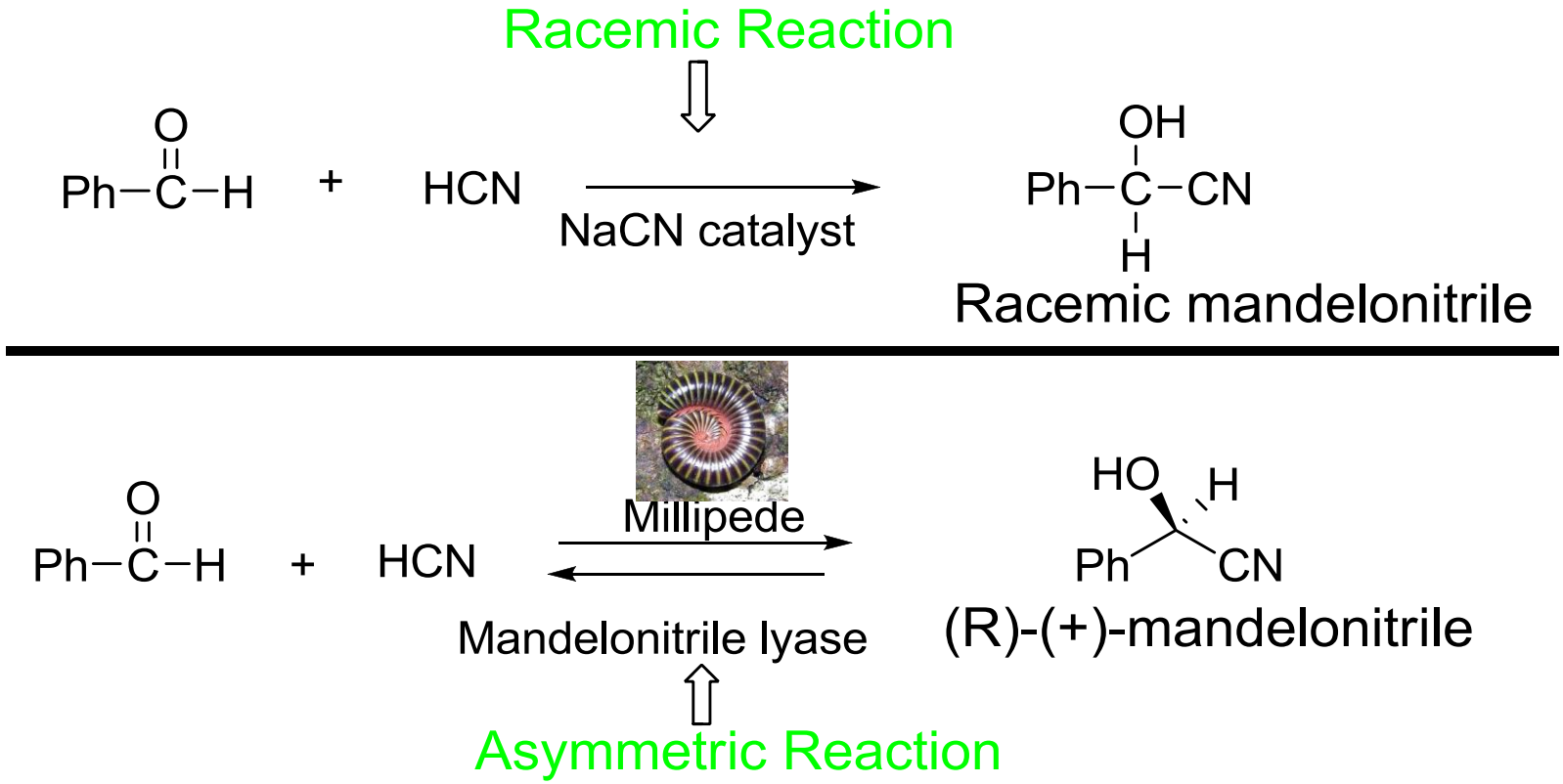
Asymmetric Synthesis

Asymmetric Synthesis

What is Asymmetric Synthesis?

Asymmetric synthesis relates to any synthetic process that introduces one or more new elements of chirality during a functional group transformation.



Asymmetric Synthesis

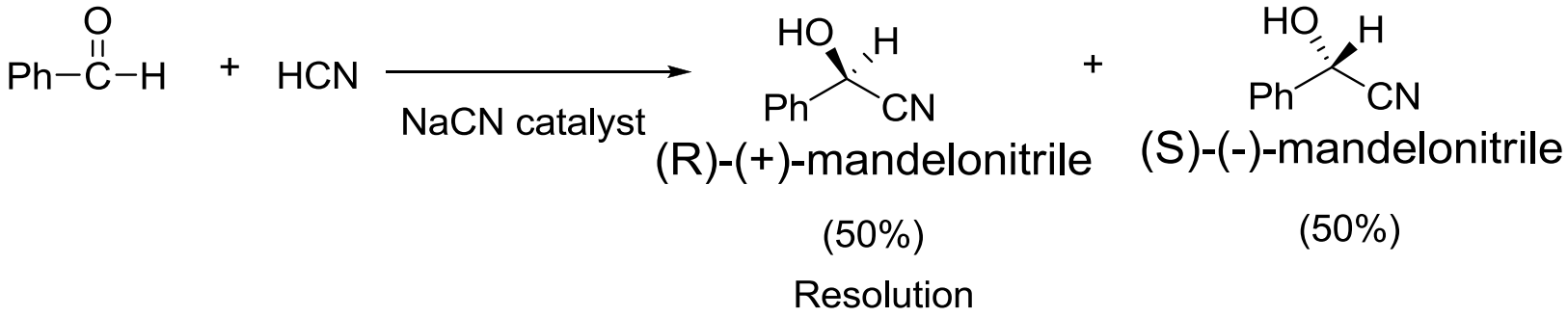
What is Asymmetric Synthesis?

In asymmetric synthesis, the reactions are either highly enantioselective (high ee) or enantiospecific (100% ee).

Prior to the development of efficient methods of asymmetric synthesis, resolution was used to access enantiopure molecules.

But, resolution is not very efficient as the maximum yield of the desired enantiomer is only 50%.

Racemic Synthesis



Asymmetric Synthesis

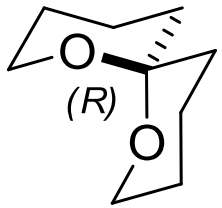
Why is Asymmetric Synthesis Important?

The ability to synthesize single enantiomers of chiral molecules is important since biological systems, where they are intended for application, are also chiral.

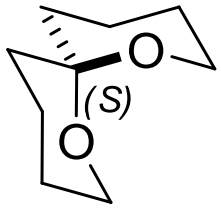
Different enantiomers often interact with the target biological receptors very differently and often with different responses.

Example

Pheromones for Olive fruit fly



Attracts male flies



Attracts female flies

Asymmetric Synthesis

The Way Forward in Asymmetric Synthesis

To access enantiomerically pure molecules for biological applications as drugs, sweeteners and moisturizers, there is need for adoption of efficient strategies for asymmetric synthesis.

