

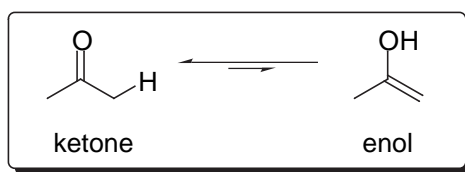
III Enolate Chemistry

Objectives

By the end of this section you will:

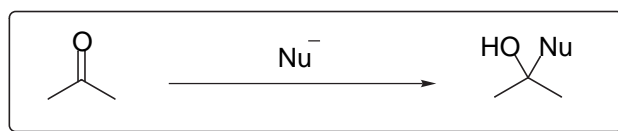
- 1) know how to use the enol tautomer of a ketone as a nucleophile;
- 2) be able to choose an appropriate base to form an enolate and relate this choice to the pK_a value of the α -C-H in the carbonyl compound;
- 3) be able to form boron and lithium enolates and silyl enol ethers stereo- and regioselectively;
- 4) be able to use the aldol reaction in the stereoselective synthesis of β -hydroxy ketones;
- 5) understand what factors control simple diastereoselectivity and diastereofacial selectivity in aldol reactions;
- 6) appreciate the importance of enolate chemistry in stereoselective C-C bond formation.

III.A. Revision

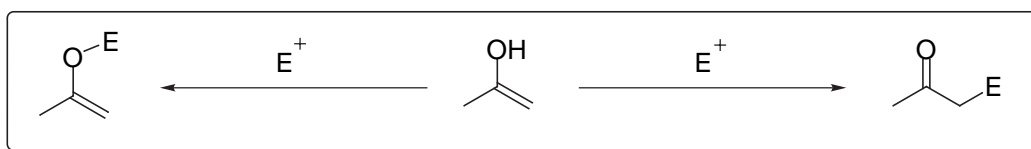


In most cases the equilibrium lies almost completely on the side of the ketone.

The ketone tautomer is electrophilic and reacts with nucleophiles:



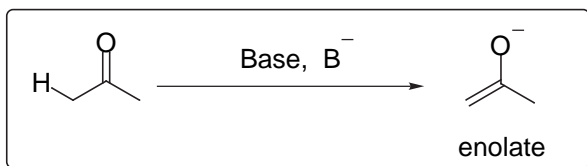
The enol tautomer is nucleophilic and reacts with electrophiles. There are two possible products - enols are *ambident* nucleophiles:



The nucleophilic enol tautomer of a ketone (and especially the enolate anionic variant) is one of the most important reactive species for C–C bond formation.

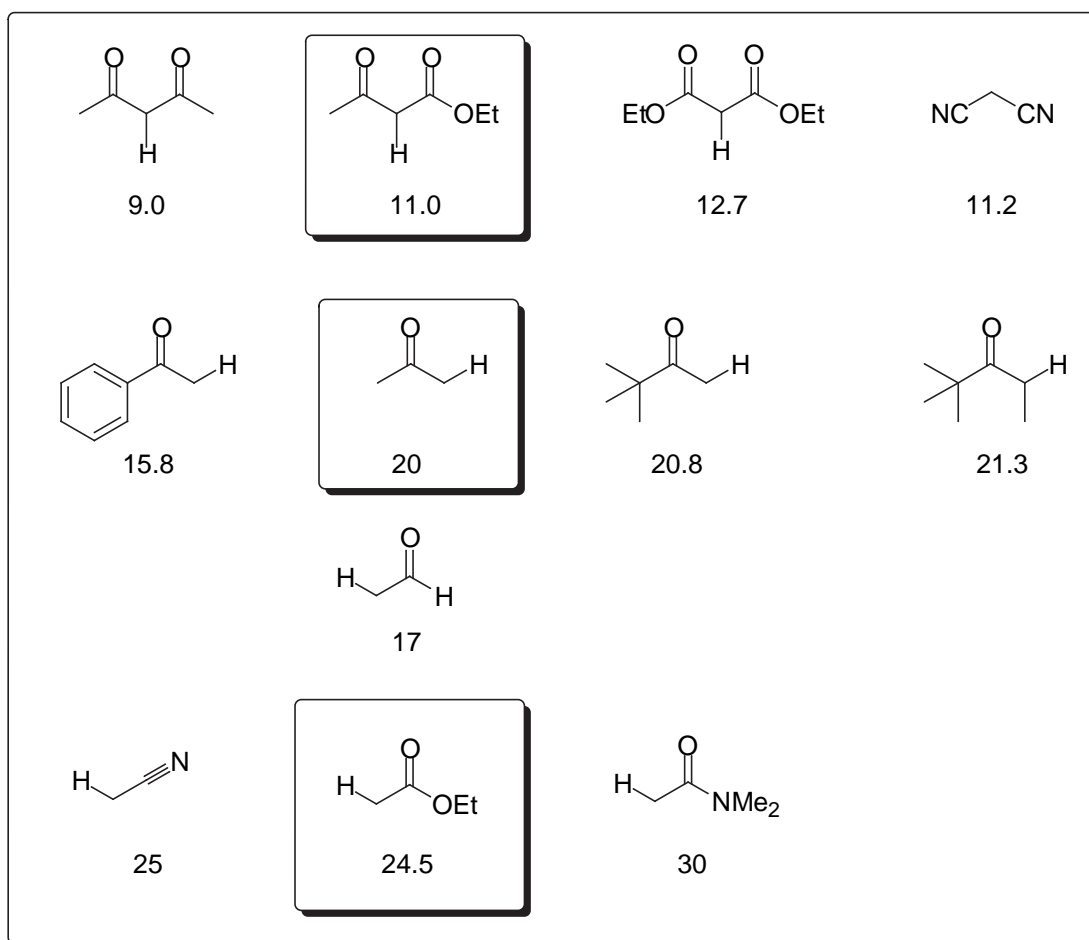
Formation of Enolates

Treat a ketone with an appropriate base and it is possible to deprotonate at the α -position to form an enolate:



Enolates are synthetically much more useful than enols (although they react analogously). We need to know what types of reaction conditions are required to form an enolate, specifically what bases we can use.

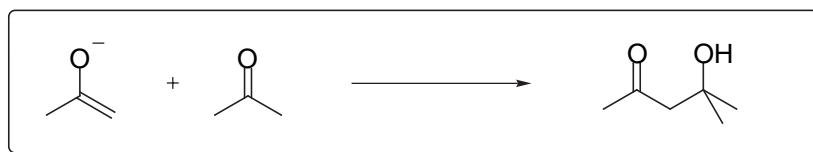
III.A.1 Some Important pK_a Values



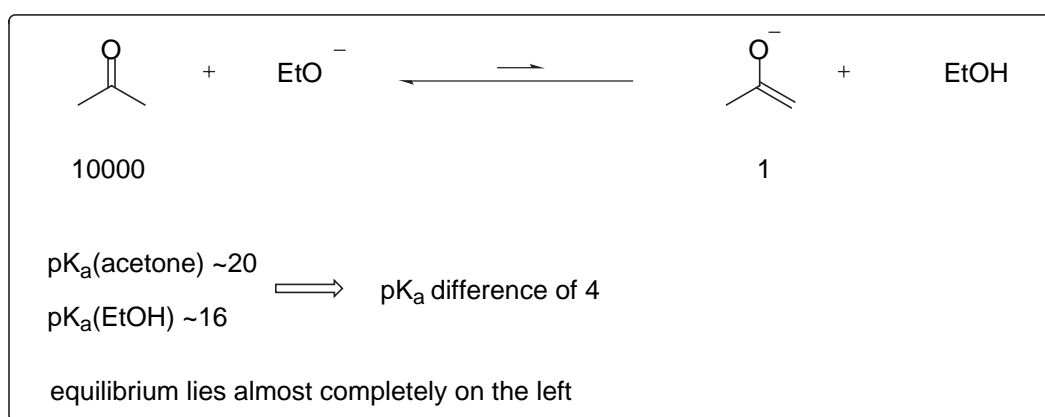
Make you can rationalise all the trends across this list of pK_a 's. It is worthwhile remembering by heart the pK_a values of the boxed compounds, as from these, you can provide a reasonable estimate of most other related systems.

By knowing the pK_a values of the relevant acidic protons in a carbonyl compound, it is possible to predict suitable bases for forming the corresponding enolates.

Enolates are nucleophiles and ketones are electrophiles - therefore there is always a potential problem of self condensation.



Sometimes this is the desired transformation, in which case we need to use a base that does not completely deprotonate the carbonyl compound *i.e.* set up an equilibrium. This is best achieved when the pK_a of the carbonyl group and conjugate acid (of the base) are similar:



$pK_a(\text{t-BuOH}) \sim 18$; thus t-BuO^- is a stronger base. pK_a difference is now 2. Therefore the ratio of ketone to enolate will be of the order 100:1 *i.e.* there will be about 1% enolate in solution.

The greater is the difference in pK_a 's the more heavily shifted is the equilibrium (to either left or right).

