Importance of the Reducing Agent in Direct Reductive Heck Reactions


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Importance of the Reducing Agent in Direct Reductive Heck Reactions

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The role of the reductant in the palladium N-heterocyclic carbene (NHC) catalyzed reductive Heck reaction and its effect on the mechanism of the reaction is reported. For the first time in this type of transformation, the palladium-NHC-catalyzed reductive Heck reaction was shown to proceed in the presence of LiOMe and PrOH even at 10 °C to give the products very efficiently in excellent yields and with exceptional chemoselectivities. This study shows that the reaction proceeds through two distinct mechanisms that depend on the nature of the reducing agent. In the presence of a protic solvent or acidic medium the reaction undergoes protonation to yield the reduced product, whereas in the absence of proton source, it proceeds through the insertion of the reductant followed by reductive elimination. The kinetic data reveal that the oxidative addition is the rate-determining step in the reaction. The reaction profiles show first-order kinetics in aryl iodide and Pd and zero-order kinetics in LiOMe, benzylideneacetone, and the excess amount of NHC ligand. In addition, the reaction progress kinetic analysis shows that neither catalyst decomposition nor product inhibition occurs during the reaction. DFT calculations of the key steps confirm that the oxidative addition step is the rate-determining step in the reaction. Deuterium-labeling experiments indicate that the product is formed by the protonation of the Pd–Caryl bond of the intermediate formed after enone insertion into the Pd–Caryl bond. Application of chiral NHC ligands in the asymmetric reductive Heck reaction only results in poor enantioselectivities (enantiomeric excess up to 20%) and is also substrate specific. DFT calculations suggest that the migration of the aryl group to the alkene of the substrate is the enantioselectivity-determining step of the reaction. It is further shown that if the steric bulk at the enone is small (a methyl group), the two transition state barriers from [Pd(arL)(Ar)(enone)] species Caryl and Caryl, which have the re and si face of the enone substrate coordinated to Pd, are very similar, in line with the experimental results. With a slightly larger group (an isopropyl substituent) a significant difference in energy barriers is calculated (2.6 kcal mol⁻¹), and in the experiment this product is formed with a modest enantiomeric excess (up to 20%).

Introduction

Despite the massive progress in Heck coupling reactions over the last decades,[1, 2] the thorough mechanistic understanding of the “direct” catalytic reductive Heck reaction remains elusive, as it is a rather unexplored reaction. Conversely, the utilization of highly reactive organometallic reagents to obtain related products has been studied extensively.[3, 4] Although numerous advances have been made in Pd-catalyzed conjugate addition with organometallic reagents (Grignards, organozincs, and boronic acids) in the past decade,[5–7] the direct Pd-catalyzed reductive Heck reaction of alkenes with aryl halides has hardly been investigated.[8–12] In general, the replacement of expensive air- and moisture-sensitive organometallic reagents with aryl halides is very tempting for industrial synthetic transformations. The reductive arylation product in the Pd-catalyzed reaction was first reported by Cacchi, and it was reasoned that the presence of trialkylamines and formic acid facilitate the reduction step by acting as the hydride source to form the hydrido-palladium-alkyl complex.[8, 9] The reductive Heck product is then produced through the reductive elimination of the complex, whereas β-hydride elimination of the palladium-alkyl complex forms the Mizoroki–Heck product (Scheme 1).

It was also proposed that formic acid plays two important roles: protonation of the Pd-alkyl species and reduction of PdII to Pd0. Alternatively, we reported the reductive Heck reaction using an N-heterocyclic carbene (NHC) palladium complex, trialkylamines (i.e., N,N-dilisopropylethylamine; DIPEA), and aprotic solvents (i.e., N-methyl-2-pyrrolidone; NMP).[10, 12]

