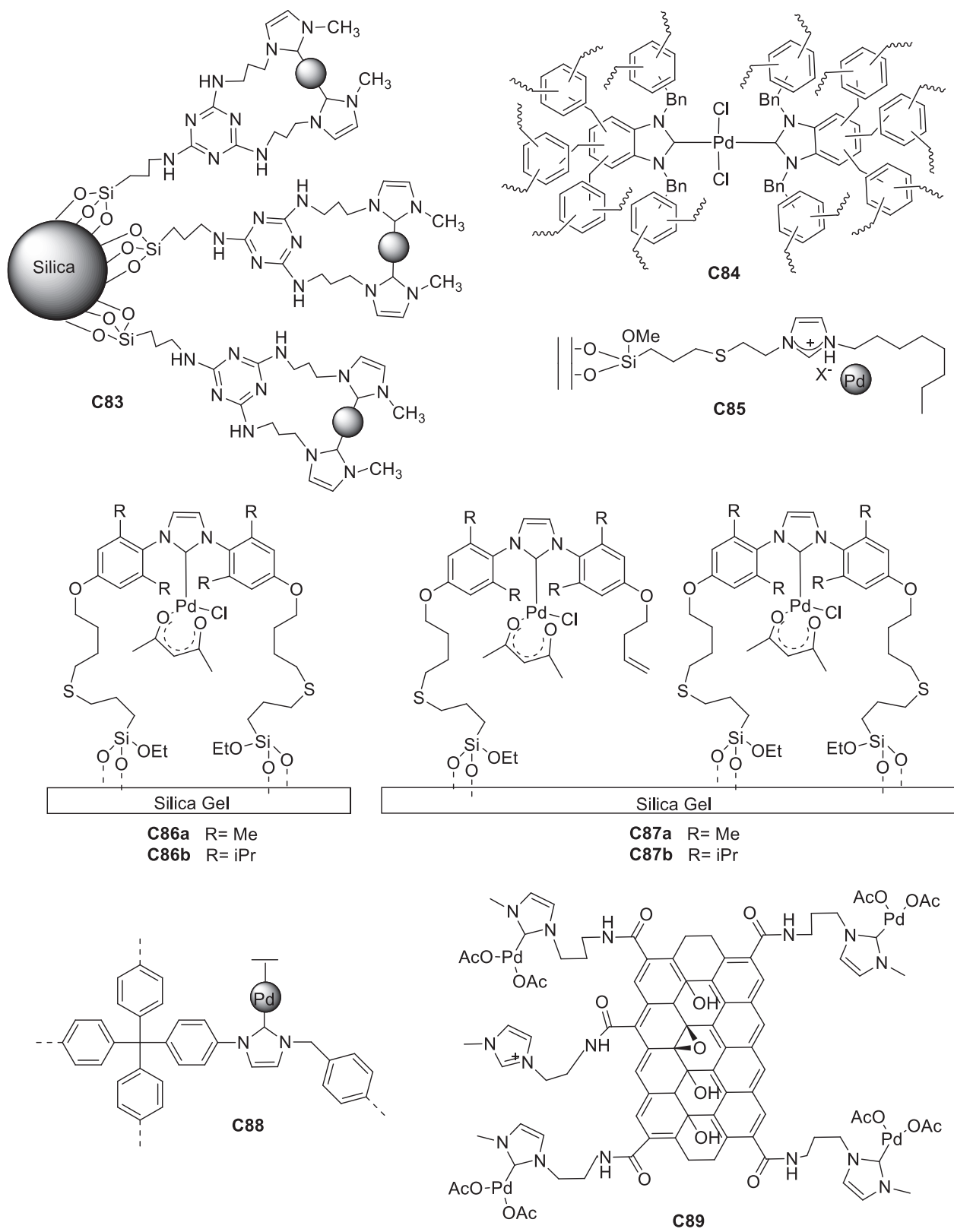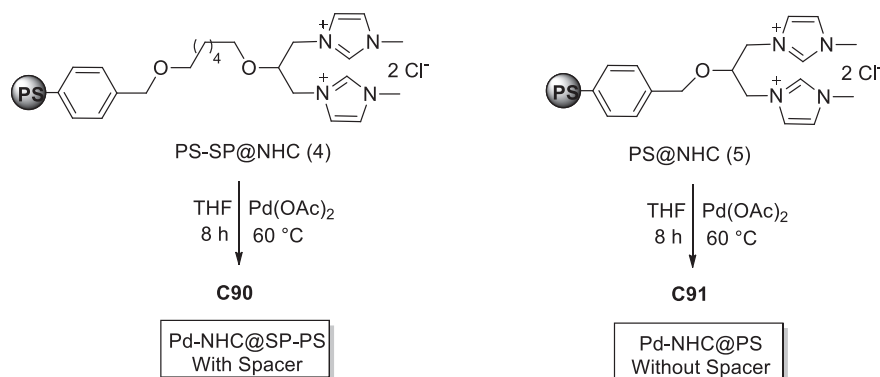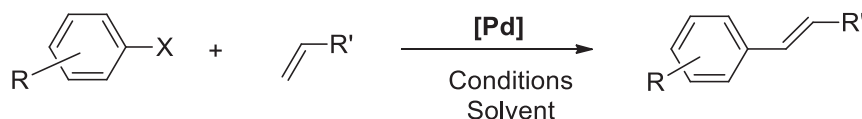
C83

C84

C85

C86a R= Me
C86b R= iPr

C87a R= Me
C87b R= iPr

C88

C89

Figure 13.

