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Review

Application of palladacycles in Heck type reactions☆

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Abstract

In the last 3 years, there have been tremendous developments in palladium catalytic systems for Heck type reactions. One of the successful approaches towards activation of less reactive substrates like aryl chlorides involves the use of palladacycles **1**, **2** and **3** as catalyst precursors. This article describes the principles of these systems with an emphasis on our own work and features the ongoing literature discussion about possible mechanisms involving Pd(0)/Pd(II) or Pd(II)/Pd(IV) catalytic cycles for this class of catalyst. © 1999 Elsevier Science S.A. All rights reserved.

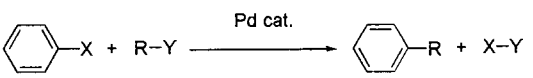
Keywords: Carbenes; Catalysis; CC-coupling; CN-coupling; Heck reaction; Palladacycles; Palladium; Phosphines

1. Introduction

Carbon–carbon and carbon–nitrogen bond forming reactions are key steps in many syntheses of organic chemicals, natural products as well as in a variety of industrial applications making these types of reaction important tools for synthetic chemists [1]. Various frequently used cross coupling reactions are mediated by palladium catalysts (Scheme 1) [2].

Unfortunately, these cross coupling reactions used to suffer from the need for high catalyst amounts (1–5 mol%) even with highly reactive aryl substrates like aryl iodides or aryl triflates. This was one of the main reasons why these reactions were not being applied to industrial processes, but only to the preparation of precious natural products and their derivatives on the laboratory scale. At the beginning of our research in this field in 1993, our interest was thus focused on the activation of more economic substrates like aryl chlorides.

It was known from the work of Osborn [3] and ourselves [4] that the oxidative addition of aryl chlorides to 14 e Pd(0)–phosphine complexes can only be achieved at elevated temperatures (Scheme 2). We believed that the oxidative addition of the aryl chloride was the rate determining step of the catalytic cycle of the cross coupling reaction. Thus, our conclusion was that one possible way for the catalytic activation of aryl chlorides could be the use of thermally stable cyclometallated Pd(II) complexes as a source for the active Pd(0) catalyst[1].



Scheme 1. Principle of palladium catalyzed cross coupling reactions. X = I, Br, Cl, OTf, COCl, CO–O–COR, $OPO(OR')_2$, $N_2^+BF_4^-$, $IR'^+X'^-$; R = aryl, vinyl, alkynyl; Y = H, MgX′, ZnX′, SnR'_3, $B(OR')_2$, Li, HgX′, AlR'_2, CuX′, Cp_2ZrCl, SiF_3.

☆ Essays on Organometallic Chemistry, part 10. For the preceding essay, see Ref. [10]. Dedicated to Professor R. Heck and to Professor J. Tsuji.

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[1] This article only describes the application of palladacycles which possess at least one Pd–C bond because of their superior thermal stability.

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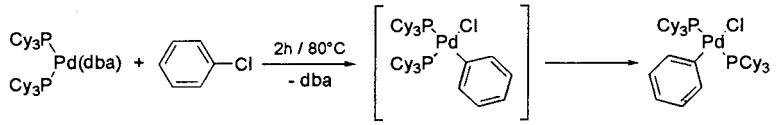


Scheme 2. Oxidative addition of chlorobenzene to $(PCy_3P)_2Pd(dba)$.

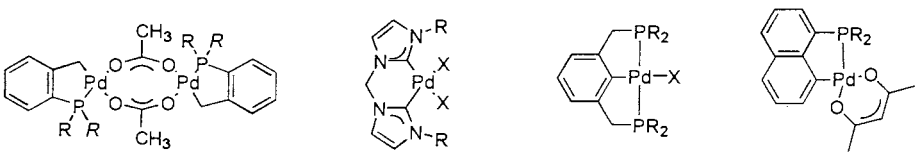


Fig. 1. Catalytic systems based on the palladacycle principle.

As a possible candidate we chose Pd(II) complexes **1** with an sp^3-metallated carbon center on a phosphorous donor ligand which had previously been prepared and characterized by Shaw [6], Alyea [7] and Heck [8], but had never been successfully used in catalytical cross coupling reactions before. Another class of cyclometallated Pd(II) complexes **2** was derived from stable *N*-heterocyclic carbenes (NHC) [9] which our group had experience in the preparation of [10] (Fig. 1).

Meanwhile, other groups have also used this concept for the preparation of Pd(II) precatalysts, e.g. Milstein produced efficient catalysis with complex **3** [11] and Shaw introduced complex **4** as a catalyst system for reactive aryl halides in the Heck reaction [12]. Additionally, there have been other prior and subsequent successful attempts to activate aryl chlorides for the Heck reaction by palladium compounds: Reetz used $(CH_3CN)_2PdCl_2 + 6\,PPh_4Cl$ [13] and a palladium colloid system [14], Beller used $Pd(OAc)_2 + 100\,P(OEt)_3$ [15] and Julia used heterogeneous Pd/C [16].

2. Chemistry of phospha–palladacycles 1

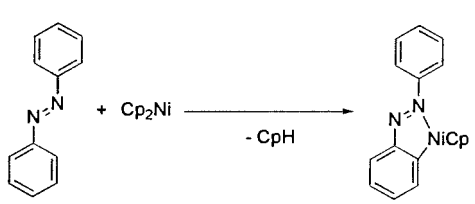
The cyclometallation reaction was discovered in 1963 by Kleinman and Dubeck [17]. They reacted azobenzene with $NiCp_2$ and obtained a five-membered metallacycle (Scheme 3). This type of reaction is particularly interesting for the understanding of CH activation in catalytic cycles [18].

Generally, metallacycles are divided into two groups: Most examples are *ortho*-metallated complexes in which an aromatic carbon atom adjacent to a functional group is bound to the metal center (e.g. **3** and **4**) and the others are complexes in which an sp^3-carbon atom is metallated (e.g. **1**).

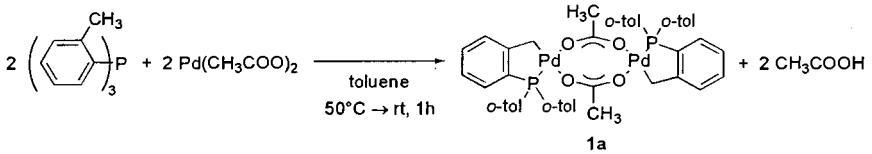
An easy and common way to obtain most metallacycles is the direct formation from the ligand and a metal salt in protic solvents at mild temperatures. In many cases, it is not necessary to neutralize the acid formed; in fact, acetic acid has even proved to be the solvent of choice in some rare cases [19]. Palladium acetate can be treated with the sterically demanding tri-*ortho*-tolyl phosphine $P(o\text{-Tol})_3$ in toluene to give the yellow, air and moisture stable cyclometallated complex *trans*-di(μ-acetato)-bis[*o*-(di-*o*-tolylphosphino)benzyl]dipalladium(II) **1a** (Scheme 4). Analogous complexes using either tri(2,4,6-mesityl) phosphine $P(Mes)_3$ [7] or $R_2P(o\text{-Tol})$ with R = *t*-Bu [6], Cy, Ph as ligand could be obtained likewise. After evaporation of the solvent and recrystallization from hexane or diethylether, the pure compounds were obtained in 80–95% yield [20].

The acetate bridged palladacycles **1** are fluxional molecules in solution as may be shown by broad $^{31}P\{^1H\}$- and ^1H-NMR resonances at room temperature. Monomer/dimer equilibria in solution due to weakly bound acetate anions as well as the participation of coordinating solvents favor bridge-splitting of the dimers and are the reason for this observation. Cooling to −70°C thus affords sharp signals. The observation of only one singlet in the $^{31}P\{^1H\}$-NMR spectrum of complex **1a** shows that the *trans*-form exclusively exists in solution. All other complexes **1** exhibit two singlets in the $^{31}P\{^1H\}$-NMR.

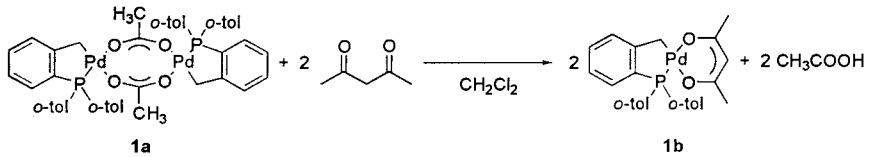
The labile acetate anions are easily exchanged by salt metathesis with tetrabutylammonium halides. The re-



Scheme 3. First example of a cyclometallated complex.



Scheme 4. Formation of *trans*-di(μ-acetato)-bis[*o*-(di-*o*-tolylphosphino)benzyl]dipalladium(II) **1a**.



Scheme 5. Formation of acetylacetonato-[*o*-(di-*o*-tolylphosphino)-benzyl]palladium(II) **1b**.

sulting dimeric complexes are equally stable, but less soluble in non-coordinating solvents like dichloromethane (DCM) or toluene [21]. Upon addition of coordinating solvents like CH_3CN or upon addition of donor ligands like PPh_3, $HNEt_2$ or pyridine, the solubility is increased due to the formation of monomeric complexes. Similarily, the addition of 2,4-pentandione results in monomeric acetylacetonato complexes, e.g. **1b**, which afforded orange prisms upon evaporation of DCM solutions (Scheme 5) [22].

The outstanding thermal stability of **1** complexes in the solid state could be measured by TG/MS. Complex **1a** does not decompose until 250°C whereas, e.g. *trans*-$Pd(PPh_3)_2(OAc)_2$ does so at about 150°C. In addition complex **1a** can be refluxed in toluene for several days without precipitation of palladium black. The inertness of the palladium–carbon bond can also be shown by the stability of complex **1a** in glacial acetic acid and even a 1:1 mixture of glacial acetic acid and concentrated sulfuric acid. This is surprising as other palladacycles of similar structure to **1** are already subject to H/D exchange in methanol-d_4 [23]. Reductive cleavage of the palladium–carbon bond of **1a** can only be achieved with NaOH in ethanol or by CO insertion into the bond followed by reductive elimination [22]. This is a severe drawback for this catalyst system as it is thus rendered useless for carbonylation reactions [24]. Although KO*t*-Bu can deprotonate the benzylic position of palladacycle **1a** under typical Heck reaction conditions resulting in its decomposition, this is not observed with NaOAc. Neither is there evidence for olefin insertion into the Pd–C bond [20]. P–C bond cleavage and aryl scrambling, both common processes in Pd(II)–phosphine chemistry [25], are not observed at reaction temperatures up to 165°C. The use of palladacycles is therefore particularly advantageous for less reactive substrates.

