

# Phospha-palladacycles and *N*-heterocyclic carbene palladium complexes: efficient catalysts for CC-coupling reactions<sup>☆</sup>

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Received 10 June 2003; accepted 30 July 2003

Dedicated to Professor Ernst Otto Fischer, our great nestor and pioneer of organometallic chemistry, on the occasion of his 85th birthday on November 10, 2003

## Abstract

Due to the great importance of palladium-catalyzed Heck-type reactions in scientific and industrial chemistry, a lot of publications and reviews have been published during the last years describing this matter under different aspects. This article presents a summary of catalytic applications of palladium complexes with phosphorus ligands containing a metallated  $sp^3$ -carbon centre (“palladacycles”) or with *N*-heterocyclic carbene ligands in C–C and C–N coupling reactions of aryl halides including recent results of mechanistic discussions about their role in the catalytic cycle.

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**Keywords:** Carbenes; Catalysis; CC-coupling; CN-coupling; Palladacycles; Palladium; Phosphines

## 1. Introduction

Carbon–carbon and carbon–nitrogen bond forming reactions are key steps in many syntheses of organic chemicals [1]. Various frequently used cross-coupling reactions are mediated by palladium catalysts (Scheme 1) [2].

For several years aryl bromides and iodides preferably were used as substrates in such reactions. The far more readily available and industrially important aryl chlorides are transformed very sluggishly by standard palladium catalysts [3].

The problem with aryl chlorides is the strength of the C–Cl bond, which impedes the oxidative addition to  $14 e^- Pd(0)$  phosphine complexes [4,5] (Scheme 2).

Looking for better catalysts that can activate aryl chlorides, we focused on thermally stable cyclometal-

lated Pd(II) complexes as a source for the active Pd(0) catalyst.

Another opportunity to overcome the difficulties of aryl chloride activation was considered in the employment of thermally stable and towards air and moisture chemically inert NHC palladium complexes [6].

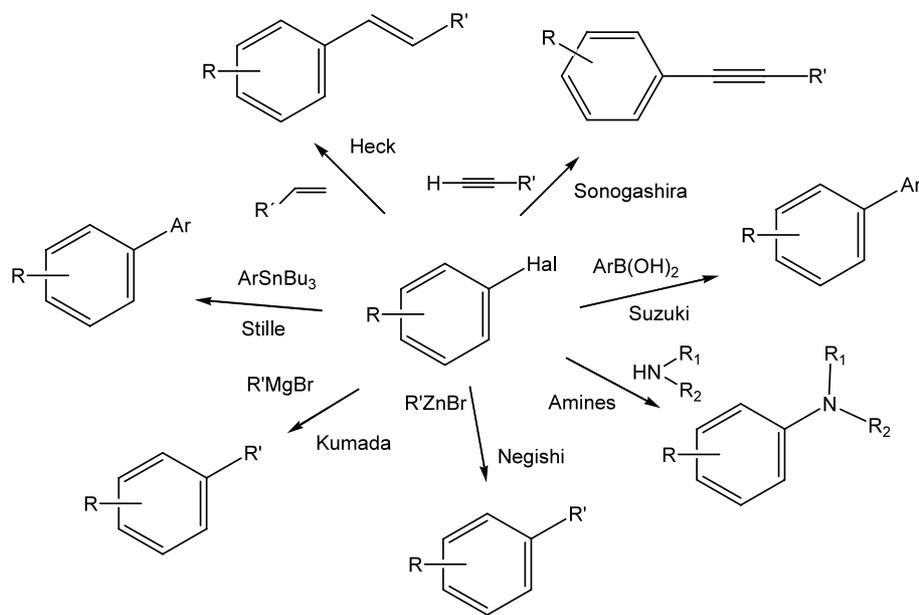
As possible candidates we chose Pd(II) complexes **1** (Fig. 1) with an  $sp^3$ -metallated centre on a phosphorus donor ligand, previously prepared and characterized by Shaw [7], Aleya [8] and Heck [9], but never successfully used in catalytic cross-coupling reactions before.

Meanwhile other groups also used *ortho*-metallated complexes as Pd(II) precatalysts in which an aromatic carbon atom adjacent to a functional group is bound to the metal centre (Fig. 1), e.g. Milstein produced efficient catalysis with complex **2** [10] and Shaw introduced complex **3** as a catalyst system into the Heck reaction [11]. Reviews dealing with nitrogen-, phosphorus- and sulfur-containing palladacycles including “pincer” complexes (Type **2**) as catalyst precursors in C–C and C–heteroatom bond forming reactions have been published by Dupont, Pfeffer and Spencer [144] and very recently by Bedford [145].

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Scheme 1. Principle of palladium catalyzed cross-coupling reactions.

## 2. Chemistry of phospho-palladacycles 1

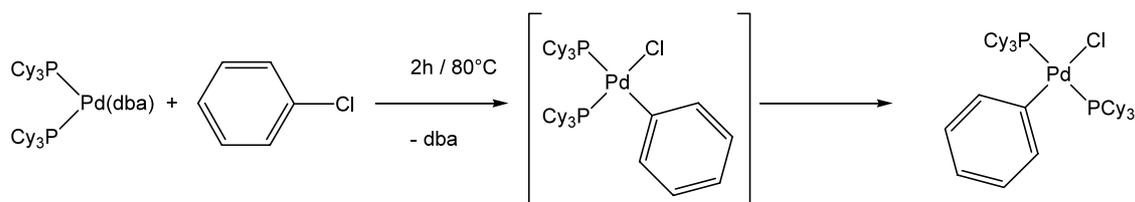
Cyclometallated complexes of type **1** are formed e.g. by reaction of palladium acetate with the sterically demanding tri-*ortho*-tolyl phosphine in toluene yielding the air and moisture stable complex *trans*-di( $\mu$ -acetato)-bis[*o*-(di-*o*-tolylphosphino)benzyl]dipalladium(II) (**1a**) (Scheme 3) [12].

The acetate-bridged palladacycles **1** are fluxional molecules in solution. Weakly bound acetate anions as well as the participation of coordinating solvents favour bridge splitting of the dimers and are the reason for this observation.

Salt metathesis with tetrabutylammonium halides yields in halogen-bridged dimeric complexes, equally stable, but less soluble in non-coordinating solvents [13]. Addition of coordinating solvents or donor ligands increases the solubility due to the formation of monomeric complexes. Similarly, the addition of 2,4-pentandione results in monomeric acetylacetonato complexes [14].

Complex **1a** is thermally stable up to 250 °C whereas *trans*-Pd(PPh<sub>3</sub>)<sub>2</sub>(OAc)<sub>2</sub> decomposes at about 150 °C. It can be refluxed in toluene for several days and is stable even in a 1:1 mixture of glacial acetic acid and

concentrated sulfuric acid. Deprotonation at the benzylic position of palladacycle **1a** under typical Heck conditions is not observed with NaOAc. The use of palladacycles is therefore particularly advantageous for less reactive substrates. Reductive cleavage of the Pd–C bond can be achieved with NaOH in ethanol or by CO insertion into the bond followed by reductive elimination [14]. For that reason this catalyst system is thus useless for carbonylation reactions [15]. Complex **1a** crystallizes in yellow prisms from DCM–hexane [16]. The crystallographic asymmetric unit contains two molecules of **1a** and one molecule of CH<sub>2</sub>Cl<sub>2</sub>. The molecules exhibit pseudo-C<sub>2</sub> symmetry. The Pd–Pd distance within the dimer of 3.115 Å rules out a metal–metal interaction. The crystal structure (Fig. 2) also confirms the *trans*-geometry of the phosphorus atoms along the Pd–P axis. Both palladium centres show square planar geometries. The Pd–C bond lengths of 2.028 Å are within observed ranges for similar complexes [13,17]. The Pd–P bond lengths are shorter (2.214 Å) than expected for a non-cyclometallated Pd phosphine complex (2.24–2.35 Å) [18]. The almost identical Pd–O distances of 2.140 and 2.119 Å verify similar *trans*-influences of alkyl and tertiary phosphine ligands [17b].



Scheme 2. Oxidative addition of chlorobenzene to a Pd(0)-phosphine complex.



of up to  $4 \times 10^4$  which had not been observed before with other catalytic systems [25].

Further increases in catalyst productivity of palladacycle **1a** combined with easy product separation and efficient catalyst recycling could be realized by using non-aqueous ionic liquids (NAILs) as media in Heck reactions [26,27]. This concept had been tested for CC-coupling reactions with convenient Palladium catalysts [28].

Scientific and industrial applications of Heck reactions catalyzed by palladacycle **1a** have been reported for the total synthesis of estrone steroid derivatives [29], the anti-leukaemia alkaloid cephalotoxin [30]. The vinylation of 2-bromo-6-methoxynaphthalene with ethylene to a single product [31] has been applied on the pilot plant-scale for the synthesis of Naproxen by Hoechst (Scheme 4).

### 3.2. The Suzuki–Miyaura coupling reaction

Coupling of aryl- and vinyl halides or triflates with aryl- or vinyl boron compounds, the Suzuki–Miyaura coupling [32] has proven extremely versatile for the preparation of unsymmetrical, bulky biaryls and is extensively used in natural product synthesis [33]. Arylboronic acids used in CC-coupling reactions are often synthesized from the corresponding Grignard or organolithium reagents [34].

