water until a colorless aqueous layer was obtained. The organic phase was extracted once with aqueous sodium hydroxide and the alkaline aqueous phase was extracted with ether (benzophenone). The aqueous phase was then acidified and again extracted with ether. The combined ether extracts were dried and, after removal of the solvent, the desired product was obtained as an orange oil (1.4 g).

This oil (1.4 g) was taken up in ether (20 mL) and esterified by using diazomethane in ether as described before. The product was chromatographed over silica gel with benzene/ethyl acetate giving the pure compound as an oil (0.45 g, 20% for two steps). The optical rotation of this compound was measured at five wavelengths (see later). ^{1}H NMR ($CDCl_3$): δ 1.30 (d, J = 8 Hz, 3 H), 2.86 (s, 3 H), 3.62 (s, 3 H), 4.32-4.86 (m, 3 H), 7.26 (s, 5 H).

***N*-Benzyl-D-alanine.** This compound was prepared from D-alanine by a method previously described.[63]

Methyl D-2-(*N*-Benzylsulfonamido)propionoate. A solution of *N*-benzyl-D-alanine (3.1 g) in methanol (30 mL) was saturated with dry HCl during which time a white solid precipitated from solution. The resultant mixture was allowed to stir for 12 h and then the solvent was removed in vacuo to give the ester hydrochloride (3.6 g, 98%) as a white solid.

(63) Quitt, P.; Hellerbach, J.; Vogler, K. *Helv. Chim. Acta* **1963**, *46*, 327.

This solid (3.6 g) was suspended in dry CH_2Cl_2 (200 mL) and triethylamine (5.3 mL) was added. The mixture was cooled to -78 °C and a solution of mesyl chloride (1.47 mL) in CH_2Cl_2 (20 mL) was added. The mixture was allowed to warm to 25 °C and was stirred at this temperature for 12 h, after which it was quenched with water. The organic layer was washed with water, followed by dilute acid and again with water, and was dried over Na_2SO_4. On removal of the solvent, the resulting oil was chromatographed as before to give (0.63 g, 14%) of the pure product having an identical ^{1}H NMR with that observed for the material obtained from allylation.

The absolute configuration of the prevailing enantiomer of the product of allylation was determined from the rotations of the D-alanine derived product. The rotations at 25 °C in $CHCl_3$, c 1.6 were $[\alpha]_{589}$ +43.21°, $[\alpha]_{578}$ +45.28°, $[\alpha]_{546}$ +51.50°, $[\alpha]_{436}$ +89.36° and $[\alpha]_{365}$ +144.42°. The values of the optical purity obtained from rotation measurements and from chiral shift experiments corresponded within 2%.

Acknowledgment. This work was supported by grants from the Natural Sciences and Engineering Research Council of Canada. B.B. was a Killam Fellow during the time of this work and is grateful to the Killam Foundation. P.B.M. was a recipient of a NSERC scholarship. We thank Dr. William Knowles for a gift of *R,R*-dipamp.

Asymmetric Synthesis. Mechanism of Asymmetric Catalytic Allylation

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Abstract: The mechanism of palladium-assisted asymmetric catalytic allylation has been investigated. It is found that the process involves two primary steps: the oxidative addition of a palladium(0)-phosphine species with an allyl acetate to form diastereomeric π-allyl intermediates which are then attacked by the nucleophile. Both steps proceed with inversion of configuration and the irreversible oxidative addition is much faster than the nucleophilic attack. The π-allyl intermediates epimerize between 10 and 10^2 times faster than nucleophilic attack occurs. The nucleophilic attack is the turnover limiting step as well as being the enantioselective step. The *major* π-allyl diastereomeric intermediate produces the *major* product enantiomer.

Homogeneous catalytic allylation with palladium complexes is a facile transformation of wide applicability.[1] The catalytic process is believed to involve two major steps. The first step is the oxidative addition of an allylic acetate (or an other suitable substrate) to a palladium(0)-phosphine complex to produce a phosphine-palladium(II)-π-allylic intermediate. This intermediate is then attacked by a "soft" nucleophile to give the allylic product with the regeneration of the palladium(0) catalyst. It has been established that, with both cyclic[2] and acyclic[3] allyl acetates, the oxidative addition step as well as the nucleophilic attack step proceed with inversion of configuration. That is, the overall process is one of net retention, although complications have been noted. Apart from this stereochemical information, little more is known quantitatively about the mechanism of this important reaction. In order to convert this catalytic process rationally for asymmetric synthesis, however, a detailed knowledge of the mechanism is required.

In the preceding paper[4] we described our attempts at orchestrating this system for asymmetric catalysis. We showed that, of all of the possible π-allyl substitution patterns, systems with the type **1** and type **2** structures (Figure 1) were the least complicated. All other 1,3-substitution patterns either possess isomeric complexity or are incapable of racemizing via the π-σ-π mechanism.[5,6] Type **1** allyls form achiral intermediates in the catalytic cycle and asymmetric synthesis occurs by enantiocenter(1,3) discrimination. The type **2** coordinated π-allyls are chiral and invert their chirality by formation of a σ-bond at the disubstituted end of the allyl during the π-σ-π process. Formation of a σ-bond at a tertiary center, however, is generally an unfavorable process when the R′ substituents are alkyl groups.[5] Such species racemize exceedingly slowly at 25 °C. Type **2** π-allyl intermediates can be derived by oxidative addition to either prochiral or chiral allyl acetates (Figure 2) and if the type **2** π-allyl intermediate were incapable of inverting its absolute configuration during its lifetime in the catalytic cycle, the optical yields for asymmetric catalysis would depend on whether a prochiral or chiral substrate were used. In the absence of epimerization of the intermediate, the optical yield would be determined at the oxidative addition stage for a type **2** prochiral substrate; i.e., oxidative addition would represent the enantioselective step. Without epimerization of the intermediate, a type **2** chiral (racemic) allyl substrate would give zero optical yield in the product. For both cases we assume that the

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Figure 1. Systems with the type **1** and type **2** structures.

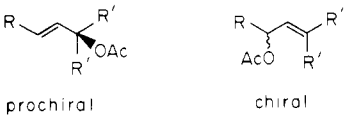

Figure 2. Allyl acetate substrates.

major steps in the catalytic cycle proceed stereospecifically. If, however, this π-allyl intermediate were capable of complete epimerization before nucleophilic attack occurred, the structure of the starting allyl acetate will be irrelevant; now the enantioselective step will be the nucleophilic attack. Clearly these latter circumstances would allow for greater flexibility in the design of the system for asymmetric catalysis. Thus both chiral and prochiral substrates could be used and, if the epimerization were much faster than nucleophilic attack (Curtin–Hammett conditions), the enantioselection would depend only on the difference in free energy of the two diastereomeric transition states. Moreover, if the enantioselective step were under reactant control, as we assumed previously,[4] the magnitude and chiral sense of the diastereomeric equilibrium of the intermediate should give an estimate of the magnitude of the optical yield as well as the chirality of the prevailing enantiomer of the product.[4] This reactant control assumption implies that the major enantiomer of the product originates from the major diastereomeric intermediate.

In an attempt to achieve these ideal conditions for asymmetric catalytic allylation, we studied a variety of diastereomeric [Pd(*S*,*S*-chiraphos)(π-allyl)]$^+$ species,[4] the putative intermediates in the catalytic cycle. We found that aryl-R′ groups caused a marked enhancement in the epimerization rate for type **2** allyls and, furthermore, anti-disposed aryl-R′ groups caused strong displacements of the diastereomeric equilibria for the [Pd(*S*,*S*-chiraphos)(π-allyl)]$^+$ complexes. Given these, and other, attributes of aryl-R′ groups, we described[4] our results of asymmetric catalytic allylation using type **2** substrates with aryl-R′ groups. A variety of phosphines and nucleophiles were used and the results seemed to be consistent with our assumptions but did not prove them. This paper addresses the validity of our mechanistic assumptions.

Catalytic Steps

We assume that the two major steps (k_1 and k_2) in asymmetric catalytic allylation are those represented in Figure 3 for type **2** allyls. If this is a correct outline of the mechanism, a number of questions require to be addressed. First, do the prochiral and chiral allyl acetates oxidatively add at similar rates and is the process reversible? Second, what is the nature of the palladium(0) chiral (chelating) phosphine? Third, what is the stereochemistry of oxidative addition? Fourth, what is the stereochemistry of the nucleophilic attack step? Fifth, what are the relative values of k_1 and k_2? Sixth, do the two diastereomeric intermediates have time to equilibrate before nucleophilic attack occurs and do Curtin–Hammett conditions obtain? Seventh, does the major enantiomer of the product originate from the major four-coordinate diastereomeric intermediate? Eighth, is the π–σ–π mechanism the only method of equilibrating the diastereomeric intermediates? Ninth, which is the enantioselective step of the catalysis? We begin by establishing the relative values of k_1 and k_2 and some of the characteristics of the palladium(0) species.

The "Turnover Limiting Step"

Although under steady-state conditions all steps in a catalytic cycle proceed at the same rate, there is usually a step which has an effective rate constant which is slower than the others so that the concentration of the appropriate catalytic intermediate builds up before this step. We shall refer to this step as the *turnover limiting step*. Thus, considering the major steps in Figure 3, if k_1 is much slower than k_2, we would expect that, during the

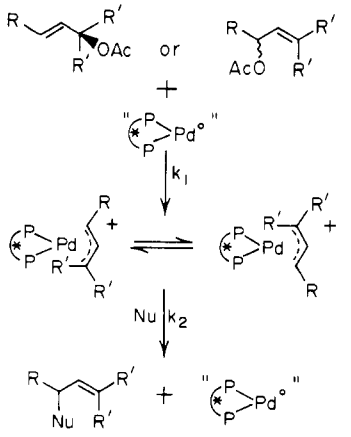

Figure 3. Major steps in catalytic allylation.

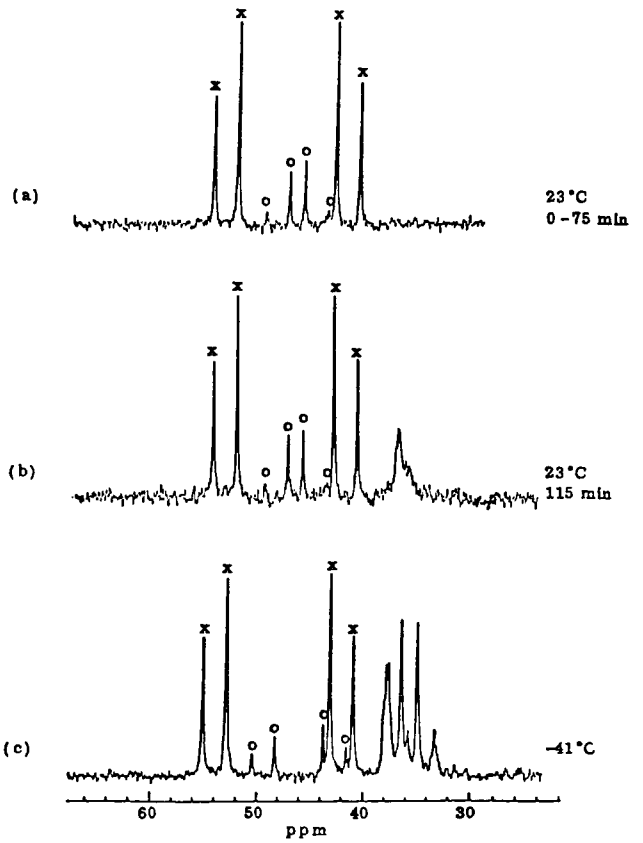

Figure 4. ^{31}P NMR spectra of the catalytic allylation of 1,1,3-triphenylprop-2-enyl acetate with sodium dimethyl malonate in THF at 23 °C using the Pd(*S*,*S*-chiraphos) catalyst.

catalysis, the palladium(0) chiral phosphine entity will be the predominant catalytic species in solution. If, however, k_2 is much slower than k_1, then the predominant catalytic species will be the palladium(II)–π-allyl intermediate.

In order to determine the turnover limiting step, we followed the catalytic reaction by ^{31}P NMR using *S*,*S*-chiraphos as the chiral ligand. Under normal catalytic conditions where 5% of catalyst is used, the catalyst concentration is too low to be effectively followed by ^{31}P NMR. We have observed, however, that if the catalyst concentration is raised to 20% and the overall reaction concentrations are doubled, the same optical yield is observed. Under these conditions, the catalytic reaction of sodium dimethyl malonate with 1,3,3-triphenylprop-2-enyl acetate (racemic type **2** allyl; R = R′ = phenyl) in THF in the presence of *S*,*S*-chiraphos palladium catalyst gave the ^{31}P NMR spectra shown in Figure 4.

For the first 75 min of reaction at 23 °C, a constant ^{31}P NMR spectrum was observed (Figure 4a). Toward the end of the reaction, a new broad upfield peak appears (Figure 4b) and,

eventually, it becomes the only ^{31}P NMR signal. On cooling the solution to −40 °C, the broad peak sharpens into a complex pattern (Figure 4c) and, on warming, it reverts to its original shape. If substrate is added at 23 °C, this broad peak immediately disappears and the original spectrum (Figure 4a) is observed. The eight-line spectrum in Figure 4a is identical with that observed for an independently prepared equilibrated sample of [Pd(*S*,*S*-chiraphos)(1,3,3-triphenyl-π-allyl)]ClO_4 in THF solution,[4] the ratio of major to minor diastereomers (~4:1) is the same in the two cases.

We interpret these observations as follows. In the presence of excess of substrate, essentially all of the catalyst exists in the form of the [Pd(*S*,*S*-chiraphos)(π-allyl)]$^+$ species. We infer, therefore, that this palladium(II) species is an intermediate in the catalytic allylation and, if this is true, the turnover limiting step is the nucleophilic attack on this species or an activated form of it. It follows that $k_1 > k_2$ (Figure 3). Furthermore, the intermediate is at diastereomeric equilibrium (~4:1) during the course of the catalytic reaction.

Given the fact that the broad high-field peak only appears at the end of the catalytic reaction, together with its chemical shift, which is characteristic of palladium(0)–phosphines,[7] we ascribe this peak to the "Pd^0(*S*,*S*-chiraphos)" species. We would expect this to be a labile species; this is confirmed by the line shape at 23 °C and the temperature variation of the spectrum. It is clear, however, that "Pd^0(*S*,*S*-chiraphos)" does not exist as a unique entity and we suppose that the palladium(0) is bound to *S*,*S*-chiraphos as well as the olefin allylation product giving a set of rapidly exchanging complexes. Despite the complexity of the "Pd^0(*S*,*S*-chiraphos)" species, oxidative addition is rapid and all of the palladium(0) is consumed.

We therefore know that, for the major part of the catalytic cycle, the oxidative addition rate constant is much faster than the nucleophilic attack rate constant, but we do not know, as yet, whether Curtin–Hammett conditions obtain for this latter (k_2) step. Further, the preceding experiment did not establish whether the oxidative addition is reversible nor did it address the issue of whether the prochiral and chiral allyl acetates (Figure 2) have different rates of oxidative addition.

Oxidative Addition

We have followed the rate of disappearance of a 1:1 mixture of the prochiral and the chiral type **2** allyl acetates (R = R′ = phenyl) under catalytic conditions by monitoring the intensities of the ^1H NMR vinylic and benzylic protons of the substrates in THF solution using the *S*,*S*-chiraphos catalyst and the sodium dimethyl malonate nucleophile. We found that the two isomeric acetates were consumed at the same rate and the initial 1:1 proportion of the two substrates remained constant during the reaction. Similarly, if the thermodynamically less stable prochiral acetate were used alone, we did not detect by ^1H NMR any of the much more stable chiral acetate during the catalytic reaction. Because the two isomeric allylic acetates do not interconvert during reaction, we conclude that the two allyl acetates react at the same rate and that oxidative addition is an irreversible step.

Rate of Epimerization of the Intermediate

The preceding experiments established that the two isomeric allylic acetates were converted rapidly, irreversibly, and at the same rate to a common intermediate, the [Pd((*S*,*S*-chiraphos)(π-allyl)]$^+$ species, which was at diastereomeric equilibrium during the catalytic cycle. We need to know, however, whether diastereomeric equilibration is much faster than nucleophilic attack. That this is probably the case was suggested by the fact that the prochiral and chiral acetates gave the same optical yield.[4] It was further supported by the following experiment for which the nucleophile was used as the limiting reagent.

The normal catalytic reaction of sodium dimethyl malonate with 1,3,3-triphenylprop-2-enyl acetate in the presence of 5% *S*,*S*-chiraphos palladium catalyst in THF at 25 °C is complete after 5 h.[4] Given that all of the catalyst is in the [Pd(*S*,*S*-chiraphos)(π-allyl)]$^+$ form for virtually all of the reaction and because the catalyst turns over 20 times for the total reaction, the average lifetime of the π-allyl intermediate is ~5/20 h = 0.25 h under these normal conditions. This lifetime can be extended as follows. A THF solution of sodium dimethyl malonate (1 equiv) was added at a constant dropping rate to 1,3,3-triphenylprop-2-enyl acetate (1 equiv) and the *S*,*S*-chiraphos catalyst (5%) in THF solution over 36 h. Under these new conditions, the lifetime of the π-allyl intermediate is 36/20 h = 1.8 h, a 7.2 lifetime increase over the normal catalytic reaction. The optical yield was the same for this reaction as was found for the normal catalytic reaction. We conclude, therefore, that the π-allyl intermediate has time to fully epimerize under the normal catalytic conditions. A similar lifetime extension experiment was performed with 4,4-diphenylbut-3-enyl acetate (type **2** allyl; R = CH_3, R′ = phenyl) substrate using the *R*-prophos catalyst.[4] No change in optical yield was observed and we draw a similar conclusion.

In order to define the problem quantitatively, we have measured the epimerization rates of the diastereomeric π-allyl intermediates. Although the equilibration of the [Pd(*S*,*S*-chiraphos)(π-allyl)]$^+$ (π-allyl = type **2** allyl; R = CH_3 or phenyl, R′ = phenyl) ion is too fast to measure at 25 °C in THF by conventional means and too slow at 25 °C to measure by NMR spin relaxation methods, the rate is extremely slow at −40 °C. Accordingly, we prepared the [Pd(1,3,3-triphenylallyl)(solvent)$_2$]CF_3SO_3 species in situ by reaction of $AgCF_3SO_3$ with the corresponding chloro-bridged dimer and allowed the solvent complex to react with *S*,*S*-chiraphos at <−40 °C in THF. As expected, the ^{31}P NMR gave a spectrum indicating equal proportions of the two diastereomers of [Pd(*S*,*S*-chiraphos)(π-allyl)]$^+$. The rate of approach to equilibrium was determined by ^{31}P NMR at −10.0, −18.1, −24.4, and at −26.0 °C and the data were processed as described later. Satisfactory first-order plots for the approach to equilibrium were obtained for all temperatures. The obtained rate constants are $k_{-10.0°C}$ = (1.82 ± 0.13) × 10^{-3}, $k_{-18.1°C}$ = (5.02 ± 0.40) × 10^{-4}, $k_{-24.4°C}$ = (2.2 ± 0.2) × 10^{-4}, and $k_{-26.0°C}$ = (1.42 ± 0.23) × 10^{-4} s^{-1}, and the observed equilibrium constants are: $K_{-3.5°C}$ = 4.66 ± 0.16, $K_{-10.6°C}$ = 4.97 ± 0.12, $K_{-18.1°C}$ = 5.06 ± 0.22, and $K_{-25.5°C}$ = 5.67 ± 0.10. From these data the forward and backward rate constants were derived. A plot of ln *K* vs. $1/T$ gave a straight line from which the thermodynamic constants for equilibrium were derived: ΔH = 1.2 kcal·mol^{-1} and ΔS = 1.3 cal·deg^{-1}·mol^{-1}. An Eyring plot was obtained for the $1/T$ variation of the logarithm of the rate constants for the minor → major diastereomer transformation, whence $\Delta H^{\ddagger}$ (minor → major) = 20 kcal·mol^{-1} and $\Delta S^{\ddagger}$ (minor → major) = 5 cal·deg^{-1}·mol^{-1}. By extrapolating the data for the thermodynamic and kinetic temperature dependence plots to 25 °C, the rate constant for *approach to equilibrium* was found to be $k_{25°C}$ = (0.28 ± 0.20) s^{-1} and the extrapolated equilibrium constant, $K_{25°C}$ = 3.80 ± 0.37, agrees with the constant determined independently in THF under catalytic conditions (Figure 4a) i.e., $K_{25°C}$ = 3.7. The substantial error quoted for the rate constant is probably an overestimate, although even with this error the conclusions are unaffected. Thus, for a rate constant of 0.48 s^{-1}, >99% equilibration would require 1 min, whereas, at the other error extreme, a rate constant of 0.08 s^{-1} would require 10 s for >99% equilibration.

We have also checked the epimerization rate of the corresponding type **2** allyl, where R = CH_3 and R′ = phenyl, complex and found that its epimerization rate is about the same as that just recorded for the triphenyl analogue. Furthermore, because the [Pd(*S*,*S*-chiraphos)(π-allyl)]$^+$ intermediate does not react with sodium dimethyl malonate below −10 °C, we have checked the epimerization rate in the presence of a stoichiometric amount of this nucleophile. No difference in epimerization rate was detected. We conclude, therefore, that the 0.28-s^{-1} rate constant is appropriate for the catalytic reaction and for both the triphenyl and methyldiphenyl substrates under catalytic conditions.

The derived rate constant is notable in two respects. First, as we noted in the first paper,[4] the type **2** allyl, where R = R′ = CH_3,

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Table I. Initial Reagent Concentrations, Ratios, and the Corresponding Rate Constants for the Catalytic Allylation Reaction in THF at 26.5 °C

	molar concentrations			ratio	
entry	$[sub]_0$	$[nu]_0$	$[cat]_0$	$[sub]_0:[nu]_0:[cat]_0$	$k(10^3)s^{-1}$
1	0.24	0.37	0.014	1:1.5:0.057	1.47 ± 0.09
2	0.24	0.37	0.007	1:1.5:0.28	1.53 ± 0.10
3	0.12	0.18	0.0035	1:1.5:0.28	1.0 ± 0.1
4	0.48	0.37	0.014	2:1.5:0.057	1.0 ± 0.1

required 3 h at 60 °C in DMF to fully equilibrate. The just described triphenyl analogue requires less than 1 min to equilibrate at 25 °C. Assuming a 10-min half-life at 60 °C and a 10-fold decrease in rate in going from 60 to 25 °C for the trimethyl system, the triphenyl analogue has an equilibration rate which is at least 10^3 times faster than the 1,3,3-trimethylallyl system. A possible explanation for this spectacular aryl substituent rate acceleration is given in the first paper[4] in terms of π-benzylic stabilization. Second, as we have noted here, the average lifetime of the π-allyl intermediate under catalytic conditions is approximately 15 min. This suggests that the nucleophilic attack step is under Curtin–Hammett control. In order to establish this quantitatively we determined the relevant catalytic rate constants.

Catalytic Rate Constants

The progress of the reaction of 1,1,3-triphenylprop-2-enyl acetate with sodium dimethyl malonate catalyzed by the palladium *S,S*-chiraphos catalyst at 26.5 ± 0.5 °C in THF solution was monitored by the ^1H NMR upfield vinylic proton doublet of the substrate. The initial concentrations and ratios are given in Table I. They span the range used for the preparative catalytic reactions. We should point out, however, that principally because of the low solubility of the nucleophile in THF, we were restricted to a narrow concentration range to study the kinetics which prevented us from determining certain details of the reaction. The substantive features, however, are secure.

The data for two half-lives of reaction for entries **1–3** obeyed the rate law

$$-d[Sub]/dt = k[Cat]$$

Since under steady-state conditions [Cat] is constant for the major part of the catalysis, zero-order plots ([Sub] vs. t) gave straight lines of slope k[Cat]. The catalytic reaction is independent of the substrate concentration and, at [Nu]:[Sub] ratios greater than 1.5:1, appears to be independent of nucleophile concentration. Under these latter conditions, therefore, the catalytic reaction is a first-order process governed by the catalyst concentration.

The first indication of a departure from first-order kinetics was evidenced by the lower k value found for entry **3** even though a satisfactory straight line was obtained for two half-lives of reaction. Because of the higher dilution of this reaction, however, the data points were obtained with less precision. The data for entry **4**, where the [Nu]:[Sub] ratio was decreased, did not give a straight line for the zero-order plot, the slope decreased with time and the departure from linearity was pronounced for the second and third half-lives. The rate constant shown in the table was derived from the first 13 points representing 1 half-life of reaction; these points fitted well. Because of the technical difficulties alluded to, we have been unable to determine the origin of this apparent nucleophile concentration dependence. It could be due to ion pairing of the nucleophile and the π-allyl intermediate which, in turn, could be complicated as the reaction progresses if there is proton exchange between the allyl product and the nucleophile anion. These details, however, do not affect the basic conclusions we wish to draw from these experiments.

We have shown that the oxidative addition step is fast compared to nucleophilic attack and that for most of the catalytic reaction the catalyst exists as the π-allyl intermediate. It follows that the measured rate constants in Table I refer to the nucleophilic attack (i.e., k_2 in Figure 3). If this is the case, then the stoichiometric reaction of the π-allyl intermediate and sodium dimethyl malonate should give the same rate constant as the catalytic reaction. The [Pd(*S,S*-chiraphos)(1,3,3-triphenylallyl)]CF_3SO_3 intermediate [0.24 M] was reacted with sodium dimethyl malonate [0.71 M] in THF at 26.5 °C in the presence of diphenylacetylene. The diphenylacetylene was used to stabilize the produced "Pd^0(*S,S*-chiraphos)" species which otherwise rapidly decompose to the metal at these high concentrations. The reaction was followed for 3 half-lives by ^{31}P NMR. The ^{31}P NMR showed no other species except the disappearing π-allyl complex (Figure 4) and a growing upfield singlet due to [Pd^0(*S,S*-chiraphos)diphenylacetylene]. The data fitted the rate law

$$-d[\pi\text{-allyl}]/dt = k[\pi\text{-allyl}]$$

and gave a straight line for the first-order plot of ln [π-allyl] vs. t for 3 half-lives. The found rate constant is, (1.27 ± 0.04) × 10^{-3} s^{-1}. The correspondence between this rate constant and those derived from the catalytic reactions (Table I) confirms that the π-allyl complex is indeed a *reactive* catalytic intermediate and that the turnover limiting step is k_2 (Figure 3).

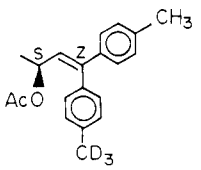
Given these results, we are in a position to answer one of the fundamental questions of the catalysis, namely, whether this turnover limiting step is under Curtin–Hammett control. If it is, then it follows that this step is also the enantioselective step in the asymmetric catalysis. Taking the upper limit for the rate of the preparative catalytic reaction as 1.6 × 10^{-3} (mol substrate)·(mol catalyst)·s^{-1}, the *minimum* average lifetime for the π-allyl intermediate is 10.4 min. We have already shown that the *maximum* time for complete epimeric equilibration of this diastereomeric intermediate is 1 min. Thus taking these "worst case" error extremes, the equilibration of the intermediate is at least 10 times faster than its average lifetime; in fact, the difference could be as much as 10^2. There seems no doubt, therefore, that the turnover limiting step is under Curtin–Hammett control and that it represents the enantioselective step. We have investigated the corresponding methyldiphenyl system briefly and it also appears to have the same characteristics as those just described for the triphenyl analogue.

Catalytic Stereocontrol

In the first paper[4] we gave reasons for expecting that the prevailing enantiomer of the product originates in the major diastereomeric intermediate. Having determined that the turnover limiting step is under Curtin–Hammett control and having identified the enantioselective step, we are now in a position to establish whether the major product enantiomer originates in the major or minor diastereomeric intermediate. In order to do this, we also have to establish the stereochemistry of the oxidative addition and nucleophilic attack steps as well as to identify the chirality of the allyl binding in the two diastereomeric intermediates. We have achieved all of this in a series of experiments which are conceptually represented in Figure 5.

The basic argument is as follows. If the allyl acetate substrate with the *S*-absolute configuration and the *Z*-disposed deuterium oxidatively adds to palladium(0) chiraphos with inversion of configuration, it will give the π-allyl intermediate with the *R*-configuration and an anti-disposed deuterium. Upon equilibration, via the π–σ–π mechanism, the first formed diastereomer will epimerize to the π-allyl intermediate with the *S*-configuration but with a syn-disposed deuterium atom. Thus the two π-allyl intermediates are distinguished by both their absolute configurations and their syn–anti deuterium positions which is a necessary consequence of the π-σ-π mechanism. Nucleophilic attack on these two intermediates will lead to four distinct products depending on which of the intermediates is attacked and on whether the nucleophilic reaction proceeds with inversion or retention. Similar arguments apply for the right side of the diagram where oxidative addition proceeds with retention. It will be noted that the same set of allylation products is produced on both sides of Figure 5, although their individual origins are different. It is necessary to identify into which equilibrium domain the oxidative addition leads.

In order to solve this puzzle we have synthesized I, a type **2** allyl of the class employed previously. Compound I was prepared



I

by the method outlined in Figure 6. Although the strategy is efficient, it lacks stereochemical control of the *Z*–*E* isomerism and an approximately 1:1 ratio of the two bromo isomers was obtained. These were partially separated with difficulty by chromatography, giving a 85:15 mixture of the *E*:*Z* bromoaryl alcohols. After separation, the steps to I proceeded cleanly.

The isomerism of I was determined by an NOE experiment at 360 MHz by irradiating the well-separated aromatic proton signals ortho to the bromo substituent in the two bromo isomers (Figure 6). The corresponding enhancements of the vinylic and methine protons for these isomers confirmed the assignments shown in Figure 6.

Compound I was subjected to asymmetric catalytic allylation using the sodium dimethyl malonate nucleophile and the *S*,*S*-chiraphos catalyst in THF at 25 °C. After converting the product to methylsuccinic acid,[4] it was found to have been produced in 64% optical yield with the predominant *R* configuration. The *Z*:*E* isomer ratio was determined from the ^{1}H NMR tolyl methyl signals which are well separated. The *Z*,*E* assignment of these protons was established by a comparison of the ^{1}H NMR of the product of the uncatalyzed reaction shown in Figure 7. It was found that the catalytic reaction gave predominantly the *E*-isomer for the *R* configuration of the product. Hence the catalytic reaction proceeds predominantly either by a double-inversion or a double-retention sequence (Figure 5).

In order to solve this ambiguity we require to know the absolute configurations of the π-allyl diastereomers and the syn–anti dispositions of the labeled tolyl groups associated with them. An absolute crystal structure of the [Pd(*S*,*S*-chiraphos)(π-allyl)]$^+$ (π-allyl = type **2** allyl; R = phenyl, R′ = 3,5-dimethylphenyl) ion showed[8] it to have the π-allyl coordinated in the *R* absolute configuration which, because of the priority rules, would be specified as *S* if a methyl group replaced the phenyl group. In order to ensure that this represented the major diastereomer in solution and to assign the ^{31}P NMR signals of the diastereomers, we dissolved the crystal in THF at −60 °C at which temperature no epimerization of the diastereomers occurs. It was found that the crystal consisted only of the major diastereomer. We have pointed out previously[4] that all of the 1,1-diphenyl-3-substituted π-allyl diastereomers give the same ^{31}P NMR patterns; the four outer peaks represent the major isomer and the minor isomer gives the four inner resonances (e.g., Figure 4a). We have used this consistency in ^{31}P NMR spectra in order to assign the absolute configuration of the π-allyl in the diastereomers derived from I; i.e., the more intense outer four ^{31}P NMR signals represent the *S* π-allyl configuration. The diastereomers derived from I give a 3.5:1, *S* to *R* ratio in the THF solution (by ^{31}P NMR and ^{1}H NMR).

The syn–anti ratio of the diastereomers derived from I was determined from the 360-MHz ^{1}H NMR of the tolyl methyl protons of the isolated intermediates after oxidative addition. The complex "Pd^0(*S*,*S*-chiraphos)" was prepared in situ in THF by the reaction of 1 equiv of sodium dimethyl malonate with [Pd(*S*,*S*-chiraphos)(η^3-C_3H_5)]$^+$ in THF. Addition of I to this solution gave the required diastereomers. The ^{1}H NMR of these diastereomers showed that the *deuterated* syn-disposed tolyl methyl group was predominantly associated with the major (*S*) diastereomer. The assignment of these tolyl methyl signals was based on the corresponding ^{1}H NMR tolyl methyl proton signals observed in the [Pd(*S*,*S*-chiraphos)(π-allyl)]$^+$ species with the three allyls shown in Figure 8. The two triphenyl allyls have chemical shifts for *syn*-tolyl methyl protons occurring at ~δ 2.28 whereas

(8) Farrar, D. H.; Payne, N. C., personal communication.

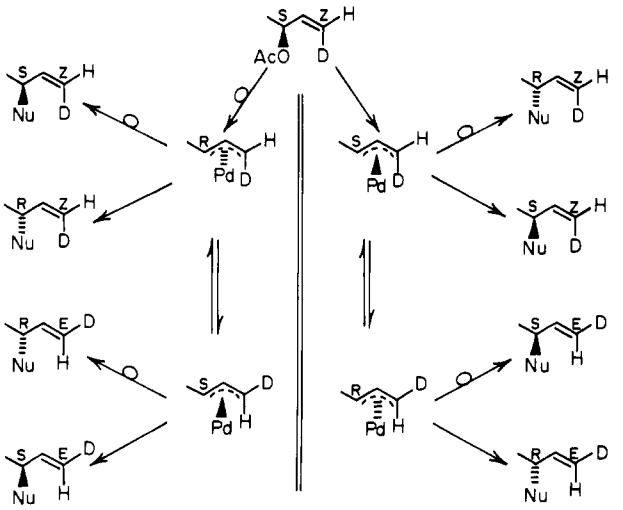


Figure 5. Pictorial representation of the structures of the possible species produced during and after allylation of the specifically labelled allyl acetate substrate using the Pd(*S*,*S*-chiraphos) catalyst.

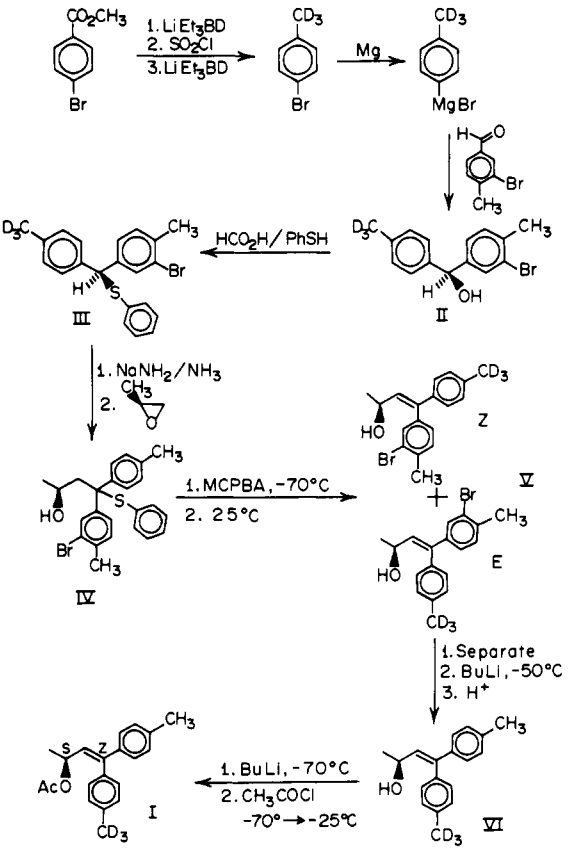


Figure 6. Outline of the synthesis of I.

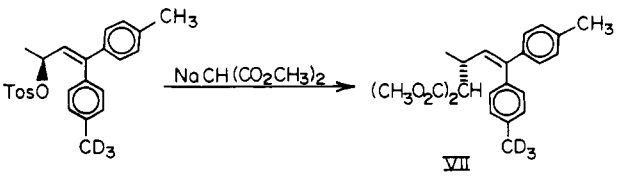


Figure 7. Product of the uncatalyzed reaction.

the corresponding anti-disposed protons occur between δ 2.32 and 2.40 at 360 MHz, whence the assignments for the methyl ditolyl allyl analogue.

Knowing that the *S*-coordinated allyl diastereomer predominates and that it is associated with a syn-disposed *deuterated* tolyl methyl group, we conclude that oxidative addition leads to the left

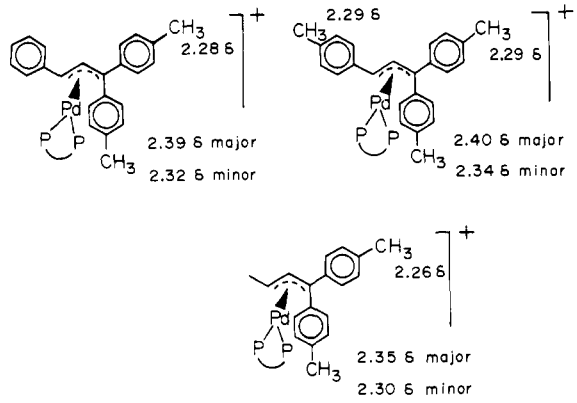


Figure 8. Chemical shifts of the respective proton signals at 360 MHz in $CDCl_3$ of the Pd(*S,S*-chiraphos) allyl complexes shown.

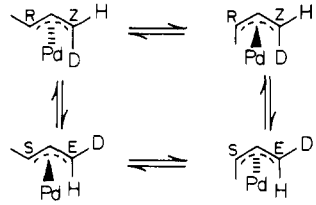


Figure 9. Possible four π-allyl isomers that are linked by the π-σ-π mechanism in the left equilibrium domain of Figure 5.

equilibrium domain (Figure 5). Since we know that the starting acetate substrate has the *S–Z* geometry, and that the major diastereomer of oxidative addition has *S*-syn-^{2}H allyl geometry and that the major enantiomer of the allylation product has the *R–E* geometry, we can draw the following conclusions. Asymmetric catalytic allylation with the present substrates involves oxidative addition with inversion, nucleophilic attack on the exo face of the coordinated allyl leading to inversion, and the *major* enantiomer of the product originates in the *major* diastereomeric intermediate.

The last conclusion is true to the extent that the major product enantiomer is the *S*-syn-^{2}H diastereomer but it does not specify whether the more reactive species has a syn- or anti-disposed methyl group because the π-σ-π mechanism admits to the presence of the four species shown in Figure 9. We were, however, unable to detect any species other than the two diastereomers with syn-disposed methyl groups by ^{1}H NMR which suggests that the anti-methyl group isomers cannot represent more than 3% of the species in solution. For the catalytic allylation to proceed predominantly via this undetected isomer, a rate acceleration over the syn isomer would have to be of the order of 10^2. In allylations of cyclic allyls[9] for which the substituents are forced to be syn or anti by the carbocylic rings, there appears to be no evidence for an acceleration in rate of this order when the substituents are forced into anti positions. In the absence of evidence to the contrary, therefore, we conclude that allylation proceeds predominantly via the syn-methyl-disposed isomer of the major diastereomer.

Stereochemical Scrambling

We have assumed throughout the preceding section that the sole route to π-allyl epimerization was via the π-σ-π mechanism which would preclude any leakage between the two equilibrium domains (Figure 5). In fact, when catalytic allylation was performed on I, 57% scrambling of the deuterated tolyl methyl groups was observed. This implies either that the primary steps of the catalytic cycle do not proceed stereospecifically or that there is a secondary mechanism for scrambling which does not impose the stereochemical restrictions of the π-σ-π mechanism. This scrambling is not a new observation[3,10,11] and has been interpreted[10,11] in terms of nonstereospecific (exo and endo) acetate attack on the coordinated allyl. Such a mechanism would, because of microscopic reversibility, challenge the conclusion that allylation is exclusively a double-inversion process. We have established that scrambling does not occur during nucleophilic attack by analyzing the product of the stoichiometric reaction between the labeled π-allyl intermediate and sodium dimethyl malonate.

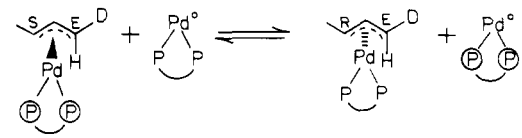


Figure 10. Proposed metal exchange mechanism for scrambling of the labels of the coordinated π-allyl groups.

Scrambling occurs after oxidative addition. Thus, in the preparation of the diastereomers derived from I by oxidative addition of "Pd^0(*S,S*-chiraphos)" to 1 equiv of I in THF at 25 °C, scrambling increased as the reaction solutions were made more concentrated and also as the time of reaction was increased in dilute [3×10^{-3} M] solutions. With only 1 equiv of I under the dilute conditions the oxidative addition is slow; it takes about 2.5 h at 25 °C in THF for completion. The best we have achieved under these conditions was 50% scrambling by quenching the reaction after 15 min, obtaining a 60% yield of product. Once the diastereomers are isolated as their perchlorate salts and purified their stereochemical integrity is retained indefinitely in $CDCl_3$ solution at 0 °C.

When these purified π-allyl diastereomers were dissolved in THF in the presence of 1 equiv of sodium acetate, the product of the oxidation addition reaction, no scrambling occurred after 23 h at 25 °C. If, however, these purified π-allyl diastereomers are allowed to react with 1 equiv of "Pd^0(*S,S*-chiraphos)" in dilute THF solution at 25 °C for 1 h, extensive scrambling is observed. We thus conclude that the source of the scrambling is not nonstereospecific acetate attack but rather occurs by the metal exchange reaction[12] depicted in Figure 10 and we believe this is the major, if not the sole, mechanism of scrambling. It will be noted that this exchange process provides for scrambling without invoking nonstereospecific mechanisms. Because this scrambling occurs during the catalytic cycle, it augments the epimerization rate of the π-allyl intermediate.

Relative Rates of Oxidative Addition

As we have just noted, the rate of oxidative addition depends on the concentration of the allyl acetate substrate. It is also probable that the oxidative addition rate is slowed in the presence of excess of phosphine so that it may be possible to find cases where the oxidative addition rate is comparable to or slower than the nucleophilic attack when an excess of phosphine is used. This is the reason we have chosen to use the "Pd^0(*S,S*-chiraphos)" species to accelerate the oxidative addition step. We also supposed that this rate would be increased by the presence of the allyl aryl substituents we have used because of the greater stability of the Pd(0)–olefin bond when the electron-withdrawing aryl groups are present.[4] In order to check this supposition we have competitively reacted "Pd^0(*S,S*-chiraphos)" with a 20-fold excess of each of the racemic type **2** allyls, R = R′ = methyl and R = methyl, R′ = phenyl in THF at 25 °C. We obtained a 2.4:1 preference for the diaryl product, suggesting that aryl substituents do indeed have an accelerating effect on the oxidative addition.

Discussion

The most important mechanistic conclusions of this paper are that the nucleophilic attack is the turnover limiting step and is also the enantioselective step, that this step is under Curtin–

(9) Trost, B. M.; Weber, L.; Strege, P.; Fullerton, T. J.; Dietsche, T. J. *J. Am. Chem. Soc.* **1978**, *100*, 3426. Trost, B. M.; Verhoeven, T. R. *J. Am. Chem. Soc.* **1980**, *102*, 4730.

(10) Trost, B. M.; Verhoeven, T. R.; Fortunak, J. M. *Tetrahedron Lett.* **1979**, *2301*, Trost, B. M.; Verhoeven, T. R. *J. Am. Chem. Soc.* **1980**, *102*, 4730.

(11) Backwall, J. E.; Nordberg, R. E. *J. Am. Chem. Soc.* **1981**, *103*, 4960.

(12) Collman, J. P.; Hegedus, L. S. "Principles and Applications of Organotransition Metal Chemistry"; University Science Books: Mill Valley, CA, 1980; p 692.

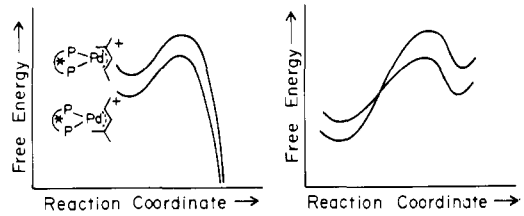


Figure 11. Reaction profiles of enantioselective steps for allylation (left) and hydrogenation (right).

Hammett control, and that the major product enantiomer originates in the major four-coordinates π-allyl diastereomeric intermediate. Because the enantioselective step is under Curtin–Hammett control, both chiral and prochiral allyl acetate substrates can be employed and presumably the olefin geometry of the substrate should not matter. In this sense the present allylation resembles the Grignard cross coupling reaction[13] which relies on the asymmetric transformation of a chiral Grignard reagent.

The only other asymmetric catalytic system which is mechanistically as well understood as allylation is asymmetric hydrogenation.[14,15] It is useful to contrast these two systems for they exemplify two extremes in asymmetric catalysis. The turnover limiting step for hydrogenation is the oxidative addition of hydrogen to the four-coordinate phosphine–substrate diastereomeric adducts whereas, for allylation, it is the nucleophilic attack on the four-coordinate π-allyl diastereomeric intermediates which is the limiting step. In both cases Curtin–Hammett conditions obtain and the turnover limiting steps are irreversible and hence are also the enantioselective steps. The two systems, however, are fundamentally different: the major product enantiomer for hydrogenation originates in the minor four-coordinate diastereomer whereas, for allylation, the prevailing product chirality is derived from the major four-coordinate diastereomer. We believe the origin of this dichotomy resides in whether the enantioselective step is under reactant or product control.[15] Figure 11 shows the reaction profiles for the enantioselective step for allylation and for hydrogenation. Since both systems are under Curtin–Hammett control, the enantioselectivities are determined only by the respecitve differences of diastereomeric transition-state energies. The enantioselective step for allylation is assumed to be exothermic whereas that of hydrogenation is assumed to be endothermic. Thus for allylation, the stabilities of the diastereomeric transition states will reflect the stabilities of the *reactant* diastereomers whereas the diastereomeric transition states for hydrogenation will resemble the stabilities of the *intermediate product* diastereomers. That is, the former is under reactant control whereas the latter is under product control. It follows that the more stable (major) diastereomeric allylation intermediate will produce the lower diastereomeric transition-state energy whereas, for hydrogenation, the stabilities of the reactant diastereomers are not directly relevant but rather it is the more stable product intermediate that connects energetically to the lower diastereomeric transition state.

These two systems serve to illustrate that asymmetric catalysis is inherently a kinetic phenomenon and that any rational development of an asymmetric catalytic system is predicated on a knowledge of the mechanism.

Experimental Section

The ^{1}H NMR spectra were obtained on a Varian model XL-200 or T-60 spectrometer or on a Nicolet NT360 spectrometer. The chemical shifts are reported in parts per million (δ scale) downfield from tetramethylsilane. The ^{31}P NMR spectra were obtained on a Bruker WP-80 spectrometer and the chemical shifts are reported in parts per million downfield from 85% H_3PO_4.

All hygroscopic solvents were dried and distilled under a nitrogen atmosphere prior to use. Diethyl ether and benzene were distilled from lithium aluminum hydride, tetrahydrofuran from sodium, and dichloromethane from calcium hydride. The reactions with the palladium compounds were carried out under an inert atmosphere as were the reactions done in hygroscopic solvents.

^{31}P NMR Monitoring of the Catalytic Reaction. Dimethyl malonate (0.225 mL, 2.6 mmol) was added to a stirred suspension of NaH (0.050 g (50% dispersion), 1.0 mmol) in THF (2.5 mL, 40% d_8) under N_2. The resultant gel was warmed to 40 °C and the now clear solution was transferred by cannulation to an NMR tube containing 1,1,3-triphenylprop-2-enyl acetate (0.171 g, 0.52 mmol) and [Pd(*S*,*S*-chiraphos)(η^3-C_3H_5)]ClO_4·$^1/_2$acetone (0.070 g, 0.10 mmol) immersed in an ice bath. The mixture was shaken at 0 °C until all of the solids dissolved. (At 0 °C allylation is very slow.) The solution was quickly warmed to 23 °C and then transferred to the NMR probe which was at 23 °C. ^{31}P NMR spectra were collected in 5-min blocks (300 pulse/block) and the spectra shown in Figure 4 were recorded.

^{1}H NMR Monitoring of the Catalytic Reaction. The progress of the catalytic allylation at 26.5 °C in THF solution was monitored by the intensities of the vinylic and benzylic proton signals of the substrates and the vinylic proton signals of the product under the same conditions as were used for the preparative scale reactions.[4]

Catalyst Lifetime Extension Experiment. A solution of sodium dimethyl malonate (0.060 M in $NaCH(CO_2CH_3)_2$ and 0.12 M in $CH_2(CO_2CH_3)_2$) was placed in a constant dropping funnel which was above a stirred mixture of 1,1,3-triphenylprop-2-enyl acetate (1.0 g, 3.0 mmol), [Pd(*S*,*S*-chiraphos)(η^3-C_3H_5)]ClO_4·$^1/_2$acetone (0.10 g, 0.14 mmol) and dimethyl malonate (0.53 mL, 6.1 mmol) in THF (40 mL). The nucleophile was added to the substrate and catalyst at a constant drop rate such that 3.0 mmol (1 equiv) of nucleophile was delivered after 36 h. A further equivalent of nucleophile was constantly added over the next 36 h and then the reaction was analyzed as described previously.[4]

^{31}P NMR Monitoring of the Stoichiometric Reaction. Finely ground bis[(1,1,3-triphenylallyl)PdCl] (0.25 g, 0.61 mmol) was dissolved in boiling CH_2Cl_2 (150 mL). Methanol (100 mL) was added and then, without delay, a solution of $AgCF_3SO_3$ (0.156 g, 0.61 mmol) in methanol (50 mL) was added. The solution was stirred for 1 h, concentrated under reduced pressure to a volume of 20 mL, and filtered through Celite. The clear yellow filtrate was cooled to 5 °C and solid *S*,*S*-chiraphos (0.259 g, 0.61 mmol) was added with stirring. After the chiraphos had dissolved, the solvent was removed to leave an orange oil. This was redissolved in methanol and filtered, and the filtrate was concentrated. The last traces of methanol were removed by concentrating the toluene solutions of the residue. A red gum remained.

Diphenylacetylene (0.217 g, 1.22 mmol) was added to the residue which was cooled to −20 °C as a solution of sodium dimethyl malonate in THF prepared from NaH (0.0712 g, 1.78 mmol), dimethyl malonate (0.52 mL, 6.01 mmol), and THF (2.5 mL, 40% d_8) was added. The resulting cold solution was added to an NMR tube and the reaction was monitored by ^{31}P NMR at 26.5 °C.

Equilibration Rates. The bis[Pd(1,1,3-triphenylallyl)Cl] complex was allowed to react with 1 equiv of $AgCF_3SO_3$ in the manner described above to give a red powder of "[Pd(1,1,3-triphenylallyl)CF_3SO_3]". This powder was dissolved in THF (30% d_8) and allowed to react with an equivalent of *S*,*S*-chiraphos at −70 °C. The solution was transferred to an NMR tube at −70 °C and the ^{31}P NMR resonances were monitored for the approach to equilibrium at −26.0, −24.4, −18.1, and −10.0 °C.

An excitation pulse of 20 μs was used and the acquisition time was 1.0255 s. Data were accumulated at fixed intervals. Each point of the kinetic rate plots does not represent an instantaneous point but rather corresponds to the accumulated data over several minutes. It is readily shown, however, that this does not affect the slope of the first-order rate plot, although the intercept is affected. In order to determine the area under the NMR peaks, a "cut-and-weigh" procedure was used. Triphenylphosphine oxide was used as an internal standard.

Preparation of (2*S*,*Z*)-4-(4-(Methyl-d_3)phenyl)-4-(4-methylphenyl)-3-buten-2-yl Acetate (I). Methyl 4-bromobenzoate[16] (43.0 g, 0.2 mol) was reduced with $LiEt_3BD$ (420 mL, 1 M) by the method of Lane[17] yielding 4-bromobenzyl-α,α-d_2 alcohol (34.2 g, 91%). This alcohol was suspended in benzene (120 mL) containing a few drops of pyridine and $SOCl_2$ (14.5 mL, 0.2 mol) in benzene (100 mL) was added dropwise. The yellow solution was refluxed for 0.5 h, and the benzene and excess $SOCl_2$ were removed under reduced pressure. The residue was dissolved in ice-cooled THF (150 mL) and $LiEt_3BD$ (400 mL, 1 M) was added dropwise after which the solution was stirred at ambient temperature for 24 h. It was then quenched at 0 °C by the dropwise addition of H_2O (5 mL), aqueous NaOH (152 mL, 3 N), and H_2O_2 (152 mL, 30%) after which the mixture was stirred for 48 h and then poured into H_2O (3000 mL) and thoroughly extracted with hexane. The combined hexane layers

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(14) Halpern, J. *Science (Washington, D.C.)* **1982**, *217*, 401; *Pure Appl. Chem.* **1983**, *55*, 99.
(15) MacNeil, P. A.; Roberts, N. K.; Bosnich, B. *J. Am. Chem. Soc.* **1981**, *103*, 2273.
(16) Hallas, G. *J. Chem. Soc. C* **1965**, 5770.
(17) Lane, C. F. *Aldrichimica Acta* **1974**, *7*, 32.

were well washed with H_2O and dried over $MgSO_4$. Upon removal of the solvent under reduced pressure, the residue was distilled to yield 4-methyl-d_3-bromobenzene (27.4 g, 87.2%, bp 86–88 °C, 35 mm). ^1H NMR (60 MHz, $CDCl_3$): δ 2.23 (br s, 0.07 H), 6.97 (d, J = 8.0 Hz, 2 H), 7.33 (d, J = 8.0 Hz, 2 H).

A solution of 3-bromo-4-methylbenzaldehyde[18] (26.0 g, 0.013 mol) in Et_2O (75 mL) was added dropwise over 1 h to an ice-cooled well-stirred solution of 4-methyl-d_3-phenyl magnesium bromide (from 4-(methyl-d_3)bromobenzene (27.4 g, 0.157 mol) and magnesium (4.21 g, 0.173 mol) in Et_2O (75 mL)). After the addition the reaction mixture was refluxed for 0.5 h, and upon cooling, was quenched with saturated aqueous NH_4Cl (150 mL). When the excess of magnesium was consumed, the layers were separated and the aqueous layer was extracted with more Et_2O. The combined Et_2O layers were washed with H_2O and brine and then were dried over $MgSO_4$. Removal of the Et_2O under reduced pressure yielded the alcohol (II) (39 g) [^1H NMR (60 MHz, $CDCl_3$): δ 2.33 (s, 3 H, 2.55 (br s, 1 H), 5.58 (s, 1 H), 6.95–7.25 (m, 6 H); 7.48 (br s, 1 H)] as a yellow oil. This oil was dissolved in benzenethiol (40.0 mL, 0.39 mol) and then formic acid (140 mL, 90%) was added. The mixture was vigorously stirred for 26 h, diluted with Et_2O (200 mL), and slowly added to an ice-cooled solution of aqueous NaOH (1000 mL, 22%). The layers were separated, and the Et_2O layer was washed thoroughly with aqueous NaOH (3 N), H_2O, and brine and was dried over $MgSO_4$. Removal of Et_2O under reduced pressure yielded the thioether (III) (50.9 g) [^1H NMR (60 MHz, $CDCl_3$): δ 2.30 (s, 3 H), 5.37 (s, 1 H), 6.88–7.33 (m, 11 H), 7.48 (d, J = 1.0 Hz, 1 H)].

A solution of thioether III (36.6 g, 0.095 mol) in Et_2O (150 mL) was added dropwise over 0.5 h to a cooled (−45 °C) stirred suspension of $NaNH_2$ (from sodium (2.2 g, 0.095 mol) in liquid NH_3 (200 mL)). The deep red-black solution was stirred 0.75 h at −45 °C and then a solution of (*S*)-(−)-propylene oxide (5.0 g, 0.086 mol) in Et_2O (50 mL) was added over 0.5 h.[19] The solution was allowed to warm to 0 °C over 3 h when the red color faded. The reaction mixture was stirred for a further 3 h at ambient temperature and was quenched by the addition of a saturated solution of aqueous NH_4Cl (450 mL). The mixture was filtered through Celite, and the layers were separated. The aqueous layer was extracted with more Et_2O, and the combined Et_2O layers were washed with aqueous NH_4Cl, H_2O, and brine and were dried over $MgSO_4$. Removal of the Et_2O under reduced pressure yielded a viscous yellow-green oil (42.5 g) which was chromatographed on Al_2O_3 (activity III, in hexane). Elution with toluene yielded a viscous yellow oil, the alcohol (IV) (30 g, 78%) as a 1:1 mixture of diastereomers. [^1H NMR (60 MHz, $CDCl_3$): δ 1.08 (br d, J = 6.0 Hz, 3 H), 2.13–2.47 (m, 2 H), 2.33 (s, 1.5 H), 2.36 (s, 1.5 H), 3.00 (s, 1 H), 3.64–4.17 (m, 1 H), 6.93–7.27 (m, 11 H), 7.40 (br s, 1 H)].

m-Chloroperbenzoic acid (4.85 g, 0.0225 mol) in CH_2Cl_2 (170 mL) was added dropwise to a solution of the alcohol (IV) (10.0 g, 0.0225 mol) in CH_2Cl_2 (350 mL) at −70 °C over 1 h.[20] The reaction mixture was stirred for 0.5 h at −70 °C and then was quickly poured into a vigorously stirred solution of aqueous Na_2SO_3 (800 mL, 10%) and Et_2O (600 mL) was added. The mixture was stirred for 1 h at room temperature whereafter the layers were separated and the aqueous layer was extracted with a little Et_2O. The combined organic layers were stirred vigorously with saturated aqueous $NaHCO_3$ (800 mL) for 24 h, and then the layers were separated and the organic volatiles were removed under reduced pressure. The residue was dissolved in Et_2O, washed with aqueous NaOH(1N), H_2O, and brine, and dried over K_2CO_3. Removal of the Et_2O under reduced pressure yielded a viscous amber oil (8.1 g) which was chromatographed on Al_2O_3 (activity III, in hexane). Elution with EtOAc/toluene, 4:1, yielded the unsaturated alcohols (V) (6.0 g, 80%), a viscous yellow-green oil, as a 1:1 mixture of geometrical isomers. [^1H NMR (360 MHz, C_6D_6): δ 1.24 (d, J = 6.0 Hz, 3 H), 1.62 (br s, 1 H), 2.26 (s, 1.5 H), 2.30 (s, 1.5 H), 4.38–4.51 (m, 1 H), 6.05 (d, J = 9.0 Hz, 0.5 H), 6.13 (d, J = 9.0 Hz, 0.5 H); 6.85–7.26 (m, 6 H), 7.66 (d, J = 1.0 Hz, 0.5 H), 7.75 (d, J = 1.0 Hz, 0.5 H)]. This sample was subjected to a NOE experiment (360 MHz, C_6D_6). Irradiating the δ 7.75 aromatic doublet produced an increase in the integrated intensity of the vinyl doublet at δ 6.05 of 5% and no increase in the integrated intensity of the methine multiplet at δ 4.38–4.51 consistent with the *E* isomer. Irradiating the δ 7.66 aromatic doublet produced no increase in the integrated intensity of the δ 6.13 vinyl doublet but did produce an increase in the integrated intensity of the methine multiplet at δ 4.38–4.51 of 1.5% consistent with the *Z* isomer. (Difference spectra obtained by subtracting a spectrum run with off-peak irradiation showed that these integrated intensity increases were real.) Repeated chromatography on Al_2O_3 (Woelm N, activity II, in benzene) and elution with 1% EtOH in benzene, produced small quantities of the unsaturated alcohol (V) enriched in the *E* isomer.

A solution of the unsaturated alcohol (V) (*E* isomer) (0.400 g, 0.0012 mol) in THF (10 mL) was cooled to −50 °C and *n*-BuLi (2.5 mL, 1.4 M) was added dropwise. The solution was stirred for 1 h at −50 °C and was quenched by the addition of saturated aqueous NH_4Cl (5 mL), and H_2O (90 mL). The mixture was thoroughly extracted with benzene and the combined benzene layers were washed with H_2O and brine and were dried over Na_2SO_4. The benzene was removed under reduced pressure yielding a light yellow viscous oil (VI) [^1H NMR (60 MHz, C_6D_6): δ 1.27 (d, J = 6.0 Hz, 3 H), 1.73 (br s, 1 H), 2.13 (s, 3 H), 4.17–4.73 (m, 1 H), 6.10 (d, J = 9.0 Hz, 1 H), 6.80–7.40 (m, 8 H)] which was dissolved in THF (10 mL) and cooled to −70 °C, *n*-BuLi (1.0 mL, 1.4 M) was added dropwise. The resultant solution was stirred at −70 °C for 0.25 h and then acetyl chloride (0.110 mL, 0.0015 mol) was added dropwise and the reaction temperature allowed to rise to −25 °C over 0.5 h. The mixture was poured into a pH 7.10 buffered solution (80 mL) and was extracted with Et_2O. The combined Et_2O layers were washed with H_2O and brine and were dried over Na_2SO_4. Removal of the Et_2O under reduced pressure yielded the acetate (I), a yellow viscous oil (0.35 g, 100%): ^1H NMR (200 MHz, C_6D_6): δ 1.28 (d, J = 6.0 Hz, 3 H), 1.70 (s, 3 H), 2.10 (s, 3 H), 5.43–6.20 (m, 2 H), 6.76–7.33 (m, 8 H). Addition of Eu(hfc)$_3$ caused the δ 2.10 acetyl methyl singlet to shift downfield and to separate into two singlets. After the addition of ~0.55 mol equiv of shift reagent, the peaks were found at δ 5.51 (*S* enantiomer) and δ 5.39 (*R* enantiomer) with an *S* to *R* ratio of 95 to 5. The tolyl methyl singlet at δ 1.70 also shifted downfield separating into three singlets which after the addition of ~0.55 mol equiv of shift reagent were found at δ 2.27 (*E* tolyl methyl, *R* and *S* enantiomer), δ 1.98 (*Z* tolyl methyl, *S* enantiomer) and δ 1.96 (*Z* tolyl methyl, *R* enantiomer) with an *E* to *Z* tolyl methyl ratio of 85 to 15. The assignments were verified with *rac*-4,4-(bis-4-methylphenyl)-3-buten-2-yl acetate which was made from 4,4-(bis-4-methylphenyl)-3-butene-2-one.[21]

Oxidative Addition Reactions. The following reactions were carried out where the π-allyl intermediate was isolated. A solution of sodium dimethyl malonate (1.2 equiv) in degassed THF was added to a stirred suspension of [Pd(*S*,*S*-chiraphos)(η^3-C_3H_5)]ClO_4·$^1/_2$acetone (1.0 equiv) and the acetate (I) (1.0 equiv) in degassed THF at 25 °C. After an appropriate length of time (see later), the reaction mixture was poured into H_2O containing a little $NaClO_4$ and the mixture was extracted with $CHCl_3$ until the extract was colorless. The combined $CHCl_3$ layers were washed several times with H_2O (containing a little $NaClO_4$) and passed through a short plug of $MgSO_4$. Almost all of the $CHCl_3$ was removed under reduced pressure yielding a yellow-orange oily residue which on treatment with hexane solidified. The hexane was decanted from the solid which was then washed with Et_2O. The solid residue was dissolved in $CHCl_3$ and this process repeated twice except that Et_2O was used to convert the oily residue to a solid. The solid was then triturated with Et_2O, filtered, washed with hexane, and air-dried. The yellow-amber solid was examined by $^1F^r$ NMR (360 MHz, $CDCl_3$) in the tolyl methyl region.

The reaction with *ra* ·,4-bis(4-methylphenyl)-3-buten-2-yl acetate (palladium concentratio).139 M, 0.5 h reaction time) was also examined by ^{31}P NMR ($CDCl_3$) and the ratio of diastereomers was found to be 3.44 to 1.0. ^1H NMR (360 MHz, $CDCl_3$): δ 2.26 (syn tolyl methyls, major and minor diastereomers), 2.30 (anti tolyl methyl, minor diastereomer), 2.35 (anti tolyl methyl, major diastereomer). Ratio of peak intensities was 4.64:1.0:3.61. The reaction was also carried out with acetate (I) (*S* to *R*, 95 to 5, and *Z* to *E*, 85 to 15) under various conditions and the products examined.

palladium concn, M	time, h	anti:syn ratio
0.176	0.5	1.08:1.0
0.0034	0.25	1.57:1.0
0.0034	2	1.20:1.0

The ratios were determined by a "cut and weigh" procedure of the relevant NMR peaks.

Reactions To Determine the Source of the Tolyl Methyl Scrambling in the π-Allyl Intermediates. A solution of the π-allyl intermediate derived from acetate (I) (ratio of anti tolyl methyls to syn tolyl methyls 1.20 to 1.0) (0.080 g, 0.000088 mol) in degassed THF (20 mL) was added to finely powdered dry NaOAc (0.010 g, 0.0001 mol) and the suspension vigorously stirred for 23 h at 25 °C. The usual workup yielded a yellow solid (0.060 g). ^1H NMR (360 MHz, $CDCl_3$) showed the ratio of anti

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tolyl methyls to syn tolyl methyls to be 1.20 to 1.0.

A solution of sodium dimethyl malonate (1.0 mL, 0.044 M in degassed THF) was added dropwise to a suspension of [Pd(*S,S*-chiraphos)(η^3-C_3H_5)]ClO_4·$^1/_2$acetone (0.030 g, 0.000042 mol) in degassed THF (9 mL) at 15-20 °C. The solution immediately turned yellow and all of the solid dissolved. After 10 min a solution of the π-allyl intermediate derived from acetate (I) (ratio of anti tolyl methyls to syn tolyl methyls 1.57 to 1.0) (0.030 g, 0.000042 mol) in degassed THF (10 mL) was added. The solution immediately darkened and became progressively blacker. After 1 h the deep brown reaction mixture was worked up in the usual manner yielding a brown solid (0.050 g) which was dissolved in THF (10 mL) and stirred vigorously with powdered Na_2SO_4 (0.50 g) for 2 h. The mixture was filtered and the filtrate worked up in the usual way yielding a yellow-brown solid (0.040 g). ^{1}H NMR (360 MHz, $CDCl_3$) showed the ratio of anti tolyl methyls to syn tolyl methyls to be 1.30 to 1.0.

Catalytic Allylation Reactions. A catalytic allylation reaction of *rac*-4,4-bis(4-methylphenyl)-3-buten-2-yl acetate under the standard conditions[4] yielded after degradation (*S*)-methylsuccinic acid (64.0% ee). The reaction was repeated on acetate (I) (*S* to *R* ratio 95 to 5, *Z* to *E* ratio 85 to 15) and the allylation product examined. ^{1}H NMR (360 MHz, $CDCl_3$) in the tolyl methyl region showed peaks at δ 2.38 and 2.30 in the ratio of 1.57 to 1.0. The reaction run at one-half the catalyst concentration, [0.003 M], showed the same ratio.

Direct Allylation. A solution of acetate(I) (*S* to *R* ratio 95 to 5, *Z* to *E* ratio 60 to 40) (0.76 g, 0.003 mol) in THF (5 mL) was cooled to -70 °C and *n*-BuLi (2.25 mL, 1.4 M) added dropwise. After 0.25 h at -70 °C toluenesulfonyl chloride (0.522 g, 0.003 mol) was added in portions. The solution was stirred 1.25 h at -70 °C and then the temperature was raised to -20 °C over 0.75 h and kept there for 0.25 h. The solution was cooled to -70 °C and a solution of sodium dimethyl malonate (20 mL, 0.2 M in THF) was added dropwise. The solution was allowed to come to room temperature over 1 h, stirred for an additional 4 h and quenched by the addition of glacial HOAc (2 mL). The reaction mixture was poured into H_2O (500 mL) and then was extracted with Et_2O, and the combined Et_2O layers were washed with H_2O, aqueous $NaHCO_3$, and brine and were dried over Na_2SO_4. The volatiles were removed under reduced pressure yielding a yellow-green oil (1.0 g) which was chromatographed on Al_2O_3 (activity III, in hexane) and the malonic ester (VII) (0.060 g) was eluted with benzene. ^{1}H NMR (200 MHz, $CDCl_3$) in the tolyl methyl region showed peaks at δ 2.38 and 2.30 in the ratio of 44 to 56.

Competition Oxidation Addition Reaction. A mixture of [Pd(*S,S*-chiraphos)(η^3-C_3H_5)]ClO_4·$^1/_2$acetone (0.100 g, 0.000142 mol) and 4,4-dimethyl-3-buten-2-yl acetate (0.403 g, 0.00284 mol) and 4,4-diphenyl-3-buten-2-yl acetate (0.755 g, 0.00284 mol) was suspended in degassed THF (20 mL) and a solution of sodium dimethyl malonate (0.75 mL, 0.215 M in THF) was added dropwise. The catalyst rapidly dissolved and after 0.5 h the amber-red solution was poured into H_2O. The usual workup yielded a yellow-orange solid (0.08 g): ^{31}P NMR ($CDCl_3$, (peak intensity)) δ 56.74 (20.7), 54.70 (25.0), 52.84 (4.9), 51.23 (9.7), 50.75 (14.24), 50.66 (14.39), 47.66 (10.3), 47.42 (12.2), 47.38 (12.1), 46.06 (5.1), 43.16 (28.0), 41.12 (18.5). This is a mixture of π-allyls derived from both acetates (aryl to alkyl ratio 2.4:1).

Acknowledgment. This work was supported by grants from the Natural Sciences and Engineering Research Council of Canada. B.B. was a Killam Fellow during the time of this work and is grateful to the Killam Foundation. P.B.M. was a recipient of an NSERC scholarship.

Structure of [Pd(η^3-C(Xyl)$_2$CHCHPh)(*S,S*-PPh$_2$(CHMe)$_2$PPh$_2$)]BPh$_4$: A Catalyst for Asymmetric Allylic Alkylation Reactions

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Abstract: The crystal structure and absolute configuration of the major diastereomeric intermediate η^3-allyl complex in [Pd(chiraphos)]$^+$ catalyzed asymmetric allylic alkylations have been determined from a single-crystal X-ray structure determination. The [Pd(η^3-C(xyl)$_2$CHCHPh)(*S,S*-chiraphos)] cation crystallizes as the tetraphenylborate salt with a molecule of ethyl acetate in a tetragonal unit cell of dimensions a = 13.578 (1) Å and c = 76.261 (3) Å, with Z = 8. Intensity data were collected with Cu radiation on an Enraf-Nonius CAD4F diffractometer, and 4007 observations with $I > 3\sigma(I)$ were used to refine 209 variables. With extensive rigid group constraints imposed, convergence was reached at R = 0.079. The known absolute configuration of the diphosphine ligand has been confirmed by measurements of anomalous scattering, and the space group was established as $P4_32_12$. The diphosphine chelate ring adopts a gauche conformation, configuration δ, which renders the phenyl substituents upon the P atoms quasi-axial and quasi-equatorial. The configuration which results for the η^3-allyl ligand is that in which the two xylyl substituents on one terminal C atom of the η^3-allyl ligand and the two phenyl rings on the adjacent P atom are staggered, thus minimizing steric interactions. The other terminal C atom, the chiral site at which nucleophilic attack occurs, is forced to adopt the *R* absolute configuration.

In the preceding two papers Mackenzie and Bosnich[2] have shown that asymmetric allylic alkylations take place through stereoselective nucleophilic attack on cationic complexes of the type [Pd(chiral-η^3-allyl)(chiral diphosphine)]$^+$. The chiral discrimination in the formation of these intermediates in the reactions has been linked to the structures of the starting Pd complexes by an elegant series of kinetic and spectroscopic experiments. With such relationships firmly established, a crystallographic study of the intermediate η^3-allyl complex would be a valuable source of information regarding the steric interactions between catalyst and substrate which are presumably the source of chiral induction. Whereas most of the complexes could only be obtained as amorphous solids, the major diastereomer of the Pd(1,1-bis(3,5-dimethylphenyl-3-phenyl-η^3-allyl))(*S,S*-chiraphos) cation does form poor crystals with a number of anions. Of these complexes, only those with the BPh_4^- anion were found to be even marginally

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0002-7863/85/1507-2054$01.50/0