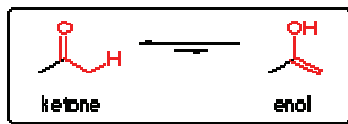


Enolate Chemistry

1. Some Basics

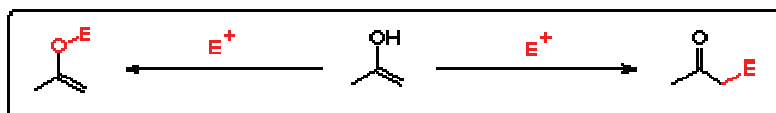


In most cases the equilibrium lies almost completely on the side of the ketone.

The ketone tautomer is electrophilic and reacts with nucleophiles:

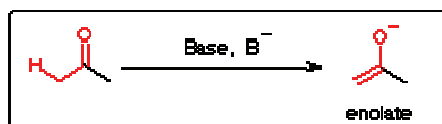


The enol tautomer is nucleophilic and reacts with electrophiles. There are two possible products - enols are *ambident* nucleophiles:



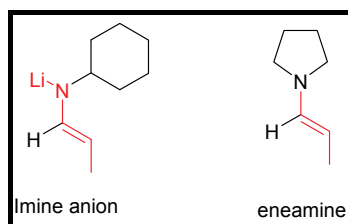
The nucleophilic enol tautomer (and especially the enolate variant) is one of the most important reactive species for C-C bond formation.

Treat a ketone with an appropriate base and can get deprotonation at the α -position to form an enolate:



Enolates are synthetically much more useful than enols (although they react analogously).

Imine anions and enamines are synthetic equivalents of enolate anions.



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

pK_a (*t*BuOH) \sim 18. A stronger base. pK_a difference of 2. Ratio of ketone to enolate will be of the order 100:1 *i.e.* there will be about 1% enolate in solution.

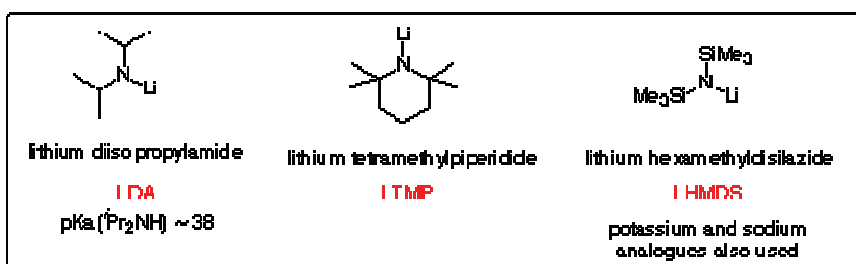
The greater is the difference in pK_a 's the more heavily shifted is the equilibrium (to either left or right).

When it is desirable to generate the enolate in small quantities, an alkoxide base is ideal (at least with standard ketones).

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. Ideally we want to use non-nucleophilic bases to avoid potential chemoselectivity problems. Most non-nucleophilic bases have the nucleophilic centre surrounded by sterically very demanding substituents.

How can we avoid self-condensation? Use a very strong base to shift the equilibrium completely over to the right.

Important 'Strong' Bases for Forming Enolates from Ketones:



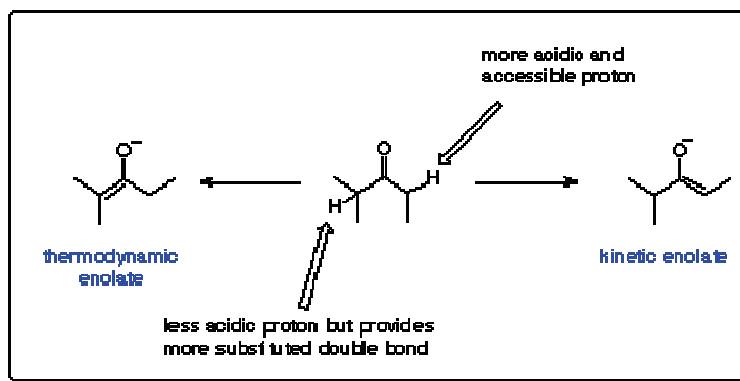
So for LDA the pK_a difference between acetone (20) and diisopropylamine (38) is 18 (*very large*). Consequently treatment of a ketone with 1 equivalent of LDA causes essentially complete deprotonation to form the corresponding lithium enolate.

Butyl Lithium (BuLi) is an excellent base and even stronger than any lithium amide, but is only very rarely used to form enolates from ketones. BuLi is a strong nucleophile with little steric hindrance.

2. Regioselective Enolate Formation

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.

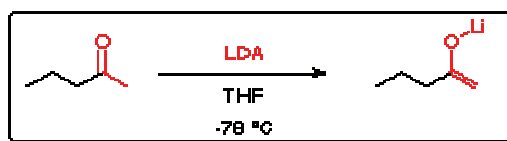
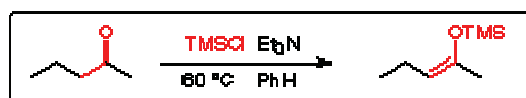


Although the pKa difference between the two sites is only 1-2 units, this difference, when combined with the steric accessibility of the α -protons, is usually enough to be able to selectively form the kinetic enolate.

