Enantioselective Synthesis

Preparation of Enantiomerically enriched Compounds

This is critically important because the two enantiomers of the same compounds often/usually have very different properties when in come to biological activity.

There are a number of different types of approaches to enantioselective synthesis. They include:

1) Substrate Control

-A situation where a chiral auxiliary is temporarily attached to the desired substrate, and a diastereoselective reaction is performed. The auxiliary is then removed to give the pure enantiomer.

2) Reagent Control – this approach has several variations, including:

i) Stoichiometric reagent

ii) Chiral Catalysis

iii) Enzyme Based processes

These are considered more elegant than substrate control, but what if you only get 80% ee (90:10 er)…what do you do?

3) Both are chiral – Double stereodifferentiation

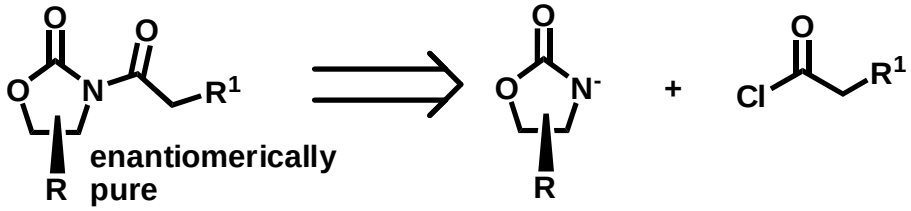
-Note: There will be cases where the substrate and reagent's chiralities reinforce each other (matched pair)

-There will also be cases where they work against each other (mismatched pair)

We will look at a few of the major cases, but will hardly be comprehensive.

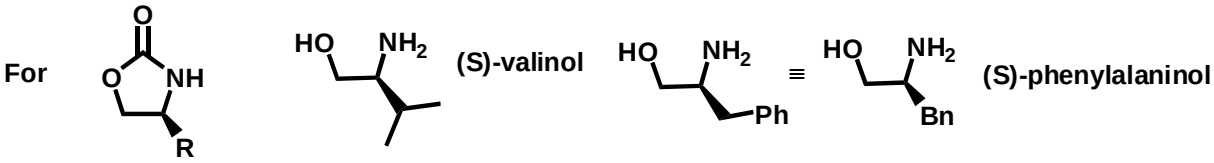
Enolate Alkylation (Evans' oxazolidinone enolates)

The basis for the most commonly employed chiral enolates involves an N-acyl oxzolidinone that enantiomerically pure in the heterocycle. This is an important example of substrate control by formation of a chiral auxiliary.

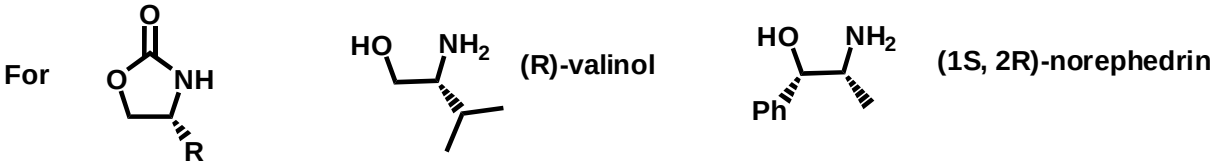


The source of chirality in the oxazolidinone is an amino alcohol, which are usually commericially available and cheap, or come from reduction of the amino acid. Recall that it's the (S)- enantiomers

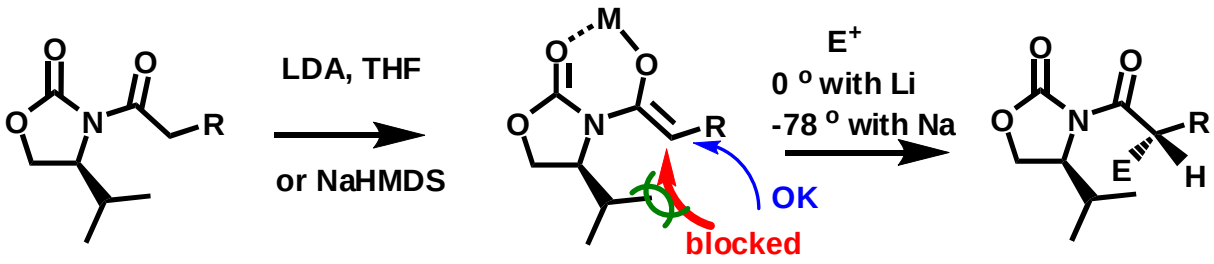
which are the natural and therefore cheap ones. The most common ones come from valine (valinol) and phenylalanine (phenylalaninol).

