# Palladium(II)-Catalyzed Exchange and Isomerization Reactions. 17. Exchange of Chiral Allyl Alcohols with Hydroxide, Methoxide, and Phenyl at High [$Cl^-$]. Stereochemistry of the Wacker Reaction

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At high [$Cl^-$] (> 2.0 M), $PdCl_4^{2-}$ catalyzes the exchange of chiral allylic alcohols with hydroxy, methoxy, and phenyl to give chiral allyl-substituted olefins. With unsymmetrical olefins, isomerization occurs along with exchange. The hydroxyl exchange occurs in aqueous solution while the other exchanges are carried out in methanol solution. At low [$Cl^-$] (0.1 M) oxidation to the corresponding $\beta$-hydroxy-, methoxy-, and phenyl-substituted carbonyl compounds occurred. The absolute configurations of the oxidation and exchange products should be the same if the same mode of addition to the Pd(II)-$\pi$-complex is operative. The absolute configurations of the oxidation and exchange products for the phenylation reaction were the same, while for hydroxy and methoxy they were different. This result indicates methanol and water must have different stereochemistries of addition at high and low [$Cl^-$]. Thus, previous studies showing anti hydroxypalladation at high [$Cl^-$] are not valid indicators of the stereochemistry at low [$Cl^-$]. If anti addition occurs at high [$Cl^-$], the addition must be syn at low [$Cl^-$].

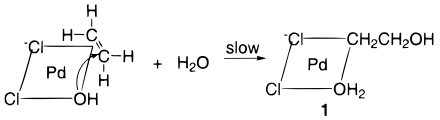
## Introduction

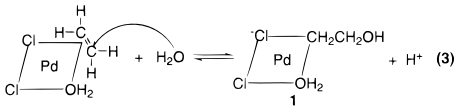
The Pd(II)-catalyzed oxidation of ethene in aqueous solution (Wacker Reaction, Scheme 1) gives exclusively acetaldehyde under the usual Wacker conditions of low [$Cl^-$] (>1.0 M).[1] Under the same conditions Pd(II) oxidizes α-olefins to methyl ketones and aldehydes. Thus, propene gives a mixture of acetone and propanal. At high chloride (>2.5 M) and high [$CuCl_2$] (>3 M), formation of ethylene chlorohydrin becomes a serious side reaction. The Wacker controversy concerns the stereochemistry of addition of the elements of Pd(II) and OH to the ethene double bond (hydroxypalladation) under the usual Wacker conditions of low [$Cl^-$].

The rate expression for the oxidation of ethene to acetaldehyde, given by eq 1, is consistent with (a) syn addition by coordinated hydroxyl on a Pd(II)−olefin $\pi$-complex to give **1** in the slow step (eq 2) or (b) anti attack by external water on the corresponding aquo-complex in an equilibrium step to give **1** (eq 3). In both mechanisms **1** decomposes to acetaldehyde and Pd(0).

The evidence for the generally accepted trans addition route for the Wacker process is based on the tacit assumption that the mode of hydroxypalladation remains the same with all olefins and under all reaction conditions.[1] Studies with chelating diolefins[2] and with simpler olefins under conditions far removed from those of the aqueous acyclic olefin oxidation[3−6] suggest an anti mode

$$\text{rate} = k[PdCl_4^{2-}][\text{olefin}]/[H^+][Cl^-]^2 \quad (1)$$




of hydroxypalladation. These results were extrapolated to the low chloride conditions of the actual oxidation. The study that uses conditions closest to those of the Wacker oxidation employs high chloride and cupric chloride concentrations ([$Cl^-$] > 3 M; [$CuCl_2$] > 2.5 M).[7] As shown in Scheme 1, under these conditions the oxidation of ethene to acetaldehyde is very slow and the main product is 2-chloroethanol. With specifically labeled ethenes as substrates, the stereochemistry of the deuterated 2-chloroethanol products was best explained by anti hydroxypalladation. It was assumed that the same intermediate, **1**, which decomposes to acetaldehyde, is intercepted by $CuCl_2$ to give chlorohydrin. The addition was thus postulated to also be anti under Wacker conditions. However, as discussed below, kinetic evidence suggests that the reaction at high [$Cl^-$] is different from that at low [$Cl^-$].[8] The present report describes a study that shows that the stereochemistry of hydroxypalladation is

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(1) For general discussion and references, see: Henry, P. M. *Palladium Catalyzed Oxidation of Hydrocarbons*; D. Reidel: Dordrecht, Holland, **1980**; pp 41−84.

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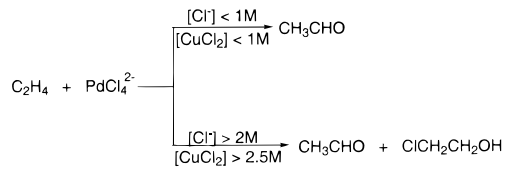
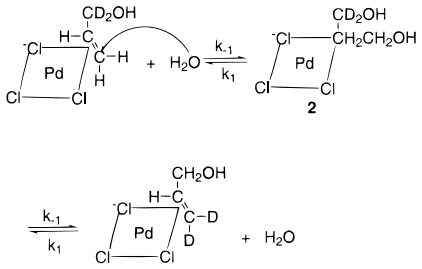
**Scheme 1**




**Scheme 2**




dissimilar at high and low chloride concentrations so the reaction pathways must, in fact, be different.