Yellow prismatic crystals of complex **1a** were obtained from DCM/hexane solutions [31]. The crystallographic asymmetric unit contains two molecules of **1a** and one molecule of DCM. This ratio could be confirmed by elemental analysis. The molecules exhibit pseudo-C_2 symmetry, and comparison of bond lengths and angles within the dimer and between the two independent dimers proves the identity of equivalent bonds within experimental errors. The Pd–Pd distance within the dimer of 3.115 Å rules out a metal–metal interaction as observed in bis(π-allylpalladiumacetate) (2.944 Å) [26]. The crystal structure also confirms the *trans*-geometry of the phosphorous atoms along the Pd–Pd axis. As expected for a d^8 complex, both palladium centers are found to be in square planar coordination geometries (the sum of the angles is 359.4°). The Pd–C bonds measure 2.028 Å and are within observed ranges for similar complexes (average is 2.050 Å) [21,27]. Due to steric strain between a square planar Pd coordination and an almost planar five membered metallacycle, the Pd–P bond lengths are shorter (2.214 Å) than expected for a non-cyclometallated palladium phosphine complex (2.24–2.35 Å) [28]. The almost identical Pd–O distances of 2.140 and 2.119 Å verify that alkyl and tertiary phosphine ligands exhibit similar *trans*-influences [27b] (Fig. 2).

3. Applications of phospha–palladacycles 1

3.1. The Heck reaction

Most of our work on palladacycle catalytic systems is focused on the arylation of olefins with aryl halides—generally referred to as the Mizoroki–Heck reaction [29]. Because of its enormous synthetic potential for generating carbon–carbon bonds and its tolerance towards a wide range of functional groups, this reaction has received increasing attention in the last decade [30].

We initially investigated the reaction of aryl bromides with *n*-butyl acrylate [31] because the resulting cinnamic ester derivatives are used industrially as UV absorbers, as anti-oxidants in plastics and as intermedi-

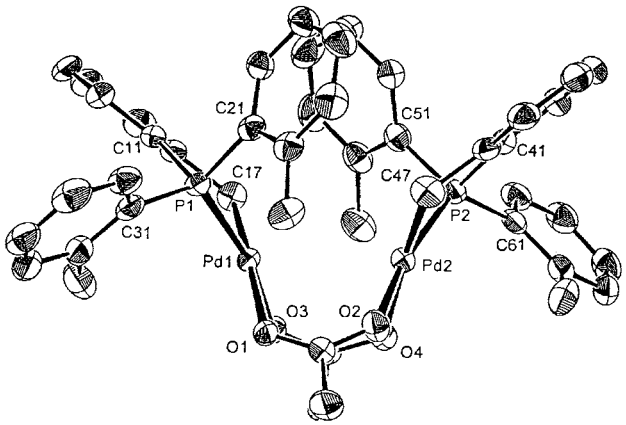


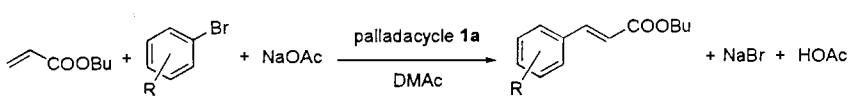
Fig. 2. Platon representation of the crystal structure of $Pd_2(\mu\text{-}OAc)_2\{o\text{-}CH_2C_6H_4P(o\text{-}Tol)_2\}_2$ **1a** showing thermal ellipsoids corresponding to 50% probability. Only one of the two independent molecules of the asymmetric unit is depicted and DCM found in the unit cell is omitted. Selected distances [Å] and angles [°]: Pd(1)–C(17) 2.021(5), Pd(1)–O(1) 2.147(3), Pd(1)–O(3) 2.111(3), Pd(1)–P(1) 2.216(1), C(16)–C(17) 1.506(7), Pd(1)–Pd(2) 3.115, P(1)–Pd(1)–C(17) 82.3(2), O(3)–Pd(1)–O(1) 87.9(1), O(3)–Pd(1)–C(17) 88.1(2), O(1)–Pd(1)–C(17) 175.8(2), P(1)–Pd(1)–O(3) 164.6(1), C(11)–P(1)–Pd(1) 103.9(2), C(16)–C(17)–Pd(1) 116.7(3), C(21)–P(1)–Pd(1) 116.2(2).

ates for pharmaceuticals [32]. C–C coupling in the presence of sodium acetate and catalytic amounts of palladacycle **1a** leads quantitatively to the desired *n*-butyl cinnamates. Table 1 summarizes the results of the catalyzed reactions [20].

Activated, electron-poor aryl bromides like 4-bromobenzaldehyde and 4-bromoacetophenone could be reacted at high turnover numbers (TON) of up to 10^6 [mol product/mol palladium]. Compared to best literature results (134 000) from in situ catalyst $Pd(OAc)_2 + 4\ P(o\text{-}Tol)_3$ [33], complex **1a** achieves a TON about 10 times greater. Turnover frequencies (TOF) generally range between 5000 and 50 000 [mol product mol palladium^{-1} h^{-1}]. Deactivated, electron-rich aryl bromides like 4-bromoanisole and 4-bromotoluene require higher catalyst amounts. Using aryl iodides as substrates showed that classical in situ catalytic systems like $Pd(OAc)_2 + 4\ P(o\text{-}Tol)_3$ are more active than palladacycle **1a** [34]. This was not only confirmed for temperatures below 80°C which are too low to activate complex **1a**, but also under the above described conditions where we observed similar TONs but lower TOFs for **1a** compared to $Pd(OAc)_2$/phosphine catalytic systems. Thus, we could confirm the former statement by Heck that palladacycles **1** were deactivated catalyst side products in his investigations because he focused his research on the activation of aryl iodides [8].

A kinetic comparison of various palladacycles **1** showed that alkyl groups (Cy, *t*-Bu) bound to phosphorous decrease catalyst activity. Higher rates for aryl substituents (*o*-Tol, Ph, Mes) can be rationalized on the basis of differing basicities of the respective P atoms, steric effects and thermal stability. The nature of the bridging group (OAc, Br or Cl) showed little effect on the reaction rate in catalytic applications which is important for small catalyst amounts because bromide or chloride anions are produced during the reaction and lead to anion metathesis. Monomeric complexes like acetylacetonato-[*o*-(di-*o*-tolylphosphino)-benzyl]palladium(II) **1b** did not show superior activity to the dimer **1a** [22].

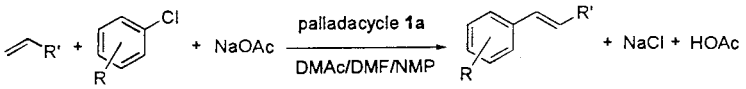
Table 1
Heck reaction of aryl bromides with *n*-butyl acrylate and palladacycle **1a** as catalyst[a]



R	Catalyst (mol% Pd)	Additive (mol%)	*T* (°C)	Reaction time (h)	Conversion (%)[b]	Yield (%)[c]	TON (mol product/mol Pd)
4-CHO	1	–	100	2	>99	>99	100
4-CHO	0.001	–	135	12	>99	>99	100 000
4-$COCH_3$	0.0001	NBu_4Br (20)	130	24	>99	>99	1000 000
4-CN	0.02	–	135	1	>99	>99	5000
4-H	2	–	140	48	>99	96	48
4-H	0.1	NBu_4Br (20)	140	48	>99	>99	1000
4-H	0.01	PPh_4Cl (1)	140	48	>99	98	9800
2-CH_3	2	–	140	48	>99	92	46
4-OCH_3	2	–	140	48	>99	94	47
4-OCH_3	1	NBu_4Br (20)	140	48	>99	>99	100

[a] One equivalent ArX, 1.1 equivalents NaOAc, 1.4 equivalents olefin. DMAc, *N*,*N*-dimethylacetamide.
[b] GC-conversion of the corresponding aryl bromide (diethyleneglycol-di-*n*-butyl ether as internal standard).
[c] Total GC-yield of all isomers (diethyleneglycol-di-*n*-butyl ether as internal standard).

Table 2
Heck reaction of aryl chlorides with palladacycle **1a** as catalyst[a]



R	R′	Catalyst (mol% Pd)	Additive (mol%)	*T* (°C)	Reaction time (h)	Yield (%)[b]	TON (mol product/mol Pd)
4-CHO	COOBu	2	-	140	24	12	6
4-CHO	COOBu	0.2	NBu_4Br (20)	130	24	81	405
4-$COCH_3$	COOBu	0.001	NBu_4Br (20)	130	72	40	40 000
4-$COCH_3$	Ph	0.1	NBu_4Br (20)	130	54	69	690
4-NO_2	Ph	0.1	PPh_4Cl (1)	140	60	91[c]	910
4-CF_3	Ph	0.1	NBu_4Br (20)	160	24	64	640
4-H	Ph	2	PPh_4Cl (12)	150	41	97	49
4-H	Ph	0.1	PPh_4Cl (1)	150	60	63	630
4-OCH_3	Ph	0.2	PPh_4Cl (1)	150	60	38[d]	190

[a] One equivalent ArX, 1.1 equivalents NaOAc, 1.4 equivalents olefin. DMF, *N*,*N*-dimethylformamide; NMP, *N*-methyl-2-pyrrolidinone.
[b] GC-yield of all isomers (diethyleneglycol-di-*n*-butyl ether as internal standard).
[c] Stilbene is formed as by-product.
[d] Plus the same amount of stilbene.

