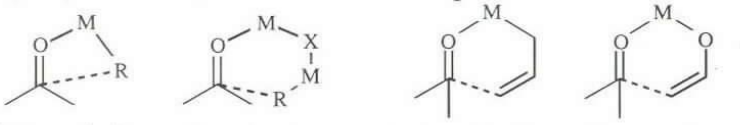
Chapter 4

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.



"σ-transfer" transition structures *"π-transfer" transition structures*

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.

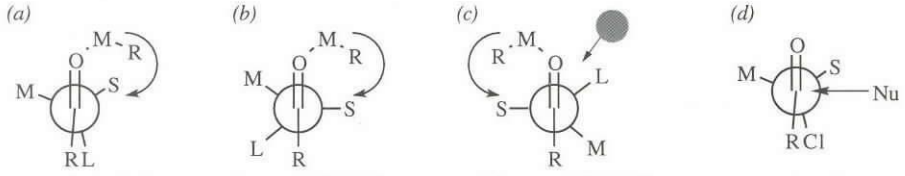


Figure 4.2. *(a-c)* Cram's models for predicting the major isomer of a nucleophilic addition to a carbonyl having a stereocenter in the α position [2,6]. *(d)* Cornforth's dipole model for α-chloro ketones [7]. S, M, and L refer to the small, medium, and large groups, respectively.

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.

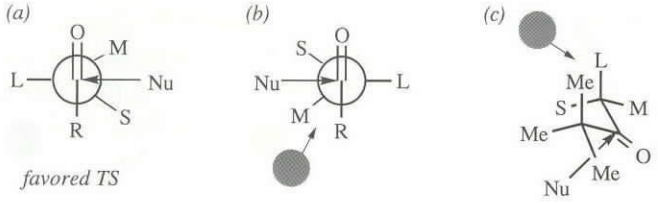


Figure 4.4. *(a-b)* Felkin's transition state models. *(c)* Destabilized 'favored' transition state with a flanking *tert*-butyl [16].

favored. 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 te 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.

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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]).

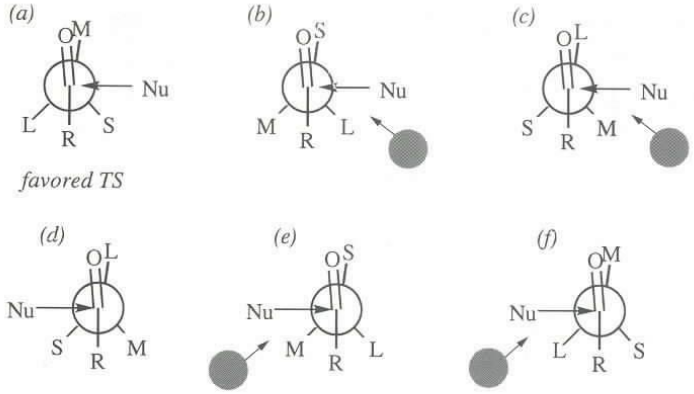

Figure 4.3. Karabatsos's transition state models [10].

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 $R_1MeCHC(=O)R_2$ by $LiAlH_4$ [16].

Large Subs.	R_2 = Me	R_2 = Et	R_2 = *i*-Pr	R_2 = *t*-Bu
R_1 = *c*-C_6H_{11}	62	66	80	62
R_1 = 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=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).

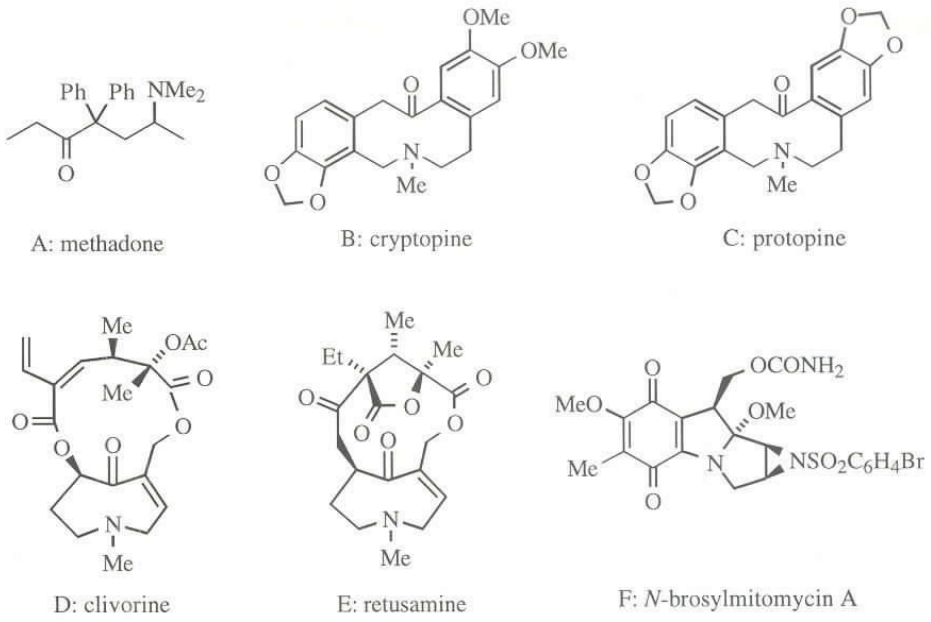

Figure 4.5. Compounds whose X-ray structures provided the basis for the "Bürgi-Dunitz" trajectory.