Oxidation of allyl alcohols occurs by the rate expression given by eq 1 at low [$Cl^-$] (<1 M).[9] The products are a mixture of hydroxyacetone and 3-hydroxypropanal, the expected Wacker oxidation products.[10] At [$Cl^-$] > 3 M, in the absence of $CuCl_2$, the oxidation of allyl alcohol effectively ceases and nonoxidative isomerization of allyl alcohol-1,1-$d_2$ into its allylic isomer, allyl alcohol-3,3-$d_2$ predominates.[8] The rate expression for the nonoxidative isomerization, given by eq 4, is most consistent with trans attack of water on an allyl alcohol Pd(II)-$\pi$-complex as

$$\text{rate} = k[PdCl_4^{2-}][\text{allyl alcohol}]/[Cl^-] \qquad (4)$$

shown in Scheme 2.

Since the isomerization shown in Scheme 2 is the predominant pathway at high [$Cl^-$], it seems reasonable that a trichloro-hydroxypalladation adduct analogous to **2** is the species intercepted by $CuCl_2$ rather than **1**. Thus a demonstration that the stereochemistry of hydroxypalladation is different at high and low [$Cl^-$] would support different mechanistic pathways for these two regions of [$Cl^-$]. Since addition is anti at high [$Cl^-$],[7] such a demonstration would be evidence for syn addition at low chloride concentration.

Studies in methanol at low and high [$Cl^-$] show that the kinetics and mechanism of the Pd(II)-catalyzed reactions in this solvent are exactly analogous to those found in aqueous solution.[11,12] Oxidation to acetals obeying eq 1 occurs at low [$Cl^-$] and isomerization obeying eq 4 is found at high [$Cl^-$].

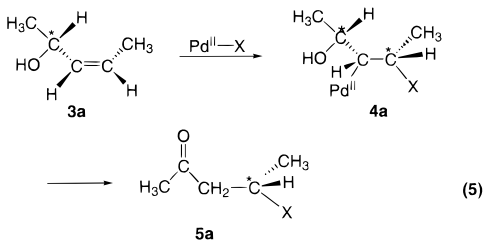
Determination of the relative modes of addition under the two regimes of chloride concentration is possible by chirality transfer.[13,14] This technique employs the directing influence of the hydroxyl group in chiral allylic alcohols. This directing ability of the hydroxyl function has been shown for several reactions of allylic alcohols.[15] Previous studies examined the exchange and isomerization of chiral tetrasubstituted allylic alcohols which cannot undergo Wacker-type oxidation. The results were consistent with different modes of addition at low and high [$Cl^-$].[14] In the present study we examine the reactions of disubstituted allylic alcohols which can undergo *both* exchange and oxidation and thus are more closely related to the allylic alcohols previously studied.

A recent study described the use of chirality transfer to suggest the probable modes of addition of $H_2O$, $CH_3OH$, phenyl, and acetate to (*R*)-(−)-(*Z*)- and (*R*)-(+)-(*E*)-3-penten-2-ol at low [$Cl^-$].[16] Equation 5 shows the general reaction scheme. The present study extends this work to high [$Cl^-$] where nonoxidative isomerization is the predominant reaction. Also included are results for the oxidation of (*R*)-(*Z*)- and (*R*)-(*E*)-3-hexen-2-ol at low [$Cl^-$].

The most relevant results of these studies has been published as a communication.[17]

## Results

The isomerization studies when X = $OCH_3$ and Ph employed (*R*)-(+)-(*E*)-3-penten-2-ol as the allyl alcohol. However when X = OH, the intermediate, **4a**, in eq 5 is symmetric and it is impossible to determine if oxidation




(5)

occurred by hydride transfer from the original chiral carbon or the new chiral center. Also, under isomerization conditions it could not be determined which OH is eliminated. Thus an unsymmetrical allyl alcohol, which gives different products for the two possible modes of oxidation and isomerization, must be used in aqueous solution.

The substrates for the oxidation studies at low [$Cl^-$] were (*R*)-(−)-(*Z*)- (**3b**) and (*R*)-(+)-(*E*)-(**3bE**)-3-hexen-2-ol. (*R*)-3-Hexyn-2-ol was prepared by the reduction of 3-hexyn-2-one with (alpine-borane) reagent.[18] A sample of **3b** was prepared in 66% ee by reduction of the triple bond with Lindlar catalyst.[19] A sample of **3bE** was prepared in 65% ee by reduction of the triple bond with

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(13) See ref 14 for a discussion of chirality transfer.
(14) (a) Francis, J. W.; Henry, P. M. *Organometallics* **1991**, *10*, 3498−3503. (b) Francis, J. W.; Henry, P. M. *Organometallics* **1992**, *11*, 2832−2836.
(15) For recent diastereofacial selection occurring with olefinic alcohols, see (a) Stork, G.; Kahne, D. E. *J. Am. Chem. Soc.* **1983**, *105*, 1072−1073. (b) Thompson, H. W.; Shah, N. V. *J. Org. Chem.* **1983**, *48*, 1325−1328. (c) Brown, J. M.; Naik, R. G. *J. Chem. Soc., Chem. Commun.* **1982**, 348−350 for hydroboration. (d) Smadja, W.; Ville, G.; Georgoulis, C. *J. Chem. Soc. Chem. Commun.* **1980**, 594−595 for isomerization. (e) Stork, G.; Kahn, M. *Tetrahedron Lett.* **1983**, 3951−3954. (f) Sha, J. K.; Christ, W. J.; Kishi, Y. *Tetrahedron Lett.* **1983**, 3943−3946, 3947−3950 for oxidation. (g) Czernecki, S.; Georgoulis, C.; Provelenghiou, C. *Tetrahedron Lett.* **1975**, 2623−26; **1979**, 4841−44 for alkoxy- and azidomercuration.
(16) Hamed, O.; Henry, P. M. *Organometallics* **1997**, *16*, 4903−4909.
(17) Hamed, O.; Thompson, C.; Henry, P. M. *J. Org. Chem.* **1997**, *62*, 7082−7083.
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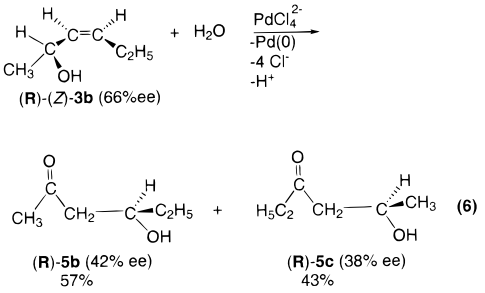
**Table 1. Stereochemistry of Addition of Phenyl, Hydroxide, and Methoxide to Chiral Allylic Alcohols**

