

Chiral Auxiliary Approach to Asymmetric Synthesis

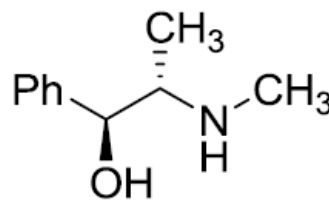
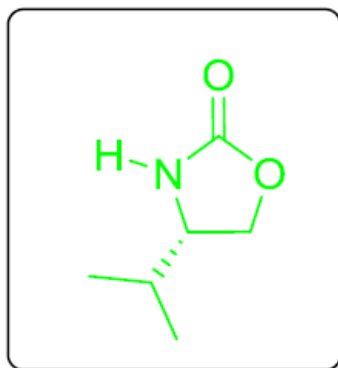
Chiral Auxiliary Approach to Asymmetric Synthesis

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.



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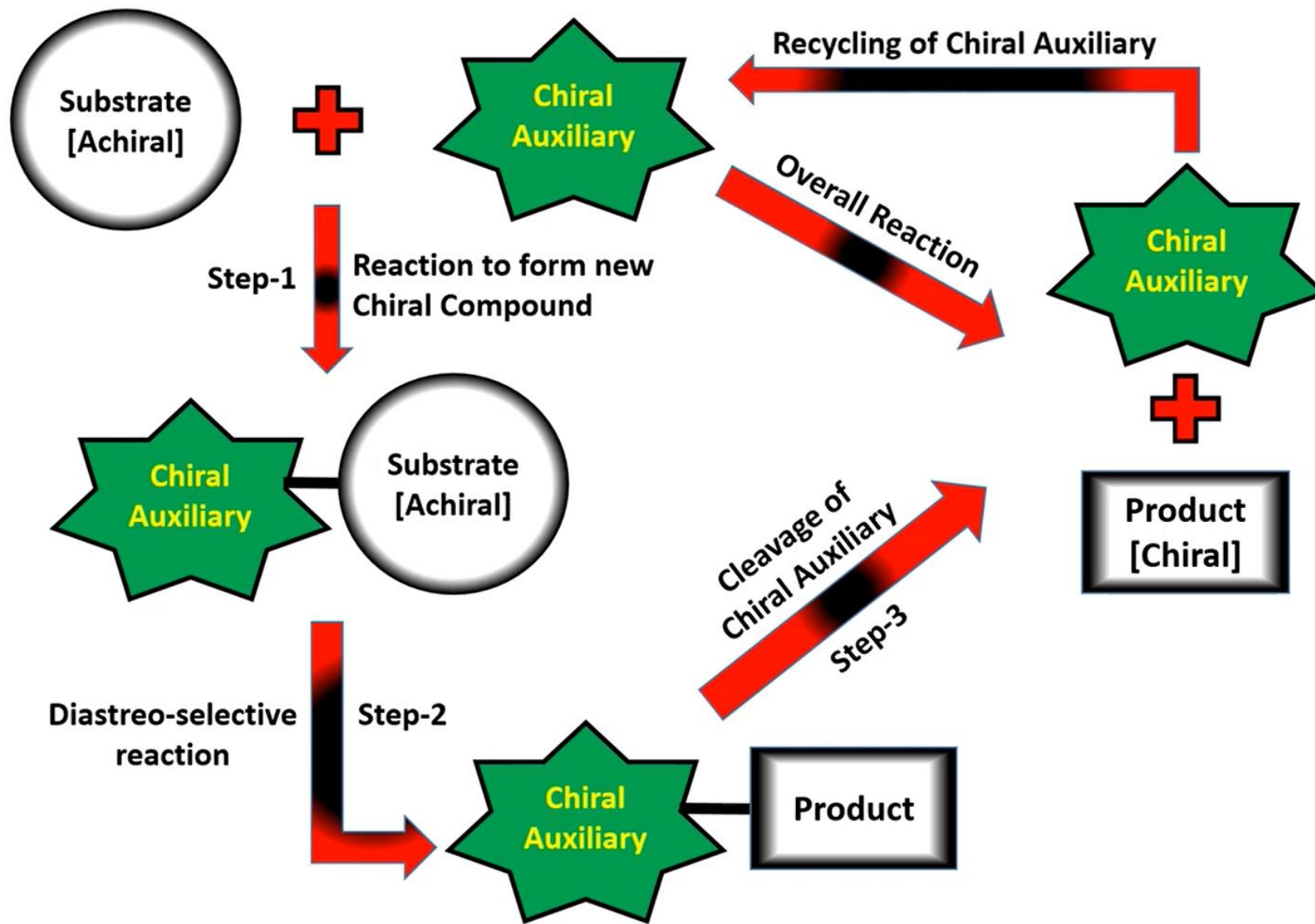
How Does a Chiral Auxiliary Work?

