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FULL PAPER

The Importance of the Reducing Agent in Direct Reductive Heck Reactions

Saeed Raoufmoghaddam,[a] Subramaniyan Mannathan,[b] Adriaan J. Minnaard,[b] Johannes G. de Vries,[b, c] Bas de Bruin,[a] Joost N. H. Reek*[a]

Dedication ((optional))

Abstract: The role of reductant in the palladium-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 iPrOH even at 10 °C, very efficiently producing the products in excellent yields and with exceptional selectivities. This study shows that the reaction proceeds through two distinct mechanism depending on the nature of the reducing agent. In the presence of the protic solvent or acidic media the reaction undergoes protonation to yield reduced product while in the absence of proton source, this proceeds through an 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 palladium, and zero order in LiOMe, benzylideneacetone and excess amount of NHC ligand. In addition, the reaction progress kinetic analysis show 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 via protonation of the Pd–C_{alkyl} bond of the intermediate formed after enone insertion into the Pd–C_{Ar} bond. Application of chiral NHC-ligands in the asymmetric reductive Heck reaction only result in poor enantioselectivities (ee up to 20%) which 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 when the steric bulk at the enone is small (a Me group), the two transition state barriers from [$Pd^{II}(L^2)$(ArI)(enone)] species $\mathbf{C_{Re}}$ and $\mathbf{C_{Si}}$, having the Re and Si face of the enone substrate coordinated to Pd, are very similar which is in line with the experimental results. With a slightly larger group (an iso-propyl substituent) a significant difference in energy barriers is calculated (2.6 kcal mol^{-1}), and indeed in the experiment this product is formed with modest ee (up to 20%).

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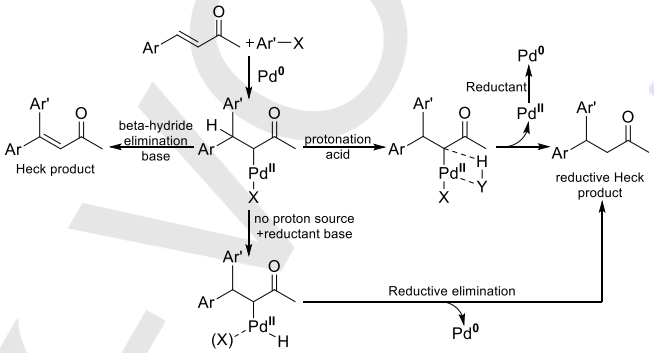

Scheme 1. Plausible mechanistic pathways; Heck product (via β-hydride elimination) versus reductive Heck product (via protonation or reductive elimination of [Pd^{II}(alkyl)(H)] species).

Introduction

Despite the massive progress in Heck coupling reactions over the last decades,[1,2] the thorough mechanistic understanding of *direct* catalytic reductive Heck reaction remains challenging, possibly due to couple of rather unexplored catalytic steps of such reactions. In contrary, the utilization of highly reactive organometallic reagents has been extensively studied.[3,4] Although numerous advances have been made in the palladium-catalyzed conjugate addition with organometallic reagents (Grignards, organozincs and boronic acids) in the past decade,[5-7] the direct palladium-catalyzed reductive Heck reaction of alkenes with aryl halides has been hardly investigated.[8-12] In general, replacing the expensive, air and moisture sensitive organometallic reagents with aryl halides is very tempting for industrial synthetic transformations. The reductive arylation product in the palladium-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 thus forming the hydrido-palladium-alkyl complex.[8,9] The reductive Heck product is then produced through 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 Pd^{II} to Pd^0. Alternatively, we recently reported the reductive Heck reaction using an N-heterocyclic carbene (NHC) palladium complex, trialkylamines (i.e. N,N-diisopropylethylamine or DIPEA) and aprotic solvents (i.e. N-methyl-2-pyrrolidone or NMP).[10,12]