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.

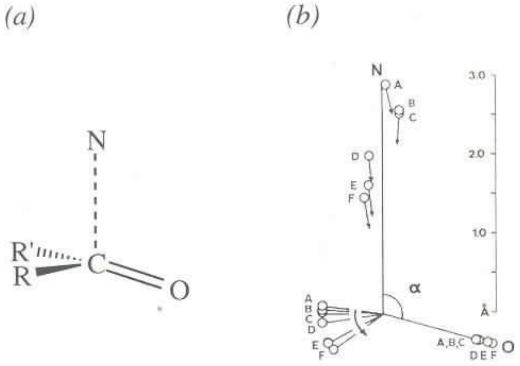

Figure 4.6. *(a)* Orientation of the superimposed carbonyl and nitrogen atoms. *(b)* Superimposed plot of the N, C, and O atoms of structures A-F, and the variance of the RRC plane from the RRO plane. α is the "Bürgi-Dunitz angle," 107°. Reprinted with permission from ref. [21], copyright 1973, American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

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.

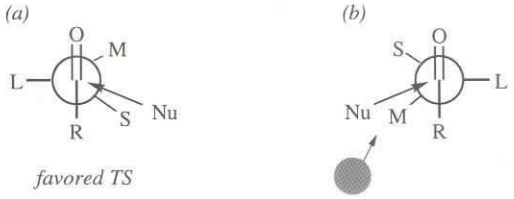

Figure 4.8. The Felkin-Anh transition state models for asymmetric induction [17,23].

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.

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

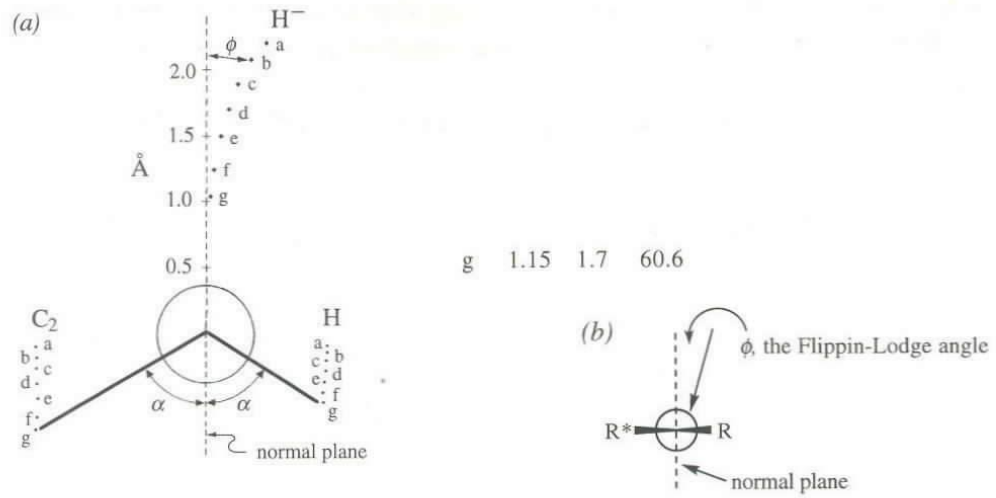


Figure 4.9. *(a)* Deviation of the attack trajectory from the normal plane in the reaction of hydride with pivaldehyde. Reprinted with permission from ref. [25], copyright 1987, American Chemical Society. *(b)* Newman projection of a ketone, with an approaching nucleophile, and the Flippin-Lodge angle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

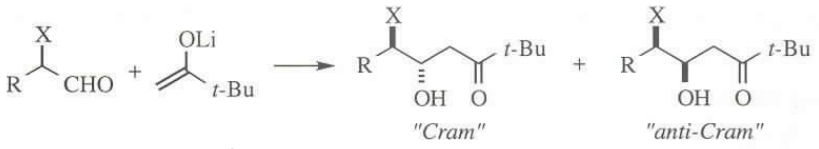
If the antiperiplanar substituents in the Felkin-Anh model (L in Figure 4.8) are those with low-lying σ* orbitals (X in Table 4.2), one would expect a gradual increase in selectivity as the steric bulk of the remaining substituent (M in Figure 4.8) increased. The data in Table 4.2 show that this is clearly 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* values[7] as a measure of steric bulk. In the phenyl series, there is no apparent pattern, and when R = *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 ($-\Delta G°$), *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*-Pr	R = *t*-Bu	R = Ph
OMe	58	76	93	93	83
Ph	78	86	70	–63	–

C_{sp^2} σ* orbital play a role. A prediction made on the basis of its bulk alone (*A* values[5]) 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 C_{sp^3}–C_{sp^3} σ* 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 C_{sp^3}–C_{sp^3} and C_{sp^3}–C_{sp^2} bonds than between carbon–carbon and carbon–heteroatom bonds.

