Kinetic Studies of Acetate Exchange in *trans*-4-Acetoxy-[η^3-(1,2,3)-cyclohexenyl]palladium Complexes. Relevance for Asymmetric 1,4-Oxidation Reactions

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The acetate/acetate-d_3 exchange reaction of the ring-bonded acetate of bis(4-acetoxy-[η^3-(1,2,3)-cyclohexenyl])palladium acetate-d_3 complexes **1a**−**c** was studied in acetic acid solutions using ^{1}H NMR spectroscopy. The reactions followed first-order kinetics in palladium, and the rates were highly affected by the presence of methanesulfonic acid or lithium acetate. The nature of the substituent in the 2-position of the complex was found to have a large impact on the reaction rate. Complexes **1a**−**c** are observed intermediates in the benzoquinone-assisted palladium(II)-catalyzed 1,4-diacetoxylation reaction of 1,3-dienes. Complex **1b** was treated with stoichiometric amounts of the enantiomerically pure ligand (*S*)-(+)-2-(4′-fluorophenylsulfinyl)-1,4-benzoquinone **4** under conditions where no exchange reaction occurs. Kinetic resolution was observed, implying that the two enantiomers of **1b** reacted to *trans*-1,4-diacetoxy-2-phenyl-2-cyclohexene with different rates. Attempts to demonstrate dynamic kinetic resolution in stoichiometric reactions between **1b** and **4** were unsuccessful. The major reason for this is presumably that with lithium acetate the equilibrium reaction between the two enantiomers of **1b** is too slow compared to the chiral benzoquinone-induced attack of acetate to give the products. Under very acidic conditions the decomposition of the (π-allyl)palladium complex is faster than benzoquinone-induced product formation. This scenario is in full agreement with our observed rates.

Introduction

The palladium(II)-catalyzed 1,4-oxidation of 1,3-dienes, developed in our laboratories over the past two decades, has become a synthetically useful reaction.[1] Different nucleophiles, including carboxylic acids, halides, alcohols, and functionalized amines, can be introduced at the 1- and 4-positions of 1,3-dienes with high regioselectivity. The stereoselectivity can easily be controlled, and a diastereomeric excess of more than 90% is usually achieved.

Enantioselective Pd(II)-catalyzed reactions are still scarce.[2] Recently, we started studying the enantioselective version of the 1,4-oxidation reaction. One approach has been to employ chiral *p*-benzoquinone derivatives as ligands since *p*-benzoquinone is known to act as a rate-accelerating ligand[3] in the reaction (Scheme 1). In the proposed mechanism, nucleophilic attack by acetate on an η^4-coordinated Pd-diene complex (**I**) yields a (π-allyl)palladium complex (**II**). Subsequent coordination of benzoquinone gives **III** and activates Pd toward a second nucleophilic attack, which yields the olefinic product and Pd(0) in an irreversible step. Finally, benzoquinone reoxidizes Pd(0) to Pd(II). Catalytic amounts of benzoquinone can be used if the hydroquinone formed is reoxidized by the use of either manganese dioxide[3,4] or molecular oxygen/iron phthalocyanine.[5] In our studies on enantioselective palladium-catalyzed 1,4-oxidation, we have so far only obtained moderate enantioselectivity, i.e., 45 and 54% e.e. in the diacetoxylation[6] and dialkoxylation[7] reaction, respectively.

It is unclear whether benzoquinone coordinates to Pd(II) during the complete reaction cycle or only during the second nucleophilic attack. For the asymmetric

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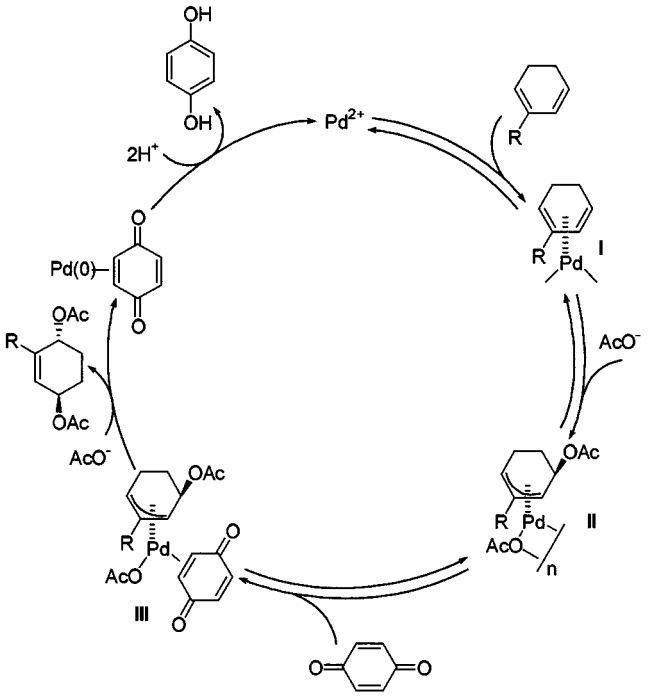
Scheme 1



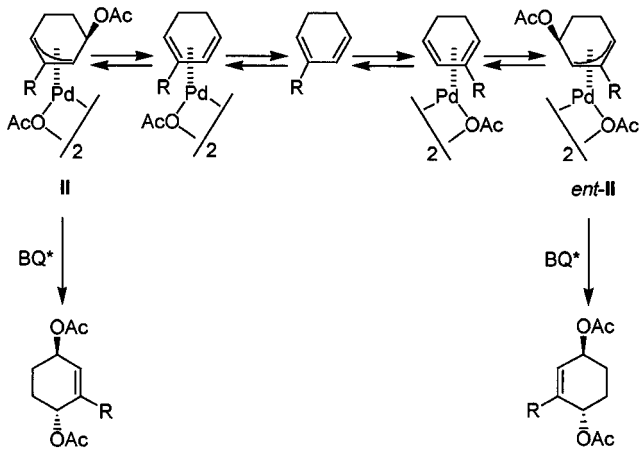
version, chiral benzoquinone ligands (BQ*) are used. These ligands contain heteroatoms which can coordinate more strongly to Pd(II). One might envision three possible ways the asymmetric induction can take place, and one of the following mechanisms should operate to obtain enantioselectivity in the catalytic reaction:

1. The ligand coordinates to Pd(II) throughout the catalytic cycle and the chirality is introduced during the first nucleophilic attack. The formation of the two possible diastereomeric (π-allyl)palladium(BQ*) complexes is irreversible, and the diastereomeric ratio of the intermediate governs the enantiomeric excess of the product.

