Structure and Reactivity

Fall Semester 2007

Summary

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Structure and Reactivity: Summary

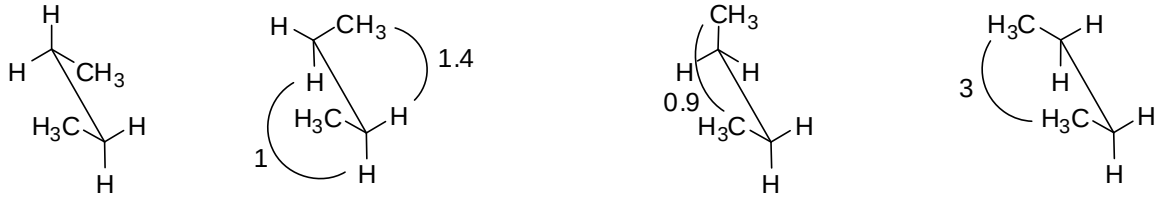
1. Conformational Analysis

(Energy Values in Kcal/mol, M = Medium, L = Large)

1.1 Alkanes

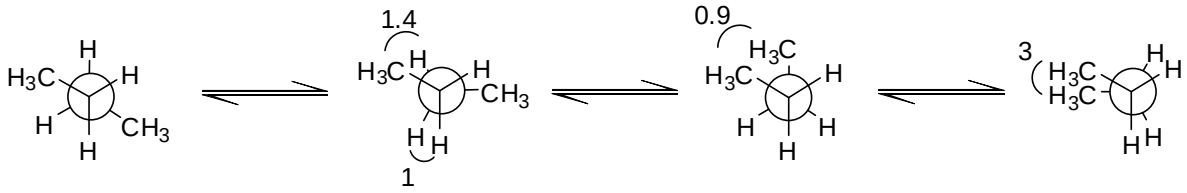
Butane

Sägebock



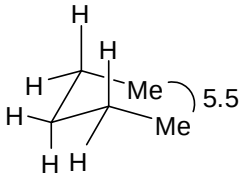
Newman

Gauche Interaction



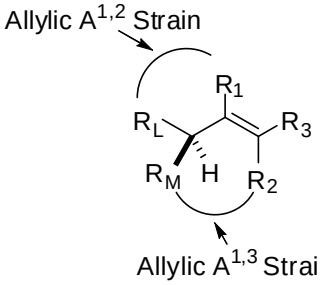
Relative Energy	**0**	**3.8**	**0.9**	**5**
	staggered antiperiplanar	eclipsed anticlinal	staggered synclinal *gauche* conformer	eclipsed synperiplanar

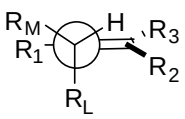
Special Interaction for Pentane:



Double Gauche Pentane or **Syn Pentane** Interaction

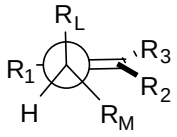
1.2 Alkenes: Allylic Strain





$A^{1,3}$ Minimized:
- R_L in free room ⊥ to DB
- H towards R_2

Favored for R_2 bigger R_1

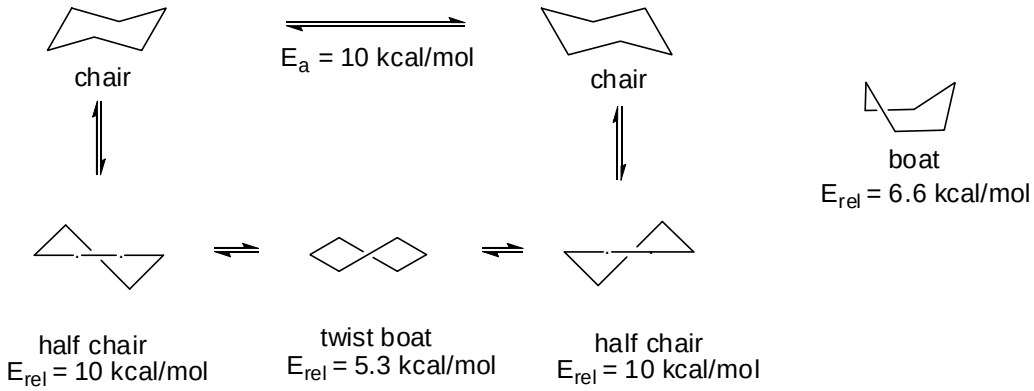


$A^{1,2}$ Minimized:
- R_L in free room ⊥ to DB
- H towards R_1

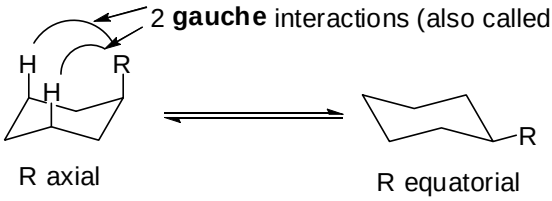
Favored for R_1 bigger R_2

- If R_1 and R_2 are of similar size, $A_{1,3}$ is more important.
- R_3 is usually less important for selectivity.

1.3 Cyclohexane



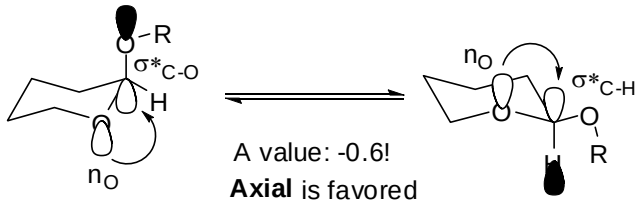
R	A value
CH_3	1.7
CH_2CH_3	1.7
$CH(CH_3)_2$	2.1
$C(CH_3)_3$	4.7
CH_2OH	1.7
CO_2Et	1.2
CN	0.2
$C \equiv C\text{-}H$	0.4
$CH = CH_2$	1.6
C_6H_5	2.8
$Si(CH_3)_3$	2.5
$Sn(CH_3)_3$	1.0
O_2CCH_3	0.7
OCH_3	0.6
N_3	0.5
F	0.3
Cl	0.6
Br	0.6
I	0.5

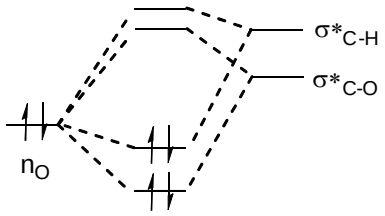


A value (R) = - ΔG (axial-equatorial)

!!! A value are exact only for monosubstituted cyclohexanes!!!

Important Exception: **Anomeric Effect**

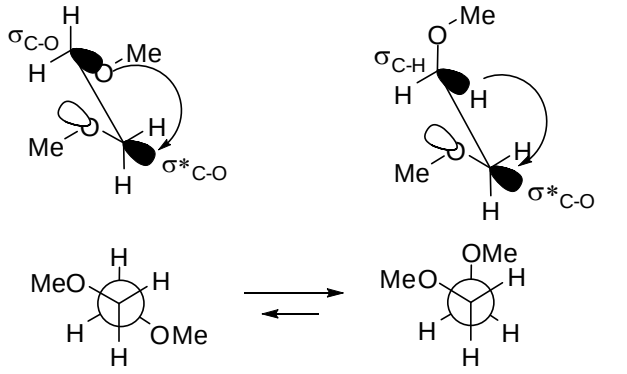




Anomeric Effect: In the axial position, a better stabilization with the more electronegative $\sigma^*_{C\text{-}O}$ is possible.

1.4 Other Important Stereoelectronic Effects

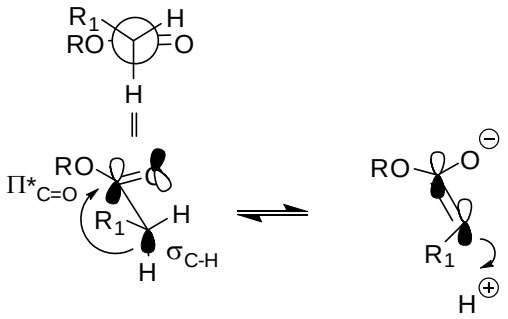
Gauche Effect



More Stable

2 good $\sigma_{C-H}\sigma^*_{C-O}$ interactions

Enolate Formation



$\Longrightarrow$ Hydrogen is acidic only $\perp$ to C=O!

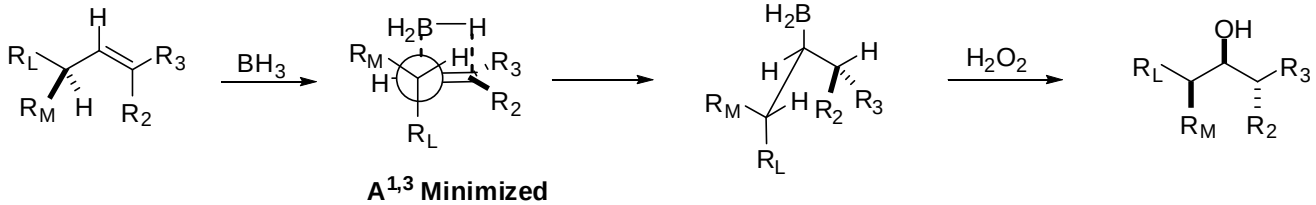
Microscopic Reversibility:

Protonation from Enolate is $\perp$ to C=C!

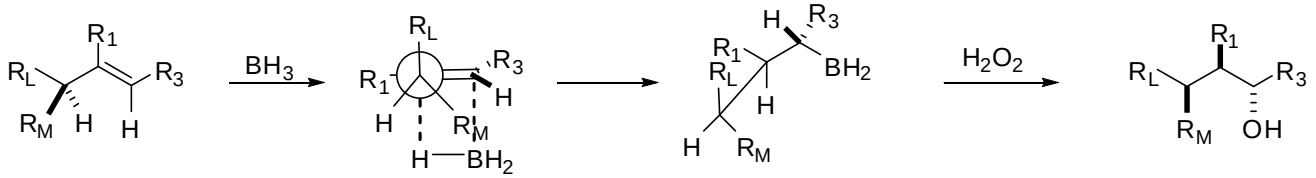
2. C=C Functionalization

2.1 Hydroboration

Hydroboration with BH_3: Minimize strongest Allylic strain, BH_3 comes opposite from R_L

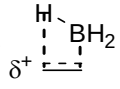


$A^{1,3}$ Minimized

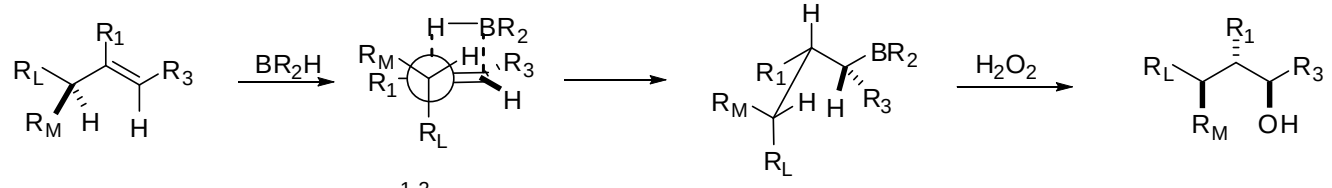


$A^{1,2}$ Minimized

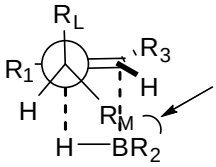
Regioselectivity: H goes to more stabilized carbocation, because the mechanism is asynchronous:

Partial positive charge  tertiary carbocation > secondary carbocation > primary carbocation

Hydroboration with bulky boron reagents: **Minimize reagent-substrate interactions**



$A^{1,2}$ **not** minimized

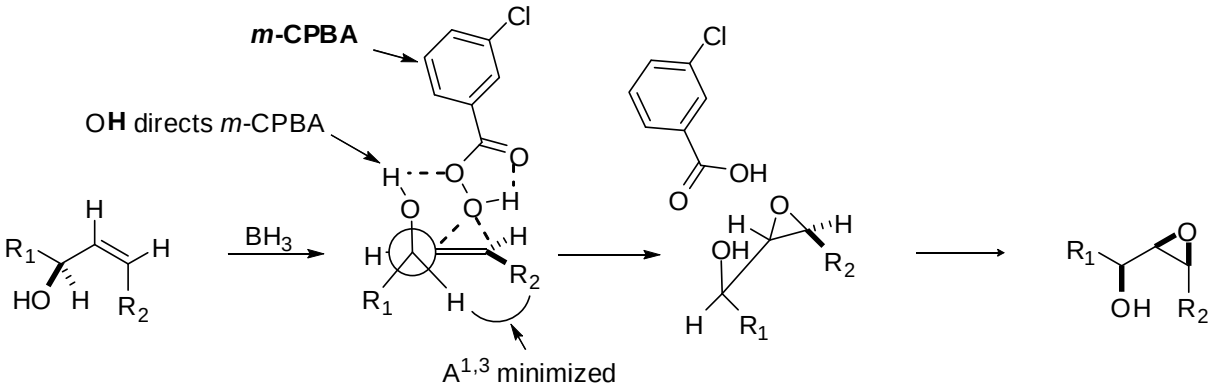


$A_{1,2}$ minimized but strong steric interaction with reagent!

$\Longrightarrow$ **Reagent control is important!**

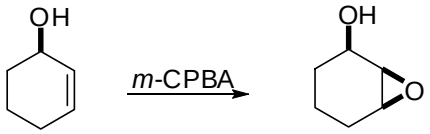
2.2 Epoxidation

Directed Epoxidation with *m*-CPBA



$A^{1,3}$ minimized

Prediction easy for cyclic substrates:

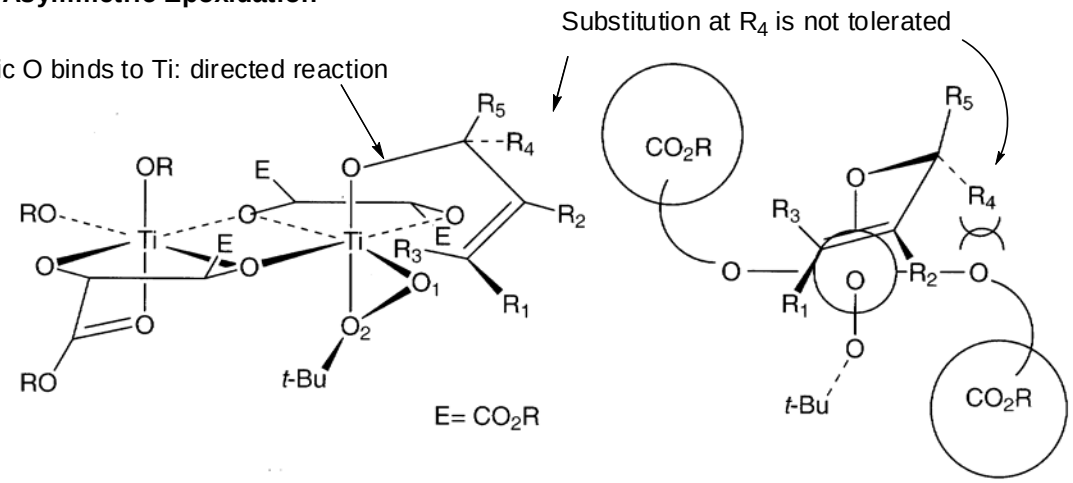


Directed reactions often allows for good selectivity in organic chemistry!

Sharpless Asymmetric Epoxidation

Substitution at R_4 is not tolerated

Allylic O binds to Ti: directed reaction



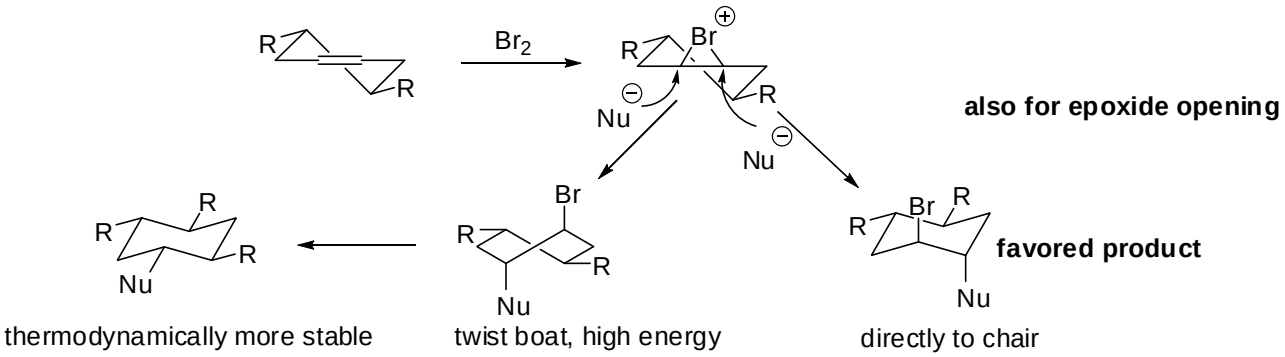
E= CO_2R

(The view down O^1-Ti bond axis)

Important:

- ^{t}BuOOH does not react until bound to Ti ⇒ Catalysis is possible
- Face of attack of the peroxide is determined by the chiral diester ligand, <u>not</u> the conformation of the substrate ⇒ very good reagent control

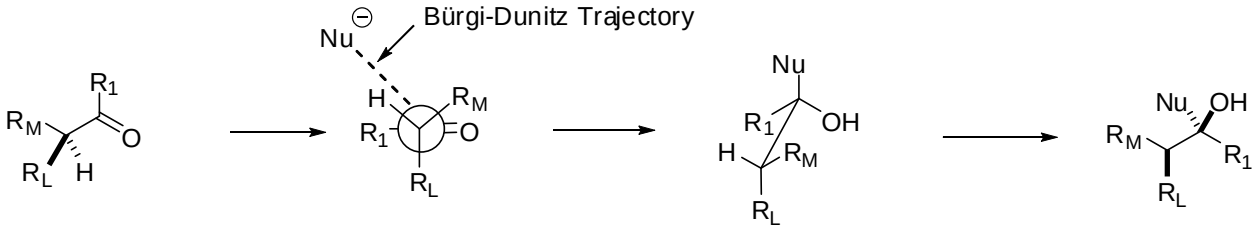
2.3. Fürst-Plattner Rule



$\Longrightarrow$ The thermodynamically more stable product is not observed, because an unvaforable twist-boat intermediate has to be formed.

3. Addition to Carbonyl Compounds

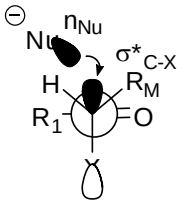
3.1. Felkin-Ahn Model



- R_L is $\perp$ to C=O
- Nu comes along the Bürgi-Dunitz trajectory (109 °C to C=O)
- Minimize Nu-Substrate interaction $\Rightarrow$ Smallest Substituent on Bürgi-Dunitz trajectory (Here H)

Polar Felkin-Ahn Rule

Electron-deficient groups behave as R_L

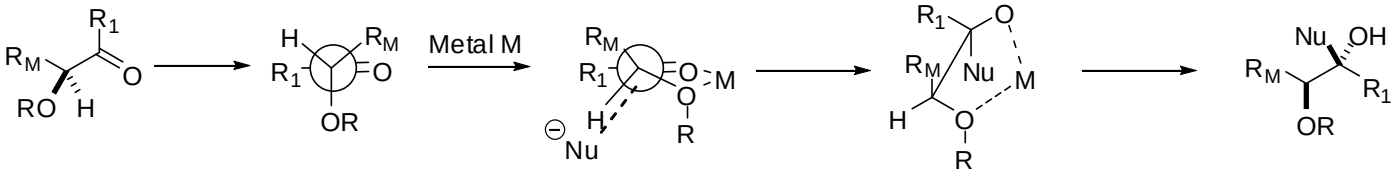


Favorable Interaction n_{Nu} to σ^*_{C-X}

X = OR, F, Cl, Br, I, ...

3.2. Addition to Carbonyl Compounds Not Following the Felkin Ahn Model

3.2.1. Chelate Control



- Metal forces two donors in plane through chelation
- Nu comes towards smallest substituent (H)

Factors favoring chelation

- R group sterically not hindered:

good: R = Me, Bn, $MeOCH_2$ (MOM), $BnOCH_2$ (BOM)

bad: R = ^tBu, $SiMe_3$, $SiMe_2{}^tBu$ (TBDMS or TBS), Si^iPr_3 (TIPS)

- non-coordinating solvents:

Toluene, CH_2Cl_2 >> Et_2O > THF >> DMF, EtOH, H_2O

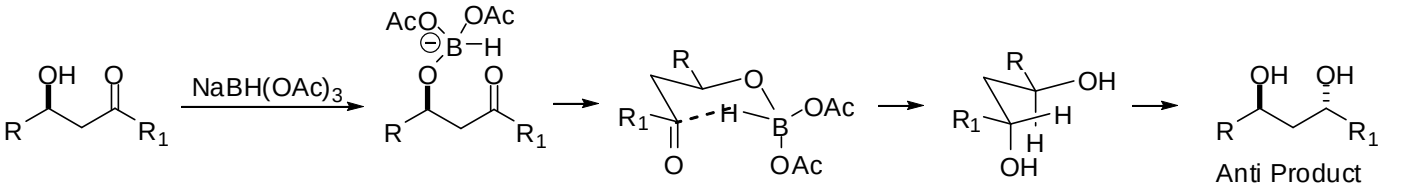
- Strong Lewis Acid, with more than one coordination site available

Bad: Na^+, K^+ (too weak Lewis Acid), BF_3 (only 1 coordination site), LiX

Good: MgX_2, ZnX_2, LiX, $TiCl_4$, $SnCl_4$, $SnCl_2$, LnX_3, $AlCl_3$,...

Importance of anion X: If X is not too tightly bond to the metal, it can dissociate generating a new free coordination site. F^-, R^- generally don't dissociate, Cl^- and OAc^- can dissociate and Br^-, I^-, OTf^- often dissociate easily. For example BF_3 is not a chelating agent, but BBu_2OTf is a chelating agent.

3.2.2. Directed Reduction



Sodium trisacetoxy borohydride is a very weak reducing reagent ⇒ Only intramolecular reduction is possible

3.2.3 Reagents Binding to Carbonyl During Addition

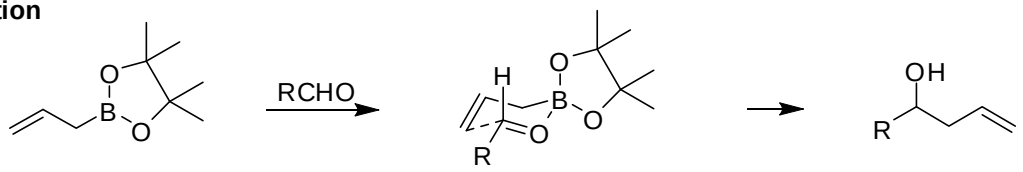
Borane Reduction

Other important examples where Felkin-Ahn models does not apply:

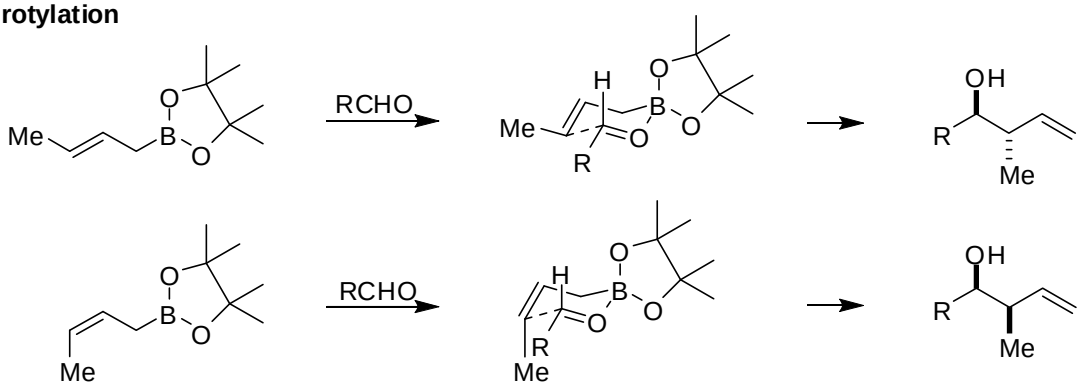
Allylation, **Aldol Reactions via Chair Transitions States**

4. Allylation

Allylation

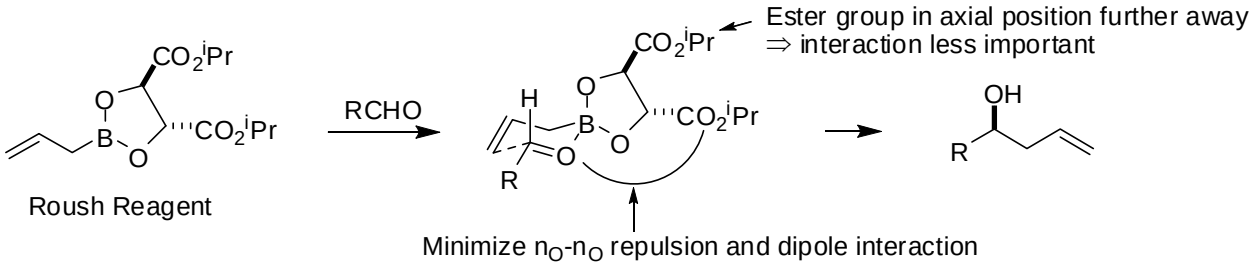


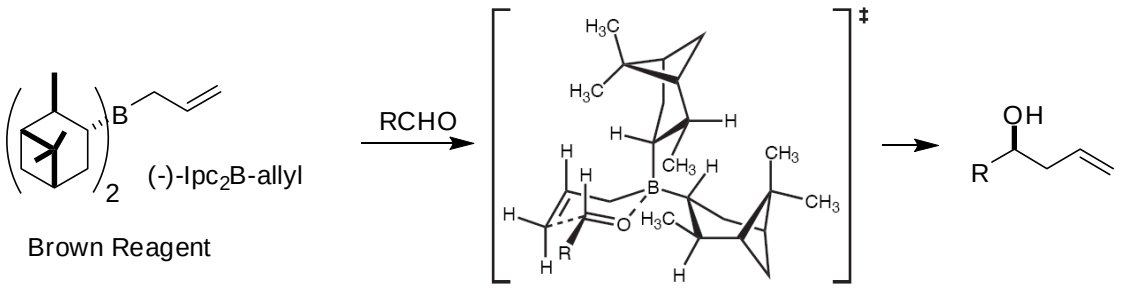
Crotylation



- 6-membered, chair transition state
- Substituent in equatorial position
- Transfer from double bond geometry to stereochemistry (*E* to anti, *Z* to cis)

Chiral Reagents For Allylation Reactions

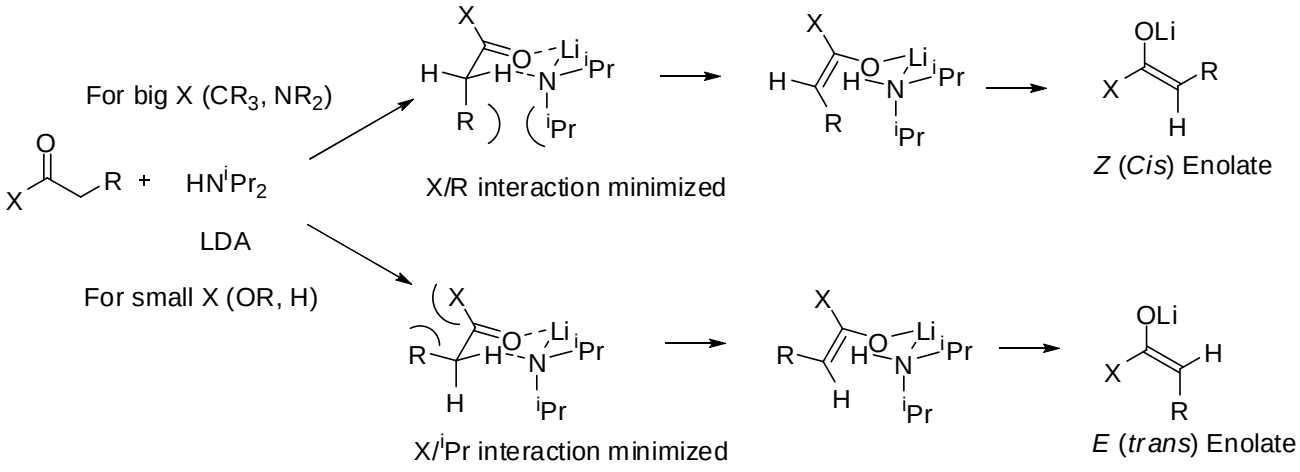




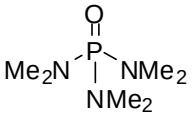
5. Aldol Reactions

5.1 Enolate Generation

With LDA

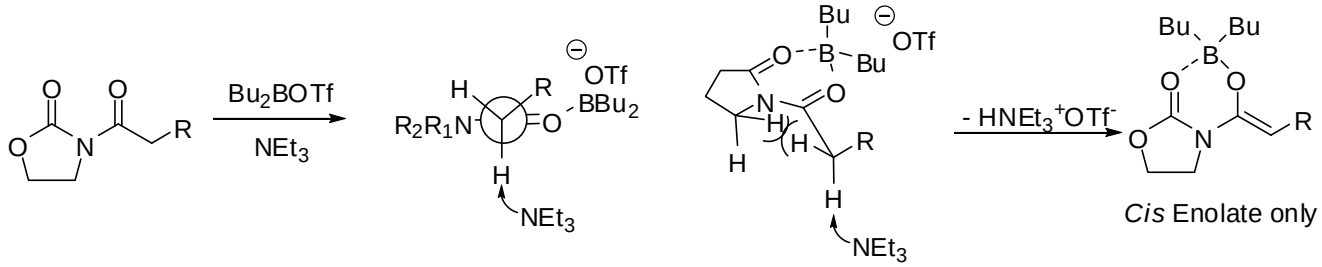


exception for esters: Adding HMPA leads to *Z* (*Cis*) Enolate

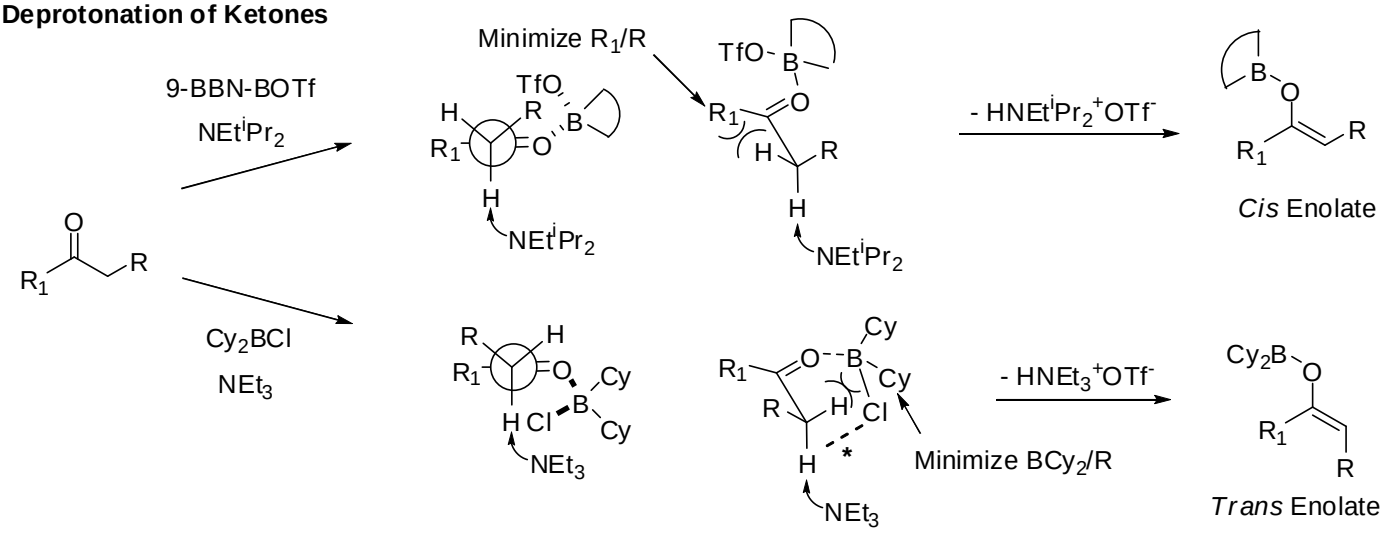


HMPA: good ligand for lithium ⇒ Cyclic transition state is partially disrupted

Deprotonation of Imides with Bu_2BOTf and NEt_3 (soft enolization)

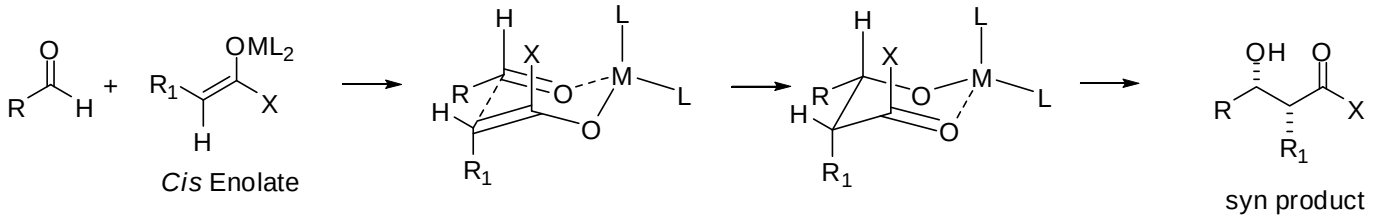


Deprotonation of Ketones



*The complete switch of selectivity is not well understood, some authors proposed an extra Cl-hydrogen interaction

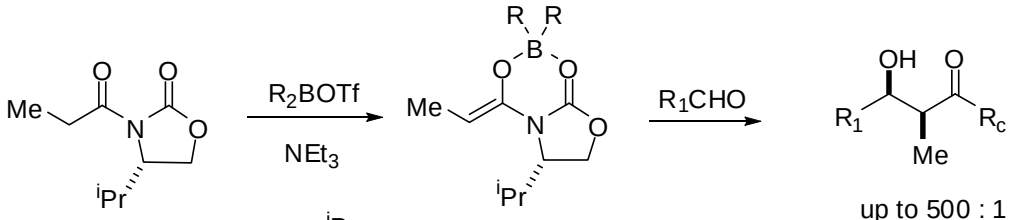
5.2 Zimmermann-Traxler Transition State



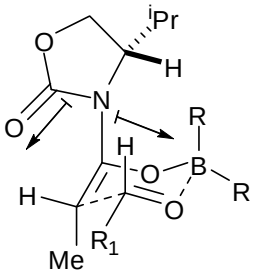
- Chair transition state (Zimmerman-Traxler)
- R group of aldehyde equatorial
- Geometry of double bond transfered to stereocenter: *cis* to syn, *trans* to anti

5.3 Evans Auxiliary

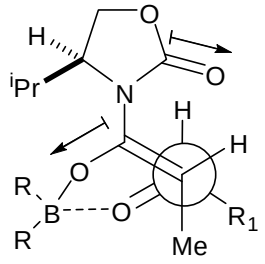
Evans Syn Aldol:



Transition States



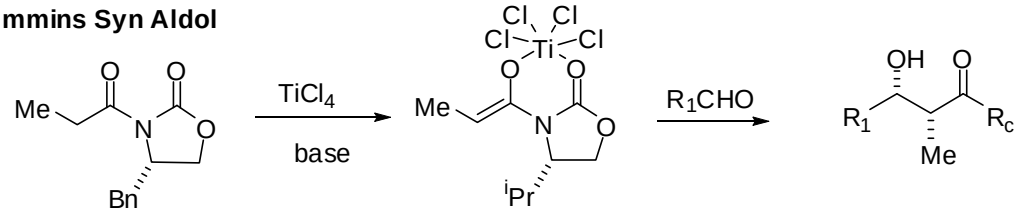
- Chair Transition State
- Minimized Dipoles
- Aldehyde comes opposite from ^{i}Pr



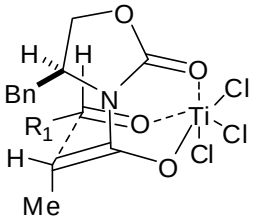
Newman view from the left

Important: In order to activate the aldehyde for addition, B has to bind to the aldehyde. As B has only two free binding sites, the oxazolidinone carbonyl is now free and rotates to minimize dipole interactions.

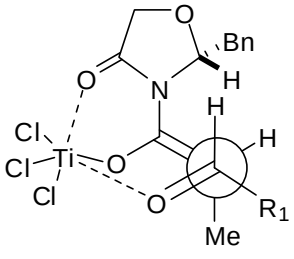
Crimmins Syn Aldol



Transition States

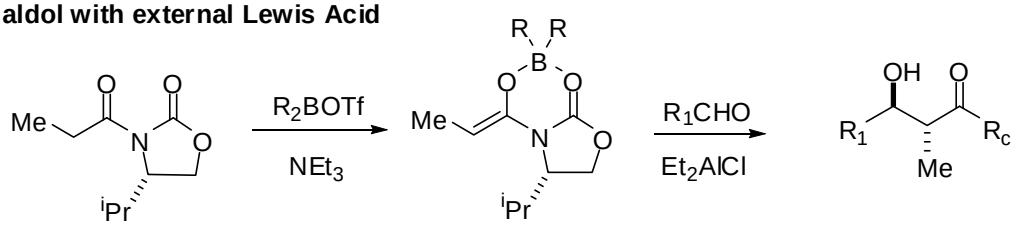


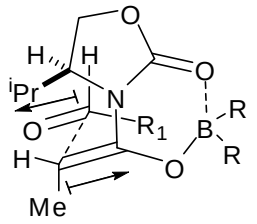
- Chair Transition State
- All Carbonyl bound to Ti
- Aldehyde comes opposite from Bn



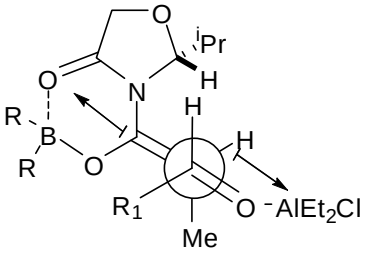
Newman view from the back

Anti aldol with external Lewis Acid



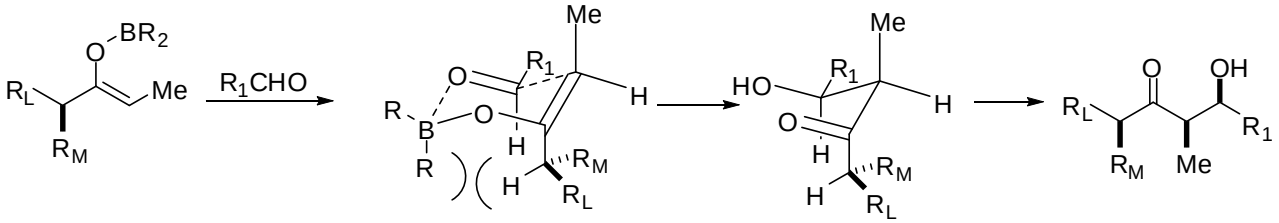


- Free transition state (no chair)
- B chelates the auxiliary
- Minimized dipoles and steric: carbonyl antiperiplanar to enolate
- Aldehyde comes opposite from ^iPr
- R_1 group away from auxiliary

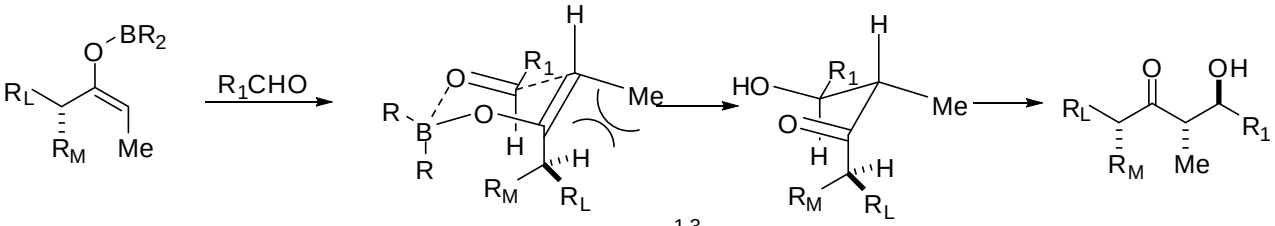


Newman view from the back

5.4 Ketone (Paterson) Aldol



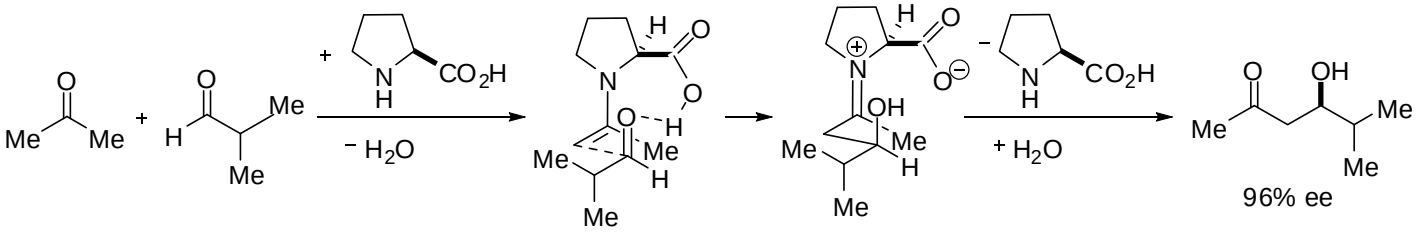
Minimized steric



Minimized $A^{1,3}$

- Chair transition state
- R_1 group of aldehyde equatorial
- position of chiral group: minimize steric interaction with BR_2 for *cis* enolate, aldehyde comes towards R_M, not R_L, minimize $A^{1,3}$ with Me of enolate for *trans* enolate, R_M and not R_L towards BR_2, aldehyde comes towards H

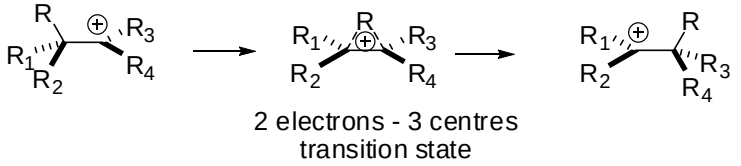
5.5 Proline Catalyzed Aldol



96% ee

6. Rearrangements

6.1 Cationic Rearrangements

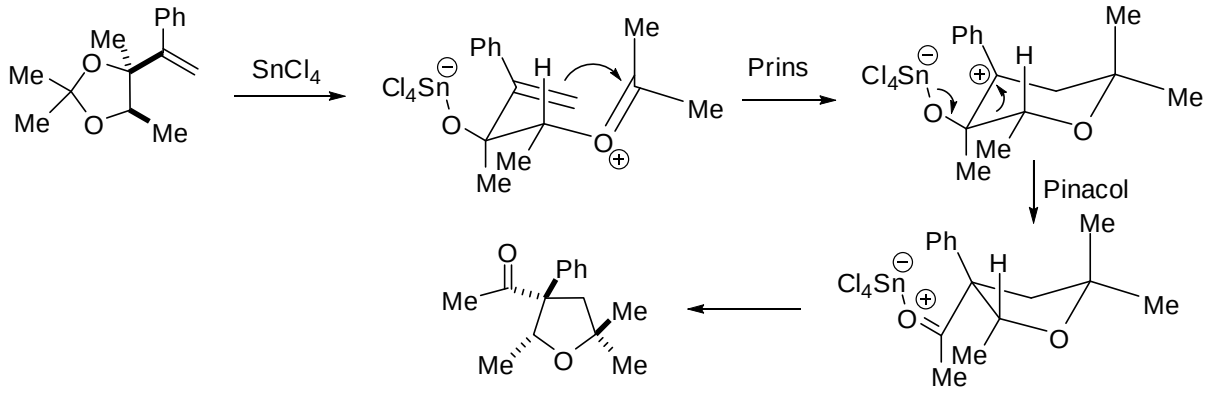


2 electrons - 3 centres transition state

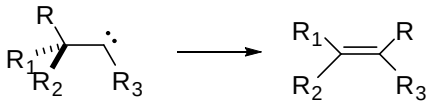
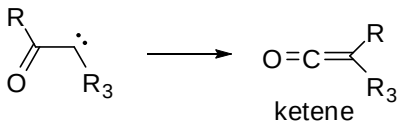
The group which stabilizes the best the cation is migrating

Name Reactions: Wagner Meerwein, Pinacol, semi-Pinacol, Prins-Pinacol.

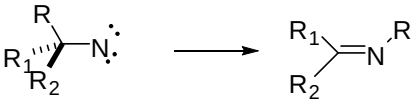
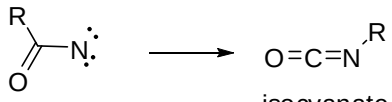
Prins-Pinacol:



6.2 Carbene and Nitrene Rearrangements

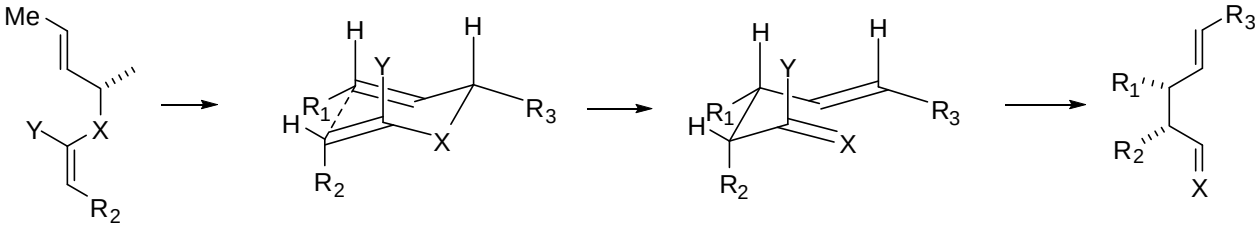
carbene  important special case: 
ketene

Name Reactions: Fritsch-Buttenberg-Wiechell, Arndt-Einstert, Wolff.

nitrene  important special case: 
isocyanate

Name Reactions: Curtius, Hofmann, Lossen, Schmidt

6.3 [3,3] Sigmatropic Rearrangements

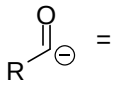
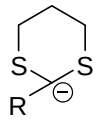


- Chair transition state (with rare exceptions)
- R groups at SP^3 centers equatorial
- Transfer of double bond geometry to stereocenter and stereocenter to double bond geometry

Name Reactions: Cope (X = C), Oxy-Cope (X = C, R_3 = OH), Anionic Oxy-Cope (X = C, R_3 = O-), Claisen (X = O), Johnson-Claisen (X = O, Y = OR), Ireland-Claisen (X = O, Y = OLi, $OSiR_3$)

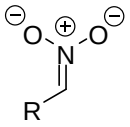
7. Umpolung

7.1 Stoichiometric Umpolung Reagents

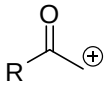
Acyl anion equivalents:  = 

Dithiane

Cyanide

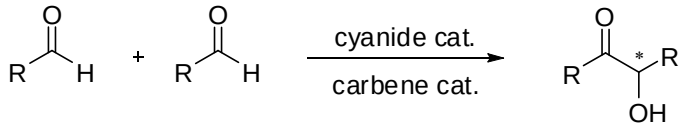


Nitronate

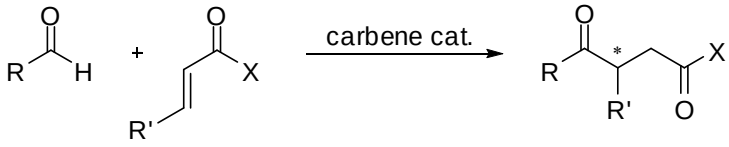
Electrophile α to carbonyl:  = 

7.2 Catalytic Umpolung

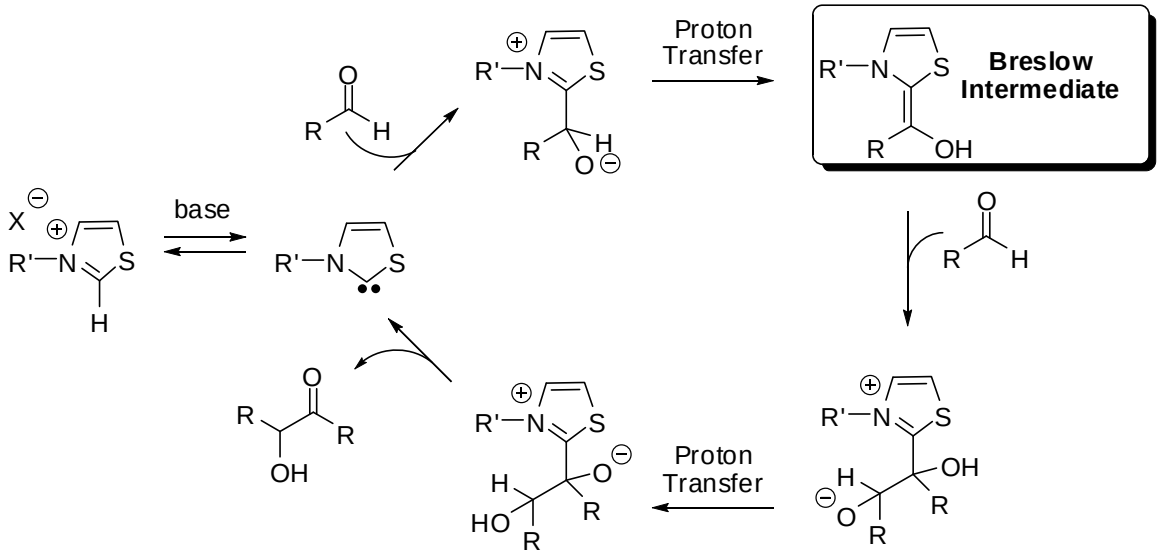
The Benzoin Condensation



The Stetter Reaction



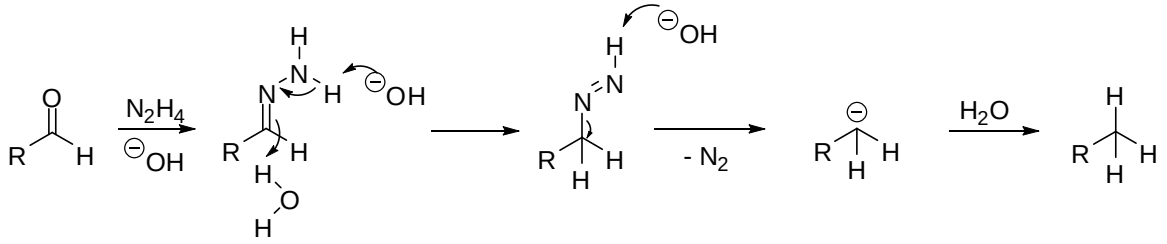
Mechanism for the carbene - catalyzed benzoin condensation:



8. Reactions Involving N-N and N-O Bonds

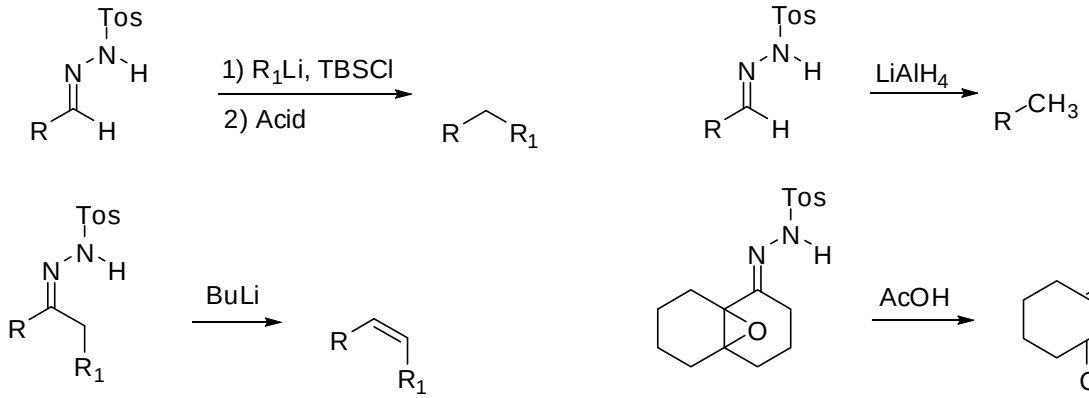
8.1 Hydrazones

Wolff-Kishner Reduction



Other reactions with hydrazones derived from hydrazine: Wharton rearrangement, Barton halogenation

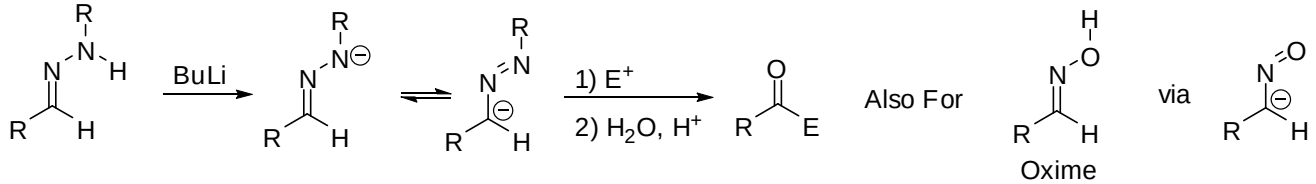
Reactions of Tosylhydrazones



Shapiro Reaction

Eschenmoser Fragmentation

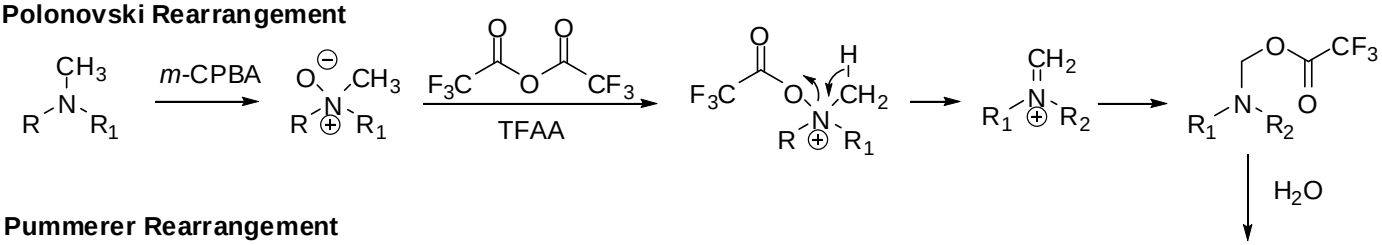
8.2 Umpolung with Hydrazones and Oximes



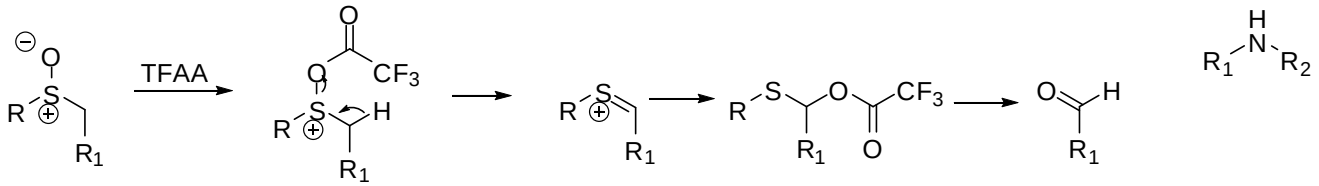
Oxime

8.3 Polonovski and Pummerer Rearrangement

Polonovski Rearrangement

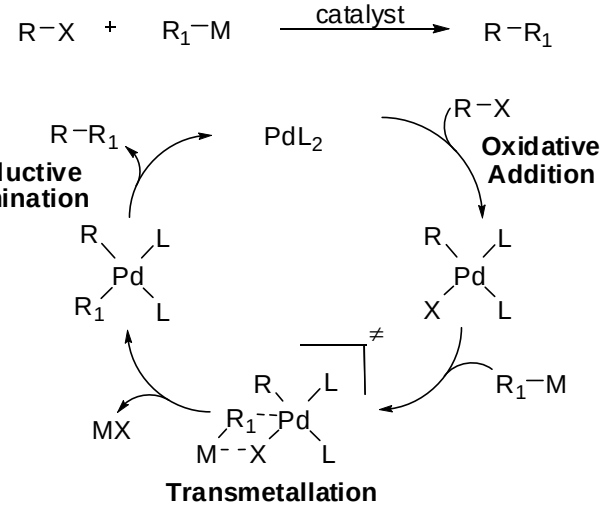


Pummerer Rearrangement



9. Cross-Coupling and Olefin Metathesis

9.1 General Mechanism for Cross Coupling



Scope:

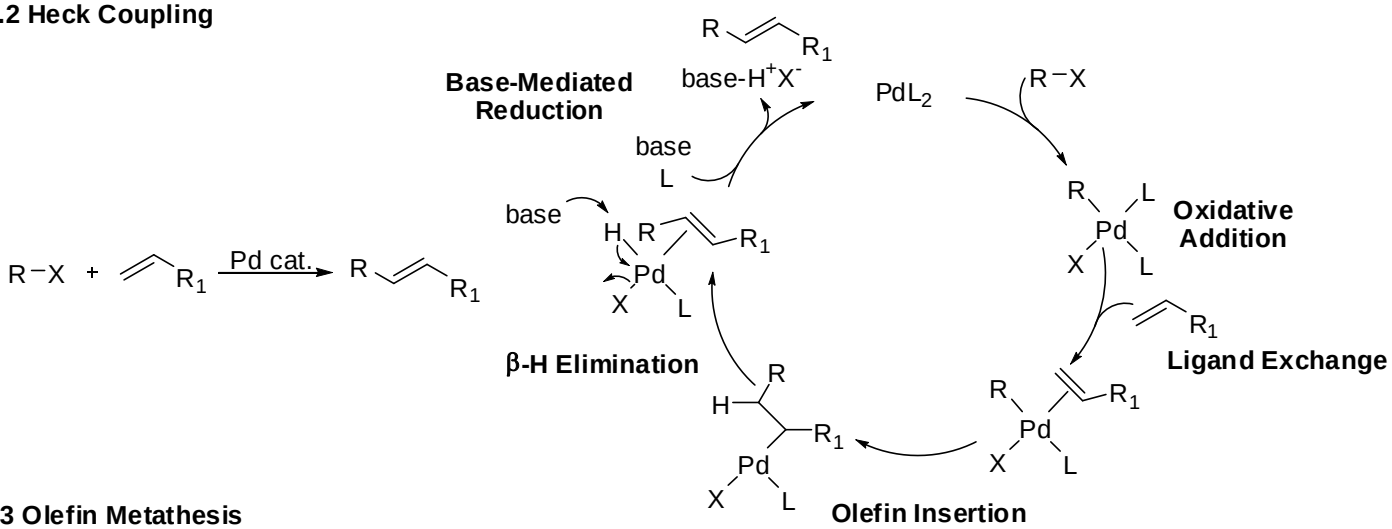
R and R_1 groups

easy: R, R_1 = aryl, alkenyl, alkynyl
difficult: R_1 = alkyl
very difficult R = alkyl (topic of current research)

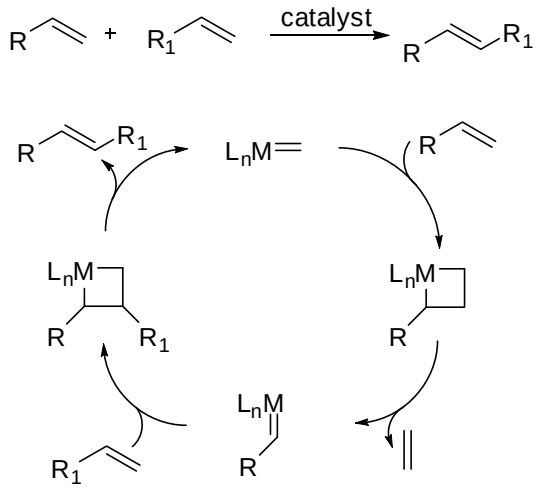
X groups

easy: I, Br, OTf
difficult but more interesting: Cl, OTos, H

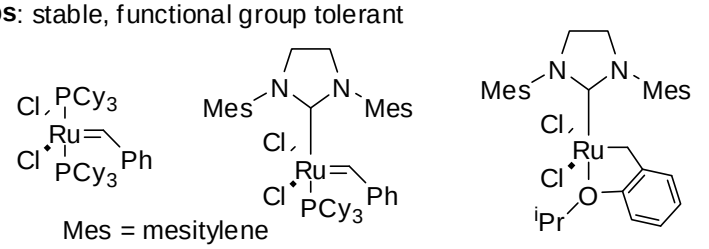
9.2 Heck Coupling



9.3 Olefin Metathesis



Grubbs: stable, functional group tolerant



Schrock: more reactive, less stable