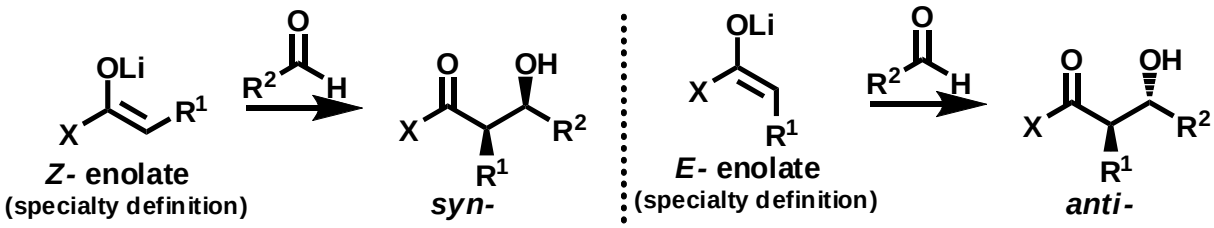
Asymmetric Synthesis

Many, if not most, of naturally occurring or biologically active organic compounds contain chiral centres. As a result, the ability to generate chiral centres with a defined geometry 'from scratch' is of much importance in synthetic organic chemistry. **Asymmetric synthesis** as defined by Morrision and Mosher, is a reaction in which an achiral unit in an ensemble of substrate molecules is converted into a chiral unit in such a manner that unequal amounts of stereoisomers are produced.[1] Since it is not immediately clear whether reactions giving diastereomerically enriched but racemic materials are included under this definition (I will include them), and for further specificity, there are many more detailed terms that should be defined.

Stereoselective Reaction A reaction in which one of a set of stereoisomers is formed predominantly. This may be further specialized into **diastereoselective** or **enantioselective** depending upon whether it is a diastereomer or an enantiomer that is being produced selectively.

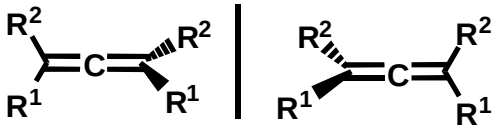
Stereospecific Reaction A reaction in which there are two (or more) starting material stereoisomers and two (or more) product stereoisomers. One of the starting material isomers produces one product isomer, while the other starting material isomer produces the other product produces the other isomer. Once again, this may be further specialized into **diastereospecific** (not used that often) and **enantiospecific** reactions. It must follow that any stereospecific reaction is *also* stereoselective, as the former is a more stringent test. An excellent example of a stereospecific reaction is the aldol condensation feature, where lithium or other enolates of *Z*- gemetry tend to form *syn* diastereomers of products, while the *E*- enolates form *anti*- products.



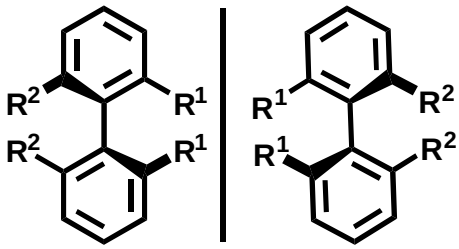
Central Chirality - This is the one you know. A chiral centre that could be *R*- or *S*-

Axial Chirality -Chirality due to restricted rotation about four groups substituted on an axis, with the partners in each pair having to be different. The most common examples are in allenes and in biaryls (with sizeable ortho substituents)

[1] Quoted from Nasipuri, D. *Stereochemistry of Organic Compounds*, 2nd Ed., New Age International, 1994.

