

1,2 and 1,4 Additions to Carbonyls

Some of the earliest attempts to understand stereoselectivity in organic reactions were the rationalizations and predictive models made in the early 1950s by Curtin [1], Cram [2] and Prelog [3] to explain the addition of achiral nucleophiles such as Grignard reagents to the diastereotopic faces of ketones and aldehydes having a proximal stereocenter.¹ In the decades since, there has been a steady stream of additional contributions to the understanding of these phenomena.

In this book, a distinction is made between additions that involve allylic nucleophiles and those that do not. For the purposes of this discussion, the addition of enolates and allylic nucleophiles will be labeled π -transfers, and nonallylic nucleophiles will be labeled σ -transfers, as illustrated in Figure 4.1. Note that for σ -transfers aggregation is possible, so that the addition may proceed through a transition state featuring either a four-membered ring or a six-membered ring. This chapter covers 1,2- and 1,4 additions to carbonyls by σ -transfer; the addition of enolates and allyls (π -transfer) is detailed in Chapter 5.

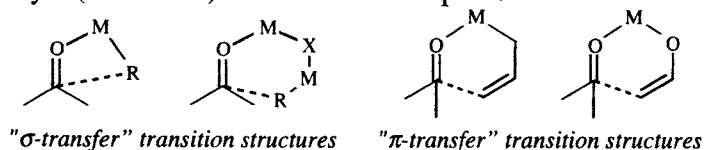


Figure 4.1. Classification of nucleophilic additions to carbonyls.

This chapter begins with a detailed examination of the evolution of the theory of nucleophilic attack on a chiral aldehyde or ketone, from Cram's original "rule of steric control of asymmetric induction" to the Felkin-Anh-Heathcock formulation. Then follows a discussion of Cram's simpler "rigid model" (chelate rule), then carbonyl additions using chiral catalysts and chiral (nonenolate) nucleophiles. The chapter concludes with asymmetric 1,4-additions to conjugated carbonyls and azomethines.

4.1 Cram's rule: open-chain model

About one hundred years ago, the stereoselective addition of cyanide to a chiral carbonyl compound, the Kiliani-Fischer synthesis of carbohydrates, was proclaimed by Emil Fischer to be "the first definitive evidence that further synthesis with asymmetric systems proceeds in an asymmetric manner" [5]. By the mid-twentieth century, enough experimental data had accumulated that attempts to rationalize the selectivity of such additions could be made. The most useful of these was made by Cram in 1952 (Figure 4.2a, [2]). In this model, Cram proposed that coordination of

¹ For a review of the early literature on the stereoselective reactions of chiral aldehydes, ketones, and α -keto esters, and also of the addition of Grignards and organolithiums to achiral ketones and aldehydes in the presence of a chiral complexing agent or chiral solvent, see ref. [4].

the metal of (for example) a Grignard reagent to the carbonyl oxygen rendered it the bulkiest group in the molecule. It would tend to orient itself between the two least bulky groups, as shown. In 1959 [6], the model was redrawn as in Figure 4.2b, which also implies a second, less favored conformation, Figure 4.2c.

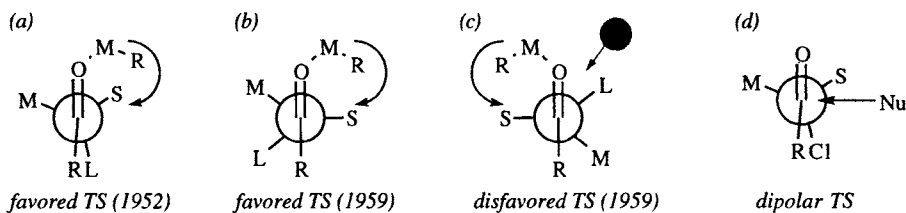


Figure 4.2. (a-c) Cram's models for predicting the major isomer of a nucleophilic addition to a carbonyl having a stereocenter in the α position [2,6]. (d) Cornforth's dipole model for α -chloro ketones [7]. S, M, and L refer to the small, medium, and large groups, respectively.

These models correctly predict the major diastereomer of most asymmetric additions. A notable exception is Grignard addition to α -chloro ketones, which led Cornforth to propose a model where the halogen plays the role of the large substituent so that the C=O and C-Cl dipoles are opposed (Figure 4.2d, [7]).

4.1.1 The Karabatsos model

The predictive value of Cram's rule notwithstanding, the rationale was speculative, and as spectroscopic methods developed, it was called into question. For example, Karabatsos studied the conformations of substituted aldehydes [8] and dimethylhydrazones [9] by NMR, and concluded that one of the ligands at the α position eclipses the carbonyl. It was felt that in the addition reaction, the organometallic probably *did* coordinate to the carbonyl oxygen as Cram had suggested, and Karabatsos used the conformations of the dimethylhydrazone as a model for the metal-coordinated carbonyl. He concluded that since the aldehyde and the hydrazone have similar conformations, so should the metal-complexed carbonyl [10]. He also assumed that the transition state is early, so that there is little bond breaking or bond making in the transition states (Hammond postulate [11]), and that the arrangement of the three ligands on the α carbon are therefore the same in the transition state as they are in the starting materials: eclipsed.

Thus Karabatsos concluded that the rationale for Cram's rule was incorrect [10]. In 1967, he published a new model, which took into account the approach of the nucleophile from either side of all three eclipsed conformers [10]. He noted that the enthalpy and entropy of activation for Grignard or hydride additions to carbonyls are 8 to 15 kcal/mole and -20 to -40 eu, respectively. Since the barrier to rotation around the sp^2 - sp^3 carbon-carbon bond is much lower [12], the selectivity must arise from Curtin-Hammett kinetics [13,14]. Of the six possible conformers (Figure 4.3), four were considered unlikely due to steric repulsion between the nucleophile and either the medium or large α -substituents. The two most likely transition states, 4.3a and 4.3d, have the nucleophile approaching closest to the smallest group on the α carbon, and are distinguished by the repulsive interactions between the carbonyl oxygen and the α substituent (either M or L), with 4.3a favored.

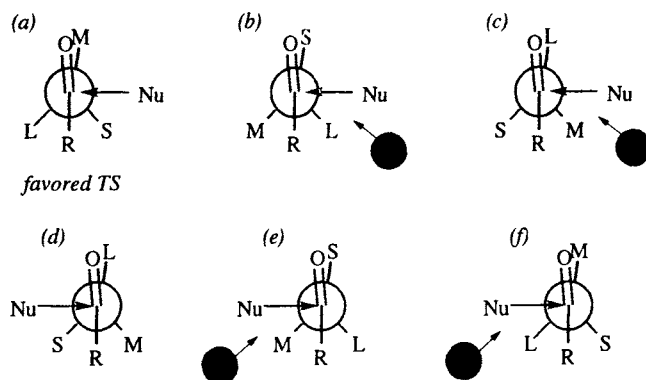


Figure 4.3. Karabatsos's transition state models [10].

4.1.2 Felkin's experiments

In 1968, Felkin noted that neither the Cram nor the Karabatsos models predict the outcome of nucleophilic addition to cyclohexanones [15], and fail to account for the effect of the size of R on the selectivity [16]. The point about cyclohexanones is particularly well-taken, since it is unlikely that the mechanisms of Grignard and hydride additions to cyclic and acyclic ketones differ significantly. The data in Table 4.1 indicate that as the size of the substituent "on the other side" increases, so does the selectivity, except for the single example where the "large" substituent is cyclohexyl and the carbonyl is flanked by a *tert*-butyl.

Table 4.1. Stereoselectivity (% ds) of reductions of $R_1\text{MeCHC(=O)R}_2$ by LiAlH_4 [16].

Large Subs.	$R_2 = \text{Me}$	$R_2 = \text{Et}$	$R_2 = i\text{-Pr}$	$R_2 = t\text{-Bu}$
$R_1 = c\text{-C}_6\text{H}_{11}$	62	66	80	62
$R_1 = \text{Ph}$	74	76	83	98

To explain these results, Felkin proposed a new model [16], in which the incoming nucleophile attacks the carbonyl from a direction that is antiperiplanar to the large substituent (Figure 4.4), while maintaining the notion of an early transition state. Whereas the Cram and Karabatsos models dictate that the nucleophile's approach eclipses (Cram dihedral 0°) or nearly eclipses (Karabatsos dihedral 30°) the small substituent on the α carbon, Felkin proposed that the nucleophile bisects the bond between the medium and small substituents, as in conformers 4.4a and 4.4b (60° dihedral). Felkin suggested that the factor controlling the relative energy of the transition states is the repulsive interaction between R and either the small or medium ligands on the stereocenter, and assumed that there is no energy differential resulting from the interaction between the carbonyl oxygen and either the small or medium substituents on the α carbon.² Thus, conformer 4.4a is

² This rationale is a major weakness of Felkin's theory [17]. First, it assumes that *intramolecular interactions in the substrate* are responsible for the selectivity of a *bimolecular* reaction. Note that the following distances are identical in both transition states: Nu–O, Nu–R, Nu–S, Nu–M. Second, it is hard to accept that $R=\text{H}$ is *more* sterically demanding than oxygen, as would be required for aldehydes (H/S and H/M interactions more important than O/S and O/M).

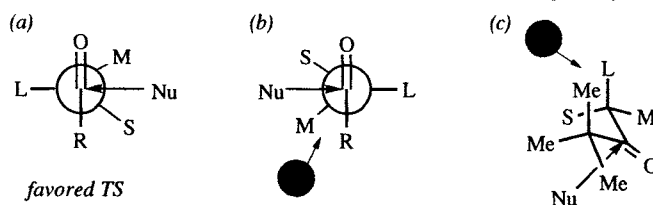


Figure 4.4. (a-b) Felkin's transition state models. (c) Destabilized 'favored' transition state with a flanking *tert*-butyl [16].

avored. The higher selectivities observed across the board (Table 4.1) when the "large" group is phenyl was explained by the greater electronegativity of phenyl over cyclohexyl (*i.e.*, increased differential between 4.4a and 4.4b). Felkin also postulated that when one of the substituents was a chlorine, it would assume the role of the "large" antiperiplanar substituent due to polar effects, thus obviating the need for the Cornforth model (Figure 4.2d). To explain the seemingly anomalous result with a *tert*-butyl substituent, Felkin suggested that the normally preferred conformation is destabilized by a severe 1,3-interaction between the large substituent and one of the methyls of the *tert*-butyl, as in 4.4c.³ An accompanying paper extended these theories to the cyclohexanone problem [15] (see also ref. [17-19]).

4.1.3 The Bürgi-Dunitz trajectory: a digression.

Note that these three models vary in their assumptions about the trajectory of the incoming nucleophile, but *all are entirely speculative*. How might the approach trajectory be determined? Professor Dunitz suggested "turning on the lights."⁴ Bürgi, Dunitz, and Schefter took the position that an observed set of static structures, obtained by X-ray crystallography, when arranged in the right sequence might provide a picture of the changes that occur along the reaction pathway [21]. The model system chosen was nucleophilic approach to a carbonyl by a tertiary amine. Figure 4.5 illustrates the series of compounds whose crystal structures were compared. In the structures of A - E, the nitrogen interacts with the carbonyl carbon to varying degrees, while in F it is covalently bonded, making an acetal. It was noted that in all cases the nitrogen, and the carbonyl carbon and oxygen atoms lie in an approximate local mirror plane (the "normal" plane), but that the carbonyl carbon deviates significantly from the plane defined by the oxygen and the two α substituents. This deviation increased as the N-C distance decreased, but the N-C-O and R-C-R' angles varied only slightly from their mean values.

³ This is a 2,3-*P*,3,4-*M* gauche pentane conformation, which is equivalent to 1,3-diaxial substituents on a cyclohexane. Note that – because the carbonyl substituent is a *tert*-butyl – it cannot be avoided by rotation around the *tert*-butyl–carbonyl bond. For further elaboration of this effect, see Figure 5.5 and the accompanying discussion. For an explanation of the *P*,*M* terminology, see the glossary, Section 1.6.

⁴ "The difference between a chemist and a crystallographer can be compared to two people who try to ascertain what furniture is present in a darkened room; one probes around in the dark breaking the china, while the other stays by the door and switches on the light." (J. D. Dunitz, quoted in ref. [20]).

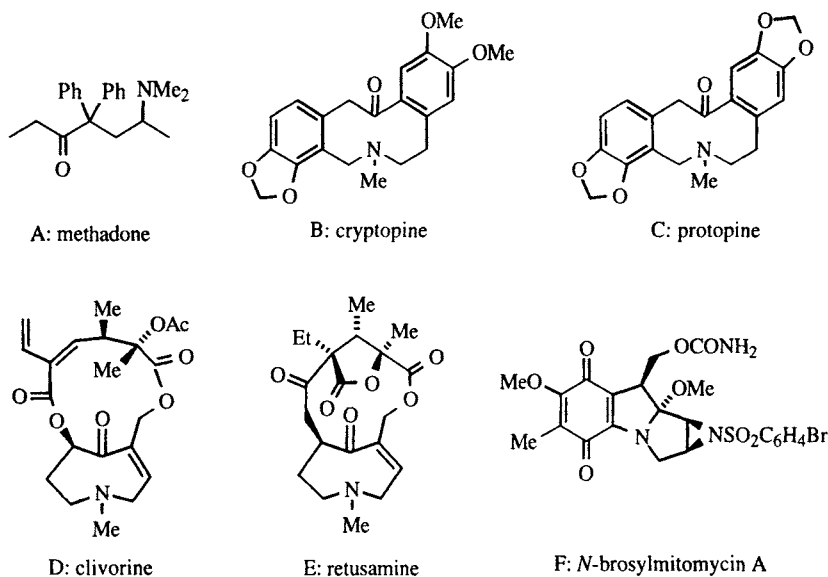
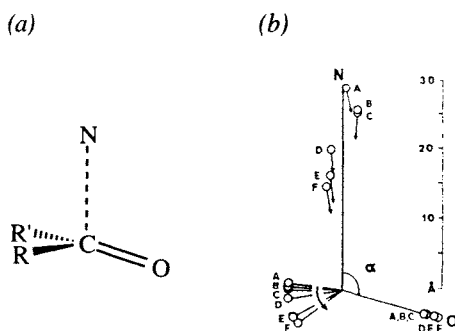


Figure 4.5. Compounds whose X-ray structures provided the basis for the “Bürgi-Dunitz” trajectory.