With palladacycle **1a** as catalyst 4-bromoacetophenone could be coupled with phenylboronic acid to 4-acetylbiphenyl with yields over 90% and TONs of up to  $7.5 \times 10^4$  using  $K_2CO_3$  instead of NaOAc as base in *o*-xylene as solvent [35]. Activated aryl chlorides like 4-chloroacetophenone can also be coupled under this conditions with yields of 82% and TONs of  $8 \times 10^3$ . Like in the Heck reaction no aryl scrambling could be observed with palladacycle **1a**.

### 3.3. The Sonogashira reaction

Arylalkynes and conjugated enynes play an important role in the assembly of bioactive natural molecules and

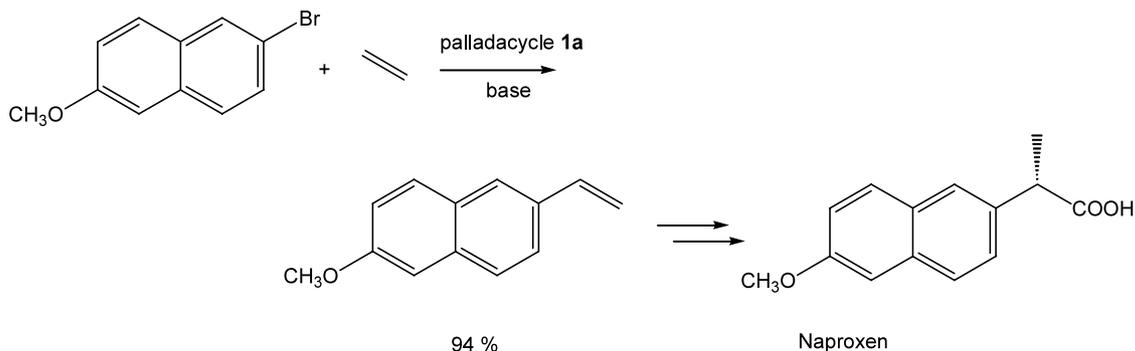
new materials [36]. The Sonogashira reaction of terminal alkynes with aryl or alkenyl halides provides a most straightforward and powerful method for their synthesis [37]. However, the palladium-catalyzed synthesis of internal alkynes via coupling of aryl halides with terminal alkynes usually affords not only high amounts of catalyst but also the addition of CuI as a co-catalyst [38].

Surprisingly, the use of palladacycle **1a** as a catalyst system for the coupling of different aryl bromides with phenylacetylene to tolane derivatives gave satisfactory results without adding CuI only in triethylamine as the solvent. TONs as high as  $8 \times 10^3$  with acceptor-substituted aryl bromides could be observed [39]. Unfortunately aryl chlorides never gave satisfactory results in triethylamine most probably due to too low reaction temperatures [40]. The reaction could not be performed with alkyl acetylenes too.

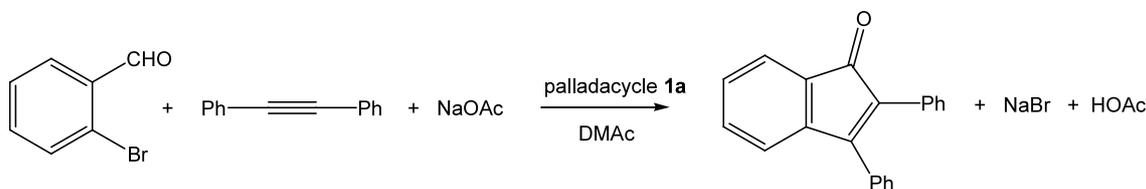
The synthesis of 2,3-diphenylindene from 2-bromobenzaldehyde and tolane was achieved with 0.1 mol% of palladacycle **1a** in 80% yield (Scheme 5) [14]. Indenone derivatives are the preliminary stage in the synthesis of indenenes which are important ligands for *ansa*-metallocenes, efficient catalysts for olefin polymerisation [41].

### 3.4. The Stille coupling reaction

The advantage of using highly toxic aryl- and vinyl stannanes in coupling reactions with aryl- or vinyl halides or –triflates—known as Stille reaction [42]—lies in their ease of access, their inertness towards air and moisture, their high chemoselectivity, and the fact that neutral conditions are applied which is useful for the synthesis of base sensitive compounds [33a,43]. Palladacycle **1a** catalyzes Stille cross-coupling reactions. TONs of 1650 could be achieved by Hartwig et al. in the reaction of  $PhSnMe_3$  with 4-bromoacetophenone [44]. Aryl chlorides did not couple in satisfactory yields [45]. Palladacycle catalyst **1a** also turned out to be a robust and active system for solid phase Stille reaction in



Scheme 4. Industrially feasible Heck reaction by palladacycle **1a**.



Scheme 5. Synthesis of 2,3-diphenylindenone from 2-bromobenzaldehyde and toluene.

coupling of aryl bromides with polystyrene-bond stannyl components [46].

### 3.5. Kumada–Tamao–Corriu and Negishi coupling reactions

The nickel [47] or palladium [48] catalyzed coupling of aryl Grignard reagents with aryl halides, triflates, ethers etc. is one of the earliest methods for the catalytic synthesis of unsymmetrical biaryls. One disadvantage is the polar nature of aryl-magnesium compounds precluding the use of several functional groups in the coupling partner [33a]. The Negishi reaction overcame this problem by using organozinc reagents to couple with aryl halides or triflates [49]. Unlike the Kumada–Tamao–Corriu coupling reaction, functional groups such as aldehydes, amides, cyano or nitro groups are tolerated. Both of these reactions can be catalyzed by palladacycle **1a** although precipitation of palladium black occurs [45]. Even aryl chlorides can be subject to coupling with this system in good yields [50,51].

### 3.6. The amination reaction

The synthesis of disubstituted anilines via palladium catalyzed amination of aryl halides by secondary amines was discovered by Buchwald and Hartwig independently in 1995 [52]. Many papers concerning this reaction have since been published [53]. Palladacycles **1** have been tested in our group as catalysts for the amination reaction. For example 4-bromoacetophenone was reacted with piperidine under conditions used in the original publications in the presence of 0.5 mol% palladacycle **1a** resulting in a yield of 89%. Extension of the methodology towards aryl chlorides afforded higher temperatures (> 135 °C), KO $t$ Bu instead of NaO $t$ Bu as base, and LiBr as co-catalyst. Thus a 55% yield of amination products was realized with 4-chlorobenzotrifluoride and piperidine [54]. With slightly higher amounts of amines and base the yield could be improved to 74%. Additionally, the *meta*-substituted regioisomer was formed in 8% yield. This finding can be explained by aryne intermediates which probably form under reaction conditions. This was proven by performing the reaction without any catalyst, resulting in a 1:1 mixture of the *para*- and the *meta*-isomer [54b].

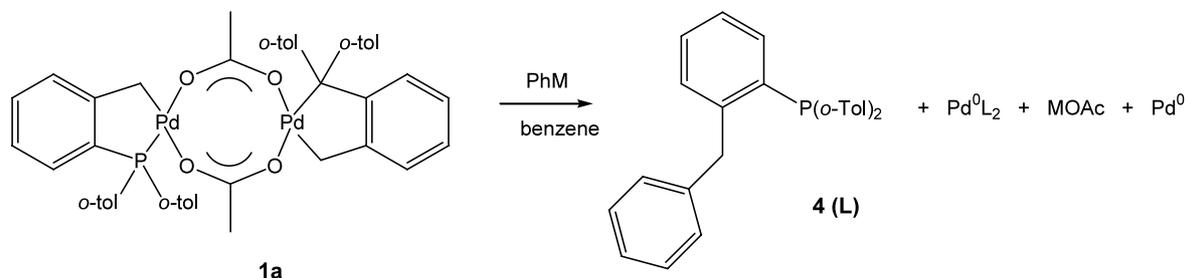
## 4. Mechanistic discussion

Heck type reactions are generally believed to work via a Pd(0)/Pd(II) redox mechanism [55]. Starting with palladacycles **1** in the oxidation state +II a reduction step prior to catalysis would be necessary.

In the cases of the Stille, Grignard, Negishi and, most probably the Suzuki–Miyaura cross-coupling reactions there is no doubt about the reduction mechanism of palladacycle **1a** to a catalytically active Pd(0) species. Heating palladacycle **1a** with PhSnMe<sub>3</sub> in benzene-*d*<sub>6</sub> and monitoring the reaction by NMR spectroscopy Hartwig et al. observed the formation of products which confirm a reduction mechanism according Scheme 6 [56]. The same observations have been made in our group when PhMgBr or PhZnCl was reacted with palladacycle **1a** [45]. Presumably the described reaction pathway (Scheme 6) is also true for the Suzuki–Miyaura reaction with phenylboronic acid.

Concerning the amination reaction, Hartwig et al. found another mechanism for the reduction of palladacycle **1a** including cleavage of the palladacycle by the secondary amine to form the monometallic amine complex **1c** (Scheme 7) which could be isolated and fully characterized [56]. Complex **1c** reacts with NaO $t$ -Bu to generate [Pd{P(*o*-Tol)<sub>3</sub>}<sub>2</sub>] in 48% yield.