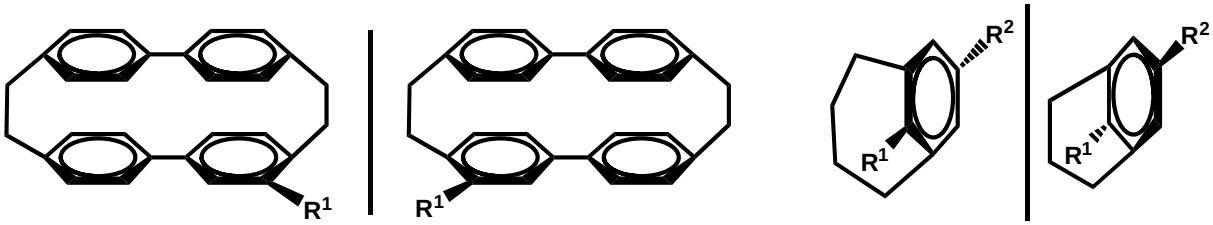


enantiomers

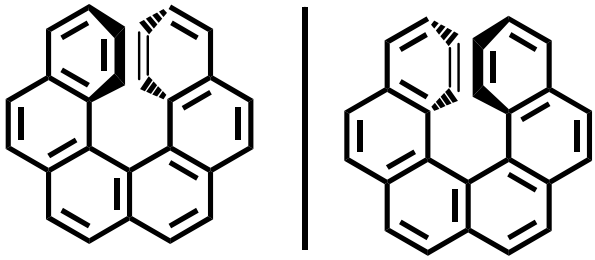


enantiomers

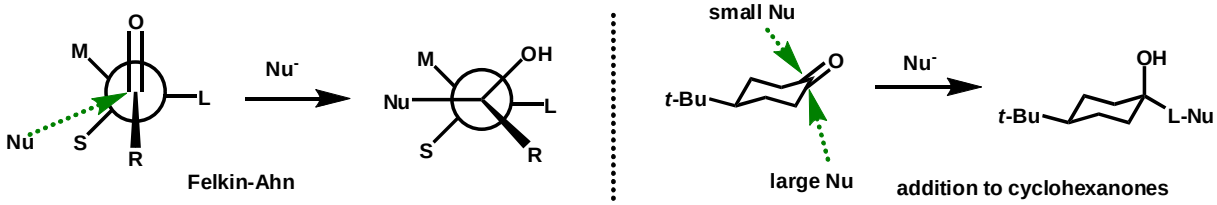
Planar Chirality -Chirality due elements in a molecule forced out of a critical reference plane of a molecule, so that the mirror image of the molecule is non- superimposable. A couple cyclophane examples are:



Helical Chirality -Chirality due a molecule assuming a helical shape that it cannot readily undo. This is often seen in polyaromatics that are (for obvious reasons) called helicenes.



Substrate Control -This is a form of stereoselective synthesis where a chiral centre already present in the molecule is responsible for selective generation of a new chiral centre. These are stereoselective reaction, and examples from 59-331 include Felkin-Ahn additions and (Cram) Chelate model additions to carbonyls.



Chiral Auxiliaries -This form of asymmetric synthesis involves an approach to asymmetric synthesis where an achiral molecule is converted to a derivative that is chiral, using a species that is readily removable to get back to the original functional group. The simplest examples of this would

include converting an aldehyde or ketone to an acetal using a chiral diol, or converting an acid derivative to an ester or amide that contains a chiral centre. This temporarily affixed group (auxiliary) then allows the creation of a new chiral centre using substrate control, and afterwards can be removed. The Evans N- acyl oxazolidinones are prime examples of this approach (see later). This could also be considered a form of substrate control

Chiral Stoichiometric Reactions -Chiral stoichiometric reactions are processes where it's the reagent that contains the chiral element that causes asymmetry. BINAL-H induced enantioselective reductions of carbonyls (see later) are prime examples of these processes.

Enantioselective Catalysis -Probably the most elegant and desired form of asymmetric synthesis, and enantiomerically pure reagents are not cheap. These involve catalysts (present in small amounts, i.e, 20 mol% or less, and the smaller the better), which are enantiomerically pure, and which bias either the orientation of the substrate or the reagent, allowing the reagent to be delivered in an enantioselective manner. This catalyst must then dissociate from the product or reagent by-product, so that it can encounter the next substrate (or reagent) molecule. The Shapless asymetric epoxidation is an excellent example of this type of asymmetric synthesis.

