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■ Cross-Coupling

Palladium(0)/NHC-Catalyzed Reductive Heck Reaction of Enones:
A Detailed Mechanistic Study**Saeed Raoufmoghaddam,^[a] Subramaniyan Mannathan,^[b] Adriaan J. Minnaard,^{*,[b]}
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Abstract: We have studied the mechanism of the palladium-catalyzed reductive Heck reaction of *para*-substituted enones with 4-iodoanisole by using *N,N*-diisopropylethylamine (DIPEA) as the reductant. Kinetic studies and in situ spectroscopic analysis have provided a detailed insight into the reaction. Progress kinetic analysis demonstrated that neither catalyst decomposition nor product inhibition occurred during the catalysis. The reaction is first order in the palladium and aryl iodide, and zero order in the activated alkene, *N*-heterocyclic carbene (NHC) ligand, and DIPEA. The experiments with deuterated solvent ($[D_7]DMF$) and deuterated base ($[D_{15}]Et_3N$) supported the role of the amine as a reductant in the reaction. The palladium complex $[Pd^0(NHC)(1)]$

has been identified as the resting state. The kinetic experiments by stopped-flow UV/Vis also revealed that the presence of the second substrate, benzylideneacetone **1**, slows down the oxidative addition of 4-iodoanisole through its competing coordination to the palladium center. The kinetic and mechanistic studies indicated that the oxidative addition of the aryl iodide is the rate-determining step. Various scenarios for the oxidative addition step have been analyzed by using DFT calculations (bp86/def2-TZVP) that supported the inhibiting effect of substrate **1** by formation of resting state $[Pd^0(NHC)(1)]$ species at the cost of further increase in the energy barrier of the oxidative addition step.

Introduction

Metal-catalyzed cross-coupling reactions are important methodologies for organic synthesis. Nowadays, a wide range of coupling reactions is available, and numerous applications in the preparation of synthetically useful compounds are known.^[1] In particular, palladium-catalyzed arylation of alkenes with aryl halides, known as the Mizoroki–Heck reaction, have been developed to synthesize a variety of new carbon–carbon bonds.^[2] In addition, the transition-metal-catalyzed conjugate addition of aryl organometallic compounds has been demonstrated to provide a powerful synthetic tool in organic chemistry.^[3] As well as copper catalysts,^[4] rhodium and palladium complexes have been applied in conjugate addition reactions; such catalysts benefit from broad functional group

tolerance and can be used under mild reaction conditions.^[5] The arylation of alkenes with aryl halides^[2h] and the reductive arylation with organometallic reagents^[6] have been intensively investigated. In contrast, the arylation of alkenes with arylboronic acids (the oxidative Heck reaction) and the direct reductive arylation have received surprisingly little attention.^[7] Although numerous advances have been developed and applied in the palladium-catalyzed reductive arylation with organometallic reagents (Grignards, organozincs, and boronic acids),^[2d] the direct palladium-catalyzed reductive arylation of alkenes with aryl halides has been rarely reported.^[7,8] The reductive arylation reaction is mostly carried out by using organometallic aryl substrates,^[9] which are produced from their corresponding aryl halides, but these compounds are often expensive and have limited air and moisture stability. As such, replacing these reagents with aryl halides is an attractive alternative and opens up new possibilities in terms of synthetic and industrial applications.

The reductive addition products in palladium-catalyzed Mizoroki–Heck reactions are often considered as side products,^[10] generally named as “reductive Heck products”. In some cases, particularly in natural product synthesis and intramolecular reactions, the reductive Heck product has been the desired product.^[11] The alkyl–palladium–halide complex, which is common to both the Heck and the reductive arylation reaction, is transformed into a hydrido–palladium–alkyl complex through reaction with formic acid or trialkylamines. Reductive elimination of this intermediate gives the reductive arylation product, whereas β -hydride elimination of the palladium–alkyl

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[**] NHC = *N*-heterocyclic carbene.

