Enantioselective Homogeneous Catalysis Involving Transition-Metal–Allyl Intermediates

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Received July 5, 1988 (Revised Manuscript Received September 29, 1988)

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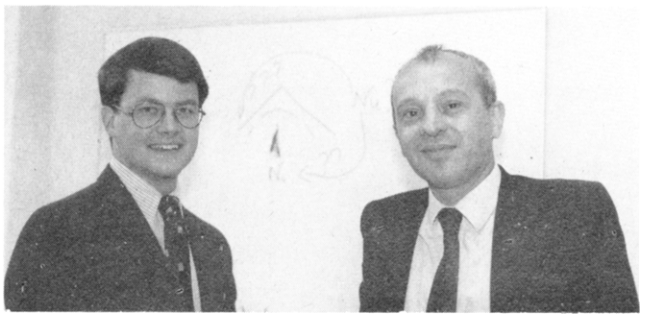

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1. Introduction

The synthesis of enantiomerically pure compounds is an extremely important undertaking and a formidable challenge to the synthetic chemist.[1] The importance of enantiomerically pure compounds stems from the central role of enantiomer recognition in biological activity.[2] Of the various ways[1,3] to induce enantioselectivity[4] in chemical reactions, the most efficient is by means of an enantiomerically pure catalyst, where a small amount of chiral material can transmit chirality information to a large amount of substrate. This type of process has been referred to as "asymmetric catalysis"[5] or, in more general terms, "asymmetric synthesis".[3] These terms, although of some historical importance,[3,6] could be advantageously substituted by the more precise term "enantioselective synthesis".[4,7] In the following discussion, we will use the term enantioselective synthesis to describe a reaction in which a chiral product, enriched in either enantiomer, is formed from either an achiral or chiral racemic substrate. By this definition, an enantioselective synthesis implies that when a substrate is chiral, the chirality of a substrate has no influence on the stereochemical outcome of the reaction. Enantioselective synthesis is therefore distinct from diastereoselective synthesis, in which chirality elements of substrates are involved in stereodifferentiation.

One way to effect an enantioselective synthesis is through enantioface selection[8] on achiral (often defined as prochiral) substrates. Enantiomer selection (also referred to as a kinetic resolution[3]) of a chiral racemic substrate will also result in an enantiomerically enriched product, but in this case, even in the event of complete enantiomer selection, the maximum yield obtainable is only 50%.[3,9]

In the design of an enantioselective catalytic reaction, it would be advantageous to be able to obtain high yields of enantiomerically enriched products from either achiral or chiral racemic substrates. For chiral racemic substrates the challenge is to convert both enantiomers of the substrate into a single enantiomer of the product. This can be achieved by a chiral catalyst when (1) reaction conditions are such that the enantiomers of the substrate interconvert on a time scale faster than the

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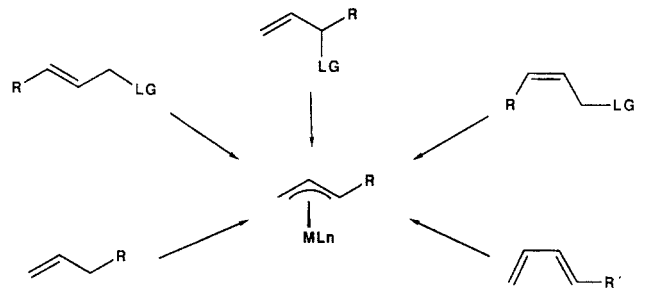
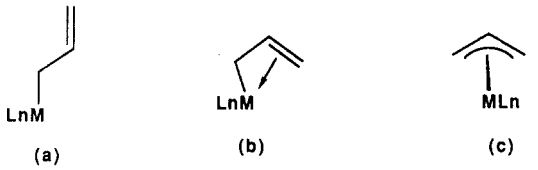
SCHEME 1[a]



[a] LG = leaving group.

SCHEME 2



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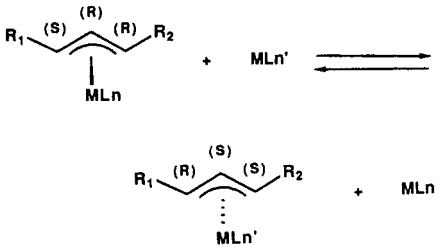


[a] For assignment of CIP priority, $R_1 > R_2$.

catalytic reaction or (2) the substrate and catalyst form an intermediate in which the chirality information of the substrate is lost. An example of the former approach is the enantioselective cross-coupling of organic halides and secondary Grignard reagents catalyzed by chiral nickel catalysts, where it was proposed that the chiral Grignard reagents racemize faster than they react with the nickel catalyst.[10] The latter approach has been applied for enantioselective allylation reactions, the subject of this review.

Catalytic systems that proceed through transition-metal–allyl intermediates offer several advantages for enantioselective synthesis, including the characteristic discussed above: the ability to produce enantiomerically enriched products from either achiral or chiral racemic substrates. Another advantage of these catalytic systems stems from the rich reaction chemistry of transition-metal–allyl complexes.[11] These complexes are reactive toward a large variety of nucleophiles and are thus useful for the enantioselective catalytic formation of not only carbon–carbon bonds but also carbon–heteroatom bonds. A further advantage of these catalytic systems is the ability to form allylic intermediates from a variety of different substrates[12] (Scheme 1): allyl intermediates can form from olefins, diolefins, or olefins containing a leaving group in the allylic position. Moreover, in the latter case, substrates with different geometries, either chiral or achiral, form identical allylic intermediates. This characteristic allows for considerable flexibility and versatility in the choice of substrate for a specific enantioselective reaction.

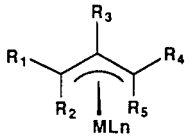


Figure 1.

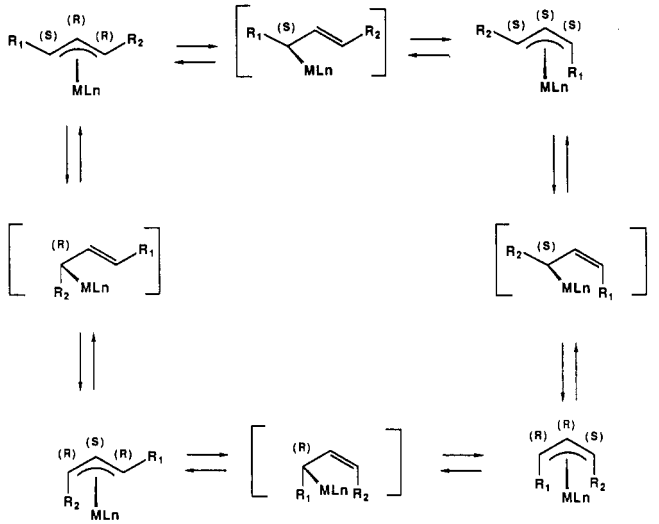
In this review, we summarize the results achieved in the field of enantioselective synthesis by transition metals where allylic intermediates are most likely involved in the catalytic cycle to form new carbon–carbon or carbon–heteroatom bonds.[13] An important aim of the review is not only to summarize important contributions to this field but to attempt to organize the results in a meaningful and mechanistically significant way. In so doing we hope to point out those systems that are well understood so that those wishing to design an enantioselective catalytic reaction will have a reasonable data base for reference. An equally important goal is to point out those areas where our understanding is on much less solid ground in the hope of stimulating additional research, for it is only through a detailed mechanistic understanding that the field of enantioselective catalysis can be elevated from its current state as an art to a science. A number of reviews on π-allyl chemistry[11,12,15] and catalytic asymmetric synthesis by transition metals[1,16,17] are available. By concentrating on enantioselective allylation reactions, we hope to provide a comprehensive treatment of an important subdiscipline of homogeneous catalysis.

2. π-Allyl Complexes: Static and Dynamic Stereochemistry

An allyl ligand, C_3R_5, can coordinate to a transition metal in three limiting ways (Scheme 2): (a) as a σ-bound ligand, (b) as a σ–π-bound ligand,[18] or (c) as a fully π-bound ligand. The manner in which an allyl ligand is coordinated to a transition-metal center and the ability of allyl ligands to change their coordination geometries will influence the stereochemistry of reactions proceeding via allyl intermediates. For the planar allyl ligand with five substituents, according to the accepted nomenclature, substituents R_1 and R_4 are termed syn and R_2 and R_5 anti (Figure 1). If the substituents at each allylic carbon atom are different, each carbon atom is a stereogenic[19,20] center. The stereochemistry of the stereogenic carbon atoms of a coordinated allyl ligand can be described unambiguously by using *R* and *S* descriptors according to the Cahn–Ingold–Prelog convention.[20,21] The static stereochemistry of the allylic moiety can thus be described by three descriptors, one for each of the stereogenic centers that constitute the allylic fragment. A change in the stereochemistry for an allylic complex can arise, in principle, in four different ways: (a) the configurations of all three stereogenic carbon atoms are changed simultaneously; (b) the configurations of the central carbon atom and one of the two external atoms are changed; (c) the configurations of the two external atoms are changed; (d) the configuration of only one atom is changed.

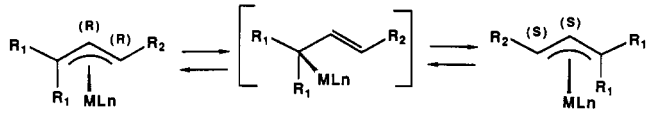
Isomerization processes of allyl ligands have been studied in some detail,[22] and of the above possibilities, two primary mechanisms have been proposed. The S_N2 type displacement of the metal center of an allyl com-

SCHEME 4[a]



[a] For assignment of CIP priority, $R_1 > R_2$.

SCHEME 5



plex by another metal fragment (Scheme 3) simultaneously inverts the stereochemistry of all three centers as in (a).[23] The well-known σ–π–σ isomerization mechanism,[24] proposed long ago to account for syn–anti interconversion in π-allyl complexes, changes the stereochemistry of two centers as in (b) (Scheme 4).

For catalytic reactions involving allyl intermediates, particularly enantioselective reactions involving optically active transition-metal species, isomerization reactions that result in a change in the stereochemistry of the allylic intermediate are very important. Of particular importance are situations under which the allylic enantioface that is complexed to the transition-metal center changes (i.e., the stereochemistry of all stereogenic carbon atoms is inverted). For example, displacement reactions such as that in Scheme 3 result in the exchange of the complexed enantiofaces. (In this case, if the transition-metal fragment is achiral, the allylic complex is racemized.) Enantioface exchange of the allyl ligand can also occur via the σ–π–σ mechanism, but only under specific conditions.[25] As seen in Scheme 4, for a π-allyl intermediate where the two external carbon atoms are stereogenic centers, the σ–π–σ process does not result in an exchange of the complexed allylic enantiofaces. Enantioface inversion (that is, the inversion of all stereogenic centers of the allyl ligand) is only possible when one of the external atoms is nonstereogenic by virtue of identical substitution, as shown in Scheme 5. The importance of enantioface inversion is that the stereochemistry of the starting substrate is lost during the isomerization process and enantioselection is then determined by the stereochemistry of the transition-metal intermediate, not the substrate.

3. Substitution Reactions of Allylic Substrates

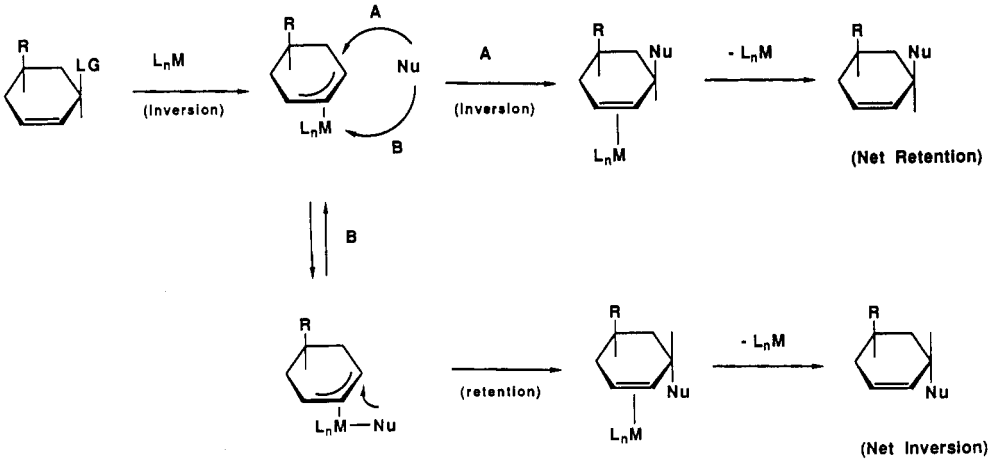
Catalytic allylic substitution involves the reaction of an olefinic substrate, generally substituted in the allylic position, with a nucleophile[11] (or electrophile[26]) in the presence of a transition-metal catalyst. Although stoichiometric allylation reactions had been investigated in the 1960s by Tsuji,[27] it was not until 1970 that the first reports of catalytic allylation reactions appeared.[28] In many cases, the allylic substrates were chiral and/or gave rise to chiral products.[29] These initial results led to a series of sustained and fruitful investigations of the stereochemistry, mechanism, and applications of allyl complexes in enantioselective catalysis.