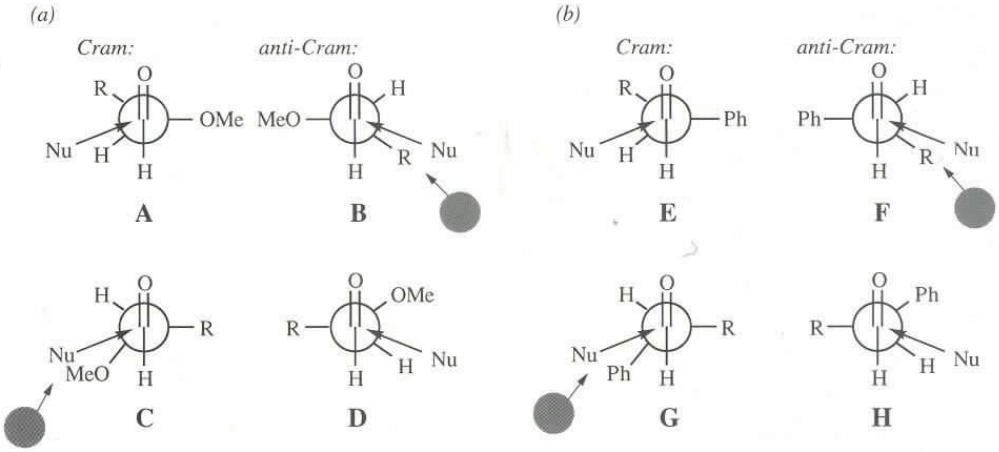


Figure 4.10. Heathcock's four-conformer model for 1,2-asymmetric induction [28]. *(a)* Electronic effects favor methoxy as anti ligand (A and B) while steric effects may favor C and D. *(b)* Electronic effects favor phenyl as anti ligand (E and F) while steric effects favor G and H for very large alkyl 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 addition reactions to carbonyl compounds originates from simple conformational effects" [30] (see also ref. [31-33]).

To predict the major stereoisomer in a "Cram's rule situation", a thorough analysis should include consideration of the following points:

1. The nucleophile will approach along the Bürgi-Dunitz trajectory, approximately 100-110° from the carbonyl oxygen (Figures 4.6 and 4.7).
2. For ketones, the approach may be in or near the normal plane, but for aldehydes, there will be a deviation from this plane, toward the hydrogen and away from the stereocenter (Figure 4.9).
3. If there is a strong electronic or steric preference by one ligand that is not offset by another ligand, the Felkin-Anh two conformer model (Figure 4.8) may be used with the following order of preference for the anti position: MeO>*t*-Bu>Ph>*i*-Pr>Et>Me>H [28].
4. A complete evaluation of the selectivity requires (at least) a four conformer analysis (Figure 4.10) with the electronic effect dictating an anti preference of MeO>Ph>R>H, while the steric effect leads to the order *tert*-Bu>Ph>*i*-Pr>Et>Me>H [28].

4.2 Cram's rule: rigid, chelate, or cyclic model

In his 1952 paper [2] Cram also considered a cyclic model that may be invoked when chelation is possible. In 1959 [6] the model was examined in detail for α-hydroxy and α-amino ketones, since the cyclic and acyclic models predict different outcomes for these systems. The cyclic model (Figure 4.11) has stood the test of time rather well, and has recently received direct experimental confirmation, in the form of NMR observation of a chelate as an intermediate in the addition of dimethylmagnesium to α-alkoxy ketones [34]. The cyclic model is applicable to cases where there is a chelating heteroatom on the α-carbon, when that carbon is also a stereocenter (reviews: [35,36]).

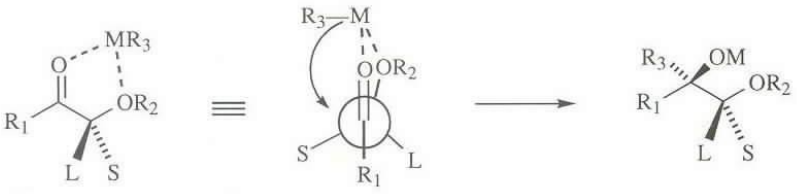
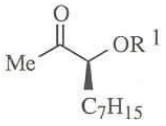
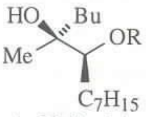
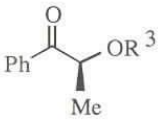
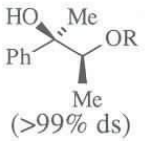
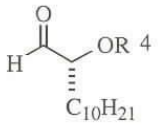
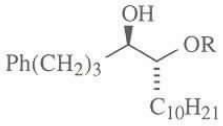
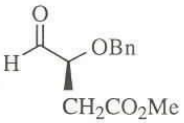
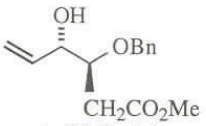
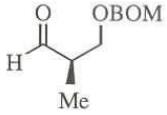
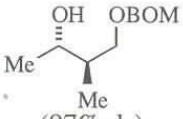
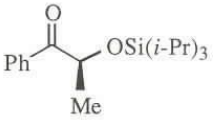
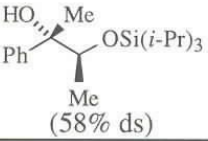


Figure 4.11. Cram's cyclic model for asymmetric induction. L and S are large and small substituents, respectively [2,6]).

