Asymmetric Catalysis. A Comparative Study of the Mechanisms of Intramolecular Hydroacylation and Hydrosilation

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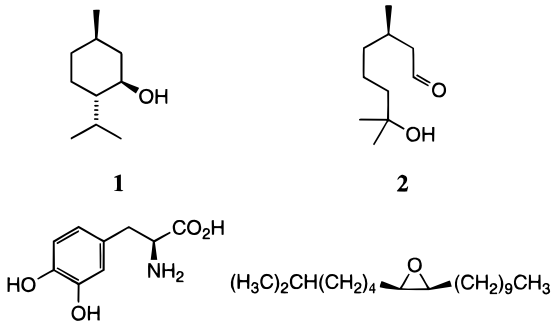
Introduction

Asymmetric catalysis is currently one of the more intensively studied subjects in synthetic chemistry. Its present status owes much to the intellectual challenges that the area presents and is driven by industrial demands for pure enantiomers that are used for the production of pharmaceuticals, fragrances, and food additives. Enantiomers are known to have biological responses that range from benign to catastrophic and, consequently, the use of pure enantiomers has become mandatory. Among the current industrial applications of asymmetric catalysis is the production of L-menthol (**1**), the fragrance component distributed under the mellifluous name of "Lily of the Valley" (**2**), the amino acid L-DOPA (**3**), and the Gypsy Moth phermone disparlure (**4**). In these examples, the key chiral centers (**1**−**4**)



1 **2** **3** **4**

are generated by asymmetric catalysis: the production of **1** and **2** relies on asymmetric catalytic double bond migration, **3** is made by asymmetric catalytic hydrogenation[2] and **4** is formed after asymmetric catalytic epoxidation[3]. Given the intense interest in this area, it is probable that many synthetic strategies will rely on asymmetric catalysis for generating key building blocks.

For its development, asymmetric catalysis relied on the discovery of new catalysts, generally organometallic species, on the synthesis of new chiral ligand types, and on an understanding of the mechanism of catalysis. It is this last question that is considered here for the examples of intramolecular hydroacylation and hydrosilation. Before these mechanisms are discussed, it is useful to outline the general mechanistic basis of asymmetric catalysis.

Catalysts accelerate the rates of reaction by opening new pathways. Sometimes these paths resemble those of the thermal reaction but, more often, the catalytic mechanism is a distinct one involving multiple steps. It is the formation of catalytic intermediates that leads to the lowering of the activation energy of the catalytic reaction. Under steady-state conditions, all steps of a catalytic reaction proceed at the same rate. This is achieved by adjustment of the concentrations of the intermediates to offset the differences in the corresponding rate constants. Catalytic reactions, therefore, do not have a "rate-determining step"; rather, the catalytic turnover frequency is controlled by the step with the lowest effective rate constant. This step is called the **turnover-limiting step**.

Asymmetric catalysis is purely a rate phenomenon; the enantiomeric excess (ee) is determined by the relative rates of production of the two enantiomers of the product. To achieve enantioselection, a chiral catalyst that can bind a prochiral substrate is required. The two (chiral) modes of binding of the prochiral substrate to the chiral catalyst will lead to two energetically distinct diastereomers. These two diastereomers will also form energetically different transition states. Consequently, the rates of conversion of the substrates to the enantiomeric products will be different leading to enantiomeric excess. Accordingly, asymmetric catalytic reactions can be described as consisting of two diastereomeric rate domains that lead to the respective enantiomers. The problem of obtaining high enantioselectivity, therefore, appears to be a simple matter; all that is required is to arrange for a large difference in the rates of reaction of the two diastereomeric rate domains. It turns out, however, that there is no simple way of determining energy differences between diastereomeric transition states. It is sometimes possible to correlate the relative energies of the diastereomeric transition states with the thermodynamic stabilities of the diastereomers that precede or succeed the transition states, depending on whether the step is under reactant or product control, respectively.[4] This correlation can only be done if there exists an identified step that controls the enantioselection. The catalytic paths leading to the enantiomeric products can be complex and may contain both reversible and irreversible steps. If, however, there exists an irreversible step that prevents the substrate from passing from one diastereomeric domain to the other, the enantioselection will be determined by the first of these

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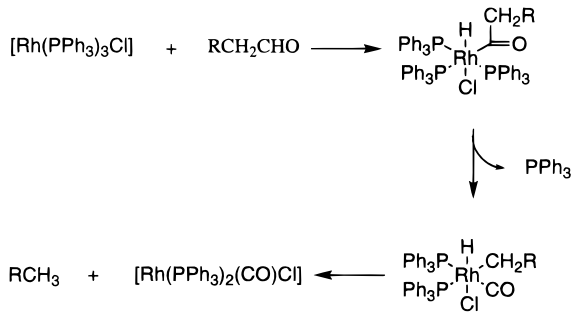
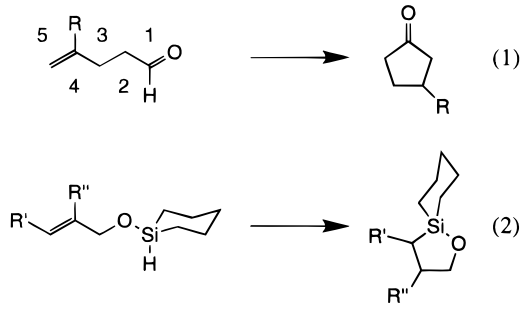
Scheme 1



steps. It is referred to as the **enantioselective step**. If such a step exists and can be identified, it is sometimes possible to correlate the enantioselectivity with the thermodynamic stabilities of diastereomers.[5] A common practice is to correlate the known enantioselection with the presumed initial diastereomers. Such models should be viewed with extreme caution for the reasons that will be illustrated presently.