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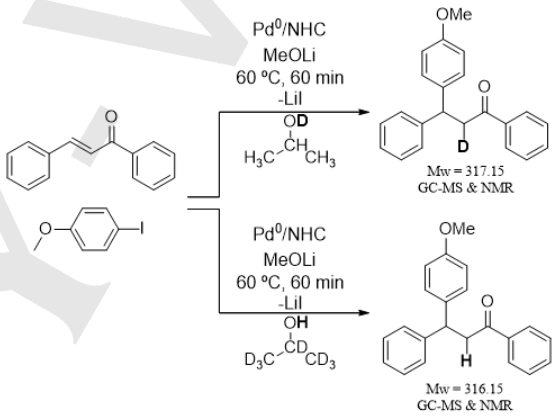
It was shown that the nature of the base and solvent have a crucial role in the reaction, and both affect the catalytic results changing the regioselectivity of the reaction. Additionally, we found that the presence of DIPEA as both reductant and base helps the reductive cleavage step and as a consequence promotes the formation of the reductive Heck product. Based on our observations in the previous studies, we proposed that the reaction does not involve protonation of the Pd-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 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 carrying out an experiment using deuterium labeled trialkylamine (Et_3N-d^{15}) which resulted in the formation of deuterated reductive Heck product.[12] This indicates that the hydride source depends on the nature of solvent (protic or aprotic) and base (reductant or non-reductant) applied in such a reaction.[13-15] In addition, studies on the asymmetric reductive Heck reaction[15,16] have also been reported by Buchwald, using aryl triflates in an intramolecular fashion to synthesize chiral 3-substituted indanones with moderate ee values in the most cases.[17] 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.[18] 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.[19] To date, the asymmetric reductive Heck reaction is rather limited to intramolecular reactions, which is particularly interesting for the synthesis of natural products.[17-24] To the best of our knowledge, there are no examples that describe the *direct intermolecular* enantioselective reductive Heck reaction with high ee%, most likely because of the challenges involved in the asymmetric induction step.

In the current contribution, we report the palladium-NHC catalyzed direct reductive Heck reaction of para-substituted benzylideneacetones with 4-iodo-anisole using isopropanol as both solvent and reductant. The reaction proceeds very efficiently even at low temperatures (10 °C). Additionally, DFT calculations, kinetics and other mechanistic studies provided 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 optimizations. To explore the role of the reductant we studied the typical reductive Heck reaction between benzylideneacetone **1** and 4-iodoanisole **2**, resulting 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 previously optimized reaction conditions,[12] but now explored various solvents in different combinations with various bases. These experiments revealed that isopropanol as a solvent in combination with K_2CO_3 as the base gave a good selectivity for the formation of product **3** with moderate conversion (65%) after 20 h (Table 1, Entries 1-10). Changing the base under the same conditions showed that LiOMe (1 equiv.) as a base is superior as it resulted in an excellent yield of **3** (93%) after just 30 min (Entry 12). Moreover, following the product formation over time revealed that the reaction proceeds to full conversion within just 30 min with nearly exclusive formation of product **3**. The use of other bases did not further improve the reaction (Entries 20-24) and also replacing isopropanol with other alcohols lowered the activity and selectivity (Entries 12-18).



Scheme 2. Deuterium labeling experiment using iPrOD-d^1 or iPrOH-d^7 in the reductive Heck coupling reaction. The reaction with iPrOD-d^1 only resulted in the incorporation of one deuterium in the product excluding the possibility of H/D exchanges between the product and iPrOD-d^1 during the reaction.

