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Mechanism of Pd(NHC)-Catalyzed Transfer Hydrogenation of Alkynes

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Abstract: The transfer semihydrogenation of alkynes to (*Z*)-alkenes shows excellent chemo- and stereoselectivity when using a zerovalent palladium(NHC)(maleic anhydride)-complex as precatalyst and triethylammonium formate as hydrogen donor. Studies on the kinetics under reaction conditions showed a broken positive order in substrate and first order in catalyst and hydrogen donor. Deuterium-labeling studies on the hydrogen donor showed that both hydrogens of formic acid display a primary kinetic isotope effect, indicating that proton and hydride transfers are separate rate-determining steps. By monitoring the reaction with NMR, we observed the presence of a coordinated formate anion and found that part of the maleic anhydride remains coordinated during the reaction. From these observations, we propose a mechanism in which hydrogen transfer from coordinated formate anion to zerovalent palladium(NHC)(MA)(alkyne)-complex is followed by migratory insertion of hydride, after which the product alkene is liberated by proton transfer from the triethylammonium cation. The explanation for the high selectivity observed lies in the competition between strongly coordinating solvent and alkyne for a Pd(alkene)-intermediate.

Introduction

The partial hydrogenation of alkynes to *cis*-alkenes is a very important transformation in synthetic organic chemistry.[1] It is particularly relevant for the synthesis of biologically important molecules such as natural products, pharmaceuticals, and fragrance chemicals, since many of these molecules incorporate carbon−carbon double bonds with defined Z or E configurations. Despite the usefulness of this reaction, it has been studied far less extensively than the similar hydrogenation of carbon−carbon double bonds.[1,2] Several homogeneous Pd-complexes that catalyze this reaction have been reported by us[3−5] and others,[6] and examples of other metal-complexes that are able to catalyze this reaction are known based on Ru-,[7,8] Rh-,[9] or Fe-complexes.[10] However, this process is often plagued by over-reduction after full conversion, leading to saturated compounds. Also cis/trans isomerization usually occurs to a considerable extent, and issues with reproducibility have been encountered.[1,11] Some examples of chemo- and stereoselective alkyne semihydrogenation have been reported, but very few studies have addressed the mechanism of the reaction or explained the observed selectivity.[4,12,13] For the development of better catalytic systems, it is of vital importance to understand the mechanism, enabling a directed search for new catalysts.

Recently, we described a system for semihydrogenation of alkynes that cleanly and reproducibly leads to *Z*-alkenes, using Pd^0(IMes)(MA) complex **1** as precatalyst, which is prepared *in situ* from our standard Pd^0-precursor Pd(tBuDAB)(MA) **2**, 1,3-bis(mesityl)imidazolium chloride, and *t*-potassium butoxide (Scheme 1). The over-reduction to alkanes is fully inhibited

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Scheme 1. Transfer Semihydrogenation of 1-Phenyl-1-propyne Using Triethylammonium Formate and *in Situ* Generated Complex **1**

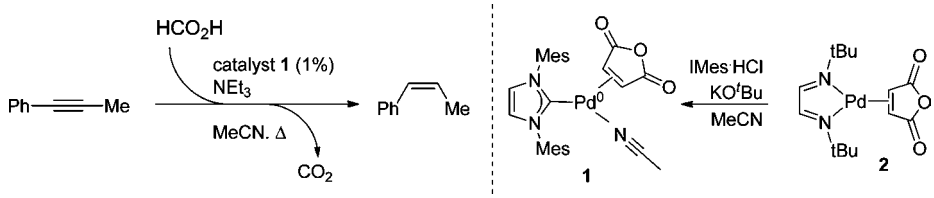

Table 1. Effect of Various Hydrogen Donors on the Hydrogenation of 1-Phenyl-1-propyne to *Z*-*β*-Methylstyrene with Precatalyst **1**[a]

entry	hydrogen donor	[donor] mol L^{-1}	base	[base] mol L^{-1}	[alkyne] mol L^{-1}	[catalyst] ($\times 10^{-3}$) mol L^{-1}	rate ($\times 10^{-3}$) mol h^{-1}	selectivity (Z/E/alkane)[b]
1	HCO_2H	0.87	NEt_3	0.87	0.16	0.90	1.50	95.2/3.9/0.9
2	HCO_2H	0.96	NEt_3	0.41	0.18	1.6	0.50	96.4/3.7/0.0
3	HCO_2H	0.94	NEt_3	0.11	0.18	1.6	0.045	96.7/3.3/0.0
4	HCO_2H	0.61	NH_3	0.61	0.10	1.2	0.041	95.3/4.0/0.7
5	HCO_2H	0.82	Na_2CO_3	0.59	0.13	1.3	0.011	93.2/2.9/3.9
6	iPrOH	13.06	-	-	0.25	2.5	0.014	1/-/-

[a] Conditions: Reactions are performed in refluxing MeCN, using *in situ* generated precatalyst **1**. [b] Selectivity reported after 24 h.

when formic acid is used as hydrogen donor in strongly coordinating solvents,[14,15] whereas the use of hydrogen gas still gives over-reduction. This increased chemoselectivity strongly hints at different modes of operation for the formic acid-mediated transfer hydrogenation versus hydrogenation with molecular hydrogen.

Mechanistic studies on transfer hydrogenation have focused on ketones and imines as the abundant substrates, and several mechanisms are known to operate depending on the catalyst, substrate, and the hydrogen donor.[16,17] However, carbonyls are more reactive than alkenes or alkynes because of the high degree of polarization of the C═O bond, and the only known alkenes subject to transfer hydrogenation are also highly polarized.[18,19] According to calculations by Comes-Vives and Lledós, the activation barriers for nonpolar substrates are approximately 10 kcal/mol higher than for polar substrates.[17] This difference is reflected in the observation that transfer hydrogenation of acetophenone has become a standard reaction for testing new catalytic systems, whereas relatively few examples are known of hydrogen transfer to alkenes[18,19] or alkynes.[8,14,15,20] Hence, the mechanism of transfer hydrogenation of carbon−carbon multiple bonds has been studied only marginally.[17,19]

This scarcity in profound mechanistic understanding for both alkene transfer hydrogenation and partial alkyne hydrogenation prompted us to thoroughly investigate the mechanism of the formic acid mediated partial alkyne transfer hydrogenation. The main issues to be addressed are (1) what is the mechanism of the Pd-catalyzed hydrogen transfer and (2) why is over-reduction inhibited in our system? We decided to study the kinetics of the transfer hydrogenation of 1-phenyl-1-propyne and the role of hydrogen donor and base on rate and selectivity. Furthermore, several catalytically relevant metal complexes were isolated and catalytic intermediates were investigated using *in situ* NMR-spectroscopy and deuterium-labeling of the precatalyst and the hydrogen donor.

Results and Discussion

1. Kinetic Studies. Knowledge about the kinetics of a reaction is essential for discussion of the mechanism. Hence, the reaction was monitored by GC and the rate of reaction and its dependence on the concentration of the reactants were obtained from the reaction profiles, using the initial rates method. This method is straightforward, reliable, and especially suitable for reactions that are not very fast. A 5-fold excess of HCO_2H/NEt_3 was used to ascertain that product selectivity toward alkene is not due to a shortage of hydrogen donor.

We initially investigated whether the acid/base-ratio affects the rate and what the influence of the base strength is. As can be seen from Table 1, the presence of base is essential for an efficient reaction, as the rate is drastically lower if HCO_2H is in excess to NEt_3, even if NEt_3 is still in excess to alkyne (Table 1, entries 1−3).

We also performed the reaction with Na_2CO_3 as base or ammonium formate as hydrogen donor (Table 1, entries 4−5), but both give inferior results compared to triethylammonium formate (TEAF). The reaction with ammonium formate is much slower than with *in situ* generated TEAF; this difference is attributed to the relative pK_b values of ammonia and triethylamine. Na_2CO_3 is too basic; the reaction was even slower than without added base. The active hydrogen donor is probably an ammonium formate species, as the reaction becomes very sluggish once the amount of NEt_3 is decreased relative to HCO_2H (Table 1, entries 1−3); therefore, we used TEAF in the kinetic studies. Isopropyl alcohol, the standard hydrogen donor for transfer hydrogenation of ketones, is not an efficient hydrogen donor for the transfer hydrogenation of alkynes (Table 1, entry 6).

1.1. Dependence of the Reaction Rate on the Catalyst Concentration. The concentration of precatalyst **1** was varied between 0.1 and 8.3 mM, keeping the initial concentration of hydrogen donor constant at 0.8 M and substrate concentration at 0.18 M. The reaction rate shows a linear dependency on the

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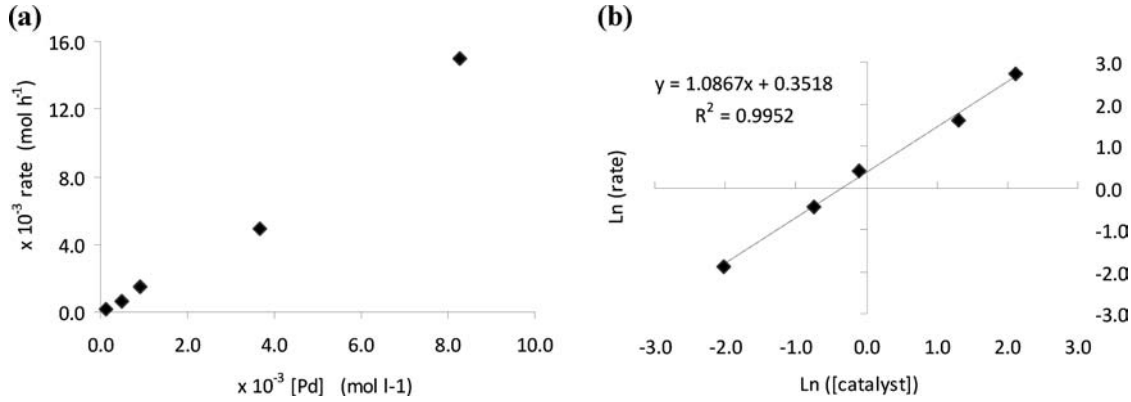

Figure 1. (a) Plot of rate of hydrogenation versus catalyst concentration. (b) Plot of ln(rate) versus ln[catalyst].

Table 2. Kinetic Data for Hydrogenation of 1-Phenyl-1-propyne to *Z*-β-Methylstyrene by *in Situ* Generated **1**, Varying [Precatalyst **1**][a]

entry	[catalyst] (x 10^{-3}) mol L^{-1}	rate ($\times$ 10^{-3}) mol h^{-1}	k_{obs} $L^{2.3}$ h^{-1} $mol^{-2.3}$	selectivity (Z/E/alkane)[b]
1	0.13	0.15	2.1	98.8/1.2/0
2	0.48	0.64	2.6	98.3/1.7/0
3	0.90	1.5	3.1	95.2/3.9/0.9
4	3.67	4.9	2.4	77.2/13.2/9.6[c]
5	8.26	15.0	3.4	68.6/16.3/15.1[d]

[a] Conditions: Reactions are performed in refluxing MeCN, using *in situ* generated precatalyst **1**, [alkyne] = 0.18 M, [TEAF] = 0.90 M. [b] Selectivity is reported after 24 h. [c] Product selectivity at 80% conversion (20 min): 97.2/2.2/0.6. [d] Product selectivity at 80% conversion (10 min): 95.3/3.3/1.4.

Table 3. Kinetic Data for Hydrogenation of 1-Phenyl-1-propyne to *Z*-β-Methylstyrene by *in Situ* Generated **1**, Varying [TEAF][a]

entry	[TEAF] mol L^{-1}	rate ($\times$ 10^{-3}) mol h^{-1}	k_{obs} $L^{2.3}$ h^{-1} $mol^{-2.3}$	selectivity (Z/E/alkane)[b]
1	0.14	0.33	4.2	98.3/1.7/0
2	0.24	0.79	5.9	97.2/2.8/0
3	0.45	1.19	4.8	96.6/2.9/0.5
4	0.83	1.24	2.8	97.2/2.8/0
5	1.76	1.91	2.1	97.4/2.4/0.2

[a] Conditions: Reactions are performed in refluxing MeCN, using *in situ* generated precatalyst **1**, [1-phenyl-1-propyne] = 0.18 M; [precatalyst **1**] = 0.92 mM. [b] Selectivity is reported after 24 h.

palladium concentration (see Figure 1a; rates are listed in Table 2). Plotting ln(rate) versus ln[Pd], as presented in Figure 1b, yields a straight line of slope 1.09, showing that the transfer semihydrogenation of 1-phenyl-1-propyne is first order in palladium. This implies that the active catalyst is a homogeneous species, and not a precatalyst that is converted into catalytically active Pd nanoparticles. It seems that a low catalyst loading improves the product selectivity for alkenes (*vide infra*).

1.2. Dependence of the Reaction Rate on Hydrogen Donor Concentration. The concentration of TEAF was varied between 0.1 and 1.6 M, keeping the concentrations of catalyst and substrate constant at 0.90 mM and 0.16 M, respectively. The reaction rate shows a linear dependency on the TEAF concentration, which levels off above 0.5 M (Figure 2a; rates are listed in Table 3). Plotting ln(rate) versus ln[TEAF], as presented in Figure 2b, yields a straight line of slope 1.06, showing that the hydrogenation of 1-phenyl-1-propyne is first order in triethylammonium formate. It has been established that the concentration of hydrogen donor has no effect on the selectivity.

1.3. Dependence of Reaction Rate on Substrate Concentration. The alkyne concentration was varied between 0.03 and 0.43 M, keeping the concentrations of catalyst and TEAF constant at 0.9 mM and 0.8 M, respectively. At alkyne concentrations below 0.15 M, the reaction rate shows a positive linear dependency with respect to the alkyne concentration, while above 0.15 M, an increase in alkyne concentration results in a decrease of the rate (Figure 3a; rates are listed in Table 4). Plotting ln(rate) versus ln[alkyne], as presented in Figure 3b, yields two straight lines, with slope +0.28 ([alkyne] < 0.15 M) and −0.75 ([alkyne] > 0.15 M). The broken orders in alkyne concentration imply that the substrate coordinates to palladium before the rate-determining step and that an equilibrium is involved between the Pd(solvent)-complex + alkyne and the Pd(alkyne) complex. This is in accordance with the strong solvent effect we had already observed in the optimization of the catalytic system.[14]

We have attempted to study the association constant of 1-phenyl-1-propyne for the catalyst using ^{1}H NMR, but no change in chemical shift was observed upon addition of precatalyst to a sample of 1-phenyl-1-propyne in DMSO-d_6.

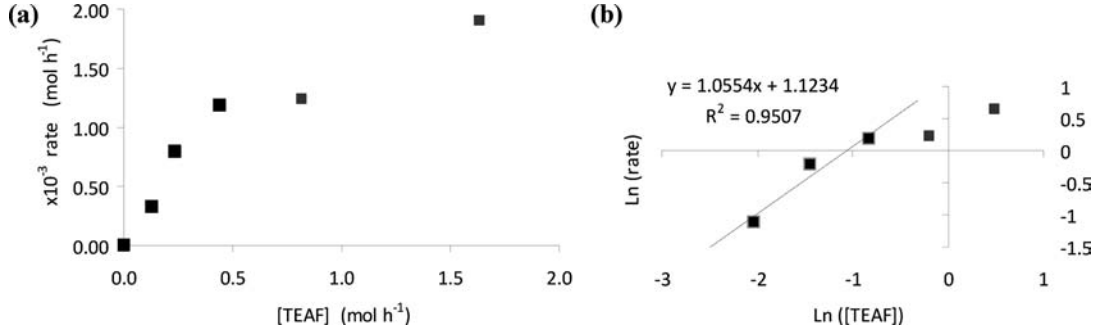

Figure 2. (a) Plot of rate of hydrogenation versus hydrogen donor concentration. (b) Plot of ln(rate) versus ln[TEAF].

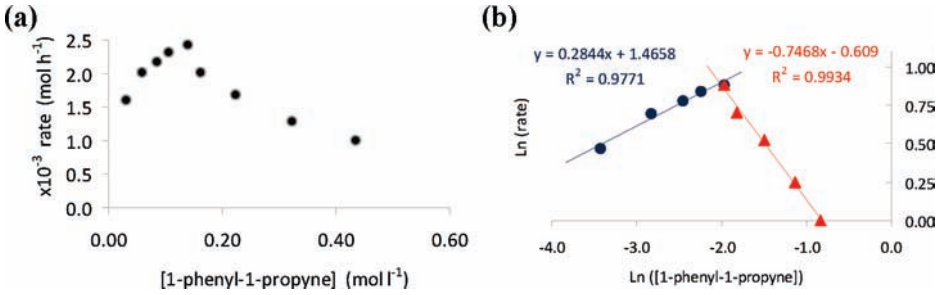

Figure 3. (a) Plot of rate of hydrogenation versus substrate concentration. (b) Plot of ln(rate) versus ln[1-phenyl-1-propyne]; circles represent values at [alkyne] < 0.15 M, triangles represent values at [alkyne] > 0.15 M.

Table 4. Kinetic Data for Hydrogenation of 1-Phenyl-1-propyne to *Z*-β-Methylstyrene by *in Situ* Generated **1**, Varying [1-phenyl-1-propyne][a]

entry	[alkyne] mol L^{-1}	rate ($\times 10^{-3}$) mol h^{-1}	k_{obs} $L^{2.3}$ h^{-1} $mol^{-2.3}$	selectivity (Z/E/alkane)[b] >90% conversion	selectivity (Z/E/alkane)[b] 24 h
1	0.03	1.6	6.2	74.9/9.4/15.6	47.1/17.1/35.8
2	0.06	2.0	6.5	90.9/3.7/5.3	47.2/21.1/31.7
3	0.09	2.2	6.2	93.4/3.9/2.7	47.2/21.1/31.7
4	0.11	2.3	5.9	94.6/3.2/2.2	61.2/17.7/21.4
5	0.14	2.4	5.8	92.7/3.4/3.9	46.2/11.7/42.0
6	0.16	2.0	4.7	n.a.	97.0/2.1/1.0
7	0.23	1.7	3.6	n.a.	97.1/2.4/0.6
8	0.32	1.3	2.4	n.a.	98.7/1.3/0.0
9	0.44	1.0	1.9	n.a.	97.9/1.6/0.5

[a] Conditions: Reactions are performed in refluxing MeCN, using *in situ* generated precatalyst **1**; [TEAF] = 0.77 M; [precatalyst **1**] = 0.95 mM. [b] Selectivity is reported after 24 h. For higher concentrations this was only determined after 24 h, even if full conversion was not attained (n.a.). Selectivity at >90% conversion is at last point before full conversion (between 90 and 99% conversion).

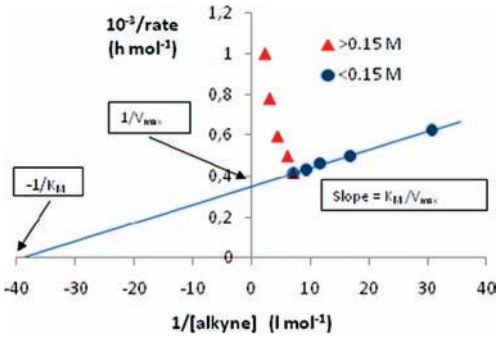

Figure 4. Lineweaver−Burke plot: 1/[alkyne] vs 1/rate. Circles represent values at [alkyne] < 0.15 M, triangles represent values at [alkyne] > 0.15 M.

Amatore and Jutand have already found that the affinity of internal alkynes for coordinatively unsaturated $Pd(PPh_3)_2$ is very low, significantly lower than that of terminal alkynes, so at low concentrations the equilibrium will be on the side of noncoordinated alkyne.[21] Because of the observed substrate inhibition, we analyzed the data for Michaelis−Menten kinetics. This gave a good fit and Figure 4 shows the Lineweaver−Burke plot of 1/[rate] as a function of 1/[alkyne], which is linear at [alkyne] < 0.15 M. Herewith, we found that V_{max} = 2.85 mmol/h (if there were no catalyst deactivation at high alkyne concentration) and K_M = 25.5 mM (substrate concentration at which rate = $^1/_2V_{max}$).[22]

From the leftmost part of Figure 3a, one sees that the slope slightly decreases with increasing alkyne concentration. At sufficiently high concentrations ([alkyne] > 0.15 M), the order in alkyne changes from a positive to a negative order. We believe this change in order occurs because the alkyne is involved in two concurrent reactions: a productive reaction with a Pd(solvento)-species to form a Pd(alkyne)-species that leads toward hydrogenation (with $[alkyne]^{0.28}$), and a side-reaction with that Pd(alkyne)-species to form a catalytically inactive complex (with $[alkyne]^{-1}$). At [alkyne] > 0.15 M, the second reaction effectively competes with the catalytically productive reaction for the alkyne present; this decreases the concentration of *active* catalyst, so the *net* reaction becomes slower at higher substrate concentration. The observed order in alkyne is the sum of the separate orders, rendering the order in alkyne −0.75. At [alkyne] ≪ 0.15 M, the concentration of the Pd(alkyne)-species is too low to significantly affect the reaction rate. The change in sign of the substrate order at higher alkyne concentration may be explained by the formation of $Pd(alkyne)_2$-complexes (substrate inhibition) or palladacylopentadiene species that act as a sink for catalyst species (Scheme 2).

We have noted this behavior before in the Pd(Ar-BIAN)(alkene)-catalyzed semihydrogenation of 4-octyne with molecular hydrogen.[4] In that system, the optimum concentration of alkyne was 0.32 M; more electron-poor alkynes give more stable metallacycles, so the concentration above which palladacycle formation effectively competes with hydrogenation will be lower for aromatic alkynes than for aliphatic alkynes.[23] Attempts to isolate these palladacyclic species from the reaction mixture were not successful. (Triphenyl)mesitylenes formed by reaction

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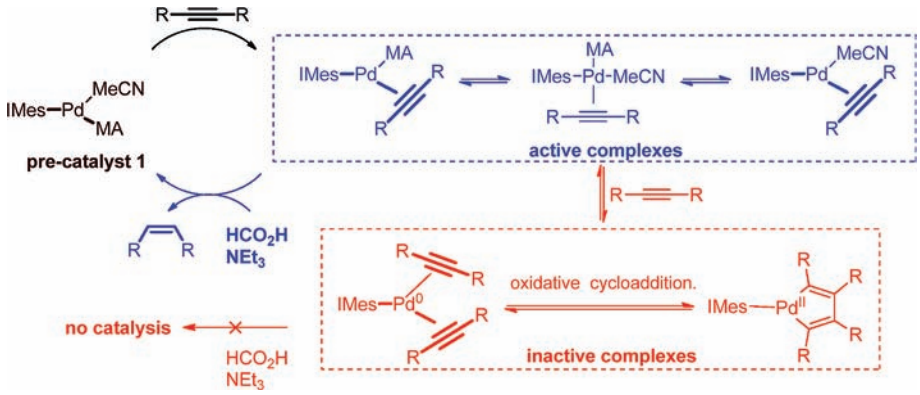
Scheme 2. The Equilibrium between Precatalyst **1** and Substrate Gives Several Potentially Active Species



of palladacyclopentadiene-species with an additional equivalent of alkyne have not been observed by NMR, nor by GC.

At high catalyst loading (Pd/alkyne-ratio), the selectivity for *Z*-alkene is seriously affected (compare entries 1, 4, and 8 in Table 4). The effect of concentration of alkyne on catalytic behavior had already been observed in the solvent screening, where more strongly coordinating solvents gave rise to a slower but more selective reaction.[14] When performing the reaction in THF, even the addition of 1 mol % of MeCN induces a higher selectivity and lower rate, and with 1 equiv of MeCN, near-full selectivity is observed (Figure 5). It is well-known that palladium(0)-complexes show highly dynamic behavior in solution and they can easily exchange weakly coordinating ligands, the equilibrium conditions depending on the nature and relative concentrations of all ligating species.[24] A lower ratio of alkyne-to-palladium will on the whole lead to less-protected palladium, which enhances the reactivity toward alkynes but also toward the product alkene, thus, increasing over-reduction to alkane.

1.4. Rate Equation. Combination of the observed rate dependencies allows us to set up an experimental rate law for palladium-catalyzed semihydrogenation of 1-phenyl-1-propyne with TEAF in acetonitrile:

$$\frac{\mathrm{d(substrate)}}{\mathrm{d}t} = -k_{\mathrm{cat}} \cdot [\mathrm{alkyne}]^{0.28} \cdot [\mathrm{TEAF}] \cdot [\mathrm{catalyst}] \quad (1)$$

Equation 1 is only valid at alkyne concentrations below 0.15 M, and shows that the reaction rate depends on the concentrations of hydrogen donor, substrate, and catalyst in a positive fashion. This means that alkyne and formate will both coordinate to a Pd species before the rate-determining step. When the alkyne concentration is increased to above 0.15 M, part of the catalyst reacts with alkyne to form a catalytically inactive species. This makes the concentrations of catalyst and alkyne interdependent, so setting up a rate law in this concentration range would be meaningless.

1.5. Mechanism—Competition. A first interpretation of the kinetic data leads to a simplified image of the catalytic cycle, shown in Scheme 3, which focuses on the role of competition between substrate and solvent for palladium. Starting from *in situ* generated complex **I**, solvent is replaced by a substrate molecule to give a complex **II**, after which the alkyne is hydrogenated by TEAF (*vide infra*), giving a complex of type **III**. The alkene product can be displaced by the more strongly coordinating solvent, closing the catalytic cycle to obtain the desired alkene product. For a more weakly coordinating solvent, complex **III** is longer lived and could react with another molecule of TEAF to give the saturated product, which is immediately displaced by solvent and thus regenerates complex **I**. This reasoning implies that the chemoselectivity of the reaction is dictated by the lifetime of complex **III**, which is determined not only by the coordinative properties of the solvent, but also by the strength of the Pd—alkene bond. The strength of the Pd—alkene bond depends on the electron density on the metal and the pi-accepting properties of the alkene. Substituents on the alkene (and alkyne) that increase the pi-accepting capacity will then lead to decreased chemoselectivity. This reasoning is in agreement with our previous finding that alkynes with electron-withdrawing substituents (e.g., dimethyl butynedioate) give significant over-reduction, while most simple aliphatic and aromatic alkynes give the *Z*-alkene in 90—99% yield.[14] Also the observed solvent-competition fits very well with this explanation. As these are all equilibrium reactions (except for the hydrogenation), part of the alkene will also be displaced by alkyne, directly transforming **III** to **II**. So, at higher catalyst/substrate ratios, the lifetime of species **III** will increase and thus give a higher tendency for over-reduction, which is what was indeed observed in the kinetics of substrate and catalyst.

Concerning the role of maleic anhydride, several possibilities can be envisaged *a priori*; (i) it may remain coordinated to the metal, (ii) it might dissociate, or (iii) it could be hydrogenated to succinic anhydride. The latter is seen in alkyne hydrogena-

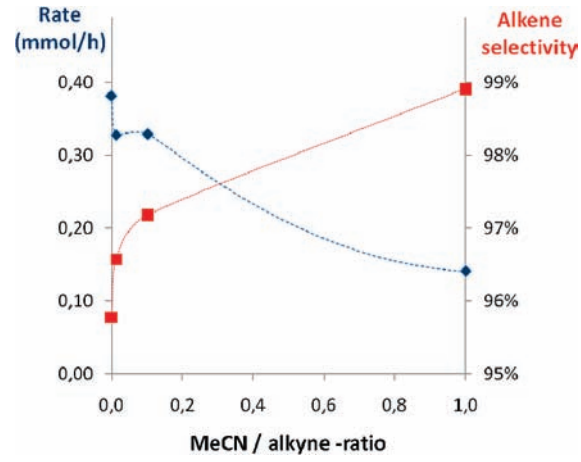


Figure 5. Transfer hydrogenation of 1-phenyl-1-propyne in THF, with increasing amounts of MeCN; MeCN/alkyne ratio vs rate and alkene selectivity. Rate is depicted in diamonds and relates to values on the primary *y*-axis; alkene selectivity is depicted in squares and relates to values on the secondary *y*-axis. Conditions: [alkyne] = 0.15 M, [catalyst] = 15 mM, [TEAF] = 0.75 M in refluxing THF.

Scheme 3. Simplified Catalytic Cycle, Focusing on the Effect of Competition between Solvent, Alkynes, and Alkenes for the Catalyst

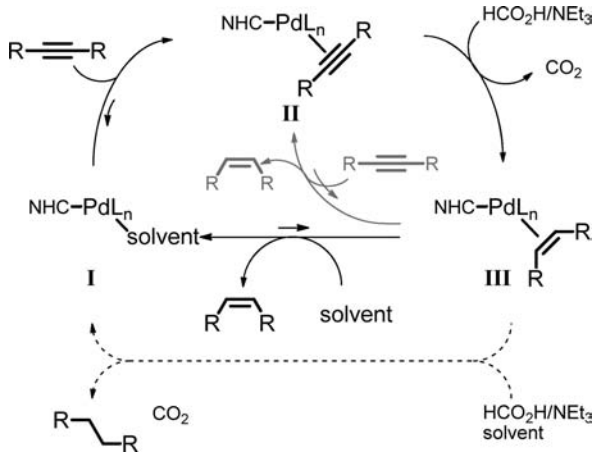


Table 5. Effect of Deuterated Formic Acids on the Rate of Transfer Hydrogenation of 1-Phenyl-1-propyne to *Z*-β-Methylstyrene by *in Situ* Generated **1**[a]

entry	formic acid	[formic acid] mol L^{-1}	rate ($\times$ 10^{-3}) mol h^{-1}	k_{cat} L$^{2.3}$ mol$^{-2.3}$ h^{-1}
1	HCO_2H	0.38	1.32 $\pm$ 0.12	5.81 $\pm$ 1.38
2	HCO_2D	0.37	0.54 $\pm$ 0.09	2.39 $\pm$ 0.82
3	DCO_2H	0.36	0.52 $\pm$ 0.10	2.38 $\pm$ 0.88
4	DCO_2D	0.36	0.34 $\pm$ 0.04	1.61 $\pm$ 0.39

[a] Conditions: Reactions are performed in refluxing MeCN, using *in situ* generated catalyst **1**; [1-phenyl-1-propyne] = 0.11 M, [NEt_3] = 0.50 M, [catalyst] = 1.05 mM, in refluxing MeCN, using *in situ* generated precatalyst **1**. All reactions were done in triplicate, values are averaged.

Table 6. Kinetic Isotope Effects of Transfer Hydrogenation of 1-Phenyl-1-propyne to *Z*-β-Methylstyrene by *in Situ* Generated **1**

	K_H/K_D
HCO_2H/DCO_2H	2.43 $\pm$ 0.33
HCO_2D/DCO_2D	1.48 $\pm$ 0.33
HCO_2H/HCO_2D	2.45 $\pm$ 0.35
DCO_2H/DCO_2D	1.47 $\pm$ 0.35
HCO_2H/DCO_2D	3.60 $\pm$ 0.27

tions with Pd(Ar-Bian)(dmfu).[4] In the current case, we have neither observed maleic anhydride nor succinic anhydride in the GC of aliquots of the reaction, nor in the NMR-spectrum of the product, so we postulate that maleic anhydride remains coordinated to the complex during reaction (*vide infra*).

2. Isotopic Labeling of the Hydrogen Donor. We investigated the role of the two different hydrogens in formic acid by performing the reaction with the various deuterium-labeled formic acids (HCO_2D, DCO_2H, and DCO_2D). It appears that the reaction rate decreases with increasing deuterium-content; note that reactions of both monodeuterated formic acids (HCO_2D and DCO_2H) proceed at the same rate (Table 5). Comparing the rates of the reactions with labeled formic acids, a primary kinetic isotope effect (KIE) of 2.4 is observed on both the formic (CH/CD) and the acidic (OH/OD) position, while the kinetic isotope effect upon double isotopic substitution is 3.6 (Table 6).

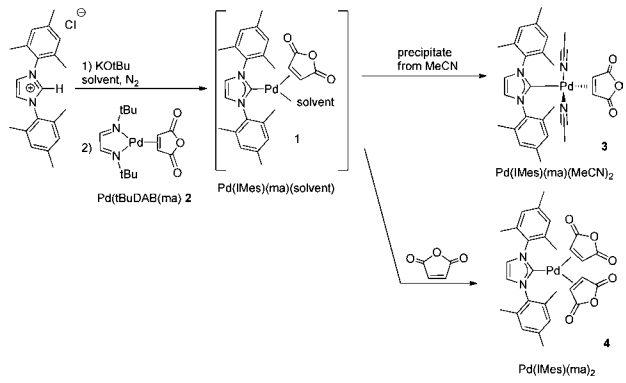
The observation of a kinetic isotope effect due to single isotopic substitution, on either the formic or the acidic position, means that both the bond to the formic hydrogen and that to the acidic hydrogen are broken or formed in the rate-determining step. Casey et al., in their studies on transfer hydrogenation of imines, have shown that the observation of a primary kinetic isotope effect does not necessarily imply that the transfers of the acidic and formic hydrogens occur in a single elementary step. They showed that the transfer of hydrogens may take place in a concerted fashion or it may involve two separate hydrogen transfer steps with approximately equal barriers, and that these processes can be distinguished.[25] For a concerted reaction in which both hydrogens are transferred in a single step, the kinetic isotope effect for the doubly labeled material should be equal to the product of the two individual isotope effects. In our case, $KIE_{CHOH/CHOD} \times KIE_{CHOH/CDOH} = 5.95$, which is appreciably larger than the experimentally observed $KIE_{CHOH/CDOD}$ of 3.60. Hence, we conclude that the acidic hydrogen and the hydridic hydrogen from formic acid are transferred in two distinct steps, and that these transfers have approximately equal activation energies.

Apart from the effect of isotopic labeling on the reaction rate, this experiment also allows us to observe whether the hydrogens retain their identity during the reaction, and if so, whether a distinction is made in the mechanism between the two carbons of the alkyne. For this, we looked at the ^{1}H NMR (integral and multiplicity) and ^{2}H NMR (integral) of the products. In the ^{1}H NMR of the hydrogenation products, we see that the distribution of protons between the two olefinic positions is roughly equal: for both monodeuterated formic acids, the integrals of both olefinic protons add up to one hydrogen compared to the five aromatic hydrogen nuclei. For the dideuterated formic acid, a minor amount of not-fully deuterated product is observed in ^{1}H NMR; the integral of the olefinic protons accounts for approximately 0.12 hydrogens relative to five aromatic hydrogens. The presence of unlabeled product is probably caused by the faster reaction with nonlabeled formic acid. This partly protonated product shows a broad singlet and a broadened quartet in ^{1}H NMR, as would be expected when the vicinal position is occupied by deuterium instead of hydrogen. In the product of unlabeled formic acid, a doublet and a doublet of quartets are seen for the olefinic protons, whereas for monodeuterated formic acids, these peaks are broadened due to the presence of mono-, as well as nondeuterated products.

The ^{2}H NMR of the products shows that the deuterium distribution depends on the position of the ^{2}H in the formic acid: for HCO_2D, the integral of the deuteron at the α-position was 15% larger than that of the deuteron at the β-position, whereas with DCO_2H and with DCO_2D, the integral of the α-deuteron was 15% smaller than that of the β-deuteron.[26] First of all, this means that the hydrogens retain their identity during the reaction. Furthermore, the first hydrogen is delivered to the more accessible β-position of the alkyne and originates from the formic position, assuming the sterically most accessible position is attacked first. In case of the 1-phenyl-1-propyne, the difference in steric demand between the Ph$-$C and C$-$CH$_3$ sites is not very large, which may explain why a preference of 'only' 15% for the β-position has been observed. For all labeled formic acids, approximately 10% of the signal in ^{2}H NMR is seen at the γ position. Indeed, monitoring the deuteration experiments

(24) Clement, N. D.; Cavell, K. J.; Ooi, L.-L. *Organometallics* **2006**, *25*, 4155–4165.
(25) Casey, C. P.; Singer, S. W.; Powell, D. R.; Hayashi, R. K.; Kavana, M. *J. Am. Chem. Soc.* **2001**, *123*, 1090–1100.
(26) We assume that the product is mostly monodeuterated, as one of the referees noted. We believe this is a reasonable assumption, based on the integrals in the ^{1}H-NMR of the product. Also, if a substantial amount would be non- or dideuterated, this would be seen in the multiplicity of the peaks in the ^{1}H-NMR.

Scheme 4. Synthesis of Various Pd(IMes)(MA)-Complexes



with GC reveals a trace of allylbenzene as a transient species, which accounts for the ^{2}H-scrambling.

2.1. Catalyst Isolation. In previous work, we have found that *in situ* generated Pd^0(NHC)(MA)-complexes are more selective catalysts for the hydrogenation of alkynes than isolated Pd-(NHC)(MA)$_2$-complexes.[3] Therefore, the transfer semihydrogenation of alkynes was developed with *in situ* generated Pd^0(IMes)(MA)-complexes,[14] where the open coordination site is occupied by solvent. As the reaction is slower but more selective in MeCN than in THF, we postulated that in acetonitrile a [Pd^0(IMes)(MA)(MeCN)] species is the source of active catalyst. To verify this, we attempted the isolation of such a species. Indeed, by concentration of a catalyst solution in MeCN, an off-white solid could be precipitated, which appeared from NMR to be complex **3**, a Pd(IMes)(MA)-complex with two coordinated acetonitrile molecules (Scheme 4).

In ^{1}H NMR, we observe that the maleic anhydride hydrogens in **3** have become inequivalent (2.91 and 3.45 ppm), while at elevated temperatures, these peaks coalesce to a broad singlet at 3.0 ppm (60 °C, 300 MHz). This indicates that at room temperature there is hindered rotation around the Pd−alkene bond and the alkene hydrogens experience inequivalent magnetic environments. This effect has been seen in similar Pd^0-(NHC^N)(MA)-complexes, and there the X-ray structure shows that one of the MA-proton signals is near the shielding region of the aromatic ring, explaining the lower chemical shift.[15] Also, the methyl peaks on the ortho-position of the IMes ligand experience different environments (2.08 and 2.10 ppm), indicating a spatial orientation of the IMes that differentiates between the two aromatic groups.

Using NOESY NMR-experiments, we found many NOE cross-peaks, most notably that of the NHC-backbone protons with the maleic anhydride protons. For a complex with square planar geometry, these C−H bonds are perpendicular to each other and further away than in a tetrahedral geometry, as is common for 18-electron Pd complexes. Despite our best efforts, attempts to grow X-ray quality crystals of **3** failed. We have optimized the geometry of this complex with density functional theory, with which we observed dissociation of one of the acetonitrile ligands (in the gas phase). In solution, the second molecule of acetonitrile may still be weakly coordinated, in accordance with the relatively small shift upon coordination and the integral of 6H of the MeCN protons. Additionally, the inequivalence of both maleic anhydride protons and both aromatic rings is clearly seen in the simulated structure of **3** (Figure 6). We have also tried to obtain the solvent-stabilized complex from a catalyst solution in THF, but this only gave decomposition to palladium black. An additional equivalent of maleic anhydride was needed, giving the previously reported complex Pd(IMes)(MA)$_2$ **4**.[3]

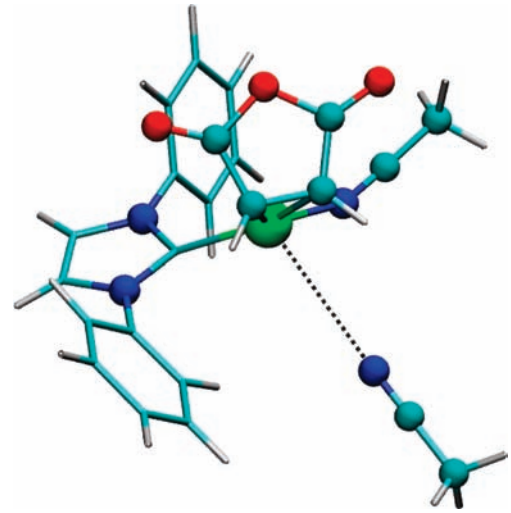
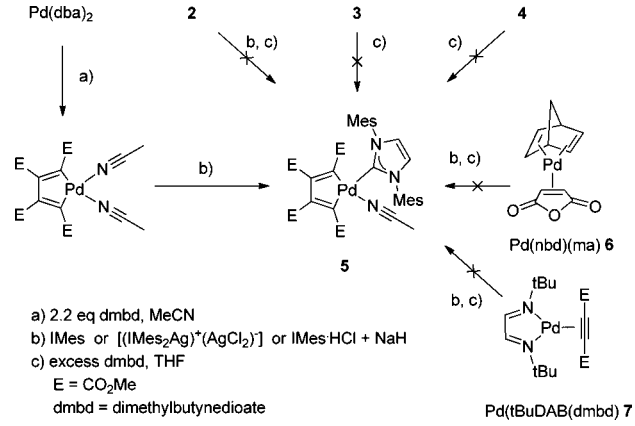


Figure 6. Simulated structure for compound **3**.

Scheme 5. Synthesis of Palladacyclopentadiene(NHC)-Complexes



2.2. Palladoles as Substrate-Inhibited Catalyst. In Scheme 2, we postulated the formation of palladacyclopentadiene species as a sink for active catalyst, to explain the inverse order in substrate at high concentrations. Although we were not able to isolate such palladoles from the reaction mixture, the synthesis of palladacycle **5** with an IMes-moiety was possible under certain conditions (Scheme 5).

For simple aromatic alkynes, the reaction of several Pd-precursors with a carbene and/or excess alkyne failed to produce the desired palladacyclopentadiene(NHC)-complexes. Substitution of alkene from solvent complexes **1** or **3**, or formation of a Pd(IMes)-complex from Pd^0-precursors **2** or **6** followed by cycloaddition of alkyne proved unsuccessful. Cycloaddition for Pd(tBuDAB)(alkyne)-complex **7** does not occur, as already shown by tom Dieck,[27] but coordination of IMes to alleviate the steric demand of the diimine ligand and subsequent cyclization with excess alkyne also did not yield the desired product. We were able to isolate complex **5** when using the more electron-withdrawing dimethyl butynedioate (dmbd), but only if the palladacyclopentadiene moiety had already been formed prior to coordination of the NHC. This shows that the

(27) tom Dieck, H.; Munz, C.; Müller, C. *J. Organomet. Chem.* **1990**, *384*, 243–255.

Table 7. Catalysts Tested in Transfer Hydrogenation of 1-Phenyl-1-propyne (Structures in Chart 1)

entry	catalyst	TOF h^{-1}	selectivity (Z/E/alkane)[a]
1	**1**	100.6	95.2/3.9/0.9
2	aged **1**[b]	74.6	87.3/9.2/3.5
3	**3**	18.0	92.3/6.1/1.6
4	**4**	25.6	80.1/10.0/9.9[c]
5	**5**	108.6	91.6/5.4/3.0
6	**5** + 1% MA	21.2	96.0/3.0/1.0
7	**8**	14.7	96.4/2.7/0.9
8	**8**, no base	1.0	95.8/4.2/0.0

[a] Selectivity determined by GC, after 24 h, conditions in Supporting Information. [b] Two months aged stock solution. [c] Selectivity after 90% conversion (3.5 h) is 93.5/5.0/1.6, TOF = 15.9 mol/(mol/h).

formation of these proposed cyclopalladated species is possible, but not straightforward under catalytic conditions, and may only occur in the presence of >150 equiv of alkyne. Reaction of *in situ* generated complex **1** with 160 equiv of 1-phenyl-1-propyne gives a complex that spectroscopically resembles **5**. Complex **5** is the first example of a palladacyclopentadiene species with a coordinated *N*-heterocyclic carbene, while complex **7** is one of the few examples of Pd−alkyne complexes that have been crystallized.[28] Because of the high electron-density on the metal, it shows very strong back-bonding, with an alkyne carbon−carbon bond distance of 1.287(2) Å) (see Supporting Information).

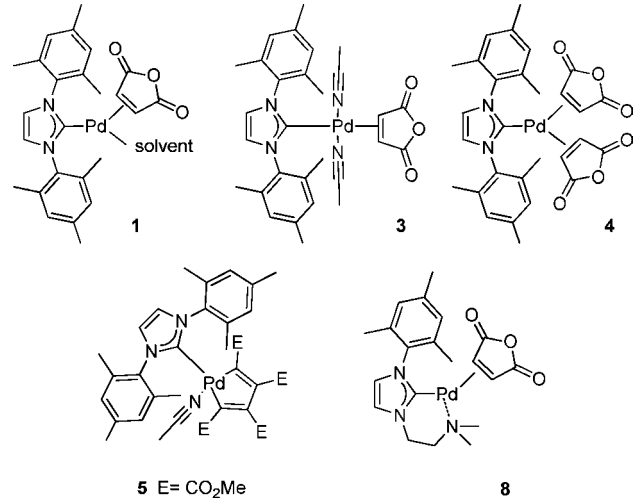
2.3. Catalytic Studies with Isolated Catalysts. To confirm whether the isolated solvent-complex **3** indeed resembles the catalytically active species, we compared its activity and selectivity with the *in situ* generated precatalyst **1**. Complex **3** exhibits the same excellent chemoselectivity as the *in situ* prepared catalyst (Table 7, entry 1 vs 3). The Z-selectivity for complex **3** is somewhat lower, but the absence of over-reduction is seen for both precatalysts. Employing the isolated complex **3** as precatalyst leads to a lower rate of transfer hydrogenation of 1-phenyl-1-propyne compared to the same reaction with the *in situ* generated precatalyst **1**; still no induction period is observed. Although one would predict the same solution-phase structures when starting from **1** and **3**, the reaction with *in situ* generated species still contains the diimine ligand from **2**. So in **1** additional ligand is present that probably facilitates a dissociative step in the mechanism to increase the rate of reaction, while at the same time aiding MeCN in the competition for Pd(alkene) intermediate **III** to give higher alkyne selectivity.

We have also repeated the reaction with a catalyst stock solution in MeCN that had been standing for 2 months and it shows only little decomposition: a decrease of rate is observed and Z-selectivity is slightly lower, but over-reduction is still marginal (Table 7, entry 2). This shows that the solvated catalyst species is very stable and that after partial decomposition it is able to isomerize alkenes but does not reduce them. In comparison, the palladium bis(maleic anhydride) complex **4** as precatalyst is neither as fast nor as selective as solvent-stabilized complexes **1** or **3**.

Although palladacyclopentadiene-complexes could not be isolated from the catalysis reaction mixture, the reaction does proceed with a relatively high reaction rate when employing palladole **5** as a catalyst precursor at [alkyne] < 0.15 M (Table 7, entry 5). The chemoselectivity is lower for **5**, compared to *in situ* generated **1** or isolated **3**, but complex **5** is equally fast as precatalyst **1**. We have previously seen that Pd^{II}-complexes are not selective transfer hydrogenation catalysts,[15] so it is

(28) McGinnety, J. A. *J. Chem. Soc., Dalton Trans.* **1974**, *59*, 1038–1043.

Chart 1. Precatalysts Tested in Transfer Hydrogenation of 1-Phenyl-1-propyne



reasonable to assume that the catalytic cycle starts from a Pd^0-complex. For complex **5**, this implies that the formation of the palladacyclopentadiene from a Pd(IMes)(alkyne)$_2$-complex is reversible under these conditions, even for the electron-poor dimethyl butynedioate. After retrocycloaddition from **5**, the formed Pd(IMes)(dmbd)$_2$ complex loses its alkynes either by dissociation or hydrogenation and generates Pd^0(IMes)-species with ligands that are only weakly coordinating compared to complex **3**. When the reaction is performed with **5** and 1 equiv of maleic anhydride to protect the 'naked' Pd^0(IMes)-species formed, the same excellent selectivity is observed as for **3**, along with a decrease in rate (Table 7, entry 6). Surprisingly, the presence of maleic anhydride on the complexes moderates the reactivity toward alkynes, and thus decreases the tendency toward over-reduction of product alkene to alkane.

From the TEAF-kinetics, we found that an equimolar amount of base to acid is required to obtain high reaction rates, but when using Pd(NHC-amine) complex **8**, the reaction also proceeds without additional base (Table 7, entries 7−8).[15] With this ligand, the hemilabile amine functions as an internal base during hydrogenation. After hydrogenation of alkyne, the amine can re-coordinate to stabilize the complex and promote the dissociation of alkene, completely suppressing the over-reduction to obtain full chemoselectivity for alkynes.

3. NMR Studies. To gain more insight into the nature of the species present during catalysis, we have monitored the reaction by ^{1}H NMR, which had to be done in DMSO-d_6 as the solubility of complex **3** in acetonitrile is too low. Prior to the reaction, a control experiment was performed without alkyne but with 1 equiv of TEAF at 60 °C. Signals that could belong to a metal hydride were not identified, but an upfield shift was observed in the *N*-ethyl signals, while the formic proton shifted downfield, indicating coordination of the formate anion to Pd and the presence of a triethylammonium cation. In the absence of alkyne, the complex decomposed to the corresponding imidazolium salt and Pd black. Also, a signal is seen at 5.97 ppm, of which the carbon resonates at 136.57 ppm ($^1J_{CH}$ = 158 Hz), indicative for maleic anhydride alkene carbons (*vide infra*). We then performed the transfer hydrogenation reaction, adding 2 equiv of 1-phenyl-1-propyne and then 2 equiv of triethylammonium formate to complex **3** in DMSO-d_6 (Figure 7). Within 10 min after addition, the formation of *Z*-*β*-methylstyrene was observed

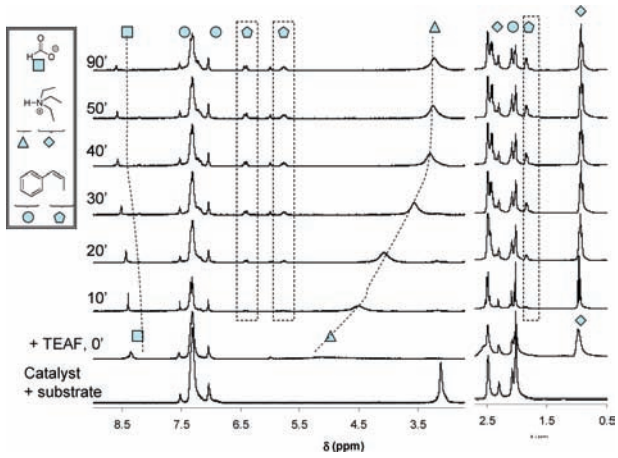


Figure 7. The 300 MHz ^{1}H NMR spectra of **3** and 1-phenyl-1-propyne in DMSO-d_6 at 60 °C, after addition of TEAF in DMSO-d_6, and during reaction. The different species are marked above the spectra: squares (formic hydrogen), circles (aromatic hydrogens and $^{im}C_{4,5}$-hydrogens of the catalyst), pentagons (alkene and methyl hydrogens of the product), triangles (ammonium proton), and diamonds (methyl and methylene peaks of triethylammonium cation).

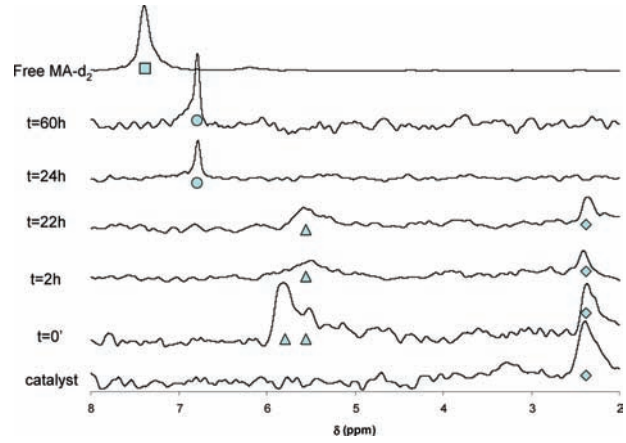


Figure 8. (a) 46 MHz ^{2}H NMR spectra of **3-*d*$_2$** during reaction with 1-phenyl-1-propyne and triethylammonium formate in DMSO at 25 °C; top spectrum is of pure, noncoordinated 2,3-dideuterio maleic anhydride. The different species are marked above the spectra: diamonds (starting catalyst **3-*d*$_2$**), triangles (active catalyst), circles (catalyst after reaction) and squares (uncoordinated maleic anhydride-d_2).

(^{1}H-signals at 6.39 ppm, 5.76 ppm and 1.85 ppm); no formation of either the corresponding E-isomer or propylbenzene was observed. The formic hydrogen shifted the same as in the control experiment (8.35 → 8.55 ppm), but now another very broad signal was observed at 5.66 ppm which is attributed to the proton on the triethylammonium cation. As the reaction proceeds, this signal shifts to 3.36 ppm, indicating that the positive charge is distributed over more than one amine as the reaction mixture becomes more basic. This shift is also seen in the ethyl signals of NEt_3, though less pronounced.

The remainder of the complex proton signals behaved in a similar manner to the control experiment, with an upfield shift of the triethylammonium peaks and downfield shift of the formate anion (Figure 7, diamonds resp. square). Notably, some decomposition of the catalyst is seen but remarkably less than in the control experiment. As the ratio of alkyne/TEAF = 1, the over-reduction at high catalyst loading is not observed.

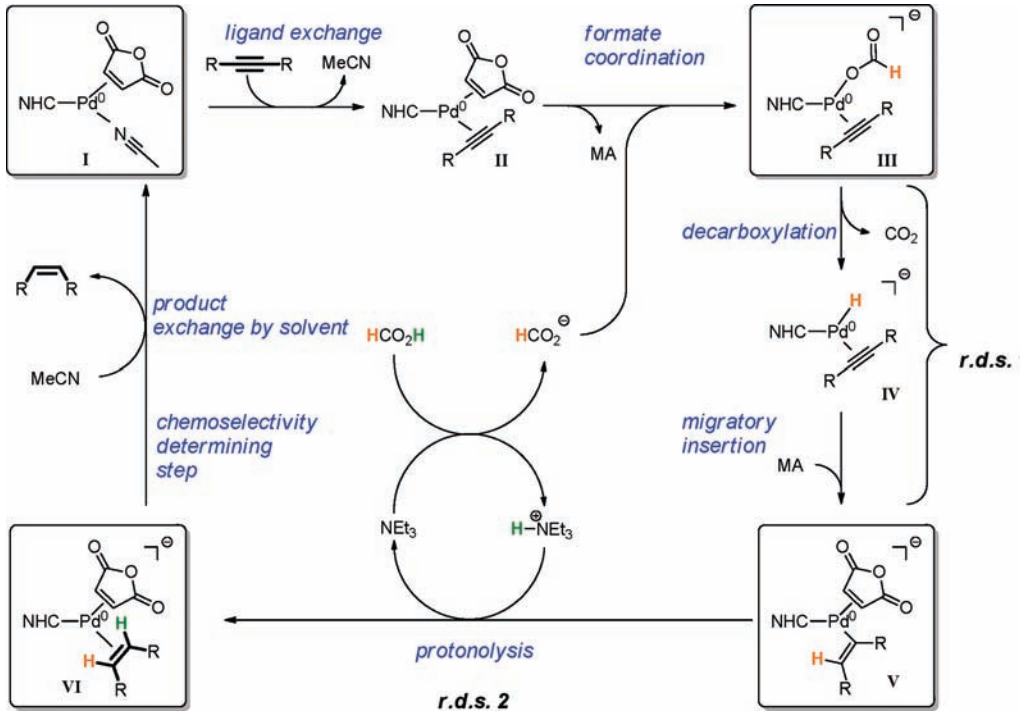
From this experiment, we conclude that a palladium formate species is formed, which in the presence of alkyne transfers a hydride to the coordinated alkyne, probably via Pd. In the absence of alkyne, the palladium formate decarboxylates to form a Pd(II) hydride which decomposes upon reductive elimination of imidazolium salt. In neither case signals were observed in the hydride region. This could indicate that the hydride is rapidly transferred to the alkyne, making the decarboxylation the first rate-determining step. However, another reason for not observing a hydride signal is fast relaxation of the hydride because of the quadrupole Pd; hence, we cannot rule out that the subsequent migratory insertion of alkyne into Pd−H is the first rate-determining step.