2. The ligand does not coordinate to Pd(II) during the first nucleophilic attack, and a racemic mixture of two enantiomeric (π-allyl)palladium complexes **II** is produced. An equilibrium between the two enantiomers exists via the diene that requires release of the diene from Pd(II). If the coordination of BQ* to **II** and *ent*-**II** is irreversible, it is the rate difference of the formation of **III** that would govern the enantioselectivity. This feature is known as dynamic kinetic resolution.[8] This case is only valid if the interconversion between **II** and *ent*-**II** is considerably faster than coordination to BQ* to **II** and *ent*-**II** (see Scheme 2), according to the Curtin−Hammett principle.[9]

3. A combination of mechanisms 1 and 2. The ligand coordinates to Pd(II) throughout the catalytic cycle and the chirality is introduced during the first nucleophilic attack. One of two possible diastereomeric (π-allyl)-palladium(BQ*) complexes is formed to a greater extent than the other. An equilibrium between the two diastereomers exists via the diene, but the rate of the second nucleophilic attack is different for both diastereomers. This rate difference as well as the diastereomeric ratio between the (π-allyl)palladium(BQ*) complexes govern the enantiomeric excess of the product. With two diastereomers in equilibrium, this mechanism is referred to as dynamic kinetic asymmetric transformation.[10]

Scheme 2



Many studies have been performed on (π-allyl)-palladium complexes, as they are common intermediates in many palladium-catalyzed reactions.[11] Szabó et al.[12] have shown that strong acid can catalyze the elimination of acetic acid from bis(4-acetoxy-[η^3-(1,2,3)-cyclohexenyl])palladium chloride complexes in chloroform−methanol solutions. However, to the best of our knowledge, nothing has been published concerning the behavior of bis(4-acetoxy-[η^3-(1,2,3)-cyclohexenyl])palladium acetate complexes in acetic acid solutions. An acid-catalyzed elimination of acetic acid under the latter conditions would facilitate a fast equilibrium between the two enantiomers of complex **II** in the diacetoxylation reaction, given that the elimination and coordination of the free diene is also fast. Knowledge of the factors that affect the equilibrium between the diene and the (π-allyl)palladium complex is of general interest for the understanding of the mechanism of the palladium-catalyzed 1,4-oxidations of 1,3-dienes and might be of major importance in the development of the asymmetric version of this reaction.

In this publication we report on ^{1}H NMR spectroscopy studies concerning equilibrium reactions of bis(4-acetoxy-[η^3-(1,2,3)-cyclohexenyl])palladium acetate complexes in acetic acid solutions and how the reaction rate is affected by the reaction conditions and substituents on the cyclohexenyl ring. The relationship between the rate of the equilibrium and the asymmetric induction has been studied in stoichiometric reactions of bis(4-

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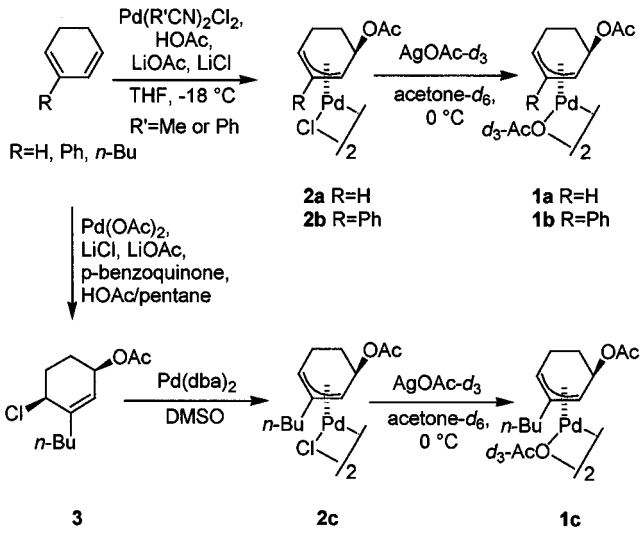
Scheme 3



acetoxy-2-phenyl-[η^3-(1,2,3)-cyclohexenyl])palladium acetate with a chiral benzoquinone ligand.

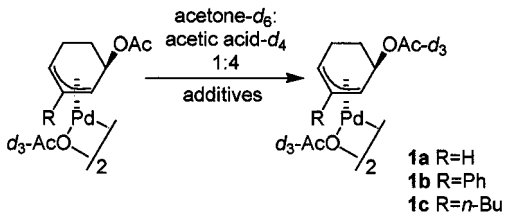
Results and Discussion

Synthesis of Starting Materials. In 1,4-oxidation reactions of 2-substituted 1,3-dienes it is known that the first attack occurs preferentially at the least substituted double bond, giving a (π-allyl)palladium intermediate with the substituent at the middle carbon of the π-allyl.[13] To study the effect of different substituents in this position, the three (π-allyl)palladium complexes **1a**−**c** were prepared. Following a literature procedure,[14] the dimeric chloropalladium complexes **2a** and **2b** were prepared by reaction of the appropriate 1,3-diene with stoichiometric amounts of $Pd(CH_3CN)_2Cl_2$ or $Pd(PhCN)_2Cl_2$ in the presence of lithium chloride and lithium acetate at −18 °C (see Scheme 3). For 2-phenyl-1,3-cyclohexadiene only one product (**2b**) was formed. However, the attempted synthesis of **2c** by this method resulted in an inseparable mixture of **2c** and 20% of the other regioisomer. Therefore, an alternative route was chosen. 2-*n*-Butyl-1,3-cyclohexadiene was oxidized in a 1,4-acetoxychlorination reaction,[15] yielding *cis*-4-acetoxy-2-*n*-butyl-1-chloro-2-cyclohexene (**3**). Compound **2c** was then obtained by an oxidative addition of **3** to $Pd(dba)_2$ in dimethyl sulfoxide.[12,16]

The acetate-d_3 complexes **1a**−**c** were obtained by treating the corresponding chloride complexes **2a**−**c** with deuterated silver acetate in acetone-d_6. Since these complexes are somewhat unstable, they were prepared shortly before the NMR experiments. Deuterated acetate was employed as bridging ligands in complexes **1a**−**c** to avoid interfering signals from palladium-bonded acetate in the ^{1}H NMR spectra.

Kinetic Experiments by ^{1}H NMR Spectroscopy. The rate of acetate/acetate-d_3 exchange in the 4-position of bis(4-acetoxy-[η^3-(1,2,3)-cyclohexenyl])palladium acetate-d_3 complexes **1a**−**c** was studied in acetic acid-d_4 by ^{1}H NMR spectroscopy at 25 °C (Scheme 4).