When the coordinates of the carbonyl carbon atoms and the direction of the C–O bonds are superimposed on a three dimensional graph, and the position of the nitrogen is plotted on the normal plane, the trajectory of approach is revealed: it “*is not perpendicular to the C–O bond but forms an angle of 107° with it*” (Figure 4.6) [21]. Also revealed is the variation in C–O bond length and the distortion of the RCR plane as the nitrogen nears bonding distance. The small arrows indicate the presumed direction of the nitrogen lone pair.

Figure 4.6. (a) Orientation of the superimposed carbonyl and nitrogen atoms. (b) Superimposed plot of the N, C, and O atoms of structures A–F, and the variance of the RRC plane from the RRO plane. α is the “Bürgi-Dunitz angle,” 107°. Reprinted with permission from ref. [21], copyright 1973, American Chemical Society.



The crystal structure data are appealing (as far as they go), but the extent to which substituent effects and crystal packing forces influenced the arrangement of the atoms could not be evaluated. Also, the structural data could provide no information about energy variations along (or variant from) the proposed reaction path. In 1974 Bürgi, Lehn, and Wipff studied the approach of hydride to formaldehyde using computational methods [22]. Thus, a hydride was placed at varying distances from formaldehyde and the minimum energy geometry was located. By superimposing these geometries, the theoretical approach trajectory could be deduced. The results (Figure 4.7), can be summarized as follows. At H^- –C distances

of $>3.0\text{\AA}$, the hydride approaches along the X axis. At an H^- -C distance of 3.0\AA , the H^- and formaldehyde hydrogens are about 2.7\AA apart. At this point, the hydride leaves the HCH plane and glides over the formaldehyde hydrogens until it senses the optimal direction for its attack on the carbonyl, $105\pm5^\circ$.

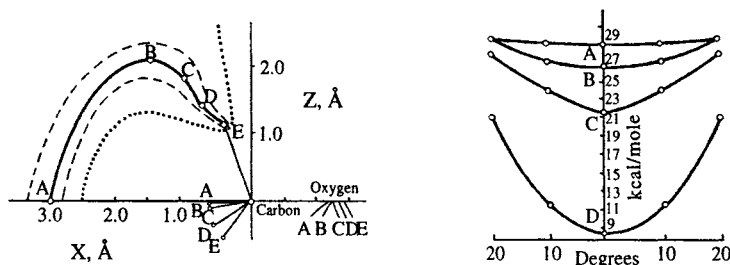


Figure 4.7. (a) Minimum energy path for addition of hydride to formaldehyde. Points A, B, C, D, and E correspond to H^- -C distances of 3.0, 2.5, 2.0, 1.5, and 1.12 \AA . The dashed and dotted curves show paths that are 0.6 and 6.0 kcal/mole higher than the minimum energy path. (b) Energy profiles for lateral displacement out of the normal (XZ) plane. Reprinted with permission from ref. [22], copyright 1974, Elsevier Science, Ltd.

Although the energy profile of the trajectory illustrated in Figure 4.7 drops continuously and never passes through a transition structure, its similarity to the X-ray structural data is striking. Taken together [22], these studies provide strong support for an approach trajectory that is at or near the Bürgi-Dunitz angle of 107° .

4.1.4 Back to the Cram's rule problem (Anh's analysis)

In 1977, Anh [23] used ab initio methods to evaluate the energies of all the postulated transition structures (Figures 4.2 - 4.4) for the reaction of 2-methylbutanal and 2-chloropropanal (the former to test the Cram, Karabatsos, and Felkin models, and the latter to test the Felkin and Cornforth models). The nucleophile was H^- , located 1.5\AA from the carbonyl carbon, at a 90° angle, on each face of the carbonyl. Rotation of the C_1 - C_2 carbon-carbon bond then provided an energy trace which included structures close to all of the previously proposed conformational models. The results for both compounds clearly showed the Felkin transition states to be the lowest energy conformers for attack on either face of the carbonyl. Inclusion of a proton or lithium ion, coordinated to the oxygen, produced similar results. It therefore appeared that Felkin's notion of attack antiperiplanar to the large substituent was correct.

The Felkin geometries have the lowest energy, but that did not necessarily mean that the Felkin rationale was correct. Recall that Felkin assumed that a hydrogen is more sterically demanding than an oxygen.² In their calculations, Anh and Eisenstein held the geometry of the carbonyl rigid (in the Felkin conformation) and varied the angle of hydride attack on the two aldehydes coordinated to a cation. They found optimum angles of 100° , but also found that the energy difference between the two transition states was *amplified* in this geometry [23]. Thus, the Felkin model was revised to include the Bürgi-Dunitz trajectory. Nonperpendicular

attack increases the eclipsing effect with either the small or medium substituents, and also increases the interaction of the nucleophile with R, while decreasing the interaction with the oxygen. With Anh's modifications, the Felkin transition states appear to be on a firm theoretical footing, as illustrated in Figure 4.8.

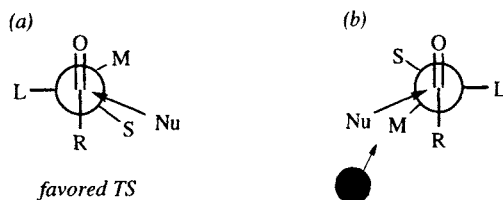


Figure 4.8. The Felkin-Anh transition state models for asymmetric induction [17,23].

4.1.5 Heathcock's refinement

Heathcock, in 1983 [24], proposed that the increase in selectivity seen as the size of the "other" substituent increased (Table 4.1, [16]), or when the carbonyl is complexed to a Lewis acid [24] might be explained by deviations of the attack trajectory from the normal plane. In 1987 [25], Heathcock reported the results of a semi empirical study of the angle of approach for the attack of pivaldehyde by hydride. The results, illustrated in Figure 4.9a, illustrate that the approach deviates significantly away from the normal plane, away from the *tert*-butyl group. Although not illustrated, the Bürgi-Dunitz component was variable, but was about the same as found for attack on formaldehyde (108-115°). Although the potential surface near the transition state for nucleophilic additions to unhindered carbonyls is fairly flat [22,26], and has room for some "wobble" in the approach (*cf.* Figure 4.7b), Heathcock showed [25] that constraining the hydride to the normal plane in approach to pivaldehyde is higher in energy, especially at longer bond distances. At 2.5 Å, the energy difference reached its maximum of 0.7 kcal/mole. Figure 4.9b shows Heathcock's rationale for Felkin's observations [16] listed in Table 4.1. When R is small, the "Flippin-Lodge angle", ϕ ,⁵ is large, and the nonbonded interactions resulting from interaction of the nucleophile with the substituents in R* are diminished. As the size of R increases, the approach trajectory is pushed back toward the normal plane, increasing the nonbonded interactions with R*, and amplifying the selectivity.

In his 1977 paper, Anh also addressed the issue of which substituent would assume the role of the "large" substituent anti to the incoming nucleophile. A simple rule was offered [23]: the substituents should be ordered according to the energies of the antibonding, σ^* orbitals. The preferred anti substituent will be that one having the lowest lying σ^* orbital, not necessarily the one that is the most demanding sterically. This rule explains the α -chloro ketone anomaly, since the σ^* orbital of the carbon-chlorine bond is lower in energy than a carbon-carbon bond. However in 1987, Heathcock tested this hypothesis [28], and concluded that the rule is only partly correct.

⁵ Professor Heathcock named this angle after his two collaborators, Lee Flippin and Eric Lodge [27].

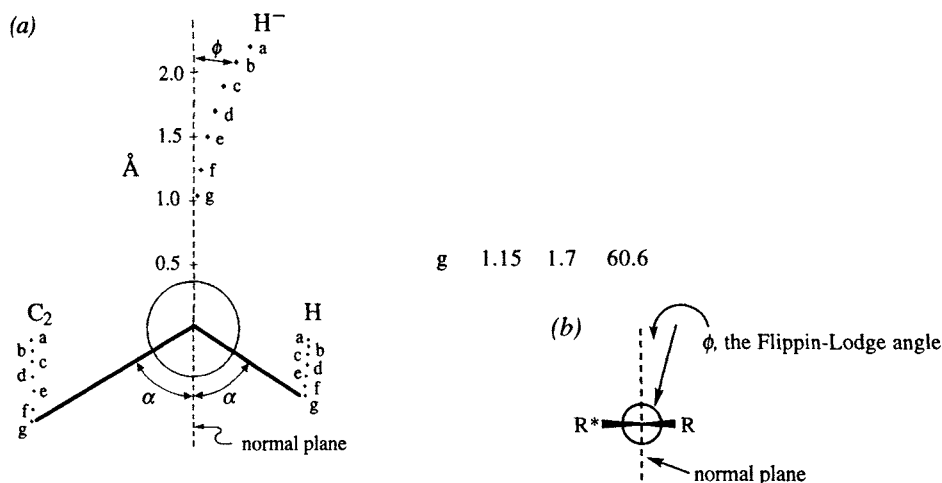


Figure 4.9. (a) Deviation of the attack trajectory from the normal plane in the reaction of hydride with pivaldehyde. Reprinted with permission from ref. [25], copyright 1987, American Chemical Society. (b) Newman projection of a ketone, with an approaching nucleophile, and the Flippin-Lodge angle of deviation from the normal plane, away from the larger substituent, R^* (after ref. [27]).

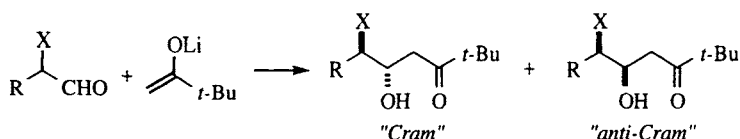
Specifically, Heathcock examined a series of aldehydes designed to evaluate the relative importance of steric and orbital energy effects. Aldehydes having a substituent with a low energy σ^* orbital (methoxy and phenyl) as well as a sterically variable substituent (methyl, ethyl, isopropyl, *tert*-butyl, phenyl) were synthesized and evaluated. The data are summarized in Table 4.2.⁶

If the antiperiplanar substituents in the Felkin-Anh model (L in Figure 4.8) are those with low-lying σ^* orbitals (X in Table 4.2), one would expect a gradual increase in selectivity as the steric bulk of the remaining substituent (M in Figure 4.8) increased. The data in Table 4.2 show that this is clearly not the case. In the methoxy series, the expected trend is observed for methyl, ethyl, and isopropyl. But the *tert*-butyl and the phenyl groups are anomalous, if one considers the standard *A* values⁷ as a measure of steric bulk. In the phenyl series, there is no apparent pattern, and when $R = \textit{tert}$ -butyl, the Anh hypothesis predicts the wrong product.

These data may be interpreted using the four-conformer model shown in Figure 4.10. Simply put, *both steric and electronic effects determine the favored anti substituent*. Thus in the methoxy series (Figure 4.10a), conformers A and B are favored when R is methyl, ethyl, or isopropyl, and attack is favored *via* conformer A. When R is *tert*-butyl, its bulk begins to compensate for the σ^* orbital effect, and conformations C and D become important, with D favored. A rationale for the observed (93% ds) selectivity for the *tert*-butyl ligand is that a very high selectivity results from the preference of A over B, but is tempered by an offsetting selectivity of D over C. When R is phenyl, the bulk of the phenyl as well as its low-lying C_{sp^3} -

⁶ Note that the nucleophile in this study is an enolate, not a Grignard reagent.

⁷ The free energy differences ($-\Delta G^\circ$), *A* values, between equatorial and axial conformations of a substituted cyclohexane ring are (kcal/mole): Cl = 0.52, MeO = 0.75, Me = 1.74, Et = 1.75, *i*-Pr = 2.15, Ph = 2.7, *t*-Bu = 4.9 (taken from ref. [29]).

Table 4.2. Cram's rule stereoselectivities (% ds) for aldol additions to aldehydes (negative value indicates anti-Cram is favored), assuming X is the large substituent in the Felkin-Anh model [28]:

X	R = Me	R = Et	R = <i>i</i> -Pr	R = <i>t</i> -Bu	R = Ph
OMe	58	76	93	93	83
Ph	78	86	70	-63	-

$\text{C}_{\text{sp}^2} \sigma^*$ orbital play a role. A prediction made on the basis of its bulk alone (A values⁵) would predict a selectivity greater than when R is isopropyl (still assuming an anti methoxy), but the phenyl σ^* orbital is lower in energy than a $\text{C}_{\text{sp}^3}-\text{C}_{\text{sp}^3} \sigma^*$ orbital, which increases the importance of conformers C and D (anti-Cram D is favored).

In the phenyl series (Figure 4.10b), when R is methyl or ethyl, conformers E and F are dominant, with E favored. Note that the selectivity in the phenyl series for methyl and ethyl ligands is greater than in the methoxy series (Table 4.2). This is because the phenyl group is bulky *and* has a low energy σ^* orbital, so that the electronic and steric effects act in concert. For the isopropyl and *tert*-butyl ligands, the importance of the G/H conformers increases, and when R is *tert*-butyl they predominate.

Heathcock refers to conformers C, D, G, and H as “non-Anh” conformations, since they have one of the ligands with a *higher* σ^* orbital energy anti to the nucleophile. The non-Anh conformations are more important in the phenyl series because there is less difference in the σ^* orbital energies between $\text{C}_{\text{sp}^3}-\text{C}_{\text{sp}^3}$ and $\text{C}_{\text{sp}^3}-\text{C}_{\text{sp}^2}$ bonds than between carbon–carbon and carbon–heteroatom bonds.

