Asymmetric Transition Metal-Catalyzed Allylic Alkylations

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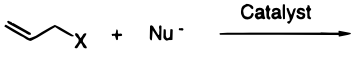
I. Introduction

Efficient and reliable amplification of chirality has borne its greatest fruit with transition metal-catalyzed reactions since enantiocontrol may often be imposed by replacing an achiral or chiral racemic ligand with one that is chiral and scalemic. While the most thoroughly developed enantioselective transition metal-catalyzed reactions are those involving transfer of oxygen (epoxidation and dihydroxylation)[1,2] and molecular hydrogen,[3] the focus of this review is on the area of enantioselective transition metal-catalyzed allylic alkylations which may involve C−C as well as C−X (X = H or heteroatom) bond formation.[4−9] The synthetic utility of transition-metal-catalyzed allylic alkylations has been soundly demonstrated since its introduction nearly three decades ago.[10−21] In contrast to processes where the allyl moiety acts as the nucleophilic partner, we will limit our discussion to processes which result in nucleophilic displacements on allylic substrates (eq 1). Such reactions have been recorded with a broad



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range of metal complexes including those derived from nickel, palladium, platinum, rhodium, iron, ruthenium, molybdenum, and tungsten.

Bringing asymmetric induction to such reactions represents an important new dimension to their use in synthesis. There are two general classes of reactions of the type represented in eq 1 which differ in the nature of the nucleophile. "Hard" nucleophiles, defined as those derived from conjugate acids whose

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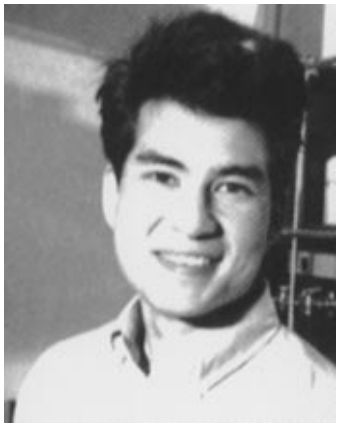
Born in Philadelphia, PA, in 1941 where he began his university training at the University of Pennsylvania (BA, 1962), Barry M. Trost obtained a Ph.D. degree in Chemistry just three years later at the Massachusetts Institute of Technology (1965). He directly moved to the University of Wisconsin where he was promoted to Professor of Chemistry in 1969 and subsequently became the Vilas Research Professor in 1982. He joined the faculty at Stanford as Professor of Chemistry in 1987 and became Tamaki Professor of Humanities and Sciences in 1990. In addition, he has been Visiting Professor of Chemistry in Germany (Universities of Marburg, Hamburg, and Munich), Denmark (University of Copenhagen), France (Universities of Paris VI and Paris-Sud), Italy (University of Pisa), and Spain (University of Barcelona). In 1994 he was presented with a *Docteur honoris causa* of the Université Claude-Bernard (Lyon I), France. Professor Trost made a major contribution early in his career with the isolation, structure determination, and synthesis of the insect juvenile hormone which initiated the concept of insect growth regulants as an alternative to pesticides. Enhancing synthetic effectiveness has been a major goal. How can the ever increasing complex molecules needed to meet the needs of society in an economical and practical fashion be created? Developing the tools, i.e., the reactions and reagents, that enhance selectivity and impart "atom economy" is the first stage. He has pursued this goal in many ways with a major thrust being the rational design of selective catalysts which may make them the "chemists' enzymes". Inserting sulfur substituents to impart synthetic versatility has created the concept of organosulfones as chemical chameleons—i.e., serving as both nucleophiles and electrophiles depending upon the environment. Coordinating a set of reactions into a sequence that permits the construction of a complex target from readily available starting materials represents the second and final stage. Over 100 total syntheses of divergent molecules ranging from antitumor agents to electrical conductors have been completed.



David L. Van Vranken was born in St. Charles, MO, in 1965. He received his B.S. degree from the University of Texas at Austin in 1987 and his Ph.D. at Stanford under the direction of Barry M. Trost as an NSF graduate fellow. His graduate work centered around the development of enantioselective palladium catalysis and the synthesis of aminocyclopentitol glycosidase inhibitors. He then did his postdoctoral with Peter G. Schultz at Berkeley as an NSF postdoctoral fellow before accepting his current position at UC Irvine. His current research interests center around the development of peptide Mannich reactions in proteins and in natural products synthesis.

pK_a > 25, normally effect such reactions by attachment of the nucleophile to the metal followed by reductive elimination as depicted in Scheme 1. This process has not been extensively developed in the achiral version. The lack of such development probably stems, in part, from its duplication of organocopper chemistry. On the other the hand, the reaction with "soft" nucleophiles, defined as those derived from conjugate acids whose pK_a < 25, normally follows a different course as outlined in Scheme 2. Intrinsic to this pathway is the fact that bond breaking and making events occur outside the coordination sphere of the metal, i.e., on the face of the π-allyl unit opposite the transition metal and its attendant ligands. Thus, the leaving group and the nucleophile are segregated from the chiral environment of the ligand by the π-allyl moiety.

The first example of an enantioselective palladium-catalyzed allylic substitution reaction with a stabilized nucleophile was reported in 1977.[22] Since this beginning, much work has been done to harness the asymmetric potential of allylic alkylations, but only recently have these reactions developed into processes where high enantioselectivities may be realized with a wide range of substrates in a predictable fashion. The lag time in this development may stem from the stereochemical requirements that the chiral ligands must somehow reach across the plane of the allyl fragment to transfer their chirality to the event responsible for the enantiodiscrimination.

This review highlights recent progress in the enantioselective allylic substitutions catalyzed by transition metals since 1988. Special attention is focused upon the expanding repertoire of amenable substrates. The review is organized so as to group together reactions which share a common source of enantioselection. Since understanding the origins of enantioselectivity is essential to the design and utilization of this process in applications, the nature of π-allyl strereodynamics is also discussed. Virtually all of the efforts to date have focused on palladium-catalyzed reactions.

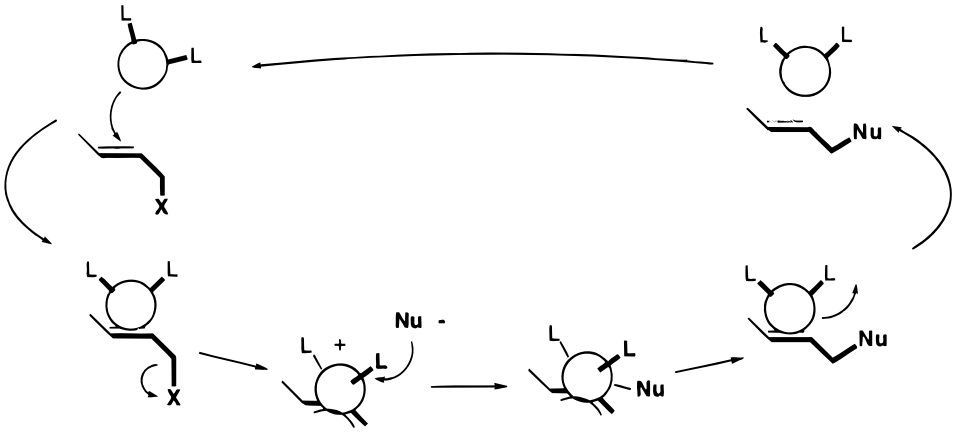
II. Considerations for Enantioselective Allylic Alkylations

A. Opportunities For Enantiodiscrimination

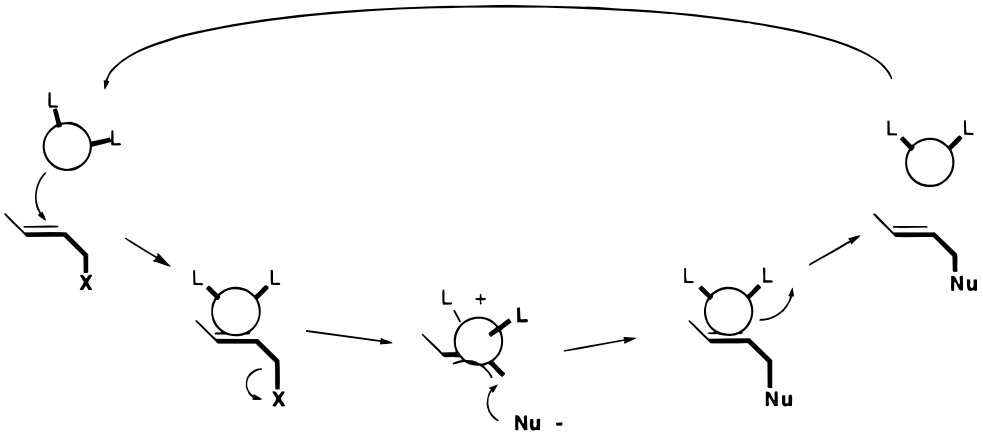
1. Overview

For a process to provide 100% enantiomeric excess in 100% yield, the enantiodetermining step must involve the distinction between enantiotopic groups or faces. All popular enantioselective transition metal-catalyzed reactions involve additions to π systems. In contrast, allylic alkylations involve displacements at sp^3 centers. The ability to convert racemic starting material into optically pure material in such an event—completely, without the waste of a kinetic resolution—presently is almost unique to transition metal-catalyzed allylic alkylations, the exception being those processes involving a dynamic kinetic resolution such as in the hydrogenation of substituted β-keto esters. The general catalytic cycle for transition metal-catalyzed allylic alkylations by stabilized nucleophiles is composed of five primary

Scheme 1. Allylic Alkylation with Hard Nucleophiles



Scheme 2. Allylic Alkylation with Soft Nucleophiles



steps (Scheme 2). Figure 1 summarizes the potential sources of enantiodiscrimination in transition metal-catalyzed allylic alkylations and serves as the basis for organization of this review. These steps are (a) metal−olefin complexation, (b) ionization, (c) enantioface discrimination of the π-allyl complex, (d) nucleophilic attack at enantiotopic termini, and (e) enantioface discrimination in the nucleophile. Decomplexation of the metal from the olefinic product cannot change the stereochemistry of the product.

The importance of organizing this review by the source of enantioselection rather than by substrate type is illustrated by eqs 2−5. The substrates in eqs 2 and 3 are structurally similar, react with the same nucleophile, and give similar levels of asymmetric induction. Yet the sources of enantioselection are quite different. In eq 2, the palladium atom will test out both faces of the olefin, but only one of these faces will lead to a complex suitable for the finicky metal to ionize the acetate (Figure 1a).[23] For the acyclic

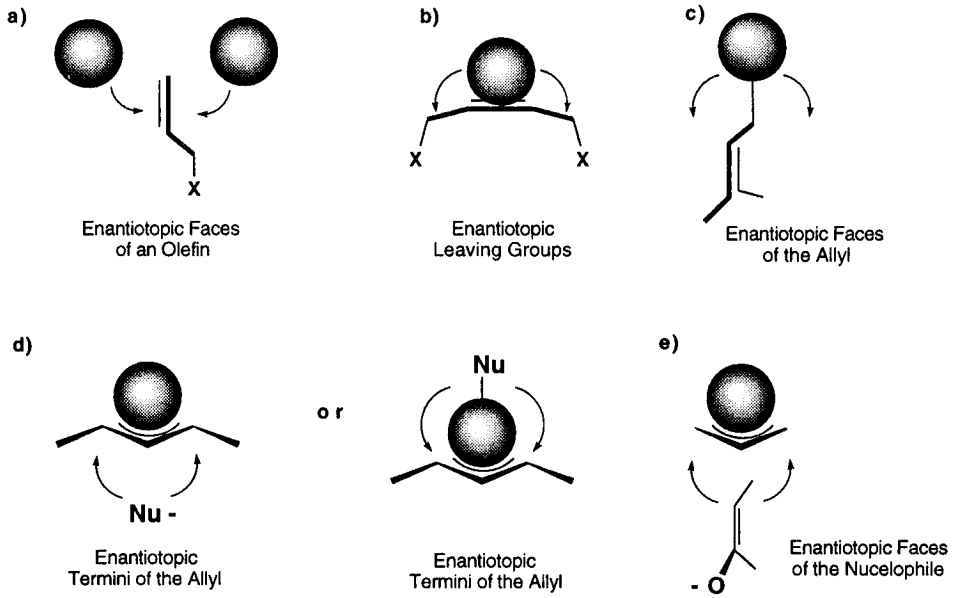
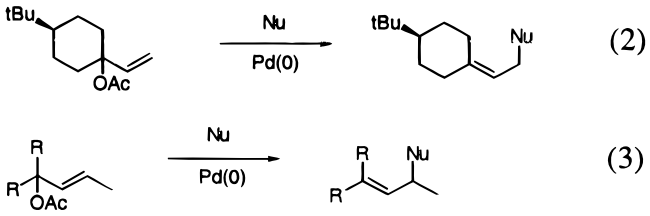
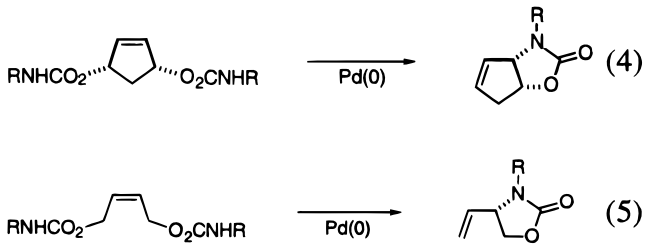


Figure 1. Sources of enantiodiscrimination in transition metal-catalyzed allylic alkylations.

substrate (eq 3), the enantiodetermining event occurs long after the acetate has parted company (Figure 1c).[24]



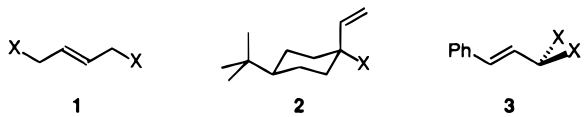
An even more dramatic comparison is shown in eqs 4 and 5. For the cyclic substrate (eq 4), the palladium catalyst can be made to deftly choose between two enantiotopic leaving groups (Figure 1b).[25] If, however, the methylene group is removed (eq 5), the palladium catalyst will explore both enantiofaces of the allyl fragment before committing to the critical enantiodetermining cyclization event (Figure 1c).[26]



2. Enantiofacial Complexation and Ionization

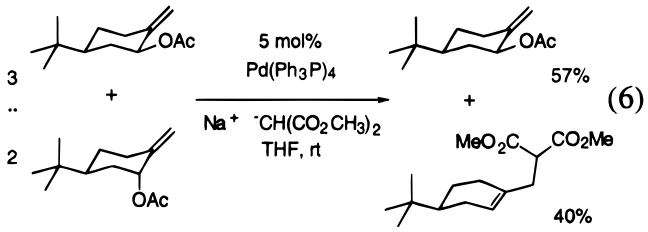
Metal−olefin complexation is a potential source of stereoselection. Unless the olefin is symmetrically C_{2h} disubstituted, the transition metal must distinguish between different faces of the olefin. The stabilities of d^{10} metal−olefin complexes vary widely (over 14 orders of magnitude) depending upon the steric and electronic properties of the olefin.[27,28] Electron-withdrawing groups (which lower the LUMO) will enhance the stability of the metal−olefin complex while bulky groups will decrease the stability via steric interactions. Halpern has elegantly demonstrated the importance of enantiofacial complexation in the asymmetric hydrogenation of olefins using rhodium.[29] In this case, the more stable metal−olefin complex is less reactive toward oxidative addition of hydrogen.

There is no evidence for selective complexation as a source of enantioselection in transition metal-catalyzed allylic alkylations, but the olefin serves as the platform for ionization and so complexation and ionization must be considered together. In the examples **1**−**3**, ionization from different enantiofaces of the olefin will afford enantiotopic allylic complexes (Figure 1a and 1c).



3. Ionization of Enantiotopic Leaving Groups

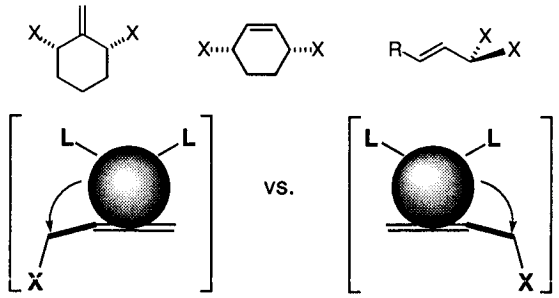
Stereoelectronic effects are important in the ionization step in palladium-catalyzed reactions. One example of this is based on the ionization of axial vs equatorial leaving groups in conformationally locked cyclohexanes—the alkylation of 5-*tert*-butyl-2-methylenecyclohexyl acetates as a 3:2 mixture of *cis* and *trans* isomers with sodium dimethyl malonate (eq 6).[30] After all of the axial acetate has reacted, the



equatorial isomer is recovered unreacted. From competition studies, it was estimated that the axial acetate reacts at least 250 times faster than the equatorial acetate.

In meso substrates with enantiotopic leaving groups at different allylic positions, enantioselection occurs from one olefinic face as shown in Scheme 3. Greater

Scheme 3. Desymmetrization of Meso-Diesters



promiscuity on the part of the leaving group is expected to lead to a reduction in enantioselectivity. This general trend has been established by experiment.[23] Geminal diesters involve both enantioface complexation and ionization in the enantiodiscriminating step (see section III.A.4).

4. Enantioface Exchange in the η^3-Allyl Complex

If the η^3-allylic intermediate is not symmetrically 1,3-disubstituted, enantioselection will be dictated by which face of the allylic fragment that the transition metal presents to the nucleophile. Selective ionization from one enantioface of the olefin is not necessarily a decisive process. The metal can switch between enantiofaces of the allylic fragment. Enantioface exchange can be either detrimental to or obligatory for enantioselectivity. This phenomenon is fundamental to allylpalladium chemistry; understanding it has helped to clarify otherwise confusing results and is sure to pave the road to future success in this field.

There are two important mechanisms for this process. In substrates with identical substituents on at least one of the allylic termini, the η^3-η^1-η^3 mechanism (Scheme 4) may be operative.[31] This mechanism involves a change in hapticity followed by rotation about a carbon−carbon bond.[32] These processes occur on the same time scale as other steps in the catalytic cycle and can also lead to a loss of stereochemical information that might have been achieved in the ionization step.

Scheme 4. Racemization of (π-Allyl)metal by η^3-η^1-η^3 Mechanism

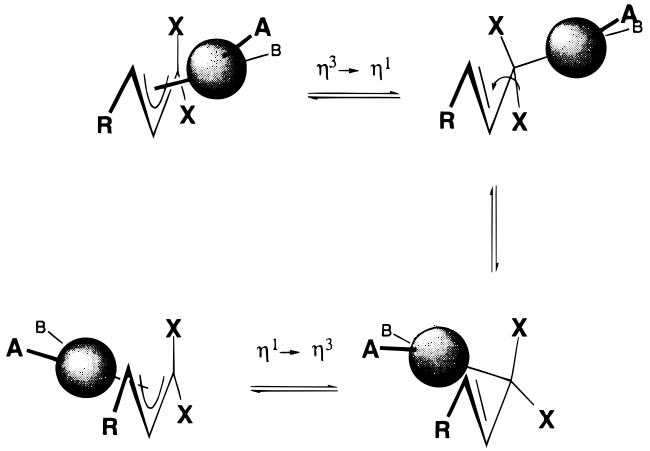


Figure 2 shows some of the substrates which can take advantage of this kind of isomerization. If this equilibration is fast relative to attack of the nucleophile, then enantiomeric excess can be obtained from racemic starting material without resorting to a kinetic resolution.

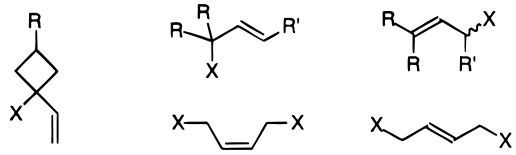
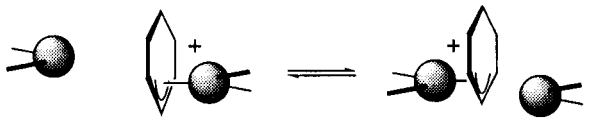


Figure 2. Substrates whose complexes may racemize by η^3-η^1-η^3 mechanism.

Cyclic substrates or unsymmetrically substituted allyls must undergo enantioface exchange through a mechanism different from that shown in Scheme 3 yet these substrates have undergone enantioselective alkylation. Evidence for alternative mechanisms has

been accumulating from many studies which probe the stereochemistry of palladium-catalyzed allylic alkylations.[24,33,34] In stoichiometric systems, the rate of diastereoface exchange in cationic allylpalladium complexes can become linearly dependent upon the concentration of Pd(0) (eq 7). The precise mechanism



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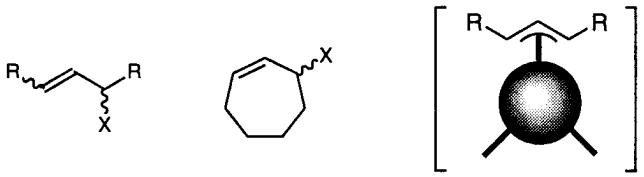
for this process is unclear at present, but the following conclusions were made. Isomerization can be inhibited by (1) a reactive allylic substrate, (2) a low Pd(0) concentration, (3) bidentate ligands, and (4) halide ions.[35] When palladium sites are isolated from each other on solid supports such pathways are shut down.[36]

5. Attack at Enantiotopic Termini of the Allyl

When the η^3-allyl moiety has C_{2h} symmetry then the allylic termini are enantiotopic. Such intermediates can be formed from racemic substrates as well as from mixtures of *E* and *Z* isomers. Since its introduction in 1973, the 1,3-disubstituted allyl system and cyclohexenyl system have become the benchmark substrates for asymmetric allylic alkylations.[37] Both stabilized and unstabilized nucleophiles can lead to enantiomeric products by control of the regioselectivity of alkylation by the ligands.



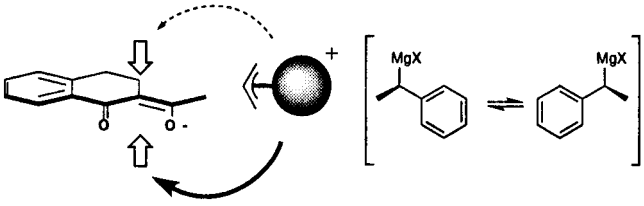
Examining Schemes 1 and 2 reveals that the ionization step normally occurs with inversion of configuration, i.e., from the face opposite the leaving group, regardless of the nature of the nucleophile. Subsequently, soft nucleophiles attack on the same face from which the leaving group departed.[38,39] This mechanism applies only to a set of nucleophiles which is often referred to as soft or stabilized and includes malonic esters, β-diketones, 1,1-bissulfonylmethanes, thiols, amines, amides, carboxylates, and alkoxides.

The term "hard" or "unstabilized nucleophile" is often used in place of its more exact mechanistic meaning: entities which attack first at the metal and are subsequently transferred to the allylic moiety. Unstabilized nucleophiles include Grignard reagents, alkylzinc halides, and hydride donors such as hydridoborates, hydridostannanes, and formates.

These two classes of nucleophiles lead to two very different stereochemical results. Allylic alkylations with stabilized nucleophiles proceed with net facial retention (ionization and alkylation occur on the side of the allylic plane opposite from the metal). Allylic alkylations with unstabilized nucleophiles lead to a net facial inversion.

6. Enantiofaces of Prochiral Nucleophiles

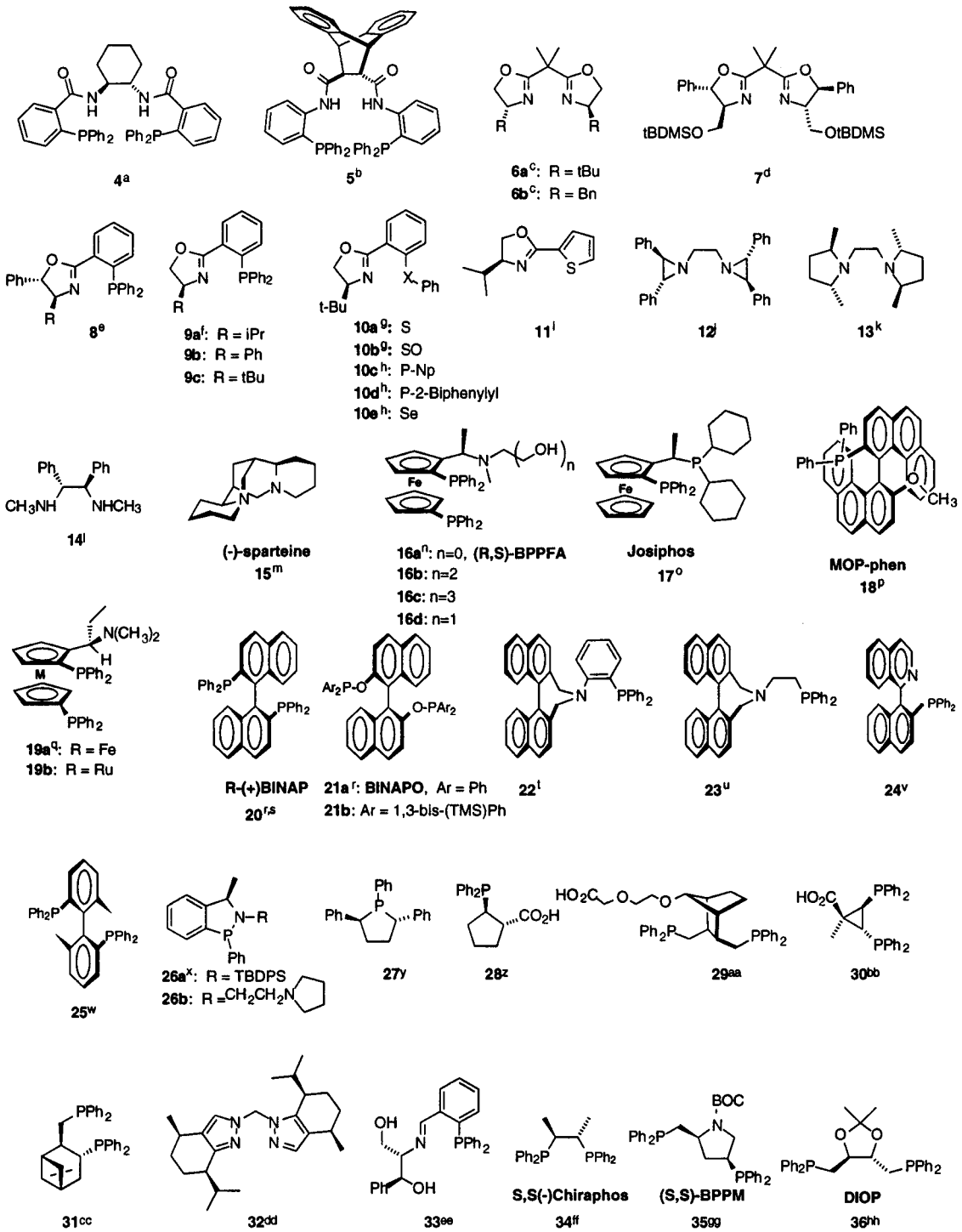
Enantioselectivity is also available by enantioface discrimination by prochiral nucleophiles or equilibrating mixtures of racemic nucleophiles. Prochiral nucleophiles like salts of β-diketones can lead to enantioselective alkylations with achiral allylic moieties as in the case where the allylic terminus is symmetrically substituted. Another mechanism of enantioselection comes from the selection of one enantiomer of nucleophile from an equilibrating mixture of enantiomers. If the allyl unit is also prochiral, double enantioselectivity becomes the issue.



B. Ligands

The potential for a simple change in ligand structure to transform, in "Cinderella fashion", racemic allylic alkylation processes into enantioselective reac-

Chart 1. Chiral Ligands Used in Allylic Alkylations



a) Ref 25. b) Ref 50. c) Ref 51. d) Ref 52. e) Ref. 53. f) Ref 54-56. g) Ref 57. h) Ref 58. i) Ref 59. j) Ref 48. k) Ref 60. l) Ref 61. m) Ref 62. n) Ref 7, 63. o) Ref 64. p) Ref 65. q) Ref 66. r) Ref 40. s) Ref 41. t) Ref 67. u) Ref 68. v) Ref 69. w) Ref 70. x) Ref 71. y) Ref 72. z) Ref 73. aa) Ref 74. bb) Ref 136. cc) Ref 76. dd) Ref 77. ee) Ref 78. ff) Ref 42. gg) Ref 79. hh) Ref 22.

tions have led to the design and screening of a plethora of chiral ligands. Many of these ligands—thoughtfully designed, meticulously synthesized—have given lackluster performances. The C_2 symmetrical ligands such as BINAP,[40,41] DIOP,[22] and CHIRAPHOS[42] which have proven to be extraordinarily successful for catalytic hydrogenation have had only modest success here.

C_2 symmetry is not required to achieve high levels of enantioselectivity. Indeed, the consensus of over 4 billion years of evolution, i.e., most enzymes, is that enantioselective catalysts should possess active sites devoid of local symmetry. For the organic chemist, however, symmetry provides a simple means of removing competing transition states which can reduce enantiofidelity.[43] Computational methods are beginning to play a role in ligand evaluation, but until more effective methods for predictive *de novo* design are available, C_2 symmetry and a substantial dose of serendipity will continue to play major roles

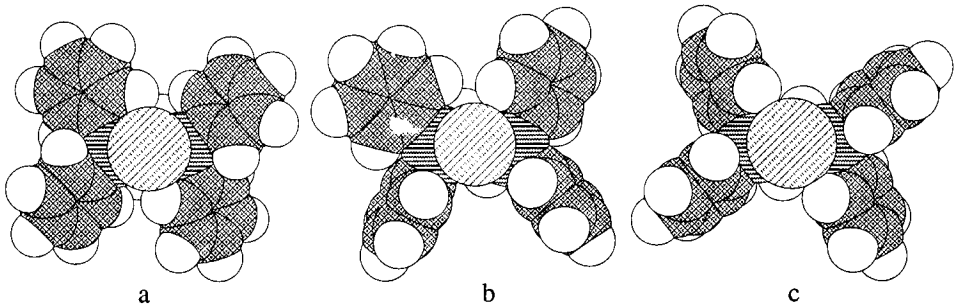


Figure 3. Some metal complexes viewed along the phosphorus−metal−phosphorous plane with phosphine ligands omitted for clarity (a) [Pd(η^3-C(Xyl)$_2$CHCHPh)(*S*,*S*-Chiraphos)]BPh$_4$,[88a] (b) (DPPE)PtCl$_2$,[88b] and (c) (η^2-diphenylphosphene)Pd(0).[88c]

in ligand design.[44−49] Chart 1 shows a selection of some of the chiral ligand designs which have been used in palladium-catalyzed allylic alkylations. Most of these have been reported only within the last few years.

So which is the best ligand to use in an enantioselective transition metal-catalyzed allylic alkylation? The answer depends upon the type of substrate being used in the reaction—a relationship that will subsequently be addressed through example. It has become evident over the past few years that solvent, counterions, and catalyst source can be extremely important in determining the outcomes of reactions. For this reason, differences in enantiomeric ratios should be interpreted with caution.

The popularity of phosphine ligands in transition metal chemistry is a result of their ability to stabilize the metal as the monomeric species while providing added control over the steric and electronic properties of the system.[80] The early successes of chiral phosphine ligands in hydrogenation reactions led to their direct recruitment for use in the area of enantioselective allylic alkylation reactions. The early results were disappointing, but steady progress has been made, with many of the new ligand designs being targeted primarily for allylic alkylations.

The different properties of the donor atoms are transmitted to the allylic substrate through the metal. In this way, the reactivity of the substrate may be fine-tuned.[81,82] These effects may be monitored via the ^{13}C shifts of the allylic complexes.[83] The lowest field allylic ^{13}C shifts are observed with complexes containing electron-withdrawing phosphite ligands (back-bonding); the highest field allylic ^{13}C shifts are observed with tertiary amine ligands (pure σ donors). Nitrogen has made its way into successful chiral ligand designs with increasing frequency.[84] The stereoelectronic predictions of the trans effect are that bonds trans to phosphorus will be longer and weaker than bonds trans to nitrogen, even when these heteroatoms are in the same ligand. These predictions are confirmed by X-ray and reactivity studies of palladium complexes of (phosphinoaryl)oxazoline ligands such as **9** and **10**.[58,85] Such factors have been claimed to be determinant for enantiodiscrimination.

C. Structural Studies of Transition Metal−Allyl Complexes

1. X-ray Structures

Advances in the design of chiral catalysts require an understanding of the nature of the transition state of the enantiodiscriminating event. Ideally, one would like to know the structure of the lowest energy diastereotopic transition state in the ionization/alkylation reaction, but as in all chemistry, we are limited to ground state complexes (metal−allyl and metal−olefin) on either side of the ever-elusive transition state. X-ray structures of these complexes have served as a major source of structural information on which many predictive models are based. There is much structural information available on transition metal−allyl complexes with chiral ligands.[29,30,45−52,58,64,69,85−90] In contrast, crystal structures of the corresponding olefinic complexes are few in number.[91] This dearth of information is unfortunate. Whether one is looking at ionization or alkylation, the metal−olefin complex represents one side of the reaction coordinate.

What does the organic fragment see when bound to a metallophosphine? The structures depicted in Figure 3 are viewed along the phosphorus−metal−phosphorus plane with other ligands removed. Even with achiral ligands such as DPPE, the steric surface presented to the organic substrate is not symmetrical. How these environments change over the course of the catalytic cycle and, most importantly, in the lowest energy transition state, is difficult to predict with certainty.

2. η^3-η^1-η^3 Isomerization

It is important to understand that, in palladium-catalyzed allylic alkylation reactions, allylpalladium complexes are often in a state of dynamic equilibrium. On the time scale of the catalytic cycle, ligands can dissociate, reassociate, and change their conformation and geometry. Substituents on allylic ligands are traditionally named according to their configuration relative to the 2 substituent. In Figure 4, the substituents which are *syn* to the 2 hydrogen are designated as "syn"; the substituents *anti* to the 2 hydrogen are labeled as "anti". On the time scale of a typical alkylation reaction, the *syn*/*anti* substituents in a palladium π-allyl complex can exchange positions tens or hundreds of times faster than alkylation.

The mechanism for *syn*/*anti* exchange shown in Scheme 4 depicts the stereochemical consequence

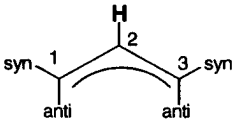
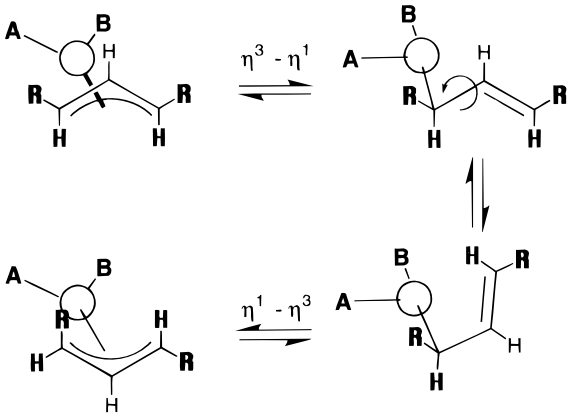


Figure 4. Stereochemical nomenclature for allyl ligands.

when having identical substituents at one allylic terminus. When the subsituents at the *syn* and *anti* positions are different, the *syn*/*anti* exchange results in an important stereochemical difference (Scheme 5). In both cases, the allylic carbons do not switch

Scheme 5. *Syn/Anti* Exchange in a π-Allyl Complex with Nonidentical *Syn/Anti* Substituents

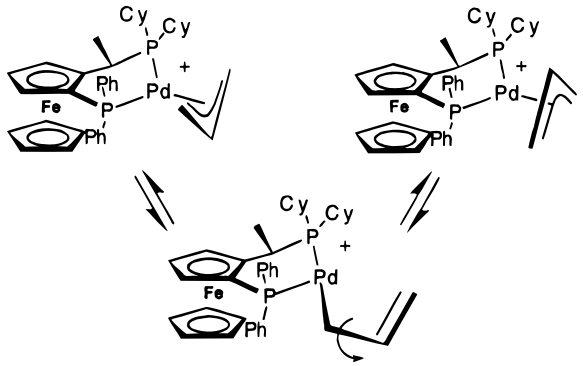


positions: the carbon *trans* (in the square-planar array) to ligand B remains *trans* to ligand B, and the carbon *trans* to ligand A remains trans to ligand A. In both cases also, the allyl ligand, which formerly occupied a geometry with the C2 carbon pointing upward, now has a geometry in which the C2 carbon points down, i.e., the palladium has effectively migrated from one face of the π-allyl unit to the other. However, in the unsymmetrical case, the two groups on carbon trans to B change from *syn* to *anti* and vice versa.

Application of modern NMR techniques to transition metal−allyl complexes has clarified the nature of many exchange processes and provided insights into potential sources of enantioselection.[41,92,93] With unambiguous assignments from improved two-dimensional and heteronuclear techniques, time-averaged spatial relationships may be extracted with nOe-based techniques.

In NMR studies of Josiphos(allyl)palladium triflate, Togni has shown that *syn*/*anti* exchange is selective (Scheme 6).[32] On the time scale of the nOe, the allylic carbon attached *trans* to the dicyclohexylphosphino group always remains *trans* to the dicyclohexylphosphino group. Thus, only the bond *trans* to the

Scheme 6. Dynamics of Complex from Josiphos



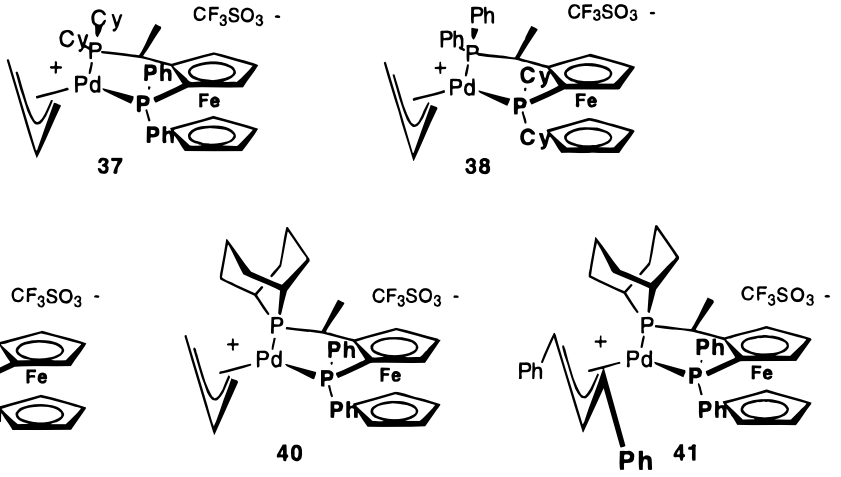
diphenylphosphino group is broken during the *syn*/*anti* exchange process.

This effect is seen in similar complexes in which the substituents on the phosphino groups are reversed (Chart 2). In both **37** and **38** exchange is observed at room temperature on the NMR time scale such that the bond *trans* to diphenylphosphino (*cis* to dicyclohexylphosphino) breaks and re-forms. The lability of these bonds cannot be simply attributed to being *trans* to diphenylphosphino nor *cis* to a dialkylphosphino group. Complexes **39** and **40** show no observable η^3-η^1-η^3 isomerization at room temperature, suggesting that the lability of particular bonds is not simply an electronic effect.[94] Diphenylallyl complex **41** exists at room temperature in solution as a mixture of two interconverting *E*,*E* and two interconverting *E*,*Z* isomers. In the *E*,*Z* isomers, one of the phenyl groups occupies an *anti* position. There is no observable exchange between the *E*,*E* and *E*,*Z* isomers.[64]

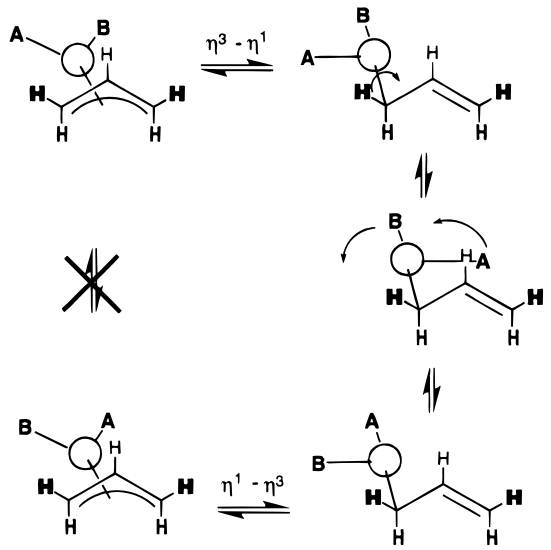
Another type of isomerization is apparent allyl rotation. There is no evidence for the simple mechanism in which the allyl moiety simply rotates about the palladium−allyl axis. A more likely mechanism is shown in Scheme 7. After a change in allyl hapticity from η^3 to η^1, a rotation occurs about the carbon−metal bond. At some point before, during, or after this rotation, the square-planar complex must change geometries to open up a coordination site trans to ligand B. The complex can then reform the η^3 allyl complex.

Syn/*anti* interchange of the allylic substituents does not occur in this process. Calculations suggest that processes which isomerize trisubstituted square-

Chart 2. Ferrocenyl Complexes

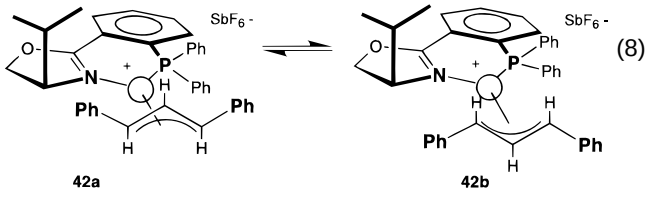


Scheme 7. Apparent Allyl Rotation



planar d^8 complexes are possible, but would be dependent upon the electronic nature (donor/acceptor properties) of the ligands attached to the metal.[95] An important conclusion from this work is that if R in $PdLR_2$ is a strong σ donor and L is a poor donor or acceptor, then the rearrangement of *trans*-$PdLR_2$ to *cis*-$PdLR_2$ will not be facile.

Helmchen has shown that the (phosphinoaryl)-oxazoline complexes **42a** and **42b** undergo apparent allyl rotation by the palladium−carbon rotation mechanism shown in Scheme 7.[58] The two isomeric complexes, **42a** and **42b**, were present in an 1:8 ratio, respectively. In contrast, the corresponding complex



(8)

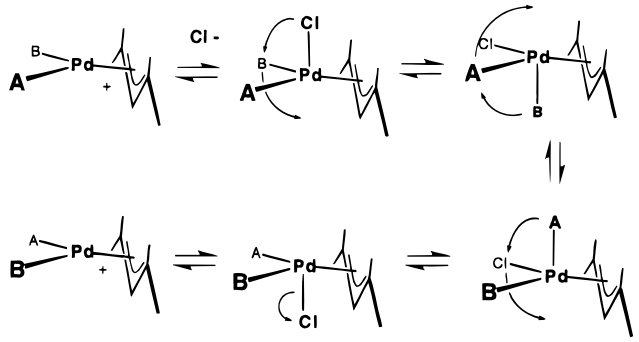
42a **42b**

of unsubstituted allyl proceeds by the carbon−carbon rotation mechanism shown in Scheme 4. Under the conditions of the reaction, the two conformations, **42a** and **42b**, interconvert at least 50 times faster than nucleophilic attack, so that no conclusions regarding the origin of stereoselection were possible (eq 8). Brown has shown that diphenylallylpalladium complexes with ligand **24** exist as equilibrating up and down diastereomers much like Scheme 6. While the ratio of these two species was solvent dependent (6:1 in CD_2Cl_2; 2:1 in $CDCl_3$), the enantiomeric product ratios (9:1) were not significantly affected.[69] Here again, the energies of the ground state intermediates, do not correlate with the relative energies of the transition states.

3. Apparent Allyl Exchange via Pseudorotation

Many groups have shown that addition of chloride ions in catalytic amounts can accelerate the process of apparent allyl rotation.[48,96] For this reason, the use of (π-allyl)palladium chloride dimer as the catalyst source may not be interchangeable with halide-free sources of palladium such as $Pd_2(dba)_3CHCl_3$. Similar effects have been attributed to the use of strongly coordinating solvents such as DMSO and acetonitrile.[69] Åkermark and Vitagliano have proposed the pseudorotation mechanism shown in Scheme 8 to account for the role of chloride in accelerating the apparent allylic rotation process.[97]

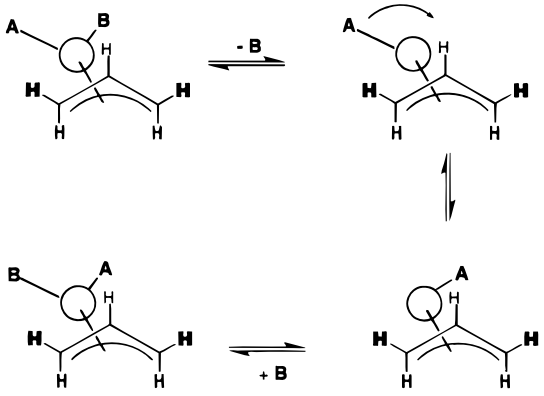
Scheme 8. Pseudorotation Mechanism for Apparent Allyl Rotation



4. Apparent Allyl Exchange via Ligand Dissociation

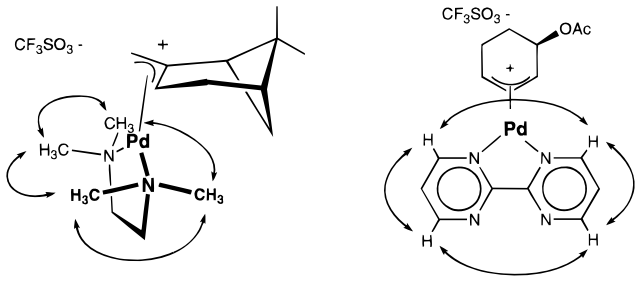
There is another mode of isomerization which corresponds to the mechanism shown in Scheme 9.

Scheme 9. Ligand Dissociation Mechanism for Apparent Allyl Rotation



In this process, dissociation of one of the ligands leads to formation of a coordinatively unsaturated square-planar complex. Isomerization of the T-shaped geometry followed by reassociation completes the process which appears as a simple allyl rotation.

Evidence for this process comes from dynamic NMR experiments on 2,2′-bipyrimidine and TMEDA allylpalladium complexes.[96,98] The EXSY spectrum of these compounds show that all of the methyl groups in **43** and all of the protons ortho to nitrogen in **44** are in chemical exchange. Addition of chloride



43 **44**

ions to these solutions has been shown to increase the rate of apparent allyl rotation. Since all four

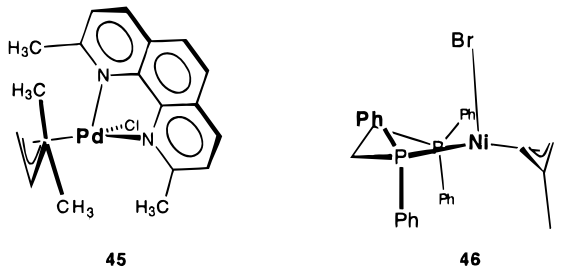


Figure 5. Pentacoordinate d^8 metal allyl halide complexes, drawn from the crystal structures.

groups in each case are shown to be in chemical exchange in this process, it is inferred that the exchange process must involve cleavage of one of the Pd−N bonds, ligand isomerization and re-formation of the Pd−N bond.

Crystal structures of pentacoordinate halide complexes (depicted in Figure 5) provide support for the intermediacy of such complexes in some apparent allyl rotation processes but does not distinguish between chloride-induced ligand dissociation and pseudorotation.[97,99] Note that in the allylpalladium complex **45**, the chloride occupies an equatorial position with respect to the square-planar array, and in the nickel complex **46**, dppe(η^3-methallyl)NiBr, the bromide occupies the axial position. The difference is probably not strictly an electronic effect. The 2,9-dimethyl substituents on the phenanthroline cause sufficient steric hindrance to prevent this ligand from binding in a simple equatorial fashion.

D. Steric Interactions—Ligand vs Nucleophile

1. Stabilized Nucleophiles

How important are the steric interactions between the nucleophile and allylic fragment? The well-known Felkin−Anh rule stresses the importance of interactions between the incoming nucleophile and carbonyl substrates in predicting the stereochemical outcomes of additions to carbonyl groups.[100,101] Development of similar models for allylpalladium systems will be important but may not be so straightforward. When a stabilized nucleophile attacks an (η^3-allyl)palladium complex, bond reorganization is also occurring between the ligands and the allylic component as the substrate undergoes a change in hapticity (Figure 6). Interactions between the chiral ligands and the allyl fragment during the η^3-η^2 bond reorganization may be just as important as interactions between the allyl fragment and the incoming nucleophile.[27,102] The effects of changes in hybridization and hapticity must be considered together.

In envisioning how chiral ligands may influence a bond-forming event on the opposite side of the allylic "plane" that separates the ligand and the trajectory of the soft nucleophile, interactions between the

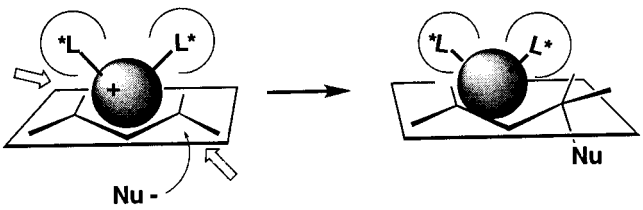


Figure 6. Steric interactions during alkylations.

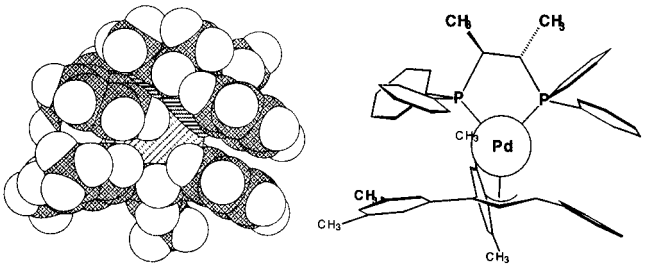


Figure 7. A Chiraphos−palladium allyl complex.

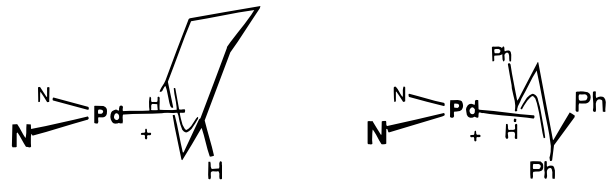


Figure 8. Cyclohexenyl- and (triphenylallyl)palladium−sparteine complexes.

ligand and the allyl unit during these bond reorganizations become a focal point for design. The crystal structure of a palladium complex bearing **34** as ligand coordinated with a triarylallyl unit clearly shows the importance of interactions between the phosphine ligand and substituents on the allyl moiety (Figure 7).[88] Here, the aryl groups of the phosphine ligand interact with the (relatively) flat surface of the arylallyl moiety. There is little possibility for the ligand to interact with a stabilized nucleophile. In crystal structures of acyclic metal−allyl complexes (1,3-diarylallyl), the aryl groups always occupy the *syn* positions.

The X-ray diffraction structures of two different allylpalladium complexes of (−)-sparteine have been determined.[86] In these crystal structures, cyclohexenyl and 1,1,3-triphenylallyl adopt opposite configurations. Cyclohexenyl is arranged so as to direct the *anti* substituents upward, whereas triphenylallyl is arranged so as to direct the two *syn* phenyl groups upward (Figure 8). Even in the absence of crystal-packing forces, the intuitive conclusion should be that cyclic and acyclic allyl ligands have different steric demands. In this case, it is clear that the steric bulk of the η^3-allyl unit orients in the same region regardless of whether the substituents are *anti* or *syn*.

The different steric demands and stereodynamics of these two structural types may translate into different requirements for asymmetric ligands for them. The current observations support this contention. Chiral ligands like **4**[103] and **5**[50] which give good enantioselectivities with cyclic substrates do not give good enantioselectivities with the 1,3-diarylallyl substrates. Conversely, those ligands like **9**, **10**,[104] **16**,[7] and **24**[69] which perform admirably with the 1,3-diarylallyl substrate do not perform well with a cyclic substrate. However, it cannot be concluded that one class of ligands cannot do well with both cyclic and substrates. For example, **4**[105] and **5**[50] perform well with the 1,3-dimethylallyl substrate and several other acyclic systems in contradistinction to their behavior with the 1,3-diarylallyl case. Steric issues appear to constitute the major design principle.

Electronic effects may complement these steric interactions. By using the electronically desymmetrized ligands like the (phosphinoaryl)oxazoline ligands

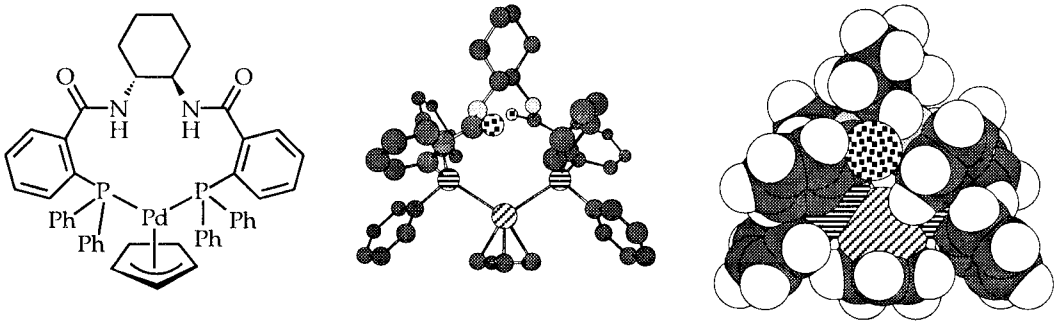


Figure 9. A chiral pocket from ligand **4**. (Hydrogens omitted for clarity in ball and stick representation.) Representations are derived from a CAChe molecular modeling program.

9 and **10**, the longer bond lengths between the metal and the allyl terminus trans to phosphine combines both electronic and steric effects to direct the enantiotopicity of nucleophilic attack.[58]

While attention is normally focused on these intrinsic structural issues between the ligand, metal, and allyl unit, it is equally important to recognize that the nucleophile is also frequently involved in the enantiodiscriminating step such as in type d asymmetric induction (Figure 1). Indeed, in virtually every case, the choice of reaction conditions associated with the nucleophile affects the ee. Ligands like **16** and **29** recognize this aspect by trying to reach across the allylic "plane" to interact with the incoming nucleophile. On the other hand, ligands like **4** and **5** attempt to envelope the reactants by creating chiral pockets as depicted in Figure 9 for the cyclopentenylpalladium complex which interact with both the allyl unit and the nucleophile. In these cases, the depth of the pocket is correlated with the P−Pd−P "bite" angle, the larger the angle, the deeper the pocket.[102]

2. Unstabilized Nucleophiles

When unstabilized nucleophiles attack the cationic η^3-allyl complex, a very different mechanism is involved. In these cases, the metal is the site of initial attack followed by a reductive elimination to give the allylated product[106] (Scheme 1). This differs from the mechanism shown in Scheme 2 in two important aspects: (1) ionization and nucleophilic attack are no longer mechanistically similar processes, and (2) the nucleophile now interacts with ligands directly, suggesting that ligand−nucleophile interactions may be very important in asymmetric induction.

III. Palladium-Catalyzed Allylations with Stabilized Nucleophiles

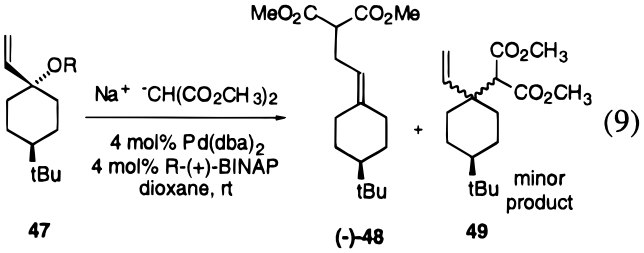
A. Enantioselective Ionization

1. Type "a" Asymmetric Induction

Type "a" asymmetric induction (Figure 1), which derives from chiral recognition in the first step of the catalytic cycle, has been investigated in the palladium-catalyzed allylic alkylation of esters of **47** using BINAP as the chiral ligand.[23,107] Ionization from opposite faces of an olefin determines the absolute stereochemistry of the product (eq 9 and Table 1). The reaction is dependent upon solvent and counterion; yields and optical rotations of products dropped with toluene as the solvent or in the presence of crown ethers. Enantioselectivities in this system were shown to correlate roughly with the leaving group ability (kinetic pK_a), better leaving groups giving poorer enantioselectivities. The plot of log ([*R*]/[*S*]) against Hammett's σ values for the 4-substituted benzoate leaving groups affords a straight line with a slope (ρ) of −0.80 and a correlation coefficient of 0.94.

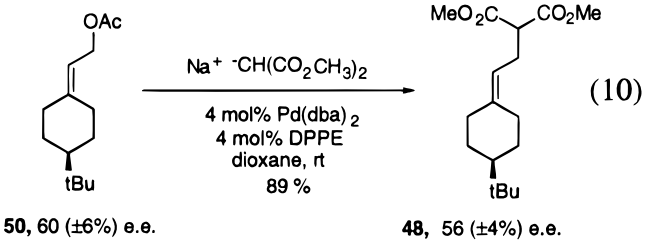
Table 1. Effect of Leaving Group on Enantiomeric Excess of 48

entry	R	% ee	σ
1	4-$O_2NC_6H_4CO$	22	0.78
2	CO_2Me	27	
3	$(CH_3)_3CCO$	30	
4	2-BrC_6H_4CO	38	
5	2,6-$(MeO)_2C_6H_3CO$	46	
6	$CON(i\text{-}Pr)_2$	47	
7	Ac	48	
8	2,4,6-$(OMe)_3C_6H_2CO$	51	
9	4-NCC_6H_4CO	60	0.63
10	4-$(CH_3)_2NC_6H_4CO$	60	−0.60
11	3,4,5-$(OMe)_3C_6H_2CO$	61	
12	$CONMe_2$	63	
13	CO(2-Np)	63	
14	CO(1-Np)	66	
15	4-BrC_6H_4CO	68	0.23
16	2,4-$(MeO)_2C_6H_3CO$	70	0
17	2-$CH_3OC_6H_4CO$	72	0
18	4-*t*-BuC_6H_4CO	73	−0.20
19	C_6H_5CO	76	0.00
20	4-$CH_3C_6H_4CO$	80	−0.17
21	4-$Et_2NC_6H_4CO$	83	−0.60
22	4-$CH_3OC_6H_4CO$	90	−0.27



(9)

Enantioface exchange is not occurring during the reaction. Thus, the enantiomeric purity is preserved in the alkylation of substrate **50** with an achiral palladium complex (eq 10).



(10)

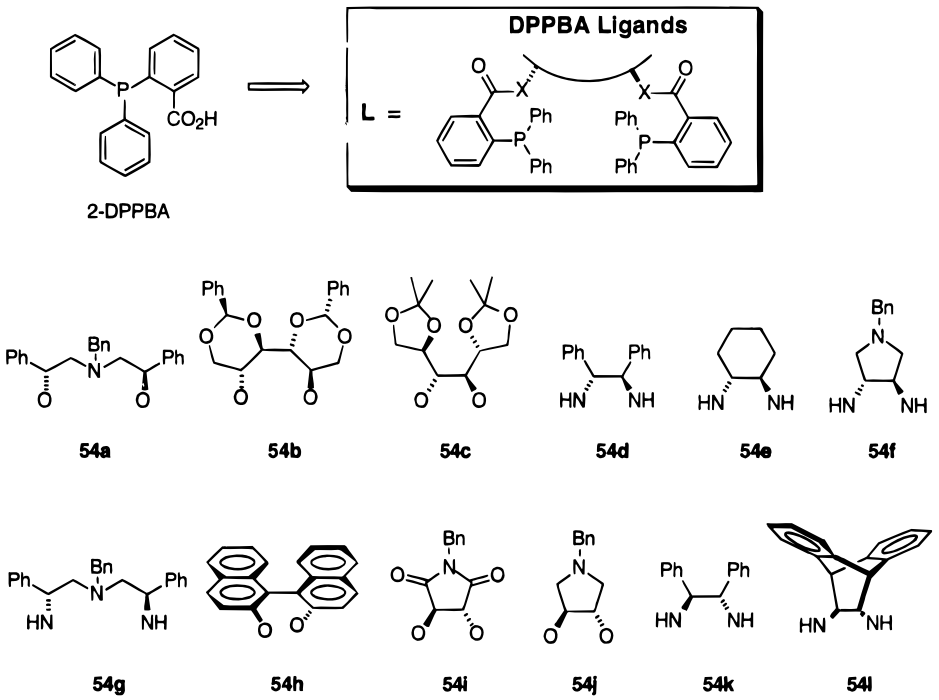
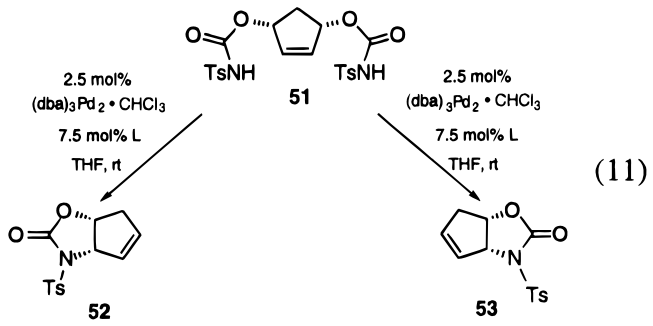


Figure 10. Ligands based upon 2-(diphenylphosphino)benzoic acid.

2. Intramolecular Type "b" Asymmetric Induction

Type "b" asymmetric induction (Figure 1) involves differentiation at the second step of the catalytic cycle—i.e., it depends upon the ability of the chiral catalyst to promote differential ionization of enantiotopic leaving groups having the metal coordinated to the face of the double bond distal to the leaving groups. Utilizing the cyclization of the bis-urethane **51** to the oxazolidin-2-ones **52** and **53** (eq 11)[108−110] as the model, a series of ligands based upon 2-(diphenylphosphino)benzoic acid (DPPBA)[111−113] with chiral diols or diamines possessing C_2 symmetry were constructed as illustrated in Figure 10.[25,102] The simplicity of this synthesis makes it easy to construct a great diversity of ligands because of the ready availability of diverse chiral diols and diamines. The results of the cyclization in which the ionization step is the sole source of enantioselection are summarized in Table 2.



(11)

This series of ligands provides the ability to predict the sense of chirality of the product based upon the chirality of the ligand. If the chiral ligand is viewed along its extended backbone, it can be seen that they have either a clockwise (as in **54a**−**g**) or counterclockwise (as in **54h**−**l**) twist. Viewing the substrate in the plane of the paper with the leaving groups below the plane and the metal above the plane correlates a ligand possessing a clockwise twist with a clockwise motion or twist of the metal with respect to the substrate or vice versa as depicted in Figure 11. Two trends emerge from the data in the DPPBA ligand series. First, the tighter amide linkage always gives higher ee's than the corresponding esters. Second, the larger the dihedral angle between the two (diphenylphosphino)benzoates on the scaffold, the higher the enantiomeric excess.

Table 2. Enantioselective Formation of Oxazolidinones 52 or 53

ligand	% yield	% ee	major enantiomer
54a	100	60	(+)-**52**
54b	98	61	(+)-**52**
54c	100	64	(+)-**52**
54d	97	80	(+)-**52**
54e	97	78	(+)-**52**
54h	87	40	(−)-**53**
54i	68	75	(−)-**53**
54k	91	79	(−)-**53**
54l	94	88	(−)-**53**
55a	29	12	(−)-**53**
55b	81	30	(−)-**53**
55c	99	88	(+)-**52**
(−)-BINAPO	53	55	(−)-**53**
(−)-DIOP	0		

An alternative platform is based upon 2-(diphenylphosphino)aniline (DPPA)[114] as illustrated in Figure 12.[50] As the data in Table 2 illustrates, only **55c** in which the dihedral angle between the two carboxamide groups is forced to be large by virtue of the rigidity of the scaffold is a satisfactory result observed. For both series, the importance of this dihedral angle derives from its effect on the P−Pd−P angle (i.e., so-called bite angle) in the alkene and allyl palladium complexes. Opening this bite angle is believed to enhance the depth of the chiral pocket in which the substrate must reside and therefore more effectively creates a chiral space to control the enantioselectivity. Indeed, an X-ray structure of a (π-allyl)palladium complex derived from **55c** has a bite angle of 110.05° well above the typical 90° so commonly observed in square-planar palladium complexes.

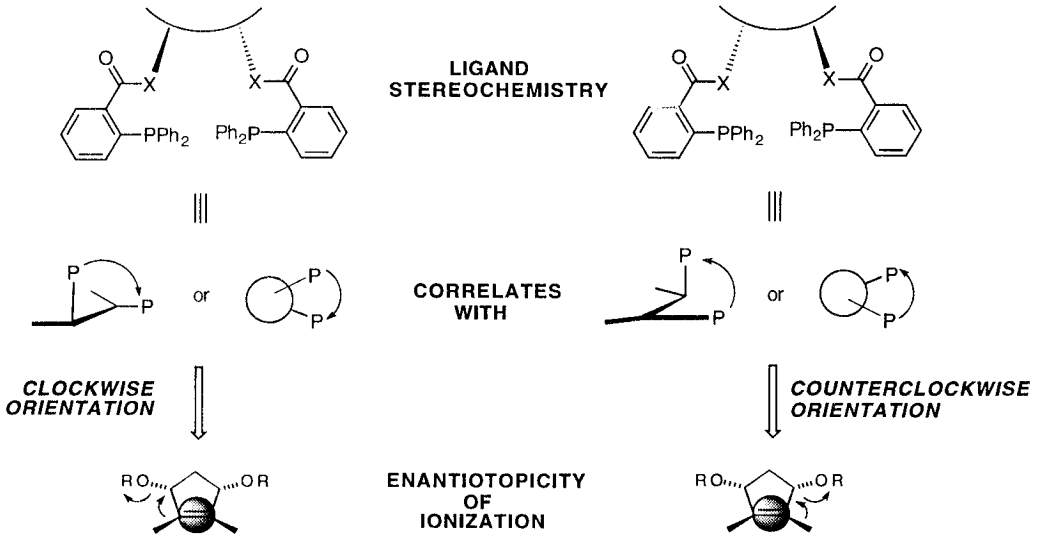


Figure 11. Correlation of ligand stereochemistry with reaction enantioselectivity.

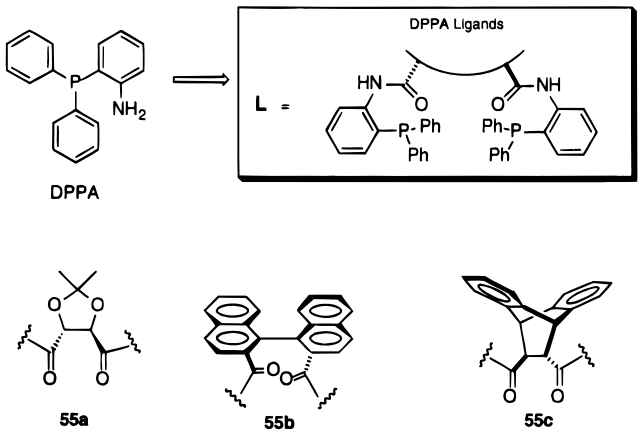
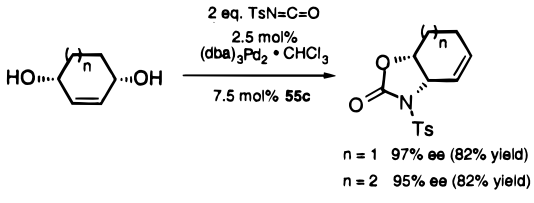


Figure 12. Amide invertomer (DPPA-based) ligands.

Strikingly, the "invertomer" ligand **55c** gives a product possessing the same ee but opposite in the sense of chirality from that obtained by the "normal" ligand **54l** which derived from a scaffold possessing the same sense of chirality. Simply inverting the amide linkage but keeping everything else the same completely inverts the sense of chiral recognition. The invertomer ligand **55c** is the best for giving high ee in oxazolidinone formation. For example, in both the six- and seven-membered ring substrates, excellent enantioselectivities are observed (eq 12). The excellent enantioselectivities (independent of ring size) contrasts sharply with biological protocols for desymmetrization.



(12)

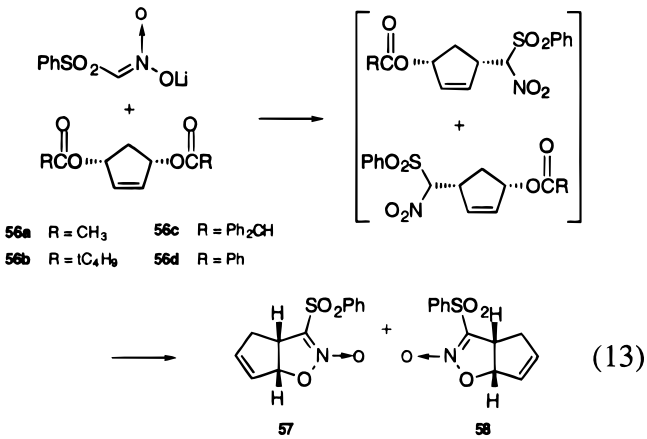
Very few other classes of ligands have been explored for this reaction. As illustrated in Table 2, DIOP failed to form an active catalyst. BINAPO gives a reasonable yield and ee but not comparable to the DPPBA and DPPA derived ligands.

3. Intermolecular Type "b" Asymmetric Induction

Since the leaving group is involved in the enantiodiscriminating step, it also plays a role in determining the ee. In the above, a urethane serves that purpose. Performing the reaction intermolecularly allows variation of this structural unit independently of the nucleophile. The effect of the variation of leaving group with a diverse array of ligands is revealed in the reaction of the esters of *cis*-3,5-cyclopentenediol and the lithium salt of (phenylsulfonyl)nitromethane to give the products of double alkylation, the isoxazoline *N*-oxides (eq 13). Table 3 summarizes the results.[115−117]

Table 3. Variation of Ligand and Leaving Group in Desymmetrization of *cis*-3,5-Cyclopentendiol Esters

entry	substrate	ligand	% yield	% ee	major isoxazoline *N*-oxide
1	**56a**	(+)-DIOP	77	6	**57**
2	**56b**	(+)-DIOP	55	6	**57**
3	**56a**	(−)-DIOP	76	6	**58**
4	**56b**	(−)-DIPAMP	nd	6	**58**
5	**56b**	(*S*,*R*)-BPPFA	50	37	**58**
6	**56c**	(*S*,*R*)-BPPFA	57	11	**57**
7	**56b**	S-BINAPO	15	23	**58**
8	**56c**	S-BINAPO	12	32	**58**
9	**56c**	**21b**	83	6	**58**
10	**56c**	**54f**	76	62	**58**
11	**56c**	**54g**	86	64	**58**
12	**56c**	**54b**	95	74	**57**
13	**56c**	**54d**	94	95	**57**
14	**56a**	**54e**	75	87	**57**
15	**56c**	**54e**	93	96	**57**
16	**56d**	**54e**	97	96	**57**

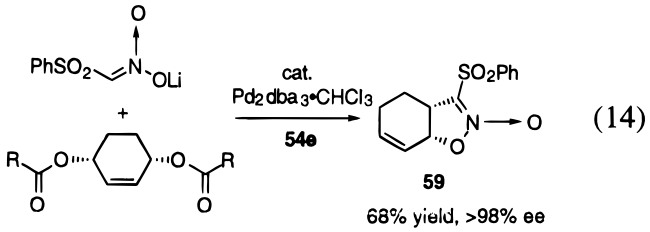


(13)

A broad array of ligands including DIOP, DIPAMP, BPPFA (**16a**), BINAPO (**21a**) and its silylated analog **21b** give rather poor selectivities. With BPPFA, a dramatic effect is observed. Changing the leaving group from pivalate to diphenylacetate inverted the sense of chirality (Table 3, entries 5 and 6). BINAPO exhibits a much less dramatic effect, a slight enhancement of ee as the steric bulk of the leaving group increases (entries 7 and 8).

The best enantioselectivities derive from catalysts generated with the DPPBA ligands (Table 3, entries 10−16). Among the DPPBA ligands, the trends mirror those observed previously—i.e., amide DPPBA ligands (entries 13−16) give higher enantioselectivities than ester DPPBA ligands (entries 10−12). Acetate as a leaving group gives a slightly lower ee (entry 14) than either diphenylacetate (entry 15) or benzoate (entry 16) which give the same selectivity.

The six-membered ring substrate gives the corresponding isoxazoline *N*-oxide **59** enantiomerically pure (eq 14). In the case of the seven-membered ring, cyclization did not occur. The sulfonyl group of **60** is easily reductively cleaved to provide the nitromethyl compound **61** of high enantiopurity.



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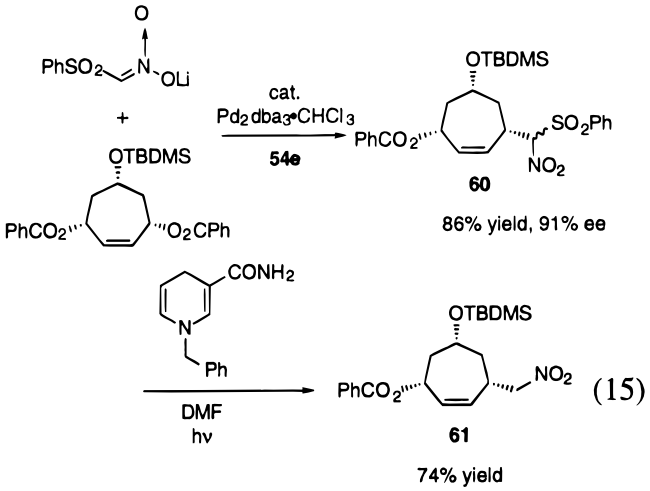
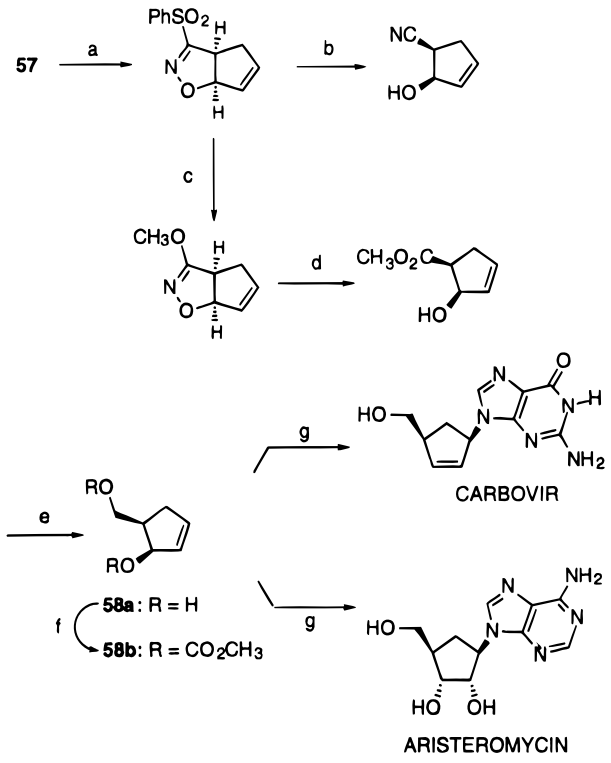


(15)

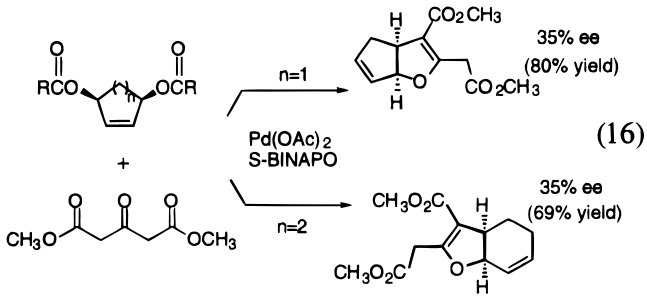
Scheme 10 illustrates the synthetic utility of the enantiopure isoxazoline *N*-oxides. The sequence constitutes the equivalent of a *cis*-hydroxycyanation or a *cis*-hydroxy methoxycarbonylation. Reduction of the latter followed by acylation provides **58b** which serves as a building block for the synthesis of the carbanucleosides aristeromycin and carbovir. This pivotal building block is available enantiomerically pure in 60% overall yield from dibenzoate **56d**. By using a second palladium-catalyzed reaction, the appropriate nucleic acid base is added with complete control of regio- and diastereoselectivity as illustrated by the facile conversion of **58** to both the antiviral agents carbovir and aristeromycin.

Scheme 10. Synthetic Conversions of Isoxazoline *N*-Oxides



a) $SnCl_2 \cdot 2H_2O$, CH_3CN, 94%. b) $Mo(CO)_6$, CH_3CN, H_2O, 94%. c) K_2CO_3, CH_3OH, 96%. d) ($Mo(CO)_6$, CH_3CN, CH_3OH, H_2O, $B(OH)_3$, 84%. e) LAH, ether, 95%. f) n-C_4H_9Li, THF, $ClCO_2CH_3$, 98%. g) See ref. 76

A similar disubstitution with dimethyl 3-ketoglutarate using BINAPO gives only modest enantioselectivities (eq 16).[118] Surprisingly, opposite enantiomers dominate by changing from the five- to the six-membered ring substrate—a result not observed with the DPPBA and DPPA platforms. BINAP (**20**), DIOP (**36**), and BPPFA (**16a**) prove to be very poor in this reaction.



(16)

The direct substitution with 2-methylcyclohexane-1,3-dione illustrates directly the difference in chiral recognition exhibited by complexes derived from diesters (Table 4, entries 1−3) vs diamides (entries 4−8) (Scheme 11). For example, ligands **54j** and **54f** differ only in that the former is a diester and the latter a diamide (in addition to being enantiomeric to each other), everything else being the same. However, the ee increased from 52% to 91%.[119] The enantioselectivity with respect to the diamides is independent of the chiral scaffold to a first approximation.

Scheme 11. Asymmetric Induction in Reaction of *cis*-3,5-Bis(benzoyloxy)cyclopentene with Carbon Nucleophile

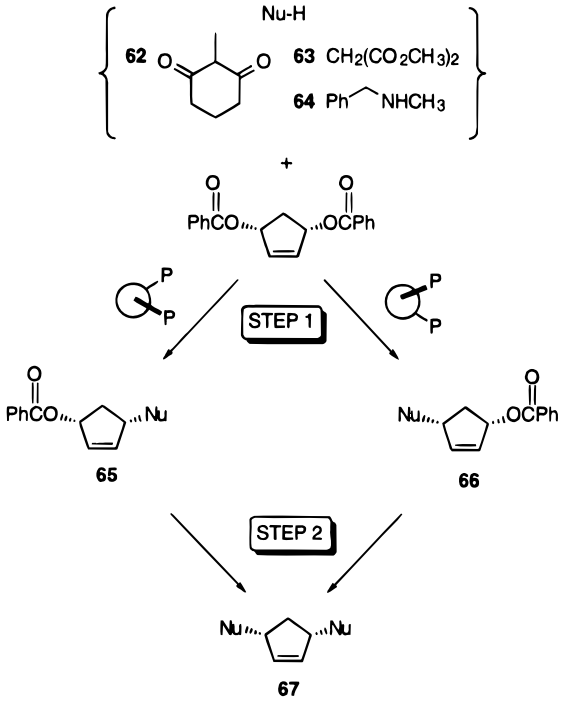


Table 4. Variation of Enantiomeric Excess in Reaction of *cis*-3,5-Bis(benzoyloxy)cyclopentene and Carbon Nucleophiles

entry	ligand	NuH	base (equiv)[a]	major enantiomer	% yield	% ee
1	**54l**	**62**	DBU (1.0)	**66**	51	54
2	**54j**	**62**	DBU (1.0)	**66**	73	52
3	**54j**	**62**	DBU (1.2)	**66**	61	60
4	**54d**	**62**	LHMDS[b] (1.0)	**65**	86	91
5	**54e**	**62**	DBU (1.0)	**65**	95	91
6	**54e**	**62**	DBU (1.2)	**65**	84	98
7	**54f**	**62**	DBU (1.0)	**65**	76	91
8	**54g**	**62**	DBU (1.0)	**65**	70	89
9	**54i**	**63**	NaH (1.0)	**66**	40	64
10	**54j**	**63**	NaH (1.0)	**66**	64	68
11	**54d**	**63**	NaH (1.0)	**65**	68	92
12	**54e**	**63**	NaH (1.0)	**65**	80	93
13	**21a**	**63**	NaH	**66**	38	57

[a] DBU = 1,8-diazabicyclo[5.4.0]undecane. [b] LHMDS = lithium hexamethyldisilazane.

Like any catalytic reaction, biological or abiological, the ee may be a function of the percent conversion. Scheme 11 illustrates this phenomenon. In the present case, enantiomer **65** derives from use of a counterclockwise ligand; the minor product **66** in such reactions constitutes an instance of a "mismatch" between the ligand and the substrate for step 1. On the other hand, for step 2, a second alkylation, the counterclockwise ligand and **66** constitute a matched pair. Thus, with such a ligand, **66** should react faster than **65** to give the dialkylated product **67** resulting in an increased ee for the remaining monoalkylated product at the expense of some yield. Indeed, with **54e**, the ee increases to 98% (Table 4, entry 6) from 91% (Table 4, entry 5) with a diminishment of yield of monoalkylated product from 95% to 84% by using 1.2 equiv of nucleophile.[102]

Since the enantiodiscriminating step involves only the ionization step, it should be independent of

Table 5. Variation of Enantiomeric Excess in Reaction of *cis*-3,5-Bis(benzoyloxy)cyclopentene with Methylbenzylamine[a,b]

entry	ligand	major enantiomer	% yield	% ee
1	**54i**	**66**	61	74
2	**54j**	**66**	80	79
3	**54d**	**66**	71	95
4	**54e**	**65**	85	78
5	**54f**	**65**	80	91
6	**54g**	**65**	95	91

[a] Reactions performed at 0 °C in THF. [b] See ref 119.

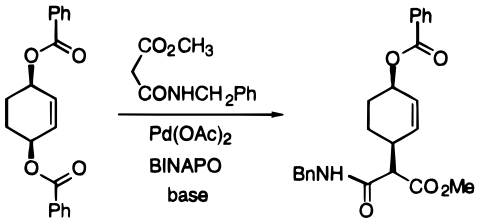
Table 6. Dependence of Desymmetrization on Generation of Nucleophile (Eq 17)[a,b]

entry	base (equiv)	additive	% yield	% ee
1	NaH (2.7)		25	2
2	LDA (2.7)	$(C_2H_5)_3SiOTf$	62	26
3	LDA (2.7)	TBDMSOTf	54	26
4	LDA (1.3)		53	49
5[b,c]	LDA (1.1)		66	41

[a] All reactions were performed in acetonitrile at 0 °C unless otherwise stated. [b] See ref 118. [c] Reaction performed at −20 °C.

nucleophile to a first approximation. Thus, as expected, the correlation of the ee with ligand for malonate as nucleophile (Scheme 11 and Table 4, entries 9−12) parallels the observations with 2-methylcyclohexane-1,3-dione.[119] In contrast to the excellent results with the DPPBA ligands, BINAPO gives only a moderate enantioselectivity in rather low yield. The use of benzylmethylamine (**64**) as a nucleophile gives similar results (Scheme 11 and Table 5). These reactions are always performed in the presence of excess triethylamine, and dialkylation is not observed unless the reactions are performed for extended periods of times at higher temperatures. Two points are noteworthy. The ee's with DPPBA diester ligands are higher with nitrogen nucleophiles than with carbon nucleophiles (cf. Table 5, entries 1 and 2 to Table 4, entries 1, 2, 9, and 10). A difference between diamide ligand 54e and the other amide ligands is observed which is not the normal case. Since amines may coordinate to palladium, their involvement in the enantiodiscriminating step may account for these observations.

With BINAPO as the asymmetric ligand, the yield and enantioselectivity are dependent upon the manner in which the nucleophile is generated (Table 6 and eq 17).[118] Switching to dimethyl malonate with

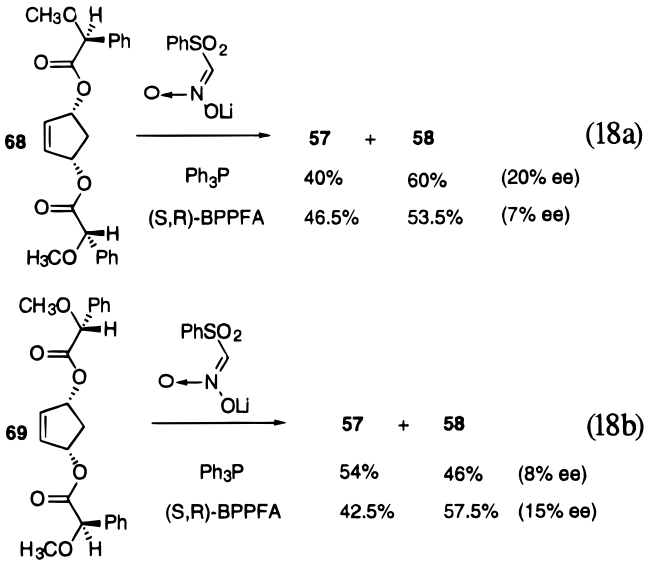


(17)

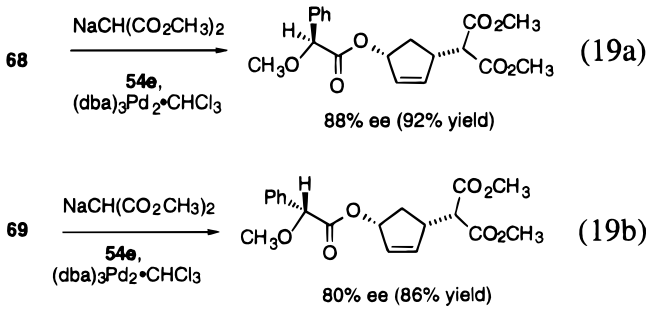
sodium hydride as base gives a 25% yield but a 47% ee under the same reaction conditions that gives only a 2% ee in the above. The source of such dependence is obscure at the moment.

Since the leaving group plays some, albeit modest, role in determining the chiral discrimination, asymmetric induction may result from the use of a chiral

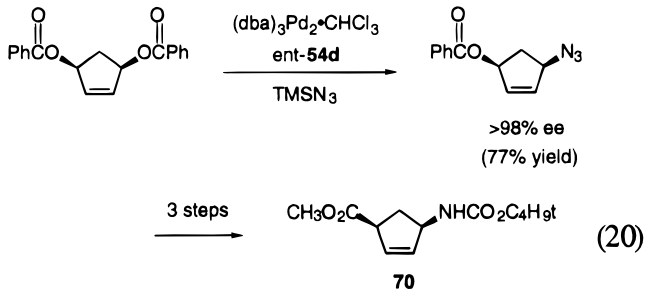
ester as the leaving group. Equations 18a and 18b reveal that with BPPFA there is a matched and mismatched pair but still rather low enantioselectivities are observed. On the other hand, the DPPBA



ligands largely override the chirality of the leaving group as shown in eqs 19a and 19b.[117]

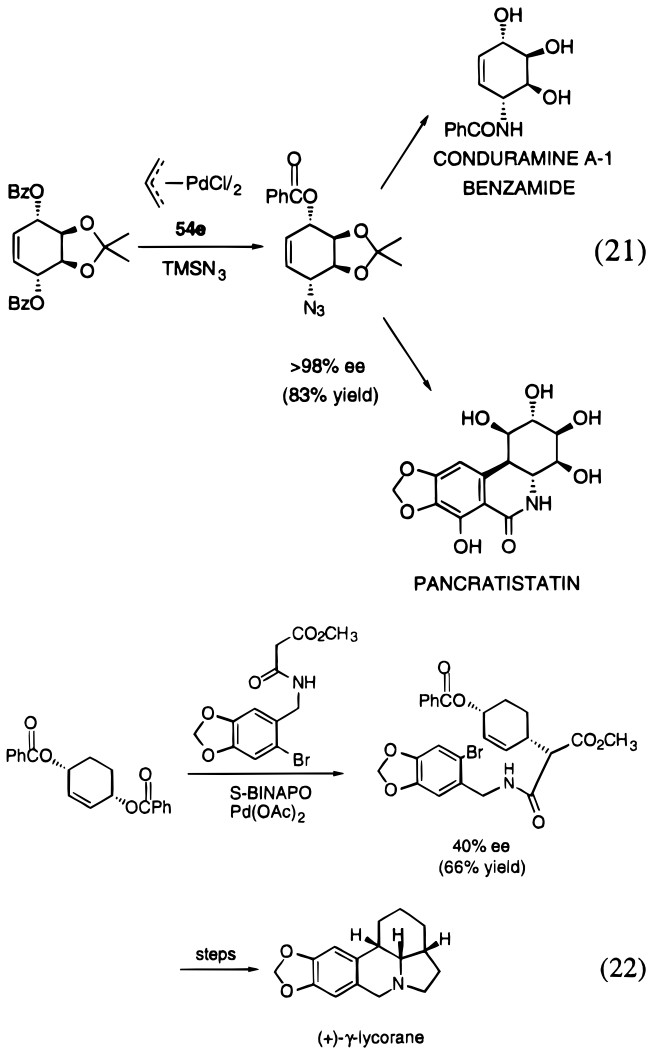


Several applications take advantage of this protocol. Azide serves as an excellent nucleophile in such processes (eq 20).[120] Only three steps transform the



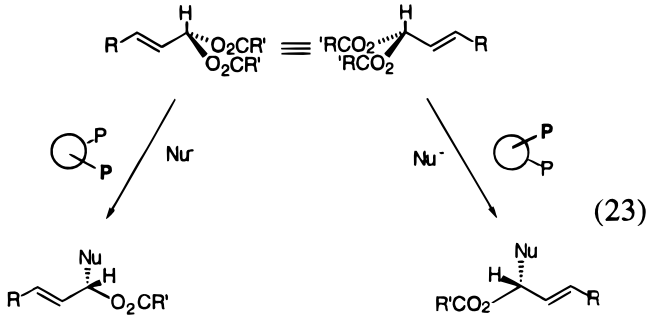
resultant product into the cyclopentene **70**, which is a common intermediate to carbanucleosides, the antiviral agent amidinomycin, and the coronary vasodilator C-NECA. Applying this methodology to a six-membered ring substrate creates a key building block for the synthesis of the conduramines and, most significantly, the anticancer agent pancratistatin (eq 21).[121]

Using BINAPO as the ligand, the alkylation shown in eq 22 gives the desired product in 66% yield and 40% ee which ultimately was transformed into the alkaloid (+)-γ-lycorane.[118]



4. Type "a" Asymmetric Induction—Geminal Dicarboxylate

Geminal dicarboxylates, easily available from aldehydes by addition of acid anhydrides catalyzed by Lewis acids, convert the problem of asymmetric addition to the enantiotopic faces of an aldehyde into asymmetric ionization of enantiopic leaving group.[122]



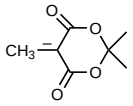
Using the DPPBA-based ligands and the normal structural preferences of π-allylmetal complexes, the substitutions depicted in eq 23 are predicted and observed. Of the various ligands, the simple 1,2-diaminocyclohexane-based ligand **54e** gives the best results. Table 7 summarizes a number of examples.

B. Desymmetrization of Meso-π-Allyl Complexes

1. Alkylation of 1,3-Diarylallyl Substrates with Carbon Nucleophiles

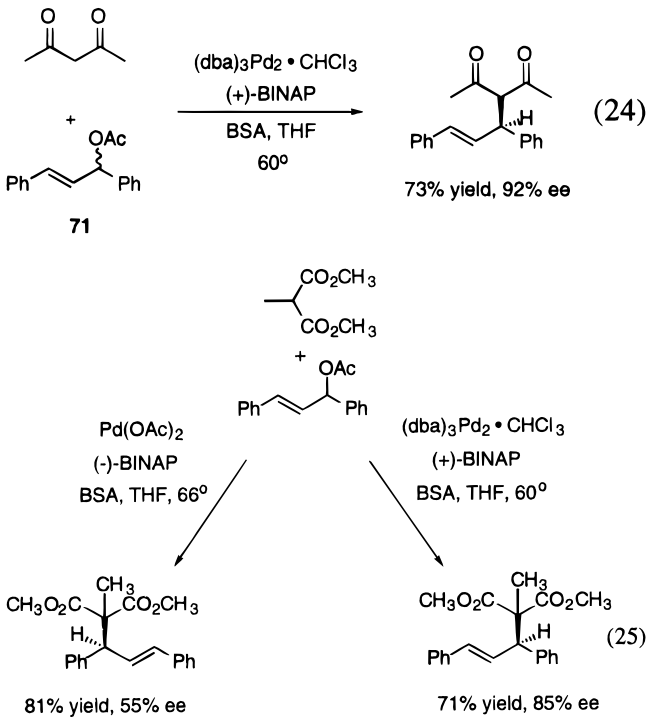
The 1,3-diphenylallyl system was introduced as a test substrate to contrast with the 1,1,3-triphenylallyl

Table 7. Desymmetrization of *gem*-Dicarboxylates with Ligand Derived from (*R*,*R*)-1,2-Diaminocyclohexane[a] (54e)

entry	R	R′	NaNu	% yield	% ee
1	Ph	CH_3	$CH_3\bar{C}(CO_2CH_3)_2$	92	>95
2	Ph	CH_3	$PhCH_2\bar{C}(CO_2CH_3)_2$	75	>95
3	*i*-C_3H_7	CH_3	$CH_3\bar{C}(CO_2CH_3)_2$	75	95
4	*i*-C_3H_7	CH_3		58	90
5	$TBDPSOCH_2$	CH_3	$CH_3\bar{C}(CO_2CH_3)_2$	76	89
6[b]	$TBDPSOCH_2$	CH_3	$CH_3\bar{C}(CO_2CH_3)_2$	85	91
7	$TBDPSOCH_2$	CH_3	$CH_3\bar{C}(CO_2CH_3)_2$	76	87
8	CH_3	CH_3	$CH_3\bar{C}(CO_2CH_3)_2$	99[c]	92
9	CH_3	C_2H_5	$CH_3\bar{C}(CO_2CH_3)_2$	99[d]	92
10	CH_3	CH_3	$CH_3\bar{C}(SO_2Ph)_2$	99	67

[a] All reactions were run at ambient temperature unless otherwise noted. [b] This reaction was performed at 0 °C. [c] A 2.9:1 ratio of regioisomers was obtained with the major one depicted in eq 25. [d] The (*S*,*S*) ligand was employed therefore producing the mirror image product. A 5.5:1 ratio of regioisomers was obtained with the major one depicted in eq 23.

system in order to probe the importance of different mechanisms for asymmetric induction.[40] Early results with BINAP and BINAPO were encouraging (eq 24). Subsequently, this substrate has become the "standard" to compare different chiral ligands. The sensitivity of this system to the reaction conditions becomes evident from the significant difference in ee which is observed when different Pd(0) sources are used (eq 25).[123]



Since the nucleophile is directly involved in the enantiodiscriminating step, its structure is expected to affect the ee. In terms of structure, both the constitution (i.e., malonate, 1,3-diketone, disulfone, etc.) and the nature of the ion pair play roles. Thus, the ee shows a dependence on how the nucleophile is generated. While the sodium salts are frequently employed, the potential for aggregate formation obfuscates the true nature of the nucleophile. For example, alkylation of **71** with dimethyl sodiomalonate using ligand **24** gives the alkylation product in 67% ee in THF and 78% ee in acetonitrile; but using the sodium salt with 15-crown-5 in acetonitrile increases it to 95%.[69] Thus, changing the nature of the ion pair has a significant effect on ee. In many cases, the best ee's are obtained by use of *N*,*O*-bis-(trimethylsilyl)acetamide (BSA), sometimes in the presence of added acetate ion.[40] Reactions performed with ligand **32** reveal an effect of halide ion under these conditions with the ee increasing from 51% with iodide and 67% with bromide to 83% with chloride.[77]

Table 8 summarizes the enantioselectivities obtained in the alkylation of the diphenylallyl system with stabilized nucleophiles using various different ligand designs (eq 26). The enantioselectivities are the best reported in the reference given (whether optimized or not).

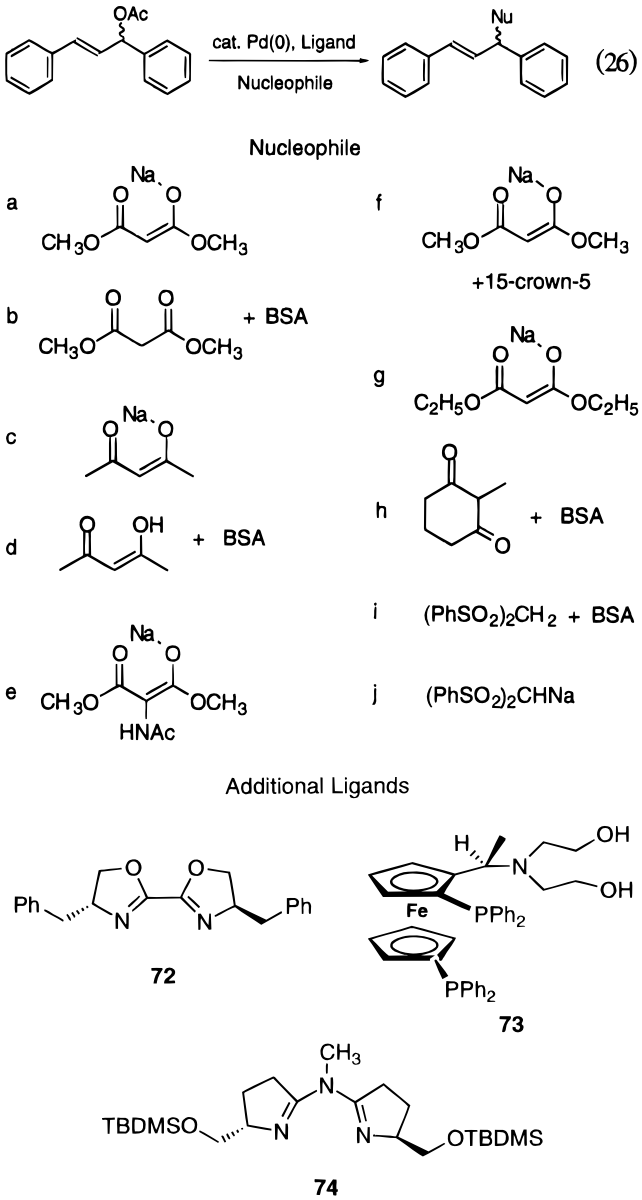


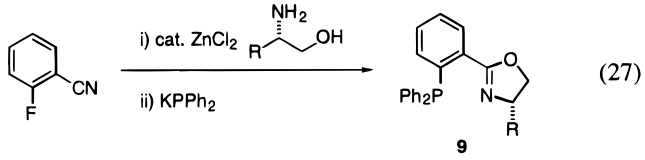
Table 8 reveals that a wide variety of bidentate ligands ranging from bisphosphines to aminophosphines to bisamines are capable of inducing high ee in this case. One notable feature of the diphenylallyl

Table 8. Allylic Alkylation of 1,3-Diphenylprop-2-enyl Acetate with Carbon Nucleophiles

entry	ligand	Nu[a]	Pd source	% yield	% ee	ref(s)
1	**24**	a[a−d]	$[C_3H_5Pd]BF_4$	nd	<79	69
2	**22**	a	$[Pd(OAc)_2]$	95	96	67
3	**15**	a[b]	$[C_3H_5Pd]PF_6$	81	95	62,125
4	**34**	a	$[C_3H_5PdCl]_2$	86	90	126
5	isosparteine	a[b]	$[C_3H_5Pd]PF_6$	87	82	62,125
6	**11**	a	$[C_3H_5PdCl]_2$	89	81	59
7	**29**	a	$[(dba)_3{\cdot}CHCl]_3$	60	49	127
8	**16b**	a	$[C_3H_5PdCl]_2$	40	92	128
9	**16c**	a	$[C_3H_5PdCl]_2$	85	96	63
10	(*S*)-(−)-BINAP	a	$[C_3H_5PdCl]_2$	80	34	129
11	PROLIPHOS	a[c]	$[C_3H_5Pd]BF_4$	99	30	87,130
12	**12**	b	$[C_3H_5PdCl]_2$	89	99	48
13	**9b**	b[b]	$[C_3H_5PdCl]_2$	99	99	54,55
14	**9a**	b[b]	$[C_3H_5PdCl]_2$	98	98	54,55,58
15	**7**	b	$[C_3H_5PdCl]_2$	97	97	52
16	**10a**	b[c]	$[C_3H_5PdCl]_2$	92	96	57,131
17	**23**	b[c]	$[C_3H_5PdCl]_2$	96	96	68
18	**74**	b[c]	$[C_3H_5PdCl]_2$	97	95	124
19	**14**	b	$[(dba)_2Pd]$	83	95	61
20	**10e**	b	$[C_3H_5PdCl]_2$	50−84	95	58
21	**17**	b[c]	$[C_3H_5PdOTf]$	nd	93	64,94
22	**10b**	b[c]	$[C_3H_5PdCl]_2$	100	92	131
23	**26a**	b[c]	$[C_3H_5PdCl]_2$	56	92	71
24	**13**	b[d]	$[C_3H_5PdCl]_2$	98	91	60
25	(*S*)-(−)-BINAP(*ent*-**20**)	b[c]	$[C_3H_5PdCl]_2$	85	90	69
26	**6b**	b[c]	$[C_3H_5PdCl]_2$	97	88	52
27	**8**	b[c]	$[C_3H_5PdCl]_2$	85	85	54
28	**32**	b[c]	$[C_3H_5Pd]PF_6$	70	84	77
29	**21a**	b	$[(dba)_3Pd_2{\cdot}CHCl]_3$	88	79	123
30	**24**	b[c]	$[C_3H_5Pd]BF_4$	nd	79	69
31	**10c**	b[c]	$[C_3H_5PdCl]_2$	98	78	58
32	**72**	a	$[C_3H_5PdCl]_2$	86	77	52
33	**26b**	b[c]	$[C_3H_5PdCl]_2$	86	60	71
34	**73b**	c	$[C_3H_5PdCl]_2$	86	81	128
35	**16b**	c	$[C_3H_5PdCl]_2$	97	90	128
36	**34**	a	$[C_3H_5Pd]ClO_4$	96	22	42
37	**36**	c	$[C_3H_5PdCl]_2$	88	0	128
38	**9b**	d[c]	$[C_3H_5PdCl]_2$	98	97	54
39	(*S*)-(−)-BINAP(*ent*-**20**)	d	$[(dba)_3Pd_2{\cdot}CHCl_3]$	73	92	123
40	(*S*)-(−)-BINAP	e	$[C_3H_5PdCl]_2$	92	95	129
41	**34**	e	$[C_3H_5PdCl]_2$	98	91	129
42	(*S*,*R*)-BPPFA	e	$[C_3H_5PdCl]_2$	79	52	129
43	**24**	f[e]	$[C_3H_5Pd]BF_4$	nd	90	69
44	**9b**	f	$[C_3H_5PdCl]_2$	98	97	54
45	**30**	g	$[Pd(OAc)_2]$	68	85	75
46	(*S*)-(−)-BINAP	h	$[(dba)_3Pd_2{\cdot}CHCl_3]$	46	66	123
47	**9a**	i	$[C_3H_5PdCl]_2$	87	88	57
48	**9a**	j[b]	$[C_3H_5PdCl]_2$	78	93	57

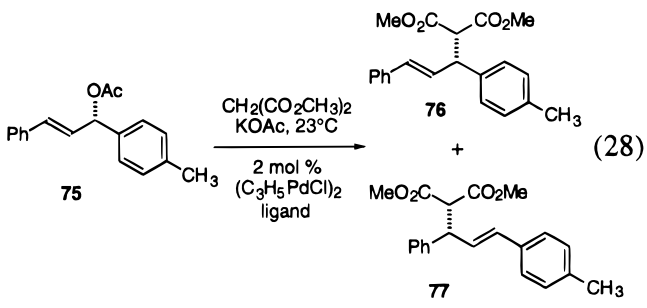
[a] In THF (for a−j, see eq 26). [b] In DMF. [c] In CH_2Cl_2. [d] In CH_3CN. [e] In CD_2Cl_2.

system is the prominence of ligands which lack C_2 symmetry.[62,77] The enantiomeric excess obtained for ligand **32** (entry 28) was more than twice as high as either of the closely related two C_2 symmetrical isomers.[77] The most extensive and general advances for acyclic substrates bearing bulky substituents have come with the development and study of (phosphinoaryl)oxazoline ligands (entries 13, 14, and 31).[54,56] These ligands give diarylallyl adducts with high enantioselectivities in excellent yields. A wide range of (phosphinoaryl)oxazolines may be easily prepared in two steps from readily available chiral amino alcohols (eq 27). The highest enantioselectivities seem to come from **9a** (R = *i*-Pr) and **9c** (R = *t*-Bu).



(27)

Oxazoline ligands (entries 13, 14, and 26) do not exchange enantiofaces during the reaction. Alkylation of optically pure (*R*)-**75** with dimethyl malonate and BSA using triphenylphosphine afforded only the regioisomers (*R*)-**76** and (*S*)-**77** in close to a 1:1 ratio with each in enantiomerically pure form (eq 28).[90]



(28)

Ligands **6b**, (+)-*ent*-**9b**, and **9b** afforded (*R*)-**76** and (*S*)-**77** in 93:7, 99:1, and 1:99 ratios, respectively.

Table 9. Asymmetric Synthesis of 1,3-Diphenylallylamines[a]

entry	ligand	X	Nu	% yield	% ee	ref
1	**9c**	OAc	$TsNH^- Na^+$	96	97	134
2	**9c**	OAc	$NaPhCONNH_2$	95	97	134
3	**16b**	OCO_2Et	$BnNH_2$	93	97	89
4	**16b**	OCO_2Et	Veratrylamine	87	95	89
5	**9b**	OCO_2Me	$BnNH_2$	98	94	134
6	**9b**	OAc	$Na(BOC)_2N$	98	86	134
7	**29**	OAc	$BnNH_2$	86	66	74

[a] $[C_3H_5PdCl]_2$ was used as the catalyst precursor.

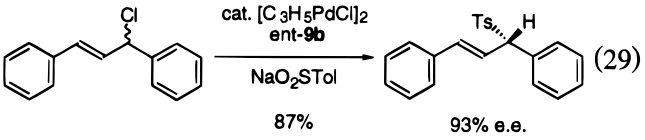
Again, these regioisomers were enantiomerically pure. This strongly suggests a double inversion mechanism without enantioface exchange. This example illustrates the ability of the ligand to dictate regiochemistry, albeit in a relatively unbiased case. The prospect for such chiral ligands to control regioselectivity is potentially an exciting solution to a long-standing issue in allylic alkylation.

In contrast to the results with oxazoline ligands, isolation of starting material from the reaction in entry 43 (ligand **24**) after 50% conversion showed that the remaining diphenylallyl acetate was racemic.[69] Either no enantiodifferentiation is occurring in the ionization, or a racemization of starting material is occurring faster than the alkylation reaction.

The many early attempts to use ligands such as BINAP and DIOP in these reactions met with disappointing results. However, entries 10, 25, 38, 39, 40, and 46 demonstrate the importance of reaction conditions in achieving good enantioselectivities. In this case, (*S*)-BINAP can give enantiomeric excesses as low as 34% with dimethyl sodiomalonate in THF or as high as 90% with dimethyl malonate/BSA in dichloromethane. The use of sodiomalonates does not preclude good ee's; if the sodium salt of 2-acetamidomalonate is used, then BINAP provides the desired alkylation product with 94% ee.[129] The factors responsible for the good enantioselectivities available with 2-acetamidomalonate may extend beyond simple steric interactions since dimethyl malonate and 2-acetamidomalonate afford products of opposite configuration. The lesson here is a simple one. Reaction conditions can and should be optimized for each new ligand/substrate/nucleophile combination in order to assess ligand efficacy.

2. Alkylation of 1,3-Diarylallyl Substrates with Heteroatom Nucleophiles

A variety of nitrogen nucleophiles also give high ee's in the diphenyl allyl system (eq 26 and Table 9) with both the (phosphinoaryl)oxazoline and ferrocenyl families of ligands. These results extend to a sulfinate nucleophile wherein the resultant sulfone of 93% ee is produced (eq 29).[135]



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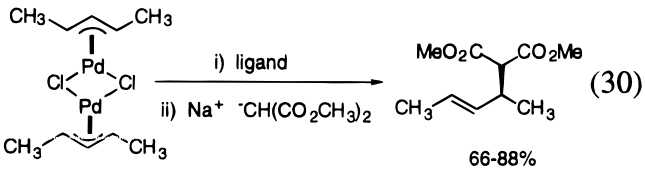
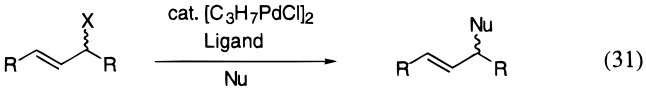
3. Alkylation of Acyclic 1,3-Dialkylallyl Substrates

Asymmetric induction in allylic alkylations were first explored in stoichiometric reactions with (1,3-dimethylallyl)palladium chloride dimer but with rather low enantioselectivities: (−)-sparteine, (+)-DIOP, and (+)-*O*-anisylcyclohexylmethylphosphine give ee's of 20%, 22%, and 24% respectively (eq 30).[37]



(30)

The corresponding catalytic reaction (eq 31, R = CH_3) with the phosphinooxazoline ligand increases that ee significantly (see Table 10 entries 4−9) but does not yet approach a magnitude that is synthetically acceptable. The recently tailored invertomer amide



(31)

ligand **5** however does give a further boost in ee to 74% with dimethyl malonate. Using dimethyl methylmalonate with this last ligand, a 93% yield of the

Table 10. Asymmetric Alkylation of 1,3-Dialkylallyl Substrates

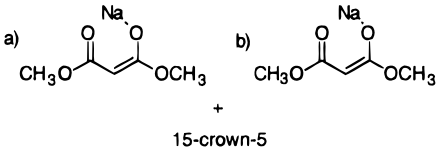
entry	ligand	R	X	Nu	% yield	% ee	ref
1	**9c**	CH_3	OAc	$NaN(BOC)_2$	44	75	134
2	**9c**	CH_3	OAc	$BnNH_2$	87	57	134
3	**9c**	CH_3	OAc	NaNHTs	61	66	134
4	**9c**	CH_3	OAc	CH_2E_2[a]/BSA	96	71	54
5	**9a**	CH_3	OAc	CH_2E_2[a]/NaH	52	62	57
6	**15**	CH_3	OAc	CH_2E_2[a]/NaH	13	5	125
7	isosparteine	CH_3	OAc	CH_2E_2[a]/NaH	83	69	125
8	**8**	CH_3	OAc	CH_2E_2[a]/BSA	62	36	54
9	**5**	CH_3	OAc	CH_2E_2[a]/NaH	90	74	50
10	**9b**	CH_3	OAc	$PhSO_2Na$	83	55	135
11	**9b**	CH_3	Cl	$PhSO_2Na$	55	52	135
12	**5**	CH_3	OAc	CH_3CHE_2[a]/NaH	93	87	50
13	**9c**	*n*-Pr	OAc	CH_2E_2[a]/BSA	96	69	54
14	**9c**	*n*-Pr	OAc	NaNHTs	90	66	134
15	**9c**	*n*-Pr	OAc	$NaN(BOC)_2$	60	59	134
16	**16b**	*i*-Pr	OCO_2Et	$BnNH_2$	88	97	89
17	**9c**	*i*-Pr	$OPO(OEt)_2$	NaNHTs	57	90	134
18	**9c**	*i*-Pr	$OPO(OEt)_2$	$NaN(BOC)_2$	29	97	134
19	**9c**	*i*-Pr	OAc	CH_2E_2[a]/BSA	88	96	54

[a] E = CO_2CH_3.

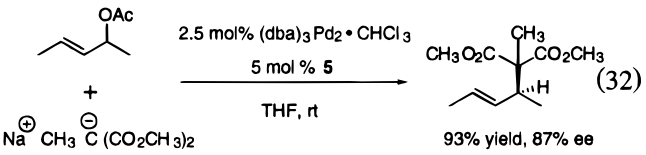
Table 11. Alkylation of Cyclohexenyl Substrates with Carbon Nucleophiles

entry	ligand	R	X	Nu[c]	% yield	% ee	ref(s)
1[a]	**4**	H	OAc	a	86	96	103
2	**16c**	CO_2CH_3	OAc	a	95	72	128
3[b]	**24**	H	OAc	b	68	67	69
4	(−)-α-iso-sparteine	H	OAc	a	63	62	62
5	**10d**	H	OAc	a	81	45	104
6	**10c**	H	OAc	a	nd	>50	58
7	**15**	H	OAc	a	82	50	62
8	**27**	H	OAc	a	74	10	72
9	(−)-DIOP	H	OAc	a	88	6	72,137
10	(−)-DIOP	CO_2CH_3	OAc	a	88	6	72,127
11	**9a**	H	OAc	a	nd	low	58

[a] In the presence of tetrahexylammonium bromide in methylene chloride. [b] In acetonitrile. [c] Nucleophiles are as follows:



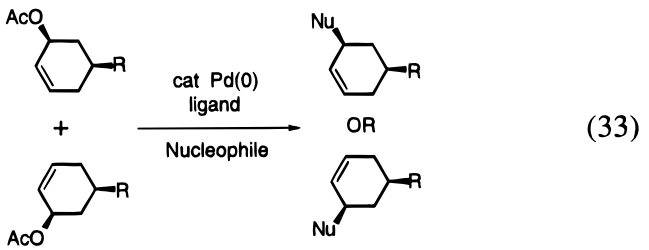
alkylation product of 87% ee is obtained (eq 32).[50] An



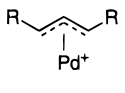
allylic substrate possessing substituents of increased steric bulk by introducing branched alkyl groups (Table 10, entries 16−19) gives excellent ee's.

4. Alkylation of Cyclic Allylic Substrates

Extrapolation from acyclic to small cyclic substrates seemingly would lead to the prediction of enhanced ee due to the greater rigidity of the cyclic framework which removes ambiguities regarding *syn* vs *anti* (π-allyl)palladium intermediates. Thus, at first glance, it is somewhat surprising that the opposite is observed with virtually all the classes of ligands that did well with the 1,3-diphenylallyl system (see eq 33 and Table 11, entries 2−11).



However, structurally, the two types of substrates involve quite different π-allyl complexes, acyclic substrates forming *syn,syn* complexes (e.g., **78**) and cyclic ones forming *anti,anti* ones (e.g., **79**).



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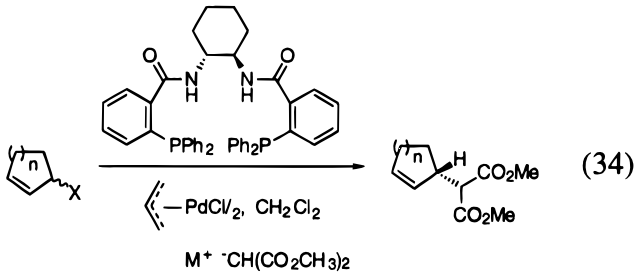
In contradistinction to these results, the DPPBA-based ligand **4** (Table 11, entry 1) gives excellent

Table 12. Dependence of Enantiomeric Excess on Nature of Ion Pair for 3-Acetoxycyclopentene

entry	M^+	solvent	% ee
1	$(CH_3)_4N^+$	THF	42
2	$(C_4H_9)_4N^+$	THF	57
3	$(C_6H_{13})_4N^+$	THF	68
4	$(C_6H_{13})_4N^+$	CH_2Cl_2	>98
5	$(C_8H_{17})_4N^+$	THF	66
6	Li^+	THF	−63[a]
7	Na^+	THF	39
8	K^+	THF	58
9	Cs^+	THF	76
10	Cs^+	CH_2Cl_2	>98

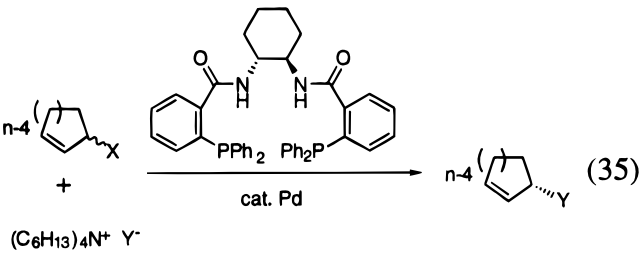
[a] A minus ee signifies the opposite enantiomer from that obtained in all the other cases with the idential ligand.

results in the presence of tetrahexylammonium bromide as counterion in methylene chloride as solvent. When this family of ligands is used, the ee shows little variation in terms of cyclic allylic substrate or anion. Thus, the cyclopentyl and cycloheptyl substrates show results comparable to that of the cyclohexyl substrate giving the alkylation products having ee's of 98% (81% yield) and 93% (99% yield), respectively (eq 34).[103] The effect of the exact nature of the



ion pair as a nucleophile is clearly revealed in the reactions of 3-acetoxycyclopentene (eq 34 and Table 12).[103,105] Two trends are revealed. Increasing the size of the counterion increases the ee within a homologous series—i.e., within the tetraalkylammonium and alkali metal series, respectively. However, clearly ionic radii of the tetraalkylammonium ions are larger than any of the alkali metal ions. Tightening the ion pair by switching from THF to methylene chloride using the better counterions has an equally dramatic effect (Table 12, entries 4 and 10 vs 3 and 9). The odd ball result is lithium (Table 12, entry 6) which, in a sense, continues the trend of the smaller cation giving more of the enantiomeric product to the extent that it is now the major product of the reaction.

Most remarkably, the escort ion, the cation, has a much bigger effect on the ee than the ion that actually bonds to the substrate, the anion. Thus, nitrogen, oxygen, and sulfur nucleophiles all give high ee's as illustrated in eq 35 and Table 13. The



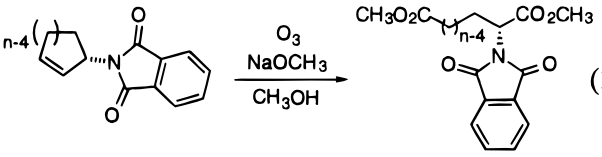
resulting phthalimides are easily cleaved to their

Table 13. Heteroatom Nucleophiles with Cyclic Allyl Substrates

entry	*n*	hetero-atom	X	Y^-	% yield	% ee	ref
1	5	N	OAc	Phth$^-$ [a]	87	94	103
2	6	N	OAc	Phth$^-$ [a]	95	97	103
3	7	N	OAc	Phth$^-$ [a]	84	98	103
4	5	O	OCO_2CH_3	$(CH_3)_3CCO_2^-$	91	97	138
5	6	O	OCO_2CH_3	$(CH_3)_3CCO_2^-$	94	92	138
6	7	O	OCO_2CH_3	$(CH_3)_3CCO_2^-$	98	98	138
7	7	O	OCO_2CH_3	$(CH_3)_3CCO_2^-$	94	94	138
8	7	O	OCO_2CH_3	$(CH_3)_3CCO_2^-$	91	99	138
9	7	O	OCO_2CH_3	$(CH_3)_3CCO_2^-$	85	95	138
10	5	S	OCO_2CH_3	$PhSO_2^-$	99	98	120
11	6	S	OCO_2CH_3	$PhSO_2^-$	95	98	120
12	7	S	OCO_2CH_3	$PhSO_2^-$	95	98	120

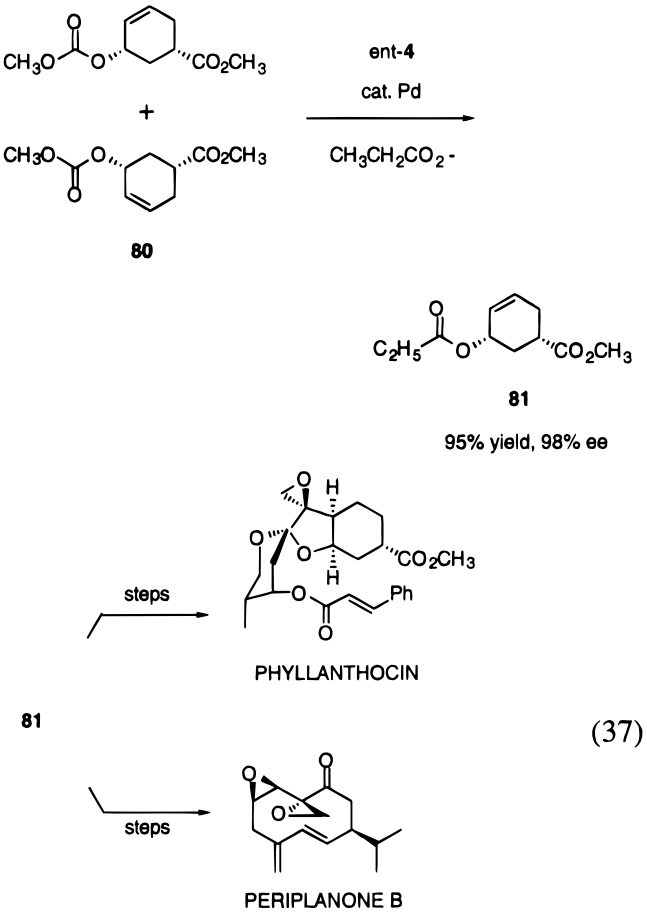
[a] Phthalimide anion.

respective amines. Alternatively, they serve as convenient precursors of unusual amino acids (eq 36).



(36)

While, at first, employment of a bulky oxygen nucleophile like pivalate was believed to be required to avoid racemization of the product, this assumption proved false. In fact, any carboxylate serves equally well. Deracemization of the allylic carbonate **80** gives the enantiomerically pure **81**[138] which has served as an important building block to a number of natural products including the antitumor agent phyllanthocin and the sex excitant of the American cockroach periplanone B (eq 37).[139] The bicyclic indenyl system



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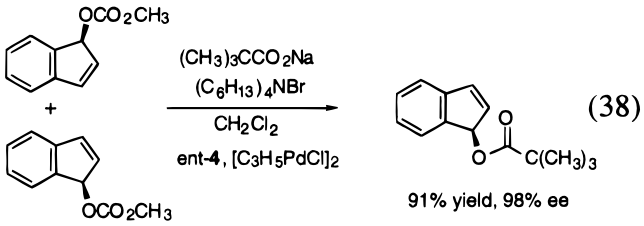
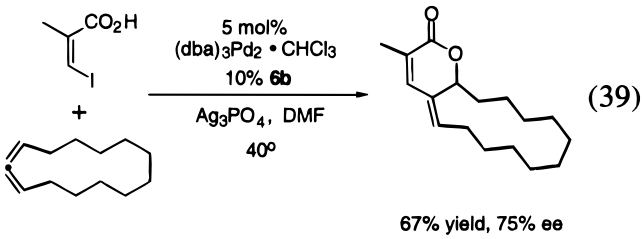
participates equally well (eq 38). Cyclic sulfones,



(38)

which have proven to be valuable building blocks, are also available with high asymmetric induction. For all of the reactions of these cyclic substrates using DPPBA-based ligands (except for the lithium salt), the mnemonic outlined in Figure 11 allows reliable correlation of product stereochemistry with ligand stereochemistry.

Generating the (π-allyl)palladium intermediate by carbametalation of an allene gives reasonable levels of ee only with a bis-oxazoline ligand **6b** as shown in eq 39.

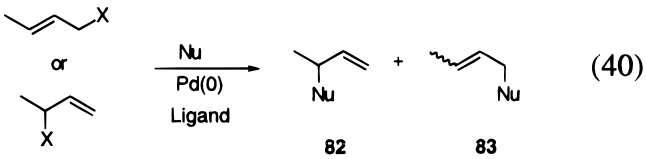


(39)

C. Enantioselection Involving Enantioface Exchange

1. Substrates Which Can Equilibrate via η^3-η^1-η^3 Processes

When both the palladium−olefin and (π-allyl)-palladium complexes lack a plane of symmetry (in the absence of chiral ligands), a mechanism must exist whereby the palladium moiety exchanges between the enantiotopic faces to allow both optical and chemical yields to exceed 50%. Electronic rather than steric effects dominate the regioselectivity of attack on (π-allyl)palladium complexes derived from crotyl systems.[144,145] As a result, the major product, **82**, in palladium-catalyzed allylic alkylations results from attack at the more substituted carbon (eq 40).



(40)

Table 14 reveals that remarkably high ee can be realized even by employing DIOP, a ligand that does not perform particularly well in other asymmetric allylic alkylations. Three types of chiral discrimination may be involved in these reactions—type a, b, or c (Figure 1). The nonidentity of the enantioselectivity starting from the achiral (*E*)-crotyl substrate (Table 14, entry 2) compared to the chiral racemic 3-acetoxy-1-butene (64% ee), although the regioselectivity and yield is the same, suggests that multiple phenomena are indeed involved and that nucleophilic addition is competitive with facial exchange.

The 1,1,3-triphenylallyl system gives excellent enantioselectivities with both CHIRAPHOS (**34**) and

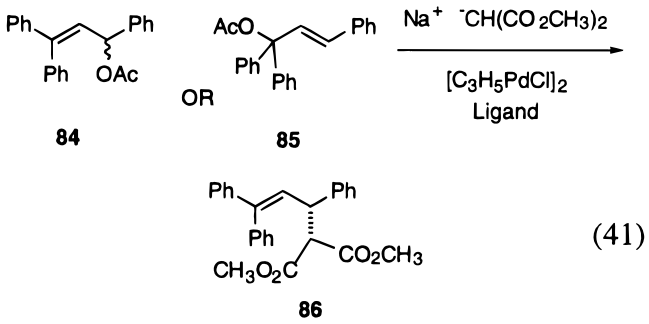
Table 14. Alkylation of Crotyl Systems

entry	L	X	Pd source	NuH	% yield of **82**	% ee	ref
1	(−)-DIOP	Cl	$(Ph_3P)_4Pd$	$TolSO_2^-$	73	88	141
2	**16b**	OAc	$Pd_2dba_3{\cdot}CHCl_3$	$BnNH_2$	84	84	142
3	(−)-BINAP	OAc	$Pd_2dba_3{\cdot}CHCl_3$	$BnNH_2$	36	41	142
4	(−)-**34**	OCO_2Ph	$Pd_2dba_3{\cdot}CHCl_3$	PhO^-	60−90	12	143
5	(−)-DIOP	OAc	$Pd_2dba_3{\cdot}CHCl_3$	$BnNH_2$	65	7	142
6	(−)-**34**	OAc	$Pd_2dba_3{\cdot}CHCl_3$	$BnNH_2$	55	9	142

Table 15. Alkylation of Triphenylallyl Systems

entry	L	substrate	% yield	% ee	ref
1	**9a**	**84**	95	97	146
2	**9a**	**85**	68	96	146
3	**34**	**84**	100	86	42
4	**34**	**85**	100	84	42

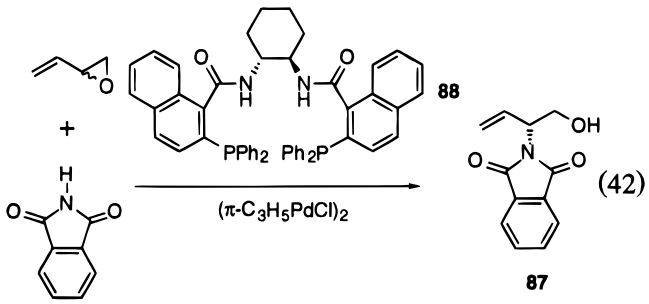
the oxazolinyl ligand **9**[146] (eq 41 and Table 15). While



(41)

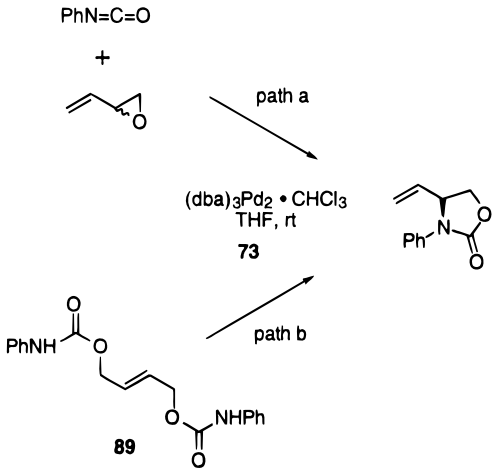
the initial investigations using 5 mol % palladium led to the conclusion that facial exchange occurred via a palladium−palladium displacement mechanism (eq 7),[24] more recent work invoked the η^3-η^1-η^3 mechanism (Scheme 4).[146]

The reaction of butadiene monoepoxide (vinyloxirane) with phthalimide using chiral amides derived from 2-(diphenylphosphino)aryl carboxylic acids give asymmetric alkylations dependent upon the nature of the arene portion of the aryl carboxylic acid. With **4** as the ligand, the ee of the major regioisomer **87** (9:1) is 76%.[105] By restricting the rotational freedom



(42)

of the carboxamide group as in ligand **88**, the ee jumped to >98% as did the regioselectivity favoring **87** to >70:1 ratio over the terminal phthalimide. The reaction of vinyloxirane with phenyl isocyanate using the ferrocenyl ligand **73** gives a related oxazolidinone in only 43% ee (eq 43, path a).[26,147] Starting with an achiral synthon of the epoxide such as **89** causes the ee to increase to 73% (80% yield). These results suggest that, under these conditions, enantioface exchange and cyclization are occurring competitively. This conclusion is reinforced by the observation that the extent of π-facial exchange increases as the reactivity of the isocyanate decreases.[148] The higher ee in the latter case presumably results from a kinetic enantioselection in the initial ionization step superimposed upon the enantiodiscrimination in the cyclization step. (+)-BINAP gives the oxazolidinone in only 27% ee.



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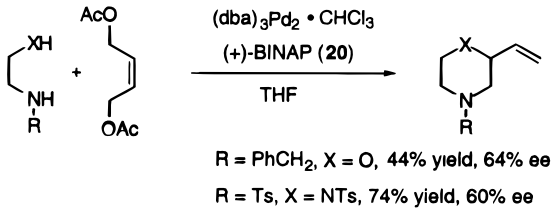
Bimolecular reactions related to the above show more modest enantioselectivities with the same ligands as shown in eqs 44 and 45.[149,150] In the



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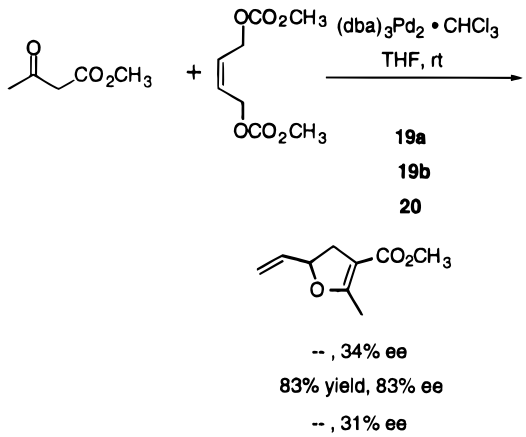
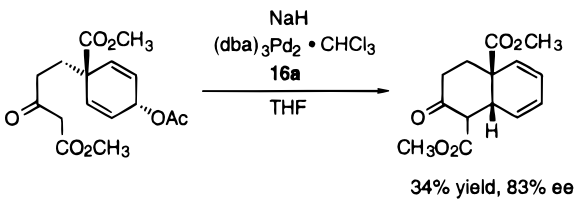


(45)

former case, BINAP gives better enantioselectivities than the ferrocenyl ligand **16b**. However, in the latter case, a ruthenocene analog **19b** of the ferrocene ligand **19a** gives better enantioselectivities than either the ferrocene ligand or BINAP (**20**).[66] The larger P−Pd−P bite angle for **19b** (100.5°) compared to **19a** (98.8°) correlates with this observation.

A related phenomenon involving potentially interconverting diastereomeric (π-allyl)palladium com-

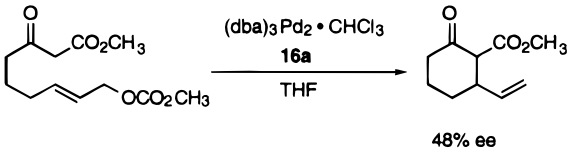
plexes may be involved in the enantiodiscrimination illustrated in eq 46.[151] Unfortunately, the major



(46)

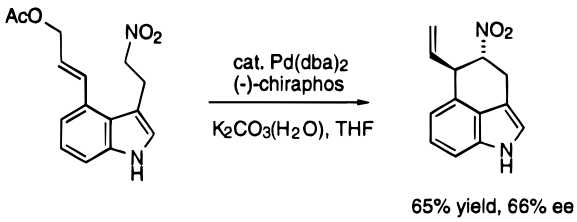
product is the achiral bicyclic[4.2.2] system. Here, too, an ambiguity arises as to whether the enantioselectivity arises from the ionization step, the cyclization step, or a combination of the two.

Simpler cyclizations yield mixed results. Effecting cyclization of a β-keto ester with the ferrocenyl ligand **16a** as the chiral inducing agent (eq 47) gives a rather modest ee.[152,153]



(47)

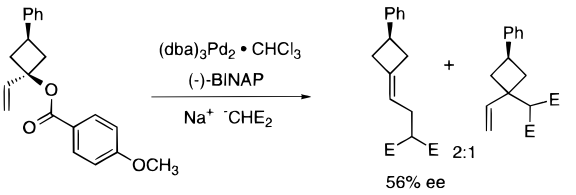
A nitroalkane as a nucleophile functions more effectively with the ee increasing to 66% (eq 48).[154]



(48)

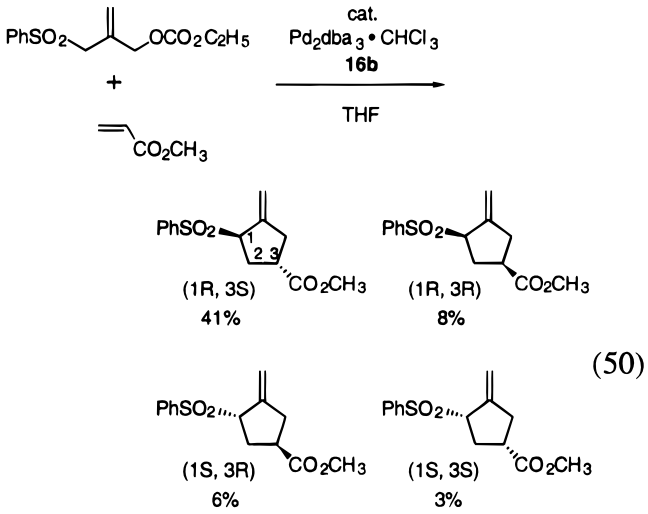
Recent studies suggest that the ee may become as high as 95% using BINAP when palladium acetate rather than $(dba)_3Pd_2 \cdot CHCl_3$ is used as the palladium source[155]—mirroring results found with the 1,3-diphenylallyl system.[123] The difficulty in displacing dba by phosphines may account for this dependency.[156] This latter cyclization serves as an entry to chanoclavins.