Upon changing the olefin from an acrylate to a styrene, we observed similar TONs with catalyst **1a**. Comparison of 4-substituted styrenes with unsubstituted styrene showed that electron-withdrawing 4-fluoro substitution increases the yield, whereas electron-donating 4-methoxy substitution decreases it significantly. Catalytic activity was also lower for the electron-rich *n*-butyl vinyl ether and the sterically demanding *n*-butyl methacrylate. Nevertheless, upon using activated aryl bromides with *n*-butyl methacrylate, good TONs of up to 8.3×10^3 could be obtained despite poor regio-selectivity and double arylation also being observed [35]. Although a productivity reduction by a factor of 3 was encountered, an improvement in the regio-selectivity towards internal olefins and thus the suppression of double arylation was achieved by a change of base from NaOAc to bulky amines like NBu_3 or *i*-Pr_2NEt [36]. This can be explained by the amine-assisted preferred elimination of the most acidic protons resulting in the internal olefin and at the same time the blocking of free coordination sites on the palladium by amine coordination which decreases the rate of oxidative addition.

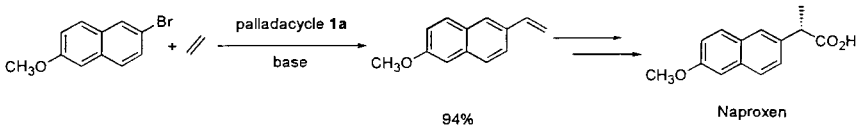
Treatment of aryl chlorides like 4-chloroacetophenone with *n*-butyl acrylate under standard conditions with palladacycle **1a** resulted in low conversions and early precipitation of palladium black at 120°C. However, addition of 20% tetrabutyl ammonium bromide [37] boosted the reaction to reasonable TONs of up to 4×10^4 which had not been observed beforehand with other homogeneous catalytic systems. Further improvement could be achieved by using tetraphenyl phosphonium chloride, although aryl scrambling on the phosphonium salt is a limiting factor for its broad application [13,38]. All these results are summarized in Table 2.

As salt additives increase the polarity of the solvent, we tested whether the reaction could also be performed in ionic liquids, i.e. using tetrabutyl ammonium bromide as a solvent at 130°C [39]. Experiments showed that good results can be obtained, e.g. the reaction of *n*-butyl acrylate with 4-bromoanisole in the presence of 1 mol% catalyst **1a** resulted in a 99% yield of 4-methoxy *n*-butyl cinnamate after 12 h [40].

The results for the Heck reaction described here led to scientific and industrial applications of catalyst **1a**. For the total syntheses of estrone steroid derivatives [41], the anti-leukaemia alkaloid cephalotaxin [42] and the blood coagulation inhibitor DX-9065a [43] various groups chose the Heck reaction catalyzed by palladacycle **1a** as the key step when higher temperatures were necessary for the substrates to react. Heck type intramolecular cyclization is also catalyzed efficiently by **1a** [5]. There is also an industrial application which uses the ability of catalyst **1a** to cleanly vinylate 2-bromo-6-methoxynaphthalene with ethylene to a single product [44]. This is applied on the pilot plant-scale as a key step for the synthesis of Naproxen by Hoechst (Scheme 6).

3.2. The Suzuki coupling reaction

Coupling of aryl- and vinyl halides or triflates with aryl- or vinyl boron compounds like boronic acids, boronic esters or boranes is known as the Suzuki coupling reaction [45]. This reaction has proven ex-



Scheme 6. Industrially feasible Heck reaction by palladacycle **1a**.

tremely versatile for the preparation of unsymmetrical, bulky biaryls and has found extensive use in natural product synthesis [46].

The reaction of 4-bromoacetophenone with phenylboronic acid under typical Heck reaction conditions, i.e. with 0.1 mol% palladacycle **1a** and a one-and-one-tenth equivalent of NaOAc as base in DMAc at 130°C, gives only a small yield of the desired product 4-acetylbiphenyl. Changing the conditions to using K_2CO_3 as base in *o*-xylene as solvent [47], the yields rose to over 90%. Thus TONs of up to 7.5×10^4 were obtained [48]. Activated aryl chlorides like 4-chloroacetophenone can also be coupled under these conditions with high TONs (Table 3). Comparison with an in situ mixture of $Pd(OAc)_2 + P(o\text{-Tol})_3$ proved that palladacycle **1a** is a superior catalyst system for biaryl formation from aryl bromides as well as chlorides.

Like in the Heck reaction, no aryl scrambling on the phosphine ligand, which leads to non-selective coupling reactions, could be observed with palladacycle **1a**. In all runs, the biphenyl was only obtained as a minor by-product ($< 5\%$). Other palladacycles **1** could also be used as catalysts for the Suzuki reaction exhibiting similar TONs. Another biaryl formation procedure with palladacycle **1a** as catalyst has been published [49]. C–H bonds of electron-rich phenols were directly activated for intramolecular coupling with aryl halides.

3.3. The Sonogashira reaction

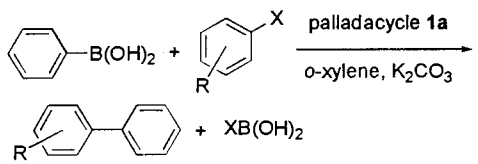
A well established method for the synthesis of internal alkynes is the palladium-catalyzed coupling of aryl iodides and bromides with terminal alkynes [50]. Nevertheless, this method suffered not only from the need for high amounts of catalyst (1–5 mol% Pd) but also from the need for the addition of 1–5 mol% CuI as a co-catalyst [51]. There are only a few exceptions reported [50b, 52].

We tried to use 0.5 mol% of palladacycle **1a** as a catalyst system for the coupling of 4-bromoacetophenone with phenylacetylene without adding CuI to the reaction mixture [53]. To our surprise, only the reaction in triethylamine as the solvent and base gave satisfactory results. In fact, the addition of co-solvents or co-bases slowed down the reaction drastically. This was also true for other amine bases, e.g. pyridine, tributylamine, piperidine and diethylamine. This effect may be explained by a sensitive association–dissociation equilibrium at the active organopalladium species and the almost quantitative precipitation of triethylammonium bromide formed during the reaction. Other palladacycles **1** performed worse under optimized conditions for **1a** [22].

Substitution of the aryl bromides effected rates and yields as expected, i.e. acceptor-substitution resulted in higher rates and yields. Unfortunately, aryl chlorides never gave satisfactory results in triethylamine most probably due to too low reaction temperatures [54]. Phenylacetylene could be coupled with a range of aryl bromides in good yields giving tolane derivatives with TONs as high as 8×10^3 (Table 4), but alkyl acetylenes did not work that well. Neither lower reaction temperature, due to lower boiling points of these acetylenes, nor the different acidity of the terminal protons can explain the low reactivity sufficiently. Thus the reason for this observation remains unclear.

The synthesis of 2,3-diphenylindenone from 2-bromobenzaldehyde and tolane was achieved with 0.1 mol% of palladacycle **1a** in 80% yield (Scheme 7) [22]. Until now there has only been published one catalytical synthetic approach that needed 5 mol% palladium(II) acetate without any phosphine ligands [55]. Indenone derivatives are the preliminary stage in the synthesis of

Table 3
Suzuki coupling of aryl halides with phenylboronic acid and palladacycle **1a** as catalyst[a]

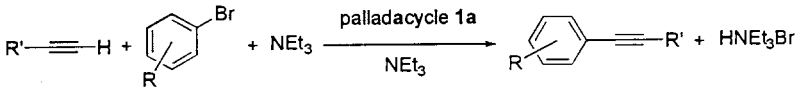


R	X	Catalyst (mol% Pd)	Yield (%)[b]	TON (mol product/mol Pd)
4-$COCH_3$	Br	0.05	92	1840
4-$COCH_3$	Br	0.001	74	74 000
4-F	Br	0.02	90	4500
4-H	Br	0.1	>99	1000
4-CN	Br	0.02	83	4150
4-OCH_3	Br	1	>99	100
4-OCH_3	Br	0.01	76	7600
4-$COCH_3$	Cl	0.1	82	8200

[a] One equivalent ArX, 1.5 equivalents $PhB(OH)_2$, two equivalents K_2CO_3; $T = 130$°C; 20 h.

[b] GC-yield using diethyleneglycol-di-*n*-butyl ether as internal standard.

Table 4
Sonogashira coupling of aryl bromides with acetylenes and palladacycle **1a** as catalyst in triethylamine[a]



R	R′	Catalyst (mol% Pd)	T (°C)	Reaction time (h)	Yield (%)[b]	TON (mol product/mol Pd)
4-$COCH_3$	Ph	0.1	90	5	99	990
4-$COCH_3$	Ph	0.01	90	24	80	8000
4-Cl	Ph	0.1	90	16	90	900
4-*n*-Bu	Ph	0.1	90	24	80	800
4-OCH_3	Ph	0.1	90	24	80	800
4-$COCH_3$	thp–O–CH_2[c]	0.1	90	24	30	300
4-$COCH_3$	tms–O–CH_2[d]	0.1	90	24	20	200
4-$COCH_3$	tms[d]	0.1	90	7	0	0
4-$COCH_3$	C_4H_9	0.1	80	24	0	0
4-$COCH_3$	HO-CH_2	0.1	70	7	0	0

[a] One equivalent ArX, 1.2 equivalents alkyne.
[b] GC-yield using diethyleneglycol-di-*n*-butyl ether as internal standard.
[c] thp = tetrahydropyran.
[d] tms = trimethylsilyl.

indenes by deoxygenation. Indenes, in turn, are important ligands for *ansa*-metallocenes which are important catalysts for olefin polymerisation [56].

Unfortunately this reaction could not be extended to terminal and unsymmetrical acetylenes under these conditions. Variations in the *ortho* functional group from aldehydes to carbonic acids, alcohols, amines or thiols failed also [22].