The nature of the base and solvent play a crucial role in the reaction and both affect the catalytic results by changing the regioselectivity of the reaction. Additionally, we found that the
presence of DIPEA as both a reductant and base helps the reductive cleavage step and, consequently, promotes the formation of the reductive Heck product. Based on our observations in the previous studies, we proposed that the reaction does not involve the protonation of the palladium-alkyl species to yield the reductive Heck product. Instead, the role of DIPEA in the reaction is to act as a reductant through its coordination to the palladium-alkyl species (after iodide dissociation) followed by β-hydride elimination of the DIPEA to form the hydride species. The reductive Heck product is formed in the final reductive elimination step. This role of DIPEA was confirmed by performing an experiment using deuterium-labeled trialkylamine (D₃)[Et₃N], which resulted in the formation of the deuterated reductive Heck product. This indicates that the hydride source depends on the nature of the solvent (protic or aprotic) and base (reductant or nonreductant) applied in such a reaction. In addition, studies on the asymmetric reductive Heck reaction have been reported by Buchwald et al. who used aryl triflates in an intramolecular fashion to synthesize chiral 3-substituted indanones with moderate enantiomeric excess (ee) values in most cases. More recently, an enantioselective palladium-phosphine-catalyzed intramolecular reductive Heck reaction of aryl halides was reported to afford 3-arylindanones with moderate to high ee values. It was proposed that the addition of trialkylammonium salts in ethylene glycol facilitates the halide dissociation through its hydrogen bond donor capacity. Another enantioselective transformation of this class was reported with the asymmetric arylative dearomatization of indoles through palladium-phosphine-catalyzed reductive Heck reaction using sodium formate in methanol. To date, the asymmetric reductive Heck reaction is rather limited to intramolecular reactions, which is particularly interesting for the synthesis of natural products. To the best of our knowledge, there are no examples that describe the "direct intramolecular" enantioselective reductive Heck reaction with a high ee, most likely because of the challenges involved in the asymmetric induction step.

In this contribution, we report the palladium-NHC-catalyzed direct reductive Heck reaction of para-substituted benzylideneacetones with 4-idoanisole using isopropanol as both the solvent and reductant. The reaction proceeds very efficiently even at low temperatures (10 °C). Additionally, DFT calculations, kinetics, and other mechanistic studies were performed to provide a detailed mechanistic picture of the reaction. We also probed the direct intermolecular asymmetric reductive Heck reaction and elucidated the enantioselectivity-determining step by performing DFT calculations.

### Results and Discussion

#### Initial optimization

To explore the role of the reductant we studied the typical reductive Heck reaction between benzylideneacetone (1) and 4-idoanisole (2) that resulted in the formation of the expected product 3 with traces of the Heck product 4 (obtained as a mixture of E/Z isomers) and 4,4'-dimethoxybiphenyl (5; Table 1). We used our reaction conditions optimized previously as a starting point to explore reaction conditions based on various solvents in different combinations with various bases. These experiments revealed that isopropanol as a sol-
vent in combination with $K_2CO_3$ as the base gave a good selectivity for the formation of 3 with a moderate conversion (65%) after 20 h (Table 1, Entries 1–10). If we changed the base to LiOMe (1 equivalent) it resulted in an excellent yield of 3 (93%) after just 30 min (Entry 12). Moreover, if we followed the product formation over time, we observed that the reaction proceeds to full conversion within just 30 min with nearly exclusive formation of 3. The use of other bases did not further improve the reaction (Entries 20–24), and also the replacement of isopropanol with other alcohols decreased the activity and selectivity (Entries 12–18).

Notably, if we used 1,1,3,3,3-hexafluoroisopropyl alcohol (HFIPA) instead of $iPrOH$, the rate of the reaction decreased substantially, and almost no substrate conversion was observed after 2 h (Entry 15). This can be explained as $iPrOH$ is a stronger reductant. The reaction in the absence of base resulted in the complete recovery of the starting materials (Entry 19).

The essential role of $iPrOH$ as the solvent/reductant in the reaction was then probed by performing two independent labeling experiments using $[D]_1iPrOD$ and $[D]_2iPrOH$ (Scheme 2). The reaction in $[D]_2iPrOD$ results in the formation of the monodeuterated product, whereas in $[D]_1iPrOH$ only the normal product was detected, which suggests that the product is likely formed by protonation of the palladium-alkyl intermediate. These results indicate that the reaction proceeds through the protonation of the palladium-alkyl complex followed by re-dissociation of $Pd^0$ to $Pd^2$, which is in contrast to that found for re-oxidation performed in the presence of DIPEA.[12]

A reductive pathway, with proton exchange between the alcohol and the product under the applied reaction conditions, is less likely as this proton exchange would also lead to the incorporation of two D atoms next to the carbonyl moiety, which is not observed. We next studied the kinetics of the re-oxidation of the palladium complex using the product formation over time and we processed the data using reaction progress kinetic analysis[29] to provide a typical rate versus substrate concentration plot. The kinetic data revealed first-order kinetics in the palladium-NHC catalyst and zero-order kinetics in base (LiOMe) and in the excess of the NHC ligand. Additionally, the reaction progress kinetic analysis showed that neither catalyst decomposition nor product inhibition plays a significant role during the reaction under the applied reaction conditions in the time studied.

