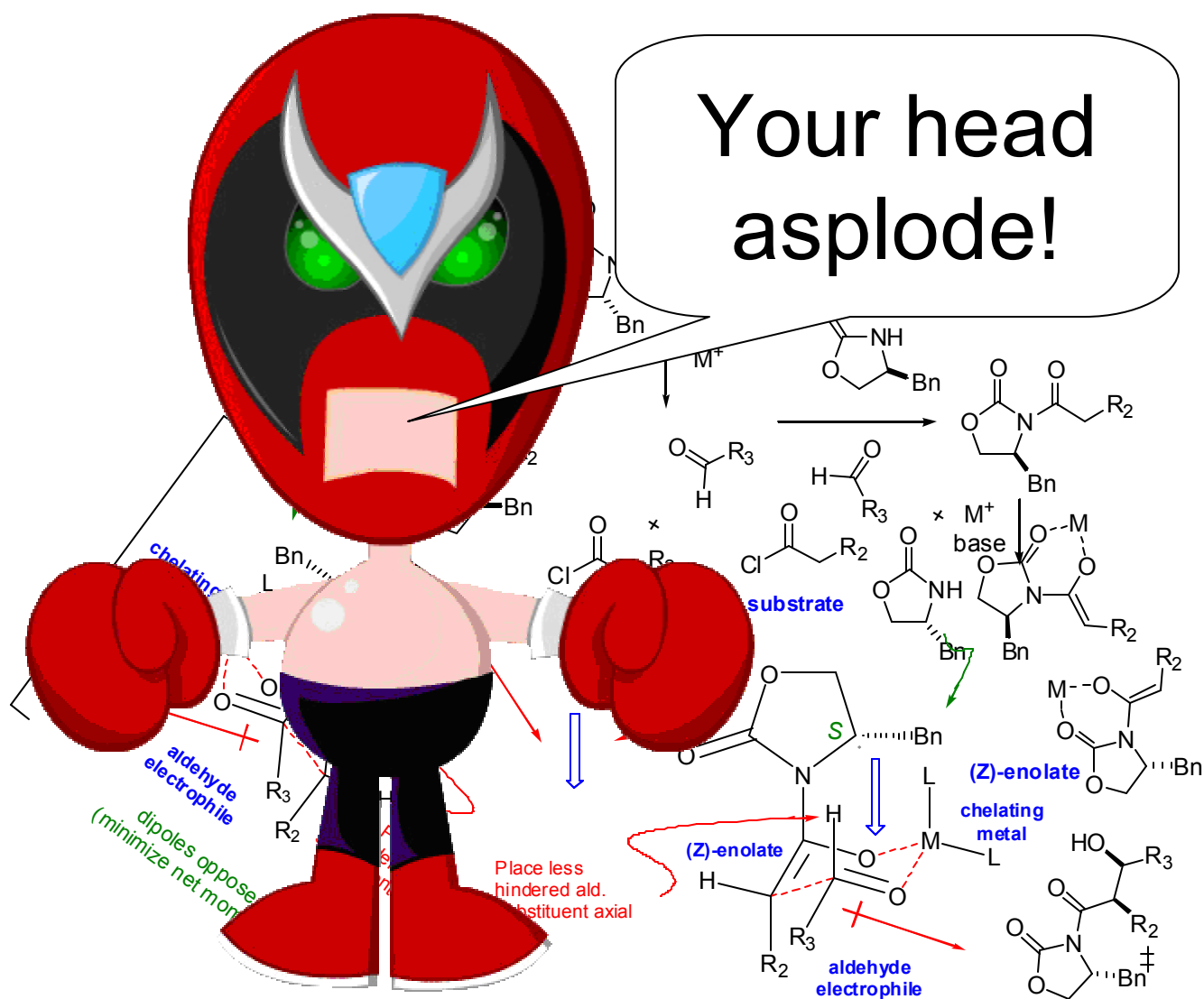


Carbonyl Chemistry IV: Enolate Alkylations and Aldols

Section Agenda

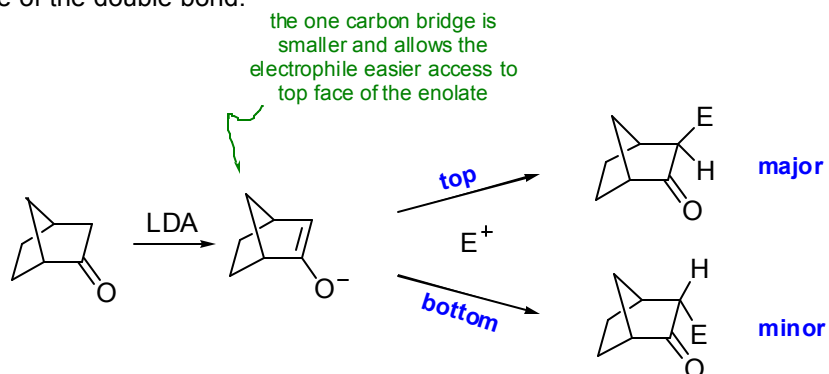
- 1) No office hours Thursday
- 2) The Great Joe Young is covering section next Monday
- 3) Handout: Carbonyl Chemistry IV

Aldol Madness

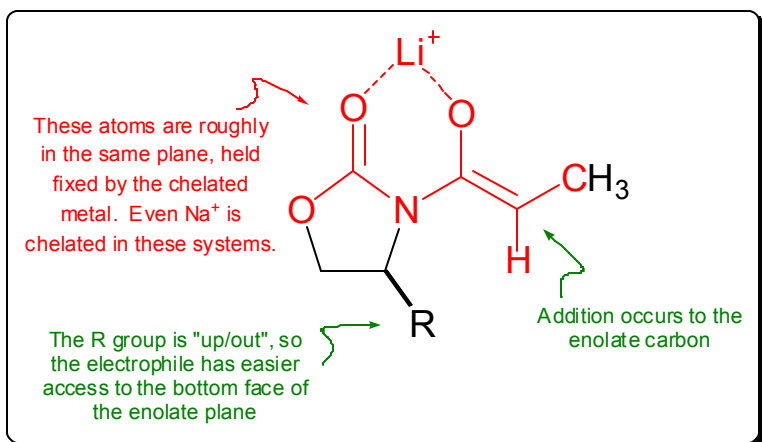
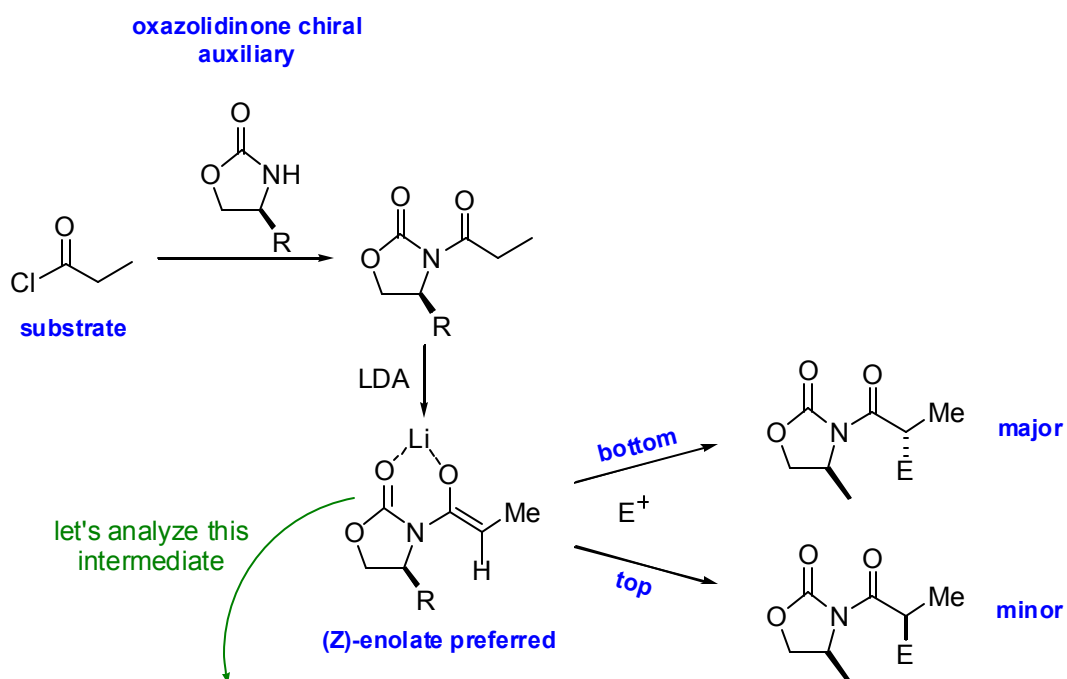


Model for Asymmetric Alkylation

- This is relatively easy. Simply draw a 3D structure of the enolate and add the electrophile to the least hindered face of the double bond.

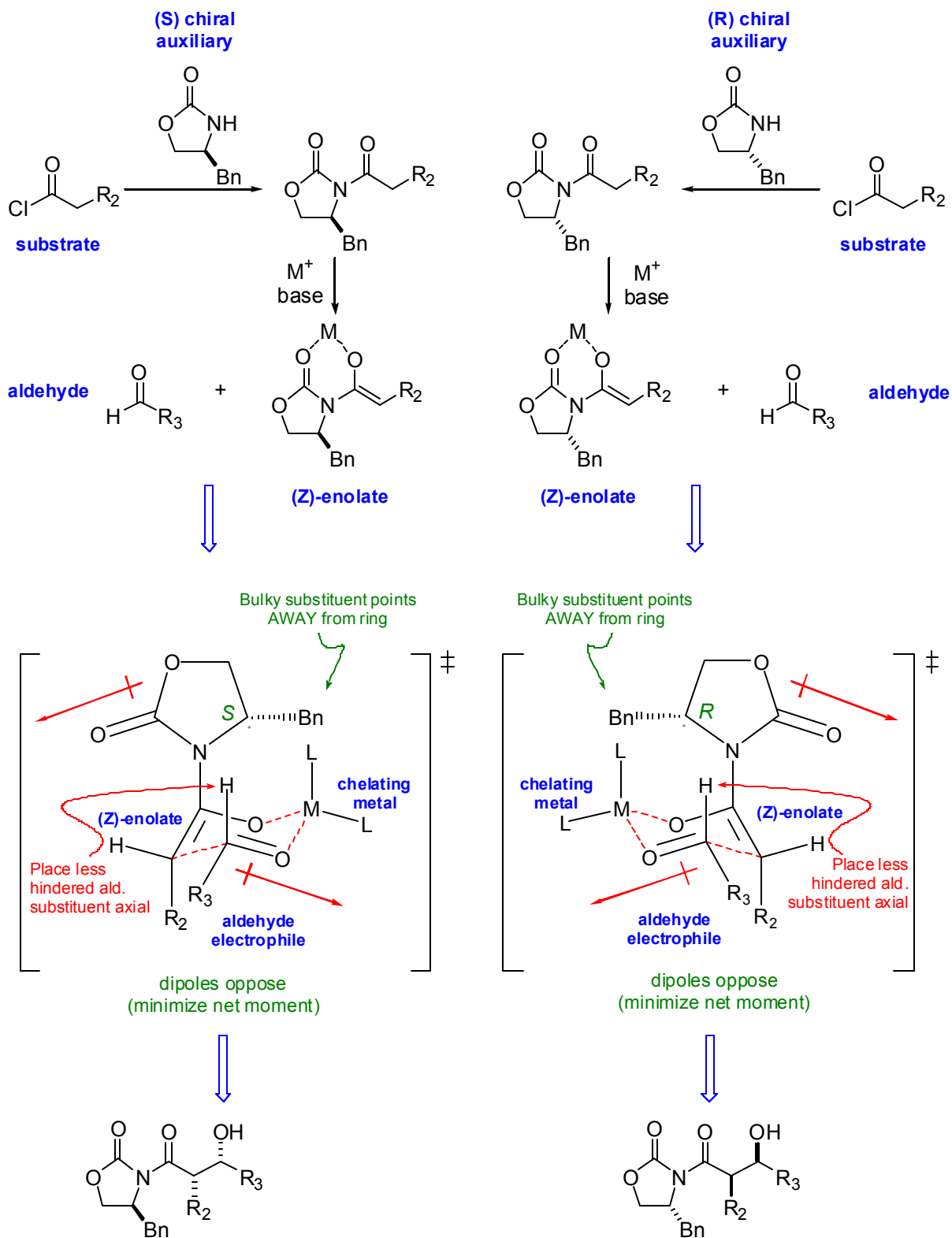


Use of oxazolidinone chiral auxiliaries:



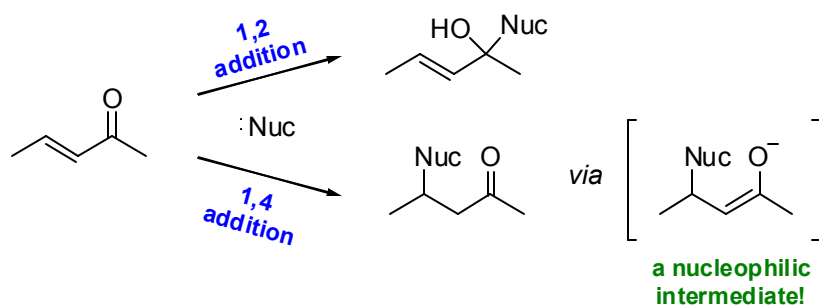
To reverse the product ratios, use the chiral auxiliary with the opposite stereochemistry

Asymmetric Aldol Reactions

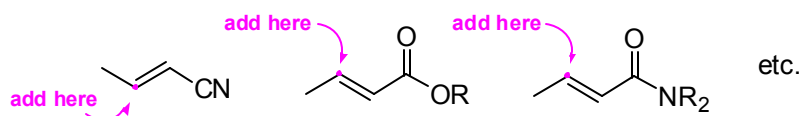


To draw the correct final product, assign *R* and *S* designations to the two stereocenters that are generated in the transition state, then add solid or dashed wedges to your Lewis structure to match these designations

Conjugate Additions



Other substrates



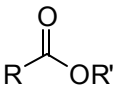

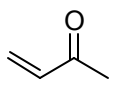
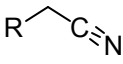


- These two additions pathways compete when a nucleophile reacts with an α,β -unsaturated substrate.
- As a general rule, most 1,2 additions are faster, but they are usually more reversible.
- “Michael” reactions are those in which an enolate adds in 1,4 fashion
- Beware of “tandem reactions” in which the enolate intermediate acts as a nucleophile

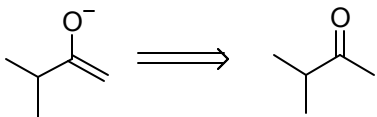
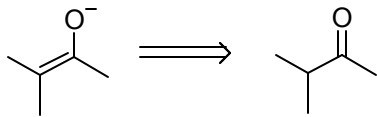
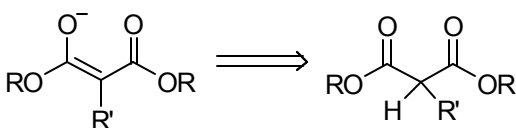
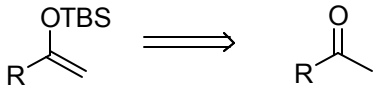
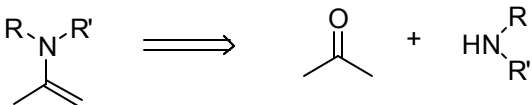
1,2 Additions	1,4 Additions
Hard nucleophiles not polarizable/high charge density Lithium Aluminum Hydride (LAH) Alkyl lithium reagents (RLi)	Soft Nucleophiles polarizable/low charge density RS^- , CN^- , enolates Organocuprates (R_2CuLi) (via an organometallic mechanism)
Note that these are the nucleophiles we normally classify as irreversible	

Synthetic Transformations

Electrophiles

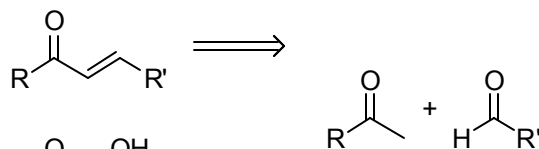
		Synthetic Preparations
aldehydes		Swern oxidation of alcohols; DIBAL-H reduction of nitriles
ketones		Oxidation of alcohols; Friedel-Crafts reaction; Oxidation of Grignard products
esters		Fischer esterification of acids and alcohols; acid chlorides and anhydrides with alcohols; Bayear-Villegier oxidation
alkyl halides		From alcohols with SOCl ₂ or PBr ₃ ; alkenes with HBr (with or w/o peroxides); alkanes by photohalogenation
α,β-unsaturated carbonyls		Aldol reactions; α-keto halogenation (Hell-Volhard-Zelinsky) then elimination of HBr
nitriles		Cyanide substitution of alkyl halides; dehydration of amides by P ₂ O ₅ ;

Nucleophiles

kinetic enolates		Irreversible bases (LDA), bulky bases
thermodynamic enolates		Reversible bases (alkoxides, hydroxides)
malonic ester enolates		Bases with pK _a >> 8 (NaH, RO ⁻)
silyl enol ethers		TBSCl and an amine base in anhydrous solvent
enamines		pH = 5 catalyzed condensation

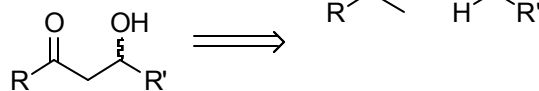
Aldol Additions

reversible
acid or base

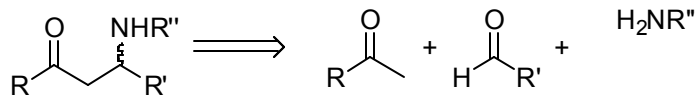


Does not work well with
ketone electrophiles

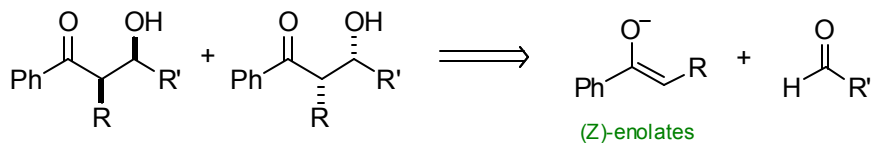
irreversible base
(e.g. LDA)



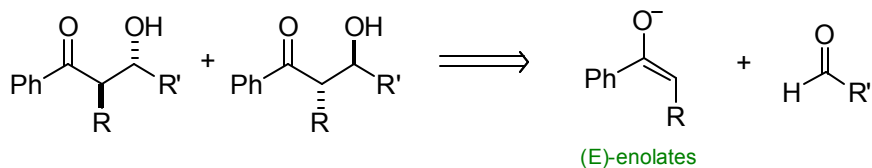
Mannich



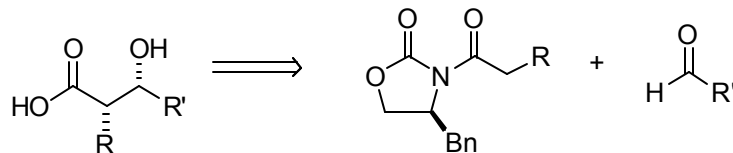
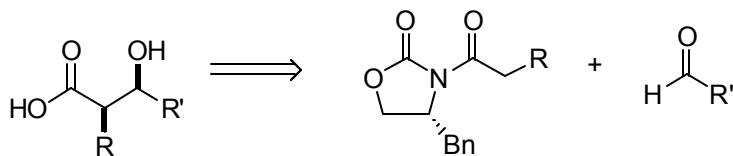
Syn Aldol
Products



Anti Aldol
Products



Evans' Aldol
Reaction

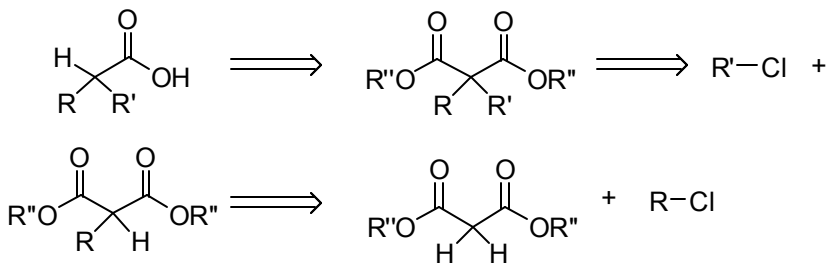


Use LAH to get terminal
alcohols

via (Z)-enolate

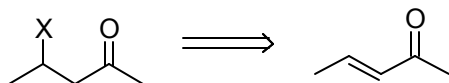
Malonic Ester Alkylation

hydrolysis and
decarboxylation



Conjugate Addition

Michael Reaction
Organocuprate Addition



Review which nucleophiles
add 1,4 vs. 1,2