3.1. Stereochemistry

As with a number of transition-metal-catalyzed reactions, catalytic allylic substitution is a stepwise process. Two important steps have been identified: (1) the reaction of a transition-metal complex with the substrate to produce a π-allyl intermediate[30] and (2) the displacement of the transition-metal species by a nucleophile[11] to give the product, possibly via an intermediate olefin complex[31] (Scheme 6).

In the absence of isomerization processes, the overall stereochemistry of the reaction will be a product of the stereochemistry of the individual steps. Overall retention of configuration occurs if both steps proceed with either retention or inversion of stereochemistry; overall inversion implies that the two steps proceed with different stereochemistry (i.e., inversion–retention or retention–inversion). Two approaches have been used to investigate the stereochemistry of allylation reactions:

SCHEME 6



(1) the use of substituted cyclic substrates, which give rise to diastereomeric products, and (2) the use of optically active substrates, which give rise to enantiomeric products. Early studies, such as the palladium-catalyzed allylation with dimethyl sodiomalonate,[32,33] utilized the first approach. Net retention of configuration was demonstrated to be the result of two steps that proceed with inversion of configuration.

In contrast, it was later discovered that alkylation reactions of allylic alcohols with Grignard reagents using nickel catalysts proceeded with net inversion of configuration,[34,35] similar to the previously investigated copper-catalyzed alkylation of allyl esters.[36] Although the relative stereochemistry of the two steps was not determined for the nickel case, the stereochemistry of the products can be rationalized in terms of an inversion–retention mechanism.

Subsequent investigations[37-66] have led to the following mechanistic and stereochemical model for allylic substitution reactions (Scheme 6):

1. Formation of the allyl complex generally occurs with inversion of configuration. Initial attack appears to occur at the double bond, although different proposals have been offered.[67] If the leaving group is disposed in an antiperiplanar orientation with respect to the metal, then formation of the π-allyl intermediate follows.[68] An exception to this general rule was recently reported;[69] oxidative addition of (*E*)-(*R*)-4-acetoxy-5-methyl-2-hexene to $(CH_3CN)_3Mo(CO)_3$ was observed to proceed with retention of configuration.

2. Attack by the incoming nucleophile directly on the allyl ligand, as occurs for "soft" nucleophiles, leads to inversion of configuration for the second step and retention for the overall reaction. Alternatively, "hard" nucleophiles attack the metal center first and then migrate to the allyl ligand.[70] This leads to retention of configuration for the second step and overall inversion of stereochemistry for the allylation reaction. Recent model studies on palladium systems give no evidence for a change in hapticity (η^1 to η^3) for this coupling step.[71,72]

The distinction between "hard" and "soft" nucleophiles is not always unambiguous. Hard nucleophiles are generally those that undergo facile transmetalation reactions, such as Grignard reagents, alkylzinc reagents, etc., whereas soft nucleophiles include stabilized carbanions, sulfur, nitrogen, phosphorus, and some oxygen nucleophiles. Selected illustrative examples are given in Table 1.

TABLE 1. Stereochemistry of Allylation Reactions of Different Nucleophiles[a]

Nu	catalytic system	net stereochem	stereochem of the two steps[f] 1	2	ref
$NaCH(COOMe)_2$	Pd/PPh_3	R	I	I	32, 33[b]
$R_3SnOC_6H_5$	Pd/PPh_3	R[g]			57[c]
$(C_2H_5)_2NH$	Pd/P[h]	R		[I][d]	37[d]
$(C_6H_5)_2P(S)Li$	Pd/PPh_3	R[g]			50
CH_3S^-[i]	Pd/PPh_3	R			62
$ArSO_2Na$[j]	Pd/PPh_3	R[g]			56
CH_3MgI	Ni/dpe	I			34[e]
C_6H_5ZnBr	Pd/dpe	I	I	R	60
$R_3SnC_6H_5$	Pd/PPh_3	I	I	R	48
$Me_2AlCH{=}CCR'$	Pd/PPh_3	I			43
CH_3COO^-	Pd/PPh_3	R, I[k]			38, 41

[a] For similar nucleophiles and/or other catalytic systems, see *b–e*. [b] References 49, 51–53, 60, 63, 65, and 68. [c] Reference 47. [d] Reference 39 and 46. [e] References 35, 36, and 58. [f] If stated or determined. [g] Some epimerization. [h] Polymeric phosphine ligand. [i] From the decomposition of the allyl dithiocarbonate. [j] The allylic sulfone is formed. [k] The stereochemistry of the reaction depends on the conditions used. R = retention; I = inversion.

3.2. Regiochemistry

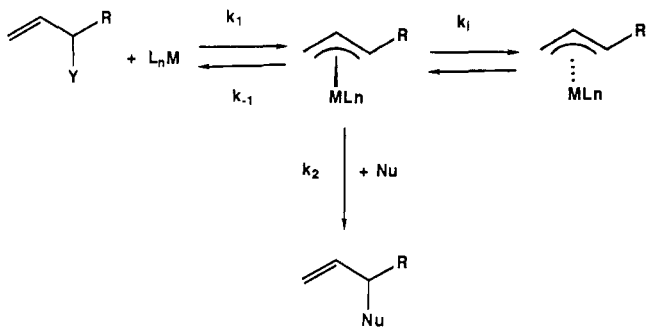
Allyl ligands that do not possess a plane of symmetry bisecting the central C–C–C angle can give rise to regioisomeric products by attack at either terminal carbon atom. Control of regioselectivity in allylation reactions remains one of the most difficult and challenging problems in this field.[73,74]

A number of variables influence the regioselectivity, including the steric environment of the catalyst, electronic factors such as charge separation on the two allylic termini and/or differences in overlap populations, and the relative stability of the intermediate olefin complexes.[73-79] The relative importance of steric and electronic factors is difficult to predict and varies with the particular metal system, the ligand array, the nucleophile, and the substitution pattern of the π-allyl intermediate.[73] For certain allylation reactions, nucleophilic attack can be the turnover-limiting step.[25] Curtin–Hammett conditions[80] apply for this exothermic step, and thus the regioselectivity is under reactant control and should be relatively insensitive to product stabilities. For other allylic substitution reactions, regioselectivity is difficult to rationalize on steric grounds, and predictions based on electronic considerations have proven useful.[76,81]

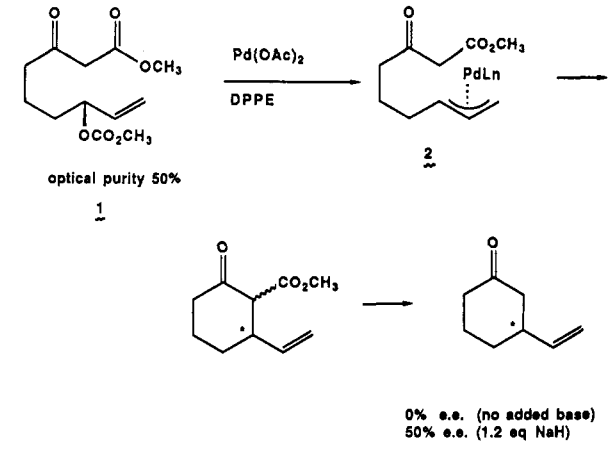
It is difficult to draw any general conclusions regarding the factors governing the regiochemistry of allylation reactions. The following examples provide some indications of the inherent complexities and general trends. The influence of different metal centers and nucleophiles on the regioselectivity was investigated for several allylation reactions catalyzed by $NiCl_2$(dppf) and $PdCl_2$(dppf) (dppf = 1,1′-bis(diphenylphosphino)ferrocene) complexes.[58] Although the stereochemistry for both the nickel- and palladium-catalyzed substitutions of 1- or 3-methyl-2-propenyl ether by PhMgCl was identical (overall inversion), the regiochemistry for the two metals was different. Substitution occurs primarily at the more substituted position for the nickel system (up to 88%) but at the less substituted position for the palladium system (up to 95%). The identical nickel system, in the presence of the soft nucleophile diethyl sodiomalonate, catalyzes substitution regioselectively at the less hindered position, in this case with overall retention of configuration.[63] This difference in regiochemistry is most likely a consequence of different mechanisms (cf. Scheme 6) involved for the different nucleophiles.

Palladium systems appear to be sensitive to steric effects, particularly for soft nucleophiles, which yield products with overall retention. In some cases, such similar allyl termini as a methyl and an *n*-propyl group can be distinguished; substitution by soft nucleophiles occurs predominantly at the methyl-substituted position in the presence of $Pd(PPh_3)_4$.[77] In contrast, substitution by PhZnCl (a hard nucleophile that yields products with overall inversion of stereochemistry) occurs primarily at the propyl-substituted position.[77]

SCHEME 7



SCHEME 8



For both the nickel and palladium systems, different ligands (phosphines, diphosphines, phosphites) can cause large variations in the regioselectivity.[63,82]

Catalytic systems of other transition metals show their own regiochemical characteristics. Tungsten systems appear to be more strongly influenced by electronic factors than the palladium systems.[49,83] Malonates react with opposite regiochemistry for molybdenum and palladium catalysts.[65,79,84] Soft nucleophiles attack at the more substituted allylic position with iron catalysts.[66]

From the preceding discussion, it can be readily appreciated that we are far from a detailed understanding of the factors that govern regioselectivity for allylation reactions and from being able to predict, a priori, the expected regiochemistry under all conditions. Nevertheless, due to the detailed studies of Tsuji,[85] Trost,[83] Hayashi,[60,61] Julia,[63,82] and Akermark,[73] a significant amount of empirical data exists that provides a degree of predictability for specific ligand/substrate/metal combinations. It should be emphasized, however, that seemingly minor modifications can have dramatic regiochemical consequences.

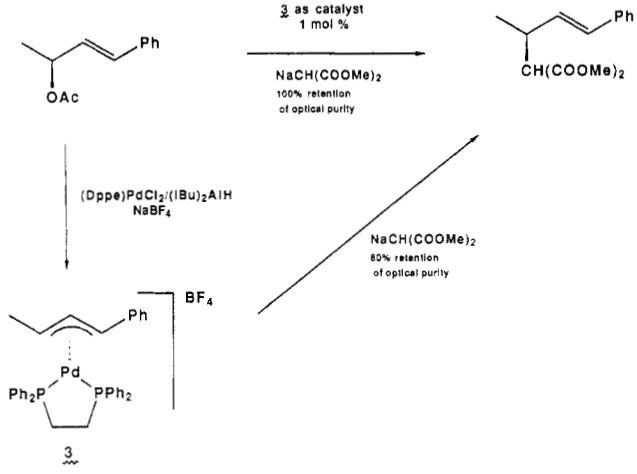
3.3. Kinetic Considerations

The relative rates of the various steps of allylic substitution reactions have a large effect on the stereochemical course of the reaction. As discussed in section 3.1, allylic substitution reactions are, in general, stereospecific. However, as discussed in section 2, the stereochemistry of the stereogenic centers of the allylic moiety can change. When conditions are such that such a change takes place or when racemization of the substrate occurs, the stereochemical information of the substrate is lost during the course of the reaction. In this section, we consider a simplified kinetic scheme for substitution reactions and discuss conditions under which the stereochemical information of the substrate is lost and, therefore, enantioselective synthesis from racemic substrates becomes possible. Presented in Scheme 7 is a general kinetic scheme for an allylic substitution reaction for a monosubstituted allylic substrate. In this scheme, k_1 represents the rate constant for formation of the π-allyl intermediate, k_i represents the rate constant(s) for all isomerization processes, and k_2 represents the rate constant for substitution of the π-allyl intermediate.