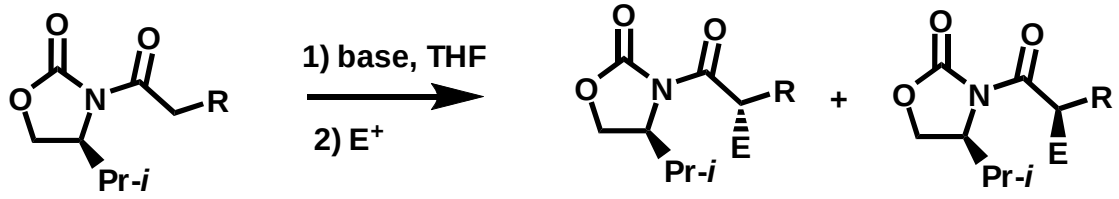


And the (R)- enantiomer? There are usually two choices: i), the (R)- enantiomer of valinol (or valine) is more expensive, but not crazily so; ii), (1S, 2R)-norephedrin has (R)- chirality at the methyl (proper) site.

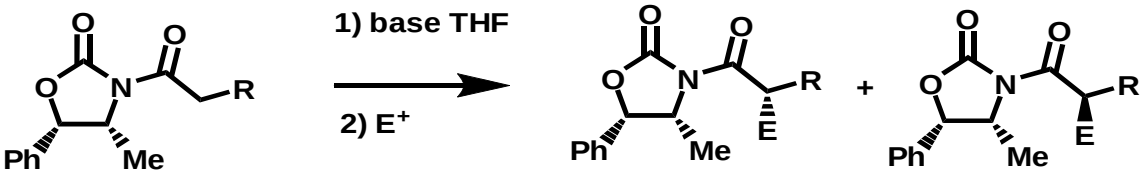


The N-acyl oxazolidinones are similar to esters in terms of ability to form enolates, most commonly with LDA or the base that functions as its sodium analogues, NaHMDS. Since these are essentially amides, the enolates are entirely the Z- isomer (using the particular definition for enolates). The metal counterion in chelated to the oxazolidinone oxygen atom, making one face of the enolate (the *re* face), away from the R of the oxazolidinone, much more available for attach on the electrophile. The selectivity obtained ranges from pretty good (smaller electrophiles, like CH_3I, EtBr) to excellent (for less small electrophiles). Some examples follow:





$E^+ = CH_3$-I (NaHMDS, -78 º)	91	9
$E^+ = PhCH_2Br$ (LDA, 0 º)	99	1

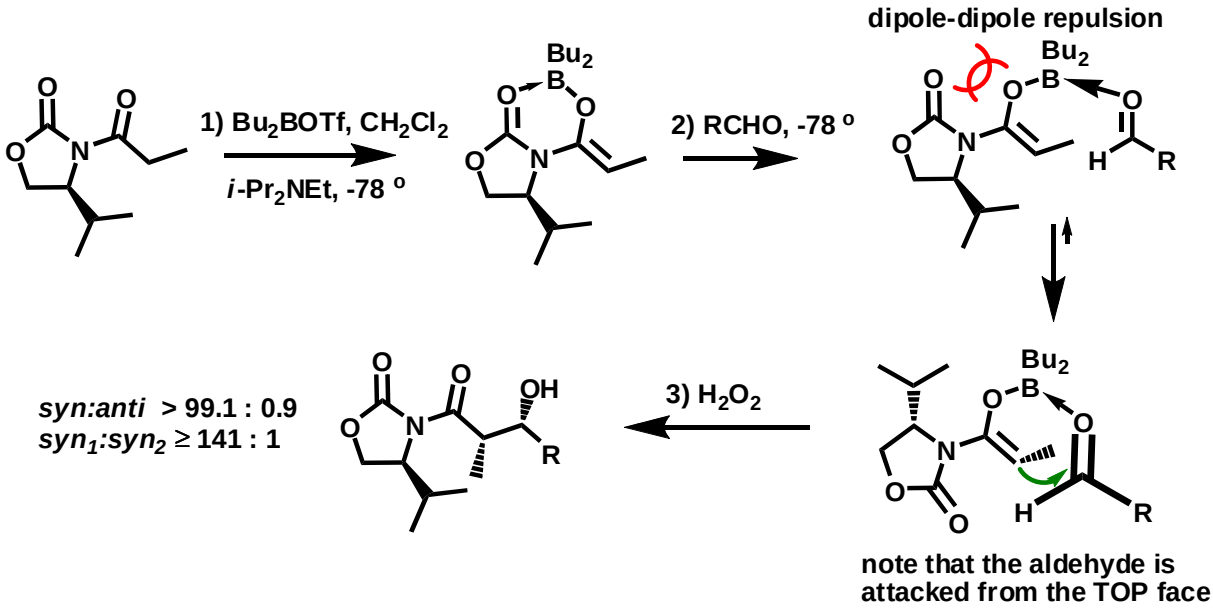


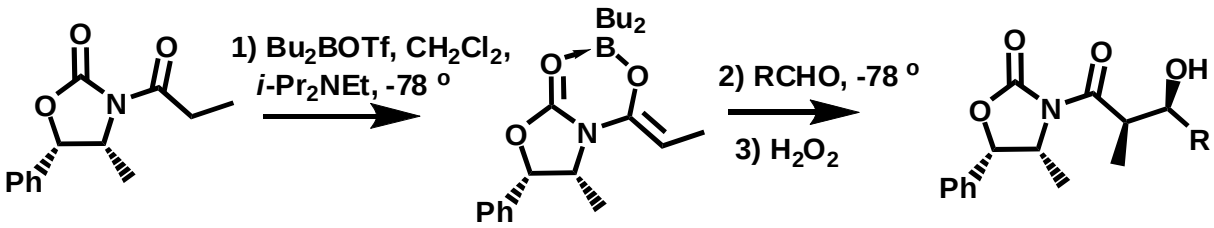
$E^+ = CH_3\text{-}I$ (NaHMDS, -78 °)	7	93
$E^+ = PhCH_2Br$ (LDA, 0 °)	2	98

Note: Other electrophiles can also be put into the Li, Na, B, Sn, or Ti enolates, such as halogenation or amination. See the reviews for detail on this.

Aldol Condensations

The Evans' N-acyloxazolidinones are wonderful at doing selective aldol condensations using their **boron** enolates. The stereoselection is even more outstanding than for alkylation, but there is (superficially) a surprise here. Firstly, because the oxazolidone is essentially an amide and of significant size, it is once again impossible to get anything other than the *Z*- enolate. The key is that even though there is a chelate in the boron enolate, when the aldol occur the chelate must fall apart (or else there is no Zimmerman-Traxler transition state). With this chelate gone, there is a repulsive dipole-dipole interaction between the oxygen atoms, so the dominant conformation flips 180 °. The result is still the *syn*- aldol product, but relative to the oxazolidine the face of attack is *opposite* from alkylations!! This is easy to miss if simply skimming the results.



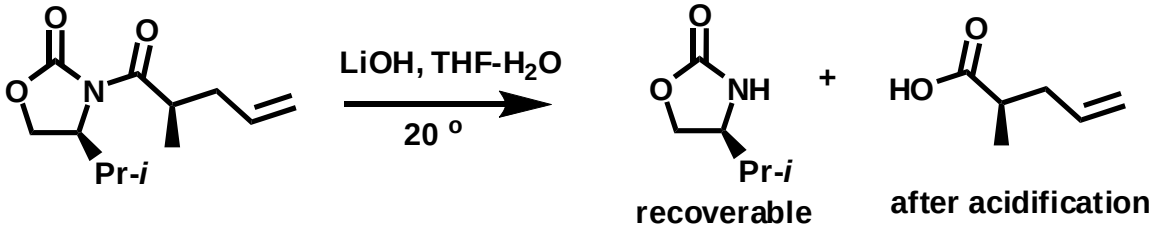


Other electrophiles can also be reacted with Li, Na, B, Sn, or Ti enolates, such as in amination or halogenation reactions. You should consult the reviews if interested.