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

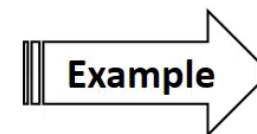
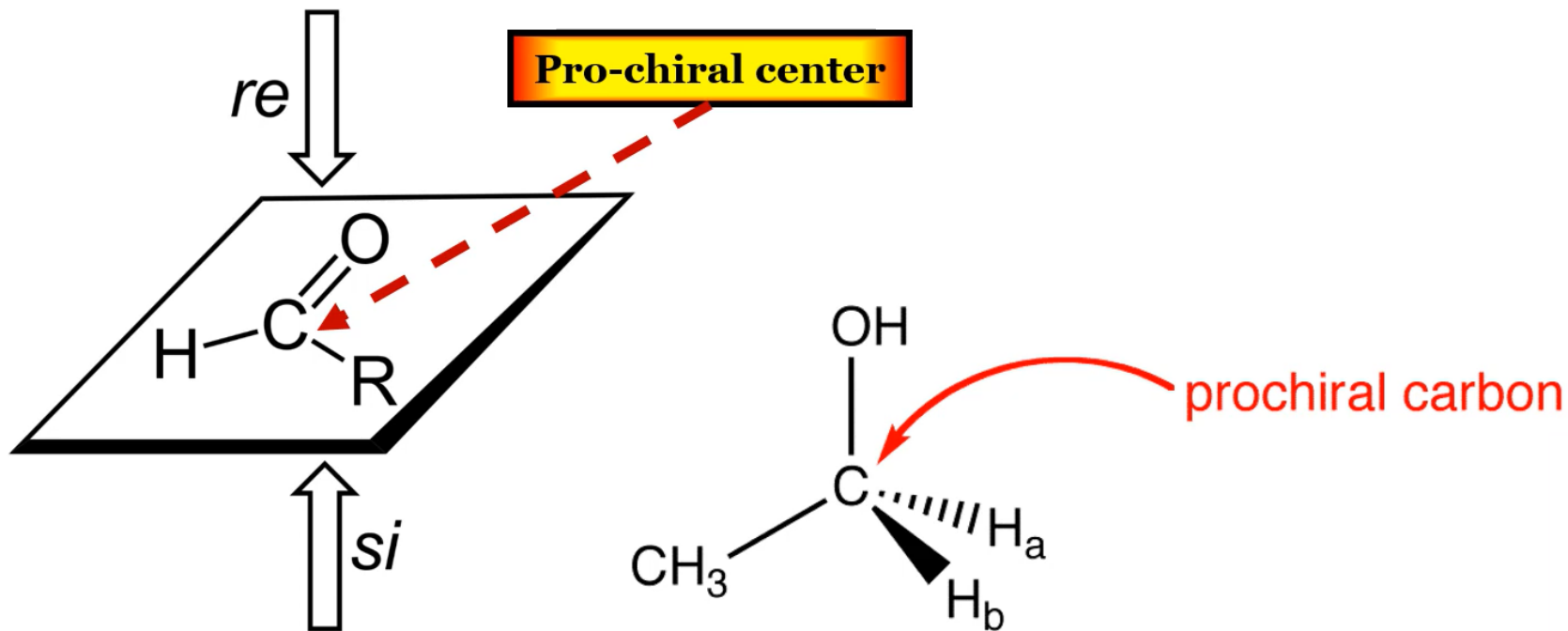
Since the chiral auxiliary is enantiopure, the two trajectories are not equivalent but diastereomeric.

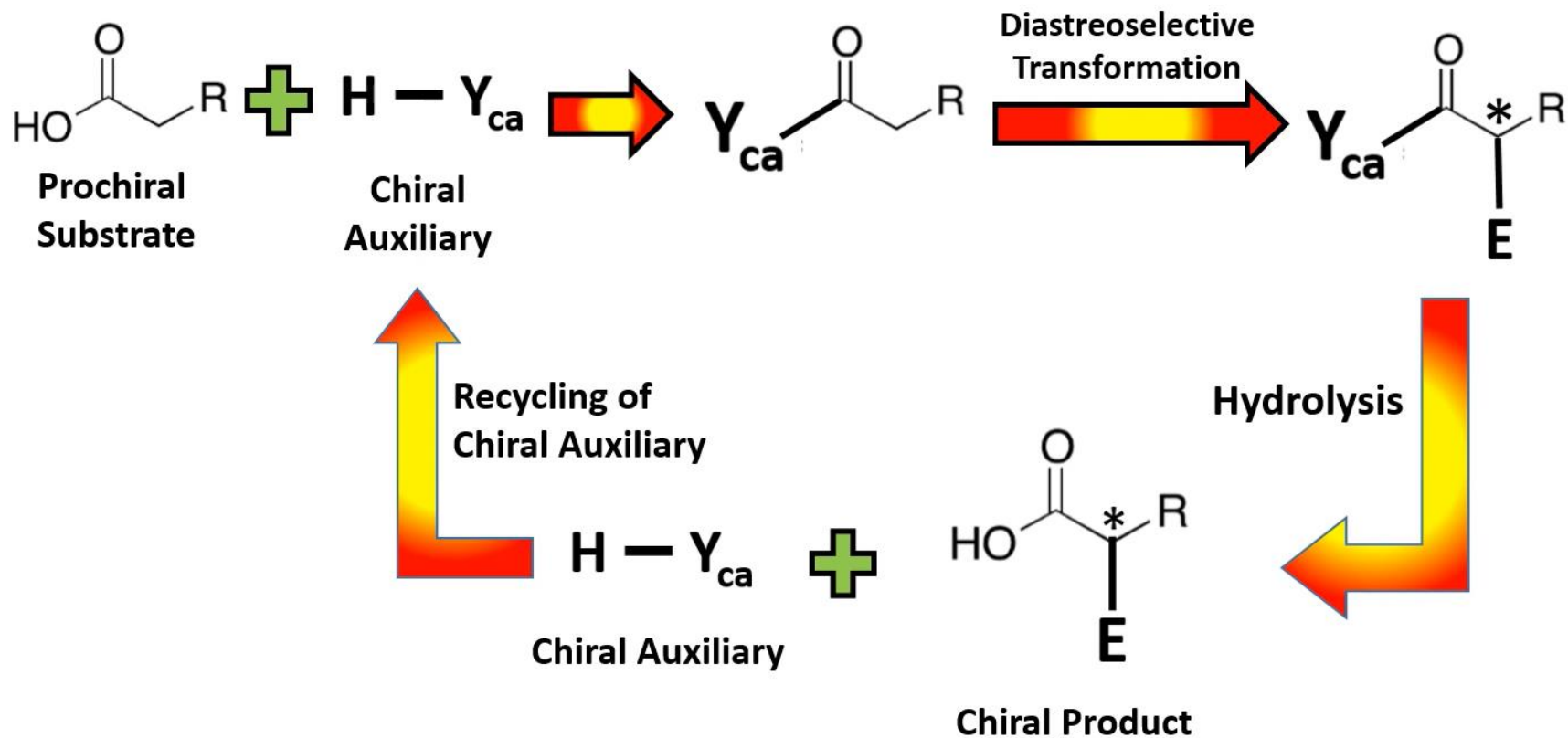
The temporary stereocenter introduced by the chiral auxiliary directs the formation of a second stereocenter.

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

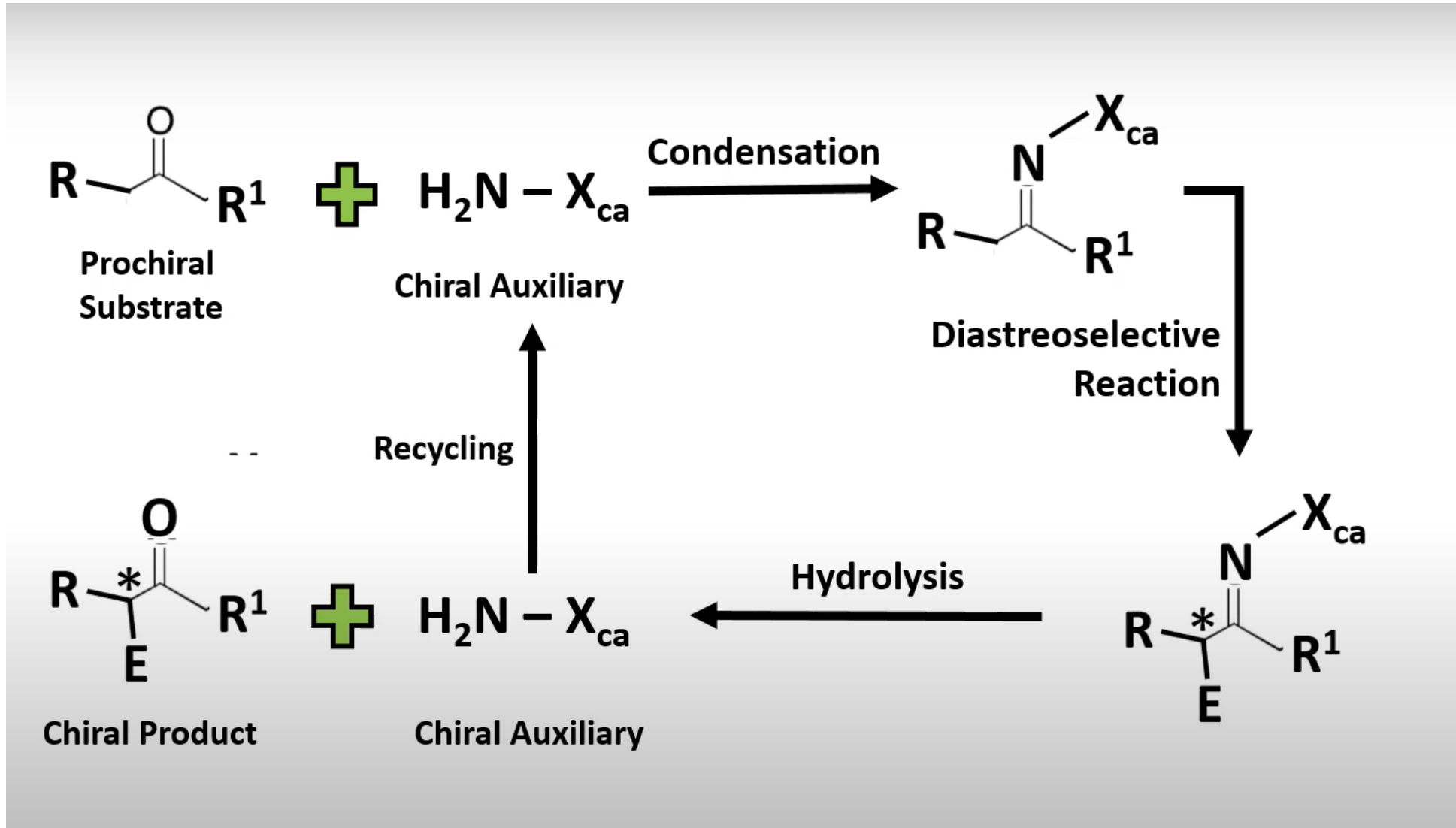


and introduce **chirality in racemic compounds or a pro-chiral center.**

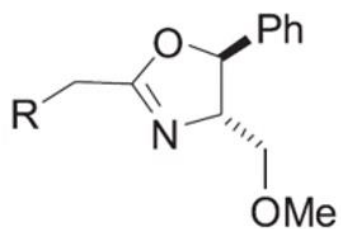




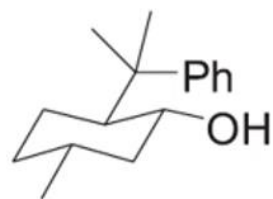
Chiral Auxiliary will guide the preferential entry of E leading to formation of excess of one Stereoisomer over the other!



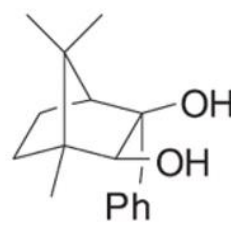
Important Chiral Auxiliaries used in Asymmetric Synthesis



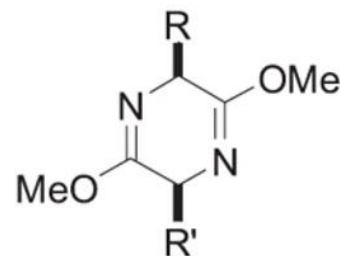
Meyers



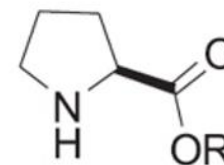
Corey



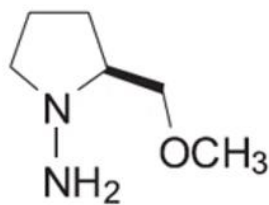
Hoffmann



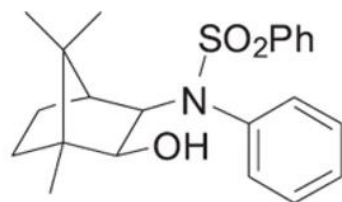
Schöllkopf



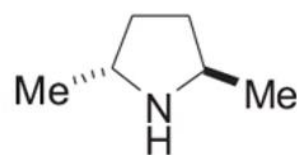
Yamada



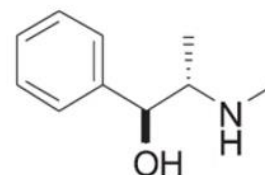
Enders



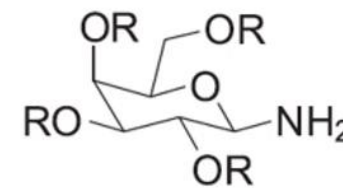
Helmchen



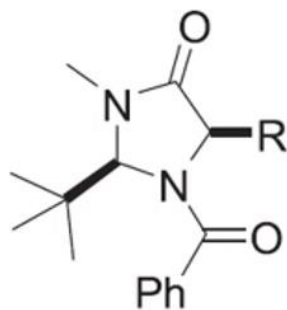
Whitesell



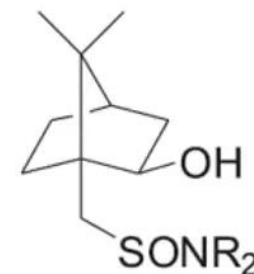
Myers



Kunz



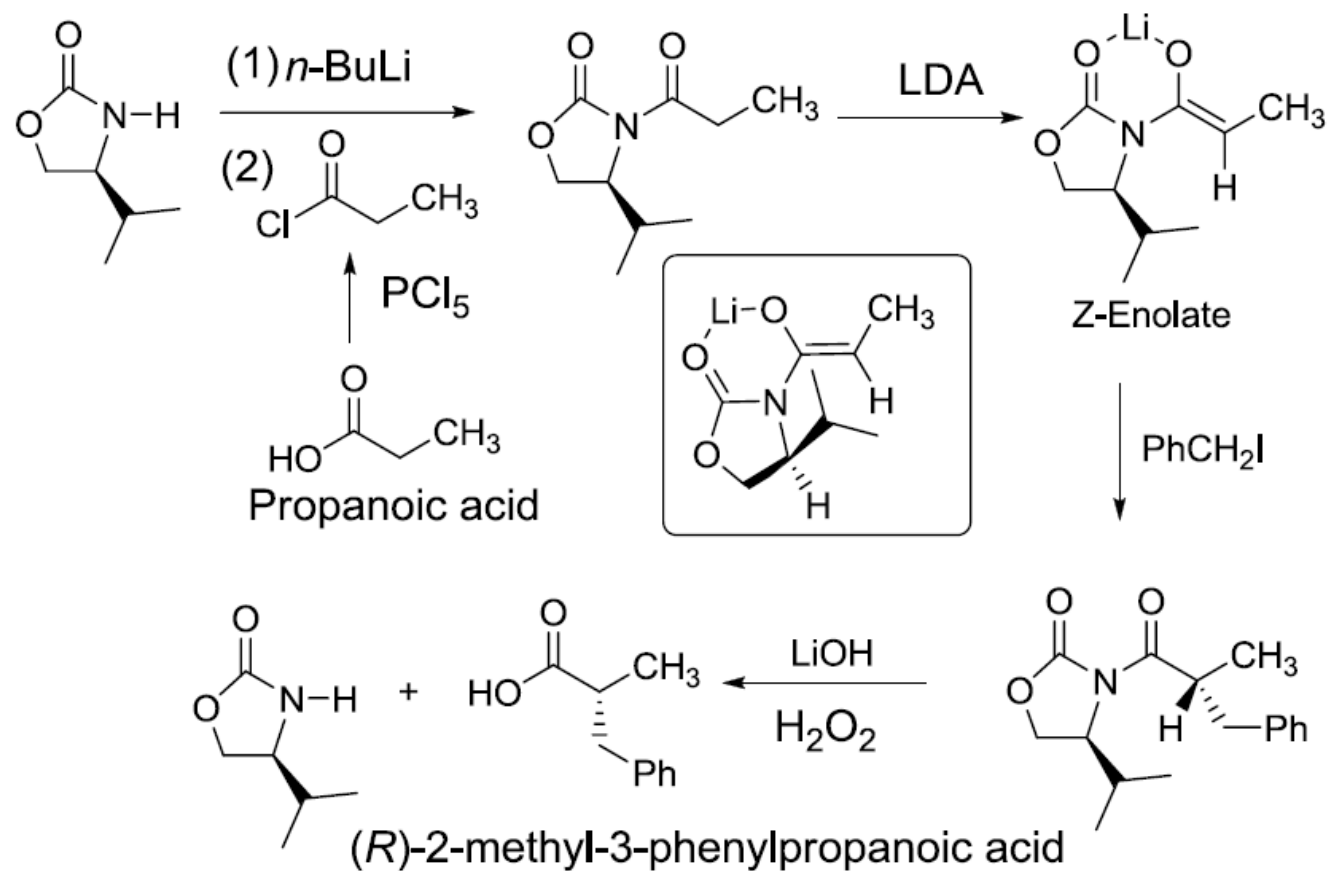
Seebach



Oppolzer

Chiral Auxiliary Approach: Asymmetric Enolate Alkylation

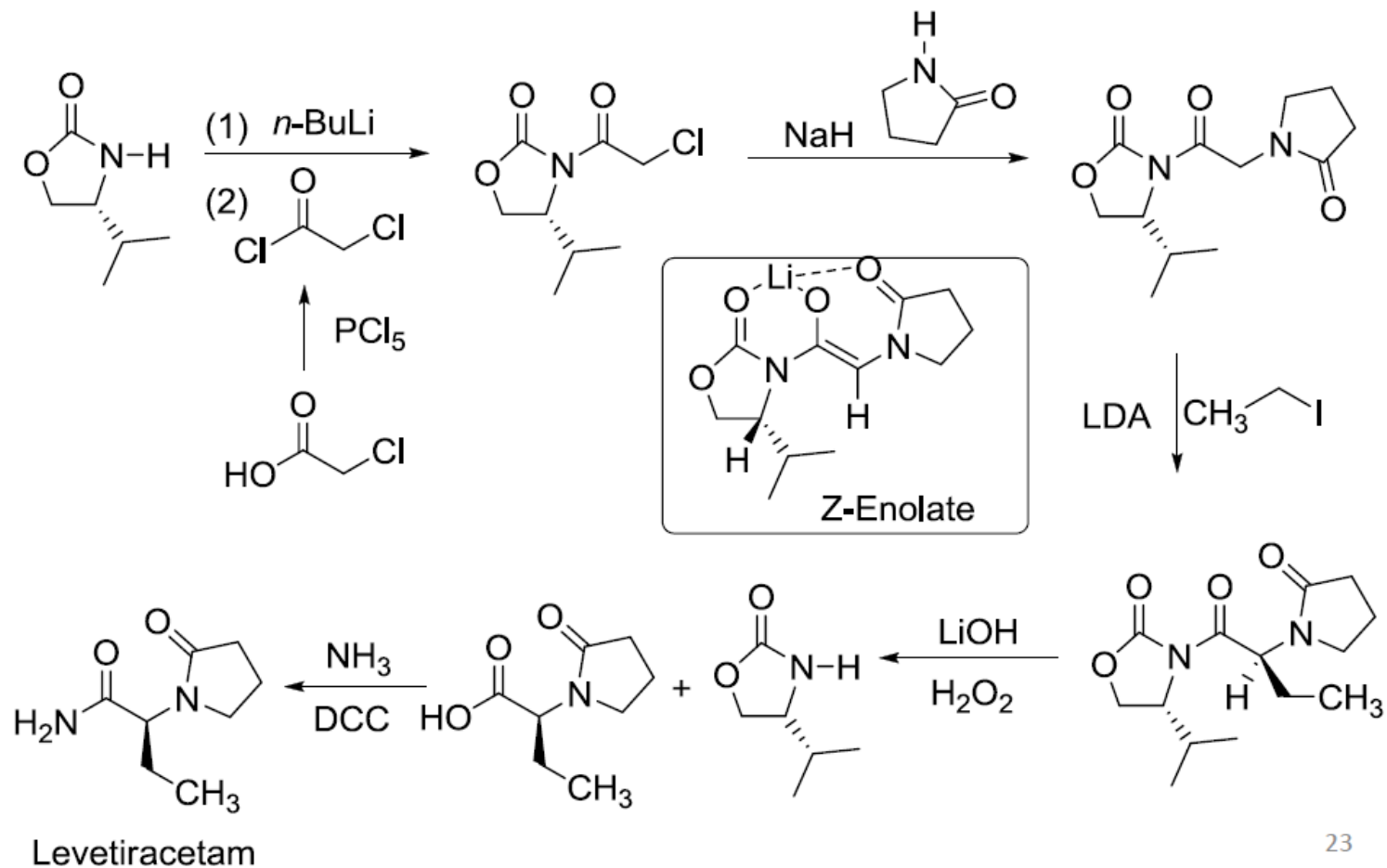
Optically active carboxylic acids can be prepared with high enantiomeric excess based on the chiral auxiliary approach to asymmetric synthesis.

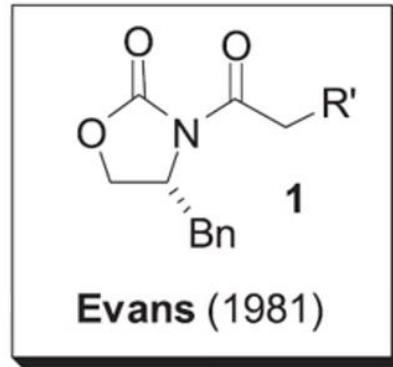


Chiral Auxiliary Approach

Asymmetric Synthesis of an Antiepileptic Drug

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

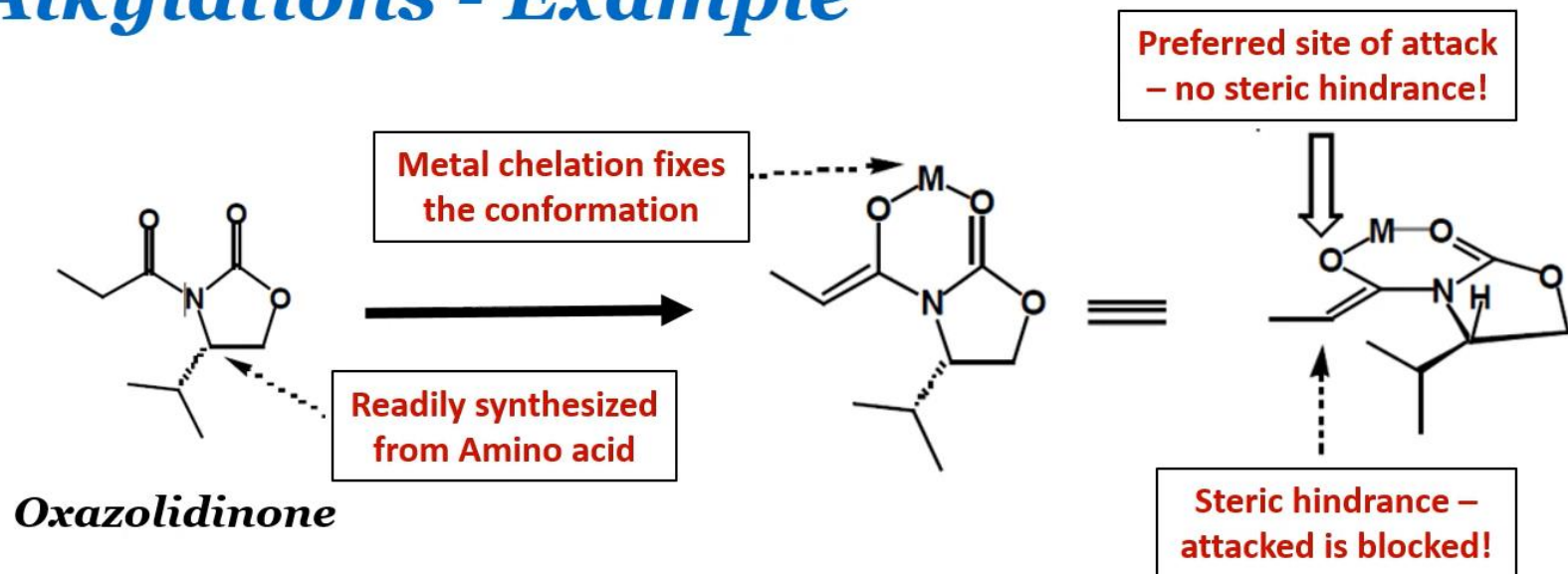




The methodology of asymmetric transformations developed with this chiral imides has been most successful in the stereoselective construction of...

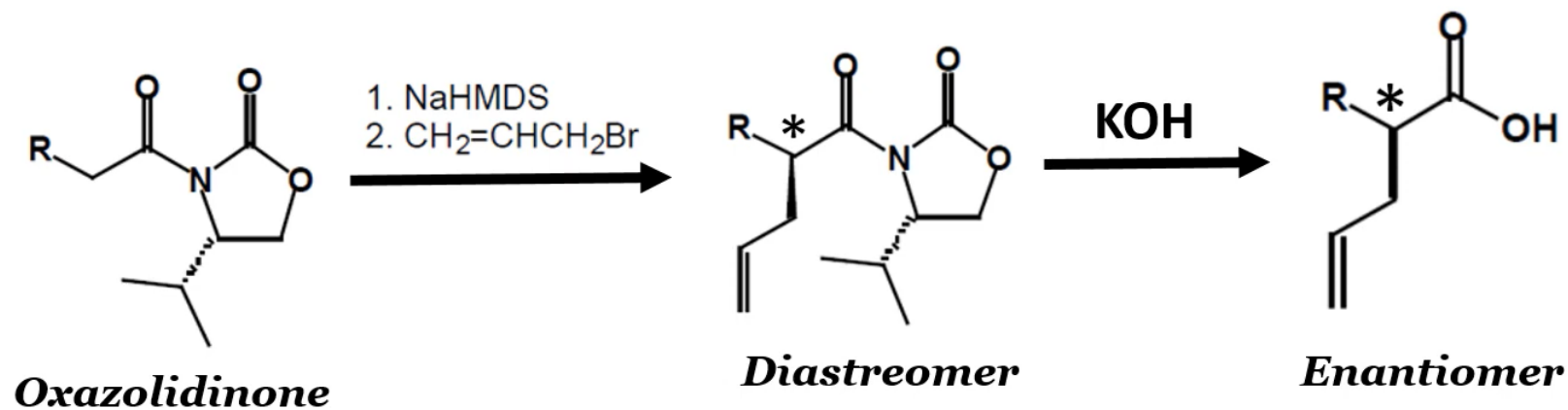
- Numerous chiral building blocks.**
- Natural products.**
- Antibiotics and**
- Medicinally important compounds.**

Evans' Oxazolidinones Alkylations - Example



Because of enolate-geometry, one of its two face is readily accessible for preferred alkylation leading to the excess formation of one stereoisomer over the other!

Evans' Oxazolidinones Alkylations



- ❑ **Enolate-chemistry- a very important Strategy in Synthesis!**
- ❑ **One of the commonest means of forming C–C bonds is *via* enolate-alkylation!**
- ❑ **If a chiral center present, it can get a *diastereoselective reaction*.**

Criteria for Chiral Auxiliaries

- Cheap!**
- Readily available!**
- Easily attached!**
- Induce stereochemistry!**
- Chemically inert!**
- Easily removed!**