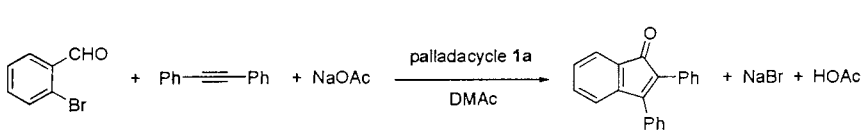
3.4. The Stille coupling reaction

Coupling of aryl- and vinyl stannanes with aryl- or vinyl halides or -triflates is known as the Stille reaction [57]. The advantage of using these highly toxic tin compounds lies in their ease of access, their inertness towards air and moisture, their high chemoselectivity, i.e. most functional groups are tolerated, and the fact that neutral conditions are applied which is extremely useful for the synthesis of base labile compounds or in the presence of base labile protecting groups [46a, 58]. Palladacycle **1a** catalyzes Stille cross-coupling reactions. Hartwig achieved TONs of 1650 in the reaction of $PhSnMe_3$ with 4-bromoacetophenone [59]. This proved to be a general observation for aryl bromides in our hands (Table 5). Aryl chlorides did not couple in satisfactory yields [60].

3.5. The Grignard and Negishi coupling reactions

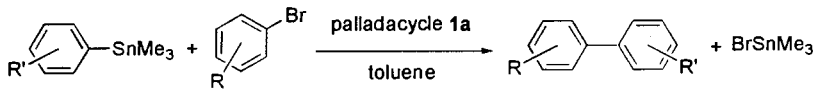
One of the earliest methods for the catalytical synthesis of unsymmetrical biaryls was the nickel [61] or palladium catalyzed [62] coupling of aryl Grignard reagents with aryl halides, triflates, ethers, sulphides or sulphones [63]. This can be further extended to the coupling of alkyl Grignard reagents and alkenyl halides. Despite the ease of access to aryl–magnesium compounds, one disadvantage is the polar nature precluding the use of several types of functional groups in the coupling partner such as aldehydes, ketones, esters and nitro groups. Thus, this method was only used in cases where none of these functional groups were present [46a].

The Negishi reaction overcame this problem by using organozinc reagents to couple with aryl- or alkenyl halides or triflates [64]. Unlike the Grignard coupling reaction, functional groups such as aldehydes, ketones, esters, amides, amines, cyano and nitro groups are tolerated. This makes the Negishi coupling a useful route to unsymmetrical biaryls [65] and other building blocks in organic synthesis [46a, 66].



Scheme 7. Synthesis of 2,3-diphenylindenone (one equivalent of 2-bromobenzaldehyde and tolane, plus a one-and-one-tenth equivalent of NaOAc and 0.1 mol% palladacycle **1a**).

Table 5
Stille coupling of aryl bromides with aryl stannanes and palladacycle **1a** as catalyst in toluene[a]



R′	R	Catalyst (mol% Pd)	Reaction time (h)	Yield (%)	TON (mol product/mol Pd)
4-H	4-$COCH_3$	5	4	96[b]	19[e]
4-H	4-$COCH_3$	0.04	12	66[b]	1650[e]
4-H	4-$COCH_3$	3	24	99[c]	33
2,4,6-CH_3	4-$COCH_3$	3	24	63[d]	21
4-H	4-H	2	24	97[c]	49
4-CH_3	4-H	3	24	90[c]	30
2,4,6-CH_3	4-H	5	24	53[d]	11
4-H	4-OCH_3	3	24	69[c]	23
4-H	2-thienyl	3	24	85[d]	28
$BzSnBu_3$	4-H	3	24	80[d]	27[f]

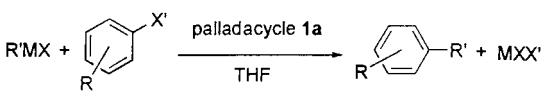
[a] One equivalent ArX, 1.5 equivalents aryl stannane; $T = 110$°C.
[b] Yield determined by ^{1}H-NMR spectroscopy.
[c] GC-yield using diethyleneglycol-di-*n*-butyl ether as internal standard.
[d] Yield determined by GC on the basis of area percentage.
[e] Results published by Hartwig et al. [59].
[f] Butylbenzene is formed as by-product.

Both of these reactions can be catalyzed by palladacycle **1a** in THF (Table 6), although early precipitation of palladium black occurs [60]. The results show that even aryl chlorides [67,68] can be subject to coupling in good yields with this system. The advantage of using aryl chlorides is that halogen–metal exchange reactions which are common for iodides and bromides do not compete here [69]. This reduces the amount of homo-coupled by-products.

3.6. The amination reaction

The synthesis of disubstituted anilines via palladium catalyzed amination of aryl halides by free secondary amines was discovered by Buchwald and Hartwig independently in 1995 [70]. Despite being known for only a short period many papers concerning this reaction have since been published [71]. We also tested the palladacycles **1** as catalysts for the amination reaction and found

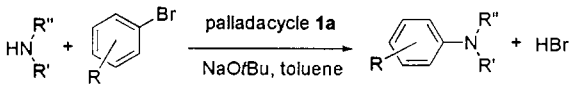
Table 6
Grignard and Negishi coupling of aryl halides with organo magnesium and zinc reagents and palladacycle **1a** as catalyst in THF[a]



R	X′	R′MX	Catalyst (mol% Pd)	Reaction time (h)	Yield (%)	TON (mol product/mol Pd)
4-H	Br	PhMgBr	2	22	>99[b]	50
4-H	Br	MeMgBr	2	18	98[b]	49
4-OCH_3	Br	PhMgBr	2	20	86[b]	43
4-CH_3	Br	MeMgBr	2	16	85[c]	43
4-H	Cl	PhMgCl	2	22	74[b]	37
4-H	Cl	MeMgBr	2	18	70[b]	35
4-$COCH_3$	Br	PhZnBr	2	16	>99[b]	50
4-H	Br	$ZnMe_2$	2	16	>99[b]	50
4-OCH_3	Br	$ZnMe_2$	2	15	78[c]	39
4-NO_2	Cl	PhZnBr	2	24	76[b]	39
4-H	Cl	PhZnBr	2	24	88[b]	44

[a] One equivalent ArX, 1.5 equivalents organometallic reagent; $T = 90$°C.
[b] GC-yield using diethyleneglycol-di-*n*-butyl ether as internal standard.
[c] Yield determined by GC on the basis of area percentage.

Table 7
Amination of aryl bromides with secondary amines and palladacycle **1a** as catalyst in toluene[a]



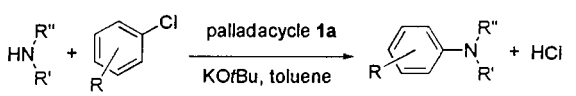
R	Amine HNR'_2	Catalyst (mol% Pd)	T (°C)	Reaction time (h)	Yield (%)[b]	TON (mol product/mol Pd)
4-$COCH_3$	Piperidine	0.5	100	24	89	178
4-CN	Piperidine	0.5	100	24	87	174
4-F	$HNBu_2$	0.5	110	24	82	164
2-CH_3	$HNPh_2$	0.5	110	48	80	160
4-H	Piperidine	0.5	110	48	83	166
4-OCH_3	$HNiPr_2$	0.5	110	48	78	156

[a] One equivalent ArBr, 1.1 equivalents NaO*t*-Bu, two equivalents amine.
[b] GC-yield using diethyleneglycol-di-*n*-butyl ether as internal standard.

that the conditions used in the original publications worked best in our case [22] (Table 7). For example 4-bromoacetophenone was reacted with piperidine in toluene in the presence of the sterically hindered base NaO*t*Bu and 0.5 mol% palladacycle **1a** resulting in a yield of 89%.

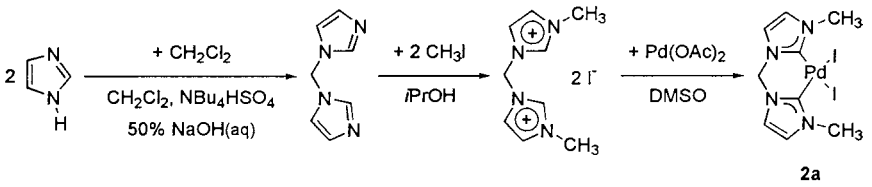
Thus, we thought about an extension of the methodology towards aryl chlorides as starting materials. Following the standard conditions developed by Buchwald and Hartwig [71] (toluene, NaO*t*Bu, 1 mol% catalyst; 100°C; 24 h) no conversion was observed with activated 4-chlorobenzotrifluoride and piperidine. However, a 55% yield of amination products was realized when the reaction was performed at higher temperatures (135°C) in the presence of 1 mol% palladacycle **1a**, a one-fifth equivalent of LiBr and KO*t*Bu as base [72]. If we used NBu_4Br instead of LiBr as co-catalyst we obtained significantly lower yields of product. With still higher amounts of amine and base the yield could be improved to 74%. This was confirmed by varying the amine as

Table 8
Amination of aryl chlorides with secondary amines and palladacycle **1a** as catalyst in toluene[a]



R	Amine (equivalents)	Catalyst (mol% Pd)	KO*t*-Bu (equivalents)	Selectivity (*para*:*meta*)	Yield (%)	TON (mol product/mol Pd)
4-CF_3	Piperidine (2.3)	1	2.0	7:1	74[b]	74
4-CF_3	Piperidine (2.3)	–	2.0	1:1	79[b]	–
4-CF_3	Piperidine (2.3)	0.1	2.0	13:1	98[c]	980
4-CF_3	$HNBu_2$ (2.0)	1	2.0	10:1	60[d]	60
4-CF_3	*N*-Methylaniline (2.0)	1	2.0	20:1	60[b]	60
4-CF_3	*N*-Methylaniline (2.0)	–	2.0	1:1	75[b]	–[e]
4-CF_3	Morpholine (2.0)	1	2.0	2:1	60[b]	60[e]
4-CF_3	Morpholine (1.2)	1	1.4	17:1	58[b]	58
4-CF_3	Morpholine (2.0)	–	2.0	1:1	62[b]	–[e]
4-COPh	Piperidine (2.3)	1	2.0	50:1	40[b]	40
4-COPh	Piperidine (2.3)	–	2.0	–	5[d]	–
4-OCH_3	Piperidine (2.0)	1	2.0	1:1	50[d]	50[e]
4-OCH_3	Piperidine (2.0)	–	2.0	1:1	60[d]	–[e]

[a] One equivalent ArCl, 0.2 equivalent LiBr; $T = 135$°C; 24 h.
[b] Isolated yields.
[c] GC-yield using hexadecane as internal standard.
[d] Determined by GC on the basis of area percentage.
[e] Results published by Beller et al. [73].



