# Lecture 5

Diastereoselective Addition into Carbonyl Compounds Containing α-Stereogenic Centres

Learning outcomes: by the end of this lecture, and after answering the associated problems, you will be able to:

1. use the Felkin-Anh T.S. to predict the stereochemical outcome of reactions carried out on carbonyl compounds that possess an α-stereogenic centre;

2. rationalise the preferential adoption of a Felkin-Anh T.S. in nucleophilic addition reactions on steric and stereoelectronic grounds;

3. understand how the presence of an α-electron-withdrawing substituent affects the Felkin-Anh T.S.;

4. use the Felkin-Anh T.S. to prepare 1,2-*syn* diols from α-alkoxy ketones;

5. use the Cram chelation model to prepare 1,2-*anti* diols from α-alkoxy ketones.

Stereoselective Addition of Nucleophiles into Ketones and Aldehydes containing α-Stereogenic Centres

The addition of a nucleophile into a chiral ketone or aldehyde provides diastereoisomers. When the stereogenic centres in the substrate are close to the reacting carbonyl group (*e.g.* 1,2-disposed), then it is often possible to exploit this stereochemical information to control the stereoselectivity of the addition reaction. This method for controlling the stereochemical outcome of a reaction is known as **substrate control**.
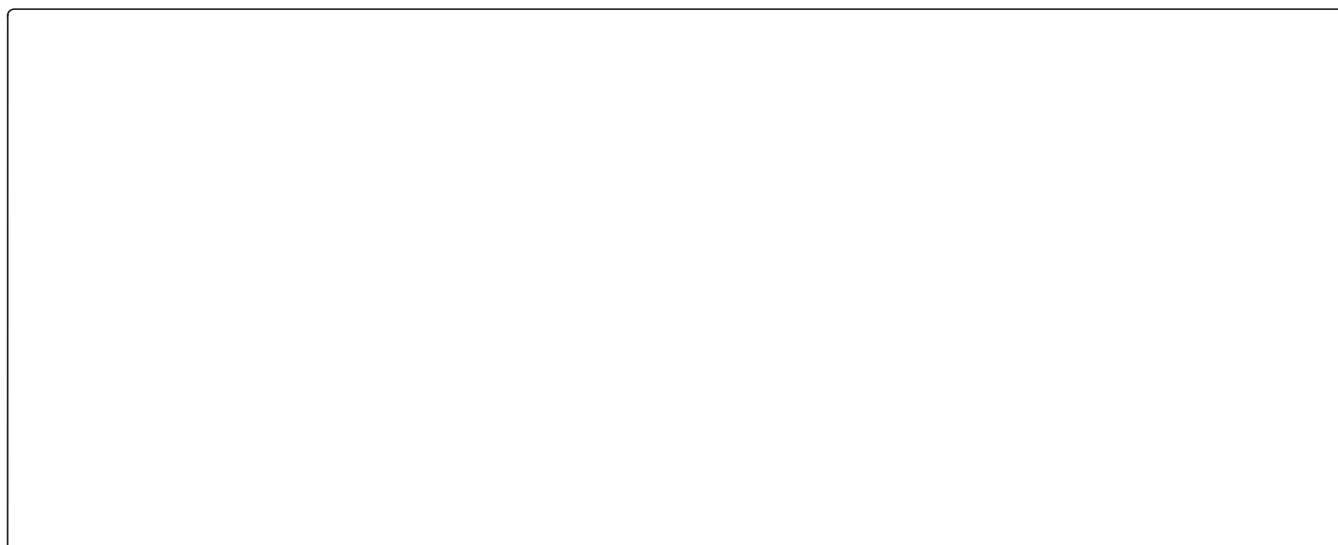
A number of models have been developed for predicting the stereochemical outcome of this type of reaction.

Felkin-Anh Model

Consider a carbonyl compound containing an α-stereogenic centre in which the three substituents at the α-site are well differentiated in size:

R^S = small substituent
R^M = medium-sized substituent
R^L = large substituent
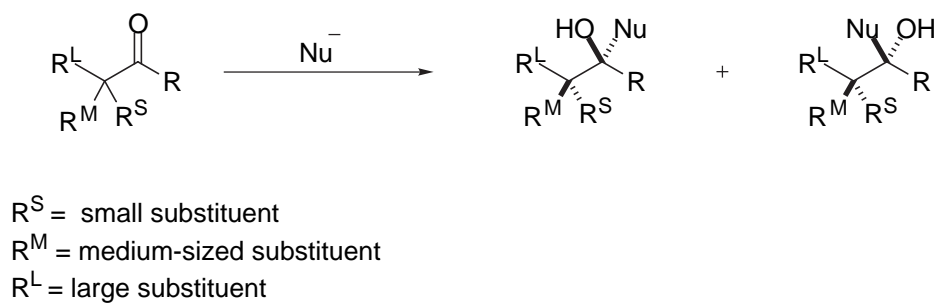
Of the two diastereoisomeric alcohol addition products, one will be formed to a greater extent than the other. Felkin and Anh proposed a T.S. to rationalise the observed stereochemical outcome of the reaction.
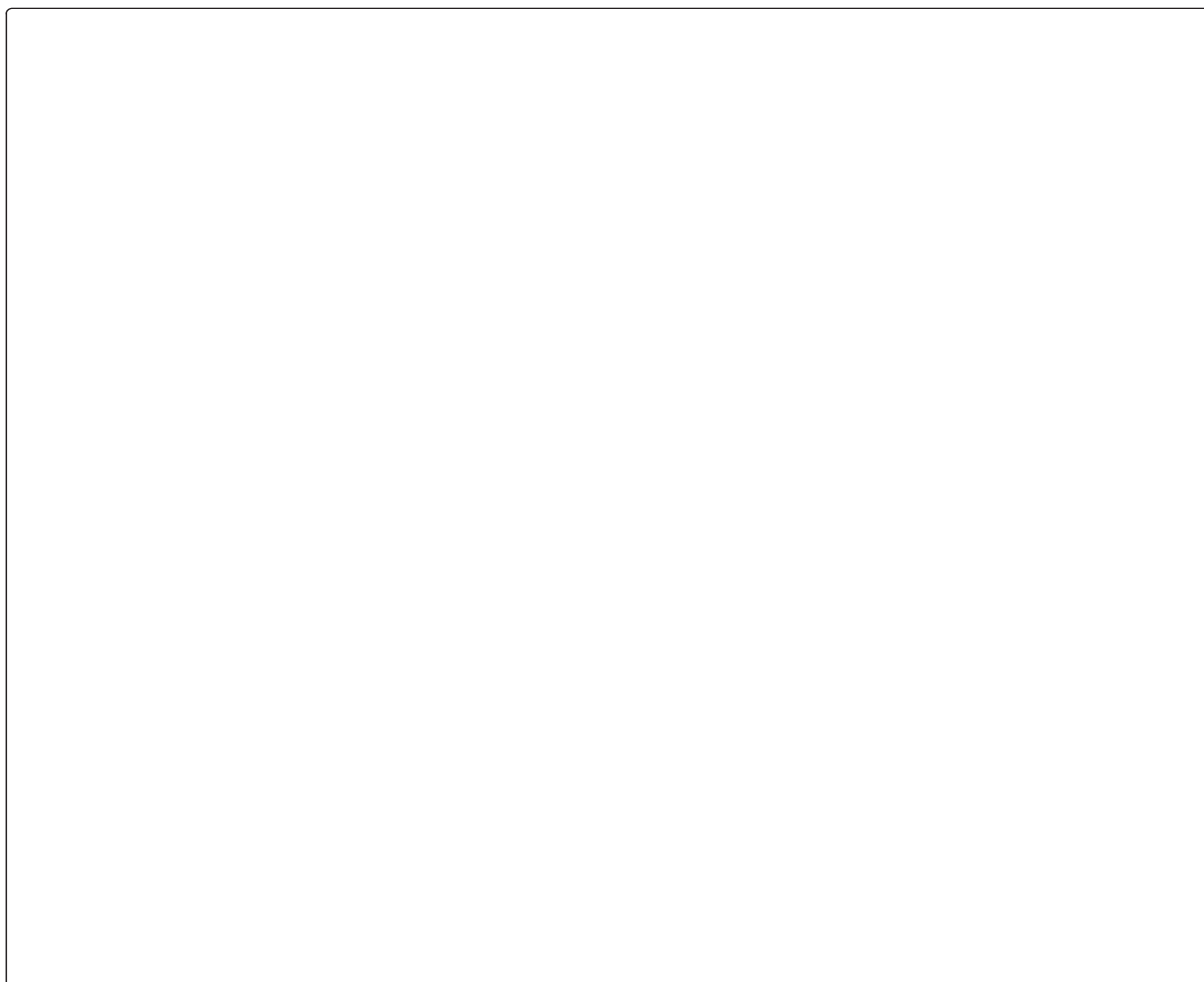
You should recognise that the model is rather similar to that which we used to account for the stereochemical outcome of hydroboration reactions on olefins containing α-stereogenic centres.

The large group at the α-site is orthogonal to the plane containing the σ-bonding framework of the C=O group. This is favourable on stereoelectronic grounds since an interaction between the $\sigma^*_{C-R}{}^L$ and π^* MOs serves to lower the energy of the LUMO.