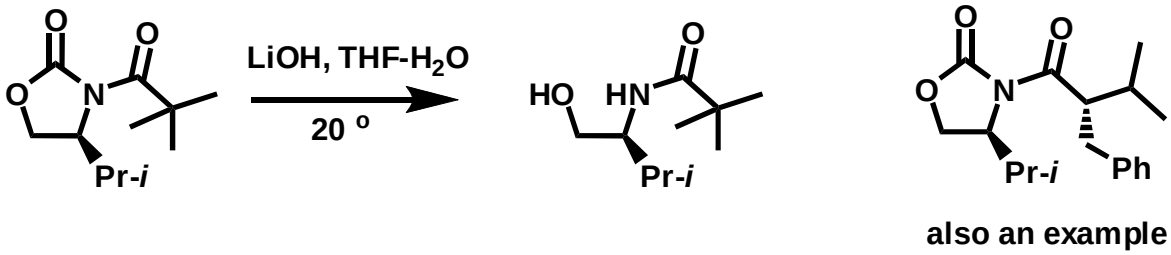
Cleavage of the Oxazolidinone

For this chemistry to be a useful enantioselective synthesis, it has to be possible to get rid of the oxazolidinone auxiliary. There are several protocols for this, but just a couple will be given.

Carbonyl Hydrolysis: The amide like carbonyl should be more susceptible to nucleophilic attack, than the carbamate carbonyl, so HO^- should be able to hydrolyze this to a carboxylic acid. When it's done, LiOH is used, because it is least likely to cause base induced side reactions, like epimerization or retro- aldol reactions.

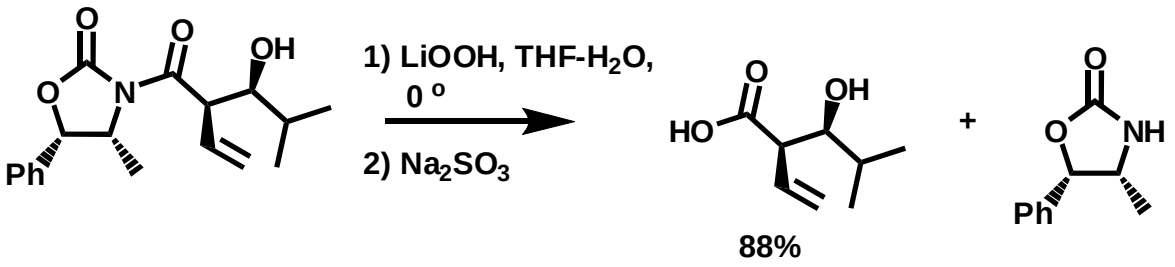


This usually works, but if the R groups on the 'amide' get too large, hydrolysis of the carbamate can start to compete.



LiOOH also works for the *intended* transformation (H_2O_2 + LiOH). As a reagent, it is sterically less hindered, and is also less basic (pK_a H_2O_2 = 10). Therefore, it's more likely to attack the 'amide' carbonyl in hindered cases, and less likely to cause undesired base initiated processes.

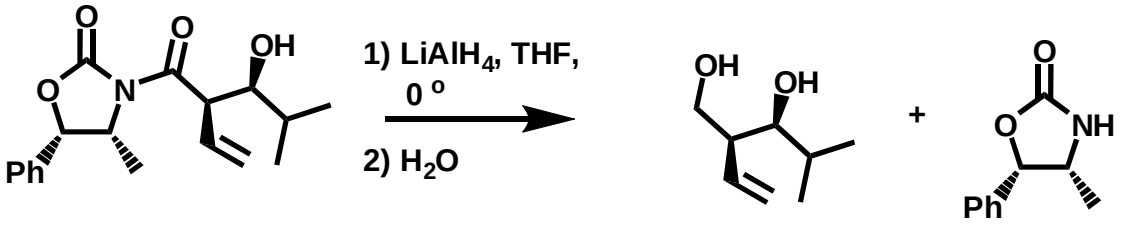
also an example



88%

Tetrahedron Lett. **1987**, *28*, 6142.

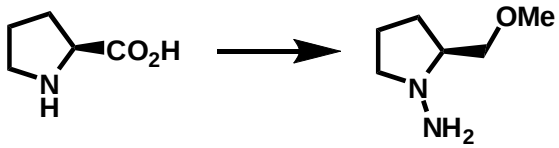
An alternative to hydrolysis of the N-acyl oxazolidinone is reduction, which can be accomplished by $LiAlH_4$ or $LiBH_4$ (more reactive that $NaBH_4$). Since the N-acyl oxazolidinone is ester-like in its reactivity, the reduction occurs twice, to give the alcohol.



We will come back to the Evans' oxazolidinones for the purposes of aldol chemistry, but the first matter to address is the question of how to do analogous enolate alkylations on ketones instead of acid derivatives.

Ketone Enolate Alkylation

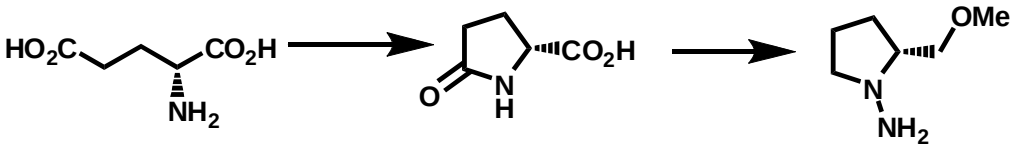
For the analogous asymmetric alkylation of ketones, the most common method involves hydrazones, which can also be derived from amino acids. In particular 1-**a**mino-2-(**m**ethoxymethyl)-**p**yrrolidine is available either as its (S)- enantiomer (SAMP) or its (R)- enantiomer (RAMP); both are commercially available but rather expensive. Since the (S)- enantiomer can be prepared from (S)-proline, it is the cheaper of the two. The (R)- enantiomer may be made from either (R)- proline or (R)-glutamic acid.



(S)- proline

(S)- 1-amino-2-(methoxymethyl)prrolidine

SAMP

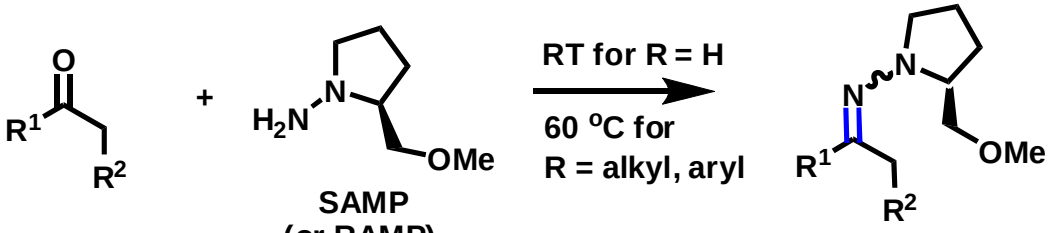


(R)-glutamic acid

(R)- 1-amino-2-(methoxymethyl)prrolidine

RAMP

When these hydrazines are subjected to exposure to ketones, the expected imine formation chemistry occurs, save that these are called hydrazones. Ultimately the C=N double bond is formed as a mixture of (E)- and (Z)- isomers, but these interconvert pretty easily and turns out to not matter.

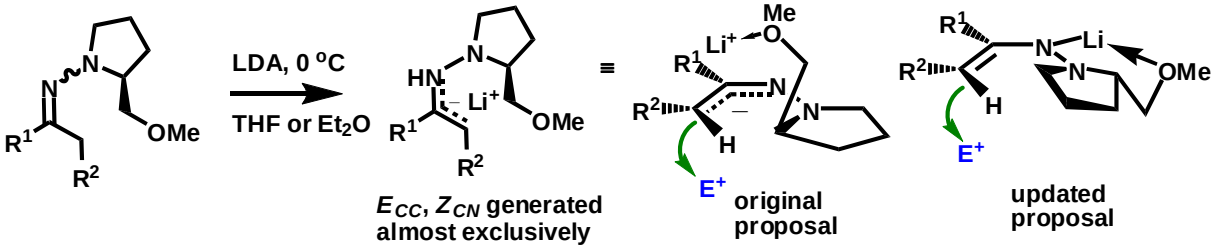


SAMP
(or RAMP)

RT for R = H

60 °C for
R = alkyl, aryl

Under kinetic conditions, this hydrazine deprotonates at the less substituted side (except for those derived from aldehydes, where only one site is possible). At 0 °C, in THF or Et_2O, only one of the 4 possible isomers is obtained.