When it is desirable to generate a ketone enolate in small quantities, an alkoxide base is ideal.

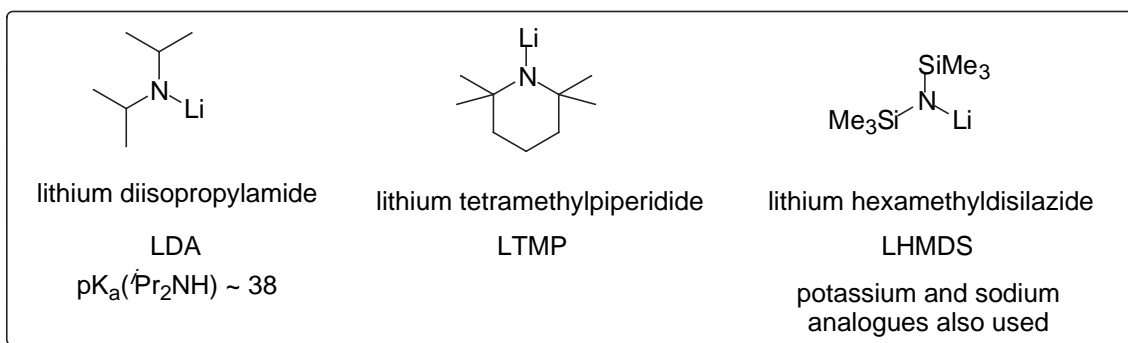
NOTE: all bases are potential nucleophiles. Alkoxide addition to the carbonyl group is reversible in the case of ketones and is therefore usually not a problem. Other side-reactions, e.g. dehydration of the aldol product, can be competing side-reactions and steps need to be taken to prevent such processes.

Using non-nucleophilic bases avoids many potential chemoselectivity problems. Most non-nucleophilic bases have the nucleophilic centre surrounded by sterically very demanding substituents.

Q? What if we want to avoid self-condensation?

A: Use a very strong base to shift the ketone-enolate equilibrium completely over to the right *i.e.* completely consume the ketone electrophile before it can react with the enolate nucleophile.

III.A.2 Important 'Strong' Bases for forming enolates from ketones:



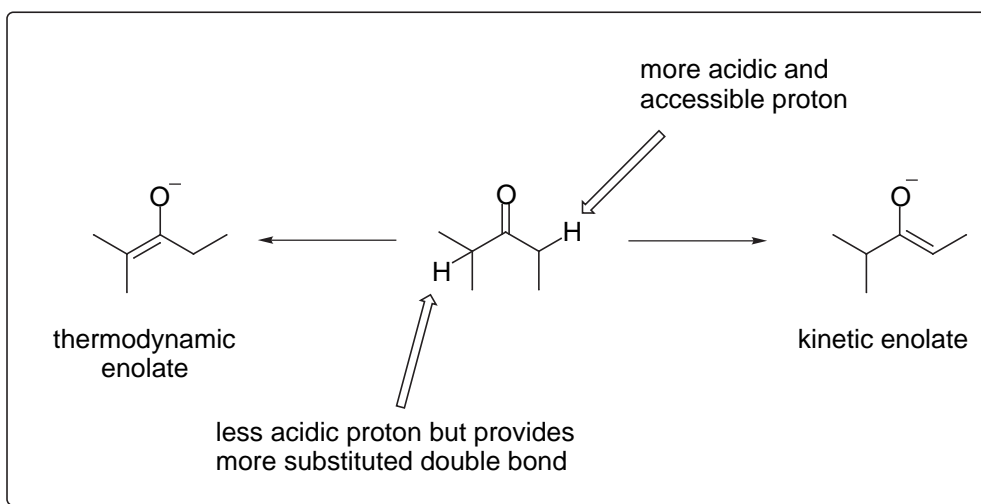
So for LDA the pK_a difference between acetone (20) and diisopropylamine (38) is 18 (*i.e.* massive). Consequently treatment of a ketone with 1 equivalent of LDA causes essentially complete deprotonation of all the ketone that is present to form the corresponding lithium enolate.

Q? Butyllithium is an excellent base (stronger than any lithium amide) but is only very rarely used to form enolates from ketones. Why?

III.B Regioselective Enolate Formation

III.B.1 Kinetic *versus* Thermodynamic Control

Consider the following unsymmetrically substituted ketone. There are two sites of proton abstraction leading to two different product enolates. It is clearly important to be able to control the site of enolate formation. Ideally we should have two sets of reaction conditions for accessing selectively either enolate.



Although the pK_a difference between the two sites is only 1-2 units, this difference, when combined with the relative steric accessibility of the α -protons, is usually enough to be able to form selectively the *kinetic* enolate.

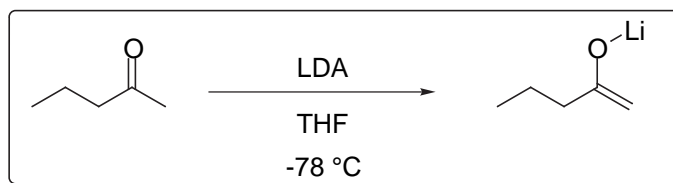
NOTE: the more substituted enolate is not always the thermodynamically more stable enolate: in some cases steric hindrance can destabilise the more substituted enolate. In these cases the kinetic and thermodynamic enolate are the same product.

Enolate formation is just an acid-base reaction. The position of the equilibrium is controlled by a variety of factors:

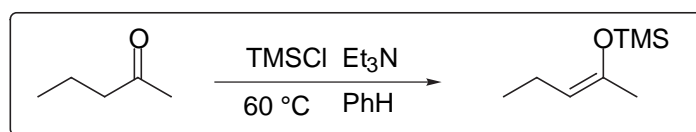
- solvent
- base
- cation
- temperature

factors favouring the formation of the kinetic enolate	factors favouring the formation of the thermodynamic enolate
aprotic solvents e.g. THF, Et ₂ O (no acidic proton to encourage the reverse reaction)	protic solvents e.g. ROH which have slightly more acidic protons than the enolate and favour formation of the enol allowing tautomerisation to the ketone (i.e. the reverse reaction)
strong bases e.g. LDA (which generate a weak conjugate acid (e.g. ⁱ Pr ₂ NH) specifically one which is less acidic than the enolate product).	weaker bases which provide a relatively strong conjugate acid.
oxophilic cations e.g. Li ⁺	
low temperature (e.g. < -78 °C)	higher temperature
short reaction times	long reaction times
<i>All these conditions suppress equilibration and ensure the reaction is essentially irreversible.</i>	<i>All these conditions encourage the reverse reaction</i>

III.B.1.i Formation of the Kinetic Enolate



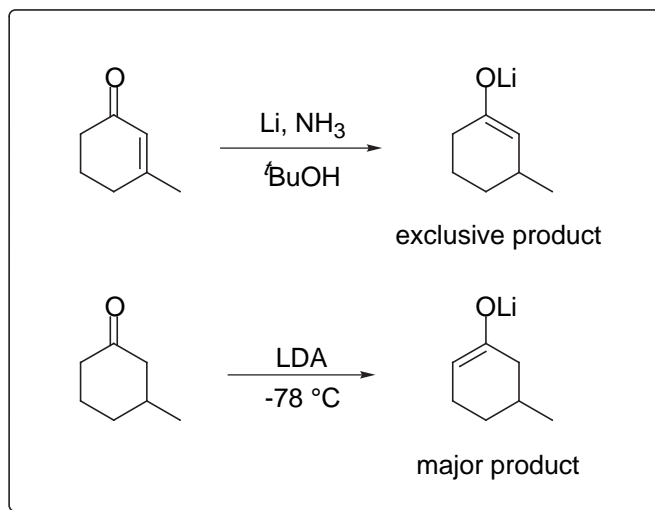
III.B.1.ii Formation of the Thermodynamic Enolate



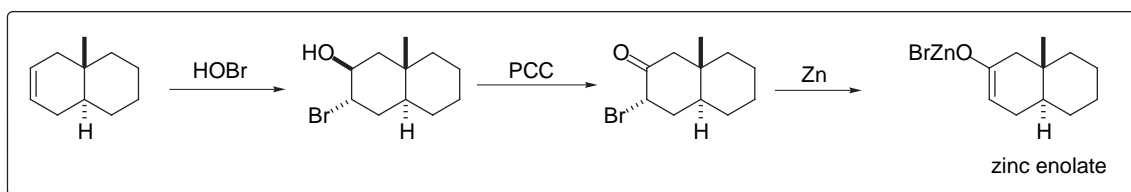
III.B.1.iii Other methods of regioselective enolate formation

It is not always necessary to rely on kinetic or thermodynamic control for forming enolates. In many cases chemical modification of pre-existing functionality (especially α,β -unsaturated ketones) can be used to regioselectively introduce the enolate:

Example 1. enone reduction

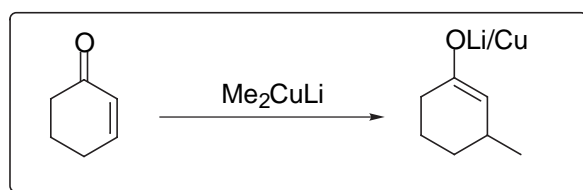


Example 2. from α -bromo ketones

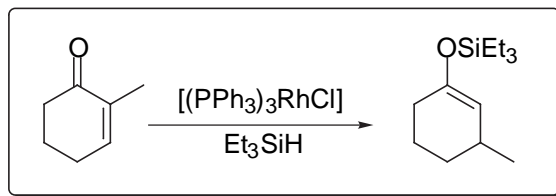


Make sure you can rationalise the selectivity in the above reactions.

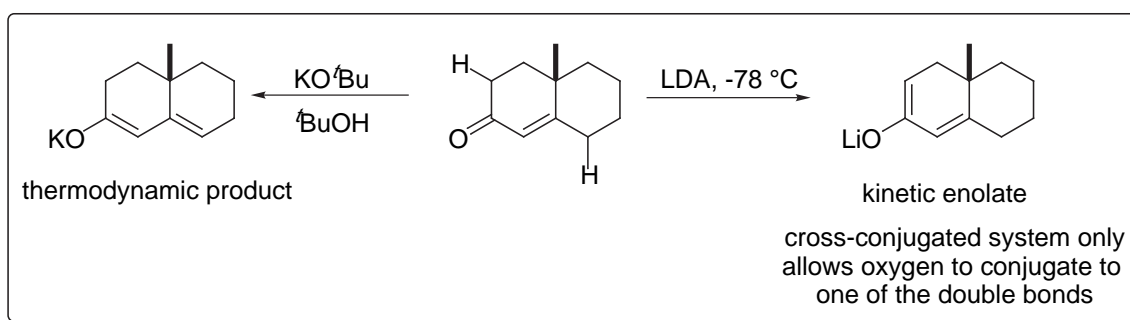
Example 3. conjugate addition of soft nucleophiles such as cuprates to enones



Example 4. Hydrosilylation of enones.



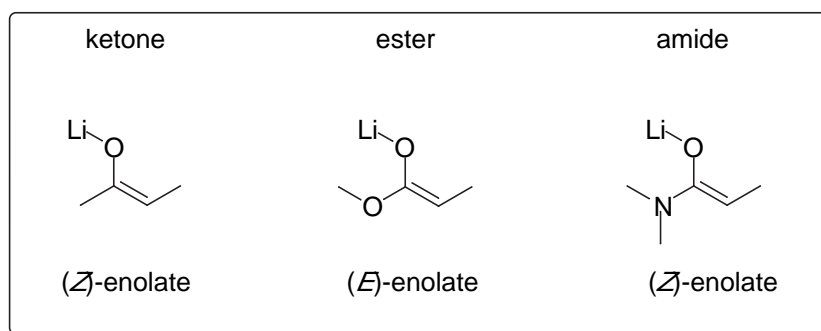
Example 5. Direct deprotonation of enones.



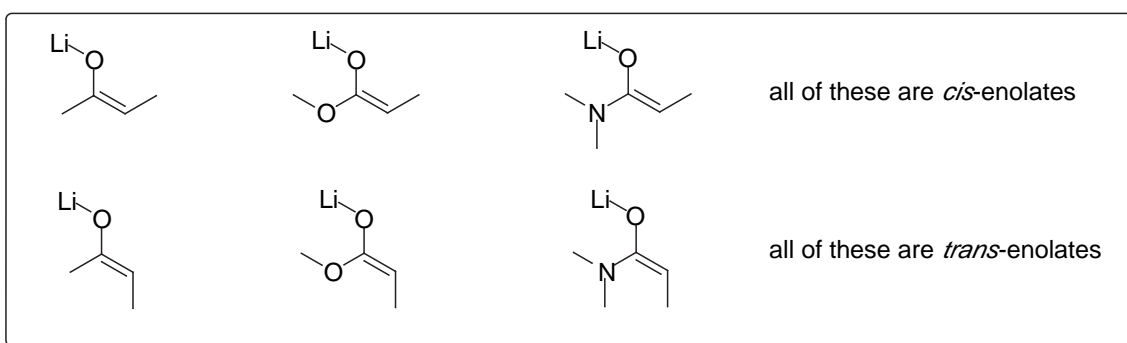
III.C Stereoselective Enolate Formation - Control of *cis/trans* Enolate Geometry

A note on stereochemical nomenclature:

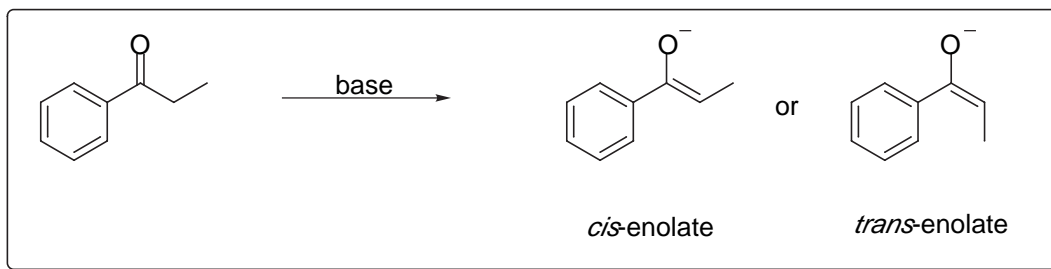
(*Z*) and (*E*) descriptors are usually used to assign the configuration of double bonds. Under normal circumstances this is more desirable than using the *cis* and *trans* nomenclature. However confusion can arise when assigning the configuration of enolates. Some examples will illustrate the point:



Therefore, in order to avoid confusion, when going from one functional group to another, we will use the *cis* and *trans* nomenclature in which the O-metal bond of the enolate always takes priority on that end of the olefin:

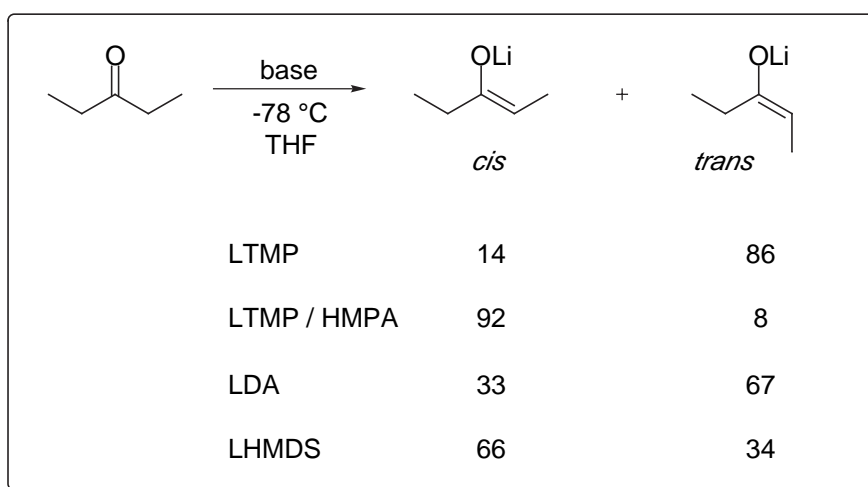


We will see later that the geometry of a substituted enolate (*cis* or *trans*) can be very important in determining the stereochemical outcome of aldol reactions. In many cases the aldol reaction is stereospecific; thus if we can access either enolate geometry at will, it should be possible to control the stereochemistry in the aldol products. This is crucial when preparing polypropionate natural products.



Make sure you know how to assign stereochemical descriptors to enolates.

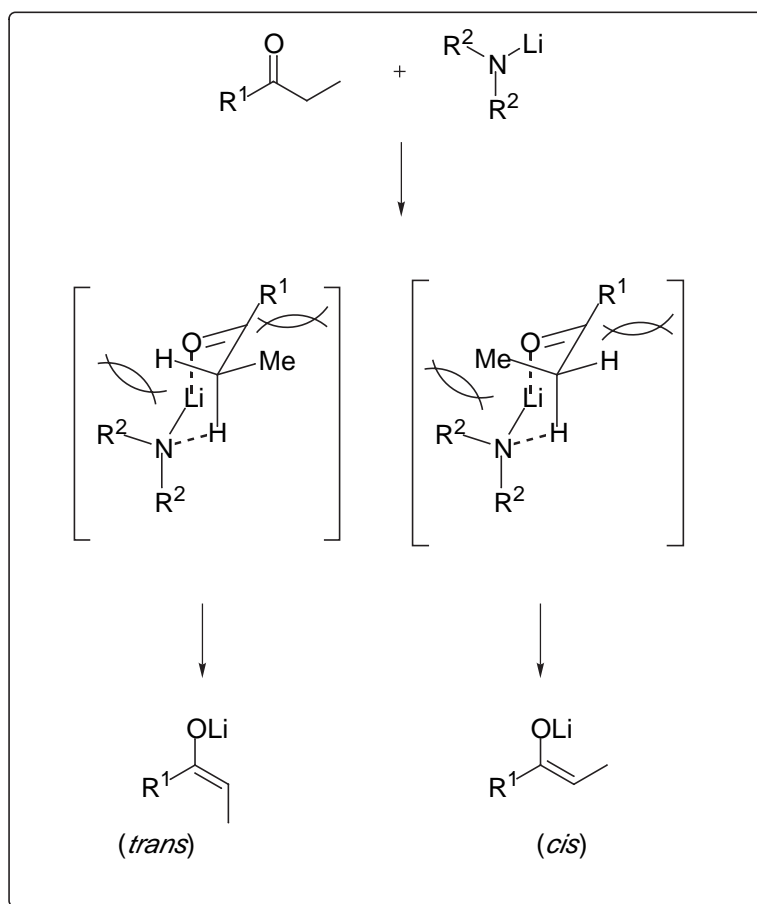
Consider the formation of lithium enolates using a variety of bases (kinetic control).



General observations:

- 1) LHMDS generally provides the *cis*-enolate as the major product
- 2) LTMP (very bulky) affords the *trans*-enolate as the major product
- 3) LDA gives intermediate results.
- 4) use of HMPA as a strongly Lewis basic donor-co-solvent can reverse selectivity.

Ireland has provided a rationale using chair-like transition states (there is little physical evidence to show that this model is an accurate representation of the deprotonation reaction).



Two interactions are deemed important for determining the stereochemical outcome of the reaction.

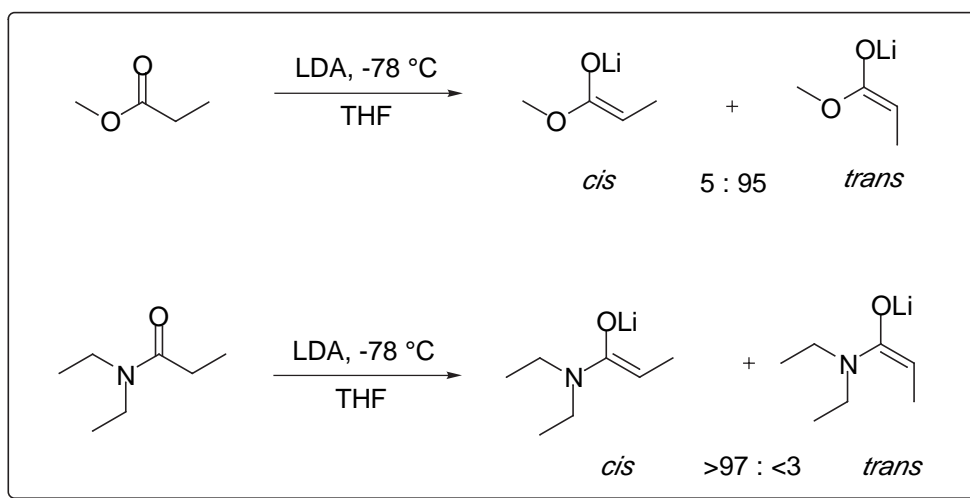
- 1) when R^1 is NOT sterically demanding and when $H \leftrightarrow R^2 \ll Me \leftrightarrow R^2$ then the *trans*-stereoisomer is favoured.
- 2) when R^1 is large (tBu is especially good) then $Me \leftrightarrow R^1 \gg H \leftrightarrow R^1$ and this overrides the $Me \leftrightarrow R^2$ interaction favouring the formation of the *cis*-stereoisomer.

The use of strongly coordinating solvents such as HMPA disrupts the transition state and the system is more complicated.

Cautionary note: the T.S. described in the Ireland model invokes a monomeric organolithium species. In reality organolithium molecules exist as oligomers (tetramers, hexamers etc). The Ireland model while fairly useful, is a gross oversimplification of the real situation.

Esters and amides also form enolates on treatment with a strong base (α -proton is less acidic in both cases than in a ketone).

In the case of esters, the *trans*-enolate is favoured whereas tertiary amides tend to form *cis*-enolates.

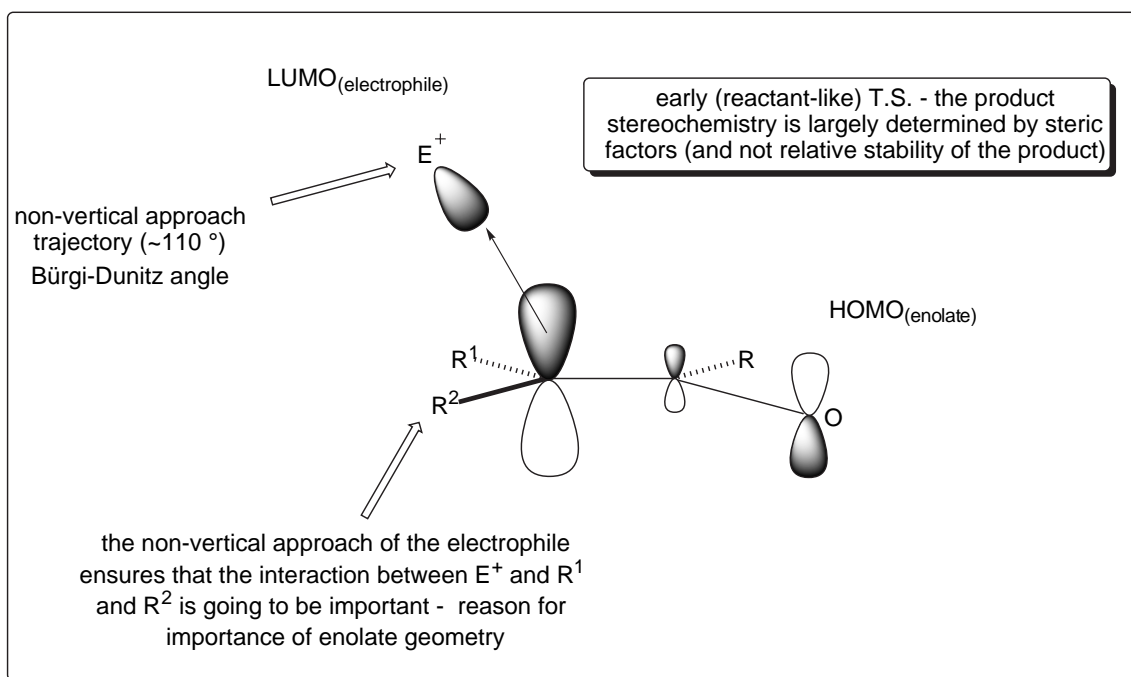


Q? Where is the most acidic proton in a primary and secondary amide? The amide enolate can still be formed - how much base is required?

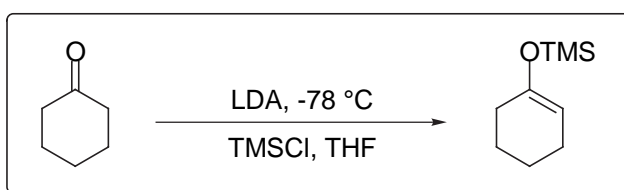
III.D Reactions of Enolates

- enolates are ambident nucleophiles and can react at either oxygen or carbon terminus.
- SOFT electrophiles (e.g. most carbon electrophiles) tend to react at carbon (soft centre).
- HARD electrophiles tend to react at oxygen (hard centre).

You should understand the differences between hard and soft centres according to frontier molecular orbital theory and electrostatics.

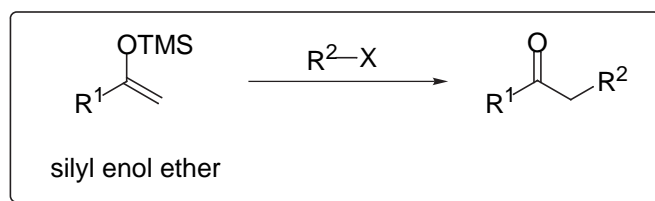


III.D.1 Silyl Enol Ethers



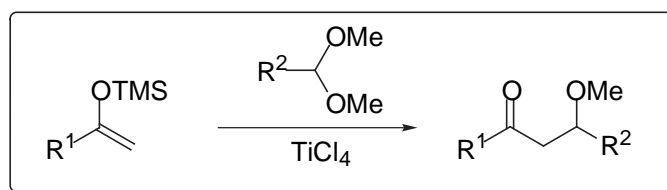
- readily formed by trapping a lithium enolate with TMSCl.
- The strong Si–O bond is responsible for O-alkylation being the major product.
- less nucleophilic than metal enolates (lithium, zinc, boron etc)
- easily prepared and readily manipulated.

III.D.1.i Alkylation with alkyl halides



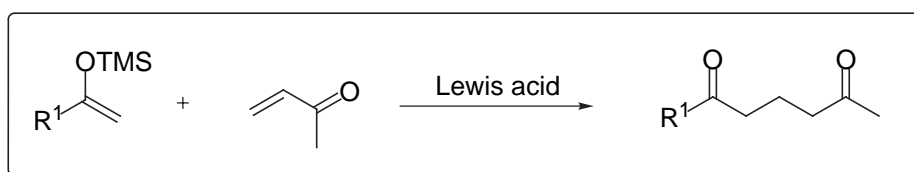
- reaction is most efficient in the presence of a Lewis acid which complexes to the halogen making it a better leaving group.
- tertiary alkyl halides, allylic and benzylic systems are particularly good electrophiles - all these systems are capable of stabilising positive charge which implies the reaction is proceeding via an S_N1 -type pathway.

III.D.1.ii Alkylation with Acetals



Q? What is the mechanism of this reaction?

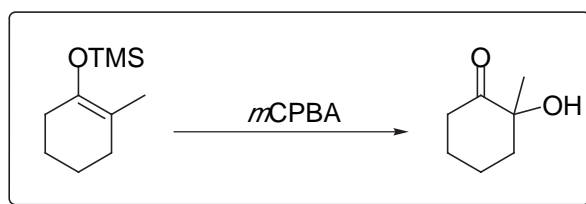
III.D.1.iii Reaction with Enones



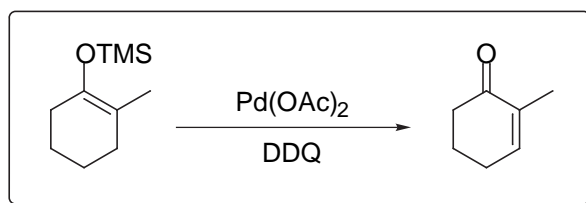
- reaction proceeds in a conjugate (Michael or 1,4-) fashion.

III.D.1.iv Oxidation of Silyl Enol Ethers

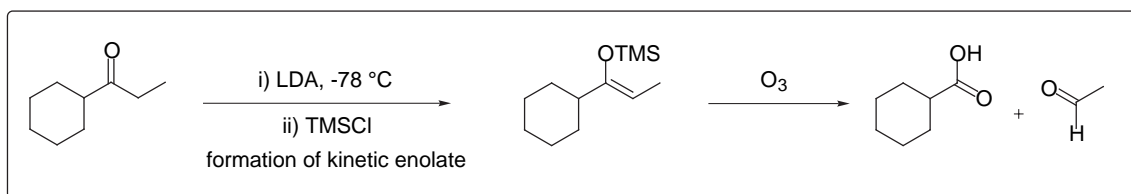
1. α -Hydroxylation of Ketones



2. Ketone \rightarrow Enone

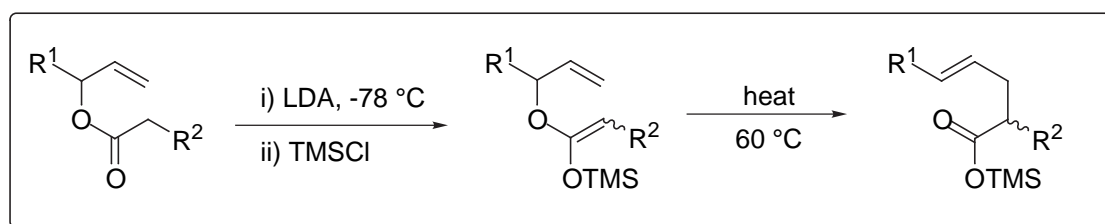


3. Oxidative Cleavage



III.D.2 Rearrangement of Silyl Enol Ethers

Claisen Rearrangement (an example of a [3,3]-sigmatropic shift)

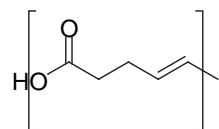


Q? How would you prepare the starting material?

Q? What is the driving force of the rearrangement reaction?

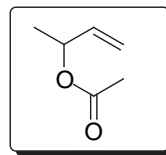
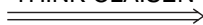
This is an important example of STRATEGIC PATTERN RECOGNITION

If you see this:



difficult to synthesise

THINK CLAISEN

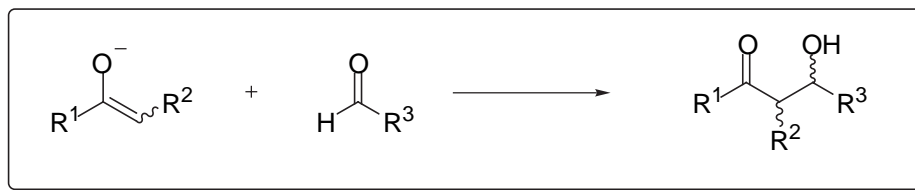


This is much easier to prepare



This is the Claisen **RETRON** *i.e. it is an enabling structural unit from which the required product can be made using a Claisen rearrangement*

III.E The Crossed Aldol Reaction



- one of the most important methods of C–C bond formation
- very widely used in organic synthesis

All the issues (and more) we have discussed previously now become very important:

- 1) regioselective enolate formation (kinetic and thermodynamic enolates)
- 2) complete or partial enolisation (self vs. cross condensation)
- 3) stereochemistry of the enolate (*cis* or *trans*)
- 4) simple diastereoselection - (*syn* and *anti* aldol products)
- 5) diastereofacial selectivity (this becomes important when chiral aldehydes react with achiral enolates and when achiral aldehydes react with chiral enolates)
- 6) double diastereodifferentiation (reaction of chiral aldehydes with chiral enolates) - matched and mismatched pairs.

In the crossed aldol reaction, the enolate of one carbonyl group reacts with the carbonyl group (usually an aldehyde) of another. To avoid self condensation, the enolate component is invariably formed beforehand.

We will consider the reaction of three types of enolate:

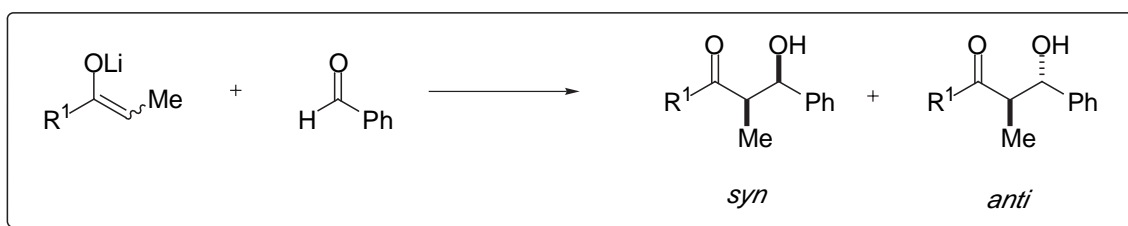
- lithium enolates (see above)
- boron enolates
- silyl enol ethers

III.E.1 Lithium Enolates in the Aldol Reaction

Reaction of lithium enolates provides a good grounding to aldol chemistry.

Simple Diastereoselection

Let us consider the reaction of achiral enolates (derived from ethyl ketones) with achiral aldehydes. There are two possible products termed *syn* and *anti*. Consider the reaction of various lithium enolates with benzaldehyde PhCHO:



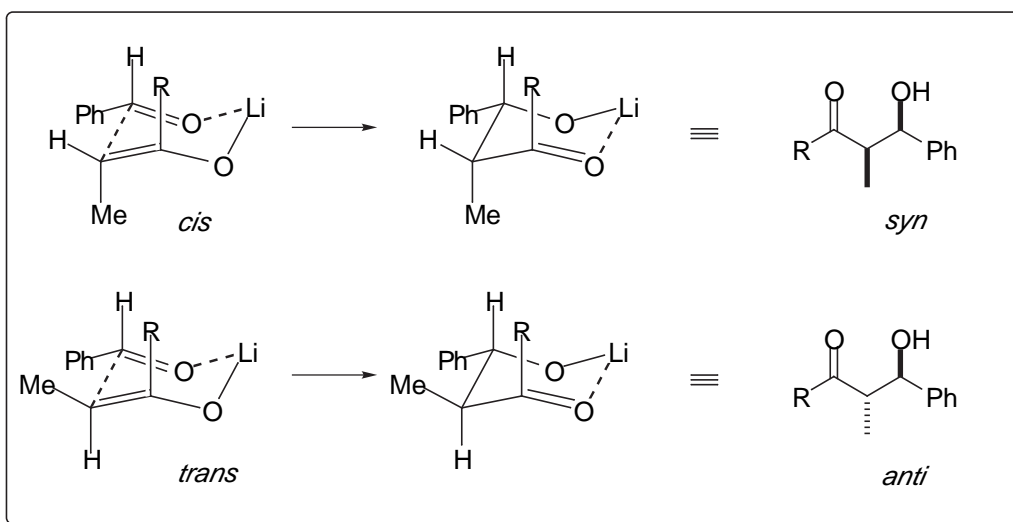
R ¹	<i>cis</i> : <i>trans</i> ratio of lithium enolate	<i>syn</i> : <i>anti</i> ratio of aldol product
Et	30 : 70	64 : 36
ⁱ Pr	0 : 100	45 : 55
ⁱ Pr	>98 : <2	90 : 10
^t Bu	>98 : <2	>98 : <2
mesityl (2,4,6,-trimethylphenyl)	8 : 92	8 : 92

Observations:

- the reaction is *sometimes* highly stereoselective (stereospecific too)
- stereospecificity is observed when R¹ is large (^tBu or mesityl)
- reaction is not always completely stereospecific in these cases in that the *cis/trans* stereochemistry of the enolate is not transferred directly to a similar ratio of *syn:anti* products. This suggests some equilibration or isomerisation processes are also occurring, or perhaps telling us something about the reaction mechanism and T.S.
- *cis*-enolates are more stereoselective than *trans*-enolates
- when the reaction is stereospecific, *cis*-enolates give *syn* products and *trans*-enolates afford the *anti* diastereoisomers.