Figure 14.

Table 11. Heck coupling reactions carried out using immobilized Pd–NHC catalysts.

Entry	Catalyst	X	R	R'	Solvent	Conditions	Yield [%]	Ref.
1	**C81**	I	H	Ph	NMP	0.5 mol% [Pd], K_2CO_3, 120 °C, 7 h	90^b	120
2	**C81**	I	4-OMe	Ph	NMP	0.5 mol% [Pd], K_2CO_3, 120 °C, 12 h	80^b	120
3	**C81**	I	2-OMe	Ph	NMP	0.5 mol% [Pd], K_2CO_3, 120 °C, 10 h	88^b	120
4	**C81**	I	H	CO_2^nBu	NMP	0.5 mol% [Pd], K_2CO_3, 120 °C, 2 h	$95^{b,c}$	120
5	**C81**	I	H	CO_2^nBu	NMP	0.5 mol% [Pd], K_2CO_3, 120 °C, 4.25 h	$80^{b,e}$	120
6	**C81**	Br	H	CO_2^nBu	NMP	0.5 mol% [Pd], K_2CO_3, 120 °C, 8 h	80^b	120
7	**C81**	I	4-OMe	CO_2^nBu	NMP	0.5 mol% [Pd], K_2CO_3, 120 °C, 6 h	95^b	120
8	**C81**	Br	4-NO_2	CO_2^nBu	NMP	0.5 mol% [Pd], K_2CO_3, 120 °C, 5 h	90^b	120
9	**C81**	Br	4-CN	CO_2^nBu	NMP	0.5 mol% [Pd], K_2CO_3, 120 °C, 4 h	93^b	120
10	**C82**	I	H	Ph	DMF	0.56 mol% [Pd], $NaHCO_3$, 120 °C, 3 h	96^b	121
11	**C82**	Br	4-COMe	Ph	DMF	0.56 mol% [Pd], $NaHCO_3$, 120 °C, 22 h	82^b	121
12	**C82**	I	H	CO_2^nBu	DMF	0.56 mol% [Pd], $NaHCO_3$, 120 °C, 3 h	$86^{b,c}$	121
13	**C82**	I	H	CO_2^nBu	DMF	0.56 mol% [Pd], $NaHCO_3$, 120 °C, 3 h	$85^{b,d}$	121
14	**C82**	Br	4-NO_2	CO_2^nBu	DMF	0.56 mol% [Pd], $NaHCO_3$, 120 °C, 22 h	72^b	121
15	**C82**	Br	2-NO_2	CO_2^nBu	DMF	0.56 mol% [Pd], $NaHCO_3$, 120 °C, 22 h	95^b	121
16	**C82**	Br	4-COMe	CO_2^nBu	DMF	0.56 mol% [Pd], $NaHCO_3$, 120 °C, 22 h	82^b	121

[a]GC yield. [b]Yield of isolated product. [c]1st cycle. [d]5th cycle. [e]12th cycle.

Cyanuric N-heterocyclic palladium complex immobilized onto silica (SiO$_2$-pA-Cyanuric-NH-Pd) (**C83**) showed excellent performance in the reaction aryl halides with phenylboronic acid under green conditions (H$_2$O). Reusability and recovery were accomplished in five sequential reaction runs (Table 12, entries 1–6).[122] **C84** afforded rapid conversions of various aryl halides and arylboronic acids even at a Pd loading of 0.057 mmol% in aqueous media (Table 12, entries 7–13). This complex could be used 5 times without significant loss of activity (Table 12, entry 8).[123]

Table 12. Suzuki coupling reactions carried out using immobilized Pd–NHC catalysts.
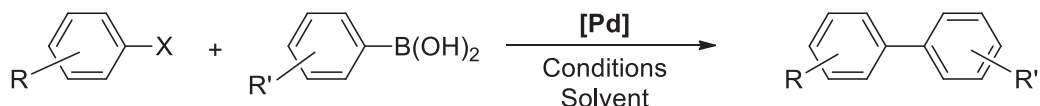
Entry	Catalyst	X	R	R'	Solvent	Conditions	Yield [%]	Ref.
1	**C83**	I	H	H	H$_2$O	0.5 mol% [Pd], K$_2$CO$_3$, 100 °C, 4 h	94[b]	122
2	**C83**	Br	H	H	H$_2$O	0.5 mol% [Pd], K$_2$CO$_3$, 100 °C, 5 h	86[b]	122
3	**C83**	I	4-Me	H	H$_2$O	0.5 mol% [Pd], K$_2$CO$_3$, 100 °C, 5 h	94[b]	122
4	**C83**	Br	4-Me	H	H$_2$O	0.5 mol% [Pd], K$_2$CO$_3$, 100 °C, 5 h	89[b]	122
5	**C83**	I	4-OMe	H	H$_2$O	0.5 mol% [Pd], K$_2$CO$_3$, 100 °C, 1.5 h	91[b]	122
6	**C83**	Br	4-NO$_2$	H	H$_2$O	0.5 mol% [Pd], K$_2$CO$_3$, 100 °C, 5 h	92[b]	122
7	**C84**	Br	H	H	EtOH/H$_2$O	0.057 mmol% [Pd], K$_2$CO$_3$, 80 °C, 5 min	99[b,c]	123
8	**C84**	Br	H	H	EtOH/H$_2$O	0.057 mmol% [Pd], K$_2$CO$_3$, 80 °C, 5 min	92[b,d]	123
9	**C84**	Cl	H	H	EtOH/H$_2$O	0.057 mmol% [Pd], K$_2$CO$_3$, 80 °C, 180 min	100[b]	123
10	**C84**	Br	H	4-OMe	EtOH/H$_2$O	0.057 mmol% [Pd], K$_2$CO$_3$, 80 °C, 10 min	95[b]	123
11	**C84**	I	4-Me	H	EtOH/H$_2$O	0.057 mmol% [Pd], K$_2$CO$_3$, 80 °C, 10 min	99[b]	123
12	**C84**	Br	H	4-Cl	EtOH/H$_2$O	0.057 mmol% [Pd], K$_2$CO$_3$, 80 °C, 15 min	93[b]	123
13	**C84**	Br	H	4-CF$_3$	EtOH/H$_2$O	0.057 mmol% [Pd], K$_2$CO$_3$, 80 °C, 60 min	98[b]	123
14	**C85**	I	4-Me	H	EtOH/H$_2$O	1.0 mmol% [Pd], K$_2$CO$_3$, 120 °C, 10 min	> 99[b]	124
15	**C85**	Br	4-Me	H	EtOH/H$_2$O	1.0 mmol% [Pd], K$_2$CO$_3$, 120 °C, 10 min	> 99[b]	124
16	**C85**	Br	3-OMe	H	EtOH/H$_2$O	1.0 mmol% [Pd], K$_2$CO$_3$, 120 °C, 10 min	88[b,d]	124
17	**C85**	Br	3-COMe	H	EtOH/H$_2$O	1.0 mmol% [Pd], K$_2$CO$_3$, 120 °C, 10 min	80[b]	124
18	**C85**	Br	4-CHO	H	EtOH/H$_2$O	1.0 mmol% [Pd], K$_2$CO$_3$, 120 °C, 10 min	> 99[b]	124
19	**C85**	Br	4-NO$_2$	H	EtOH/H$_2$O	1.0 mmol% [Pd], K$_2$CO$_3$, 120 °C, 10 min	> 99[b]	124
20	**C86b**	Br	2,4-(Me)$_2$	4-OMe	H$_2$O	2.0 mol% [Pd], Cs$_2$CO$_3$, 60 °C, 5 h	87[a]	125
21	**C87a**	Br	2,4-(Me)$_2$	4-OMe	H$_2$O	1.5 mol% [Pd], Cs$_2$CO$_3$, 60 °C, 20 h	35[a]	125
22	**C87b**	Br	2,4-(Me)$_2$	4-OMe	H$_2$O	1.5 mol% [Pd], Cs$_2$CO$_3$, 60 °C, 20 h	85[a]	125
23	**C87b**	Br	2,4-(Me)$_2$	4-OMe	H$_2$O	1.0 mol% [Pd], Cs$_2$CO$_3$, 60 °C, 5 h	88[a]	125
24	**C87b**	Br	2,4-(Me)$_2$	4-OMe	H$_2$O	2.0 mol% [Pd], Cs$_2$CO$_3$, 60 °C, 5 h	> 95[a]	125
25	**C88**	Br	H	H	MeOH/H$_2$O	0.2 mmol% [Pd], K$_2$CO$_3$, 60 °C, 1 h	93[a]	126
26	**C88**	Br	H	4-Me	MeOH/H$_2$O	0.2 mmol% [Pd], K$_2$CO$_3$, 60 °C, 2 h	99[a]	126
27	**C88**	Br	4-Me	H	MeOH/H$_2$O	0.2 mmol% [Pd], K$_2$CO$_3$, 60 °C, 3.5 h	95[a]	126
28	**C88**	Br	4-OMe	H	MeOH/H$_2$O	0.2 mmol% [Pd], K$_2$CO$_3$, 60 °C, 3.5 h	96[a,c]	126
29	**C88**	Br	4-OMe	H	MeOH/H$_2$O	0.2 mmol% [Pd], K$_2$CO$_3$, 60 °C, 3.5 h	97[a,d]	126
30	**C88**	Br	4-COMe	H	MeOH/H$_2$O	0.2 mmol% [Pd], K$_2$CO$_3$, 60 °C, 1.5 h	> 99[a]	126
31	**C89**	I	H	H	DMF/H$_2$O	1.0 mmol% [Pd], Cs$_2$CO$_3$, 60 °C, 1 h	98[a]	126
32	**C89**	Br	4-Me	H	DMF/H$_2$O	1.0 mmol% [Pd], Cs$_2$CO$_3$, 50 °C, 1 h	89[a,c]	126
33	**C89**	Br	4-Me	H	DMF/H$_2$O	1.0 mmol% [Pd], Cs$_2$CO$_3$, 50 °C, 1 h	79[a,d]	126
34	**C89**	I	4-OMe	H	DMF/H$_2$O	1.0 mmol% [Pd], Cs$_2$CO$_3$, 60 °C, 1 h	99[a]	126
35	**C89**	I	4-NO$_2$	H	DMF/ H$_2$O	1.0 mmol% [Pd], Cs$_2$CO$_3$, 60 °C, 1 h	98[a]	126
36	**C89**	I	OH	H	DMF/H$_2$O	1.0 mmol% [Pd], Cs$_2$CO$_3$, 60 °C, 1 h	96[a]	126
37	**C89**	Br	4-CHO	H	DMF/H$_2$O	1.0 mmol% [Pd], Cs$_2$CO$_3$, 60 °C, 1 h	98[a]	126

[a]GC yield. [b]Yield of isolated product. [c]1st cycle. [d]5th cycle.

The palladium catalyst **C85** based on modified halloysite nanotubes displayed good activity, allowing the synthesis of several biphenyl compounds in high yield working with only 0.1 mol% palladium loading (Table 12, entries 14–19). The application of microwave irradiation decreased the reaction time and also improved

conversion with respect to traditional heating. Recycling investigations were carried out using catalyst at 1 mol% in the reaction between phenylboronic acid and 3-bromoanisole (Table 12, entry 16).[124]

Silica-immobilized Pd–NHC precatalysts (**C86**–**C87**) were active in the reaction of aryl chlorides and bromides bearing sterically hindered substituents (Table 12, entries 20–24).[125] A Pd–NHC porous polymeric network, **C88**, with opened pore channels in the polymeric network revealed high activity in the coupling of arylbromides in MeOH –H_2O at 60 °C (Table 12, entries 25–30).[126] Additionally the catalyst could be reused five times without loss of activity (Table 12, entry 29).

Graphene oxide was functionalized with a N-heterocyclic carbene (NHC) precursor, 3-(3-aminopropyl)-1-methylimidazolium bromide for the immobilization of palladium catalyst.[127] The supported NHC complex **C89** showed excellent catalytic activity and fast reaction kinetics in the aqueous-phase Suzuki reaction of aryl bromides and chlorides at relatively mild conditions (Table 12, entries 31–37). The Pd catalyst **C89** was reused five times without any loss of its catalytic activity (Table 12, entry 33).

Reusability of the complex **C83** in the Sonogashira reaction was also investigated in the model reaction of iodobenzene and phenylacetylene under optimized conditions.[122] Recovery was accomplished in five sequential reaction runs (Table 13, entries 1–7).

Table 13. Sonogashira coupling reactions carried out using immobilized Pd–NHC catalysts.