The nucleophile then approaches the C=O group from the face opposite to the large group, R^L, to minimise unfavourable steric interactions.

However, the nucleophile approaches along the Bürgi-Dunitz trajectory, which is different to the approach trajectory for a borane on an olefin. This is an important difference since the incoming nucleophile now comes much closer to one of the substituents at the α-site rendering substrate-reagent interactions much more important in this type of reaction.

Placing the small substituent, R^S, in the position shown, minimises such interactions with the approaching nucleophile (as well as 1,2-interactions with the R group in the substrate).

Caveat:
This model assumes that interactions between the R^M substituent and the carbonyl oxygen are not important, which is clearly not always going to be the case. In particular, reactions that require a Lewis acid, or some form of pre-association between the carbonyl oxygen and reagent, can lead to increased interactions between the carbonyl oxygen and an α-substituent. In such cases, the stereochemical outcome is better understood by considering a T.S. in which the R^S and R^M substituents have been swapped around.

Examples
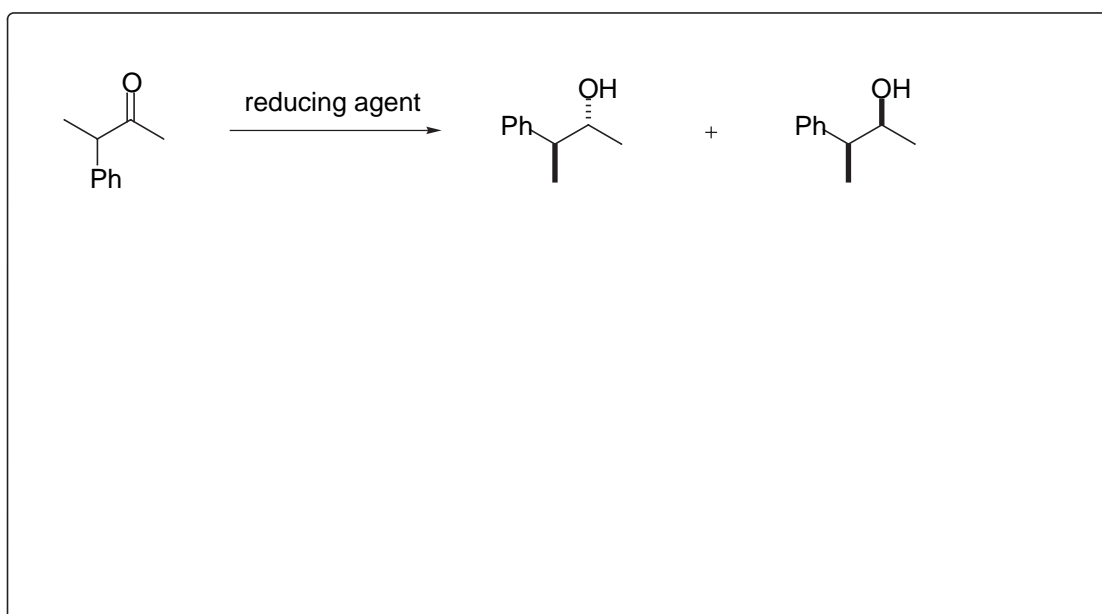
From these two examples it is clear that the steric bulk of the reducing agent can have a profound effect on the stereoselectivity of the reaction. In both cases, however, the major diastereoisomer is that predicted by the Felkin-Anh T.S.
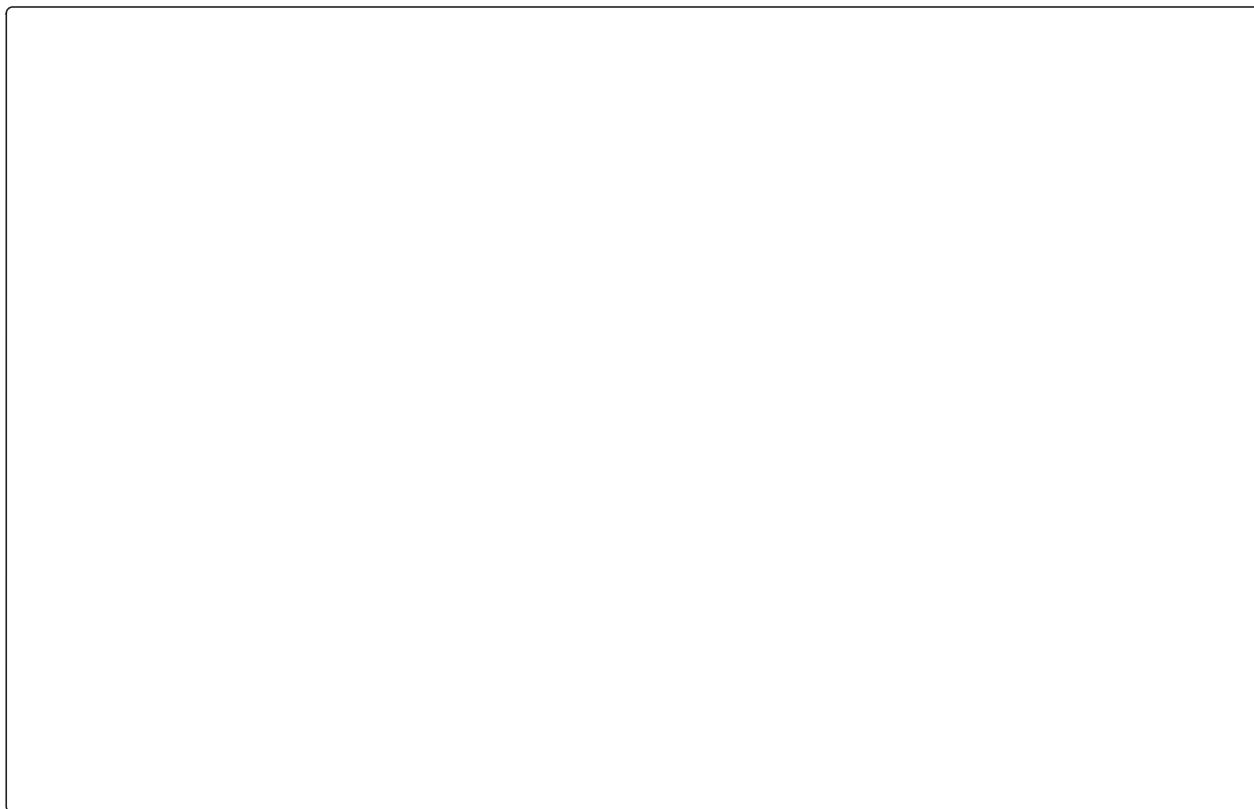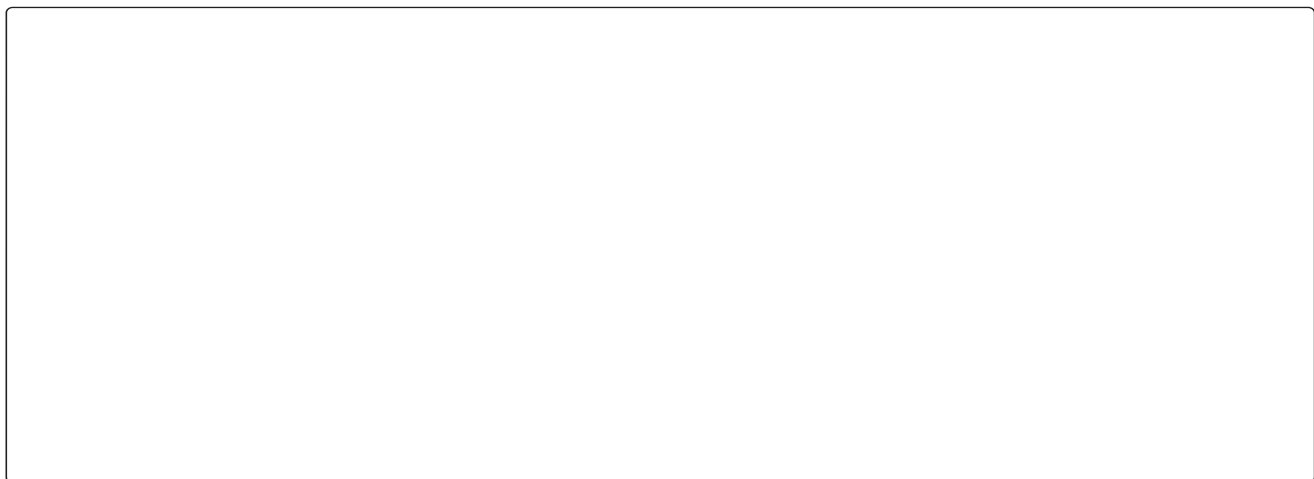
Diastereoselective Addition into Carbonyl Compounds containing an α-Electron-Withdrawing Group

Consider the stereoselectivity of the following reaction:
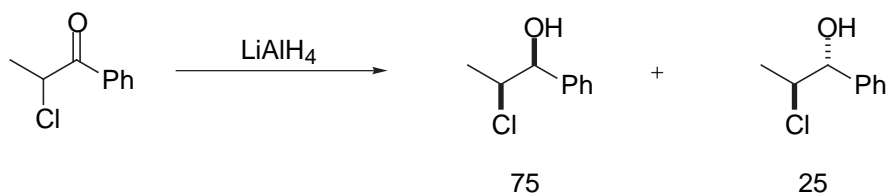
If we apply the Felkin-Anh model to try and rationalise the stereoselectivity of this reduction reaction, we see that the electron-withdrawing chlorine substituent is *behaving* as the large group.

In such situations, assuming chelation between the α-heteroatom and the carbonyl oxygen is *not* important (see below), we can rationalise the stereoselectivity of these reactions by assuming that the electron-withdrawing group is the 'large group'.

A modified Felkin-Anh Model
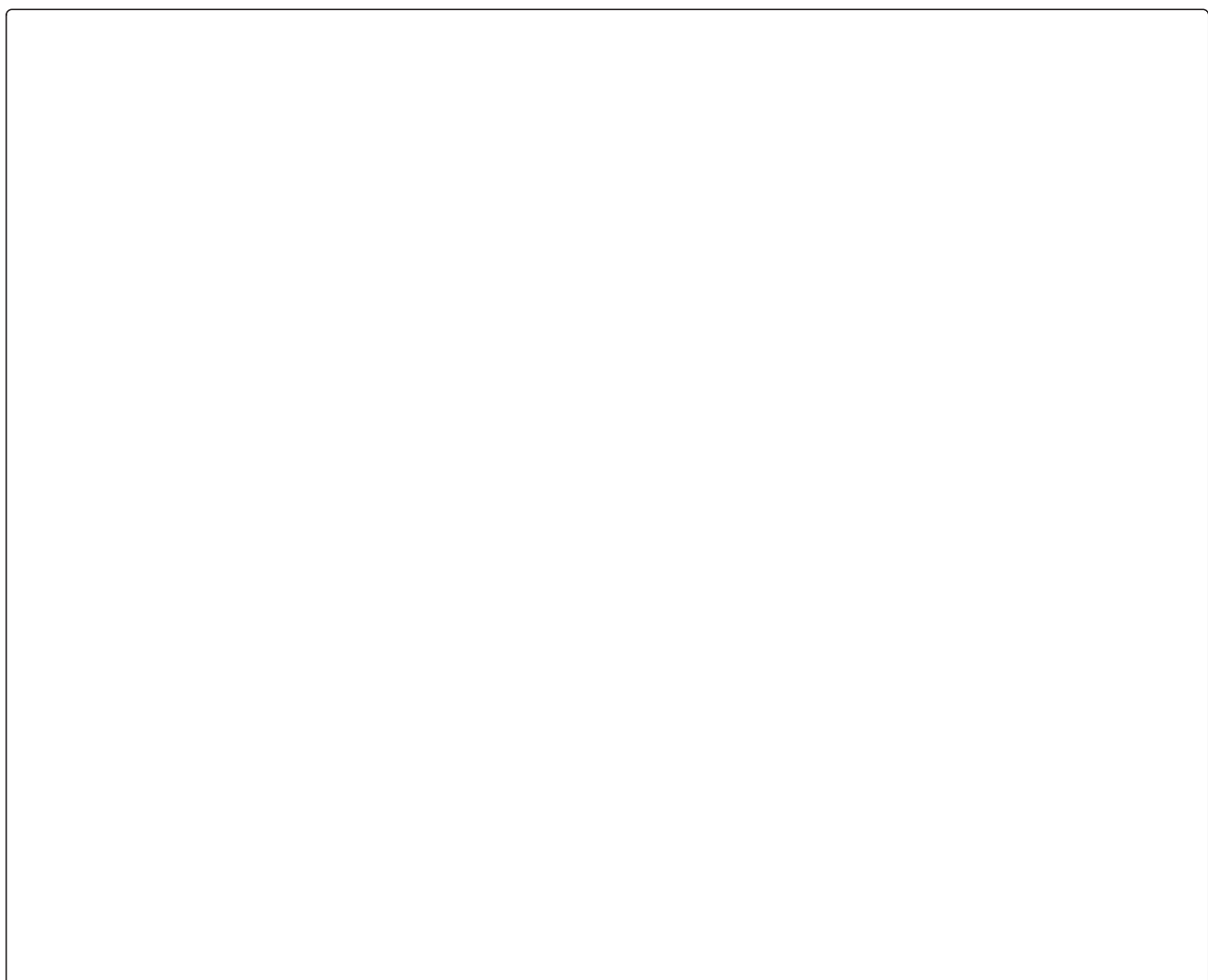
It has been proposed that the reactive-state conformation in which the electron-withdrawing group lies orthogonal to the C=O bond is favoured by an energetically favourable stereoelectronic interaction between the HOMO of the nucleophile and the σ^*_{C-X} MO, which will serve to lower the energy of the T.S.
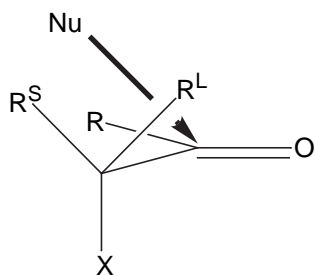
Stereoselective Synthesis of 1,2-Diols

1,2-Diols are widespread in natural products. The stereoselective reduction of α-hydroxy ketones provides a reliable route for incorporating such functionality.

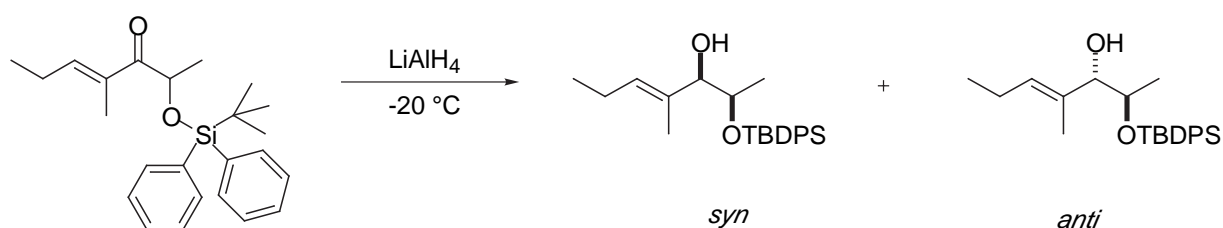*Diastereoselective 1,2-reduction:*
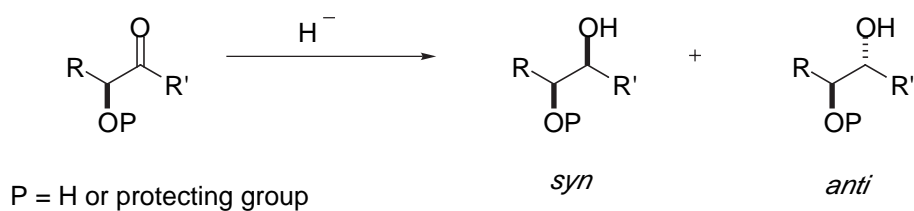
For a discussion on this area:

- F. A. Carey, R. J. Sundberg, *Advanced Organic Chemistry: Volume B*, Plenum Press, New York, 1990 (3rd Edition), pp 241-244.
- M. B. Smith, *Organic Synthesis*, McGraw-Hill, New York, 1994, pp 400-417.
- E. L. Eliel, S. H. Wilen, *Stereochemistry of Organic Compounds*, Wiley, New York, 1994, pp 858-938 for an indepth discussion of this area of Chemistry

Diastereoselective Synthesis of *Syn*-1,2-Diols

In the previous example involving reduction of an α-chloro ketone, we saw that the *syn* diastereoisomer was the major product. Reaction through a Felkin-Anh T.S. where the chloro substituent behaved as the 'large' group, accounted for the observed stereoselectivity. We can use the same analysis to prepare 1,2-*syn*-diols providing we make a careful choice of protecting group, specifically one that suppresses chelate formation. A sterically very bulky protecting group will further improve levels of Felkin-Anh selectivity - large silyl protecting groups are therefore ideal.

Example

For other examples:

T. Takahashi, M. Miyazawa, J. Tsuji, *Tetrahedron Lett.*, 1985, **26**, 5139-5142.

L. E. Overman, R. J. McCready, *Tetrahedron Lett.*, 1982, **23**, 2355-2358.

**Diastereoselective Formation of *Anti*-1,2-Diols - Cram Chelation**

We have seen how to prepare *syn* 1,2-diols from α-alkoxy carbonyl compounds. To obtain high levels of diastereoselectivity in these reactions, it was vital to choose an alcohol protecting group that prevented the possibility of chelation between the two oxygen atoms, since this leads to an erosion in the *syn* selectivity.

Deliberate choice of a protecting group that allows efficient chelation can therefore be used to prepare *anti* 1,2-diols.

To exploit chelation control, we require:

i)   a free alcohol *or* a protected alcohol in which the protecting group can still form a chelate *i.e.* the oxygen must still be able to behave as a Lewis base (alkyl ethers are good examples that allow this).

ii)   a metal which can form a chelate (typical metals include Zn(II), Mg(II), Ti(IV) *etc.*)

The formation of a chelated intermediate generates a much more conformationally rigid molecule that sterically differentiates the two diastereotopic faces of the carbonyl group. This approach to controlling the stereoselectivity of a reaction is known as **Cram chelation** (after Donald Cram, UCLA).
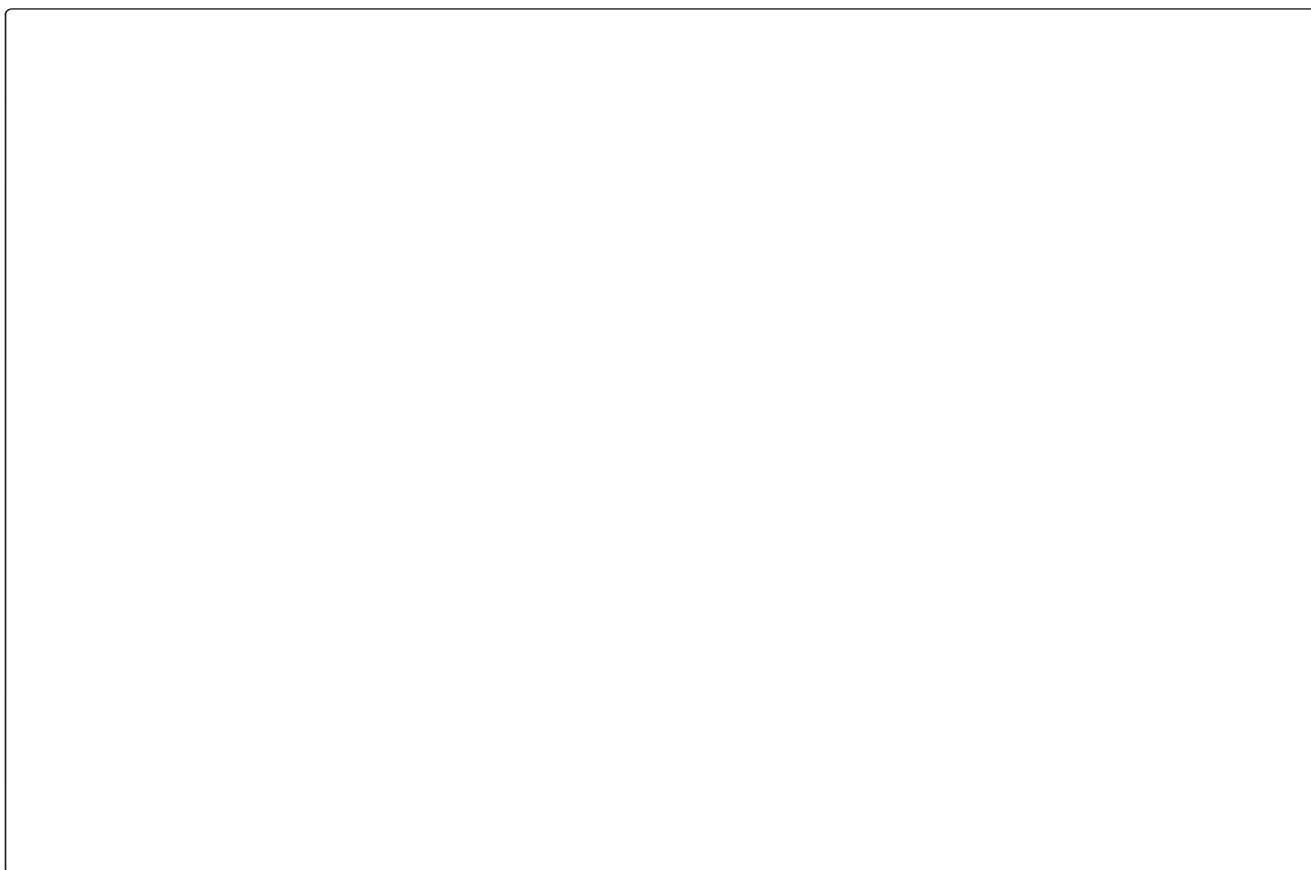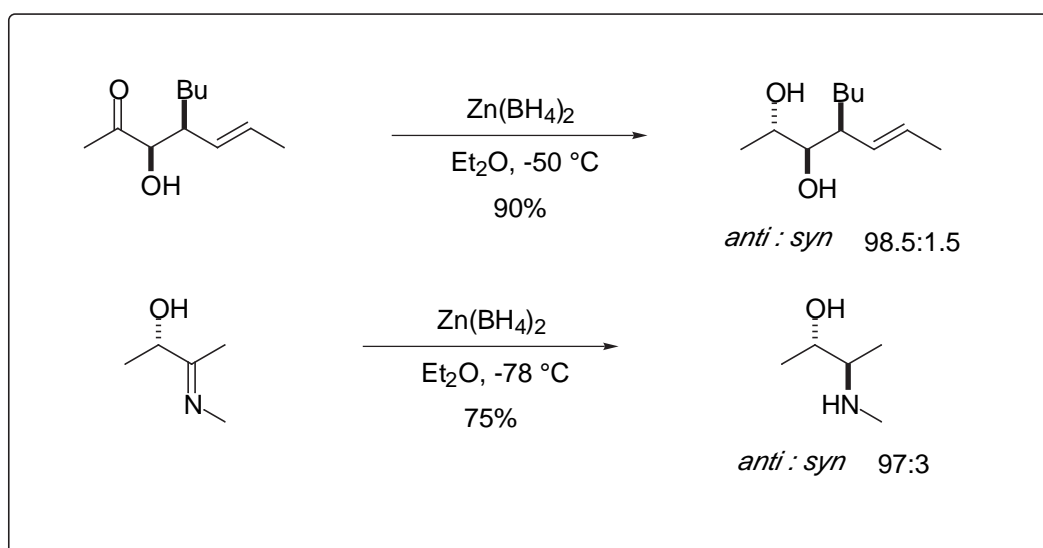
Example
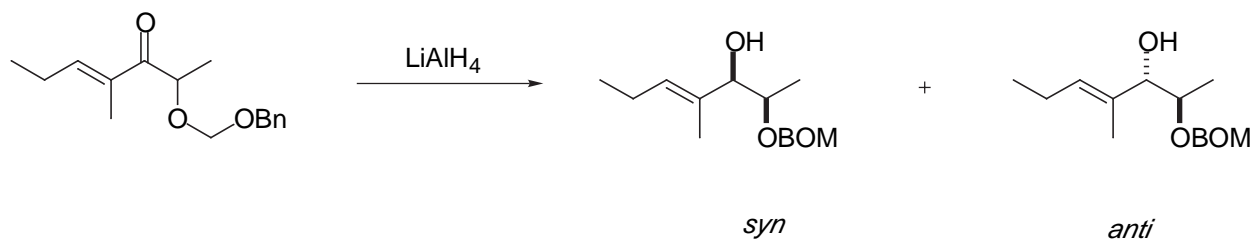
Using the same α-hydroxy ketone as in the example above, by changing the protecting group on the alcohol from a bulky silyl group, which precludes chelation, to a BOM ether, which is particularly good at participating in chelation, we can reverse the stereoselectivity of the reduction.

Other examples:

Summary

The presence of a stereogenic centre α-to a carbonyl group allows us to use *substrate control* to govern the stereochemical outcome of reactions at the carbonyl centre. The substituents present at the α-stereogenic centre, as well as the nucleophile used, dictate the stereochemical outcome.

The Felkin Anh T.S. provides a particularly useful model for predicting the stereochemical outcome of reactions involving carbonyl groups containing α-stereogenic centres. Providing the substituents at the α-centre are well differentiated in size, reaction through this T.S. can lead to products with excellent levels of stereocontrol.

The Felkin-Anh T.S. has some physical base. On steric grounds, the incoming nucleophile attacks the *diastereotopic* face that is opposite to the large group since this minimises interactions between the substrate and reactant. These interactions are further minimised by placing the small substituent closest to the trajectory along which the incoming nucleophile approaches the carbonyl group. On stereoelectronic grounds, by placing a substituent orthogonal to the reacting π-system, the π^* LUMO is lowered in energy (interaction with an appropriately aligned σ^* MO) making frontier orbital interactions (between the LUMO and the HOMO on the nucleophile) more favourable.

For substrates where the α-stereogenic centre contains an electron-withdrawing group, such as a chloro substituent, the stereochemical outcome of a nucleophilic addition reaction can still be predicted. In this case we need to use a modified Felkin-Anh T.S. in which the electron-withdrawing substituent behaves as the 'large' group, even if it is not the sterically most demanding substituent. A stereoelectronic argument has been used to account for this observation.

The addition of nucleophiles into α-hydroxy ketones generates synthetically useful 1,2-diol products. Careful choice of protecting group and nucleophile allows the selective synthesis of either the *syn* or *anti* diol product. The Felkin-Anh T.S. rationalises the obtention of the 1,2-*syn* diol product when a very bulky alcohol protecting group, which prevents chelation, is used. When protecting groups that allow chelation are used, in conjunction with reagents that contain a chelating metal, the Cram chelation model readily rationalises the preferential formation of 1,2-*anti* products.