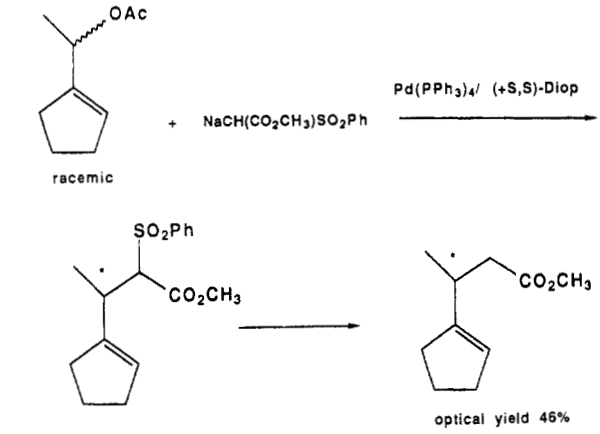
Because allylic substitution reactions are stereospecific, in cases where $k_i < k_2[\mathrm{Nu}]$ the stereochemistry of the substrate will determine the stereochemistry of the product. Thus, as discussed in section 3.1, with soft nucleophiles one obtains products with overall retention of substrate stereochemistry. If, however, $k_i > k_2[\mathrm{Nu}]$, then the stereochemical information of the substrate will be lost during the course of the reaction if isomerization processes result in exchange of the π-allyl enantiofaces. The reaction in Scheme 8 provides a good example.[86] The palladium-catalyzed cyclization of the enantiomerically enriched carbonate 1 with an achiral catalyst in the absence of an added base yielded, after decarboxylation, *rac*-3-vinylcyclohexanone. However, if the substrate was deprotonated prior to addition of the catalyst (by the addition of NaH), complete retention of optical purity was observed. These results can be rationalized by considering the relative rates of isomerization and substitution of the π-allyl intermediate. In the presence of an added base, the initially formed π-allyl intermediate is trapped rapidly by the preformed enolate nucleophile, giving rise to optically active products. In the absence of added base, the rate of isomerization of the π-allyl intermediate is greater than the rate of intramolecular nucleophilic attack (due to the low concentration of the nucleophile), leading to loss of optical activity. In this case, because one of the external atoms of the initially formed π-allyl intermediate **2** is not a stereogenic center, isomerization via the σ–π–σ process results in exchange of the enantiofaces of the π-allyl intermediate (see Scheme 5). As discussed in section 3.4.B, this result can be used to effect an enantioselective synthesis using a chiral catalyst precursor.

Even in the absence of σ–π–σ isomerization processes, the stereochemical course of the reaction can be affected if the rate of formation of the π-allyl intermediate is comparable with that of substitution (i.e., $k_1[\mathrm{LnM}] = k_2[\mathrm{Nu}]$) and the concentration of the catalyst is high. Under these conditions, enantioface inversion of the allyl moiety, the process outlined in Scheme 3, can become important. This phenomenon is a likely cause of the different stereospecificities for the stoichiometric and catalytic reactions presented in Scheme 9. In the presence of catalytic amounts of **3**, optically active (*E*)-3-acetoxy-1-phenyl-1-butene is stereospecifically alkylated by dimethyl sodiomalonate with 100% retention of optical purity.[51,52,60] In contrast, treatment of the allyl acetate with a stoichiometric amount of palladium followed by alkylation results in a 20% loss of optical purity. As discussed in section 2, allylic intermediates such as **3** cannot racemize by the σ–π–σ mechanism, and thus loss of optical purity is most likely

SCHEME 9



SCHEME 10



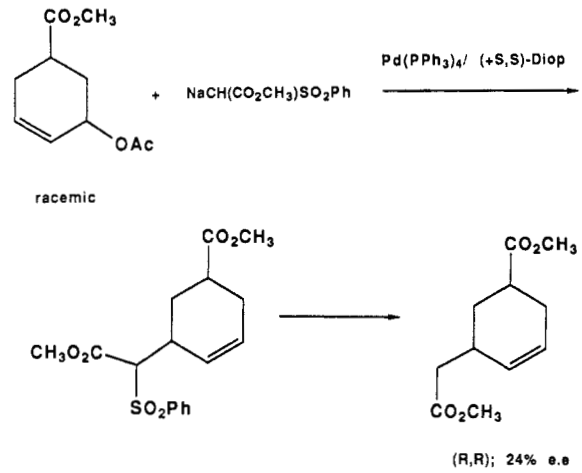
due to partial enantioface inversion by the displacement process as outlined in Scheme 3, due to excess of the Pd(0) compound.

Furthermore, the formation and substitution of the π-allyl intermediates are not always irreversible, and thus racemization is possible through reversible processes involving formation and nonstereospecific substitution of the allyl intermediate. For example, the regioselective coupling reaction of Scheme 10 (one of the first successful examples of asymmetric allylic alkylation) gave up to 46% asymmetric induction using $Pd(PPh_3)_4$/(*S*,*S*)-diop as a catalyst precursor.[87] Apparently, racemization at the level of the starting material occurs and thus permits enantioselective synthesis from a racemic starting material. Racemization in this case is probably due to the reversibility of formation of the allyl intermediate (i.e., k_1, $k_{-1} > k_2$) and the nonstereospecific attack of the acetate nucleophile.[88]

3.4. Prochiral or Chiral Allylic Substrates and Carbon Nucleophiles

Most of the investigations on enantioselective allylation reactions have been carried out by using chiral or prochiral allyl substrates and achiral nucleophiles. In some cases, however, chiral nucleophiles have been used, and this gives rise to the formation of products having two chiral centers. However, rarely has the diastereomeric composition been determined; in general, the chiral center of the nucleophile is removed (see Scheme 10) and the enantioselectivity of the reaction

SCHEME 11



is determined on the basis of the chiral center formed at the allylic moiety.

The following discussion will be organized according to the type of allylic intermediate and the various stereodifferentiating processes involved. The first case to be considered is reactions involving allylic intermediates that have identical substituents on the two allylic termini. In this case, for any given nucleophile, the enantioselectivity is determined by the regiochemistry of the nucleophilic attack.[89] Reactions involving allylic intermediates bearing different substituents on the allylic termini are more complicated. For these reactions, enantioselectivity is associated with enantioface selection[8] (section 3.4.B) and/or with enantioselectivity derived from differential regioselectivities on the two allylic enantiofaces (section 3.4.C).

A. Intermediates Having Identical Substituents on the Allylic Termini

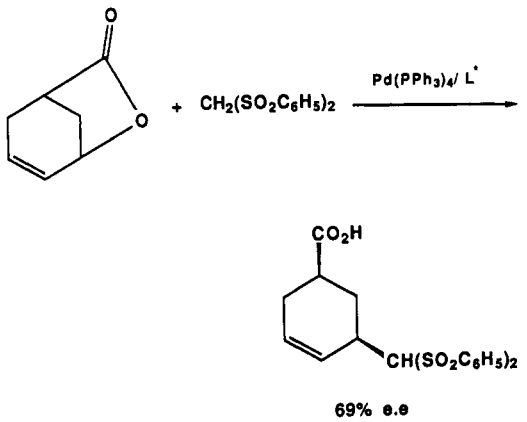
The first examples of an enantioselective allylation reaction that gave products with asymmetric carbon atoms in the allylic moiety were reported by Trost and Strege[87] (Scheme 11). *rac-cis*-3-Acetoxy-5-carbomethoxycyclohexene was coupled with the sodium salt of methyl (phenylsulfonyl)acetate in the presence of $Pd(PPh_3)_4$ and (*S*,*S*)-diop with 24% enantioselectivity, as determined on the desulfonated product. The experimental results were interpreted in terms of a π-allyl intermediate, but this interpretation was subsequently disputed,[91] primarily on the basis of the following observations made on an analogous system:

(1) The optical yields obtained from optically active substrates in the presence of the related chiral catalyst ($Pd(DBA)_2$/(*R*,*R*)-diop) were different from those obtained with racemic substrates. (A symmetric π-allyl intermediate should afford identical optical yields.)

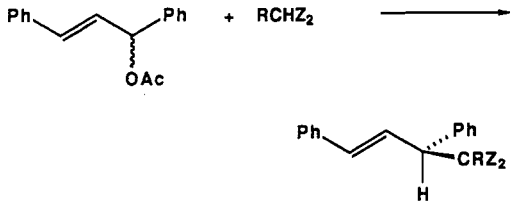
(2) Residual optical activity was observed in products obtained from chiral substrates and an achiral catalytic system (where 1,4-butanediylbis(diphenylphosphine) was used as a ligand).

The controversy has never been fully resolved[92] but could be ascribed to a different composition or nature in the ligands used. In subsequent work, a π-allyl intermediate has been assumed. On the basis of this assumption, Trost and co-workers proposed a model for asymmetric induction based on steric interactions between the incoming nucleophile and the "chiral pocket"

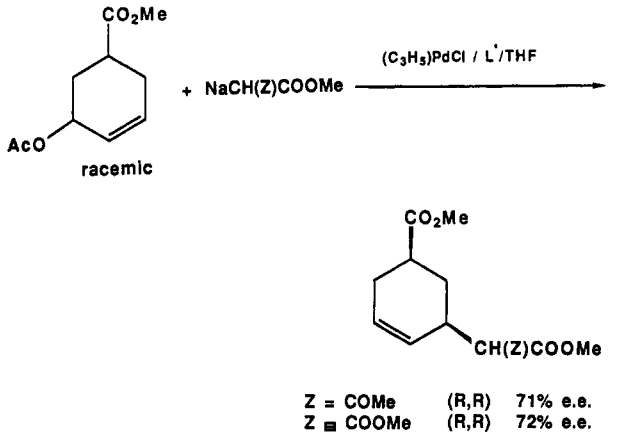
SCHEME 12



SCHEME 13



SCHEME 14



created by the four phenyl substituents of the chiral phosphine ligands.[93] In this model, it was proposed that the poor asymmetric induction in the reaction of Scheme 11 was due to the fact that the nucleophile approaches the allylic intermediate distal to the chiral phosphine ligands. To improve the optical yields in this system, ligands were designed to reduce the size of the "chiral pocket" to render the asymmetric bias of the phosphine ligands more effective. As seen in Scheme 12, in the presence of 2,2′-(1,1′-binaphthyldiyl)bis-[(3,5-bis(trimethylsilyl)phenyl) phosphinite], an enantiomeric excess of up to 70% was achieved by using this approach. Similar optical yields were obtained in the reaction of 1,3-diphenyl-2-propenyl acetate with different nucleophiles (Scheme 13; R = CH_3, H; Z = $COOCH_3$, $SO_2C_6H_5$).[93] Optical yields of up to 77% were recently reported for the same reaction using the alkaloid (−)-sparteine as the chiral ligand.[94]

A different approach for improving the optical yields in this type of reaction was devised by Hayashi et al.[95] They have prepared a number of chiral 1,1′-ferrocenediylbis(diphenylphosphine) (BPPF) ligands

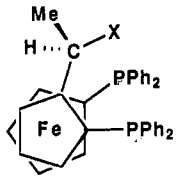


Figure 2.

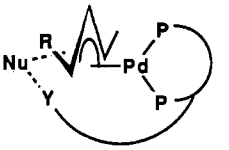


Figure 3.

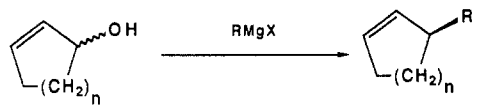
TABLE 2. Asymmetric Allylation of Some Nucleophiles by (*E*)-1,3-Diphenyl-3-acetoxy-1-propene Using $[(\eta\text{-}C_3H_5)PdCl]_2$/(*R*,*S*)-BPPF-X as the Catalyst Precursor[95] at 40 °C

(*R*,*S*)-BPPF-X			allylation prod ee (%)
compd	X	Nu	and ac
4	$NMeCH(CH_2OH)_2$	NaCH(COMe)COPh	87 (*S*)
4	$NMeCH(CH_2OH)_2$	NaCH(COMe)COOMe	83 (*S*)
4	$NMeCH(CH_2OH)_2$	$NaCH(COOMe)_2$	48 (*S*)
4	$NMeCH(CH_2OH)_2$	$NaCH(COMe)_2$	90 (*S*)
5	$NMeC(CH_2OH)_3$	$NaCH(COMe)_2$	96 (*S*)
6	$N(CH_2CH_2OH)_2$	$NaCH(COMe)_2$	81 (*S*)
7	$NMeCH_2CH_2OH$	$NaCH(COMe)_2$	71 (*S*)
8	NMe_2	$NaCH(COMe)_2$	62 (*S*)
9	$N(CH_2)_5$	$NaCH(COMe)_2$	44 (*S*)
10	Me	$NaCH(COMe)_2$	10 (*R*)
11	OH	$NaCH(COMe)_2$	46 (*R*)

(Figure 2) bearing a functional group on a pendant side chain that was expected to direct the incoming nucleophile preferentially to one of the two diastereotopic carbon atoms of the allylic intermediate, as represented in Figure 3. In the presence of the chiral ligand 4 (Figure 2, X = $NMeCH(CH_2OH)_2$), optical yields in excess of 70% were obtained in the reaction of Scheme 14 using a palladium catalyst precursor. Optical yields of up to 96% have been obtained in allylation reactions of 1,3-diphenyl-2-propenyl acetate (Scheme 13) using a variety of chiral BPPF-X ligands (Table 2). From these studies, it was shown that the enantioselectivity was highly dependent on the presence and position of the hydroxyl group on the side chain of the ferrocenyl diphosphine ligand, as well as on the nucleophile.

The coupling reaction with hard nucleophiles occurs by a different mechanism from that for soft nucleophiles, as evidenced by stereochemical studies (section 3.1). Hard nucleophiles attack the metal center rather than the allyl ligand, and thus, at one point during the reaction, the organic moieties to be coupled are bound simultaneously to the metal catalyst. In principle, the asymmetric bias of the phosphine ligands on the metal atom should be greater with hard nucleophiles. However, the situation is also more complicated since the reaction intermediate responsible for the formation of the allylation products has one more stereogenic center (associated with the M–Nu bond), and thus, there are twice the number of possible reaction intermediates for hard nucleophiles as there are for soft nucleophiles. In addition, for reactions involving hard nucleophiles, enantioselectivity could be determined not only in the coupling of the two (σ and π bonded) organic ligands but also at a step involving formation of an η^1-allyl

SCHEME 15



n = 1,2
R = CH_3, C_2H_5

intermediate prior to reductive elimination of the products. Although model studies suggest that η^1–η^3 isomerization is unlikely for palladium catalysts,[71] it could be important for nickel and other catalyst systems.

In view of the aforementioned complications, a useful criterion that has been applied for reactions involving hard nucleophiles has been to utilize chiral ligands having C_2 symmetry in order to minimize the number of possible reaction intermediates.[96] The first results[97] reported involved the alkylation of cyclopent-2-en-1-ol and cyclohex-2-en-1-ol with methyl or ethyl Grignard reagents in the presence of [(−)-phenphos]$NiCl_2$ as the catalyst precursor (Scheme 15). These substrates give rise to intermediates with homotopic allylic faces, and thus enantioselectivity is due to diastereotopos selection as in the reaction of Scheme 11.[8] Optical yields for these reactions were on the order of 15–40%.[97] Use of the C_2-symmetric chiraphos ligand led to improved optical yields in most cases. In the case of 3-phenoxycyclopentene, optical yields of up to 90% were observed (Table 3). For acyclic substrates, the best optical yields are generally lower,[98–100] possibly due to the fact that the same product can arise from attack of the nucleophile on homochiral stereogenic centers of different diastereofaces of the π-allyl intermediate. The enantioselectivity in these reactions is very sensitive to the nucleophile (compare CH_3 and C_2H_5 in Table 3). Yields also depend on the nucleophile due to competing reduction of the allylic substrate.[101] In the case of cyclohexenyl derivatives, no substantial influence of the leaving group was observed,[98] and solvent effects on the enantioselectivity appear to be minimal. In some cases, enantiomer selection of the allylic substrates was checked, but the difference in reactivity between the two enantiomeric substrates was found to be very small.[98]

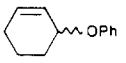
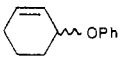
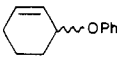
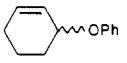
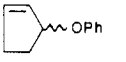
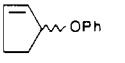
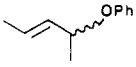
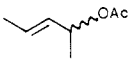
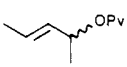
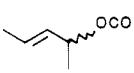
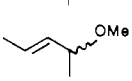
Palladium systems containing homologues of 1,2-ethanediylbis(diphenylphosphine) were found to be inactive for allylation reactions in the presence of Grignard reagents. However, the use of zinc reagents affords reasonable yields of allylation products (up to 80%).[100] For reactions with phenylzinc chloride, monophosphines such as NMDPP or DMPP were found to give better chemical and optical yields than chelating phosphines such as chiraphos or diop. These results were interpreted by assuming that chiraphos and diop behave as monodentate ligands, although this seems improbable in the case of chiraphos.[98] However, due to the limited number of experiments with organozinc reagents,[100] the scope and limitations of these reactions remain to be analyzed.

B. Enantioselectivity Connected with Enantioface Selection

The most thoroughly investigated examples of allylation reactions involve reactions in which enantioselectivity is associated with enantioface selection. For chiral racemic substrates this involves formation of diastereomeric π-allyl complexes, which interconvert, generally by the σ–π–σ mechanism. This process provides a mechanism for interconverting the enantiofaces of the π-allyl intermediate. However, as previously discussed, the requirements for enantioface exchange via σ–π–σ isomerization of a π-allyl intermediate are rather stringent: the π-allyl intermediate must contain one terminal nonstereogenic center and the rate of isomerization must be fast relative to substitution.

For these reactions, either chiral or achiral allylic substrates can be used. For chiral substrates, enantiomer selection during formation of the π-allyl intermediate can take place, but under conditions where isomerization of the allylic intermediate is fast relative to substitution, enantiomer selection should not influence the overall enantioselectivity of the reaction. This was shown for example in Scheme 8, where in the presence of an achiral catalyst, the cyclization of optically active (*R*)-3-oxo-7-((methoxycarbonyl)oxy)-8-nonanoate occurred with complete loss of optical activity.[86] In the presence of a chiral catalyst ((*S*,*R*)-BPPFA (8) as ligand), the identical system afforded optical yields of up to 30%, regardless of whether (*E*)-3-oxo-9-(methoxycarbonyl)oxy)-7-nonanoate or *rac*-3-oxo-7-((methoxycarbonyl)oxy)-8-nonanoate was used as the substrate.[102] Optical yields of up to 48% were reported for this system. This system also ex-

TABLE 3. Asymmetric Allylation of Some Organomagnesium (or Organozinc) Compounds in the Presence of [(*S*,*S*)-chiraphos]$NiCl_2$ as the Catalyst Precursor[98–100]

allylic substrate	organomet compd	allylation prod opt purity (%) and ac
	CH_3MgBr	1.3 (*S*)
	C_2H_5MgBr	51.2 (*R*)
	CH_2=$CHMgBr$	24.2 (*S*)
	C_6H_5MgBr C_6H_5ZnCl[a]	5.8 (*S*) 1.0 (*S*)
	CH_3MgBr	13.5 (*R*)
	C_2H_5MgBr	90.4 (*R*)
	C_2H_5MgBr	34.1 (*S*)
	6-CH_3O-2-$C_{10}H_6MgBr$	68.0 (*R*)
	6-CH_3O-2-$C_{10}H_6MgBr$	67.0 (*R*)
	6-CH_3O-2-$C_{10}H_6MgBr$	41.0 (*R*)
	C_6H_5MgBr	47.0 (*R*)

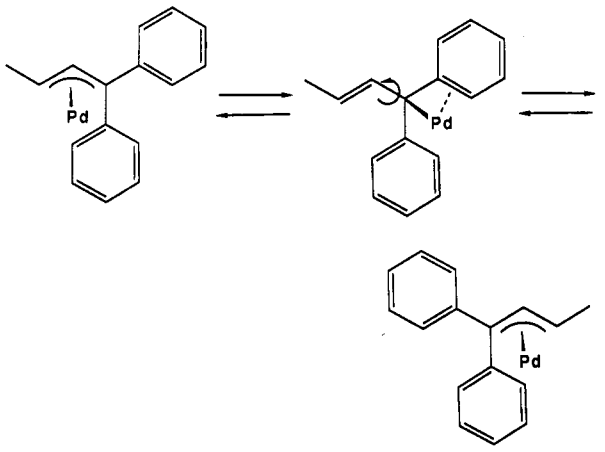
[a] Cyclohexenyl acetate as the substrate and $Pd(dba)_2$/(*S*,*S*)-chiraphos as the catalyst precursor.[100] [b] Pv = pivalate.

TABLE 4. Asymmetric Allylation of $NaCH(COOCH_3)Z$ Nucleophiles Using $[Pd\{(S,S)\text{-chiraphos}\}(\eta\text{-}C_3H_5)]ClO_4$ as the Catalyst Precursor[103]

allylic substrate	nucleophile Z =	solvent[a]	opt yield, %
(*R*,*S*)-Ph(AcO)CHCH=CPh_2	$COOCH_3$	THF	84
(*E*)-PhCH=CHC(OAc)Ph_2	$COOCH_3$	THF	84
	$COOCH_3$	DMF	86
(*R*,*S*)-CH_3(AcO)CHCH=CPh_2	$COOCH_3$	THF	65
	$COOCH_3$	DMF	67
	$SO_2(p\text{-}CH_3C_6H_4)$[b]	THF	65
	$COCH_3$	THF	67
(*R*,*S*)-Ph(AcO)CHCH=CAr_2[c]	$COOCH_3$	THF	64
(*R*,*S*)-(*E*)-Ph(AcO)CHCH=CHPh	$COOCH_3$	THF	22

[a] THF = tetrahydrofuran; DMF = dimethylformamide. [b] Reaction temperature, 55 °C; the other reactions were carried out at 25 °C. [c] Ar = 3,5-$(CH_3)_2C_6H_3$.

SCHEME 16



hibited complete regioselectivity, probably due to the greater stability of the 6-membered ring relative to the 8-membered ring that would form via cyclization to the less substituted termini of the allylic intermediate (see Scheme 8).

One thoroughly investigated example of asymmetric induction connected with enantioface selection was reported by Bosnich and co-workers.[25,103] These authors investigated substrates of the type $RCH{=}CHCAr_2Y$ and $RCHYCH{=}CAr_2$ (Y = leaving group, Ar = aryl), which, in the presence of palladium/chiraphos catalysts, undergo attack exclusively at the less substituted carbon atom of the allylic intermediate.[103] These substrates were chosen for the additional reason that exchange of the allylic enantiofaces is rapid relative to substitution. The high isomerization rates of these types of π-allyl intermediates were attributed to a σ-π-σ process involving η^3-benzyl participation, as shown in Scheme 16. A summary of these authors' results is presented in Table 4. Distinctive features of this catalytic system are summarized as follows:

(1) A correlation was established between the type and extent of enantioface discrimination in the π-allyl intermediate and the enantioselectivity of the reaction. That is, the diastereomeric equilibrium for the two enantiofaces of the syn diastereomers of the π-allyl intermediates provided an indication of the extent and sense of asymmetric induction in the reaction.

(2) Optical yields do not depend on the geometry of the substrate (Table 4, entries 1 and 2).

(3) The structure of the nucleophile has little effect on the optical yields.

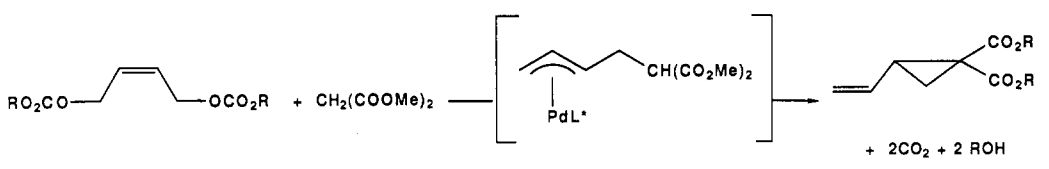
(4) Optical yields depend on the chiral ligand: chiraphos was superior to prophos; this could be partially explained on the basis of a reduced number of reaction intermediates in the presence of the C_2-symmetric chiraphos ligand.[103a]

(5) The prevailing enantiomer formed appears to result from attack of the nucleophile on the *syn*-allyl intermediate; the existence of the anti isomers could not be detected by solution NMR studies.

In a recent report, similar optical yields were obtained in the same reaction with (−)-sparteine as the chiral ligand, but in this case, the chemical yields were lower (61%).[94] In the reaction of dimethyl sodiomalonate with (*Z*)- and (*E*)-4-*tert*-butyl-1-vinylcyclohexyl acetate in the presence of palladium catalysts and chiral diphosphines, optically active dimethyl 2-((4-*tert*-butylcyclohexylidene)methyl)malonate was produced in optical yields of up to 40%.[177] In this paper, it was suggested that the enantioselectivity could be ascribed to the selection of one of two chiral conformers of the substrate; another possibility is that the enantioselectivity results from a diastereomeric equilibrium between the intermediate π-allyl complexes.

An intramolecular version of this type of reaction recently appeared.[104] In this case, optically active vinylcyclopropanes were obtained from (*Z*)-2-butylene dicarbonate in the presence of dimethyl malonate and a chiral $Pd_2(dba)_3$/(*R*,*S*)-BPPFFA catalyst system. This reaction apparently occurs in several steps involving the initial formation of the monocarbonate followed by formation of the π-allyl 12 and intramolecular substitution to give the cyclopropane derivative (Scheme 17). Optical yields of up to 70% were obtained with this system; chemical yields were between

SCHEME 17



12

SCHEME 18

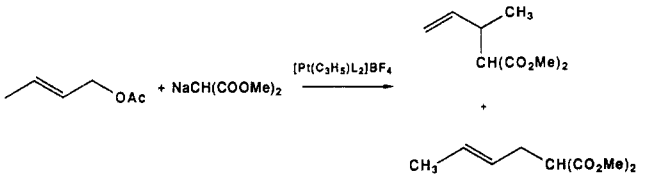


TABLE 5. Enantioselective Allylation of But-2-enyl Acetate Using $[Pt(L)(C_4H_7)]BF_4$ as the Catalyst Precursor[105]

ligand	(S)-dimethyl (buten-2-yl)malonate yield,[a] %	opt yield, %
(R,R)-diop	83	11
(R,R)-diop[b]	50	13
(R,R)-diop-dbp	75	0
(R,R)-2-MeO-diop	20	23
(S,S)-dipamp	56	13

[a] With respect to the sum of all alkylation products. [b] The corresponding palladium complex was used as the catalyst.