R≡≡ + Ar-X $\xrightarrow[\text{Condition Solvent}]{\text{[Pd]}}$ R≡≡Ar
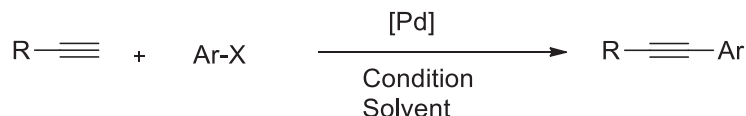
Entry	Catalyst	X	R	Ar	Solvent	Conditions	Yield [%]	Ref.
1	**C83**	I	Ph	Ph	DMF/H_2O	0.5 mol% [Pd], NaOAc, 80 °C, 3 h	96[b,c]	122
2	**C83**	I	Ph	Ph	DMF/H_2O	0.5 mol% [Pd], NaOAc, 80 °C, 3 h	96[b,d]	122
3	**C83**	Br	Ph	Ph	DMF/H_2O	0.5 mol% [Pd], NaOAc, 80 °C, 4.5 h	83[a]	122
4	**C83**	I	Ph	4-OMePh	DMF/H_2O	0.5 mol% [Pd], NaOAc, 80 °C, 4 h	93[a]	122
5	**C83**	I	Ph	4-MePh	DMF/H_2O	0.5 mol% [Pd], NaOAc, 80 °C, 3.5 h	91[a]	122
6	**C83**	I	Ph	4-MePh	DMF/H_2O	0.5 mol% [Pd], NaOAc, 80 °C, 5 h	82[a]	122
7	**C83**	Br	Ph	4-NO_2Ph	DMF/H_2O	0.5 mol% [Pd], NaOAc, 80 °C, 4.5 h	87[a]	122
8	**C90**	Br	Ph	4-Ph	-	1 mol% [Pd], NEt₃, 90 °C, 1.5 h	95[a]	128
9	**C90**	Br	Ph	4-MePh	-	1 mol% [Pd], NEt₃, 90 °C, 2 h	89[a]	128
10	**C90**	Br	Ph	4-MePh	-	1 mol% [Pd], NEt₃, 90 °C, 2.5 h	90[a]	128
11	**C90**	Br	Ph	4-NO_2Ph	-	1 mol% [Pd], NEt₃, 90 °C, 2 h	75[a,d]	128
12	**C90**	Br	Ph	4-CHOPh	-	1 mol% [Pd], NEt₃, 90 °C, 3 h	91[a]	128
13	**C90**	Br	Ph	4-MeOCPh	-	1 mol% [Pd], NEt₃, 90 °C, 2.5 h	89[a]	128
14	**C91**	Br	Ph	4-Ph	-	1 mol% [Pd], NEt₃, 90 °C, 3 h	88[a]	128
15	**C91**	Br	Ph	4-MePh	-	1 mol% [Pd], NEt₃, 90 °C, 4,5 h	87[a]	128
16	**C91**	Br	Ph	4-MePh	-	1 mol% [Pd], NEt₃, 90 °C, 4 h	88[a]	128
17	**C91**	Br	Ph	4-NO_2Ph	-	1 mol% [Pd], NEt₃, 90 °C, 4 h	70[a,d]	128
18	**C91**	Br	Ph	4-CHOPh	-	1 mol% [Pd], NEt₃, 90 °C, 5 h	85[a]	128
19	**C91**	Br	Ph	4-CNPh	-	1 mol% [Pd], NEt₃, 90 °C, 3.5 h	86[a]	128

[a]Yield of isolated product. [b]GC yield. [c]1st cycle. [d]5th cycle.

Applications of a polymer supported air-stable palladium NHC complex with a spacer (catalyst **C90**, Pd–NHC@SP–PS) and without a spacer (catalyst **C91**, Pd–NHC@PS) have been studied for the Sonogashira cross-coupling reaction.[128] Catalyst **C90** has been found to be more active than catalyst **C91**, due to the greater accessibility of active catalytic sites, for a variety of aryl bromides and terminal alkynes in solvent and copper-free Sonogashira cross-coupling reactions under aerobic conditions. After the first reaction, which gave a

quantitative yield of the desired coupling product (95%), the catalyst was recovered and successively subjected to the next run under the same conditions to afford the product in good to excellent yields for up to five cycles (Table 13, entries 8–19).

3.6. Buchwald–Hartwig amination

Buchwald–Hartwig amination is basically a cross-coupling reaction of an aryl halide with an amine to make a carbon–nitrogen bond using palladium as a catalyst and a strong base. The reaction begins by oxidative addition of the aryl halide to the palladium, followed by coordination of the amine to the palladium. The strong base then abstracts a proton from the amine, forming an amide, which in turn attacks the palladium and ejects the halide as a leaving group. Reductive elimination then produces the final aryl amine product and regenerates the catalyst.[129,130] Some NHC ligand and palladium NHC complexes used in amination reactions are presented in Figure 15.
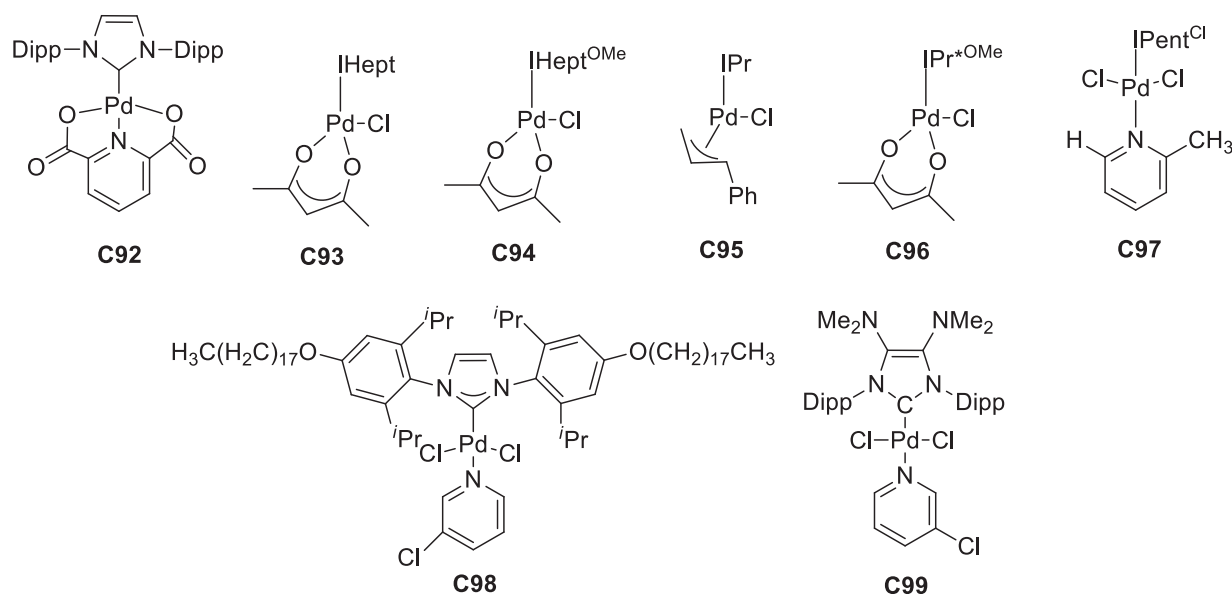
Figure 15.

The catalytic potential of the arsine- and stibine-stabilized carbene palladium complexes **C57** and **C58** for Pd-mediated transformations was investigated with various substrates in Buchwald–Hartwig aminations.[89] The reactions indeed proceeded smoothly to afford the corresponding products in good yields when performed in dried dioxane (Table 14, entries 1–4). Both electron-poor and electron-rich aryl chlorides reacted with amines to afford the corresponding products in high yields.

The well-defined NHC–Pd complexes incorporating a pyridine-2-carboxylate or pyridine-2,6-dicarboxylate ligand (**C92**) exhibited prominent catalytic activity in the coupling of a variety of aliphatic amines with sterically encumbered aryl chlorides at elevated temperature but relatively inferior reactivity at low temperature (Table 14, entries 5–7).[131]

The influence of IPent ligands and other substituents p-position of the Ar group on the N-atoms in arylamination of aryl chlorides with aniline derivatives has been examined by Nolan's group. The overall positive effect attributed to the length of the R-alkyl chains appeared to be maximal with the IHept ligand.[132] The system showed excellent catalytic activity for the coupling of various deactivated aryl chlorides with anilines,

Table 14. Buchwald–Hartwig amination reactions carried out using Pd–NHC catalysts.
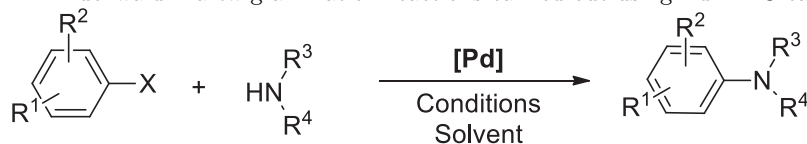
Entry	Catalyst	X	R^1	R^2	R^3	R^4	Solv.	Conditions	Yield [%]	Ref.
1	**C57a–d**	Cl	4-Me	H	H	Ph	Dioxane	0.5 mol% [Pd], ^{t}BuOK, 110 °C, 4 h	90–94^b	89
2	**C57a–d**	Cl	4-OMe	H	H	Ph	Dioxane	0.5 mol% [Pd], ^{t}BuOK, 110 °C, 4 h	92–97^b	89
3	**C58a–d**	Cl	4-OMe	H	H	Ph	Dioxane	0.5 mol% [Pd], ^{t}BuOK, 110 °C, 4 h	93–97^b	89
4	**C58a–d**	Cl	4-OMe	H	H	PhMe$_2$-2,6	Dioxane	0.5 mol% [Pd], ^{t}BuOK, 110 °C, 4 h	82–88^b	89
5	**C92**	Cl	2-Me	6-Me	H	C$_4$H$_8$N	Dioxane	1 mol% [Pd], NaOBu^t, 100 °C, 0.5 h	95^b	131
6	**C92**	Cl	2-Me	6-Me	Me	Ph	Dioxane	1 mol% [Pd], NaOBu^t, 100 °C, 15 min	91^b	131
7	**C92**	Cl	H	H	C$_4$H$_9$	C$_4$H$_9$	Dioxane	1 mol% [Pd], NaOBu^t, 100 °C, 15 min	95^b	131
8	**C93**	Cl	4-Me	H	Bu	Bu	Toluene	0.2 mol% [Pd], ^{t}BuOK, 110 °C, 4 h	92^b	132
9	**C93**	Cl	4-OMe	H	C$_5$H$_4$N	PhF-4	Toluene	0.1 mol% [Pd], ^{t}BuOK, 80 °C, 2 h	97^b	132
10	**C93**	Cl	2-OMe	6-OMe	Me	Ph	Toluene	0.1 mol% [Pd], ^{t}BuOK, 80 °C, 2 h	87^b	132
11	**C94**	Cl	2-Me	6-Me	H	PhF-4	Toluene	0.05 mol% [Pd], KO^{t}Am, 80 °C, 3 h	91^b	133
12	**C94**	Cl	4-OMe	H	H	PhCF$_3$-3	Toluene	0.2 mol% [Pd], KO^{t}Am, 110 °C, 6 h	91^b	133
13	**C94**	Cl	2-OMe	H	H	PhF-4	Toluene	0.05 mol% [Pd], KO^{t}Am, 80 °C, 3 h	96^b	133