Table 4.3 lists selected examples where exceptionally high stereoselection has been encountered. Solvent effects play an important role in achieving high selectivity. For example the >99% diastereoselectivities for the addition of

Grignard reagents to α-alkoxy ketones in THF (entry 1) were greatly diminished in ether, pentane, or methylene chloride [37]. Eliel demonstrated similar selectivites 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_2Mg THF, –70°	 (>99% ds)	[34]
3		$Ph(CH_2)_3MgBr$ Et_2O,[5] –78°	 (94% ds)	[39]
4		$MgBr_2{\cdot}OEt_2$ CH_2=CHMgBr CH_2Cl_2,[5] –78°	 (>99% ds)	[40]
5		Me_2CuLi Et_2O, –78°	 (97% ds)	[38]
6		Me_2Mg THF, –70°	 (58% ds)	[34]

1 R = MEM (methoxyethoxymethyl-), MOM (methoxymethyl-), MTM (methylthiomethyl-), CH_2–furyl, Bn (benzyl-), BOM (benzyloxymethyl-).

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

3 R = Me, $SiMe_3$.

4 R = Bn, MOM

5 THF affords much lower selectivity.

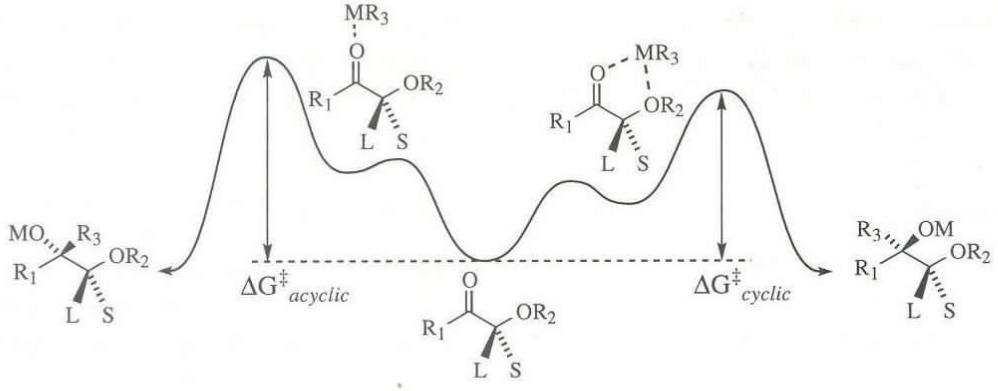


Figure 4.12. Energetics of the Cram-chelate (acyclic) model. $\Delta G^{\ddagger}_{acyclic} > \Delta G^{\ddagger}_{cyclic}$ (after ref. [34]).

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 combination of both) would raise the transition state energy for the chelate path and the primary addition mode could be shifted to the less selective nonchelated mechanism.[10]

Because of the high selectivities observed in chelation-controlled additions, it is often used in stereoselective total syntheses. For example, highly selective additions of Grignards were used in the synthesis of the ionophores monensin [43,44] and lasalocid [45,46], shown in Figure 4.13.

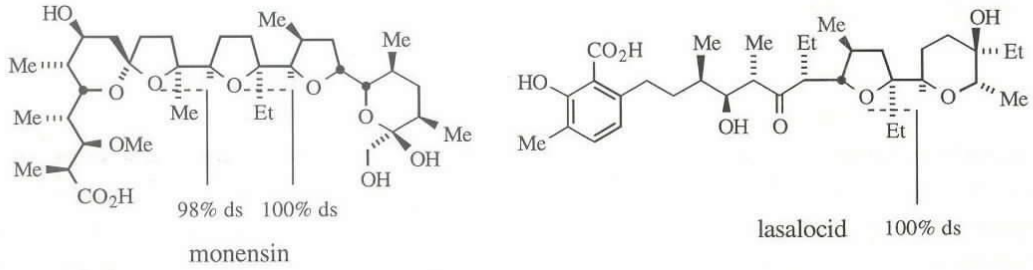


Figure 4.13. Chelation-controlled addition of Grignards to ketones figured prominently in the synthesis of monensin [43] and lasalocid [45,46]. The disconnections used and the selectivities achieved are indicated for the stereocenters formed by the Grignard addition.