Scheme 4



Although these reactions are in equilibria, they can be considered irreversible in our experiments since the deuterated acetic acid is present in large excess. The acetate exchange, which should reflect the equilibrium between the two enantiomeric (π-allyl)palladium complexes via the free diene (cf. Scheme 2), was carried out under reaction conditions similar to those of the catalytic 1,4-oxidations of 1,3-dienes. Thus, acetone-d_6/acetic acid-d_4 1:4 was chosen as the solvent for the NMR experiments.[6] However, the 1,4-oxidation reactions are carried out in the presence of various additives, depending on the type of reaction. For example, the 1,4-diacetoxylation reaction is usually performed in the presence of lithium acetate to obtain a high stereoselectivity,[3] whereas the 1,4-dialkoxylation reaction requires the addition of methanesulfonic acid.[17] DFT calculations have shown that protonation of the ring-bonded acetate enhances the rate of elimination of acetic acid from 4-acetoxy-[η^3-(1,2,3)-cyclohexenyl]palladium complexes, yielding (η^4-cyclohexadiene)palladium.[12] Furthermore, 0.5 equiv of sulfuric acid per palladium metal center was used in the 1,4-alkoxy-acetoxylation of 1,3-dienes to destabilize the bis(4-acetoxy-[η^3-(1,2,3)-cyclohexenyl])palladium complex that is formed as an undesired intermediate.[18]

The effect on the kinetics of the addition of acid or lithium acetate was studied by varying the concentrations of these additives. For the acid-catalyzed exchange reactions, sulfuric acid was used initially. Substantial amounts of decomposition of the reacting (π-allyl)-palladium complexes were observed though, the reason probably being the presence of small amounts of water. Even after severe drying of the acetone-d_6/acetic acid-d_4 solvent mixture by the addition of 5% acetic anhydride-d_6 it was impossible to obtain reliable values for the rates of the exchange reactions because of traces of water in the sulfuric acid. We therefore changed to methanesulfonic acid as the proton source, which gave more reproducible results. Furthermore, the exact amount of added acid could be determined by integration. The following three conditions were compared in the exchange reactions:

A. acetone-d_6/acetic acid-d_4 1:4, 5% acetic anhydride-d_6

B. acetone-d_6/acetic acid-d_4 1:4, 5% acetic anhydride-d_6, methanesulfonic acid

C. acetone-d_6/acetic acid-d_4 1:4, lithium acetate-d_3

The exchange of acetate for acetate-d_3 was monitored by ^{1}H NMR spectroscopy by measuring the correspond-

(13) The regiochemistry can be explained by the proposed mechanisms for 1,4-acetoxychlorination and acyloxyalkoxylation reactions; see also refs 15 and 18.

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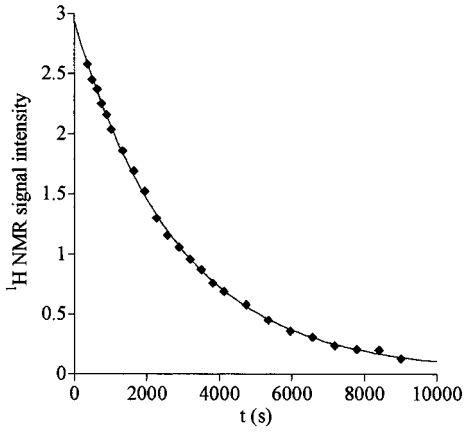


Figure 1. Example of a ^{1}H NMR measurement. Complex **1b** in acetone-d_6/acetic acid-d_4, 1:4, 0.1 M lithium acetate-d_3.

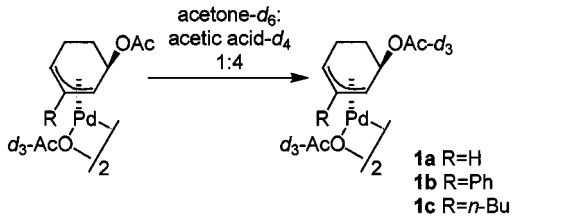
ing decrease of the 4-acetoxy resonance. The production of CH_3COOD was concurrently observed as it appeared as a new signal. The integral of the 4-acetoxy signal was compared to the integral of one of the allyl proton signals, which was employed as an internal reference within the (π-allyl)palladium complexes. The ratio of the integrals of the signals was plotted against time and was under all conditions in nice agreement with pseudo-first-order kinetics (Figure 1).

Decomposition of (π-Allyl)palladium Complexes during Measurements. In all experiments, a small amount of decomposition of the (π-allyl)palladium complexes was observed. The decomposition was followed by ^{1}H NMR using 1,4-dimethoxybenzene as an internal standard.[19] The intensity of the methoxy group signal of the internal standard was compared to the signal of one of the allyl protons. The decomposition was neglected in the calculations of the observed rate constants (k_{obs}). It should therefore be kept in mind that, due to the decomposition, the true rate constants might be slightly higher than those reported.

Two kinds of decomposition were observed. In the presence of water, we believe the 4-acetoxy-(π-allyl)-palladium complexes are converted to the corresponding alcohol complexes, as new allyl signals were observed. This side reaction was largely suppressed by adding 5% of acetic anhydride. For the slower reactions the signals became broader after longer reaction times, presumably due to the generation of paramagnetic palladium(0). Among the new signals that appeared in the ^{1}H NMR spectra, some characteristic signals for the aromatized organic precursor were observed (benzene, biphenyl, and *n*-butylbenzene). Also in the 1,4-oxidation reactions of 1,3-dienes, aromatization of the starting materials is usually observed. This side-reaction probably proceeds via the intermediate (π-allyl)palladium complexes. The rate of decomposition was faster for the *n*-butyl-substituted complex **1c** than for the other two substrates, and 20−30% decomposition was observed for this complex under all conditions. With lithium acetate all complexes showed up to 30% decomposition during the reaction. The decomposition was less than 7% for all other reactions.

(19) The presence of 1,4-dimethoxybenzene did not affect the rate of reaction. The same values for k_{obs} were obtained, both with and without the internal standard, for the acetate exchange reaction of substrate **1b**.

Table 1. k_{obs} for Substrates 1a−c Under Different Reaction Conditions



	k_{obs} (s^{-1}) × $10^{4\,b}$		
conditions[a]	**1a**	**1b**	**1c**
A	n.r.	1.0	1.4
B[c]	n.r. (0.72 equiv)	1.4 (0.91 equiv)	0.95 (0.81 equiv)
	>80 (1.05 equiv)	78 (1.38 equiv)	>80 (1.10 equiv)
C	0.53	7.8	8.9
D		1.8	

[a] Deuterated solvents were used in all experiments. A: acetone/acetic acid, 1:4, 5% acetic anhydride; B: acetone/acetic acid, 1:4, 5% acetic anhydride, methanesulfonic acid; C: acetone/acetic acid, 1:4, 0.4 M LiOAc; D: acetone/acetic acid, 1:4, 0.4 M $LiClO_4$. [b] R = 0.998-0.999 for all values except substrate 1b, conditions D (R = 0.990). [c] Equivalents of methansulfonic acid in parentheses.

Results of Measurements. The rate constants were obtained from a first-order three-parameter (k_{obs}, I_0, and I_∞) least-squares fit, employing the equation $I = I_\infty + (I_0 - I_\infty)e^{-k_{obs}t}$, and are presented in Table 1.