14	**C95**	Cl	2-Me	6-Me	H	PhMe$_2$-2,6	-	1 mol% [Pd], KO^{t}Am, 25 °C, 5 min	98^b	134
15	**C95**	Br	2-Me	H	H	PhMe$_2$-2,6	-	1 mol% [Pd], KO^{t}Am, 25 °C, 5 min	99^b	134
16	**C95**	Cl	4-Me	H	H	PhMe$_2$-2,6	-	1 mol% [Pd], KO^{t}Am, 25 °C, 5 min	99^b	134
17	**C95**	Cl	2-OMe	H	H	PhMe$_2$-2,6	-	1 mol% [Pd], KO^{t}Am, 25 °C, 24 h	94^b	134
18	**C96**	Cl	2-Me	H	Me	Ph	Dioxane	0.02 mol% [Pd], KO^{t}Am, 110 °C, 21 h	98^b	135
19	**C96**	Br	4-Me	H	Me	Ph	Dioxane	0.005 mol% [Pd], KO^{t}Am, 110 °C, 21 h	91^b	135
20	**C96**	Cl	4-OMe	H	H	C$_4$H$_8$O	Dioxane	0.05 mol% [Pd], KO^{t}Am, 110 °C, 21 h	93^b	135
21	**C96**	Cl	4-OMe	H	Me	Ph	Dioxane	0.02 mol% [Pd], KO^{t}Am, 110 °C, 21 h	92^b	135
22	**C97**	Cl	4-OMe	H	H	PhCO$_2$Me-3	DME	3 mol% [Pd], Cs$_2$CO$_3$, r.t., 24 h	86^a	136
23	**C97**	Cl	2-OMe	H	H	PhF-2	DME	3 mol% [Pd], Cs$_2$CO$_3$, r.t., 24 h	99^b	136
24	**C98**	Cl	2-Me	H	H	C$_4$H$_8$O	THF	0.5 mol% [Pd], ^{t}BuOK, 30 °C, 0.5 h	94^b	137
25	**C98**	Cl	H	6-Me	H	CH$_2$Ph	THF	0.5 mol% [Pd], ^{t}BuOK, 60 °C, 1.0 h	91^b	137
26	**C98**	Cl	H	6-Me	H	Dipp	THF	0.5 mol% [Pd], ^{t}BuOK, 50 °C, 2 h	98^b	137
27	**C98**	Cl	4-OMe	H	H	C$_4$H$_8$O	THF	0.5 mol% [Pd], ^{t}BuOK, 50 °C, 0.5 h	97^b	137
28	**C99**	Cl	4-Me	H	H	Ph	Dioxane	0.01 mol% [Pd], ^{t}BuOK, 80 °C, 18 h	98^b	138
29	**C99**	Cl	4-OMe	H	H	Ph	Dioxane	0.02 mol% [Pd], ^{t}BuOK, 80 °C, 18 h	95^b	138
30	**C99**	Cl	2-Me	H	H	Ph	DME	2 mol% [Pd], Cs$_2$CO$_3$, 80 °C, 24 h	99^b	139
31	**C99**	Cl	4-OMe	H	H	PhCH$_3$-4	DME	2 mol% [Pd], Cs$_2$CO$_3$, 80 °C, 24 h	91^b	139
32	**C99**	Cl	4-OMe	H	H	C$_4$H$_8$O	DME	1 mol% [Pd], Cs$_2$CO$_3$, 80 °C, 24 h	97^b	139
33	**C99**	Cl	H	H	H	Ph	DME	2 mol% [Pd], Cs$_2$CO$_3$, 80 °C, 24 h	97^b	139

^{a}GC yield. ^{b}Yield of isolated product. ^{c}Yield determined by NMR spectroscopy. ^{d}GCMS yield.

particularly with electron-poor anilines, which are reported to be highly disfavored coupling partners (Table 14, entries 8–10). The results demonstrated the excellent catalytic activity of **C93** in Buchwald–Hartwig arylamination reaction and confirmed that the "flexible steric bulk" concept is essential in securing high catalytic activity with Pd–NHC complexes. The conformationally flexible [Pd(IHept^{OMe})(acac)Cl] complex **C94** was superior to that of its analogue **C93**, proving the positive effect of the methoxy group (Table 14, entries 11–13).[133]

A highly effective solvent-free protocol for the Buchwald–Hartwig amination of unactivated aryl chlorides was realized by use of **C95** without the addition of an external source of heat. Aryl bromides displayed higher activities, leading to the formation of the desired products in slightly shorter times (Table 14, entries 14–17).[134]