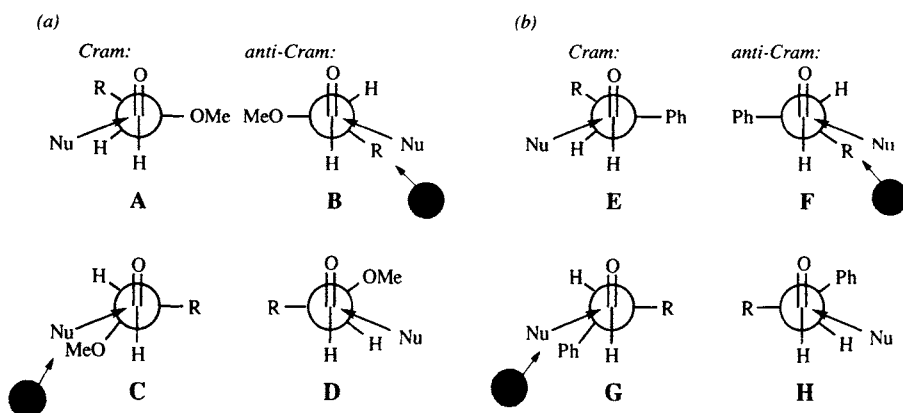


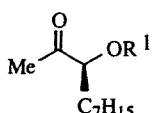
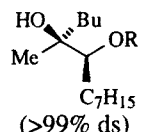
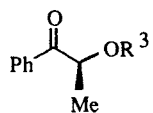
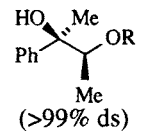
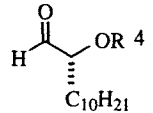
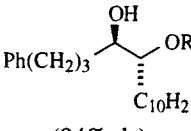
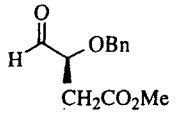
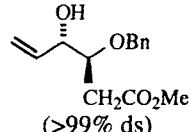
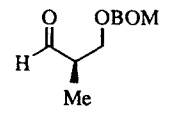
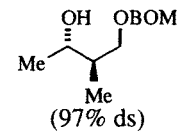
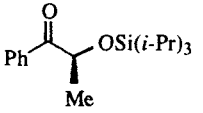
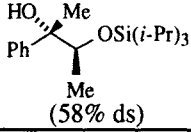
Figure 4.10. Heathcock's four-conformer model for 1,2-asymmetric induction [28]. (a) Electronic effects favor methoxy as anti ligand (A and B) while steric effects may favor C and D. (b) Electronic effects favor phenyl as anti ligand (E and F) while steric effects favor G and H for very large alkyl groups.

4.1.6 The bottom line (*hasn't been written yet*)

Theoretical investigations into the origins of Cram's rule selectivity continue. For example, Dannenberg has shown that the energies of the frontier orbitals change as a function of the dihedral angle [19], and Frenking has concluded that "the most important factor for the π -facial diastereoselectivity in nucleophilic

Grignard reagents to α -alkoxy ketones in THF (entry 1) were greatly diminished in ether, pentane, or methylene chloride [37]. Eliel demonstrated similar selectivities for additions by dimethylmagnesium in THF (entry 2). With aldehydes, there have been conflicting reports. Still reported a 90% diastereoselectivity in the reaction of methylmagnesium bromide with 2-(benzyloxymethoxy)propanal [38], but Eliel [39] and Keck [40] observed poor selectivities in THF. Eliel found good selectivities (90–94% ds) in ether (*e.g.*, entry 3) for the addition of a Grignard to the benzyl or MOM ethers of a 2-hydroxyundecanal. For a number of additions of less reactive

Table 4.3. Selected examples of nucleophilic addition to α -alkoxy carbonyls.

Entry	Educt	Conditions	Product (%ds)	Reference
1		BuMgBr THF, ² -78°	 (>99% ds)	[37]
2		Me ₂ Mg THF, -70°	 (>99% ds)	[34]
3		Ph(CH ₂) ₃ MgBr Et ₂ O, ⁵ -78°	 (94% ds)	[39]
4		MgBr ₂ ·OEt ₂ CH ₂ =CHMgBr CH ₂ Cl ₂ , ⁵ -78°	 (>99% ds)	[40]
5		Me ₂ CuLi Et ₂ O, -78°	 (97% ds)	[38]
6		Me ₂ Mg THF, -70°	 (58% ds)	[34]

¹ R = MEM (methoxyethoxymethyl-), MOM (methoxymethyl-), MTM (methylthiomethyl-), CH₂-furyl, Bn (benzyl-), BOM (benzyloxymethyl-).

² Pentane, ether, and methylene chloride afforded much lower selectivities.

³ R = Me, SiMe₃.

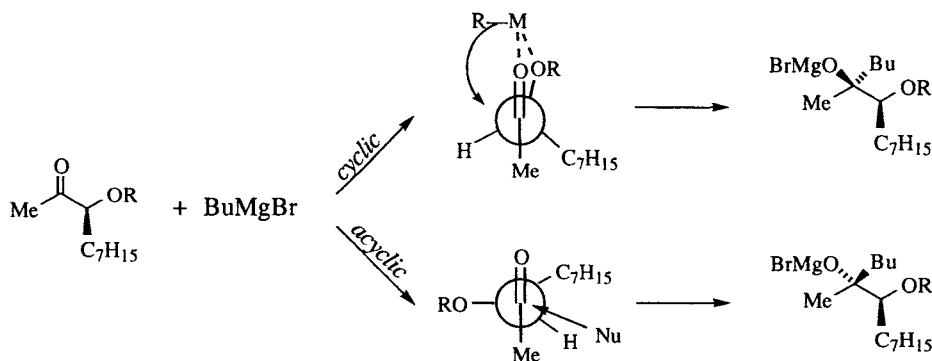
⁴ R = Bn, MOM

⁵ THF affords much lower selectivity.

nucleophiles, Reetz has shown that prior organization of the chelate by complexation with a Lewis acid improves results with aldehydes [41]. Along these lines, Keck has reported [40] that prior coordination of an α -alkoxy aldehyde with magnesium bromide in methylene chloride, followed by addition of a vinyl Grignard affords excellent selectivity (entry 4). In order to achieve high selectivity, the THF in which the Grignard was formed had to be distilled away and replaced by methylene chloride [40].

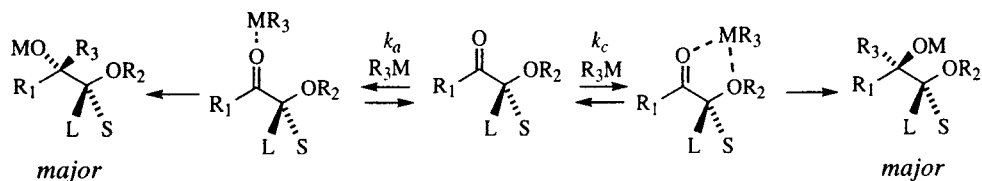
The cyclic model applies mainly for α -alkoxy carbonyls (*5-membered chelate*), whereas β -alkoxy carbonyls (*6-membered chelate*) are less selective in most cases. An exception is the addition of cuprates to β -alkoxy aldehydes having an α -stereocenter (entry 5).

Two features of the cyclic model are particularly important synthetically. The first is that the selectivities can be significantly higher than for the acyclic category. Compare entries 2 and 6 of Table 4.3: the methoxy and trimethylsilyloxy groups chelate the magnesium (entry 2) whereas the triisopropylsilyloxy group does not (entry 6). This poorly selective example reacts by the acyclic pathway (also compare entries 1-5 with Tables 4.1 and 4.2). The second noteworthy point is that the product predicted by the cyclic and acyclic models are sometimes different. As shown in Scheme 4.1, the predictions of the acyclic and cyclic models are different for Table 4.3, entry 1 (see also entries 2 and 6).



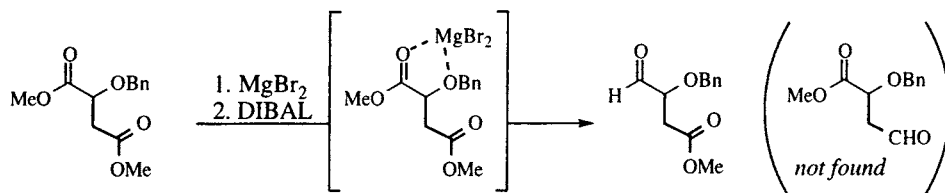
Scheme 4.1. Cyclic and acyclic models often predict opposite outcomes.

Study of the mechanism of Grignard addition (RMgX) via the chelate pathway is complicated by the presence of Schlenk equilibria, but Eliel has examined the mechanism of the addition of dimethylmagnesium (R_2Mg) to α -alkoxy ketones (e.g., Table 4.3, entries 2 and 6) in detail, since dimethylmagnesium is a well-characterized monomer in THF solution. Scheme 4.2 summarizes the current picture of the mechanism [34]. Beginning with the educt in the middle of the scheme, there are two competing pathways for the addition reaction. One involves chelated (cyclic) intermediates (to the right of the scheme), while the other involves nonchelated (acyclic) intermediates (shown on the left). One should also recognize that there are two distinct issues that must be considered for these competing pathways: their *relative rates*, and their *stereoselectivities*.



Scheme 4.2. The acyclic and cyclic mechanisms compete for the consumption of substrate.

The chelate rule will only be applicable if addition via the chelate is faster than addition by the acyclic mechanism (*i.e.*, $k_c > k_a$ in Scheme 4.2). Because the chelate is rigid, it is often considerably more stereoselective as well.⁸ *However, the relative rate issue is independent of the stereoselectivities of the two processes.* For example, chelation can be used to control regiochemistry: selective reduction of a diester is achieved by preferential chelation to a 5-membered ring over a 6-membered ring by magnesium bromide (Scheme 4.3, [40]).



Scheme 4.3. Independent of stereochemical issues, chelation can determine reactivity [40].

For the chelate path to be faster than the acyclic path, chelation must lower the energy of activation relative to the acyclic path, as shown in Figure 4.12 [34]. The two individual steps illustrated in this diagram deserve comment. First, note that the chelated intermediate is lower in energy and has a smaller energy of activation for its formation than the monodentate intermediate on the acyclic pathway. That the chelate is more stable than the monodentate complex is no surprise. However, the increased organization of the chelated transition state (ΔS^\ddagger less positive) and the increased steric interactions that result (ΔH^\ddagger more positive) would seem to dictate a slower reaction,⁹ but these effects are offset by the enthalpy gained by complexation of the alkoxy ligand to the metal and the entropy gained by liberation of an additional solvent from the metal by the bidentate ligand. Regarding the second step, whereby the chelate reacts faster than the monodentate complex, it is pertinent that the kinetics of the addition of dimethylmagnesium are first order in organometallic [34]. This requires the intramolecular transfer of an R_3 ligand *via* a four-membered ring transition state. The distance between the metal ligand (R_3) and the carbonyl carbon is greater in the (linear) acyclic transition state than in the chelated one, so the chelate is further along the reaction coordinate than the linear complex [34].

⁸ This may seem contrary to the reactivity-selectivity principle, wherein one expects a decrease in selectivity to accompany an increase in reactivity, but this principle has a number of limitations. For an extensive discussion of the reactivity-selectivity principle, see ref. [42].

⁹ Recall (Chapter 1) that $k = \left(e^{-\Delta H^\ddagger/RT} \right) \left(e^{\Delta S^\ddagger/R} \right)$.

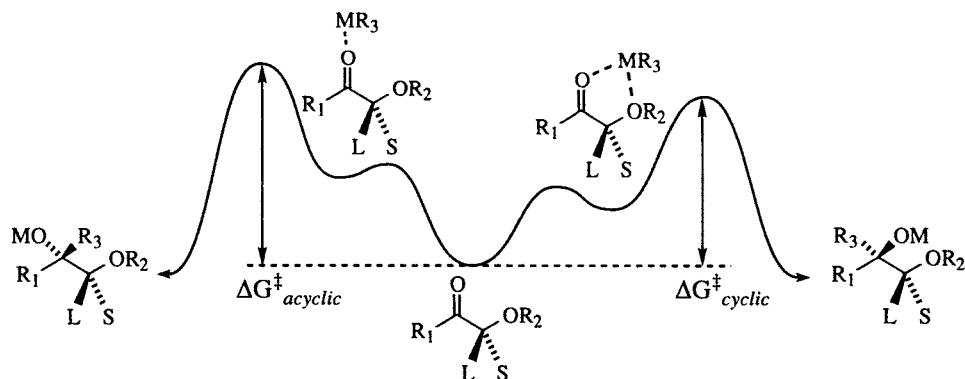
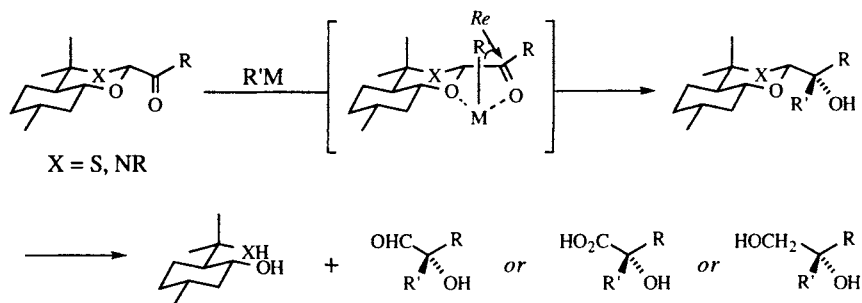


Figure 4.12. Energetics of the Cram-chelate (acyclic) model. $\Delta G^\ddagger_{acyclic} > \Delta G^\ddagger_{cyclic}$ (after ref. [34]).