LDA, 0 °C

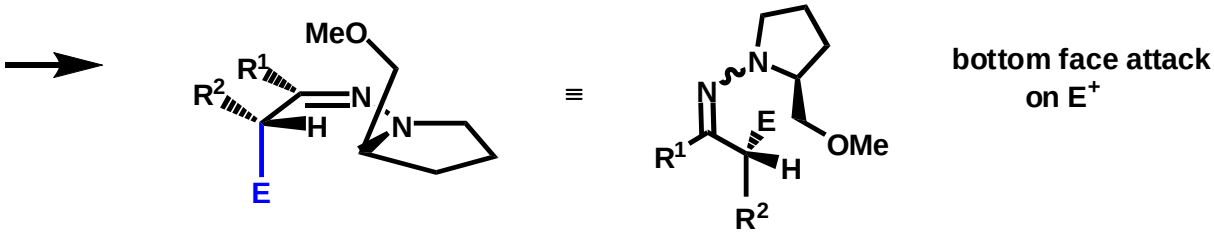
THF or Et_2O

E_{CC}, Z_{CN} generated almost exclusively

original proposal

updated proposal

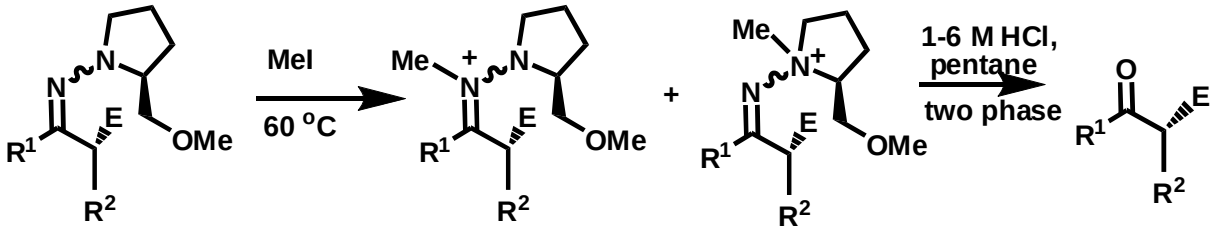
The temperature is then dropped very low (to -78 °C or even lower), and an electrophile such as an alkyl halide is added. With the auxiliary blocking the top face, electrophile attack on the bottom face is almost exclusive to generate a new chiral centre.



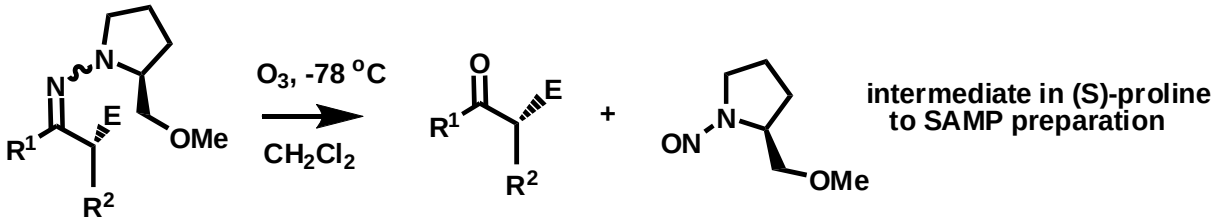
bottom face attack on E^+

Hydrolysis – Hydrazones are types of imines and therefore can be hydrolyzed in strong acid at reflux. Unfortunately, these vigourous conditions cause racemization at the careful crafted chiral centre due to acid catalyzed keto-enol tautomerism (also called epimerization). There are two solutions to this problem:

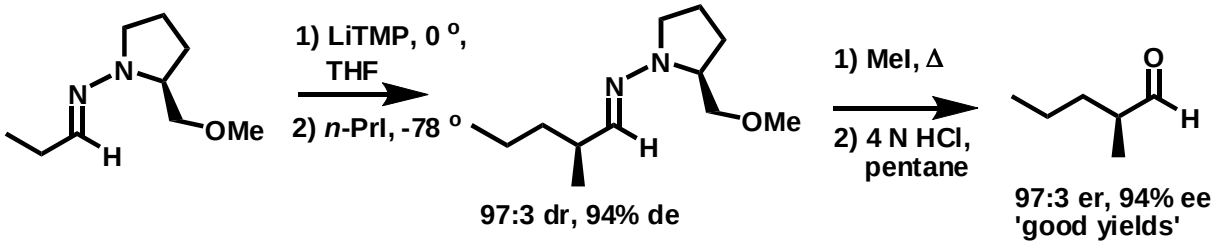
i) Quaternize then hydrolyze – Subjecting the hydrazine to MeI alkylates mostly the nitrogens. This ionic species is more readily hydrolyzed, and acidic but less aggressive conditions can be found for the hydrolysis without racemizations.



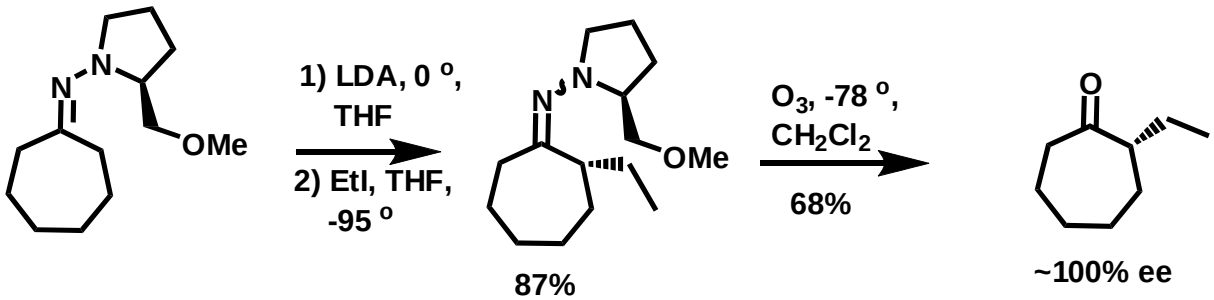
ii) Oxidation/ozonolysis – Instead, one can pretend that the imine is more like an alkene and cleave the double bond similarly, with ozone (or other oxidants). The advantage here is that the recovered hydrazine derivative is an intermediate in the (S)-proline to SAMP preparation.



A couple of specific examples of asymmetric alkylation of ketones by way of Enders SAMP hydrazones follow.



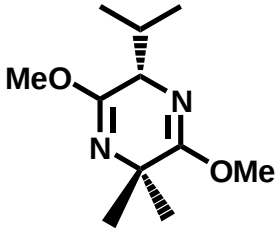
Tetrahedron Lett. **1998**, *39*, 7823



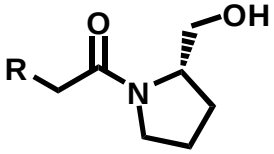
Enders has also done aldol chemistry with these, but this area will not be covered. For reviews, see:

Enders, D. *Asymmetric Synthesis* **1984**, *3*, 275; *Comprehensive Organic Synthesis,* Vol 3, 38.

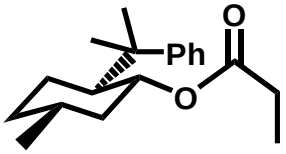
There are other very important chiral enolate sources. I will show some of them below, without further discussion.



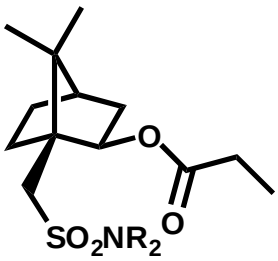
Schollkopf



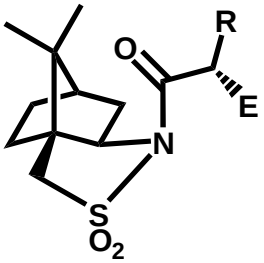
Evans



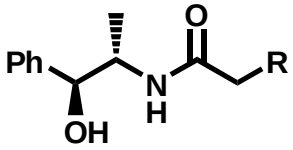
Whitesell
***CR*, 1992, *92*, 953**
8-phenylmenthol



Oppolzer
***Tetrahedron* 1987, *43*, 1969**



Oppolzer
camphor sultams



Myers
pseudoephedrine
amides