Scheme 8. Synthesis of diiodo-(1,1′-methylene-3,3′-dimethylimidazolin-2,2′-ylidene)palladium(II) **2a**.

well as using different alkyl and aryl chlorides (Table 8). Much to our surprise additionally the *meta*-regioisomer was obtained in 9% yield. A side mechanism with aryne intermediates being responsible for this finding was proven by performing the reaction under the same conditions in the absence of a catalyst. Both regioisomers were obtained in a 1:1 ratio in 79% yield. Kinetic studies of the reaction of 4-chlorobenzotrifluoride and piperidine revealed that the selectivity is not dependent on conversion [73]. We thus conclude, that the catalyst does not become deactivated. Surprisingly LiO*t*Bu and NaO*t*Bu resulted in only low conversions ($< 10\%$) although they have been reported to work well with other catalytic systems [73].

4. Chemistry of carbene–palladacycles 2

For many years carbenes were seen simply as a laboratory curiosity [74] and even the interest of Fischer who introduced them as ligands into inorganic chemistry could not focus attention on this class of compound beyond academic study [75]. Since then, carbenes and especially carbene complexes have claimed their place in the repertoire of synthetic chemists, e.g. for olefin metathesis [76] or cyclopropanation reactions [77].

Over the past few years, our group has been investigating transition metal complexes of *N*-heterocyclic carbenes derived from imidazole [10]. The chemistry of these special 'free' carbenes started with publications of Öfele [78] and Wanzlick [79] in 1968 who independently isolated the first complexes **5** and **6** with this family of ligands (Fig. 3). Many years later, Arduengo was even able to isolate stable free carbenes of this type [9]. The stability of *N*-heterocyclic carbenes is achieved by π-donation of both neighbouring nitrogen atoms which has been confirmed by ab initio calculations [80]. Some

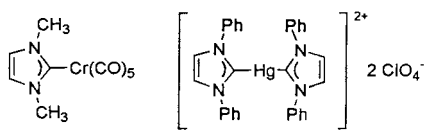


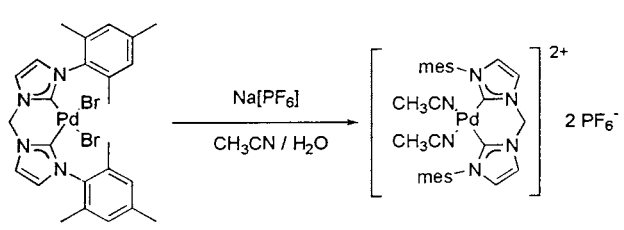
Fig. 3. Transition metal complexes of *N*-heterocyclic carbenes first isolated in 1968.

interesting properties of these ligands in addition to the facts that they are cheap, non-toxic and easy to prepare, are the high thermal stability of their metal complexes and their nucleophilic behaviour which is similar to Lewis basic phosphines. Both of these aspects suggested potential catalytic applications for the complexes [81].

Bridged dicarbenes can be used as chelating ligands. The ligands are prepared from imidazole by reaction with dichloromethane in the presence of tetrabutylammonium hydrogen sulfate in 50% NaOH (aq.) [82]. After isolation, quaternisation can be achieved by standard methods (Scheme 8). Palladium complexes **2** can then be obtained by dissolving one equivalent of $Pd(OAc)_2$ and of the diimidazolium salt in DMSO and evaporating the solvent in vacuo at 150°C. Soxhlet extraction of the residue by acetonitrile gives the desired complexes **2** in 70–80% yield [83] (Scheme 8). Earlier publications of our group suggested the use of THF as solvent but it turned out that an alternative route described in [84] gives significantly higher yields.

Dibromo - (1,1′ - methylene - 3,3′ - dimesitylimidazolin-2,2′-ylidene)palladium(II) **2b** with mesityl substituents is prepared analogously, however the diimidazolium dibromide salt must be prepared by quaternization of 1(2-,4-,6-mesityl)imidazole with CH_2Br_2. Dicationic complexes like **2c** can further be achieved via the exchange of bromide anions by non-coordinating anions with $Ag[BF_4]$ or $Na[PF_6]$ (Scheme 9). Complex **2c** was isolated as an air and moisture stable bis(acetonitrile) adduct.[2]

Orange prisms could be grown from a DCM solution of complex **2a** [83]. The crystal structure determination



Scheme 9. Preparation of the dicationic complex **2c** from dibromo-(1,1′-methylene-3,3′-dimesitylimidazolin-2,2′-ylidene)palladium(II) **2b**.

[2] Concerning the catalytical activity and structural details of complex **2c** see reference [84].

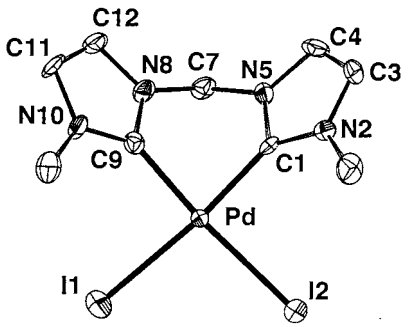


Fig. 4. Platon representation of the crystal structure of diiodo-(1,1′-methylene-3,3′-dimethylimidazolin-2,2′-ylidene)palladium(II) **2a** showing thermal ellipsoids corresponding to 50% probability. Selected distances [Å] and angles [°]: Pd–I(1) 2.645(1), Pd–I(2) 2.657(1), Pd–C(1) 1.989(8), Pd–C(9) 1.988(7), C(1)–Pd–C(9) 83.2(3), C(1)–Pd–I(2) 92.0(2), I(1)–Pd–I(2) 93.2(1), I(1)–Pd–C(9) 90.8(2), C(1)–N(5)–C(7) 119.7(7), C(9)–N(8)–C(7) 120.3(7), N(5)–C(7)–N(8) 108.6(6), N(2)–C(1)–N(5) 104.5(7), N(8)–C(9)–N(10) 105.3(6).

revealed the chelating nature of the ligand resulting in monomeric diiodide complexes possessing non-crystallographic C_s symmetry, the mirror plane passing through the palladium and methylene carbon centers (Fig. 4). The six membered metallacycle is fixed in a boat like conformation in accordance with previously reported tetracarbene complexes [85]. The two heterocyclic ring systems deviate from the coordination plane of the palladium center by an average of 51.9°. The Pd–C bond distances of 1.988 Å are in the same range as reported for the non-chelating dicarbene complex diiodo-bis(1,3-dimethylimidazolin-2-ylidene)palladium-(II) [86] but shorter than those in a tetracarbene complex because of the *trans* influence of the iodide anions [85]. The formation of the metallacycle does not distort the coordination geometry of the palladium center, with the C(1)–Pd–C(9) ligand bite angle being close to ideal at 89.2(3)°.

5. Application of carbene–palladacycles 2

5.1. The Heck reaction

Palladium di(monocarbene) complexes efficiently catalyze the Heck reaction with aryl bromides and activated aryl chlorides [86]. Taking these results into account, it was to be expected that complexes of chelating dicarbene ligands should also exhibit catalytic activity. Experiments confirmed this and showed that the catalytic activity of chelating dicarbene and di(monocarbene) Pd(II) complexes are comparable [83]. With activated 4-bromoacetophenone and *n*-butyl acrylate TONs of 1000 were obtained applying defined Pd(II) carbene complexes like **2a** [22,83]. Using $Pd_2(dba)_3 \cdot dba$ and two equivalents of free monocarbene ligand in situ resulted even in TONs as high as 3.3×10^5. Table 9 shows the results obtained with complex **2a**.

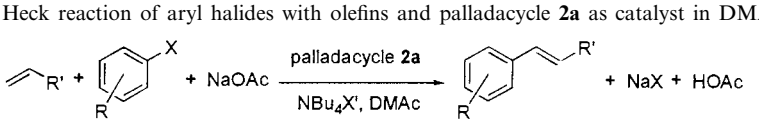
5.2. The Suzuki reaction

Further investigations concerning the catalytic activity of complex **2a** were carried out on the coupling of aryl halides with phenylboronic acid [83]. The Suzuki coupling reaction was chosen because it is one of the most important synthetic tools for making unsymmetrical biaryl building blocks [46]. The results obtained in toluene with K_2CO_3 as base show that aryl bromides can be coupled with phenylboronic acid in good to excellent yields with 0.5 mol% of catalyst **2a** (Table 10).

5.3. The Sonogashira reaction

Being an important tool for the synthesis of internal alkynes, the Sonogashira reaction was also performed with palladacycle **2a** [83]. Good results could be obtained with activated aryl bromides and phenylacetylene (Table 11). Like in the case of palladacycle **1a** NEt_3 had to be used as both the base and solvent.

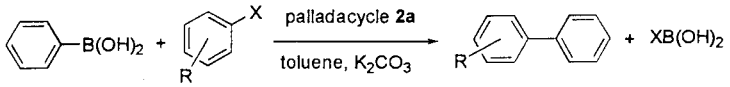
Table 9
Heck reaction of aryl halides with olefins and palladacycle **2a** as catalyst in DMAc[a]



R	X	R′	Catalyst (mol% Pd)	NBu_4X' (mol%)	*T* (°C)	Reaction time (h)	Yield (%)[b]	TON (mol product/mol Pd)
4-$COCH_3$	Br	COOBu	0.1	Br (20)	130	5	>99	1000
4-OCH_3	Br	Ph	0.17	Br (20)	135	24	85	500
4-OCH_3	Br	COOBu	0.5	OAc (30)	140	12	95	190
4-$COCH_3$	Cl	Ph	0.2	Br (20)	140	24	70	350
4-$COCH_3$	Cl	COOBu	0.5	OAc (30)	140	24	60	120

[a] One equivalent ArX, 1.2 equivalents NaOAc, 1.4 equivalents olefin.
[b] GC-yield using diethyleneglycol-di-*n*-butyl ether as internal standard.

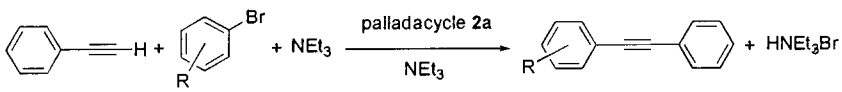
Table 10
Suzuki coupling of aryl halides with phenylboronic acid and palladacycle **2a** as catalyst in toluene with K_2CO_3 as base[a]



R	X	Catalyst (mol% Pd)	Reaction time (h)	Yield (%)[b]	TON (mol product/mol Pd)
4-$COCH_3$	Br	0.5	18	93	186
4-NO_2	Br	0.5	12	99	198
4-H	Br	0.5	12	87	174
4-NH_2	Br	0.5	24	78	156
4-OCH_3	Br	0.5	22	80	160
4-$COCH_3$	Cl	0.5	48	60	120

[a] One equivalent ArX, 1.1 equivalents phenylboronic acid, two equivalents K_2CO_3; $T = 120°C$.
[b] GC-yield using diethyleneglycol-di-*n*-butyl ether as internal standard.

Table 11
Sonogashira coupling of aryl bromides with phenylacetylene and palladacycle **2a** as catalyst in triethylamine[a]



R	Catalyst (mol% Pd)	Reaction time (h)	Yield (%)[b]	TON (mol product/mol Pd)
4-$COCH_3$	1	48	76	76
4-F	1	48	71	71

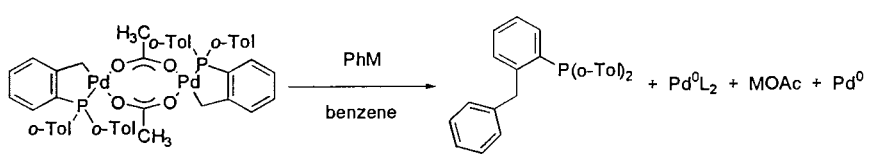
[a] One equivalent ArX, 1.2 equivalents alkyne; $T = 90°C$.
[b] GC-yield using diethyleneglycol-di-*n*-butyl ether as internal standard.

6. Mechanistic discussion

6.1. Mechanism of phospha–palladacycle systems *1*

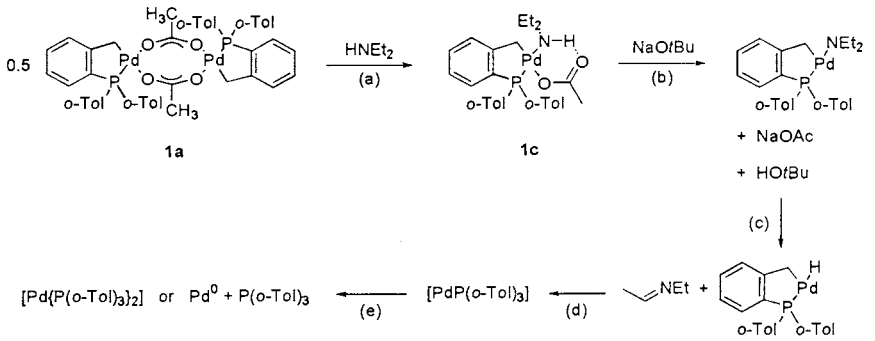
Heck type reactions that have been covered in this article are generally believed to work via a Pd(0)/Pd(II) redox mechanism [87]. Starting with palladacycles **1** in the oxidation state + II it would be necessary to have a reduction step prior to catalysis. If no reduction occurred a catalytic cycle via Pd(II)/Pd(IV) had to be postulated [31,53,88].

In the cases of the Stille, Grignard, Negishi and, most probably, the Suzuki cross coupling reaction there is no doubt about the reduction mechanism of palladacycle **1a** to the Pd(0) species strongly suggesting that these are the catalytically active molecules. In order to examine the reduction mechanism in the Stille reaction, Hartwig et al. heated palladacycle **1a** in the presence of $PhSnMe_3$ in benzene-d_6 for 2.5 h [59]. Monitoring the reaction by NMR spectroscopy showed the conversion of the resonances for **1a** into two new $^{31}P\{^1H\}$-NMR resonances for complexed and free P(*o*-Tol)$_2$(C_6H_4-*o*-CH_2Ph) **7** at $\delta = 8.1$ ppm (δ [Pd{P(*o*-Tol)$_3$}$_2$] = 6.7 ppm) and at $\delta = 29.9$ ppm (δ P(*o*-Tol)$_3$ = 29.1 ppm), respectively. When the reaction had ceased, phosphine **7** and P(*o*-Tol)$_3$ were isolated in a 5:1 ratio and with a total yield of 87%. The same observations for C–C bond-forming reductive methylene bridge cleavage have been made when PhMgBr or PhZnCl was reacted with palladacycle **1a** [38]. In these cases a greater amount of free P(*o*-Tol)$_3$ was detected. Presumably the described reaction pathway to the Pd(0) species is also true for



1a **7,L**

Scheme 10. Schematic reduction of palladacycle **1a** to Pd(0) species by PhM (M = $SnMe_3$, MgBr, ZnCl).



Scheme 11. Postulated mechanism for the formation of $[Pd\{P(o\text{-}Tol)_3\}_2]$ during the amination reaction: (a) dimer cleavage (b) deprotonation (c) β-H elimination (d) reductive elimination (d) disproportionation.

the Suzuki reaction with phenylboronic acid (Scheme 10).

Concerning the amination reaction, Hartwig et al. also found another mechanism for the formation of Pd(0) compounds from palladacycle **1a** [59]. Palladacycle **1a** was cleaved by the secondary amine $HNEt_2$ to form the monometallic amine complex **1c** which could be isolated and fully characterized. Crystal structure determination and low temperature NMR spectra revealed a rigid and puckered metallacycle exhibiting strong hydrogen bonding between the amine NH proton and the acetic acid carbonyl oxygen which was confirmed in the crystal structure and by IR data. Amine complex **1c** reacts with $NaOtBu$ to generate $[Pd\{P(o\text{-}Tol)_3\}_2]$ in 48% yield being almost quantitatively based on the number of phosphines (Scheme 11). The formation of Pd(0) along with the aryl amine products has been shown to occur for amine-ligated aryl halide complexes upon addition of base to deprotonate the amine and generate a Pd(II) amido species [89]. Further comparison of the catalytical activity of metallacycles **1a** and **1c** and of $[Pd\{P(o\text{-}Tol)_3\}_2]$ in the amination reaction revealed no significant differences, suggesting that indeed Pd(0) phosphine complexes are the catalytically active species in this reaction.

Despite the findings already mentioned, speculation concerning the mechanism of the Heck reaction with palladacycles **1** and **3** still gives rise to the possibility of a pathway via Pd(II)/Pd(IV) intermediates. This possibility was first proposed by ourselves [31] and has been theoretically justified and described in detail by Shaw recently [88].

Various observations and facts made us think about a mechanism being different to that expressed in standard textbooks [87]. First of all, no visible palladium black formation is observed during catalysis at moderate temperatures. As this was believed to be a sign of Pd(0) species being present during the reaction, we wondered whether Pd(0) was produced in our system at all. The fact that the palladacycles **1** can be isolated as the halide bridged isomers from catalytic reactions in yields up to 70% lead us to propose a mechanism which would leave the catalyst in a resting state in which it at least could form back into a metallacycle. It has to be stressed that cyclometallation of this kind is known to occur exclusively with Pd(II) compounds. It was also known that Pd(II) salts are reduced in situ to Pd(0) complexes by phosphine and base [90] but we could not detect phosphine oxide nor any other oxidized by-products during catalysis. In addition, it was known that Pd(IV) complexes can be isolated and that they can form cross coupling type products by reductive elimination in stoichiometric and catalytic reactions [91]. Thus, we followed the reaction of 4-bromobenzaldehyde with *n*-butyl acrylate in the presence of palladacycle **1a** at relatively low temperatures [31]. The only species we could detect in the $^{31}P\{^1H\}$-NMR spectra resulted from anion exchange (OAc vs. Br) and the formation of anionic, monomeric palladacycles (Fig. 5). No resonances assignable to Pd(0)–phosphine complexes were measured, nor could any signals resulting from free phosphine be detected.

Next we tried to achieve oxidative addition of aryl bromides to palladacycles **1** but could never isolate the desired Pd(IV) complexes. Heating in the presence of only an olefin resulted in partial palladium black formation if no aryl halide was present. But no oxidation products or insertion of the olefin into the Pd–C bond could be detected. In order to see whether the metallacycle opens during catalysis we analyzed the retained palladacycles **1** after reaction of 4-bromobenzaldehyde with styrene-d_8. No incorporation of deuterium into the methylene bridge was detected [92].

On the other hand, unknown reduction pathways of palladacycles **1** to Pd(0) cannot be ruled out. Hartwig et al. obtained 20% of the non-arylated $P(o\text{-}Tol)_3$ after reaction of palladacycle **1a** with $PhSnMe_3$ which could not have been liberated by the mechanism described. The fact that diphenyl amine also works equally well in the amination reaction shows that a β-H atom in the amine is not necessary to obtain an active Pd(0) catalyst [72]. Thus, we investigated other possible reduction

pathways for the palladacycles **1**. Olefins are not capable of inserting into the Pd–C bond and a Wacker type oxidation of the olefin resulting in reduction of the palladacycle was not detected. In both these cases we

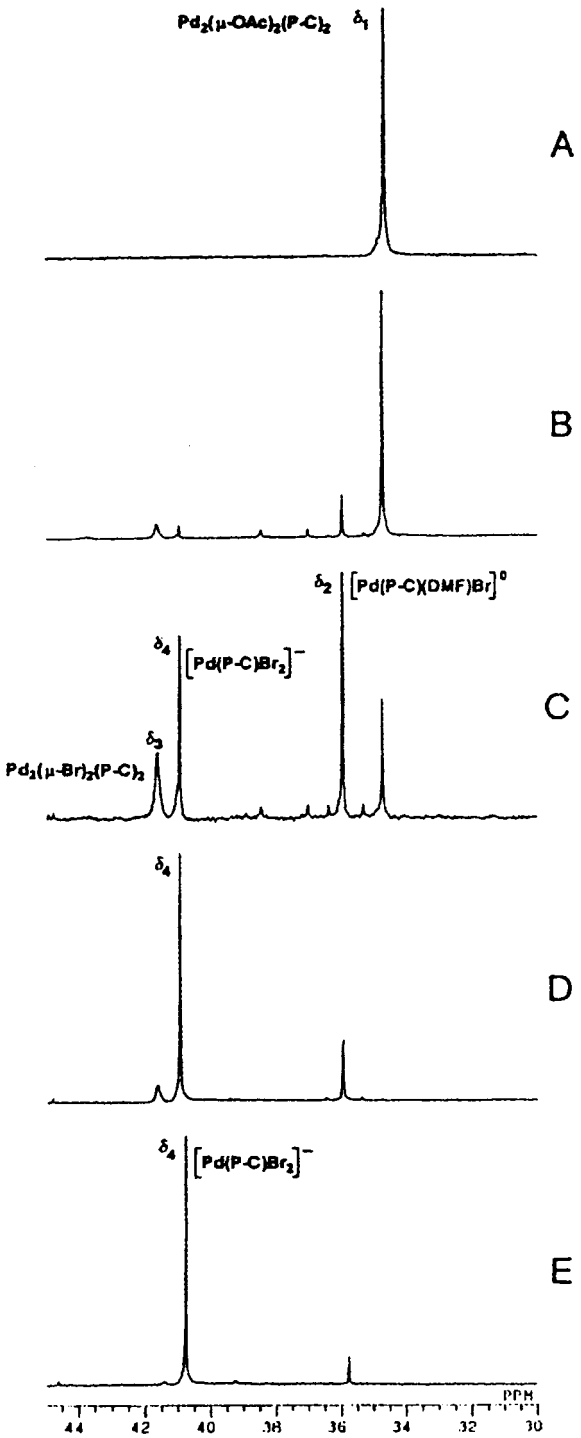


Fig. 5. $^{31}P\{^{1}H\}$-NMR investigation (40°C, DMF-d_7, 161.85 MHz) on the Heck olefination of 4-bromobenzaldehyde with *n*-butyl acrylate in DMF-d_7; $T = 80$°C, palladacycle **1a** as catalyst. (A) at the start (conversion $x = 0$); (B) after 10 min ($x = 2\%$); (C) after 1 h ($x = 5\%$); (D) after 1.5 h ($x = 8\%$); (E) after 5 h ($x = 10$–12%). (P–C) = *o*-$CH_2C_6H_4P(o\text{-Tol})_2$.

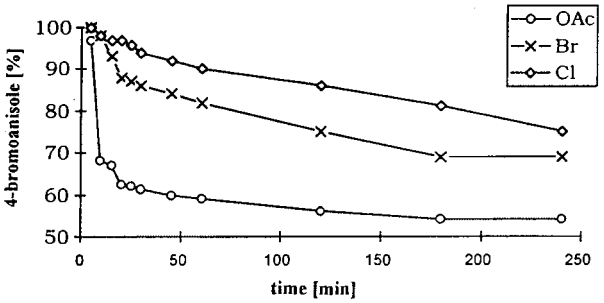


Fig. 6. Time-conversion diagrams of the Heck reactions of 4-bromoanisole with *n*-butyl acrylate without base in the presence of three palladacycles $Pd_2(\mu\text{-}X)_2\{o\text{-}CH_2C_6H_4P(o\text{-Tol})_2\}_2$ **1** (X = OAc, Br, Cl).

failed to detect appropriate by-products. Acetic acid, which is formed during catalysis, is unable to cleave the Pd–C bond which was shown by experiments with CD_3COOD and can additionally be justified by DFT calculations [93]. On the other hand, NaOAc is also not strong enough to deprotonate the methylene group. Only strong bases like alkaline *t*-butoxides can lead to the degradation of the palladacycles **1**. The olefin is thus not the reducing agent, nor is it the base or the formed acid.

As it is known that palladium(II) salts are easily degraded to palladium black if heated in any solvent we thought about correlating the thermal stability of the palladacycles **1** with their reactivity in the Heck reaction. Taube et al. showed that the redox stability of Pd(II) compounds with respect to the anion followed the series Cl > Br > OAc [94]. It is crucial to choose an appropriate aryl halide for mechanistic studies as this determines what step in the catalytic cycle will be the rate determining one (ligand dissociation, olefin insertion [95] or oxidative addition). As our aim was to see which species catalyzes the reaction of normally unreactive aryl halides we performed the reaction of 4-bromoanisole with *n*-butyl acrylate without base in the presence of three different palladacycles **1** which differed in their anion. Time-conversion diagrams revealed that the reactivity decreased according to the series OAc > Br > Cl (Fig. 6). This finding can be interpreted as an enhanced activity if the system is more easily reduced thermally, i.e. a thermally induced heterolytical Pd–C bond cleavage with subsequent reduction of the under-coordinated Pd(II) center [22]. A similar finding was obtained when thermally more stable alkyl phosphine substituted palladacycles **1** were applied in Heck catalysis and performed significantly worse than palladacycles **1** derived from triaryl phosphines [20].

The observation regarding the reactivity of different palladacycles **1** is also an argument against a Pd(II)/Pd(IV) catalytic cycle because it is known that σ-donors, like alkyl ligands, on the palladium, are necessary to achieve oxidative addition to Pd(II) complexes. As the σ-donor ability of phosphines increases

upon exchanging aryl for alkyl substituents one would expect a greater reactivity of palladacycles **1** derived from $Cy_2P(o\text{-Tol})$ or $t\text{-Bu}_2P(o\text{-Tol})$ than those derived from $P(o\text{-Tol})_3$ or $PMes_3$. This is not the case [20].

Shaw also stressed the necessity of strong σ-donor ligands to achieve oxidative addition to the Pd(II) centers. His mechanism suggests a reversible nucleophilic attack by acetate or halide anions on the Pd(II)-coordinated olefin and thus the formation of σ-bound alkyl ligands to be the key step in the promotion of oxidative addition of the aryl halide [88]. As we never found side reaction products for the reversible π-σ-bonding of the olefins, e.g. phenylvinyl acetate from the elimination of a β-hydride instead of the postulated β-acetate, we cannot give further credence to a Pd(II)/Pd(IV) mechanism being operative in our case.

In summary we are confident in believing that Heck type reactions catalyzed by phospha–palladacycles **1** are catalyzed by Pd(0) species. This implies that the palladacycles constitute a reservoir for a highly active catalyst species which is produced by thermally induced heterolytical Pd–C bond cleavage and subsequent reduction to Pd(0). In turn, the catalytically active species produced must then be responsible for higher turnovers than the ones calculated from the amount of palladacycle **1a** used.

We presumed that the catalytically active species is formed by anion coordination to a Pd(0)–monophosphine compound. This assumption could be confirmed by DFT calculations [96]. In order to test this finding we tried to prepare the postulated complexes from an alternative route. Upon addition of an excess of NBu_4OAc and other salts, which are soluble in organic solvents, to a solution of $[Pd\{P(o\text{-Tol})_3\}_2]$ in benzene-d_6 we observed a change in the $^{31}P\{^1H\}$-NMR resonances (Fig. 7). The signal for $[Pd\{P(o\text{-Tol})_3\}_2]$ disappeared and two new signals appeared in a ratio of about 1:1. As one of the signals could be assigned to free $P(o\text{-Tol})_3$ we suggested that the other signal belongs to the postulated complex $[(AcO)Pd\{P(o\text{-Tol})_3\}]$. Varying the anion showed that salts which have proved to be activating and catalyst stabilizing in the Heck reaction, like NBu_4Br or NBu_4OAc, shift the equilibrium towards the side of the anionic complex because no signal for $[Pd\{P(o\text{-Tol})_3\}_2]$ remained. Salts containing non-coordinating anions which showed no effect in the Heck reaction like NBu_4BF_4 exhibited only a small effect on the species distribution [22].

On the other hand, we cannot rule out a Pd(II)/Pd(IV) side mechanism which should be conducted by much less productive Pd(II) catalysts compared to the Pd(0) catalysts. If two mechanisms were active in the Heck reaction at the same time but at different rates, one should observe this in product distribution. It is unlikely that the two distinct mechanisms have exactly the same isomer distribution. Thus, if the product ratio differed with the reaction time one would have to consider a change of mechanism during the reaction as the amount of Pd(II) catalyst decreases while the amount of Pd(0) catalyst increases with the reaction time. To our knowledge no one has yet observed this phenomenon with phospha–palladacycles **1** making us confident in our above mentioned opinion. Redox reactions on the metal center of palladacycle catalysts could further be revealed by cyclovoltametry. Electrochemical studies like the ones on Pd/PPh_3 systems [90b,c,95] could give insight into a possible Pd(II)/Pd(IV) pathway or in turn further support a classical Pd(0)/Pd(II) mechanism.

6.2. Mechanism of carbene–palladacycle systems **2**

Mechanistic discussions about the carbene–palladacycle systems have never considered Pd(II)/Pd(IV) pathways although the carbene ligands constitute strong σ-donors. The observation of induction periods in the Heck and the Suzuki reaction suggested the in

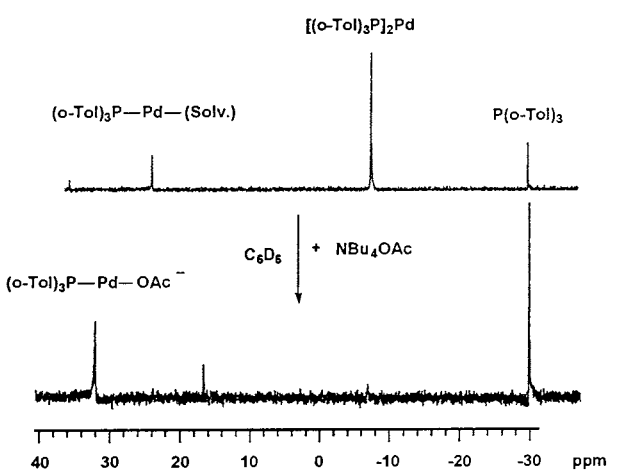


Fig. 7. Effect of the addition of NBu_4OAc to a solution of $[Pd\{P(o\text{-Tol})\}_2]$ in benzene-d_6 on the $^{31}P\{^1H\}$-NMR spectrum.

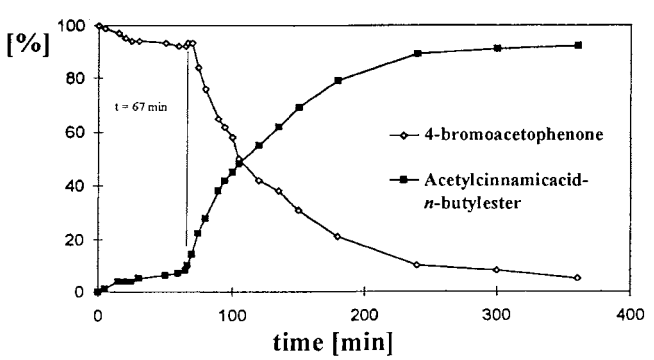


Fig. 8. Conversion/time diagram for the Heck reaction of 4-bromoacetophenone with *n*-butyl acrylate to form *n*-butyl 4-acetylcinnamate catalyzed by a palladium–dicarbene complex. Addition of 85 μl hydrazine hydrate after 67 min.

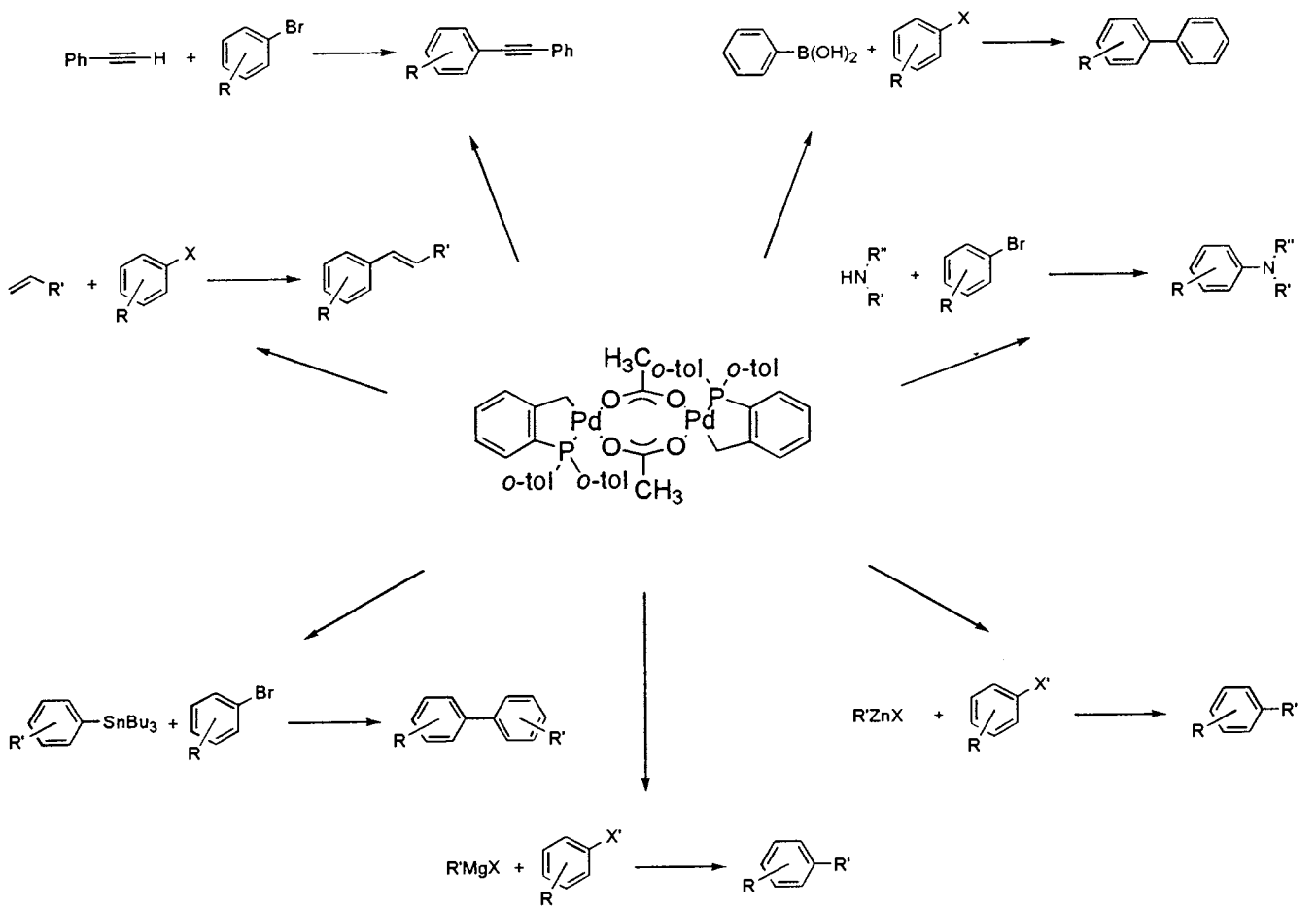


Fig. 9. Heck type reactions catalyzed by phospha–palladacycle **1a**.

situ reduction of the Pd(II) complexes **2** and a standard Pd(0)/Pd(II) mechanism. This was proven by adding reducing agents like hydrazine hydrate or sodium formate to the reaction mixtures. A typical kinetic observation with di(monocarbene) complexes of palladium(II) in the Heck reaction of 4-bromoacetophenone and *n*-butyl acrylate is shown in Fig. 8. The reaction commenced only after the addition of hydrazin hydrate [86].

7. Conclusions

Improved catalyst efficiency compared to all previously published procedures has been realized by palladacycles **1** and **2** in the Heck type reactions with aryl chlorides and aryl bromides. Advantages with regard to conventional catalyst mixtures are based on the possible use of more economic aryl halides, high activity at low palladium/ligand ratio (1:1) and improved thermal stability and life-time in solution. The spectrum of reactions covered by this new principle of the catalyst has been shown to be broad (Figs. 9 and 10).

The advantages of the palladacycle system over in situ catalytic systems offer a sophisticated way to choose the appropriate catalyst system for a large range of possible needs. For easy to activate aryl iodides, triflates or diazonium salts, in situ systems are good enough to obtain high yields in Heck type reactions. But if the steric requirements of the substrates dictate higher reaction temperatures or if it were more appropriate to use aryl bromides or even chlorides for coupling, the described palladacycle systems should be the catalysts of choice. This market has already been met by Lancaster Synthesis who made *trans*-di(μ-acetato)-bis[*o*-(di-*o*-tolylphosphino)benzyl]dipalladium(II) **1a** commercially available in their latest catalogue for 1997–1999[3]. This now offers even those groups not willing to make the easy to prepare catalyst on their own the opportunity to use it nevertheless in both established and new applications.

Concerning the mechanism of Heck type reactions catalyzed by palladacycles, it is becoming clear from the

[3] Lancaster synthesis, Eastgate, Uk offers palladacycle **1a**: order no. 16948.

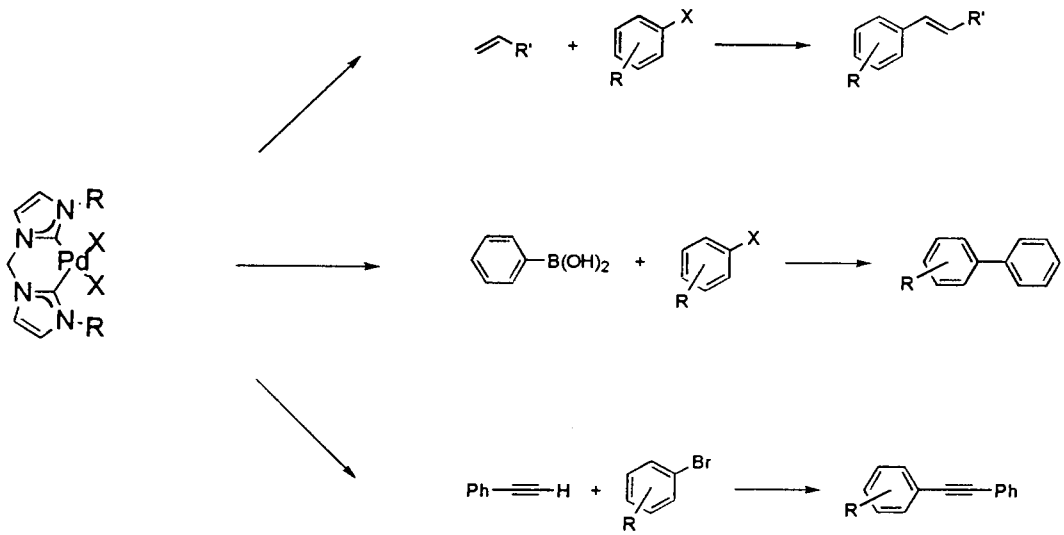


Fig. 10. Heck type reactions catalyzed by palladium–carbene complex **2a**.

contributions of different groups that the most active species in all cases is a Pd(0) compound. The palladacycle catalysts constitute only a thermally stable reservoir for the active species. Although we cannot definitely rule out a Pd(II)/Pd(IV) mechanism working in competition, we are nevertheless confident to have shown that it could only be a side mechanism which cannot be responsible for the high turnovers observed.

8. Supplementary material

Crystallographic data for the structures have been deposited with the Cambridge Crystallographic Data Centre. Supplementary publication no. CSD-59103 for **1a**. Copies of the information can be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (Fax: +44-1223-336-033; e-mail: deposit@ccdc.cam.ac.uk or www: http://www.ccdc.cam.ac.uk.

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