4.2.1 Cram's cyclic model in asymmetric synthesis

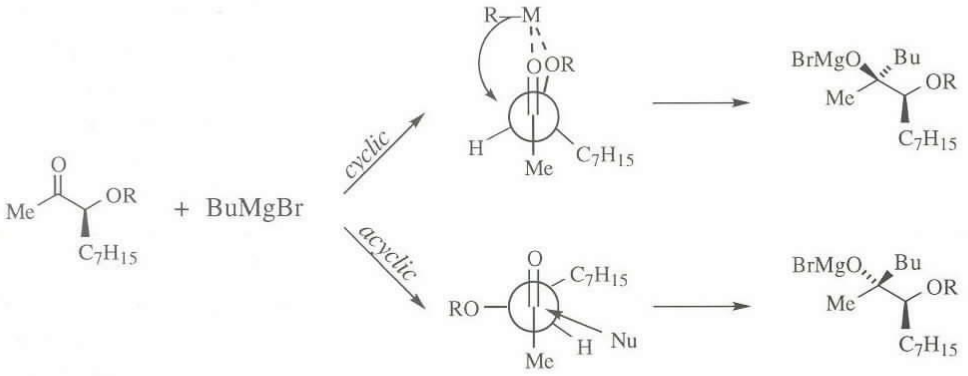
Auxiliaries have been designed to exploit the high selectivities of chelation-controlled processes in asymmetric synthesis. Among these are the oxathiane [35,47-50]

[10] Another possibility is that the intrinsic selectivity of reaction *via* a 6-membered chelate is lower.

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).

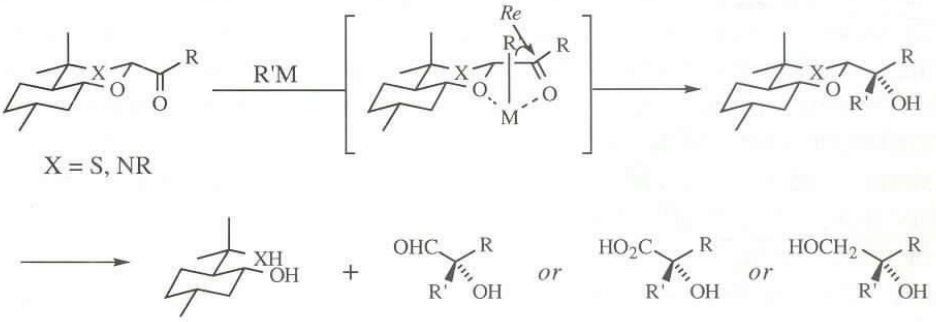


Scheme 4.1. Cyclic and acyclic models often predict opposite outcomes.

Study of the mechanism of Grignard addition (RMgX) via the chelate pathway is complicated by the presence of Schlenck 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.*

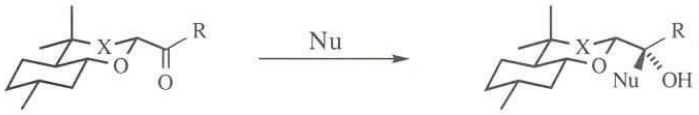
and oxazine [51,52] systems developed by Eliel. As shown in Scheme 4.4, the heterocyclic system is held rigid by its *trans*-decalin-like geometry. In both heterocyclic systems, the metal is chelated by the carbonyl oxygen and the ether oxygen (the latter in preference to either the sulfur or the nitrogen).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

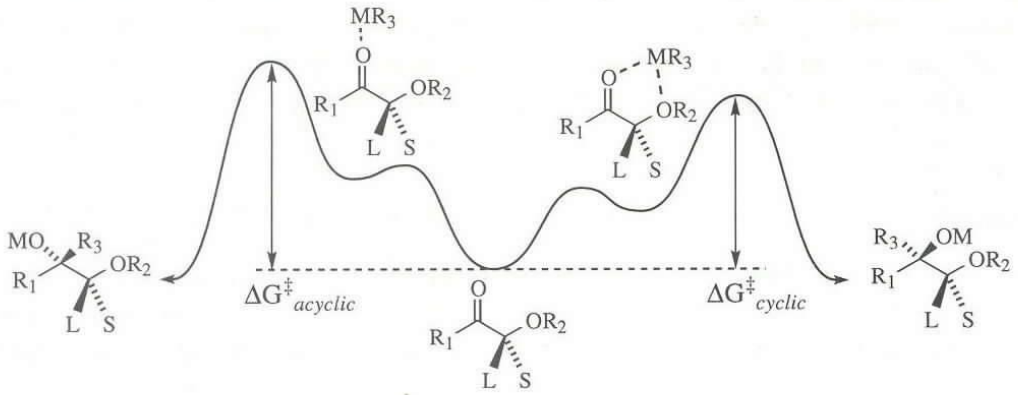


Scheme 4.4. Eliel's asymmetric addition to carbonyls using Cram's chelate model.