Strategies of Asymmetric Synthesis

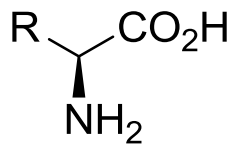
We will cover the two main strategies of asymmetric synthesis:

- Chiral pool synthesis or chiron approach
- Chiral auxiliary approach

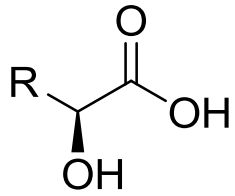
Chiral Pool

Chiral pool refers to a collection of enantiomerically pure molecules available from nature.

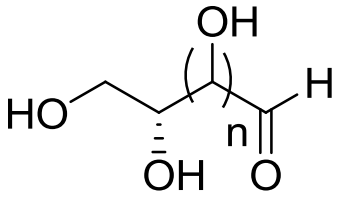
Common chiral starting materials derived from nature include amino acids, chiral carboxylic acids and monosaccharides.



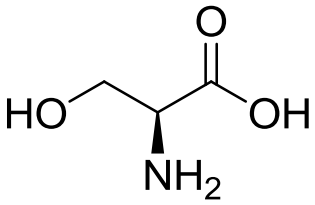
Natural L-Amino acids



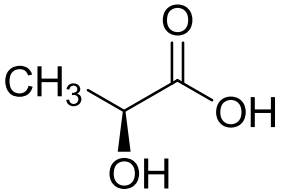
α-Hydroxy acids



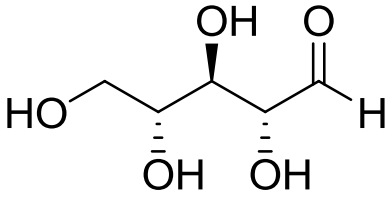
Natural D-Sugars



L-Serine



(S)-Lactic acid
(Milk)



D-Ribose

Chiron Approach to Asymmetric Synthesis

A chiron approach or chiral pool synthesis refers to a synthetic process that employs a member of the chiral pool as a starting material (SM) in the synthesis of a target molecule (TM).

The chiral centre(s) in the starting material are (but not all are always) preserved in the target molecule (TM).

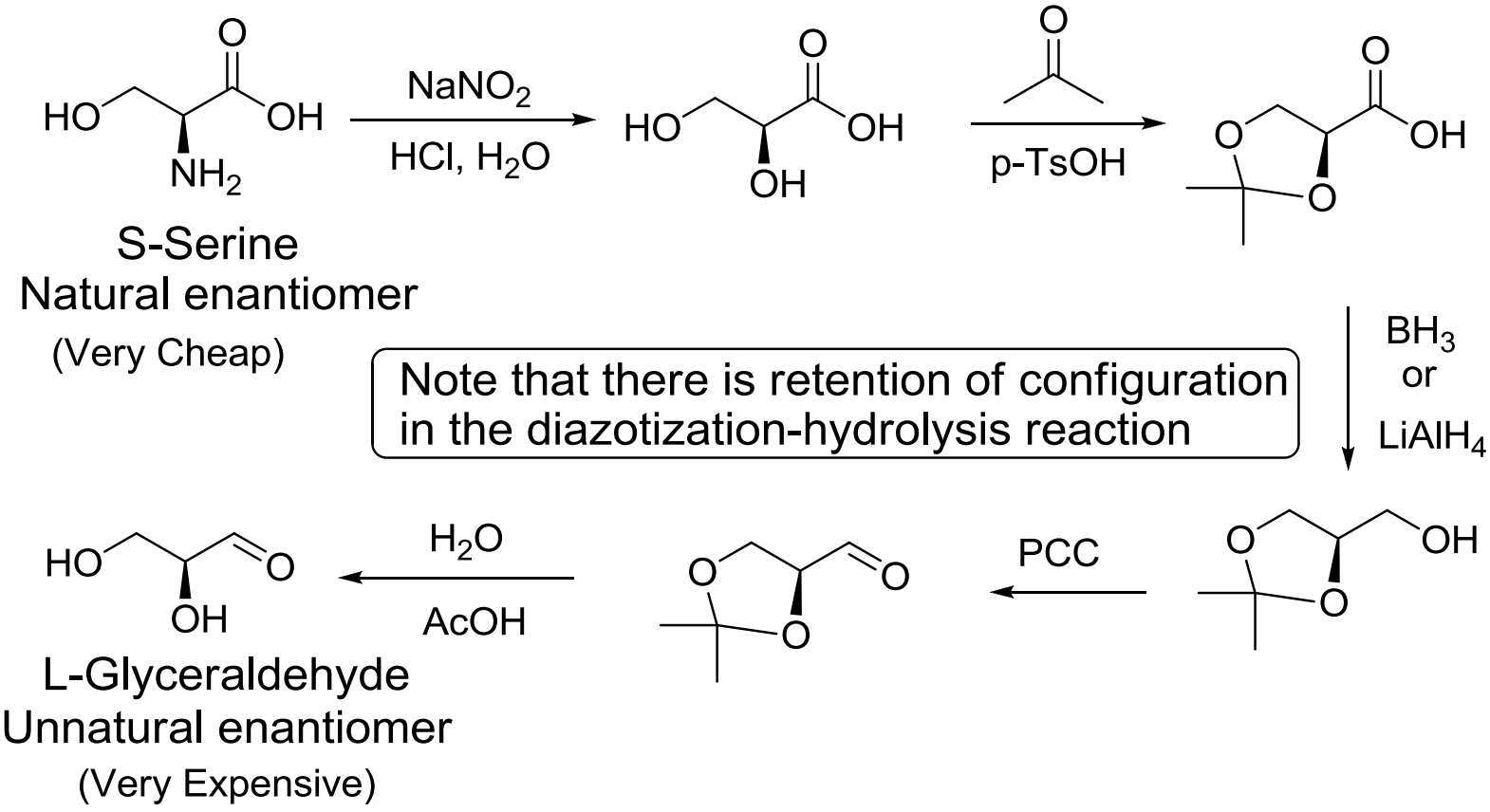
It may use pre-existing chiral centres from the chiral pool substrate to influence formation of new chiral centres.

The new chiral centres can be generated through substitution or addition reactions.

