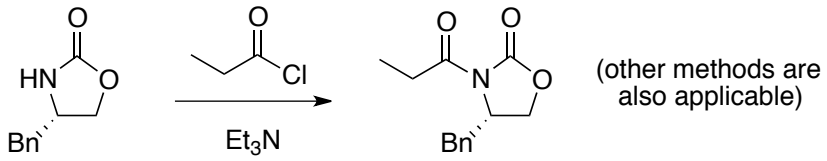
CHEM 330

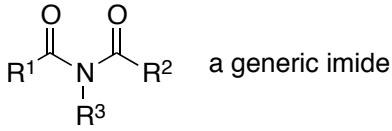
Topics Discussed on Nov. 16

Preparation of Evans auxiliaries from natural L-aminoacids, e.g phenylalanine, valine...

Attachment of enolizable carbonyl segments to an Evans auxiliary, e.g.:

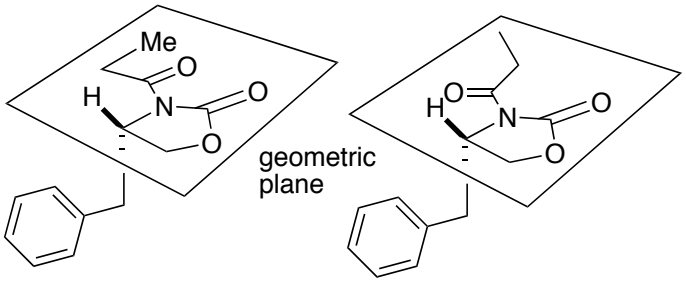


Imides: structures in which 2 carbonyl groups are connected to the same N atom

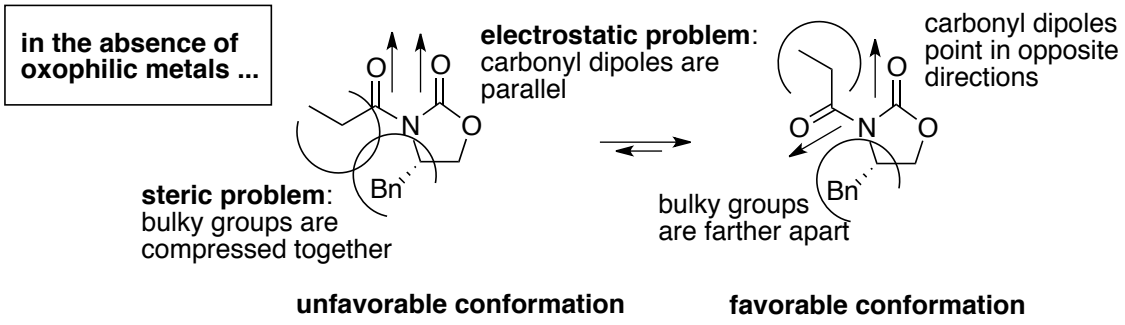


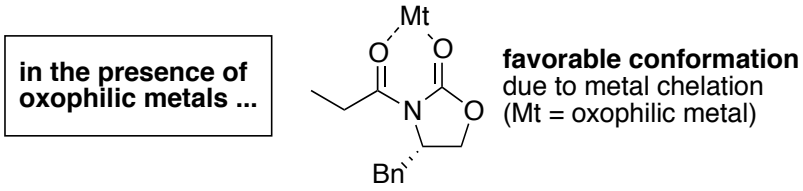
Evans imides: another name for the Evans *N*-acyl-oxazolidinones

Substantial planarity of Evans imides due to resonance interactions and existence of two non-equivalent conformations on which such interactions are maximal:



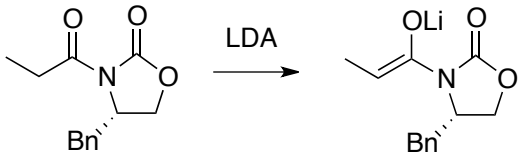
Conformational properties of Evans complexes in the absence and in the presence of chelating, oxophilic metals:



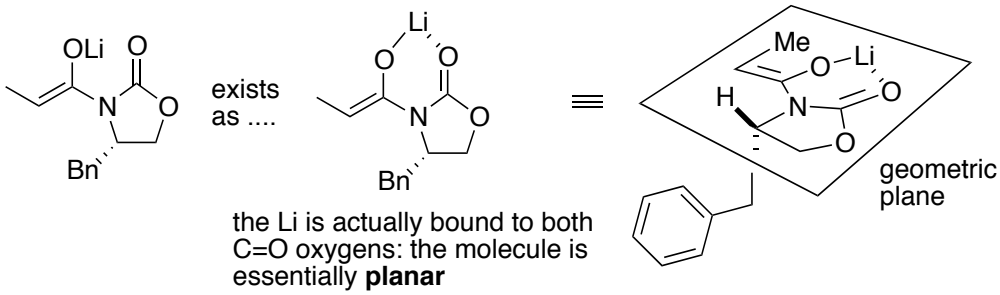


Note: all conformations are substantially planar to maximize resonance interactions

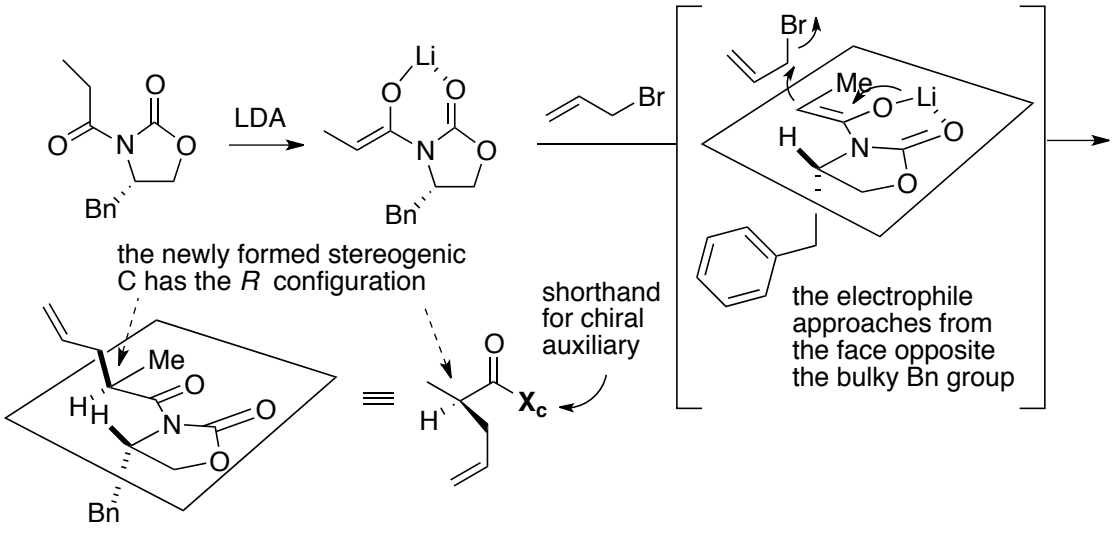
Principle: like amides, Evans complexes form Z enolates selectively, e.g.:



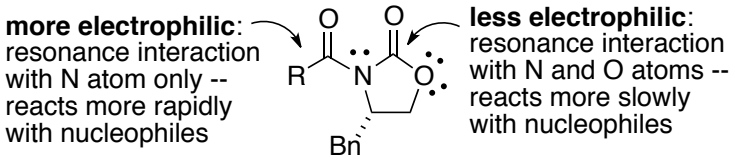
Conformational properties of Evans enolates: formation of a chelate:



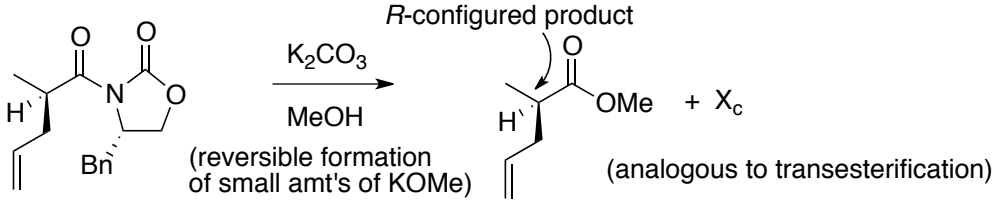
Alkylation of Evans enolates: preferential attack from the face of the enolate *opposite* the bulky benzyl group (minimization of steric interactions), e.g.:



Relative electrophilic character of the 2 carbonyls of an Evans complex:

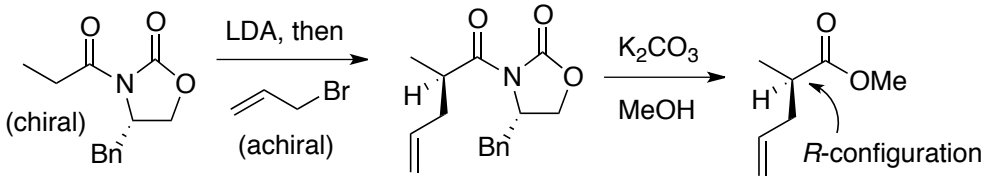


Facile removal of the Evans auxiliary from alkylated derivatives of Evans imides, e.g. by transesterification:



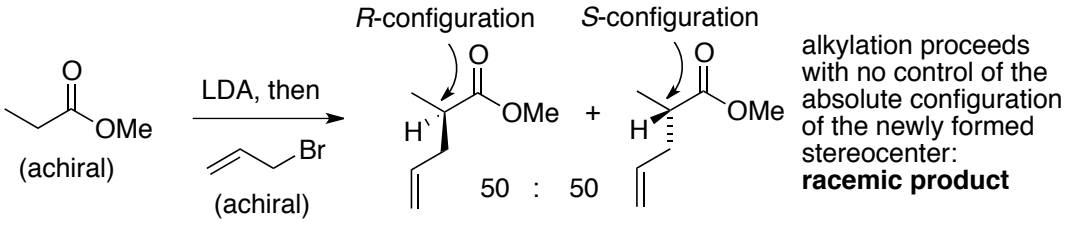
Note: saponification and transesterification reactions run under the above conditions are much faster than α-deprotonation. So, exposure of the products to LiOH or K_2CO_3 in MeOH for a short period of time induces rapid saponification / transesterification with no erosion of stereochemical integrity of the enolizable center.

Net result of alkylating an Evans enolate: control of the absolute configuration of the product (=asymmetric alkylation):



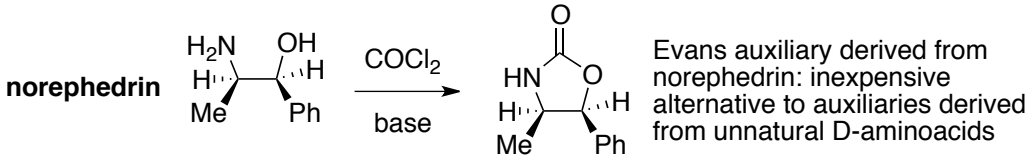
alkylation has now occurred with control of the absolute configuration of the newly formed stereocenter: **enantioenriched product**

but if one were to prepare the above ester by deprotonation (e.g., LDA) of methyl propionate and allylation of the resultant enolate, the product thus obtained would be *racemic*:

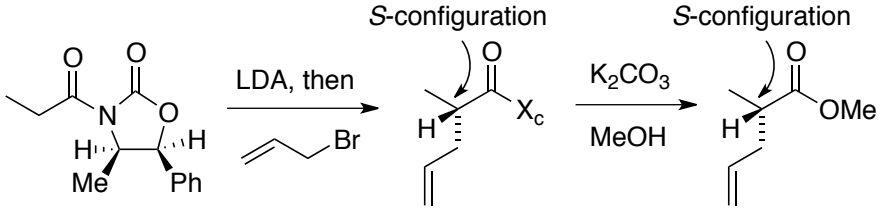


Principle: the stereoselective preparation of the *enantiomers* of the alkylation or aldol products obtained as seen above would require the enantiomeric form of Evans auxiliary, i.e., one derived from an unnatural D-aminoacid. While some D-aminoacids are inexpensive, others, such as (D)-phenylalanine, (D)-valine, etc., are costly

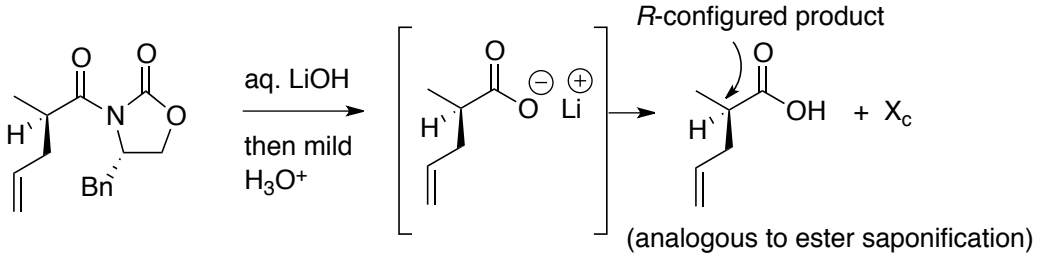
Norephedrin and Evans auxiliary derived from it:

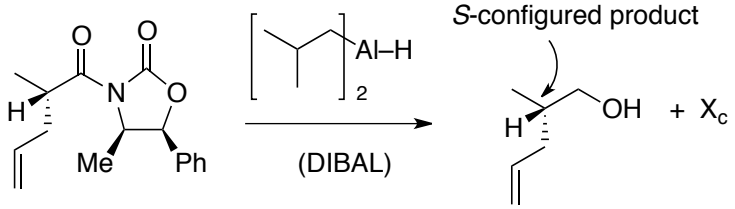


Norephedrin-derived Evans auxiliary in the preparation of the enantiomer of the alkylation product seen earlier:

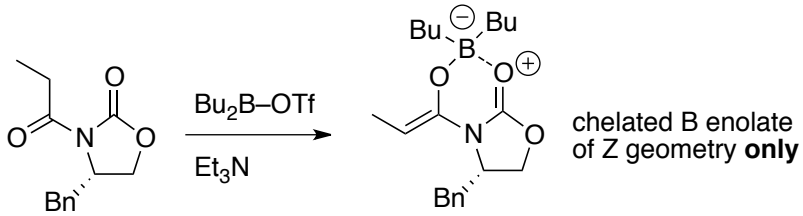


Saponification and reduction of products of Evans enolate alkylation leading to enantioenriched acids and alcohols, respectively; e.g.:



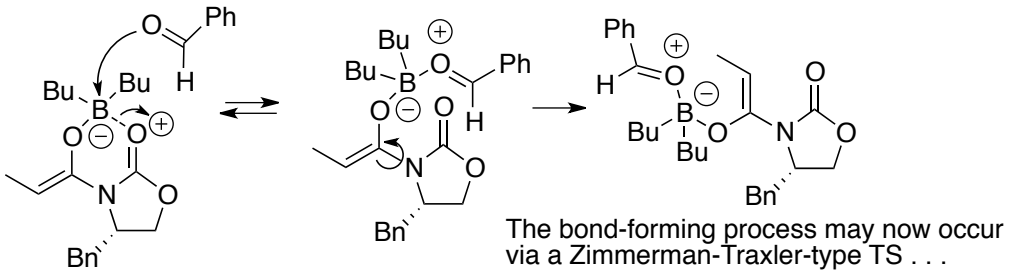


Evans aldol reactions: use of dibutylboron enolates



Note: the mechanism of formation of the Evans boron enolate is substantially the same as that seen earlier for ketones (notes of November 9)