Notably, upon using 1,1,1,3,3,3-hexafluoroisopropyl alcohol (HFIPA) instead of iPrOH, the rate of the reaction dropped substantially, and almost no substrate conversion was observed after 2 h (Entry 15). This can be explained as it is less prone to be oxidized compared to iPrOH. The reaction in the absence of base resulted in complete recovery of the starting materials (Entry 19). The essential role of iPrOH as solvent/reductant in the reaction was then probed by two independent labeling experiments using iPrOD-d^1 and iPrOH-d^7 (Scheme 2). It was found that the reaction in iPrOD-d^1 results in the formation of the mono-deuterated product whereas in iPrOH-d^7 only the normal product was detected, suggesting that the product is likely formed by protonation of the Pd-alkyl intermediate. These results indicate that the reaction proceeds through protonation of the palladium-alkyl complex followed by reduction of Pd^{II} to Pd^0, which is in contrast to what we found for the reactions carried out with DIPEA.[12]

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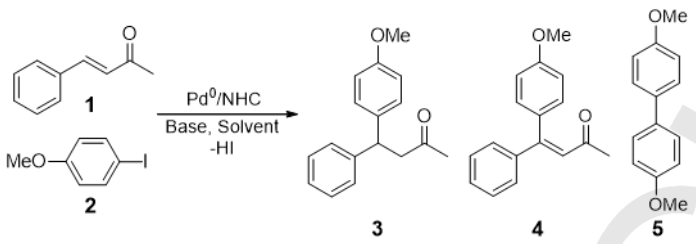
Table 1. Palladium-catalyzed reductive arylation[a]



No.	Base (equivalent)	t h	Solvent (v/v)	Conversion[b] %	Yield%[b] 3	4	5
1	DIPEA (2)	4	NMP	100	90	8	1
2	K_2CO_3 (1)	20	NMP	96	0	96	0
3	K_2CO_3 (1)	20	NMP/iPrOH (1.5/0.5)	87	13	74	0
4	K_2CO_3 (1)	20	NMP/iPrOH (1/1)	75	32	43	0
5	K_2CO_3 (1)	20	NMP/iPrOH (0.5/1.5)	66	48	18	0
6	K_2CO_3 (1)	20	NMP/iPrOH (0.25/1.75)	64	50	14	0
7	K_2CO_3 (1)	20	NMP/iPrOH (0.1/1.9)	63	53	10	0
8	K_2CO_3 (1)	20	acetone/iPrOH (0.25/1.75)	60	54	6	0
9	K_2CO_3 (1)	20	H2O/iPrOH (0.25/1.75)	20	12	7	0
10	K_2CO_3 (1)	20	iPrOH	65	59	5	0
11	Cs_2CO_3 (1)	6	THF/iPrOH (0.25/1.75)	89	66	4	19
12[c]	LiOMe (1)	0.5	iPrOH	99	93	3	3
13	LiOMe (1)	1	MeOH/iPrOH (1/1)	100	93	4	3
14	LiOMe (1)	0.5	EtOH	100	44	4	52
15	LiOMe (1)	2	HFIPA	5	4	1	0
16	LiOMe (1)	2	iBuOH	87	73	13	0
17	LiOMe (1)	1	$PhCH(OH)CH_3$	100	83	16	0
18	LiOMe (1)	1	Cyclopentanol	81	65	3	12
19	-	2	iPrOH	1	-	-	-
20	Na_2CO_3 (1)	20	iPrOH	60	55	5	0
21	Cs_2CO3 (1)	2	iPrOH	99	82	0	16
22	DIPEA (1)	20	iPrOH	16	13	3	0
23	Et_3N (1)	20	iPrOH	13	9	4	0
24	CsPiv (1)	20	iPrOH	44	3	41	0

[a] Reaction conditions: **1** (1.65 mmol), **2** (1.10 mmol), $Pd(L^1)(MA)_2$ (0.75 mol%) (MA = maleic anhydride; L^1 = 1,3-bis(2,4,6-trimethylphenyl)-imidazolium), base (1-2 equiv.), T= 60 °C, solvent (1.5 mL), internal standard = decane, *t* = 0.5 - 20 h. [b] GC Yields and conversions based on 4-iodoanisole. [c] ~88% isolated yield.

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 incorporation of two deuterium atoms next to the carbonyl moiety, which is not observed. We next studied the kinetics of the reaction, monitoring the product formation in time and processed the data using reaction progress kinetic analysis[25] that provides the typical graphical rate vs substrate concentration. These kinetic data revealed first order kinetics in the Pd-NHC catalyst and zero order in base (LiOMe) and zero order 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-span studied.

