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.

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	3^o and 2^o Substrates	1^o and 2^o Substrates
Nucleophile	Good nucleophile works	Strong nucleophile best
Leaving Group	Good leaving group	Good leaving group

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

Asymmetric Synthesis

SN_2 Reactions: Good Leaving Groups Needed

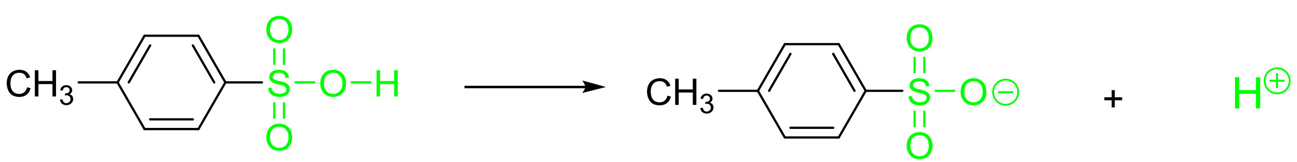
A **leaving group** is an atom (or a group of atoms) that is displaced as stable species taking with it the bonding electrons.

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

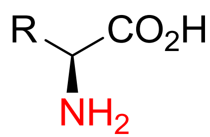
p-Toluenesulphonate
p-TsO⊖

pKa = -2.8

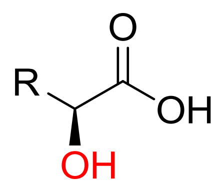
Chiral Pool Synthesis

New Chiral Centres through Substitution Reactions

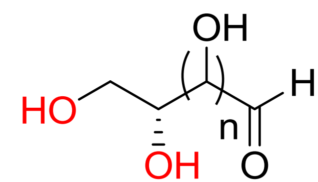
Chiral pool substrates that are commonly used in organic synthesis contain functional groups that are poor leaving groups.



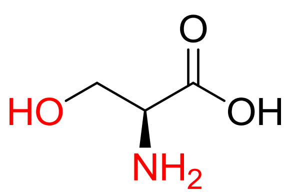
Natural L-Amino acids



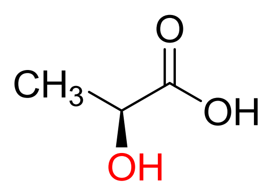
α-Hydroxy acids



Natural D-Sugars

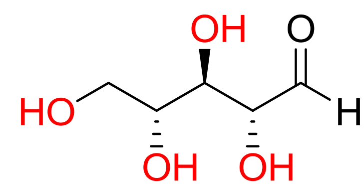


L-Serine



(S)-Lactic acid

(Milk)



D-Ribose

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