Diastereoselectivity

34

Connections

Building on:

- Stereochemistry ch16
- Conformation ch18
- Controlling double bond stereochemistry ch31
- Determining stereochemistry by NMR ch32
- Controlling stereochemistry in cyclic compounds ch33

Arriving at:

- How to make single diastereoisomers from single geometrical isomers
- How to predict and explain the reactions of chiral carbonyl compounds
- How chelation to metal ions can change stereoselectivity
- How to predict and explain the reactions of chiral alkenes
- Stereoselectivity in the aldol reaction
- How to make *syn* aldol products
- How to make *anti* aldol products

Looking forward to:

- Saturated heterocycles ch42
- Asymmetric synthesis ch45
- Organic synthesis ch53

Looking back

You have had three chapters in a row about stereochemistry: this is the fourth, and it is time for us to bring together some ideas from earlier in the book. We aim firstly to help you grasp some important general concepts, and secondly to introduce some principles in connection with stereoselective reactions in acyclic systems. But, first, some revision.

We introduced the stereochemistry of structures in Chapter 16. We told you about two types of stereoisomers.

Enantiomers and diastereoisomers

- **Enantiomers**—stereoisomers that are mirror images of one another
- **Diastereoisomers**—stereoisomers that are not mirror images of one another

In this chapter we shall talk about how to make compounds as single diastereoisomers. Making single enantiomers is treated in Chapter 45. Chapter 33 was also about making single diastereoisomers, and we hope that, having read that chapter, you are used to thinking stereochemically.

In this chapter we shall talk about two different ways of making single diastereoisomers.

Reactions that make single diastereoisomers

- **Stereospecific reactions**—reactions where the mechanism means that the stereochemistry of the starting material determines the stereochemistry of the product and there is no choice involved
- **Stereoselective reactions**—reactions where one stereoisomer of product is formed predominantly because the reaction has a choice of pathways, and one pathway is more favourable than the other

These terms were introduced in Chapter 19 in connection with elimination reactions, and many of the reactions we mention will be familiar from earlier chapters (particularly Chapters 17–20 and 26–27).

Making single diastereoisomers using stereospecific reactions of alkenes

The essence of the definition we have just reminded you of is much easier to grasp with some familiar examples. Here are two.

- S_N2 reactions are stereospecific: they proceed with inversion so that the absolute stereochemistry of the starting material determines the absolute stereochemistry of the product

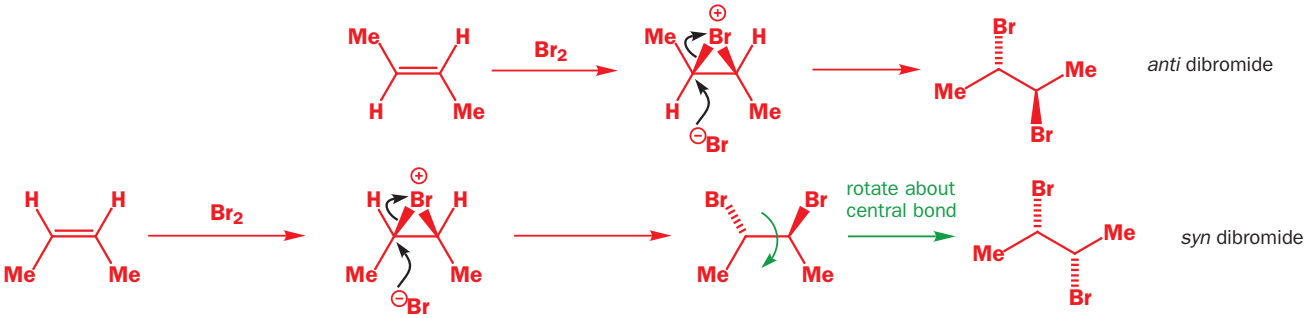
■ This is discussed in Chapter 17, p. 000.

- E2 reactions are stereospecific: they proceed through an anti-periplanar transition state, with the relative stereochemistry of the starting material determining the geometry of the product

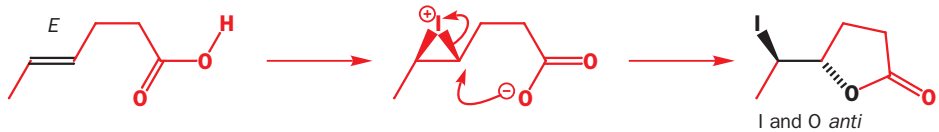
Both of these examples are very interesting because they show how, once we have some stereochemistry in a molecule, we can change the functional groups but keep the stereochemistry—this is the essence of a stereospecific reaction. In the second example, we change the bromide to a double bond, but we keep the stereochemistry (or 'stereochemical information') because the geometry of the double bond tells us which bromide we started with.

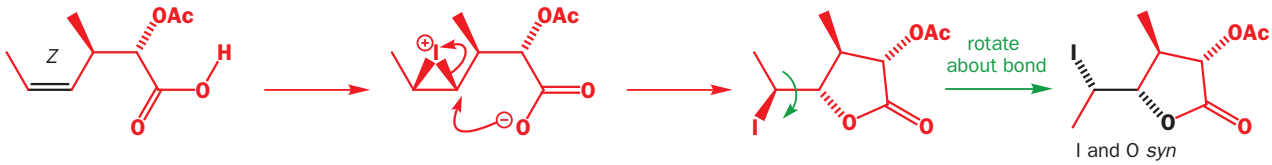
This is a good place to begin if we want to make single diastereoisomers, because we can reverse this type of reaction: instead of making a single geometry of alkene from a single diastereoisomer, we make a single diastereoisomer from a single geometry of double bond. Here is an example of this—again, one you have already met (Chapter 19). Electrophilic addition of bromine to alkenes is stereospecific and leads to *anti* addition across a double bond. So if we want the *anti* dibromide we choose to start with the *trans* double bond; if we want the *syn* dibromide we start with the *cis* double bond. The geometry of the starting material determines the relative stereochemistry of the product.

■ Chapter 31 described the methods available for controlling the geometry of double bonds.



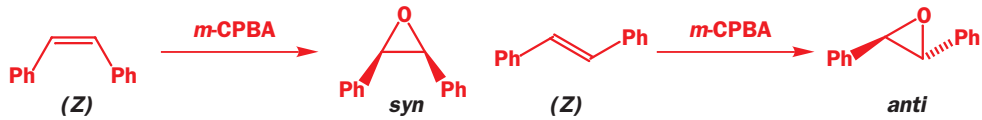
Iodolactonization has a similar mechanism; notice how in these two examples the geometry of the double bond in the starting material defines the relative stereochemistry highlighted in black in the product.



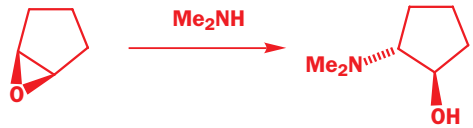


For a stereospecific alkene transformation, choose the right geometry of the starting material to get the right diastereoisomer of the product. Don't try to follow any 'rules' over this—just work through the mechanism.

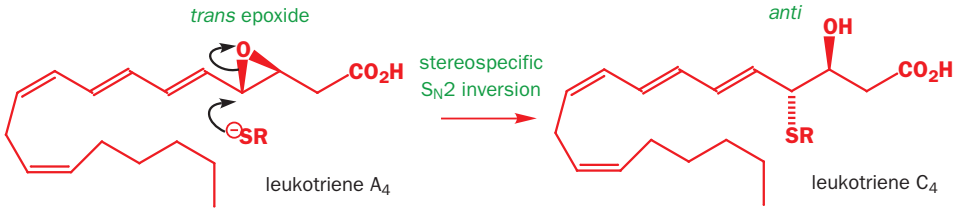
Now for some examples with epoxides. Epoxides are very important because they can be formed stereospecifically from alkenes: *cis*-alkenes give *cis* (or *syn*) -epoxides and *trans*-alkenes give *trans* (or *anti*) -epoxides.



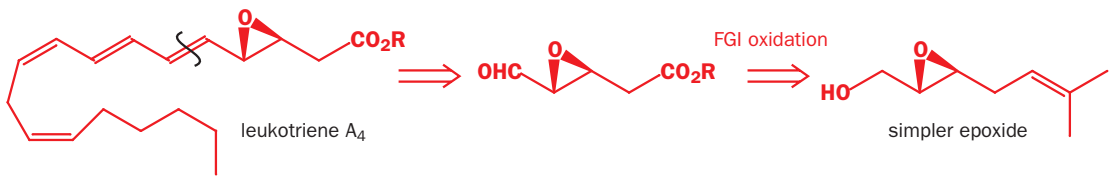
Epoxides also react stereospecifically because the ring-opening reaction is an S_N2 reaction. A single diastereoisomer of epoxide gives a single diastereoisomer of product.



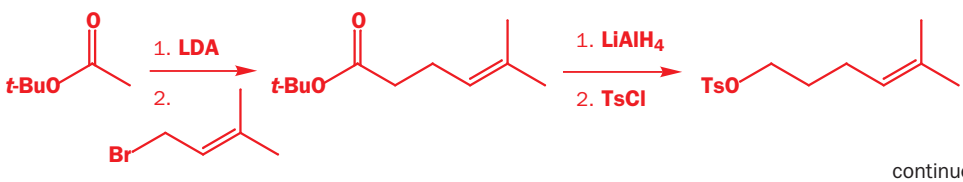
We have mentioned **leukotrienes** before: they are important molecules that regulate cell and tissue biology. Leukotriene C_4 (LTC_4) is a single diastereoisomer with an *anti* 1,2 S,O functional group relationship. In nature, this single diastereoisomer is made by an epoxide opening: since the opening is S_N2 the epoxide must start off *anti* and, indeed, the epoxide precursor is another leukotriene, LTA_4.



When Corey was making these compounds in the early 1980s he needed to be sure that the relative stereochemistry of LTC_4 would be correctly controlled, and to do this he had to make a *trans* epoxide. Disconnecting LTA_4 as shown led back to a simpler epoxide.



The *trans* allylic alcohol needed to make this compound was made using one of the methods we introduced in Chapter 31: reduction of an alkynyl alcohol with $LiAlH_4$. Here is the full synthesis: alkylation of an ester enolate with prenyl bromide gives a new ester, which itself is turned into an alkylating agent by reduction and tosylation. The alkyne is introduced as its lithium derivative with the alcohol protected as a THP acetal. Hydrolysis of the acetal with aqueous acid gives the hydroxyalkyne needed for reduction to the *E* double bond, which is then epoxidized.

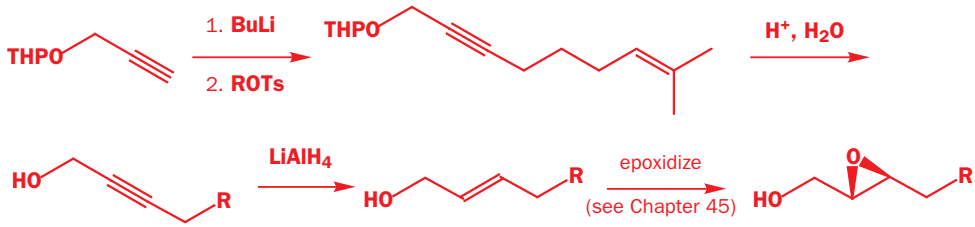


continued overleaf

There are two more stereogenic centres in the second example here and, although they do not affect the relative stereochemistry shown in black, they do affect how those two new stereogenic centres relate to the two that are already present in the starting material. We discuss how later in the chapter.

Chapter 20, p. 000.

Chapters 17 (p. 000) and 19 (p. 000).



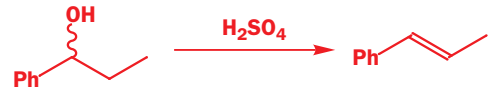
■ The epoxide was, in fact, made as a single enantiomer using the Sharpless epoxidation, which we will describe in Chapter 45.

Stereoselective reactions

For most of the rest of the chapter we shall discuss stereoselective reactions. You have already met several examples and we start with a summary of the most important methods.

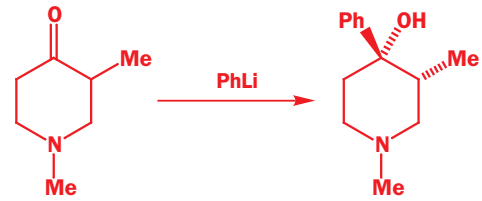
■ Chapter 18, p. 000.

- E1 reactions are stereoselective: they form predominantly the more stable alkene



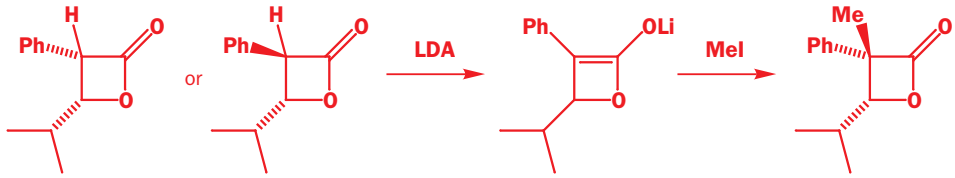
■ Chapter 33, p. 000.