The relative energies of the intermediates and transition structures along the reaction coordinates are subject to the influence of solvation, which may alter relative stabilities and rates. This may explain the solvent effects discussed earlier (*cf.* Table 4.3, entries 1, 3 and 4). The energetic features outlined above may also explain the lack of selectivity in the nucleophilic additions to β -alkoxy carbonyl compounds. It is possible that even though 6-membered chelates are formed, their rates of formation are slower than addition via the nonchelated path, or that they are less reactive than a 5-membered chelate. Either of these circumstances (or a

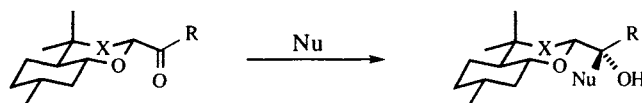
and oxazine [51,52] systems developed by Eliel. As shown in Scheme 4.4, the heterocyclic system is held rigid by its *trans*-decalin-like geometry. In both heterocyclic systems, the metal is chelated by the carbonyl oxygen and the ether oxygen (the latter in preference to either the sulfur or the nitrogen). Approach of the electrophile from the less hindered *Re* face is favored.

Both auxiliaries are synthesized from (+)-pulegone, with the sulfur version available as an *Organic Syntheses* prep [47]. Hydrolysis of the acetal after the addition removes the chiral auxiliary (recovered in good yield) and liberates an α -hydroxy aldehyde, which may be reduced to a glycol or oxidized to an α -hydroxy acid. Table 4.4 lists several examples of the addition. Entries 2/3 and 7/10 illustrate the selective formation of either possible stereoisomer by reversal of the "R" and "Nu" groups. Entries 4 and 5 illustrate a case of matched and mismatched double asymmetric induction (Chapter 1), where the distal stereocenter of the chiral nucleophile affects the selectivity of the addition. Comparison of entries 1-6 and 7-12 indicate that both the sulfur and the nitrogen auxiliaries are useful, so that the conditions necessary for cleavage may dictate the choice of auxiliary. Figure 4.14 shows several natural products that have been synthesized using this methodology.



Scheme 4.4. Eliel's asymmetric addition to carbonyls using Cram's chelate model.

Table 4.4. Asymmetric addition of nucleophiles to oxathianes and oxazines.



Entry	X	R	Nu	% ds	Reference
1	S	Me	$\text{CH}_2=\text{CHMgBr}$	92	[53]
2	S	Me	BnMgBr	>98	[54]
3	S	Bn	MeMgBr	>98	[54]
4	S	<i>n</i> -C ₉ H ₁₉	(<i>S</i>)-MeCHPh(CH ₂) ₂ MgBr	97.5	[55]
5	S	<i>n</i> -C ₉ H ₁₉	(<i>R</i>)-MeCHPh(CH ₂) ₂ MgBr	89	[55]
6	S	<i>n</i> -C ₁₀ H ₂₁	$\text{LiBH}(\textit{s}\text{-Bu})_3$	91	[39]
7	NBn	Me	PhMgBr	95.5	[52]
8	NBn	Me	EtMgBr	92	[52]
9	NBn	Me	NaBH_4	95.5	[52]
10	NBn	Ph	MeMgBr	>98	[51]
11	NBn	Ph	EtMgBr	>98	[51]
12	NMe	Ph	MeMgBr	96	[52]

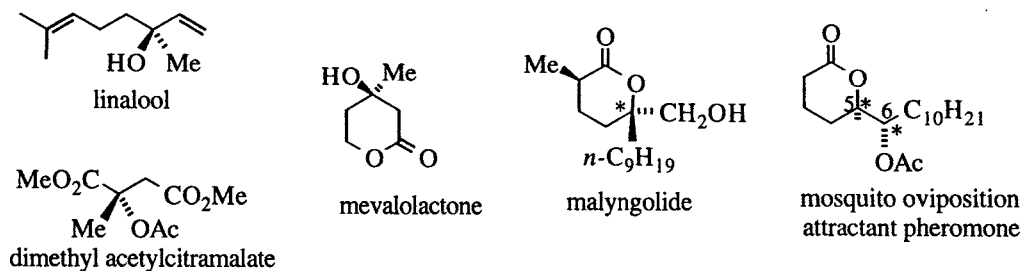


Figure 4.14. Applications of oxathianes: linalool [53], dimethyl acetylcitramalate [54], mevalolactone [56], malyngolide [55], and the mosquito oviposition attractant [39]. For the latter, the C-5 stereocenter was formed by a chelate-controlled reduction while the C-6 position could be produced as either epimer by a chelate or acyclic mechanism, depending on the reducing agent.

4.3 Additions using chiral catalysts or chiral nucleophiles

The preceding discussion summarizes a great deal of work done over the last forty years on the stereoselective additions of achiral carbanionic nucleophiles to carbonyls having a neighboring stereocenter. The knowledge gained during these studies has aided in the development of two different approaches to stereoselective additions to heterotopic carbonyl faces: (i) those using chiral nucleophiles with achiral carbonyl compounds [57]; and (ii) a potentially more useful process, one in which neither partner is chiral, but a chiral catalyst is used to induce stereoselectivity (reviews: [58-60] and chapter 5 in ref. [61]).

All of the reactions discussed in this chapter require coordination of a carbonyl to a metal. This coordination activates the carbonyl toward attack by a nucleophile, and may occur by two intrinsically different bonding schemes: σ or π (Figure 4.15). The best evidence to date indicates that σ coordination predominates for Lewis acids such as boron or tin [62,63], and (more importantly) σ -bonding produces a more reactive species [64]. In the following discussions, it will be assumed that σ bonding to the carbonyl oxygen is operative.



Figure 4.15. Geometries and relative reactivities of coordinated carbonyls [64].

The potential utility of an asymmetric addition to a prochiral carbonyl can be seen by considering how one might prepare 4-octanol (to take a structurally simple example) by asymmetric synthesis. Figure 4.16 illustrates four possible retrosynthetic disconnections. Note that of these four, two present significant challenges: asymmetric hydride reduction requires discrimination between the enantiotopic faces of a nearly symmetrical ketone (a), and asymmetric hydroboration-oxidation requires a perplexing array of olefin stereochemistry and regiochemical issues (b). In contrast, the addition of a metal alkyl to an aldehyde offers a much more realistic prospect (c) or (d).

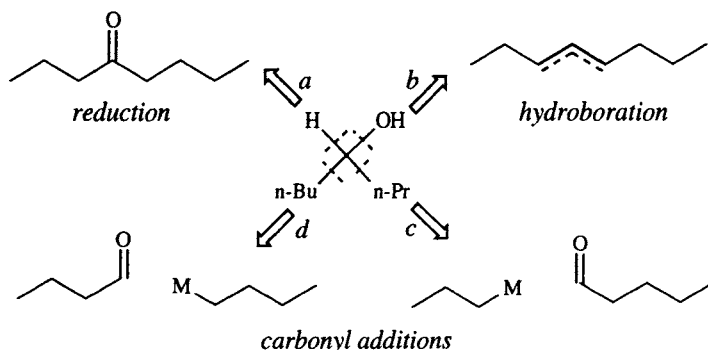


Figure 4.16. Simple retrosynthetic strategies for synthesis of 4-octanol.

4.3.1 Catalyzed Addition of organometallics

A number of organometals have been evaluated for this type of reaction, but because of fewer side reactions (such as deprotonation of the aldehyde), the substrate studied most often is benzaldehyde. Perhaps the best understood of these reactions is the addition of organozincs, especially dimethyl- and diethylzinc (reviews: [58-60,65-68]). The reactivity of alkylzincs is low, and at or below room temperature the rate of addition of, for example, diethyl zinc to benzaldehyde is negligible. Addition of a Lewis acid, however, causes rapid addition. Replacement of one of the alkyl substituents with an alkoxide produces a more reactive species as well, and amino alcohols have been found to be very useful catalysts for the addition reaction [69,70]. At least part of the reason for the increased reactivity is a rehybridization of the zinc from linear to bent upon complexation to an alkoxide, and to tetrahedral upon bidentate coordination. Additionally, donor ligands such as oxygen and nitrogen render the alkyl group more nucleophilic. Figure 4.17 illustrates some of the catalysts that afford good yields and high enantioselectivities in the diethylzinc reaction with benzaldehyde.

The mechanisms that have been proposed for the amino alcohol-catalyzed reaction all involve two zinc atoms, one amino alcohol and three alkyl groups on the active catalyst [65,71-74]. A composite mechanism is illustrated in Scheme 4.5 for a “generic” β -amino alcohol.¹¹ NMR evidence [71] indicates dynamic exchange of the alkyl groups on zinc as shown in the brackets (a bridged species has also been proposed [71]). In experiments done with a polymer-bound amino alcohol catalyst, Frechet has noted that the alkoxide product is not bound to the catalyst and that the alkyl transfer must have therefore occurred from diethylzinc in solution.

It might be expected that use of an amino alcohol of less than 100% enantiomeric purity would place an upper limit on the enantiomeric purity of the product. However, Noyori reported that when a catalyst (Figure 4.17b) of 15% ee was used in the diethylzinc reaction, 1-phenyl-1-propanol of 95% ee was isolated in 92% yield [71]. As it turns out, the zinc alkoxide produced after the reaction of one equivalent of diethylzinc dimerizes (Scheme 4.6). When both enantiomers of the amino alcohol are present, both homochiral and heterochiral dimers may be formed.

¹¹ For a discussion of the various mechanistic models and a detailed analysis, see ref. [58,75].

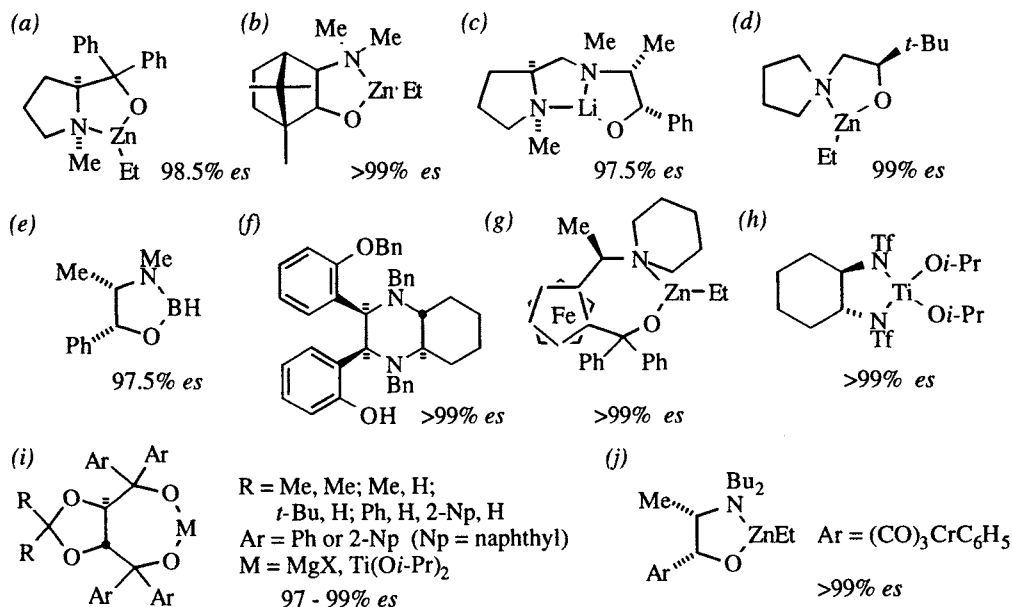
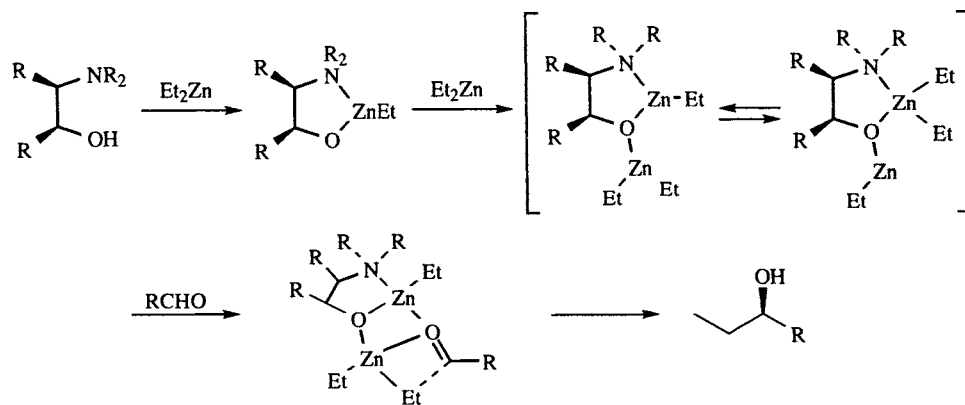


Figure 4.17. Catalysts for the diethylzinc reaction with benzaldehyde: (a), [76]; (b), [71]; (c), [73]; (d), [77]; (e), [78]; (f), [79]; (g), [80]; (h), [81,82]; (i), [83,84]; (j), [85].



Scheme 4.5. Proposed mechanistic scheme for amino alcohol catalyzed diethylzinc reaction (after ref. [60])

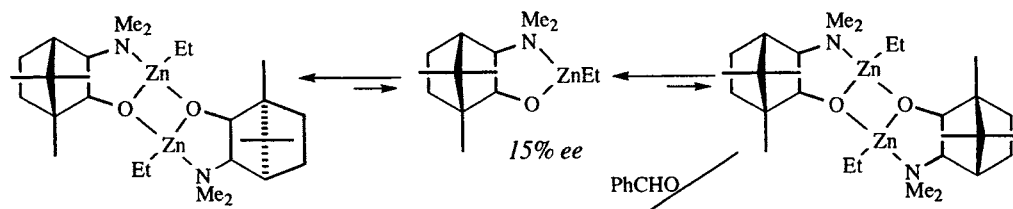
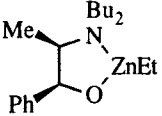
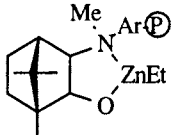
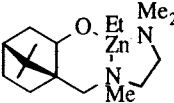
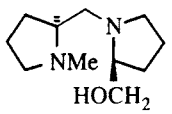


Table 4.5. Catalyzed additions of organometallics (RM) to aldehydes and ketones. Numbers in the catalyst column refer to Figure 4.17.