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



Entry	X	R	Nu	% ds	Reference
1	S	Me	CH_2=CHMgBr	92	[53]
2	S	Me	BnMgBr	>98	[54]
3	S	Bn	MeMgBr	>98	[54]
4	S	*n*-C_9H_{19}	(*S*)-MeCHPh$(CH_2)_2$MgBr	97.5	[55]
5	S	*n*-C_9H_{19}	(*R*)-MeCHPh$(CH_2)_2$MgBr	89	[55]
6	S	*n*-$C_{10}H_{21}$	LiBH(*s*-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]



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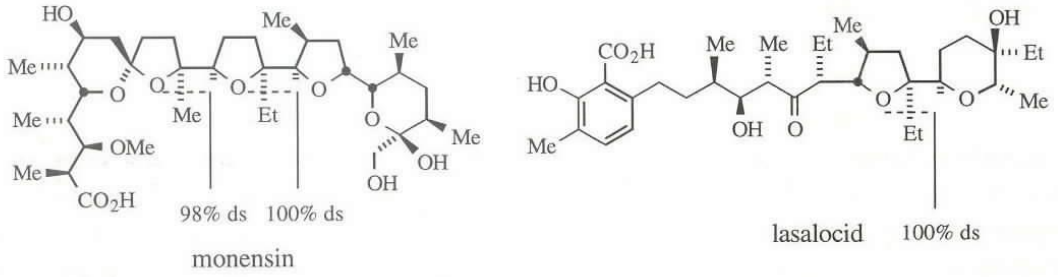

Figure 4.13. Chelation-controlled addition of Grignards to ketones figured prominently in the synthesis of monensin [43] and lasalocid [45,46]. The disconnections used and the selectivities achieved are indicated for the stereocenters formed by the Grignard addition.

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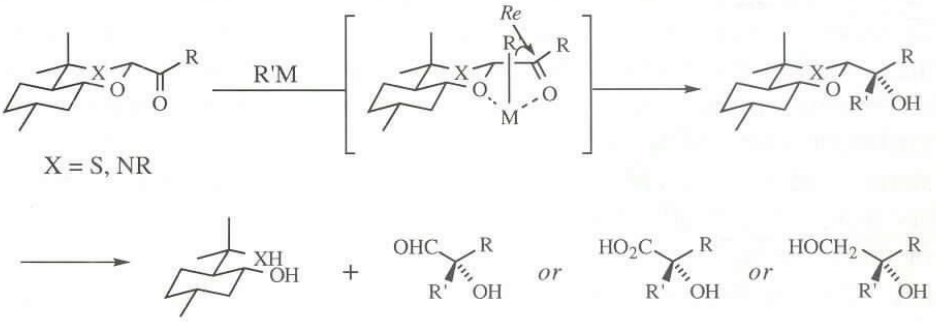
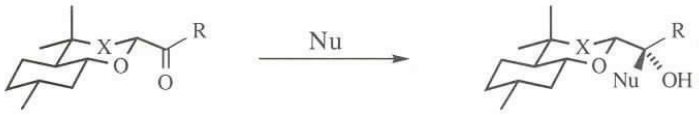


Scheme 4.4. Eliel's asymmetric addition to carbonyls using Cram's chelate model.

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



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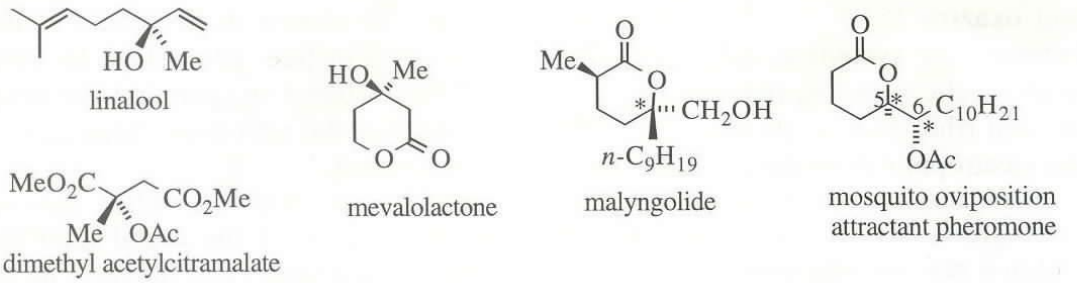

Figure 4.14. Applications of oxathianes: linalool [53], dimethyl acetylcitramalate [54], mevalolactone [56], malyngolide [55], and the mosquito oviposition attractant [39]. For the latter, the C-5 stereocenter was formed by a chelate-controlled reduction while the C-6 position could be produced as either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

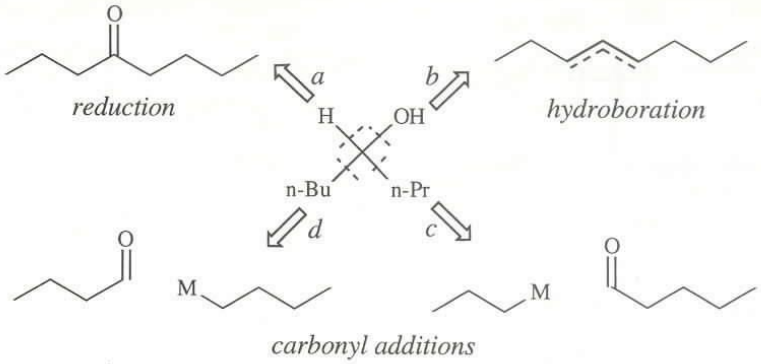

Figure 4.16. Simple retrosynthetic strategies for synthesis of 4-octanol.