Chiral Pool Synthesis

Functional Group Interconversion

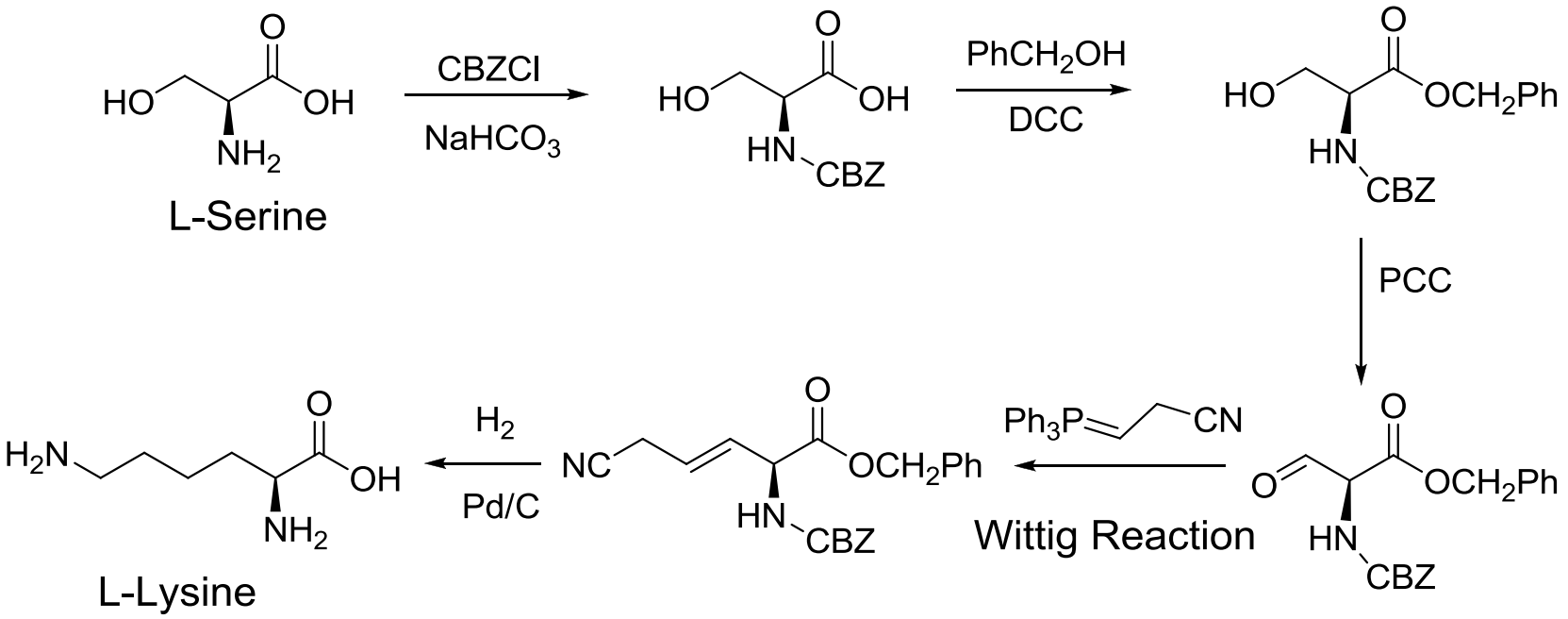
Chiral pool synthesis of L-glyceraldehyde, the unnatural sugar, from the natural amino acid L-Serine.



Chiral Pool Synthesis

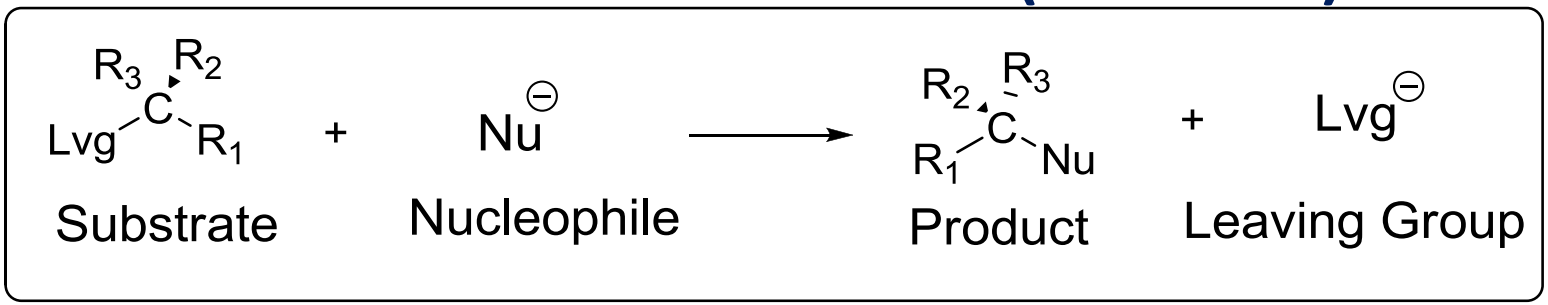
Functional Group Interconversion

Chiral pool synthesis of the essential amino acid, L-lysine from the natural non-essential amino acid L-serine can also be achieved.



Asymmetric Synthesis

Via Substitution Reactions (Revisited)



SN_1 vs SN_2: Which is best for asymmetric synthesis?

Attribute	SN_1	SN_2
Kinetics	First Order	Second Order
Mechanism	Stepwise Reaction	Concerted Reaction
Stereochemistry	**Non Stereospecific** **Racemization occurs**	**Stereospecific** **Complete inversion**
Best Substrates	3º and 2º Substrates	1º and 2º Substrates
Nucleophile	Good nucleophile works	Strong nucleophile best
Leaving Group	Good leaving group	Good leaving group

For being stereospecific, SN_2 reactions on 2º substrates are more reliable in asymmetric synthesis.

Asymmetric Synthesis

SN_2 Reactions: Strong Nucleophile Needed

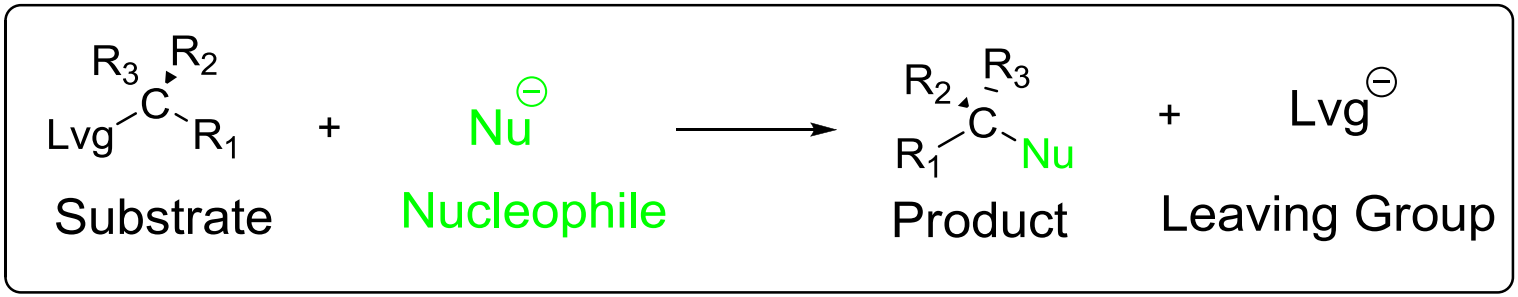
A nucleophile is an electron rich species that has a negative charge or at least a lone pair of electrons.