In acetone-d_6/acetic acid-d_4, the exchange reaction was very slow for all complexes, and for the nonsubstituted complex **1a** no exchange could be observed. With methanesulfonic acid the rate showed to be highly dependent on the amount of acid present in the reaction. When less than 1 equiv of methanesulfonic acid was added, no rate enhancement was observed. On the other hand, the reactions were very fast when just over 1 equiv of acid was added. These rates could be measured for phenyl-substituted complex **1b** up to the addition of 1.4 equiv, where the reaction was complete within 10 min. The other two complexes reacted at such enhanced rates already with 1.10 equiv of acid that no starting material could be detected after only 2 min, making it impossible to measure any reaction rates. The values for k_{obs} of complexes **1a** and **1c** are therefore estimated by comparison with k_{obs} for **1b**. In the presence of lithium acetate-d_3 a slow exchange reaction was observed for complex **1a**. Phenyl- and *n*-butyl-substituted complexes **1b** and **1c** gave a 10-fold increase of k_{obs}, the reactions being complete in slightly less than 1 h.

Rate Dependence on Methanesulfonic Acid. The effect of the amount of added methanesulfonic acid on the rate of the exchange reaction was investigated. The reactions were carried out using 0.043 M of 2-phenyl-substituted complex **1b**, with different concentrations of methanesulfonic acid in acetic acid-d_4. The number of equivalents of methanesulfonic acid per palladium was plotted against the measured values of k_{obs} (Figure 2). The plot shows that a small amount of acid (less than 1 equiv) does not affect the rate of the reaction. As mentioned before, a tremendous increase in rate is observed upon addition of slightly more than 1 equiv of acid to the reacting complex. After addition of more than

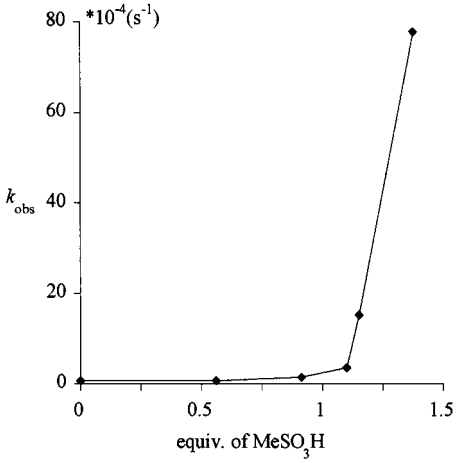


Figure 2. Dependence of k_{obs} on the amount of methanesulfonic acid for complex **1b**.

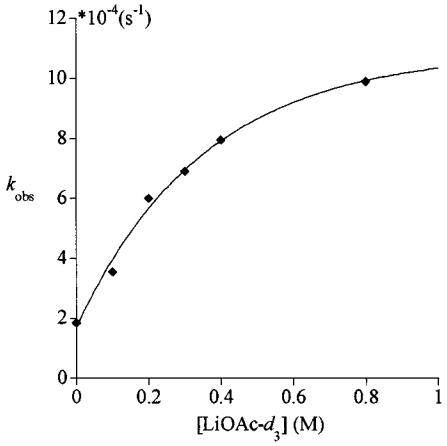


Figure 3. Dependence of k_{obs} on the concentration of lithium acetate-d_3 for complex **1b**.

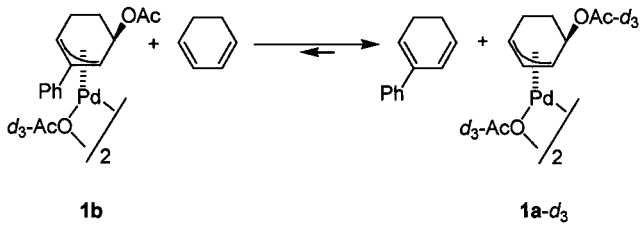
1.4 equiv the reactions became too fast to be measured by the NMR spectroscopy methods used for our experiments.

Salt Effects. To exclude a rate enhancement by lithium acetate as a result of a higher ionic strength, a control experiment with the 2-phenyl-substituted complex **1b** was performed, using a 0.4 M solution of lithium perchlorate instead of lithium acetate-d_3. Only a small rate-acceleration was observed. The nucleophilicity of the perchlorate ion is very low compared to the acetate ion, and it can be neglected for the purpose of the experiment. The observed rate constant k_{obs} was found to be 1.85×10^{-4} s^{-1}, which is only 22% of the lithium acetate-induced rate enhancement under otherwise identical reaction conditions, indicating that the ionic strength has only a minor effect on the rate of the exchange (Table 1, substrate **1b**, conditions A, C, and D). Thus, a sole ionic strength effect can be ruled out to be responsible for the rate enhancement by the addition of lithium acetate.

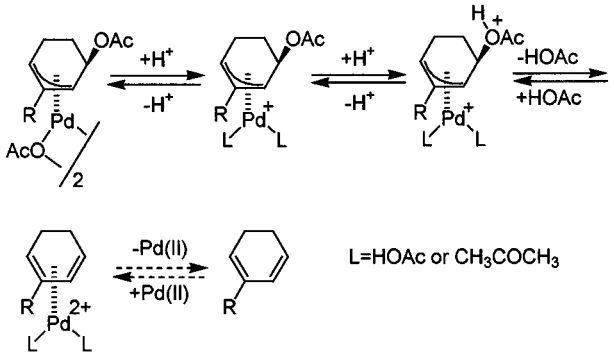
Rate Dependence on Lithium Acetate. The effect of the acetate concentration on the rate of exchange was investigated by performing the ^{1}H NMR spectroscopy experiments using 0.1, 0.2, 0.3, 0.4, and 0.8 M lithium acetate-d_3. These reactions were carried out using the 2-phenyl-substituted complex **1b** at a constant concentration of 0.043 M. To rule out a salt effect, lithium perchlorate was added in all experiments to obtain a total ion concentration (LiOAc-d_3 + $LiClO_4$) of 0.4 M. Only the 0.8 M lithium acetate-d_3 experiment thus had higher ionic strength. The observed rate constants were plotted against the concentration of lithium acetate-d_3; see Figure 3. A nonlinear increase in the rate of the exchange reaction with respect to lithium acetate-d_3 concentration was observed, giving rise to a plot with a shape that might indicate saturation kinetics.

Release of Diene from (η^4-Cyclohexadiene)palladium. The acetate/acetate-d_3 exchange reaction studied might in principle take place without the release of diene from Pd(II) (see Scheme 2). However, to determine whether the exchange reaction is a relevant measure of the racemization, the exchange reaction on complex **1b** in acetone-d_6/acetic acid-d_4 1:4, 0.4 M lithium acetate-d_3 (condition C) was repeated with the addition of 1 equiv of 1,3-cyclohexadiene. During the exchange reaction, the peaks belonging to the starting complex

Scheme 5



Scheme 6



and the free diene decreased, while new signals belonging to 2-phenyl-1,3-cyclohexadiene and bis(4-acetoxy-d_3-[η^3-(1,2,3)-cyclohexenyl])palladium acetate-d_3 (**1a**) appeared (Scheme 5). Since under these conditions the exchange reaction is much faster with complex **1b** than **1a** (Table 1), net formation of **1a**-d_3 was observed. The experiment shows that the diene, at least in the presence of excess free diene, is indeed released from palladium, making racemization possible under the conditions employed for the catalytic reactions.