10% and 30%. The optical yields decrease with increasing reaction time, apparently due to the reversibility of the vinylcyclopropane formation. The chemoselectivity for this reaction is a function of the nucleophile; methyl acetoacetate or acetylacetone nucleophiles show a different chemoselectivity and yield dihydrofuran derivatives (see section 3.5).

Platinum complexes appear to be much less reactive than the corresponding palladium systems in allylation reactions.[105] However, the use of the less reactive platinum systems has proven useful for mechanistic studies designed to observe reaction intermediates. In the reaction of Scheme 18, optical yields were quite low (Table 5). In the presence of diop both the syn and anti diastereomeric allyl intermediates could be observed by NMR, in contrast to the palladium system investigated by Bosnich. At equilibrium, the anti isomer accounted for 37% of the allylic intermediates. Moreover, NMR studies on the isomeric olefin complex intermediates produced by nucleophilic attack of the π-allyl intermediates indicated that both syn and anti isomers are attacked by soft nucleophiles.

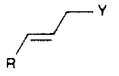
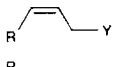
For hard nucleophiles the majority of studies have been carried out with nickel catalysts. The first examples involved the formation of 3-methyl-1-pentene with low optical yields (1–4%) in the ethylation of 2-buten-1-ol and the methylation of 1-penten-3-ol by Grignard reagents in the presence of [(R)-1-phenyl-1,2-ethanediylbis(diphenylphosphine)]nickel dichloride.[97] Subsequently, the reaction of methylmagnesium bromide with the three isomeric pentenols using [(R,R)-diop]$NiCl_2$ as the catalyst precursor was investigated (Table 6).[106] Although the isomeric product composition was not reported, the fact that *rac*-1-buten-3-ol gives optically active 3-methyl-1-pentene was interpreted in terms of a rapid equilibration of the allylic intermediate prior to alkylation. However, for this system it is likely that the rate of isomerization of the allylic intermediate is comparable with alkylation since in a related system, 25% retention of optical activity has been observed in the phenylation of (S)-but-1-en-3-ol in the presence of the achiral catalyst $(PPh_3)_2NiCl_2$.[35] An alternative interpretation of the experimental results that was evidently not considered is that the overall reaction enantioselectivity could be due to different regioselectivities on the two enantiofaces. This point will be considered in more detail in section 3.4.C.

In contrast to the system described above, the three isomeric butenyl phenyl ethers yielded the same product when alkylated in the presence of [(S,S)-chiraphos]$NiCl_2$.[98] The enantiomeric and isomeric compositions of the products were identical for all three ethers when treated with either EtMgBr or PhMgBr (Table 6). Optical yields were higher in the presence of the chiraphos ligand; this difference could be due to the stronger chelating power of the chiraphos ligand relative to diop.[107] Small differences in the isomeric and enantiomeric compositions in the reactions of butenyl esters with the Grignard reagent of 2-methoxy-6-bromonaphthalene[99] could arise from possible competing noncatalyzed reactions between the allylic substrate and the Grignard reagent. Furthermore, as seen in Table 6, there is a substantial influence of the nucleophile on the optical yield, in contrast to the previously discussed case involving soft nucleophiles and palladium catalysts.[103]

C. Enantioselectivity as a Result of Regioselectivity

Several years ago, it was observed that for addition reactions of unsymmetrical addenda to olefinic double bonds, enantioselectivity can be caused merely by different regioselectivities of attack on the two olefinic enantiofaces, even in the absence of enantioface selection.[108] This is also possible for allylic enantiofaces due to the unsymmetrical nature of the final adduct (see

TABLE 6. Nickel-Catalyzed Coupling Reactions of Allyl Substrates with Grignard Reagents

	optical purity (%) and asymmetric center			
	A[a] R = C_2H_5, Y = OH[106]	B[b] R = CH_3, Y = OC_6H_5[98]	C[c] R = CH_3, Y = OC_6H_5[98]	D[d] R = CH_3, Y = O_2C-*t*-Bu[99]
	1.2 (S)	22.3 (S)	58.0 (R)	88 (R)
	14.9 (R)	18.5 (S)	58.5 (R)	nr[e]
	8.5 (R)	17.5 (S)	60.0 (R)	81 (R)

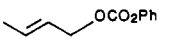
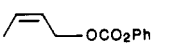
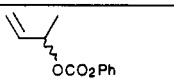
[a] Grignard reagent, CH_3MgBr; catalytic system, [(R,R)-diop]$NiCl_2$; chiral product, 3-methyl-1-pentene. [b] Grignard reagent, C_2H_5MgBr; catalytic system, [(S,S)-chiraphos]$NiCl_2$; chiral product, 3-methyl-1-pentene. [c] Grignard reagent, C_6H_5MgBr; catalytic system, [(S,S)-chiraphos]$NiCl_2$; chiral product, 3-phenyl-1-butene. [d] Grignard reagent, 6-MeO-2-$C_{10}H_6MgBr$; catalytic system, [(S,S)-chiraphos]$NiCl_2$; chiral product, 3-(6-methoxy-2-naphthyl)-1-butene. [e] Not reported.

TABLE 7. Enantioselective Coupling of Substituted Propenyl Acetates ($Ar^1CH(OAc)CH{=}CHAr^2$) with Sodium Acetylacetonate[109]

Ar^1	Ar^2	molar ratio A/B	ee of A[b]	ee of B[b]	$k_{1(S)}/k_{2(R)}$[c]	$k_{2(S)}/k_{1(R)}$[c]
C_6H_5	$3\text{-}CH_3OC_6H_4$	56:44	80 (*S*)	95 (*S*)	98:2	88:12
$1\text{-}C_{10}H_7$	C_6H_5	54:46	75	94	97:3[a]	87:13[a]
$4\text{-}ClC_6H_4$	C_6H_5	54:46	70	87	94:6[a]	84:16[a]
$4\text{-}CH_3C_6H_4$	C_6H_5	55:45	72	86	94:6[a]	84:16[a]
$2\text{-}CH_3C_6H_4$	C_6H_5	69:31	24	80	93:7[a]	50:50[a]

[a] Calculated assuming the same absolute configuration (*S*) for both coupling products. [b] A and B represent the products arising from attack at C1 and C3, respectively. [c] See Scheme 19.

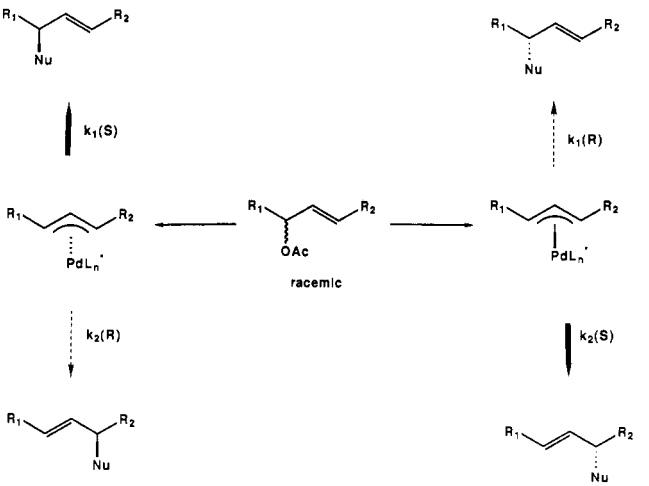
TABLE 8. Enantioselective Formation of Allyl Ethers via CO_2 Extrusion from Allyl Carbonates Catalyzed by Metal/Diphosphine Complexes[111,115]

							
ligand	metal complex	i.r.[a]	opt yield[b]	i.r.[a]	opt yield[b]	i.r.[a]	opt yield[b]
(*S,S*)-chiraphos	$Pd_2(dba)_3$	83/17	11.6 (*R*)	83/17	13.3 (*R*)	83/17	11.6 (*R*)
(*S,S*)-chiraphos	$Ni(COD)_2$	nd[d]	nd	nd	nd	88/12	15.8 (*R*)
(*S,S*)-chiraphos	$[Rh(NBD)Cl]_2$	96/4	23.4 (*S*)	98/2	7.4 (*S*)	nd	nd
(*R,R*)-BCO-DPP[c]	$Pd_2(dba)_3$	53/47	1.0 (*S*)	73/27	8.9 (*R*)	nd	nd

[a] 3-Phenoxy-1-butene/4-phenoxy-2-butene ratio. [b] Optical purity and absolute configuration of 3-phenoxy-1-butene. [c] BCO-DPP = 2,3-bicyclo[2.2.2]octanediylbis(methylene)bis(diphenylphosphine). [d] Not determined.

Scheme 19). A recent example of this phenomenon involved the palladium-catalyzed coupling reaction of racemic allylic acetates having the general formula (*E*)-$R^1CH(OCOCH_3)CH{=}CHR^2$ (R = aryl) with sodium acetylacetonate (Scheme 19 and Table 7)[109,110] in the presence of $[Pd(\pi\text{-}C_3H_5)Cl]_2$ and (*R*)-*N*-methyl-*N*-(bis(hydroxymethyl)methyl)-1-[(*S*)-1′,2-bis(diphenylphosphino)ferrocenyl]ethylamine (see Figure 2). For the racemic substrate (*E*)-1-(3-methoxyphenyl)-3-phenyl-3-acetoxy-1-propene nucleophilic attack occurs preferentially at C_1 for the (1***S***,2*R*,3*R*) allylic face but at C_3 for the (1*R*,2*S*,3***S***) face to give the two coupling products having (*S*) absolute configurations and ee's of 80% and 95%, respectively. This corresponds to ratios of regioselectivities on the two allylic enantiofaces of 98:2 and 12:88, respectively. For the other examples reported in Table 7, the absolute configurations of the products have not been reported,[109] but the results can be rationalized in a similar way. The same catalytic system shows a rather remarkable substrate enantiomer selection for substrates having one aryl and one alkyl substituent. In this case, enantiomer selection has an effect on the reaction enantioselectivity. With this system, the relative rate ratio for the two enantiomers of 1-[(*E*)-styryl]-2-methylpropyl acetate is $k_{(S)}/k_{(R)}$ = 14, which allows a kinetic resolution of the substrate: at conversions higher than 68%, practically enantiomerically pure (>99%) unreacted starting material could be recovered from the reaction mixture.[110] The regioselectivity ratios for the two allylic enantiofaces, calculated from the reported ee's and the total regioselectivity, are approximately 25:1 for the (1*R*,2*R*,3*S*) enantioface and 1:1.25 for the (1*S*,2*S*,3*R*) enantioface (reactivity at C1 with respect to C3). This substantial difference in regioselectivities for the two enantiofaces causes a remarkable change in the prevailing absolute configuration for the product arising from attack at C1 (bearing the phenyl group) from (*R*) to (*S*) when the conversion is increased from 40% to 80%. Enantiomer selection is lower ($k_{(S)}/k_{(R)}$ = 6) when dimethyl sodiomalonate is used as the nucleophile or when 1-[(*E*)-styryl]ethyl acetate is the substrate ($k_{(S)}/k_{(R)}$ = 1.2). The latter case is comparable to the very low enantiomer selection observed with hard nucleophiles in the nickel-catalyzed allylation reaction.[96,97]

SCHEME 19

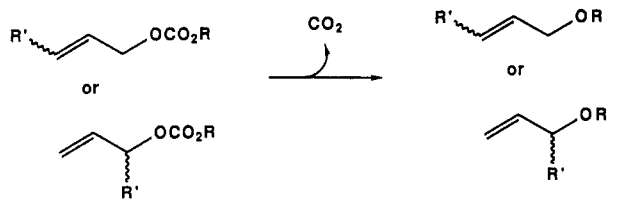


3.5. Non-Carbon Nucleophiles

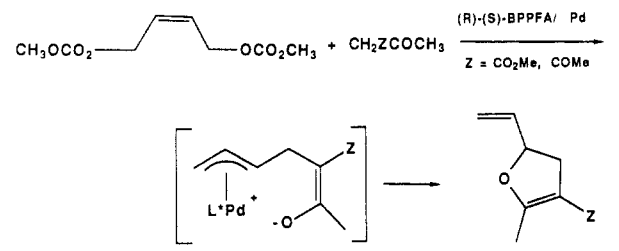
For non-carbon nucleophiles, the reversibility of the allylation reaction can cause considerable difficulties. If the product has a reactivity similar to that of the substrate, then, under low catalyst concentrations, racemization of the products results.