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

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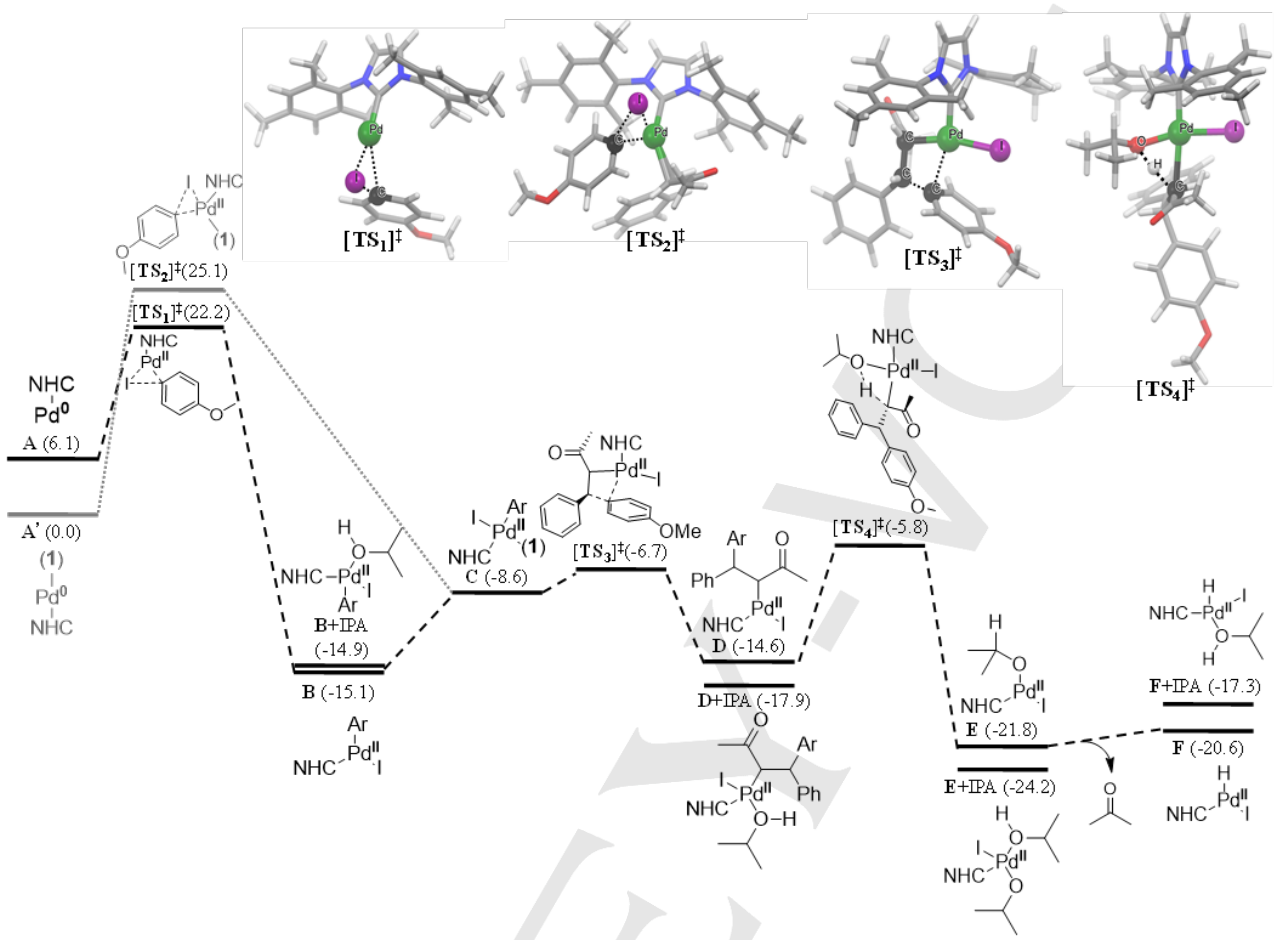

Figure 1. Gibbs free energy diagram (ΔG^0_{298K} in kcal mol^{-1}) of the DFT computed reductive Heck reaction (BP86, def2-TZVP).