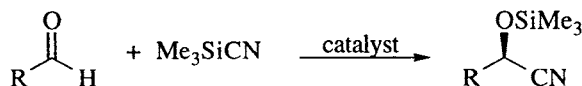
Entry	Carbonyl	RM	Catalyst	% Yield	%es	Ref
1	<i>n</i> -C ₆ H ₁₃ CHO	Et ₂ Zn	4.17a	96	95.5	[76]
2	<i>i</i> -BuCHO	Et ₂ Zn		92	96.5	[72]
3	<i>n</i> -C ₆ H ₁₃ CHO	Me ₂ Zn	"	70	95	[72]
4	2-NpCHO	Ph ₂ Zn	"	83	90	[86]
5	<i>c</i> -C ₆ H ₁₁ CHO	Et ₂ Zn	4.17g	92	99	[80]
6	<i>t</i> -BuCHO	Et ₂ Zn	4.17g	93	99	[80]
7	<i>n</i> -C ₆ H ₁₃ CHO	Et ₂ Zn	4.17h	78	>99	[81]
8	PhCHO	Et ₂ Zn		91	96	[73]
9	PhCHO	Vinyl ₂ Zn		96	93.5	[87]
10	<i>n</i> -C ₅ H ₁₁ CHO	Vinyl ₂ Zn	"	90	98	[87]
11	<i>c</i> -C ₆ H ₁₁ CHO	Vinyl ₂ Zn	"	83	91	[87]
12	<i>c</i> -C ₆ H ₁₁ CHO	Bu ₂ Zn	4.17i, M = Ti(Oi-Pr) ₂	35	95	[88]
13	PhCHO	(MOMO-(CH ₂) ₆) ₂ Zn	4.17i, M = Ti(Oi-Pr) ₂	68	92	[88]
14	PhCHO	(C ₂ H ₃ -(CH ₂) ₂) ₂ -Zn	4.17i, M = Ti(Oi-Pr) ₂	83	95	[88]
15	1- or 2-Np	Et ₂ Zn	4.17j	98	>99	[85]
16	PhCHO	<i>n</i> -BuLi		77	97.5	[70]
17	PhCHO	Et ₂ Mg	"	74	96	[70]
18	PhCOCH ₃	EtMgBr	4.17i, M = MgX	62	99	[89]

With the Noyori catalyst, the heterochiral dimer is considerably more stable than the homochiral dimer. The latter decomposes to the active, monomeric catalyst immediately upon exposure to a dialkylzinc or an aldehyde, whereas the heterochiral dimer does not. Thus, the minor enantiomer of the catalyst is "tied up" by the major enantiomer.¹²

To provide an overview of the scope of such processes, Table 4.5 lists some of the more selective examples of this type of addition for a variety of substrates and organometallics. It would be premature to say that the process of asymmetric additions of achiral nucleophiles is a general procedure at this time (*i.e.*, that any organometallic and carbonyl can be made to couple enantioselectively), but the current rate of progress suggests that the realization of this goal will not be long in coming. Particularly noteworthy are the isolated examples of organolithium and Grignard additions (entries 16-18).

4.3.2 Hydrocyanations

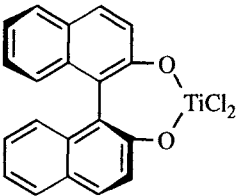
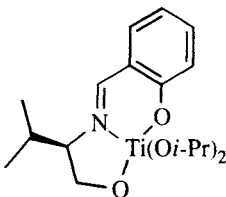
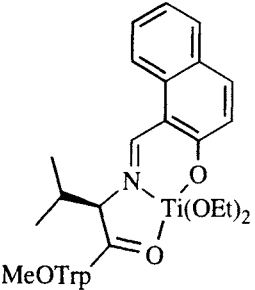
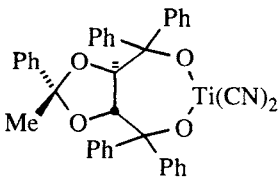
The addition of cyanide to an aldehyde or ketone (hydrocyanation) is an old reaction, but it has been the subject of renewed interest since Reetz's discovery that a chiral Lewis acid could be used to catalyze the asymmetric addition of trimethylsilylcyanide to isobutyraldehyde ([91]; reviews: [59,92]). The general process, illustrated in Scheme 4.7, usually employs trimethylsilylcyanide because hydrogen cyanide itself catalyzes the addition as well (nonselectively). Most of the catalysts are chiral titanium complexes; some of the more selective examples are shown in Table 4.6. A clear mechanistic picture of the titanium catalyzed additions has not yet emerged.¹³



Scheme 4.7. General asymmetric addition of trimethylsilylcyanide to an aldehyde.

Experiments described by Corey constitute a noteworthy example of *double asymmetric induction where neither participant in the reaction is chiral* [95]! As illustrated in Figure 4.18 two different catalysts are necessary to achieve the best results. Control experiments indicated that the nucleophile is probably free cyanide, introduced by hydrolysis of the trimethylsilylcyanide by adventitious water, and continuously regenerated by silylation of the alkoxide product. Note that the 82.5% enantioselectivity in the presence of the magnesium complex shown in Figure 4.18a is improved to 97% upon addition of the bisoxazoline illustrated Figure 4.18b as a cocatalyst. Note also that the bisoxazoline 4.18b alone affords almost no enantioselectivity and that the enantioselectivity is much less when the enantiomer of the

Table 4.6. Catalytic asymmetric hydrocyanation of aldehydes. Numbers in the catalyst column refer to Figure 4.18 (p. 142).

Entry	Carbonyl	Catalyst	% Yield	%es	Ref
1	<i>i</i> -BuCHO		85	94	[96]
2	PhCHO		67	92	[94]
3	2-NpCHO	"	76	86	[94]
4	<i>E</i> -CH ₃ CH=CHCHO	"	70	94	[94]
5	PhCHO (Trp = tryptophan)		83	95	[93]
6	2-NpCHO	"	55	95	[93]
7	<i>n</i> -C ₈ H ₁₇ CHO		85	96	[97]
8	Ph(CH ₂) ₂ CHO	"	88	95	[97]
9	<i>n</i> -C ₆ H ₁₃ CHO	4.18a & 4.18b	88	97	[95]
10	Et ₂ CHCHO	"	86	95	[95]
11	<i>c</i> -C ₆ H ₁₁ CHO	"	94	97	[95]
12	<i>t</i> -BuCHO	"	57	95	[95]
13	<i>E</i> - <i>n</i> -PrCH=CHCHO	"	59	93	[95]

for the matched pair has the hydrogen cyanide complexed to 4.18a and the aldehyde complexed to the magnesium atom of 4.18b.

4.3.3 Additions to the C=N bond

The stereoselective addition of organometallics to azomethines (C=N bond) has not been as fully developed as additions to carbonyls for several reasons (review: [98]). First, imines are not as electrophilic as carbonyls, and so are less susceptible

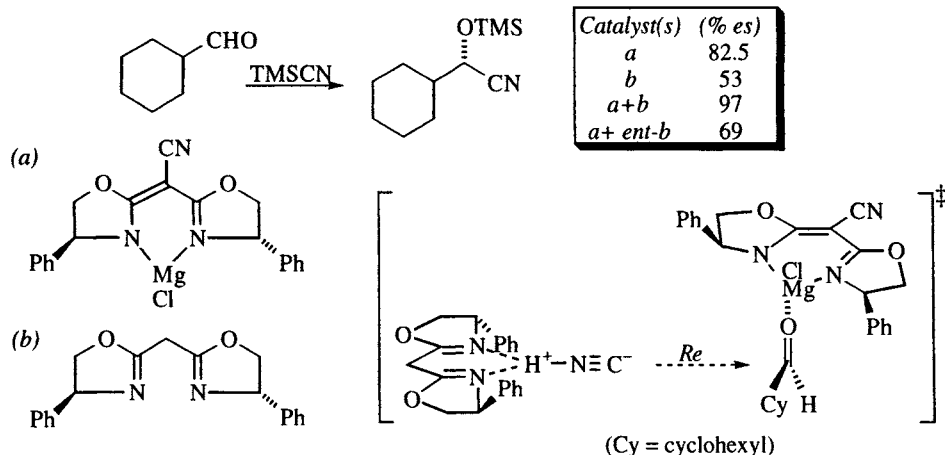
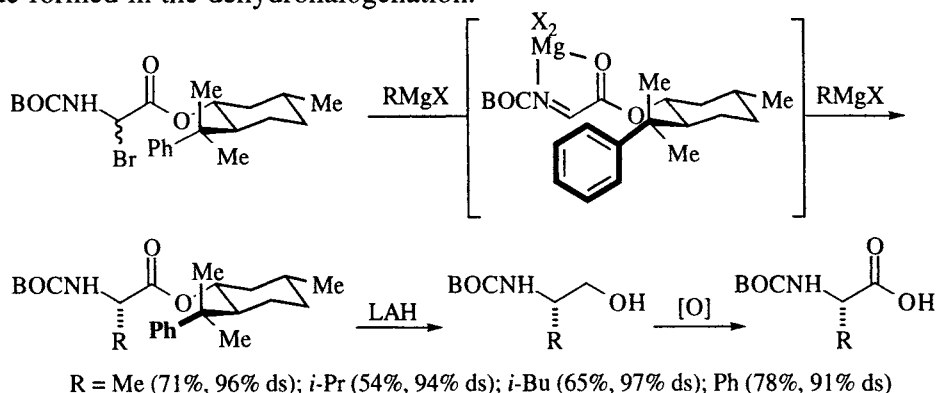


Figure 4.18. Corey's dual catalyst system for asymmetric hydrocyanation of aldehydes [95].

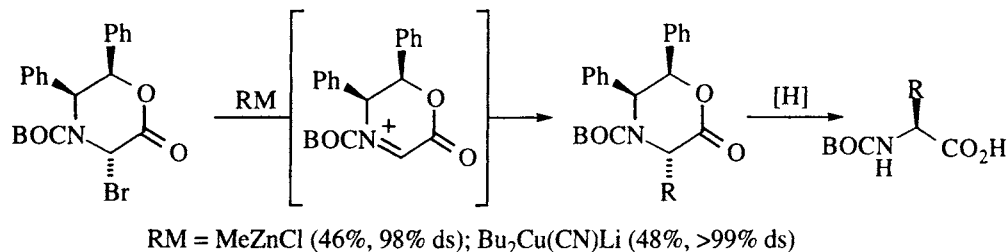
to nucleophilic attack. Second, many organometallic reagents are sufficiently basic that the preferential mode of reaction is abstraction of an α proton. Third, imines are susceptible to *E/Z* isomerization (often catalyzed by the Lewis acids that are a prerequisite to nucleophilic attack), which complicates the issue of stereochemical predictability. Nevertheless, the importance of amines in chemistry and medicine has furnished ample motive to pursue this method of synthesis. In fact, since the nitrogen is substituted ($C=NR$ instead of $C=O$), azomethines provide an opportunity for auxiliary-based stereochemical control that is not available to carbonyls. The following examples are arranged according to the charge on the nitrogen: addition to imines and hydrazones (neutral nitrogen) is followed by addition to iminium ions.

An asymmetric synthesis of amino alcohols by asymmetric addition of Grignard reagents to chiral α -bromoglycine esters provides a convenient synthesis of α -amino esters (Scheme 4.8, [99]). Hydrolysis of the product ester produces racemized amino acids, but reduction affords amino alcohols that can be subsequently oxidized to the amino acids with no loss of enantiomeric purity. Note that in the proposed transition structure, the phenyl effectively shields the *Re* face (toward the viewer) of the imine, which is chelated to the carbonyl by magnesium halide formed in the dehydrohalogenation.



Scheme 4.8. Synthesis of amino alcohols and amino acids by nucleophilic additions [99].

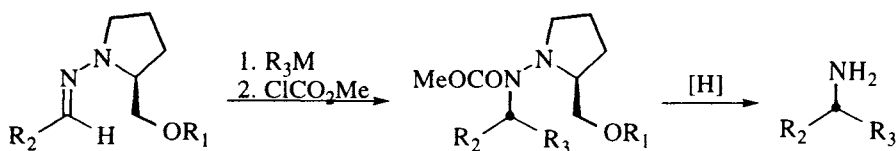
A strategy similar to that shown in Scheme 4.8 employs a Grignard addition to a cyclic α -bromoglycine derivative. As shown in Scheme 4.9, elimination of bromide affords an iminium ion that is selectively attacked on the *Si*-face, opposite the two phenyl groups [100]. Reductive cleavage of the benzylic C–N and C–O bonds provides ready access to amino acids.



Scheme 4.9. Oxazinones as chiral electrophilic glycine equivalents [100].

The addition of organometallics to SAMP and RAMP hydrazones has been studied by the Enders [101–106] and Denmark groups [107–109]. The best selectivities result from addition of organolanthanide reagents; table 4.7 illustrates several of the more highly selective examples. In conjunction with reductive cleavage of the hydrazone by hydrogenolysis [101,102] or dissolving metal reduction [110], the addition provides a convenient synthesis of α -branched primary amines (*c.f.*, Figure 4.16, p. 137). The intermediate hydrazines are somewhat unstable, but *N*-acylation makes for easier handling [105,110]. A mechanistic model has not been proposed to account for the observed configuration.

Table 4.7. Asymmetric addition of organoceriums to hydrazones.



