Second Comes First: Switching Elementary Steps in Palladium-Catalyzed Cross-Coupling Reactions

Marlene Kolter and Konrad Koszinowski[a]

Abstract: The electron-poor palladium(0) complex \( L_3\text{Pd} \) (\( L = \text{tris(3,5-bis(trifluoromethyl)phenyl)phosphine} \)) reacts with Grignard reagents \( RMgX \) and organolithium compounds \( RLi \) via transmetalation to furnish the anionic organopalladates \( [L_2\text{Pd}R]^- \), as shown by negative-ion mode electrospray-ionization mass spectrometry. These palladates undergo oxidative additions of organyl halides \( R'X \) (or related \( SN_2 \)-type reactions) followed by further transmetalation. Gas-phase fragmentation of the resulting heteroleptic palladate(II) complexes results in the reductive elimination of the cross-coupling products \( RR' \). This reaction sequence corresponds to a catalytic cycle, in which the order of the elementary steps of transmetalation and oxidative addition is switched relative to that of palladium-catalyzed cross-coupling reactions proceeding via neutral intermediates. An attractive feature of the palladate-based catalytic system is its ability to mediate challenging alkyl–alkyl coupling reactions. However, the poor stability of the phosphine ligand \( L \) against decomposition reactions has so far prevented its successful use in practical applications.

Introduction

Palladium-catalyzed cross-coupling reactions provide an extremely efficient means for the formation of new carbon–carbon bonds. These reactions are known to proceed through a common catalytic cycle characterized by the elementary steps of oxidative addition, transmetalation, and reductive elimination (Scheme 1).[1] This sound mechanistic understanding has proven invaluable for the rational design of new phosphine and N-heterocyclic carbene ligands, without which cross-coupling reactions would not have reached their current level of reliability and versatility.[2–7]

Despite the power of modern palladium-catalyzed cross-coupling reactions, shortcomings of these transformations remain. One of the most pressing problems is the difficulty of alkyl–alkyl coupling. These reactions are hindered by the reluctance of conventional palladium catalysts to undergo oxidative additions of alkyl halides. Even if such oxidative reactions take place, the resulting intermediates are prone to \( \beta \)-hydrogen elimination if the palladium-bound organyl group bears a hydrogen atom in \( \beta \) position, as is the case for most alkyl residues.[8–10]

An intriguing way to overcome these difficulties makes use of anionic organopalladate(0) complexes. As Kambe and co-workers have shown, the nucleophilicity of these palladates exceeds that of conventional neutral palladium(0) complexes such that they readily react with alkyl halides.[11] The catalyst used by Kambe and co-workers included 1,3-dienes as additives, which play an essential role in stabilizing the anionic organopalladate(0) complexes. 1,3-Dienes have the advantage of being cheap, but they do not offer the same flexibility as phosphines for fine-tuning the catalytic activity. We therefore wondered whether phosphine-containing palladium complexes could also participate in a catalytic cycle, in which the elementary step of the transmetalation precedes that of the oxidative addition.

As we have shown previously, electron-poor phosphines, such as \( L \) and, to a lesser extent \( L^{(Ph)} \) (Figure 1) stabilize anionic...
**Results**

**Transmetalation of **$\text{L}_2\text{Pd}$

Negative-ion mode ESI mass-spectrometric analysis of solutions of $\text{L}_2\text{Pd}$ and BuMgCl in tetrahydrofuran (THF) showed the organopalladate(0) anion $[\text{L}_2\text{PdBu}]^-$ as base peak (Figure 2, Table S1 and Figures S1–S10 in the Supporting Information). In addition, several other palladate species were present, which contained fragments of the phosphine ligand. The transfer of aryl substituents from the phosphine ligand onto the palladium center has been observed before for the case of triphenylphosphine-palladium complexes.\(^{19-21}\) We cannot rule out that even some of the ions assigned as $[\text{L}_2\text{PdBu}]^-$ actually correspond to $[\text{LPd}(\text{Ar}^F\text{Bu})\text{Ar}^F]^-$, in which an exchange of the palladium-bound butyl group with the aryl substituent of the phosphine ligand has taken place (see below). Among the detected ions, the dinuclear complex $[\text{LPd}(\text{PAr}^F)\text{Bu}]^+$ was remarkable because it is a rare example of a dianionic organometallic complex detectable by ESI mass spectrometry.

When the Grignard reagent was changed from BuMgCl to PhMgCl, the transmetalation product $[\text{L}_2\text{PdPh}]^-$ (or possibly its $[\text{LPd}(\text{Ar}^F\text{Ph})\text{Ar}^F]^-\text{isomer}$) formed in analogy to the previous experiment, although only in rather low abundance, whereas palladates bearing fragments of the phosphine L predominated in the resulting negative-ion mode ESI mass spectrum (Figures S11–S15). Upon the reaction of $\text{L}_2\text{Pd}$ with BnMgCl, the expected organopalladate(0) $[\text{L}_2\text{PdBn}]^-$ was not detected (Figures S16–S18). Instead, palladate(II) complexes, such as $[\text{LPdAr}^F\text{Bn}]^-$ and $[\text{LPdBn}]^-$ were observed and pointed to the operation of oxidation processes. Such oxidation processes could possibly involve traces of O\(_2\) or residual BnCl as a contaminant of the BnMgCl reagent.\(^{22}\)

We next examined whether other organometallic reagents also brought about the transmetalation of $\text{L}_2\text{Pd}$. The reaction of the latter with BuLi afforded $[\text{L}_2\text{PdBu}]^-$, but at the same time furnished more ligand decomposition products as well as palladate(II) complexes (Figure S19). The reaction with BnZnClLiCl gave $[\text{LPdCl}]^-$ and $[\text{LPd}(\text{PAr}^F)\text{Ar}^F]^-\text{as main products together with several heterobimetallic complexes, such as [LPdZnBuCl]}^-$ (Figures S20–S26). As it is not immediately obvious whether the butyl substituent of this species was bound to the Pd or Zn center, we defer the answer to this question to the analysis of its gas-phase fragmentation behavior (see below).

We went on to probe the influence of the phosphine ligand on the formation and stability of the organopalladate(0) anions. The treatment of $[\text{Pd(PPh)\text{Ar}^F}]_2$ with BuMgCl did not yield any anionic palladates detectable by ESI mass spectrometry. When a palladium complex of $[\text{L}_2\text{Pd}]^+$ (formed in situ by the reaction of Pd(dbac), with 4 equiv of L\(^{\text{PHI}}\)) was added BuMgCl, the main anion observed was $[\text{L}_2\text{PdAr}^F\text{Bu}]^-$ along with further organopalladate(II) and minor -palladate(0) species, but no $[\text{L}_2\text{Pd}\text{Bu}]^-$ (Figures S27–S36). Apparently, neither PPh\(_3\) nor L\(^{\text{PHI}}\) was effective in stabilizing alkylpalladate(0) complexes.

To obtain additional information on the organopalladate(0) anions, we also investigated their gas-phase fragmentation behavior (Table S2). Both $[\text{L}_2\text{PdBu}]^-$ and $[\text{LPdPh}]^+$ preferentially afforded $[\text{LPdAr}^F]^-\text{upon collision-induced dissociation (CID)}$ (Eq. (1) with $R=\text{Bu}$ and Ph, respectively) (Figures S37 and S38).

$$[\text{L}_2\text{Pd}]^+ ightrightarrows [\text{LPdAr}^F]^- + [\text{PAr}^F,R]$$

It is not clear whether the neutral fragments of these reactions corresponded to a phosphine $\text{PAr}^F,R$ or to separate entities. The former possibility would be in accordance with the facile transformation of the reactant ion into its

---

**Figure 1.** Phosphine ligands used for the generation of palladate complexes.

**Figure 2.** Negative-ion mode ESI mass spectrum of a solution of $[\text{Pd(PAr}^F)_3]\_2$ ($\text{L}_2\text{Pd}, 3 \text{mM}$) and BuMgCl (12 mM) in THF ($a = [\text{L}_2\text{Pd}(\text{PAr}^F)\text{Bu}]^+$, $b = [\text{LPd}(\text{PAr}^F)\text{Bu}]^+$, $c = [\text{LPdH}]^+$).
[LPd(Ar²PR)Ar²]⁻ isomer (see above). Further fragmentation reactions of interest resulted in the loss of a ligand L, either alone or in combination with the product of a putative \( \beta \)-hydrogen elimination [Eq. (2) and (3), respectively]. These reactions clearly demonstrate that at least part of the reactant complexes did not undergo isomerization and contained the intact ligand L.

\[
\begin{align*}
[L_2\text{PdPh}]^+ & \rightarrow [L\text{PdPh}]^+ + L \quad (2) \\
[L_2\text{PdBu}]^+ & \rightarrow [L\text{PdH}]^+ + C_6H_6 + L \quad (3)
\end{align*}
\]

For determining the connectivity of the \([L_2\text{PdZnBuCl}_3]^–\) complex formed from \(L\)Pd and BuZnCl-LiCl (see above), we analyzed its gas-phase fragmentation. CID of this complex mainly gave \([L_2\text{PdZnBuCl}_2]^–\) [Eq. (4)], but also \([L_2\text{PdCl}]^–\) [Eq. (5)], which suggests that the butyl group had not been transferred from Zn to Pd, or at least that such a transfer, if occurring, must be easily reversible (Figure S39). This assumption is further supported by the observation that the related anion \([L_2\text{PdZnBuCl}(\text{PAr})]^–\) showed the elimination of BuZnCl as the main fragmentation pathway (Figure S40).

\[
\begin{align*}
[L_2\text{PdZnBuCl}_3]^– & \rightarrow [L_2\text{PdZnBuCl}_2]^– + L \quad (4) \\
[L_2\text{PdZnBuCl}_2]^– & \rightarrow [L_2\text{PdCl}]^– + \text{BuZnCl} \quad (5)
\end{align*}
\]

Reactions of organopalladates with organyl halides

When solutions of \([L_2\text{PdBu}]^–\) and \([L_2\text{PdPh}]^–\) palladates formed in situ were treated with alkyl iodides \(R_1, R_1 = \text{Et and Pr}\), small amounts of the heteroleptic organopalladate(II) complexes \([L_2\text{PdBu}_2]^–\) and \([L_2\text{PdPh}_2]^–\) (or possibly isomers thereof) were observed together with the organyl-free palladate(0) anion \([L_2\text{Pd}]^–\) and various ligand decomposition products (Figure 3, Table S3, and Figures S41–S59). In a control experiment, the reaction of \(L\)Pd with EtI was probed in the absence of any Grignard reagent and was found to furnish no detectable heteroleptic palladate complexes. The addition of LiI to the sample solution ensured that any formed neutral heteroleptic palladium(II) products would have been readily ionized by the coordination of I⁻.\(^{[12]}\)

We then examined the reactions of \([L_2\text{PdBu}]^–\) with further substrates. With \(\text{PrBr}\), the heteroleptic product complex \([L_2\text{PdBu}_2\text{Pr}]^–\) was formed again, although more slowly than in the reaction with \(\text{PrI}\) as a comparison of the signal intensity of the product ion relative to that of \([L_2\text{PdBu}]^–\) indicated (Figures S60 and S61). In contrast, no reaction took place with \(\text{PrCl}\) (Figure S62). With the sterically more hindered \(\text{ iPBr}\), the \([L_2\text{PdBu}_2\text{iP}]^–\) product ion could be observed, but only in very low signal intensities (Figure S63). The addition of (2-phenyl)ethyl bromide also led to the expected product ion when \(L\) was used as a ligand (Figures S64–S66). In contrast, no oxidative addition reaction could be observed upon treatment of in situ formed palladium complexes of the less electron-withdrawing \(\text{L}^\text{PHI}\) with \(\text{BuMgCl}\) and (2-phenyl)ethyl bromide.

When allyl bromide was added to solutions of \([L_2\text{PdBu}]^–\), the yellow reaction mixture rapidly turned colorless, thus, suggesting the occurrence of a chemical reaction. However, the resulting negative-ion mode ESI mass spectrum displayed only poor signal intensities and did not show the expected allyl-containing heteroleptic palladate(II) ions, possibly due to the operation of fast consecutive reactions (Figure S67). Analogous experiments with ethyl 4-bromobenzoate (ArBr) as substrate afforded the heteroleptic product ions \([L_2\text{PdBu}_2\text{Ar}]^–\) and \([L_2\text{PdArBuAr}]^–\) together with further ligand decomposition products, which again exhibited the highest signal intensities (Figures S68–S80).

In a different type of experiment, we subjected mass-selected \([L_2\text{PdBu}]^–\) ions to gas-phase reactions with different organyl iodides \(R_1 (R_1 = \text{Me, Et, allyl, vinyl, Ph})\) for times of up to 2 s. In no case, the product of an oxidative addition could be observed, which implies that such reactions, if proceeding at all, were relatively inefficient and slower than the time scale of our experiment (Figure S81 for the example of vinyl iodide). Alternatively, the \([L_2\text{PdBu}]^–\) ions might also react with the \(R_1\) substrates in an \(S_n\text{,}2\)-type fashion to afford neutral heteroleptic palladium(II) complexes along with I⁻. Although we did not observe the formation of I⁻, this negative result does not rigorously rule out the occurrence of \(S_n\text{,}2\)-type reactions because the low-mass cut-off of the used quadrupole-ion trap mass spectrometer renders the detection of light product ions (relative to the precursor ion) notoriously difficult.

For comparison, we also analyzed the bimolecular gas-phase reactivity of \([\text{Pd(PAr)}_{2}]^–\), a species detected among the various ions originating from the decomposition of the phosphine ligand \(L\). \([\text{Pd(PAr)}_{2}]^–\) underwent a fast oxidative addition of PhI [Eq. (6)] (Figures S82 and S83). Due to the relatively low signal intensity of the precursor ion and a competing reaction with residual traces of O₂ present in the vacuum system of the mass spectrometer, no reliable determination of the rate constant of this reaction was feasible.

\[
\text{[Pd(PAr)}_{2}]^– + \text{PhI} \rightarrow \text{[PhPd(PAr)}_{2}]^–
\]
Gas-phase fragmentation of heteroleptic organopalladates

Upon CID, the putative heteroleptic organopalladate anions \([LPdR]^-\) (for the possible involvement of different isomers, see below) produced inter alia \([LPdR]^+\) fragment ions (Figure 4, Table S4, Figures S84–S97). Most likely, the neutral byproduct of this reaction corresponded to the cross-coupling product \(RR'\) (Eq. (7)) and not to separate \(R\) and \(R'\) radicals. The stepwise release of such radicals would not only be energetically strongly disfavored, but should also give rise to intermediates resulting from the loss of only a single organyl radical, which in no case were detected, however. Likewise, the liberation of the homo-coupling product \(R_2\) was not observed either.

\[
[LPdR,R']^- \rightarrow [LPdR]^+ + RR'
\]  

(7)

Further fragmentation reactions, several of which were quite prominent, again involved the decomposition of the phosphine ligand as well as the loss of alkanes \(RH\) and \(R'H\). In addition, the observation of oxygen-containing product ions once more pointed to the operation of reactions with traces of \(O_2\) present in the mass spectrometer.

Analysis of neutral reaction products

For obtaining further insight, we used gas chromatography to analyze the neutral products formed in the reactions of Grignard reagents with alkyl halides in the presence of 2 mol% of the palladium catalyst \(L_2Pd\) under synthetic conditions. In the reactions of \(BuMgCl\) with decyl iodide and (2-phenyl)ethyl iodide as well as that of \(HexMgCl\) with ethyl bromide, we did observe the cross-coupling products. However, control experiments showed that these products also formed in the absence of the palladium catalyst. In contrast, no cross-coupling product could be detected for the reaction of \(BuMgCl\) with (2-phenyl)ethyl bromide, not even when the more reactive so-called turbo-Grignard reagent \(BuMgCl\cdot LiCl\) was used.\(^{29}\) In all experiments with the \(L_2Pd\) catalyst, we observed decomposition products of the electron-poor phosphine ligand, such as the cleaved-off arene moiety 1,3-bis(trifluoromethyl)benzene.

Discussion

Transmetalation

As our experiments have shown, the reactions between the palladium complex \(L_2Pd\) and Grignard reagents \(RMgCl\), \(R = Bu\) and \(Ph\), or the organolithium compound \(BuLi\) furnish the anionic transmetalation products \([LPdR]^+\); these species resemble the previously observed organyl-free palladates \([LPdX]^+\), \(X = Cl, Br, I, OAc\).\(^{12}\) The fact that the organozinc reagent \(BuZnCl\cdot LiCl\) failed to afford the corresponding organopalladate(0) complex suggests that only highly reactive organometallics, such as \(RMgCl\) and \(RLi\), are capable of transferring their organyl group to the palladium(0) center of \(L_2Pd\). This behavior resembles the transmetalation of palladium diene complexes,\(^{46}\) but contrasts that of typical palladium(II) complexes, whose reactivity toward organozinc compounds and even milder transmetalation reagents is well known and forms the basis of synthetically most useful transformations, for example, Negishi and Suzuki–Miyaura cross-coupling reactions.\(^{24,25}\)

Besides the organometallic reagent, the phosphine ligand is also of crucial importance for the formation and stabilization of anionic alkylpalladate(0) complexes. These complexes could only be observed for the particularly electron-poor phosphine \(L\), but not for the less electron-poor \(L^\text{Ph}1\) or for \(PPh_3\). Apparently, only the former sufficiently stabilizes the anionic palladium(0) complex by a \(π\) back donation from the occupied \(d\) orbitals of the metal center into the empty \(π^*\) orbitals of the C–P bonds of the phosphine. In this context, a comparison with the organyl-free palladate(0) complexes \([\text{phosphine}]_2PdX]^+\), \(X = Cl, Br, I, n = 1–3\), is of interest. These species proved to be stable not only for phosphine \(L\), but also for phosphine \(L^\text{Ph}1\). This behavior is indicative of the organyl-free palladate(0) complexes \([\text{phosphine}]_2PdX]^+\) having an electron density at the palladium center not quite as high as that of their organopalladates(0) counterparts. Indeed, it appears plausible that the binding of a carbanion \(R^\text{-}\) raises the electron density of a palladium center more than that of a halide \(X^\text{-}\) does. Moreover, the organyl-free palladates typically bear three phosphine ligands instead of the two observed for the organopalladates. The coordination of the additional electron-poor phosphine supposedly further stabilizes the anionic palladium(0) center by abstracting more electron density. The different coordination numbers found for \([LPdR]^+\) on the one hand and for \([LPdX]^+\) on the other presumably reflect the larger size of the carbanion \(R^\text{-}\) in comparison to the halide \(X^\text{-}\), which renders the coordination of an additional ligand unfavorable.

Differences between the organopalladates(0) and their organyl-free counterparts also manifested themselves in their unimolecular reactivity. The former reacted mainly via ligand decomposition whereas the latter preferentially lost intact phosphine ligands \(L\). This comparison again shows the stronger binding of the phosphine \(L\) to the palladium center in the
\[ \text{[L}_2\text{PdR}^-] \] than in the \([\text{L}_2\text{PdX}]^-\) complexes. Moreover, it specifically points to the importance of the \(\pi\) back donation in the organopalladates, which transfers electron density from the metal-centered \(d\) orbitals into the anti-bonding \(C-P\) \(\sigma^*\) orbital of the ligand. In this way, the \(C-P\) bond of the phosphine is activated for its dissociation.

**Oxidative addition**

The observation of heteroleptic organopalladates \([\text{LPdR}_2\text{R}']^-\) formed in the reactions of \([\text{L}_2\text{PdR}]^-\) with alkyl halides \(\text{RX}\) (for the possible involvement of different isomers, see below) points to the occurrence of an oxidative addition or related process followed by a second transmetalation along with a ligand dissociation (Scheme 2). The dissociation of one of the two phosphine ligands reflects the relatively low stability of penta-coordinated palladium(II) complexes.\(^{26-28}\)

\[
\begin{align*}
\text{[L}_2\text{PdR}]^- & \quad \text{R}^- - \text{X}^- & \quad \text{[L}_2\text{PdRR}']^- + \text{X}^- & \quad \text{RMgCl} \quad \stackrel{\text{MgCl}_2X}{\text{[L}_2\text{PdR}^-]} \quad \text{L}^- \\
\end{align*}
\]

**Scheme 2.** Oxidative addition of an alkyl halide to \([\text{L}_2\text{PdR}]^-\) with subsequent transmetalation.

The absence of an analogous heteroleptic palladium(II) complex in the control experiment without added Grignard reagent indicates that the latter is required for the reaction. Apparently, the electron-poor neutral \(\text{L}_2\text{Pd}^-\) complex is not sufficiently nucleophilic to undergo oxidative additions of substrates \(\text{RX}\), but becomes activated by its transformation into an anionic palladate \([\text{L}_2\text{Pd}^-]\). Likewise, organyl-free palladates \([\text{L}_2\text{PdX}]^-\) do not appear to react with alkyl halides efficiently.

In solution, heteroleptic organopalladate products form both for \(sp^3\)- and \(sp^3\)-hybridized organic halides \(\text{RX}\). The latter, but not the former, are typical substrates for classical oxidative additions. The situation is just the opposite for \(S_2\)-type reactions, which Kambe and co-workers proposed to occur for diene-containing palladate(0) anions.\(^{111}\) Hence, the observed reactivity pattern does not allow for a straightforward distinction between the two mechanistic pathways in the present case. The higher efficiency of the reactions with \(\text{R}^-\) than of those with \(\text{R}\)\(\text{Br}\) does not permit a differentiation either because this result is expected for both pathways. In general, the two pathways could be distinguished by analyzing the stereochemical outcome of a cross-coupling reaction with an enantiopure chiral substrate \(\text{RX}\). Inversion of the stereochemistry at the reactive center would point to the operation of an \(S_2\)-type reaction, whereas retention would be consistent with a classical oxidative addition. However, such experiments would be rather difficult in the present case owing to the occurrence of the uncatalyzed background reaction.

The failure of the gaseous \([\text{L}_2\text{PdR}]^-\) complexes to react with various substrates \(\text{R}^-\) at measurable rates implies that these gas-phase reactions must be rather slow. Addition processes, such as classical oxidative additions, often proceed only sluggishly in the diluted gas phase because the exothermicity of these reactions cannot be efficiently carried away by third-body collisions, but remains in the formed adducts and causes them to re-dissociate easily. In contrast, \(S_2\) reactions in the gas phase do not suffer from this constraint because the exothermicity can be effectively released as kinetic energy of the two reaction products.\(^{29}\) Indeed, \(S_2\) reactions are commonly found to proceed much faster in the gas phase than in solution.\(^{30,31}\) In the present case, the technical difficulties of detecting the possibly formed \(\text{L}^-\) ions again prevent an unambiguous mechanistic assignment.

**Reductive elimination**

The gas-phase fragmentation of the heteroleptic organopalladate(II) complexes \([\text{LPdR}_2\text{R}']^-\) afforded evidence for the formation of the cross-coupling products \(\text{RR'}\). These reactions correspond to reductive eliminations, which regenerate the palladium(0) catalyst. However, the occurrence of several competing reactions results in a rather low selectivity of the reductive eliminations.

A remarkable feature of the reductive elimination from the putative \([\text{LPdBu}_2\text{R}']^-\) complexes, \(\text{R} = \text{Et}\) and \(\text{Pr}\), is the non-occurrence of homo-coupling reactions. Given the electronic similarities of the alkyl groups, it is not clear how the catalyst could differentiate between them. A possible explanation of this behavior could be the involvement of a different isomer. If the reactant palladate(0) complex did not correspond to \([\text{L}_2\text{PdBu}]^-\), but to the isomerized species \([\text{LPd(Ar}^2\text{Bu)}\text{Ar}^2\text{Bu}]^-\) (see above), its reaction with the substrates \(\text{RX}\) and subsequent transmetalation would afford \([\text{LPd(Ar}^2\text{Bu)}\text{Ar}^2\text{BuR}]^-\). In these heteroleptic complexes, the electronic properties of the palladium-bound \(\text{Ar}^2\) group on the one hand and of the alkyl residues on the other strongly differ, which could rationalize the selectivity of the gas-phase fragmentation with the exclusive formation of the \(\text{BuR}\) cross-coupling product.

**Catalytic cycle and catalyst stability**

The present results demonstrate that anionic organopalladate complexes can react in a catalytic cycle that differs from that of conventional palladium-catalyzed cross-coupling reactions in that the order of the transmetalation and oxidative addition is reversed (Scheme 3). For the product-forming step of the reductive elimination, we consider two different possibilities: (i) The reductive elimination occurs for \([\text{L}_2\text{PdRR}']\), that is, the same type of complex also invoked in the conventional catalytic cycle. (ii) Alternatively, this complex may first undergo a further transmetalation to afford an anionic palladate(II) species, which then can release the cross-coupling product in a reductive elimination and, thus, directly regenerates the reactive organopalladate(0) intermediate. Presumably, the two alternative modes of reductive elimination compete with each other, with their relative weights depending on the reaction conditions (e.g., nature and concentration of the transmetalating reagent).
Although the separate elementary steps of this cycle are all feasible, the overall cross-coupling reaction proceeds only very sluggishly. The low efficiency of the catalyzed reactions results from the facile decomposition of the electron-poor ligand L, which opens up competing processes and, even more importantly, reduces the concentration of the active catalyst. The degradation of phosphine ligands in palladium-catalyzed reactions has been previously observed in numerous instances.\cite{20,21,32,33} However, the combination of a particularly electron-poor phosphine with a highly nucleophilic organometallic reagent in the present case severely aggravates this problem.

**Conclusions**

The use of negative-ion mode ESI mass spectrometry permits the observation of organopalladates(0) [L₂PdR]⁻ formed from the electron-poor palladium complex [L₄Pd] and Grignard or organolithium reagents, RMgX or RLi, respectively. Thus, the present study extends the scope of known palladate(0) anions. The fact that reactions with less electron-poor phosphines or with R₂ZnX as milder transmetalation reagents do not afford the analogous palladates points to the considerable reluctance, with which the very electron-rich [L₂PdR]⁻ complexes form.

The high electron density and, thus, nucleophilicity of the [L₂PdR]⁻ palladates can be exploited for their reaction with organyl halides and, in particular, alkyl halides R’X. As gas-phase fragmentation experiments show, the resulting heteroleptic organopalladate(II) complexes undergo reductive eliminations and release cross-coupling products R’R. Overall, this reaction sequence corresponds to a catalytic cycle, in which the elementary step of transmetalation precedes that of oxidative addition and which therefore differs from that of conventional palladium-catalyzed cross-coupling reactions. An analogous mechanism has previously been found for reactions catalyzed by palladate anions containing dienes, but not for those mediated by phosphine-coordinated palladium complexes.

Despite the potential of the present organopalladates for catalyzing challenging alkyl-alkyl cross-coupling reactions and the significant interest in these transformations, these systems themselves are not suited for practical applications because of the facile catalyst degradation under the reaction conditions. This problem arises from the electron-poor character of the phosphine, which is needed for stabilizing the electron-rich palladate center by a π back donation to the ligand. The partial occupation of the anti-bonding C–P orbital weakens this bond and activates it for degradation reactions with the highly reactive organometallics present in the reaction mixture. Thus, the practical utilization of the new catalytic pathway requires the development of phosphines that combine an electron-poor character with a high stability.

**Experimental Section**

**General:** All experiments were carried out under standard Schlenk conditions to exclude moisture and oxygen. THF was dried over sodium/benzophenone and freshly distilled before use. [L₄Pd] was synthesized according to literature procedures (see the Supporting Information).\cite{20,21} BNMe₃ was synthesized according to standard procedures. BuZnCl·LiCl was prepared in situ from ZnCl₂ and BuLi. All other organometallic reagents as well as the palladium complexes Pd₃, Pd(PPh₃)₃ and Pd(db), were purchased. The concentrations of the organometallic reagents were determined by iodicometric titration.\cite{22}

Sample solutions were prepared by dissolving the palladium catalyst and, if necessary, an additional phosphine ligand in dry THF. The organometallic reagent and, in some experiments, the organyl halide were added at 195 K. The resulting solutions were analyzed immediately.

**ESI mass spectrometry:** Sample solutions were fed into the ESI source of a micrOTOF-Q II mass spectrometer (Bruker Daltonik) with gas-tight syringes at typical flow rates of 8 μL min⁻¹. The ESI source was operated at a voltage of 3500 V. N₂ was used as nebulizer gas (flow rate of 5 L min⁻¹) and drying gas (0.7 bar backing pressure, temperature of 333 K). In simple MS³ experiments, all generated ions with 50 ≤ m/z ≤ 3000 were allowed to pass the quadrupole mass filter of the instrument. In gas-phase fragmentation experiments, ions of interest were mass-selected in the quadrupole-mass filter, subjected to a kinetic energy E_kin, and allowed to collide with N₂ gas. Residual precursor ions and fragment ions were then detected after passage through the TOF analyzer. An external calibration with a mixture of CF₃COOH and phosphazenes in H₂O/CH₃CN allowed for typical accuracies of the measured m/z ratios of ≤ 25 ppm. In some cases, an additional internal calibration had to be applied. To this end, the m/z scale was adjusted to match the theoretical m/z ratio of an ion, whose identity could be independently established with certainty (indicated for each experiment). Theoretical exact m/z ratios and isotope patterns were calculated with the Compass DataAnalysis software package (Bruker Daltonik).

Ion-molecule reactions in the gas phase were analyzed by means of an HCT quadrupole-ion trap mass spectrometer (Bruker Daltonik). Defined mixtures of neutral reactants and helium were prepared and introduced into the three-dimensional quadrupole ion trap using a mixing device, which has been described in detail previously.\cite{23}
GC analysis: The Grignard reagent (1.5 mmol) and the organyl halide (1.0 mmol) were added dropwise to solutions of LiPd (0.02 mmol) in THF (5 mL) held at 195 K. After warming up, the resulting mixtures were stirred for reaction times ranging from 3 h to 48 h before they were treated with brine (2 mL) and extracted with THF (3×2 mL). The combined organic layers were dried over Na₂SO₄ and filtrated through silica gel. The resulting solutions were analyzed by GC-MS with a Trace DSQ instrument (Thermo Finnigan) equipped with a VF-5 ms column (Agilent).

Acknowledgements

We thank Mr. Marius Deuker for carrying out some of the ESI-mass spectrometric experiments and the anonymous reviewers for helpful comments. We gratefully acknowledge funding from the CaSuS (Catalysis for Sustainable Synthesis) program (scholarship for M.K.). Open access funding enabled and organized by Projekt DEAL.

Conflict of interest

The authors declare no conflict of interest.

Keywords: cross-coupling • mass spectrometry • palladium • phosphines • reactive intermediates

[1] Metal-Catalyzed Cross-Coupling Reactions and More (Eds.: A. de Meijere, S. Bräse, M. Oestreich), Wiley-VCH, Weinheim, 2014.
[2] E. R. Strieter, D. G. Blackmond, S. L. Buchwald, J. Am. Chem. Soc. 2003, 125, 13978–13980.
[3] E. A. B. Kantchev, C. J. O'Brien, M. G. Organ, Angew. Chem. Int. Ed. 2007, 46, 2768–2813; Angew. Chem. 2007, 119, 2824–2870.
[4] G. C. Fu, Acc. Chem. Res. 2008, 41, 1555–1564.
[5] N. Marion, S. P. Nolan, Acc. Chem. Res. 2008, 41, 1440–1449.
[6] C. C. Johansson Seechurn, M. O. Kitching, T. J. Colacot, V. Snieckus, Angew. Chem. Int. Ed. 2012, 51, 5062–5085; Angew. Chem. 2012, 124, 5150–5174.
[7] N. Hazari, P. R. Melvin, M. M. Beromi, Nat. Rev. Chem. 2017, 1, 1–16.
[8] T.-Y. Luh, M. Leung, K.-T. Wong, Chem. Rev. 2000, 100, 3187–3204.
[9] A. C. Frisch, M. Beller, Angew. Chem. Int. Ed. 2005, 44, 674–688; Angew. Chem. 2005, 117, 680–695.
[10] R. Jana, T. P. Pathak, M. S. Sigman, Chem. Rev. 2011, 111, 1417–1492.
[11] a) J. Terao, H. Watanabe, A. Ikumi, H. Kuniyasu, N. Kambe, J. Am. Chem. Soc. 2002, 124, 4222–4223; b) J. Terao, Y. Naitoh, H. Kuniyasu, N. Kambe, Chem. Lett. 2003, 32, 890–891; c) J. Terao, Y. Naitoh, H. Kuniyasu, N. Kambe, Chem. Commun. 2007, 0, 825–827; d) J. Terao, N. Kambe, Acc. Chem. Res. 2008, 41, 1545–1554; e) N. Kambe, T. Iwasaki, J. Terao, Chem. Soc. Rev. 2011, 40, 4937–4947.
[12] M. Kolter, K. Böck, K. Karaghiosoff, K. Koszinowski, Angew. Chem. Int. Ed. 2017, 56, 13244–13248; Angew. Chem. 2017, 129, 13427–13431.
[13] For early reports on anionic palladate complexes with triphenylphosphine ligands, see: a) C. Amatore, M. Azzabi, A. Jutand, J. Am. Chem. Soc. 1991, 113, 8375–8384; b) C. Amatore, A. Jutand, Acc. Chem. Res. 2000, 33, 314–321.
[14] a) M. Kolter, K. Koszinowski, Chem. Eur. J. 2016, 22, 15744–15750; b) M. Kolter, K. Koszinowski, Chem. Eur. J. 2019, 25, 13376–13384.
[15] a) A. Putau, H. Brand, K. Koszinowski, J. Am. Chem. Soc. 2012, 134, 613–622; b) C. Schnegelsberg, S. Bachmann, M. Kolter, T. Auth, M. John, D. Stalke, K. Koszinowski, Chem. Eur. J. 2016, 22, 7752–7762; c) F. Keyvenschmidt, S. E. Meurer, K. Koszinowski, Chem. Eur. J. 2019, 25, 5912–5921; d) T. Parchomyk, S. Demeshko, F. Meyer, K. Koszinowski, J. Am. Chem. Soc. 2018, 140, 9709–9720.
[16] B. H. Lipshutz, J. Keith, D. J. Buzard, Organometallics 1999, 18, 1571–1574.
[17] a) K. L. Vikse, M. A. Henderson, A. G. Oliver, J. S. McIndoe, Chem. Commun. 2010, 46, 7412–7414; b) T. K. Trefz, M. A. Henderson, M. Y. Wang, S. Collins, J. S. McIndoe, Organometallics 2013, 32, 3149–3152;
[18] a) H. S. Ziljstra, A. Joshi, M. Linnolahti, S. Collins, J. S. McIndoe, Eur. J. Inorg. Chem. 2019, 2346–2355.
[19] J. Váňa, T. Terencio, V. Petrovič, O. Tischler, Z. Novák, J. Raithová, Organometallics 2017, 36, 2072–2080.
[20] R. Qian, Y.-X. Liao, Y.-G. Guo, H. Guo, J. Am. Chem. Soc. Mass Spectrom. 2006, 17, 1582–1589.
[21] D. Agrawal, E.-L. Zins, D. Schroder, Chem. Asian J. 2010, 5, 1667–1676.
[22] V. V. Grushin, Organometallics 2000, 19, 1888–1900.
[23] T. Gartner, W. Henze, R. M. Gschwind, J. Am. Chem. Soc. 2007, 129, 11362–11363.
[24] A. Krasovskij, P. Knochel, Angew. Chem. Int. Ed. 2004, 43, 3333–3336; Angew. Chem. 2004, 116, 3396–3399.
[25] a) A. J. Casares, P. Espinet, B. Fuentes, G. Salas, J. Am. Chem. Soc. 2007, 129, 3508–3509; b) B. Fuentes, M. Garcia-Melchor, A. Lledös, F. Masera, J. A. Casares, G. Ujaje, P. Espinet, Chem. Eur. J. 2010, 16, 8596–8599;
[26] a) J. I. Brauman, W. N. Olmstead, C. A. Lieder, J. Am. Chem. Soc. 1974, 96, 4030–4031; b) W. N. Olmstead, J. I. Brauman, J. Am. Chem. Soc. 1977, 99, 4219–4228.
[27] a) D. K. Bohme, L. B. Young, J. Am. Chem. Soc. 1970, 92, 7354–7358; b) D. K. Bohme, A. B. Rakshit, J. Am. Chem. Soc. 1984, 106, 3447–3452.
[28] A. J. Laerdahl, E. Uggerud, Int. J. Mass Spectrom. 2002, 214, 277–314.
[29] a) W. A. Herrmann, C. Brömler, K. Öfele, M. Beller, H. Fischer, J. Organomet. Chem. 1995, 491, C1–C4; b) W. A. Herrmann, C. Brömler, K. Öfele, M. Beller, H. Fischer, J. Mol. Cat. A 1995, 103, 133–146.
[30] S. A. Macgregor, Chem. Soc. Rev. 2007, 36, 67–76.
[31] A. Jakab, Z. Dalicsék, T. Holczbauer, A. Hamza, I. Pápai, Z. Finta, G. Timár, T. Szös, Eur. J. Org. Chem. 2015, 60–66.
[32] A. Krasovskiy, P. Knochel, Synthesis 2006, 0890–0891.
[33] T. Parchomyk, K. Koszinowski, J. Mass Spectrom. 2019, 54, 81–87.

Manuscript received: February 27, 2020
Revised manuscript received: May 11, 2020
Accepted manuscript online: May 19, 2020
Version of record online: September 7, 2020