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Scheme 1. The Heck product (through β -hydride elimination) versus the reductive Heck reaction or conjugate addition (through protonation or reductive elimination of Pd(alkyl)(H) species).

complex gives the Mizoroki–Heck product (Scheme 1). The reductive Heck (or reductive arylation) reaction was first studied by Cacchi^[7a,8] and it was proposed that the formation of the reductive arylation product is facilitated by the addition of both acid (i.e., formic acid) and base (i.e., Et₃N) as a result of protonation of the alkyl Pd intermediate species. It was also proposed that the use of formic acid would affect both protonation of the alkyl Pd species and reduction of Pd^{II} to Pd⁰. On the other hand, the reductive Heck reaction was recently reported with a palladium–N-heterocyclic carbene (NHC) complex^[12] in comparison with the Heck reaction.^[7b] In this case, it was shown that the nature of the base governs the formation of the major product (either Heck or reductive Heck). Additionally, it was found that the presence of tributylamine as a reductant and base forces the reductive cleavage step and, therefore, promotes the formation of the reductive Heck product. The absence of formic acid did not lower the yield of the reductive Heck product; therefore, it was suggested that the reaction does not necessarily proceed through the protonation of the alkyl Pd species (Scheme 1).

Herein, we report an optimized palladium-catalyzed reductive Heck reaction that proceeds at a relatively moderate temperature of 60 °C in only 4 h (Scheme 2), and a reaction mechanism is proposed based on experimental evidences and DFT calculations.

Scheme 2. The reductive Heck reaction.

Results and Discussion

Initial optimization

The previously reported reaction conditions^[7b] (Table 1, entry 1) were further optimized in terms of reaction time, catalyst loading, reaction temperature, base/reductant, and solvent. A slight excess of benzylideneacetone than 4-iodoanisole was used. Analysis of the reaction mixture after a typical reductive arylation reaction revealed a mixture of the expected conjugate addition product **3**, the Mizoroki–Heck product **4**

Table 1. Palladium-catalyzed reductive arylation reaction.^[a]

Entry	Ligand	Base/reductant [(equivalent)]	<i>t</i> [h]	<i>T</i> [°C]	Solvent	Conv. [%]	Yield [%] ^[b]		
							3	4	5
1 ^[c,d]	L ¹	<i>n</i> Bu ₃ N (4.5)	18	80	DMF	full	82	5	10
2 ^[d]	L ¹	DIPEA (4.5)	18	80	DMF	full	82	10	8
3	L ¹	DIPEA (4.5)	4	60	NMP	full	91	9	–
4	L ¹	DIPEA (2)	4	60	NMP	full	90^[e]	8	1
5	L ¹	DIPEA (1)	4	60	NMP	71	56	11	4
6	L ¹	DIPEA (2)	4	60	CH ₃ CN	32	25	6	1
7	L ¹	DIPEA (2)	4	60	THF	52	44	7	1
8 ^[d]	L ¹	<i>n</i> Bu ₃ N (2)	4	60	NMP	31	18	11	1
9 ^[d]	L ¹	<i>i</i> Bu ₃ N (2)	4	60	NMP	18	12	6	–
10 ^[d]	L ¹	Et ₃ N (2)	4	60	NMP	32	14	18	1
11	L ²	DIPEA(2)	4	60	NMP	99	91	8	–
12	L ³	DIPEA (2)	4	60	NMP	39	28	11	–
13	L ⁴	DIPEA (2)	4	60	NMP	3	3	–	–
14	L ⁵	DIPEA (2)	4	60	NMP	31	21	11	–
15	L ⁶	DIPEA (2)	4	60	NMP	19	7	12	–
16	L ⁷	DIPEA (2)	4	60	NMP	34	15	20	–
17	L ⁸	DIPEA (2)	4	60	NMP	31	14	18	–
18	L ⁹	DIPEA (2)	4	60	NMP	5	5	–	–
19	L ¹⁰	DIPEA (2)	4	60	NMP	22	11	11	–
20	L ¹¹	DIPEA (2)	4	60	NMP	27	16	11	–

[a] Reaction conditions: **1** (1.65 mmol), **2** (1.10 mmol), [Pd(L)(MA)₂] (0.75 mol %) (MA = maleic anhydride), DIPEA (0.25–4.5 equiv), *T* = 60–80 °C, solvent = DMF, MeCN, THF, or NMP (1.5 mL), internal standard = decane, *t* = 4–18 h. [b] GC yields that are based on iodoanisole. [c] Reaction conditions as previously reported: **1** (2.72 mmol), **2** (1.14 mmol), 80 °C, 18 h. [d] Biphasic reaction medium. [e] ≈ 85% yield of isolated product.

(obtained as a mixture of *E/Z* isomers), and 4,4'-dimethoxybiphenyl (**5**) (Table 1).