| run | $[Cl^-]$ (M) | X | solvent | allyl alcohol (%ee) | product(%ee)[a] |
|---|---|---|---|---|---|
| 1[b] | 0.1 | Ph | $CH_3OH$ | (*R*)-(*Z*)-**3a** (53) | (*R*)-$CH_3C(=O)CH_2CH(Ph)CH_3$, (*R*)-**5a″** (30) |
| 2 | 2.5 | Ph | $CH_3OH$ | (*S*)-(*Z*)-**3a** (74) | (*S*)-(*Z*)-$CH_3CH=CHCH(Ph)CH_3$, (*S*)-(*Z*)-**3a″** (68) |
| 3 | 0.1 | OH | $H_2O$ | (*R*)-(*Z*)-**3b** (66) | (*R*)-$CH_3C(=O)CH_2CH(OH)C_2H_5$, (*R*)-**5b** (42) |
| 4 | 0.1 | OH | $H_2O$ | (*R*)-(*E*)-**3b** (65) | (*R*)-$CH_3C(=O)CH_2CH(OH)C_2H_5$, (*R*)-**5b** (28) |
| 5 | 2.0 | OH | $H_2O$ | (*R*)-(*Z*)-**3c** (76) | (*S*)-(*Z*)-$C_2H_5CH=CHCH(OH)CH_3$, (*S*)-(*Z*)-**3b** (76) |
| 6[b] | 0.1 | $OCH_3$ | $CH_3OH$ | (*R*)-(*Z*)-**3a** (53) | (*R*)-$CH_3C(=O)CH_2CH(OCH_3)CH_3$, (*R*)-**5a′** (42) |
| 7 | 2.5 | $OCH_3$ | $CH_3OH$ | (*S*)-(*Z*)-**3a** (74) | (*R*)-(*Z*)-$CH_3CH=CHCH(OCH_3)CH_3$, (*R*)-(*Z*)-**3a′** (68) |

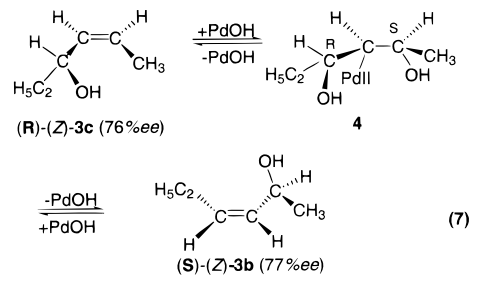
[a] Products were identified by $^1H$ and $^{13}C$ NMR. [b] Data from reference 16.

$LiAlH_4$. As shown in eq 6, the oxidation of **3b** at low $[Cl^-]$ (0.1 M) gave a mixture of 4-hydroxy-2-hexanone (**5b**) and




5-hydroxy-3-hexanone (**5c**) in 57% and 43% yield, respectively. A pure sample of the **5b** isomer, which gives the desired stereochemical information, was isolated from the reaction mixture by preparative GLC. $^1H$ NMR analysis of **5b** in the presence of the chiral shift reagent, $Eu(hcf)_3$, showed the presence of the two enantiomers of **5b** in the ratio 1:2.5 (42% ee). The absolute configuration of the major enantiomer was found to be *R* by converting the enantiomers to their Mosher's esters and studying the shift of the two $CH_3$ signals in the presence of $Eu(hcf)_3$.[20] The oxidation of **3bE** gave a mixture of **5b** and **5c** in 29% and 71% relative yields. A pure sample of the **5b** isomer was isolated and analyzed as described above. Its configuration was *R*, and its optical purity was 28% ee.

The isomerization studies were conducted with (*R*)-(−)-(*Z*)-4-hexen-3-ol (**3c**), prepared in 76% ee by a procedure analogous to that for **3b**. As shown in eq 7,

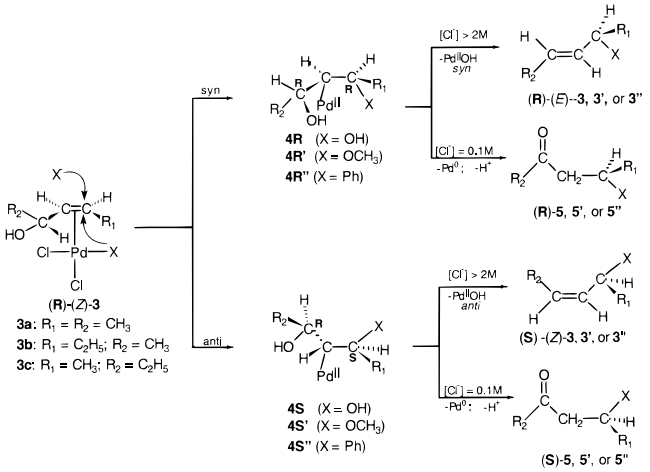



comparison of the $^1H$ NMR in the presence and absence of $Eu(hcf)_3$ with authentic samples showed that the products consisted of a 1:1 mixture of (*S*)-(*Z*)-**3c** and (*R*)-(*Z*)-**3b** in 74% and 77% ee, respectively. Table 1 lists the data. Some data from ref 16 are added for comparison purposes.