**DFT calculations**

To gain additional insight into the mechanism, we performed DFT calculations to investigate the various pathways of the catalytic cycle (Figure 1). The geometry optimizations were performed by using the TURBOMOLE program package[26] using BP86 functional[27, 28] together with the def2-TZV[P basis set.[29] The given minima comprise no imaginary frequencies, and the transition states contain only one imaginary negative frequency (for detailed data and all minima and optimized geometries see the Supporting Information).

From the experimental results, we considered a pathway that involves the oxidative addition of the ArI substrate 2, coordination and insertion of the enone substrate 1 into the Pd–C$_{Ar}$ bond, followed by protonation of the resulting Pd–C$_{alkyl}$ bond by a coordinated $iPrOH$ moiety (Figure 1). The energy of the various intermediates and transition states indicates that the oxidative addition is irreversible and the rate-determining step of the catalytic reaction. This is in agreement with our kinetic experiments that show first-order kinetics in $[12]$ and zero-order kinetics in $[1]$ (see Supporting Information for details). As we reported previously, the oxidative addition step may proceed via various transition state (TS) species with slightly different activation barriers ($\Delta G^\ddagger$[1] = $\Delta G^\ddagger$[0] + 2.9 kcal mol$^{-1}$), which depends on the reaction conditions. In this respect, the transition state of the oxidative addition step can be decreased in energy ($\approx$ 3 kcal mol$^{-1}$) by the de-coordination of 1.

In general, the oxidative addition energy profile indicates that it is an overall exergonic process to form species B or C. The formation of species C from species B is an endergonic process. Species C undergoes migratory insertion to give species D, which proceeds via a low-barrier-energy transition state (TS$_D$). Here, a palladium-O-enolate species (D') can also be formed through isomerization, but it is energetically less favored ($\approx$ 2.7 kcal mol$^{-1}$ higher in energy; $\Delta G^\ddagger_{298K}$ (D') = −11.9 kcal mol$^{-1}$). Species D and E can be stabilized by the coordination of $iPrOH$ ($\approx$ 3 kcal mol$^{-1}$ lower in energy). The next step considered in the reaction path is palladium-alkyl protonation to form the product. This is followed by β-hydrogen elimination from alkoxide E to form acetone and the palladium-hydride species F. The computed barrier for this step is low (12 kcal mol$^{-1}$ from D (+$iPrOH$), which is in good agreement with the labeling experiments (Scheme 2) and suggests that protonation is a key step in product formation. Reformation of the $Pd^0$ species A is proposed to involve the base-assisted reductive elimination of HI (LiOMe as a base), which is overall slightly endergonic.

![Scheme 2. Deuterium-labeling experiment using $[D]_1iPrOD$ or $[D]_2iPrOH$ in the reductive Heck coupling reaction. The reaction with $[D]_1iPrOD$ only resulted in the incorporation of one D in the product, which excludes the possibility of H/D exchange between the product and $[D]_2iPrOD$ during the reaction.](image_url)
Mechanism of the reaction

From the kinetic data and DFT calculations, we propose the mechanism depicted in Scheme 3. Several species, possibly in equilibrium, may be present for the oxidative addition step with different energy barriers. We envision that the catalytic cycle starts with the formation of species A and A'. The oxidative addition of 2 to palladium(0)-NHC then takes place to give both species A and A', and therefore, afford species B or C. According to our kinetic data and DFT calculations, the oxidative addition is the rate-determining step.