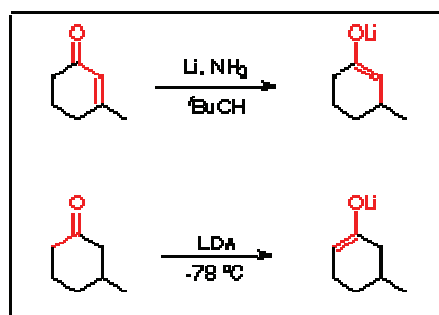
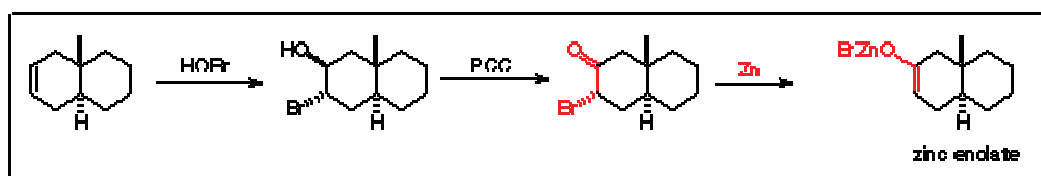
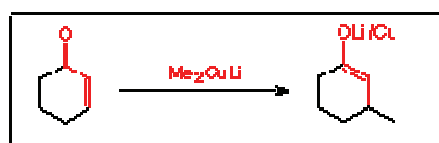
NOTE: The more substituted enolate is not always the thermodynamically more stable enolate; in some cases steric hindrance can destabilise the more substituted enolate; thus in these cases the kinetic and thermodynamic enolate are the same product.

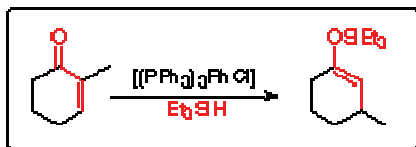
Enolate formation is essentially just an acid-base reaction. The position of the equilibrium is controlled by a variety of factors: **solvent, base, cation, temperature.**

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

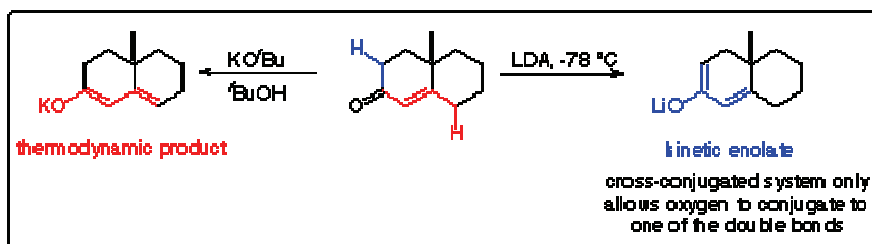
Formation of the Kinetic Enolate**Formation of the Thermodynamic Enolate****Other Methods of Regioselective Enolate Formation**

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****Example 3. Conjugate addition of soft nucleophiles such as cuprates to enones.****Example 4. Hydrosilylation of enones.**

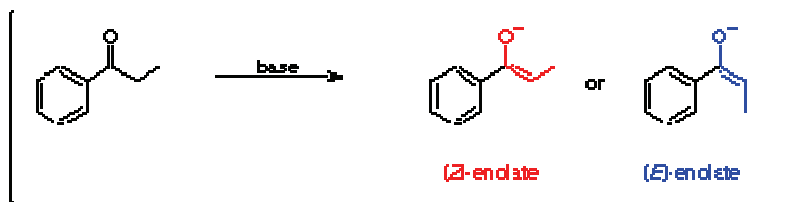


Example 5. Direct deuteration of enones.



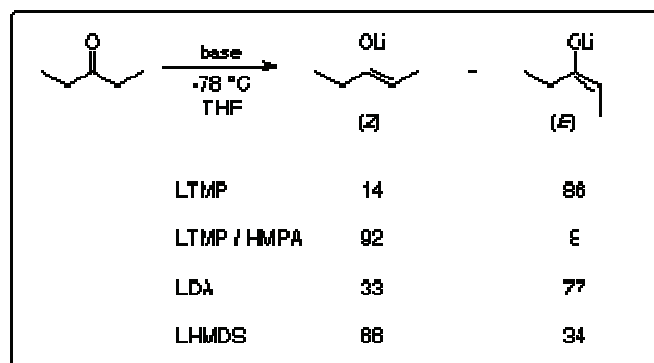
3. Stereoselective Enolate Formation - Control of *E*/*Z* Enolate Geometry

We will see that the geometry of a substituted enolate (*E* or *Z*) 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 for stereoselective synthesis.



Reminder: You must know how to assign stereochemical descriptors (E/Z) to enolates.

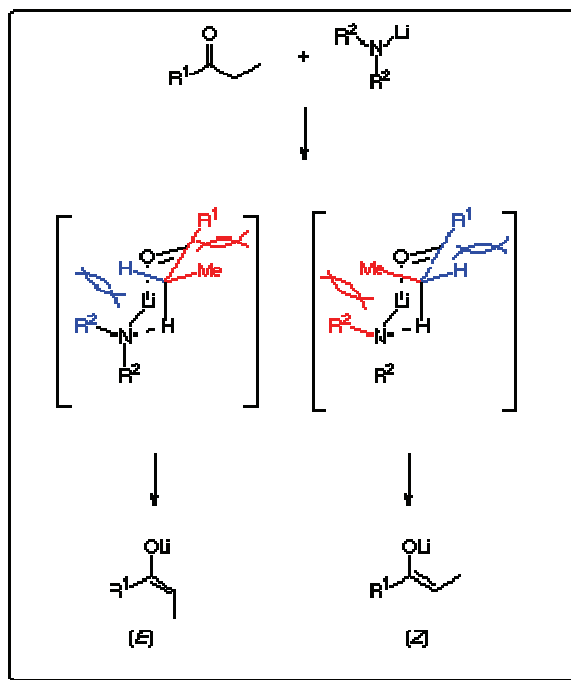
Consider the formation of lithium enolates using a variety of bases (kinetic control).



General observations:

1. LHMDS generally provides the (*Z*)-enolate as the major product
2. LTMP (very bulky) affords the (*E*)-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 (there is NO physical evidence to show that the model is an accurate representation of the deprotonation reaction) using chair-like transition states:



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

1. when R_1 is NOT sterically demanding or when $H \ll R_2 \ll Me \ll R_2$ then the (*E*)-stereoisomer is favoured.
2. when R_1 is large (*t*Bu is especially good) then $Me \ll R_1 \gg H \ll R_1$ and this overrides the $Me \ll R_2$ interaction and favours the formation of the (*Z*)-stereoisomer.

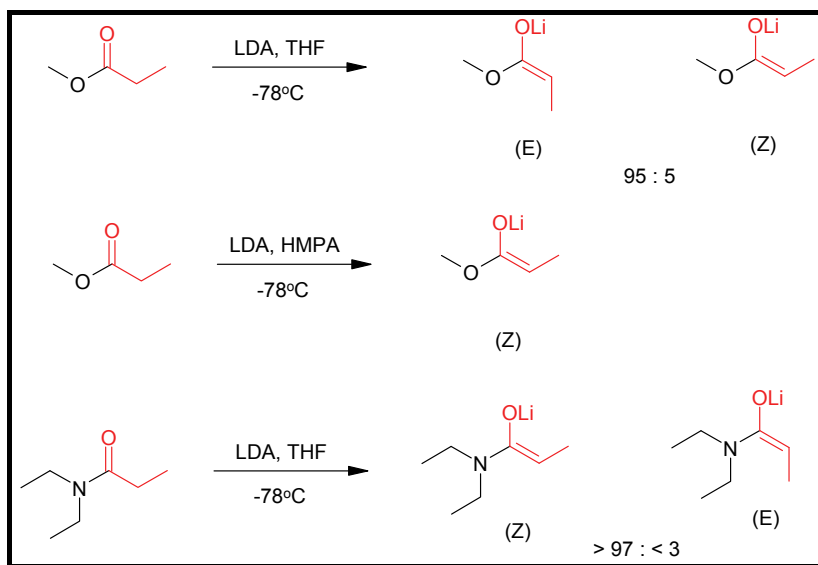
The use of strongly coordinating solvents such as HMPA disrupts the transition state and the system is more complicated.

Cautionary note: the T.S. described invokes a monomeric organolithium species. In reality organolithium molecules exist as oligomers (tetramers, hexamers *etc*). The Ireland model while fairly useful, is a 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 (*E*)-enolate is favoured with LDA in THF. Addition of HMPA leads to a preferential formation of the (*Z*)-enolate, which is explained by the strong solvation of the lithium ion by the HMPA leading to a loose, perhaps acyclic transition state. Tertiary amides

tend to form (*Z*)-enolates due to the steric hindrance of nitrogen substituents with the double bond substituent.

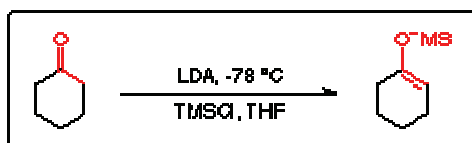


4. Reactions of Enolates

- 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).

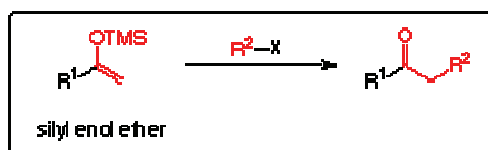
4.1. Silyl Enol Ethers

- 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.*).
- BUT they are easily prepared and readily manipulated.

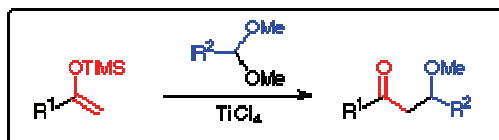
Alkylation with Alkyl Halides



- 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 the best - all these systems are capable of stabilising positive charge which implies the reaction is proceeding *via* an S_N1-type pathway.

Alkylation with Acetals



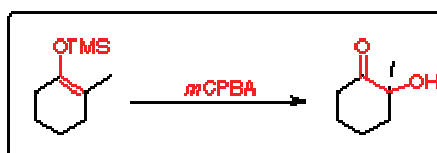
Reaction with Enones



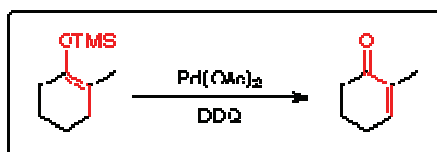
- Reaction proceeds in a conjugate (Michael or 1,4-) fashion.

Oxidation of Silyl Enol Ethers

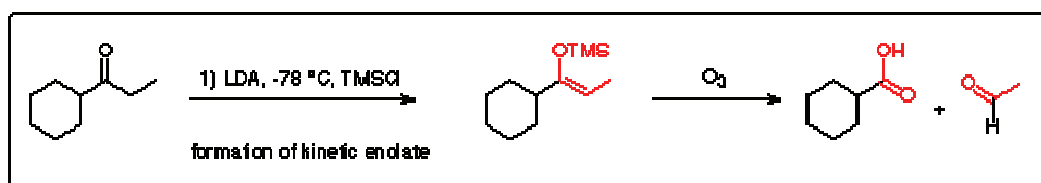
1.



2.

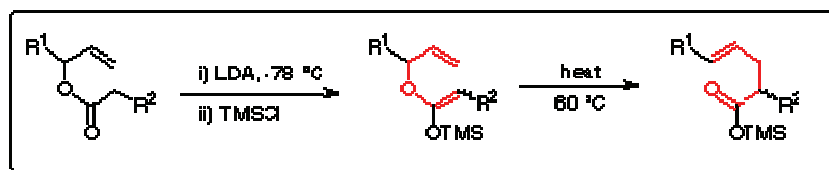


Oxidative Cleavage

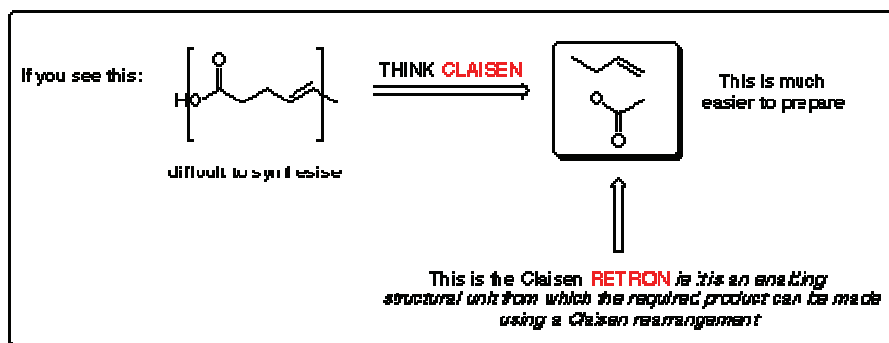


Rearrangement of Silyl Enol Ethers

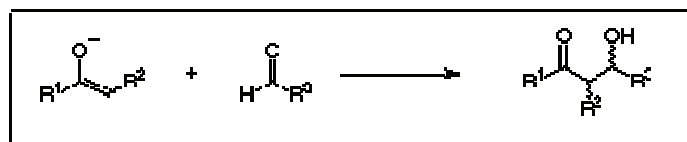
Claisen Rearrangement (an example of a [3,3]-sigmatropic shift)



This is an important example of STRATEGIC PATTERN RECOGNITION



4.2 The Crossed Aldol Reaction



- One of the most important methods for C-C bond formation.
- Very widely used in organic synthesis.

All the issues previously discussed (1-3) and more (4-6) 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 (*E* or *Z*)
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 formed beforehand.

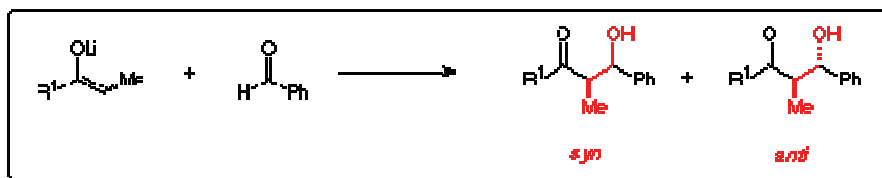
We will consider the reaction of three types of enolate:

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

Lithium Enolates in the Aldol Reaction

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:

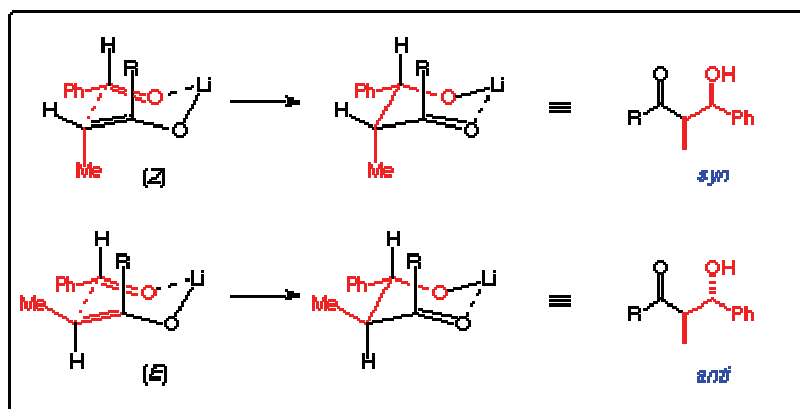


R(1)	(<i>Z</i>) : (<i>E</i>) ratio of lithium enolate	<i>syn</i> : <i>anti</i> ratio of aldol product
Et	30 : 70	64 : 36
<i>i</i> Pr	0 : 100	45 : 55
<i>i</i> Pr	>98 : <2	90 : 10
<i>t</i> Bu	>98 : <2	>98 : <2
mesityl (2,4,6-trimethylphenyl)	8 : 92	8 : 92

Observations:

- The reaction is *sometimes* highly stereoselective (stereospecific too).
- Stereospecificity is observed when R(1) is large (*t*Bu or mesityl).
- Reaction is not always completely stereospecific in these cases in that the (*E* / *Z*) 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.
- (*Z*)-enolates are more stereoselective than (*E*)-enolates.
- When the reaction is stereospecific, (*Z*)-enolates give the *syn* products and (*E*)-enolates afford the *anti* product.

Reaction through a chair-like Zimmerman-Traxler T.S. can rationalize the stereochemistry.



However the requirement for 1) a bulky group α -to the enolate and 2) a good method for stereoselective formation of lithium enolates has restricted the synthetic utility of these species. The search for increased stereocontrol has led to the development of boron enolates.

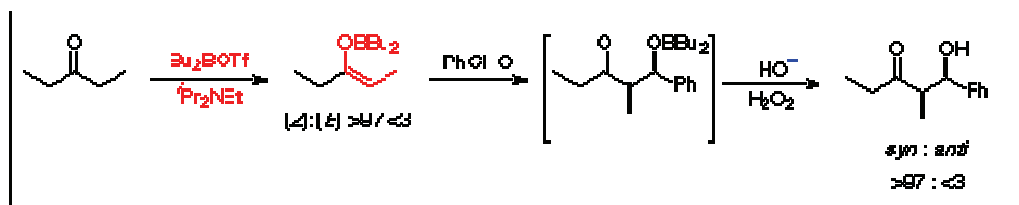
Boron Enolates in Aldol Reactions

- Usually much more stereoselective than lithium enolates.
- Reaction is highly stereospecific (*Z*)-boron enolate gives the *syn* aldol product and (*E*)-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 - leads to a tighter T.S. and accounts for the improved stereoselectivity.

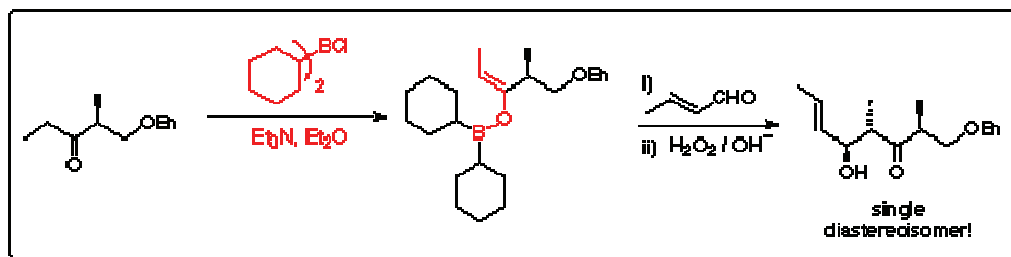
Preparation of Boron Enolates

Usually formed from a dialkylboron halide or triflate and a sterically hindered tertiary amine base such as triethylamine or Hünig's base (*i*Pr₂NEt).

Example



- Under most conditions, (*Z*)-boron enolates are formed with high stereoselectivity.
- (*E*)-boron enolates can be formed under carefully chosen reaction conditions (e.g. (cyclohexyl)₂BCl / Et₃N in Et₂O):

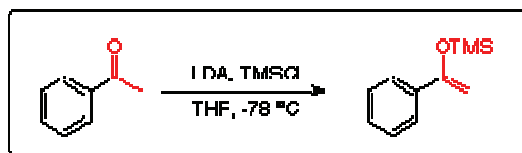


Note that water is not sufficient to cleave the O-B bond in the aldol product. Oxidative cleavage with alkaline peroxide is the standard method of work-up.

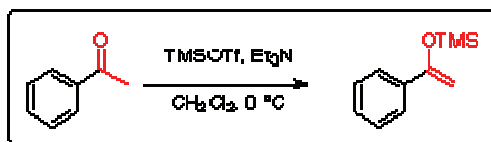
Silyl Enol Ethers in Aldol Reactions (Mukaiyama Aldol Reaction)

Preparation of TMS enol ethers

1) basic conditions - trap lithium enolate

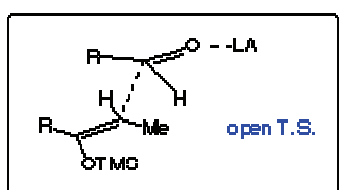


2) Lewis acidic conditions - TMSOTf or TMSCl in the presence of a tertiary amine (requires temperatures >0 C).



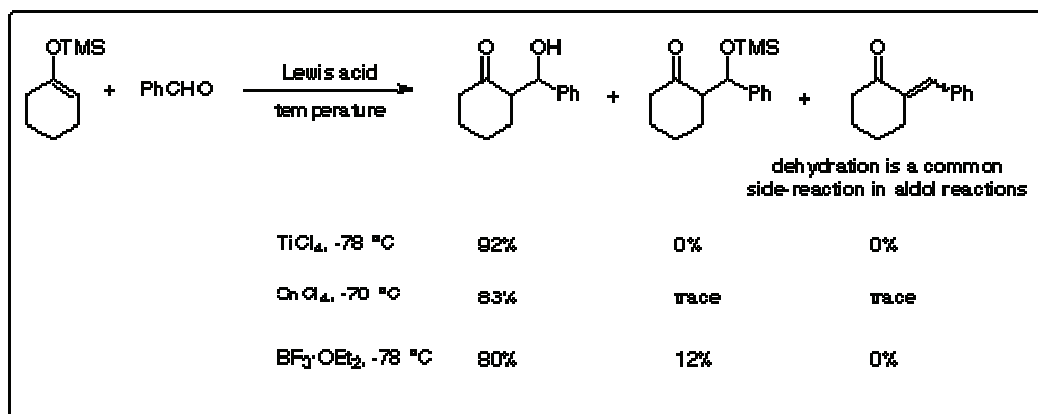
Mukaiyama Aldol Reaction

- 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.

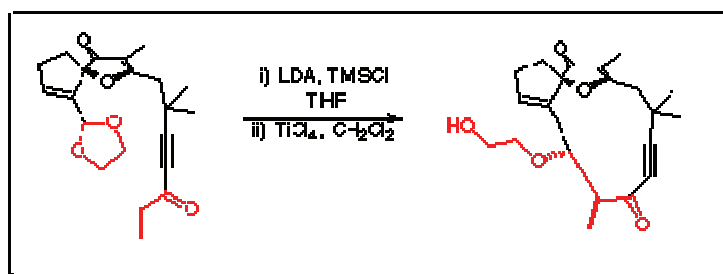


Stereoselectivity of the reaction is usually low.

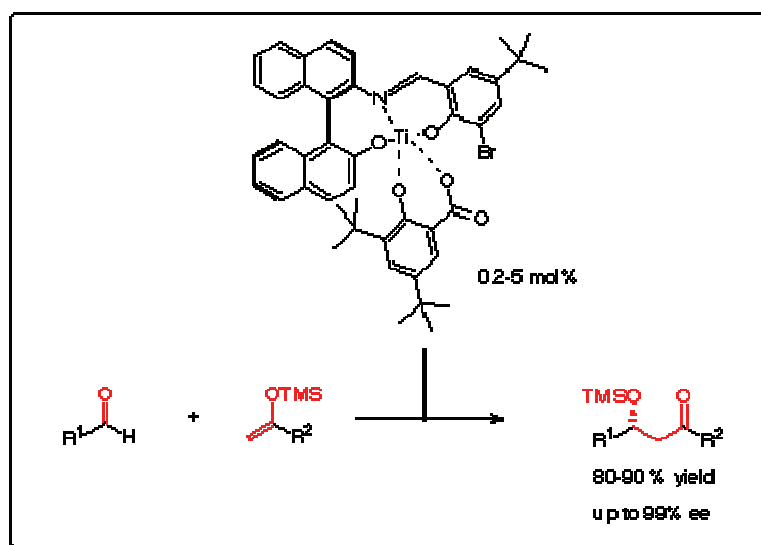
Examples:



The Lewis acid activation conditions allows 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:



S.V.Ley and L. R. Cox, *Chemtracts: Org. Chem.*, 1997, **10**, 853-857.

Diastereofacial Selectivity

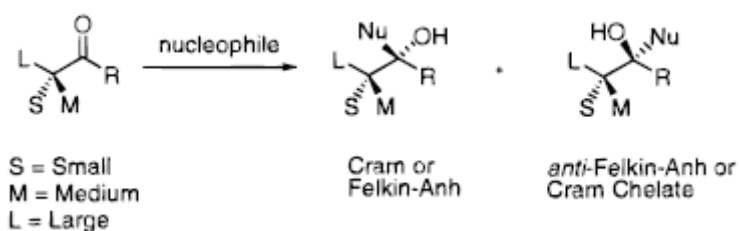
So far we have discussed three types of enolates which sometimes give high levels of simple diastereoselectivity (*syn* or *anti* product). In most cases the relative stereocontrol is determined by the geometry of the enolate (cyclic T.S. with boron or lithium enolates).

To control the absolute stereochemistry of the reaction requires facial selectivity of the prochiral carbonyl group. There are three methods to do this:

1. **substrate control** in which stereochemical information in the substrate(s) directs the stereochemical outcome of the reaction.
2. **auxiliary control** involves the use of a temporary directing group usually attached to the enolate
3. **reagent control** in which chiral ligands on the metal enolate or a chiral Lewis acid provides stereocontrol.

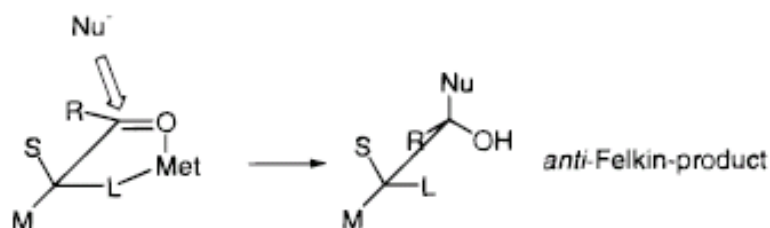
Substrate Control

Models for 1,2- induction

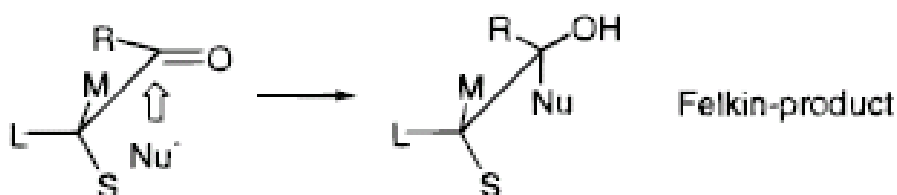


1,2-induction in a α -chiral carbonyl compound

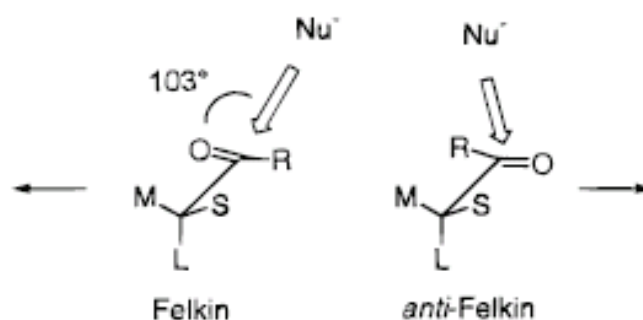
Cram-chelate model (L = OR', NHR' etc)



Cram model



Felkin-Ahn model

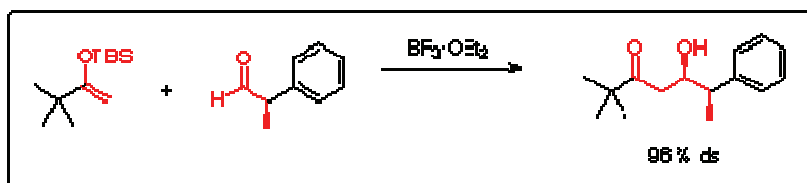


O. Reiser, A. Mengel *Chem. Rev.* **1999**, *99*, 1191.

Chiral Aldehyde and Achiral Enolate

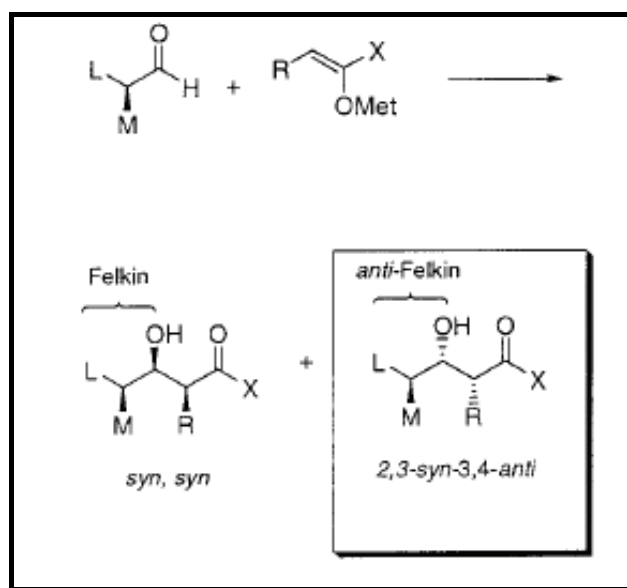
- Aldehydes which possess an α -stereogenic centre often react with high levels of stereocontrol.
- The nature of the groups attached to the stereogenic centre as well as the precise reaction conditions will determine which type of T.S. is important.