Investigations on the mechanism of the Mizoroki–Heck reaction during the last few years led us to the conclusion that a different catalytic cycle compared to the classical Heck reaction pathway must be operative with palladacycles **1** as catalysts. Catalysts of this type can be recovered without rupture of the metallacycle in yields up to 70% from Heck reactions [57]. There is no proof for the reduction of the palladacycle under Heck reaction conditions to a Pd(0)(PR<sub>3</sub>)<sub>2</sub> species [45], the usually supposed catalytically active intermediate in Heck reactions [45,55,58,62]. For that reason, the possibility of a non-classical pathway via Pd(II)/Pd(IV) intermediates was discussed for palladacycle-catalyzed Heck reactions [57,59]. Although this mechanism including oxidative addition of the aryl halide to Pd(II) has been theoretically justified and described in detail by Shaw [60], any attempts to form potential Pd(IV) intermediates from palladacycles **1** have failed [57,61]. Recent competition experiments with palladacycle **1a** and the standard catalyst intermediates [Pd{P(*o*-Tol)<sub>3</sub>}<sub>2</sub>] **5** and [{PdAr{P(*o*-Tol)<sub>3</sub>}Br]<sub>2</sub>] **6** revealed that the

Scheme 6. Reduction of palladacycle **1a** to Pd(0) species by PhM (M = SnMe<sub>3</sub>, MgBr, ZnCl).

characteristics of aryl bromide vinylations with catalyst **1a** deviate slightly from those with catalysts **5** and **6**. Since for a substantially different catalytic cycle more pronounced effects are to be expected, a modified classical catalytic cycle is proposed with a novel, cyclometallated, anionic palladium(0) species **7**. It assumes the reduction of **1a** without cleavage of the metallacycle (Scheme 8) [59].

### 5. NHC palladium complexes as effective catalysts for CC-coupling reactions

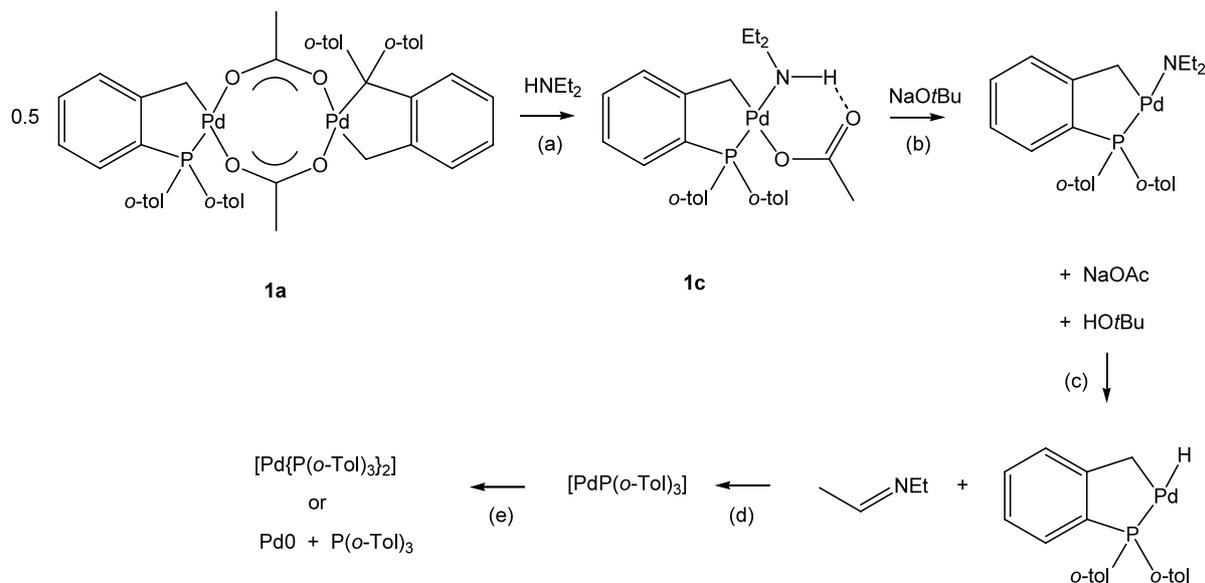
The use of phosphine ligands in organometallic chemistry and catalysis is widespread [55,58,62]. Recently, Buchwald [63] and Fu [64] have reported phosphine-modified palladium-mediated Suzuki–Miyaura coupling reactions which employ inexpensive aryl chlorides as substrates. The use of a bulky phosphine (P<sup>t</sup>Bu<sub>3</sub>) or a phosphine-containing moiety (Pcy<sub>3</sub>) in ancillary ligation was shown to be fundamental in triggering the observed catalytic behaviour.

Nucleophilic *N*-heterocyclic carbenes, the imidazol–2-ylidenes or so-called “phosphine mimics”, have attracted considerable attention as possible alternatives for the widely used phosphine ligands in homogeneous catalysis [65,66]. These catalysts exhibit therefore a second possible way for the effective activation of aryl chlorides in CC-coupling reactions.

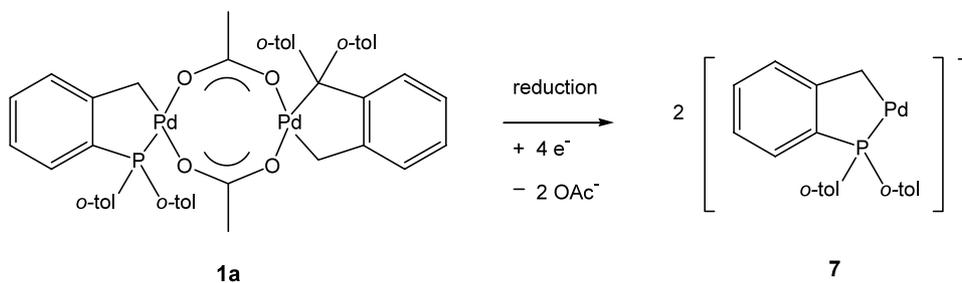
*N*-Heterocyclic carbenes in fact behave like typical σ-donor ligands that can substitute classical 2e<sup>−</sup> donor ligands such as amides, ethers, and phosphines in metal coordination chemistry [67]. It was determined in 1993 that “heterocarbenes show bonding properties similar to those of trialkylphosphines and alkylphosphinates” [68]. Nolan et al. concluded from structural and thermochemical studies that “in general these ligands behave as better donors than the best phosphine donor ligands with the exception of the sterically demanding (adamantyl) carbene” [69].

#### 5.1. Heck and Suzuki–Miyaura coupling reaction

One of the most successful examples of catalysts containing NHC ligands are found in palladium-cata-



Scheme 7. Postulated mechanism for the formation of a Pd(0) species during the amination reaction: (a) dimer cleavage (b) deprotonation (c) β-H elimination (d) reductive elimination (e) disproportionation.

Scheme 8. Reduction of palladacycles **1** without rupture of the carbon–palladium bond.

lyzed carbon–carbon bond formations. The catalyst development has focused in particular on Heck-type reactions, especially the Mizoroki–Heck reaction itself [70–73], and the Suzuki–Miyaura cross-coupling reaction (Scheme 1).

#### 5.1.1. Palladium(II) pre-catalysts

Because of their convenient preparation from palladium(II) acetate and the corresponding imidazolium salts, palladium(II) complexes were first examined as potential catalysts for the Mizoroki–Heck reaction in our group [74]. In this work, the first Heck coupling of aryl bromides and aryl chlorides was communicated: Complexes **8** and **9** (Fig. 3) are active upon smooth reduction with formate or hydrazine, thus generating the active Pd<sup>0</sup> species. The low catalyst loadings (10<sup>−3</sup> mol% in the case of aryl bromides, and 0.1–1 mol% for aryl chlorides) necessary to obtain yields >99% were quite unexpected and are based on the advantageous properties of the new catalyst type described here.

The advantages of this “New structural principle for catalyst in homogeneous catalysis” [74] were stated as follows: “The new catalyst type described here has a series of advantageous properties and potential for development: a) high thermal and hydrolytic durability resulting from exceptionally stable M–C bonds (long shelf-life, stability to oxidation), b) easy accessibility, and c) no need for an excess of the ligand. The prospects for derivatization to water-soluble catalysts (two-phase catalysis), immobilization, and chiral modification seem promising because of the constitution of the ligands [74,75]. These predictions have since been shown to be

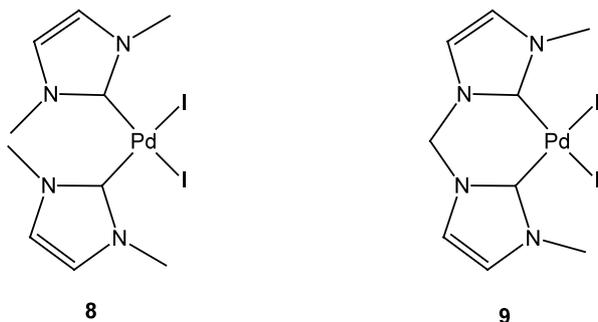


Fig. 3. Pd complexes with monodentate and bidentate NHC ligands.

correct. Later on the synthesis of this Pd–NHCs could be improved by replacing the initially used solvent THF with the higher boiling solvent Me<sub>2</sub>SO [75–77].

These catalysts are exceptionally stable toward heat, oxygen, and moisture; moreover, carbene dissociation has never been detected. All these properties make these palladium–carbene complexes suitable for the Heck reaction (Scheme 1), particularly for the activation of chloro arenes [64]. Promising results have also been obtained for alkyne (Sonogashira reaction, see below) and Suzuki–Miyaura (Scheme 1) coupling reactions [65].

Based on this work more examples of Heck coupling with complexes of monodentate NHC [78–80] such as **8** as well as the complexes of chelating ones such as **9** [81–84] have been described in literature.

An increase in activity for catalysts like **8** was achieved using molten salts as the solvent [27,85–87]. This ionic-liquid concept [27,88] was taken up by the group of Calò [89,90]. They used related palladium complexes of benzothiazole carbene type ligands **10** [89b] (Fig. 4) in a melt of tetra(*n*-butyl)ammonium salts to carry out the coupling of aryl bromides with 3-hydroxy-2-methylene alkanates.  $\beta$ -Arylketones are thus formed in good yields. The improved catalyst efficiencies compared to all previously described molecular solvents have been observed for reactions of bromo arenes and even chloro arenes. Advantages with regard to conventional solvents are based on high activity as well as improved thermal stability and catalyst life-time during the reaction.

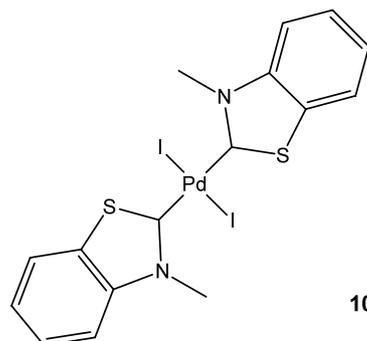
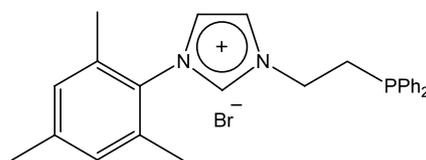


Fig. 4. Pd(II) complex with benzothiazole carbene ligands.

Following the strategy that has been very efficient for olefine metathesis, palladium(II) complexes such as **11** containing both phosphine and NHC ligands were used in catalysis [91,92]. Therefore a variety of mixed palladium(II) complexes bearing *N*-heterocyclic carbenes and triaryl- and trialkylphosphines [NHC]Pd(PR<sub>3</sub>)<sub>2</sub> have been synthesized, according to Scheme 9 and tested as catalysts in Mizoroki–Heck, Suzuki–Miyaura and Stille reactions as well as in the dimerization of phenylacetylene. The mixed complexes **11** were prepared from a dichloromethane solution of the well soluble mono(NHC) complexes **12** [(NHC)PdI<sub>2</sub>]<sub>2</sub> by addition of one equivalent of phosphine at ambient temperature. Increased activities in the Mizoroki–Heck and in the Suzuki–Miyaura reaction were observed. These catalysts combine the advantageous stability of bis(carbene) complexes and the good activity of the bis(phosphine) complexes in these reactions. The replacement of one of the phosphine ligands by an NHC ligand being a strong  $\sigma$ -donating ligand alters the electron density on the palladium centre, which provides an easier activation of halogen aryl bonding. Both arylbromides and arylchlorides can therefore be used as substrates. An important feature seems to be the necessity of bulky NHC ligands, whereas the phosphine has to be optimized for each type of reaction [93].

In the Suzuki–Miyaura reaction boronic acid derivatives are used as the transmetallating reagent [94]. Biaryl moieties are important structural units in drugs [95] as well as in non-linear optical materials [96]. In this cross-coupling reaction the steric bulk of the residues both on the NHC and the phosphine are decisive factors governing activity [96] including practical advantages over the Stille reaction that the boron-containing by-products are non-toxic and that they are easily separable from the desired product. The basic trialkyl phosphines P(*t*-Bu)<sub>3</sub> and PCy<sub>3</sub> (Cy = cyclohexyl) prove to be superior to triarylphosphines, when they were employed directly together with complexes of the type **12** in the Suzuki–Miyaura reaction. No difference in activity was observed if the pre-isolated complexes **11** or a mixture of



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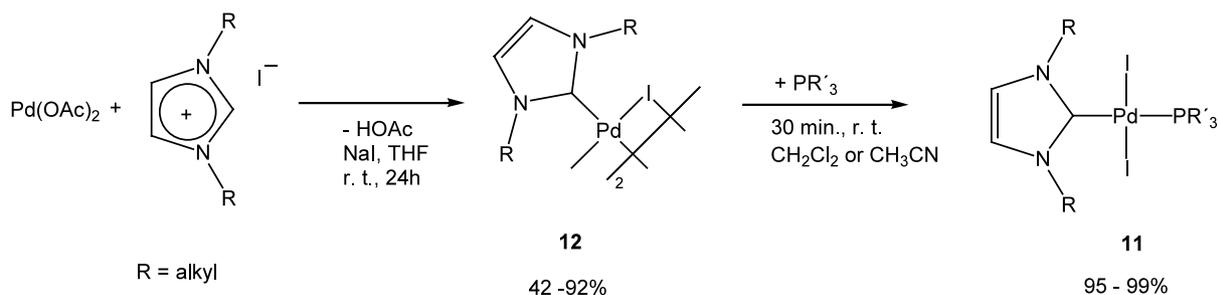
Fig. 5. Precursor of a C–P-chelating NHC ligand.

**12** and the corresponding phosphine were used. In coupling of different aryl halides and phenylboronic acids the optimized catalyst in this system is the complex **11** with R = CH(CH<sub>3</sub>)C<sub>6</sub>H<sub>5</sub> and R' = cyclo-C<sub>6</sub>H<sub>11</sub>, which was identified by the reaction of 4-bromoanisole and phenylboronic acid in xylene. The use of Cs<sub>2</sub>CO<sub>3</sub> increases the yields, especially in the case of non-activated chloroarenes. Comparison with diiodo-bis(1,3-dimethylimidazol-2-ylidene) palladium(II) stresses the need for the phosphine ligand to be present: the bis(NHC)complex does not show any catalytic activity with 4-chloroanisole in the Suzuki–Miyaura reaction under the conditions described above.

The reduction of catalysts of type **11** to the catalytically active palladium(0) species can be forced by the addition of sodium formate as a reducing agent. Catalysis is then commenced without an induction period. But this procedure is accompanied by visible palladium black formation and reduced activity of the catalysts in terms of turnover numbers (TON).

High efficiencies in Heck reactions of aryl bromides were reported by the Nolan group [97] who used palladium in the presence of C,P-chelating NHC ligands derived from the sterically demanding imidazolium salt **13** (Fig. 5). A catalyst loading of 0.5 mol% based on palladium was sufficient to obtain good yields. Cesium carbonate turned out to be the most efficient base, much better than KO*t*-C<sub>4</sub>H<sub>9</sub>, NaOAc and K<sub>2</sub>CO<sub>3</sub> [97].

High TONs in Heck reactions even in the coupling of aryl chlorides were achieved by very stable “pincer-type” tridentate C,N,C-ligands of type **14** [98–100] (Fig. 6).



Scheme 9. Synthesis of mixed carbene complexes bearing NHC and phosphines.

