Stereoselective Synthesis

Dr Michael Perkins, Flinders University

Reference Texts:

“Stereochemistry of organic compounds” Ernest L. Eliel New York : Wiley & Sons, c1994. Chapter 12 on stereoselective synthesis by Lewis N. Mander.

“Stoichiometric Asymetric Synthesis”

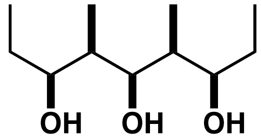
by Mark Rizzacasa and Michael Perkins,

Sheffield Academic Press 2000

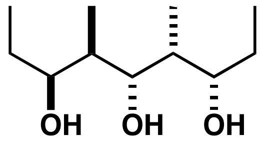
10 Minute Problem

i. Indicate which of the following compounds are chiral and mark any stereocentres

ii. For the stereocentres bearing 4 different groups assign the configuration as *R* or *S*



A



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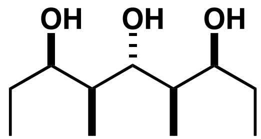

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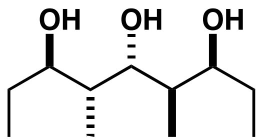
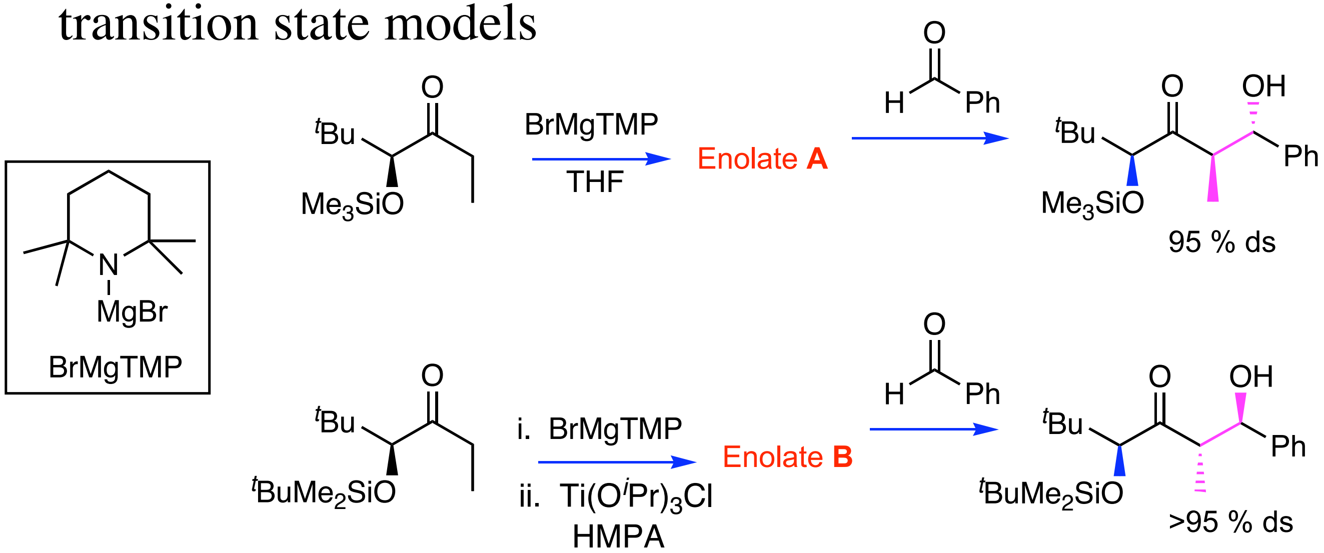


D

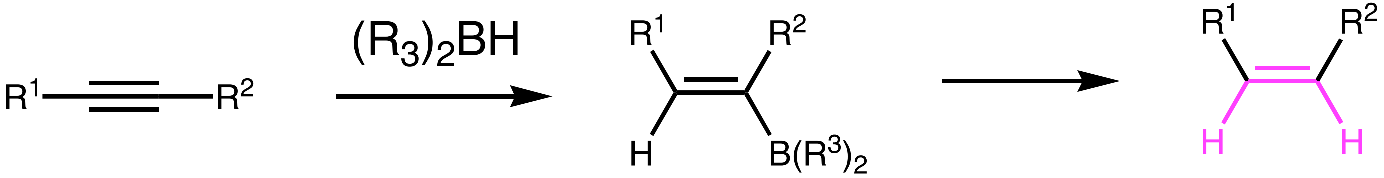
iii. Give the structures for the enolates A and B and explain the stereochemical outcomes of the following aldol reactions using transition state models