Double Stereodifferentiation If both the substrate and reagent are chiral, there is the possibility for double (dia)stereodifferentiation, where both effect asymmetric synthesis

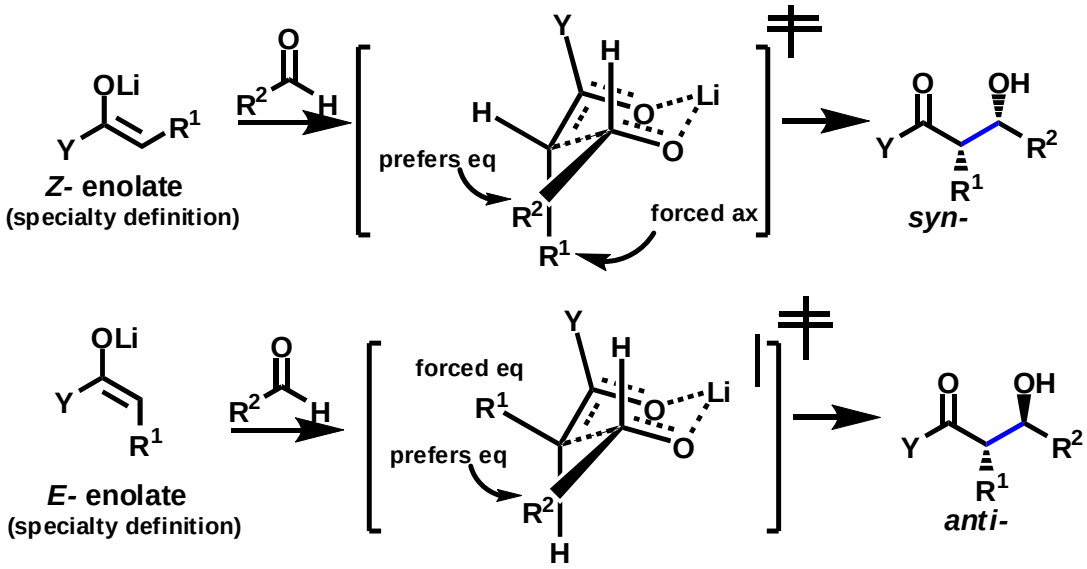
-Note: There will be cases where the substrate and reagent's chiralities reinforce each other (matched pair)
-There will also be cases where they work against each other (mismatched pair)

The following is a brief survey of selected forms of asymmetric synthesis, meant to be built upon reactions studied in 59-331. Due to time constraints, in no way can this be considered even approaching comprehensive. If you are interested in further forms of asymmetric synthesis, see:

Lin, G.-Q.; Li, Y.-M.; Chan, A. S. C. *Principles and Applications of Asymmetric Synthesis*, Wiley: Chichester, 2001.
Gawley,R. E.; Aubé.J. Principles of Asymmetric Synthesis, 2nd Ed.; Elsevier: Oxford, 2012.

1. Diastereoselective/specific Aldol Condensations

It should be recalled from 59-331 that geometrically defined enolates tend to give one diasteromer of kinetic aldol product, rationalized though a cyclic transition state called the Zimmerman-Traxler transition state. As a result, Z- enolates (specially denoted where the R on the α- carbon is *cis* to the OLI) give *syn*- aldols, while the *E*- enolates (where the R on the α-carbon is *trans* to the OLi) give *anti*- aldols.



As it turns out, this doesn't work perfectly well for Li enolates, due to relatively long O-Li bonds, the fact the this is probably not a monomeric species, and the belief through calculation that the chair is very much flattened. Normally:

For large Y, the Z- enolate to *syn*- aldol works decently, while

For small Y, the *E*-enolate to *anti*- aldol is much more hit and miss.