Based on the experimental results we considered a pathway involving 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 (see Figure 1). The energy of the various intermediates and transition states indicate 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 in [iodo anisole 2] and zero order in [benzylideneacetone 1] (see SI for detailed information). As we reported previously,[12] the oxidative addition step may proceed through various species with slightly different activation barriers ($[TS_2]^‡$ = $[TS_1]^‡$ + 2.9 kcal mol^{-1}), depending on the reaction conditions. In this respect, the transition state of the oxidative addition step can be slightly lowered (~3 kcal mol^{-1}) by de-coordination of the enone 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, proceeding via a low barrier transition state (TS_3). Here, a Pd-O-enolate species (D') can also be formed through isomerization, but is energetically less favored (~2.7 kcal mol^{-1} higher in energy; $\Delta G^0_{298\,K}$ (D')= -11.9 kcal mol^{-1}). Species D and E can be stabilized by the coordination of iPrOH (~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 beta-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+IPA) which is in good agreement with the labeling experiments, described above in Scheme 2, suggesting protonation as a key step in product formation. Reformation of the Pd^0 species A is proposed to involve base assisted reductive elimination of HI (LiOMe as a base), which is overall slightly endergonic.

Mechanism of the reaction. Based on the kinetic data and DFT calculations, we propose a mechanism as 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'. Oxidative addition of iodoanisole (2) to Pd^0-NHC then takes place to both species A and A', thus affording species B or C.

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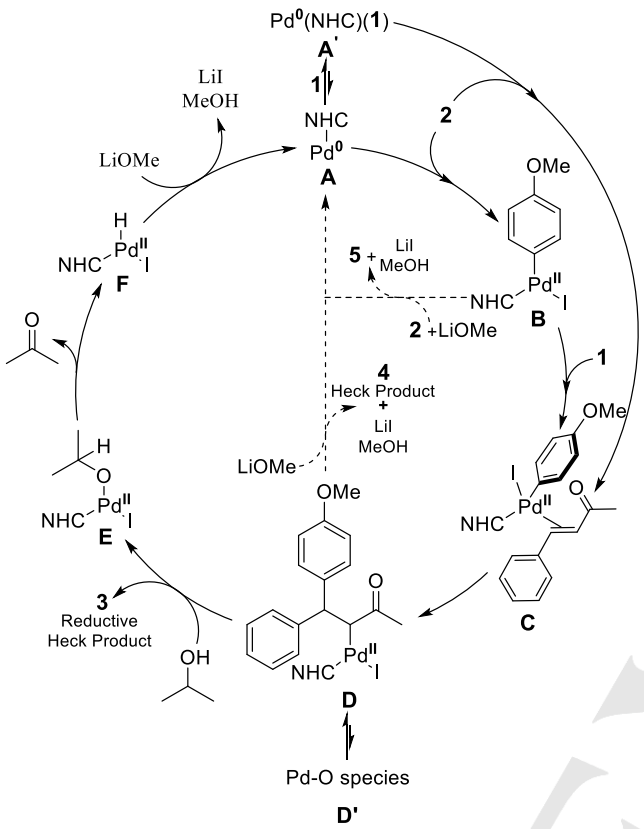
According to our kinetic data and DFT calculations, the oxidative addition is the rate-determining step.



Scheme 3. Proposed mechanism of the reductive Heck reaction; empty coordination sites may be occupied by solvent molecules or halides.

As previously reported for similar reactions,[31-36] activated alkenes slow down the oxidative addition step by coordinating to the palladium zero species, thereby stabilizing the Pd species through delocalization of the electron density from the electron rich Pd^0. The resulting species C undergoes migratory insertion into benzylideneacetone to form species D, which is in equilibrium with the energetically less favored Pd-O-enolate species D' (~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 protonation of this species, which should be with 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 for reductive elimination reactions to proceeds through the Pd-C species, [30] the reaction most like goes via D.