There are generally three factors that determine the trend in nucleophilicity of a reactant:

1) Size- Generally, the more linear or smaller the nucleophile, the *more* nucleophilic it will be. It avoids steric hinderance if it is smaller or linear.
2) Electronegativity- The more electronegative an atom is, the *less* nucleophilic it will be. Nucleophilicity decreases across the periodic table (C > N > O > F)
3) Polarizability- The more polarizable an atom is, the *more* nucleophilic it will be. Generally, polarizability increases down the periodic table (I > Br > Cl > F)

Asymmetric Synthesis

SN_2 Reactions: Strong Nucleophiles Needed



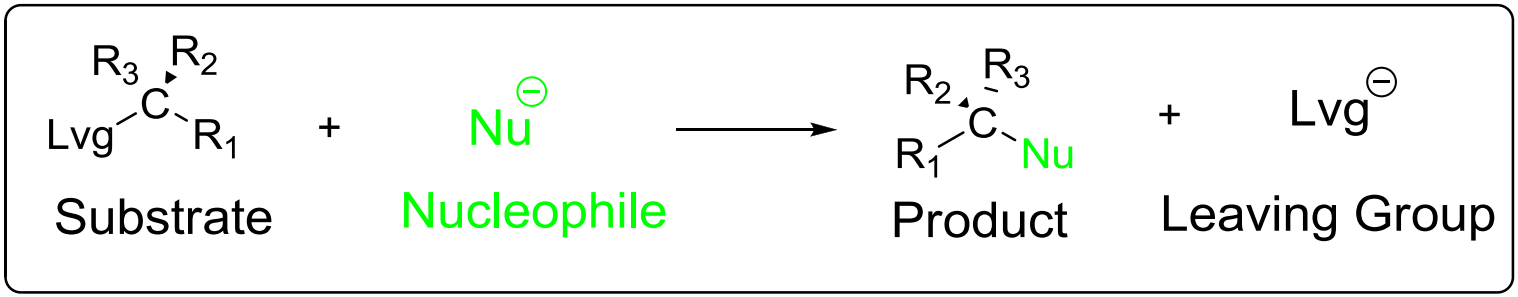
Categories of Nucleophiles

Very Good nucleophiles	HS^-, I^-, RS^-
Good nucleophiles	Br^-, HO^-, RO^-, CN^-, N_3^-
Fair nucleophiles	NH_3, Cl^-, F^-, RCO_2^-
Weak nucleophiles	H_2O, ROH
Very weak nucleophiles	RCO_2H

The best nucleophiles should also be weak bases to limit the competition between substitution and elimination.

Asymmetric Synthesis

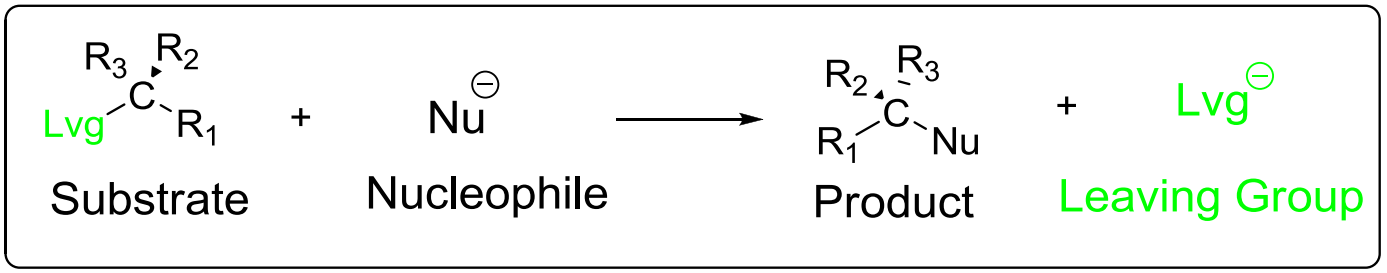
Synthetically Important Nucleophiles



Nucleophile	Source	Synthetic Targets
-SH	NaSH	Thiols such as cysteine
RS-	RSNa	Thioglycosides
I-	NaI	Alkyl iodides
Br-	NaBr	Alkyl bromides
-CN	NaCN	Cyanohydrins and 1º amines
$-N_3$	NaN_3	Chiral amines and amino acids

Asymmetric Synthesis

SN_2 Reactions: Good Leaving Groups Needed



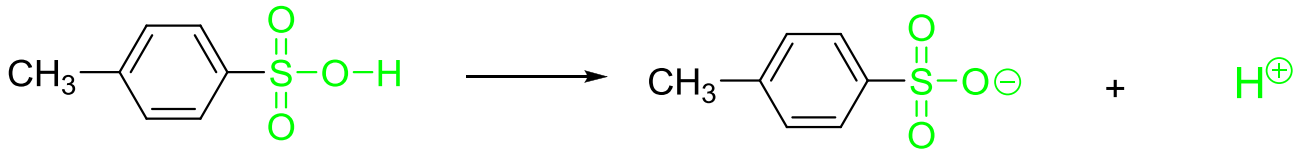
A **leaving group** is an atom (or a group of atoms) that is displaced as stable species taking with it the bonding electrons.

The leaving group may be an anion (*e.g.* I^-) or a neutral molecule (*e.g.* H_2O).

The better the leaving group, the more likely it is to depart: The more the stable a **Lvg**$^-$ is, the more it favours its "leaving".

A good leaving group is the conjugate base of a strong acid.

Some of the strongest organic acids are the sulphonic acids.



p-Toluenesulphonic acid
p-TsOH

p-Toluenesulphonate
p-TsO⊖

pKa = -2.8

Asymmetric Synthesis

SN_2 Reactions: The Good Leaving Groups

Classification of Leaving Groups

Excellent leaving groups	TsO^-, MsO^-
Very Good leaving groups	I^-, H_2O
Good leaving groups	Br^-
Fair leaving groups	Cl^-
Poor leaving groups	F^-
Very poor leaving groups	HO^-, NH_2^-, RO^-

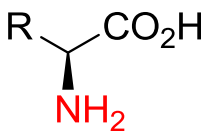
Generally, the order of leaving group ability is as follows:

TsO- (Excellent) > I^- > Br^- > Cl^- > F^- (Poor)

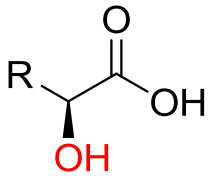
Chiral Pool Synthesis

New Chiral Centres through Substitution Reactions

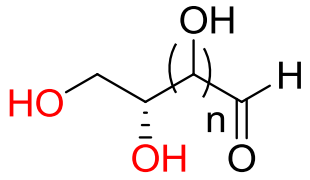
Chiral pool substrates that are commonly used in organic synthesis contain functional groups that are poor leaving groups.



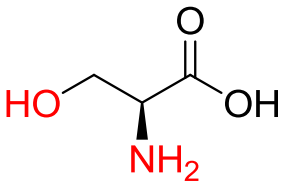
Natural L-Amino acids



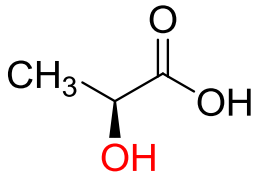
α-Hydroxy acids



Natural D-Sugars

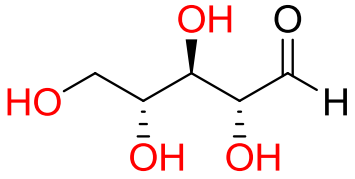


L-Serine



(S)-Lactic acid

(Milk)



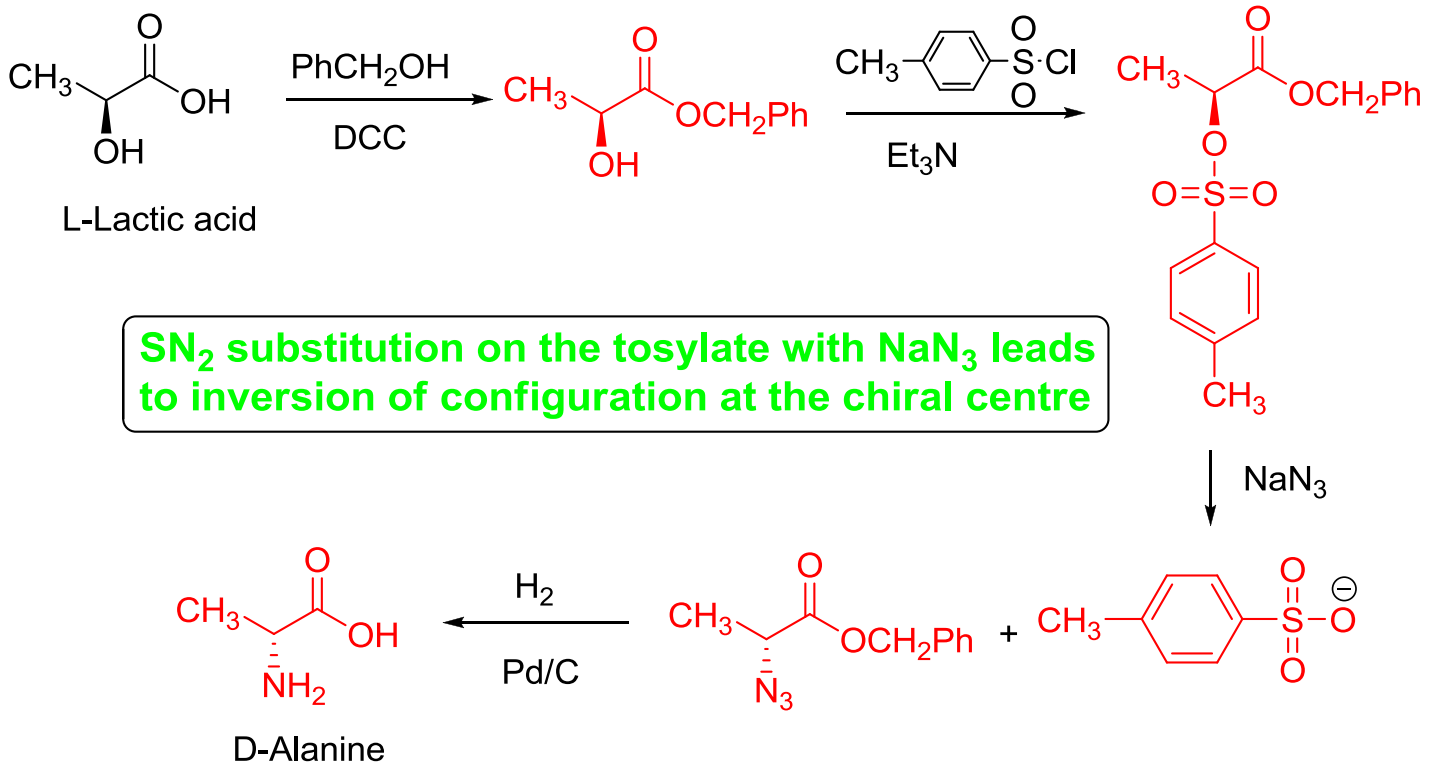
D-Ribose

These functional groups have to be converted into good leaving groups that can be used in substitution reactions.

Chiral Pool Asymmetric Synthesis

Synthesis of Unnatural Amino Acids

The chiral pool synthesis of D-alanine from L-lactic acid can be achieved via conversion to *p*-toluenesulphonate.

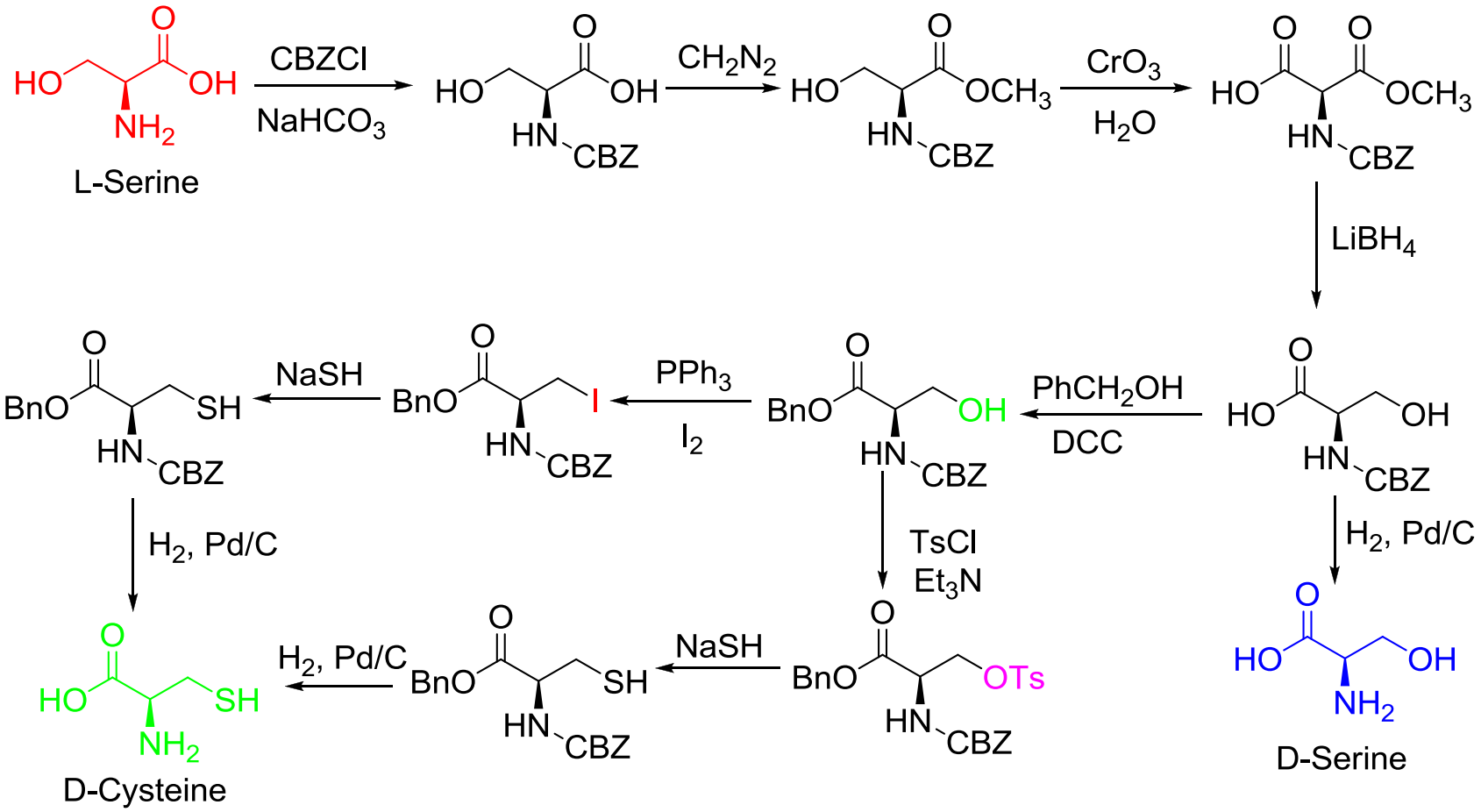


Any synthetic success dictates for a judicious introduction of protecting groups in the starting material to assist subsequent functionalization to the target molecule.

Chiral Pool Asymmetric Synthesis

Synthesis of Unnatural Amino Acids

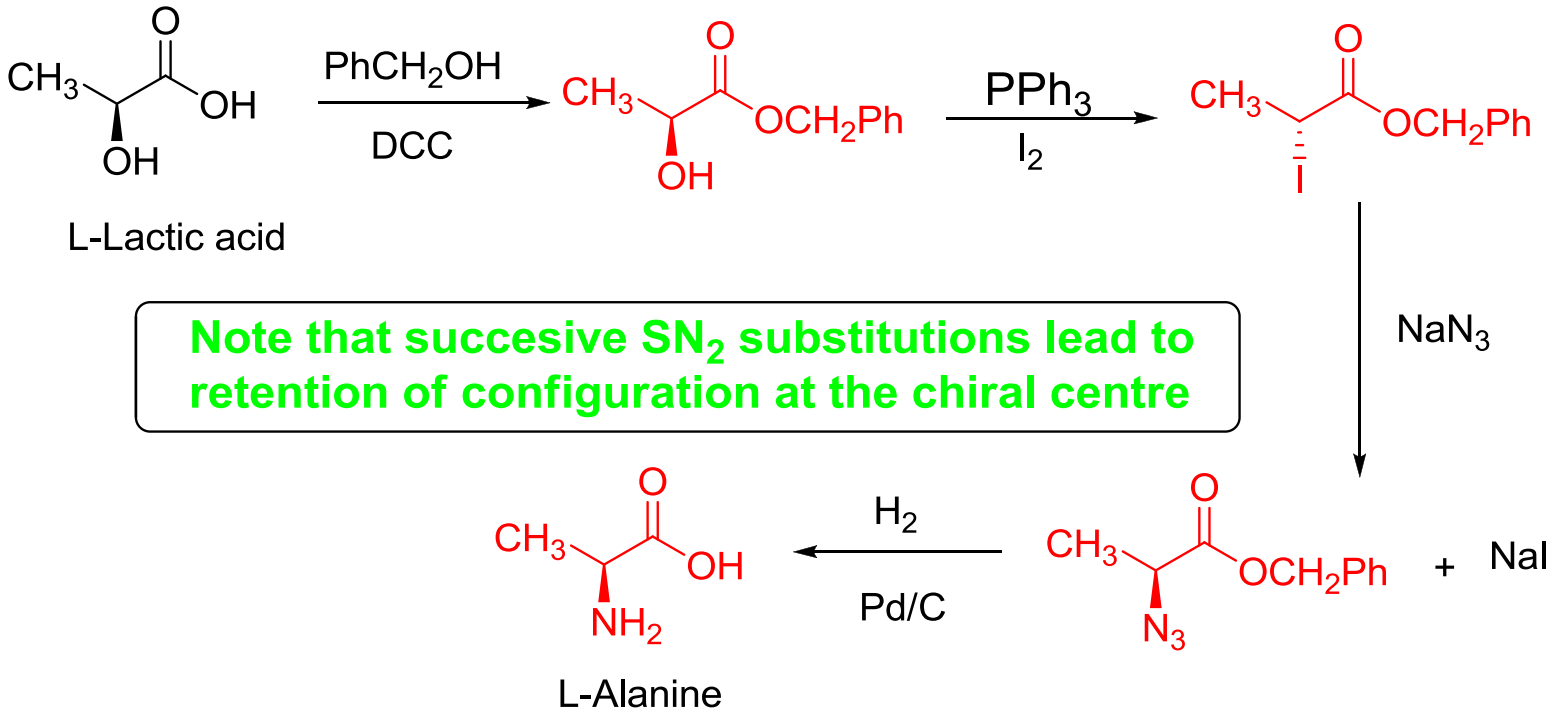
Chiral pool synthesis of the unnatural amino acid, D-cysteine, from the natural L-serine is feasible.



Chiral Pool Asymmetric Synthesis

Synthesis of Natural Amino Acids

The chiral pool synthesis of L-alanine from L-lactic acid can be achieved via double inversion through an iodide.



Note that the iodination with PPh_3/I_2 follows an SN_2 pathway leading to inversion of configuration during the formation of the iodide from benzyl lactate.

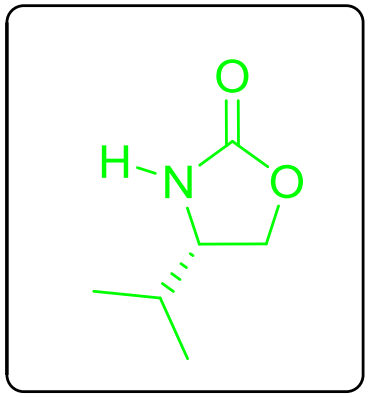
Chiral Auxiliary Approach to Asymmetric Synthesis

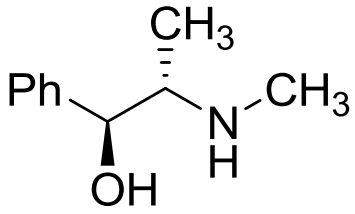
What is a Chiral Auxiliary?

A chiral auxiliary is a chiral molecular unit that can be temporarily incorporated in an achiral substrate to guide selective formation of one of a possible pair of enantiomers.

Chiral auxiliaries are optically active compounds and introduce chirality in otherwise achiral starting materials.

Examples of chiral auxiliaries used in the alkylation of enolates.





Chiral Auxiliary Approach to Asymmetric Synthesis

How Does a Chiral Auxiliary Work?

A chiral auxiliary physically blocks one of two possible trajectories of attack on an achiral substrate, leaving only the desired trajectory open for reaction.

Since the chiral auxiliary is enantiopure, the two trajectories are not equivalent but diastereomeric.

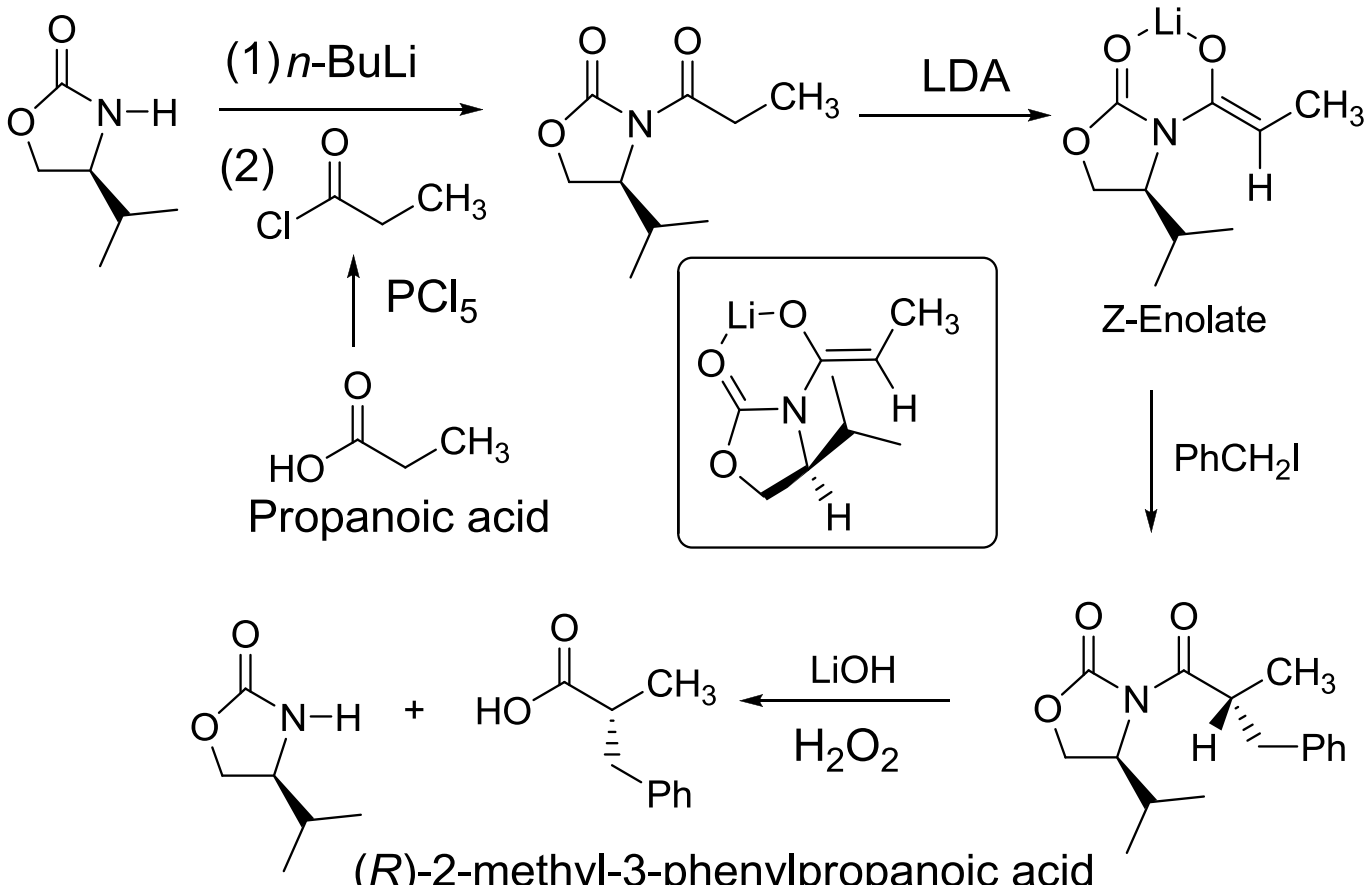
The temporary stereocenter introduced by the chiral auxilliary directs the formation of a second stereocenter.

The stereochemistry of the new chiral centre can be rationalized based on steric considerations.

Chiral Auxiliary Approach:

Asymmetric Enolate Alkylation

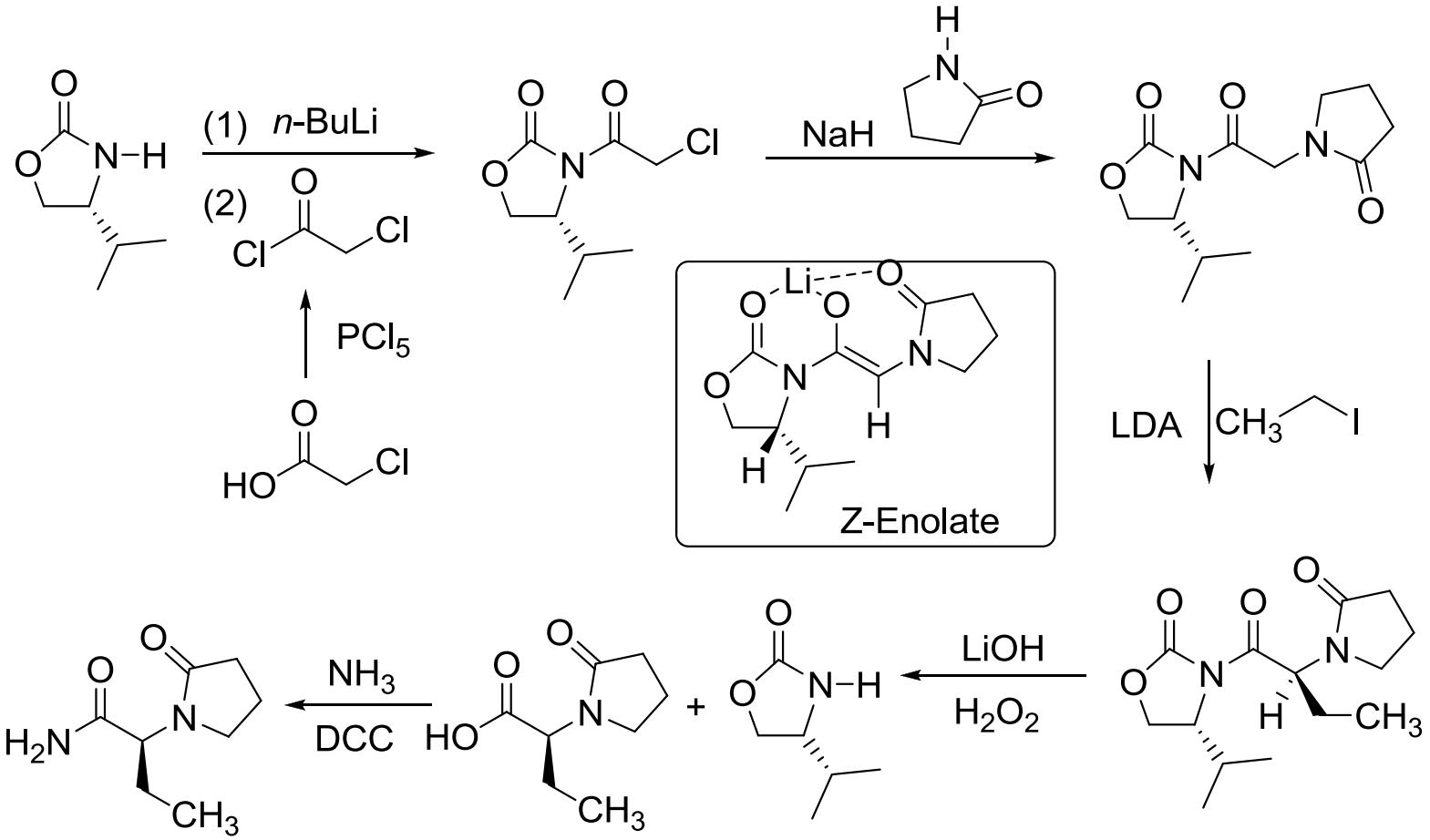
Optically active carboxylic acids can be prepared with high enantiomeric excess based on the chiral auxiliary approach to asymmetric synthesis.



Chiral Auxiliary Approach

Asymmetric Synthesis of an Antiepileptic Drug

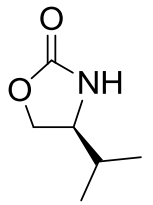
The antiepileptic drug, levetiracetam, can be synthesized based on the chiral auxiliary approach outlined below.



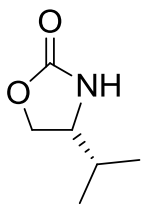
Chiral Auxiliaries

Qualities of a Good Chiral Auxiliary

(a) Needs to be available in both enantiomeric forms

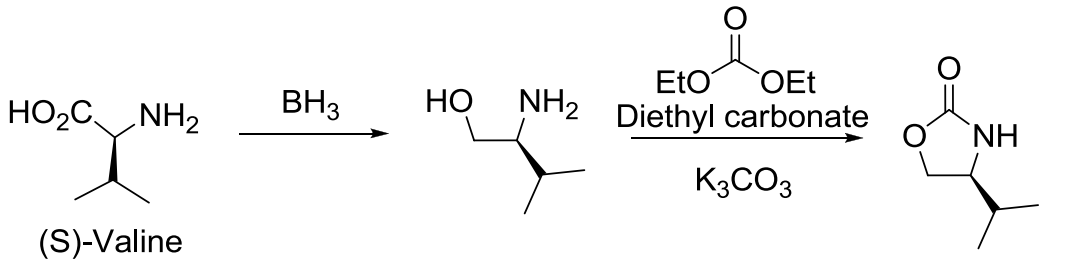


(S)-Enantiomer



(R)-Enantiomer

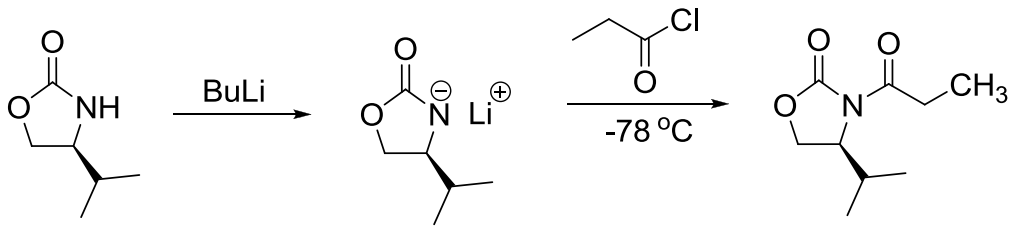
(b) Needs to be easy and quick to synthesize



(S)-Valine
Natural and Cheaper

(S)-(-)-4-Isopropyl-2-oxazolidinone

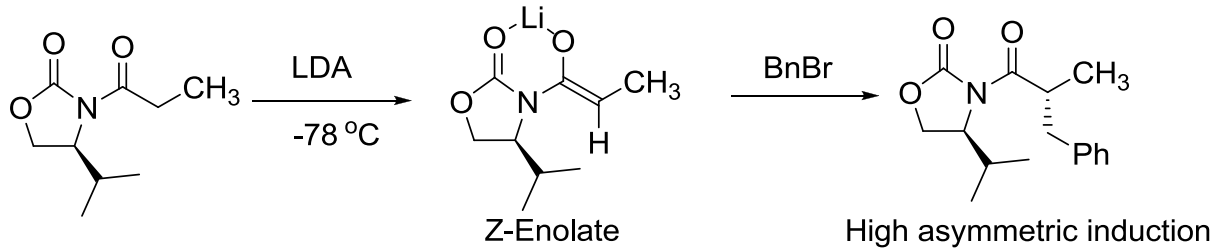
(c) Must be readily incorporated onto an achiral substrate



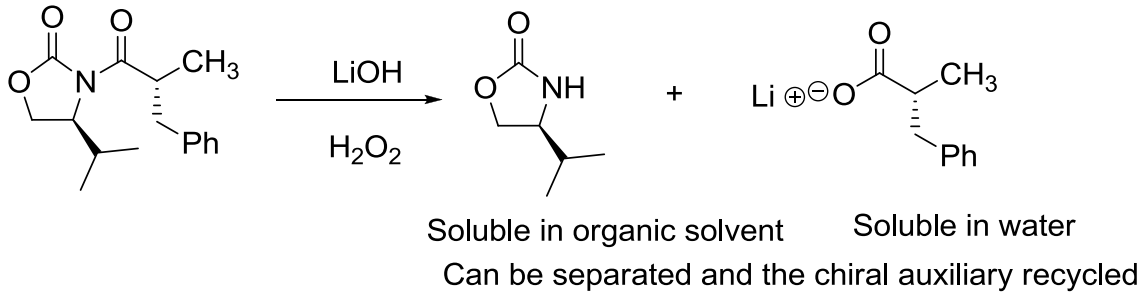
Chiral Auxiliaries

Qualities of a Good Chiral Auxiliary

(d) It should provide good levels of asymmetric induction leading to high enantiomeric excess (ee). Steric bias plays a major role in facial differentiation.



(e) Needs to be selectively cleaved from the substrate under mild conditions



(f) Must be recoverable and re-useable

Terminology of Chiral Auxiliary Approach to Asymmetric Synthesis

Asymmetric Induction

Asymmetric induction refers to the control of stereoselectivity exerted by an existing chiral centre on the formation of a new chiral centre.

This is one property that many strategies in asymmetric synthesis have in common. The aim being to convert enantiomers into diastereomers. Since diastereomers have different reactivities, there will be preferential formation of one diastereomer.

A chiral auxiliary with a high asymmetric induction provides high enantiomeric excesses.

Terminology of Chiral Auxiliary Approach to Asymmetric Synthesis

Enantiomeric excess (ee)

The enantiomeric excess (ee) is defined as the excess of one enantiomer over the other generated in an enantioselective reaction and is usually expressed as a percentage of the whole. It usually gives a measure of the efficiency of the enantioselective reaction.

$$ee = \left(\frac{(R - S)}{(R + S)} \right) \times 100$$

(Where R and S are the amounts of each enantiomer in the mixture)

Chiral Auxiliary Approach to Asymmetric Synthesis

Advantages of Using Chiral Auxiliaries

(a) The levels of diastereofacial control in the reactions are usually high leading to high ee.

(b) The diastereomers generated from the use of chiral auxiliaries can be separated by the use of conventional methods (such as chromatography and crystallization).

(c) Chiral auxiliaries can be recycled (re-used) thus reducing the expenses of buying the chiral reagent routinely.

(d) The sense of configuration at the newly formed chiral centre can be determined by X-ray crystallography.

Chiral Auxiliary Approach to Asymmetric Synthesis

Disadvantages of Using Chiral Auxiliaries

(a) Both enantiomers of a chiral auxiliary are usually not readily available. More often, one enantiomer may be far more expensive than the other.

(b) Chiral auxiliaries need to be synthesized.

(c) As with protecting groups, there are extra steps associated with the use of chiral auxiliaries. The chiral auxiliary has to be introduced and then removed once it purpose has been accomplished.

(d) A stoichiometric amount of the chiral template (chiral auxiliary) is usually required.