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 occured 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.

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

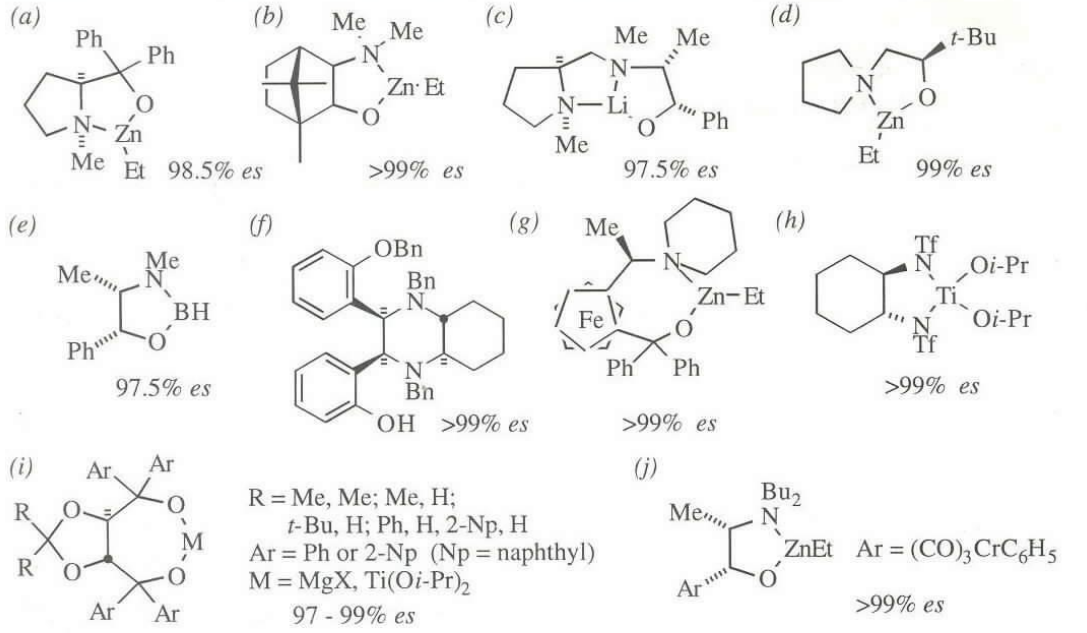
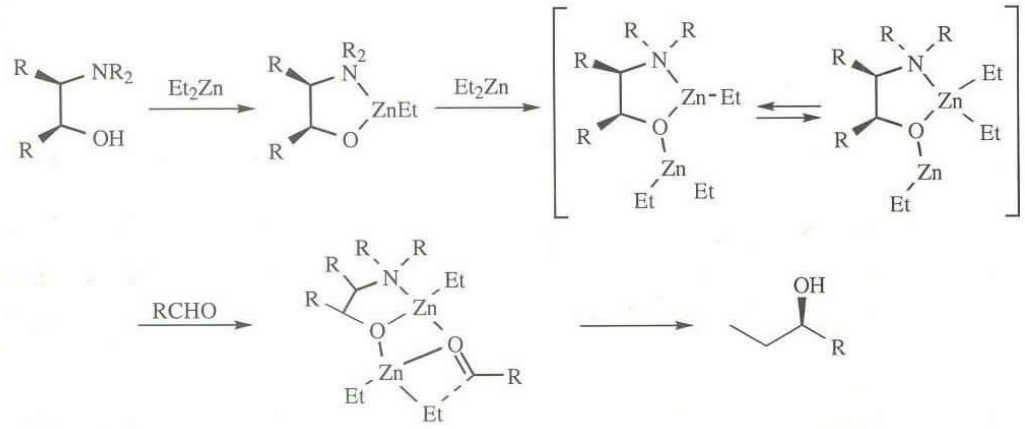
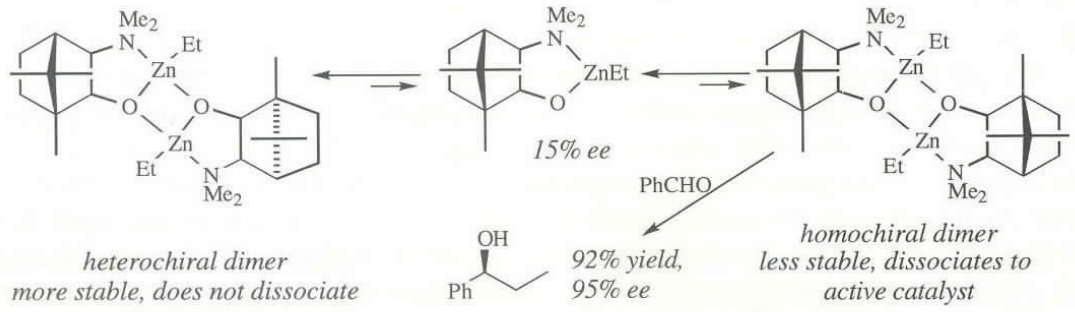


Figure 4.17. Catalysts for the diethylzinc reaction with benzaldehyde: *(a)*, [76]; *(b)*, [71]; *(c)*, [73]; *(d)*, [77]; *(e)*, [78]; *(f)*, [79]; *(g)*, [80]; *(h)*, [81,82]; *(i)*, [83,84]; *(j)*, [85].