The first approach to this kind of reaction[111] took advantage of the higher reactivity of allyl phenyl carbonates with respect to allyl phenyl ethers.[112] Allyl phenyl carbonates undergo CO_2 extrusion[113] to give allyl phenyl ethers (Scheme 20). In the case of allyl alkyl carbonates, the reaction was found to give low yields and to be nonstereospecific.[47] Some results obtained in the enantioselective CO_2 extrusion reaction involving allyl aryl carbonates are shown in Table 8.[111] This reaction can be catalyzed by different metal complexes, each having its own stereochemical characteristics.[114]

SCHEME 20



SCHEME 21



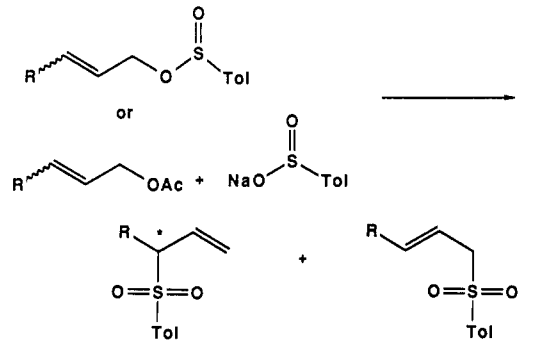
In the case of the reaction catalyzed by $Pd(DBA)_2$/(*S*,*S*)-chiraphos, optical yields and isomeric product compositions are independent of the structure of the butenyl phenyl carbonate substrate. For all isomeric carbonate substrates, (*R*)-3-phenoxy-1-butene having an optical purity of 12–13% is formed as the major product. These results are consistent with a rapidly isomerizing π-allyl intermediate. It is also worth mentioning that the (*R*) enantiomer is formed prevailingly when (*E*)-1-phenoxy-2-butene isomerizes to 3-phenoxy-1-butene. The (*R*) enantiomer also preferentially isomerizes with respect to the (*S*) isomer when this catalytic system is used.[115]

In the presence of a different chiral ligand, (*S*,*S*)-2,3-bicyclo[2.2.2]octanediylbis(methylene)bis(diphenylphosphine), the optical yield and the isomeric product composition depend on the structure of the substrate. It appears that in this case and in the case of $[Rh(NBD)Cl]_2$/(*S*,*S*)-chiraphos, isomerization of the π-allyl intermediate is slower than product formation. The extent of asymmetric induction for these reactions is low, the best reported optical yield being 23%. This is possibly due to the fact that attack of the phenoxy nucleophile on the allylic intermediate appears to be less stereospecific than it is for other nucleophiles.[115]

Better optical yields (up to 70%) have been reported for the reaction of 2-butylene dimethyl carbonate with methyl acetylacetonate catalyzed by $Pd_2(dba)_3$/(*R*,*S*)-BPPFA (Scheme 21) to yield dihydrofurans.[104] With this nucleophile, there is no competing cyclization to the vinylcyclopropane (see section 3.4.B). In addition, the vinyldihydrofuran products are only slowly ring-opened under the reaction conditions, and thus racemization of the products does not occur to a great extent. Similar products were obtained with acetylacetone nucleophiles, although the optical yields have not been reported.

The sulfonylation of allylic sulfinates or acetates (Scheme 22)[116] yields optically active sulfones in high optical yields.[117-119] The palladium-catalyzed rearrangement of (*Z*)- and (*E*)-2-butenyl *p*-toluenesulfinate (**13**) in the presence of (*R*,*R*)-diop afforded (*R*)-1-buten-3-yl *p*-tolyl sulfone with 87% ee (Table 9). Chiral monophosphines such as NMDPP and (*S*)-(2-methylbutyl)diphenylphosphine also yielded high degrees of enantioselectivity. Curiously, asymmetric induction in

SCHEME 22



SCHEME 23

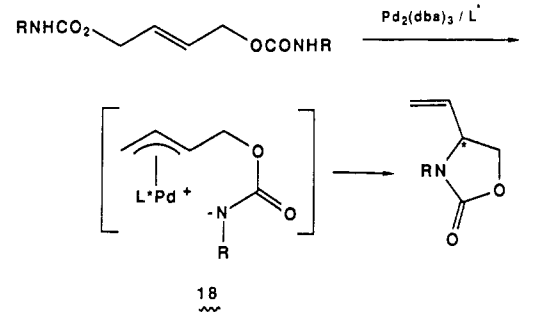


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TABLE 9. Enantioselective Synthesis of Allyl Sulfonates via Rearrangement of Sulfinates or Sulfonylation of Allyl Acetates Catalyzed by $Pd(PPh_3)_4$/(*R*,*R*)-diop[118]

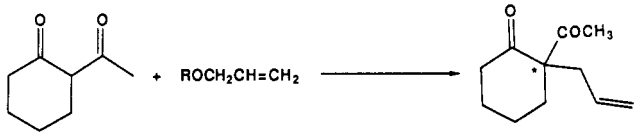
substrate	achiral product yield, %	chiral product yield, %	chiral product ee, % (config)
	R = CH_3		
(*E*)-**13**	15	77	87.0 (*R*)
(*Z*)-**13**	15	73	86.0 (*R*)
(*E*)-**14**	24	73	88.0 (*R*)
(*Z*)-**14**	23	70	88.0 (*R*)
	R = *n*-C_3H_7		
(*E*)-**15**	37	55	78.5 (*R*)
(*E*)-**16**	39	59	78.8 (*R*)
(*Z*)-**16**	38	58	70.3 (*R*)
	R = *n*-C_5H_{11}		
(*E*)-**17**	17	70	83.0 (*R*)
(*E*)-**17**	21	74	69.5 (*R*)

the formation of the sulfone is not affected if the reaction is carried out starting from the corresponding acetates and sodium *p*-toluenesulfinates, although the isomeric ratio changes. The choice of solvent in these reactions is critical. When THF is used as a solvent, (*R*)-1-buten-3-yl *p*-tolyl sulfone is the major product,[119] but when a mixture of THF and methanol is used as the solvent, the kinetically formed sulfone with the external double bond isomerizes under the reaction conditions to the thermodynamically more stable achiral sulfone with the internal double bond.[118]

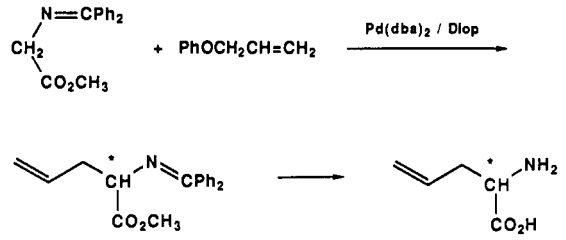
When benzylamine was used as a nucleophile in the substitution reaction of *rac*-1,1-diphenyl-3-butenyl acetate in the presence of $[Pd(C_3H_5)$((*S*,*S*)-chiraphos)$]ClO_4$, the substitution product (1,1-diphenyl-3-(benzylamino)-1-butene) had a prevailing (*R*) absolute configuration in 63% ee.[103] In this case the type and extent of enantioface selection are the same as those reported for stabilized carbon nucleophiles.

Carbamates can also be used as nucleophiles as shown in Scheme 23. The cyclization of 2-butylene di-

SCHEME 24



SCHEME 25



carbamates catalyzed by chiral ferrocenyl–phosphine–palladium complexes yields 4-vinyl-2-oxazolidones, which can be hydrolyzed to 2-amino-3-butenols.[120] Several chiral ligands have been investigated; the best optical yields (73%) for (*E*)-2-butylene *N*,*N*-diphenylcarbamates were obtained by using compound 4. Slightly better optical yields (77%) were obtained for the (*Z*)-butylene carbamates.

A similar reaction intermediate has been proposed for the reaction of racemic vinyloxiranes with phenyl isocyanates.[120,121] In the case where compound 4 was used as the chiral ligand, (*S*)-4-vinyl-*N*-phenyl-2-oxazolidones were formed in 43% optical yields. This result implies that epimerization of intermediate 18 is fast relative to cyclization; however, complete epimerization does not appear to take place.[120]

3.6. Achiral–Nonprochiral Allylic Substrates/Chiral Nucleophiles

For enantioselective reactions involving achiral–nonprochiral allylic substrates, a chirality center must be present in the nucleophile. With few exceptions, unsubstituted allylic electrophiles (CH_2=$CHCH_2Y$) have been coupled with either stabilized carbon nucleophiles or secondary Grignard reagents. A common feature of these nucleophiles is that they have stereochemically labile centers of chirality.

A. Reactions with Stabilized Nucleophiles

The first example of this reaction was reported by Kagan et al.[122] for the reaction of 2-acetylcyclohexanone with allyl phenyl ether in the presence of [(*S*,*S*)-diop]$PdCl_2$ and a basic cocatalyst such as sodium phenolate (Scheme 24). Optical yields for these reactions were quite low (up to 7% ee) and were found to depend on the solvent, on the counterion of the basic cocatalyst (Li vs Na), and on the leaving group of the allylic electrophile (AcO vs MeO vs C_6H_5O). Similarly, low enantioselectivities were observed for 2-acetyl-1-tetralone and hydratropaldehyde (10% and 8% ee, respectively). The low enantioselectivities were attributed to the distance of the chiral ligand from the developing asymmetric center. However, some years later[123] the same catalytic system was used with better success (up to 62% ee) for the reaction of the methyl ester of glycine benzophenone imine with allyl phenyl ether or allyl acetate (Scheme 25). The same catalytic system has been used for the reaction of the zinc enolate of 3-pentanone with 2,3-dichloropropene to give 6-chloro-4-methyl-6-hepten-3-one with 34% ee.[124]

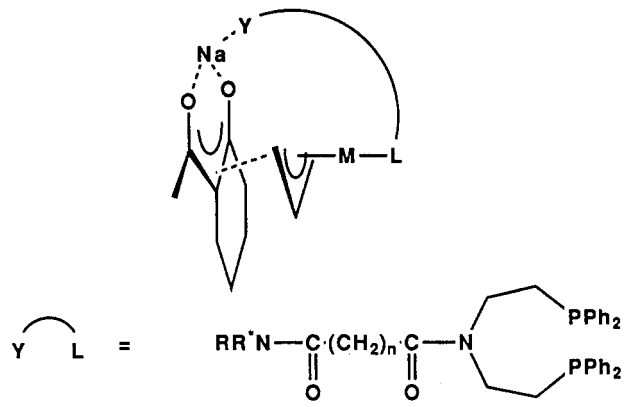


Figure 4.

TABLE 10. Asymmetric Allylation of 2-Acetylcyclohexanone with Allyl Acetate in the Presence of Palladium Catalysts[126,127]

(*R*,*S*)-BPPF-X X =	temp, °C	ee, % (config)
$NMeCH_2CH_2OH$	15	16 (*S*)
	0	27 (*S*)
	−10	42 (*S*)
	−30	53 (*S*)
	−50	73 (*S*)
	−60	81 (*S*)
$NHCH_2CH_2OH$	−50	62 (*S*)
$N(CH_2CH_2OH)_2$	−50	62 (*S*)
OCH_2CH_2OH	−50	53 (*S*)
$NMeCH(CH_2OH)_2$	−50	49 (*S*)
$NH(CH_2)_3OH$	−50	46 (*S*)
$NHCH_2CMe_2OH$	−30	31 (*S*)
OH	−30	30 (*S*)
NH_2	−30	15 (*S*)
$NHCH_2CH_2OCH_2CH_2OH$	−30	0
$NHCH_2CH_2OMe$	−30	6 (*R*)
OCOMe	−30	16 (*R*)
Me	−30	19 (*R*)
$NMeCH_2CH_2NHMe$	−30	20 (*R*)
NMe_2	−30	22 (*R*)

To improve the asymmetric induction in these reactions, Hayashi, Kumada, and co-workers have devised chiral ligands bearing polar groups that were expected to interact with the attacking nucleophile in order to obtain a better enantioface selection of the enolate moiety. This approach is represented schematically in Figure 4, together with the type of ligand employed. Substitution of allyl acetate in the presence of [(C_3H_5)$PdCl]_2$ using the ligand shown in Figure 4 (n = 2, NRR* = NHC*H(i-C_3H_5)$COOCH_3$) at −50 °C proceeded with 52% ee.[125] Subsequently, the ferrocenyl diphosphine ligands discussed previously were developed for the same reaction.[126,127] The most successful ligand (Table 10, X = $N(CH_3)CH_2CH_2OH$) gave optical yields of up to 82% at −60 °C. The results summarized in Table 10 show the effects that different substituents on the ferrocenyl phosphine ligand have on the asymmetric induction in these reactions. Studies of the temperature dependence on the optical yields using these diphosphine ligands revealed a sharp decrease in the optical yield with increasing temperature.[127,128] This catalytic system was also found to be effective for the asymmetric allylation of 2-acetyl-1-tetralone (82% ee), hydratropaldehyde (53% ee), and other dicarbonyl compounds (58–70% ee)[129] but is less effective for α-

SCHEME 26

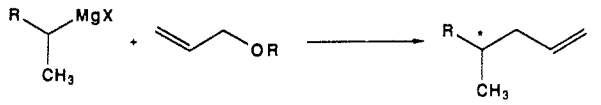


TABLE 11. Enantioselective Allylation of Grignard Reagents in the Presence of [P-P]$NiCl_2$ Derivatives[98]

RCH-(CH_3)-MgX				yield,	opt yield,
R	X	Y	P-P	%	%
C_2H_5	I	OC_6H_5	(*R*)-phenphos	10	1.3 (*R*)
C_6H_5	Cl	OC_6H_5	(*R*)-prophos	81	14.0 (*S*)
C_6H_5	Cl	OC_6H_5	(*R*)-phenphos	86	10.1 (*S*)
C_6H_5	Cl	OC_6H_5	(*S,S*)-chiraphos	87	58.3 (*R*)
C_6H_5	Br	OC_6H_5	(*S,S*)-chiraphos	87	47.0 (*R*)
C_6H_5	Br	OC_6H_5	(*R,R*)-cyphenphos	50	31.2 (*S*)
C_6H_5	Cl	$PO(OC_2H_5)_2$	(*R,R*)-chiraphos	65	37.2 (*R*)
C_6H_5	Cl	$PO(OC_6H_5)_2$	(*R,R*)-chiraphos	75	13.4 (*R*)
C_6H_5	Cl	OC_2H_5	(*R,R*)-chiraphos	55	47.3 (*R*)
C_6H_5	Cl	SCH_3	(*R,R*)-chiraphos	70	56.8 (*R*)
C_6H_5	Br	SCH_3	(*R,R*)-chiraphos	55	46.2 (*R*)

isocyano carboxylates (39% ee).[130]

B. Reactions with Grignard Reagents

Chiral products can be obtained with achiral allylic substrates when a secondary Grignard reagent is used in the presence of a chiral catalyst. The asymmetry-inducing step is most likely the alkylation of the metal complex by the Grignard reagent, as in the case of the widely investigated cross-coupling reactions of Grignard reagents with alkyl halides.[10,131-133]

The majority of studies have been carried out with nickel catalysts since only recently have palladium systems been found to react cleanly with hard nucleophiles.[58,100] For the nickel catalysts, low optical and chemical yields were reported[97] for the reaction of *sec*-butylmagnesium iodide with allyl alcohol in the presence of [(*R*)-phenphos]$NiCl_2$ (Scheme 26; R = C_2H_5, X = I, R = H) to give 4-methyl-1-hexene. Optical yields were better but still low for (1-phenylethyl)magnesium chloride with the same catalytic system. Optical yields appear to be influenced by the halide of the Grignard reagent but not by the leaving group, at least under conditions where there is no competing reaction from the noncatalyzed reaction. Much better optical yields (up to 58%) (Table 11) were obtained with the cyphenphos and chiraphos ligands, which may be due to the fact that these ligands are C_2 symmetric.[98]

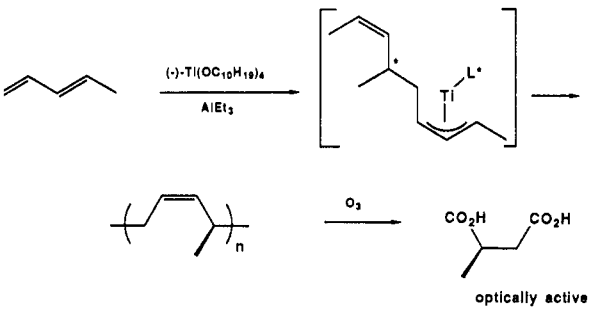
4. Dienes as Substrates

Despite the fact that the first report[134] of enantioselective catalysis by homogeneous transition-metal catalysts involved the polymerization of butadiene via allyl intermediates,[135] the activity and progress in this field have been much lower than in the previously discussed substitution reactions. Clearly, the same possibilities for enantioselectivity exist, but for these processes it is generally more difficult to obtain information about the asymmetry-inducing step.

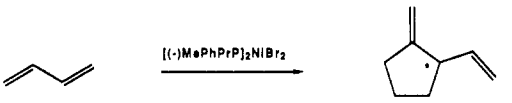
4.1. Poly-, Oligo-, and Telomerization

The first proposal that transition-metal catalytic systems could transmit chiral information came from studies of stereospecific polymerizations.[136] The same research group carried out the first attempts to chirally modify a homogeneous transition-metal system. The polymerization of 1,3-pentadiene[134] in the presence of triethylaluminum and tetramenthoxytitanium (Scheme 27) yielded an optically active polymer with a prevailing cis-1,4 structure. Ozonolysis of the polymer yielded optically active methylsuccinic acid, thus demonstrating that optical activity was associated with the presence of asymmetric carbon atoms in the polymer chain. The structure of the postulated[135] reaction intermediate is also shown in Scheme 27. A similar polymer was obtained some years later with a catalytic system based on tribenzylaluminum/tetrabenzyltitanium/(−)-menthol.[137] This catalytic system is quite complicated as demonstrated by the change in the optical rotation of the polymer samples obtained from two catalysts that differed only in the order of mixing of the catalyst components. More recently, neodymium trichloride modified with optically active sulfoxides in the presence of aluminum alkyls has been used as the catalyst precursor for the preparation of the same polymer.[138]

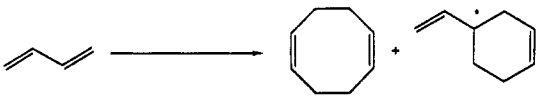
SCHEME 27



SCHEME 28



SCHEME 29



Ziegler–Natta catalyst systems such as diethylaluminum chloride/tetramenthoxytitanium catalyze the cyclotrimerization of 1,3-pentadiene to a mixture of trimethylcyclododecatrienes.[139] The crude reaction mixture exhibited optical activity. Oligomers obtained from optically active tetrakis(2-methylbutoxy)titanium showed lower optical activity.

Nickel complexes catalyze the cyclodimerization of 1,3-dienes. The cyclodimerization of butadiene with a catalytic system derived by reduction of bis[(−)-(methylphenyl)-*n*-propylphosphine]nickel dibromide with butyllithium yielded 1-methylene-2-vinylcyclopentane in 30% yield (Scheme 28). Although the products were optically active, the enantiomeric composition was not determined.[140] The involvement of a π-allyl intermediate is probable in these reactions.[141] The selectivity of butadiene oligomerization is different in the presence of bis(1,5-cyclooctadiene)nickel(0) and phosphines such as (*S*)-phenyl-*tert*-butylisopropylphosphine and (−)-phenyldimenthylphosphine or diphosphines such as

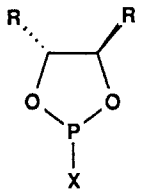


Figure 5.

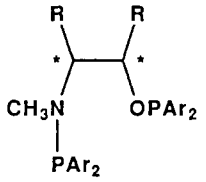


Figure 6.

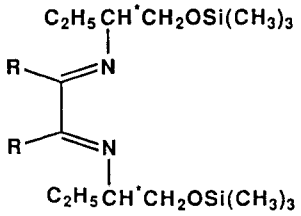


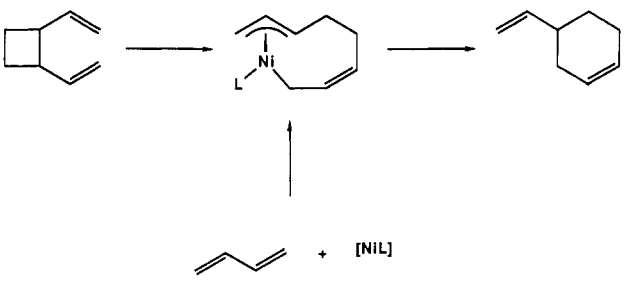
Figure 7.

diop.[141] In this case 1,4-cyclooctadiene is formed preferentially along with 4-vinylcyclohexene (Scheme 29). The optical purity of the vinylcyclohexene is only 12% at monophosphine/nickel ratios of 8/1 and lower for diop. The use of the 1,3,2-dioxaphospholanes led to minor improvements in selectivity for 4-vinylcyclohexene and in the enantioselectivity. Optical yields decrease with increasing temperature for these reactions; the best optical yield (35% ee) was obtained with 2-*tert*-butyl-4,5-dicarboethoxy-1,3,2-dioxaphospholane (Figure 5, X = t-C_4H_9, R = $COOC_2H_5$) at 20 °C. The same system catalyzes the rearrangement of *cis*-1,2-divinylcyclobutane to 4-vinylcyclohexene with the identical asymmetric induction.[143] This result has been taken as evidence for a common intermediate, most likely the (η^3-octadienediyl)nickel complex (Scheme 30).

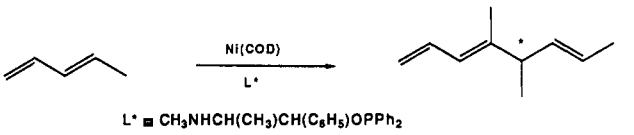
A series of ligands derived from amino acids (Figure 6) have also been used for this dimerization reaction catalyzed by nickel complexes.[144,145] Optical yields of up to 26% were reported for this system. Similar enantioselective cyclooligomerizations of butadiene (Scheme 29) have been carried out by using a diazadiene iron(II) chloride complex and a fourfold excess of ethylmagnesium iodide. Optical yields of 9.2% and 16.4% were obtained with the two diazadienes (Figure 7, R = H, CH_3), respectively.[146]

Bis(1,5-cyclooctadiene)nickel(0)-based catalytic systems containing amino phosphinite ligands $Ph_2POCHRCHR'NHCH_3$ were found to oligomerize 1,3-dienes mostly to linear dimers. The (1*R*,2*S*) ligand derived from ephedrine (R = C_6H_5, R′ = CH_3) causes the regioselective formation (approximately 90%) of optically active *cis*- and *trans*-4,5-dimethyl-1,3,5-octatrienes of unknown optical purity (Scheme 31).[145] The same system catalyzes the cyclodimerization of isoprene in 40% yield. Of the products formed, limonene (6%) was found in 10% enantiomeric excess.[145] Optically active 4-vinylcyclohexene was obtained as a side product in the telomerization of butadiene (vide infra) with

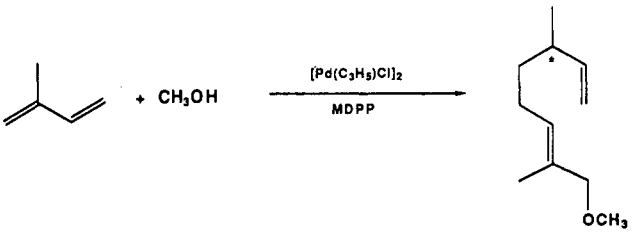
SCHEME 30



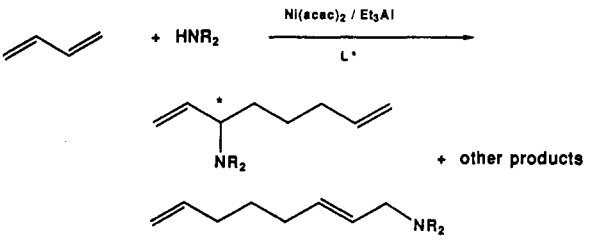
SCHEME 31



SCHEME 32



SCHEME 33

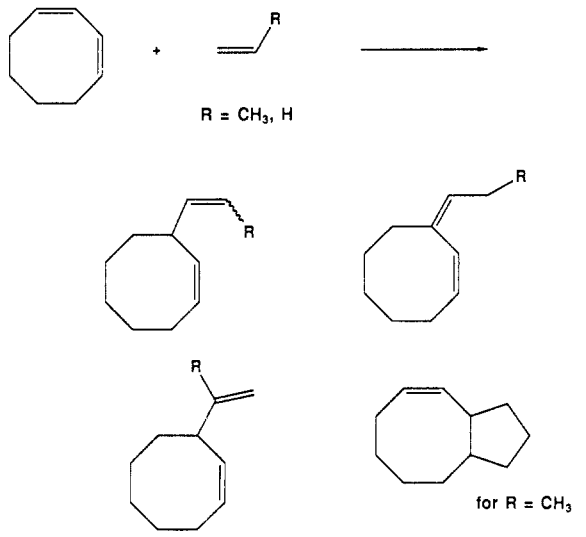


piperidine in the presence of $Ni(acac)_2/AlEt_3$ and $PPh(OR)_2$ (R = menthyl).[147] According to the reported optical rotation, the product should be of high optical purity (90%).