Mechanistic Considerations

The experiments clearly show an increased rate of exchange on addition of strong acid (methanesulfonic acid) or lithium acetate to the reaction mixture. Because of the different nature of these additives, they most probably catalyze the reactions in different ways.

I. Addition of Methanesulfonic Acid. For the acid-catalyzed exchange reaction, we propose the general mechanism outlined in Scheme 6.

A strong acid will probably protonate the bridging acetate ligands of the dimeric complex first and give a

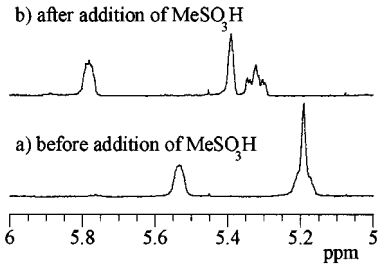


Figure 4. Selected parts of the ^{1}H NMR spectra for **1b**, showing the shift changes for signals H-1, H-3, and H-4 upon addition of 0.91 equiv of methanesulfonic acid.

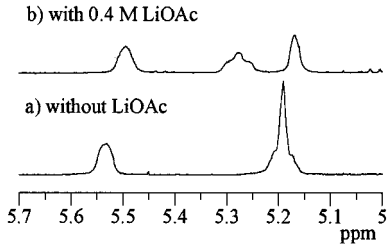


Figure 5. Selected parts of the ^{1}H NMR spectra for **1b**, showing the different shifts for signals H-1, H-3, and H-4 in acetic acid-d_4/acetone-d_6, 4:1, with and without lithium acetate.

monocationic intermediate. As Figure 2 shows, one full equivalent of acid does not influence the rate of the exchange reaction. When larger amounts of acid are added, also the ring-bonded acetate can become protonated, making it a good leaving group. We believe that this labilized intermediate then eliminates acetic acid to give a cationic palladium-diene species, which in turn can give free diene. It should be noted that the release of diene was demonstrated in the presence of added diene (vide supra). However, if an associative diene/diene exchange mechanism is operating, the release of diene might be slow under the present conditions.

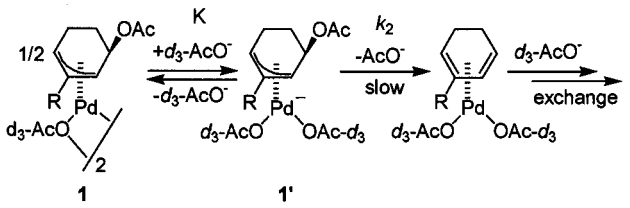
The ^{1}H NMR spectra might provide evidence for the monocationic intermediate in Scheme 6. Upon the addition of 0.91 equiv of methanesulfonic acid to substrate **1b**, the signals for H-1, H-3, and H-4 are shifted 0.2−0.3 ppm downfield (Figure 4). Since the rate of exchange is very low under these conditions, we believe the dicationic intermediate is not present and therefore the signals probably belong to the monocationic intermediate.

Dictated by the principle of microscopic reversibility, the reverse reaction has to proceed by the same pathway. Furthermore, the presence of acetate ions is negligible under the reaction conditions. Therefore, nucleophilic attack of acetic acid on a cationic η^4-coordinated diene-palladium complex followed by loss of two protons gives back the (π-allyl)palladium complex.

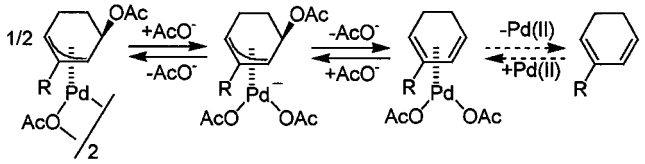
Support for this mechanism is given by the effects of the different substituents on the exchange rate. The electron-withdrawing properties of the phenyl substituent in complex **1b** make the ring-bonded acetate oxygen atoms less basic and therefore slightly less susceptible to protonation than the corresponding oxygen atoms in complexes **1a** and **1c**, which lack electron-withdrawing groups in the 2-position. This mechanism is in agreement with the lower rate enhancement observed for complex **1b** compared to the other complexes.

II. Addition of Acetate. In the presence of added lithium acetate, the protonation step as described above is less likely. Since the rate exhibits a dependence on the acetate concentration (Figure 3), a simple dissociation of the ring-bonded acetate (S_N1) from the dimeric palladium species can be ruled out as the exchange mechanism. Instead, acetate is believed to attack the dimeric palladium species in an associative fashion to yield a monomeric, negatively charged diacetate complex in a reversible step. Facilitated by anchimeric assistance from palladium, the ring-bonded acetate will be eliminated, yielding a diene-palladium complex (Scheme 7).

Scheme 7



Scheme 8



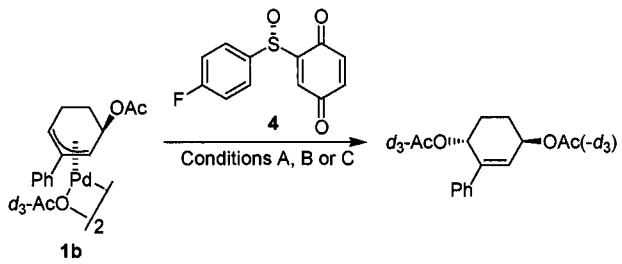
A preequilibrium between the dimeric palladium species **1** and the anionic palladium monomer **1′**, followed by an irreversible rate-determining elimination of nondeuterated acetate (since the reactions are performed in acetic acid-d_4) is assumed. At low concentrations of acetate-d_3, the rate will be dependent on the concentrations of both palladium and acetate-d_3. However, at higher concentrations of acetate-d_3 the preequilibrium will be completely shifted to the right, and this leads to saturation kinetics and the exchange rate will become equal to k_2[**1′**]. This explains the saturation effect shown in Figure 3 at high acetate concentrations.

The change in chemical shift for the signals of H-1, H-3, and H-4 for substrate **1b**, with and without lithium acetate (Figure 5), is much smaller than upon the addition of methanesulfonic acid. However, as all other signals are unaffected, we believe the signals belong to the monoanionic intermediate **1′** (Scheme 7).

For the exchange reaction in the general case, i.e., in the presence of nondeuterated acetate, we propose the general mechanism outlined in Scheme 8. By the principle of microscopic reversibility, the reverse order of these steps then applies for the back reaction.