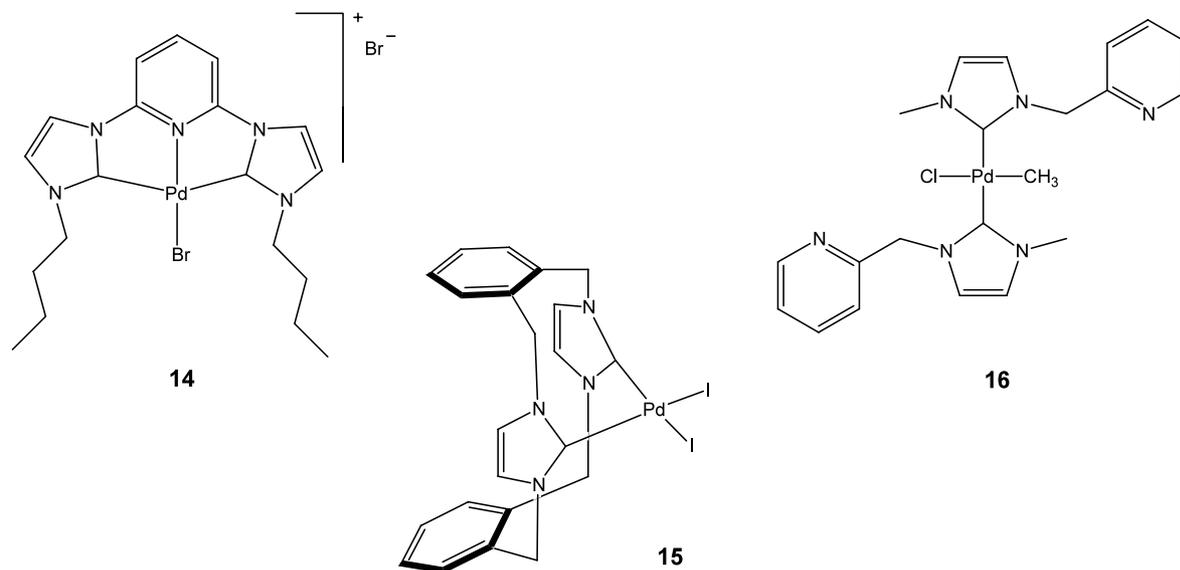


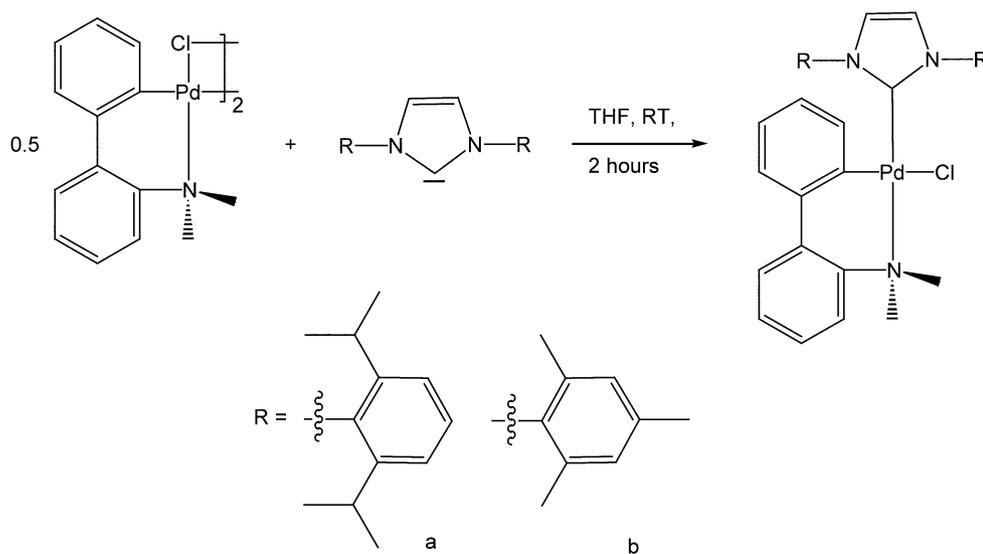
Fig. 6. Pd(II) complexes with “pincer-type”-NHC, *ortho*-cyclophane-NHC and NHC with dangling substituents.

Complex **14** shows excellent air and thermal stability at elevated temperatures (165 °C) and is an active catalyst for CC-coupling reactions. It maintains activity with reuse and allows markedly high TONs in the Heck olefination of activated aryl chlorides. The TONs of 47 500–75 000 obtained with  $210^{-3}$ – $210^{-4}$  mol% **14** are among the highest yet reported for aryl chlorides.

Dicarbenes derived from imidazolium-linked *ortho*-cyclophanes of type **15** form exceptionally stable complexes of nickel and palladium [101,102]. The palladium–cyclophane complexes show high activity as catalysts for Heck coupling reactions of aryl bromides and iodides with remarkable activities. (TONs  $7.110^6$  for

iodobenzene–*n*-butylacrylate at 140 °C;  $6.810^5$  for 4-bromo-nitrobenzene–*n*-butylacrylate at 140 °C).

Highly active and very stable catalysts for Heck and Suzuki–Miyaura coupling reactions were discovered in certain palladium(II) complexes of NHC with “dangling” N-substituents. Catalyst **16** performed particularly well, giving turnover numbers (TONs) of  $1.7 \times 10^6$  (Heck) and  $1.1 \times 10^5$  (Suzuki–Miyaura) at > 85% conversion of 4-bromoacetophenone with butyl acrylate and phenylboronic acid, respectively [103]. Additionally these catalysts are very selective in the Heck reaction. Analysis of the product from bromoacetophenone coupling showed predominately *n*-butyl (*E*)-4-acetylcinnamate, with the only other product being the *Z* isomer



Scheme 10. Synthesis of NHC modified N-C-palladacycles.

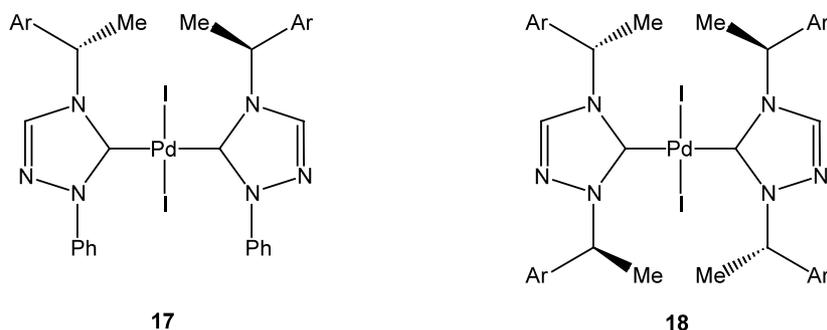


Fig. 7. Pd complexes with chiral NHC ligands.

(<10%). This is an important result, as byproducts resulting from aryl dehalogenation and aryl–aryl coupling are often found during Heck couplings, but this was not the case with the present catalysts [103]. Moreover the methyl group in this kind of complexes is supposed to have an activating influence on catalyst formation. This was already shown previously by the same group [103,80]. It is thought that the methyl group provides a facile route to (catalytically active) Pd(0), possibly through insertion of the olefine and subsequent  $\beta$ -hydride elimination [104]. This “methyl effect” was again exploited in preparing highly active catalysts (showing no induction period) with the functionalized carbenes [103].

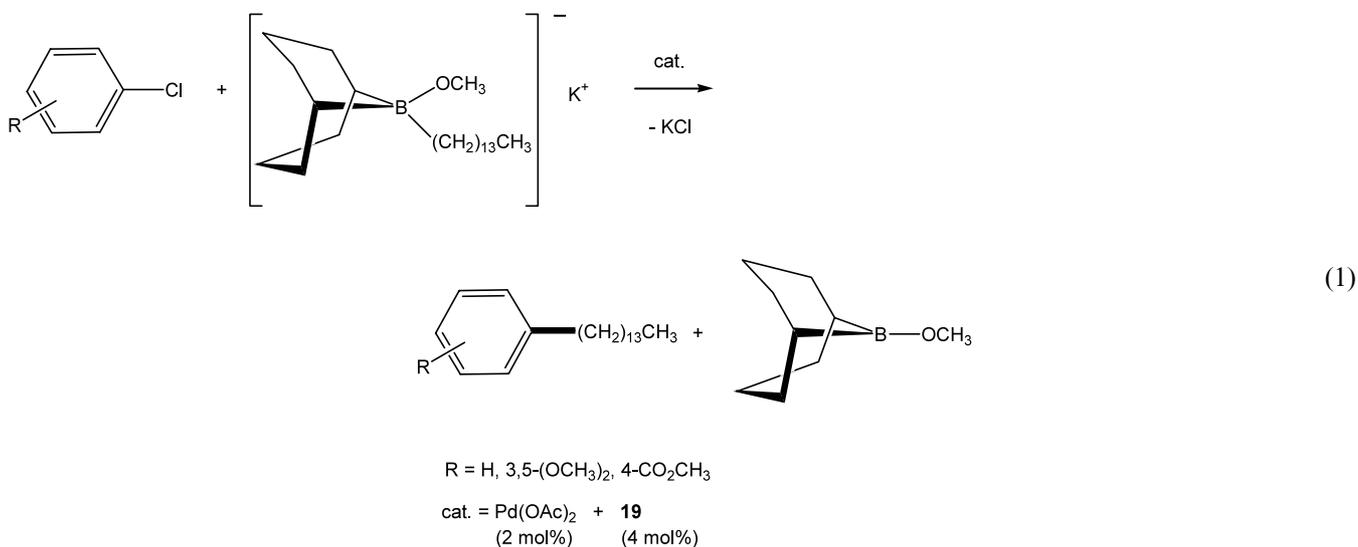
A new class of catalytically active “mixed ligand” complexes was recently developed by Studer and Nolan, combining a N–C–palladacycle framework with a sterically demanding NHC ligand (Scheme 10). These catalysts combine the important donating properties of NHC with the stability induced by the palladacycle framework. They turned out to be very active in cross-

coupling of aryl chlorides or triflates with amines and/or ketones [146].