The activity of Pd–NHC catalysts is directly linked to the properties of the NHCs. Their steric bulk enables stabilization of a low-valent active intermediate and favors reductive elimination, while the strong σ-donor character facilitates the oxidative addition of aryl halides. Complex **C96** was proven to be superior to its [Pd(IPr*)(acac)Cl] congener (Table 14, entries 18–21).[135] In this context, (IPent^{Cl})PdCl$_2$(o-Picoline) (**C97**) catalyzed the coupling of strongly deactivated oxidative addition partners and amines with a diverse array of sensitive functionality at room temperature (Table 14, entries 22 and 23).[136]

The complex **C98** was shown to be much more active than the corresponding IPr-based compound. The increase in activity was attributed to the electron-donor ability of the IPrO scaffold's alkoxy tethers (Table 14, entries 24–27).[137]

A further and complementary optimization can be accomplished through a skeleton modification of IPr-type NHCs through electron-donating NMe$_2$ substituents (**C99**).[138] Excellent catalytic activities were obtained for various substrates using 0.005–0.1 mol% of precatalyst **C99** (Table 14, entries 28–33). Furthermore, anilines were also found to be suitable coupling partners, by 100% selectivity in the monoarylation of ArNH$_2$ (Table 14, entries 28 and 29). In particular, the performance of **C99** in terms of activity, low catalyst loading, and substrate scope was found to be greatly superior to that of the unmodified precatalyst Pd–PEPPSI–IPr, and even slightly better than that of Organ's highly efficient second generation complex Pd–PEPPSI–IPent when challenging alkylamines were used as the coupling partners (Table 14, entries 30–33).[139]

4. Conclusions

NHC–Pd complexes have been introduced as less complicated and environmentally more desirable alternatives to the original Pd–phosphane catalysts. They are employed in numerous homogeneously catalyzed processes, such as Heck, Kumada, Negishi, Suzuki, Sonogashira, Stille, and Hiyama coupling reactions, owing to their remarkable σ-donating properties and high thermal stabilities. The steric bulk and strong σ-donating properties of NHCs have made them particularly convenient for coupling reactions. The steric effects of ligands can be modified through nitrogen substituents. This prompted researchers to introduce ever bulkier groups, rather than trying to optimize a ligand for the conversion of a certain substrate. In terms of efficiency, mono NHC–Pd complexes bearing nitrogen ligands gave very promising results in numerous cross-coupling reactions. In this regard, NHC–PdCl(cinnamyl) is a family of other NHC–Pd complexes.

The variety of ligands and complexes reported in recent years is significant. NHC–Pd(II) complexes are remarkably resilient towards air, moisture, and thermal decompositions. These properties are rationalized by stabilization. Such factors favor catalyst lifetime and efficiency. They are now established as one of the most explored systems in coordination chemistry and catalysis. Due to their ease of handling and the above-mentioned

properties, it appears that they can be applied to any synthetic procedure where phosphane complexes are used as catalyst.

In contrast to bis NHC–Pd(II) complexes, monoNHC–Pd complexes containing a throwaway ligand (like 3-chloropyridine, ammines, tertiary phosphane, or N-methyl imidazole) are more efficient than the bisNHC–Pd(II) complexes. However, bis NHC–Pd(II) complexes and pincer analogues are found to be better than mono NHC complexes for Heck coupling. Moreover, the substitution of a C-2 azolylidene for a 1,2,3-triazolylidene ligand in the precatalyst has a profound impact on the mode of action of the catalyst system and results in the formation of nanoparticles (heterogeneous system in contrast to C-2/C-5 system).

Numerous NHC–Pd catalytic systems were generated over the last 3 years. It was not our intention to conduct an exhaustive analysis of the literature in this fast growing field of organic chemistry. Rather, we had to be selective due to the space limitation. It is found to be useful to represent the recent results in various tables. Nevertheless, even with the results presented here, it reflects many new and exciting possibilities for studying the transformations of these relatively new reagents that have only become available recently. It is highly likely that NHC–Pd complexes will find significant applications in a range of studies that include C–H activation. Chirality and immobilization is a field ripe for further investigation.

In this review, we aim to provide a concise overview of the properties and broad range of applications of NHCs, which we hope will serve as a useful introduction for scientists interested in studying and applying these important compounds. After an initial summary of the general structure and properties of NHCs, the reactivity and applications in modern chemistry are loosely categorized in three sections. Each section contains a brief overview of the key features and major applications with references to seminal publications. Also covered are the current state of the art and future trends as an ever-increasing number of NHCs continue to find new and exciting applications in the synthetic field.

The immobilization and aqueous application of the NHC–Pd complexes onto a suitable support offer several advantages in terms of catalyst recycling and their use. Easy preparation and separation of the catalyst and excellent catalytic performance make it a good heterogeneous system and a useful alternative to other heterogeneous palladium catalysts. At present, the use of NHC–Pd complexes in industry is still limited. However, it is envisaged that metal NHCs will become more attractive for general use in important industrial processes.

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