Inorganic Chemistry Cite This: Inorg. Chem. XXXX, XXX, XXX-XXX

Article pubs.acs.org/IC

Understanding Anionic "Ligandless" Palladium Species in the Mizoroki-Heck Reaction

Felix Schroeter and Thomas Strassner*

Physikalische Organische Chemie, TU Dresden, Bergstrasse 66, 01062 Dresden, Germany

Supporting Information

ABSTRACT: The anionic complex $[NBu_4][Pd(DMSO)Cl_3]$, as a "ligandless" system, was shown to be an active catalyst in the Mizoroki-Heck coupling of aryl chlorides in the absence of strongly σ -donating ligands. To investigate the experimentally observed influence of halides and the amount of water on the catalytic activity, we employed a combination of experiments and theoretical calculations. The presence of water was shown to be critical for the formation of the active palladium(0) species by oxidation of in situ generated tributylamine. Oxidative addition to an anionic palladium(0) species was found to be the ratedetermining step of the catalytic cycle. For the ensuing steps, both neutral and anionic pathways were considered. It was shown that, in the absence of strongly σ -donating neutral ligands, chloride ions stabilize the catalytic intermediates. Therefore, an



anionic pathway is preferred, which explains the need for tetrabutylammonium chloride as an additive. The study of the influence of bromide ions on the catalytic activity revealed that the strongly exergonic displacement of the neutral substrates by bromide ions lowers the catalytic activity.

INTRODUCTION

As one of the organic transformations honored with the Nobel Prize,¹⁻⁴ the Mizoroki–Heck reaction⁵⁻⁷ has been and still is being intensely studied experimentally and theoretically.⁸⁻¹² The development of this powerful palladium-catalyzed C-C bond-forming process enabled the facile synthesis of stilbenes from styrene derivatives and aryl halides as target molecules for medicinal¹³⁻¹⁷ and materials¹⁸⁻²⁰ chemistry on a laboratory²¹⁻²³ and industrial²⁴⁻²⁷ scale. A multitude of catalyst systems has been established for the Mizoroki-Heck reaction, 28,29 among them not only phosphines^{30–33} and N-heterocyclic carbenes (NHCs)^{34–50} as ligands but also preformed palladium nanoparticles^{51–54} and "ligand-free" systems⁵⁵⁻⁶⁶ in ionic liquids.⁶⁷⁻⁷⁴ While aryl bromides are typically the coupling partner, many developed systems are also able to couple the less reactive aryl chlorides.⁷⁵⁻

The performance of these systems was rationalized on the basis of the identified mechanism of the reaction (Scheme 1).^{9,81-85} At first, a palladium(II) precursor is reduced to a neutral palladium(0) species (Scheme 1A). Then, oxidative addition of an aryl halide takes place (Scheme 1B), followed by ligand exchange (Scheme 1C) and migratory insertion of a styrene derivative (Scheme 1D). The resulting palladium alkyl complex undergoes β -hydride elimination, preferably yielding the coordinated (E)-alkene, which subsequently dissociates (Scheme 1E). Base-mediated reductive elimination (Scheme 1F) regenerates the catalytically active species. In this mechanism, all species involved in the catalytic cycle are

neutral. Intense investigation of the oxidative addition step by Amatore and Jutand led to the proposal of an anionic catalytic cycle with short-lived pentacoordinate intermediates (Scheme 1G, H).^{86–88} Anionic species have been later identified in other cross-couplings⁸⁹⁻⁹⁵ and encouraged the use of anionic palladium precatalysts in cross-coupling reactions.^{96–105} Both mechanistic pathways have been the subject of detailed theoretical calculations.^{106–127}

We recently reported on the catalytic activity of an anionic "ligandless" palladium complex in the Mizoroki-Heck reaction.¹⁰⁵ The $[Pd(DMSO)Cl_3]^-$ anion (DMSO = dimethyl sulfoxide) is capable of coupling activated aryl chlorides in relatively short reaction times.

During the course of the optimization, we observed the following:

(1) The presence of a small amount of water was crucial for product formation. The role of water in transition-metal catalysis has often been neglected, although it can play an important role.^{128–130} For example, Rh- and Ir-catalyzed hydrogenations are largely both positively and negatively influenced by the presence of water, depending on its concentration.^{131–133} In the Suzuki–Miyaura cross-coupling, water is thought to be responsible to form an anionic boronate complex which is required for efficient transmetalation.^{134–136} In Mizoroki-Heck and related cross-coupling reactions, water

Received: January 25, 2018

Scheme 1. Commonly Proposed Mechanism of the Mizoroki–Heck Reaction a



"Legend: (A) catalyst activation; (B) oxidative addition to a neutral Pd(0) species; (C) ligand displacement; (D) migratory insertion; (E) β -hydride elimination and liberation of the product; (F) "classical" reductive elimination, (G) formation of an anionic Pd(0) species; (H) oxidative addition to an anionic Pd(0) species; (I) reductive elimination via an anionic pathway; (J) reversible nanoparticle formation; (K) irreversible palladium black formation.

has been demonstrated to induce and/or accelerate the reduction of a palladium(II) precursor to palladium($0^{9,137,138}$ by base-mediated oxidation of a phosphine ligand to the corresponding phosphine oxide, ^{86,139,140} by Wacker oxidation,¹⁴¹ or by oxidation of tertiary amines.^{142–146}

(2) Product formation required the presence of tetrabutylammonium chloride (TBACI) as stabilizer. Jeffery was the first to report that tetrabutylammonium salts enhance the performance of catalysts in the Mizoroki–Heck reaction.^{55,147} It is commonly proposed that the salt provides "electrosteric" stabilization¹⁴⁸ and size control¹⁴⁹ of nanoparticles, which serve as a reservoir for soluble palladium(0) species,^{59,150} and that the halide aids in the formation of an anionic palladium species.⁸⁷ The latter observation is especially relevant to our catalytic system, since in the absence of strong σ -donating ligands (e.g., NHCs, phosphines), the catalytic intermediates may be stabilized by anionic halido ligands, which serve as moderately strong σ -donors and π -acceptors.^{151,152}

(3) The presence of bromide ions in the reaction mixture had a detrimental influence on the catalytic activity. This finding was somewhat counterintuitive, since many catalyst systems for the Mizoroki–Heck reaction rely on tetrabutyl-ammonium bromide (TBABr) as an additive.^{153–156}

To rationalize these findings and to understand the origin of the high catalytic activity of the $[Pd(DMSO)Cl_3]^-$ anion, we used a combined experimental and theoretical approach. For density functional theory (DFT) calculations, we chose the M06L functional, which has proven its reliability in thermochemical calculations of transition metals and treatment of noncovalent interactions,¹⁵⁷ along with the 6-31+G* basis set for treatment of anions.^{158–161} Solvent effects were treated implicitly with the SMD method,¹⁶² to account for the large influence of solvation effects on charged structures. First, we turned our attention to the precatalyst activation step. Then, we calculated the mechanism of the Mizoroki–Heck reaction, where we considered both an anionic and a neutral pathway. Finally, we investigated the influence of bromide ions on representative key steps of the catalyst activation and catalytic cycle.

RESULTS AND DISCUSSION

Catalyst Activation. *Experimental Observations.* At first, the palladium(II) precatalyst has to be reduced to palladium(0) in order to enter the catalytic cycle. We looked into the Wacker oxidation and treated complex 1a-NBu₄ with styrene in the absence of an aryl halide (Scheme 2a). Indeed, formation of

Scheme 2. Experimentally Observed Reduction of Palladium a



^{*a*}Legend: (a) reaction via Wacker oxidation; (b) reaction with styrene and NBu₃, respectively, at room temperature; (c) competition experiment between styrene and NBu₃. All products were identified by GC-MS (respectively NMR) and compared to reference samples.

palladium black occurred. Moreover, GC analysis of the reaction mixture revealed trace amounts of acetophenone (see Figure S1 in the Supporting Information). The presence of a base significantly accelerated the reaction, in accordance with the mechanism of the Wacker oxidation, where key steps such as deprotonation of a palladium aqua complex¹⁶³ and nucleophilic attack of a water molecule or hydroxide ion on the coordinated alkene^{164,165} are discussed.

However, we also found trace amounts of tributylamine, which are also always present in a typical catalytic experiment (see Figure S2 in the Supporting Information). These result from base-mediated Hofmann elimination of the tetrabutylammonium cation. Additionally, in another control experiment, formation of palladium black also occurred in the absence of styrene. In an NMR experiment, precatalyst 1a-NBu4 did not react with styrene (Scheme 2b). Neither coordination of styrene to the metal center nor reduction was observed. In contrast, if precatalyst la-NBu4 is treated with excess tributylamine (NBu₃), formation of palladium black occurs within 24 h (Scheme 2b) at room temperature. This observation is accompanied by the disappearance of the NMR peak assigned to ligated DMSO and the appearance of two new signals, which can be assigned to butyraldehyde (see Figure S3 in the Supporting Information). This is in accordance with the findings by Shmidt and Trzeciak, who investigated the reduction of palladium(II) by tertiary amines.^{143,144,166} In the last work, the aldehyde oxygen atom was found to originate

from trace amounts of water, and it was also stated that water accelerated the reduction of palladium.

In a competition experiment between styrene and tributylamine in dimethylacetamide (DMAc), using compound **1a-Na** in the absence of tetrabutylammonium ions, no acetophenone was found. Instead, butyraldehyde formed, which was identified as its *p*-chlorophenyl hydrazone derivative (Scheme 2c; see Figures S4 and S5 in the Supporting Information). Thus, the latter pathway appears to be preferred for catalyst activation. Additionally, other stabilizers, which are not able to undergo Hofmann elimination or β -hydride elimination, were tested in the Mizoroki–Heck reaction with **1a-NBu**₄.¹⁰⁵ These reactions did not lead to product formation. This is another sign that, under catalytically relevant conditions, the oxidation of a tertiary amine is necessary for efficient catalyst activation.

The thermolysis of palladium acetate $^{167-171}$ as a productive catalyst activation pathway could be excluded, since using palladium acetate as a precatalyst did not lead to product formation.¹⁰⁵ In addition, the reaction proceeds efficiently with other bases in the absence of acetate ions (see Table S1, entries 2–4, in the Supporting Information).

On the basis of these results, both the Wacker oxidation and the reduction by tributylamine may account for catalyst activation. It has to be emphasized that both activation pathways require stoichiometric amounts of water to take place, which might explain the need for water in the Mizoroki– Heck reaction using our catalyst system.

Theoretical Investigation: Relevant Pd(II) and Pd(0)Species. Since these experiments suggest two plausible activation pathways, we used theoretical calculations to further gain insight into this step. Therefore, we considered several palladium(II) species as possible starting points for the reduction (Chart 1a; see Figure S6 in the Supporting Information). The displacement of the neutral DMSO ligand with styrene, forming the anion 1b, is slightly exergonic. Similarly, formation of the anionic tributylamine complex 1c is

Chart 1. Plausible Palladium(II) and Palladium(0) Species in the Reaction Mixture $\!\!\!\!^a$

a) Palladium(II) complexes



 ${}^{a}\Delta H^{298}$ (ΔG^{298}) in kcal/mol. Energies are relative to 1a (2a, respectively).

favored. In contrast, several neutral palladium(II) species are higher in energy than 1a (see Chart S1 in the Supporting Information). We also considered the coordination of another chloride ligand, yielding 1d. Compound 1d is slightly favored in terms of free energy, in comparison to 1a. Species 1a,d both coexist in solution, as will be discussed later (Table 2, see below). Formation of a dimeric palladium(II) species, as in 1e, is also disfavored. Thus, displacement of the DMSO ligand by styrene or tributylamine, yielding the anionic complexes 1b,c, respectively, seems to initiate the reduction step.

We compared the energies of different palladium(0) complexes to see which palladium(0) species would most likely result from reduction (Chart 1b). Starting from a dicoordinated species, which is often discussed as the species entering oxidative addition,^{84,101} we compared different ligands in compounds 2a-c. Only styrene was able to efficiently stabilize Pd(0) (2b), in contrast to other ligands (see Chart S2 in the Supporting Information). Upon comparing different tricoordinated complexes, we identified the neutral complex 2d and the anionic complex 2e as the most thermodynamically favorable compounds, which also most likely coexist in solution, on the basis of their energies. We chose compound 2e as our reference point, since the anionic ligand renders the palladium atom more electron rich, which in turn facilitates the following oxidative addition. This will be discussed later in detail.

It should be mentioned that the Pd(0) compound **2e** is most likely in equilibrium with palladium nanoparticles,^{172,173} which may be catalytically active by themselves; however, these nanoparticles are most frequently discussed to be a resting state of the reaction.^{82,150,174–179} The formation of palladium nanoparticles has been confirmed by a mercury poisoning test, where the yield dropped from 94%¹⁰⁵ to 7%. These nanoparticles might aggregate in the presence of a large excess of water, as has been shown for related Ru and Ir nanoparticles.^{131,133} Such a process in the present case might explain why an excess of water larger than 50 μ L is detrimental to the catalytic activity of **1a-NBu**₄.¹⁰⁵

Wacker Oxidation. As one of the most important industrially relevant homogeneously catatalyzed reactions,¹⁸⁰⁻¹⁸³ the Wacker oxidation has been subject to extensive experimental and theoretical studies.¹⁸⁴ Typically, the oxidation of ethylene to acetaldehyde is performed in acidic aqueous solution at a low chloride ion concentration. Two major mechanistic alternatives have been proposed. (1) An inner-sphere attack of a hydroxido ligand occurs on the coordinated alkene. This syn pathway may be operative at low [Cl⁻]; however, some ambiguity remains.^{163,185-188} (2) An outer-sphere attack of a water molecule takes place on the coordinated alkene.^{164,165,189–192} Nowadays, there is general consensus that this so-called anti pathway is operative at high [Cl⁻].¹⁸⁴ Many groups strove to correlate experimental and theoretical results, ^{122,193–198} and a great deal of effort was put into the accurate description of water as a solvent, mostly by employing explicit solvation models in static quantum mechanical approaches,^{199–204} as well as molecular dynamics simulations.²⁰⁵⁻²⁰⁸ The conditions employed in our work differ greatly from the typical Wacker oxidation conditions. In dimethylacetamide as solvent, the concentration of water is ca. 100 times lower than that in pure water. In addition, basic instead of acidic conditions are employed. Thus, we modeled both syn and anti pathways.

In the syn pathway, the DMSO ligand of **1a** is displaced by styrene (Scheme 3; see Figure S7 in the Supporting Information).

Scheme 3. Catalyst Activation by Wacker Oxidation: Syn Pathway a



 ${}^{a}\Delta H^{298}$; ΔG^{298} ; ΔG^{413}) in kcal/mol. rds denotes the potentially rate determining step. Energies are relative to **1a**.

Then, in an endergonic step, a chlorido ligand in 1b has to be displaced by water. At room temperature, the corresponding transition state TS1b-3 correlates with a barrier of +15.5 kcal/ mol, which is approximately as high as the ensuing transition state for hydroxypalladation TS4_{Cl}-5a, commonly deemed the rate-determining step. However, due to the entropic effect, TS1b-3 becomes the sole rate-limiting step at 140 °C with a barrier of +19.1 kcal/mol. For hydroxypalladation to take place via $TS4_{CI}\mbox{-}5a,$ deprotonation of 3 to 4_{CI} occurs first, which is feasible under the basic conditions. Dechelation in 5a leads to the tricoordinate intermediate $5b_{Cl}$. Thus, β -hydride elimination can take place via **TS5b-6**, which is linked to a relatively small barrier of +9.6 kcal/mol. Ligand displacement in the palladium hydride complex 6 by styrene and subsequent tautomerization liberates acetophenone and the palladium complex 7, which undergoes quick reductive elimination, as will be discussed later in detail. Overall, this activation pathway is strongly exergonic by -43.3 kcal/mol.

In the anti pathway, the neutral species 8 has to form, which is sufficiently electrophilic for the nucleophilic attack by water (Scheme 4; see Figure S8 in the Supporting Information). The formation of strongly nucleophilic hydroxide ions from the mildly strong acetate base is endergonic by +32.5 kcal/mol and is thus unlikely. Following the water-chain model proposed by Siegbahn,²⁰⁰ we calculated the attack of a water trimer on the more stable complex 8_t. However, the transition state TS8_t-9_t· 3H₂O has a free energy of +24.6 kcal/mol, which is significantly higher than the highest barrier of the syn addition. The attack Scheme 4. Catalyst Activation by Wacker Oxidation: Anti
 Pathway a



 ${}^{a}\Delta H^{298}$ ($\Delta G^{298};\Delta G^{413}$) in kcal/mol. Energies are relative to 1a.

of a single water molecule on complex 8 is even less favorable (see Scheme S1 in the Supporting Information). Thus, the syn pathway appears to be preferred for this particular system.

Reduction by Tributylamine. The reduction of palladium-(II) by tertiary amines is less well understood. At first, the DMSO ligand in 1a is displaced by tributylamine. Following a mechanistic proposal by Trzeciak, the palladium amine complex 1e is subjected to a concerted metalation-deprotonation (cmd) reaction (Scheme 5; see Figure S9 in the Supporting Information).¹⁴⁴ This reaction pathway has frequently been reported for similar systems.²⁰⁹⁻²¹³ In complex 1c, two chlorido ligands can be replaced by one acetate ligand in a η^2 fashion. The corresponding associative displacement of the chlorido ligand by acetate (TS1c-1f) is connected to a high barrier, especially at 140 °C. However, if the loss of a chloride ligand occurs first, the resulting compound 10 can easily add an acetate anion. Then, the acetato ligand can displace another chlorido ligand via $TS1f-11_{Cl}$ forming the chelate 11_{Cl} . With 11_{Cl} being 3.3 kcal/mol higher in energy than 1c, this process is only slightly endergonic. Then, an intramolecular cmd process can take place via $TS11_{Cl}-12_{Cl}$, with a corresponding transition state free energy of +14.6 kcal/mol. At 140 °C, this energy is slightly lowered to +14.0 kcal/mol. This step appears to be the rate-limiting step for this pathway. As can be seen in the transition state geometry, the deprotonation is concerted and involves a palladium-hydrogen interaction (Figure 1a). Displacement of the formed acetic acid in complex 12_{CI} by a chlorido ligand yields compound 13. The corresponding intermolecular process is disfavored. However, the transition state geometry of TS10-13 is similar to that of TS10_{CI}-11_{CI} and also involves a palladium-hydrogen interaction (Figure 1b)

The alkyl palladium complex 13 can easily undergo reductive elimination, as is known for alkyl palladium complexes (Scheme 6; see Figure S10 in the Supporting Information).⁹ Opening of the chelate to compound 14 results in a free coordination site, and the subsequent β -hydride elimination can easily take place. The corresponding transition state TS14-15a is only +2.7 kcal/ mol higher in energy than the reactant 14. In the resulting enamine complex 15a, displacement of the enamine by styrene yields compound 7, which is prone to reductive elimination, as described above. Also, facile hydrolysis of the enamine to butyraldehyde takes place and constitutes another major driving force of the reaction. The corresponding formation of the

Scheme 5. Concerted Metalation-Deprotonation of Tributylamine^a



 $^{a}\Delta H^{298}\left(\Delta G^{298};\Delta G^{413}
ight)$ in kcal/mol. Energies are relative to 1a.



Figure 1. Transition state geometries for (a) $TS11_{CI}$ - 12_{CI} and (b) TS10-13. Color code: H, white; C, gray; N, blue; O, red; Cl, green; Pd, turquoise.

allylamine complex 15b is associated with a significantly higher reaction barrier of +8.9 kcal/mol and is thus less likely. Overall, this activation process is exergonic by -35.6 kcal/mol.

A nucleophilic substitution in compound 13 by hydroxide ions or C–N bond cleavage in 13 is considered unlikely (see Scheme S2 in the Supporting Information). In addition, the β hydride elimination from complex 10¹⁴⁶ is less favorable (see Scheme S3 in the Supporting Information).

To conclude, it was shown experimentally and theoretically that both Wacker oxidation and reduction by tributylamine are viable pathways for the reduction of Pd(II) to Pd(0). However, in direct comparison, reduction by tributylamine is more likely because butyraldehyde was the only product observed in the competition experiment between styrene and tributylamine. In addition, a solution of tributylamine and **1a-NBu**₄ forms Pd(0) at room temperature, whereas a solution of **1a-NBu**₄ and styrene is stable for weeks. This pronounced difference can be explained by the theoretical calculations described above. The rate-determining step in the Wacker oxidation is the endergonic displacement of a chloride ligand by water (**TS1-b3**, $\Delta G^{\ddagger,413}$ =

Scheme 6. β -Hydride Elimination of the Alkyl Palladium Complex 10^a



+19.1 kcal/mol). In contrast, the highest barrier for the reduction with tributylamine is calculated to be +14.0 kcal/mol at 140 °C (TS11_{Cl}-12_{Cl}). Thus, the calculations support the preference for the latter activation mechanism.

Catalytic Cycle. Oxidative Addition. In the next step, oxidative addition of the aryl halide takes place (Table 1; see



Figure S11 in the Supporting Information). Therefore, one styrene ligand in **2e** has to be displaced by the substrate, yielding the η^2 -aryl complex **16**. This process is endergonic and contributes to the overall barrier that has to be overcome during the oxidative addition. To find out, if a neutral or an anionic palladium species undergoes oxidative addition more easily, we chose the anionic complex **16**_{Cl} and the neutral complexes **16**_S and **16**_D, having another styrene ligand or a DMSO ligand, respectively, as model systems. The η^2 -aryl compounds **16**_{Cl} and **16**_D are similar in energy, with respect to **2e**, while **16**_S is lower in energy.

TS16_{Cl}-17_{Cl} is the transition state with the lowest barrier height, relative to 2e, while TS16_D-17_D and TS16_S-17_S are higher in energy. Although coordination of an anionic chlorido ligand in 16_{Cl} is less favored than that of the styrene ligand in 16_s, it renders the palladium center more electron rich and facilitates the following oxidative addition. The same applies if the free energies at 140 °C are considered. On comparison of these energies, it is highly likely that oxidative addition occurs from an anionic complex. Both transition state geometries are similar and show similar bond lengths for the bonds that are being formed and cleaved (Figure 2).



Figure 2. Transition state geometries of (a) $TS16_{CI}$ - 17_{CI} and (b) $TS17_{S}$ - 17_{S} . Bond lengths are given in Å. Color code: H, white; C, gray; N, blue; O, red; Cl, green; Pd, turquoise.

The resulting complex 17_{Cl} can isomerize to the trans isomer 17t, which has been reported for related structures (Scheme 7).^{214–221} However, 17_t is higher in energy than 17_{Cl} and thus is no resting state in this catalytic cycle.

Migratory Insertion. The following migratory insertion of the styrene ligand into the palladium–aryl bond determines the regioselectivity of the reaction (Scheme 7; see Figure S12 in the Supporting Information). From 17_{Cl} , either terminal insertion

Scheme 7. Migratory Insertion^a



 ${}^{a}\Delta H^{298} (\Delta G^{298}; \Delta G^{413})$ in kcal/mol. Energies are relative to **2e**. Ar = 4-acetylphenyl.

via $TS17_{CI}$ -18_T or geminal insertion via $TS17_{CI}$ -18_G is possible. Due to the negligible steric effect of the chlorido ligands, the calculated free energy difference of both transition states is as low as 3.1 kcal/mol at 140 °C. This difference should correspond to a terminal/geminal product ratio of about 98/2, which is consistent with GC analyses of the reaction mixture, where no geminal product isomer was identified.

In the neutral pathway, the barrier of $TSS8_T-S9_T$ for migratory insertion is reduced to +15.0 kcal/mol (relative to $S8_T$), (see Scheme S4 in the Supporting Information). The energy difference of +16.5 kcal/mol in the anionic pathway between $TS17_{CI}-18_T$ and 17_{CI} is slightly higher. This dependence on the charge of the complex has been reported in the literature.¹¹⁹ However, displacement of a chlorido ligand in 17_{CI} by a neutral ligand, such as DMSO, to form $S8_T$ is highly endergonic, thus rendering the neutral pathway less favorable overall. The selectivity-determining energy difference of 2.6 kcal/mol between $TSS8_G-S9_G$ and $TSS8_T-S9_T$ corresponds to a similar terminal/germinal ratio of about 96/4.

 β -Hydride Elimination. Compound 18_T is in equilibrium with its other rotamers 18_E and 18_Z (Scheme 8; see Figure S13 in the Supporting Information). In compound 18_E , both aryl groups are in a gauche arrangement, and subsequent β -hydride elimination via $TS18_E$ - 19_E leads to the *E*-configured alkene.

Scheme 8. β -Hydride Elimination^{*a*}



 ${}^{a}\Delta H^{298}$ ($\Delta G^{298}; \Delta G^{413}$) in kcal/mol. Energies are relative to 2e.

The (*Z*)-alkene is accessible by β -hydride elimination from isomer $\mathbf{18}_{\mathbf{Z}}$ with ecliptic arrangement of the aryl groups. The transition state free energy difference of 4.8 kcal/mol largely favors the *E* isomer, with a calculated *E*/*Z* ratio of >99/1. In a typical catalytic run, the *E*/*Z* ratio was about 98/2. In the β hydride elimination, the neutral pathway is linked to both a higher relative and absolute reaction barrier, but a comparable *E*/*Z* ratio of >99/1, although the neutral palladium alkyl complexes $\mathbf{S9}_{\mathrm{T}}$, $\mathbf{S9}_{\mathrm{E}}$, and $\mathbf{S9}_{\mathrm{Z}}$ are slightly enthalpically favored in comparison to their anionic congeners $\mathbf{18}_{\mathrm{T}}$, $\mathbf{18}_{\mathrm{E}}$, and $\mathbf{18}_{\mathrm{Z}}$ (see Scheme S5 in the Supporting Information).

Reductive Elimination. The last step to regenerate the catalyst is reductive elimination (Scheme 9; see Figure S14 in

Scheme 9. Plausible Reductive Elimination Pathways^a



 ${}^{a}\Delta H^{298}$ ($\Delta G^{298};\Delta G^{413}$) in kcal/mol. Energies are relative to **2e**. denotes a vacant coordination site. In compound **23**_v the chlorido ligand is located trans to the styrene ligand, whereas in **23**_c these ligands are arranged in a cis fashion.

the Supporting Information). Replacement of the stilbene ligand by styrene liberates the reaction product and produces complex 7, which also has been discussed as an intermediate in the catalyst activation step (see above). We considered direct attack of an acetate molecule via intermediate 22. However, we were not able to locate 22, since it readily dissociates to form the dicoordinate species 2b, acetic acid, and a free chloride anion. Despite our efforts, we were not able to identify a transition state for this transformation, but we believe it to proceed in a nearly barrierless fashion. After coordination of another styrene molecule, the anionic species 2e is regenerated.

We also considered initial displacement of a chlorido ligand in 7 by styrene, which is an endergonic process. However, addition of one acetate molecule to **20** again led to dissociation of acetic acid and generation of compound **2e** without the location of intermediate **21**. A coordination of acetic acid to the palladium center was only observed in the tricoordinate intermediate **24**, which has to be formed via compound **23**_t. In **24**, the Pd–H bond length is 2.21 Å, which is significantly longer than in **23**_t (1.55 Å). Thus, complex **24** can be described as a palladium(0) complex with coordinated acetic acid. A relaxed potential energy surface scan of the Pd–H bond showed that formation of **24** from **23**_t proceeded smoothly downhill, even upon incorporation of explicit microsolvation of acetate by a water molecule, which shows that the reductive elimination proceeds via a very small barrier, if any at all.

Overall, the catalytic cycle is exergonic by -37.9 kcal/mol and thus thermodynamically favorable. At 140 °C, the overall reaction free energy is reduced to -25.5 kcal/mol, which still signals a highly favorable process.

Bromide Influence. Having established the overall reaction mechanism, we turned our interest to the influence of bromide ions on the catalyst performance. During catalysis, we noticed a decrease in catalytic activity of complex **1a-NBu**₄, if bromide ions were present, even in small quantities.¹⁰⁵ First, we investigated if bromide ions are able to replace the chloride ions in the anionic species **1a**. By calculating the energies of the bromide-containing complexes **1g–i**, we found that each displacement of a chlorido ligand by a bromido ligand leads to a stabilization of the complex by about 8.6 kcal/mol (Chart 2a; see Figure S15 in the Supporting Information). This trend is in accordance with experimental studies.⁹

Chart 2. Influence of Bromide Ions on the Complex Stability a

a) Pd(II) complexes



 $^{a}\Delta H^{298}$ (ΔG^{298} ; ΔG^{413}) in kcal/mol. Energies are relative to 1a and 2l, respectively.

Additionally, the dianionic complex 1j is lower in its free energy than complex 1i, which shows that also a neutral ligand can be displaced by bromide ions. The dimeric species 1l is comparably favorable. In the palladium(0) anion 2e, displacement of chloride by bromide, yielding 2f, is exergonic by -6.1kcal/mol (Chart 2b; see Figure S15 in the Supporting Information). These calculations show a clear preference for palladium bromido species.

A similar observation can be made if 1a-NBu₄ is treated with the corresponding tetrabutylammonium halide salt (Table 2). Using NMR, the displacement of the DMSO ligand by halides can be monitored as the relative intensities of bound vs free DMSO. Addition of 1 equiv of TBACl led to no change in the relative intensity and thus nearly no displacement of DMSO. With a 10-fold excess of TBACl, the ratio of 1a to 1d is about 1.6/1, which shows that both species coexist in equilibrium. However, if 1 equiv of TBABr is added, much more free DMSO

Table 2. NMR Titration of 1a-NBu₄ Leading to the Displacement of DMSO



is detected. Ten equivalents of TBABr are able to completely displace the DMSO ligand in **1a-NBu**₄. This experiment shows that bromide ions are more efficient in displacing neutral ligands in comparison to chloride ions in complex **1a-NBu**₄. This effect might be intensified by the increased tendency to form dimeric μ -bromido palladium species. The displacement of neutral ligands and formation of dimeric species in catalysis was also observed by Hartwig and others.^{93,222–224} In their work, μ -halido complexes as a resting state were identified in the presence of bromide and iodide ions, but not for chloride ions.

To prove if a dimeric μ -bromido palladium complex could also be the resting state of the presented reaction, we investigated the reaction of $17_{C\nu}$ which is the product of the oxidative addition, with chloride and bromide ions (Scheme 10; see Figure S16 in the Supporting Information).

Scheme 10. Potential Catalyst Resting States^a



 $^{a}\Delta H^{298}$ (ΔG^{298} ; ΔG^{413}) in kcal/mol. Energies are relative to 17_{Cl}.

Displacement of the styrene ligand in 17_{Cb} forming the μ chlorido compound 25_{Cb} is only slightly exergonic at 140 °C, indicating that both species can exist in equilibrium, with a sufficient amount of 17_{Cl} still present to undergo intramolecular migratory insertion. Exergonic displacement of chloride by bromide ions leads to complex 17_{Br} . Starting from 17_{Br} , displacement of the styrene ligand to form the μ -bromido species 25_{Br} is exergonic by -17.8 kcal/mol at 140 °C. This difference in energy is high enough that only small quantities of 17_{Br} should exist in solution. This ultimately slows down the migratory insertion. Judging from the experimental and theoretical data, the presence of bromide ions in the reaction mixture provides access to dimeric catalyst resting states, which in turn slows the ensuing reaction steps. We also looked at the influence of bromide ions on the key steps of the catalyst activation (Scheme 11; see Figure S17 in the Supporting Information).

Scheme 11. Influence of Bromide Ions on Key Steps of the Catalyst $\operatorname{Activation}^a$



 ${}^{a}\Delta H^{298}$ (ΔG^{298} ; ΔG^{413}) in kcal/mol. Energies are relative to 4 and 11, respectively.

For example, the difference in the transition state energies of the C–O insertion of the Wacker oxidation $(TS4_{Cl}-5a_{Cl} \text{ and } TS4_{Br}-5_{Br})$ is within the accuracy range of the DFT method (Scheme 11a). For the oxidation of tributylamine, the effect is somewhat more pronounced (Scheme 11b). In both cases, the presence of bromide ions renders the process only slightly less favorable. This is in accordance with the observation that the complex [NBu]₄[Pd(DMSO)Br₃] (1i-NBu₄)¹⁰⁵ also decomposes in the presence of tributylamine at room temperature, yielding butyraldehyde and Pd black.

Finally, we investigated the influence of bromide ions on the oxidative addition, which is the rate-determining step of the catalytic cycle (Table 3; see Figure S18 in the Supporting Information). Displacement of chloride by bromide in compounds $16_{\rm Cl}$ and $17_{\rm Cl}$ is energetically favored, but the relative reaction barrier height stays nearly the same. At 140 °C, the energy difference between $TS16_{\rm Cl}$ - $17_{\rm Cl}$ and $16_{\rm Cl}$ is just

Table 3. Energies of the Oxidative Addition in the Presence of Bromide $Ions^a$



^aIn kcal/mol. Energies are relative to 2e.

1.1 kcal/mol higher than the difference between $TS16_{Br}$ - 17_{Br} and 16_{Br} . Thus, the influence of bromide ions on the oxidative addition is negligible.

CONCLUSION

We have used experimental data together with computational chemistry to gain insight into the mechanism of the Mizoroki–Heck reaction of aryl chlorides catalyzed by the anionic complex **1a-NBu**₄. It was shown experimentally that catalyst activation from Pd(II) to Pd(0) takes place by oxidation of tributylamine generated in situ, even at room temperature. We present a viable mechanistic pathway for this oxidation by theoretical calculations, which support the preference of this activation pathway over the Wacker oxidation. This activation pathway requires the presence of water to effectively function, thus explaining the need for trace amounts of water in the reaction. Several other activation pathways, e.g., Wacker oxidation, could be excluded. The presence of palladium nanoparticles as a catalyst reservoir has been confirmed by mercury poisoning tests.

Subsequently, the mechanism of the Mizoroki–Heck reaction itself was assessed. Oxidative addition to an anionic palladium(0) species was found to be the rate-determining step for this system. For the following steps, i.e. migratory insertion, β -hydride elimination, and reductive elimination, a reaction pathway comprising anionic palladium species is proposed. These anionic species are stabilized by TBACl, which ensures a sufficiently high chloride ion concentration. The selectivities were explainable by the calculated energy differences of the transition states. Overall, the reaction is exergonic by -37.9 kcal/mol.

The previous experimental work indicated a detrimental influence of the presence of bromide ions on the catalytic activity. Titration of compound **1a-NBu**₄ with TBABr and investigation by NMR and quantum chemical calculations show that halide exchange from chloride to bromide is favored, yielding palladium bromide intermediates. These were considered as active catalytic species; however, the calculations show that the presence of bromide ions does not significantly alter the relative height of the transition states in the respective catalytic steps. Instead, bromido ligands strongly facilitate the formation of μ -halido palladium dimers, thus displacing the neutral substrates, which eventually leads to decreased catalytic activity.

Overall, the experimental observations fit well with the theoretical insight gained by computations. Furthermore, the results show that under "ligandless" conditions and in the presence of halide sources, soluble anionic palladium species should be considered as the active species for all parts of the catalytic cycle.

EXPERIMENTAL SECTION

General Considerations. All activation experiments were performed under an argon atmosphere, except for NMR measurements, which were performed in air. Dimethylacetamide (DMAc) was distilled from CaH prior to use. Sodium acetate was dried at 130 °C. Tetrabutylammonium chloride was dried at 60 °C overnight under high vacuum and stored in an MBraun glovebox. **1a-NBu**₄, **1a-Na** and **1j-NBu**₄ were synthesized according to our previously reported procedure.¹⁰⁵ All other chemicals were purchased from commercial suppliers and used as received. ¹H NMR spectra were acquired on a Bruker NMR Avance 300 spectrometer and referenced internally using the solvent residual signal (7.26 ppm for CDCl₃). GC-MS measurements were carried out on an Agilent 7890A gas chromatograph and an Agilent 5975 Series MSD.

Representative Catalytic Procedure. In a 10 mL crimp vial were placed sodium hydrogen carbonate (185 mg, 2.2 mmol) and tetrabutylammonium chloride (143 mg, 0.5 mmol), and the vial was closed with a butyl rubber septum. The vial was evacuated and filled with argon three times. Then, DMAc (5 mL), 4-chloroacetophenone (130 μ L, 1 mmol), styrene (162 μ L, 1.4 mmol), water (50 μ L, 3 mmol), and the calculated amount of a catalyst stock solution in DMAc were added via syringe. The vial was placed in a preheated aluminum block and the solution stirred for 6 h at 140 °C. Then, 0.1 mL of the solution was removed, diluted with 4 mL of diethyl ether, and filtered over a plug of silica, which was then rinsed by addition of 1 mL of DCM. The resulting solution was analyzed by GC. The yield is given as an average of two runs.

Representative Catalyst Activation Experiment. In a 10 mL crimp vial was placed **1a-Na** (5 mg, 16 μ mol), and the vial was closed with a butyl rubber septum. The vial was evacuated and filled with argon three times. Then, DMAc (2 mL), tributylamine (20 μ L, 84 μ mol), styrene (9 μ L, 80 μ mol), and water (20 μ L, 1.1 mmol) were added via syringe. The vial was placed in a preheated aluminum block and the solution stirred for 2 min at 140 °C, during which it turned from orange to black. The solution was cooled to room temperature, 4-chlorophenylhydazine hydrochloride (20 mg, 0.1 mmol) was added, and the solution was stirred for another 30 min. Then, 0.1 mL of the solution was removed, diluted with 2 mL of diethyl ether, and filtered over a plug of silica, which was then rinsed by addition of 1 mL of DCM. The resulting solution was analyzed by GC.

Computational Details. All calculations were carried out with the Gaussian 09, Rev. B.01 program package.²²⁵ The M06L functional^{226,227} was chosen as an established and reliable method for the calculation of thermochemistry of transition-metal compounds.¹⁵⁷ The Hay-Wadt ECP was used for palladium.²²⁸ Bromine atoms were treated with the 6-311G* basis set.²²⁹ The 6-31+G* basis set was used for all other atoms.¹⁵⁸⁻¹⁶¹ For a more reliable optimization, the keyword Grid = UltraFine was employed. All calculations were performed with the continuum solvation model SMD with DMAc as solvent.¹⁶² All geometries were optimized without any restriction. Frequency calculations were used to confirm the presence of a ground state or transition state. Additional IRC calculations were performed for ambiguous transition states.^{230,231} Thermochemical data were taken from frequency calculations at 298.15 and 413 K, respectively. If not stated otherwise, all discussed values are the ΔG^{298} values. Images were created with CYLview.²³²

ASSOCIATED CONTENT

S Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.inorg-chem.8b00175.

Gas chromatograms, mass spectra, and NMR spectra of representative activation experiments, additional schemes and tables as described in the text, discussions of the geometries of the intermediates and transition states, and Cartesian coordinates and ZPEs of all compounds (PDF)

AUTHOR INFORMATION

Corresponding Author

*E-mail for T.S.: thomas.strassner@chemie.tu-dresden.de.

ORCID 💿

Thomas Strassner: 0000-0002-7648-457X

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We would like to thank the Zentrum für Informationsdienste und Hochleistungsrechnen (ZIH) for allocating computing time.

REFERENCES

(1) Wu, X. F.; Anbarasan, P.; Neumann, H.; Beller, M. From noble metal to Nobel Prize: Palladium-catalyzed coupling reactions as key methods in organic synthesis. *Angew. Chem., Int. Ed.* **2010**, *49*, 9047–9050.

(2) Bäckvall, J.-E. Palladium-Catalyzed Cross Couplings in Organic Synthesis - Scientific Background on the Nobel Prize in Chemistry, 2010.
(3) Negishi, E.-i. Magical power of transition metals: past, present, and future (Nobel Lecture). Angew. Chem., Int. Ed. 2011, 50, 6738– 6764.

(4) Johansson Seechurn, C. C. C.; Kitching, M. O.; Colacot, T. J.; Snieckus, V. Palladium-Catalyzed Cross-Coupling: A Historical Contextual Perspective to the 2010 Nobel Prize. *Angew. Chem., Int. Ed.* **2012**, *51*, 5062–5085.

(5) Mizoroki, T.; Mori, K.; Ozaki, A. Arylation of Olefin with Aryl Iodide Catalyzed by Palladium. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 581– 581.

(6) Heck, R. F.; Nolley, J. P. Palladium-catalyzed vinylic hydrogen substitution reactions with aryl, benzyl, and styryl halides. *J. Org. Chem.* **1972**, *37*, 2320–2322.

(7) The Mizoroki-Heck Reaction; Oestreich, M., Ed.; Wiley: Chichester, U.K., 2009.

(8) de Meijere, A.; Meyer, F. E. Fine Feathers Make Fine Birds: The Heck Reaction in Modern Garb. *Angew. Chem., Int. Ed. Engl.* **1995**, *33*, 2379–2411.

(9) Beletskaya, I. P.; Cheprakov, A. V. The Heck reaction as a sharpening stone of palladium catalysis. *Chem. Rev.* **2000**, *100*, 3009–3066.

(10) Alonso, F.; Beletskaya, I. P.; Yus, M. Non-conventional methodologies for transition-metal catalysed carbon-carbon coupling: a critical overview. Part 1: The Heck reaction. *Tetrahedron* **2005**, *61*, 11771–11835.

(11) Sigman, M. S.; Werner, E. W. Imparting Catalyst Control upon Classical Palladium-Catalyzed Alkenyl C-H Bond Functionalization Reactions. *Acc. Chem. Res.* **2012**, *45*, 874–884.

(12) Beletskaya, I. P.; Cheprakov, A. V. Modern Heck Reactions. In *New Trends in Cross-Coupling: Theory and Applications;* Colacot, T., Ed.; The Royal Society of Chemistry: Cambridge, U.K., 2015; pp 335–478.

(13) Nakamura, I.; Yamamoto, Y. Transition-Metal-Catalyzed Reactions in Heterocyclic Synthesis. *Chem. Rev.* 2004, 104, 2127–2198.

(14) Prashad, M. Palladium-catalyzed Heck arylations in the synthesis of active pharmaceutical ingredients. *Top. Organomet. Chem.* **2004**, *6*, 181–203.

(15) Tietze, L. F.; Kinzel, T. Synthesis of natural products and analogs using multiple Pd-catalyzed transformations. *Pure Appl. Chem.* **2007**, *79*, 629–650.

(16) Kotora, M.; Hessler, F.; Eignerová, B. Transition-Metal-Mediated or -Catalyzed Syntheses of Steroids and Steroid-Like Compounds. *Eur. J. Org. Chem.* **2012**, 2012, 29–42.

(17) Czajkowska-Szczykowska, D.; Morzycki, J. W.; Wojtkielewicz, A. Pd-catalyzed steroid reactions. *Steroids* **2015**, *97*, 13–44.

(18) Schiedel, M.-S.; Briehn, C. A.; Bauerle, P. C-C Cross-coupling reactions for the combinatorial synthesis of novel organic materials. *J. Organomet. Chem.* **2002**, *653*, 200–208.

(19) Tietze, L. F.; Düfert, A. Multiple Pd-catalyzed reactions in the synthesis of natural products, drugs, and materials. *Pure Appl. Chem.* **2010**, *82*, 1375–1392.

(20) Hang, C.; Wu, H.-W.; Zhu, L.-L. π -Conjugated cyanostilbenebased optoelectric functional materials. *Chin. Chem. Lett.* **2016**, 27, 1155–1165. (21) Dounay, A. B.; Overman, L. E. The Asymmetric Intramolecular Heck Reaction. *Chem. Rev.* **2003**, *103*, 2945–2963.

(22) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. Palladium-catalyzed cross-coupling reactions in total synthesis. *Angew. Chem., Int. Ed.* 2005, 44, 4442–4489.

(23) Heravi, M. M.; Hashemi, E.; Ghobadi, N. Development of Recent Total Syntheses Based on the Heck Reaction. *Curr. Org. Chem.* **2013**, *17*, 2192–2224.

(24) de Vries, J. G. The Heck reaction in the production of fine chemicals. *Can. J. Chem.* 2001, *79*, 1086–1092.

(25) de Vries, J. G. Palladium-Catalysed Coupling Reactions. In Organometallics as Catalysts in the Fine Chemical Industry; Beller, M., Blaser, H.-U., Eds.; Springer: Berlin, Heidelberg, 2012; pp 1–34.

(26) Beller, M.; Dumrath, A.; Lübbe, C. Palladium-Catalyzed Cross-Coupling Reactions-Industrial Applications. In *Palladium-Catalyzed Coupling Reactions: Practical Aspects and Future Developments*; Molnár, Á., Ed.; Wiley-VCH: Weinheim, Germany, 2013; pp 445–489.

(27) Biajoli, A. F. P.; Schwalm, C. S.; Limberger, J.; Claudino, T. S.; Monteiro, A. L. Recent progress in the use of Pd-catalyzed C-C crosscoupling reactions in the synthesis of pharmaceutical compounds. *J. Braz. Chem. Soc.* **2014**, *25*, 2186–2214.

(28) Farina, V. High-turnover palladium catalysts in cross-coupling and Heck chemistry: A critical overview. *Adv. Synth. Catal.* **2004**, *346*, 1553–1582.

(29) Kumar, A.; Rao, G. K.; Kumar, S.; Singh, A. K. Formation and Role of Palladium Chalcogenide and Other Species in Suzuki– Miyaura and Heck C–C Coupling Reactions Catalyzed with Palladium(II) Complexes of Organochalcogen Ligands: Realities and Speculations. *Organometallics* **2014**, *33*, 2921–2943.

(30) Beller, M.; Riermeier, T. H. First efficient palladium-catalyzed Heck reactions of aryl bromides with alkyl methacrylate. *Tetrahedron Lett.* **1996**, *37*, 6535–6538.

(31) Stambuli, J. P.; Stauffer, S. R.; Shaughnessy, K. H.; Hartwig, J. F. Screening of homogeneous catalysts by fluorescence resonance energy transfer. Identification of catalysts for room-temperature heck reactions. *J. Am. Chem. Soc.* **2001**, *123*, 2677–2678.

(32) Littke, A. F.; Fu, G. C. A versatile catalyst for heck reactions of aryl chlorides and aryl bromides under mild conditions. *J. Am. Chem. Soc.* **2001**, *123*, 6989–7000.

(33) Lee, J.-Y.; Shen, J.-S.; Tzeng, R.-J.; Lu, I. C.; Lii, J.-H.; Hu, C.-H.; Lee, H. M. Well-defined palladium(0) complexes bearing Nheterocyclic carbene and phosphine moieties: efficient catalytic applications in the Mizoroki–Heck reaction and direct C–H functionalization. *Dalton Trans.* **2016**, *45*, 10375–10388.

(34) Gründemann, S.; Albrecht, M.; Loch, J. A.; Faller, J. W.; Crabtree, R. H. Tridentate carbene CCC and CNC pincer palladium(II) complexes: Structure, fluxionality, and catalytic activity. *Organometallics* **2001**, *20*, 5485–5488.

(35) Hillier, A. C.; Grasa, G. A.; Viciu, M. S.; Lee, H. M.; Yang, C.; Nolan, S. P. Catalytic cross-coupling reactions mediated by palladium/ nucleophilic carbene systems. *J. Organomet. Chem.* **2002**, *6*53, 69–82.

(36) Selvakumar, K.; Zapf, A.; Beller, M. New Palladium Carbene Catalysts for the Heck Reaction of Aryl Chlorides in Ionic Liquids. *Org. Lett.* **2002**, *4*, 3031–3033.

(37) Lebel, H.; Janes, M. K.; Charette, A. B.; Nolan, S. P. Structure and Reactivity of "Unusual" N-Heterocyclic Carbene (NHC) Palladium Complexes Synthesized from Imidazolium Salts. J. Am. Chem. Soc. 2004, 126, 5046–5047.

(38) Hahn, F. E.; Jahnke, M. C.; Gomez-Benitez, V.; Morales-Morales, D.; Pape, T. Synthesis and Catalytic Activity of Pincer-Type Bis(benzimidazolin-2-ylidene) Palladium Complexes. *Organometallics* **2005**, *24*, 6458–6463.

(39) Ahrens, S.; Zeller, A.; Taige, M. A.; Strassner, T. Extension of the Alkane Bridge in BisNHC-Palladium-Chloride Complexes. Synthesis, Structure, and Catalytic Activity. *Organometallics* **2006**, *25*, 5409–5415.

(40) Taige, M. A.; Zeller, A.; Ahrens, S.; Goutal, S.; Herdtweck, E.; Strassner, T. New Pd-NHC-complexes for the Mizoroki–Heck reaction. J. Organomet. Chem. 2007, 692, 1519–1529.

Article

(41) Meyer, D.; Taige, M. A.; Zeller, A.; Hohlfeld, K.; Ahrens, S.; Strassner, T. Palladium Complexes with Pyrimidine-Functionalized N-Heterocyclic Carbene Ligands: Synthesis, Structure and Catalytic Activity. *Organometallics* **2009**, *28*, 2142–2149.

(42) Sie, M. H.; Hsieh, Y. H.; Tsai, Y. H.; Wu, J. R.; Chen, S. J.; Kumar, P. V.; Lii, J. H.; Lee, H. M. A heteroleptic palladium(II) complex containing a bidentate carbene/amido ligand and 3-(trifluoromethyl)-5-(2-pyridyl)pyrazolate: Fast catalyst activation in the heck coupling reaction. *Organometallics* **2010**, *29*, 6473–6481.

(43) Fortman, G. C.; Nolan, S. P. N-Heterocyclic carbene (NHC) ligands and palladium in homogeneous cross-coupling catalysis: a perfect union. *Chem. Soc. Rev.* **2011**, *40*, 5151–5169.

(44) Lin, Y.-C.; Hsueh, H.-H.; Kanne, S.; Chang, L.-K.; Liu, F.-C.; Lin, I. J. B.; Lee, G.-H.; Peng, S.-M. Efficient PEPPSI-Themed Palladium N-Heterocyclic Carbene Precatalysts for the Mizoroki– Heck Reaction. *Organometallics* **2013**, *32*, 3859–3869.

(45) Hopkinson, M. N.; Richter, C.; Schedler, M.; Glorius, F. An overview of N-heterocyclic carbenes. *Nature* **2014**, *510*, 485–496.

(46) Gallop, C.; Zinser, C.; Guest, D.; Navarro, O. Mizoroki–Heck Reactions Catalysed by (N-Heterocyclic carbene)PdCl2(Et3N) Complexes. *Synlett* **2014**, *25*, 2225–2228.

(47) Hsu, Y. C.; Shen, J. S.; Lin, B. C.; Chen, W. C.; Chan, Y. T.; Ching, W. M.; Yap, G. P. A.; Hsu, C. P.; Ong, T. G. Synthesis and isolation of an acyclic tridentate bis(pyridine)carbodicarbene and studies on its structural implications and reactivities. *Angew. Chem., Int. Ed.* **2015**, *54*, 2420–2424.

(48) Gürbüz, N.; Karaca, E. Ö.; Özdemir, İ.; Çetinkaya, B. Cross coupling reactions catalyzed by (NHC)Pd(II) complexes. *Turk. J. Chem.* **2015**, *39*, 1115–1157.

(49) Balinge, K. R.; Bhagat, P. R. Palladium-N-heterocyclic carbene complexes for the Mizoroki–Heck reaction: An appraisal. *C. R. Chim.* **2017**, *20*, 773–804.

(50) Astakhov, A. V.; Khazipov, O. V.; Chernenko, A. Y.; Pasyukov, D. V.; Kashin, A. S.; Gordeev, E. G.; Khrustalev, V. N.; Chernyshev, V. M.; Ananikov, V. P. A New Mode of Operation of Pd-NHC Systems Studied in a Catalytic Mizoroki–Heck Reaction. *Organometallics* **2017**, 36, 1981–1992.

(51) Tsuji, Y.; Fujihara, T. Homogeneous nanosize palladium catalysts. *Inorg. Chem.* 2007, *46*, 1895–1902.

(52) Balanta, A.; Godard, C.; Claver, C. Pd nanoparticles for C-C coupling reactions. *Chem. Soc. Rev.* **2011**, *40*, 4973–4973.

(53) Wang, W.; Yang, Q.; Zhou, R.; Fu, H. Y.; Li, R. X.; Chen, H.; Li, X. J. Palladium nanoparticles generated from allylpalladium chloride in situ: A simple and highly efficient catalytic system for Mizoroki–Heck reactions. *J. Organomet. Chem.* **2012**, *697*, 1–5.

(54) Leyva-Pérez, A.; Oliver-Meseguer, J.; Rubio-Marqués, P.; Corma, A. Water-stabilized three- and four-atom palladium clusters as highly active catalytic species in ligand-free C-C cross-coupling reactions. *Angew. Chem., Int. Ed.* **2013**, *52*, 11554–11559.

(55) Jeffery, T. Palladium-catalysed Vinylation of Organic Halides under Solid-Liquid Phase Transfer Conditions. J. Chem. Soc., Chem. Commun. **1984**, 1287–1289.

(56) Schmidt, A. F.; Smirnov, V. V. Simple method for enhancement of the ligand-free palladium catalyst activity in the Heck reaction with non-activated bromoarenes. *J. Mol. Catal. A: Chem.* **2003**, *203*, 75–78. (57) De Vries, A. H. M.; Parlevliet, F. J.; Schmieder-van De Vondervoort, L.; Mommers, J. H. M.; Henderickx, H. J. W.; Walet, M. A. M.; De Vries, J. G. A Practical Recycle of a Ligand-Free Palladium

Catalyst for Heck Reactions. *Adv. Synth. Catal.* **2002**, 344, 996–1002. (58) de Vries, A. H. M.; Mulders, J. M. C. A.; Mommers, J. H. M.; Henderickx, H. J. W.; de Vries, J. G. Homeopathic Ligand-Free Palladium as a Catalyst in the Head Paratism A Comparison with a

Palladium as a Catalyst in the Heck Reaction. A Comparison with a Palladacycle. *Org. Lett.* **2003**, *5*, 3285–3288. (59) Reetz, M. T.; de Vries, J. G. Ligand-free Heck reactions using

(S) Reetz, M. 1.; de Vries, J. G. Ligand-free Fleck reactions using low Pd-loading. *Chem. Commun.* 2004, 1559–1563.

(60) Albéniz, A. C.; Espinet, P.; Martín-Ruiz, B.; Milstein, D. Catalytic system for the Heck reaction of fluorinated haloaryls. *Organometallics* **2005**, *24*, 3679–3684.

(61) Fairlamb, I. J. S.; Kapdi, A. R.; Lee, A. F.; McGlacken, G. P.; Weissburger, F.; De Vries, A. H. M.; Schmieder-Van De Vondervoort, L. Exploiting noninnocent (E,E)-dibenzylideneacetone (dba) effects in palladium(0)-mediated cross-coupling reactions: Modulation of the electronic properties of dba affects catalyst activity and stability in ligand and ligand-free reaction systems. *Chem. - Eur. J.* **2006**, *12*, 8750–8761.

(62) Palmisano, G.; Bonrath, W.; Boffa, L.; Garella, D.; Barge, A.; Cravotto, G. Heck reactions with very low ligandless catalyst loads accelerated by microwaves or simultaneous microwaves/ultrasound irradiation. *Adv. Synth. Catal.* **2007**, *349*, 2338–2344.

(63) Kleist, W.; Pröckl, S. S.; Köhler, K. Heck reactions of aryl chlorides catalyzed by ligand free palladium salts. *Catal. Lett.* **2008**, *125*, 197–200.

(64) Tao, L.-M.; Li, Q.-G.; Liu, W.-Q.; Zhou, Y.; Zhou, J.-F. An efficient and reusable PdCl₂/TBAF system for the Heck reaction under ligand- and solvent-free conditions. *J. Chem. Res., Synop.* **2010**, 2010, 2010, 211–213.

(65) Amini, M.; Bagherzadeh, M.; Moradi-Shoeili, Z.; Boghaei, D. M. Pd(OAc)2 without added ligand as an active catalyst for Mizoroki–Heck reaction in aqueous media. *RSC Adv.* **2012**, *2*, 12091–12091.

(66) Jadhav, S.; Kumbhar, A.; Rode, C. V.; Salunkhe, R. S. Ligandfree Pd Catalyzed Cross-coupling Reactions in Aqueous Hydrotropic Medium. *Green Chem.* **2016**, *18*, 1898–1911.

(67) Kaufmann, D. E.; Nouroozian, M.; Henze, H. Molten Salts as an Efficient Medium for Palladium-Catalyzed C-C Coupling Reactions. *Synlett* **1996**, *1996*, 1091–1092.

(68) Herrmann, W. A.; Böhm, V. P. W. Heck reaction catalyzed by phospha-palladacycles in non-aqueous ionic liquids. *J. Organomet. Chem.* **1999**, *572*, 141–145.

(69) Böhm, V. P. W.; Herrmann, W. A. Nonaqueous ionic liquids: superior reaction media for the catalytic Heck-vinylation of chloroarenes. *Chem. - Eur. J.* **2000**, *6*, 1017–1025.

(70) Zou, G.; Wang, Z.; Zhu, J.; Tang, J.; He, M. Y. Developing an ionic medium for ligandless-palladium-catalysed Suzuki and Heck couplings. *J. Mol. Catal. A: Chem.* **2003**, *206*, 193–198.

(71) Singh, R.; Sharma, M.; Mamgain, R.; Rawat, D. S. Ionic liquids: A versatile medium for palladium-catalyzed reactions. *J. Braz. Chem. Soc.* **2008**, *19*, 357–379.

(72) Wang, L.; Li, H.; Li, P. Task-specific ionic liquid as base, ligand and reaction medium for the palladium-catalyzed Heck reaction. *Tetrahedron* **2009**, *65*, 364–368.

(73) Bellina, F.; Chiappe, C. The heck reaction in ionic liquids: Progress and challenges. *Molecules* **2010**, *15*, 2211–2245.

(74) Gaikwad, D. S.; Park, Y.; Pore, D. M. A novel hydrophobic fluorous ionic liquid for ligand-free Mizoroki–Heck reaction. *Tetrahedron Lett.* **2012**, *53*, 3077–3081.

(75) LeBlond, C. R.; Andrews, A. T.; Sun, Y.; Sowa, J. R. Activation of Aryl Chlorides for Suzuki Cross-Coupling by Ligandless, Heterogeneous Palladium. *Org. Lett.* **2001**, *3*, 1555–1557.

(76) Zapf, A.; Beller, M. Palladium catalyst systems for cross-coupling reactions of aryl chlorides and olefins. *Chem. - Eur. J.* **2001**, *7*, 2908–2915.

(77) Bedford, R. B.; Cazin, C. S. J.; Holder, D. The development of palladium catalysts for C-C and C-heteroatom bond forming reactions of aryl chloride substrates. *Coord. Chem. Rev.* **2004**, *248*, 2283–2321.

(78) Pröckl, S. S.; Kleist, W.; Köhler, K. Design of highly active heterogeneous palladium catalysts for the activation of aryl chlorides in Heck reactions. *Tetrahedron* **2005**, *61*, 9855–9859.

(79) Srinivas, P.; Likhar, P. R.; Maheswaran, H.; Sridhar, B.; Ravikumar, K.; Kantam, M. L. N4-tetradentate dicarboxyamidate/ dipyridyl palladium complexes as robust catalysts for the Heck reaction of deactivated aryl chlorides. *Chem. - Eur. J.* **2009**, *15*, 1578–1581.

(80) Lee, D.-H.; Taher, A.; Hossain, S.; Jin, M.-J. An Efficient and General Method for the Heck and Buchwald-Hartwig Coupling Reactions of Aryl Chlorides. *Org. Lett.* **2011**, *13*, 5540–5543.

(81) Jutand, A. The Use of Conductivity Measurements for the Characterization of Cationic Palladium(II) Complexes and for the

Determination of Kinetic and Thermodynamic Data in Palladium-Catalyzed Reactions. *Eur. J. Inorg. Chem.* 2003, 2003, 2017–2040.

(82) Phan, N. T. S.; Van Der Sluys, M.; Jones, C. W. On the Nature of the Active Species in Palladium Catalyzed Mizoroki-Heck and Suzuki-Miyaura Couplings – Homogeneous or Heterogeneous Catalysis, A Critical Review. *Adv. Synth. Catal.* **2006**, *348*, 609–679.

(83) Schmidt, A. F.; Al Halaiqa, A.; Smirnov, V. V. Interplays between reactions within and without the catalytic cycle of the Heck reaction as a clue to the optimization of the synthetic protocol. *Synlett* **2006**, 2006, 2861–2878.

(84) Knowles, J. P.; Whiting, A. The Heck-Mizoroki cross-coupling reaction: a mechanistic perspective. *Org. Biomol. Chem.* **2007**, *5*, 31–44.

(85) Rauf, W.; Brown, J. M. Reactive intermediates in catalytic alkenylation; pathways for Mizoroki–Heck, oxidative Heck and Fujiwara-Moritani reactions. *Chem. Commun.* **2013**, *49*, 8430–8440.

(86) Amatore, C.; Jutand, A. Mechanistic and kinetic studies of palladium catalytic systems. *J. Organomet. Chem.* **1999**, *576*, 254–278.

(87) Amatore, C.; Jutand, A. Anionic Pd(0) and Pd(II) Intermediates in Palladium-Catalyzed Heck and Cross-Coupling Reactions. *Acc. Chem. Res.* **2000**, 33, 314–321.

(88) Jutand, A. Dual role of nucleophiles in palladium-catalyzed Heck, Stille, and Sonogashira reactions. *Pure Appl. Chem.* **2004**, *76*, 565–576.

(89) Kozuch, S.; Shaik, S.; Jutand, A.; Amatore, C. Active anionic zero-valent palladium catalysts: Characterization by density functional calculations. *Chem. - Eur. J.* **2004**, *10*, 3072–3080.

(90) Goossen, L. J.; Koley, D.; Hermann, H.; Thiel, W. The mechanism of the oxidative addition of aryl halides to Pd-catalysts: a DFT investigation. *Chem. Commun.* **2004**, 2141–2143.

(91) Goossen, L. J.; Koley, D.; Hermann, H. L.; Thiel, W. The palladium-catalyzed cross-coupling reaction of carboxylic anhydrides with arylboronic acids: A DFT study. *J. Am. Chem. Soc.* **2005**, *127*, 11102–11114.

(92) Goossen, L. J.; Koley, D.; Hermann, H. L.; Thiel, W. Palladium Monophosphine Intermediates in Catalytic Cross-Coupling Reactions: A DFT Study. *Organometallics* **2006**, *25*, 54–67.

(93) Carrow, B. P.; Hartwig, J. F. Ligandless, anionic, arylpalladium halide intermediates in the heck reaction. *J. Am. Chem. Soc.* **2010**, *132*, 79–81.

(94) Proutiere, F.; Schoenebeck, F. Solvent effect on palladiumcatalyzed cross-coupling reactions and implications on the active catalytic species. *Angew. Chem., Int. Ed.* **2011**, *50*, 8192–8195.

(95) Schmidt, A. F.; Kurokhtina, A. A.; Larina, E. V.; Yarosh, E. V.; Lagoda, N. A. Direct Kinetic Evidence for the Active Anionic Palladium(0) and Palladium(II) Intermediates in the Ligand-Free Heck Reaction with Aromatic Carboxylic Anhydrides. *Organometallics* **2017**, *36*, 3382–3386.

(96) Zawartka, W.; Trzeciak, A. M.; Ziółkowski, J. J.; Lis, T.; Ciunik, Z.; Pernak, J. Methoxycarbonylation of iodobenzene in ionic liquids. A case of inhibiting effect of imidazolium halides. *Adv. Synth. Catal.* **2006**, 348, 1689–1698.

(97) Yang, X.; Fei, Z.; Geldbach, T. J.; Phillips, A. D.; Hartinger, C. G.; Li, Y.; Dyson, P. J. Suzuki coupling reactions in etherfunctionalized ionic liquids: The importance of weakly interacting cations. *Organometallics* **2008**, *27*, 3971–3977.

(98) Zawartka, W.; Gniewek, A.; Trzeciak, A. M.; Ziółkowski, J. J.; Pernak, J. PdII square planar complexes of the type [IL]2[PdX4] as catalyst precursors for the Suzuki-Miyaura cross-coupling reaction. The first in situ ESI-MS evidence of [(IL)xPd3] clusters formation. *J. Mol. Catal. A: Chem.* **2009**, 304, 8–15.

(99) Song, H.; Yan, N.; Fei, Z.; Kilpin, K. J.; Scopelliti, R.; Li, X.; Dyson, P. J. Evaluation of ionic liquid soluble imidazolium tetrachloropalladate pre-catalysts in Suzuki coupling reactions. *Catal. Today* **2012**, *183*, 172–177.

(100) Silarska, E.; Trzeciak, A. M.; Pernak, J.; Skrzypczak, A. [IL]2[PdCl4] complexes (IL = imidazolium cation) as efficient catalysts for Suzuki–Miyaura cross-coupling of aryl bromides and aryl chlorides. *Appl. Catal., A* **2013**, *466*, 216–223.

(101) Guest, D.; Menezes da Silva, V. H.; de Lima Batista, A. P.; Roe, S. M.; Braga, A. A. C.; Navarro, O. (N-Heterocyclic Carbene)-Palladate Complexes in Anionic Mizoroki–Heck Coupling Cycles: A Combined Experimental and Computational Study. *Organometallics* **2015**, *34*, 2463–2470.

(102) Silarska, E.; Trzeciak, A. M. Oxygen-promoted coupling of arylboronic acids with olefins catalyzed by [CA]2[PdX4] complexes without a base. *J. Mol. Catal. A: Chem.* **2015**, *408*, 1–11.

(103) Bivona, L. A.; Giacalone, F.; Carbonell, E.; Gruttadauria, M.; Aprile, C. Proximity Effect using a Nanocage Structure: Polyhedral Oligomeric Silsesquioxane-Imidazolium Tetrachloropalladate Salt as a Precatalyst for the Suzuki-Miyaura Reaction in Water. *ChemCatChem* **2016**, *8*, 1685–1691.

(104) Silarska, E.; Majchrzak, M.; Marciniec, B.; Trzeciak, A. M. Efficient functionalization of olefins by arylsilanes catalyzed by palladium anionic complexes. *J. Mol. Catal. A: Chem.* **2017**, *426*, 458–464.

(105) Schroeter, F.; Soellner, J.; Strassner, T. Cross-Coupling Catalysis by an Anionic Palladium Complex. *ACS Catal.* **2017**, *7*, 3004–3009.

(106) Albert, K.; Gisdakis, P.; Rösch, N. On C-C Coupling by Carbene-Stabilized Palladium Catalysts: A Density Functional Study of the Heck Reaction. *Organometallics* **1998**, *17*, 1608–1616.

(107) Sundermann, A.; Uzan, O.; Martin, J. M. L. Computational study of a new Heck reaction mechanism catalyzed by palladium(II/IV) species. *Chem. - Eur. J.* **2001**, *7*, 1703–1711.

(108) Senn, H. M.; Ziegler, T. Oxidative Addition of Aryl Halides to Palladium(0) Complexes: A Density-Functional Study Including Solvation. *Organometallics* **2004**, *23*, 2980–2988.

(109) Lee, M.-T.; Lee, H. M.; Hu, C.-H. A Theoretical Study of the Heck Reaction: N-Heterocyclic Carbene versus Phosphine Ligands. *Organometallics* **2007**, *26*, 1317–1324.

(110) Svennebring, A.; Sjoeberg, P. J. R.; Larhed, M.; Nilsson, P. A mechanistic study on modern palladium catalyst precursors as new gateways to Pd(0) in cationic Heck reactions. *Tetrahedron* **2008**, *64*, 1808–1812.

(111) Surawatanawong, P.; Fan, Y.; Hall, M. B. Density functional study of the complete pathway for the Heck reaction with palladium diphosphines. *J. Organomet. Chem.* **2008**, *693*, 1552–1563.

(112) Wang, C.; Fu, Y.; Li, Z.; Guo, Q.-X. Theoretical study on catalyst activation of palladacycles in Heck reaction. *Chin. J. Chem.* 2008, 26, 358–362.

(113) Baecktorp, C.; Norrby, P.-O. A DFT comparison of the neutral and cationic Heck pathways. *Dalton Trans.* **2011**, *40*, 11308–11314.

(114) Wu, X.-F.; Jiao, H.; Neumann, H.; Beller, M. Progress in Carbonylative-Heck Reactions of Aryl Bromides: Catalysis and DFT Studies. *ChemCatChem* **2011**, *3*, 726–733.

(115) Peng, Q.; Yan, H.; Zhang, X.; Wu, Y.-D. Conjugate Addition vs Heck Reaction: A Theoretical Study on Competitive Coupling Catalyzed by Isoelectronic Metal (Pd(II) and Rh(I). *J. Org. Chem.* **2012**, 77, 7487–7496.

(116) Sumimoto, M.; Kuroda, T.; Yokogawa, D.; Yamamoto, H.; Hori, K. Theoretical study on a new active species for the Pd(II)catalyzed Mizoroki–Heck reaction. *J. Organomet. Chem.* **2012**, *710*, 26–35.

(117) Nilsson Lill, S. O.; Ryberg, P.; Rein, T.; Bennstroem, E.; Norrby, P.-O. tBu or not tBu? *Chem. - Eur. J.* **2012**, *18*, 1640–1649. (118) Derat, E.; Maestri, G. Understanding palladium complexes structures and reactivities: beyond classical point of view. *Wiley Interdisciplinary Reviews: Computational Molecular Science* **2013**, *3*, 529–541.

(119) Allolio, C.; Strassner, T. Palladium Complexes with Chelating Bis-NHC Ligands in the Mizoroki–Heck Reaction – Mechanism and Electronic Effects, a DFT Study. *J. Org. Chem.* **2014**, *79*, 12096–12105.

(120) Dang, Y.; Qu, S.; Wang, Z.-X.; Wang, X. A Computational Mechanistic Study of an Unprecedented Heck-Type Relay Reaction: Insight into the Origins of Regio- and Enantioselectivities. *J. Am. Chem. Soc.* **2014**, *136*, 986–998.

(121) Gruber, R.; Fleurat-Lessard, P. Density Functional Study of Indole Formation by an Intramolecular Heck Reaction. *Organometallics* **2014**, *33*, 1996–2003.

(122) Xu, L.; Hilton, M. J.; Zhang, X.; Norrby, P.-O.; Wu, Y.-D.; Sigman, M. S.; Wiest, O. Mechanism, Reactivity, and Selectivity in Palladium-Catalyzed Redox-Relay Heck Arylations of Alkenyl Alcohols. J. Am. Chem. Soc. **2014**, *136*, 1960–1967.

(123) Sperger, T.; Sanhueza, I. A.; Kalvet, I.; Schoenebeck, F. Computational Studies of Synthetically Relevant Homogeneous Organometallic Catalysis Involving Ni, Pd, Ir, and Rh: An Overview of Commonly Employed DFT Methods and Mechanistic Insights. *Chem. Rev.* 2015, *115*, 9532–9586.

(124) Fiebig, L.; Held, J.; Schmalz, H.-G.; Schaefer, M. Individual steps of the Mizoroki–Heck reaction and intrinsic reactivity of intermediate organopalladium complexes studied in the gas phase. *Eur. J. Mass Spectrom.* **2015**, *21*, 623–633.

(125) Menezes da Silva, V. H.; Braga, A. A. C.; Cundari, T. R. N-Heterocyclic Carbene Based Nickel and Palladium Complexes: A DFT Comparison of the Mizoroki–Heck Catalytic Cycles. *Organometallics* **2016**, *35*, 3170–3181.

(126) Liu, L.; Liu, Y.; Ling, B.; Bi, S. Mechanistic investigation into Et₃N C-H activation and chemoselectivity by Pd-Catalyzed intramolecular heck reaction of N-Vinylacetamides. *J. Organomet. Chem.* **2017**, 827, 56–66.

(127) Menezes da Silva, V. H.; de Lima Batista, A. P.; Navarro, O.; Braga, A. A. C. Theoretical study on selectivity trends in (Nheterocyclic carbene)-Pd catalyzed mizoroki-heck reactions: Exploring density functionals methods and molecular models. *J. Comput. Chem.* **2017**, 38, 2371.

(128) Köhler, K.; Heidenreich, R. G.; Krauter, J. G. E.; Pietsch, J. Highly active palladium/activated carbon catalysts for heck reactions: Correlation of activity, catalyst properties, and Pd leaching. *Chem.* - *Eur. J.* **2002**, *8*, 622–631.

(129) Bergbreiter, D. E.; Osburn, P. L.; Frels, J. D. Mechanistic studies of SCS-Pd complexes used in Heck catalysis. *Adv. Synth. Catal.* **2005**, 347, 172–184.

(130) Liu, C.; Ni, Q.; Hu, P.; Qiu, J. Oxygen-promoted PdCl₂catalyzed ligand-free Suzuki reaction in aqueous media. *Org. Biomol. Chem.* **2011**, *9*, 1054–1060.

(131) Lin, Y.; Finke, R. G. A More General Approach to Distinguishing "Homogeneous" from "Heterogeneous" Catalysis: Discovery of Polyoxoanion- and Bu₄N⁺-Stabilized, Isolable and Redissolvable, High-Reactivity Ir_{~190-450} Nanocluster Catalysts. *Inorg. Chem.* **1994**, 33, 4891–4910.

(132) Bianchini, C.; Meli, A.; Moneti, S.; Oberhauser, W.; Vizza, F.; Herrera, V.; Fuentes, A.; Sánchez-Delgado, R. A. Mimicking the HDS activity of ruthenium-based catalysts 2: The hydrogenation of benzo[b]thiophene to 2,3-dihydrobenzo[b]thiophene. J. Am. Chem. Soc. **1999**, 121, 7071–7080.

(133) Widegren, J. A.; Finke, R. G. Anisole hydrogenation with wellcharacterized polyoxoanion- and tetrabutylammonium-stabilized Rh(0) nanoclusters: Effects of added water and acid, plus enhanced catalytic rate, lifetime, and partial hydrogenation selectivity. *Inorg. Chem.* **2002**, *41*, 1558–1572.

(134) Amatore, C.; Le Duc, G.; Jutand, A. Mechanism of palladiumcatalyzed Suzuki-Miyaura reactions: multiple and antagonistic roles of anionic "bases" and their countercations. *Chem. - Eur. J.* **2013**, *19*, 10082–10093.

(135) Lennox, A. J. J.; Lloyd-Jones, G. C. Transmetalation in the Suzuki – Miyaura Coupling: The Fork in the Trail. *Angew. Chem., Int. Ed.* **2013**, *52*, 7362–7370.

(136) Thomas, A. A.; Denmark, S. E. Pre-transmetalation intermediates in the Suzuki-Miyaura reaction revealed: The missing link. *Science* **2016**, 352, 329–332.

(137) Rosner, T.; Le Bars, J.; Pfaltz, A.; Blackmond, D. G. Kinetic studies of heck coupling reactions using palladacycle catalysts: Experimental and kinetic modeling of the role of dimer species. *J. Am. Chem. Soc.* **2001**, *123*, 1848–1855.

(138) Adrio, L. A.; Nguyen, B. N.; Guilera, G.; Livingston, A. G.; Hii, K. K. Speciation of Pd(OAc)₂ in ligandless Suzuki–Miyaura reactions. *Catal. Sci. Technol.* **2012**, *2*, 316–323.

(139) Amatore, C.; Jutand, A.; Medeiros, M. J. Formation of zerovalent palladium from the cationic complex Pd(PPh3)2(BF4)2 in the presence of PPh3 and water in DMF. *New J. Chem.* **1996**, *20*, 1143–1148.

(140) Amatore, C.; El Kaïm, L.; Grimaud, L.; Jutand, A.; Meignié, A.; Romanov, G. Kinetic data on the synergetic role of amines and water in the reduction of phosphine-ligated palladium(II) to palladium(0). *Eur. J. Org. Chem.* **2014**, 2014, 4709–4713.

(141) Machado, A. H. L.; Milagre, H. M. S.; Eberlin, L. S.; Sabino, A. A.; Correia, C. R. D.; Eberlin, M. N. "Dba-free" palladium intermediates of the Heck-Matsuda reaction. *Org. Biomol. Chem.* **2013**, *11*, 3277–3281.

(142) McCrindle, R.; Ferguson, G.; Arsenault, G. J.; McAlees, A. J. Reaction of Tertiary Amines with Bis(benzonitrile)dichloropalladium-(II). Formation and Crystal Structure Analysis of Di-µ-chloro-dichlorobis[2-(N,N-di-isopropyliminio)ethyl-C]dipalladium(II). J. Chem. Soc., Chem. Commun. **1983**, 571–572.

(143) Shmidt, A. F.; Khalaika, A.; Bylkova, V. G. Role of a Base in the Catalytic Arylation of Olefins. *Kinet. Catal.* **1998**, *39*, 194–199.

(144) Trzeciak, A. M.; Ciunik, Z.; Ziółkowski, J. J. Synthesis of Palladium Benzyl Complexes from the Reaction of $PdCl_2[P(OPh)_3]_2$ with Benzyl Bromide and Triethylamine: Important Intermediates in Catalytic Carbonylation. *Organometallics* **2002**, *21*, 132–137.

(145) Jiang, M. Y.; Shin, J.-Y.; Patrick, B. O.; Dolphin, D. Structure, formation and catalytic studies of a meso-palladioporphyrin intermediate in a Heck reaction. *Dalton Trans.* **2008**, 2598–2598.

(146) Muzart, J. On the behavior of amines in the presence of Pd0 and PdII species. J. Mol. Catal. A: Chem. 2009, 308, 15–24.

(147) Jeffery, T. Heck-type Reactions in Water. *Tetrahedron Lett.* **1994**, 35, 3051–3054.

(148) Deraedt, C.; Astruc, D. Homeopathic" Palladium Nanoparticle Catalysis of Cross Carbon-Carbon Coupling Reactions. *Acc. Chem. Res.* **2014**, 47, 494–503.

(149) Jin, M.; Liu, H.; Zhang, H.; Xie, Z.; Liu, J.; Xia, Y. Synthesis of Pd nanocrystals enclosed by {100} facets and with sizes < 10 nm for application in CO oxidation. *Nano Res.* **2011**, *4*, 83–91.

(150) de Vries, J. G. A unifying mechanism for all high-temperature Heck reactions. The role of palladium colloids and anionic species. *Dalton Trans.* **2006**, 421–429.

(151) Fagnou, K.; Lautens, M. Halide Effects in Transition Metal Catalysis. *Angew. Chem., Int. Ed.* **2002**, *41*, 26–47.

(152) Fairlamb, I. J. S.; Taylor, R. J. K.; Serrano, J. L.; Sanchez, G. Halide and pseudohalide effects in Pd-catalysed cross-coupling reactions. *New J. Chem.* **2006**, *30*, 1695–1695.

(153) Herrmann, W. A.; Brossmer, C.; Öfele, K.; Reisinger, C.-P.; Priermeier, T.; Beller, M.; Fischer, H. Palladacycles as Structurally Defined Catalysts for the Heck Olefination of Chloro- and Bromoarenes. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1844–1848.

(154) Calò, V. Regio- and stereo-selective carbon-carbon bond formation in ionic liquids. *J. Mol. Catal. A: Chem.* **2004**, *214*, 45–56. (155) Tao, L.-M.; Li, Q.-G.; Liu, W.-Q.; Zhou, Y.; Zhou, J.-F. Water-promoted palladium-catalysed Heck cross-coupling reactions of aryl halides with alkenes in TBAB. *J. Chem. Res.* **2011**, *35*, 154–156.

(156) Gao, T.-T.; Jin, A.-P.; Shao, L.-X. N-Heterocyclic carbenepalladium(II)-1-methylimidazole complex catalyzed Mizoroki–Heck reaction of aryl chlorides with styrenes. *Beilstein J. Org. Chem.* **2012**, *8*, 1916–1919.

(157) Zhao, Y.; Truhlar, D. G. Density functionals with broad applicability in chemistry. *Acc. Chem. Res.* **2008**, *41*, 157–167.

(158) Hariharan, P. C.; Pople, J. A. The influence of polarization functions on molecular orbital hydrogenation energies. *Theor. Chim. Acta* **1973**, *28*, 213–222.

(159) Krishnan, R.; Binkley, J. S.; Seeger, R.; Pople, J. A. Selfconsistent molecular orbital methods. XX. A basis set for correlated wave functions. *J. Chem. Phys.* **1980**, *72*, 650–654. (160) Francl, M. M.; Pietro, W. J.; Hehre, W. J.; Binkley, J. S.; Gordon, M. S.; DeFrees, D. J.; Pople, J. A. Self-consistent molecular orbital methods. XXIII. A polarization-type basis set for second-row elements. *J. Chem. Phys.* **1982**, *77*, 3654–3665.

(161) Clark, T.; Chandrasekhar, J.; Spitznagel, G. W.; Schleyer, P. v. R. Efficient diffuse function-augmented basis sets for anion calculations. III. The 3-21+G basis set for first-row elements, Li-F. J. Comput. Chem. 1983, 4, 294–301.

(162) Marenich, A. V.; Cramer, C. J.; Truhlar, D. G. Unviersal solvation model based on solute electron density and a contiuum model of the solvent defined by the bulk dielectric constant and atomic surface tensions. *J. Phys. Chem. B* 2009, *113*, 6378–6396.

(163) Henry, P. M. Kinetics of the Oxidation of Ethylene by Aqueous Palladium(II) Chloride. *J. Am. Chem. Soc.* **1964**, *86*, 3246–3250.

(164) Backvall, J. E.; Akermark, B.; Ljunggren, S. O. Stereochemistry of the hydroxypalladation step in the Wacker process. *J. Chem. Soc., Chem. Commun.* **1977**, 264–265.

(165) Baeckvall, J. E.; Akermark, B.; Ljunggren, S. O. Stereochemistry And Mechanism For The Palladium(II)-Catalyzed Oxidation Of Ethene In Water (The Wacker Process). *J. Am. Chem. Soc.* **1979**, *101*, 2411–2416.

(166) Shmidt, A. F.; Khalaika, A. The Heck catalytic reaction as an example of the self-controlled system. *Kinet. Catal.* **1998**, *39*, 803–809. (167) Reetz, M. T.; Lohmer, G. Propylene carbonate stabilized nanostructured palladium clusters as catalysts in Heck reactions. *Chem. Commun.* **1996**, 1921–1922.

(168) Reetz, M. T.; Maase, M. Redox-Controlled Size-Selective Fabrication of Nanostructured Transition Metal Colloids. *Adv. Mater.* **1999**, *11*, 773–777.

(169) Reetz, M. T.; Westermann, E. Phosphane-free palladiumcatalyzed coupling reactions: The decisive role of Pd nanoparticles. *Angew. Chem., Int. Ed.* **2000**, *39*, 165–168.

(170) Chen, Y.; He, B.; Liu, H. Preperation and Characterization of Palladium Colloidal Nanoparticles by Thermal Decomposition of Palladium Acetate with Microwave Radiation. *J. Mater. Sci. Technol.* **2005**, *21*, 187–190.

(171) Santra, S.; Ranjan, P.; Bera, P.; Ghosh, P.; Mandal, S. K. Anchored palladium nanoparticles onto single walled carbon nanotubes: Efficient recyclable catalyst for N-containing heterocycles. *RSC Adv.* **2012**, *2*, 7523–7533.

(172) Ananikov, V. P.; Beletskaya, I. P. Toward the ideal catalyst: From atomic centers to a "cocktail" of catalysts. *Organometallics* **2012**, *31*, 1595–1604.

(173) Eremin, D. B.; Ananikov, V. P. Understanding Active Species in Catalytic Transformations: from Molecular Catalysis to Nanoparticles, Leaching, "Cocktails" of Catalysts and Dynamic Systems. *Coord. Chem. Rev.* **2017**, 346, 2–19.

(174) Pröckl, S. S.; Kleist, W.; Gruber, M. A.; Köhler, K. In situ generation of highly active dissolved palladium species from solid catalysts - A concept for the activation of aryl chlorides in the heck reaction. *Angew. Chem., Int. Ed.* **2004**, 43, 1881–1882.

(175) Weck, M.; Jones, C. W. Mizoroki–Heck coupling using immobilized molecular precatalysts: Leaching active species from Pd pincers, entrapped Pd salts, and Pd NHC complexes. *Inorg. Chem.* **2007**, *46*, 1865–1875.

(176) Köhler, K.; Kleist, W.; Pröckl, S. S. Genesis of coordinatively unsaturated palladium complexes dissolved from solid precursors during heck coupling reactions and their role as catalytically active species. *Inorg. Chem.* **2007**, *46*, 1876–1883.

(177) Schmidt, A. F.; Al-Halaiqa, A.; Smirnov, V. V. New approaches to heck reaction testing for homogeneity-heterogeneity. *Kinet. Catal.* **2008**, *49*, 395–400.

(178) Schmidt, A. F.; Kurokhtina, A. A. Distinguishing between the homogeneous and heterogeneous mechanisms of catalysis in the Mizoroki–Heck and Suzuki-Miyaura reactions: Problems and prospects. *Kinet. Catal.* **2012**, *53*, 714–730.

(179) Kurokhtina, A. A.; Larina, E. V.; Shmidt, A. F. Study of the differential selectivity of cross-coupling reactions for elucidating the nature of the true catalyst. *Kinet. Catal.* **2015**, *56*, 190–196.

(180) Michel, B. W.; Steffens, L. D.; Sigman, M. S. Wacker Oxidation, The. Org. React. 2014, 75-414.

(181) Smidt, J.; Hafner, W.; Jira, R.; Sieber, R.; Sedlmeier, J.; Sabel, A. Palladium chloride-catalyzed oxidation of olefins. *Angew. Chem.* **1962**, 74, 93–102.

(182) Jira, R. Oxidations. In *Applied Homogeneous Catalysis with Organometallic Compounds;* Cornils, B., Herrmann, W. A., Eds.; Wiley-VCH: Weinheim, Germany, 2002; Vol. 1.

(183) Jira, R. Acetaldehyde from Ethylene-A Retrospective on the Discovery of the Wacker Process. *Angew. Chem., Int. Ed.* **2009**, *48*, 9034–9037.

(184) Stirling, A. S.; Nair, N. N.; Lledó, A.; Ujaque, G. Challenges in modelling homogeneous catalysis: new answers from ab initio molecular dynamics to the controversy over the Wacker process. *Chem. Soc. Rev.* **2014**, *43*, 4940–4952.

(185) Henry, P. M. Deuterium isotope effects in the palladium(II) and thallium(III) oxidation of ethylene. J. Org. Chem. **1973**, 38, 2415–2416.

(186) Wan, W. K.; Zaw, K.; Henry, P. M. Oxidation of olefins by palladium(II). 11. Kinetics and mechanism of the oxidation of allyl alcohol by PdCl42- in aqueous solution. *Organometallics* **1988**, *7*, 1677–1683.

(187) Francis, J. W.; Henry, P. M. Palladium(II)-catalyzed exchange and isomerization reactions. 14. Kinetics and stereochemistry of the isomerization and water exchange of 2-(methyl-d3)-4-methyl-1,1,1,5,5,5-hexafluoro-3-penten-2-ol in aqueous solution catalyzed by PdCl42-. Two new mechanistic probes for catalytic chemistry. *Organometallics* **1991**, *10*, 3498–3503.

(188) Francis, J. W.; Henry, P. M. Oxidation of olefins by palladium(II). Part XIV. Product distribution and kinetics of the oxidation of ethene by PdCl3(pyridine)- in aqueous solution in the presence and absence of CuCl2: a modified Wacker catalyst with altered reactivity. J. Mol. Catal. A: Chem. 1995, 99, 77–86.

(189) Stille, J. K.; Divakaruni, R. Stereochemistry of the hydroxypalladation of ethylene. Evidence for trans addition in the wacker process. J. Am. Chem. Soc. **1978**, 100, 1303–1304.

(190) Majima, T.; Kurosawa, H. Isolation of stable β -alkoxyethylpalladium complexes and the first direct evidence for trans alkoxypalladation of ethylene. *J. Chem. Soc., Chem. Commun.* **1977**, 610–611.

(191) Åkermark, B.; Söderberg, B. C.; Hall, S. S. The Mechanism of the Wacker Process. Corroborative Evidence for Distal Addition of Water and Palladium. *Organometallics* **1987**, *6*, 2608–2610.

(192) Francis, J. W.; Henry, P. M. Palladium(II)-catalyzed exchange and isomerization reactions. 15. Kinetics and stereochemistry of the isomerization of 2-(methyl-d3)-4-methyl-1,1,1,5,5,5-hexafluoro-3-penten-2-ol in aqueous solution catalyzed by PdCl42- at high chloride concentrations. *Organometallics* **1992**, *11*, 2832–2836.

(193) Nelson, D. J.; Li, R.; Brammer, C. Correlation of Relative Rates of PdCl2 Oxidation of Functionalized Acyclic Alkenes versus Alkene Ionization Potentials, HOMOs, and LUMOs. *J. Am. Chem. Soc.* **2001**, *123*, 1564–1568.

(194) Eisenstein, O.; Hoffmann, R. Transition-metal complexed olefins: how their reactivity toward a nucleophile relates to their electronic structure. *J. Am. Chem. Soc.* **1981**, *103*, 4308–4320.

(195) Fujimoto, H.; Yamasaki, T. A theoretical analysis of catalytic roles by paired interacting orbitals. Palladium(II)-catalyzed nucleophilic additions to carbon-carbon double bonds. *J. Am. Chem. Soc.* **1986**, *108*, 578–581.

(196) Kragten, D. D.; van Santen, R. A.; Lerou, J. J. Density Functional Study of the Palladium Acetate Catalyzed Wacker Reaction in Acetic Acid. J. Phys. Chem. A **1999**, 103, 80–88.

(197) Keith, J. A.; Nielsen, R. J.; Oxgaard, J.; Goddard, W. A. Unraveling the wacker oxidation mechanisms. J. Am. Chem. Soc. 2007, 129, 12342–12343.

(198) Baeckvall, J. E.; Bjoerkman, E. E.; Pettersson, L.; Siegbahn, P. Reactivity of coordinated nucleophiles toward cis migration in (π -olefin)palladium complexes. J. Am. Chem. Soc. **1984**, 106, 4369–4373.

Ν

(199) Siegbahn, P. E. M. New Perspectives on the Nucleophilic Addition Step in the Wacker Process. J. Am. Chem. Soc. 1995, 117, 5409–5410.

(200) Siegbahn, P. E. M. Two, Three, and Four Water Chain Models for the Nucleophilic Addition Step in the Wacker Process. *J. Phys. Chem.* **1996**, *100*, 14672–14680.

(201) Beyramabadi, S. A.; Eshtiagh-Hosseini, H.; Housaindokht, M. R.; Morsali, A. Mechanism and kinetics of the wacker process: A quantum mechanical approach. *Organometallics* **2008**, *27*, 72–79.

(202) Beyramabadi, S. A.; Eshtiagh-Hosseini, H.; Housaindokht, M. R.; Morsali, A. H-Transfer steps of the Wacker process: A DFT study. *J. Mol. Struct.: THEOCHEM* **2009**, *903*, 108–114.

(203) Keith, J. A.; Oxgaard, J.; Goddard, W. A., III Inaccessibility of β -Hydride Elimination from -OH Functional Groups in Wacker-Type Oxidation. *J. Am. Chem. Soc.* **2006**, *128*, 3132–3133.

(204) Keith, J. A.; Nielsen, R. J.; Oxgaard, J.; Goddard, W. A.; Henry, P. M. Comment on "Mechanism and Kinetics of the Wacker Process: A Quantum Mechanical Approach. *Organometallics* **2009**, *28*, 1618–1619.

(205) Nair, N. N. Ligand Exchanges and Hydroxypalladation Reactions of the Wacker Process in Aqueous Solution at High Cl-Concentration. J. Phys. Chem. B 2011, 115, 2312–2321.

(206) Imandi, V.; Kunnikuruvan, S.; Nair, N. N. Hydroxypalladation Precedes the Rate-Determining Step in the Wacker Oxidation of Ethene. *Chem. - Eur. J.* 2013, *19*, 4724–4731.

(207) Comas-Vives, A.; Stirling, A.; Lledos, A.; Ujaque, G. The Wacker Process: Inner- or Outer-Sphere Nucleophilic Addition? New Insights from Ab Initio Molecular Dynamics. *Chem. - Eur. J.* **2010**, *16*, 8738–8747.

(208) Kovacs, G.; Stirling, A.; Lledos, A.; Ujaque, G. The Nature of [PdCl2(C2H4)(H2O)] as an Active Species in the Wacker Process: New Insights from Ab Initio Molecular Dynamics Simulations. *Chem.* - *Eur. J.* **2012**, *18*, 5612–5619.

(209) Petrovic, V. P.; Markovic, S.; Petrovic, Z. D. A new aspect of Heck catalyst formation. *Monatsh. Chem.* **2011**, *142*, 141–144.

(210) Lu, C. C.; Peters, J. C. Synthetic, structural, and mechanistic aspects of an amine activation process mediated at a zwitterionic Pd(II) center. *J. Am. Chem. Soc.* **2004**, *126*, 15818–15832.

(211) Yap, J. S. L.; Ding, Y.; Yang, X.-Y.; Wong, J.; Li, Y.; Pullarkat, S. A.; Leung, P. H. Mechanistic insights into the PdII-catalyzed chemoselective N-demethylation vs. cyclometalation reactivity pathways in 1-Aryl-N,N-dimethylethanamines. *Eur. J. Inorg. Chem.* 2014, 2014, 5046–5052.

(212) McNally, A.; Haffemayer, B.; Collins, B. S. L.; Gaunt, M. J. Palladium-catalysed C–H activation of aliphatic amines to give strained nitrogen heterocycles. *Nature* **2014**, *510*, 129–133.

(213) Zhang, Q.; Yu, H.; Fu, Y. Mechanism of Pd-catalyzed selective C-H activation of aliphatic amines via four-membered-ring cyclometallation pathway. *Sci. China: Chem.* **2015**, *58*, 1316–1322.

(214) Cardin, D. J.; Cetinkaya, B.; Cetinkaya, E.; Lappert, M. F.; Manojlović-Muir, L. J.; Muir, K. W. trans/cis-isomerism and isomerisation of PdII and PtII carbene complexes; The crystal and molecular structures of cis- and trans-PtCl2 [C(NPhCH2)2]PEt3. J. Organomet. Chem. 1972, 44, C59–C62.

(215) Redfield, D. A.; Nelson, J. H. Equilibrium Energetics of cis-Trans Isomerization for two Square-Planar Palladium(II)-Phosphine Complexes. *Inorg. Chem.* **1973**, *12*, 15–19.

(216) Casado, A. L.; Espinet, P. On the Configuration Resulting from Oxidative Addition of RX to $Pd(PPh_3)_4$ and the Mechanism of the cis-to- trans Isomerization of $[PdRX(PPh_3)_2]$ Complexes (R = Aryl, X = Halide). Organometallics **1998**, 17, 954–959.

(217) Chamizo, J. A.; Morgado, J.; Castro, M.; Bernès, S. Synthesis and structure of cis-palladium(II) carbene complexes containing the 1,3-diallylimidazolidin-2-ylidene Ligand: Trans \rightarrow cis rearrangement. *Organometallics* **2002**, *21*, 5428–5432.

(218) Goossen, L. J.; Koley, D.; Hermann, H. L.; Thiel, W. Mechanistic pathways for oxidative addition of aryl halides to palladium(0) complexes: A DFT study. *Organometallics* **2005**, *24*, 2398–2410.

(219) Huynh, H. V.; Han, Y.; Ho, J. H. H.; Tan, G. K. Palladium(II) complexes of a sterically bulky, benzannulated N-heterocyclic carbene with unusual intramolecular C-H-Pd and C carbene-Br interactions and their catalytic activities. *Organometallics* **2006**, *25*, 3267–3274.

(220) Akbari, A.; Hoseinzade, F.; Morsali, A.; Beyramabadi, S. A. Quantum mechanical study on the mechanism and kinetics of the cisto-trans isomerization of [Pd(C6Cl2F3)I(PH3)2]. *Inorg. Chim. Acta* **2013**, *394*, 423–429.

(221) Xu, X.; Pooi, B.; Hirao, H.; Hong, S. H. CH- π and CF- π interactions lead to structural changes of n-heterocyclic carbene palladium complexes. *Angew. Chem., Int. Ed.* **2014**, *53*, 1283–1287.

(222) Evans, J.; O'Neill, L.; Kambhampati, V. L.; Rayner, G.; Turin, S.; Genge, A.; Dent, A. J.; Neisius, T. Structural characterisation of solution species implicated in the palladium-catalysed Heck reaction by Pd K-edge X-ray absorption spectroscopy: palladium acetate as a catalyst precursor. *J. Chem. Soc., Dalton Trans.* **2002**, 2207–2212.

(223) Schmidt, A. F.; Al-Halaiqa, A.; Smirnov, V. V.; Kurokhtina, A. A. State of palladium in ligandless catalytic systems for the Heck reaction of nonactivated bromobenzene. *Kinet. Catal.* **2008**, *49*, 638–643.

(224) Pelagatti, P.; Carcelli, M.; Costa, M.; Ianelli, S.; Pelizzi, C.; Rogolino, D. Heck reaction catalysed by pyridyl-imine palladium(0) and palladium(II) complexes. *J. Mol. Catal. A: Chem.* **2005**, *226*, 107–110.

(225) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, O.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. Gaussian 09, Revision B.01; Gaussian Inc., Wallingford, CT, 2010.

(226) Zhao, Y.; Truhlar, D. G. A new local density functional for main-group thermochemistry, transition metal bonding, thermochemical kinetics, and noncovalent interactions. *J. Chem. Phys.* **2006**, *125*, 194101.

(227) Zhao, Y.; Truhlar, D. G. The M06 suite of density functionals for main group thermochemistry, thermochemical kinetics, non-covalent interactions, excited states, and transition elements: Two new functionals and systematic testing of four M06-class functionals and 12 other functionals. *Theor. Chem. Acc.* **2008**, *120*, 215–241.

(228) Hay, P. J.; Wadt, W. R. Ab initio effective core potentials for molecular calculations. Potentials for K to Au including the outermost core orbitals. *J. Chem. Phys.* **1985**, *82*, 299–310.

(229) Curtiss, L. A.; McGrath, M. P.; Blaudeau, J.-P.; Davis, N. E.; Binning, R. C.; Radom, L. Extension of Gaussian-2 theory to molecules containing third-row atoms Ga–Kr. *J. Chem. Phys.* **1995**, *103*, 6104–6113.

(230) Fukui, K. The path of chemical reactions - the IRC approach. *Acc. Chem. Res.* **1981**, *14*, 363–368.

(231) Hratchian, H. P.; Schlegel, H. B. Using Hessian Updating To Increase the Efficiency of a Hessian Based Predictor-Corrector Reaction Path Following Method. *J. Chem. Theory Comput.* **2005**, *1*, 61–69.

(232) Legault, C. Y. CYLview 1.0b; Université de Sherbrooke, 2009.