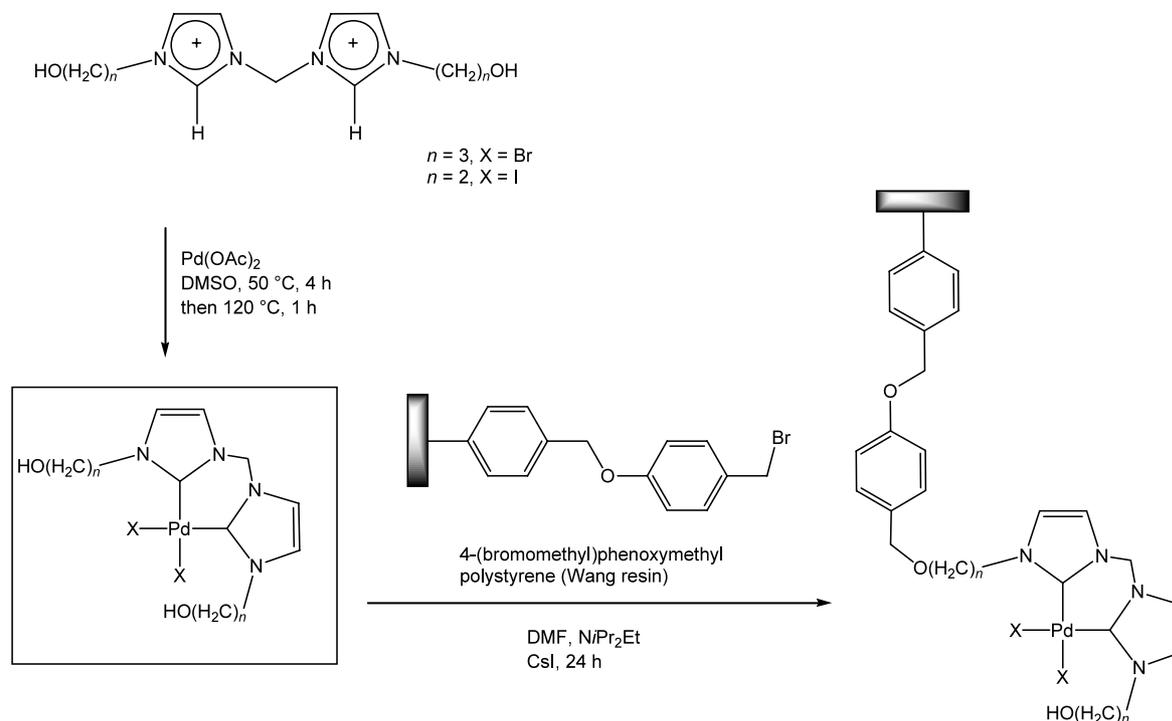
Until now the attempt to employ chiral NHC complexes of palladium in enantioselective Heck coupling reactions failed. Enders et al. prepared the related palladium complexes **17** and **18** featuring two chiral 1,2,4-triazol-5-ylidene ligands, but their use in asymmetric Heck reactions has not yet resulted in a significant optical induction ( $ee > 8\%$ ) [105] (Fig. 7).

There have been some reports in literature concerning chiral palladium(II) NHC complexes [106–108], but up to now none of them have been successfully employed in asymmetric Heck coupling reactions.

Palladium/imidazolium salt systems were found to be efficient in mediating the Suzuki–Miyaura cross-coupling of aryl chlorides and aryl triflates [115] with various arylboronic acids. In several cases, the in situ technique is more efficient than the use of the preformed palladium catalyst. Electron-rich and electron-poor aryl chlorides, as well as sterically hindered substrates, lead to high conversions under general conditions using Pd(0)/IPr·HCl **19** or Pd(II)/IMes·HCl **20** (Fig. 8). The







Scheme 11. Effective immobilization from pincer-type Heck catalysts on MK 10.

unreactive C–Br and C–Cl bonds, providing high yields in the C–Br case.)

### 5.1.2. Well-defined palladium(0) catalysts

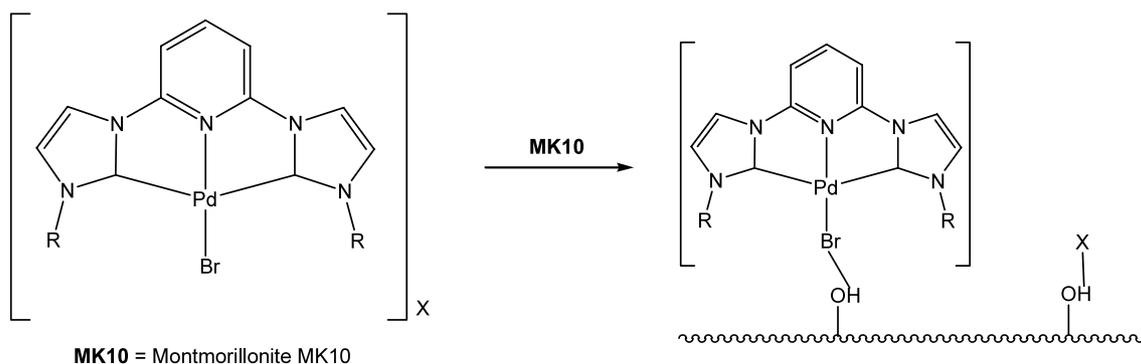
The mechanistic requirement for a palladium(0) complex regarding the initiation of the catalytic cycle in Heck and Suzuki–Miyaura-type reactions suggests the preparation of suitable palladium(0) complexes of NHC **21** and **22**. Therefore heteroleptic palladium(0) complexes (Fig. 9) containing NHC and an electron-deficient olefin for stabilization were synthesized and successfully used as catalysts in the Mizoroki–Heck reaction of aryl iodides [128].

Beller et al. were able to show for the first time that defined monocarbene palladium(0) complexes of the type **23** are suitable catalysts for the Pd-catalyzed Heck reaction of activated and nonactivated aryl

chlorides [129]. It is shown that tetraalkylammonium halides constitute superior high-temperature solvents for this type of Heck reaction.

Since it has been demonstrated that the coordination of olefins to palladium(0) catalysts generally slows down the reaction rate of the oxidative addition [130], the synthesis of homoleptic palladium(0)–NHC complexes (Fig. 10) was expected to furnish more active catalysts. The vapour phase deposition of palladium metal in the presence of a sublimable free NHC like 1,3-di-*tert*-butylimidazolin-2-ylidene allows the isolation of complex **24** (Scheme 13) [131a].

In contrast to the Suzuki–Miyaura reaction (see below), application of the complex **24** in the Mizoroki–Heck reaction did not reveal higher activity than the previously examined palladium(II) complexes.



Scheme 12. Synthesis of palladium(0)–NHC complexes.

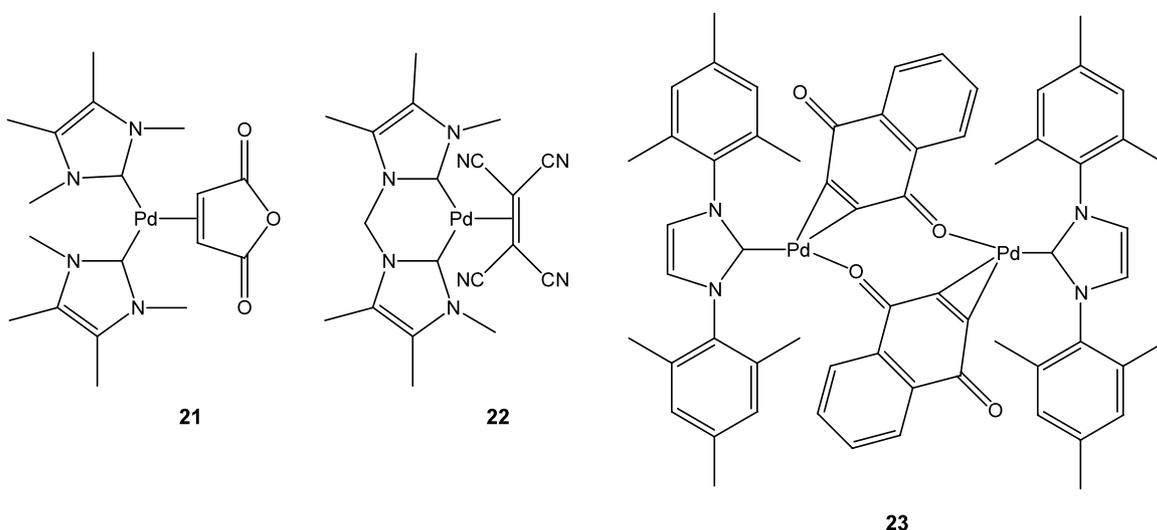


Fig. 9. Heteroleptic palladium(0) complexes containing NHC and an electron deficient olefin.

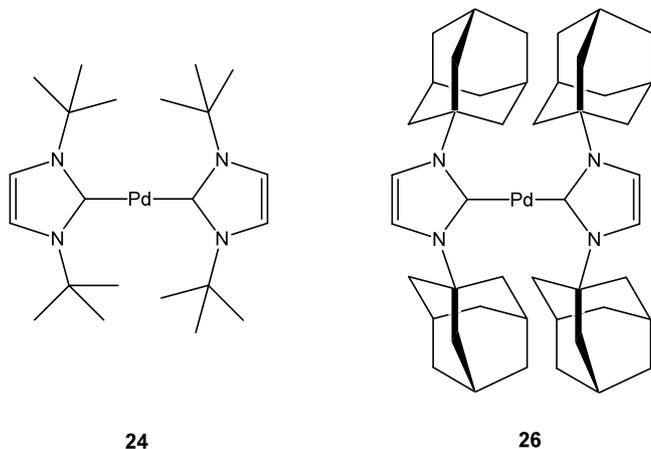


Fig. 10. Homoleptic Pd(0) NHC complexes.

As this method is limited to sublimable, thermally stable NHC, a more general route to this type of complex is desirable for the evaluation of ligand effects in catalysis. Our group established a synthetic procedure for homoleptic bis(NHC)-complexes of palladium(0) by ligand exchange in bis(tri-*ortho*-tolylphosphine)palladium(0) (Scheme 13) [131b]. In the case of sterically demanding NHCs the isolation of the intermediate mixed phosphine–NHC complex **25** is possible [127]. The catalytic activity of these complexes strongly depends on the steric bulk of the NHC ligand. 1,3-Bisadamantylimidazolin-2-ylidene, as one of the most bulky NHC ligands, [132] represents a good candidate for palladium(0) catalysts of high activities in the Suzuki–Miyaura cross-coupling. However, even in presence of an excess of the carbene only one phosphine ligand was exchanged, which resulted in the formation of complex **25** [120] (Fig. 11).

There is only one other example of an isolated mixed NHC–phosphine complex of palladium(0) in the litera-

ture [121]. Furthermore, **25** is the first NHC-complex to catalyze the Suzuki–Miyaura cross-coupling of 4-chlorotoluene with phenylboronic acid at ambient temperature (20% conversion).

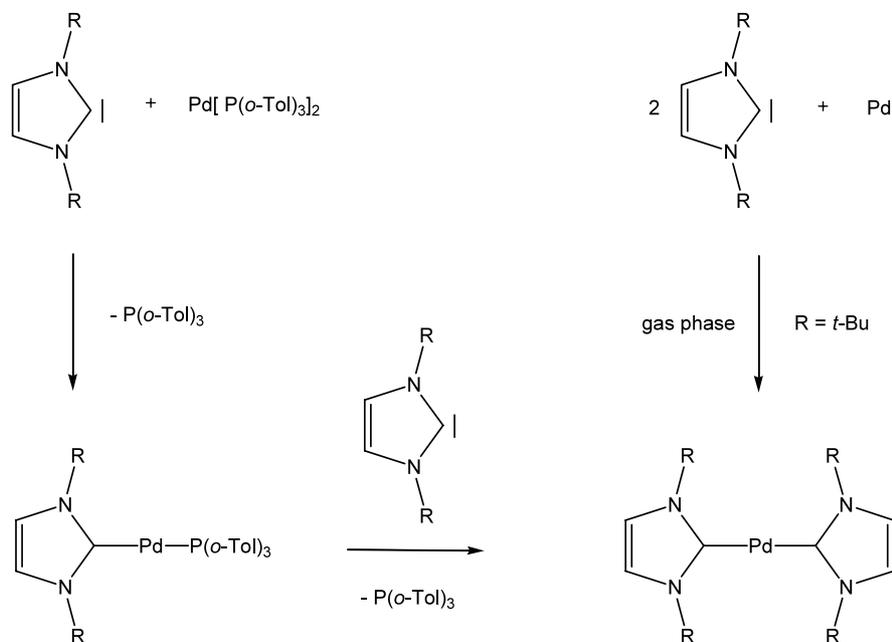
The homoleptic palladium(0) complex **26** catalyzes the Suzuki–Miyaura cross-coupling and exhibits the highest TON with aryl chlorides at room temperature reported so far.

For example, 4-chlorotoluene is coupled to phenylboronic acid in the presence of 3 mol% of **26** and two equivalents of CsF in 97% yield at 80 °C within 20 min. At room temperature, the same result is obtained after 6 h. The starting turnover frequency (TOF) [turnover frequency determined after 1 min] of 1100 [mol product mol Pd<sup>-1</sup> h<sup>-1</sup>] and the turnover number (TON) of 573 are the highest reported to date for aryl chlorides under these conditions, thus illustrating the activity of catalyst **26**. The use of 1,4-dioxane as well as two equivalents of CsF gives the best results [120].

The phosphine-free NHC catalyst **26**, either as the isolated complex or generated in situ, represents the most active coupling agent for aryl chlorides to form (substituted) biphenyls in the Suzuki–Miyaura cross-coupling. Reaction times between 2 and 48 h are sufficient at room temperature, while at 80 °C the productivity is approximately six times better [120]. In sharp contrast to the observations with mixed palladium(II) complexes, mixed palladium(0) complexes showed inferior activity in the Heck coupling in all tested reactions, rendering this type of catalyst useless for activation of aryl chlorides.

### 5.1.3. Mechanism

Studies regarding the nature of the catalytically active species for NHC complexes in Heck-type reactions have focused on the Mizoroki–Heck reaction and have consistently revealed a palladium(0) species as the active



Scheme 13. Proposed mechanism for Heck coupling with dicarbene–Pd complexes.

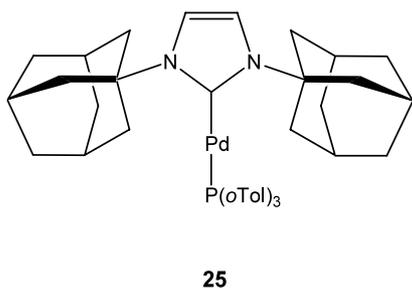


Fig. 11. Mixed phosphine–NHC complex.

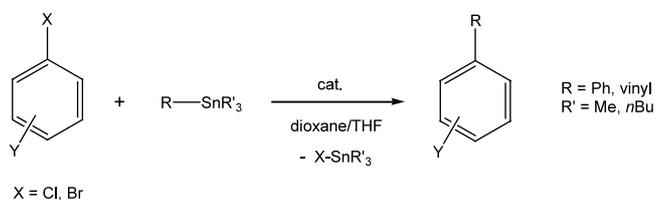
catalyst. The induction period is shortened upon addition of a reducing agent [133]. Postulated intermediates of the reaction were isolated and characterized as well as employed in stoichiometric and catalytic reactions by the Cavell group [128,104]. The following steps in the catalytic cycle of the Heck reaction have been investigated: in situ synthesis of a dicarbene–Pd(0) complex, oxidative addition to the Pd(0)–carbene complex and

olefin insertion into the Pd–C bond of a hydrocarbylpalladium–carbene complex.

These investigations led to a proposal of an overall mechanism for the Heck reaction catalyzed by these complexes (Scheme 14).

The first step in the catalytic cycle is thought to consist of oxidative addition of the aryl halide to a zero valent active species (formed in situ) yielding a Pd(II)–aryl complex (i). Coordination and insertion of the olefin into the Pd–C bond could then occur (ii), followed by  $\beta$ -hydride elimination to generate a short lived Pd(II)–hydride complex (iii). Reductive elimination (iv) in the presence of a base could then regenerate the active Pd(0) species allowing the cycle to proceed again. The mechanism is essentially the same as the one proposed for the Pd–phosphine catalyzed Heck reaction. Theoretical studies using DFT calculations confirm this result [134].

Mechanistically, palladium-to-ligand ratio studies support an active palladium species bearing one nucleophilic carbene ligand [95].



cat. = Pd(OAc)<sub>2</sub> + 20

(3)

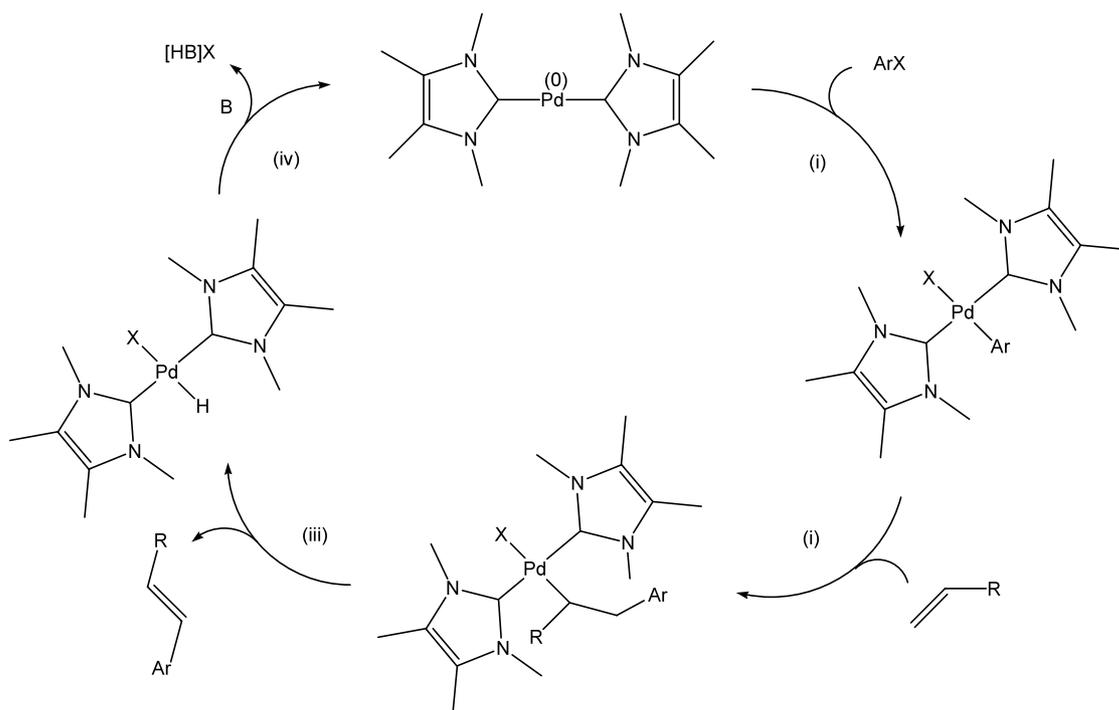
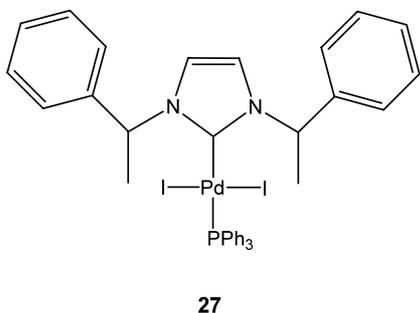
Scheme 14. Simple synthesis of Pd(0) bis(carbene) **24**.

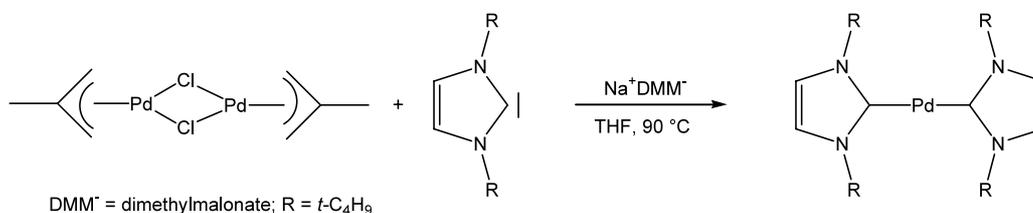
Fig. 12. Most active catalyst for the Stille reaction.

The formation of similar reactive intermediates has been proposed by Buchwald in the Suzuki–Miyaura reaction with phosphine ligands [135].

## 5.2. Stille reaction

Mixed NHC complexes of palladium like **27** (Fig. 12) also turned out to act as catalysts in the Stille reaction [94]. The identification of complex **27** as the most active catalyst was achieved by the coupling of 4-bromoacetophenone and phenyltributylstannane in toluene without any promoting additives. In contrast to the Suzuki–Miyaura reaction, the less basic and less sterically demanding triphenylphosphine PPh<sub>3</sub> is the most active one [136]. With this catalyst aryl bromides can be coupled with good turnover numbers but the system fails in the case of aryl chlorides. Nolan and coworkers used a Pd(OAc)<sub>2</sub>/imidazolium chloride system to mediate the catalytic cross coupling of aryl halides with organostannanes (Eq. (2)) [137].

The imidazolium salt **19**·HCl in combination with TBAF (t-Bu<sub>4</sub>NF) was found to be most effective for the cross coupling of aryl bromides and electron-deficient aryl chlorides with aryl and vinyl stannanes.

**24**

Scheme 15.

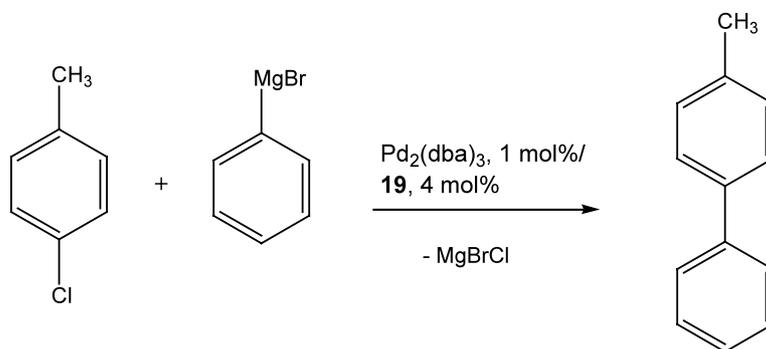


Fig. 13. Carbamoyl-substituted heterocyclic carbene Pd(II).

### 5.3. Sonogashira reaction

The bis(carbene)palladium(0) species **24**, which is active in the Heck and the Suzuki–Miyaura C–C coupling, can also be employed to furnish a Sonogashira-type coupling to get the bromo-enyne **28** (Eq. (3)) [138]. Particularly encouraging is the good conversion using only 1 mol% of **24** which is comparable with the use of the standard catalyst  $[\text{Pd}(\text{PPh}_3)_4]$  [139,140]. Furthermore the authors presented a new, simple synthesis of Pd(0) bis(carbene) complexes: ( $\pi$ -allyl)palladium(II) chloride is treated with the free carbene under reducing conditions (Scheme 15).

A palladium/imidazolium chloride system has been successfully applied to the Sonogashira coupling of arylhalides with alkynesilanes by the Nolan group [141]. The system  $\text{Pd}(\text{OAc})_2/\mathbf{20}$  has proven to be a highly efficient catalytic system in the cross-coupling reactions of a variety of arylbromides with alkynesilanes. The coupling reaction proceeds rapidly even under copper-free conditions, although the addition of CuI as cocatalyst can facilitate the reaction especially for deactivated arylhalides. Remarkably, the catalytic system was also effective for chloro benzene in moderate yield.

A very recent approach to facilitate a Sonogashira reaction under mild conditions (room temperature, 2–24 h) was described by Batey and coworkers [142]. They successfully employed the *N*-carbamoyl-substituted heterocyclic carbene Pd(II) **29** (Fig. 13) in the cross-

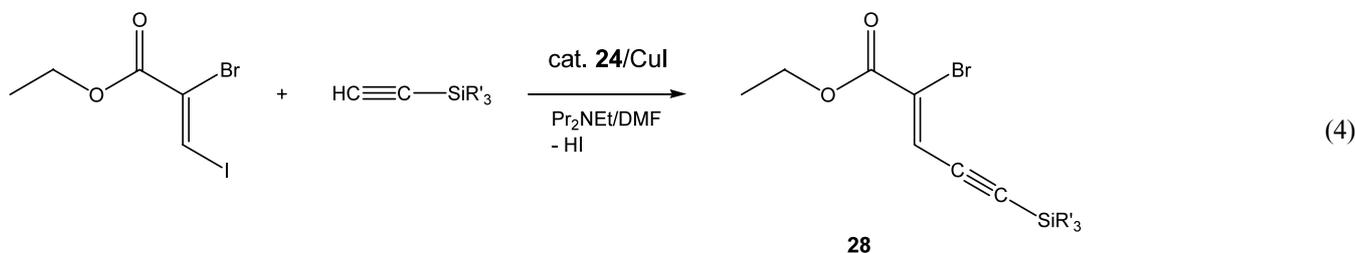
coupling reaction of a variety of arylhalides with several terminal alkynes.

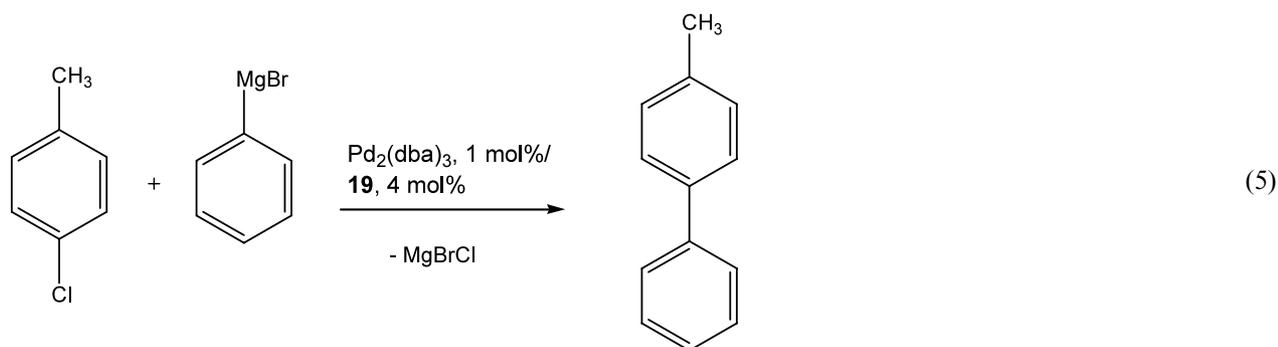
### 5.4. Kumada Tamao Corriu coupling

Although the Kumada Tamao Corriu Coupling (Eq. (4)) reaction prefers nickel(0) containing catalysts, Nolan and coworkers could find a suitable NHC palladium catalyst system, that was generated in situ from 1 mol%  $\text{Pd}_2(\text{dba})_3$  and 4 mol% **19**, but it renders less active than comparable nickel(0) systems [143].

## 6. Conclusion

Phospha-palladacycles of the type **1** and Pd(II) NHC-complexes turned out to be very efficient and robust precatalysts for CC-coupling and similar reactions. During the catalytic cycle neither the stable palladacycle undergo cleavage nor the NHC ligands dissociate from the metal centre. In contrast to conventional Pd catalysts bearing phosphine ligands, both can be employed in reactions with prolonged periods at elevated temperature without decomposition and formation of palladium black, thus achieving highest TON and TOF. Consequently, if the steric requirements of the substrates dictate higher reaction temperatures or if it is more appropriate to use deactivated aryl bromides or even





chlorides for coupling, the described palladacycles and palladium NHC-complexes could be the catalysts of choice. Molten salts as alternative solvents stabilize and activate even more and enable consecutive runs of the same catalyst after distillation of the volatile products.

The synthesis of palladacycles **1** is straightforward, starting with easily accessible educts. However, they do not offer much versatility concerning the phosphorus ligand and the anionic bridging group. Higher diversity in the design of palladacycle catalysts for coupling reactions is enabled using palladacycles of type **2** and **3**, particularly involving nitrogen- and sulfur-containing systems as cited by Bedford [145].

Structural versatility is a great advantage of N-heterocyclic carbenes as developed mainly in our group: chirality, functionalization, immobilisation and chelate effects can be achieved by easy means. Complexes like **11**, containing both NHC and phosphine ligands, combine the advantages of *stability* of bis(carbene) complexes with the good activity of phosphine complexes in C–C-coupling reactions. This strategy turned out to be very efficient also in catalysts for olefin metathesis. A promising concept in the design of efficient catalysts for coupling reactions was found by Studer and Nolan, generating a novel class of NHC substituted palladacycles.

### Acknowledgements

The research covered in this article was supported by the German Science Foundation (DFG) and the Bayerische Forschungsverbund Katalyse (FORKAT).

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