- Nucleophilic attack on six-membered ring ketones is stereoselective: small nucleophiles attack axially and large ones equatorially



■ Chapter 33, p. 000.

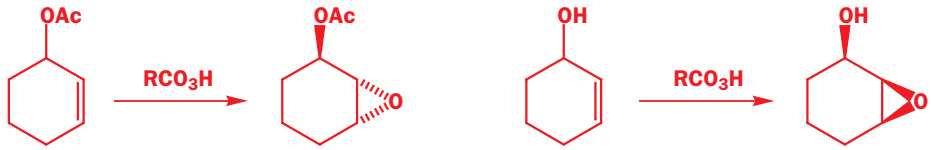
- Alkylation of cyclic enolates is stereoselective, with reaction taking place on the less hindered face (four- or five-membered rings) or via axial attack (six-membered rings)



■ Chapter 33, p. 000.

▶ For a *stereoselective* reaction we can specify two different stereoisomers of the starting material and get the same product (first and third examples). In a *stereospecific* reaction, different starting material stereochemistry means different product stereochemistry.

- Epoxidation of cyclic alkenes is stereoselective, with reaction taking place on the less hindered face, or directed by hydrogen bonding to a hydroxyl group

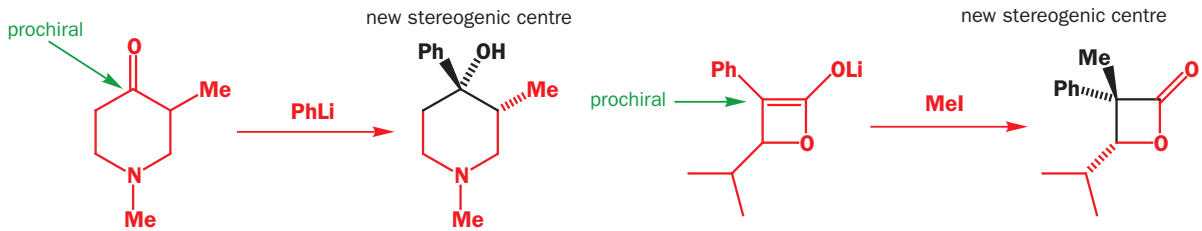


■ Chapter 33, p. 000.

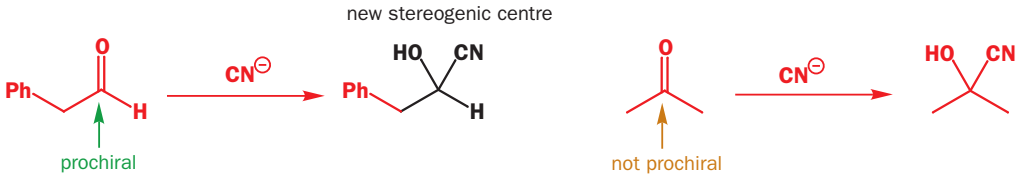
▶ A common misapprehension is that stereospecific means merely very stereoselective. It doesn't—the two terms describe quite different properties of the stereochemistry of a reaction.

Prochirality

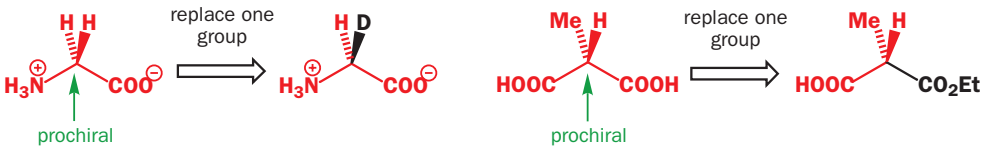
Take another look at all the reactions in the chapter so far—in particular those that give single diastereoisomers (rather than single enantiomers or geometrical isomers)—in other words, those that are **diastereoselective**. They all involve the creation of a new, tetrahedral stereogenic centre at a carbon that was planar and trigonal. This leads us to our first new definition. Trigonal carbons that aren't stereogenic (or chiral) centres but can be made into them are called **prochiral**.



At the very start of Chapter 17, we introduced stereochemistry by thinking about the reactions of two sorts of carbonyl compounds. They are shown again here: the first has a prochiral carbonyl group. The second, on the other hand, is not prochiral because no stereogenic centre is created when the compound reacts.



Tetrahedral carbon atoms can be prochiral too—if they carry two identical groups (and so are not a chiral centre) but replacement of one of them leads to a new chiral centre, then the carbon is prochiral.

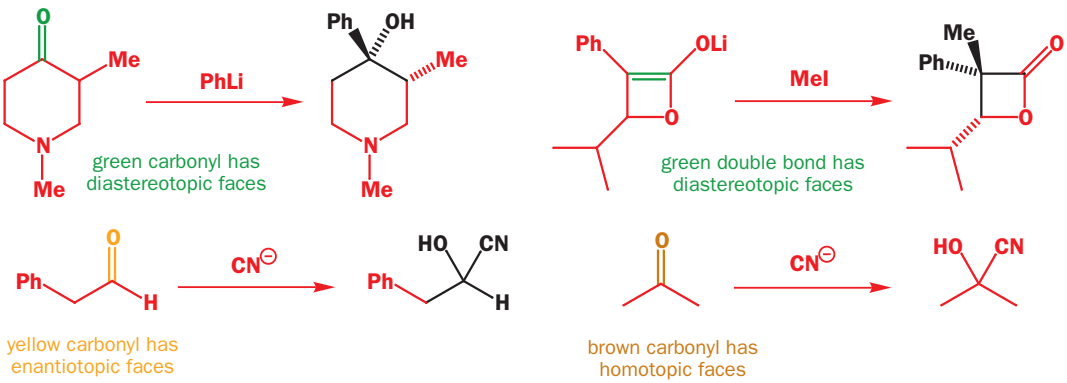


Glycine is the only α amino acid without a chiral centre, but replacing one of the two protons on the central carbon with, say, deuterium creates one: the CH_2 carbon is prochiral. Similarly, converting malonate derivative into its monoester makes a chiral centre where there was none: the central C is prochiral.

Now, does this ring any bells? It should remind you very much of the definitions in Chapter 32 of **enantiotopic** and **diastereotopic** in connection with NMR spectra. Replacing one of two enantiotopic groups with another group leads to one of two enantiomers; replacing one of two diastereotopic groups with another group leads to one of two diastereoisomers. Diastereotopic groups are chemically different; enantiotopic groups are chemically identical.

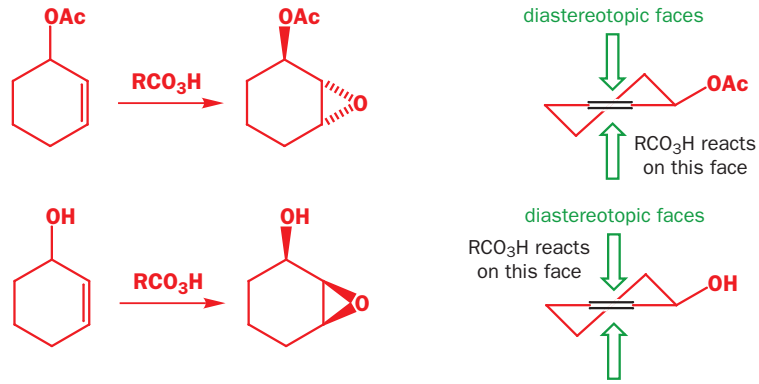
Enantiotopic and diastereotopic protons and groups are discussed in Chapter 32, p. 000.

Exactly the same things are true for the faces of a prochiral carbonyl group or double bond. If reaction on one of two faces of the prochiral group generates one of two enantiomers, the faces are enantiotopic; if the reaction generates one of two diastereoisomers, the faces are diastereotopic. We will now apply this thinking to the first few reactions in this chapter: they are shown again below. The first two examples have prochiral C=C or C=O bonds with diastereotopic faces: choosing which face of the double bond or carbonyl group to react on amounts to choosing which diastereoisomer to form. In the third example, the faces of the prochiral carbonyl group are enantiotopic: choosing which face to attack amounts to choosing which enantiomer to form. In the fourth example, the two faces of C=O are **homotopic**: an identical product is formed whichever face is attacked.



Knowing this throws some new light on the last chapter. Almost without exception, every stereoselective reaction there involved a double bond (usually C=C; sometimes C=O) with diastereotopic

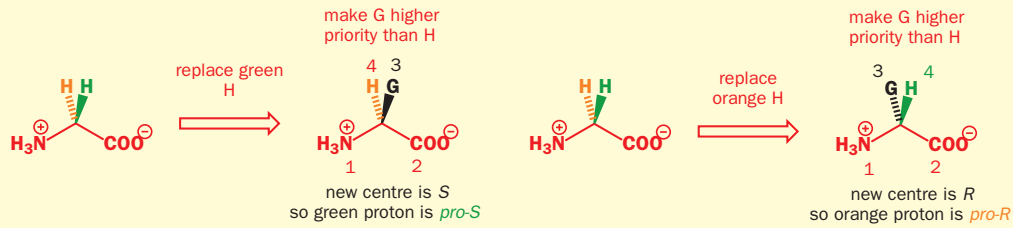
faces. The diastereotopic faces were distinguished by steric hindrance, or by a nearby hydrogen-bonding group, and so were able to react differently with an incoming reagent.



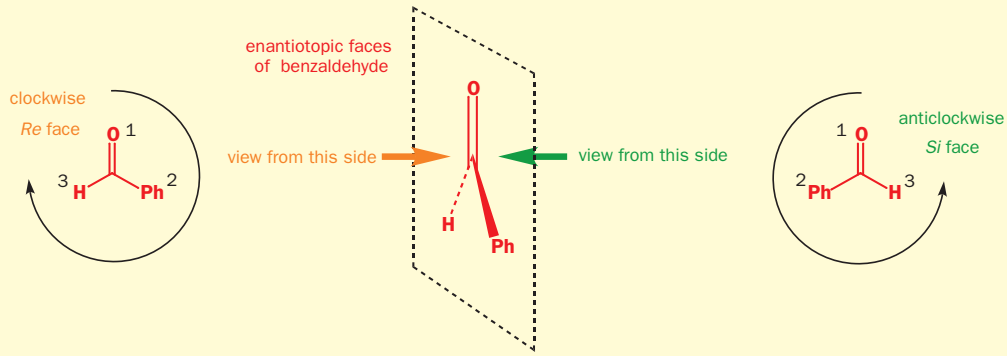
Using an *R*/*S*-type system to name prochiral faces and groups

Just as stereogenic centres can be described as *R* or *S*, it is possible to assign labels to the enantiotopic groups at prochiral tetrahedral carbon atoms or the enantiotopic faces of prochiral trigonal carbon atoms. The basis of the system is the usual *R,S* system for stereogenic centres, but *pro-R* and *pro-S* are used for groups and *Re* and *Si* for faces.

Pro-R and *pro-S* can be assigned to a pair of enantiotopic groups simply by using the usual rules to assign *R* or *S* to the centre created *if* the group in question is artificially elevated to higher priority than its enantiotopic twin. We'll use G to replace H as we did in Chapter 32: just assume that G has priority immediately higher than H. The method is illustrated for glycine.

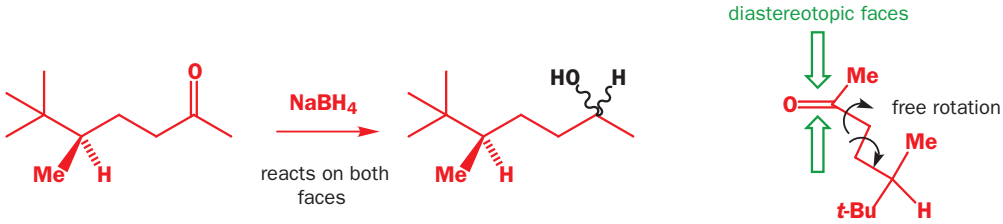


Faces of a prochiral trigonal carbon atom are assigned *Re* and *Si* by viewing the carbon from that side and counting down the groups in priority 1–3. Counting round to the right (clockwise) means the face is *Re*; counting round to the left (anticlockwise) means it's *Si*. Remember our advice from Chapter 16: think of turning a steering wheel in the direction of the numbers: does the car go to the right or the left?



Like *R* and *S*, these stereochemical terms are merely labels: they are of no consequence chemically.