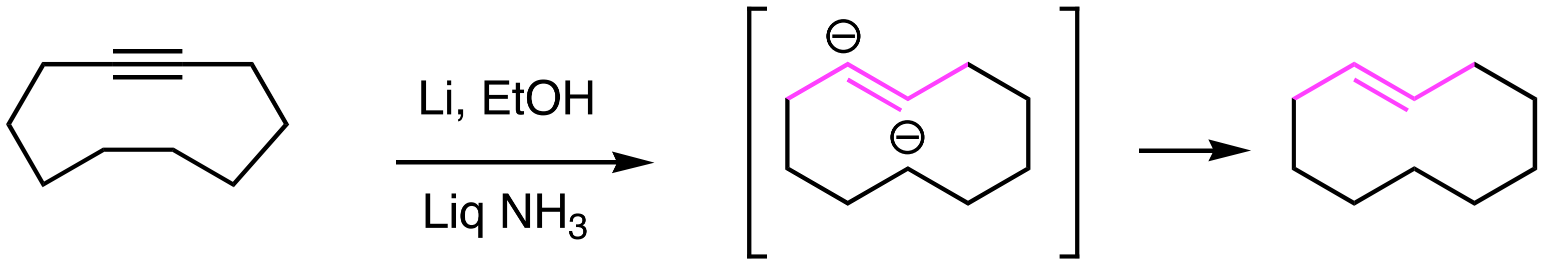


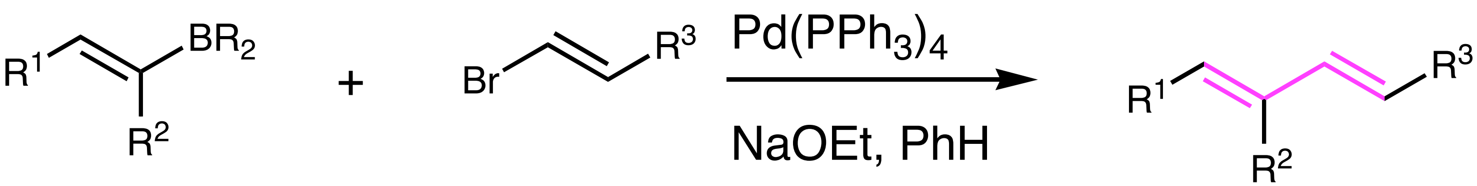
Diastereoselective Synthesis

Synthesis of Achiral Compounds

Reduction Methods



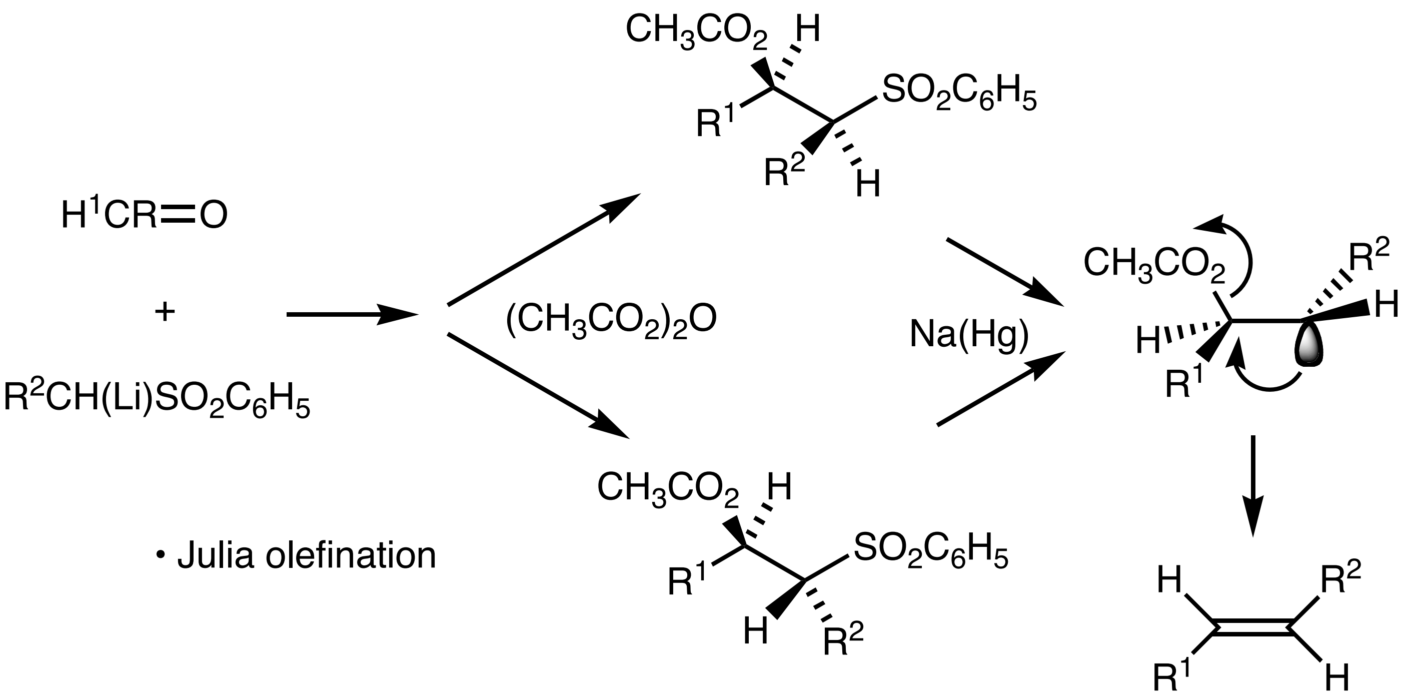




- Suzuki stereocontrolled synthesis of dienes

Diastereoselective Synthesis

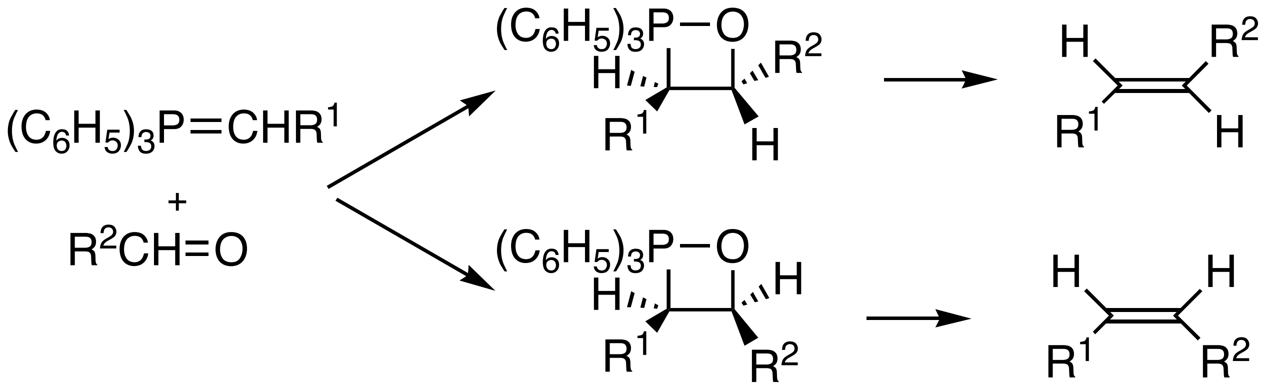
Synthesis of Achiral Compounds



• Julia olefination

Diastereoselective Synthesis

Synthesis of Achiral Compounds



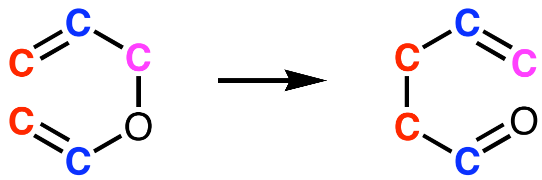