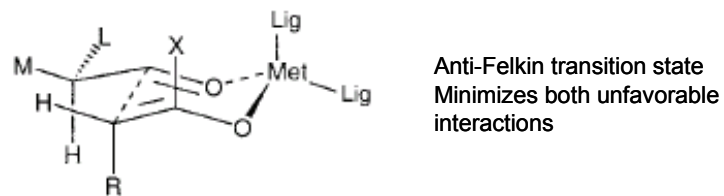
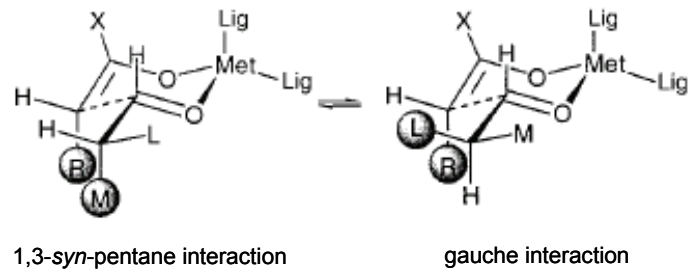
Example 1.



Example 2.

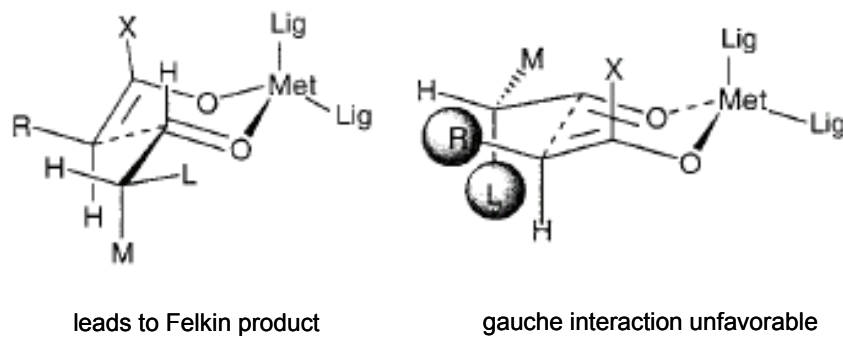
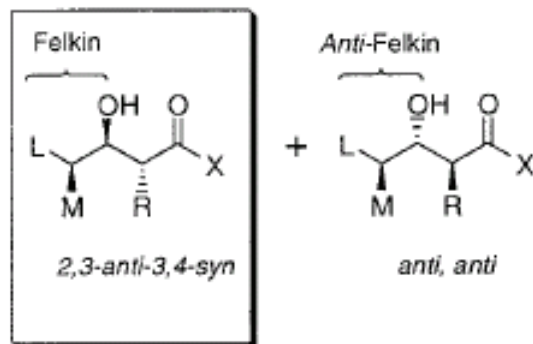
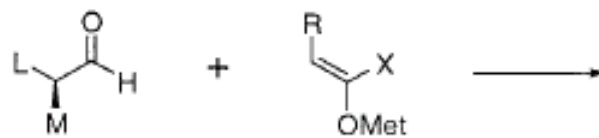
Aldol reaction of α -chiral aldehyde and Z-enolate

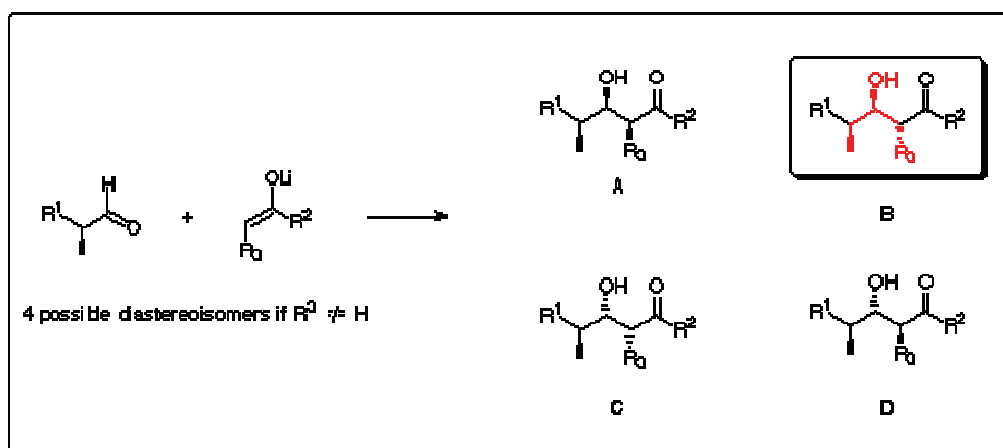




Example 3.

Aldol reaction of α -chiral aldehyde and E-enolate

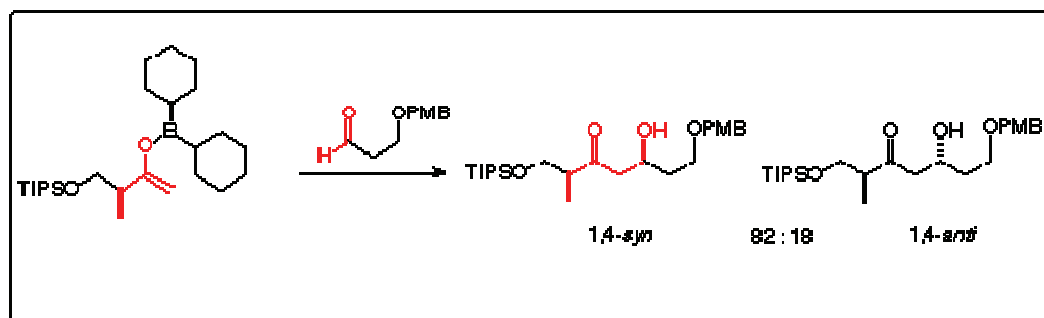




The (*E*)-enolate should provide the *anti* aldol product (cyclic T.S.) *i.e.* **B** and **D**. The α -stereogenic centre in the aldehyde favours product **B** (Felkin-Anh T.S.)