Replacement of *n*Bu₃N by *N,N*-diisopropylethylamine (DIPEA) under the same conditions resulted in a slightly better yield of product **3** (entry 2). The reaction carried out in *N*-methyl-2-pyrrolidone (NMP) instead of DMF was monophasic and led to a considerably increased yield of product **3**; this allowed the use of a lower reaction temperature and a shorter reaction time (entry 3). Lowering the amount of amine (as a base/reductant) from 4.5 to 2 equivalents did not affect the yield of the desired product **3**, whereas a further decrease to 1 equivalent resulted in incomplete conversion (entries 3–5). This was expected as at least 1 equivalent of the amine is required for the reduction, and when present in stoichiometric amount this may become rate limiting. Other variations in solvent and amine did not further improve the yield of product **3** (entries 6–10).^[13] By using these optimized conditions, we examined various NHC ligands (Figure 1) in this reaction, and the results are shown in Table 1. L¹ and L² were identified as the best ligands, which give the product **3** in ≈ 90% yield (entries 4 and 11). The use of L³–L¹¹ did not give better yields or conversions (entries 12–20).

Figure 1. Various NHC ligands used in the reductive Heck reaction.

Dynamic light scattering (DLS) measurements and reaction poisoning studies

To confirm that the reaction proceeds through a molecular catalyst and is not catalyzed by nanoparticles, we used DLS to detect nanoparticles that may have formed during the reaction. On the basis of the DLS measurements, we did not observe any nanoparticles in the reaction mixture in the presence of substrate **1** (1.5 equiv with respect to the substrate **2**). It was also found that the excess amount of substrate **1** stabilized the catalyst, which prevented the nanoparticle formation in the reaction mixture.^[14] In addition, the presence of mercury, tetramethylthiourea (TMTU), or 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) resulted in only slightly lower conversions (≈ 2 –4% lower in the presence of thiourea or TEMPO and $\approx 8\%$ lower in the presence of Hg), which also indicated that the reaction is catalyzed by a molecular palladium catalyst (see the Supporting Information, Figure S1–S3).^[15]

Reaction kinetics

We next studied the reaction kinetics by monitoring the reaction over time by GC analysis, and the initial reaction rates were calculated from the slope of the concentration/time plot at the beginning of the reaction. In addition, the data were processed by using reaction progress analysis, which gave the typical graphical rate versus substrate concentration plots.^[16] These plots were used to determine the order of each reactant (Figure 2); accordingly, we observed first order kinetics in [iodoanisole (**2**)] and zero order kinetics in [benzylideneacetone (**1**)] (Figure 2a). These results revealed that the oxidative addition was the rate-determining step. Additionally, reactions with very low concentrations of substrate **1** were carried out. To our surprise, we found that, under these conditions, the reaction was no longer zero order in [substrate **1**]; indeed, it became nearly inverse first order. This suggests that the order of the reaction with respect to substrate **1** varies as follows: At concentrations between 0.0–0.3 M, an increase in the amount of sub-

Figure 2. Kinetic analysis of the reductive arylation reaction: a) Rate versus substrate concentration for concentrations > 0.3 M. b) Rate versus benzylideneacetone concentration; different reaction kinetics were observed at low and high concentrations of **1**.

strate **1** led to a decrease in the reaction rate, which is possibly due to a decrease in the concentration of the active palladium species through its coordination to the substrate **1**. However, at concentrations higher than 0.3 M, the reaction rate was not further lowered by any increase in the concentration of substrate **1** (Figure 2b). Similar decelerating effects, which were caused by the presence of alkenes, have been reported by the group of Jutand in the oxidative addition of aryl iodides to Pd^0 complexes in Heck and cross-coupling reactions.^[17] They observed that the rate of the oxidative addition was lower in the presence of dibenzylideneacetone (dba), and they reasoned that more than one reactive species must be involved in the equilibrium.

To gain additional mechanistic insight, we probed the effect of the electronic properties of the 4-substituent in substrate **1** on the reaction rate (Table 2). Variation of the electron density in substrate **1** did not result in significant changes in the reaction rate profile at concentrations > 0.3 M, which is in line with the reaction kinetics (zero order in substrate **1**).^[18]

The kinetic data obtained at various catalyst concentrations showed first order kinetics in the Pd –NHC catalyst (Figure 3a), which is in line with a rate-determining step that involves oxidative addition to the Pd^0 species. Additionally, the changes in the concentration of DIPEA did not change the reaction rate, which indicated that the reaction was zero order in the base/reductant (Figure 3b).^[19] Furthermore, with different concentrations of **L**¹, the rate of the reaction was not changed, which shows that the reaction is zero order in **L**¹ (Figure 3c). This implies that ligand (de-)coordination was not involved in the rate-determining step, which is in agreement with the published data by Hartwig et al. that concerned the oxidative