Axial chirality may be created in allylic alkylations as previously noted (eq 9). While such reactions may involve enantiodiscrimination in the ionization as suggested earlier, facial equilibration may compete or be faster than alkylation leading to enantiodiscrimination in the alkylation step as has been proposed in the case of eq 49.[157] A more complicated



(49)

situation tries to bring asymmetric induction to palladium-catalyzed cycloadditions involving trimethylenemethane intermediates (eq 50). While results using (+)-DIOP or (*R*)-cyclohexyl-2-anisylmethylphosphine give poor levels of enantioselection,[158] the ferrocenyl ligand **16b** sets the sulfone center with 71% ee and the ester center with 50% ee.[159]

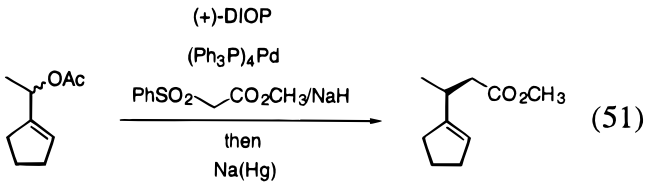


(50)

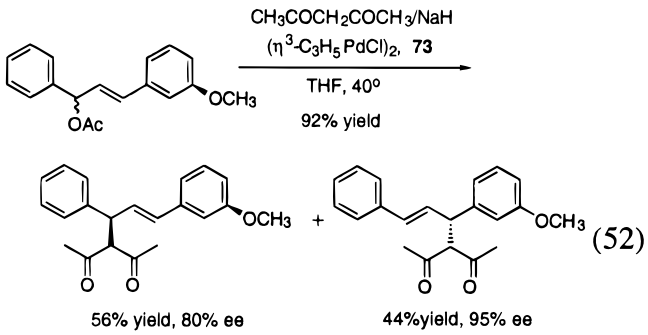
2. Substrates Which Cannot Equilibrate via η^3-η^1-η^3 Processes

If both termini of the allyl system are unsymmetrically substituted, the situation is much more complex as revealed in Figure 13. Using a chiral palladium template and an enantiomerically pure substrate can produce eight different η^3-allylic intermediates that are interconvertible by η^3-η^1-η^3 and allyl rotational (i.e., rotation of allyl plane relative to palladium) processes. The 16 possible trajectories for nucleophilic attack with a stabilized anion may form four different products. If the starting material is racemic, there are 16 different η^3-allyl complexes and enantioface exchange must occur to keep the reaction from being a kinetic resolution.

Although the situation looks intimidating, initial results lead to optimism. One of the first examples of asymmetric induction involved just such a case in which an 84% yield of the product of 46% ee was obtained (eq 51).[22] An acyclic unsymmetrical diaryl substrate gave each of the regioisomers with good to excellent enantioselectivities (eq 52).[128] In this case, the results imply that each enantiomer of the starting material is the precursor of one of the regioisomeric products and that racemization of the starting material or the intermediate is not involved. With aryl alkyl unsymmetrical systems, the results have been less satisfying.[159−161]



(51)



(52)

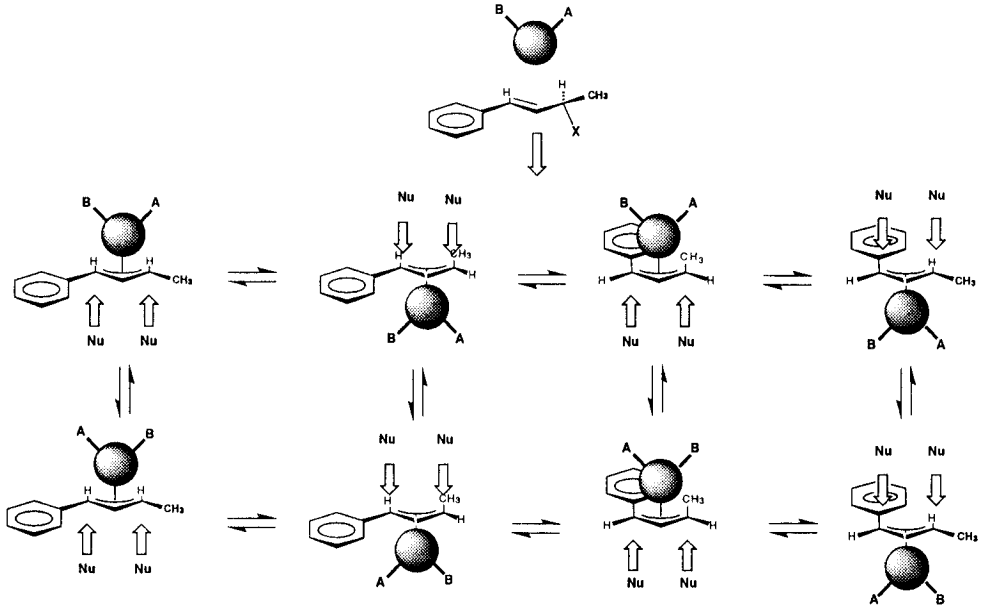
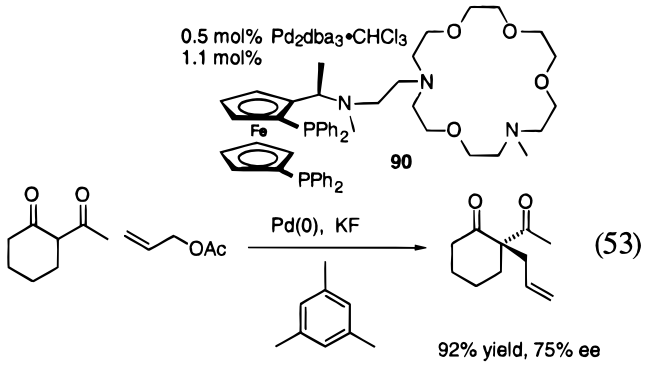


Figure 13. Possible complexes of unsymmetrical nonterminal π-allyl systems.

D. Enantioselective Allylation of Prochiral Nucleophiles

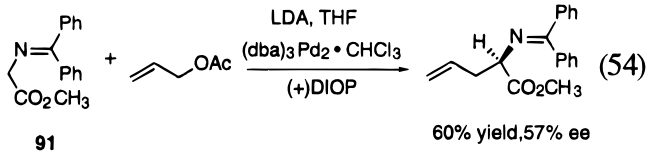
One of the first efforts to effect asymmetric allylic alkylations involved the use of a prochiral nucleophile, 2-acetyltetralone. Using DIOP as a ligand, the optical yield was only 10%.[162] Increasing the enantioselectivity requires increasing ligand/nucleophile interaction. Attaching a crown ether to a ferrocenyl ligand as in **90** and using a hydrophobic solvent such as mesitylene to maximize ion pairing of the nucleophile dramatically increased the ee as in eq 53.[163] Somewhat surprisingly, a simple hydroxyethyl group as in ligand **16** gave similar yields and enantioselectivity (60% ee).[133]



(53)

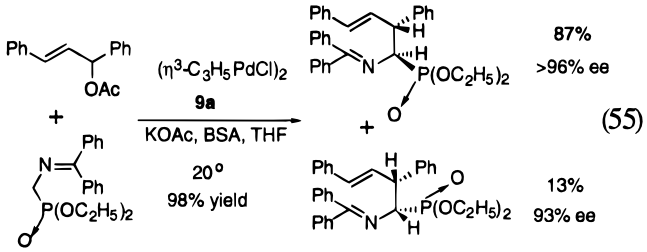
Allylation of 1,5-dimethylbarbituric acid gave only a 12.7% ee with iminophosphine ligand **33** as the chiral ligand.[78] Since the difference between the enantiotopic faces of this nucleophile is rather subtle due to its nearly meso nature, such a low ee is not surprising.

The imine **91** gave a remarkable 57% ee in its allylation using (+)-DIOP at −60 °C (eq 54).[164] A



(54)

similar reaction with the phosphonate analog of **91** gave only 19% ee with the oxazoline ligand **9c**.[165] On the other hand, when the 1,3-diphenylallyl system which involves a double stereodifferentiation was used, excellent enantioselectivity and good diastereoselectivity was obtained (eq 55).

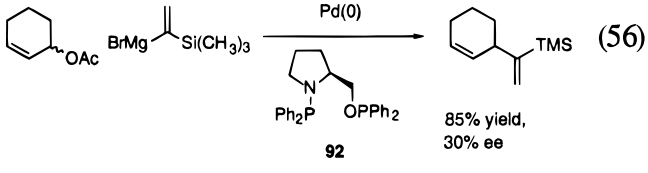


(55)

IV. Palladium-Catalyzed Allylations with Unstabilized Nucleophiles

Palladium-catalyzed alkylation of allylic substrates with "hard" nucleophiles has received far less attention than the reaction with "soft" nucleophiles in general. Since such processes normally are thought to transfer the nucleophile first to palladium and then collapse to product by reductive elimination, the enantiodiscrimination occurs within the coordination sphere of the palladium and might be thought to give rise more easily to high ee. While the studies are very limited at present, the results have been disappointing.

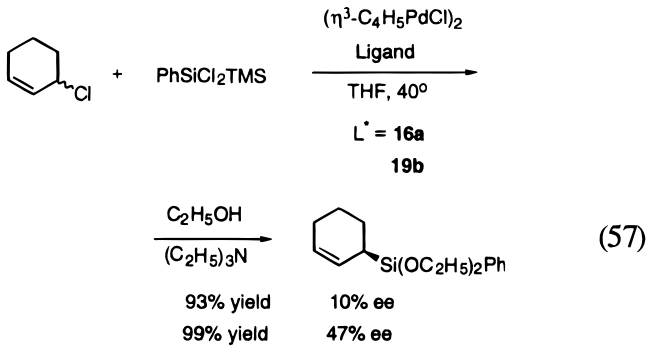
Cross-coupling of phenylzinc chloride with 3-acetoxycyclohexene gave a 10% ee with chiral ligand **27**[72] and 9% with DIOP **36**.[167] A somewhat better enantioselectivity was observed in the cross-coupling of a Grignard reagent in the presence of PROLIPHOS **92** (eq 56).[168] Significantly better results were obtained



(56)

with silyl transfer using the metallocene ligands (eq 57).[66] As noted previously, increasing the P−Pd−P

bite angle by switching from the ferrocene to the ruthenocene complex increased the ee. The acyclic crotyl substrate gave an exciting 92% ee but a mixture of regioisomers. It is noteworthy that the regioselectivity favoring the more substituted product increased also with the ruthenocene complex.



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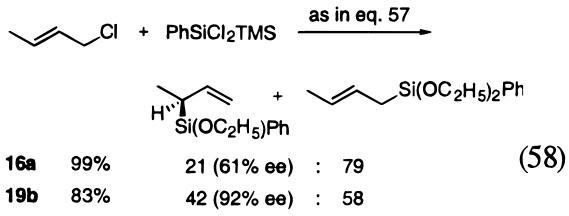
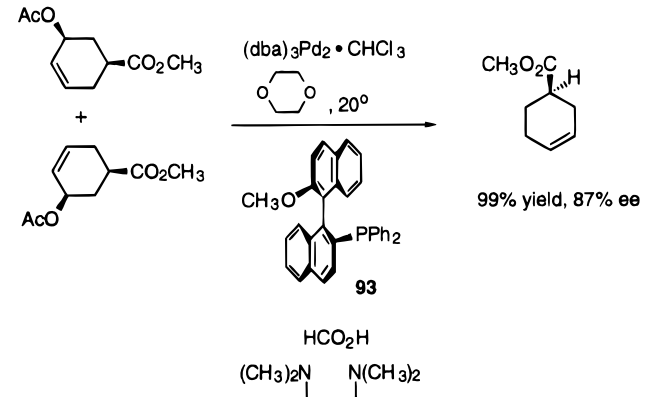


(58)

The most successful asymmetric induction of non-stabilized nucleophiles involves transfer of hydride with formate serving as the hydride donor.[169] The monophosphines R-MOP (**93**) and R-MOP-phen (**18**) have been used as the preferred ligands for the cyclic (eq 59)[65] and acyclic (eq 60)[106,170] cases respectively. The stereochemistry of the optically active allylsilane in the latter case translates into the stereochemistry of a homoallylic alcohol by Lewis acid promoted addition to an aldehyde with excellent chirality transfer.



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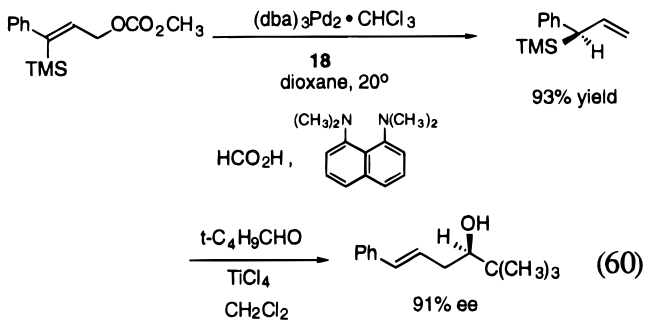


(60)

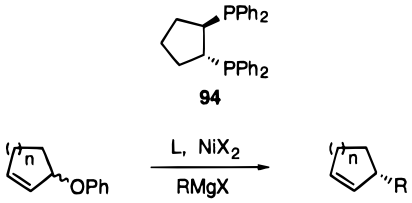
Table 16. Nickel Catalyzed Allylic Alkylation

entry	L	ring size	R	% yield	% ee	ref
1	**34**	5	C_2H_5	60	90	171
2	(*S*)-BINAP (*ent*-**20**)	5	C_2H_5	67	82	172
3	**94**	5	C_2H_5	91	83	173
4	**25**	5	C_2H_5	90	94	173
5	**25**	5	CH_3	53	51	173
6	**25**	5	*n*-C_3H_7	10	61	173
7	**25**	5	*i*-C_3H_7	8	36	173
8	**34**	6	C_2H_5	80	36	173
9	(*S*)-BINAP (*ent*-**20**)	6	C_2H_5	11	65	172
10	**94**	6	C_2H_5	99	74	173
11	**25**	6	C_2H_5	84	84	173

V. Enantioselective Allylations Catalyzed by Other Metals

A. Nickel

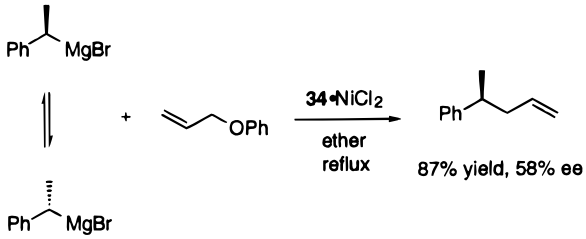
Nickel-catalyzed allylic alkylations have mainly involved unstabilized nucleophiles with allyl substrates bearing rather poor leaving groups. Like in the case of the palladium-catalyzed reactions with "hard" nucleophiles, the reactions are generally believed to involve an inner-sphere mechanism where the nucleophile initially bonds to the metal. Table 16 and eq 61 summarize the alkylation with cyclic allyl phenyl ethers in which several trends are noted.



(61)

First, the five-membered ring substrate gave better enantioselectivity than the six-membered ring (Table 16, entries 1−4 vs 8−11). Second, the yields and enantioselectivities with the atropisomeric ligand **25** exceeded those of its close sibling BINAP (Table 16, entries 4 and 11 vs 2 and 9). Third, there was a dramatic variation in ee with the structure of the nucleophile (Table 16, entries 4−7).

Asymmetric induction in the nucleophilic partner of this alkylation reaction has also been examined. Thus, a nickel complex generated from (*S*,*S*)-CHIRAPHOS (**34**) catalyzed the coupling of racemic (α-phenethyl)magnesium bromide and allylphenyl ether (eq 62). With the bis-phosphine **94**, the yield and



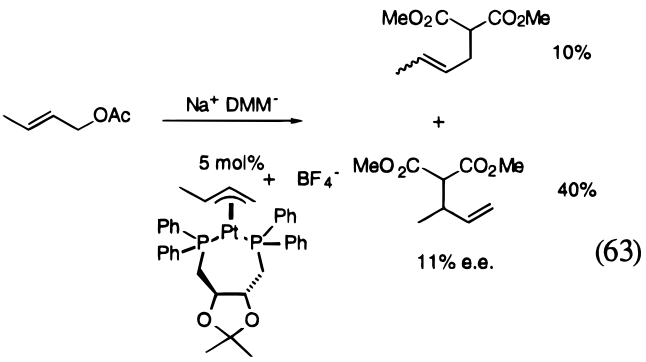
(62)

enantioselectivity were only 50% and 31% respectively.[174] The high yield and ee in the former case precludes a simple kinetic resolution of the racemic Grignard reagent.

B. Platinum

Only one study explored the area of platinum-catalyzed allylic alkylations, which suffer from low

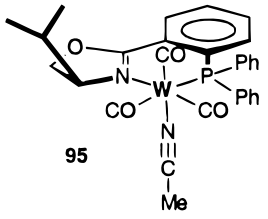
turnover numbers.[175] The enantioselectivities attained with the difficult substrate (*E*)-crotyl acetate ranged from 11% (*R*,*R*-diop) to 23% (*R*,*R*-dipamp) (eq 63).



(63)

C. Tungsten

Simple cinnamyl substrates do not lead to chiral products with palladium catalysts because substitution occurs at the less substituted allylic terminus. Tungsten is the transition metal of choice when selectivity complementary to palladium is sought.[144,176] An exciting extension of the work using (phosphinoaryl)oxazoline ligands has come with the move to tungsten-based catalyst systems.[177] The complex **95** was prepared and the stereochemistry was confirmed by X-ray diffraction.[85] This complex served effectively as a catalyst in the alkylation of (*E*)-cinnamyl diethyl phosphate (**96**) with dimethyl sodiomalonate. In this case, alkylation at the more substituted benzylic position is preferred affording a 3:1 mixture of **97** and **98**, respectively, in 89% yield (eq 66). The enantiomeric excess of **97** is 96%. Notably, the tungsten complexes are not subject to *syn*−*anti* and apparent allyl rotation processes that are prevalent in palladium-catalyzed reactions. The corresponding molybdenum complex was not catalytic in this reaction.



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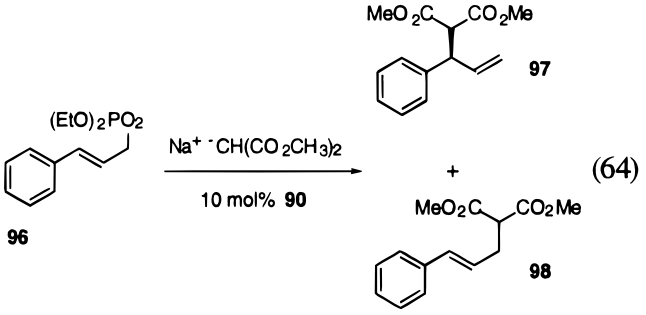

96
(64)

D. Other Metals

Other metals have been shown to catalyze allylic alkylation reactions and are postulated to proceed through allylic intermediates. Notable among these metals are molybdenum,[178,179] cobalt,[180] and rhodium.[181,182] The results of iron-catalyzed allylic alkylations with $Bu_4N[Fe(CO)_3NO]$ are not consistent with η^3-allylic intermediates.[183] These catalytic systems have not been fully investigated for their synthetic potential, and, understandably, lag far behind palladium in efforts to bring asymmetry.

VI. Summary and Conclusions

It should be clear from this review that great strides have been made in developing the asymmetric potential of palladium-catalyzed allylic alkylations. Many reactions have been developed which rival the enantioselectivities of other commonly used transition metal-catalyzed reactions. The stereodynamic processes involved in the catalytic cycle provide different mechanisms for enantioselection. Each of these has been utilized, with varying degrees of success. As other transition metals are recruited for asymmetric allylic alkylations, complementary patterns of substrate tolerance may emerge. In this way, even the least cooperative substrates (unsymmetrically substituted racemic allylic substrates) may eventually yield to the continued efforts to develop these processes for use in enantioselective organic synthesis.

VII. Acknowledgments

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