• Wittig reaction

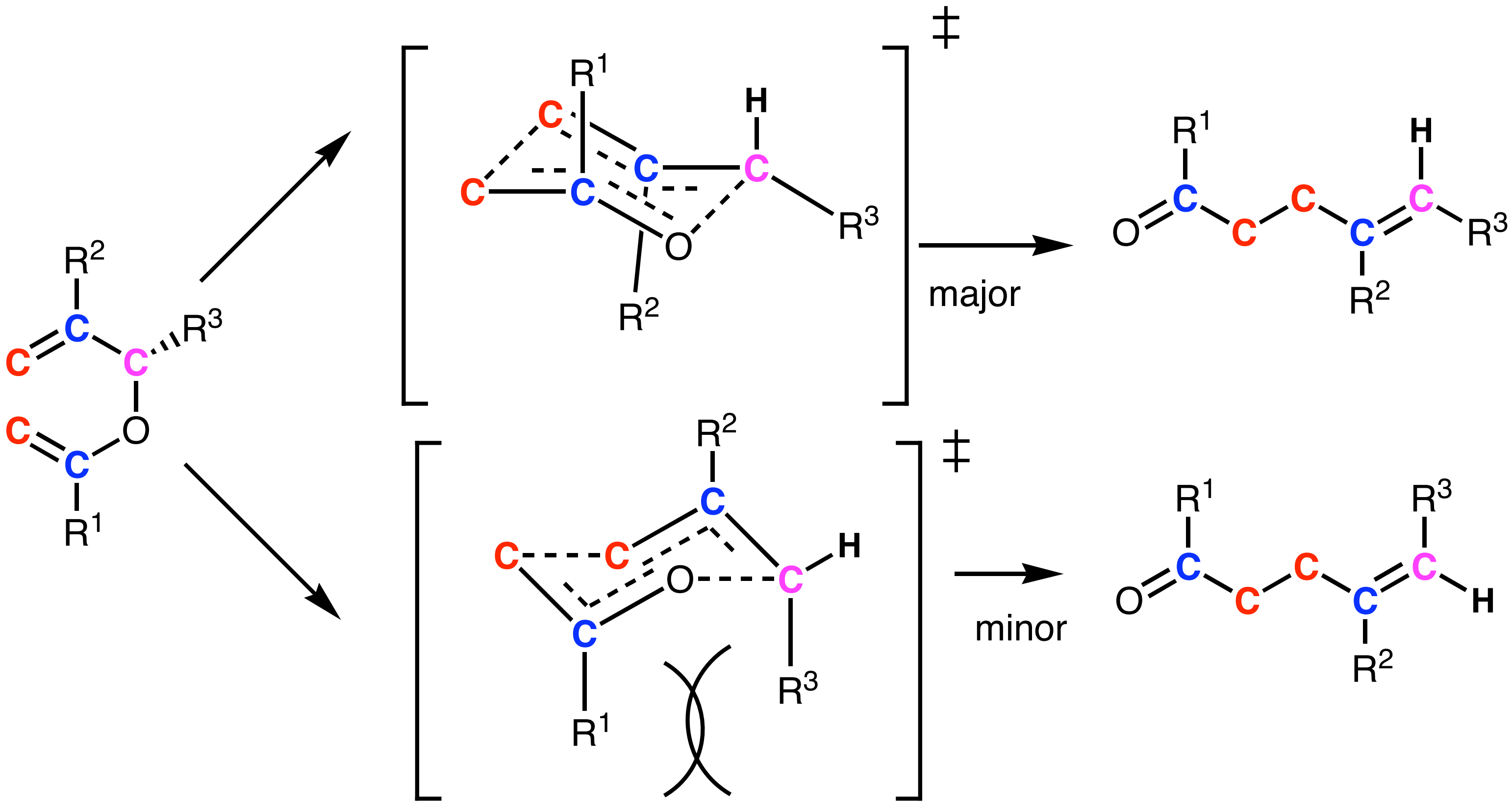
Diastereoselective Synthesis

Synthesis of Achiral Compounds

Pericyclic Reactions

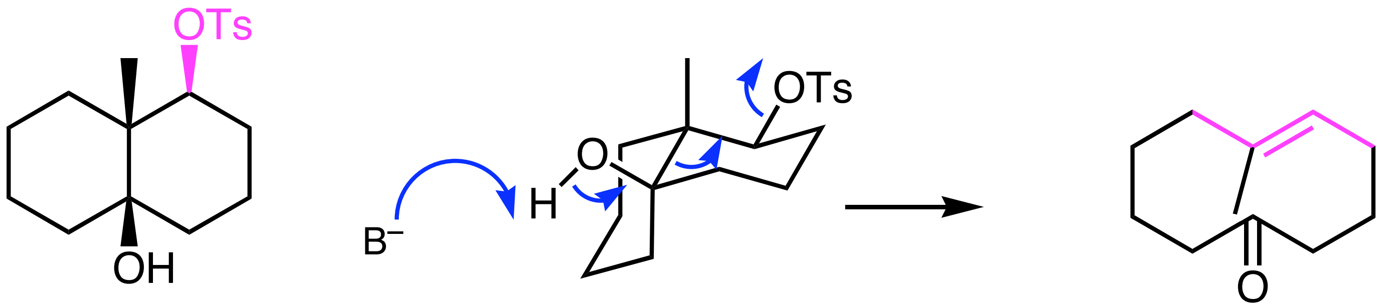
• Claisen rearrangement

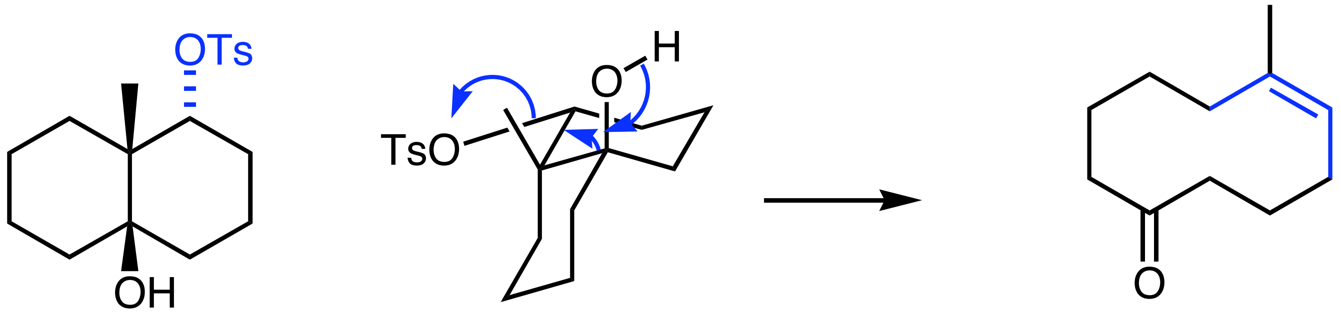




Ring Fragmentations

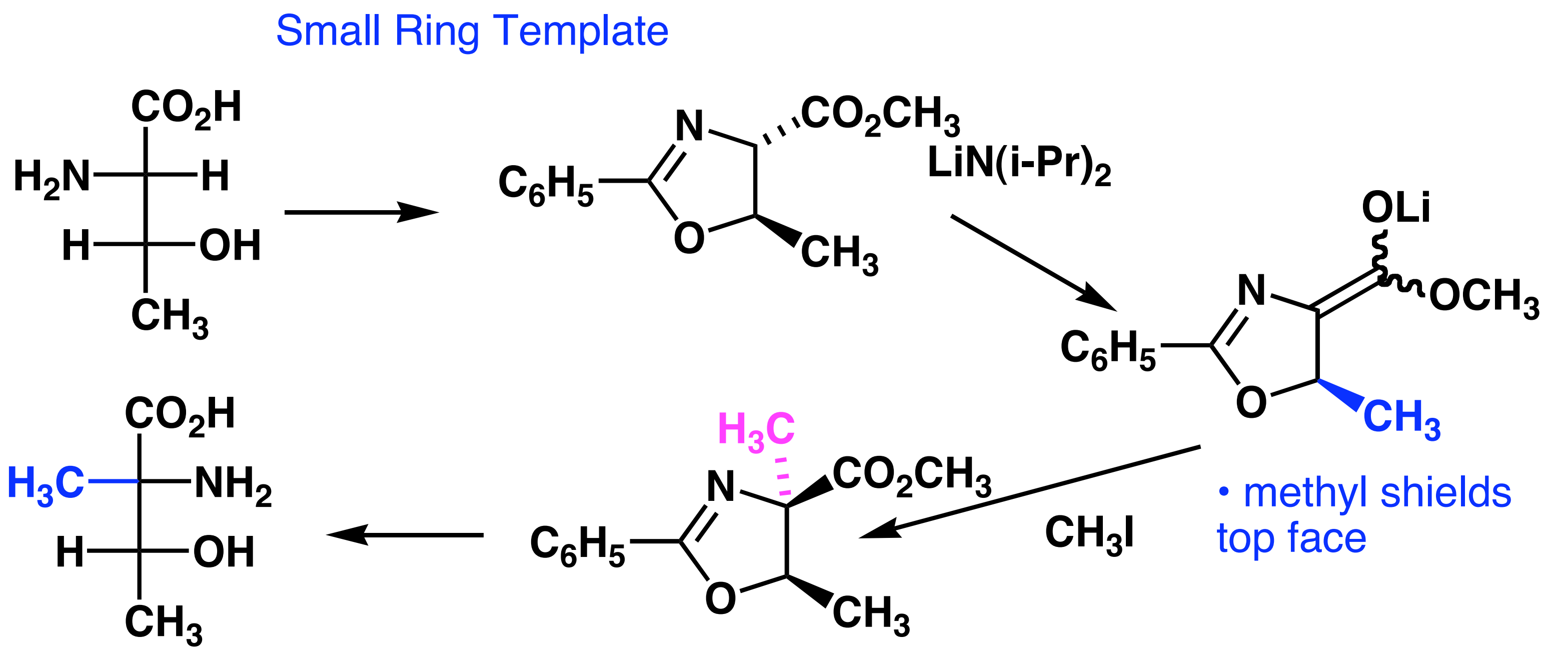
• stereoelectronic control

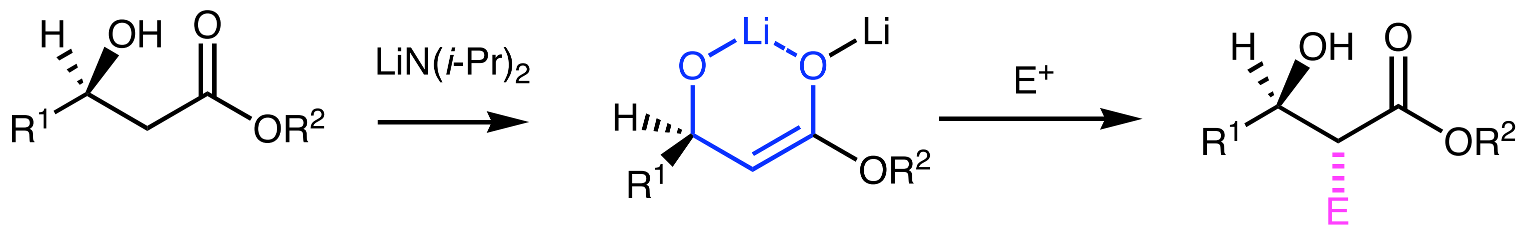




Reactions of Acyclic Enolates and Related Substrates

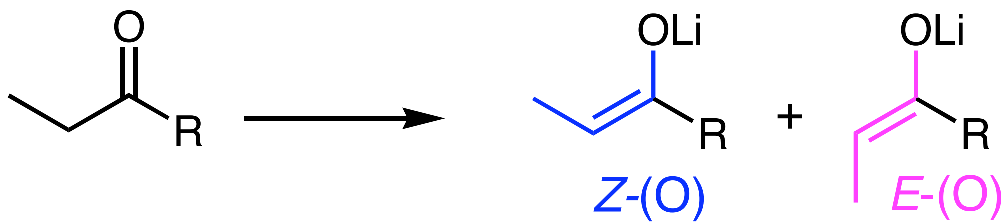
Alkylations:

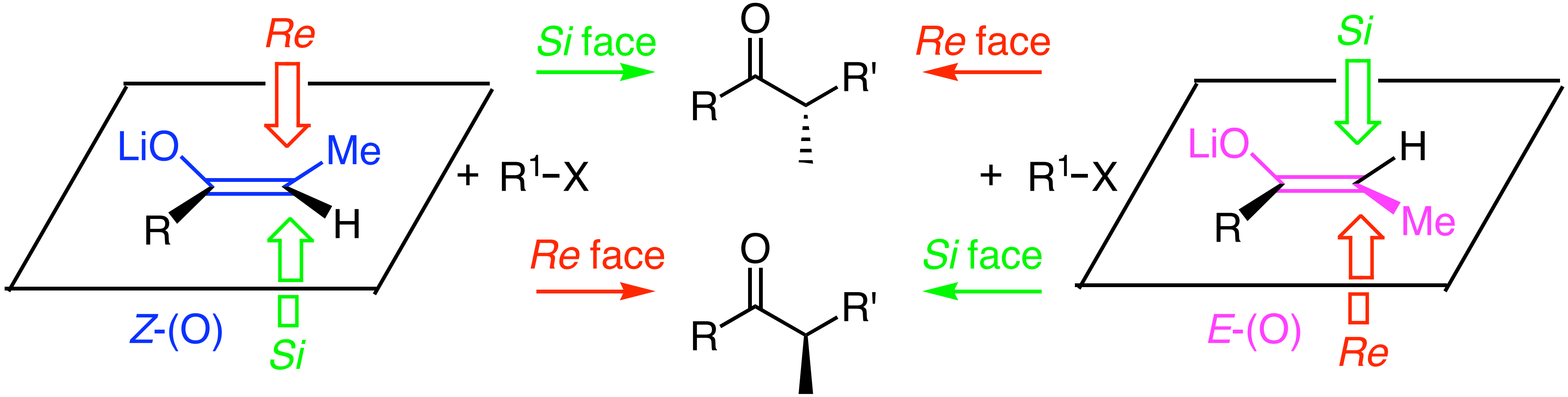


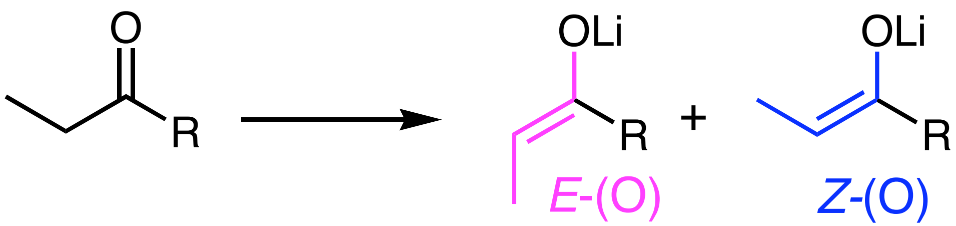


Reactions of Acyclic Enolates and Related Substrates

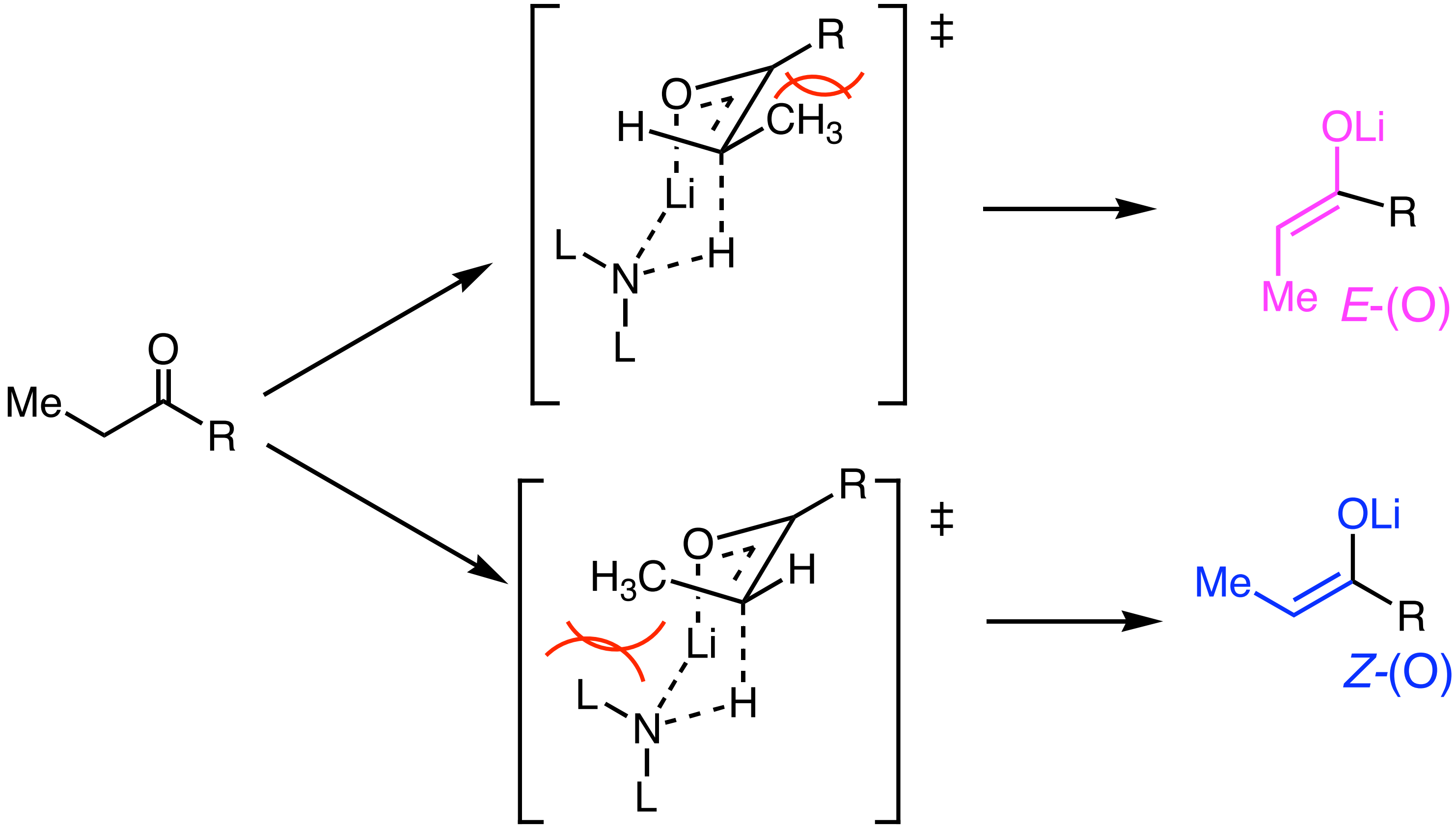
Enolate Geometry?







R	Base	Solvent	*E*-(O) Enolate	*Z*-(O) Enolate	Ref.
–Et	LDA	THF	70	30	28
–Et	LTMP	THF	84	16	28
–Et	LDA	THF-23 % HMPT	8	92	29
–Et	LHMDS	THF	34	66	28
$-OCH_3$	LDA	THF	95	5	28
OCH_2H_3	LDA	THF	94	6	31
OCH_2H_3	LDA	THF-23 % HMPT	15	85	31
$-O^tBu$	LDA	THF	95	5	32,33
$-S^tBu$	LDA	THF	90	10	34
$-NEt_2$	LDA	THF	<3	>97	15
$C(CH_3)_3$	LDA	THF	2	98	28
$-C_6H_5$	LDA	THF	2	98	28



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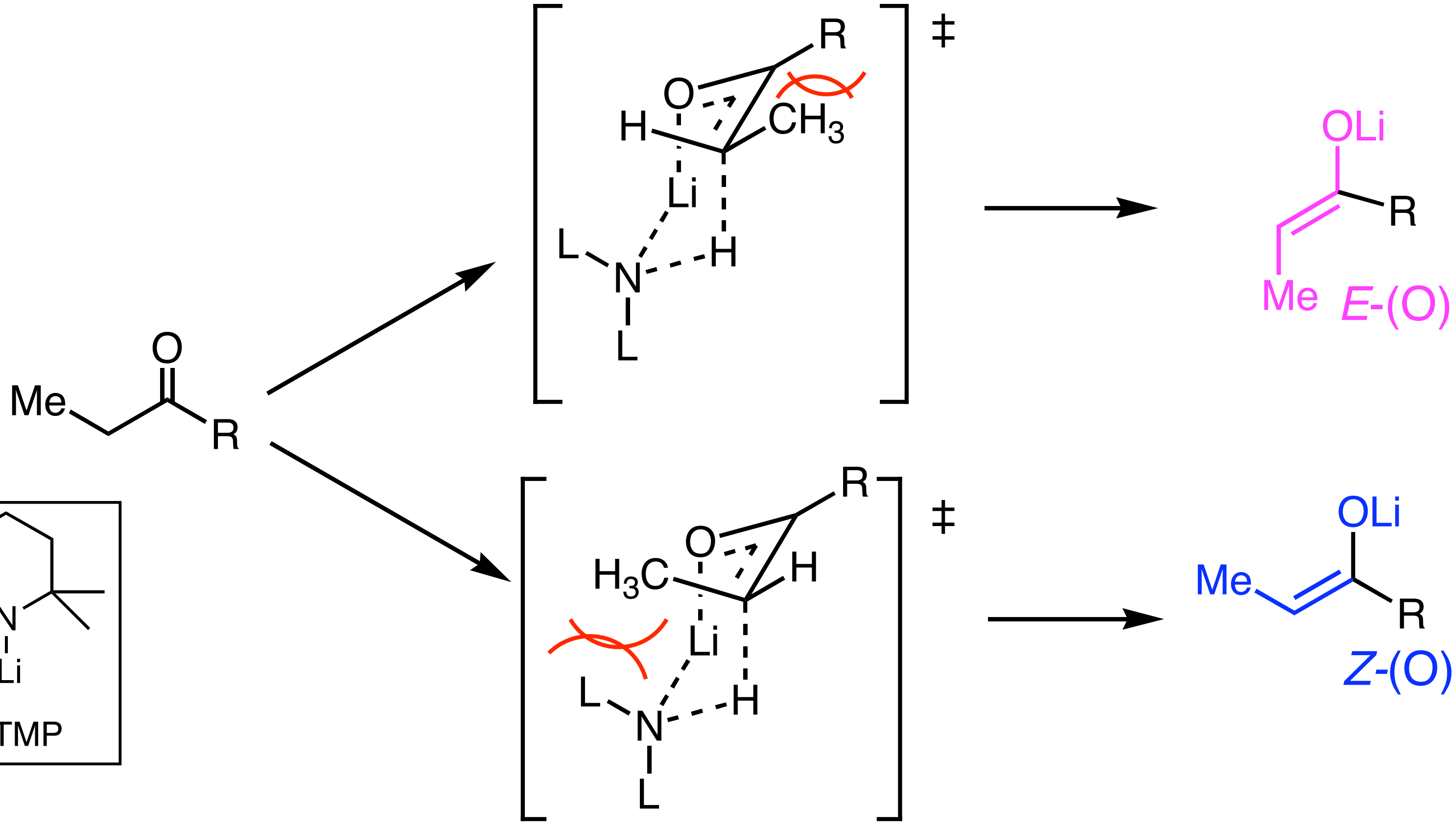