## Discussion

The interpretation of the results in Table 1 require a closer look at the possible modes of chirality transfer

**Scheme 3**




shown in eq 5. Chirality transfer must result from the direction of the Pd(II) to one face or the other of the double bond by the hydroxyl group. The face to which the hydroxyl directs the Pd(II) depends on the steric interactions between the two methyl groups. The most stable $\pi$-complex is the one which has the $R_1$ and $R_2$ groups farthest apart. Scheme 3 shows the possible stereochemical outcomes starting with the most stable $\pi$-complex. If, as shown, (*R*)-(*Z*)-**3** is the allylic alcohol, syn addition to the most stable $\pi$-complex will form the intermediate, **4**, with the (*R*,*R*) configuration. The exchange (**3**) and oxidation (**5**) products will retain this chiral center and thus will have the (*R*)-absolute configuration. Anti addition will produce the intermediate, **4**, with the (*R*,*S*) configuration. The final products, **3** and **5** will have the (*S*)-absolute configuration. Other combinations of events will produce different absolute configurations. In general anti addition to the most stable $\pi$-complex with either (*R*)- or (*S*)-(*Z*)-**3** will give products with the opposite absolute configuration from that of the starting material while syn addition will give products with the same absolute configuration. On the other hand anti addition to the *least stable* $\pi$-complex will give the same absolute configuration as the starting material.[21] The important result is *that one type of addition to a given* $\pi$*-complex will give both isomerization and oxidation products with the same absolute configuration*.

The approach assumes *only* that the same $\pi$-complex is attacked at high and low $[Cl^-]$. It would be very unlikely that one mode of addition occurs to one $\pi$-complex at low $[Cl^-]$ and another mode of addition to the other $\pi$-complex at high $[Cl^-]$. To test Scheme 3, a

(20) (a) Yamaguchi, S.; Yasuhara, F. *Tetrahedron Lett.* **1977**, 89−92. (b) Dale, D. L.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512−519.

(21) It is possible the product arises from the least stable $\pi$-complex. This is the case with asymmetric hydrogenation of some olefinic systems for which the unstable $\pi$-complex is so reactive that it leads to the major product.[22]

nucleophile, whose mode of addition is known and is the same at both low and high chloride, is required. Such a nucleophile is the phenyl group. As shown in eq 8, the phenylation (Heck reaction) of allyl alcohol at low [$Cl^-$] gives a $\beta$-phenyl ketone analogous to **5″**.[23] The actual

$$CH_2{=}CHCH_2OH + PhHgCl \xrightarrow{PdCl_2} PhCH_2CH_2CHO \qquad (8)$$

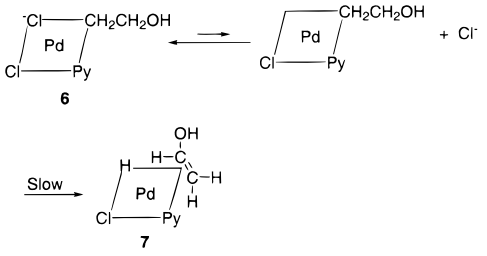
reagent in the Heck reaction is "phenylpalladium" (PhPdCl) formed by exchange of the PhHgCl with $PdCl_2$.[24] This nucleophile was chosen because, being a carbanoid species, it can only exist in hydroxylic solvents bonded to Pd(II). Thus, it must add syn under all Experimental conditions, and syn addition has been demonstrated for this nucleophile.[25] For solubility reasons, methanol was the solvent. As discussed above, methanol behaves in the same fashion as water in Wacker chemistry.

Runs 1 and 2 in Table 1 support the reaction sequence shown in Scheme 3. *Thus, as predicted by Scheme 3, the products from syn phenylation had the same absolute configuration as the starting allylic alcohol at both high and low [Cl⁻].* This result is strong evidence for addition to the most stable $\pi$-complex at both high and low [$Cl^-$]. The remainder of the data in Table 1 can now be interpreted in light of this analysis. The most significant result is the relative configurations of the oxidation and exchange products in runs 3 and 4. The product of oxidation of (*R*)-(*Z*)-**3b** is (*R*)-**5** while the product of isomerization of (*R*)-(*Z*)-**3c** is (*S*)-(*Z*)-**3b**. *Thus, according to Scheme 3, the stereochemistry of hydroxypalladation must be opposite at high and low [Cl⁻]!* The results are best accommodated by syn addition at low [$Cl^-$] and anti addition at high [$Cl^-$]. This interpretation is consistent with kinetic studies discussed above and with the stereochemistry studies in the presence of $CuCl_2$.[7]

Runs 5 and 6 confirm the mechanistic similarity of water and methanol solvents. The results parallel those in water with different modes of addition at high and low [$Cl^-$]. Thus the phenylation results in runs 1 and 2 are valid models for the results in aqueous solution.

The reason for the change in mode of addition as well as the switch from oxidation to isomerization products in going from low to high [$Cl^-$] very likely results from the difference in the coordination sphere of the palladium(II) catalyst. Wacker-type oxidations obey the rate expression given by eq 1. The $1/[Cl^-]^2$ inhibition term arises from the need to have both olefin and hydroxide in the coordinate sphere to give the intermediate in eq 2 that undergoes syn addition to give **1**. Because of the squared chloride inhibition, increasing [$Cl^-$] strongly retards the rate of the Wacker oxidation. Finally, at chloride concentrations greater than about 2 M, the predominant reaction becomes anti attack on a trichloropalladium(II) complex to give an intermediate analogous to **2** in Scheme 2. Since **2** does not have a labile aquo ligand in its coordination sphere, it is stabilized against decomposition by hydride transfer to give Wacker oxidation products. Its choices are then either reversal of the hydroxypalladation to give isomerization or reaction with $CuCl_2$, if it is present, to give chlorohydrins. Thus the same factor that encourages anti addition,

**Scheme 4**




coordination saturation, also stabilizes the intermediate toward decomposition to Wacker oxidation products.

Previous reports support this analysis. In addition to the study at high [$Cl^-$] in aqueous solution discussed above, most of the previous stereochemistry studies which gave anti addition were carried out under conditions that put extra neutral ligands in the coordination sphere. In one case chelating diolefins were the substrates.[2] In another, the strongly complexing ligands, phosphine and $\eta^5$-$C_5H_5$, were present in the coordination sphere of Pd(II).[3] In others, CO, which coordinates very strongly to Pd(II), was present.[4,5]

In recent studies the effect of a neutral ligand on reactivity was demonstrated.[26] As shown in Scheme 1, $PdCl_4^{2-}$ gives 2-chloroethanol only at both high [$Cl^-$] *and* high [$CuCl_2$]. Addition of a neutral pyridine ligand to the coordination sphere to give $PdCl_3$(pyridine)$^-$ has two dramatic effects. First, the rate constant, *k*, in eq 1 for Wacker type oxidation of ethene is decreased by a factor of 750. Second, in the presence of $CuCl_2$, 2-chloroethanol is observed at chloride concentrations as low as 0.2 M. With $PdCl_4^{2-}$, at [$Cl^-$] = 0.2 M, 2-chloroethanol would not be formed *at any CuCl₂ concentration*.

Both effects are explained by charge factors involved in replacing a chloride ligand with a more labile aquo ligand. For the syn addition shown in eq 2 to occur, water must be introduced into the coordination sphere of the Pd(II). As shown in eq 9, this would involve the formation of a positively charged complex with the $\pi$-complex

$$PdCl_2(py)(C_2H_4) + H_2O \underset{}{\overset{K}{\rightleftharpoons}} PdCl(py)(H_2O)(C_2H_4)^+ + Cl^- \qquad (9)$$

formed from $PdCl_3$(pyridine)$^-$. This would be an energetically unfavorable process so syn addition leading to Wacker type oxidation is strongly retarded. If syn addition is retarded, anti addition occurs to give an intermediate hydroxypalladation adduct with a nonlabile pyridine ligand rather than the labile aquo ligand in **1** in eq 2. Thus, to produce a vacant coordination site required for the hydride transfer leading to Wacker-type decomposition, a chloride must dissociate. The dissociation of a negative $Cl^-$ from the coordination sphere of Pd(II) is much less favorable with **6** than is the displacement of a labile water from **1**. The reaction sequence is shown in Scheme 4 where **7** decomposes to Pd(0) and $CH_3CHO$.

Studies with the chiral tetrasubstituted allylic alcohol, (*E*)-2-methyl-$d_3$-4-methyl-1,1,1,5,5,5-hexafluoro-3-penten-2-ol, and the chiral trisubstituted allylic alcohol, (*E*)-4-methyl-1,1,1,5,5,5-hexafluoro-3-penten-2-ol indicated that Wacker-type oxidation with $PdCl_3$(pyridine)$^-$ can occur by both initial displacement of chloride by water to give

(22) Halpern, J. *Science* **1982**, *217*, 401−407.
(23) Heck, R. F. *J. Am. Chem. Soc.* **1968**, *90*, 5526−5531.
(24) Heck, R. F. *J. Am. Chem. Soc.* **1968**, *90*, 5518−5526.
(25) (a) Heck, R. F. *J. Am. Chem. Soc.* **1969**, *91*, 6707−6714. (b) Henry P. M.; Ward, G. A. *Ibid*. **1972**, *94*, 673−674.
(26) Francis, J. W.; Henry, P. M. *J. Mol. Catal. A: Chem*. **1995**, *99*, 77−86.

an aquo complex analogous to **1** (eq 9) or by Scheme 4. Both routes were much slower than oxidation by $PdCl_4^{2-}$.[27]

The fact that 2-chloroethanol is formed at low [$Cl^-$] is explained by the extra stability of the intermediate **6** over that for the intermediate **1** (eq 1) which contains a labile neutral aquo ligand. Thus, **1** more readily forms the open coordination site required for $\beta$-hydride transfer from the alcoholic carbon to initiate decomposition to acetaldehyde. The intermediate **6** is more readily intercepted by $CuCl_2$ to form 2-chloroethanol than is **1**.

Such information about the details pathways of a catalytic system can be very useful in designing new syntheses. Thus, a recent report describes the development of a novel asymmetric chlorohydrin synthesis based on the effect of neutral ligands on the reactivity of Pd(II).[28]

The higher degrees of chirality transer (defined as %ee of product/%ee of starting alcohol) for isomerization as compared with oxidation is surprising. The are in the range of 92−100% for isomerization but only in the range of 55−80% for oxidation. If, as shown in Scheme 3, both arise from a common intermediate, **4**, the degree of chirality transfer should be the same for both processes. One possible explanation is that the steps in the decomposition route for oxidation are reversible to some extent. The present results do not justify speculation as to the exact nature of this loss of optical purity. It is noteworthy that the original chiral center in the oxidation of (*R*)-(*Z*)-**3b** to form (*R*)-**5c** (eq 6) racemized to some extent.

As expected the degree of chirality transfer was higher with the *Z*-isomer (run 3) than with the *E*-isomer (run 4). The steric interactions in the $\pi$-complexes formed from the *E*-isomer are much less pronounced than those in the $\pi$-complexes formed from the *Z*-isomer.[16]

## Experimental Section

**Materials.** All chemicals were purchased from Aldrich Chemical Co., unless otherwise specified, and were used as received. 3-Hexyn-2-ol and 4-hexyn-3-ol and chromium trioxide were purchased from Lancaster Synthesis Inc. and used without further purification. $Pd(OAc)_2$ was purchased from Alfa Aesar and used without further purification. THF was dried over sodium benzophenone ketyl, distilled, and stored over $CaH_2$ under argon. All other chemicals were of reagent grade. Stock solutions in water of the following composition were prepared: 0.2 M in $K_2PdCl_4$, and 0.2 M in HCl. Stock solutions in methanol of the following composition were prepared: 0.2 M in $Li_2PdCl_4$, and 0.2 M in LiCl. Reaction mixtures were prepared using the stock solutions.

**Preparation of Pyridinium Chlorochromate.** To 46.0 mL of 6.0 M HCl was added 25.0 g (0.25 mol) of $CrO_3$ rapidly with stirring. After about 5 min, the homogeneous solution was cooled to 0 °C followed by the careful addition of 16.3 mL of pyridine (15.8 g, 0.2 mol) over approximately 10 min. Cooling again to 0 °C produced a yellow orange solid which was collected by suction filtration and dried in a vacuum.

**Preparation of 3-Pentyn-2-ol.** The preparation involved the reaction of propenylmagnesium bromide with acetaldehyde. The experimental procedure has been described.[16]

**Preparation of 3-Pentyn-2-one.** The preparation involved the oxidation of 3-pentyn-2-ol with pyridinium chlorochromate. The procedure has been described.[16]

**Preparation of (*R*)-(+)-3-Pentyn-2-ol.** The procedure involved the reduction of 3-pentyn-2-one with 9-borabicyclo-[3.3.1]nonane in the presence of α-pinene (alpine-borane reagent).[18] The experimental procedure has been described.[16]

**Preparation of (*R*)-(−)-*Z*-3-Penten-2-ol.** The preparation involved the reduction of (*R*)-(+)-3-pentyn-2-ol with Lindlar catalyst.[19] The experimental procedure has been described.[16]

**Preparation of (*S*)-(+)-3-pentyn-2-ol.** An oven-dried 500 mL three-necked round-bottom flask, equipped with a septum-capped sidearm, magnetic stirring bar, reflux condenser, and stopcock adapter connected to a mercury bubbler, was assembled hot and flushed with a stream of Ar. After the apparatus cooled, it was charged, via a double-ended syringe, with 303 mL of a 0.5 M THF solution of 9-borabicyclo[3.3.1]-nonane (0.15 mol). Then 27 mL (23.2 g, 0.17 mol) of (−)-α-pinene was added. After the solution was refluxed for 4 h, the excess α-pinene and THF was removed first by water aspirator and then by vacuum pump at 40 °C to provide a thick clear oil. The flask was then cooled in an ice bath, and 10.2 mL (8.86 g, 0.108 mol) of 3-pentyn-2-one was added under Ar. Stirring was continued for 8 h, the first 2 h at 0 °C. Then 8.4 mL of acetaldehyde was added to the solution and stirring continued for another 1 h. Liberated α-pinene was removed under vacuum. Then 75 mL of THF and 57 mL of 3 M NaOH were added followed by 57 mL of 30% $H_2O_2$ dropwise. The mixture was stirred for 4 h at 40 °C and extracted with $Et_2O$ (3 × 50 mL). The ether layers were combined, dried over $MgSO_4$, filtered, and concentrated to give an oil. Distillation under vacuum provided 6.3 g (76 mmol) of 3-pentyn-2-ol, 70% yield. Examination of the $^1H$ NMR spectrum in the presence of Eu(hfc)$_3$ indicated an enantiomeric mixture containing 92% (*S*) (84% ee).

**Preparation of (*S*)-(−)-(*Z*)-3-Penten-2-ol (3a).** A low-pressure hydrogenation apparatus was charged with 5 mL of hexane, 2.2 mL (2.1 g, 25 mmol) of (*S*)-(+)-3-pentyn-2-ol, 0.1 g of Pd on $CaCO_3$ with Pb (Lindlar's catalyst), and 10 drops of quinoline. The apparatus was evacuated and hydrogen was admitted to give a pressure slightly above 1 atm. The contents of the flask were shaken until absorption of hydrogen stopped. The catalyst was removed by filtration, hexane was distilled off, and the residue upon distillation at 50 mmHg at 61−63 °C gave 1.5 g (70%) of colorless liquid. GC analysis of the product indicated it to be 98% pure *Z* isomer.

Examination of the $^1H$ NMR spectrum in the presence of Eu(hfc)$_3$ indicated an enantiomeric mixture containing 87% (*S*) (74% ee).

**Preparation of 3-Hexyn-2-one.** In a 250-mL round-bottomed flask fitted with a reflux condenser and magnetic stirring bar, 12.9 g (0.06 mol) of pyridinium chlorochromate in 50 mL of $CH_2Cl_2$ was suspended. 3-Hexyn-2-ol (4.4 mL, 3.9 g, 0.04 mol) in 10 mL of $CH_2Cl_2$ was then added in one portion to the stirred mixture. After 2 h, 100 mL of ether was added and the supernatant was decanted from the black gum. Next the black gum was washed three times with 50 mL portions of ether. The combined ether washings were dried over $MgSO_4$ and distilled under reduced pressure to give 3.0 g (0.03 mol) of 3-hexyn-2-one, 77% yield.

**Preparation of (*R*)-3-Hexyn-2-ol.** An oven-dried 500 mL round-bottom flask equipped with a septum-capped sidearm, magnetic stirring bar, reflux condenser, and stopcock adapter connected to a mercury bubbler, was assembled hot and flushed with a steam of Ar. After the apparatus was cooled, it was charged, via a double-ended syringe, with 309 mL of a 0.5 M THF solution of 9-BBN (0.152 mol). Then 27.0 mL (23.2 g, 0.17 mol) of α-pinene was added. After the solution was refluxed for 4 h, the excess α-pinene and THF was removed first by water aspirator and then by vacuum pump at 40 °C to provide a thick clear oil. The flask was then cooled in an ice bath, and 12 mL (10.8 g, 0.108 mol) of 3-hexyn-2-one was added under Ar. Stirring was continued for 2 h at 0 °C and for 6 h at 25 °C. Then 8.4 mL of acetaldehyde was added to the solution, and stirring was continued for another 1 h. Next, liberated α-pinene was removed under vacuum. Then 75 mL of THF and 57 mL of 3 M NaOH were added followed by dropwise addition of 57 mL of 30% $H_2O_2$. The mixture was stirred for 4 h at 40 °C and extracted with $Et_2O$ (3 × 50 mL). The ether layers were combined, dried over $MgSO_4$, filtered,

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(28) El-Qisairi, A.; Hamed, O.; Henry, P. M. *J. Org. Chem.* **1998**, *63*, 2790−2791.

and concentrated to yield an oil. Distillation under vacuum provided 7.7 g (0.079 mol) of 3-hexyn-2-ol, 73% yield. Examination of the $^1$H NMR spectrum in the presence of Eu(hfc)$_3$, indicated an enantiomeric mixture containing 84% (*R*) (68% ee).

**Preparation of (*R*)-(−)-(*Z*)-3-Hexen-2-ol (3b).** A low-pressure hydrogenation apparatus was charged with 10 mL of hexane, 3.5 mL (3.2 g, 0.032 mol) of (*R*)-(+)-3-hexyn-2-ol, 0.2 g of Pd on $CaCO_3$ poisoned with lead (Lindlar's catalyst), and 20 drops of quinoline. The apparatus was evacuated, and hydrogen was admitted to a pressure slightly above 1 atm. The contents of the flask was shaken until absorption of hydrogen stopped. The catalyst was removed by filtration, hexane was distilled off, and the residue upon distillation under vacuum produced 2.2 g (0.022 mol, 71% yield) of colorless liquid which was found by GLC analysis to be a 98% pure *Z* isomer. $^1$H NMR study of the product in the presence of Eu(hfc)$_3$ indicated the sample was 83% (*R*) (66% ee).

**$Li_2PdCl_4$-Catalyzed Phenylation of (*R*)-(+)-(*Z*)-3-Penten-2-ol.** To a stirred solution of 0.1 M $Li_2PdCl_4$ in methanol (15.0 mL) was added 0.5 mL (3.7 mmol) of $Et_3N$, 0.5 g (3.7 mmol) of $CuCl_2$, 1.1 g (3.5 mmol) of PhHgCl, and 0.35 mL (0.3 g, 3.5 mmol) of (*R*)-(*Z*)-3-penten-2-ol (ee = 53%). After stirring for 2 h at room temperature, the reaction was diluted with water. The precipitate was removed by filtration, and the filtrate and the precipitate were extracted with ether (3 × 30 mL). The ether layers were combined and dried over $MgSO_4$, and solvent was removed under vacuum. The residue was purified twice by column chromatography (silica gel, 8/2 hexane/ether) to give 0.47 g (84% yield) of 4-phenyl-2-pentanone. Lanthanide shift determination showed the presence of 65% *R* (30% ee).

**Phenylation of (*S*)-(*Z*)-3-Penten-2-ol (ee = 74%) in the Presence of High [LiCl].** A 100-mL two-necked round-bottom flask, containing a magnetic stirring bar and LiCl (1.6 g, 37.7 mmol) fitted with a septum-cap, was evacuated on a vacuum line at 100 °C for 2 h. To this were added $PdCl_2$ (0.11 g, 0.6 mmol), $CuCl_2$ (0.67 g, 5 mmol), and 15 mL of methanol. After stirring the solution for 30 min, PhHgCl (0.70 g, 3.5 mmol) and (*S*)-(*Z*)-3-penten-2-ol (0.35 mL, 0.30 g, 3.5 mmol) were added. The stirring was continued for 48 h at room temperature, and then the reaction mixture was diluted with 100 mL of $CH_2Cl_2$ and washed with 30 mL of water. The organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Analysis of the residue by GLC and NMR showed the presence of 4-phenyl-(*Z*)-2-pentene (**3a″**), phenylbenzene, and 4-phenyl-2-pentanone (**5a″**) in relative yields of 70%, 25%, and 5%, respectively.

The enantiomeric purity of **3a″** and its absolute configuration were determined by converting pure sample of **3a″** obtained by preparative GLC to 4-phenyl-2-pentanone (**5a″**) as described below.