1. Substrates and Catalysts

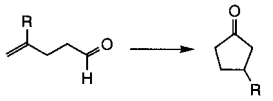
The two catalytic reactions discussed here are intramolecular hydroacylation (eq 1) and intramolecular hydrosilation (eq 2).



Intermolecular hydrosilation is a well-known process that is catalyzed by a variety of metal complexes.[6] Generally, the process is accompanied by double-bond migration, and a variety of regioisomers of the hydrosilated products are found. There is, however, a tendency for the silicon to locate at the terminal carbon atom. Intramolecular hydrosilation of the type illustrated in eq 2 ensures that only the 5-membered ring products are formed.[7] Although other silicon substituents can be used, the silacyclohexane substituent gave good turnover frequencies as well as high ee values for certain allylic fragments and catalysts.[8] The possibility of observing hydroacylation was prompted by the observation that Wilkinson's catalyst, $[Rh(PPh_3)_3Cl]$, decarbonylated aldehydes[9] by the presumed mechanism illustrated in Scheme 1.

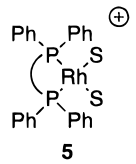
The steps shown in Scheme 1 suggest that it might be possible to obtain hydroacylation of olefins provided hydride−olefin insertion were to occur at the hydrido−acyl intermediate. Intermolecular hydroacylation does not occur with Wilkinson's catalyst because the rates of the steps shown in Scheme 1 are much faster than hydride−olefin insertion. The probability that an intramolecular process would enhance the rate of hydride−olefin insertion was soon recognized and attempted.[10] Wilkinson's catalyst and its variants promoted intramolecular hydroacylation (eq 1) but little or no catalytic turnover was observed because the catalytically inactive carbonyl complexes (Scheme 1) were formed rapidly.

Table 1. Asymmetric Catalytic Intramolecular Hydroacylation of 4-Substituted-4-pentenals Using $[Rh(chiral\ diphosphine)(S)_2]^+$ at 25 °C



		chiral diphosphine		
entry	R	(*S*)-binap ee% (config)	(*S*,*S*)-chiraphos ee% (config)	(*S*,*S*)-Me-duphos ee% (config)
1	^{t}Bu	>99 (S)	29 (R)	44 (S)
2		>99 (S)	41 (R)	–
3	Me_3Si	>99 (S)	8 (R)	64 (S)
4	$PhMe_2Si$	>99 (S)	15 (R)	61 (S)
5		87 (S)	13 (R)	–
6		94 (S)	64 (R)	–
7		>99 (S)	35 (S)	–
8		>99 (S)	11 (R)	–
9	Me	78 (S)	42 (S)	94 (S)
10	Et	60 (S)	45 (S)	95 (S)
11	^{n}Bu	–	–	94 (S)
12	Bn	–	–	94 (S)
13	^{i}Pr	60 (S)	45 (S)	96 (S)
14	C_5H_9	81 (S)	41 (S)	96 (S)
15	C_6H_{11}	69 (S)	50 (S)	94 (S)
16	Ph	70 (S)	78 (S)	46 (R)

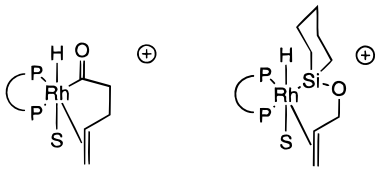
Because it is known that carbonyl ligands are less stable when they are trans to phosphine ligands and when the complexes are cationic, it was considered[11] likely that Rh(I) complexes of the type **5** would suppress decarbonylation of aldehydes (S = weakly coordinating solvent such as acetone or CH_2Cl_2).



