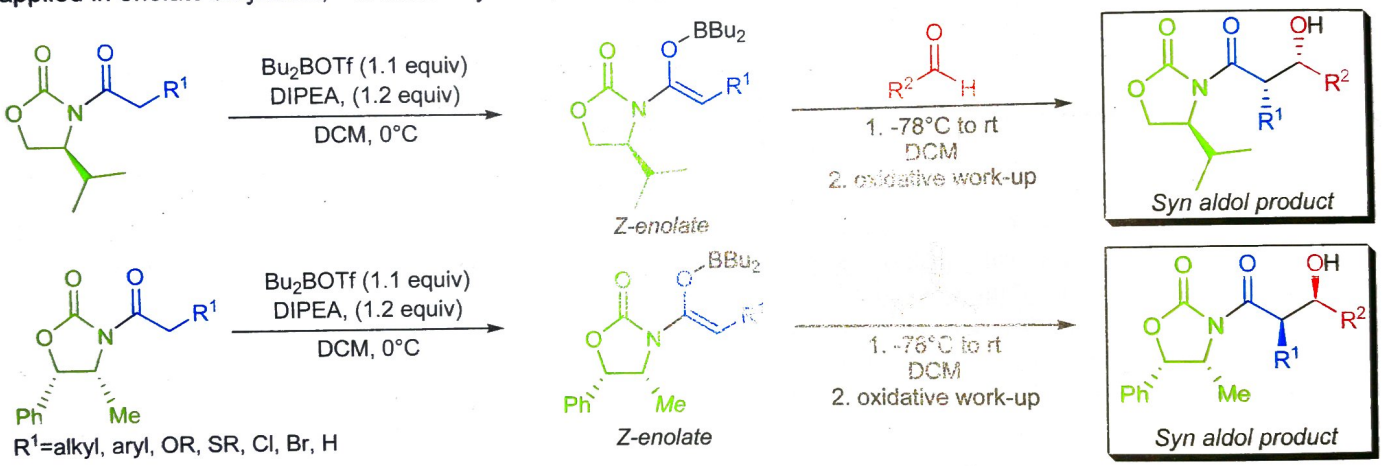
EVANS ALDOL REACTION

(References are on page 583)

Importance:

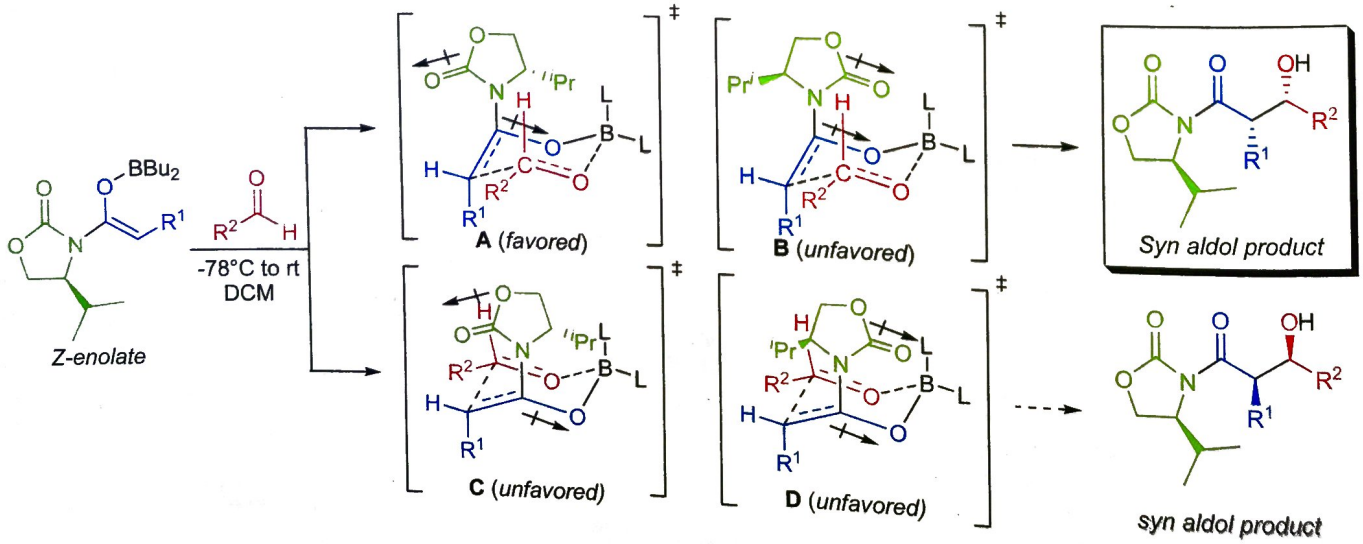
[*Seminal Publication*[1]; *Reviews*[2-10]; *Modifications & Improvements*[11-22]; *Theoretical Studies*[23-28]]

The boron mediated *aldol reaction* is a powerful method for highly stereoselective carbon-carbon bond formation. The high diastereoselectivity of this process can be attributed to the relatively short boron-oxygen bond length (1.36-1.47 Å) in the boron enolate,[29] which upon reacting with an aldehyde leads to a tight, six-membered chairlike transition state. Reaction of (*Z*)-boron enolates with aldehydes gives the *syn* aldol product while, (*E*)-boron enolates lead to formation of the *anti* aldol product with high diastereoselectivity.[30,31] Control of the absolute stereochemistry can be achieved through the application of covalently attached chiral auxiliaries in the enol component. D.A Evans and his co-workers developed a pair of oxazolidinone based chiral auxiliaries, which could be obtained from (*S*)-valinol and (1*S*,2*R*)-norephedrine with excellent enantiopurity.[1] *Asymmetric aldol reactions* relying on the application of these chiral auxiliaries are called the *Evans aldol reaction*. General features of the *Evans aldol reaction* are: 1) enolization of the *N*-acyl oxazolidinones under standard conditions (1.1 equiv Bu_2BOTf, 1.2 equiv diisopropylamine, 0 °C, 30 min) affords the (*Z*)-enolates with excellent selectivity;[1] 2) *aldol reaction* of the resulting (*Z*)-boron enolates with a wide variety of aldehydes yields the *syn* aldol product with very high diastereo- and enantioselectivity;[1] 3) when a chiral aldehyde is used, the facial bias of the enolate overrides the π-facial selectivity of the chiral aldehyde;[32] 4) aldol reaction of boron enolates derived from *N*-acetyloxazolidinone (R^1=H) provide the products with low stereoselectivity, but this can be overcome by the incorporation of a heteroatom substituent in the α-position, such as a thioalkyl group (R^1=SR), which can be reductively removed;[1] and 5) there are several methods for the nondestructive removal and recovery of the chiral auxiliary: hydrolysis and transesterification (LiOH, LiOOH, LiOR, LiSEt),[33-35] reductive removal ($LiAlH_4$),[33,36] and transamination to Weinreb amide (Me(OMe)NH, Me_3Al).[37] Since the introduction (S)-4-isopropyl-oxazolidin-2-one and (1*S*,2*R*)-4-methyl-5-phenyl-oxazolidin-2-one chiral auxiliaries by D.A. Evans, several modifications have been reported.[11-22] Besides the *aldol reaction*, the Evans chiral auxiliaries were successfully applied in enolate alkylation,[33] enolate acylation,[33] enolate amination,[38-41] and hydroxylation[42] processes.



Mechanism:[2]

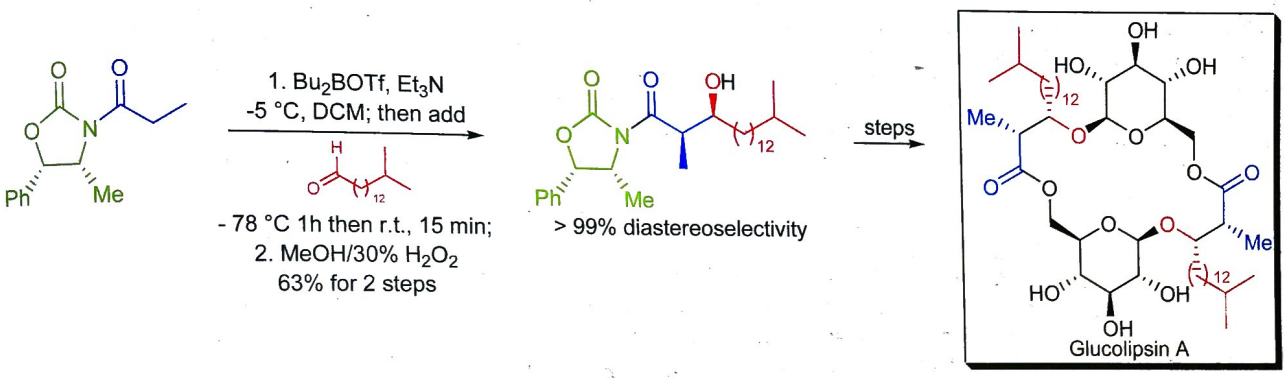
The observed stereoselectivity in the *Evans aldol reaction* can be explained by the *Zimmerman-Traxler* transition state model.[2] There are eight possible transition states, four of which would lead to the *anti* aldol product. These, however, are disfavored due to the presence of unfavorable 1,3-diaxial interactions (not depicted below). The possible transition states leading to the *syn* aldol product are shown below. The preferred transition state leading to the product is transition state **A**, where the dipoles of the enolate oxygen and the carbonyl group are opposed, and there is the least number of unfavored steric interactions.