**$Pd(OAc)_2$-Catalyzed Oxidation of 4-Phenyl-(*Z*)-2-pentene.** A 2 mL conical vial fitted with a magnetic stirring bar and a reflux condenser was charged with acetonitrile (0.9 mL), $H_2O$ (0.1 mL), benzoquinone (20 mg, 0.19 mmol), $HClO_4$ (10 μL), 4 -phenyl-Z-2-pentene (**3a″**) (0.015 g, 0.1 mmol), and $Pd(OAc)_2$ (0.0011 g, 0.005 mmol). The resulting solution was stirred at 50 °C for 6 h. Then it was diluted with $CH_2Cl_2$ (5 mL), washed with water (5 mL), and dried over $MgSO_4$. $CH_2Cl_2$ was removed under reduced pressure. Analysis of the residue by $^1$H NMR showed the presence of one product, 4-phenyl-2-pentanone (**5a″**). Its ee was 56%, and comparison of its $^1$H NMR spectrum with that of an authentic sample, both in the presence of Eu(hfc)$_3$, showed that its absolute configuration was *S*.

**Methoxylation of (*S*)-(*Z*)-3-Penten-2-ol ((*S*)-(*Z*)-3a) (ee = 74%) in the Presence of High [LiCl].** A 100-mL two-necked round-bottom flask, containing a magnetic stirring bar and LiCl (1.6 g, 37.7 mmol, 2.5 M) fitted with a septum-cap, was evacuated on a vacuum line at 100 °C for 2 h. To this were added $PdCl_2$ (0.11 g, 0.6 mmol), $CuCl_2$ or benzoquinone (5 mmol), and 15 mL of methanol. After stirring for 30 min, (*S*)-*Z*-3-penten-2-ol (0.35 mL, 0.30 g, 3.5 mmol) was added. The stirring was continued for 48 h at room temperature, followed by dilution with 100 mL of $CH_2Cl_2$ and washing with 30 mL of water. The organic layer was dried over anhydrous $MgSO_4$ and distilled to remove the solvent. Analysis of the residue by GLC and NMR showed the presence of only one product that was identified by NMR spectroscopy as 4-methoxy-(*Z*)-2-pentene (**3a′**).

The enantiomeric purity of **3a′** was 68%. As described next its absolute configuration was found to be *R* by converting pure sample of **3a′**, obtained by preparative GLC, to 4-methoxy-2-pentanone (**5a′**).

**$Pd(OAc)_2$-Catalyzed Oxidation of 4-Methoxy-(*Z*)-2-pentene (Z-3a′).** For procedure, see $Pd(OAc)_2$-catalyzed oxidation of 4-phenyl-(*Z*)-2-pentene. Comparison of the $^1$H NMR spectrum of the **5a′** product with that of an authentic sample, both in the presence of Eu(hfc)$_3$, showed that the absolute configuration was *R*.

**Oxidation of (*R*)-(−)-(*Z*)-3-Hexen-2-ol (3b).** The reaction solution (50.0 L), which was (0.1 M) in $K_2PdCl_4$, 0.1 M in HCl, and 0.1 M in benzoquinone was put into an open, round-bottom flask. (*R*)-(−)-(*Z*)-**3b** (0.65 mL; 0.11 M) was gradually added over a period of 20 min. The solution was stirred for another 20 min, followed by addition of Zn powder. After another 10 min of stirring, the mixture was extracted with ether (3 × 50 mL). The combined extracts were combined and dried over anhydrous $MgSO_4$. Analysis of the product by GLC and $^1$H NMR showed that the product is a mixture of two compounds **5b** and **5c** in relative yields of 57% and 43%, respectively. Preparative GLC yielded pure samples of **5b** and **5c**. The ee of **5b** and **5c** were 42% and 38%, respectively.

**Preparation of (*R*)-(−)-MTPA Derivative of 4-Hydroxy-2-hexanone (5b).** The reagents were injected by a syringe into a 1 mL conical vial fitted with a rubber septum in the following order: dry pyridine (300 μL), carbon tetrachloride (300 μL), (+)-MTPA-Cl (37 μL, 0.15 mmol), and **5b** (11.5 mg, 0.15 mmol). The reaction mixture was stirred at room temperature for about 48 h. Excess 3-(dimethylethylamino)-2-propylamine (24 μL, 20 mg, 0.2 mmol) was added, and the mixture was stirred for another 10 min. It was then diluted with ether and washed with cold dilute HCl, cold saturated $Na_2CO_3$, and saturated NaCl. After drying over $MgSO_4$, the ether was removed under vacuum. The $^1$H NMR spectrum of the residue was taken in the presence of Eu(hfc)$_3$.

**Preparation of (*R*)-(+)-MTPA Derivative of 5-Hydroxy-3-hexanone (5c).** See preparation of (*R*)-(+)-MTPA derivative of 4-hydroxy-2-hexanone.

**Isomerization of (*R*)-(−)-(*Z*)-4-Hexen-3-ol (3c).** The reaction solution (25.0 mL) was 0.05 M in $Li_2PdCl_4$, 0.2 M in benzoquinone, 2.0 M in LiCl, and 0.06 M in (*R*)-(−)-(*Z*)-(**3c**). The reaction mixture was stirred for 30 min at room temperature, and $CH_2Cl_2$ was used to extract the product (3 × 30 mL). The extracts were combined, dried over $MgSO_4$, and evaporated. A pure sample of the product was collected by preparative gas chromatography. The product was identified by $^1$H and $^{13}$C NMR as a mixture of equal amounts of (*R*)-(−)-(*Z*)-(**3c**) and (*S*)-(−)-(*Z*)-(**3b**). The ee's were determined by $^1$H NMR in the presence of the chiral shift reagent Eu(hfc)$_3$.

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**Supporting Information Available:** $^1$H and $^{13}$C NMR and IR spectra data, as well as optical rotations, of (*S*)-(+)-3-pentyn-2-ol, (*R*)-3-hexyn-2-ol, **3a**, **3a′**, **3a″**, **3b**, **5a′**, **5a″**, **5b**, **5c** (3 pages). This material is available free of charge via the Internet at http://pubs.acs.org.

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