Table 2. Rates of Pd-catalyzed reductive arylation of iodoanisole **2** with various 4-substituted benzylideneacetone **1**.^[a]

Entry	R	Rate ^[b] [Mh ⁻¹]
1	H	0.32
2	Me	0.31
3	OMe	0.35
4	NMe ₂	0.35
5	Cl	0.31
6	NO ₂	0.29

[a] Reaction conditions: **1** (1.65 mmol), **2** (1.10 mmol), [Pd(L¹)(MA)₂] (0.75 mol%), DIPEA (2 equiv), *T* = 60 °C, solvent = NMP (1.5 mL), internal standard = decane, *t* = 30 min. [b] The rate of the reactions was determined by GC analysis.

Figure 3. Reaction kinetics: a) Rate versus Pd/NHC catalyst concentration. b) Rate versus base/reductant (DIPEA) concentration. c) Rate versus L¹ concentration (see the Supporting Information for full experimental details).

addition of iodoarenes to trialkylphosphine palladium complexes.^[20]

To further analyze the reaction kinetics, progress kinetic analysis, introduced by Blackmond,^[16] was conducted to give typical rate versus substrate concentration plots (Figure 4b).

Figure 4. Reaction profile for the Pd/NHC-catalyzed addition of 4-iodoanisole to benzylideneacetone: a) Product formation versus time. b) Rate versus substrate concentration; different initial substrate concentrations with the same excess were examined: 1) [1]/[2] = 0.44:0.66 M, 2) [1]/[2] = 0.38:0.60 M, 3) [1]/[2] = 0.30:0.52 M.

The change in concentration of substrate **1** and products **3**, **4**, and **5** over time has been plotted (Figure 4a), and the results revealed that full conversion was obtained after 4 h with nearly exclusive formation of the product **3**. The power of this analysis is that information can be directly extracted by visual inspection of these plots; if the plots of two reactions that have different starting concentrations of the substrate do overlay then there is no catalyst deactivation or product inhibition during the reaction. For reactions with two different substrates, experiments were performed with the same excess of one of the two substrates. The parameter called the “excess” is defined as the initial concentration difference between the two reactants, which remains constant from the beginning to the end of the reaction. The kinetic data are then used to make overlay plots to judge the reaction kinetics and also to graphically evaluate product inhibition/catalyst deactivation events. Three reactions with the same excess values and different absolute initial concentrations of the substrates were performed. Figure 4b reveals that the reaction plots overlay perfectly, which indicates that neither catalyst decomposition nor product inhibition occurs during the reaction.

According to the kinetic data, the oxidative addition is the rate-determining step. For a related Heck arylation reaction, it

has been proposed that dba slows down the oxidative addition reaction by coordination to the Pd^0 species, and benzylidene **1** probably has similar coordination properties.^[17,21] In Suzuki couplings and Heck reactions, it has been shown that coordination of dba (or other alkene π -acids) influences the reaction rate, especially when electron-donating ligands, such as basic phosphines or NHC ligands, are used.^[21]

To further study this in detail, we monitored the oxidative addition of the Pd –NHC complex to iodoanisole by using stopped-flow UV/Vis kinetics to measure the rate of this step under various conditions. The stopped-flow apparatus provides instantaneous mixing and is able to record changes in the absorption on a millisecond, second, or minute timescale (by rapidly mixing two solutions in a flow cell and then subsequently recording data). We examined the rates of the oxidative addition of substrate **2** in the presence of various amounts of substrate **1** by monitoring the changes in the absorption peak at 325 nm, which is the wavelength at which the maximum difference in the UV/Vis spectra is observed (Figure 5). The results show that the rate of the oxidative addition is fastest in the absence of substrate **1**, as judged from the decays. Increasing the concentration of substrate **1** led to a decrease in the rate of the oxidative addition step. The inhibiting effect of substrate **1** is likely due to a pre-equilibrium that arises between intermediates **A**, **A'**, and **A''** in solution.

Figure 5. Stopped-flow kinetic analysis of the oxidative addition step: change in absorbance at 325 nm versus time; $[\text{Pd}(\text{L}^1)(\text{MA})_2]/\text{ArI}$ (**2**)/enone (**1**) = 1:10:0.1–0.3 in NMP. In a typical experiment $[\text{Pd}(\text{L}^1)(\text{MA})_2]$ (0.4 mM), ArI (**2**) (4 mM), and enone (**1**) (0.04–0.12 mM) were used in NMP as the solvent on a timescale of 0–10 s, MA = Maleic anhydride (see the Supporting Information, Figure S6–S12).

Spectroscopic data reported in the literature indicates that the most reactive Pd^0 species in the oxidative addition with aryl halides are unsaturated complexes, that is, those complexes with the lowest number of ligands (L_1Pd^0 ; Figure 5, species **A**).^[22] Coordination of substrate **1** to species **A** to form species **A''** stabilizes the electron-rich d^{10} Pd^0 center by removing the electron density from the metal center, and it

consequently diminishes the concentration of the active catalyst species **A** in the oxidative addition step. A similar effect was observed for dba and other olefinic π -acids in cross-coupling reactions.^[17b,21,23] The coordination of benzylideneacetone **1** to the Pd^0 complex was also confirmed by 2D-DOSY NMR spectroscopy, in which 25 equivalents of substrate **1** was introduced at ambient temperature (see the Supporting Information, Figure S14).^[24]

DFT calculations

Various scenarios for the oxidative addition step to give **A** and **A''** were computed by using DFT calculations to further confirm the effect of substrate **1**. The geometry optimizations were performed with the TURBOMOLE program package^[25] by using the bp86 functional^[26] together with the def2-TZVP basis set.^[27]

The given minima contained no imaginary frequency, and the transition states contained only one imaginary negative frequency (for detailed data, all minima, and optimized geometries see the Supporting Information).

DFT calculations confirmed that the coordination of substrate **1** to the Pd^0 center stabilized the catalyst by delocalizing the electron density from the Pd^0 species, as reported in both experimental and theoretical studies on the Heck reaction.^[17a,28] Additionally, the DFT-calculated species **A'**, **A''**, and **A'''** are the energetically most favorable Pd^0 species (Figure 6).

The different transition states for the oxidative addition step were examined (Figure 7), and this revealed that the energy barrier for the oxidative addition step was slightly higher for the transition state $[\text{C}_{\text{TS}}]^+$ than for $[\text{B}_{\text{TS}}]^+$ (≈ 3 kcal), which suggests that the reaction mainly proceeds through the dissociation of substrate **1**. This is in agreement with the inhibiting effect of substrate **1** on the rate of oxidative addition that was observed experimentally (Figure 7a). As the coordination of alkenic π -acid **1** lowers the energy of the Pd^0 complex, the intermediate species **A'** and **A''** are lower in energy than species **A** and, therefore, are the resting state of the reaction if sufficient substrate **1** is present in solution. Based on the calculations, we conclude that the dominant pathway for the oxidative addition step is from the resting state **A''** (as an energetically preferred species) through the dissociation of compound **1** to give intermediate **A** and then formation of transition state $[\text{B}_{\text{TS}}]^+$.

Figure 6. DFT-calculated (bp86/def2-TZVP) HOMO plot for the species **A** ($[\text{Pd}^0(\text{NHC})]$), **A'** ($[\text{Pd}^0(\text{NHC})(\text{NMP})]$), **A''** ($[\text{Pd}^0(\text{NHC})(\text{MA})_2]$), **A¹** ($[\text{Pd}^0(\text{NHC})(1)(\text{MA})]$), and **A²** ($[\text{Pd}^0(\text{NHC})(1)]$); (see the Supporting Information, Figure S53, for DFT-calculated HOMO and LUMO plots of all species).

Mechanism of the reaction

Based on the kinetic data and DFT calculations, we propose the mechanism that is depicted in Scheme 3. Palladium species **A** or **A²** may be the starting point for the oxidative addition step, each of which has different energy barriers associated to the subsequent reaction. These starting species are formed by the loss of MA (maleic anhydride) and coordination of substrate **1** to the palladium centre, and they are presumably in equilibrium. The most stable Pd^0 complexes are $[\text{Pd}^0(\text{NHC})(1)]$ (**A²**) and $[\text{Pd}^0(\text{NHC})(\text{MA})]$, whereas the most active Pd^0 species for oxidative addition is $[\text{Pd}^0(\text{NHC})]$ (probably with a molecule of solvent), and its presence depends on the concentration of

compound **1** in the reaction mixture. When $[1] > 0.3 \text{ M}$, species **A²** is predominantly present in the mixture, which was confirmed by DOSY NMR spectroscopy and DFT calculations. In principle, the oxidative addition of aryl iodide **2** can occur with both species **A** and **A²**, but the main pathway will start from the resting state (lowest energy intermediate) and proceed through the lowest energy barrier. At a low concentration of **1**, the reaction starts from intermediate **A²** to form species **A**, and a subsequent oxidative addition step provides intermediate species **B**. Based on the experimental evidence that the reaction rate is lower at higher concentrations of substrate **1** and the fact that the reaction rate levels off at $[1] > 0.3 \text{ M}$ to a constant, lower rate, the oxidative addition step may, alternatively, proceed through the direct oxidative addition onto species **A²** at high concentrations of substrates **1**. Both kinetic data and DFT calculations indicated that this oxidative addition step was the rate-determining step in the reductive Heck reaction ($\Delta G_{298 \text{ K}}^\circ = -11.21$ and $-10.81 \text{ kcal mol}^{-1}$ for the formation of species **B** and species **B** with one molecule of NMP, respectively). After coordination of substrate **1**, species **C** ($\Delta G_{298 \text{ K}}^\circ = -4.68 \text{ kcal mol}^{-1}$) undergoes migratory insertion (carbopalladation) to form intermediate **D** ($\Delta G_{298 \text{ K}}^\circ = -17.02$, -14.34 , and $-20.37 \text{ kcal mol}^{-1}$ for species **D**, $\text{Pd}-\text{O}$ species, and species **D** with one molecule of NMP, respectively), which is then followed by either coordination of the reductant DIPEA towards intermediate **E** or β -hydride elimination to form the Heck product **4**, thereby regenerating the species **A**. The coordination of DIPEA occurs after iodide dissociation, which then undergoes β -hydride elimination to generate species **E** ($\Delta G_{298 \text{ K}}^\circ = -5.53$ and $-4.13 \text{ kcal mol}^{-1}$ for species **E** and species **E** with one molecule of NMP, respectively). Finally, reductive elimination completes the catalytic cycle to provide the desired product **3** and regenerate the resting-state catalytic species **A**.^[29]

The structures of the aryl palladium halide complexes depend on the identity of the halide as well as the steric bulk

Figure 7. DFT-calculated (bp86/def2-TZVP) Pd species for the oxidative addition step, $\Delta G_{298 \text{ K}}^\circ$ is in kcal mol^{-1} . a) Calculated geometries of transition-state species $[\text{B}'\text{TS}]^\ddagger$, $[\text{BTS}]^\ddagger$, and $[\text{CTS}]^\ddagger$. b) Effect of **(1)** on the Gibbs energy of the species **A**, **A¹**, **A²**, $[\text{BTS}]^\ddagger$, and $[\text{CTS}]^\ddagger$; the species may be stabilized by coordination of solvent molecules. MA = Maleic anhydride. The calculation of the transition-state species that involved solvent (NMP) did not result in a species with NMP coordinated to the palladium center, which indicated that the oxidative addition proceeds through species **A** or **A²**.

Scheme 3. Proposed mechanism of the reductive Heck reaction and the DFT-calculated optimized geometries of the selected species (with and without NMP); empty coordination sites may be filled by solvent molecules or halides.

of the ligands.^[30] The aryl palladium iodide complex is a monomeric, three-coordinate complex in the presence of a sterically hindered ligand (i.e., NHC). This is in agreement with the findings of Hartwig et al., who reported the formation of three-coordinate complexes in both solution and solid state for aryl palladium bromide and iodide complexes, whereas aryl palladium chloride analogues formed monomers in solution and dimers in the solid state.^[20]

Two possible mechanisms can be envisioned for the oxidative addition of substrate 1 to the Pd⁰ species (Scheme 4). In the first mechanism, oxidative addition goes through direct reaction of compound 1 with species A (or species A' after NMP dissociation) to form a three-coordinate aryl palladium iodide B. Alternatively, the oxidative addition of compound 1 can take place with species A², which is the most stable Pd⁰ complex and resting state, to form a four-coordinate species C. If

Scheme 4. Two possible pathways for the oxidative addition of substrate 1 to palladium complexes A or A².

substrate 1 is in large excess (at least > 0.3 M), the reaction rate remains first order (or pseudo first order) in 2 and zero order (or pseudo zero order) in 1 owing to the saturation effect; otherwise, the reaction rate will depend on the concentration of both substrates 1 and 2. The fact that the reaction order is independent of [1] indicates that the equilibrium that provides the reactive species is much faster than the oxidative addition step. Under these conditions, the oxidative addition step is the rate-determining step, and the overall reaction rate remains first order in compound 2. The oxidative addition of substrate 1 onto intermediate A' was also studied by DFT calculations; as we could not find a transition state, this path requires the dissociation of NMP before the oxidative addition step can proceed. The reaction rate for this pathway would be first order in substrate 2 and independent of the concentration of substrate 1.