Alternatively, species C could form from a halogen-bridged dimeric species (analogues to B), in particular, when bulky ligands are involved, possibly leading to the isomeric form of C.[37,38] This alternative Pd species C and its transition states with aryl group cis-positioned to the NHC ligand were also calulated by DFT-calculated (see SI, Figure S31) and demonstrated to be similar in energy (~0.3 kcal lower in energy). Also 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 β-hydride elimination, the Heck side-product **4** is formed. Species E converts to species F through β-hydride elimination resulting in the formation of acetone, which was also detected experimentally by GC and GC/MS. The final steps in the mechanism that ultimately leads to reformation of species A, involve β-hydride elimination from the alcoholate E to produce acetone (as observed in the reaction mixture), followed by reductive deprotonation by LiOMe as a base, thereby forming 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 for an enantioselective *intra*molecular Heck reaction using monodentate phosphoramidite ligands.[40] The reactions with the model enone 1 (R=Me) using chiral ligand L^4 under different conditions (in iPrOH at 60 ºC 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-C_{Ar} 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 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, moving on from a methyl to an isopropyl group in the enone substrate increased the ee% value from <1% to 8% (Entry 8). Unfortunately, the experiments with the bulkier 1-adamantyl or t-butyl substituted enones with greater steric influences gave no product 3 simply because these substrates are too bulky to coordinate to the palladium center. As a consequence, the reaction merely resulted in the formation of homo-coupling product (Entries 9-10). Additionally, the reaction with the *i*Pr substituted enone at lower temperatures (room temperature and even at 10 ºC) gave excellent yields of the product 3 (90-94%) with slightly higher ee% values of 16% and 19% (Entries 11-12). Further lowering the temperature to 0 ºC did not result in conversion as the substrates were recovered unchanged (Entry 13), indicating that 10 ºC is the lowest reaction temperature at which the reaction still progresses. The reactions with various chiral NHC ligands were therefore carried out at 10 ºC, 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 aryl migration step. The DFT calculations show that the energy difference between the species C_{Re} and C_{Si}, having the enone coordinated to Pd center with its Re face and Si face, respectively, is very smal. We next optimized the geometries of species C using enones with different R groups (methyl and isopropyl) coordinated to the palladium center.

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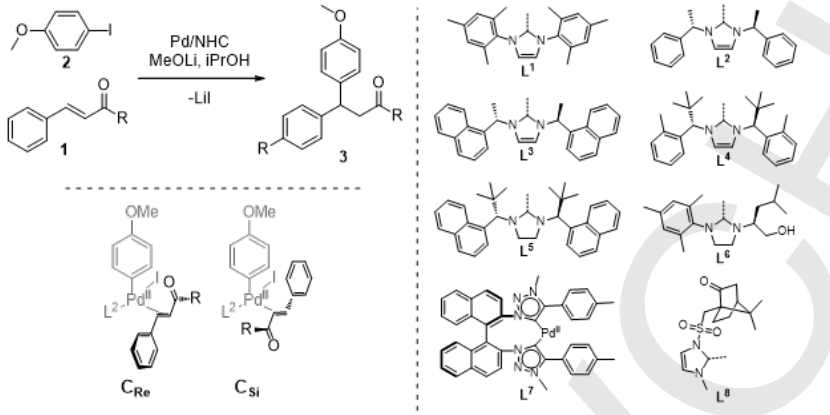
Table 2. Palladium-catalyzed enantioselective reductive arylation [a]