Q? How can we rationalise some of these observations?

Reaction through a chair-like Zimmerman-Traxler T.S. is useful.



This reaction T.S. accounts for the stereospecificity of the reactions. More refined T.S.s have been developed to rationalise the reduced stereoselectivity of *trans*-enolates.

Note however that the requirement for i) a bulky group α -to the enolate, ii) a good method for stereoselective formation of lithium enolates, and iii) their relatively high basicity restricts the synthetic utility of Lithium enolates. The search for increased stereocontrol has led to the development of boron enolates.

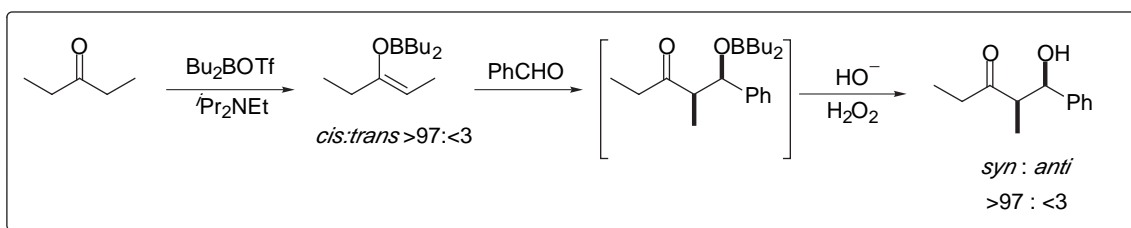
III.E.2 Boron Enolates in Aldol Reactions

- usually much more stereoselective than lithium enolates
- reaction is highly stereospecific: the *cis*-boron enolate gives the *syn* aldol product; the *trans*-boron enolate provides the *anti* aldol product.
- the stereospecificity can be readily rationalised by invoking chair-like Zimmerman-Traxler T.S.s (see above)
- The shorter B–O bond - compared with Li–O. This results in a tighter T.S. and accounts for the improved stereoselectivity.

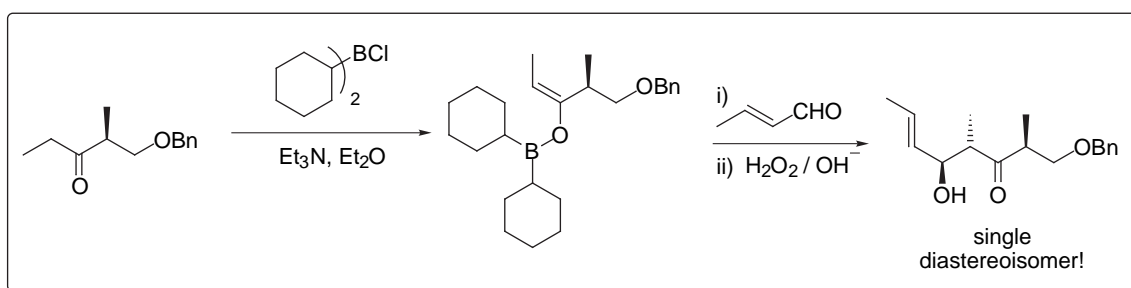
Preparation of Boron Enolates

Usually formed from a dialkylboron halide or triflate and a sterically hindered tertiary amine base such as triethylamine or Hünig's base ($i\text{-Pr}_2\text{NEt}$).

Example



- Under most conditions, *cis*-boron enolates are formed with high stereoselectivity
- *trans*-boron enolates can be formed under carefully chosen reaction conditions (e.g. $(\text{cyclohexyl})_2\text{BCl} / \text{Et}_3\text{N}$ in Et_2O):

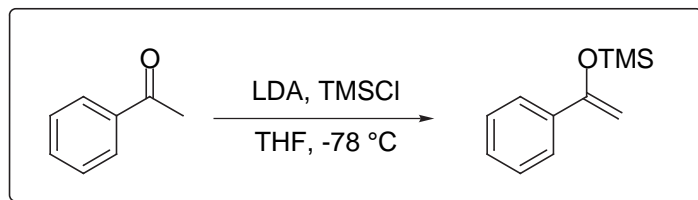


- Note that water is not sufficient to cleave the O–B bond efficiently in the aldol product. Oxidative cleavage with alkaline peroxide is the standard method of work-up. **You should know the mechanism of this cleavage reaction.**

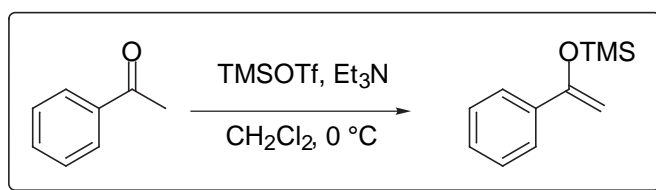
III.E.3 Silyl Enol Ethers in Aldol Reactions (Mukaiyama Aldol Reaction)

Preparation of TMS enol ethers

i) basic conditions - trap lithium enolate

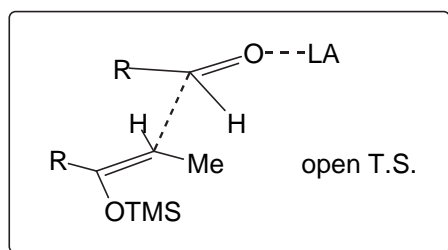


ii) Lewis acidic conditions - TMSOTf or TMSCl in the presence of a tertiary amine (requires temperatures >0 °C).



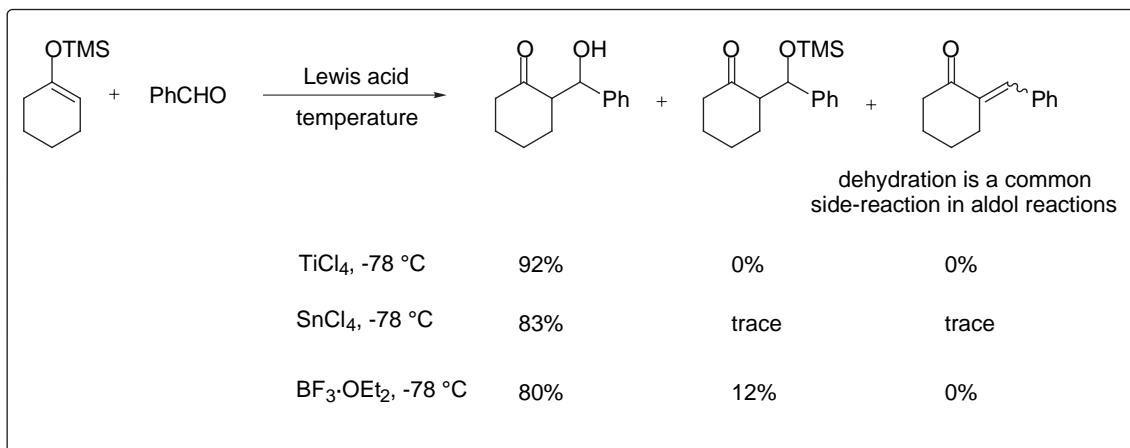
III.E.3.i Mukaiyama Aldol Reaction

- TMS enol ethers are much less nucleophilic than boron or lithium enolates and do not react directly with aldehydes
- Lewis acid complexation increases the electrophilicity of aldehydes and this is sufficient to allow reaction.
- the reaction mechanism is quite different to that of lithium or boron enolates described above. Internal coordination and reaction through a 6-membered T.S. is not possible with silicon since the silicon atom is not Lewis acidic.
- reaction proceeds through an open T.S.

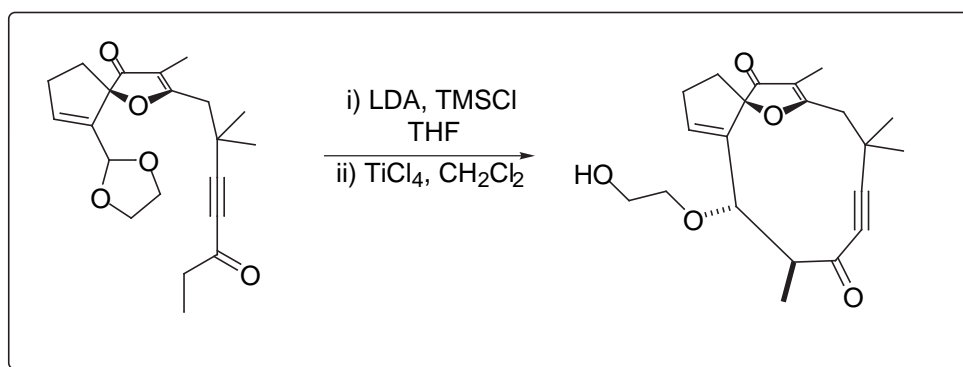


- stereoselectivity of the reaction is usually low (this can be attributed to there being several low energy T.S.s through which reaction can proceed).