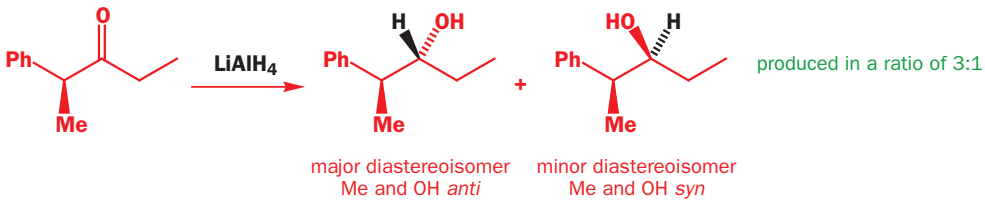
Just like diastereotopic signals in an NMR spectrum, diastereotopic faces are always different in principle, but sometimes not so in practice. The very first reaction of Chapter 33 is a case in point: this C=O group has two diastereotopic faces, which, due to free rotation about single bonds, average out to about the same reactivity, so we cannot expect any reasonable level of diastereoselectivity.



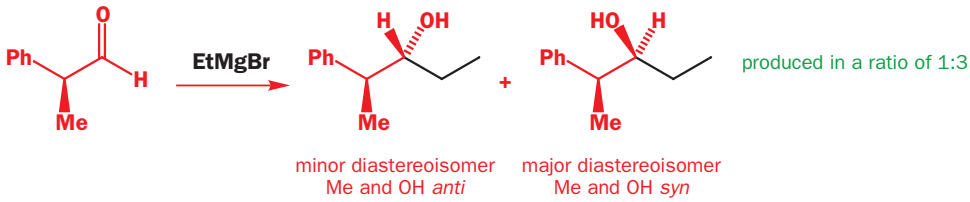
We put Chapter 33 first because in rings conformation is well defined, and this 'averaging' effect is held at bay. We are about to let it out again, but we will show you how it can be tamed to surprisingly good effect.

Additions to carbonyl groups can be diastereoselective even without rings

What happens if we bring the stereogenic centre closer to the carbonyl group than it was in the last example? You might expect it to have a greater influence over the carbonyl group's reactions. And it does. Here is an example.



There is three times as much of one of the two diastereoisomeric products as there is of the other, and the major (*anti*) diastereoisomer is the one in which the nucleophile has added to the front face of the carbonyl group as drawn here. We can make these same two diastereoisomers by addition of an organometallic to an aldehyde. For example, this Grignard reagent gives three times as much of the *syn* diastereoisomer as the *anti* diastereoisomer. The major product has changed, but the product still arises from attack on the front face of the carbonyl as shown.

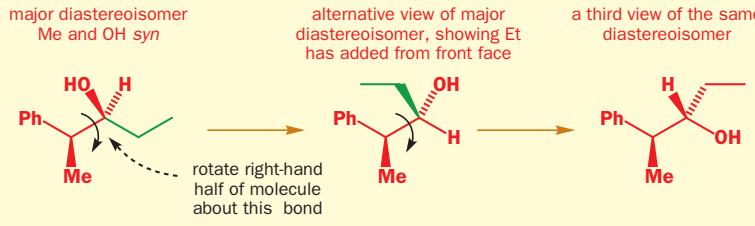


▶ In Chapter 32 we showed that homotopic and enantiotopic protons are identical by NMR. Similarly, homotopic faces or groups are always chemically identical. Enantiotopic faces are also chemically identical, provided that all the reagents in the reaction in question are achiral or racemic. In Chapter 45, we will consider what happens to enantiotopic faces when enantiomerically pure reagents are used.

▶ We have termed the major diastereoisomer *anti* because the two substituents (Me and OH) are on opposite sides of the chain as drawn. There is no formal definition of *anti* and *syn*: they can only really be used in conjunction with a structural drawing.

Drawing diastereoisomers of acyclic molecules

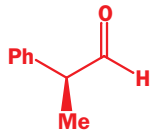
If you find it hard to see that these are still the same two diastereoisomers, try mentally rotating the right-hand half of the molecule about the bond shown below. The next three structures all show the same diastereoisomer (the major product from the last reaction), but in three different conformations (we are just rotating about a bond to get from one to another).

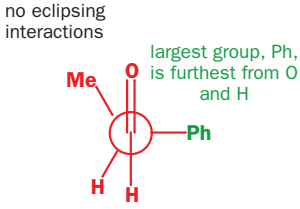


Which is the best? A good guideline, which we suggested in Chapter 16, is to place the longest carbon chain zig-zagging across the page in the plane of the paper, and allow all the smaller substituents to extend above or below that chain. The first structure here is drawn like that. But this is only a guideline, and the second structure here is a bit more informative regarding the reaction because,when it is drawn like this, you can clearly see from which direction the ethyl group has attacked the carbonyl. Our advice would be that you first of all draw the product of any reaction in more or less the same conformation as the starting material to ensure you make no mistakes, and then rotate about a single bond to place the longest chain in the plane of the paper.

If you still have problems manipulating structures mentally—for example, if you find it hard to work out whether the substituents that aren't in the plane should be in front of or behind the page—build some models.

■ We shall draw heavily on the first part of Chapter 18 here: if you haven't read it recently, now might be a good time to refresh your memory.





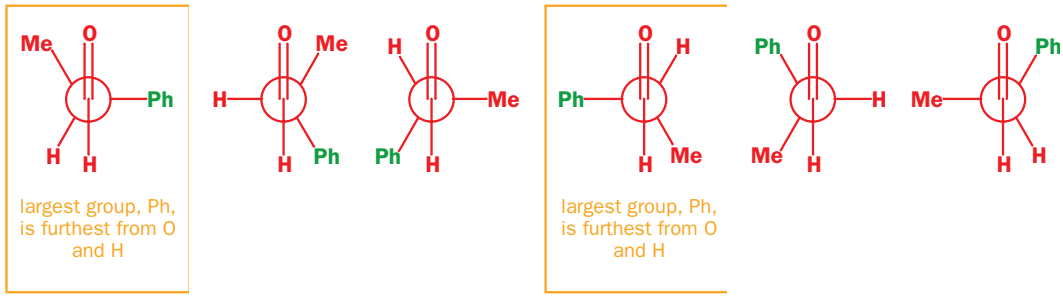
Newman projection of one possible conformation

These two reactions are not nearly as diastereoselective as most of the reactions of cyclic compounds you met in the last chapter. But we do now need to explain why they are diastereoselective at all, given the free rotation possible in an acyclic molecule. The key, as much with acyclic as with cyclic molecules, is **conformation**.

The conformation of a chiral aldehyde

What will be the conformation of the aldehyde in the margin? Using the principles we outlined in Chapter 17, we can expect it to be staggered, with no eclipsing interactions, and also with large substituents as far apart from one another as possible. A Newman projection of one of the possible conformers might look like the one shown in the margin. There are no eclipsing interactions, and the large phenyl group is held satisfactorily far away from the O and the H atoms of the aldehyde.

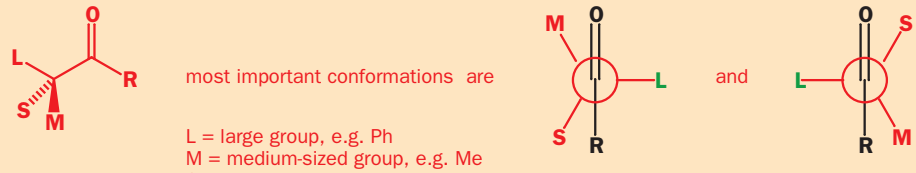
By rotating about the central bond of the aldehyde (the one represented by a circle in the Newman projection) we can suggest a series of possible conformations. Provided we move in 60° steps, none of them will have any eclipsing interactions. The full set of six conformers is shown here. Look at them for a moment, and notice how they differ.



Only two of them, boxed in yellow, place the large Ph group perpendicular to the carbonyl group. These yellow boxed conformations are therefore the lowest-energy conformers and, for the purpose of the discussion that follows, they are the only ones whose reactions we need to consider.

● Lowest energy conformations of a carbonyl compound

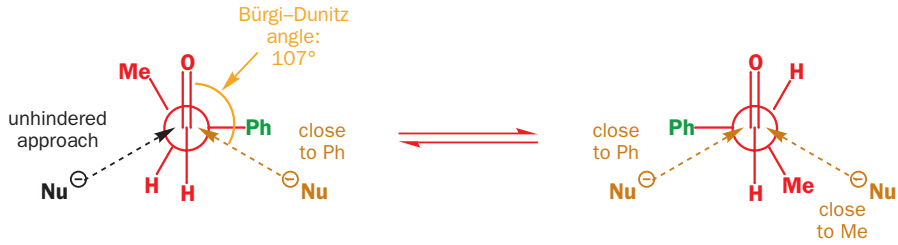
The most important conformations of a carbonyl compound with a stereogenic centre adjacent to the carbonyl group are those that place the largest group perpendicular to the carbonyl group.



■ We introduced the idea that attack on a C=O group followed this trajectory in Chapter 6.

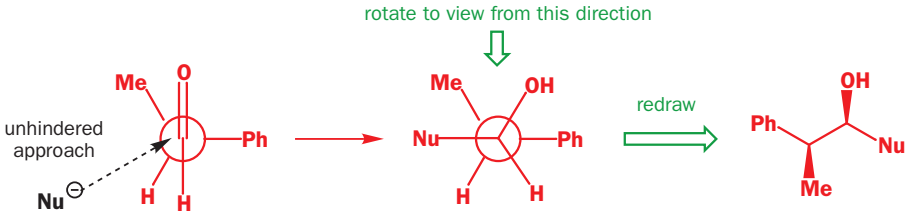
The major product arises from the most reactive conformer

Now that we have decided which are the important conformations, how do we know which gives the product? We need to decide which is the *most reactive*. All we need to do is to remember that any nucleophile attacking the carbonyl group will do so from the Bürgi–Dunitz angle—about 107° from the C=O bond. The attack can be from either side of C=O, and the following diagrams show the possible trajectories superimposed on the two conformations we have selected, which are in equilibrium with one another.



the black flight path is the best — the three brown flight paths are hindered by Ph or Me

Not all four possible 'flight paths' for the nucleophile are equally favourable. For the three shown in brown, the nucleophile passes within 30° or so of another substituent. But, for the one shown in black, there is no substituent nearby except H to hinder attack: the conformation on the left is the most reactive one, and it reacts to give the diastereoisomer shown below.



With Nu = Et we have the right product and, more importantly, we can be pretty sure it is for the right reason: this model of the way a nucleophile attacks a carbonyl compound, called the **Felkin–Anh model**, is supported by theoretical calculations and numerous experimental results. Notice that we don't have to decide which is the lower energy of the two conformations: this is not necessary because the attack in black will occur even if the conformer on the left is the minor one in the mixture.

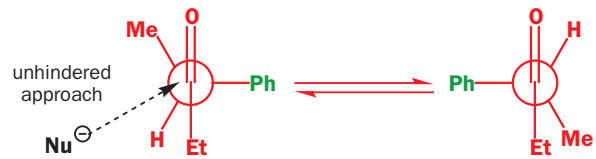
▶ Remember our guideline: draw the product in a conformation similar to that of the starting material; then redraw to put the longest chain in the plane of the paper. Here, this just means drawing the view from the top of the Newman projection—there is no need to rotate any bonds in this case.

▶ This is an example of the **Curtin–Hammett principle**, which says that it is the relative energies of the transition states that control selectivity, not the relative energies of the starting materials. It's really more of a reminder not to make a mistake than a principle.

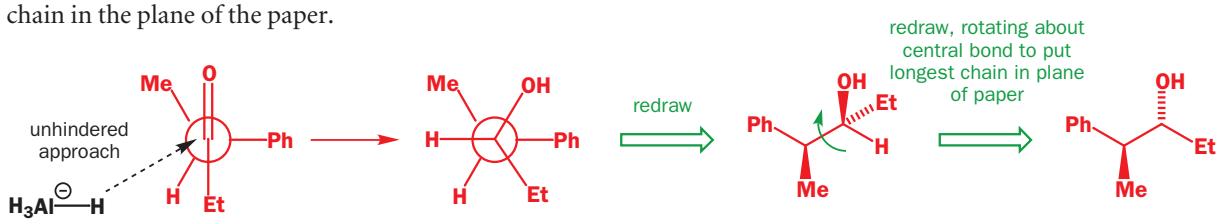
Cram's rule

You may hear 'Cram's rule' used to explain the outcome of reactions involving attack on chiral carbonyl compounds. Cram was the first to realize that these reactions could be predicted, but we now know why these compounds react in a predictable way. We will not describe Cram's rule because, although it often does predict the right product, in this case it does so for the wrong reason. Explanations and clear logical thinking are more important than rules, and you must be able to account for and predict the reactions of chiral aldehydes and ketones using the Felkin–Anh model.

The same reasoning accounts for the diastereoselectivity of the reduction on p. 000: first we need to draw the two important conformers of the ketone; the ones that have the large group (Ph) perpendicular to the C=O group.

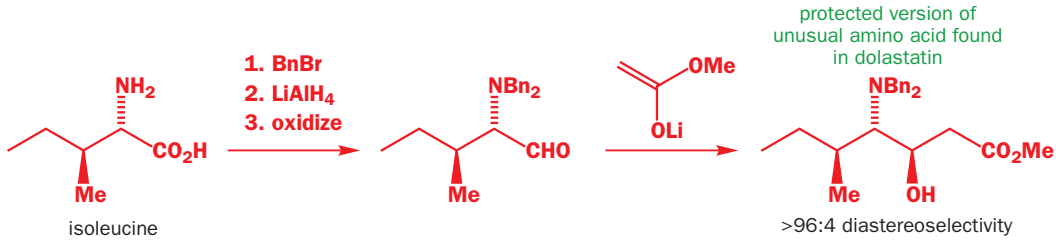


Now choose the angle of attack that is the least hindered, and draw a Newman projection of the product. Finally, redraw the Newman projection as a normal structure, preferably with the longest chain in the plane of the paper.



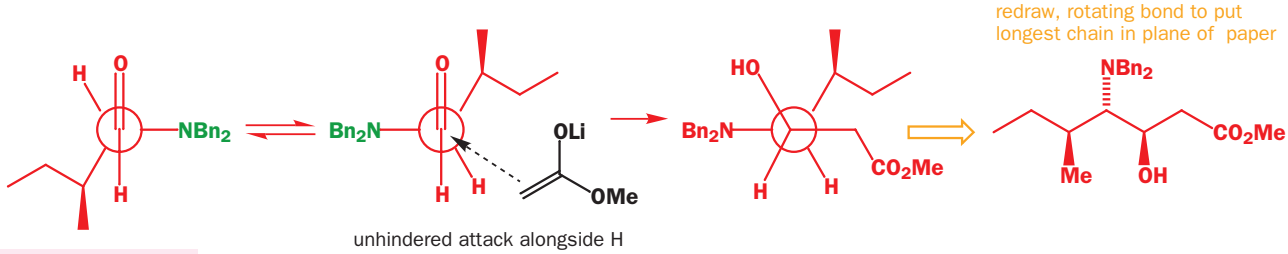
The effect of electronegative atoms

One of the most powerful anticancer agents known is dolastatin, isolated from the sea-hare *Dolabella*. Dolastatin contains an unusual amino acid, with three stereogenic centres, and chemists in Germany managed to exploit Felkin–Anh control very effectively to make it from the much more widespread amino acid isoleucine. This is the sequence of reactions.



The key step is the aldol reaction of the enolate of methyl acetate with the protected amino aldehyde. To rationalize the stereoselectivity, we first need to draw the two most important conformations of this aldehyde with the large group perpendicular to C=O. The trouble is—which do we choose as 'large': the $-NBn_2$ group or the branched alkyl group? Since we know which diastereoisomer is produced we can work backwards to find that it must be the NBn_2 group that sits perpendicular to C=O in the reactive transition state, and not alkyl.

▶ Try for yourself putting alkyl perpendicular to C=O: you will get the wrong diastereoisomer.



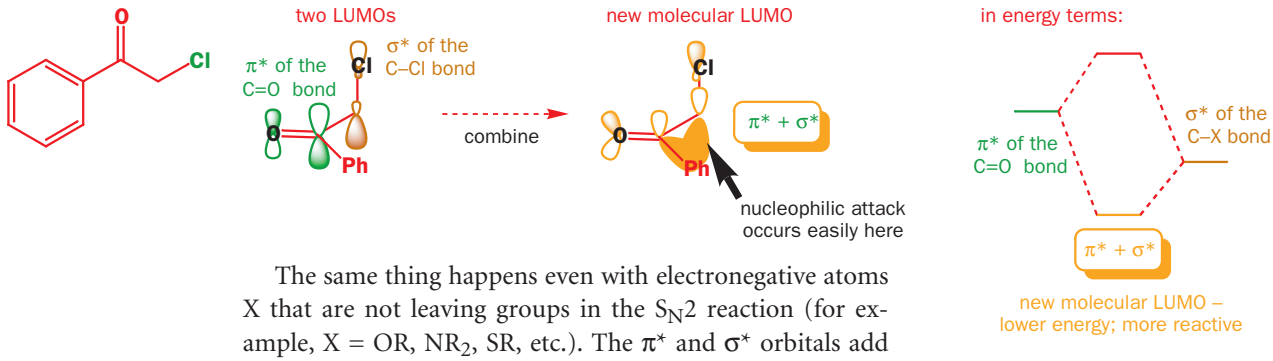
Now look at the diastereoselectivity of the reaction: it is much greater than the 3:1 we saw before—more like 20:1. This really does suggest that there is a further factor at work here, and that further factor is the electronegative N atom.

▶ When you see a selectivity given as 'greater than' something, it means that the other diastereoisomer was undetectable, but here 96:4 was the limit of detection by the method used—possibly NMR.

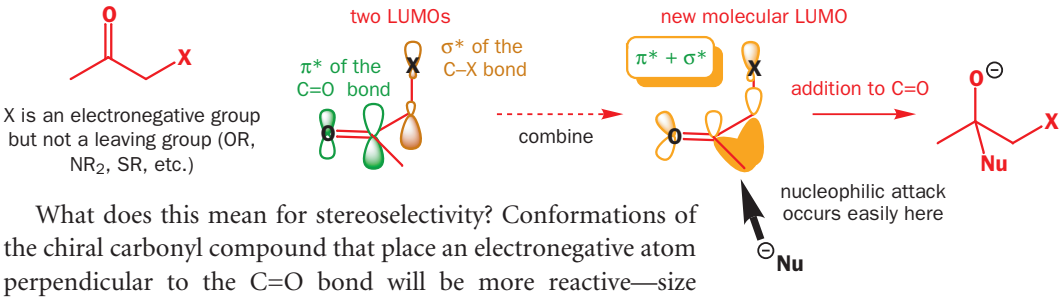
Carbonyl groups increase the reactivity of adjacent leaving groups towards nucleophilic substitution by several orders of magnitude. This was an effect that we noted in Chapter 17, where we showed that the ketone below reacts by the S_N2 mechanism 5000 times as fast as methyl chloride itself.

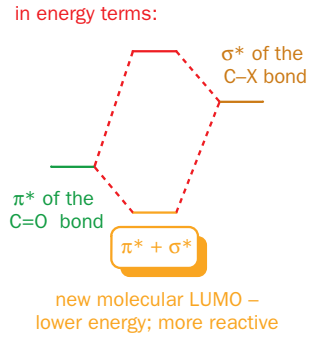
■ This is discussed on p. 000 of Chapter 17.

We explained this effect by saying that the π* of the C=O and the σ* of C–Cl overlap to form a new, lower-energy (and therefore more reactive) LUMO. What we did not note then, because it was not relevant, is that this overlap can only occur when the C–Cl bond is perpendicular to the C=O bond, because only then are the π* and σ* orbitals aligned correctly.



The same thing happens even with electronegative atoms X that are not leaving groups in the S_N2 reaction (for example, X = OR, NR_2, SR, etc.). The π* and σ* orbitals add together to form a new, lower-energy molecular orbital, more susceptible to nucleophilic attack. But, if X is not a leaving group, attack on this orbital will result not in nucleophilic substitution but in addition to the carbonyl group. Again, this effect will operate only when the C–X and C=O bonds are perpendicular so that the orbitals align correctly.





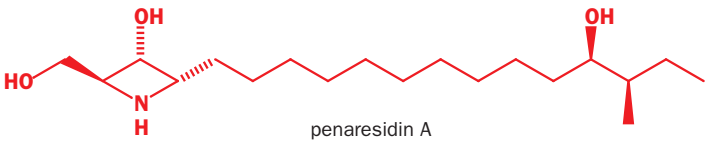
What does this mean for stereoselectivity? Conformations of the chiral carbonyl compound that place an electronegative atom perpendicular to the C=O bond will be more reactive—size doesn't matter. So, in the dolastatin amino acid example, the conformations with NBn_2 perpendicular to C=O are the only conformations we need to consider.

Using the Felkin–Anh model

To predict or explain the stereoselectivity of reactions of a carbonyl group with an adjacent stereogenic centre, use the Felkin–Anh model.

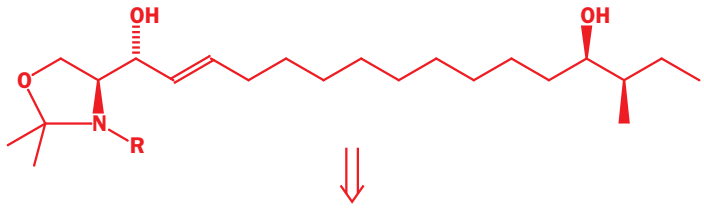
- **Draw Newman projections of the conformations of the starting material that place a large group or an electronegative group perpendicular to C=O**
- **Allow the nucleophile to attack along the least hindered trajectory, taking into account the Bürgi–Dunitz angle**
- **Draw a Newman projection of the product that arises from attack in this way**
- **Carefully flatten the Newman projection on to the page to produce a normal structure, preferably with the longest chain of C atoms in the plane of the page. Check that you have done this last step correctly: it is very easy to make mistakes here. Use a model if necessary, or do the 'flattening out' in two stages—first view the Newman projection from above or below and draw that; then rotate some of the molecule about a bond if necessary to get the long chain into the plane of the page.**

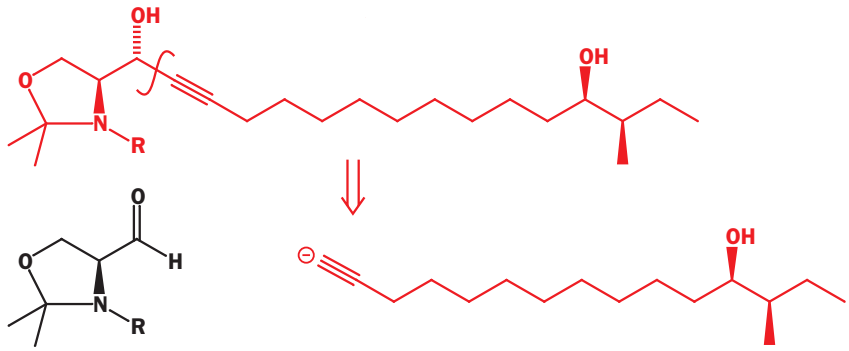
As an illustration of two sorts of diastereoselectivity, our next example is a natural product called penaresidin A. It was isolated from a Japanese sponge in 1991, and has the structure shown below



penaresidin A

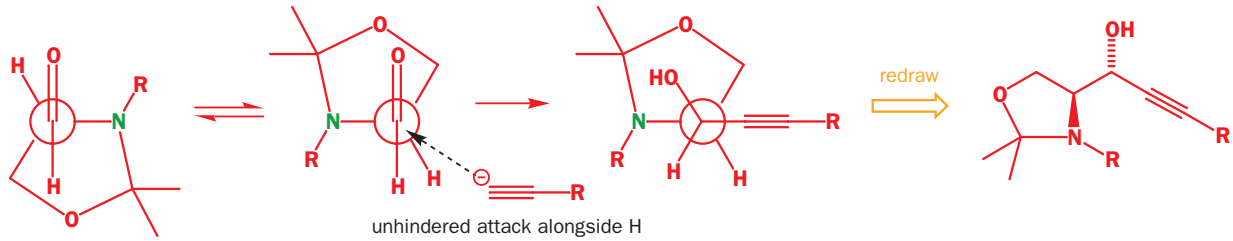
or something like this, because at the time of writing the relative stereochemistry between the two remotely related groups of chiral centres is still not known for sure. What is sure is the stereochemistry around the ring: NMR (the methods of Chapter 32) gives that. What Mori and his co-workers set out to do was to make, using unambiguous stereoselective methods, all the possible diastereoisomers of penaresidin A to discover which was the same as the natural product. It was fairly straightforward to get to the target molecule from the structure below and overleaf, so that's the compound whose synthesis we need to consider. If we imagine getting the *E*-alkene by stereoselective reduction of the alkyne, disconnection to an alkynyl anion equivalent reveals an aldehyde with a chiral centre next to the carbonyl group.

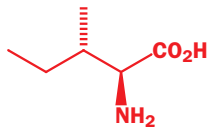




chiral aldehyde

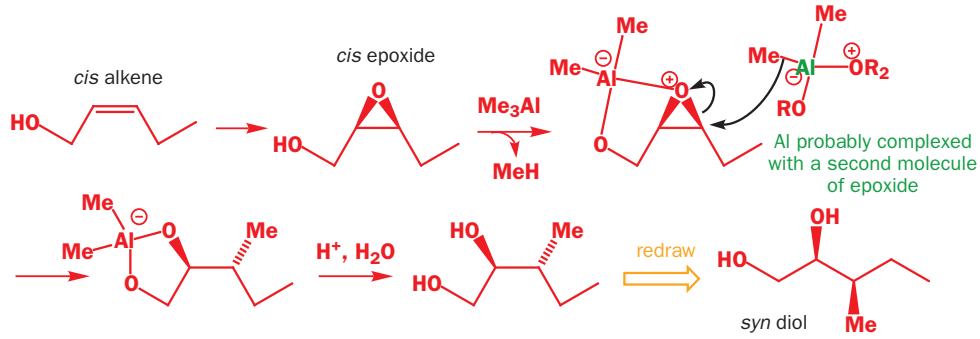
How will this aldehyde (which can be made from the amino acid serine) react with nucleophiles such as lithiated alkynes? Consider a Felkin–Anh transition state: again, we know that the nitrogen, being electronegative, will lie perpendicular to the carbonyl group in the most reactive conformation, so we need only consider these two. The least hindered direction of attack is shown, and that indeed gives the required product.



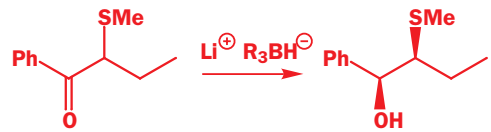


isoleucine

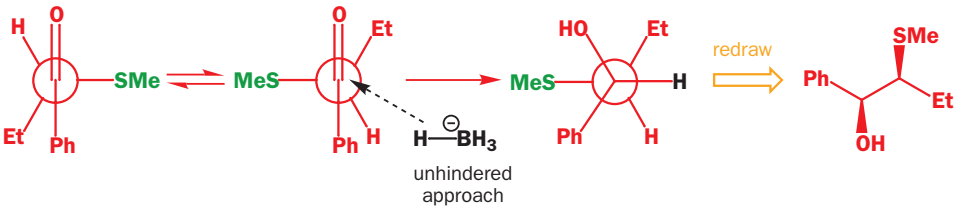
The other two chiral centres need to be controlled separately. The *trans* relative configuration could be obtained from another amino acid, which itself has two stereogenic centres—isoleucine. The *cis* was harder. The chemists decided to make it by starting with the *cis* diol shown, which could come from ring opening of an epoxide with an aluminium reagent. Since the ring opening goes with inversion, the epoxide needs to be *cis*, so the ultimate starting material was chosen to be a *cis* allylic alcohol. It turned out that the *cis* stereochemistry was right.



Chelation can reverse stereoselectivity

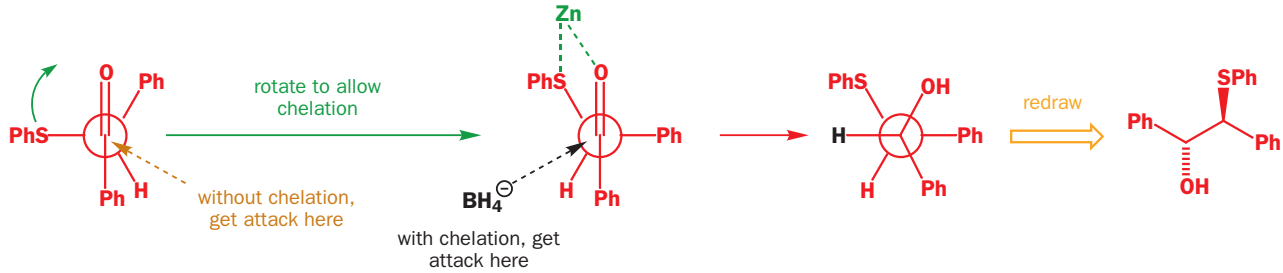


You should now be in a position to explain the outcome of this reaction without much difficulty. Sulfur is the electronegative atom, so the conformations we need to consider are the two following. Unhindered attack on the second gives the diastereoisomer shown.



But, from what we have told you so far, the next reaction would present a problem: changing the metal from sodium to zinc has reversed the stereoselectivity. Using the simple Felkin–Anh model now does not work: it gives the wrong answer.

The reason is that zinc can chelate sulfur and the carbonyl group. **Chelation** is the coordination of two heteroatoms carrying lone pairs to the same metal atom, and here it changes the conformation of the starting material. No longer does the most reactive or most populated conformation place the electronegative S atom perpendicular to C=O; instead it prefers S to lie as close to the carbonyl oxygen as possible so that Zn can bridge between S and O, like this.



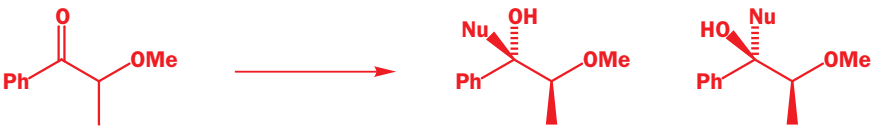
When chelation is possible, this is the conformation to consider—the one with the carbonyl O and the other chelating atom almost eclipsing one another. It is the most populated, because it is stabilized by the chelation, and it is also the most reactive, because the Lewis-acidic metal atom increases the reactivity of the carbonyl group. Attack is still along the less hindered pathway, but this now leads to the other face of the carbonyl group, and the stereochemical outcome is reversed.

Two things are needed for chelation to occur:

- a heteroatom with lone pairs available for coordination to a metal
- a metal ion that prefers to coordinate to more than one heteroatom at once. These are mainly more highly charged ions as shown in the table

Metals commonly involved in chelation	Metals not usually involved in chelation
Li^+ sometimes	Li^+ often
Mg^{2+}	Na^+
Zn^{2+}	K^+
Cu^{2+}	
Ti^{4+}	
Ce^{3+}	
Mn^{2+}	

Here is another example of a reversal in selectivity that can be explained using a nonchelated Felkin–Anh model with Na^+ and a chelated model with Mg^{2+}.

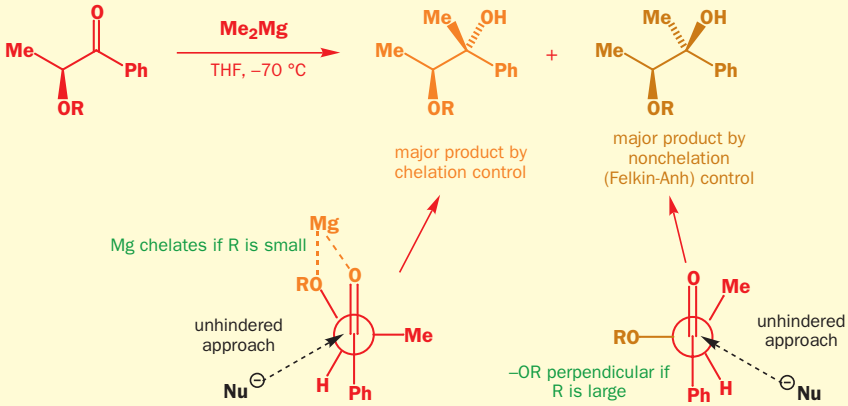


$NaBH_4$ (Nu = H)	73%	27%
Me_2Mg (Nu = Me)	1%	99%

Not only does chelation control reverse the stereoselectivity, but it gives a much higher *degree* of stereoselectivity. Stereoselectivities in chelation-controlled additions to C=O groups are typically >95:5. But this fits in nicely with the ideas we presented at the end of the last chapter: stereoselectivity is likely to be high if a cyclic transition state is involved. Chelation involves just such a transition state, so it should be no surprise that it lets us achieve much higher levels of control than the acyclic Felkin–Anh model does.

Chelation, rate, and stereoselectivity

The correlation of rate of addition with diastereoselectivity was demonstrated in a series of experiments that involved reacting Me_2Mg with protected α-hydroxy-ketones. As the protecting group was changed from a methyl ether to a trimethylsilyl ether and then through a series of increasingly bulky silyl ethers, both the rate of the reaction and the diastereoselectivity decreased. With small protecting groups, the reaction takes place through the chelated transition state—the selectivity shows this—and the rate is faster because of the activating effect of the Lewis-acidic magnesium ion. But with larger protecting groups, chelation of Mg^{2+} between the two oxygen atoms is frustrated: the rate drops off, and the selectivity becomes more what would be expected from the Felkin–Anh model.

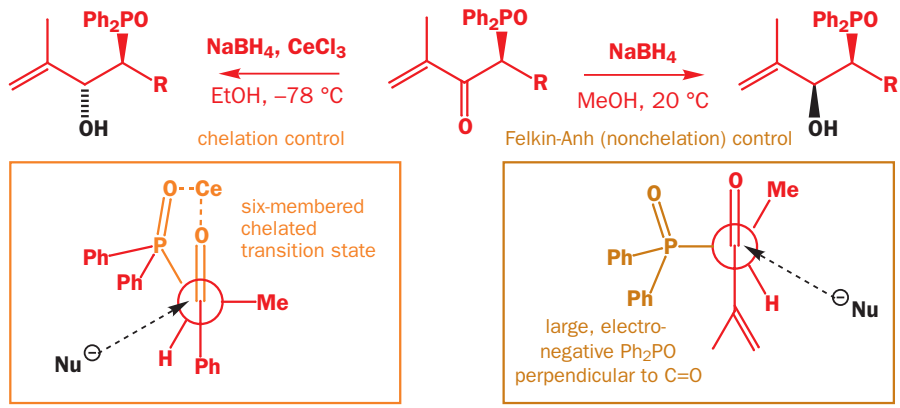


R	Ratio	Relative rate
Me	>99:1	1000
$SiMe_3$	99:1	100
$SiEt_3$	96:4	8
$SiMe_2t$-Bu	88:12	2.5
$SiPh_2t$-Bu	63:37	0.82
$Si(i\text{-}Pr)_3$	42:58	0.45

Chelation

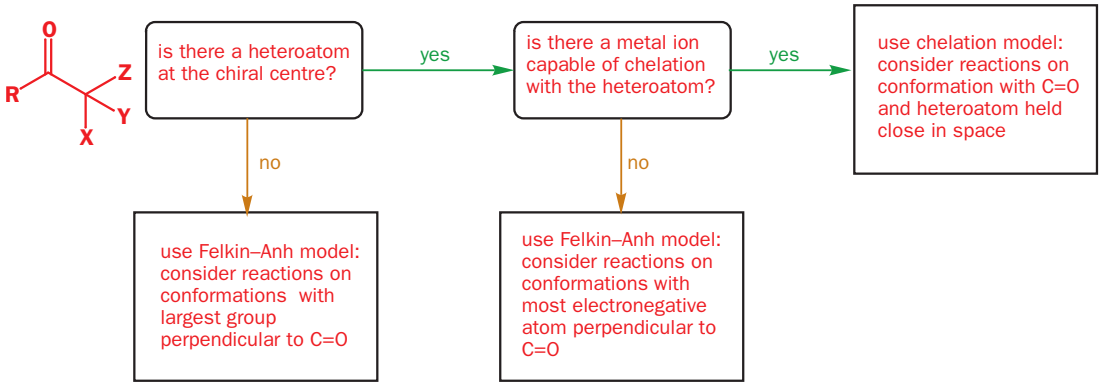
- may change the direction of diastereoselectivity
- leads to high levels of diastereoselectivity
- increases the rate of the addition reaction

Chelation is possible through six- as well as five-membered rings, and the reduction of the ketone below is a nice example of the reversal of diastereoselectivity observed when chelating Ce^{3+} ions are added to a normal sodium borohydride reduction. The products were important for making single geometrical isomers of alkenes in a modification of the Wittig reaction (Chapter 31). Notice too how the rate must change: with Ce^{3+} the reaction can be done at –78 °C.



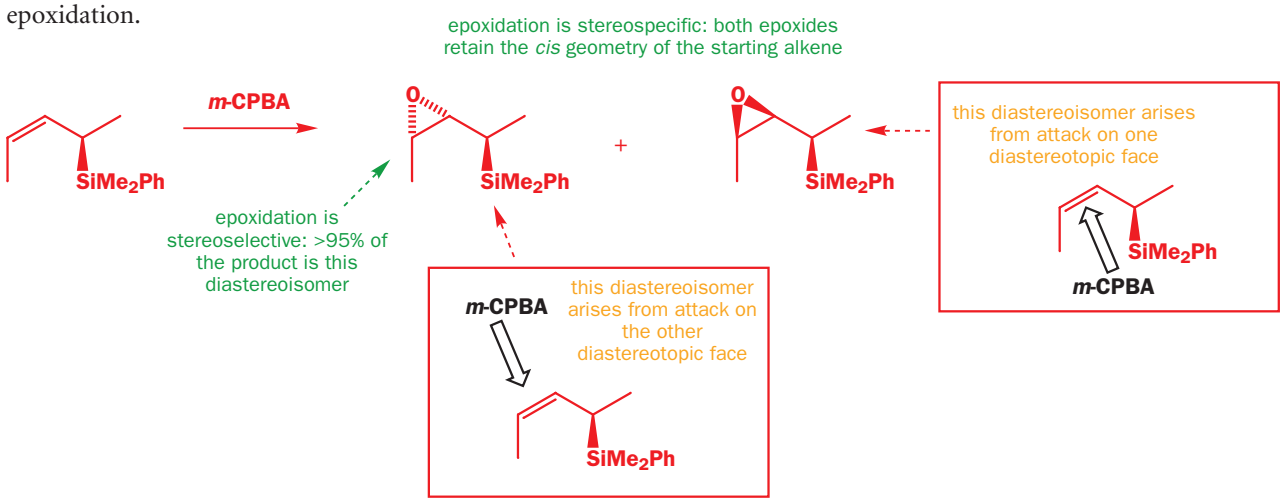
Attack on α chiral carbonyl compounds: summary

The flow chart summarizes what you should consider when you need to predict or explain the stereochemical outcome of nucleophilic attack on a chiral carbonyl compound.



Stereoselective reactions of acyclic alkenes

Earlier in the chapter we discussed how to make single diastereoisomers by stereospecific additions to double bonds of fixed geometry. But if the alkene also contains a chiral centre there will be a stereoselective aspect to its reactions too: its faces will be diastereotopic, and there will be two possible outcomes even if the reaction is fully stereospecific. Here is an example where the reaction is an epoxidation.

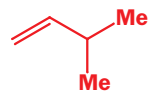


The Houk model

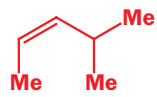
In order to explain reactions of chiral alkenes like this, we need to assess which conformations are important, and consider how they will react, just as we have done for chiral carbonyl compounds. Much of the work on alkene conformations was done by K.N. Houk using theoretical computer models, and we will summarize the most important conclusions of these studies. The theoretical studies looked at two model alkenes, shown in the margin.

The calculations found that the low-energy conformations in each case were those in which a substituent eclipses the double bond. For the simple model alkene **1**, the lowest-energy conformation is the one that has the proton in the plane of the alkene. Another low-energy conformation—only 3.1 kJ mol^{-1} higher—has one of the methyl groups eclipsing the double bond, so that when we start looking at reactions of this type of alkene, we shall have to consider both conformations.

■ K.N. Houk works at the University of California in Los Angeles. He has provided explanations for a number of stereochemical results by using powerful computational methods.

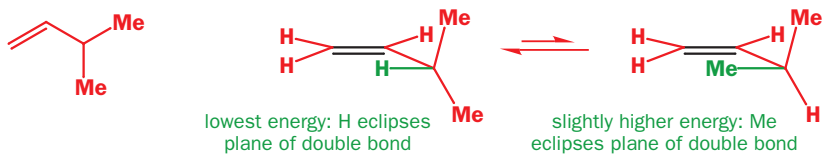


model alkene **1**



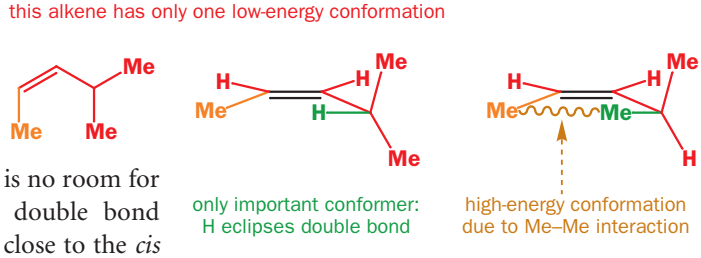
model alkene **2**

this alkene has two low-energy conformations



▶ This effect—the control of conformation by a *cis* substituent—is known as **allylic strain** or $A^{1,3}$ strain. The groups involved are on carbons 1 and 3 of an allylic system.

For the model alkene 2, with a *cis* substituent, the conformation is more predictable and the only low-energy conformer is the one with the hydrogen eclipsing the double bond. There is no room for a methyl group to eclipse the double bond because if it did it would get too close to the *cis* substituent at the other end of the double bond.



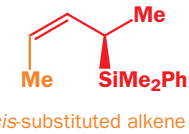
The message from the calculations is this:

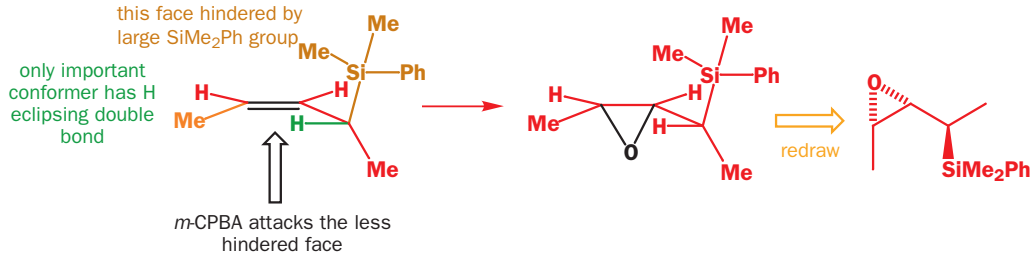
- The lowest-energy conformation of a chiral alkene will have H eclipsing the double bond
- If there is a *cis* substituent on the alkene, this will be the only important conformation; if there is no *cis* substituent, other conformations may be important too

Now we can apply the theoretical model to some real examples.

Stereoselective epoxidation

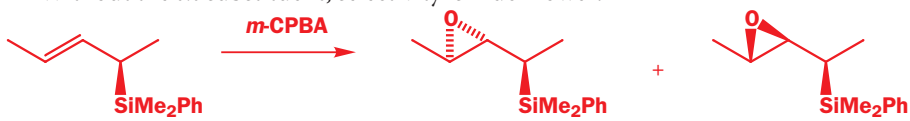
We started this section with a diastereoselective epoxidation of an alkene. The alkene was this one, and it has a substituent *cis* to the stereogenic centre. We can therefore expect it to have one important conformation, with H eclipsing the double bond. When a reagent—*m*-CPBA here—attacks this conformation, it will approach the less hindered face, and the outcome is shown.



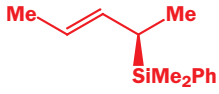


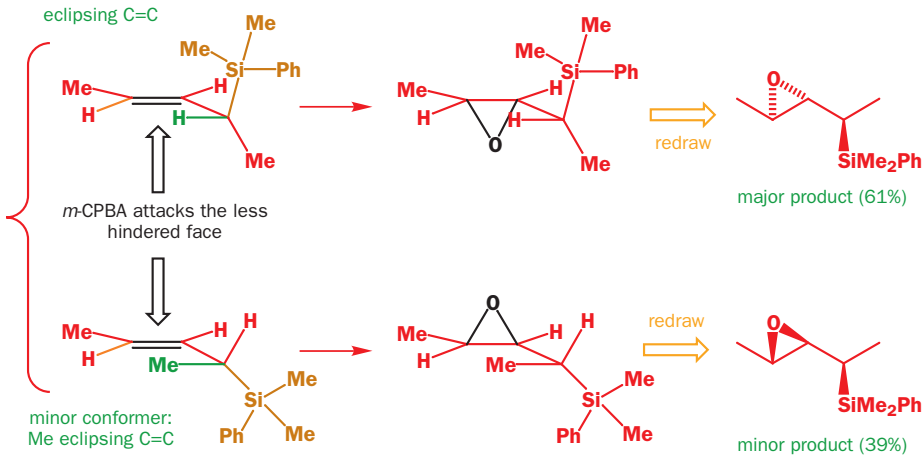
▶ Again—draw the product in the same conformation as the starting material, then flatten into the plane of the page.

Without the *cis* substituent, selectivity is much lower.



m-CPBA still attacks the less hindered face of the alkene, but with no *cis* substituent there are two low-energy conformations: one with H eclipsing the double bond, and one with Me eclipsing. Each gives a different stereochemical result, explaining the low stereoselectivity of the reaction.

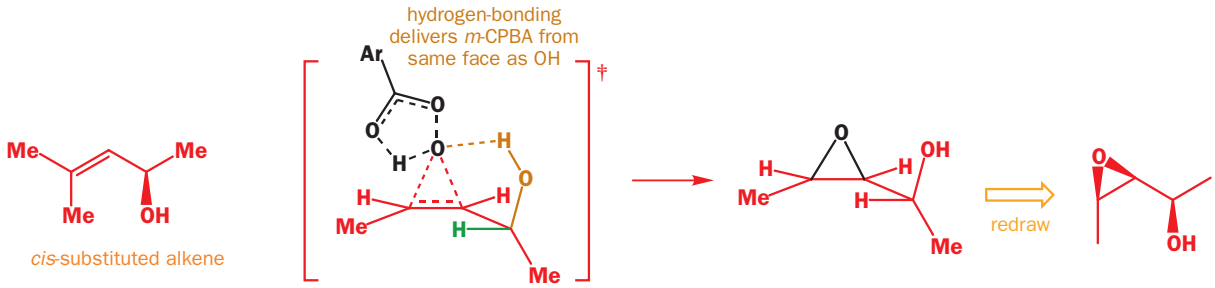




You saw at the end of the last chapter that the reactions of *m*-CPBA can be directed by hydroxyl groups, and the same thing happens in the reactions of acyclic alkenes. This allylic alcohol epoxidizes to give a 95:5 ratio of diastereoisomers.

95:5 ratio of diastereoisomers

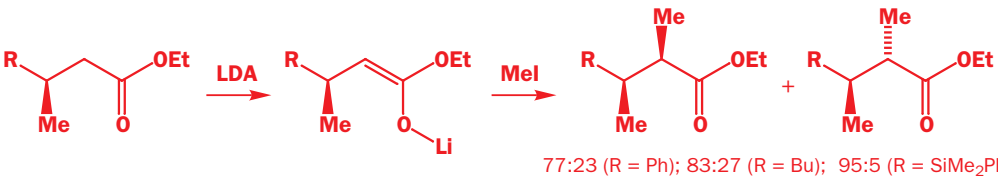
Drawing the reactive conformation explains the result. The thing that counts is the *cis* methyl group: the fact that there is a *trans* one too is irrelevant as it is just too far away from the stereogenic centre to have an effect on the conformation.



- **To explain the stereoselectivity of reactions of chiral alkenes:**
  - **Draw the conformation with H eclipsing the double bond**
  - **Allow the reagent to attack the less hindered of the two faces or, if co-ordination is possible, to be delivered to the face *syn* to the coordinating group**
  - **Draw the product in the same conformation as the starting material**
  - **Redraw the product as a normal structure with the longest chain in the plane of the paper**

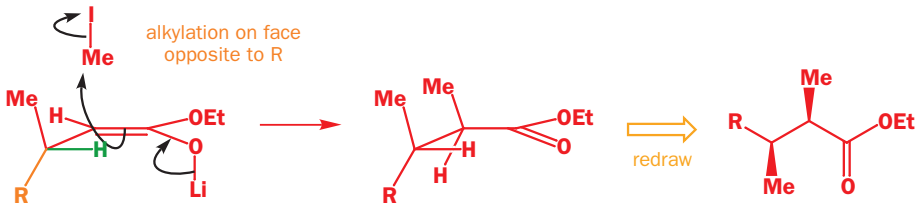
Stereoselective enolate alkylation

Chiral enolates can be made from compounds with a stereogenic centre β to a carbonyl group. Once the carbonyl is deprotonated to form the enolate, the stereogenic centre is next to the double bond and in a position to control the stereoselectivity of its reactions. The scheme below shows stereoselectivity in the reactions of some chiral enolates with methyl iodide.



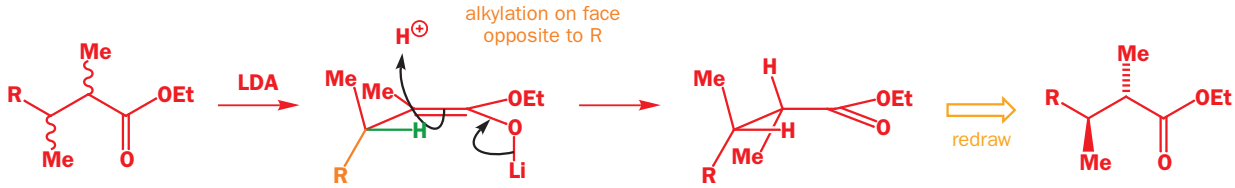
77:23 (R = Ph); 83:27 (R = Bu); 95:5 (R = $SiMe_2Ph$)

The enolate is a *cis*-substituted alkene, because either O^- or OEt must be *cis* to the stereogenic centre, so that to explain the stereoselectivity, we need consider only the conformation with H eclipsing the double bond. Notice how the diastereoselectivity increases as the group R gets bigger, because there is then more contrast between the size of Me and R. In each case, the electrophile adds to the less hindered face, opposite R.



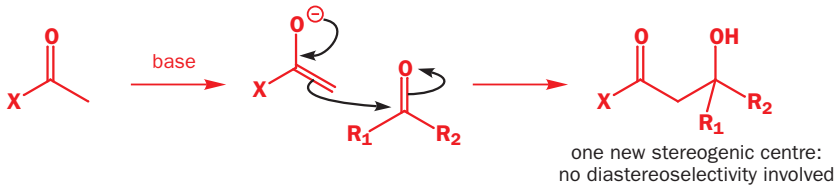
▶ The relative stereochemistry of the starting material is lost in the enolization step, so either diastereoisomer, or a mixture, can be used.

The other diastereoisomer can be made just by having the methyl group in place first and then protonating the enolate. The selectivities are lower (because a proton is small), but this does illustrate the way in which reversing the order of introduction of two groups can reverse the stereochemical outcome of the reaction.



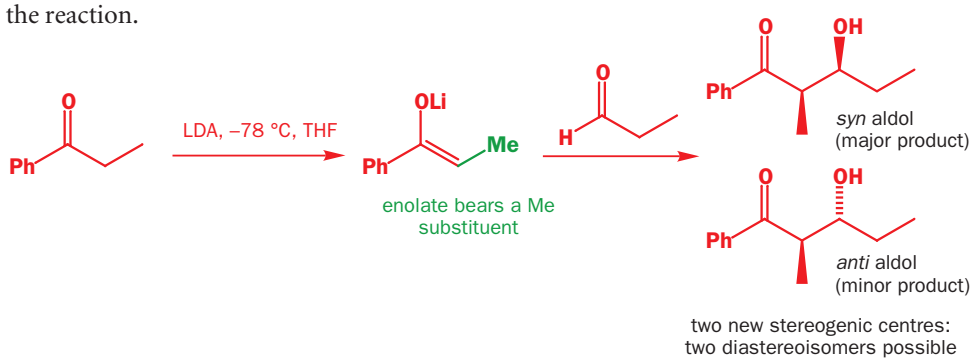
Aldol reactions can be stereoselective

In Chapter 27 you met the **aldol reaction**: reaction of an enolate with an aldehyde or a ketone. Many of the examples you saw approximated to this general pattern.



Only one new stereogenic centre is created, so there is no question of diastereoselectivity. But with substituted enolates, two new stereogenic centres are created, and we need to be able to predict which diastereoisomer will be formed. Here is an example from p. 000. We did not consider stereochemistry at that stage, but we can now reveal that the *syn* diastereoisomer is the major product of the reaction.

▶ This reaction is diastereoselective not because of stereoselective attack on one of two diastereotopic faces, but because of the way in which two prochiral reagents, each with two enantiotopic faces, come together.

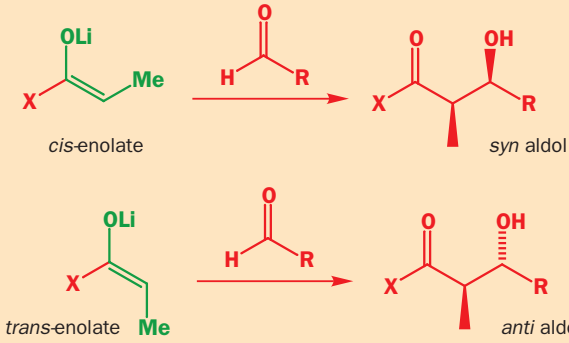


■ This is a very general rule and there are many exceptions—the enolates of some metals (Sn(II), Zr, Ti) give *syn* aldols regardless of enolate geometry. Some related reactions are discussed in Chapter 47.

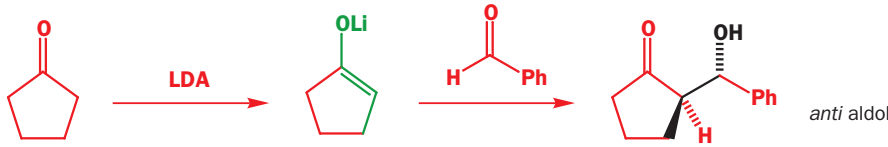
The important point about substituted enolates is that they can exist as two geometrical isomers, *cis* or *trans*. Which enolate is formed is an important factor controlling the diastereoselectivity because it turns out that, in many examples of the aldol reaction, *cis*-enolates give *syn* aldols preferentially and *trans*-enolates give *anti* aldols preferentially.

Diastereoselectivity in aldol reactions

Generally (but certainly not always!) in aldol reactions:

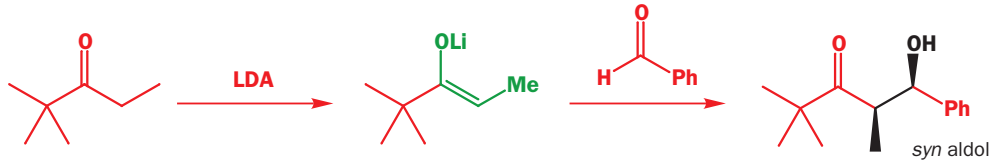


Let's start by showing some examples and demonstrating how we know this to be the case. Some enolates can only exist as *trans*-enolates because they are derived from cyclic ketones. This enolate, for example, reacts with aldehydes to give only the *anti* aldol product.



only *trans*-enolate can form

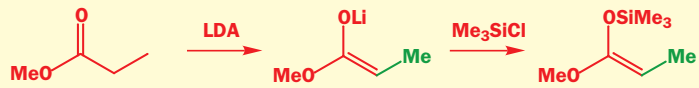
If we choose the group 'X', next to the carbonyl group, to be large, then we can be sure of getting just the *cis*-enolate. So, for example, the lithium enolate of this *t*-butyl ketone forms just as one geometrical isomer, and reacts with aldols to give only the *syn* aldol product.



cis-enolate avoids Me and *t*-Bu coming into contact

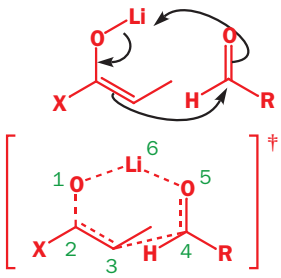
cis and *trans*, *E* and *Z*, *syn* and *anti*

Before going further, there are two points we must clarify. The first is a problem of nomenclature, and concerns the enolates of esters. Here are two closely related ester enolate equivalents, drawn with the same double bond geometry. Is it *E* or *Z*?



The answer is both! For the Li enolate, the usual rule makes OLi of lower priority than OMe, so it's *E*, while the silyl enol ether (or 'silyl ketene acetal') has OSi of higher priority than OMe, so it's *Z*. This is merely a nomenclature problem, but it would be irritating to have to reverse all our arguments for lithium enolates simply because lithium is of lower atomic number than carbon. So, for the sake of consistency, it is much better to avoid the use of *E* and *Z* with enolates and instead use *cis* and *trans*, which then always refer to the relationship between the substituent and the anionic oxygen (bearing the metal).

The other point concerns *syn* and *anti*. We said earlier that there is no precise definition of these terms: they are a useful way of distinguishing two diastereoisomers provided the structure of at least one of them is presented in diagrammatic form. For aldol products the convention is that *syn* or *anti* refers to the enolate substituent (the green Me in the last example) and the new hydroxyl group, provided the main chain is in the plane of the paper, the way we have encouraged you to draw molecules.



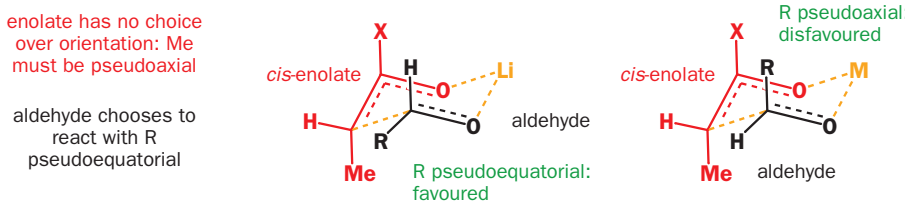
■

The six-membered ring transition state for the aldol reaction was proposed by Zimmerman and Traxler and is sometimes called the **Zimmerman–Traxler transition state**.

The aldol reaction has a chair-like transition state

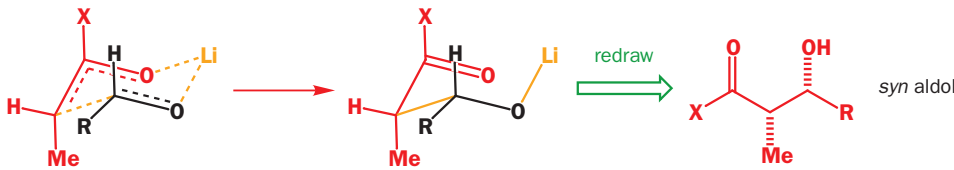
These are the experimental facts: how can we explain them? Aldol reactions are another class of stereoselective process with a cyclic transition state. During the reaction, the lithium is transferred from the enolate oxygen to the oxygen of the carbonyl electrophile. This is represented in the margin both in curly arrow terms and as a transition state structure.

A six-membered ring is involved, and we can expect this ring to adopt more or less a chair conformation. The easiest way to draw this is first to draw the chair, and then convert atoms to O or Li as necessary. Here it is.

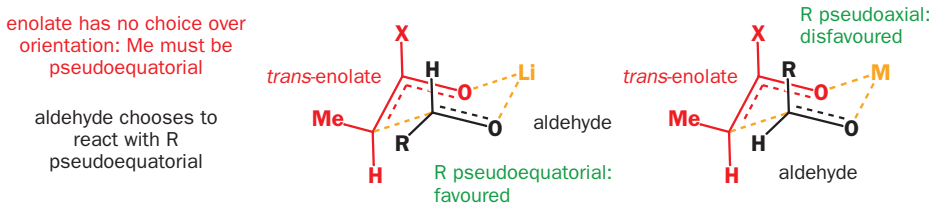


In drawing this chair, we have one choice: do we allow the aldehyde to place R equatorial or axial? Both are possible but, as you should now expect, there are fewer steric interactions if R is equatorial. Note that the enolate doesn't have the luxury of choice. If it is to have three atoms in the six-membered ring, as it must, it can do nothing but place the methyl group pseudoaxial.

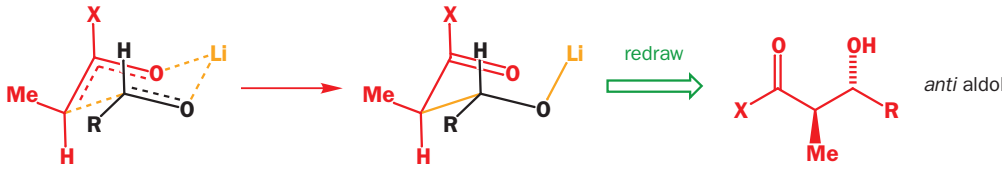
The aldol formed from the favoured transition state structure, with R pseudoequatorial, is shown below—first in the conformation of the transition state, and then flattened out on to the page, and it is *syn*.



We can do the same for a *trans*-enolate. The enolate has no choice but to put its methyl substituent pseudoequatorial, but the aldehyde can choose either pseudoequatorial or pseudoaxial. Again, pseudoequatorial is better



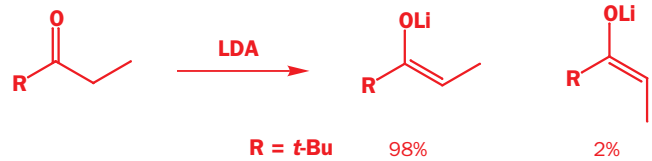
and the reaction gives the product shown—the *anti* aldol.

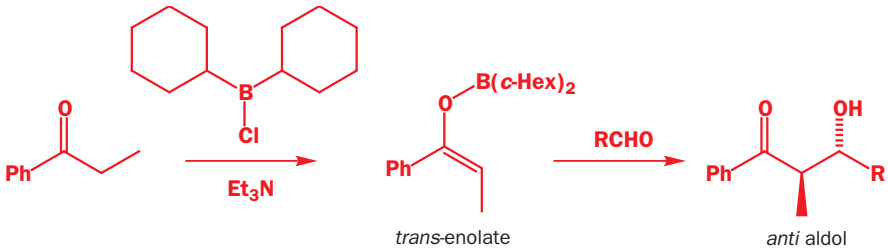


Stereoselective enolization is needed for stereoselective aldols

The cyclic transition state explains how enolate geometry controls the stereochemical outcome of the aldol reaction. But what controls the geometry of the enolate? For lithium enolates of ketones the most important factor is the size of the group that is not enolized. Large groups force the enolate to adopt the *cis* geometry; small groups allow the *trans*-enolate to form. Because we can't separate the lithium enolates, we just have to accept that the reactions of ketones with small R will be less diastereoselective.

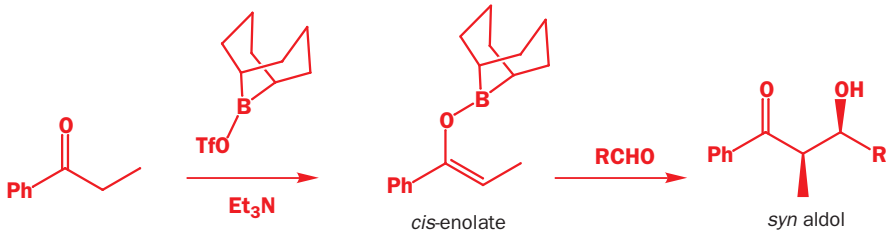
With *boron* enolates, we don't have to rely on the structure of the substrate—we choose the groups on boron—and we can get either *cis* or *trans* depending on which groups these are. Boron enolates are made by treating the ketone with an amine base (often Et_3N or *i*-$PrNEt_2$) and R_2B–X, where X^- is a good leaving group such as chloride or triflate ($CF_3SO_2^-$). With bulky groups on boron, such as two cyclohexyl groups, a *trans*-enolate forms from most ketones. The boron enolate reacts reliably with aldehydes to give *anti* aldol products through the same six-membered transition state that you saw for lithium enolates.





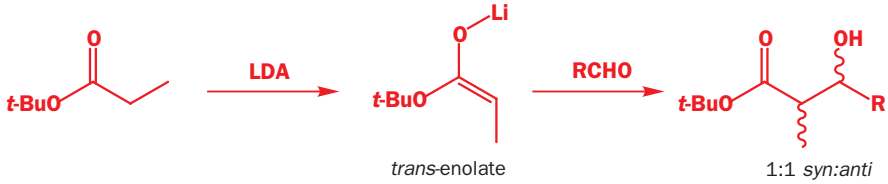
In fact, geometrically defined boron enolates give the aldol products with greater stereospecificity than do lithium enolates, possibly because the B–O bonds are shorter than Li–O bonds, so the six-membered ring is 'tighter'.

With smaller B substituents, the *cis*-enolate forms selectively. Here, the boron is part of a bicyclic structure known as 9-BBN (9-borabicyclononane—you will meet this in Chapter 47). The bicyclic part may look large but, as far as the rest of the molecule is concerned, it's 'tied back' behind the boron, and the methyl group can easily lie *cis* to oxygen. The *cis*-enolate then gives *syn* aldol products. Di-*n*-butylboron triflate (Bu_2BOTf) also gives *cis*-enolates.

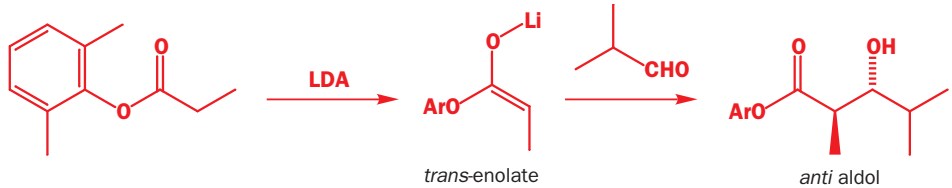


Stereoselective ester aldols

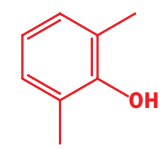
We have talked mainly about aldol reactions of ketones (as the enolate component). Esters usually form the *trans* lithium enolates quite stereoselectively. You might therefore imagine that their aldol reactions would be stereoselective for the *anti* product. Unfortunately, this is not the case, and even pure *trans*-enolate gives about a 1:1 mixture of *syn* and *anti* aldols.



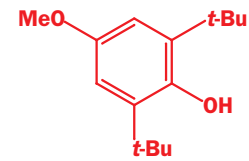
There is one important exception, and that is a class of esters of hindered phenols. The *trans*-enolates of these compounds react selectively with aldehydes to give the *anti* aldol products.



hindered phenols:

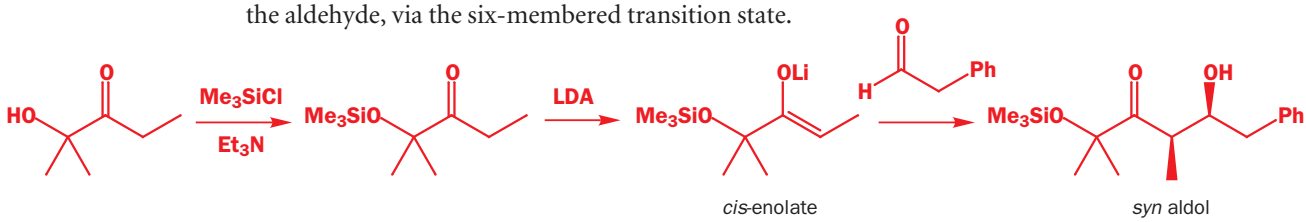


2,6-dimethylphenol

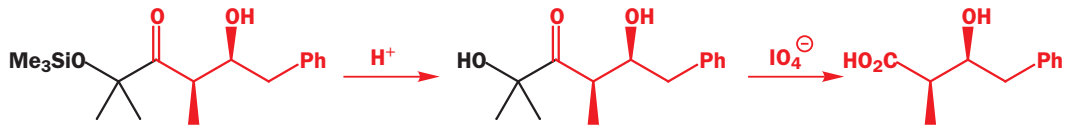


'butylated hydroxyanisole', BHA

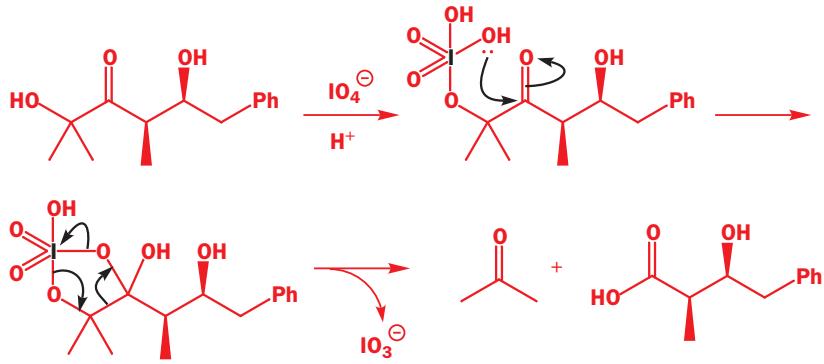
An ingenious way of getting a *syn* ester aldol product is to do the more reliable ketone *syn* aldol with a bulky group (to ensure the *cis*-enolate is formed) and then to oxidize off the bulky group. Here's what we mean. The starting material is very like the *t*-butyl ketone that you saw enolize stereoselectively above: only the *cis*-enolate can form. The enolate reacts highly *syn* selectively with the aldehyde, via the six-membered transition state.



At this point, the bulky group is no longer needed. The oxygen is deprotected in acid and, in the same step, periodate ions oxidatively cleave the C–C bond between the two oxygen substituents. The product is the acid parent of a *syn* ester aldol product.



We shall show you the mechanism of the cleavage, because it leads us nicely into the next chapter. The first step is rather like the first step of many oxidations—formation of an inorganic ester (here a periodate). The periodate can form a cyclic ester by attack on the carbonyl group. Next, we can push the arrows round the ring to reduce the iodine from I(VII) to I(V), cleave the double bond, and generate acetone and the acid.



You will see many more cyclic mechanisms in the next two chapters, including some more C–C cleavage reactions.

Summary: How to make *syn* and *anti* aldols

To make *syn* aldols of ketones:

- with a ketone RCOEt with bulky R, use lithium enolate
- use boron enolate with 9-BBN-OTf or Bu_2BOTf

To make *syn* aldols of esters:

- use a bulky 2-alkoxyketone and cleave to an acid

To make *anti* aldols of ketones:

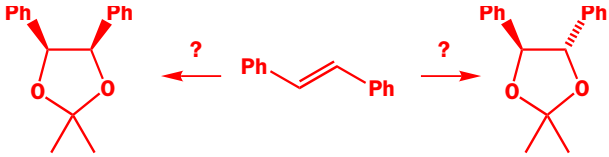
- with a cyclic ketone, use lithium enolate
- use boron enolate with dicyclohexylboron chloride

To make *anti* aldols of esters:

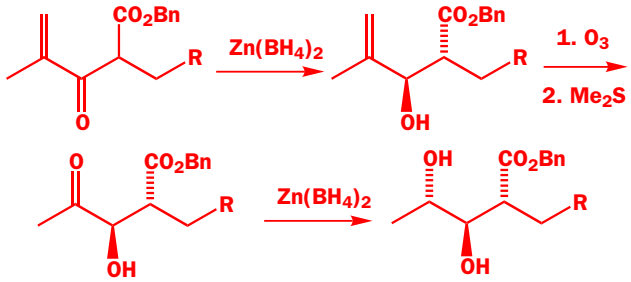
- use the ester of a hindered phenol

Problems

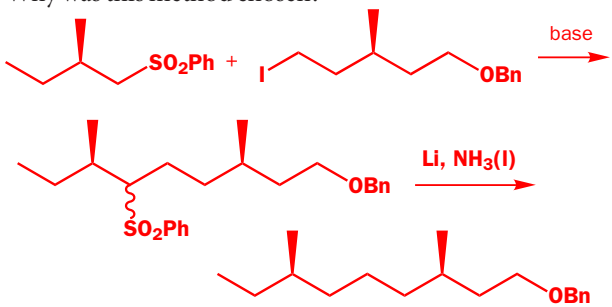
1. How would you make each diastereoisomer of this product from the same alkene?



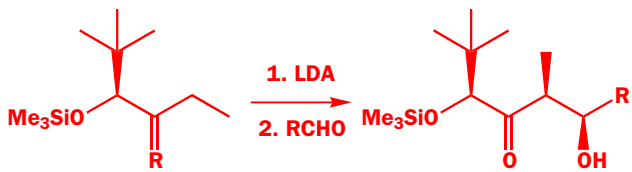
2. Explain the stereoselectivity shown in this sequence of reactions.



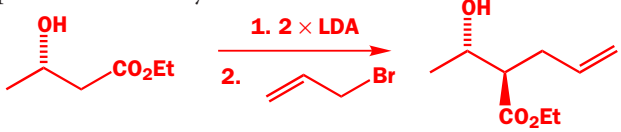
3. How is the relative stereochemistry of this product controlled? Why was this method chosen?



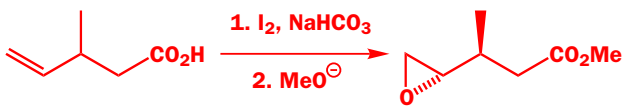
4. Explain the stereochemical control in this reaction, drawing all the intermediates.



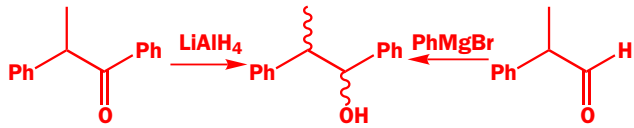
5. When this hydroxy-ester is treated with a twofold excess of LDA and then alkylated, one diastereoisomer of the product predominates. Why?



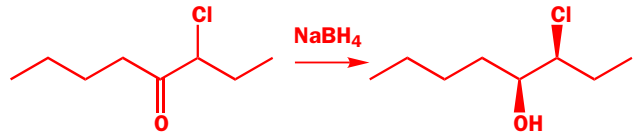
6. Explain how the stereochemistry of this epoxide is controlled.



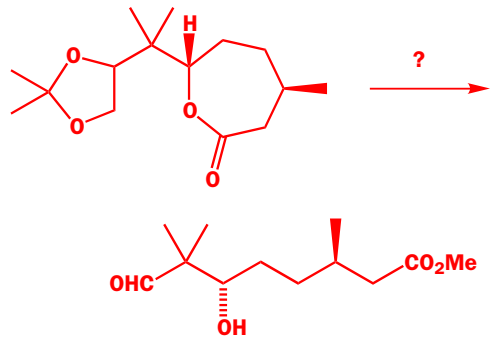
7. Explain how these two reactions give different diastereoisomers of the product.



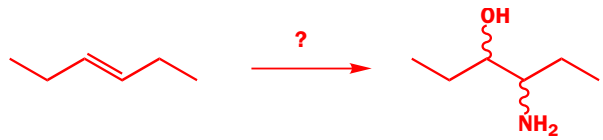
8. Explain the stereoselectivity in this reaction. What isomer of an epoxide would be produced on treatment of the product with base?



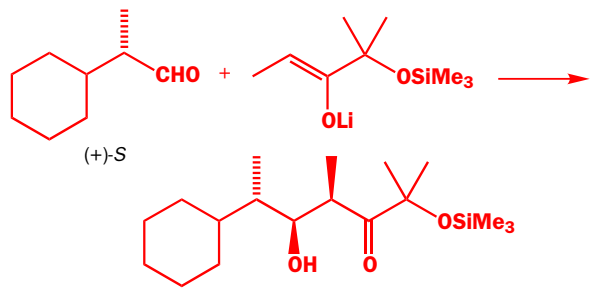
9. How could this cyclic compound be used to produce the open-chain compound with correct relative stereochemistry?



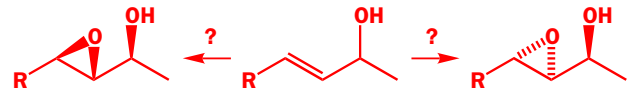
10. How would you transform this alkene stereoselectively into either of the diastereoisomers of the amino-alcohol?



11. Explain the formation of essentially one stereoisomer in this reaction.



12. How would you attempt to transform this allylic alcohol into both diastereoisomers of the epoxide stereoselectively? You are not expected to estimate the degree of success.



13. Revision. Here is an outline of the AstraZeneca synthesis of a thromboxane analogue. Explain the reactions, giving mechanisms for each step, and explain how the stereochemistry is controlled. In what way could this be considered an example of the control of open-chain stereochemistry when all of the molecules are cyclic?