III. No Additives. In the absence of additives, complexes **1b** and **1c** react slowly while **1a** does not react at all. We proposed two different mechanisms for the lithium acetate- and acid-catalyzed reactions. Without any additives, we believe a reaction can occur after protonation by acetic acid, and the mechanism is as shown in Scheme 6. The difference in reactivity between the complexes may be explained by the effect of the

Scheme 9



2-substituent in **1b** and **1c**, which should weaken the bond between C-4 and the acetoxy group.[20]

Application to the Asymmetric 1,4-Diacetoxylation Reaction

After having determined the factors that affect the equilibrium reaction, the consequences for the asymmetric 1,4-oxidation reaction were investigated. We therefore studied stoichiometric reactions between bis(4-acetoxy-2-phenyl-[η^3-(1,2,3)-cyclohexenyl])palladium acetate-d_3 **1b** and the chiral ligand (*S*)-(+)-2-(4′-fluorophenylsulfinyl)-1,4-benzoquinone **4** (Scheme 9) by ^{1}H NMR spectroscopy. The yield of *trans*-1,4-diacetoxy-2-phenyl-2-cyclohexene was measured by the use of an internal standard. The enantiomeric excess of the product was determined by HPLC. We chose ligand **4** for practical reasons, since it was available in our laboratories in larger quantities. In a catalytic diacetoxylation reaction with 2-phenyl-1,3-cyclohexadiene, ligand **4** had previously given 20% ee.[21] The ligand was synthesized according to the Andersen methodology,[22] and studies on similar benzoquinones have been published before.[6,23]

No Additives (Conditions A). In the absence of a fast equilibrium between the two starting enantiomers of racemic **1b**, a stoichiometric reaction with chiral ligand **4** theoretically should give racemic product. When the reaction was performed in acetone-d_6/acetic acid-d_4, 1:4, the reaction leading to the diacetoxylation product was observed to take 30 min. Almost 50% ee was observed in the very beginning of the reaction, which then decreased to about 15% ee at 100% conversion (79% yield by ^{1}H NMR). This clearly indicates the occurrence of kinetic resolution where one of the enantiomers of the (π-allyl)palladium complex reacts faster with the chiral ligand than the other and where the equilibrium is not fast enough to give a fully dynamic process (dynamic kinetic resolution). Addition of 1 equiv of ligand **4** in several small portions, to decrease the rate of the product-forming step, did not increase the enantiomeric excess.

Addition of Methanesulfonic Acid. In the presence of more than 1 equivalent of methanesulfonic acid (conditions B) the exchange reaction is very rapid. Since the time observed for complete exchange can be as short as 2 min (see Table 1), there might be a probability that dynamic kinetic resolution can be obtained. Unfortunately, the formation of *trans*-1,4-diacetoxy-2-phenyl-2-cyclohexene is very slow under these reaction conditions, the reaction leading mainly to decomposition of the acetoxy-(π-allyl)palladium complex and less than 10% yield of diacetate. The methanesulfonic acid-catalyzed exchange reaction is therefore not compatible with the 1,4-diacetoxylation reaction.

Addition of Lithium Acetate. The stoichiometric reaction of **1b** with chiral ligand **4** was then carried out under conditions C. Also in this case conversion was complete in 30 min. The enantiomeric excess measured in the very beginning of the reaction was almost 50%. After complete conversion 65% yield and 28% ee were obtained. From our data we know that the exchange rate is higher under conditions C than under conditions A, and this may be reflected by the slight increase of enantioselectivity. However, the rate of equilibration between the enantiomeric (π-allyl)palladium complexes is too slow to give a fully dynamic process (dynamic kinetic resolution).

The low enantiomeric excess may also be caused by very slow or no release of the diene from palladium. Since we showed that, in the exchange reactions, the diene is released from palladium at least in the presence of an excess of diene, a stoichiometric reaction between **1b** and chiral benzoquinone **4** was performed in the presence of 10 equiv of 2-phenyl-1,3-cyclohexadiene. However, no improvement of the yield or ee was observed.

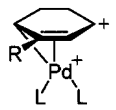
Concluding Remarks

We have synthesized a series of bis(4-acetoxy-2-phenyl-[η^3-(1,2,3)-cyclohexenyl])palladium acetate-d_3 complexes **1a**−**c**. By treating the complexes with acetic acid-d_4 solutions we have shown that an exchange reaction of the ring-bonded acetate with the acetic acid-d_4 takes place. The reaction has been studied by ^{1}H NMR spectroscopy under different conditions. The results show that the exchange reaction is first-order in palladium. The presence of either methanesulfonic acid or lithium acetate dramatically enhanced the rate of the exchange reaction. Therefore we have postulated two different mechanisms. Furthermore, we have found that the nature of the substituent in the 2-position of the complex has a profound effect on the reaction rate.

Finally, we have observed that the benzoquinone-assisted palladium(II)-catalyzed 1,4-diacetoxylation reaction, in which the bis(4-acetoxy-[η^3-(1,2,3)-cyclohexenyl])palladium acetate complexes are observed intermediates, gives kinetic resolution in stoichiometric reactions of complex **1b** and chiral benzoquinone **4**. Attempts to demonstrate dynamic kinetic resolution in stoichiometric reactions between **1b** and the chiral benzoquinone **4** were unsuccessful.

In the presence of lithium acetate, the interconversion between the enantiomeric (π-allyl)palladium complexes, which was studied by the exchange of acetate, is too slow compared to the chiral benzoquinone-induced attack of

(20) The positive charge at C-4 developed when the acetoxy group is leaving would be stabilized by a butyl or phenyl substituent at C-2. The stabilizing effect is evident from the σ,π resonance form.



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acetate to give the products. To obtain a higher asymmetric induction in the catalytic reactions, it is therefore necessary to increase the equilibration between the enantiomeric (π-allyl)palladium under the catalytic reaction conditions.

Experimental Section

General Remarks. ^{1}H (400 or 300 MHz) and ^{13}C (100 or 75 MHz) NMR spectra were recorded on a Varian Mercury spectrometer. Chemical shifts (δ) are reported in ppm, using residual solvent proton resonance or tetramethylsilane as internal standard. IR spectra were obtained using a Perkin-Elmer 1600 FT-IR instrument, and the samples were examined on NaBr plates. Only the strongest/structurally most important peaks (cm^{-1}) are listed. Merck silica gel 60 (240−400 mesh) was used for flash chromatography, and analytical thin-layer chromatography was performed on Merck precoated silica gel 60-F_{254} plates. Analytical high-pressure liquid chromatography (HPLC) was performed on a Waters liquid chromatograph using a Daicel Chiralcel OD-H column. Unless otherwise noted, all materials were obtained from commercial suppliers and used without further purification. Tetrahydrofuran (THF) was freshly distilled from sodium benzophenone ketyl prior to use. Dimethyl sulfoxide (DMSO) was distilled from calcium hydride prior to use. Methanesulfonic acid and 1,3-cyclohexadiene were freshly distilled prior to use. 2-Phenyl-1,3-cyclohexadiene and 2-*n*-butyl-1,3-cyclohexadiene were prepared according to a known procedure.[24] $Pd(dba)_2$,[25] $Pd(PhCN)_2Cl_2$,[26] and $Pd(CH_3CN)_2Cl_2$ [26] were prepared according to known procedures.

Bis(4-acetoxy -[η^3-(1,2,3)-cyclohexenyl])palladium Chloride (2a). To a suspension of $Pd(PhCN)_2Cl_2$ (998 mg, 2.5 mmol), lithium acetate (383 mg, 3.75 mmol), acetic acid (215 μL, 3.75 mmol), and lithium chloride (53 mg, 1.25 mmol) in THF (20 mL) at −18 °C was added dropwise 1,3-cyclohexadiene (200 mg, 2.5 mmol). The reaction was complete after 2 h. The material was concentrated in vacuo to approximately 2 mL and purified by column chromatography (pentane/diethyl ether, 3:1 → 1:3). **2a** (787 mg, 0.70 mmol, 56%) was obtained as a yellow powder. The NMR data were in agreement with those reported in the literature.[27]

Bis(4-acetoxy-2-phenyl-[η^3-(1,2,3)-cyclohexenyl])palladium Chloride (2b). To a suspension of $Pd(CH_3CN)_2Cl_2$ (649 mg, 2.5 mmol), lithium acetate (383 mg, 3.75 mmol), acetic acid (215 μL, 3.75 mmol), and lithium chloride (53 mg, 1.25 mmol) in THF (20 mL) at −18 °C was added dropwise 2-phenyl-1,3-cyclohexadiene (390 mg, 2.5 mmol). The mixture was stirred for 2 h and then left in a freezer at −14 °C overnight. Water was added, and the material was extracted with dichloromethane. The aqueous phase was back-extracted with dichloromethane, and the combined organic phases were dried over magnesium sulfate. After removal of the solvent in vacuo and purification by column chromatography (pentane/diethyl ether, 3:1 → 1:3), 540 mg (0.76 mmol, 60%) of **2b** was obtained as a yellow powder. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.42 (br m, 2H, ArH), 7.35 (br m, 3H, ArH), 5.41 (br m, 1H, H-1), 5.30 (br m, 1H, H-4), 5.16 (dd, J = 2.7, 1.5 Hz, 1H, H-3), 2.50−2.28 (br m, 1H, H-5), 2.10−1.95 (br m, 4H, CH_3 + H-6), 1.74−1.61 (br m, 1H, H-6′), 1.36−1.23 (br m, 1H, H-5′). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 170.3, 136.1, 129.7, 129.2, 126.6, 117.3, 78.5, 71.2, 69.9, 27.5, 25.3, 21.4. IR (neat): 3025, 2927, 1728, 1462, 1372, 1241, 1022, 966 cm^{-1}.

***cis*-4-Acetoxy-2-*n*-butyl-1-chloro-2-cyclohexene (3).** Palladium acetate (76 mg, 0.34 mmol), lithium acetate (1.39 g, 13.6 mmol), lithium chloride (0.575 g, 13.6 mmol), and *p*-benzoquinone (1.47 g, 13.6 mmol) were dissolved in pentane (35 mL) and acetic acid (22 mL). 2-Butyl-1,3-cyclohexadiene (0.925 g, 6.8 mmol) was added with a syringe pump over 2 h. After stirring for 22 h at room temperature, brine and diethyl ether were added and the solution was stirred for an additional 5 min. The phases were separated, and the aqueous phase was filtered through Celite and extracted with pentane/diethyl ether, 80:20. The combined organic phases were washed with water, saturated aqueous potassium carbonate, and 2 M sodium hydroxide. The aqueous phases were back-extracted with pentane/diethyl ether, 80:20. The combined organic phases were dried over sodium sulfate. The solvent was removed in vacuo, and the material was purified by column chromatography (pentane/ethyl acetate, 9:1), yielding 765 mg (49%) of **3** as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.52 (dq, J = 1.2, 2.4 Hz, 1H, H-3), 5.36−5.28 (br m, 1H, H-4), 4.44 (br t, J = 4.6 Hz, 1H, H-1), 2.24−2.09 (m, 4H, H-6, CH_2 of Bu), 2.07 (s, 3H, C═OCH_3), 2.03−1.91 (m, 2H, H-5), 1.53−1.24 (m, 4H, CH_2 of Bu), 0.91 (t, J = 7.2 Hz, 3H, CH_3 of Bu). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 171.1, 142.4, 125.4, 69.9, 57.1, 34.2, 30.9, 29.7, 23.8, 22.7, 21.6, 14.2. IR (neat): 3400, 2958, 2872, 1735, 1562, 1407, 1373, 1240, 1024 cm^{-1}.

Bis(4-acetoxy-2-*n*-butyl-[η^3-(1,2,3)-cyclohexenyl])palladium Chloride (2c). *cis*-4-Acetoxy-2-*n*-butyl-1-chloro-2-cyclohexene **3** (0.439 g, 1.56 mmol) was dissolved in DMSO (20 mL), and $Pd(dba)_2$ (0.938 g, 1.64 mmol) was added. After stirring for 3 h at room temperature, the material was cooled to 0 °C. Water was added, and the material was extracted with dichloromethane. The organic phase was washed with water and dried over sodium sulfate, and the solvent was evaporated in vacuo. The material was purified by column chromatography (dichloromethane/diethyl ether, 100:0 → 0:100), yielding 129 mg (25%) of **2c** as a yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.15 (dt, J = 5.4, 3.0 Hz, 1H, H-4), 4.89 (ddd, J = 3.9, 3.0, 1.5 Hz, 1H, H-1), 4.64 (dd, J = 3.0, 1.5 Hz, 1H, H-3), 2.39 (dddd, J = 13.8, 7.1, 6.6, 5.4 Hz, 1H, H-5), 2.18 (t, J = 7.6 Hz, 2H, CH_2 of Bu), 1.96 (s, 3H, C═OCH_3), 1.90 (dt, J = 17.1, 6.6, 3.0 Hz, 1H, H-6), 1.55−1.41 (m, 3H, H-6′ + CH_2 of Bu), 1.40−1.31 (m, 2H, CH_2 of Bu), 1.30−1.18 (m, 1H, H-5′), 0.88 (t, J = 7.3 Hz, 3H, CH_3 of Bu). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 170.1, 120.9, 79.7, 72.6, 69.8, 36.0, 32.2, 27.7, 25.0, 22.2, 21.2, 14.1. IR (neat): 2931, 2871, 1733, 1456, 1437, 1370, 1235, 1184, 1017, 965 cm^{-1}.