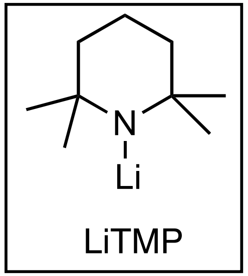

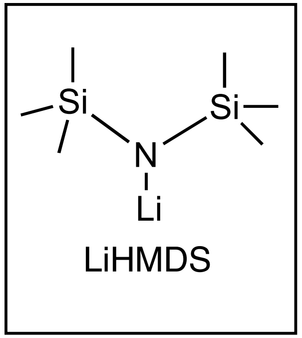

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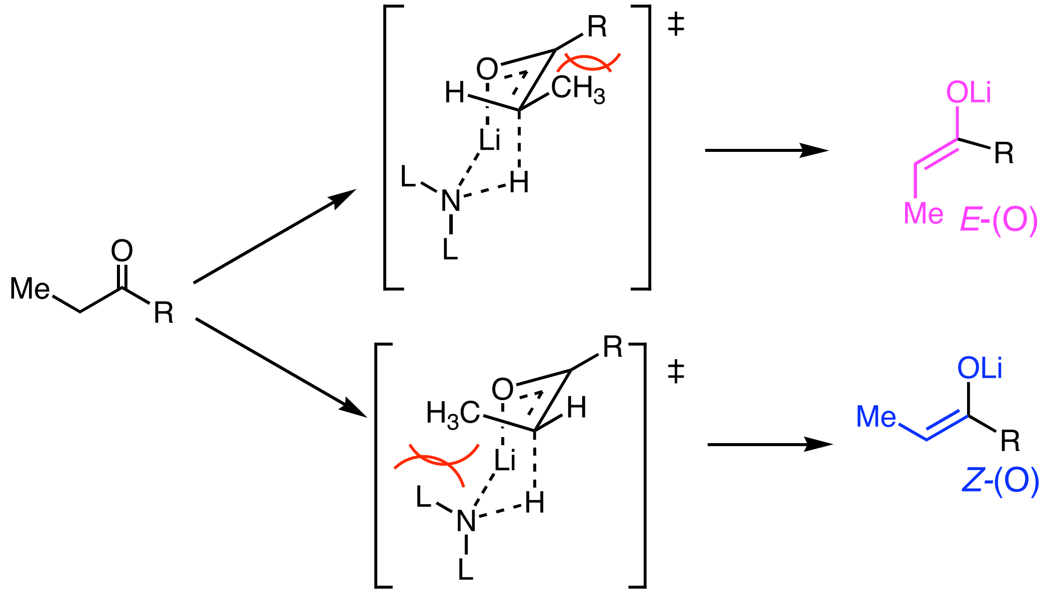

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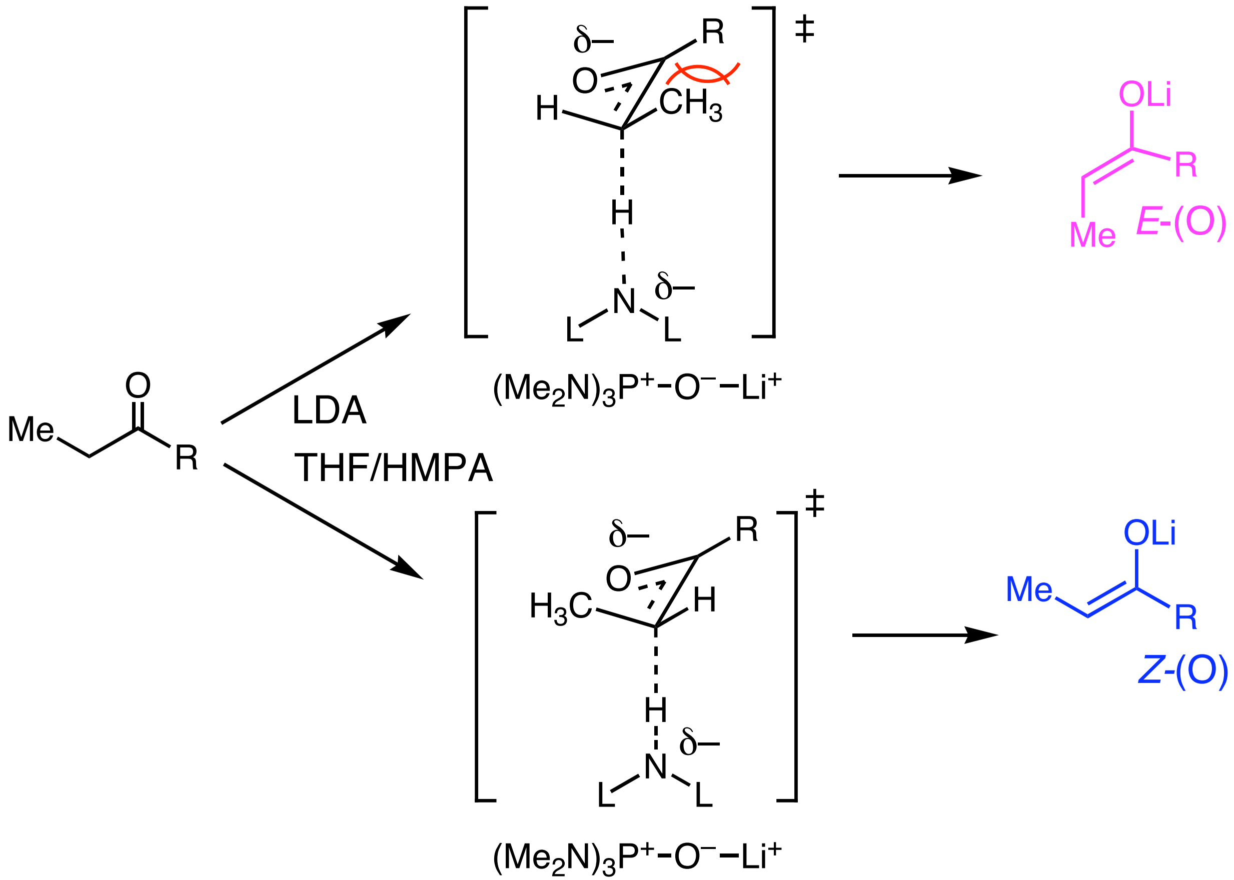

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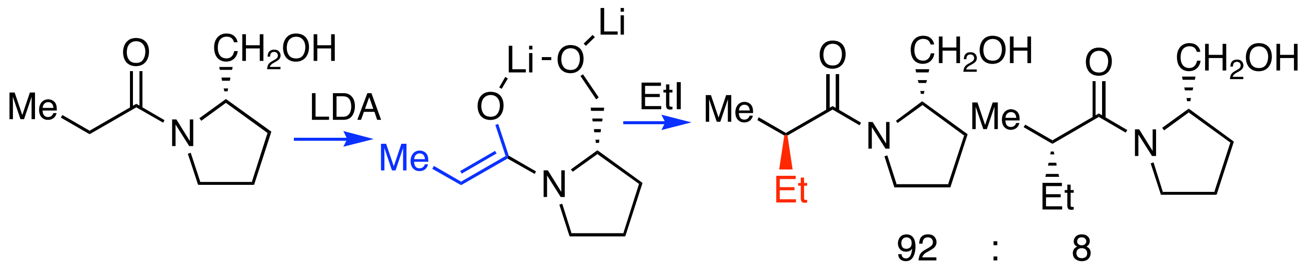
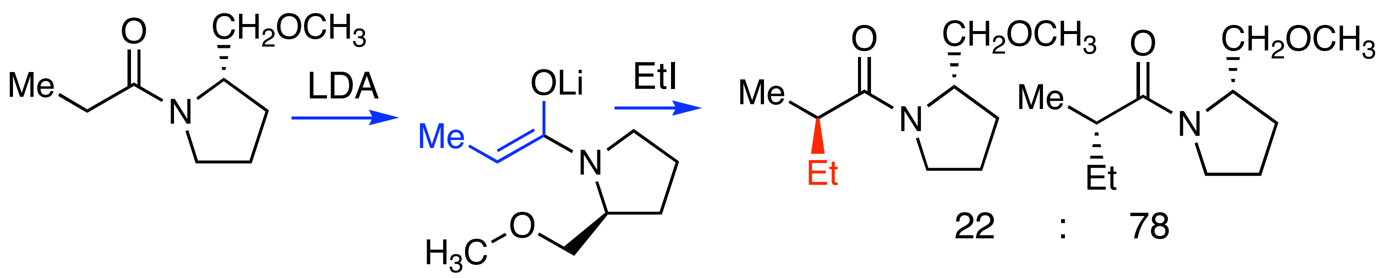
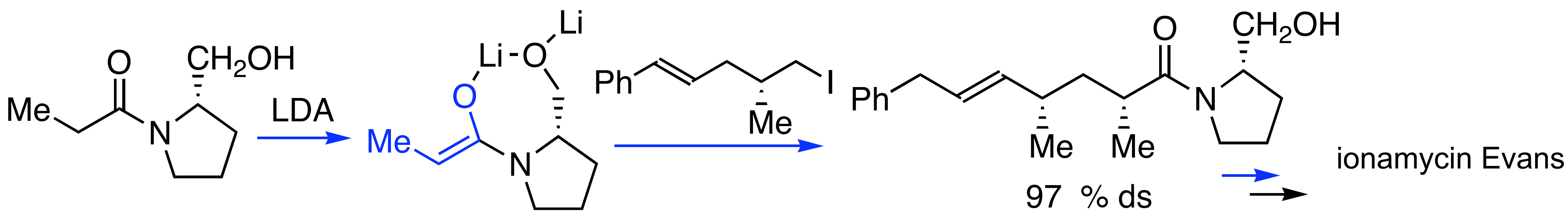
OCH$_2$H$_3$	LDA	THF-23 % HMPT	15	85	31

Alkylation of Acyclic Chiral Enolates







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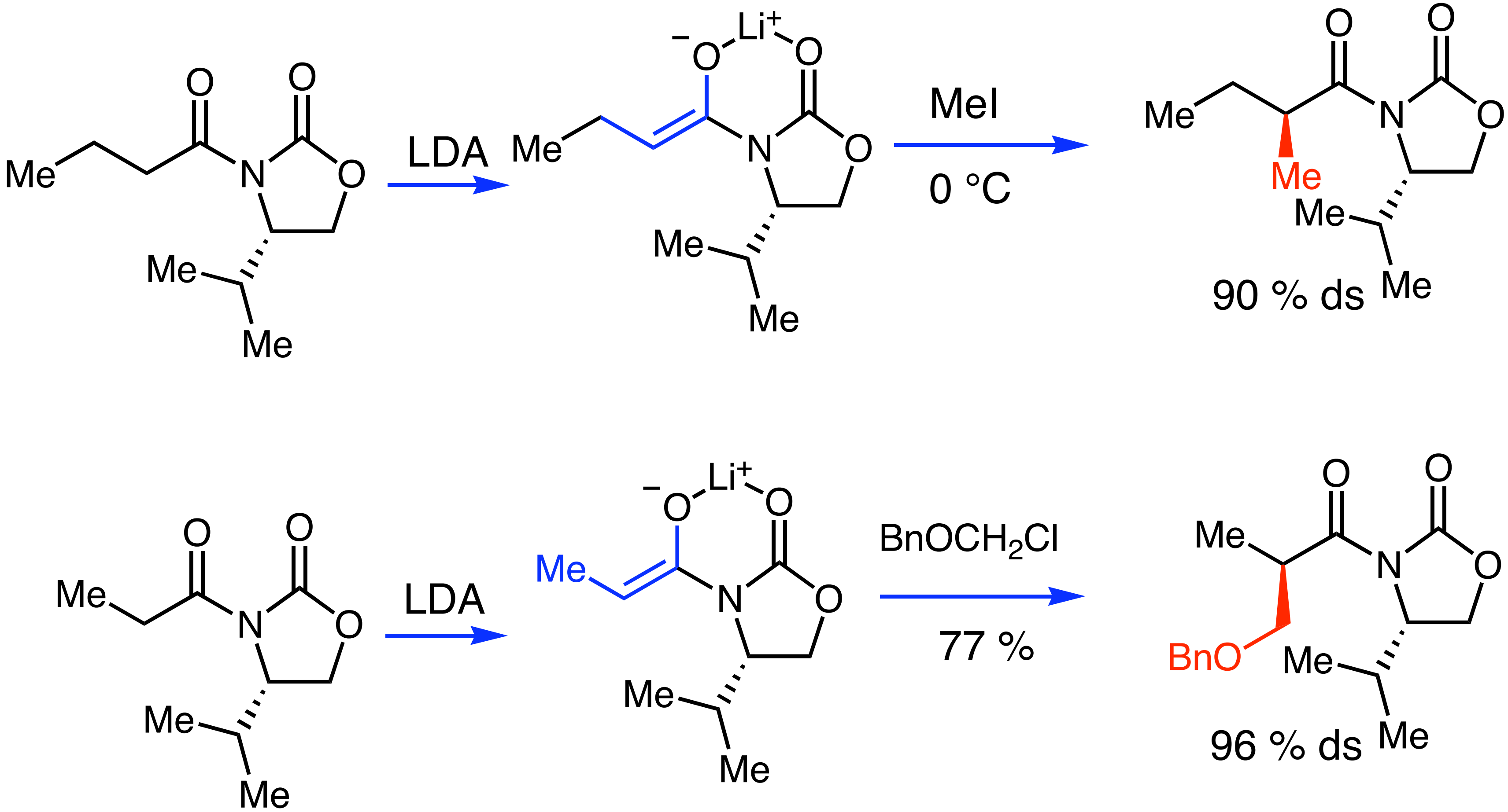
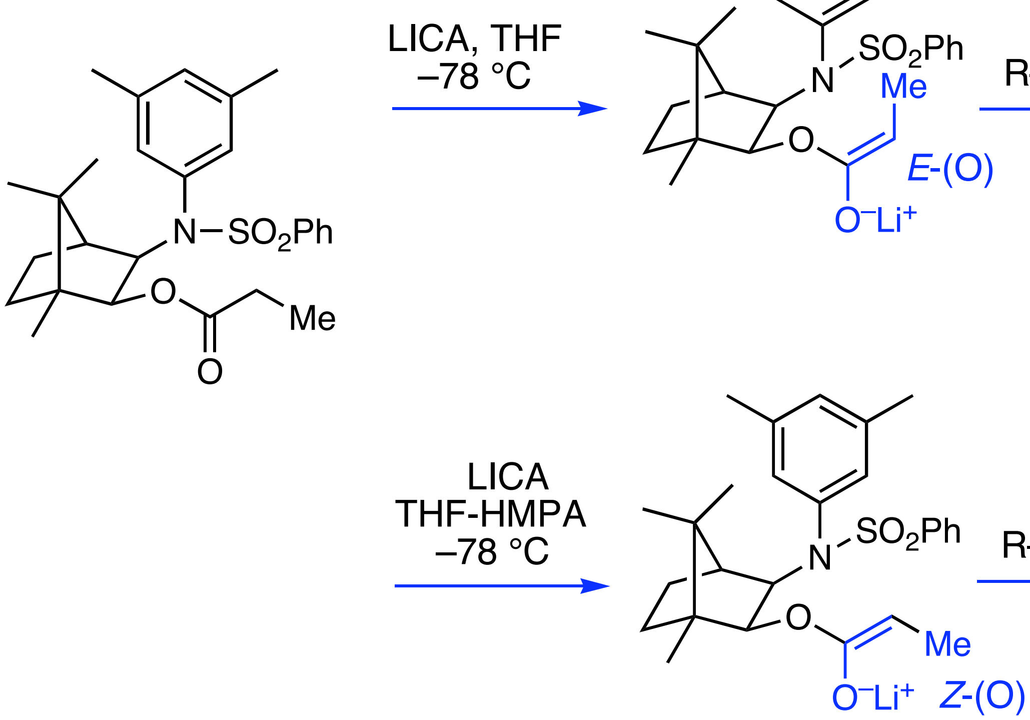


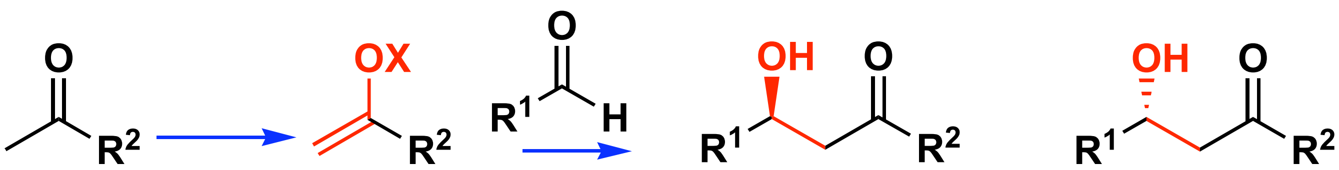
Alkylation of Acyclic Chiral Enolates

LICA = lithium
N-isoprpycyclohexylamide



Aldol Reactions

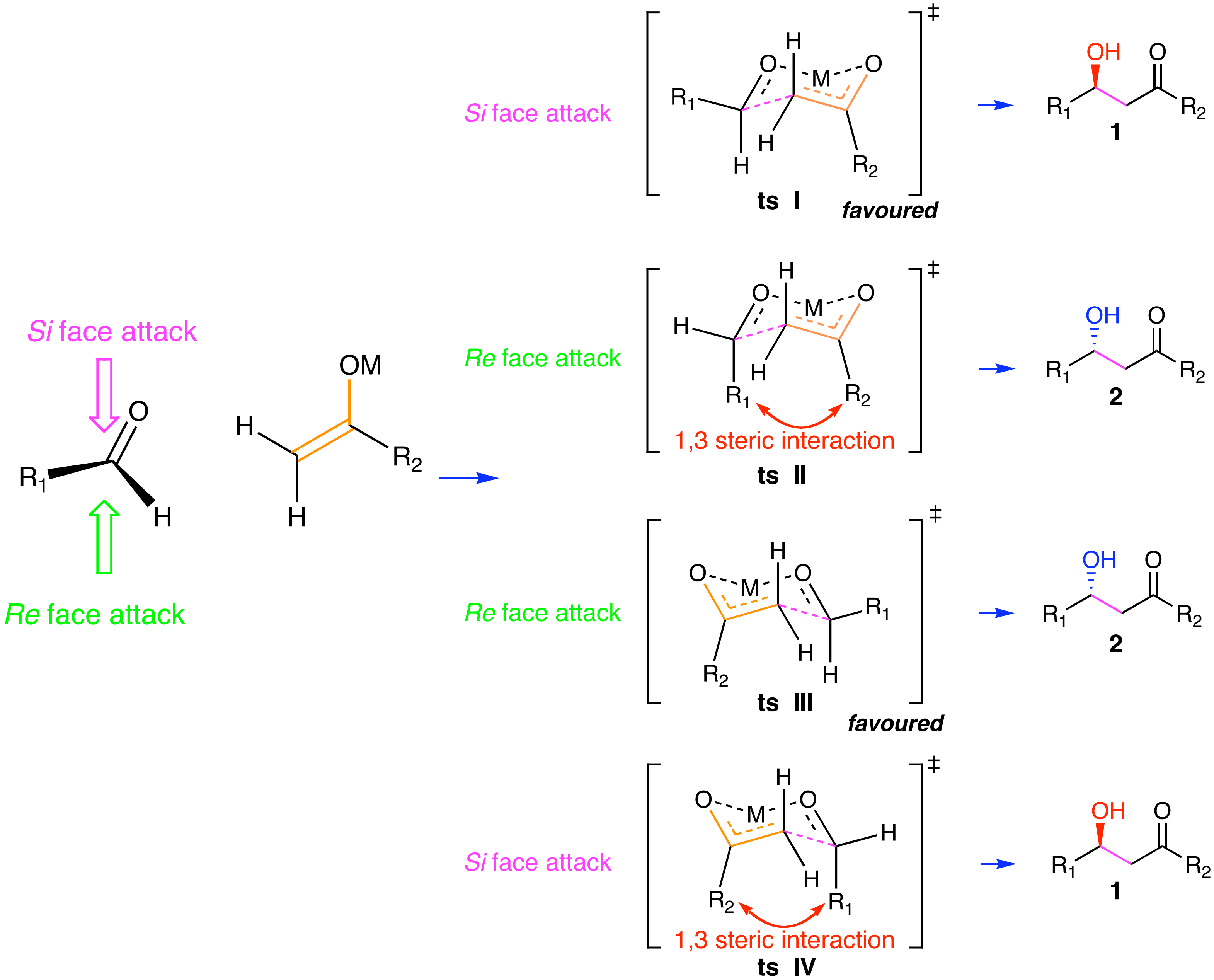
- The quest for efficient methods to construct polyketide natural products has driven the development of stereocontrolled acyclic crossed aldol reactions between aldehydes and ketones.
- These reactions are usually considered to occur *via* closed six membered cyclic Zimmerman-Traxler transition states, in which coordination between the aldehyde carbonyl oxygen and the enolate metal centre occurs.
- First consider the simple case where the enolate is not substituted at the α-carbon, then reaction with an aldehyde produces one stereocentre (ie. 2 isomers, which are enantiomers if R^1 and R^2 are achiral, but diastereisomers if R^1 or R^2 are chiral, Scheme 4.1).



enantiomers if R^1 and R^2 achiral
diastereosiomers if R^1 or R^2 chiral

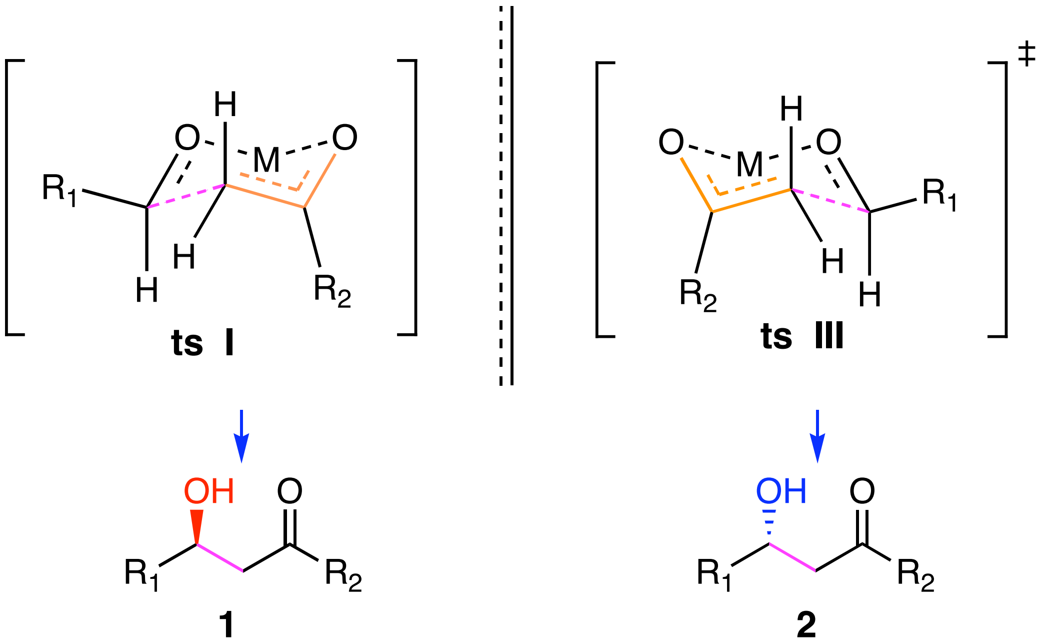
2 possible isomers

Aldol Reactions

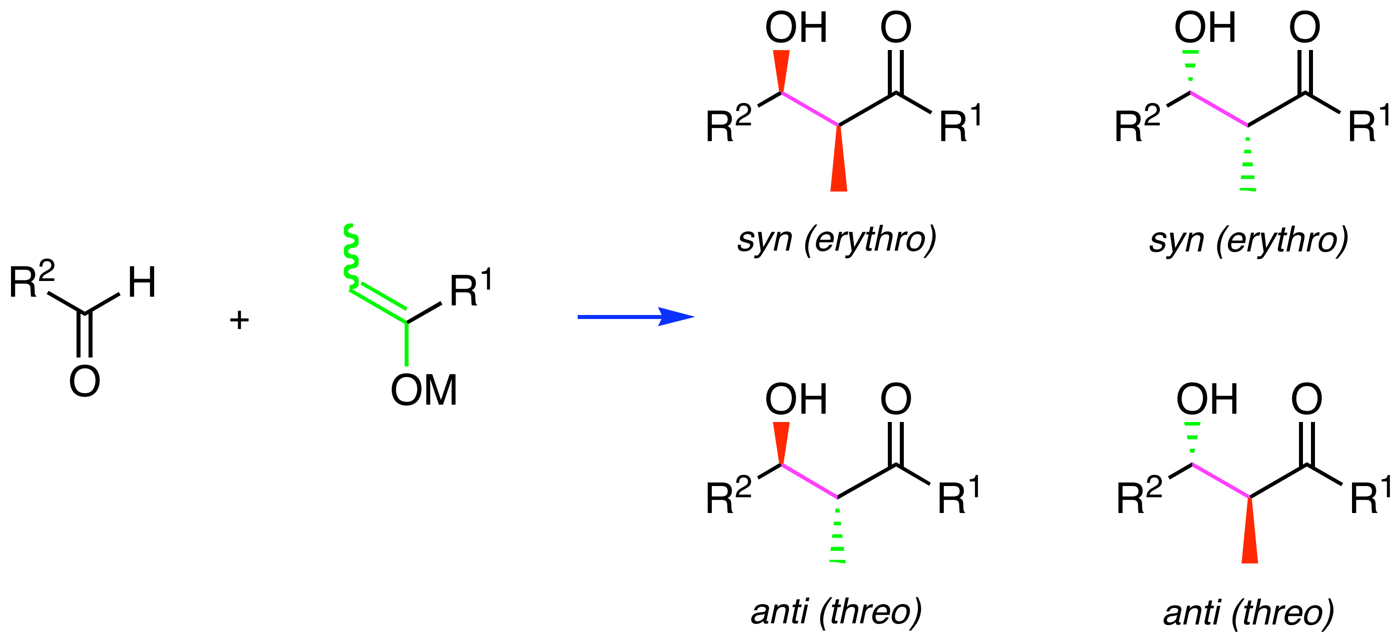


Aldol Reactions

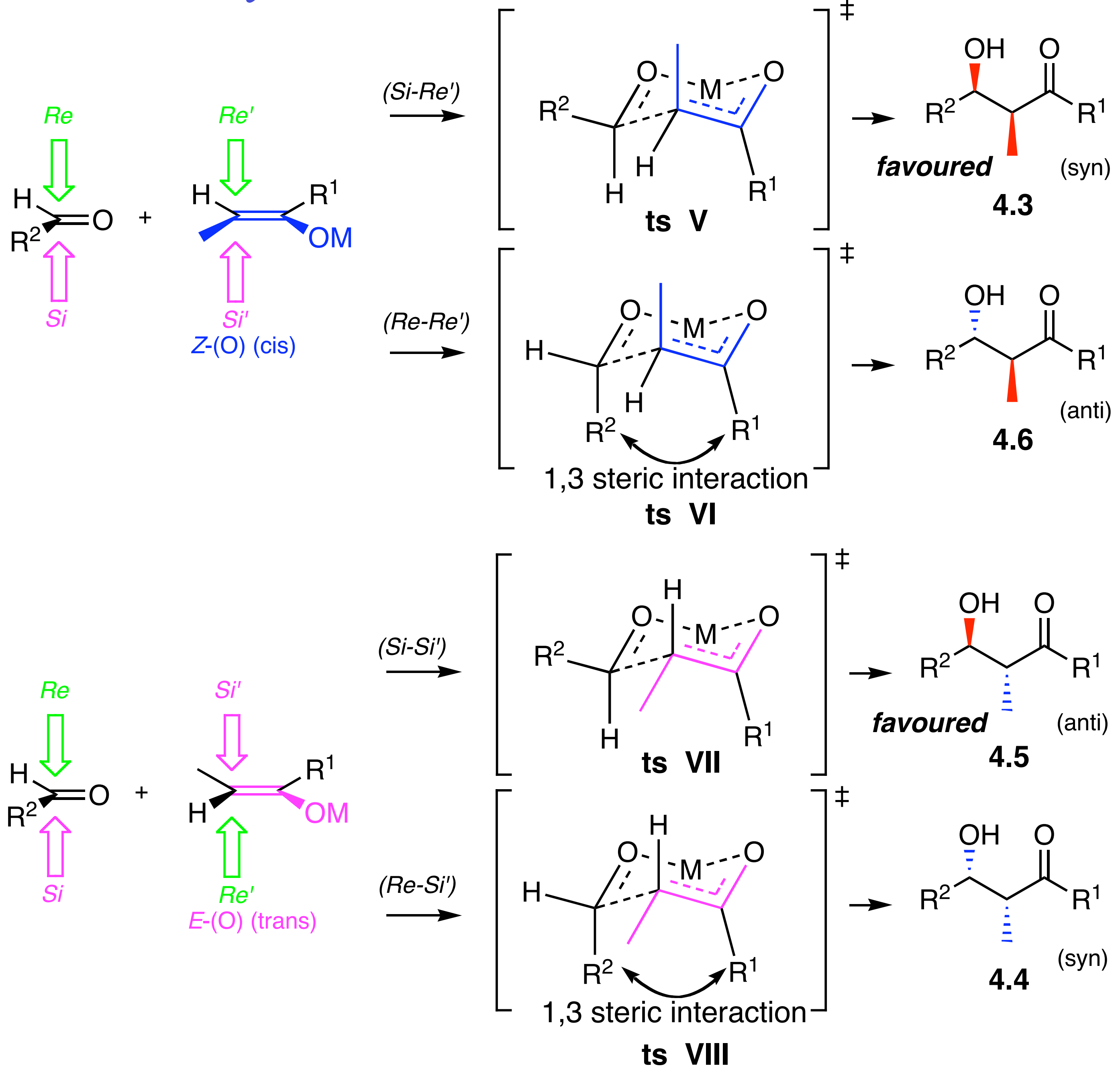
enantiomers provided R_1 and R_2 do not contain stereogenic elements



Ethyl Ketone Aldol Reactions



Ethyl Ketone Aldol Reactions



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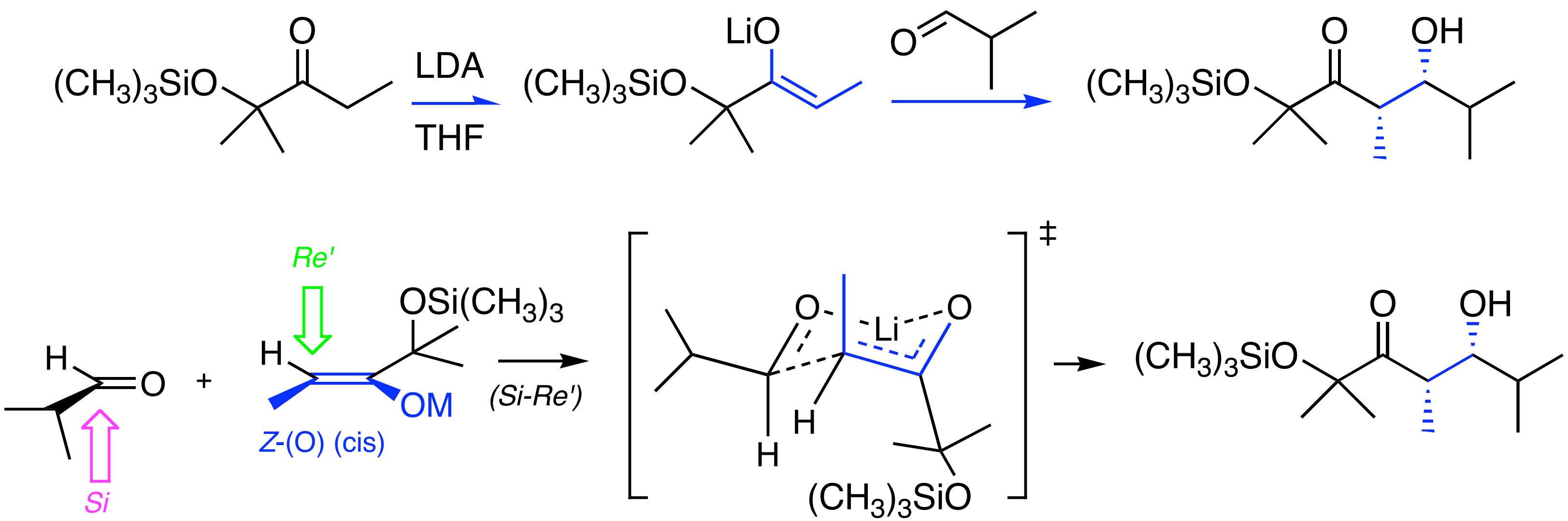
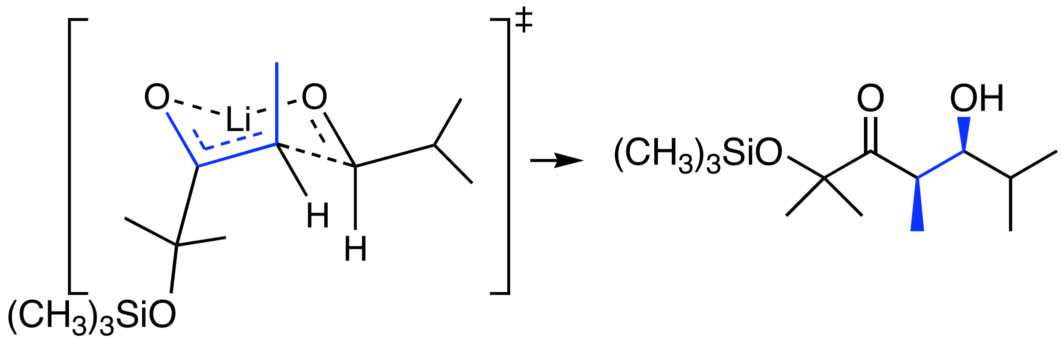
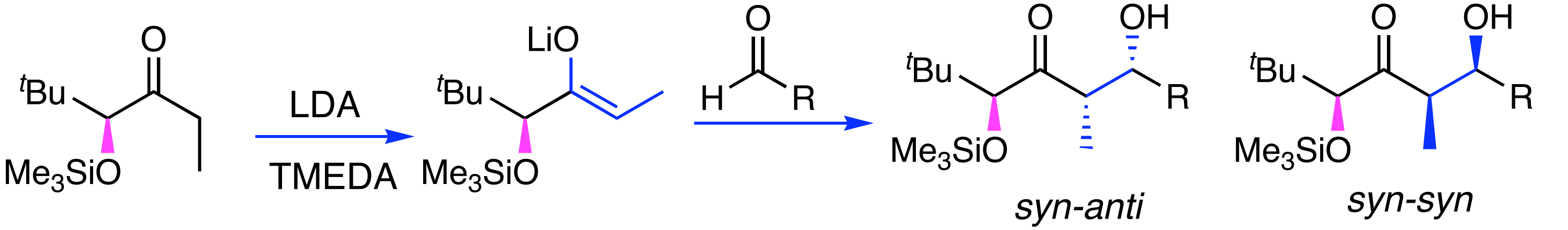




Ethyl Ketone Aldol Reactions



R	% *syn-anti*	% *syn-syn*
Ph, ^{t}Bu, ^{i}Pr	>95	<5
Ph CH_2	87	13
Ph_2CH	>90	<10