Telomerization of dienes involves dimerization or oligomerization with concomitant addition of a nucleophile. The telomerization of isoprene with methanol catalyzed by a combination of $[Pd(\pi\text{-}C_3H_5)Cl]_2$, CH_3O-Na, and menthyldiphenylphosphine or neomenthyldiphenylphosphine afforded 1-methoxy-2,6-dimethyl-octa-2,7-diene in 65% yield (Scheme 32).[148] A minimum optical yield of 17.6% was obtained with menthyldiphenylphosphine, as determined from the optical activity of the (-)-citronellol derived from that telomer. In the presence of neomenthyldiphenylphosphine the other enantiomer was produced with an optical purity of only 8.6%. The formation of the "tail-to-tail" telomer 1-methoxy-2,7-dimethyl-2,7-octadiene also occurs. Relatively high selectivities for the chiral telomer (up to 86%) have been reached with $PR(OMe)_2$ (R = menthyl), but in this case, the optical yields were only 8%.[149] Of the various chiral monophosphines investigated, menthyldiisopropylphosphine yielded the highest enantio- and regioselectivities (35% and 63%, respectively).

Amine telomers have been obtained in similar reactions involving the coupling of butadiene with nickel catalysts in the presence of phosphonite ligands derived

SCHEME 34



from menthol, 1,2,5,6-diisopropylideneglucose, or cholesterol (Scheme 33).[147] Two telomers are formed along with the simple addition products (see section 4.3) and cyclic dimers. The linear telomers are the major products with the phosphines investigated. The optical yield was only determined for the morpholine telomer (37% ee), which was obtained in 30% yield using PR(OR')$_2$ (R = *i*-Bu, R' = menthyl). A patent report[150] indicated that palladium systems catalyze similar reactions in the presence of chiral diphosphine ligands; however, no data on the optical yields of the telomers were given.

4.2. Codimerization with Olefins

The first example of an enantioselective codimerization of olefins with dienes involved the coupling of propylene or ethylene with 1,3-cyclooctadiene using nickel–allyl systems modified with (−)-tris(*trans*-myrtanyl)phosphine (Scheme 34).[151] Optically active (−)-3-isopropenylcyclooctene and (+)-bicyclo[6.3.0]undec-3-ene of unknown optical purity were obtained in the reaction with propylene. The (−)-3-vinylcyclooctene isolated from the reaction with ethylene had an optical purity of 10%. A number of different phosphine ligands have been investigated for this reaction;[152] in the presence of dimenthylmethylphosphine, optical yields could be improved from 23.5% at 0 °C to 53% at −75 °C. The best optical yield (70%) was obtained at 0 °C with dimenthylisopropylphosphine where the phosphine/nickel molar ratio was 3.8.[152] Lower ratios caused a decrease in the enantioselectivity.[153] The selectivity of these reactions is not very high; trimers of ethylene are also formed. Selectivities of 99% for the codimerization of 1,3-cyclohexadiene with ethylene were obtained with (COD)$_2$Ni, diethylaluminum chloride, and chiral aminophosphine ligands.[154] In the presence of (−)-(*R*)-(methyl(1-phenylethyl)amino)diphenylphosphine, (*S*)-3-vinylcyclohexene was obtained in 87% yield.[154,155] From a more recent, careful determination of the maximum optical rotation of 3-vinylcyclohexene,[155] the optical yield of this reaction can be calculated to be 47%. Better enantioselectivities were obtained with ligands derived from amino acids (Figure 6). With these ligands, optical yields of up to 93% were obtained at −30 °C.[145]

TABLE 12. Enantioselective Addition of Amines to Butadiene Catalyzed by Ni(acac)$_2$/Et$_3$Al in the Presence of Chiral Phosphonites[147]

chiral ligand[a]	amine	NRR yield, %	$[\alpha]_D$, deg	opt purity, %
(MenO)$_2$P(*i*-C$_4$H$_9$)		10	−0.41	52
(MenO)$_2$P(*i*-C$_4$H$_9$)		8	−0.1	ng[b]
(MenO)$_2$P(*i*-C$_4$H$_9$)		8	+1.8	58
(MenO)$_2$P(*i*-C$_4$H$_9$)		11	+2.12	77.5
(GluO)PPh$_2$		ng[b]	+0.63	78
(GluO)PPh$_2$		ng[b]	+0.21	26

[a] Men = menthyl; Glu = 1,2:5,6-diisopropylidene-3-glucosyl. [b] ng = not given.

4.3. Addition of Amines

In the addition of nucleophiles to 1,3-dienes, the selectivity for telomerization versus simple addition of the nucleophile to the diene depends on a number of factors, including the transition-metal catalyst. Palladium catalysts exhibit high selectivities for the simple 1:1 addition reactions.[157] Optically active products have recently been obtained from the addition of amines to butadiene using the nickel systems discussed in section 4.1.[158] Selected results are presented in Table 12. These reactions are slow, requiring 30 days at −8 °C, and the selectivity is quite low, but the enantioselectivity of the reaction can be as high as 78%.

Similar reactions have been carried out by using palladium acetate and chiral diphosphines such as dipamp and diop.[150] Optical yields of 14% and selectivity of 27% were obtained for the addition of ammonia to 1,3-butadiene in the presence of diop; dipamp afforded a higher selectivity for the addition product (35%), but a lower enantioselectivity (3%). Other amine nucleophiles such as aniline and pyrrolidine add to 1,3-butadiene and 1,3-cyclohexadiene to give optically active products, but the optical purities of the products are unknown.[150]

4.4. Addition of Hydrosilanes

The addition of hydrosilanes to conjugated dienes to form chiral allylsilanes was first carried out by using palladium[159] and nickel[160] catalysts and menthyldiphenylphosphine, neomenthyldiphenylphosphine, or benzylmethylphenylphosphine as the chiral ligands. With cyclopentadiene or 1,3-cyclohexadiene as the substrate, optically active (2-cycloalkenyl)trichlorosilanes or dichloromethylsilanes were obtained. The optical yields were not determined in these first experiments.[161]

In the presence of (PPFA)PdCl$_2$ (PPFA = (*R*)-*N*,*N*-dimethyl-1-[(*S*)-2-(diphenylphosphino)ferrocenyl]-ethylamine), (2-cyclopentenyl)dichloromethylsilane was obtained in 22–25% optical yield.[162] The enantioselectivity was lower for 1,3-cyclohexadiene. Better re-

SCHEME 35

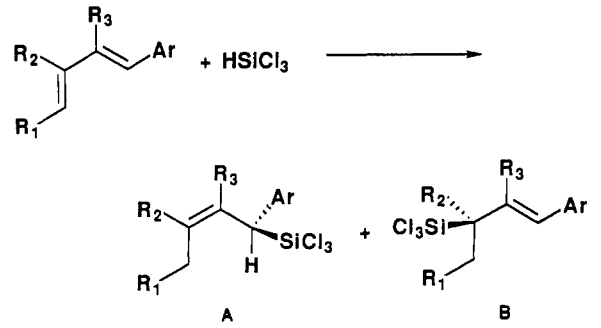


TABLE 13. Enantioselective Hydrosilation of 1-Arylbutadienes ($R^1CH{=}CR^2CR^3{=}CHAr$) with $HSiCl_3$ Using $(PPFA)PdCl_2$ as the Catalyst Precursor[163,164]

substrate[a]				isomeric	ee, % (config)	
R^1	R^2	R^3	Ar	ratio A/B[a]	A[a]	B[a]
H	H	H	C_6H_5	94/6	64 (*S*)	30 (*R*)
H	H	H	1-$C_{10}H_7$	49/51	29 (*S*)	55 (*R*)
CH_3	H	H	C_6H_5	93/7	31 (*S*)	nr[b]
H	CH_3	H	C_6H_5	100/0	50 (*S*)	
H	H	CH_3	C_6H_5	99/1	39 (*S*)	nr[b]

[a] Refer to Scheme 35. [b] nr = not reported.

sults were achieved for the hydrosilation of 1-arylbutadienes using the same catalyst precursor, the best reported optical yield being approximately 64% (Scheme 35 and Table 13).[163,164] On the basis of the regioisomers produced in this reaction, the results were interpreted in terms of a common π-allyl–silylpalladium intermediate having an aryl group in a syn position and a methyl group in an anti position.[163] However, there is no proof that this is the only intermediate involved in the formation of the prevailing enantiomers for both regioisomers (compare Scheme 4).

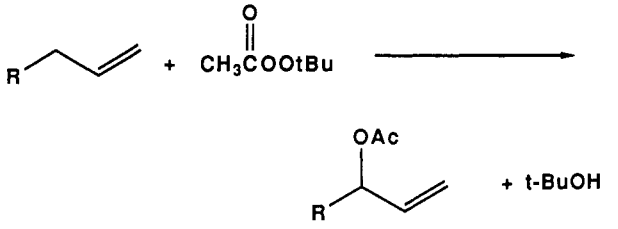
Ruthenium complexes in the presence of chiral diazadienes have been claimed to give optically active 3-methyl-4-(triethoxysilyl)-1-butene in the addition of triethoxysilane to isoprene.[165] However, neither the optical activity nor the enantiomeric excess for this compound has been reported.

5. Olefins as Substrates

Catalytic allylic substitution reactions of olefinic hydrocarbons by homogeneous transition-metal complexes are not very common[166] and their scope appears limited,[167] with the possible exception of the peroxy ester oxidation reactions of Scheme 36.[168] Copper salts are the catalysts of choice for these reactions. A peculiar feature of these allylic oxidations is that terminal olefins are selectively oxidized in the 3-position.[169] The first attempt of an enantioselective oxidation with this type of reaction utilized *tert*-butyl hydroperoxides as oxidants in the presence of copper salts of α-ethyl camphorate or diacetyl tartarate.[170] In this case stoichiometric amounts of the chiral-inducing reagents were used. The enantioselectivity of the reaction was quite low. Alcohols derived from acyclic olefins showed no appreciable optical activity.

Oxidations that are catalytic with respect to the chiral-inducing reagents have been reported only in the patent literature.[171] Optically active ligands derived from Schiff bases were used in situ "together with copper salts". Optically active products were obtained

SCHEME 36



in these cases from both acyclic and cyclic olefins, but in many cases the optical purity could not be calculated since the optical rotations of the optically pure compounds are unknown. The highest reported enantioselectivity (approximately 16–17%) was obtained in the oxidation of cyclohexene with *tert*-butyl peroxybenzoate in the presence of bis(L-prolinato)copper(II).

A number of different mechanisms for enantioselectivity can be envisioned for this reaction, depending on the type of intermediate involved in the product-forming step.[169] Enantioselectivity could be determined by the attack of the allyl radical on the copper catalyst, or in the formation of an allyl–copper intermediate. However, little is known of the mechanism of this reaction, and clearly more work is needed to define the scope and limitations of these copper-catalyzed allylic oxidations.

6. Conclusion

Enantioselective catalysis via transition metal–allyl intermediates is a powerful methodology for the synthesis of enantiomerically enriched compounds. Optical yields of up to 96% have been obtained by using this methodology.[95] One of the most impressive features of this methodology is the ability to replace existing centers of chirality of chiral racemic compounds with new centers of desired configuration. The rich reaction chemistry of transition-metal–allyl complexes can be exploited for the catalytic synthesis of carbon–carbon as well as carbon–heteroatom bonds from a variety of different substrates.

This methodology is not without limitations. The dual requirements of high selectivity and efficient asymmetric bias require a measure of control over the catalytic system that has been achieved only in isolated cases. One of the more severe limitations hindering further development of allylic substitution reactions is regiochemical control in the nucleophilic attack. This is particularly troublesome for substrates yielding allylic intermediates where one of the allylic termini is unsubstituted. Attack at the unsubstituted position (as might be expected for sterically demanding nucleophiles) yields achiral products. This for example is a serious shortcoming for the possible exploitation of the decarboxylative carbonylation of allylic carbonates[172] in order to prepare chiral β,γ-unsaturated esters.

Enantioselective catalysis is fundamentally a kinetic phenomenon. Control of the kinetic factors that influence the enantioselectivity requires a detailed mechanistic understanding of the catalytic system. For allylic substitution reactions, conversion of chiral racemic substrates into a single enantiomerically enriched product requires a rapid isomerization of the allylic intermediate or substrate prior to nucleophilic attack. The rate of these isomerization processes is governed

by numerous factors, including the transition metal, the chiral ligands, and the substitution pattern on the allylic ligand. A clear rationale for influencing the rate of these isomerization processes is still lacking, although the work of Bosnich[103] and co-workers demonstrates the usefulness of a mechanistic approach to this problem.

The enormous potential of these catalytic systems and the remarkable results that have been achieved underscore the value of further research in this fruitful area. These studies need not be restricted to allylic substitution reactions; interesting results have already been obtained with the related palladium trimethylenemethane intermediates for enantioselective reactions.[173] Other intriguing possibilities are suggested by results involving nucleophilic attack at the central carbon of allylic intermediates to produce transition-metal metallacyclobutanes.[174] Transition-metal–enolate (oxyallyl) complexes have been employed in stoichiometric enantioselective reactions,[175] but few catalytic enolate reactions have been reported.[176] Clearly, additional research in these and related areas will result in new and interesting applications for organic synthesis.

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