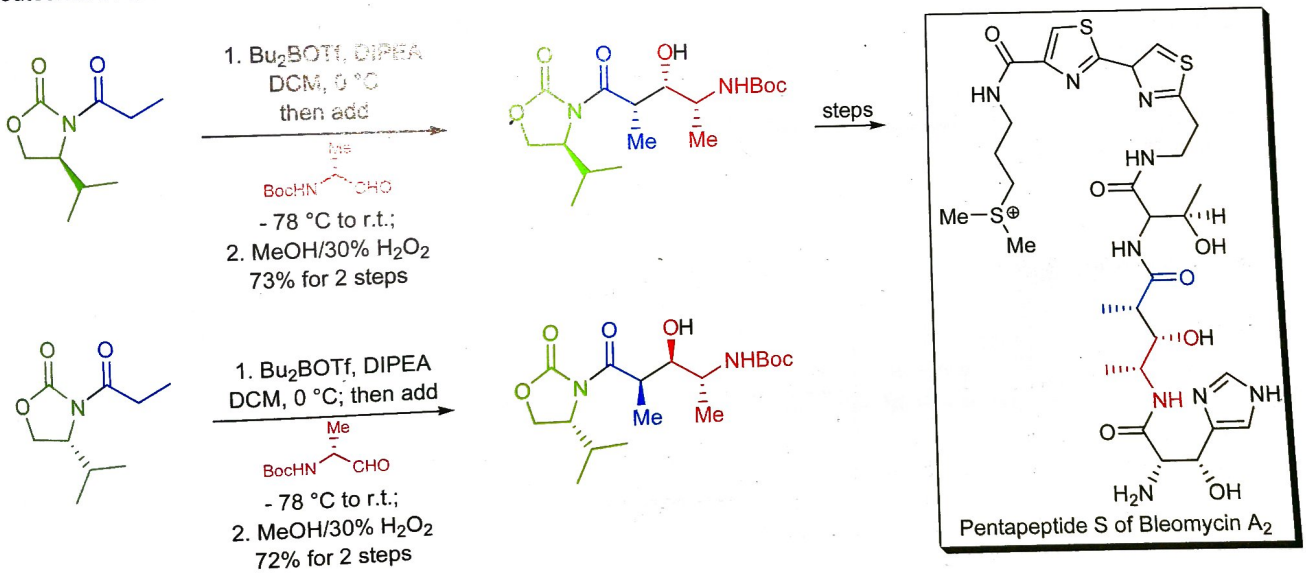
EVANS ALDOL REACTION

Synthetic Applications:

Glucolipsin A, a glycolipid possessing glycokinase-activating properties, was discovered at Bristol-Myers Squibb, but the absolute stereochemistry of the natural product remained elusive. A. Fürstner and co-workers elucidated the absolute stereochemistry *via* synthesis and spectroscopic analysis of the natural macrolide and its C_2-symmetric stereoisomers.[43] In their approach, they utilized the *Evans aldol reaction* that provided the *syn* aldol product with good yield and excellent diastereoselectivity.



D.L Boger et al. reported the total synthesis of bleomycin A_2. They devised an efficient synthesis for the construction of the tripeptide S, tetrapeptide S, and pentapeptide S subunits of the natural product.[44,45] In their strategy, they utilized an *Evans aldol* reaction between the (*Z*)-enolate derived from (*S*)-4-isopropyl-3-propionyl-oxazolidin-2-one and *N*-Boc-D-alaninal. In order to synthesize one of the diastereomers of the pentapeptide S subunit, they carried out an *Evans aldol reaction* between the same aldehyde and the (*Z*)-enolate of (*R*)-4-isopropyl-3-propionyl-oxazolidin-2-one. The formation of the diastereomeric *syn* aldol product in this reaction clearly shows that the stereochemical outcome of the transformation is determined by the chiral auxiliary.



The asymmetric total synthesis of cytotoxic natural product (–)-FR182877 was accomplished by D.A. Evans and co-workers.[46,47] To establish the absolute stereochemistry, a boron mediated aldol reaction was utilized applying (*R*)-4-benzyl-*N*-propionyl-2-oxazolidinone[48] as a chiral auxiliary to yield the *syn* aldol product.