Examples:



- The Lewis acid activation conditions allow the use of acetals as masked aldehydes.

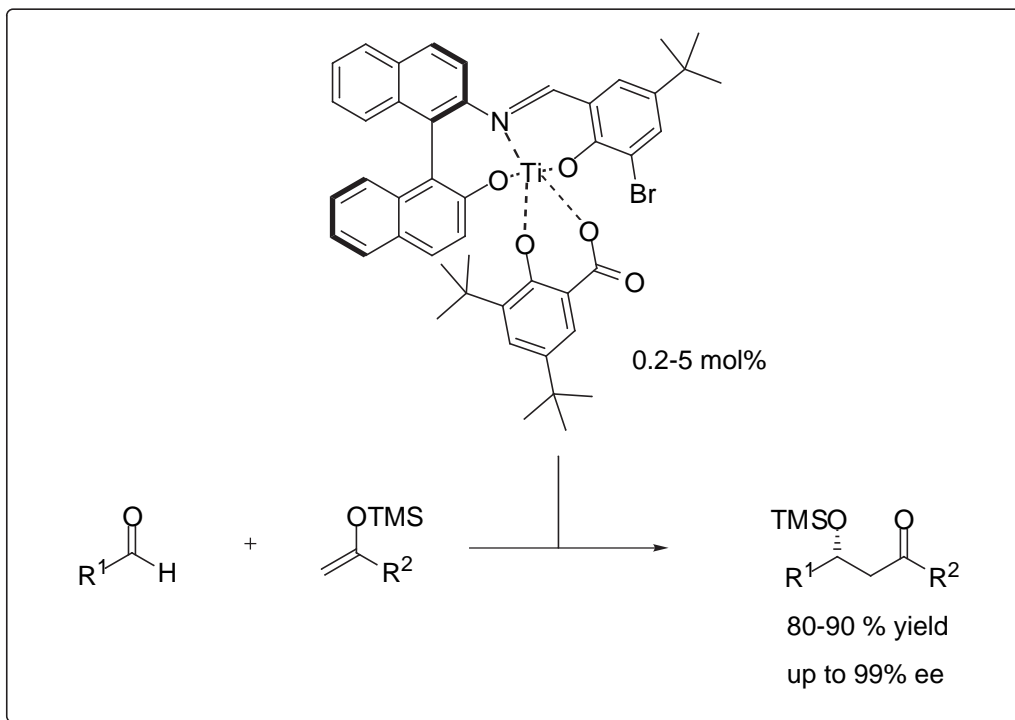


- The use of chiral Lewis acids in sub-stoichiometric quantities provides one important method for controlling the stereoselectivity of this reaction and is rapidly becoming a very useful method. One example developed by Carreira will serve to illustrate the idea:

E. M. Carreira *et al.*, *J. Am. Chem. Soc.*, 1994, **116**, 8837-8838.

E. M. Carreira *et al.*, *J. Am. Chem. Soc.*, 1995, **117**, 3649-3650.

E. M. Carreira *et al.*, *J. Am. Chem. Soc.*, 1995, **117**, 12360-12361.



III.E.4 Diastereofacial Selectivity

So far we have discussed three types of enolate which sometimes give high levels of simple diastereoselectivity (*syn* or *anti* product) in the aldol reaction. In most cases, relative stereocontrol is determined by the geometry of the enolate (cyclic T.S. with boron or lithium enolates).

To control the absolute stereochemistry of the reaction requires π -facial selectivity. There are three methods for tackling this problem:

substrate control in which stereochemical information in the substrate(s) directs the stereochemical outcome of the reaction.

auxiliary control involves the use of a temporary directing group usually attached to the enolate.

reagent control in which chiral ligands on the metal enolate or a chiral Lewis acid provide the stereocontrol.

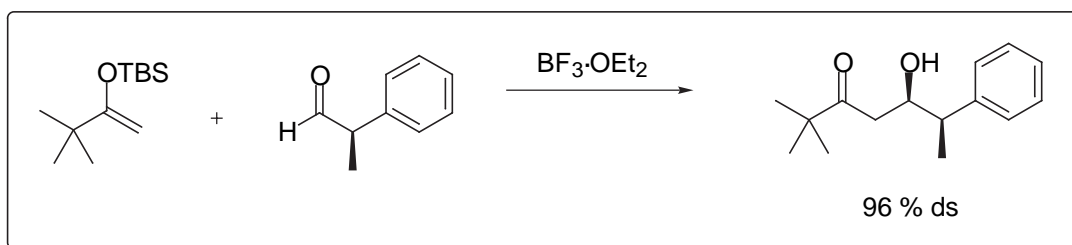
We will consider each in turn.

III.E.4.i Substrate Control

Chiral Aldehyde and Achiral Enolate

- Aldehydes which possess an α -stereogenic centre often react with high levels of stereocontrol.
- The nature of the groups attached to the stereogenic centre as well as the precise reaction conditions will determine which type of T.S. is adopted.

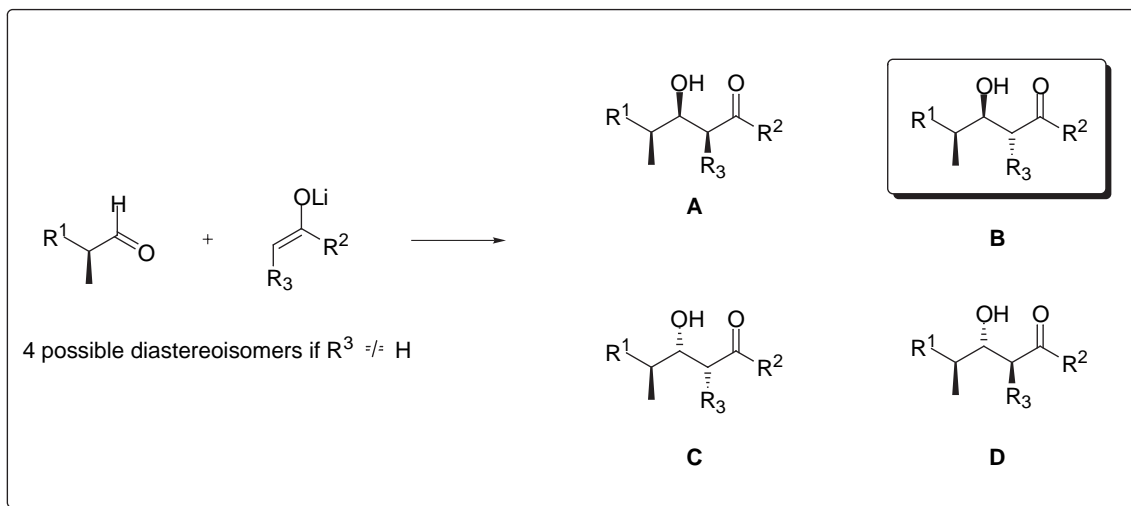
Example1



Make sure you can rationalise the outcome of this reaction using the Felkin-Anh T.S. model.

In the case of substituted enolates, relative *and* absolute stereocontrol must be considered. Use the enolate geometry to control the relative stereochemistry and the stereogenic centre in the aldehyde to control the π -facial (*i.e.* absolute) stereochemistry.

Example 2



The *trans*-enolate should provide the *anti* aldol product (cyclic T.S.) *i.e.* **B** and **D**.

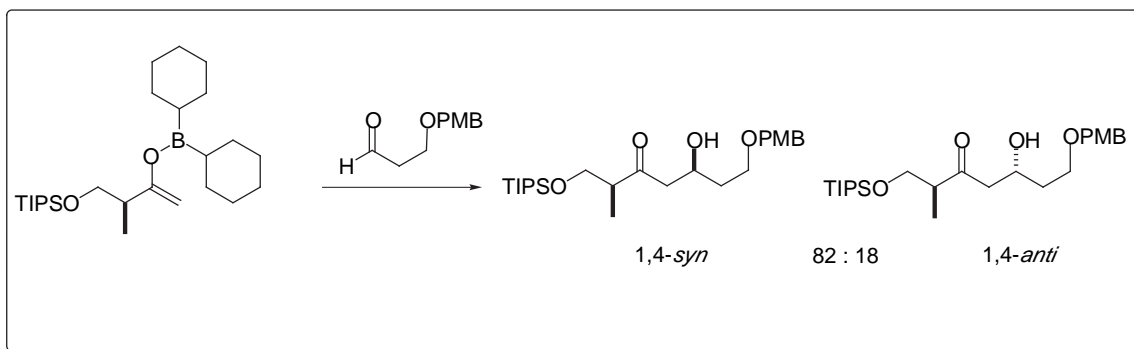
The α -stereogenic centre in the aldehyde favours product **B** (Felkin-Anh T.S.)

You should be able to predict that B will be the major product.

Chiral Enolate and Achiral Aldehyde

The presence of a stereogenic centre α -to the enolate can sometimes provide a good method for controlling diastereofacial selectivity.

Example



Double Diastereodifferentiation

The problem is complicated when both aldehyde and enolate substrates are chiral and possess controlling stereogenic centres (usually α).

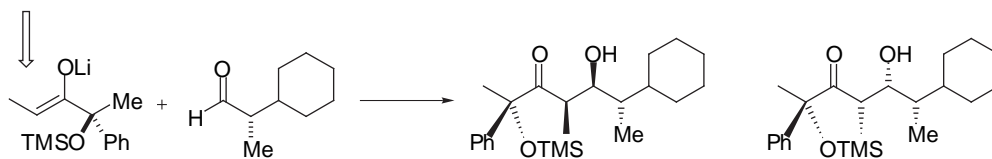
This is a common problem in complex natural product synthesis.

In this case each substrate has an inherent facial bias. When both substrates have the same bias, they reinforce the facial selectivity leading to improved stereoselectivity (reinforced stereoselection). **Matched** case.

When the inherent facial bias in one substrate opposes that in the other, stereoselectivity is reduced. **Mismatched** case.

One substrate usually exerts a stronger facial bias than the other and on occasion can completely override the inherent facial preference of its partner. In this case one substrate controls the stereochemical outcome entirely. This can be desirable.

cis-enolate will give the *syn* product



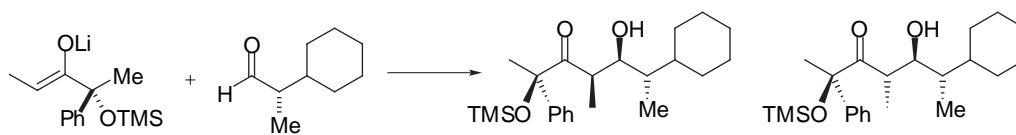
MATCHED CASE

major

9 : 1

minor

(both stereogenic centres have the same facial bias)



MISMATCHED CASE

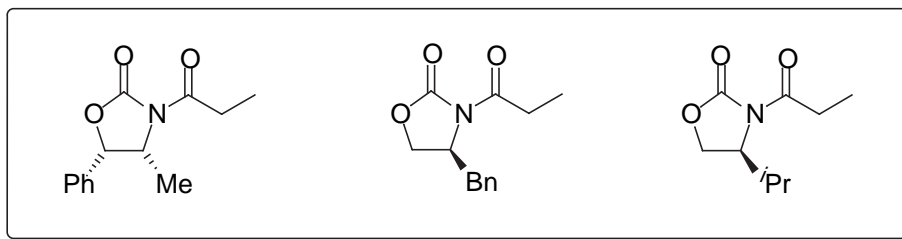
major

1.3 : 1

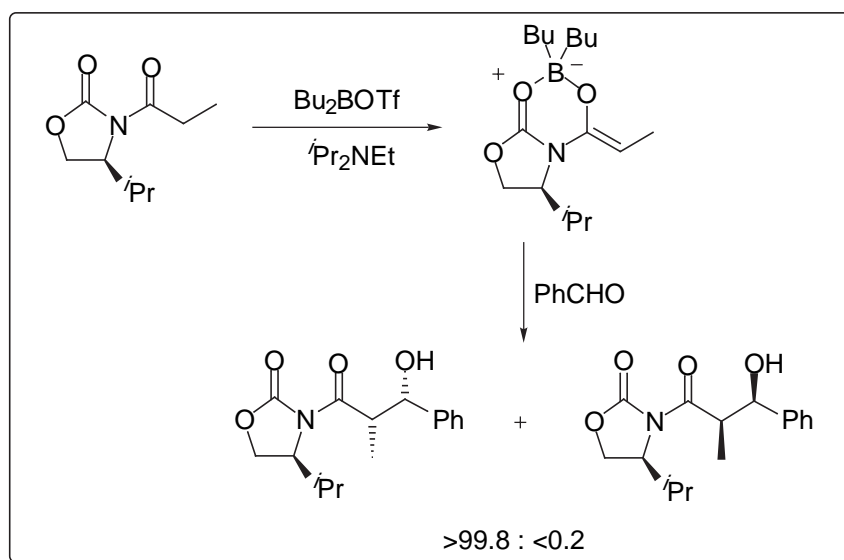
minor

III.E.4.ii Auxiliary Control

- many successful chiral auxiliaries have been developed for controlling the stereochemical outcome of the aldol reaction.
- only one example will be discussed here - chiral oxazolidinones developed by Evans.



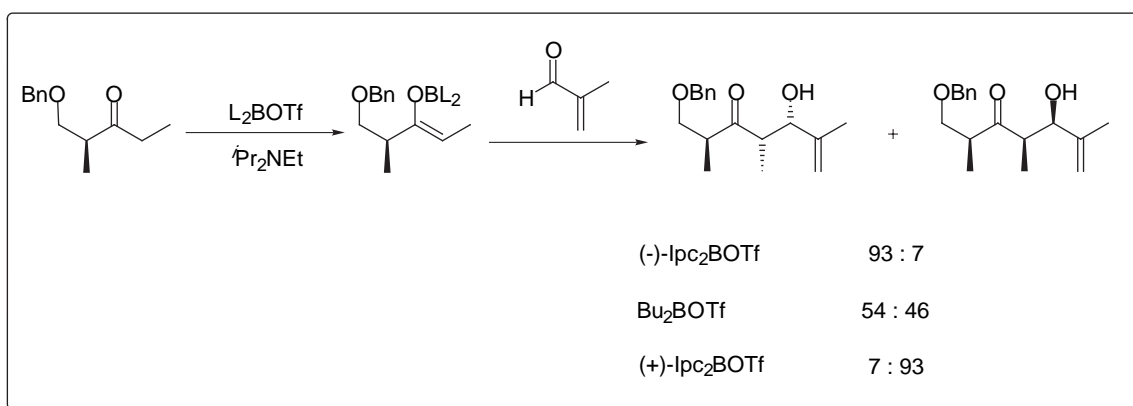
- Lithium enolates derived from these species give poor stereoselectivity
- Boron (and titanium) enolates however give excellent levels of stereocontrol
- *Cis*-enolates are invariably formed and reaction proceeds through a cyclic T.S. to provide the *syn* products (almost exclusively)
- The substituent(s) on the oxazolidinone controls the facial selectivity. The norephedrine-derived auxiliary provides one product and the phenylalanine- and valine-derived auxiliaries exert the opposite facial selectivity.
- These auxiliaries are so powerful in their facial directing ability that they often override the inherent facial bias of chiral aldehydes - (*i.e.* even the mismatched pair can provide high levels of stereoselectivity)



III.E.4.iii Reagent Control

- Use of chiral ligands at the metal centre provides an alternative and powerful approach to controlling the stereochemical outcome of reactions.
- The most widely used system is to prepare the boron enolate from (bis-isopinocampheyl)boron triflate or chloride.
- This system is usually used to reinforce or overturn the inherent stereochemical bias of a chiral ketone or aldehyde and is particularly useful at later stages of synthesis.

Example



Summary

Enolates are one of the most important classes of Carbon nucleophiles; their most important application is in the formation of β -hydroxy ketones in the crossed aldol reaction. This versatile functional motif is readily manipulated in a wide variety of stereoselective ways and finds particular application in the preparation of natural products derived from the polyketide biosynthetic pathway.

Before employing an aldol reaction as a key step in a synthesis all the usual issues of selectivity need to be considered and addressed. In the specific case of enolates the following factors are particularly important:

- 1) which base to form the enolate
- 2) is the thermodynamic or kinetic enolate required?
- 3) in the case of B-enolates the ligands on boron and the tertiary amine are important.

Zimmerman-Traxler chair-like T.S.s are very useful for determining the stereochemical outcome of the reaction of Li- and B-enolates with aldehydes (simple diastereoselection).

In the case of silyl enol ethers, these nucleophiles react with aldehydes and acetals under Lewis acid activation (Mukaiyama aldol reaction) through an open T.S. As a result, these reactions are often less stereoselective than those which can react through a closed T.S. Chiral Lewis acids however can be useful in imparting very high levels of stereoselectivity.

The chair T.S. is useful for evaluating simple diastereoselectivity. Other features however need to be considered when trying to account for the absolute stereochemical outcome of the reaction. In particular proximal stereogenic centres in the form of:

- 1) chiral auxiliaries
- 2) chiral Lewis acids
- 3) chiral ligands on the metal
- 4) other stereochemical information in either substrate, especially α -stereogenic centres.

When all things are considered the aldol reaction becomes a very powerful method for stereoselective C–C bond formation; the aldol disconnection is very often a *strategic bond disconnection* in a retrosynthesis.