5

This was found to be the case[11] for 4- and 3-substituted 4-pentenals for which >500 rapid turnovers were observed

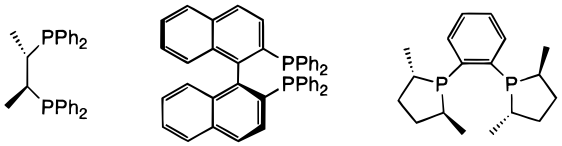
before the formation of the dicarbonyl complex, [Rh(diphosphine)$(CO)_2]^+$, which is a very poor catalyst. Substituents at the 5- and 2- positions of the pentenal, however, lead to poor turnover frequencies and numbers. The efficiency of catalysts of the type **5** is related to the rapid displacement of the solvent molecules and to the availability of at least three vacant coordination positions at the catalyst to accommodate the hydride, acyl, and olefin ligands of a putative catalytic intermediate **6**. When these coordination positions are occupied by nonlabile ligands such as, for example, acetonitrile, the catalytic frequency is very low and is dependent on the rate of dissociation of these ligands. The same types of catalysts, **5**, were expected to promote intramolecular hydrosilation where a similar intermediate, **7**, was proposed. This also proved to be the case.[8]



6 **7**

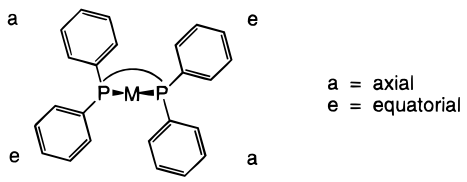
2. Asymmetric Catalysis

A number of chiral analogues of **5** were investigated to determine whether high enantioselectivities could be obtained with 4-substituted 4-pentenals. Catalysts derived from the chiral diphosphines (*S*, *S*)-chiraphos, **8**,[12] (*S*)-binap, **9**,[13] and (*S*, *S*)-Me-duphos, **10**[14] provided interesting results.



8 **9** **10**

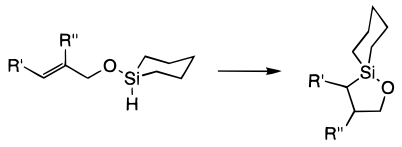
For catalysts formed by **8** and **9**, the major source of chiral induction is expected to arise from the chiral array of phenyl groups, the chiral orientation of which is determined by the chirality of the chelate ring.[12,15] Both (*S*,*S*)-chiraphos and (S)-binap have the same chirality of the phenyl groups, **11**, but the precise orientations differ.



11

The chiral induction of **10** emanates mainly from the methyl groups of the phosphacyclopentane substituents, the chelate ring is planar. Because **8** and **9** are structurally similar, it might be concluded that their catalysts would produce similar ee values and have the same sense of induction for both hydroacylation and hydrosilation substrates.

Table 2. Asymmetric Catalytic Intramolecular Hydrosilation Using [Rh(chiral diphosphine)$(S)_2]^+$ Catalysts in Acetone Solutions at 25 °C



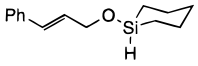
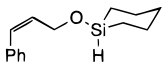
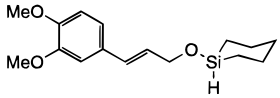
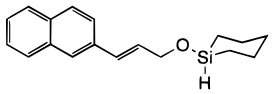
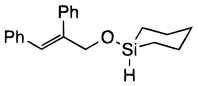
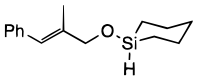
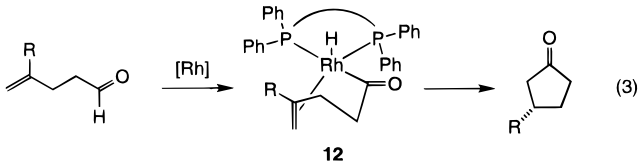
		chiral diphosphine	
substrate		(*S*)-binap ee% (config)	(*S*,*S*)-chiraphos ee% (config)
1		96 (R)	74 (R)
2		96 (R)	–
3		97 (R)	–
4		94 (R)	–
5		88 (?)	55 (?)
6		90 (RR)	0

Table 1[16] lists a number of the ee values observed with catalysts derived from the phosphines **8**, **9**, and **10** at 25 °C. Catalyst loadings were between 2 and 4 mol %. The solvents used were CH_2Cl_2 and acetone. The chemical yields in all cases were >95%. The reaction times were usually <2 h. The results are interesting in a number of respects. First, substrates bearing tertiary and ester groups give products that are essentially entiomerically pure with the (*S*)-binap catalyst. Second, substrates with acyl substituents give high ee values with the same catalyst. Third, substrates bearing *n*-alkyl or isoalkyl groups produce products with consistently high ee values with the Me-duphos catalyst. Fourth, despite the fact that the (*S*, *S*)-chiraphos and (*S*)-binap catalysts have the same twist sense for the phenyl groups, **11**, opposite absolute configurations of the products are produced in many cases and for most cases the chiraphos catalyst gives low ee values. Overall, the results in Table 1 suggest that the (*S*)-binap and (*S*, *S*)-Me-duphos catalysts give consistently high ee values for certain classes of substrates, and that seemingly small changes in the catalyst structure can have a large effect on the enantioselection.

A collection of results for hydrosilation using the (*S*)-binap and (*S*,*S*)-chiraphos catalysts is shown in Table 2.[8] The reactions were generally complete in 4 h at 25 °C, and the chemical yields were >90%. It will be noted that the (*S*)-binap catalyst gives consistently high ee values for

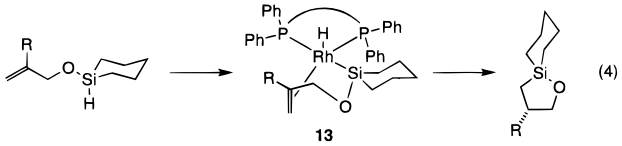
substrates bearing terminal aryl groups. Especially intriguing is the observation that the two isomeric substrates (entries 1 and 2) give identical enantioselection, and the rates of catalysis are identical for the two isomers. These results will be discussed later.

At this stage it is common to propose a model to rationalize the enantioselectivity. Given that the substrates, entries **1** to **8** in Table 1, give high enantioselectivity to produce the (*S*)-cyclopentanones in all cases using the (*S*)-binap catalyst, it might be concluded that the prevailing enantiomer of the product proceeds by the mechanism illustrated in eq 3.



12 (3)

The chirality of the olefin coordination in the putative intermediate, **12**, mechanistically connects with the known absolute configuration of the cyclopentanone product. The enantioselection is sometimes discussed in terms of the steric interactions in an intermediate such as **12**, that leads to the preferred diastereomeric intermediate. Using such arguments for hydrosilation, it might be tempting to conclude that a similar intermediate, **13** (eq 4), might control the enantioselectivity.

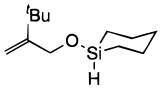
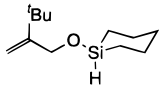
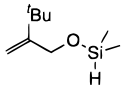
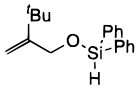
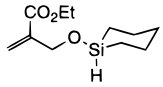
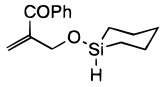
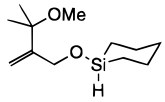
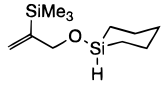


13 (4)

Of course the silacyclohexane group is different from an acyl group in terms of steric interactions; nonetheless, it could be supposed that substrates bearing tertiary, acyl, or ester groups might give high ee values with the (*S*)-binap catalysts as was observed for hydroacylation (Table 1, entries **1** to **8**).

Some of the results testing this analogy are collected in Table 3.[17] The first four entries indicate that the enantioselection depends on both the solvent and on the silicon substituent. Although the substituent and solvent effects are large, an inspection of the ee values observed for entries **1**, **5**−**8** might suggest that an analogy between intramolecular hydroacylation and hydrosilation exists. All of these products (entries **1**, **5**−**8**) generated by the (*S*)-binap catalyst have the same sense of induction. (The (*R*) and (*S*) designations vary according to the priority rules). The assumption that the prevailing enantiomers of the products originate in the olefin face-selection as shown in **13** is not the case, however, because the sense of induction for hydrosilation is **opposite** to that observed for hydroacylation using the (*S*)-binap catalyst. Thus, despite the fact that the analogy models appeared to be successful to the extent that high ee values were observed for hydrosilation, the analogy is clearly fanciful because the sense of chiral induction is opposite to that predicted.

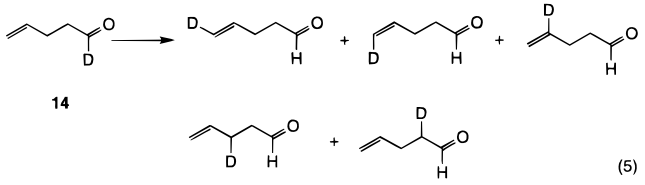
Table 3. Asymmetric Catalytic Intramolecular Hydrosilation Using [Rh((S)-binap)(S)$_2$]$^+$ at 25 °C

	substrate	solvent	ee% (config)
1		acetone	96 (R)
2		CH_2Cl_2	32 (S)
3		acetone	69 (R)
4		acetone	51 (R)
5		CH_2Cl_2	69 (S)
6		CH_2Cl_2	96 (S)
7		acetone	95 (S)
8		CH_2Cl_2	78 (R)

To understand why there cannot be any simple analogy between hydroacylation and hydrosilation, a detailed understanding of the mechanisms is required.

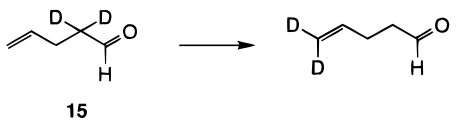
3. Hydroacylation Mechanism

Because no intermediates could be detected, the mechanism of intramolecular hydroacylation was inferred mainly from deuterium scrambling studies.[18] Among these studies was the hydroacylation of the deuterated substrate, **14**, with the chiraphos catalyst. During catalysis, deuterium is observed at all of the positions of the substrate (eq 5) before complete hydroacylation occurs.



14 (5)

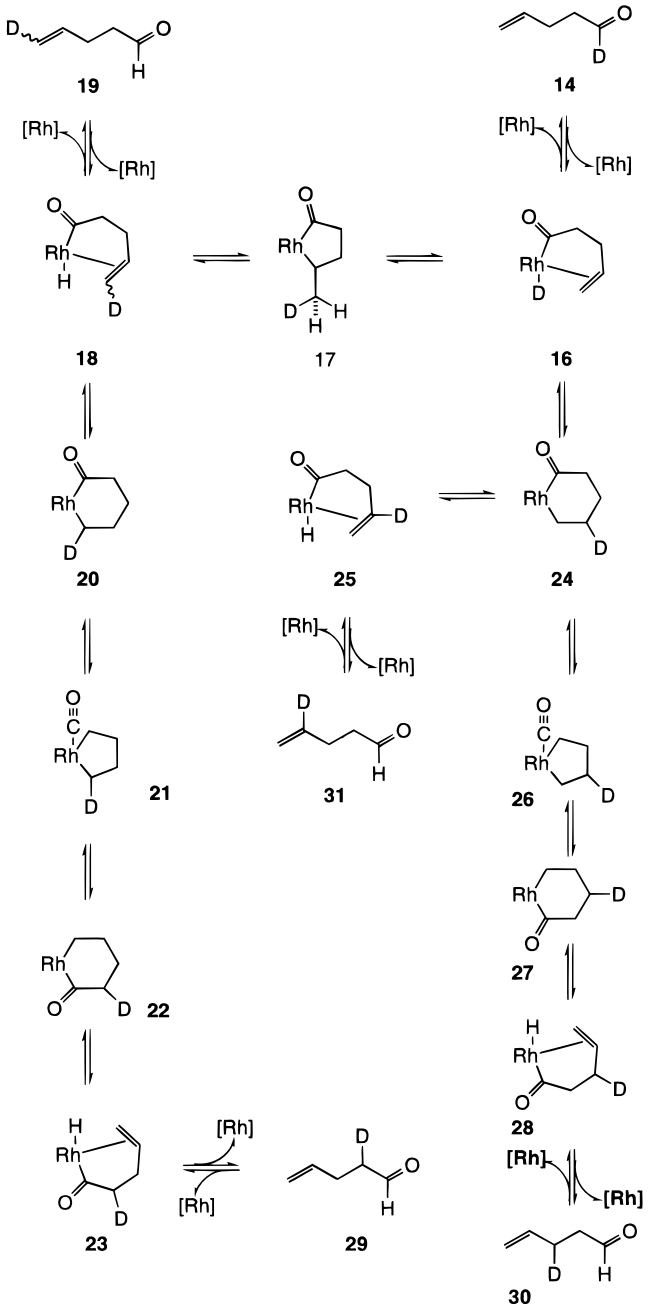
In another experiment, the deuterated substrate **15** underwent a small amount of the conversion shown in eq 6 during catalysis.



15 (6)

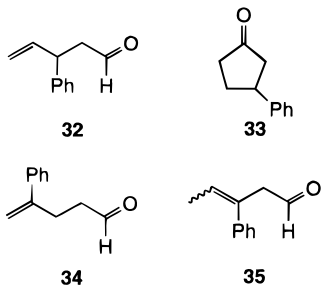
The deuterium relocations shown in eqs 5 and 6 are a

Scheme 2



consequence of the mechanism of hydroacylation and are not the result of other concurrent events such as double bond migration.[18] The extraordinary scrambling of the deuterium indicates that the catalytic mechanism is unusually complex and that numerous intermediates are formed before the final irreversible formation of the product. A mechanism that is consistent with the deuterium relocations illustrated in eqs 5 and 6 is shown in Scheme 2. Oxidative addition of the deuterated substrate, **14**, to the Rh(I) catalyst leads to the formation of the deutero-acyl-Rh(III) intermediate, **16**. The deutereo ligand of **16** can transfer to either of the carbon atoms of the double bond. Transfer to the terminal carbon atom leads to the five-membered metallocycle **17**, which leads back to **16** after β-deuterium elimination, or leads to **18** upon β-hydride elimination to give the two deutero-double bond isomers depending on which of the protons is β-hydride eliminated. Upon reductive elimination, **18** gives the two isomers of **19.** Transfer of the deutero ligand of **16** to the inner carbon atom of the double bond leads the six-membered metallocycle **24**, which can undergo β-deutero elimination back to **16** or can engage in β-hydride elimination to give **25**. Reductive elimination of **25** gives the deuterated substrate **31**. Decarbonylation of **24** gives an intermediate, **26**, where the CO ligand can reinsert either back to **24** or to **27**. β-Hydride elimination of **27** gives **28**, which, in turn, can produce the substrate **30.** The formation of the other possible deuterated substrate, **29**, follows a similar process starting from, **18**, via **20**, **21**, **22**, and **23**. The transformation shown in eq 6 is consistent with the decarbonylation−insertion steps, **24**−**26** − **27** or **20**−**21** − **22**. Further, the formation of the deuterated substrates (eq 5) indicates that all of the catalytic steps shown in Scheme 2 are reversible. It is remarkable that all of these steps can occur before intramolecular hydroacylation is complete. The final irreversible step is the reductive elimination of the 6-membered metallocycles (**24**, **27**, **20**, **22**) to give the cyclopentanone products. No cyclobutanones are formed despite the presence of the 5-membered metallocycles, **17**.

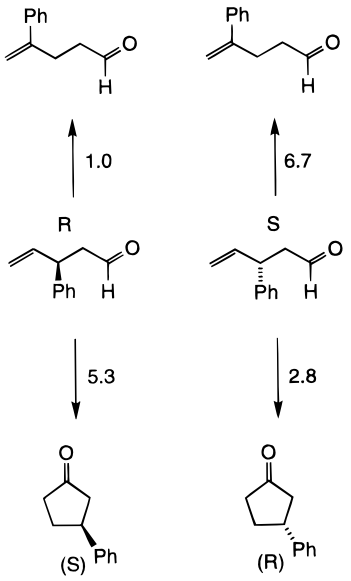
The mechanism illustrated in Scheme 2 is a necessary prelude to understanding the origins of the enantioselectivity. To try to understand the mechanistic basis for the enantioselectivity, a number of experiments[19] were devised, that, at first glance, appear to be inconsequential, but are implicit in the mechanism outlined (Scheme 2). Racemic 3-phenyl-4-pentenal, **32**, undergoes hydroacylation with the (*S*)-binap catalyst in CH_2Cl_2 solutions at 25 °C to give initially 51% of β-phenylcyclopentanone, **33**, as expected, but also 42% of 4-phenyl-4-pentenal, **34** is produced, together with ≅ 7% of 3-phenyl-3-pentenal, **35**. The latter is formed irreversibly by a double-bond migration mechanism. At a rate that is 20 times slower than the rate of disappearance of **32**, the 4-phenyl-4-pentenal, **34**, is converted to the cyclopentanone.



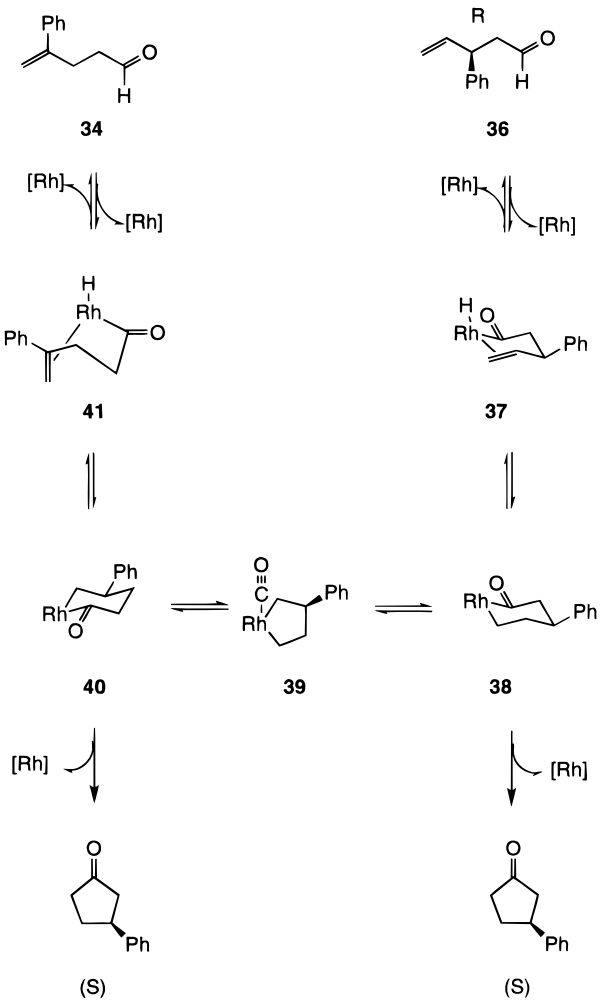
The relative rate constants for the initial kinetic resolution of racemic **32** are illustrated in Scheme 3.

The relative rate constants indicate that the two enantiomers of **32** react at different rates to both the chiral cyclopentanones and to the achiral 4-phenylpentenals. The kinetic amplification in the formation of (*S*)-β-phenylcyclopentanone is controlled by the faster catalytic conversion of the (*R*)-3 phenylpentenal to (*S*)-β-phenyl-

Scheme 3



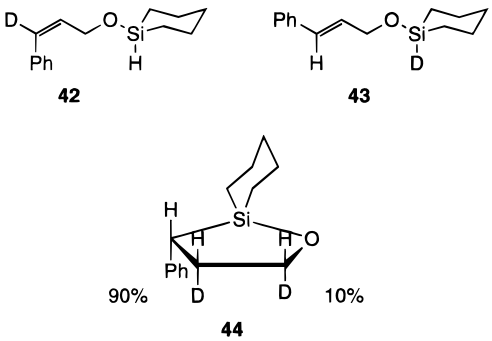
Scheme 4



cyclopentanone and by the more rapid conversion of the (*S*)-3-phenylpentenal to 4-phenylpentenal, **34**. The mechanism for these catalytic transformations follows from Scheme 2 and is outlined in Scheme 4 using the example of (*R*)-3-phenyl-4-pentenal. The β-phenylcyclopentanone product can form by reductive elimination of either of the two metallocycle intermediates **38** or **40**, which, presumably, will form the product at different rates. The carbonyl migration leads to the formation of **34** from **36.** Although all of the steps connecting **34** with **36** are reversible, equilibrium is not established because, if it were, the ee would be the same starting from either the 4- or 3-phenyl-4-pentenals. This is not the case. The different rates of production of the 4-phenylpentenals from the enantiomers of 3-phenylpentenal (Scheme 3) indicate that the catalytic intermediates are selectively formed. Hence, the enantioselectivity will depend on the relative rates of formation of the diastereomeric 6-membered metallocyclic intermediates (**38** and **40** and their corresponding diastereomers) and on their rates of reductive elimination to the enantiomeric products. It is clear that for hydroacylation there is no single enantioselective step and that the ee is controlled by a complex mix of rates. Consequently, it is not possible to present a simple model that describes the origins of the enantioselectivity, and the putative intermediate **12** (eq 3) represents merely the connection between the known preferred chirality of the product and the face orientation of the prochiral olefin, which may or may not represent the preferred orientation. Similar circumstances obtain for asymmetric intramolecular hydrosilation.

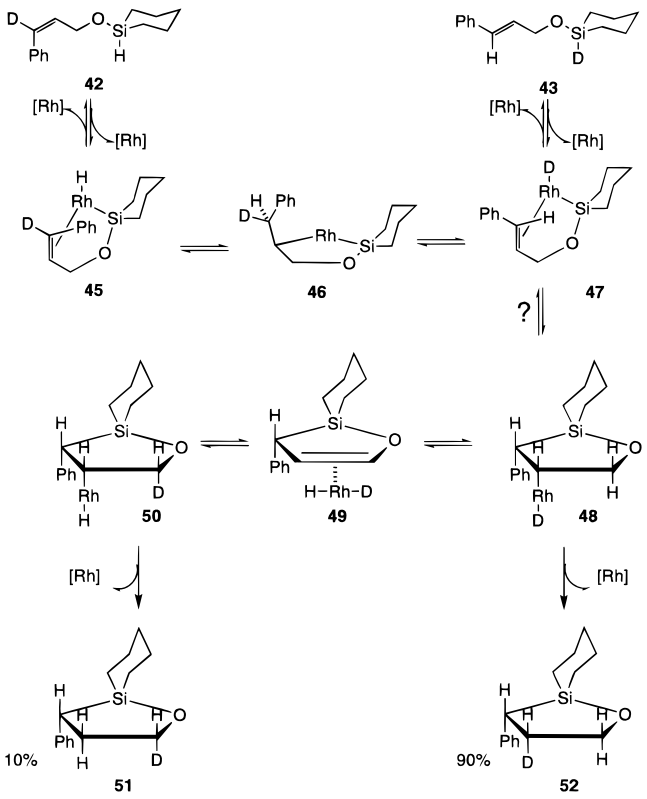
4. Hydrosilation Mechanism

Until recently, the commonly accepted mechanism for the hydrosilation of olefins was the Chalk−Harrod process[20] where, after oxidative addition of the silane to the metal, hydride−olefin insertion occurs followed by alkyl−silicon reductive elimination to give the product. The possibility that silyl−olefin insertion might be an alternative mechanism was generally regarded as improbable despite evidence to the contrary.[21,22] The mechanism for asymmetric catalytic intramolecular hydrosilation was inferred from label distribution experiments using the (*S*)-binap catalyst and the substrate, **42** (Table 2).[23]



It was found that, before any product was detected, the substrate, **42**, completely isomerized to **43**, with the simultaneous transfer of the deuterium atom from the olefin carbon atom to the silicon atom. Consequently, all of the catalysis proceeds by way of the trans substrate, **43**, and, as a result, the apparent rate and ee is the same as was observed for the trans substrate (Table 2). In

Scheme 5



addition to the isomerism and deuterium transfer process, the deuterium atom appears at two stereochemically defined positions in the product, as shown in **44**. It should be noted that the deuterium atoms and the phenyl group in **44** are all cis disposed. A mechanism consistent with these observations is outlined in Scheme 5. Oxidative addition of the silicon−hydrogen bond of **42** to the Rh(I) catalyst leads to the intermediate **45**, which after hydride−olefin insertion gives **46**. If β-hydride elimination occurs in **46**, the intermediate **45** is reformed. In order for β-deuteride elimination to occur, the phenyl substituent must adopt a trans disposition and, consequently, the deuterio intermediate **47** has a trans-oriented phenyl group. Reductive elimination of **47** necessarily gives **43**, a substrate with a trans olefin geometry and a deuterated silicon atom. This process is analogous to some of the steps proposed in the hydroacylation mechanism (Scheme 2). The intermediate **47** can also proceed to products but, to account for the presence of **51** (Scheme 5) in the product, a silyl−olefin insertion step is proposed. Such a step would provide the intermediate **48**, where the cis-phenyl-Rh geometry is a consequence of the silyl−olefin insertion mechanism. Reductive elimination of **48** leads to the product, **52**, but β-hydride elimination of **48** would lead to the intermediate **49**. It will be noted that the cyclic system constrains the β-hydride elimination to occur cis to the Rh atom. Olefin−deuterium insertion gives **50**, which, upon reductive elimination, produces the product **51**. The observed percentages of the two deuterated products are shown. It is difficult to conceive how the Chalk−Harrod mechanism could give **51**. Aside from the final steps to the products, the other steps are, in principle, reversible, even the silyl−olefin insertion step[21] (**47**−**48**). No evidence was obtained that would establish the reversibility of the silyl−olefin insertion step, however.

If the silyl−insertion step is indeed irreversible, it would represent the enantioselective step. Were this the case, however, it is not possible to conclude that the thermodynamic preference of prochiral olefin binding in **47** will correlate with the prevailing enantiomer of the product because the minor diastereomer may react faster than the major diastereomer. If silyl−olefin insertion is reversible, then the ee will depend on a complex mix of rates analogous to that described for hydroacylation.

5. Discussion

A number of important observations can be drawn from the preceding description of the mechanisms of hydroacylation and hydrosilation. First, the mechanisms of catalysis are much more complicated than would have been predicted. Once the substrate enters the catalytic cycle it is transformed by numerous steps that are rapid compared with the overall reaction. Second, for both hydroacylation and hydrosilation there appears to be no single step in the catalytic cycle that determines the enantioselectivity. The enantioselectivity is governed by many steps, the majority of which are reversible. Third, as a consequence of the mechanisms it is not possible to provide a simple model that represents the factors controlling the enantioselection.

It is somewhat disconcerting that, after >20 years of intensive study, success in asymmetric catalysis is largely dependent on a mixture of luck, intuition, and perseverance. During this time, the mechanistic basis for asymmetric catalysis has been laid out and many spectacular achievements have been realized. These achievements, however, have tended to obscure the lack of predictability. The lack of predictability is perhaps not surprising because high ee values require only a difference of $\approx$3 kcal mol^{-1} in diastereomeric activation energies. Electronic and steric effects are generally considered in assessing differences in diastereomeric activation energies. The electronic effects serve to control the reaction trajectory but it is ultimately steric effects within a reaction trajectory that determine the chiral discrimination. This chiral discrimination is subtle because it represents the discriminatory part of the total interaction that occurs in diastereomers. As such, the discriminatory part may be constituted of many small interactions that are not readily identified.

Under certain circumstances, however, the situation is not as intractible as the preceding discussion may imply. Provided there exists a single enantioselective step, the difference in activation energies can be estimated. Three reaction profiles are illustrated in Figure 1 and refer to the enantioselective step and assume rapid diastereomeric equilibration before the activation barrier is transversed. In all of the cases, the conventional assumption is made that the relative transition state energies will reflect the relative thermodynamic stabilities of the diastereomers,

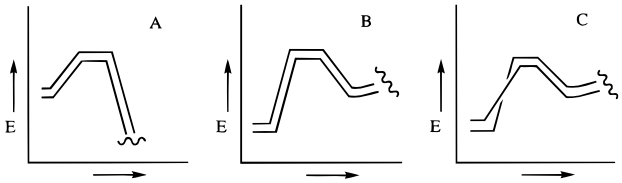


FIGURE 1. Three reaction profiles of the enantioselective step of an asymmetric reaction. Each profile has two reactions referring to the two diastermers and their corresponding transition states.

which are closer to the transition states in energy. For A, the enantioselective step is exothermic, whereas the same step for B and C is endothermic, and the reactions are said to be under reactant (A) and product (B and C) control. Thus, if it is possible to determine the thermodynamic stabilities of the diastereomers preceding the transition states in A, these relative energies should reflect the relative energies of the transition states. Similarly, the relative energies of the product diastereomers in B and C should reflect the corresponding transition state energies. In the case of C, the less stable reactant diastereomer is more reactive. Determining the thermodynamic stabilities of the diastereomers in the exothermic reaction A can be done by either direct measurement or by computational methods. For the endothermic cases B and C, determination of the stabilities of the product diastereomers requires calculation. It has been demonstrated for palladium-catalyzed allylation that the condition illustrated in A exists[5,24] and moreover, a semiquantitative relationship between thermodynamic and transition state energies was established. The enantioselective step for hydrogenation of amino acid precursors with cationic Rh(I) diphosphine catalysts probably is represented by profile C, where the minor reactant diastereomer is more reactive.[25] It is clear that before these correlations can be applied, the detailed mechanism of catalysis has to be established. Such simple correlations do not exist for the hydroacylation and hydrosilation reactions discussed here.

It is clear from the two examples presented here that asymmetric catalysis is generally a complex rate phenomenon that is not amenable to simple interpretation. Further, without a detailed understanding of the mechanism it is not possible to provide a rational model for the enantioselection. Perhaps in the future, when more sophisticated catalysts resembling enzymes are developed, a greater degree of rationality in design will be possible. The current systems have the virtue of simplicity and practicality at the cost of a lack of predictability.

I thank my co-workers for both their dedicated work and their many conceptual contributions. Their names appear in the references. This work was supported by grants from the NIH. This review is dedicated to Warren Roper, an unusually inventive organometallic chemist.

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