Silver Acetate-d_3.[28] Silver acetate (250 mg, 167 mmol) was suspended in acetic acid-d_4 (2.5 mL) and stirred for 2 days at room temperature. The solvent was removed in vacuo. The procedure was repeated and the material was dried in vacuo, resulting in a quantitative yield of silver acetate-d_3. The material was stored in darkness.

Bis(4-acetoxy-[η^3-(1,2,3)-cyclohexenyl])palladium Acetate-d_3 (1a). General Procedure for the Preparation of the Acetate Complexes 1. Bis(4-acetoxy-[η^3-(1,2,3)-cyclohexenyl])palladium chloride **2a** (12.2 mg, 0.022 mmol) was dissolved in acetone-d_6 (0.5 mL), and the solution was cooled to 0 °C. Silver acetate-d_3 (7.7 mg, 0.045 mmol) was added, and the mixture was stirred for 45 min. After filtration through Celite, the solvent was removed in vacuo to give a yellow solid. The product is unstable and was hence prepared immediately before the NMR experiments. The ^{1}H NMR data were in agreement with those reported in the literature, with the exclusion of the acetate-d_3 ligand peak at 2.13 ppm.[27]

Bis(4-acetoxy-2-phenyl-[η^3-(1,2,3)-cyclohexenyl])palladium Acetate-d_3 (1b). 1b was prepared from **2b**, according

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(28) Silver acetate-d_3 was prepared by a method for purification of nondeuterated silver acetate described by: Perrin, D. D.; Armarego, W. L. F.; Perrin, D. R. *Purification of Laboratory Chemicals*; Pergamon Press: Oxford, UK, 1980; p 520.

to the general procedure. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.46 (br m, 2H, ArH), 7.34 (br m, 3H, ArH), 5.20 (br m, 1H, H-1), 5.12 (br m, 1H, H-4), 4.94 (br m, 1H, H-3), 2.18−1.96 (br m, 4H, H-5 + CH_3), 1.88−1.67 (br m, 1H, H-6), 1.64−1.46 (br m, 1H, H-6′), 1.13−0.99 (br m, 1H, H-5′). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 179.9, 170.3, 136.2, 129.6, 129.2, 126.6, 116.7, 72.0, 70.7, 65.2, 27.0, 25.1, 24.5, 21.4. IR (neat): 2945, 2242, 1729, 1651, 1547, 1407, 1234, 1185, 1019 cm^{-1}.

Bis(4-acetoxy-2-*n*-butyl-[η^3-(1,2,3)-cyclohexenyl])palladium Acetate-d_3 (1c). Prepared from **2c**, according to the general procedure. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.19 (dt, J = 5.4, 2.7 Hz, 1H, H-4), 4.73 (ddd, J = 3.9, 2.7, 1.2 Hz, 1H, H-1), 4.49 (dd, J = 2.7, 1.2 Hz, 1H, H-3), 2.42 (dddd, J = 13.2, 12.0, 6.6, 5.4 Hz, 1H, H-5), 2.28 (t, J = 7.4 Hz, 2H, CH_2 of Bu), 2.00 (s, 3H, C═OCH_3), 1.93 (ddt, J = 16.8, 6.6, 2.7 Hz, 1H, H-6), 1.60−1.46 (m, 3H, H-6′ + CH_2 of Bu), 1.44−1.32 (m, 2H, CH_2 of Bu), 1.26−1.13 (m, 1H, H-5′), 0.92 (t, J = 7.4 Hz, 3H, CH_3 of Bu). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 180.1, 170.4, 120.8, 73.5, 70.6, 67.0, 36.4, 33.2, 27.7, 25.0, 24.7, 22.3, 21.4, 14.2. IR (neat): 2932, 2871, 1732, 1552, 1456, 1426, 1370, 1235, 1184, 1017, 958 cm^{-1}.

Lithium Acetate-d_3. Lithium deuteride (70 mg, 7.8 mmol) was suspended in THF (5 mL) and cooled to 0 °C. Acetic acid-d_4 (0.50 g, 7.8 mmol) was diluted with THF (3 mL) and added dropwise to the slurry. The material was stirred at room temperature for 3 days, after which the solvent was removed in vacuo, giving a quantitative yield of lithium acetate-d_3.

General Procedure for ^{1}H NMR Experiments to Determine the Rate of Acetate Exchange. The experiments were recorded on a 300 MHz Varian spectrometer. Acetone-d_6/acetic acid-d_4, 1:4, and acetone-d_6/acetic acid-d_4, 1:4, 0.4 M LiOAc-d_3 solutions, were prepared prior to use. The acetate complex (0.022 mmol) was dissolved in 0.5 mL of the appropriate solvent mixture, and 1,4-dimethoxybenzene (0.98 mg, 0.007 mmol) was added. The solution was subsequently transferred to an NMR tube. When methanesulfonic acid was used, it was added to the solution as a 2 M solution in acetic acid-d_4. The exact amount of added methanesulfonic acid was obtained from the ^{1}H NMR integrals of the methyl and one of the allyl signals. An array of scans was recorded to follow the disappearance of the nondeuterated ring-bonded acetate signal over a time interval of 5 min to 11 h, depending on the rate of the reaction.

^{1}H NMR Experiments on Stoichiometric Reactions of Bis(4-acetoxy-2-phenyl-[η^3-(1,2,3)-cyclohexenyl])palladium Acetate-d_3 1b with Chiral Benzoquinone 4. Bis(4-acetoxy-2-phenyl-[η^3-(1,2,3)-cyclohexenyl])palladium chloride **2b** (16 mg, 0.022 mmol) was suspended in 1.0 mL of the appropriate solvent mixture in an NMR tube, and silver acetate-d_3 (7.9 mg, 0.047 mmol) was added. 1,4-Dimethoxybenzene (0.98 mg, 0.007 mmol) was added and used as an internal standard. The formation of the corresponding acetate complex, followed by ^{1}H NMR, was almost instantaneous. When methanesulfonic acid was used, it was then added to the solution as a 2 M solution in acetic acid-d_4. (*S*)-(+)-2-(4′-Fluorophenylsulfinyl)-1,4-benzoquinone **4** (11.2 mg, 0.045 mmol) was dissolved in 0.2 mL of the appropriate solvent solution and added to the reaction mixture. An array of scans was recorded to follow the formation of *trans*-1,4-diacetoxy-2-phenyl-2-cyclohexene. The enantiomeric excess was determined by HPLC analysis using a Chiralcel OD-H column (hexane/2-propanol 98/2, flow rate 0.5 mL/min): t_R (major) = 14.1 min, t_R (minor) = 16.2 min.

Acknowledgment. Financial support from the Swedish Research Council is gratefully acknowledged.

Supporting Information Available: ^{1}H and ^{13}C NMR spectra of compounds **1b**, **1c**, **2b**, **2c**, and **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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