Entry	R	Ligand	T(h)	T (˚C)	Conv.[b] (%)	Yield **3** (%)[b]	ee%[c]
1	methyl	L^1	0.5	60	99	93	0
2	methyl	L^4	1	60	78	66	<1
3[d]	methyl	L^4	4	60	80	63	<1
4	methyl	L^4	8	rt	51	50	<1
5	phenyl	L^4	1	60	98	91	<1
6	9-anthracenyl	L^4	-	-	-	-	-
7	ethyl	L^4	-	-	-	-	-
8	isopropyl	L^4	2	60	99	96	8
9[e]	t-butyl	L^4	20	60	93	0	-
10[e]	1-adamantyl	L^4	20	60	91	0	-
11	isopropyl	L^4	15	rt	96	94	16
12	isopropyl	L^4	20	10	91	90	19
13	isopropyl	L^4	20	0	<2	0	-
14	isopropyl	L^2	20	10	88	82	14
15	isopropyl	L^3	20	10	89	83	14
16	isopropyl	L^5	20	10	90	81	19
17	isopropyl	L^6	20	10	68	65	17
18	isopropyl	L^7	20	60	<1	0	-
19	isopropyl	L^8	20	10	14	13	17
20	isopropyl	L^8	20	rt	49	47	15

[a] Reaction conditions: 1 (1.65 mmol), 2 (1.10 mmol), Pd(L)$(MA)_2$ (0.75 mol%) (MA = maleic anhydride), LiOMe (1 eq), T= 0 - 60 °C, solvent = iPrOH (2 mL), *t* = 0.5 - 20 h, Internal standard = decane. [b] The conversion and yield determined by GC based on iodo anisole. [c] ee% determined by chiral HPLC. [d] (S)-(−)-1-Phenylethanol used as a solvent. [e] homo-coupling product (5) as a major product and other by-products formed.

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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 exergonic processes to give species D*. However, the energy barrier for the two transition states starting from the species C_{Re}(Me) and C_{Si}(Me) revealed almost no differences (0.1 kcal mol^{-1}), whereas the transition states of the species C_{Re}(iPr) and C_{Si}(iPr) gave larger differences of 2.6 kcal mol^{-1}, indicating 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.

It is also noteworthy to mention that the relative energy barriers at ambient or elevated temperatures (or due to absence of explicit solvent effects) may become even closer which rationalizes the fact that we did not obtain any ee values higher than 20%.

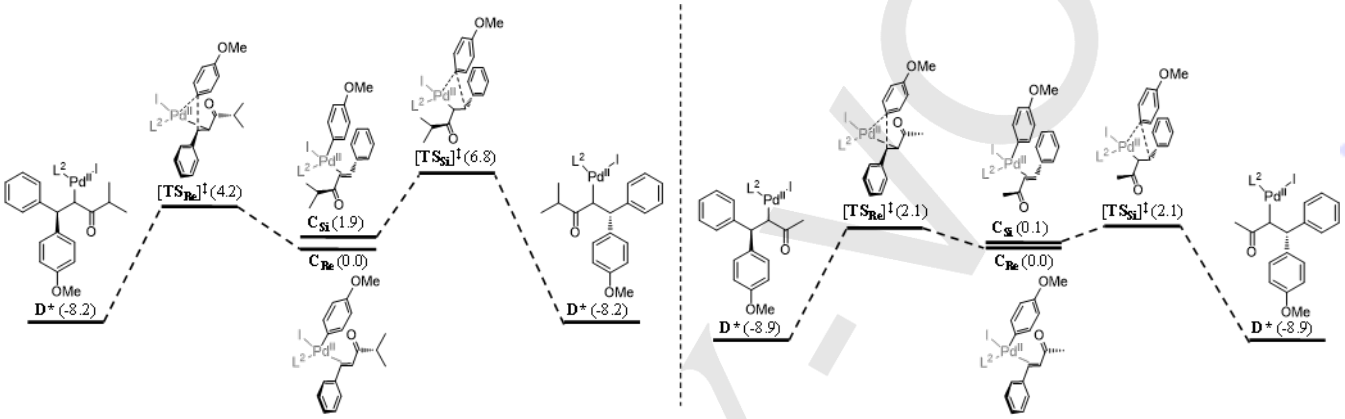

Figure 2. Migratory insertion step and the corresponding transition states of the palladium species (DFT calculations, BP86/def2-TZVP) in the reductive Heck reaction, $\Delta G^{0}_{298\ K}$ is in kcal mol^{-1}. Alternative transition states with aryl group cis-positioned to the NHC ligand were also calculated (see the supporting info, Figure S31) which resulted in 2.1 kcal energy difference between the species C_{Re}(iPr) and C_{Si}(iPr) indicating similar energy barrier (only 0.5 kcal lower compared to the trans-positioned species) in the migratory insertion step.

Conclusions

The effect of reducing agent on palladium-NHC catalyzed direct reductive Heck reaction of para-substituted benzylideneacetones with 4-iodo anisole has been investigated. Compared to previous studies, the reaction conditions lead to faster reactions as full conversion was achieved within 30 min at 60 °C. It was further shown 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 protonation of the Pd-alkyl intermediate, as is clear from deuterium labeling experiments. This is in contrast to the use of DIPEA, for which was 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 DFT calculations. Various chiral NHC ligands were synthesized and evaluated in the asymmetric reductive Heck reaction, which showed no ee for the bench-mark substrate. In line with this, the difference in the transition state barriers of the crucial aryl migration step of the two [Pd^{II}(L^{2})(ArI)(enone)] species **C_{Re}** and **C_{Si}** is negligible. In contrast, the same transition states for the complexes with a slightly more bulky substrate (iPr-enone) are 2.6 kcal mol^{-1} different in energy, and indeed for this reaction significant, but low ee values (up to ~20%) have been obtained. Further optimization of asymmetric reductive reaction could proceed along these lines.

Experimental Section

General procedure for the reductive arylation reaction.

In a flame-dried Schlenk tube, equipped with a stopper and a stirring bar, 1.1 mmol (1 equiv.) of base (LiOMe, 1 M in THF) was added. The solvent (THF) was then removed under reduced pressure to obtain a white powder. The Schlenk tube was then charged with Pd^{0}(L)(MA)$_2$ (0.75 mol%), 4-iodo anisole 2 (1.1 mmol), and benzylideneacetone 1 (1.65 mmol) and subsequently flushed 3 times with a cycle of vacuum-argon. The solvent isopropyl alcohol (iPrOH) (2 mL) containing decane as internal standard was then transferred into the Schlenk tube which was then placed into a preheated oil bath at 60 ºC. Upon reaction completion (after 30 minutes; judged by GC), the reaction mixture was cooled down to room temperature and a sample of 10 µL was taken and diluted to 1 ml with dichloromethane (DCM) and subsequently subjected to GC/GC-MS analysis (for more detailed data, see supporting information).

DFT calculation details.

All calculations and geometry optimizations were performed using the Turbomole program package[26], coupled to the PQS Baker optimizer[41] via the BOpt package[42] at the spin unrestricted ri-DFT level using the BP86 functional[27,28] and the def2-TZVP basis set[29] for the geometry optimizations. All geometries of minima with no imaginary frequencies and

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transition states with one imaginary frequency were characterized by numerically calculating the Hessian matrix (for detailed information see SI).

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Keywords: Reductive Heck; Reductive arylation, Reducing agent; Pd-catalyed reaction; Asymmetric reductive Heck; isopropanol

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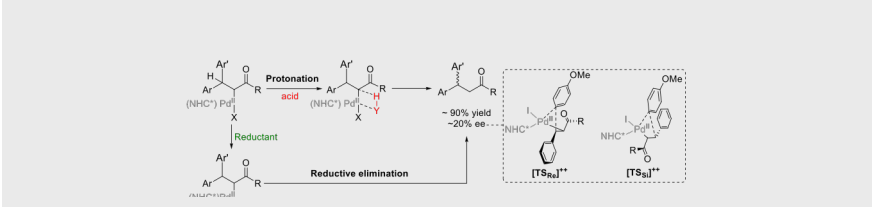

The role of reductant in the palladium-NHC catalyzed reductive Heck reaction and its effect on the mechanism of the reaction is reported.

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The Importance of the Reducing Agent in Direct Reductive Heck Reactions

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