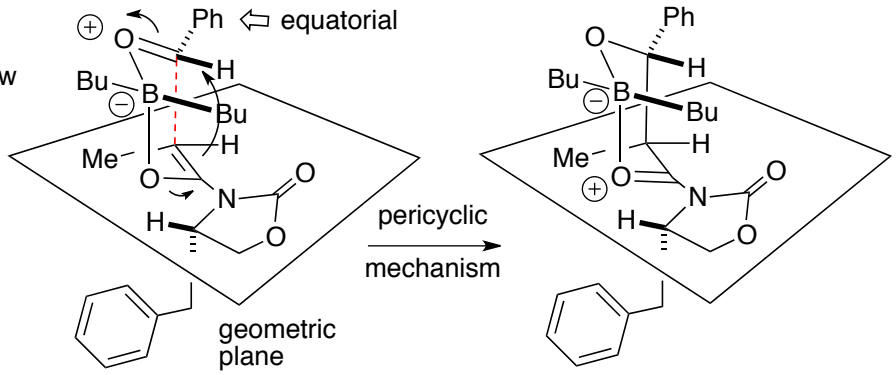
First interaction between an aldehyde (e.g. benzaldehyde) and an Evans boron enolate: release of the dative bond between the B and the oxazolidinone oxygen atoms and consequent internal rotation leading to a more stable conformation:

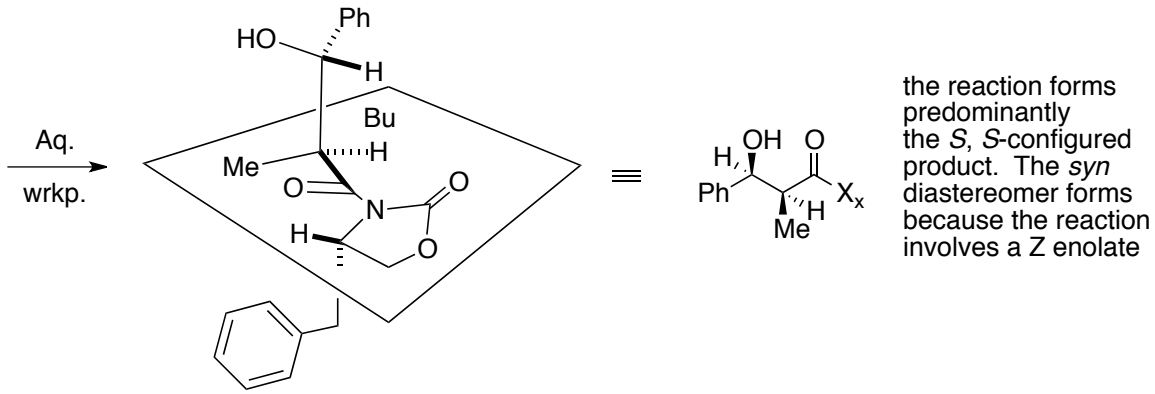


Transition state model for the Evans aldol reaction:

the activated complex above folds into a Zimmerman-Traxler conformation to allow the nucleophilic and electrophilic centers to interact. This occurs so as to minimize steric interactions. Notice the equatorial orientation of the phenyl group.

In red: incipient bond





the reaction forms predominantly the *S*, *S*-configured product. The *syn* diastereomer forms because the reaction involves a *Z* enolate

Principle: the conduct of the same Evans aldol reaction with an enolate based on a norephedrine-derived auxiliary would result in formation of a product of *R*, *R*-configuration: