Mechanism of the Heck Reaction Using a Phosphapalladacycle as the Catalyst: Classical versus Palladium(IV) Intermediates**

Volker P. W. Böhm[a, b] and Wolfgang A. Herrmann*[a]

Abstract: The mechanism of the (Mizoroki–)Heck vinylation of aryl bromides catalyzed by the phosphapalladacycle $[\{\overline{\mathrm{PdCH_2C_6H_4P}}(o\text{-Tol})_2(\mathrm{OAc})\}_2]$ (**1**) was investigated in order to determine whether palladium(IV) intermediates play a significant role in the catalytic cycle. The phosphapalladacycle **1** was compared to the related palladium(0) catalyst $[\mathrm{Pd}\{\mathrm{P}(o\text{-Tol})_3\}_2]$ (**2**) and an intermediate of the classical catalytic cycle $[\{\mathrm{PdAr}\{\mathrm{P}(o\text{-Tol})_3\}\mathrm{Br}\}_2]$ (**3**) obtained by oxidative addition of an aryl bromide to **2**. Small, yet measurable deviations of the phosphapalladacycle **1** from the other catalysts **2** and **3** in the product distribution of styrene, in competition experiments of styrene and *n*-butyl acrylate, in the isotope effect on styrene, and the Hammett correlation on aryl bromides led to the conclusion that a different catalytic cycle is operative. Nevertheless, due to only small differences in these competition experiments a modified classical catalytic cycle with a novel, cyclometallated, anionic palladium(0) species **6** is proposed rather than palladium(IV) intermediates. Species **6** accounts for the observed high activity and stability of palladacycle catalysts in the Heck reaction. Palladium(IV) intermediates can be ruled out by taking into account the experiments performed here and recently published by others.

Keywords: Heck reaction · homogeneous catalysis · metallacycles · palladium · reaction mechanisms

Introduction

The palladium-catalyzed vinylation of aryl halides, known as the Mizoroki–Heck or simply the Heck reaction,[1, 2] offers a convenient method for the synthesis of olefinic intermediates for pharmaceuticals,[3] for fine chemicals,[4] and for building blocks of polymers.[5] However, industrially important but less reactive aryl halides are transformed very sluggishly with standard catalysts.[6] An important class of catalysts for the transformation of these unreactive reagents are palladacycles, like **1**,[7, 8] which resemble thermally stable palladium(II) complexes.[9] Subsequently, these catalysts can be used over prolonged periods at elevated temperatures, thus achieving highest turnover numbers (TON).[7, 8, 10, 11]

Despite those outstanding characteristics, mechanistic details about this class of catalysts remain unsolved. In particular, the question of whether the stable palladium(II) complexes allow palladium(IV) intermediates to be formed in an alternative catalytic cycle of the Heck reaction has attracted substantial interest,[12] as this potential mechanism would complement the classical catalytic cycle involving a palladium(0) intermediate as shown in Scheme 1.[2] The postulated palladium(IV) species are supported by the isolation of related, stable organometallic complexes[13] as well as by Heck-type catalytic reactions that have been proven to proceed via palladium intermediates of the oxidation state +IV.[13, 14]

Results

trans-Di(μ-acetato)bis[*ortho*-(di-*ortho*-tolylphosphino)benzyl]dipalladium(II) (**1**)[7] was the first example of a number of palladacyclic catalysts[10, 11] and has received much attention in the literature.[8] Nevertheless, mechanistic investigations on this and related catalysts in the Heck reaction are rare. Although ^{31}P NMR spectroscopic studies[7a] and time-conversion analyses[15] were conducted with **1**, conclusions about the mechanism remained contradictory. Only for related

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[a] Prof. Dr. W. A. Herrmann, Dr. V. P. W. Böhm
Anorganisch-chemisches Institut
der Technischen Universität München, Lichtenbergstrasse 4
85747 Garching bei München (Germany)
Fax: (+49) 89-289-13473
E-mail: lit@arthur.anorg.chemie.tu-muenchen.de

[b] Dr. V. P. W. Böhm
Present address: Department of Chemistry
University of North Carolina at Chapel Hill
Chapel Hill, NC 27599-3290 (USA)

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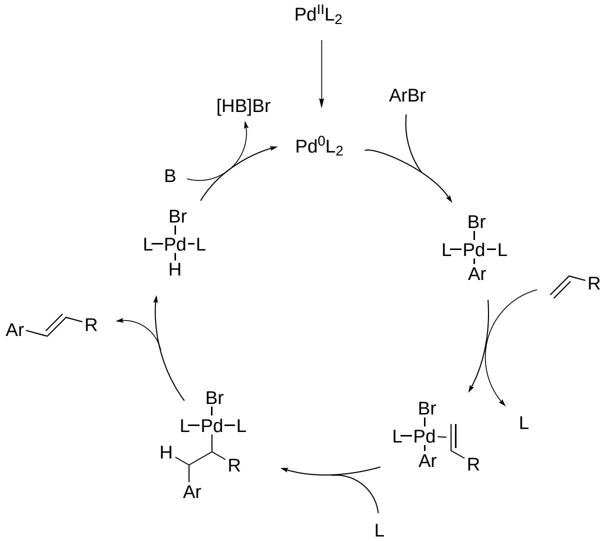

Scheme 1. Classical catalytic cycle of the Heck reaction employing aryl bromides [B = base, L = ligand (neutral or anionic)].

cross-coupling reactions and the Buchwald–Hartwig amination has a reduction mechanism for **1** and, thus, a classical catalytic cycle been verified.[8a, 16] Yet, the reagents necessary for the reduction pathways identified within these reactions are not present in the Heck reaction. This leaves the problem of the oxidation state of the palladium catalyst in the Heck reaction to be solved.

Abstract in German: *Der Mechanismus der (Mizoroki–) Heck-Vinylierung von Arylbromiden katalysiert von Phospha-Palladacyclus* $[\{\overline{PdCH_2C_6H_4P}(o\text{-}Tol)_2(OAc)\}_2]$ (***1***) *wurde untersucht, um die Frage zu klären, ob Palladium(IV)-Intermediate eine Rolle im Katalysecyclus spielen. Der Phospha-Palladacyclus* ***1*** *wurde dabei mit dem verwandten Palladium(0)-Katalysator* $[Pd\{P(o\text{-}Tol)_3\}_2]$ (***2***) *und einem Intermediat des klassischen Katalysecyclus* $[\{PdAr\{P(o\text{-}Tol)_3\}Br\}_2]$ (***3***) *verglichen. Komplex* ***3*** *entsteht durch oxidative Addition eines Arylbromids ArBr an* ***2***. *Geringe, jedoch messbare Unterschiede zwischen Phospha-Palladacyclus* ***1*** *einerseits und den Katalysatoren* ***2*** *und* ***3*** *andererseits in der Produktverteilung bei der Reaktion von Styrol, bei Konkurrenzreaktionen von Styrol und n-Butylacrylat, beim Isotopeneffekt mit Styrol und bei der Hammett-Korrelation der Arylbromide führen zu dem Schluss, dass unterschiedliche Katalysecyclen durchlaufen werden. Die geringen Unterschiede in diesen Konkurrenzreaktionen deuten allerdings nicht auf Palladium(IV)-Intermediate sondern vielmehr auf einen veränderten klassischen Katalysecyclus hin. Als Schlüsselintermediat dieses modifizierten Katalysecyclus wird ein neuartiger, cyclometallierter, anionischer Palladium(0)-Komplex* ***6*** *vorgeschlagen. Diese Spezies* ***6*** *kann sowohl die hohe Aktivität als auch Stabilität der Palladacyclen in der Heck-Reaktion erklären. Das Auftreten von Palladium(IV)-Intermediaten kann auf Grund der hier durchgeführten Experimente sowie kürzlich publizierter Resultate anderer Arbeitsgruppen in der untersuchten Reaktion ausgeschlossen werden.*

Standard methods in the evaluation of reaction mechanisms like in situ analysis or kinetic studies by NMR spectroscopy show difficulties in the Heck reaction with palladacycle catalysts due to the high temperatures of over 100 °C, the presence of catalytic intermediates at very low concentrations, and uncertainties about induction periods, effective catalyst concentrations, and monomer-dimer equilibria.[17, 18] Furthermore, any attempts to stoichiometrically form potential palladium(IV) intermediates have failed.[8a, 19] Due to these problems, kinetic studies with an azapalladacycle by highly sensitive reaction calorimetry were reported only recently.[17, 18]

As an alternative to the investigation of intermediates of a reaction by direct observation or kinetic behavior, macroscopic characteristics of the reaction can be monitored. Generally, these experiments are more easily conducted and analyzed even at very low catalyst concentrations because they focus on bulk properties of the products—typically at the point of full conversion. In particular competition constants serve as diagnostic tools in physical organic chemistry for different reactions proceeding via identical intermediates because of the possibility to determine selectivities in steps other than the rate-limiting one.[20]

Considering as a working hypothesis that palladacycle **1** is reduced to a palladium(0) species by an unspecified mechanism as shown in Scheme 2 allows its comparison to bis(tri-*ortho*-tolylphosphine)palladium(0). This is the case because under the conditions of the Heck reaction, that is, an excess of Na(OAc), both catalysts should predominantly form the anionic 14-electron palladium(0) species **4**.[8a, 21] Complex **3** is the product of the oxidative addition of an aryl halide, here ArBr, to complex **2**.[22, 23] Cleavage of the dimeric complex **3** by Na(OAc) under reaction conditions furnishes complex **5**, a required intermediate of the classical catalytic cycle (Scheme 1).[2, 21] Intermediate **5** is also formed from species **4** during the first elemental step of the classical catalytic cycle, the oxidative addition of the aryl halide. Therefore, all three "pre-catalysts" **1**–**3** should show identical macroscopic characteristics in the Heck reaction if the assumption regarding the reduction of palladacycle **1** was correct. The comparison of **2** and **3** serves as a verification of all the other assumptions made above and as an approximation for the analytical errors, because both of these species pass through the classical mechanism and should therefore exhibit similar characteristics (Scheme 1).[2]

If the reaction conditions are held constant and *only* the catalysts are changed, the competition constants are characteristic of the catalytically active species formed from either of the catalysts. In turn, substantial deviations are diagnostic of non-identical mechanisms for the catalysts. Furthermore, in the presented case the discrepancy between catalysts **2** and **3** serves as an estimate for the accuracy of the measurement (vide supra).

Stability of palladium(0) species: To rule out a more complex catalytic system that would arise from a reversible reduction of the palladacycle **1**, we tested whether palladacycle **1** can be formed from **2** under the reaction conditions. No signals of **1** in the ^{31}P NMR could be detected during and after catalysis

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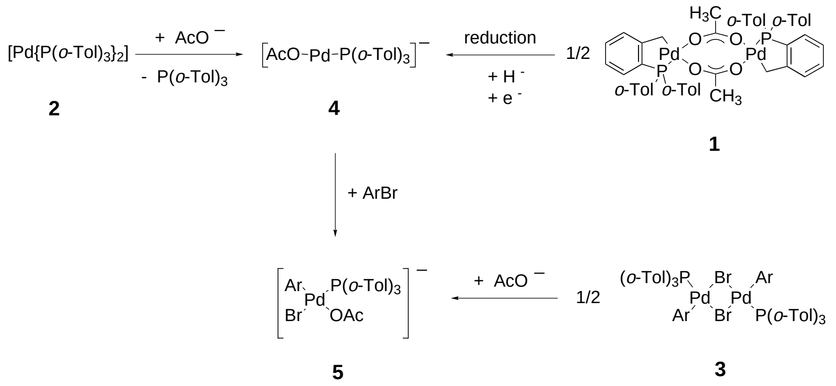


Scheme 2. Formation of the intermediate **5** of the classical catalytic cycle from the catalysts **1**, **2**, and **3** [L = P(*o*-Tol)$_3$, OAc$^-$].

with catalyst **2**. Thus, the reduction of **1** is presumably irreversible. Further support of this finding is given by the lack of reports about this type of reaction in the literature.

Therefore, palladium(IV) intermediates can be ruled out for the catalysts **2** and **3**. Identical competition constants of **1**, **2**, and **3** would in turn be a strong indicator for classical intermediates with catalyst **1**. Although a coincidental similarity is possible, the probability for this accidental occurring can be narrowed down statistically by increasing the number of *different* experiments conducted. Only if *all* of these experiments exhibit identical competition constants for the three catalysts **1**–**3**, can a classical catalytic cycle with *identical* intermediates be assumed with high accuracy. In order to assure this, four different competition experiments were conducted and combined for this investigation.

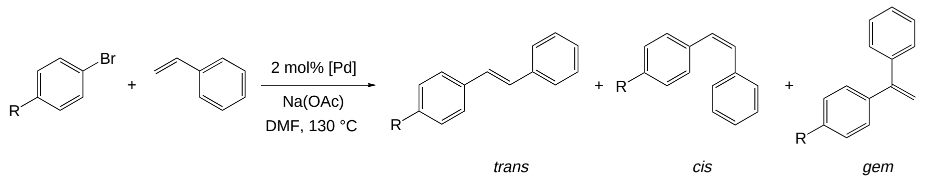
In the experiments conducted, we used aryl bromides rather than aryl chlorides owing to their good reactivity with all catalysts **1**–**3**. As the aryl group in complex **3** we chose 4-*n*-butylphenyl because its product, which is formed during the initial turnover of the catalytic reaction, can be easily distinguished from the desired reaction products generated from the distinct aryl bromide reagents.

Isomer distribution with styrene: The isomer distribution of the products from the reaction with styrene was examined in the first experiments. Styrene was used because of the good reactivity yet poor regioselectivity of α versus β substitution. The isomer distribution of catalysts **1**–**3** lay within experimental error; nevertheless, product ratios from palladacycle **1** deviated slightly from the ones furnished by **2** and **3** (Table 1). The selectivity of β over α substitution is characteristic of the aryl transfer, whereas the *cis*/*trans*-ratio is diagnostic of the β-hydride elimination step. Taking the similar values for all three catalysts into account, these results suggest that the elemental steps mentioned above most likely proceed via related intermediates. In order to rule out the isomerization of the products in a side reaction, *trans*-stilbene was subjected to the reaction conditions in the presence of catalysts **1**–**3** and Na(OAc). It was recovered unchanged.

Competition between styrene and *n*-butyl acrylate: Competition experiments[20] between styrene and *n*-butyl acrylate under pseudo-first-order conditions with respect to the aryl bromide were used to determine the relative rates for the reaction of catalysts **1**–**3** with olefins. Treating an equimolar mixture of the two olefins in a tenfold excess with different aryl bromides shows that *n*-butyl acrylate is preferred over styrene for all three catalysts (Table 2). Although there is an observable difference between palladacycle **1** and the catalysts **2** and **3**, the difference in product ratios is still too close to the margin of error of the GC analysis. As the aryl bromides influence the product ratios, the olefin-discriminating steps must involve the aryl moiety. This indicates that the aryl group is already attached to the palladium center at that stage. The fact that the aryl halide reacts with the catalyst prior to the olefin is in accord with the classical mechanism (Scheme 1). Subjecting a given mixture of the products to the reaction conditions showed the product ratio to be stable in the presence of **1**–**3**. Thus, product scrambling can be ruled out.

Isotope effects: The kinetic isotope effect is a special case of a competition constant, as the selectivity towards different isotopes rather than molecules is monitored.[20] Analysis of the

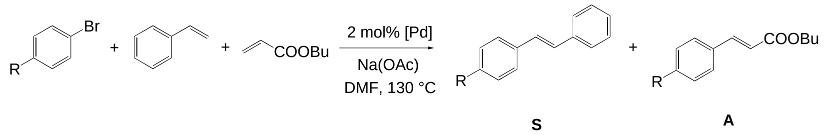
Table 1. Product isomer ratios in the reaction of aryl bromides and styrene.[a] GC yield was determined with diethyleneglycol di-*n*-butyl ether as the internal standard. Averages of two independent runs.



	R	Catalyst	*trans* [%]	*cis* [%]	K_{SI}[b]	*gem* [%]	K_{RI}[c]
1	C(O)CH$_3$	**1**	93.7	2.6	0.03	3.7	0.04
2	C(O)CH$_3$	**2**	88.2	6.8	0.08	5.0	0.05
3	C(O)CH$_3$	**3**	89.5	5.4	0.06	5.1	0.05
4	H	**1**	94.2	1.9	0.02	3.9	0.04
5	H	**2**	93.5	2.2	0.02	4.3	0.04
6	H	**3**	93.9	2.3	0.02	3.8	0.04
7	OCH$_3$	**1**	94.9	0.8	0.01	4.3	0.04
8	OCH$_3$	**2**	93.8	1.1	0.01	5.1	0.05
9	OCH$_3$	**3**	94.0	1.0	0.01	5.0	0.05

[a] 1.0 equiv aryl bromide, 1.5 equiv styrene, 1.5 equiv Na(OAc). [b] Stereoisomer ratio K_{SI} = *cis*/*trans*. [c] Regioisomer ratio $K_{RI} = \alpha/\beta$. β = sum of *trans* and *cis* isomers, α = geminal isomer (*gem*).

Table 2. Olefin competition constants K_O in the reaction of styrene (**S**) and *n*-butyl acrylate (**A**) with different aryl bromides.[a] GC yield was determined by using diethyleneglycol di-*n*-butyl ether as the internal standard. Averages of two independent runs.



	R	Catalyst	**S** [%]	**A** [%]	$K_O = \mathbf{S}/\mathbf{A}$
1	C(O)CH$_3$	**1**	4.0	96.0	0.04 ± 0.04
2	C(O)CH$_3$	**2**	3.0	97.0	0.03 ± 0.03
3	C(O)CH$_3$	**3**	1.8	98.2	0.02 ± 0.03
4	H	**1**	37.3	62.7	0.59 ± 0.09
5	H	**2**	32.8	67.2	0.49 ± 0.07
6	H	**3**	30.9	69.1	0.45 ± 0.10
7	OCH$_3$	**1**	36.1	63.9	0.56 ± 0.11
8	OCH$_3$	**2**	29.8	70.2	0.42 ± 0.09
9	OCH$_3$	**3**	31.8	68.2	0.47 ± 0.09

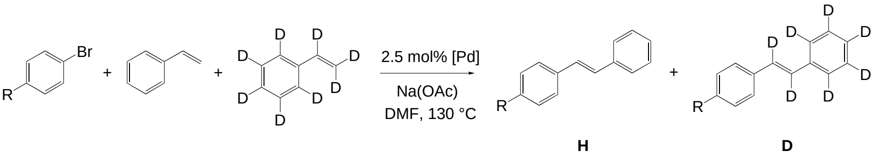
[a] 1.0 equiv aryl bromide, 5.0 equiv styrene, 5.0 equiv *n*-butyl acrylate, 1.5 equiv Na(OAc).

deuterium–hydrogen isotope effect is most convenient because it is most pronounced; both isotopes are stable, and labeled starting materials are commercially available. The competition experiments between [H$_8$]styrene and [D$_8$]styrene were conducted by treating an equimolar mixture of the olefins in a sixfold excess with different aryl bromides and subsequent analysis of the product ratios by GC. The excess of olefin during the reaction ensures pseudo-first-order kinetics with respect to the aryl bromide. Inverse isotope effects in the order of secondary ones are observed for all three catalysts (Table 3). Yet again, despite deviation of palladacycle **1** from the catalysts **2** and **3**, the difference is too close to call. No isotope scrambling between the products or reactants was observed, confirming the isotope effect to originate only from the catalyzed C–C bond-forming reaction.

As the competition isotope effect resembles the product of all elemental steps in which the olefins are involved, mechanistic interpretation of the values observed in terms of the transition state structure is difficult. Nevertheless, the aryl transfer from the palladium center to the olefin that induces the change of hybridization of the carbon atom from sp^2 to sp^3 can explain the inverse isotope effect observed and should, therefore, play a decisive role in the isotope discrimination. The close involvement of the aryl moiety in this step as shown by the influence of the aryl bromide on the isotope effect supports this interpretation. It is also in agreement with the observations made above that the aryl bromides influence the selectivity of the catalysts towards different olefins.

Hammett correlations: Substituent effects of aryl reagents are best expressed in terms of a linear free-energy relationship by the Hammett correlation.[20] Generally, it is difficult to extract relevant mechanistic information from this procedure if multi-step reaction sequences are investigated, because all of the individual steps involved affect the final value, and it is impossible, a priori, to separate these contributions from each other. This problem is similar to the one discussed for the kinetic isotope effect. Nevertheless, both the kinetic isotope effect and the Hammett correlation are of enormous value as a competition constant for the discussion presented here, because *only the differences between the constants for the catalysts **1**–**3** but not their absolute values* are of interest. Despite the problem regarding the mechanistic interpretation in multi-step catalytic reactions, the usefulness of Hammett correlations has been demonstrated in this regard.[24]

Table 3. Isotope effects in the reaction of styrene with aryl bromides.[a] Relative amounts of deuterated (**D**) and protiated products (**H**) were determined by the ratio of the abundance of the molecular ions in the GC-MS spectrum. Averages of two independent runs.



	R	Catalyst	$K_{H/D} = \mathbf{H}/\mathbf{D}$
1	CF$_3$	**1**	0.79 ± 0.05
2	CF$_3$	**2**	0.86 ± 0.06
3	CF$_3$	**3**	0.90 ± 0.08
4	C(O)CH$_3$	**1**	0.82 ± 0.02
5	C(O)CH$_3$	**2**	0.88 ± 0.03
6	C(O)CH$_3$	**3**	0.93 ± 0.03
7	H	**1**	0.84 ± 0.04
8	H	**2**	0.93 ± 0.03
9	H	**3**	0.93 ± 0.03
10	OCH$_3$	**1**	0.90 ± 0.09
11	OCH$_3$	**2**	0.94 ± 0.03
12	OCH$_3$	**3**	0.97 ± 0.04

[a] 1.0 equiv aryl bromide, 3.0 equiv [H$_8$]styrene, 3.0 equiv [D$_8$]styrene, 1.5 equiv Na(OAc).

An equimolar mixture of bromobenzene and a substituted aryl bromide were treated in tenfold excess with *n*-butyl acrylate to ensure pseudo-first-order conditions with respect to the olefin. *n*-Butyl acrylate was chosen because of both its activity and selectivity which makes the GC-analysis easier. The product ratios equal the relative rate constants of the aryl bromides, since the products are stable to the reaction conditions. Plotting the product ratios against σ values did not result in linear behavior.[25] However, a plot against σ^- values yielded linear behavior with positive slopes for all catalysts (Figure 1).[26] For **2** and **3** similar values of $\rho = 1.01$ and 1.00, respectively, were obtained. These deviate from palladacycle **1** with $\rho = 1.58$; this indicates a substantial variation in the active species during the steps discriminating the aryl bromides. Although these values are a product of the combination of all elemental steps of the catalytic cycle, the correlation to σ^- values rather than σ constants indicates that conjugation of π-electron density with the *para* substituents occurs in the most influential transition state. Additionally, the positive slope ρ shows that electron-withdrawing substituents accelerate the reaction—a commonly encountered phenomenon in the Heck reaction.[27] Both of these observations are in accordance with the oxidative addition of the aryl bromide having strong influence on the Hammett correlation.

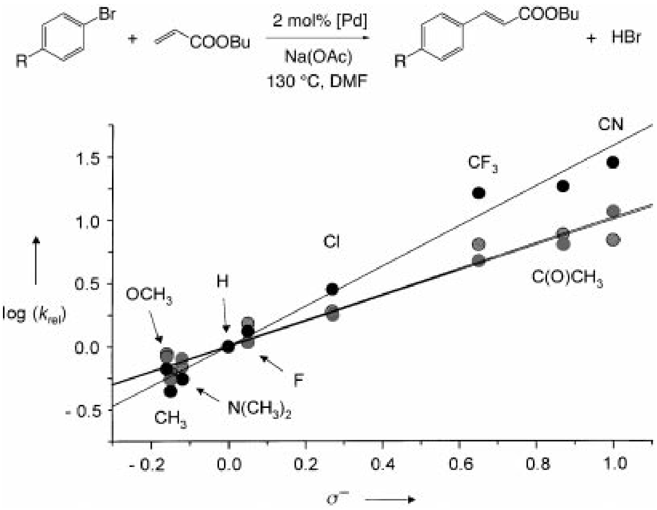


Figure 1. Hammett correlation of the reaction of aryl bromides with *n*-butyl acrylate plotted against σ^- values. $k_{rel} = k/k_0$ was determined from the product ratios of binary reaction mixtures of aryl bromides, as determined by GC analysis by using diethyleneglycol di-*n*-butyl ether as the internal standard. Averages of two independent runs.[25] Palladacycle **1**, $\rho = 1.58 \pm 0.06$ (black circles); $[Pd\{P(o\text{-Tol})_3\}_2]$ (**2**), $\rho = 1.01 \pm 0.03$ (dark gray circles); $[Pd\{(4\text{-}n\text{-}C_4H_9)C_6H_4\}Br\{P(o\text{-Tol})_3\}]_2$ (**3**), $\rho = 1.00 \pm 0.07$ (light gray circles).

In further support of the use of σ^- values in these experiments, apart from the linear correlation obtained, is the linearization of the oxidative addition of aryl chlorides to a palladium(0) complex[28] and of the palladium-catalyzed Suzuki reaction of aryl bromides with phenylboronic acid against the same constants in the literature.[24] The ρ value reported in the latter publication for an azapalladacycle catalyst in the Suzuki reaction is in the same range as the values obtained for catalysts **2** and **3**.[24]

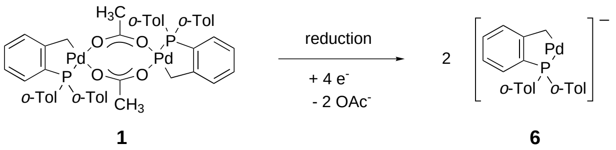
Discussion

Palladacycle **1** represents an advantageous case of a catalyst for competition experiments in the Heck reaction, because related catalysts leading to intermediates of the classical catalytic cycles, that is, complexes **2** and **3**, are readily available for comparison. Evaluation of these three catalysts reveals that the characteristics of catalysis by palladacycle **1** deviate from those of catalysts **2** and **3**. Thus, the Heck reaction catalyzed by palladacycle **1** must involve different active species than those involved in the catalysis by **2** and **3**. As all experimental data are within very good agreement for these last two catalysts, the active species formed from **2** and **3** during catalysis are probably identical as was assumed and expected (vide supra).

The different behavior of palladacycle **1** can either be accounted for by a nonclassical catalytic cycle involving palladium(IV) intermediates[12] or by a significant deviation from **2** and **3** within the classical catalytic cycle (Scheme 1).[2] We believe that palladium(IV) intermediates are not very likely to be responsible for the measured differences in data. Deviations in the competition experiments are small with the exception of the Hammett correlation, and more pronounced effects in all of these experiments are to be expected for a substantially different catalytic cycle. This conclusion is strongly supported by the recent fitting of kinetic data of an azapalladacycle in the Heck reaction to a classical mechanism.[17] The palladacycle **1** exhibited similar behavior, which also is in agreement with palladium(0) intermediates.[17]

The competition experiments were conducted by treating the starting materials as a mixture at the same time and analyzing the product ratios after approximately full conversion. As a result of using this method, the isotope effect and the Hammett correlation are not diagnostic of the transition state in the rate-determining step. In consequence, an interpretation of the values in these terms, as would be feasible based on kinetic measurements, is impossible. Nevertheless, our experiments serve their purpose to indicate different reaction pathways for related catalysts because in this case *only the differences between the constants for the catalysts but not their absolute values* are of importance.

The discrepancy of the catalysts is most pronounced for the competition of the aryl bromides, that is, the Hammett correlation. For the other three competition experiments, which focus on the behavior towards olefins, the catalysts exhibit quite similar characteristics. This leads to the conclusion that the active species should differ mostly during steps in the catalytic cycle that involve aryl bromides but not olefins. The most likely step explaining this behavior is the oxidative addition, that is, the first step of the classical catalytic cycle (Scheme 1). In conclusion, the structure of the active species **4**, which is formed from **2** and **3**, is not being formed by palladacycle **1**. As a possible explanation we offer an alternative structure **6**, which assumes the reduction of **1** to occur without rupture of the carbon–palladium bond [Eq. (1)].



(1)

Species **6** bears an anion that is forced into *cis*-position with respect to the phosphine ligand. This is advantageous in terms of stability and reactivity of the active species, since it is documented that *cis*-chelating ligands[29] as well as coordinated anions[21, 30] both enhance the stability of palladium(0) catalysts in Heck-type reactions and the rate of oxidative addition of aryl halides.

Conclusion

Based on our experiments and recent findings in the literature,[17] palladium(IV) intermediates in the Heck reaction catalyzed by palladacycle **1** can be ruled out for the activation of aryl bromides. The discrepancy found with respect to the classical catalytic cycle in Scheme 1, as operative for the catalysts **2** and **3**, can be conveniently explained by the proposed formation of a highly active, anionic palladium(0) species **6** [Eq. (1)]. This species is different from the linear intermediate **4** formed by standard catalysts like **2** in the Heck reaction (Scheme 2).

Experimental Section

General procedures: Pd(OAc)$_2$ and 4-*n*-butylbromobenzene were obtained from Merck-Schuchardt. P(*o*-Tol)$_3$ was prepared from the corresponding Grignard reagent and PCl$_3$ by a literature method.[31, 32] Complex **3** was synthesized according to a published procedure.[22, 33] Other chemicals were bought from Fluka and Aldrich. All chemicals were used as received without further treatment. Except for the workup of the reactions, all operations were carried out with the use of vacuum line, Schlenk, and syringe techniques under an atmosphere of dry nitrogen. DMF (*N*,*N*-dimethylformamide) was degassed prior to use and stored over molecular sieves 4 Å. Other solvents were carefully dried and degassed according to standard procedures.[34, 35]

Physical and analytical methods: NMR spectra (^{1}H, ^{13}C, ^{31}P) were recorded on a Jeol JMX-GX 400 instrument and are referenced to residual protons in the solvent (^{1}H), the solvent ^{13}C signal (^{13}C) or 85 % H_3PO_4 as an external standard (^{31}P).

GC-MS spectra were measured on a Hewlett Packard gas chromatograph GC5890 A equipped with a mass selective detector MS5970 B with diethyleneglycol di-*n*-butyl ether as the internal standard. The C–C coupling products were identified by comparison of GC-MS data with authentic samples.

Synthesis of *trans*-di(*μ*-acetato)-bis[*o*-(di-*o*-tolylphosphino)benzyl]dipalladium(II) (1):[7, 32] A Schlenk flask was charged with Pd(OAc)$_2$ (220 mg, 1.0 mmol) in toluene (20 mL) under an atmosphere of dry nitrogen. P(*o*-Tol)$_3$ (400 mg, 1.3 mmol) was added, and the orange mixture was heated to 50 °C for 3 min. When the color changed to yellow the mixture was rapidly cooled to RT with an ice bath and stirred at RT for an additional 45 min. After evaporation of 15 mL of the solvent, hexane (20 mL) was added to precipitate the product. Filtration and drying in vacuo afforded yellow microcrystals that could be recrystallized from toluene/hexane (1:1) at -35 °C (440 mg, 0.93 mmol, 93 % yield). Analytical data were found to be in agreement with the literature.[7, 32]

Synthesis of bis(tri-*o*-tolylphosphine)palladium(0) (2):[36, 37] [Pd(Cp)(allyl)] (400 mg, 1.88 mmol) was dissolved in CH$_3$CN (90 mL) under an atmosphere of dry nitrogen. P(*o*-Tol)$_3$ (1720 mg, 5.65 mmol) was added slowly over a period of 10 min as a solid against a positive stream of dry nitrogen; this resulted in the precipitation of the yellow product after several minutes. The reaction was stirred for a total of 24 h at RT, and the yellow product was filtered and washed twice with cold hexane (30 mL) to give **2** (1277 mg, 1.78 mmol, 95 % yield). Analytical data were found to be in agreement with the literature.[33] [(η^5-C$_5$H$_5$)(η^3-C$_3$H$_5$)Pd] was prepared following procedures in the literature starting from [(η^3-C$_3$H$_5$)Pd(μ-Cl)]$_2$ and Na(C$_5$H$_5$).[36, 38] An alternative method for the synthesis of **2** starts from [Pd$_2$(dba)$_3$] and P(*o*-Tol)$_3$.[33]

General conditions for the (Mizoroki–)Heck reaction: The catalyst (0.01 mmol or 0.02 mmol, 2 mol % [Pd]), 4-bromoacetophenone (199 mg, 1.0 mmol) and anhydrous Na(OAc) (123 mg, 1.5 mmol) were weighed into a Schlenk tube and put under an atmosphere of dry nitrogen. The internal standard diethyleneglycol di-*n*-butyl ether (50 mg), styrene (172 μL, 1.5 mmol), and DMF (2 mL) were added. The suspension was stirred for 2 min at RT before it was put into a pre-heated oil bath at 130 °C. After 10 h, the suspension was allowed to cool to RT to stop the reaction and was diluted with CH$_2$Cl$_2$ (2 mL). After filtration, the reaction mixture was examined by GC-MS.

Determination of the isotope effect: The equimolar mixture of [H$_8$]styrene and [D$_8$]styrene, which was used for all experiments, was prepared by weighing both components in a molar ratio of 1:1 into a Schlenk tube under an inert atmosphere. Analysis of the abundance of the molecular ions in the GC-MS spectrum showed the mixture to contain 50 ± 1 mol % of [D$_8$]styrene.

The reactions were conducted as illustrated in the general conditions for the Heck reaction. Instead of 1.5 equivalents of styrene, 6.0 equivalents of the previously prepared equimolar mixture of [H$_8$]styrene and [D$_8$]styrene were used. The volume of the mixture added was determined by calculating the theoretical volume of 6.0 equivalents [H$_8$]styrene, assuming the molar density of the mixture and pure [H$_8$]styrene to be the same. Relative amounts of deuterated and protiated products were determined by the ratios of the abundance of the molecular ions in the GC-MS spectra. Two independent runs were conducted for every data point, and each run was evaluated five times independently.

Hammett correlation: The reactions were conducted as described in the general conditions for the Heck reaction. Instead of a single aryl bromide (1.0 mmol), bromobenzene (5.0 mmol, 526 μL) and a *para*-substituted aryl bromide (5.0 mmol) were employed. Instead of styrene, *n*-butyl acrylate (1.0 mmol, 143 μL) was employed. Relative amounts of the products were determined by GC-MS analysis by the method of internal standardization. Two independent runs were conducted for all data points; each run was evaluated five times independently.

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