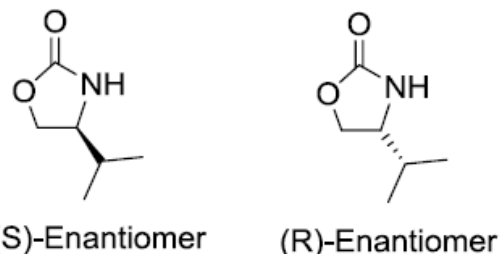


C R I T E R I A

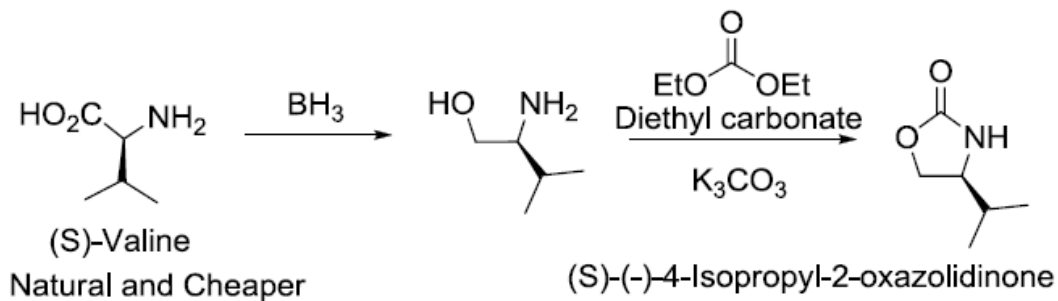
Chiral Auxiliaries

Qualities of a Good Chiral Auxiliary

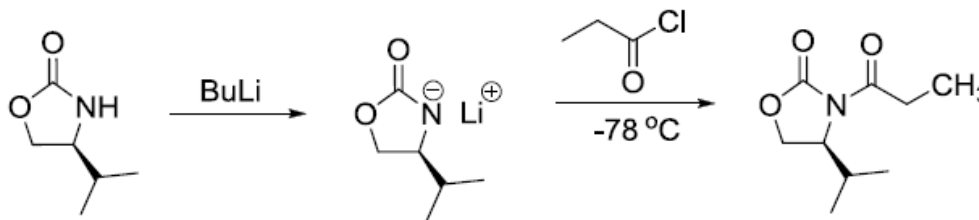
(a) Needs to be available in both enantiomeric forms



(b) Needs to be easy and quick to synthesize



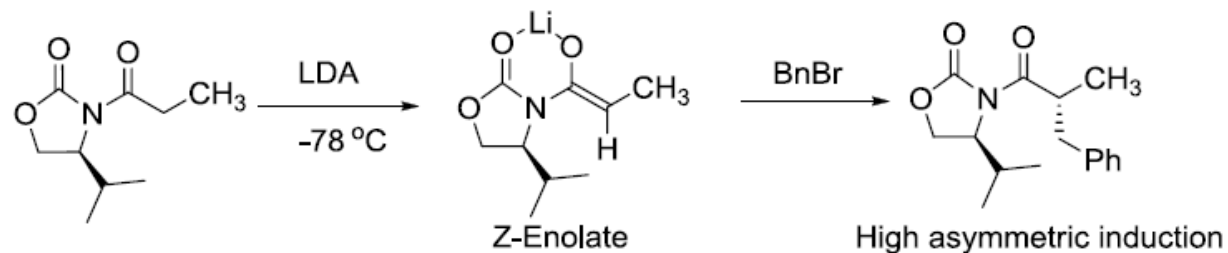
(c) Must be readily incorporated onto an achiral substrate



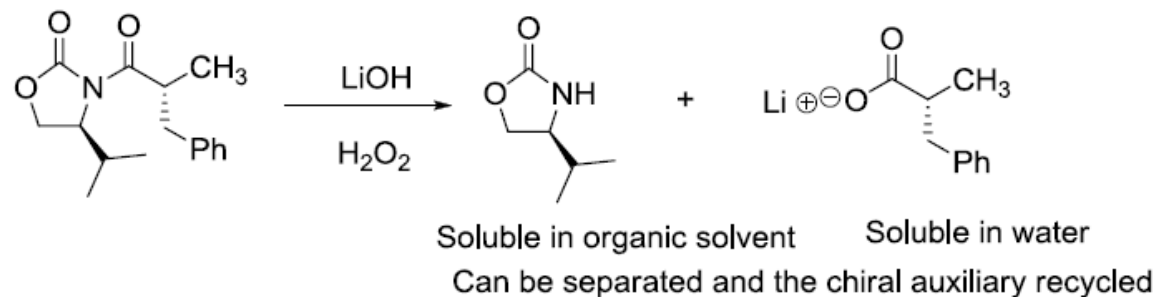
Chiral Auxiliaries

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

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 its purpose has been accomplished.
- (d) A stoichiometric amount of the chiral template (chiral auxiliary) is usually required.

1. What is the enantiomeric excess of an adrenaline sample that has a specific rotation of -47.7 ? Pure adrenaline has a specific rotation of -53 .

$$\text{Optikçe saflık} = \frac{\text{gözlenen özgül çevirme}}{\text{saf enantiyomerin özgül çevirmesi}} \times 100$$

$$ee = 47.7/53 \times 100$$

$$ee = \%90$$

2. How many percent of cholesterol and its enantiomer are present in a sample with an observed specific rotation of -22.4° ? The specific rotation of pure cholesterol is -32° .

$$ee = 22.4/32 \times 100$$

$$ee = \%70$$