Entry	R ₁	R ₂	R ₃	% Yield	% ds	Ref
1	Me	(EtO) ₂ CH	EtLi/CeCl ₃	91	96	[102]
2	Me	"	<i>n</i> -BuLi/CeCl ₃	92	97	[102]
3	Me	Ph(CH ₂) ₂	MeLi/CeCl ₃	81	98	[107]
4	Me	"	PhLi/CeCl ₃	72	96	[107]
5	Me	PhCH ₂	MeLi/CeCl ₃	66	96	[107]
6	Me	<i>E</i> -CH ₃ CH=CH	"	82	96	[107]
7	Me	TBSO(CH ₂) ₄	<i>n</i> -PrLi/YbCl ₃	83	>99	[105]
8	Me	<i>n</i> -Pr	TBSO(CH ₂) ₄ Li/ YbCl ₃			[105]
9	(CH ₂) ₂ OMe	Ph(CH ₂) ₂	<i>n</i> -BuLi/CeCl ₃	72	97	[107]
10	"	Me	Ph(CH ₂) ₂ Li/CeCl ₃	53	97	[108]
11	"	<i>t</i> -Bu	"	60	98	[108]
12	"	Ph	"	80	97	[108]

Stereoselective addition of Grignards to chiral pyridinium ions has been used to gain access to an important class of chiral heterocycles: substituted piperidines. Marazano uses *N*- α -methylbenzyl pyridiniums obtained by exchange of α -methylbenzyl amine with an *N*-2,4-dinitrophenylpyridinium [111], while Comins uses an *N*-acylpyridinium obtained by acylation with 8-phenylmenthyl chloroformate or a similar derivative (Table 4.8, [112–115]). Note that these processes are complicated by the symmetry of the ring system: *Si*-face attack at C-2 and *Si*-face attack at C-6 are equivalent (*i.e.*, the *Si*-faces of C-2 and C-6 are homotopic, Figure 4.19a). As a result of this equivalence, face selectivity at C-2 is topologically equivalent to regioselectivity (C-2 vs. C-6) from a single face. Thus, in a transition structure where (for example) attack of a nucleophile comes exclusively from the direction of the viewer, addition to C-2 and C-6 produce the same set of isomers that would result from attack at the front and back of only C-2 (Figure 4.19b). To circumvent this complication, Comins puts a large (removable) blocking group at C-3, which also blocks addition at C-4 (Figure 4.19c). Figure 4.20 illustrates several alkaloids synthesized using this approach.

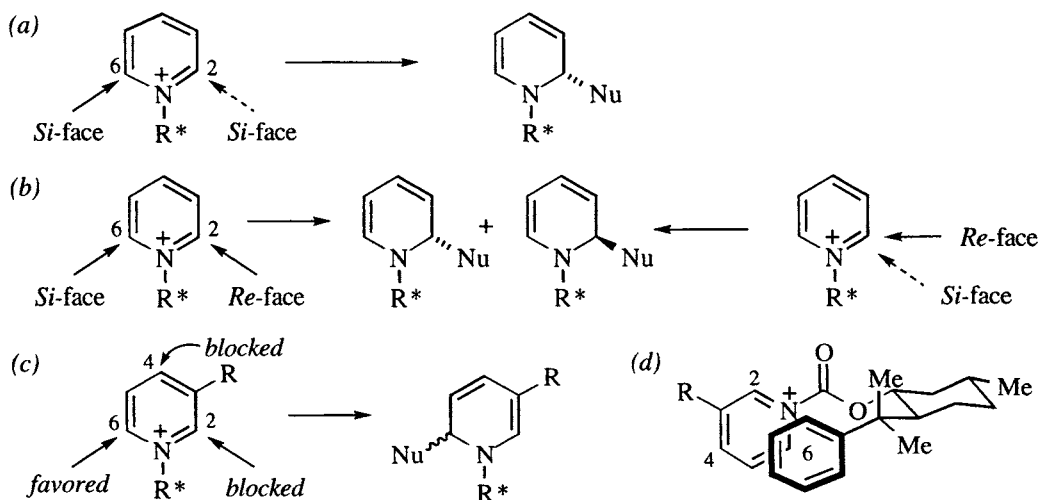


Figure 4.19. Complications of pyridinium additions due to ring symmetry. (a) Homotopic faces of C-2 and C-6; (b) Equivalence of 100% selective addition to only the front face with no regioselectivity and 100% regioselectivity with no face selectivity; (c) A bulky group at C-3 simplifies the situation by blocking attack at C-2 (and coincidentally C-4); (d) Comins's conformational model favoring *Re*-face (back side) attack at C-6 of an acylpyridinium ion [112].

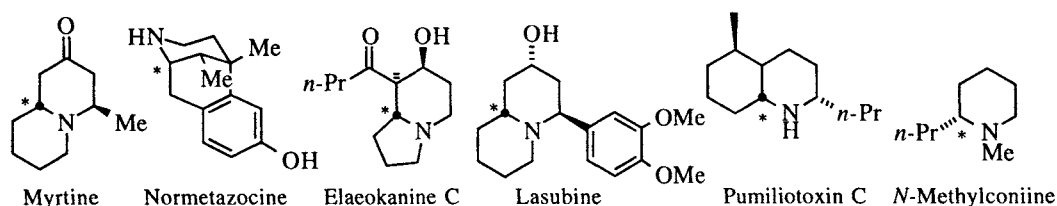
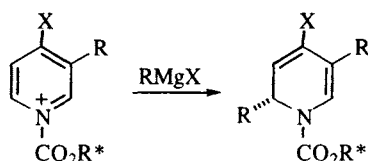


Figure 4.20. Alkaloids synthesized by asymmetric addition to chiral pyridiniums: myrtine ([116], normetazocine [100], elaeokanine C [117], lasubine [116], pumiliotoxin C [118], and *N*-methylconiine [113]. The stereocenter created in the addition reaction is indicated (*).

Table 4.8. Asymmetric additions to chiral acylpyridinium esters. For the structure of R*, see Figure 4.19d.

Entry	Educt	R	% Yield	% ds	Ref
1		<i>n</i> -Pr	72	91	[113]
2	"	<i>c</i> -C ₆ H ₁₁	81	95	[113]
3	"	PhCH ₂	58	88	[113]
4	"	CH ₂ =CH	71	95	[113]
5	"	Ph	85	94	[113]
6		Me	92	95	[112]
7	"	<i>i</i> -Bu	95	96	[112]
8	"	<i>c</i> -C ₆ H ₁₁	90	90	[112]
9	"	Ph	88	96	[112]

4.4 Conjugate additions¹⁴

Two strategies have been used for asymmetric 1,4-additions: those that are based on a chiral auxiliary that is covalently attached to one of the reactants, and those that rely on chiral ligands on the metal (reviews: [120-122]). As yet the former afford the higher selectivities, but progress is being made in the development of the latter, which has the most potential for cost effectiveness via chiral catalysis. The following discussion is organized by electrophile.

4.4.1 Esters

Since esters exhibit a strong preference for a conformation in which an alkoxy C-H is synperiplanar to the carbonyl, the job of the auxiliary is to then project an appendage back over the enoate π -system, leaving only one face open to attack by a nucleophile. Figure 4.21 illustrates three of the more selective auxiliaries for this purpose. These auxiliaries are illustrated with the esters in their most stable

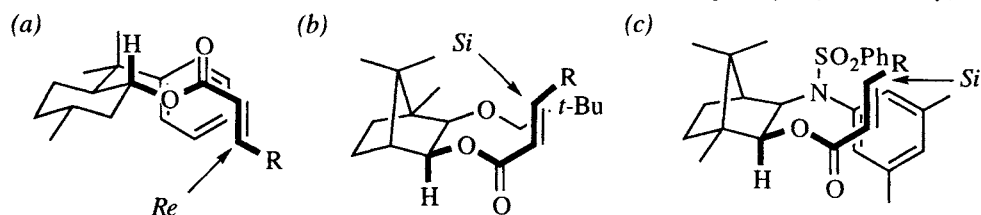
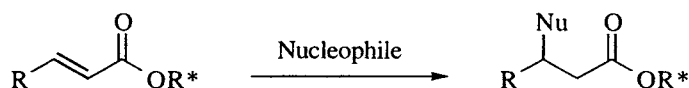


Figure 4.21. Chiral auxiliaries for asymmetric 1,4-addition to (the illustrated front face) of esters. Note the C–H/C=O coplanarity and the *s*-trans enone in the illustrated ground state conformations. (a) [123,124]; (b) [124]; (c) [125].

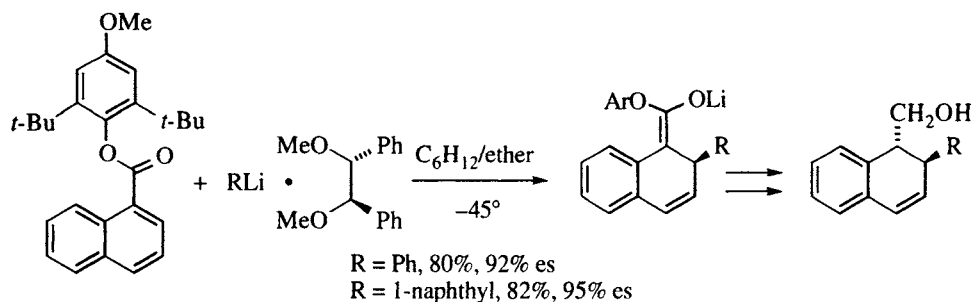
in the *s*-trans conformation. Presumably the ground state preference for this conformation is also felt in the transition state, which has the rear face shielded. Table 4.9 lists several examples of asymmetric additions to *E*-enoates. Less success has been realized in asymmetric additions to *Z*-enoates and to di- and trisubstituted double bonds.

Interligand asymmetric induction is observed in the 1,4-addition of certain organolithiums to hindered aryl esters in the presence of a chiral ligand. For example, Tomioka has shown that a chiral diether ligand affords good to excellent enantioselectivities in the conjugate additions of aryllithiums to the BHA esters shown in Scheme 4.10 [126]. Addition of butyllithium is much less selective, but similar selectivities can be achieved in aryllithium additions to BHA esters of 2-naphthoic acid. The additions are about 10–20% less selective when the ligand is used in catalytic quantities (10–20 mol%), but control experiments showed that the ligand accelerates the addition when the reaction is conducted in toluene.

Table 4.9. Asymmetric 1,4-addition to unsaturated esters of chiral alcohols. Numbers in the OR* column refer to Figure 4.21.



Entry	R	OR*	Nucleophile	% Yield	% es	Ref
1	Me	4.21a	PhCuBF ₃	76	>99	[123]
2	"	4.21c	"	97	>99	[125]
3	"	4.21c	VinylCuBF ₃	94	>99	[125]
4	"	4.21c	EtCuBF ₃	90	>99	[125]
5	"	4.21a	<i>n</i> -BuCuBF ₃	75	>99	[123]
6	"	4.21b	Me ₂ C=C(CH ₂) ₂ - CuP(<i>n</i> -Bu) ₃ BF ₃	81	99	[124]
7	"	4.21c	<i>i</i> -PrCuBF ₃	92	>99	[125]
8	Et	4.21c	MeCuBF ₃	86	99	[125]
9	<i>n</i> -Bu	4.21a	MeCuP(<i>n</i> -Bu) ₃ BF ₃	96	93	[124]
10	"	4.21b	"	82	97	[124]
11	<i>n</i> -C ₈ H ₁₇	4.21b	"	90	99	[124]
12	<i>i</i> -Pr	4.21c	MeCuBF ₃	92	>99	[125]



Scheme 4.10. Ligand induced asymmetric addition to naphthoic acid BHA (butylated hydroxy anisole esters) [126].

Figure 4.22 illustrates several natural products synthesized using auxiliary-modified esters. Particularly noteworthy is the ability of the method to produce the correct relative and absolute configuration of the alkyl branches on these acyclic frameworks. The illustrated structure for norpectinatone is the one originally postulated [127], but was proven incorrect by asymmetric synthesis [128].

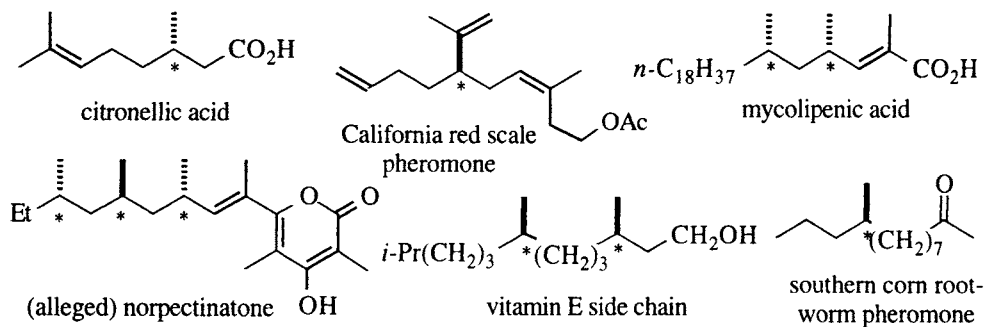
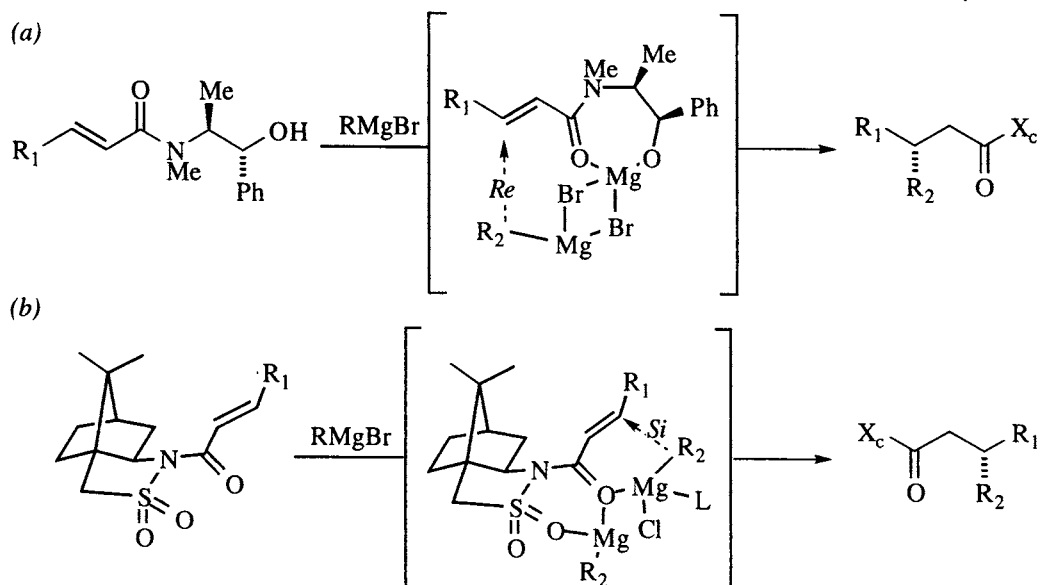


Figure 4.22. Natural products synthesized by asymmetric 1,4-addition of cuprates to esters: citronellic acid [124]; California red scale pheromone [129]; mycolipenic acid (W. Oppolzer; T. Godel, unpublished, quoted in [130]); the alleged norpectinatone [128]; vitamin E side chain (W. Oppolzer; R. Moretti, unpublished, quoted in [130]); southern corn rootworm pheromone [131]. Stereocenters created in the asymmetric conjugate addition are marked (*).

4.4.2 Amides and imides

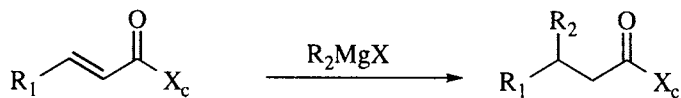
A number of amides have been screened for their selectivity in conjugate additions of organometallics to acyclic enamides [120]. Two of the more useful auxiliaries are illustrated in Scheme 4.11. Both systems add Grignard reagents with considerable selectivity. Mukaiyama's ephedrine amides (Scheme 4.11a) require excess Grignard, and work best with organomagnesium bromides [132]. Oppolzer's sultam imide (Scheme 4.11b) offers several useful features [133]: in addition to the usual crystallinity of camphor derivatives (helpful for purification and diastereomer enrichment), the enolate may be alkylated (recall Scheme 3.18 and Table 3.7) with 87-88% selectivity for one of the four possible α,β -disubstituted stereoisomers. Additionally, 2-methacryloyl sultams can be protonated with a high degree of selectivity, giving 2-methyl-3,3-dialkyl amides of >97% purity [133].



Scheme 4.11. Auxiliaries for the asymmetric 1,4-addition of Grignards to acyclic amides [132,133].

The transition structures illustrated in Scheme 4.11 have been proposed by the authors to account for the absolute configuration of the major product. Note that both groups invoke aggregation of the nucleophile with a magnesium species chelated by the enone carbonyl and a heteroatom on the auxiliary. This chelation reduces conformational motion in the ground state as well as the transition state, and reduces the possible number of competing nucleophile approach trajectories. For the ephedrine amides, the stereocenters on the auxiliary are quite remote from the site of attack. Although attack on the face opposite the methyl and phenyl groups in this chelate (as drawn) accounts for the configuration of the product, it is not clear how this steric effect is transmitted across the metallocycle chelate to the external double bond. It may be that the methyl and phenyl substituents induce a

Table 4.10. Asymmetric 1,4-additions to enamides (auxiliaries illustrated in Scheme 4.11).

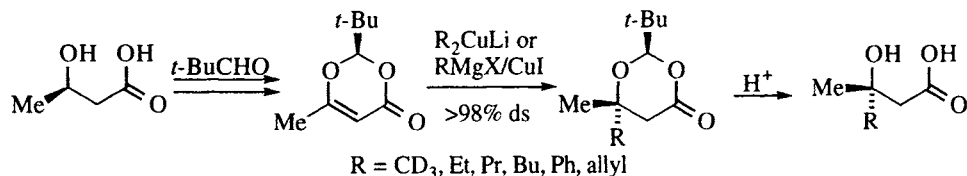


Entry	R ₁	R ₂ MgX	Auxiliary	% Yield	% ds	Ref
1	Me	PhMgBr	a	63	95	[132]
2	Me	EtMgBr	a	79	98	[132]
3	Ph	"	a	48	98	[132]
4	Et	PhMgBr	a	76	93	[132]
5	Et	<i>n</i> -C ₄ H ₉ MgBr	a	59	79	[132]
6	<i>n</i> -C ₄ H ₉	EtMgBr	a	69	99	[132]
7	Me	EtMgCl	b	80	94	[133]
8	Me	<i>i</i> -Pr	b	92	86	[133]
9	Et	<i>n</i> -C ₄ H ₉ MgCl	b	89	95	[133]

curved shape to the chelate ring that favors approach from the convex face, or perhaps the substrate is an aggregate of unknown structure. For the sultam (Scheme 4.11b), the situation is more clear: the bridge methyls of the camphor hinder approach from the *Re* face, similar to the situation with enolate alkylation of the same auxiliary (Scheme 3.18). Table 4.10 lists several examples of additions to these auxiliaries.

4.4.3 Dioxinones.

Incorporation of an auxiliary into a cyclic system has been used for the diastereoselective addition of cuprates to unsaturated 6-membered ring dioxinones, which are perhaps less important for their synthetic potential than for the mechanistic insight they provide. The dioxinones shown in Scheme 4.12a were obtained from *R*-3-hydroxybutanoic acid using the “self-regeneration of chirality centers” concept discussed in Chapter 3 (*cf.*, Scheme 3.9 and 3.10). After the addition, hydrolytic removal of the “achiral auxiliary” (pivaldehyde) liberates a 3-alkyl-3-hydroxybutyrate that is essentially enantiomerically pure [134].



Scheme 4.12. Asymmetric conjugate addition of cuprates to dioxinones [134].

The additions are all >98% diastereoselective (the limit of detection), which is surprising since the dioxinone ring is in a sofa conformation, with only the acetal carbon significantly out of plane, leaving approach from either face essentially unhindered (recall the low selectivities for alkylation of *t*-butylcyclohexanone enolates, Scheme 3.7). Interestingly, examination of a number of X-ray crystal structures revealed that dioxinone acetals such as these have the common feature of pyramidalized carbonyl and β -carbon atoms [134]. Empirically, additions occur from the direction of the β -carbon's pyramidalization (see also ref. [135]). The reason for the pyramidalization in the substrate is the relief of torsional strain (however, calculations indicated that the energy required to flatten the pyramidal atoms is very small, ~ 0.1 kcal/mole). Seebach suggests [134] that approach of the nucleophile from the direction of pyramidalization should minimize the strain even more (see also ref. [15]). Since the reaction is kinetically controlled, and the selectivity is therefore determined in the transition state ($\Delta\Delta G^\ddagger$), this hypothesis (which is based on ground state arguments) may seem a risky infringement of the Curtin-Hammett principle [13,14]. Nevertheless, the strain that produces the pyramidalization (ΔG for the flat and pyramidal geometries) in the ground state and the energy differences in the transition state ($\Delta\Delta G^\ddagger$) have the same origin, and approach from the direction of pyramidalization relieves the strain while approach from the opposite direction increases it (Figure 4.23a). Thus, the energy difference between the two pyramidal ground states is *amplified* in the transition state (see

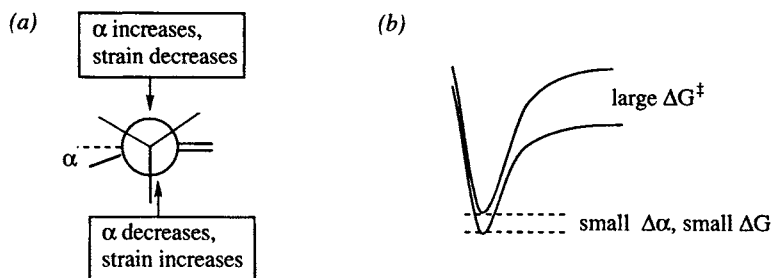
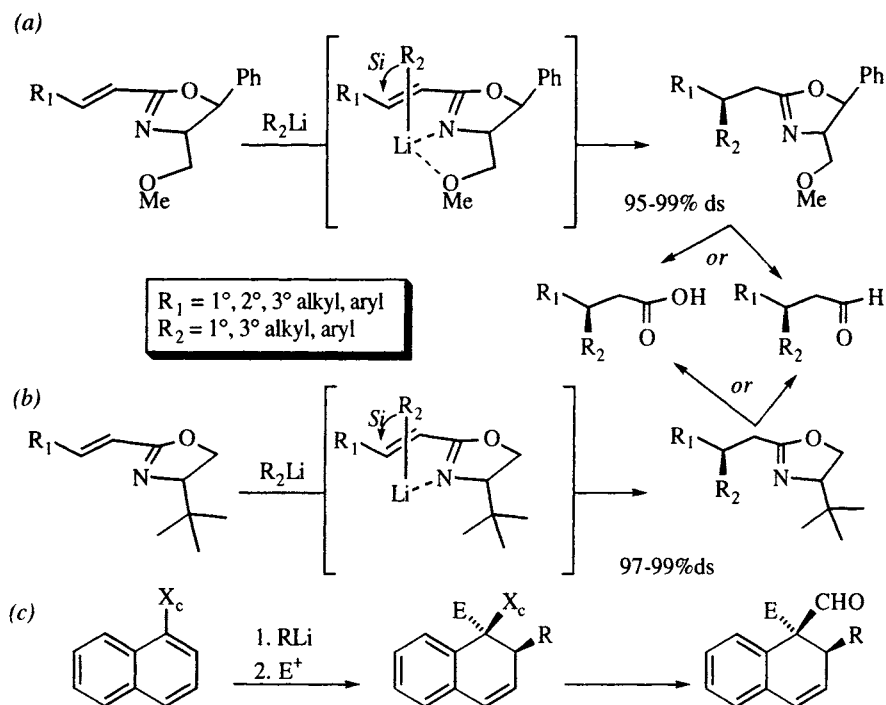


Figure 4.23. (a) Schematic showing how torsional strain is affected by the direction of attack on a pyramidalized trigonal center. (b) Linear perturbation of a Morse function that produces small distortions in the ground state can lead to large energy differences in the transition structure. (After ref. [134]).



Scheme 4.13. Asymmetric addition of organolithiums to oxazolines: (a) [136,137]; (b) [140]; (c) Tandem asymmetric addition and alkylation of naphthalenes.

operation. Depending on the method, the two alkyl groups may be introduced in either a *cis* or a *trans* fashion. For example, the naphthalene oxazolines (Figure 4.24a-c) alkylate *trans* to the first alkyl group, whereas the cycloalkenyl imines (Figure 4.24f) may alkylate either *cis* or *trans* selectively, depending on the method used. A generalized example (for 1-naphthalenes) is shown in Scheme 4.13c.

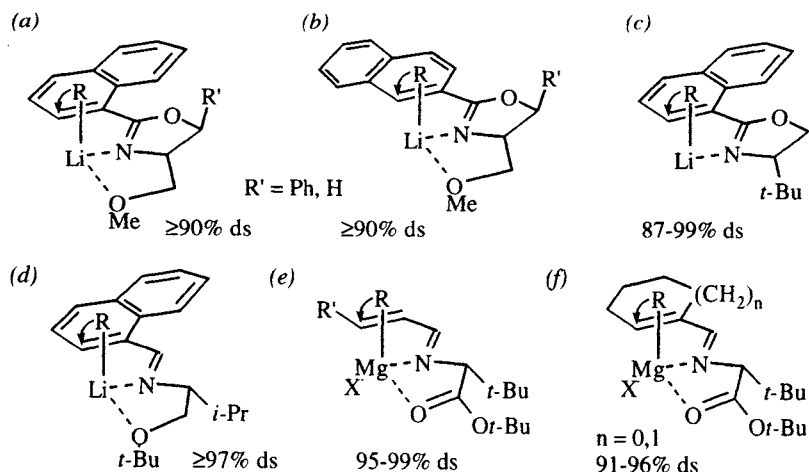
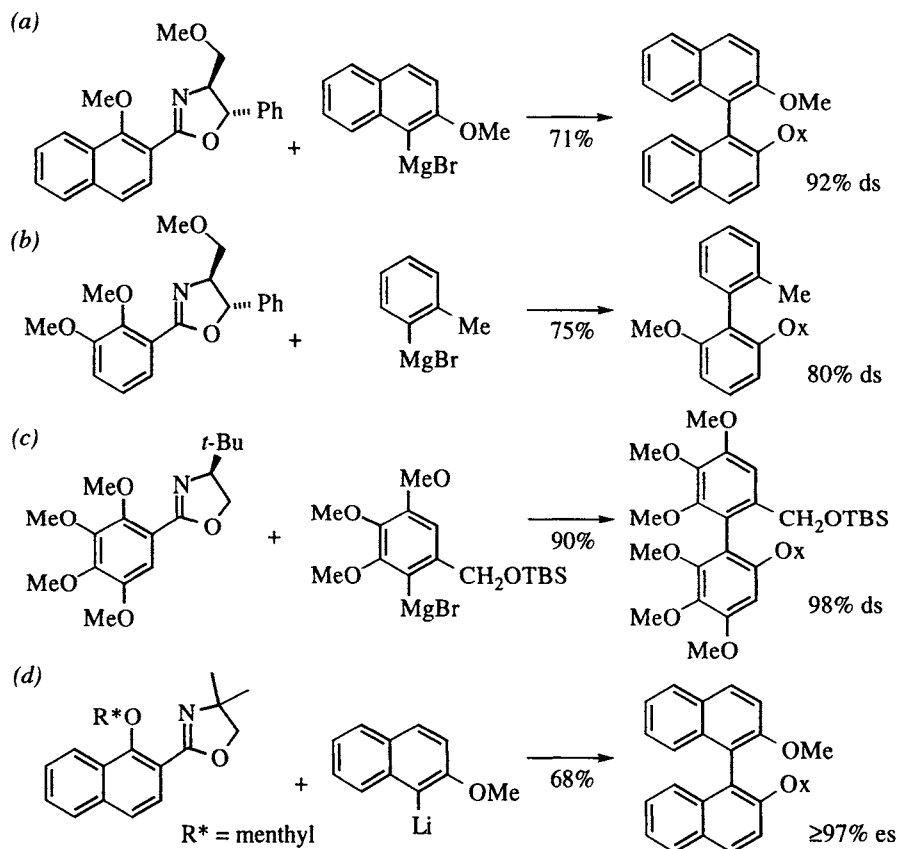


Figure 4.24. (a) Addition to 1-naphthyloxazolines [142]; (b) Addition to 2-naphthyloxazolines [142]; (c) addition to 1-naphthyloxazolines lacking a chelating group [144]; (d) addition to 1-naphthaldehyde imines [145]; (e) addition to crotyl amino acid imines [146,147]; (f) addition to cyclohexene and cyclopentene aldehyde amino acids imines [148].