As reported previously for similar reactions,[[30–35] activated alkenes slow down the oxidative addition step by coordinating to the Pd species, thereby stabilizing the Pd species through the delocalization of the electron density from the electron-rich Pd. The resulting species C undergoes migratory insertion into benzylideneacetone to form species D, which is in equilibrium with the energetically less favored palladium-O-enolate species D' ($\approx 2.7$ kcal mol$^{-1}$ higher in energy). Although this species is less favored in terms of stability, we cannot rule out that the product is formed by the protonation of this species, which should have a low barrier as it is after the rate- and selectivity-determining step. As we were unable to find the transition state for this step and it was reported that reductive elimination reactions proceed through Pd-species,[[36] the reaction most likely proceeds via D.

Alternatively, species C could form from a halogen-bridged dimeric species (analogous to B), in particular, if bulky ligands are involved, which could lead to the isomeric form of C.[[37, 38]

This alternative Pd species C and its transition states with the aryl group positioned cis to the NHC ligand were also calculated by using DFT (Figure S31) and were demonstrated to be similar in energy ($\approx 0.3$ kcal lower in energy). Additionally, the energy barriers for the migratory insertion step from these species are similar. As observed in the labeling experiment, protonation of the palladium-alkyl complex in iPrOH occurs to form product 3 and species E. If species D undergoes $\beta$-hydride elimination, the Heck side-product 4 is formed. Species E converts to species F through $\beta$-hydride elimination to result in the formation of acetone, which was also detected experimentally by using GC and GC–MS. The final steps in the mechanism that ultimately leads to reformation of species A involve $\beta$-hydride elimination from the alcoholate E to produce acetone (as observed in the reaction mixture), followed by reductive deprotonation by LiOMe as a base, to form MeOH and LiI. The abstraction of a proton from a palladium-hydride species by a base can occur without an activation barrier.[[39]
Asymmetric reductive Heck reactions

With a clear picture of the kinetics and mechanism of the reaction in hand, we next conducted experiments to study the challenging direct intermolecular asymmetric reductive Heck reaction using chiral NHC ligands (Table 2). Recently, we showed that this reaction lends itself to an enantioselective intramolecular Heck reaction using monodentate phosphoramidite ligands.[46] The reactions with the model enone 1 (R = Me) using chiral ligand L1 under different conditions (in iPrOH at 60 °C and room temperature or in (S)-(−)-1-phenylethanol) resulted in < 1% ee (entries 2–4). The mechanism dictates that the insertion of enone 1 into the Pd–Cα bond of species C is the asymmetric induction step, which should be controlled by the chiral NHC ligands. It is anticipated that more sterically hindered enone substrates will be more prone to the induction of enantioselectivity by the ligand. As such, we explored the reaction by using other enones with bulkier R groups (phenyl, 9-anthracenyl, ethyl, isopropyl, tert-butyl, and 1-adamantyl). Interestingly, if we moved from a methyl to an isopropyl group in the enone substrate, the ee value increased from < 1 to 8% (Entry 8). Unfortunately, the experiments with the bulkier 1-adamantyl- or tert-butyl-substituted enones with greater steric influences gave no product simply because these substrates are too bulky to coordinate to the Pd center. Consequently, the reaction resulted in the formation of the homocoupling product (Entries 9–10). Additionally, the reactions with the iPr-substituted enone at lower temperatures (room temperature and at 10 °C) gave excellent yields of 3 (90–94%) with slightly higher ee values of 16 and 19% (Entries 11–12). A further decrease of the temperature to 0 °C did not result in conversion as the substrates were recovered unchanged (Entry 13), which indicates that 10 °C is the lowest reaction temperature at which the reaction still progresses. The reactions with various chiral NHC ligands were, therefore, performed at 10 °C, however, this did not further improve the ee values (Entries 14–20).

According to the mechanism supported by our DFT calculations, the enantioselectivity is determined by an aryl migration step. The DFT calculations show that the energy difference between the species Cα and Cβ in which the enone is coordinated to the Pd center with its re and si face, respectively, is very small. We next optimized the geometries of species C using enones with different R groups (methyl and isopropyl) coordinated to the Pd center.

Table 2. Pd-catalyzed enantioselective reductive arylation.[46]

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<th>T [°C]</th>
<th>Conv.[b] (%)</th>
<th>Yield of [c] (%)</th>
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[a] Reaction conditions: 1 (1.65 mmol), 2 (1.10 mmol), Pd(L)(MA) (0.75 mol %) (MA = maleic anhydride), LiOMe (1 equiv.), T = 0–60 °C, solvent = iPrOH (2 mL), t = 0.5–20 h, internal standard = decane. [b] The conversion and yield were determined by using GC based on 2. [c] ee determined by using chiral HPLC. [d] (S)-(−)-1-Phenylethanol used as a solvent.

[e] Homocoupling product 5 was formed as the major product and other byproducts formed.
To further study the asymmetric induction step of the reaction mechanism, we also probed the migratory insertion step of these two enones into the Pd center through DFT calculations of the corresponding transition states (Figure 2). They both undergo migratory insertion through exerogenic processes to give species D*. However, the energy barrier for the two transition states if we start from the species C_{iPr}(Me) and C_{iPr}(Me) revealed almost no differences (0.1 kcal mol\(^{-1}\)), whereas the transition states of the species C_{iPr}(iPr) and C_{iPr}(iPr) had larger differences of 2.6 kcal mol\(^{-1}\), which indicates that one pathway is more preferred than the other. This energy barrier difference observed for the more bulky substrate is in line with the experiment as for this substrate the product was produced in 19% ee.

Notably, the relative energy barriers at ambient or elevated temperatures (or because of the absence of explicit solvent effects) may become even closer, which rationalizes the fact that we did not obtain any ee values higher than 20%.

Conclusions
The effect of the reducing agent on the palladium N-heterocyclic carbene catalyzed direct reductive Heck reaction of para-substituted benzylideneacetones with 4-iodoanisole has been investigated. Compared to that of previous studies, the reaction conditions lead to faster reactions as full conversion was achieved within 30 min at 60 °C. We further showed that the reaction proceeds even at 10 °C. Importantly, the mechanism of the product-forming step can be different and depends on the nature of the reducing agent. In the presence iPrOH, the product is formed through the protonation of the palladium-alkyl intermediate, which is clear from deuterium-labeling experiments. This is in contrast to the reaction in the presence of N,N-disopropylethylamine, for which we found that the product is formed by reductive elimination from the alkyl-hydride species. The kinetic data indicate that under both conditions the oxidative addition is the rate-determining step, which is in line with the results of our DFT calculations. Various chiral NHC ligands were synthesized and evaluated in the asymmetric reductive Heck reaction, which showed no enantiomeric excess for the benchmark substrate. In line with this, the difference in the transition state barriers of the crucial aryl migration step of the two [Pd(L)(Ar(ene))] species C_{Me} and C_{Me} is negligible. In contrast, the same transition states for the complexes with a slightly more bulky substrate (isopropyl enone) are 2.6 kcal mol\(^{-1}\) different in energy, and indeed for this reaction significant but low enantiomeric excess values (up to \(\approx 20\%\)) were obtained. Further optimization of asymmetric reductive reaction could proceed along these lines.

Experimental Section
General procedure for the reductive arylation reaction.
To a flame-dried Schlenk tube equipped with a stopper and a stirring bar, LiOMe (1 m in THF, 1.1 mmol, 1 equiv.) was added. The solvent (THF) was then removed under reduced pressure to obtain a white powder. The Schlenk tube was then charged with Pd(L)(MA), (0.75 mol%), 2 (1.1 mmol), and 1 (1.65 mmol) and flushed three times with vacuum and Ar. iPrOH (2 mL) that contained decane as an internal standard was then transferred into the Schlenk tube, which was then placed into a preheated oil bath at 60 °C. Upon reaction completion (after 30 min; judged by using GC), the reaction mixture was cooled to RT, and a sample of 10 μL was taken and diluted to 1 mL with dichloromethane and subsequently analyzed by using GC/GC–MS (for more detailed data, see Supporting Information).

DFT calculations
All calculations and geometry optimizations were performed by using the Turbomole program package\(^{[26]}\) coupled to the PQS Baker optimizer\(^{[41]}\) with the BP0t package\(^{[42]}\) at the spin-unrestricted n-DFT level using the BP86 functional\(^{[27, 28]}\) and the def2-TZVP basis set\(^{[26]}\) for the geometry optimizations. All geometries of minima with no imaginary frequencies and transition states with one imaginary frequency were characterized by calculating the Hessian matrix numerically (for detailed information see the Supporting Information).
Acknowledgements

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Conflict of interest

The authors declare no conflict of interest.

Keywords: carbene ligands • density functional calculations • palladium • reaction mechanisms • reduction