Oxidation of Olefins by Palladium(II). 15.[1] Oxidation of (*R*)-(−)-(*Z*)- and (*R*)-(+)-(*E*)-3-Penten-2-ol Using Several Nucleophiles To Give Chiral *β*-Substituted Ketones. A Method of Finding Modes of Palladation of Olefins Using Chirality Transfer

Othman Hamed and Patrick M. Henry*

Department of Chemistry, Loyola University of Chicago, Chicago, Illinois 60626

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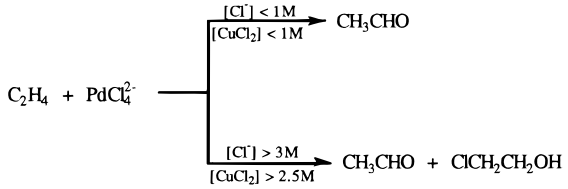
The oxidation of (*R*)-(−)-(*Z*)- and (*R*)-(+)-(*E*)-3-penten-2-ol with Pd(II) using hydroxyl, methoxyl, acetate, and phenyl as nucleophiles produced *β*-substituted ketones. The ketone products are optically active, indicating the hydroxyl group was preferentially directing the Pd(II) to one of the two faces of the double bond in forming the initial *π*-complex. The absolute configuration of the product depends on the absolute configuration of the starting alcohol, the *π*-complex face to which the nucleophile adds, and the stereochemistry of addition. Because of steric interactions between the two terminal methyl groups, one *π*-complex is more stable than the other. Phenylpalladium, a reagent which is known to add syn, gave (*R*)-4-phenyl-2-pentanone, a result that is consistent only with syn addition to the most stable *π*-complex. With this information, determination of the stereochemistries of addition of the other nucleophiles is possible. In aqueous solution and methanol at low [Cl^-], the 4-hydroxy, and 4-methoxy-2-pentanone products had the *R* configuration, indicating syn addition. These results are consistent with recent stereochemical and kinetic studies. A surprise was the finding of the *R* configuration, indicating syn addition, for the 4-acetoxy-2-pentanone product in acetic acid solvent. Previous kinetic studies were interpreted in terms of anti addition. Another unexpected result was the reversal of addition to anti at high [Cl^-] in acetic acid. As expected, the *Z*-isomer gave higher degrees of chirality transfer than the *E*-isomer.

Introduction

The Pd(II)-catalyzed oxidation of ethene in aqueous solution (Wacker reaction, Scheme 1) gives acetaldehyde exclusively under the usual Wacker conditions of low [Cl^-] (>1.0 M).[2] 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) concentrations, formation of ethylene chlorohydrin becomes a serious side reaction. The Wacker controversy concerns the stereochemistry of the addition of Pd(II) and OH to the ethene double bond (hydroxypalladation) under the usual Wacker conditions of low [Cl^-]. 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.[2] Studies with chelating diolefins[3] and with simpler olefins under conditions far removed from those of the aqueous acyclic olefin oxidation[4,5] suggest an anti mode of hydroxypalladation. These results were extrapolated to the low chloride conditions of the actual oxidation.

Scheme 1



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).[6] 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 the substrates, formation of the deuteriated 2-chloroethanol products occurred via anti hydroxypalladation. It was assumed that the same intermediate 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, kinetic evidence suggests that the reaction at high [Cl^-] is different from that at low [Cl^-].[7]

Thus, there is a need for a stereochemical probe which identifies the modes of addition under the actual reaction conditions of interest. A potential technique uses chirality transfer. There are several demonstrations of the directing influence of the hydroxyl group for epoxi-

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Table 1. Results for the Oxidation of (*R*)-(*Z*)-Pent-3-en-2-ol with Various Nucleophiles (% ee = 53%)

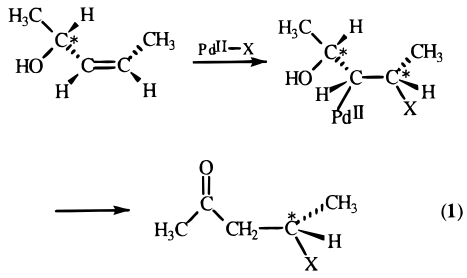
run	catalyst species[a]	X	solvent	absolute configuration	% ee	% chirality transfer
1	Li_2PdCl_4[b]	OH	H_2O	*R*	33.4 ± 0.6[e]	63
2	"$Pd(OAc)_2$"[c]	CH_3O	CH_3OH	*R*	36	68
3	Li_2PdCl_4	CH_3O	CH_3OH	*R*	41.6 ± 0.4[e]	78
4	Li_2PdCl_4	Ph	CH_3OH	*R*	30 ± 1.0[e]	57
5	$Li_2Pd_2Cl_6$	Ph	CH_3CN	*R*	36	68
6	$Li_2Pd_2(OAc)_6$[d]	OAc	HOAc	*R*	28	53
7	$Li_2Pd_2Cl_6$	OAc	HOAc	*R*	41.4 ± 0.6[e]	79
8	$Li_2Pd_2Cl_6$ ([LiCl] = 1M)	OAc	HOAc	*S*	31 ± 1.5[f]	58

[a] The formulas are the form of the catalytic species under the reaction conditions (see ref 2; pp 11−15). [b] Also 0.1 M in HCl. [c] State of catalyst unknown. [d] Also 0.8 M in LiOAc. [e] Duplicate runs. [f] Run in triplicate.

dation reactions[8−10] as well as for other reactions.[11] In one study, on the Simmons−Smith reaction with *cis* allylic alcohols, over 99% stereoselectivity was found.[12] The directing influence of the hydroxyl group in Pd(II) catalytic chemistry is well-documented. The product distributions for the oxidation of allyl alcohol,[13a] crotyl alcohol,[13b] and 2-cyclohexenol-*1-d*[13c] are best explained by direction of the Pd(II) by the hydroxyl group. Thus, asymmetric synthesis by chirality transfer with optically active allylic alcohols seems to be a promising preparative procedure. The palladium(II)-catalyzed addition of a phenyl group (Heck reaction) to chiral 3-methyl-but-3-en-2-ol occurred with partial 1,2 chirality transfer.[14] Recent studies of the exchange of chiral tetrasubstituted allylic alcohols with water solvent show chirality transfer can be very high (>98%).[15] However, despite these promising early results, asymmetric synthesis by chirality transfer in Pd(II) catalysis has been, as yet, largely unexploited.

The simplest types of chirality transfer involve relocating the optically active center from one part of the molecule to another. The final product for secondary alcohols under most reaction conditions is a ketone. Equation 1 shows the general reaction sequence using chiral *Z*-pent-3-en-2-ol as the olefin. X could be phenyl, methoxy, acetate, vinyl, or other carbon nucleophiles such as the carboxyl ester group. Formation of the ketone occurs when the Pd(II) species undergoes oxidative decomposition. These procedures provide a means of constructing a new type of chiral center.

However, their most exciting use could be as a mechanistic tool in learning the stereochemistries of the addition of several nucleophiles under different reaction conditions. Convenient allylic alcohols for these studies



(1)

are the (*Z*)- and (*E*)-pent-3-en-2-ols since the optical isomers for both geometry's are known. Also, the absolute configurations of the ketone products when phenylpalladium(II) is the reagent are also known.[14] The main advantage of such a stereochemical probe would be the fact that it can be used under the actual experimental conditions of interest. As discussed above, such a probe would be useful in determining the modes of the addition under the usual Wacker conditions ([Cl^-] < 1 M).

Results

Table 1 shows the results for the reaction of the *Z*-isomer using several nucleophiles. The % chirality transfer is the % ee of the product divided by the % ee of the starting pentenol. The % chirality transfer varied from about 50% to 80%. The absolute configuration of the major β-hydroxyketone product in run 1 was determined to be *R* by converting the product to its Mosher's esters and determining the shift of the methoxy and methyl signals of the Mosher ester in the presence of $Eu(hfc)_3$.[16] The standards for the methoxy product in runs 2 and 3 and the acetoxy product in runs 6−8 were prepared from this hydroxyketone product. The phenylation (Heck) reaction was run in methanol since this system is close to the Wacker conditions and in acetonitrile to imitate the conditions of the original Heck reaction.[17] The absolute configuration of the 2-phenyl-4-pentanone product was determined to be *R* by comparing its specific rotation with that reported in the literature.[18]

Several of the runs in Table 1 were duplicate experiments, and one run (run 8) was the average of three experiments. The reproducibility was quite good, less

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(12) Ratier, M. C.; Castaing, M.; Godet, J.-Y. G.; Pereyre, M. *J. Chem. Res. (Miniprint)* **1978**, 2309.
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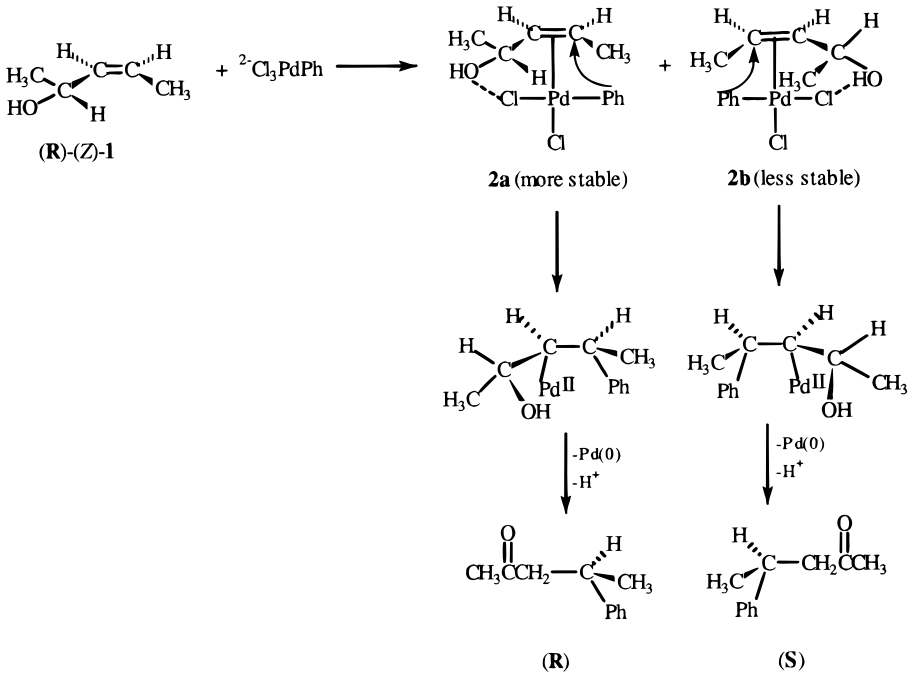
Table 2. Results for the Oxidation of (*R*)-(*E*)-Pent-3-en-2-ol with Various Nucleophiles (% ee = 51%)

run	catalyst species[a]	X	solvent	absolute configuration	% ee	% chirality transfer
1	$Pd(OAc)_2$[b]	CH_3O	CH_3OH	*R*	28	55
2	Li_2PdCl_4	CH_3O	CH_3OH	*R*	8	15.6
3	Li_2PdCl_4	Ph	CH_3OH	*R*	14	27
4	$Li_2Pd_2Cl_6$	Ph	CH_3CN	*R*	16	31
5	$Li_2Pd_2(OAc)_6$[c]	OAc	HOAc	*R*	12	23.5

[a] The formulas are the form of the catalytic species under the reaction conditions (see ref 2; pp 11−15). [b] State of catalyst unknown. [c] Also 0.8 M in LiOAc.

Scheme 2



than ±2%. Thus, the difference among 63% chirality transfer in run 1 and 68% chirality transfer in runs 2 and 5 is statistically significant.

Table 2 lists the results for the (*R*)-*E*-isomer with methoxy, phenyl, and acetoxy nucleophiles. A problematic side reaction in the $Pd(OAc)_2$-catalyzed runs in methanol solvent (run 2 in Table 1 and run 1 in Table 2) was the formation of 3-penten-2-one. This side product appeared in 40% yield with (*R*)-*Z*-**1** in Table 1 and in 60% yield with (*R*)-*E*-**1** in Table 2. In the chloride containing system (run 3 in Table 1), the unsaturated ketone was a minor product.

Discussion

The interpretation of the results in Tables 1 and 2 require a closer look at the possible mechanisms of the chirality transfer shown in eq 1. The logical starting point is the phenylation reaction since the addition of Pd(II) and phenyl is known to be syn.[19] 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) is depends on the steric interactions between the two methyl groups. As shown in Scheme 2, the most stable complex should be the one which has the methyl's farthest apart. With the *R*-configuration, this is **2a**. However, it is possible that the product arises from addition to the least stable π-complex, **2b**. This is the case with asymmetric hydrogenation of some olefinic systems for which the unstable π-complex is so reactive that it leads to the major product.[20] The experimental result, formation of the *R* optical isomer, is consistent with syn addition occurring from the most stable π-complex, **2a**. The above considerations lead to the conclusion that, in the present system, addition occurs to the most stable rotamer.

This deduction now explains the remainder of the data in Table 1. Table 1 contains some intriguing results. The β-hydroxyketone formed in run 1 has the *R* absolute configuration, indicating syn addition. This result is in apparent contradiction to stereochemical results at high chloride-concentrations that indicate anti addition to ethylene. However, stereochemical studies of the isomerization of chiral allylic alcohols showed that the mode of hydroxypalladation is opposite at low- and high-chloride concentrations.[15] The combination of the two studies implies syn addition at low $[Cl^-]$. The present result is consistent with this analysis. Actually, the fact the β-hydroxyketone was chiral indicates that the new chiral center must have the *R* absolute configuration. As shown in Scheme 3, the formation of an optically active hydroxyketone is not possible if addition to form the palladium(II) hydroxypalladation intermediate had been anti. Thus, the intermediate in Scheme 3, resulting from syn addition to the most stable

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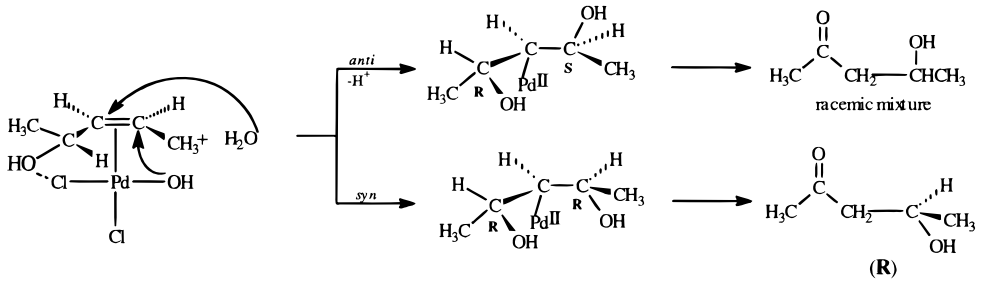
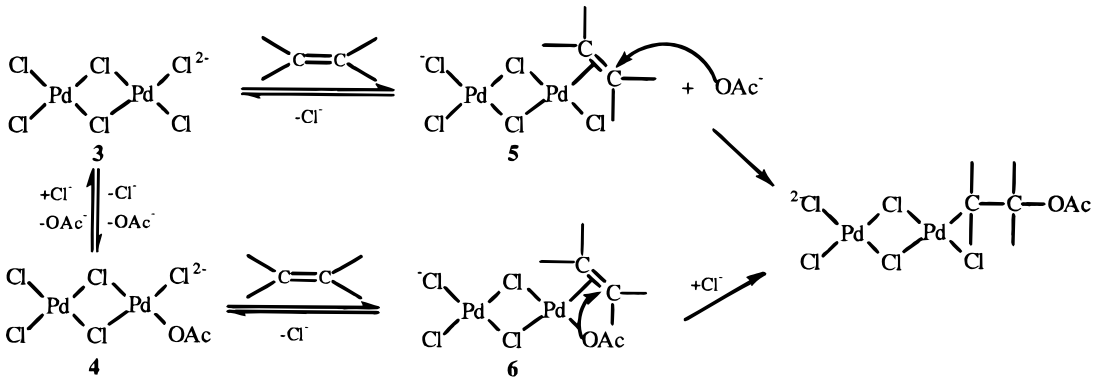
Scheme 3



Scheme 4



rotamer, has the (*R*,*R*) configuration. Thus, even if $R_1 = R_2 = CH_3$, as in the present case, the intermediate gives an optically active product. On the other hand, as shown in Scheme 3, anti addition gives the (*R*,*S*)-isomer, which, in the present case, would lead to a racemic product. The absolute configuration of the product confirmed this analysis. As expected, the hydroxyketone had the (*R*) configuration, indicating syn addition.

In the light of the result of run 1, the finding of the *R* configuration for methoxypalladation in the chloride containing system (run 3), indicating syn addition, is not surprising. Ethene oxidation in methanol at low [Cl^-] follows a rate expression that is identical to ethene oxidation in water.[21] Thus, both must proceed by similar mechanisms. In the chloride-free system, the ether product also had the *R* configuration, indicating syn addition. This result is of some interest, but the lack of equilibrium and kinetic studies in this system preclude any detailed mechanistic discussion of the finding.

The results for the acetoxypalladation studies are unexpected. In chloride-free media (run 6), previous studies had suggested anti addition[22] while the *R* configuration found is consistent only with syn addition. The complexity of the system is the probable explanation for the difference. "$Pd(OAc)_2$" exists in three forms in acetic acid; trimer, dimer, and monomer.[23] The relative amount of each form depends on acetate concentration. Some aggregations could undergo syn addition and others anti. The low % chirality transfer is perhaps an indication of the presence of both syn and anti modes. Under the conditions of the experiment, both dimer and monomer would be present. Complete definition of the system requires determination of absolute configuration at various [LiOAc].

A *real surprise* was the finding of syn acetoxypalladation in the chloride containing system in acetic acid. The original postulate of anti acetoxypalladation for the exchange of vinyl and allylic esters with acetate in acetic acid[24] was based on equilibrium studies in the absence of acetate ion.[25] The equilibrium studies indicated that the predominate species under these conditions was **3**, Scheme 4. There was only a single chloride inhibition in the rate expression for exchange,[24] and this most likely resulted from the equilibrium reaction with olefin to form **5**. Since putting an acetate in the coordination sphere of Pd(II) for syn addition requires a second chloride inhibition, the logical assumption was that addition was anti. Oxidation studies with deuteriated cyclohexene as the substrate supported this conclusion.[26] However, cyclohexene behaves differently from acyclic olefins,[13c] so this finding may not apply to the present system.

The present results suggest that **4** is the most important species in the presence of acetate ion at low-chloride concentration. In an equilibrium step, **4** must react with olefin to give **6**, which is capable of undergoing syn addition. The reversal of stereochemistry in the presence of 1 M LiCl can be explained by conversion of **4** to **3** under these conditions. The intermediate **3** can only react with olefin to give **5**, which can only undergo anti addition. Thus, anti addition becomes the preferred route at high [Cl^-]. This reversal of mode of addition at high-chloride concentration is reminiscent of that found in the aqueous system discussed above. The reaction in acetic acid requires an equilibrium study in the presence of acetate to determine if **4** is the predomi-

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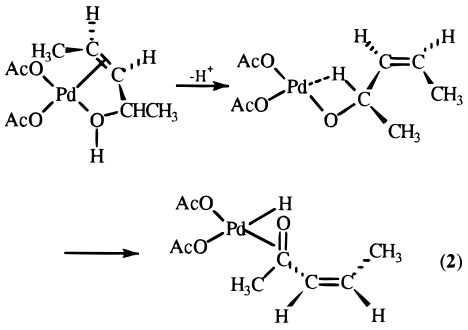
nate species at low-chloride concentration in the presence of acetate.

As expected, the % chirality transfers for (*R*)-*E*-3-penten-2-ol listed in Table 2 are lower than those for the *Z*-isomer. This decrease must result from the fact that the steric interactions in the π-complexes formed from this isomer experience less-pronounced steric interactions than with the *Z* isomer. The net result is that the energy difference between the two rotomers corresponding to **2a** and **2b** is less and that there is less preference for addition to the more stable rotamer. It is noteworthy that the chloride-free system in methanol (run 1) gives the highest % chirality transfer. This result is peculiar since with the (*Z*)-isomer the % chirality transfer is not exceptionally high.

These very encouraging preliminary results suggest a general procedure for learning the modes of addition of various Pd(II) and other metal reagents under a variety of reaction conditions. Unfortunately, the degree of chirality transfer is probably too low for practical asymmetric synthesis. The reason for this low chirality transfer could result from an inherently ineffective chirality transfer. However, as discussed in the Introduction, % chirality transfers are often very high in other reactions involving chirality transfer. These include isomerization and carbonylation, which were studied in these laboratories. The chirality transfer approaches 100% in these cases.[27] Thus, the loss in chirality transfer may result from the decomposition step. Future publications, which compare different types of chirality transfer syntheses, will explore this possibility in more detail.

The ketone product, 3-penten-2-one, is analogous to the acrolein product found in the oxidation of allyl alcohol in aqueous solution.[13a] As shown in eq 2, it most likely is formed by direct hydride transfer from the alcohol carbon by Pd(II). However, the formation of this



(2)

product by acetic acid elimination from the 4-acetoxy-2-pentanone product cannot be completely ruled out.

Experimental Section

Starting Materials. Palladium(II) chloride and acetate were purchased from Aesar. All other chemicals were purchased from Aldrich, except as noted, and were used as received. Propyne was obtained from Lancaster Synthesis, Inc.

Physical Measurements. ^{1}H NMR data were recorded on a Varian VRX 300 NMR spectrometer. All ^{1}H NMR spectra in the presence of Eu(hfc)$_3$ were carried out in $CDCl_3$. GLC analysis was carried out using a GOW-MAC 350 gas chromatograph fitted with Carbowax 10 M on 80−100 mesh Chromosorb W-NAW column. IR spectra were recorded on a ATI Mattson Genesis FT-IR or a Perkin-Elmer 1310 infrared spectrometer. All chemical shifts are reported relative to tetramethylsilane as an internal standard.

Preparation of 3-Pentyn-2-ol. A clean oven-dried three-necked 1 L flask equipped with a magnetic stirring bar, a dropping funnel, and a reflux condenser connected with a drying tube of anhydrous $CaCl_2$ was used for this experiment. Acetaldehyde (22 g, 0.50 mol) in 50 mL of anhydrous ether was gradually added to a solution of propenylmagnesium bromide obtained by passing propyne into a solution of ethylmagnesium bromide. After 5 h of stirring, ice-cold saturated aqueous ammonium chloride (500 mL) was added. The ethereal layer was separated, dried over anhydrous $MgSO_4$, and fractionated, giving 22 g (52%) of 3-pentyne-2-ol. Bp 117−119 °C (lit.[28] 118−121 °C). IR (neat) cm^{-1}: 3350, 2220.

Preparation of 3-Pentyn-2-one. In a 500 mL round-bottomed flask fitted with a reflux condenser and magnetic stir bar was suspended 64.6 g (0.300 mol) of pyridinium chlorochromate in 100 mL of CH_2Cl_2. 3-Pentyn-2-ol (19 mL, 17 g, 0.20 mol) in 20 mL of CH_2Cl_2 was added in one portion to the stirred solution. After 2 h, 200 mL of ether was added and the supernatant decanted from the black gum. The gum was washed three times with 100 mL portions of ether. The combined ether washings were dried over $MgSO_4$ and distilled at 56−58 °C at 50 mmHg to give 12 g (0.15 mol) of 3-pentyn-2-one, 75% yield. ^{1}H NMR ($CDCl_3$) δ: 2.02 (s, 3H), 2.32 (s, 3H).

Preparation of (*R*)-(+)-3-Pentyn-2-ol. An oven-dried 500 mL three-necked round-bottomed flask, equipped with a septum-capped side arm, 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 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. The mixture continued to stir for 8 h, the first 2 h at 0 °C. Then 8.4 mL of acetaldehyde was added to the solution, and the mixture continued to stir 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 at 64−66 °C at 50 mmHg provided 6.3 g (76 mmol) of 3-pentyn-2-ol, 70% yield. IR (neat) cm^{-1}: 3350, 3005, 2220, 720. ^{1}H NMR ($CDCl_3$) δ: 4.48 (m, 1H), 2.55 (variable, br, 1H, OH) 1.82 (s, 3H), 1.42 (d, 3H). Optical rotation $[\alpha]^{24}_D = +19.71$ (neat). Examination of the ^{1}H NMR spectrum in the presence of Eu(hfc)$_3$ indicated an enantiomeric mixture containing 78.5% (*R*), 57% ee.

Preparation of (*R*)-(−)-*Z*-3-Penten-2-ol. A low-pressure hydrogenation apparatus was charged with 5 mL of hexane, 2.2 mL (2.1 g, 25 mmol) of (*R*)-(+)-3-pentyn-2-ol, 0.1 g of Pd on $CaCO_3$ with Pb (Lindlar 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 (lit.[28] bp 118−121 °C) gave 1.5 g (70%) of a colorless liquid. GC analysis of the product indicated it to be 98% pure *Z* isomer. Optical rotation $[\alpha]^{24}_D = -8.2$ (neat), IR (neat) cm^{-1}:

(27) Hamed, O. Ph.D. Thesis, Loyola University, Chicago, IL, 1996.

(28) Brudrenghien, J. *Chem. Abstr.* **1929**, *23*, 4196.

3350, 3005, 1605, 720. ^{1}H NMR ($CDCl_3$) δ: 5.52 (m, 1H), 5.40 (m, 1H), 4.65 (dq, J = 18.6 and 6.28 Hz, 1H), 2.15 (br, 1H), 1.68 (d, J = 6.5 Hz, 3H), 1.25 (d, J = 6.35 Hz, 3H). Examination of the ^{1}H NMR spectrum in the presence of Eu(hfc)$_3$ indicated an enantiomeric mixture containing 76.5% (*R*), 53% ee.

Preparation of (*R*)-(+)-*E*-3-Penten-2-ol. A 100 mL flask was dried in an oven and cooled down to room temperature under a stream of argon. The flask was equipped with a magnetic stirring bar and a refluxing condenser connected to a drying tube of anhydrous $CaCl_2$. A 200 mL sample of dry THF was introduced into the flask, followed by 1.3 g (30 mmol) of $LiAlH_4$ and 3.5 mL (3.2 g, 38 mmol) of (*R*)-(+)-3-pentyn-2-ol. The mixture was stirred for 3 h at room temperature. Hydrolysis was affected by careful dropwise addition of H_2O (3.0 mL), 15% NaOH (2.0 mL), and H_2O (6.0 mL). The mixture was filtered, and the precipitate was washed with ethyl ether (2 × 30 mL). The organic layers were combined and dried over anhydrous $MgSO_4$. The residue, upon distillation at 62−64 °C at 50 mmHg gave 2.5 g (77%) of a colorless liquid that was >98% pure *E* isomer by GLC. Optical rotation $[\alpha]^{24}_D = +5.21$ (c = 5, methanol). IR (neat) cm^{-1}: 3350, 3005, 1605, 980. ^{1}H NMR ($CDCl_3$) δ: 5.7 (dd, J = 6.32 and 15.3 Hz, 1H), 5.52 (dq, J = 6.43 and 15.3 Hz, 1H), 4.25 (dq, J = 6.3 and 19 Hz, 1H), 2.10 (br, 1H, OH) 1.54 (d, J = 6.45 Hz, 3H), 1.22 (d, J = 6.50 Hz, 3H). Study of the NMR in the presence of the lanthanide shift reagent Eu(hfc)$_3$ showed that the product is a mixture of the two enantiomers containing 75.5% (*R*), 51% ee.

Oxidation of (*R*)-(−)-(*Z*)-3-Penten-2-ol in Aqueous Solution. The reaction was carried out in an open round-bottomed flask. The reaction solution (50 mL) was 0.1 M in K_2PdCl_4, 0.1 M in HCl, and 0.1 M in benzoquinone. A 1.0 mL (0.89 g, 0.10 mol) sample of (*R*)-*Z*-2-penten-3-ol was gradually added over a period of 20 min. The solution was stirred for another 20 min, Zn powder was added, and the mixture was stirred for another 10 min, followed by extraction with ether (3 × 50 mL). The combined extracts were dried over anhydrous $MgSO_4$ and evaporated to give 0.65 g of 4-hydroxy-2-pentanone (65% yield). The ee (34%) of the product was determined by ^{1}H NMR in the presence of Eu(hfc)$_3$. ^{1}H NMR ($CDCl_3$) δ: 4.2 (m, J = 6.4 Hz, 1H), 3.05 (b, 1H), 2.62 (dd, J = 3.2 and 17.8 Hz, 1H), 2.52 (dd, J = 8.6 and 17.8 Hz, 1H) 2.16 (s, 3H), 1.69 (d, 3H, J = 6.4 Hz). ^{13}C NMR ($CDCl_3$) δ: 209.6, 63.8, 51.4, 30.8, 22.4.

Preparation of (*R*)-4-Hydroxyl-2-pentanone α-Methoxy-α-(trifluoromethyl)phenyl Acetate and Determination of Absolute Configuration. 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 mL), carbon tetrachloride (300 mL), (+)-α-Methoxy-α-(trifluoromethyl)-phenylacetyl chloride (37 mL, 0.15 mmol),[15a] and 4-hydroxy-2-pentanone (13 mg, 0.15 mmol). The reaction mixture was stirred at room temperature for 48 h. Excess 3-(dimethylethylamino)-2-propylamine (24 mL, 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 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)$_3$. The shift of the two CH_3 signals indicated the absolute configuration was (*R*).[16]

Preparation of an Authentic Sample of (*R*)-Methoxy-2-pentanone. O-Methylation of (*R*)-4-Hydroxy-2-pentanone. A 25 mL flask, equipped with a magnetic stirring bar and a refluxing condenser connected to a mercury bubbler, was charged with 5.0 mL of methyl iodide, 0.17 mL (0.16 g, 1.6 mmol) of (*R*)-4-hydroxy-2-pentanone, 0.15 g of $CaSO_4$, and 0.37 g of silver(I) oxide. The stirred mixture was heated in the absence of light in a 60 °C oil bath for 27 h. Then 20 mL of ethyl ether was added, the mixture was filtered by suction using a sintered glass funnel, and the solid residue was washed with 2 × 20 mL portions of ethyl ether. The ether washes were combined, and solvent was removed by distillation. A pure sample of the product was obtained from the residue by preparative gas chromatography

Preparation of an Authentic Sample of 4-Acetoxy-2-pentanone. An oven-dried 25 mL flask, equipped with a rubber septum and a magnetic stirring bar, was charged with 1.5 mL of CCl_4, 1.5 mL of pyridine, 0.11 mL (0.102 g, 1 mmol) of *R*-4-hydroxy-2-pentanone, and 0.085 mL (0.0942 g) of acetyl chloride. The mixture was stirred at room temperature for 1 h. It was then diluted with ether, washed with cold diluted HCl, cold saturated $NaHCO_3$, and H_2O, and dried over $MgSO_4$. Ether was removed by distillation. A pure sample of the product was collected by GLC.

Pd(OAc)$_2$-Catalyzed Methoxylation of (*R*)-*Z*-1. To a solution of 0.25 mL (0.21 g, 2.5 mmol) of (*R*)-*Z*-**1** (ee = 53%) in 5.0 mL of methanol under Ar was added 0.63 g (2.5 mmol) of $Pd(OAc)_2$. After the mixture was stirred for 2 h at room temperature, it became black. The mixture continued to stir for another 10 h. The reaction mixture was then diluted with water and filtered to remove the black precipitate. The filtrate was extracted with CH_2Cl_2 (3 × 10 mL). The CH_2Cl_2 extracts were combined, dried over $MgSO_4$, and evaporated to yield 0.21 g (47%) of a yellow liquid. Analysis by GLC and NMR identified one product as 4-methoxy-2-pentanone. ^{1}H NMR ($CDCl_3$) δ: 3.78 (m, J = 6.4 Hz, 1H), 3.29 (s, 3H), 2.70 (dd, J = 7.3 and 15.9 Hz, 1H), 2.40 (dd, J = 5.1 and 15.7 Hz, 1H), 2.15 (s, 3H), 1.15 (d, J = 6.4 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ: 207.2, 73.2, 56.3, 50.6, 31.1, 19.l3. The other compound was identified as 3-penten-2-one in 40% yield. ^{1}H NMR ($CDCl_3$) δ: 6.82 (m, 1H), 6.1 (dd, 1H), 2.2 (s, 3H), 1.90 (d, 3H). Examination of the ^{1}H NMR spectrum of the 4-methoxy-2-pentanone product in the presence of Eu(hfc)$_3$ indicated an enantiomeric mixture containing 68% (*R*), 36% ee.

Pd(OAc)$_2$-Catalyzed Methoxylation of (*R*)-(+)-(*E*)-1. See methoxylation of (*R*)-(−)-(*Z*)-**1**. The mass of the product was 0.16 g (35%, yield). GLC analysis showed the presence of 4-methoxy-2-pentanone and 3-penten-2-one in 40% and 60% yields, respectively. Examination of the ^{1}H NMR spectrum of the 4-methoxy-2-pentanone product in the presence of Eu(hfc)$_3$ indicated an enantiomeric mixture containing 64% (*R*), 28% ee.

Li_2PdCl_4-Catalyzed Methoxylation of (*R*)-(−)-(*Z*)-1. A solution of 0.1 M Li_2PdCl_4, 0.1 M LiCl, and 0.1 M benzoquinone in 25 mL of methanol was prepared. To this solution was added 0.35 mL (0.3 g, 0.35 mmol) of (*R*)-(−)-*Z*-**1** (ee = 53%). The system was placed under Ar and stirred for 8 h at room temperature. The mixture was then diluted with water, and the aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic phase was dried over $MgSO_4$, and solvent was removed by distillation. Analysis of the residue by gas chromatography showed the presence of 4-methoxy-2-pentanone and 3-penten-2-one in 95% and 5% relative yields, respectively. Examination of the ^{1}H NMR spectrum in the presence of Eu(hfc)$_3$ indicated the 4-methoxy-2-pentanone was an enantiomeric mixture containing 71% (*R*), 42% ee.

Li_2PdCl_4-Catalyzed Methoxylation of (*R*)-(+)-(*E*)-1. See Li_2PdCl_4-catalyzed methoxylation of (*R*)-(−)-(*Z*)-**1**. Examination of the ^{1}H NMR spectrum in the presence of Eu(hfc)$_3$ indicated an enantiomeric mixture containing 54% (*R*), 8% ee.

$LiPdCl_3$-Catalyzed Phenylation of (*R*)-(−)-(*Z*)-1. To a stirred solution of (*R*)-(−)-(*Z*)-3-penten-2-ol (53% ee), 1.89 mL (1.68 g, 20.0 mmol) in 5.0 mL of acetonitrile, under Ar at room temperature were sequentially added Et_3N (2.7 mL, 3.3 g, 20 mL), phenylmercuric chloride (2.73 g, 20.0 mmol), cupric chloride (2.73 g, 20.0 mmol), and 20 mL of 0.l M $LiPdCl_3$ in acetonitrile. The reaction mixture was stirred overnight. Water (50 mL) was added, and the insoluble material and the aqueous solution were extracted with hexane (3 × 50 mL). The combined extracts were washed twice with water and dried over $MgSO_4$. After evaporation of solvent, the yellow oily material was purified twice by column chromatography (silica gel, 8/2 hexane/Et_2O) to give 1.5 g (53% yield) of 4-phenyl-2-

pentanone. IR (neat) cm^{-1}: 3030, 3010, 2990, 1720. ^1H NMR ($CDCl_3$) δ: 7.22 (m, 5H), 3.30 (m, J = 7.0 Hz, 1H), 2.72 (dd, J = 6.7 and 16.3 Hz, 1H), 2.68 (dd, J = 7.9 and 16.2 Hz), 2.07 (s, 3H), 1.69 (d, J = 7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ: 207.8, 146.2, 128.6, 126.6, 126.3, 52.0, 35.5, 30.6, 22.0. Optical rotation $[\alpha]^{24}_D = -25.2$ (c = 10, benzene).[18] Lanthanide shift determination showed the presence of 68% (*R*) (36% ee). Using the value of the published rotation (−74.5), the % ee of the *R* isomer is calculated to be 34%.[18]

LiPdC1$_3$-Catalyzed Phenylation of (*R*)-(+)-(*E*)-3-Penten-2-ol. See phenylation of (*R*)-(−)-(*Z*)-3-penten-2-ol. A 1.89 mL (1.68 g, 0.0200 mol) sample of (*R*)-(*E*)-3-penten-2-ol (51% ee) afforded 1.4 g (50% yield) of 4-phenyl-2-pentanone. A lanthanide shift determination showed the product to be 58% (*R*), 16% ee.

Li$_2$PdC1$_4$-Catalyzed Phenylation of (*R*)-(+)-(*Z*)-3-Penten-2-ol. To a stirred solution of 0.1 M Li_2PdCl_4 in methanol (15 mL) were added 0.50 mL (3.7 mmol) of Et_3N, 0.50 g (3.7 mmol) of $CuCl_2$, 1.1 g (3.5 mmol) of PhHgCl, and 0.35 mL (0.30 g, 3.5 mmol) of (*R*)-(*Z*)-3-penten-2-ol (53% ee). After the mixture was stirred 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 the 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. A lanthanide shift determination showed the presence of 65% (*R*), 30% ee.

Li$_2$PdC1$_4$-Catalyzed Phenylation of (*R*)-(+)-(*E*)-3-Penten-2-ol. See phenylation of (*R*)-(−)-(*Z*)-3-penten-2-ol. A 0.35 mL sample of (*R*)-(*E*)-3-penten-2-ol (51% ee) afforded 0.38 g (68% yield) of 4-phenyl-2-pentanone. A lanthanide shift determination showed the presence of 57% (*R*), 14% ee.

Pd(OAc)$_2$-Catalyzed Acetoxylation of (*R*)-(−)-(*Z*)-3-Penten-2-ol. To a stirred solution of $Pd(OAc)_2$ (0.1 g, 0.44 mmol), $LiOAc{\cdot}2H_2O$ (0.41 g, 4.0 mmol), and benzoquinone (0.11 g, l.0 mmol) in acetic acid (5.0 mL) was added MnO_2 (0.36 g, 4.1 mmol), followed by 0.31 mL (0.26 g, 3 mmol) of (*R*)-(−)-(*Z*)-3-penten-2-ol (53% ee). The reaction was stirred at room temperature for 12 h and diluted with water (10 mL), and the precipitate was extracted with petroleum ether−ether (l:l) (3 × 30 mL). The combined extracts were washed with saturated NaCl (30 mL), saturated $NaHCO_3$ (2 × 30 mL), and finally water (2 × 10 mL). The organic phase was dried ($MgSO_4$) and evaporated to give 0.33 g (76% yield) of product. ^1H NMR ($CDCl_3$) δ: 5.25 (m, J = 6.3 Hz, lH), 2.78 (dd, J = 7.3 and 16.5 Hz, lH), 2.55 (dd, J = 5.9 and 16.4 Hz, lH), 2.15 (s, 3H), 1.96 (s, 3H), 1.25 (d, J = 6.3 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ: 205.2, 170.1, 67.0, 49.5, 30.5, 21.2, 20.7. A lanthanide shift determination showed the presence of 64% (*R*), 28% ee.

Pd(OAc)$_2$-Catalyzed Acetoxylation of (*R*)-(+)-(*E*)-3-Penten-2-ol. See acetoxylation of (*R*)-(−)-(*Z*)-3-penten-2-ol. A 0.3 mL sample of (*R*)-(*E*)-3-penten-2-ol afforded 0.30 g of product (70% yield). A lanthanide shift determination showed the presence of 56% (*R*), 12% ee.

Li$_2$PdCl$_4$-Catalyzed Acetoxylation of (*R*)-(−)-(*Z*)-3-Penten-2-ol. To a stirred solution of 0.1 M Li_2PdCl_4 in acetic acid (5.0 mL) containing $LiOAc{\cdot}2H_2O$ (0.41 g, 4.0 mmol) and benzoquinone (0.11 g, 1.0 mmol) was added MnO_2 (0.36 g, 4.1 mmol), followed by 0.3 mL (0.28 g, 3 mmol) of (*R*)-(−)-(*Z*)-3-penten-2-ol (53% ee). The reaction was stirred at room temperature for 12 h and diluted with water (10 mL), the precipitate was extracted with petroleum ether−ether (1:1; 3 × 30 mL) and washed finally with water (2 × 10 mL). The combined extract was washed with saturated NaCl (30 mL), saturated $NaHCO_3$ (2 × 30 mL), and finally water (2 × 10 mL). The organic phase was dried ($MgSO_4$) and evaporated to give 0.36 g (83% yield) of product. A lanthanide shift determination showed the presence of 71% (*R*), 42% ee.

Li$_2$PdCl$_4$-Catalyzed Acetoxylation of (*R*)-(−)-(*Z*)-3-Penten-2-ol in the Presence of LiCl. Same as Li_2PdCl_4-catalyzed acetoxylation of (*R*)-(*Z*)-3-penten-2-ol except in this case the reaction was carried out in the presence of LiCl (1.0 M) and 0.2 mL (0.17 g, 3.0 mmol) of (*R*)-(*Z*)-3-penten-2-ol. A 0.20 mL (0.17 g, 3 mmol) sample afforded 0.15 g (42% yield) of product. A pure sample of the product was obtained by GLC. The ee (32%) of the product was determined by ^1H NMR in the presence of $Eu(hfc)_3$. The absolute configuration of the major enantiomer was found to be (*S*).

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