Based on the observation that neither acid nor protic solvent are required for the selective formation of the reductive Heck product 3, we postulate that the reaction does not involve protonation of the alkyl Pd species D to yield the product 3. Additionally, an experiment in the absence of base/reductant and in the presence of one equivalent of the palladium catalyst (with respect to the substrate) resulted in the formation of a mixture of products ($\approx 65\%$ Heck product 4 and $\approx 35\%$ reductive Heck product 3). As the Heck reaction produces $[\text{Pd}^{\text{II}}(\text{L}^1)\text{HI}]$, reductive elimination releases acidic HI, which can subsequently protonate species D. This experiment shows that a mechanism that involves protonation of the alkyl palla-

dium complex followed by reduction of Pd^{II} to Pd^0 with trialkylamine is equally possible if a proton source (acid or protic solvent) is available. Additionally, a similar reaction in the presence of one equivalent of base (K_2CO_3) resulted in merely formation of Heck product **4** (see the Supporting Information, Figure S19 and S20). In principle, $[\text{Pd}^{\text{II}}(\text{L}^1)\text{HI}]$ can re-insert into the Heck product in a conjugate reduction to give product **3**. A control experiment that was carried out under catalytic conditions, in which a Heck product was added at the start of the reaction, resulted in the complete recovery of this product, which suggested that, in the presence of an amine, the formation of the reductive Heck product is not a result of a sequential Heck–reduction pathway.^[7b]

The role of the base/reductant and the solvent during the reaction was also investigated by carrying out experiments with $[\text{D}_7]\text{DMF}$ (solvent) and $[\text{D}_{15}]\text{Et}_3\text{N}$ (reductant/base) (Scheme 5). The use of deuterated DMF as the solvent merely

Scheme 5. Deuterium-labeling experiment by using $[\text{D}_7]\text{DMF}$ or $[\text{D}_{15}]\text{Et}_3\text{N}$ in the reductive Heck reaction.

resulted in the formation of product **3**, whereas employing deuterated Et_3N yielded a mixture of $3^{\text{D}}/3$ (55:45), which showed that the amine (and not the solvent) was the source of the terminal hydride under the applied conditions (see the Supporting Information, Figure S4–S6, S51, and S52). This type of reactivity has precedent as it has been previously proposed that iminium hydrides of Pd^{II} complexes are intermediates in trialkylamine exchange reactions that are catalyzed by palladium^[31]. In the current example, a Pd^{II} /iminium hydride intermediate is formed by oxidative insertion of Pd^0 into the C–H bond of the coordinated trialkylamine. Palladium reduction by amine bases was also reported in the presence of water, and it was shown that the $[\text{Pd}^{\text{II}}(\text{L})_2\text{Cl}_2]$ complex (L =phosphite) is reduced to $[\text{Pd}^0(\text{L})_4]$ by tertiary amines in the presence of nucleophiles.^[29,32] Moreover, the Peter group suggested that the β -hydride elimination from a Pd^{II} species is the C–H bond-cleaving step.^[33] For complexes based on other metals, similar reactions have been reported, such as the formation of Os^{III} /iminium hydride species through β -hydride elimination of an Os^{III} /amine complex^[34] and formation of iridium^{III}/dihydride

complexes by the dehydrogenation of tertiary amines to produce enamines.^[35] More recently, the Peter group reported dehydrogenation of a variety of trialkylamines by a cationic (or zwitterionic) Pd complex through a β -hydride elimination/iminium salt reinsertion process to give the corresponding three-membered palladacycle.^[33] It was also shown that the selectivity in the activation of tertiary and secondary C–H bonds in trialkylamines was solely towards secondary C–H bonds owing to steric hindrance.^[34b]

The H/D scrambling that occurred during the reaction may be caused by the $\text{Pd}^{\text{II}}\text{--H}$ species that is present in the reaction mixture as a minor byproduct, which was formed from either a classical Heck reaction or reaction with traces of water in the reaction mixture, as hydride anions exchange quickly in palladium complexes. Additionally, the reaction with *N,N*-diisopropylmethylamine (DIPMA) as a reductant/base resulted in a lower yield of product **3** ($\approx 52\%$ after 4 h) and poor selectivity, which suggests that the ethyl moiety in DIPEA is oxidized. This is in line with previous results, in which it was demonstrated that the amine is oxidized during the reaction to form an enamine (via the iminium ion), which is hydrolyzed during work up (see the Supporting Information, Figure S18).^[2h,7b,36]

Conclusion

The reductive Heck reaction of aryl halides with Michael acceptors presents a facile C–C bond forming reaction under mild conditions with unsaturated ketones and nitro compounds as the substrates, which makes this a comparatively versatile catalytic transformation. A palladium/NHC complex has been thoroughly investigated as the catalyst for this reaction by using benzylideneacetone and 4-iodoanisole as substrates and various spectroscopic techniques, which included kinetic analysis and DFT calculations. Deuterium-labeling experiments indicated that the amine was the hydride source in the reaction. Kinetic analysis, in accordance to Blackmond, showed that neither catalyst decomposition nor product inhibition occurred during the reaction. The kinetic data further showed that the oxidative addition was the rate-determining step in the reaction. For concentrations in the range 0.3–1.0 M, the reaction rate profile revealed first order kinetics in aryl iodide **2** and the palladium catalyst, zero order in DIPEA and L^1 , and zero order in benzylideneacetone (**1**). When the concentration of benzylideneacetone (**1**) was below 0.3 M, we observed that the reaction rate increased slightly. Independent experiments that used stop-flow UV/Vis spectroscopy revealed that the presence of benzylideneacetone (**1**) reduced the rate of the oxidative addition of iodoanisole onto the $\text{Pd}\text{--NHC}$ complex. DFT computations further showed that the coordination of substrate **1** to the palladium/NHC complex both stabilized this resting state and increased the energy level of the transition state of for oxidative addition. These data provided evidence for a mechanism in which there is a pre-equilibrium between the more stable palladium complex with benzylideneacetone (A^2) and the palladium/NHC complex (**A**), and a subsequent (rate-determining) oxidative addition of the aryl iodide to the palladium/NHC complex **A**. Based on the energy

differences between the two calculated transitions states, only a small fraction of the reaction may proceed by oxidative addition to give **A**². Having established the mechanism of this reaction, we are currently focusing on the asymmetric version by employing chiral NHC ligands.

Experimental Section

General information

All reactions were performed in dry glassware under an argon atmosphere by using standard Schlenk techniques, unless stated otherwise. THF, CH₂Cl₂, and CH₃CN were distilled from sodium under dinitrogen. NMP and DIPEA were distilled, degassed, dried, and kept over molecular sieves (4 Å). Deuterated solvents were degassed in freeze-pump-thaw fashion and dried over molecular sieves (4 Å). NMR spectra were measured on a Bruker AMX 400 (¹H: 400.1 MHz and ¹³C: 100.6 MHz).

General procedure for the reductive arylation reaction

A flame-dried Schlenk tube, equipped with stopper and stirrer bar, was charged with [Pd⁰(L¹)(MA)₂] catalyst (0.75 mol %), 4-iodoanisole (**2**) (1.1 mmol), and benzylideneacetone (**1**) (1.65 mmol). The reductant, for example, *N,N*-diisopropylethylamine (DIPEA) (2.2 mmol), *N*-methylpyrrolidone (NMP) (1.5 mL), and decane, as an internal standard, were transferred into the Schlenk tube, which was then placed into a preheated oil bath at 60 °C. Upon reaction completion (after 4 h; as judged by GC), the reaction mixture was cooled down to room temperature and an aliquot (10 µL) was taken, diluted to 1 mL with CH₂Cl₂, and subsequently subjected to GC/GC-MS analysis (for more detailed data see the Supporting Information).

DFT calculations details

All calculations and geometry optimizations were performed using the Turbomole program package^[25] coupled to the PQS Baker optimizer^[37] via the BOpt package^[3b] at the spin unrestricted RI-FT level using the BP86 functional^[26] and the def2-TZVP basis set^[27] for the geometry optimizations. All geometries of minima with no imaginary frequencies and transition states with one imaginary frequency were characterized by numerically calculating the Hessian matrix (for detailed information see the Supporting Information).

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