3.1. Labeled Catalyst. In previous research, we have shown that during alkyne hydrogenation with Pd^0(Ar-BIAN)(alkene)-complexes as catalysts, the alkene is hydrogenated off to form the active catalyst.[4] We wondered whether this would also be the case for our current NHC-based precatalysts **1** or **3**. However, by ^{1}H NMR this cannot be verified, because the hydrogens of noncoordinated maleic anhydride would be obscured by the aromatic hydrogens of the mesityl-substituent on the carbene ligand. Therefore, we prepared complex **3-*d*$_2$** in which the maleic anhydride is deuterium-labeled, and performed the reaction in an NMR-tube while monitoring by ^{2}H NMR. The reaction was carried out at 25 °C to decrease the reaction rate, because the low solubility of the catalyst requires longer acquisition time, and spectra were recorded every hour over a 72 h period. Figure 8 shows that during the reaction only part of the catalyst is in the native state (diamonds, 2.4 ppm), while part of the catalyst bears maleic anhydride with a more downfield shift (triangles) around 5.5 ppm. The pi-backdonation should be significantly diminished to shift the maleic anhydride signal downfield to such an extent; either an additional very strong pi-acceptor is coordinated, or the orbital overlap is decreased because of steric congestion by incoming substrate, or a Pd(II) hydride is formed. To the best of our knowledge there is no precedent of coordinated maleic anhydride signals at such low field, and we are hesitant to claim this with such limited evidence. Another possibility is that hydrolysis of (uncoordinated) maleic anhydride to maleic acid occurs, which causes an upfield shift of the alkene ^{1}H signals to around 6.0 ppm. However, after the reaction, this signal shifts to 6.8 ppm, and upon addition of an additional equivalent of MA-d_2 after the reaction, the signal at 6.8 ppm increases and only after addition of more than 5 equiv of MA-d_2 some uncoordinated MA-d_2 is observed at 7.4 ppm. This observation shows that exchange of coordinated and uncoordinated maleic anhydride is fast on the NMR time scale, implying that free maleic anhydride is already present during the reaction. By comparison with ^{2}H NMR spectra of authentic samples of succinic anhydride, we have ascertained that this is not present in the reaction medium, so maleic anhydride is not hydrogenated off to activate the complex. Although we cannot conclusively identify the nature of the formed species, it is clear that part of the maleic anhydride remains coordinated during the reaction.

3.2. Proposed Catalytic Cycle. With the catalytic cycle of alkyne hydrogenation proposed for Pd(diimine)-complexes in mind,[29] we initially thought that the mechanism would consist of oxidative addition of the formic acid O−H-bond, migratory insertion of the hydride into the Pd−alkyne bond, decarboxylation of the formyl anion to CO_2, and reductive elimination from a Pd(alkenyl)(hydride). On the basis of our current

(29) Dedieu, A.; Humbel, S.; Elsevier, C.; Grauffel, C. *Theor. Chem. Acc.* **2004**, *112*, 305–312.

Scheme 6. Proposed Catalytic Cycle for Transfer Hydrogen of Alkynes to *Z*-Alkenes, Catalyzed by Complex **1** with Triethylammonium Formate As Hydrogen Donor



experimental results, this hypothesis must clearly be revised. For the hydrogen donor, we found that (1) a Pd(formate) intermediate is involved, (2) the nature and concentration of base is important, and (3) the kinetic isotope effects dictate two rate-determining steps with similar activation energies, involving both hydrogens of formic acid. The studies of the catalyst and kinetics showed that (4) maleic anhydride is not hydrogenated off as expected previously, but is partly coordinated during reaction and moderates the catalytic activity; also (5) substrate and formate are coordinated to Pd before the rate-determining steps. Furthermore, (6) the coordination of solvent versus the alkyne is competitive and strongly influences the chemoselectivity. We therefore propose a mechanism that starts from species **I**, a Pd^0-complex containing an *N*-heterocyclic carbene ligand, maleic anhydride, and acetonitrile (Scheme 6).

Displacement of solvent from **I** by alkyne, and subsequent coordination of formate anion forms complex **III**, probably with dissociation of maleic anhydride to retain a 16-electron configuration. Jutand and Amatore have shown that similar anionic Pd(0)-species containing, for example, chloride or acetate as anions are *the* active species in Heck and cross-coupling reactions, much more reactive than their neutral counterparts.[30] From species **III**, the coordinated formate decarboxylates to give palladium hydride species **IV**, which after migratory insertion into the Pd−alkyne bond gives species **V**; one of these is the first rate-determining step. The alkene is obtained by protolytic cleavage, which is the second rate-determining step to give the Pd−alkene species **VI**, and the alkene is displaced by solvent or alkyne to close the catalystic cycle. The lifetime of species **VI** determines the amount of over-reduction, and thus the chemoselectivity. The groups of Lledós and Joó have shown by calculations that for alkyne hydrogenation with $[\{RuCl_2(m\text{tppms})_2\}_2]$ in water the Z/E-selectivity is determined by the order in which the proton and hydride are added to the alkyne, and this mechanism resembles our proposed catalytic cycle.[13] For a mechanism in which the hydride is added first and the Pd−alkenyl bond is broken by protonolysis, the product is the *Z*-alkene; the *E*-alkene is formed if the proton is added to alkyne prior to hydride transfer. The reason they give for the high Z-selectivity is that the approach of the proton to the Pd(alkenyl)-species is hindered by the aryl-group, disfavoring formation of *E*-alkene. This rationalizes two of our observations, namely, that (1) bulky diphenylacetylene is hydrogenated in higher (>99% Z) selectivity than 1-phenyl-1-propyne, and (2) Pd(NHC^amine)(MA) complex **8** is a more selective catalyst toward *Z*-alkene in the absence of an external base.

Conclusion

The mechanism of Pd^0(IMes)-catalyzed transfer hydrogenation of alkynes has been elucidated for the case of 1-phenyl-1-propyne. Kinetics and several observations allow us to propose a viable catalytic cycle for this transformation. A number of similarities but also differences are seen when comparing to transfer hydrogenation of carbonyls or to alkyne hydrogenation using molecular hydrogen. We have found that the transfer of hydrogens from the hydrogen donor to the substrate takes place in two separate rate-determining steps. These hydrogens keep their identity during the reaction, as seen from the distribution of the ^{2}H-label across the alkene bond when formic acid isotopomers were used. When these observations are compared with transfer hydrogenation of ketones, a resemblance with an inner-sphere monohydride mechanism comes to mind, but a metal-hydride species for such a mechanism could not be observed. Concerning other known alkyne semihydrogenations, a comparison of Pd^0(NHC)(alkene) with Pd^0(Ar-BIAN)(alkene) is obvious. However, in the present study, we have a monodentate NHC ligand instead of a bidentate BIAN-ligand; hence, in the current case, the alkene need not be hydrogenated off to

(30) Amatore, C.; Jutand, A. *Acc. Chem. Res.* **2000**, *33*, 314–321.

obtain a catalytically active complex. This allows the maleic anhydride ligand to moderate the electron-density of the metal, a property we found of importance for the chemoselectivity of the reaction. The main difference between the known hydrogenation of alkynes with molecular hydrogen and the current catalytic system involving transfer hydrogenation is a strong competition between substrate and solvent for a Pd(alkene) intermediate occurring in the transfer hydrogenation, which is not observed in the hydrogenation with molecular H_2. This competition ensures negligible concentration of unsaturated Pd(alkene) species, decreasing the chance of reaction with a second equivalent of hydrogen. As such this competition between substrate and solvent is important for the selectivity of the transfer hydrogenation and in fact determines the complete absence of over-reduction, a selectivity that has proven to be difficult to obtain for other systems for catalytic hydrogenation of alkynes.

Prospectively, the stability of the Pd(product alkene) intermediate **VI** might be tuned by adjusting the electronic properties of the catalyst precursor, which may lead to higher selectivity for alkynes with electron-withdrawing groups. In this way, our mechanistic investigation does not only explain the details of the reaction itinerary, but it also provides new insights, upon which new catalysts for transfer hydrogenation reactions may be designed.

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Supporting Information Available: Concentrations and reaction rates for kinetic measurements depicted in Tables 2−5 and 7, kinetic study methodology, general experimental methods, experimental details and characterization for **3**, **3-d_2**, **5**, **7** and the palladacyclopentadiene bis(acetonitrile)-complex (PDF); compound I (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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