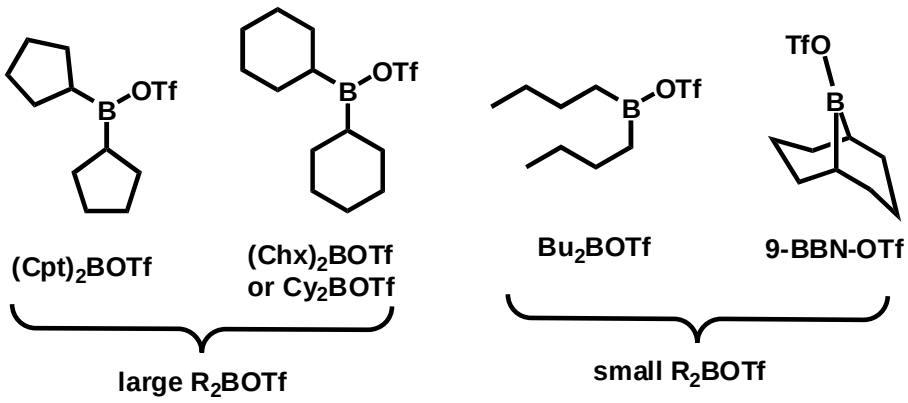
The most commonly employed alternative uses boron enolates, since the B-O bond is shorter, and since B is a first row element, the transition state is 'tighter' and is better approximated by a true chair; in other words, the Zimmerman-Traxler works better. As a result,

For large Y, the Z- enolate to *syn*- aldol very well, while

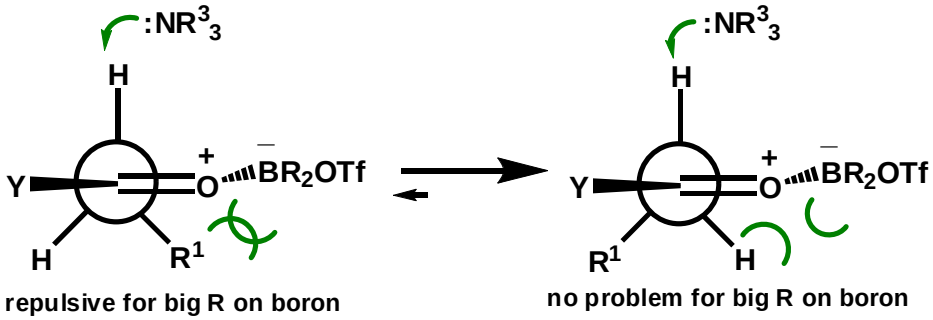
For small Y, the *E*-enolate to *anti*- aldol works decently.

The stereochemistry of boron enolate formation is incredibly complex, and a complete discussion of factors is beyond the scope of this course by far. General features include the following trends:

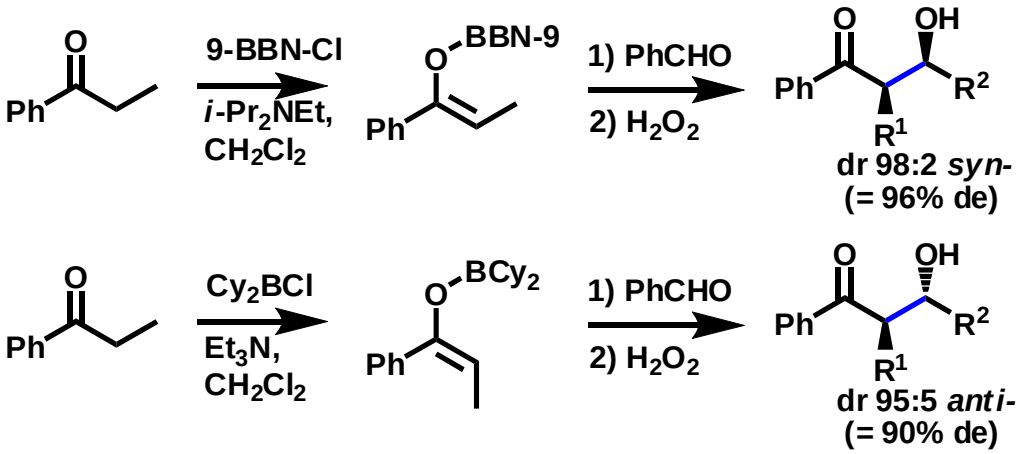
1) Enolate generation occurs by use of a dialkylboron triflate (R_2B-OTf) or dialkylboron halide (R_2B-X, X = I, Br, or Cl) and an amine, such as *i*-Pr_2NEt or NEt_3. It can be done for alkyl ketones, aryl ketones, esters (Y = OR), thioesters (Y = SR), amides (Y = NR_2), and modified amides such as N-acyl oxazolidinones (see later).
2) As for Li enolates, large Y's tend to give *Z*- enolates, while smaller X's tend to give *E*- enolates.
3) There is a lot of room for playing around with stereochemistry for ketones and thioesters.
4) The larger the R groups on boron, there greater the tendency for *E*- enolate formation. For smaller R groups on boron, the tendency is for *Z*- enolate formation. As for what is large and what is small here.



The argument is for 9-BBN-OTf, the R groups are 'tied back', and therefore have a much smaller steric displacement than would appear. There is a rationale here, in that big ligands on boron interact repulsively with R^1 (the α- substituent) during deprotonation, making it favour a situation where it is away from the O atom.



The base in the *Z*- selective cases is almost always *i*-Pr_2NEt. In the *E*- selective cases, sometimes the smaller Et_3N is used as base, but this is by no means unilaterally done.



As stated before, the combinations here can get very detailed and these are generalities. For a more detailed discussion, see:

Comprehensive Organic Synthesis, vol. 2, p. 239 (Ch. 1.17)

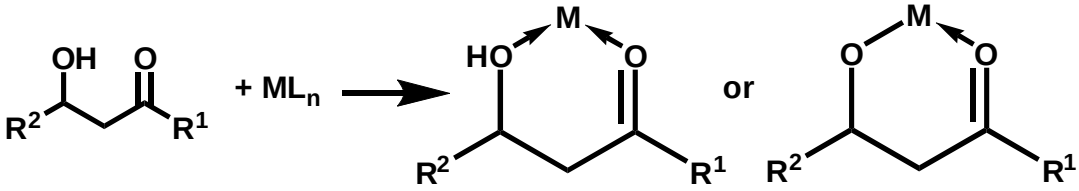
Alternatives to boron enolates include those of Ti^{IV} and Sn^{II} (see *J. Am. Chem. Soc.* **1995**, *117*, 9073, and *Org. React*. **1994**, *46*, 1).

2. Synthesis of *Syn*- and *Anti*- 1,3-Diols

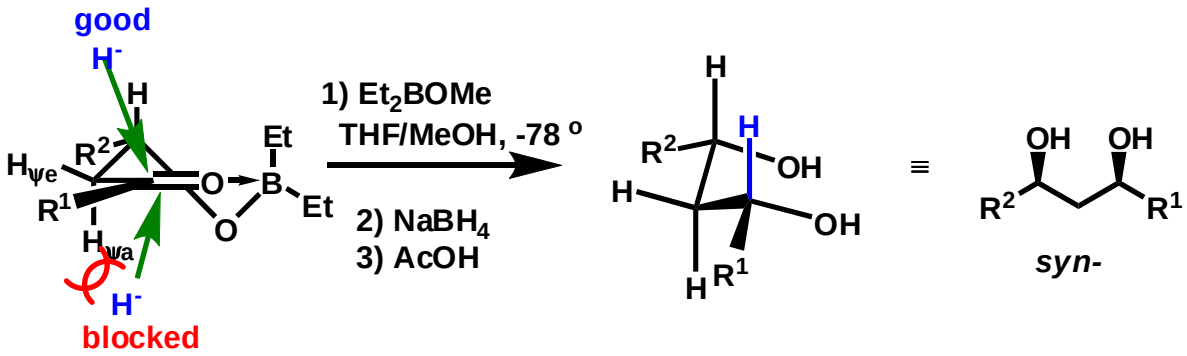
One of the other classic substrate control examples of asymmetric synthesis involves the formation of 1,3-diols with a defined relative stereochemistry; either the *syn*- or *anti*- diastereomer may be made by careful choice of reagent. Since the 1,3-diol unit is heavily represented in natural products and since this clearly relates to the aldol chemistry we've discussed in 59-331, and previously here, it is worth addressing. Each uses the β- hydroxyl ketone precursor and a source of hydride.

For the *syn*- diastereomer:

The approach that is used for *syn*- diastereomer synthesis involved the idea that the alcohol is converted to a simple derivative, that is also capable of complexation by the carbonyl oxygen. This six membered chelate is pretty restricted in conformation; the subsequently added hydride source then has a preferred attack route to the carbonyl carbon, giving one diastereomer mostly.



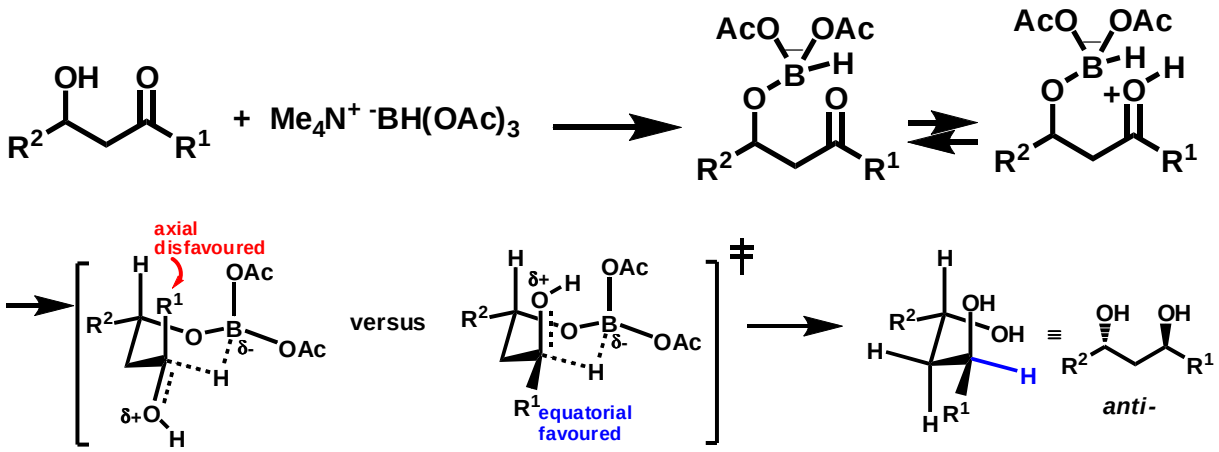
The trick here is that the model everything is based on for the structure of the chelate is cyclohex*ene* instead of cyclohexane. Cyclohexene exists as a half-chair conformation, and therefore a half-chair model is proposed here. The hydride, attacking from the bottom face in the following structure, has to get by the pseudoaxial (ψe) hydrogen on the next carbon - although hydrogen is small, it is very nearly eclipsing and its competitor is essentially nothing. The top face (in the diagramme) attack results into the H^- coming near nothing at all, and is preferred. This gives the *syn*- diastereomer after workup, with 95:5 ratios (dr = 95:5, de = 90%) common. Since the most common reagent set is to add 1) Et_2BOMe in THF/MeOH at -78 °C, then 2) $NaBH_4$, and finally 3) CH_3CO_2H for hydrolysis, I'll use that in the drawings.



There are many other sets of reagents that do the same thing: LiCl followed by $LiAlH_4$; zinc borohydride ($Zn(BH_4)_2$) on its own, or H_2/Pt-C.

For the *anti-* diastereomer:

The alternative to the above approach is to have a reagent that coordinates or covalently binds to the alcohol function, but instead of just chelating to the carbonyl oxygen it has the hydride source within the reagent. The hydride is therefore delivered to the ketone in an intramolecular fashion. This creates a whole different set of restrictions on the conformations, but we can be back at modeling the transition state as a cyclohexane- type chair again. The question is whether the protonated carbonyl oxygen is going to be axially or equatorially disposed: since the OH was a relatively small group (smaller than methyl, which is the least R^1 we could have), it is reasonable to expect that the $=O^+$-H is also axially preferred. The result gives the *anti-* diastereomer, again with 95:5 ratios (dr = 95:5, de = 90%) being commonplace. The most common reagent is $Me_4N^+ {}^-BH(OAc)_3$ on CH_3CO_2H/MeCN at -40 ^oC, with the alcohol replacing one acetate. Once again, that one will be used in the models below.



Again, there are alternative reagents such as 1) *i*-Pr_2SiHCl, pyridine, then 2) a Lewis acid that are fairly straightforward variations on the same method and uses the same principles. For a good example of both the *syn-* and *anti-* diol approaches being used, see Evans, D. A. *j. Org. Chem.* **1991**, *56*, 741.