When the site of nucleophilic attack has an alkoxy substituent, the azaenolate adduct undergoes spontaneous elimination of alkoxide. Since aryllithiums add efficiently to 2-alkoxyaryloxazolines, the process may be used in an asymmetric synthesis of chiral biaryls. Two strategies for auxiliary-based asymmetric induction have been evaluated: using an oxazoline as a chiral auxiliary [149-152], and using a chiral alkoxide (leaving group) as an auxiliary [153]. Scheme 4.14 illustrates several examples. Note that here again, the early reports used an oxazoline that contains a chelating substituent (Scheme 4.14a,b), but later reports indicated that a bulky substituent at the oxazoline 4-position will suffice (Scheme 4.14c). Figure 4.25 illustrates several natural products that have been made using asymmetric addition to unsaturated azomethines.



Scheme 4.14. Asymmetric synthesis of biaryls: (a) binaphthyls using a chelating oxazoline [149]; (b) biphenyls using a chelating oxazoline [150]; (c) biphenyls using a nonchelating oxazoline [151]; (d) binaphthyls using a chiral leaving group [153].

An interesting development in asymmetric additions to azomethines employs chiral ligands (chelating agents) on the organometallic. Tomioka has shown that the same ligand used for addition of aryllithiums to unsaturated esters (*cf.* Scheme 4.10) also works for unsaturated imines, as illustrated in Scheme 4.15 [154].¹⁶ The

¹⁶ For a related study of the stereoselectivity of addition/alkylation to cyclohexylimines in the racemic series, see ref. [155].

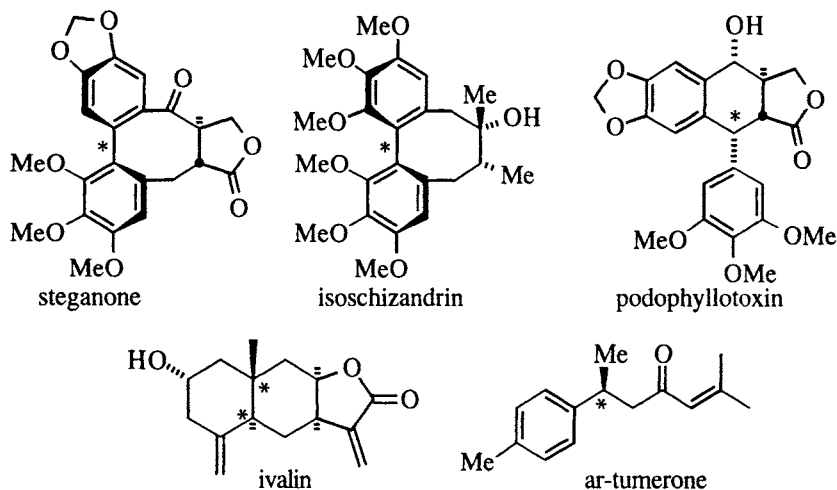
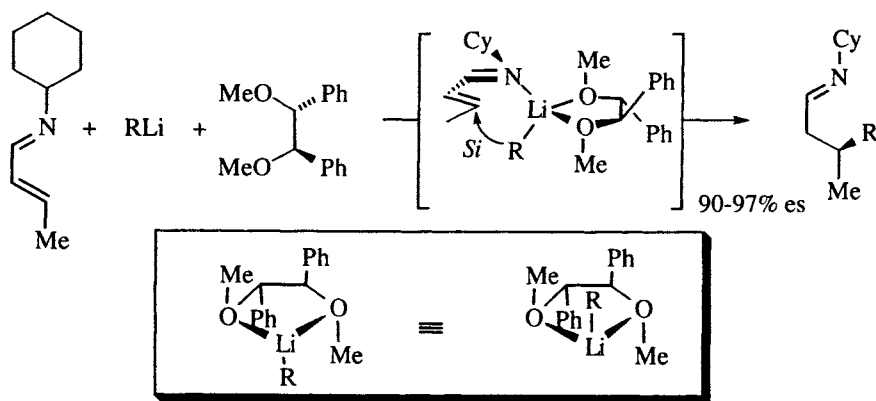


Figure 4.25. Natural products synthesized using asymmetric addition to chiral azomethines: steganone [156], isoschizandrin [157], podophyllotoxin [158], ivalin [159], ar-tumerone [160]. The stereogenic units formed in the conjugate addition step are marked (*).

C₂-symmetric ether is thought to chelate the alkyllithium (and thereby break up the alkyllithium aggregate), which then coordinates to the azomethine nitrogen. Note that the phenyls force the methyls into a conformation that places each of them trans to the neighboring phenyl in the chelate (see inset). Upon complexation of the azomethine to the vacant site on the lithium, the large cyclohexyl is oriented into the vacant quadrant of the chelate, as shown.¹⁷ Suprafacial transfer of the alkyl group then gives the observed product with enantioselectivities above 90%, and usually in the 97-99% range. Examples include crotyl, cycloalkenyl, and 1-naphthyl imines [154]. Using the same ether and the 2,6-diisopropylphenyl imine of 1-fluoro-2-naphthaldehyde, a chiral binaphthyl is formed by asymmetric addition of 1-naphthyllithium in >99% yield and 95% es [161].



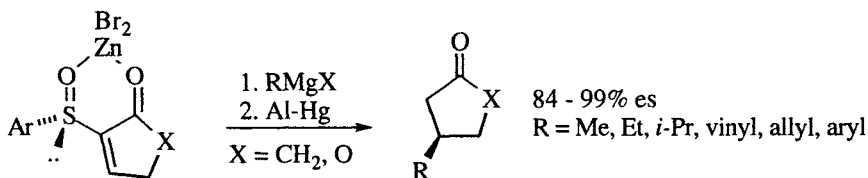
Scheme 4.15. Interligand asymmetric induction in the conjugate addition of an alkyllithium to an unsaturated imine [154].

¹⁷ Note that because of symmetry, the lithium is not stereogenic, so the vacant sites available by inversion of the tetrahedral lithium are equivalent.

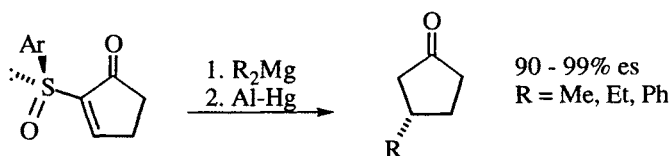
4.4.5 Ketones and lactones

In addition to the “self-regeneration of chirality” principle discussed in Section 4.4.3, strategies for the asymmetric 1,4-addition to enones have included both auxiliary-based methods and interligand asymmetric induction. The most fully developed auxiliary method is Posner's use of vinyl sulfoxides, illustrated in Scheme 4.16 (reviews: [162-164]). The sulfur atom is pyramidal, and therefore stereogenic. The method is most useful with 5-membered α,β -unsaturated ketones and lactones (butenolides), and may employ strategies in which chelates are involved (Scheme 4.16a) or not (Scheme 4.16b), as illustrated. Zinc bromide is the most effective for chelating the sulfoxide and carbonyl oxygens. In the ‘non-chelate’ strategy, dialkylmagnesiums are used as the organometallic, sometimes in the presence of crown ethers. The authors’ mechanistic rationale has the organometallic adding from the side that is opposite the aryl group of the sulfoxide in either the chelate or opposing-dipole (non-chelate) conformations; improved selectivities resulted when anisyl sulfoxides were used in place of tosyl [165], and when the poorly coordinating dimethyltetrahydrofuran was used as solvent. Figure 4.26 illustrates several natural products synthesized using this method.

(a) *chelate control*:



(b) *non-chelate control*:



Scheme 4.16. Asymmetric addition of organomagnesiums to vinylic sulfoxides [162-164].

Schultz has reported a conceptually related method, which affords higher selectivities for cyclohexenones than is possible with the sulfoxide method, as shown in Scheme 4.17 [166]. The 2-carboxamidocyclohexenones are prepared by Birch reduction and hydrolysis of the 2-methoxybenzamide. Conjugate addition of Grignard reagents in the presence of Lewis acids, affords good yields of addition products with high selectivities for most nucleophiles (allyl is the notable exception). Presumably, the stereochemical rationale is similar, with the Lewis acid chelating the two carbonyls and the nucleophile approaching from the face opposite the methoxymethyl. Hydrolysis of the auxiliary and decarboxylation affords the 3-substituted cyclohexanones.

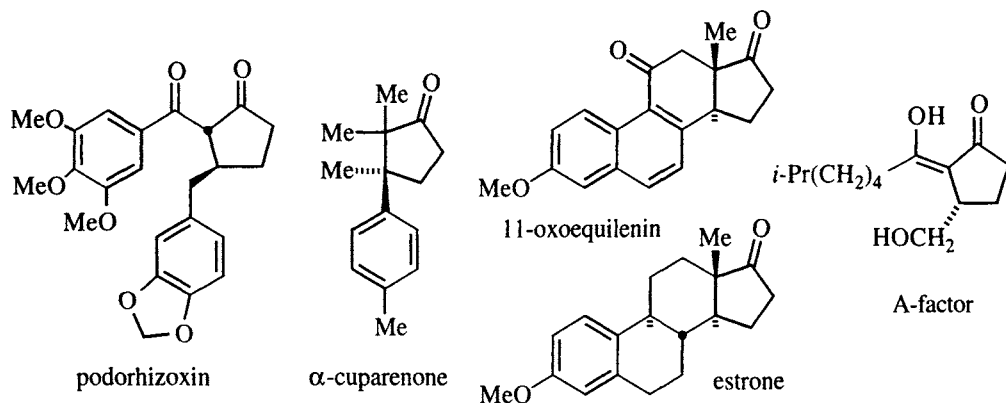
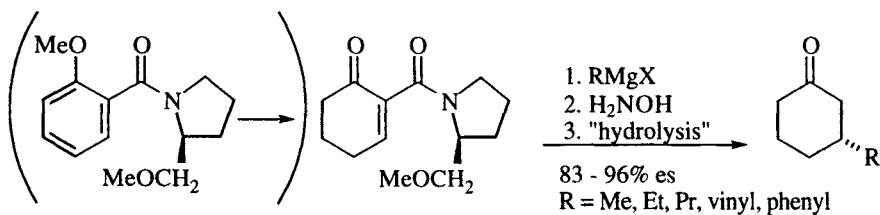


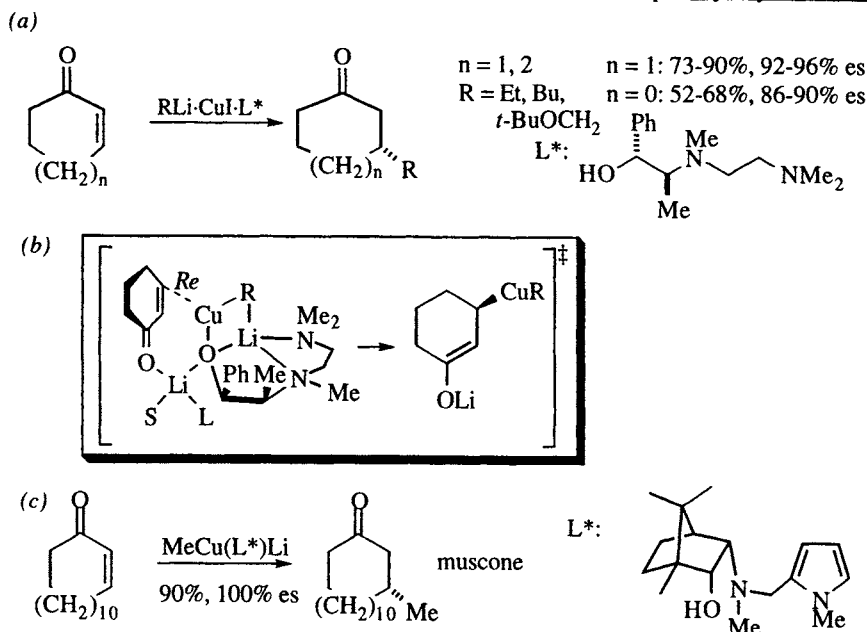
Figure 4.26. Natural products synthesized by 1,4-addition to unsaturated cyclopentenones and butenolides: podorhizoxin [167], α -cuparenone [168], 11-oxoequilenin [169], estrone [169,170], A-factor [163].

The asymmetric addition of cuprates to achiral cycloalkenones using a chiral ligand on the metal (interligand asymmetric induction) has been studied extensively,¹⁸ but obtention of uniformly high yields with a variety of substrates and nucleophiles has not been achieved because the selectivity is dependent on a number of factors, including substrate and cuprate structure, solvent, concentration, temperature, and the presence of added salts. Two of the more highly selective ligands are illustrated in Scheme 4.18, and a mechanistic rationale for the first is also shown. Unfortunately, these processes are reported to be hypersensitive to the presence of impurities in the reaction mixture. In the first example (Scheme 4.18a), the presence of alkoxides in the alkyllithium diminishes the selectivity, and methyl iodide must be added to the recipe as an alkoxide scavenger [171]. A related approach uses a phosphine ligand, but the selectivity of these additions are highly dependent on the source of the copper [172]. The second example (Scheme 4.18b) is an optimized procedure for the asymmetric synthesis of muscone [173].



Scheme 4.17. Asymmetric addition of Grignards to cyclohexenones [166].

¹⁸ For a survey of the ligands tested, see ref. [120].



Scheme 4.18. (a) Asymmetric addition of cuprates to cycloalkenones [171]. (b) Mechanistic rationale for a [171]. (c) Asymmetric synthesis of muscone [173].

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