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.



Double Diastereodifferentiation

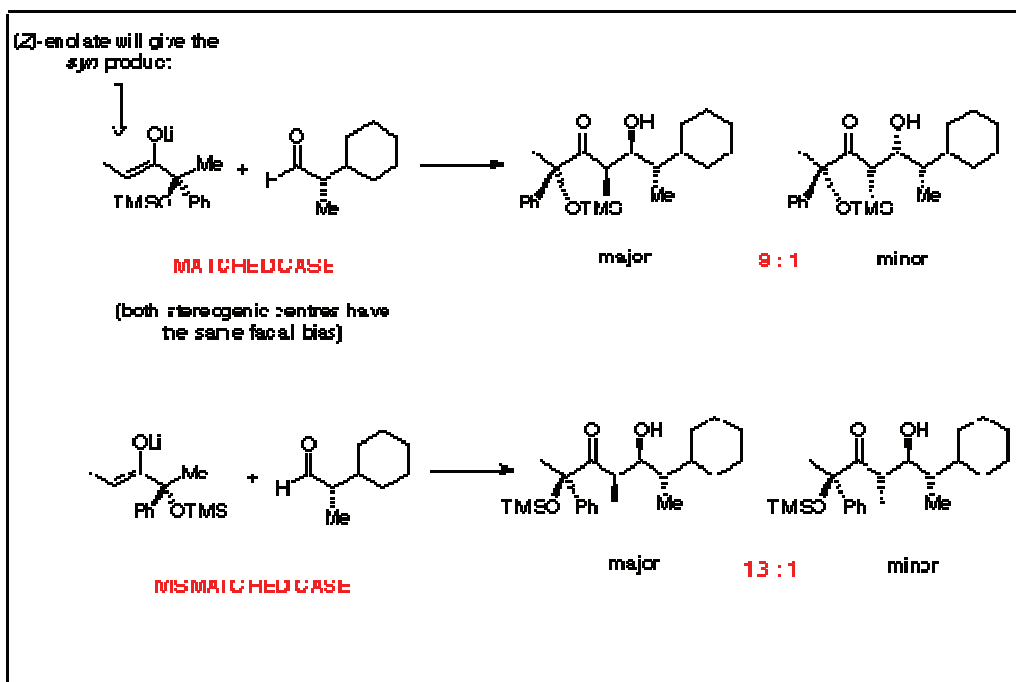
The problem is complicated when both aldehyde and enolate substrates are chiral and possess controlling stereogenic centres (usually α).

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.

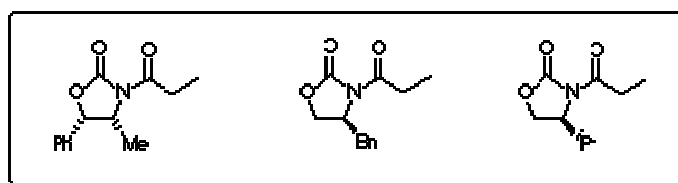
When the inherent facial bias in each substrate opposes one another, stereoselectivity is reduced. **Mismatched** case.

One substrate usually has a stronger facial bias than the other and can completely override the facial preference of its partner. In this case one substrate controls the stereochemical outcome entirely.

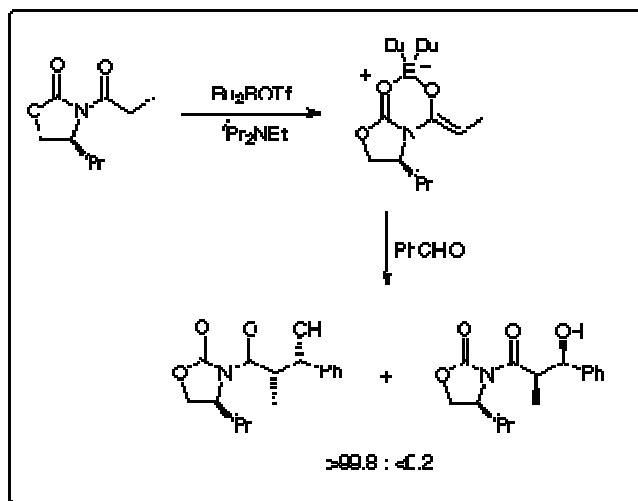


Auxiliary Control

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

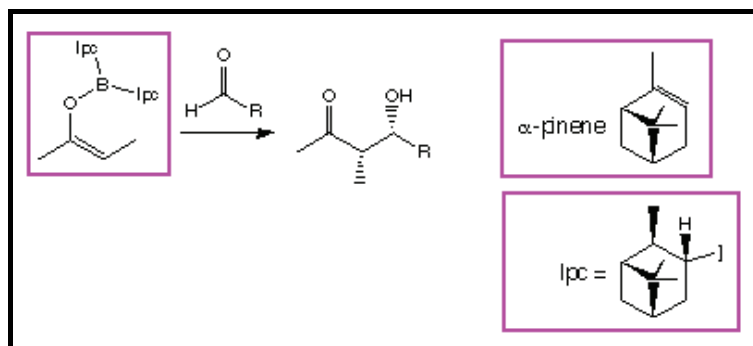


- Lithium, boron and titanium enolates allow stereocontrol of enolate alkylation or aldol reactions
- Metal cations form chelates
- (Z)-enolates are invariably formed and reaction proceeds through a cyclic T.S. to provide the *syn* products (almost exclusively).
- The substituent(s) on the oxazolidinone controls the facial selectivity. The norephedrine-derived auxiliary provides one product and the phenylalanine- and valine-derived auxiliaries give the opposite facial selectivity.
- These auxiliaries are so powerful in their facial directing ability that they usually override the inherent facial bias of chiral aldehydes and even the mismatched pair can provide high levels of stereoselectivity.



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 diisopinocampheyl boron triflate or chloride. Other systems are derived from menthone.
- 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:

