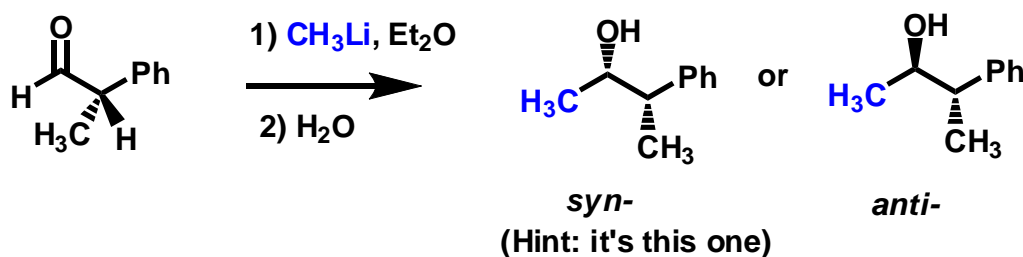**Nucleophilic Additions to Carbonyls- Stereoselectivity of Addition**

1. **Felkin-Ahn Addition**

In many cases, there are additions of an organometallic reagent (or as we'll see later, a hydride source) to a ketone or an aldehyde with a existing chiral centre α- to the carbonyl. For example:

1) CH_3Li, Et_2O

2) H_2O

H, Ph, H_3C, H, O

OH, H_3C, Ph, CH_3
syn-
(Hint: it's this one)

or

OH, H_3C, Ph, CH_3
anti-

In such reactions, both *syn-* and *anti-* diastereomeric products are possible. Which of these two the reaction gives predominantly is predictable; the model used to predict the product is called the **Felkin-Ahn** model. It is worth noting that an <u>outdated</u> model that normally gives the same predicted result is known as Cram's Rule, and that the term 'Cram addition' still gets used informally, despite this. We'll go through the Felkin-Ahn.

Assuming that there isn't an unusually electronegative atom on the carbon next to the carbonyl, the largest group (and use the **A value table** for this measure) prefers a conformation where it is perpendicular to the carbonyl C=O. This gives two relatively competitive lowest energy conformations, with the medium and smallest groups differing in their proximity to the carbonyl oxygen.

(M) Me, O, (L) Ph, H (S), H

(S) H, O, (L) Ph, Me (M), H

L = large
M = medium
S = small
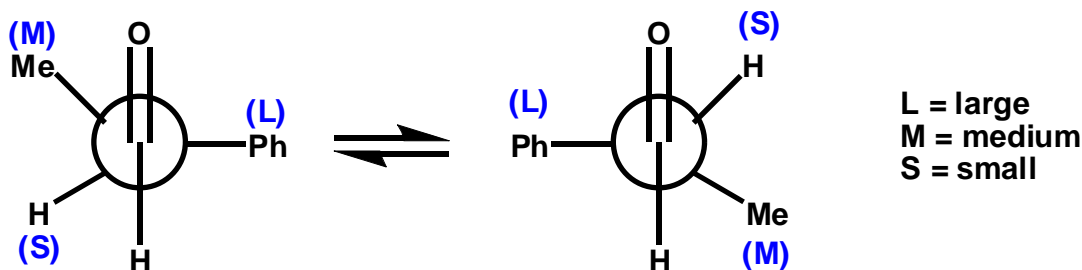
With this feature in hand, the other important consideration is that nucleophiles prefer to attack carbonyls not at a bond angle of 90° to the C=O, but at an angle closer to the classic tetrahedron bond angle (actually about 107°). This trajectory of approach is called the **Burgi-Dunitz** trajectory). Not surprisingly, the nucleophile prefers attack away from the large group. This leaves two possibilities: for the nucleophile to attack nearest to the small group, or for it to attack nearest to the medium group. The 'nearer to the small group' attack is preferred, and therefore one diastereomer is preferred. Keep in mind that in most cases (but by no means all) the *large* group will be part of main chain in the product and the incoming nucleophile will the other end of the main chain; in these cases, the major diastereomer will be the *syn-* diastereomer.
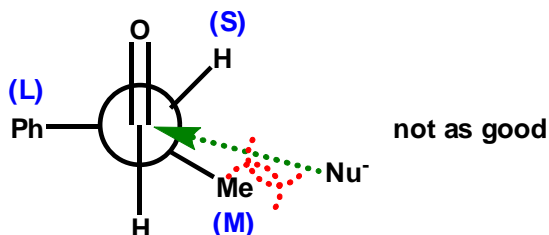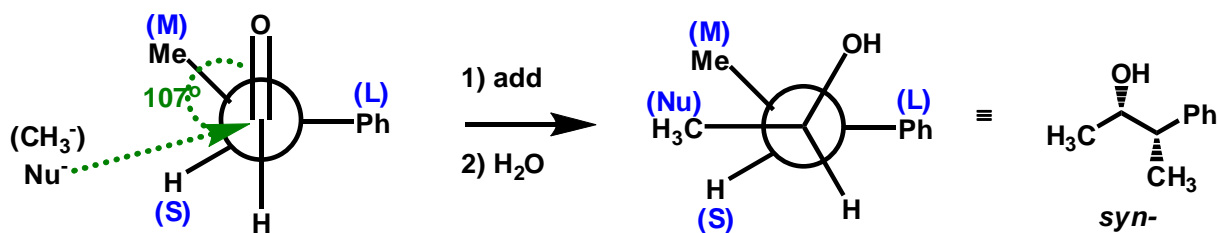
b. with electronegative α-groups

If, however, there is an electronegative atom or group at the site α- to the carbonyl, there is a slight change. For the purposes of this course, we will limit electronegative groups (X) to halogens, OR, NR_2, or SR groups. This 'slight change' is that this electronegative group becomes the equivalent of the 'large' group in the Felkin-Ahn model. The reason for this that the energy of the C-X σ* antibonding orbital is rather low, and so it overlaps with the π*of the carbonyl to make a new, lower energy LUMO (lowest unoccupied molecular orbital). What this really means is that this conformational arrangement is **more reactive** than any other. With this change in mind, the Felkin-Ahn type addition now proceeds as before. What that tends to mean in most cases (not all), is that the 'medium' group ends up being part of the product's main chain, and most often this means that the ***anti-*** diastereomer is the one formed.
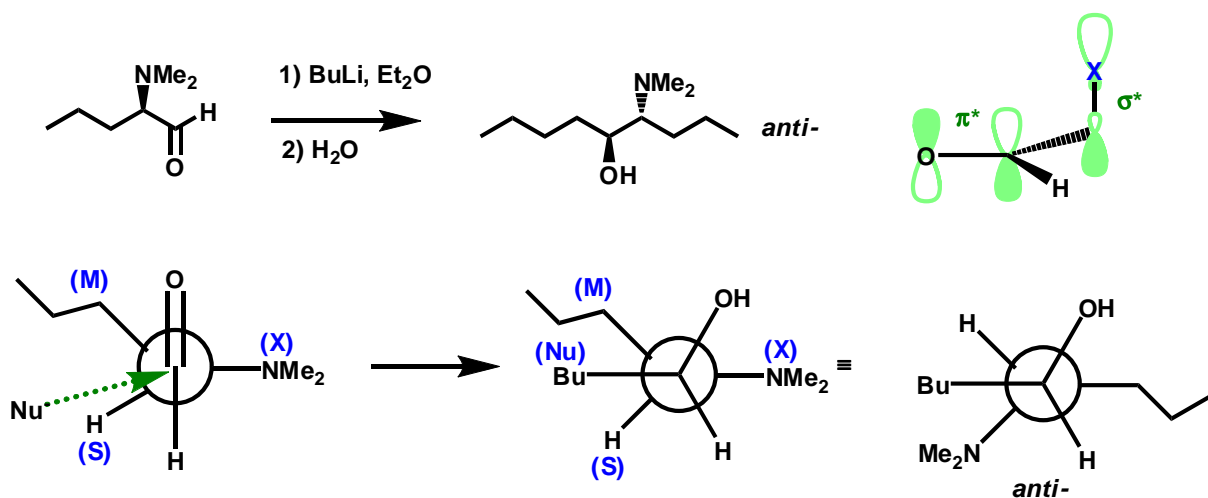

2. **Chelation and Addition – The Cram Chelate Rule**

These α- heteroatom substituted cases can be more complex for one additional reason – that these heteroatom based functional groups (in particular OR, NR_2, and SR) are Lewis basic for metals. As a result, with some organometallic systems, the carbonyl C=O: and the –X: group will combine to chelate the metal; this changes the pathway of addition significantly.

When does this chelate **not** occur? - When the metal is Li^+ (usually), Na^+, K^+ (so follow the Felkin-Ahn)

When **does** this chelation occur? – When the metal is Mg^{2+} (usually), **Zn^{2+}, Cu^{2+}, Ti^{4+}, Ce^{3+}, Mn^{2+}**
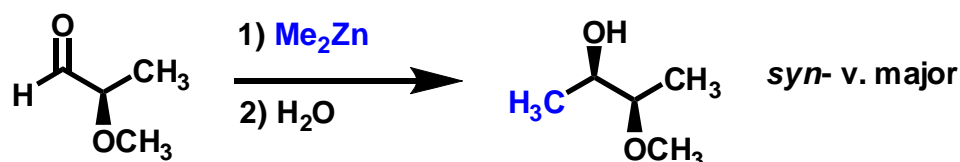
So what happen in the chelating cases is that this feature forces the –X: group to be held close to the carbonyl C=O (closest to the position of the 'M' group in the Felkin-Ahn). Since nucleophile attack is still at about the Burgi-Dunitz trajectory, this will invert the result from the electronegative α-group situation above (in b.), and in the most common cases (but not all) mean a **syn-** diastereomeric product again as the major.

Chelated - puts Lewis basic group at normal 'M' position
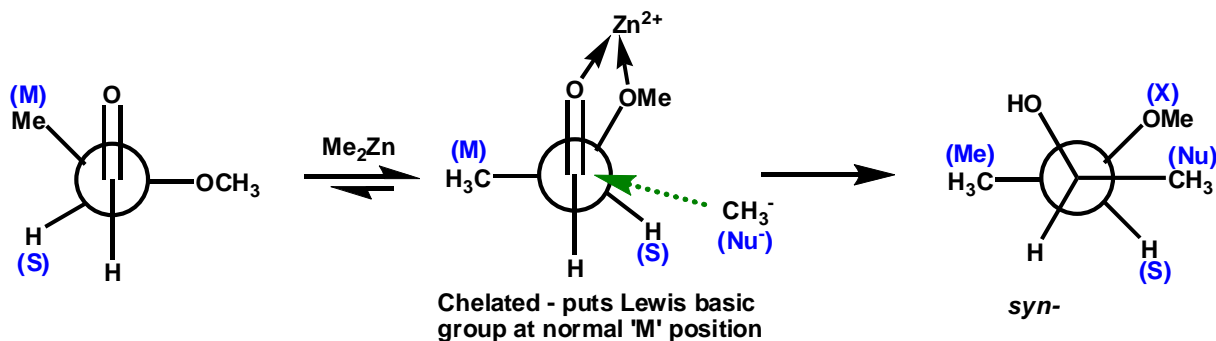
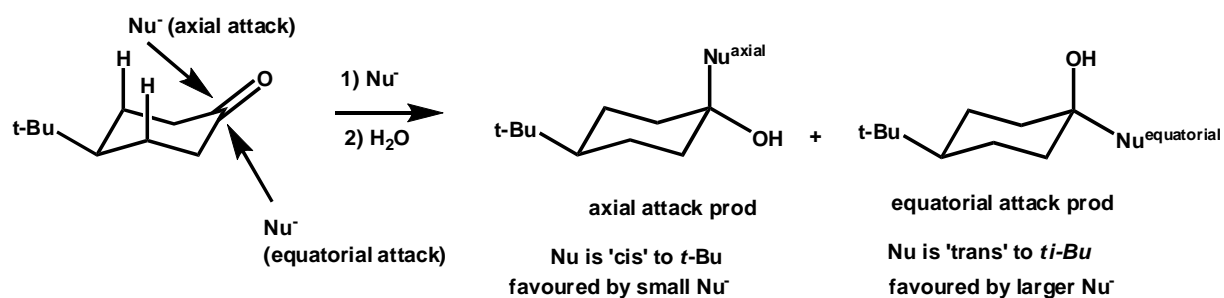**Stereochemistry of Additions to Cyclohexanones**

Different considerations are involved if the ketone being attacked is cyclic, since the conformation of the ring system is now of paramount importance. Since cyclohexanes are the most well understood ring systems in terms of conformation, we will look at them only.

We will start by taking 4-*t*-Bu cyclohexanone, since we need a substituent to see anything, and due to the fact that *t*-Bu demands an equatorial position. An incoming nucleophile can therefore attack either axial or equatorial in direction. If the nucleophile has **zero** size, it would reasonable to assume that the O^- is *becoming* axial if the attack was equatorial, and this would be slightly *disfavoured* because any group larger than H prefers an equatorial orientation. So our prediction – a really **small** nucleophile prefers **axial** attack. We will really discuss H^- attack later in more detail, but it shouldn't surprise than attack by hydride sources falls into this category.

On the other hand, if the nucleophile is larger, *it* would be the axial group if axial attack occurred (in truth, there starts to be trouble getting by the C-3 axial H's during the attack). The O^- isn't *very* large (yes, larger than H, but not much else), so we would predict mostly **equatorial** attack for **large** nucleophiles.

So over all, a good prediction is……**small** nucleophiles, **axial** attack

Large nucleophile, **equatorial** attack.

Nu⁻ (axial attack)

Nu⁻ (equatorial attack)

1) Nu⁻
2) H_2O

axial attack prod

Nu is 'cis' to *t*-Bu
favoured by small Nu⁻

equatorial attack prod

Nu is 'trans' to *ti-Bu*
favoured by larger Nu⁻

Nu⁻	A value	% axial attack	% equatorial attack
$LiAlH_4$	0	90	10
H-C≡C-Li (or Na)	0.45	88	12
MeLi	1.7	65	35
EtMgBr	1.8	29	71
i-PrMgBr	2.1	18	82
t-BuMgBr	>4.5	0	100