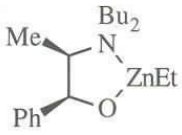
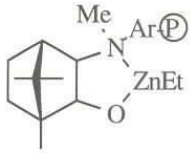
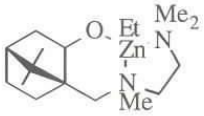
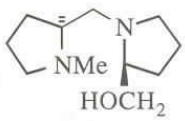


Scheme 4.5. Proposed mechanistic scheme for amino alcohol catalyzed diethylzinc reaction (after ref. [60])



Scheme 4.6. Amplification of enantiomer excess by the Noyori catalyst [71].

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	*n*-$C_6H_{13}CHO$	Et_2Zn	4.17a	96	95.5	[76]
2	*i*-BuCHO	Et_2Zn		92	96.5	[72]
3	*n*-$C_6H_{13}CHO$	Me_2Zn	"	70	95	[72]
4	2-NpCHO	Ph_2Zn	"	83	90	[86]
5	*c*-$C_6H_{11}CHO$	Et_2Zn	4.17g	92	99	[80]
6	*t*-BuCHO	Et_2Zn	4.17g	93	99	[80]
7	*n*-$C_6H_{13}CHO$	Et_2Zn	4.17h	78	>99	[81]
8	PhCHO	Et_2Zn		91	96	[73]
9	PhCHO	$Vinyl_2Zn$		96	93.5	[87]
10	*n*-$C_5H_{11}CHO$	$Vinyl_2Zn$	"	90	98	[87]
11	*c*-$C_6H_{11}CHO$	$Vinyl_2Zn$	"	83	91	[87]
12	*c*-$C_6H_{11}CHO$	Bu_2Zn	4.17i, M = $Ti(Oi\text{-}Pr)_2$	35	95	[88]
13	PhCHO	$(MOMO\text{-}(CH_2)_6)_2Zn$	4.17i, M = $Ti(Oi\text{-}Pr)_2$	68	92	[88]
14	PhCHO	$(C_2H_3\text{-}(CH_2)_2)_2\text{-}Zn$	4.17i, M = $Ti(Oi\text{-}Pr)_2$	83	95	[88]
15	1- or 2-Np	Et_2Zn	4.17j	98	>99	[85]
16	PhCHO	*n*-BuLi		77	97.5	[70]
17	PhCHO	Et_2Mg	"	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 bisoxazoline (Figure 4.18b) when used as the cocatalyst. Thus 4.18a and 4.18b constitute a "matched pair" of co-catalysts and 4.18a and *ent*-4.18b are a "mismatched pair" (see Chapter 1 for definitions). The proposed transition structure

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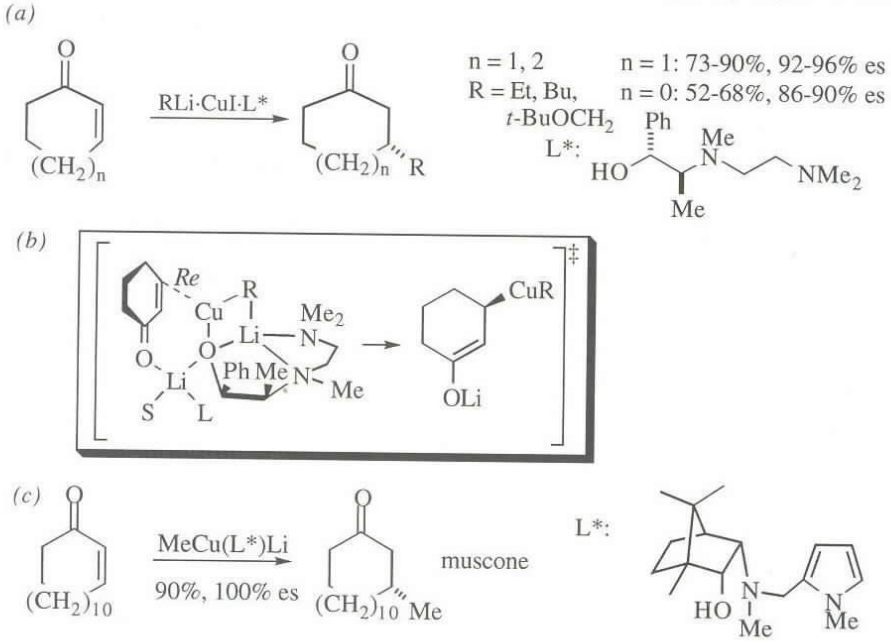
[12] The phenomenon of nonlinear optical yields is sometimes called asymmetric amplification. For detailed analyses, see ref. [58,75,90].

[13] For mechanistic hypotheses, see ref. [93,94].



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

4.5 References

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