Structure and Reactivity

Fall Semester 2008

Summary

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Supplementary Material

- Prerequired Knowledge (required for exam)
- General Mechanism for Diels Alder Reaction (required for exam)
- Polyketides and Drugs (**not** required for exam)

Structure and Reactivity: Summary

1. Introduction and Literature

Warning: This summary is meant as an help to check the note taken in the lecture and contains only the most important concepts and transition states, it cannot replace the blackboard notes!

Important Supporting Material

- Prerequired Knowledge Summary (necessary to solve exam problems!)
  repetition of easy concepts from bachelor

- Evans CHEM 206 (on the internet via google)
  probably the best lecture on the net on advanced organic chemistry, contains most of the topics of this lecture and much more

- Carey Sundberg: Advanced Organic Chemistry Part A and B
  Comprehensive books, focusing mostly on reactivity, but weaker on selectivity.

- March's: Advanced Organic Chemistry
  Book good for consultation, not for learning

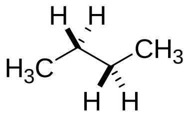
- Kurti-Czako: Strategic Applications of Named Reactions in Organic Synthesis
  One of the best book for named reactions, very good to revise mechanism and scope of specific reactions

2. Conformational Analysis

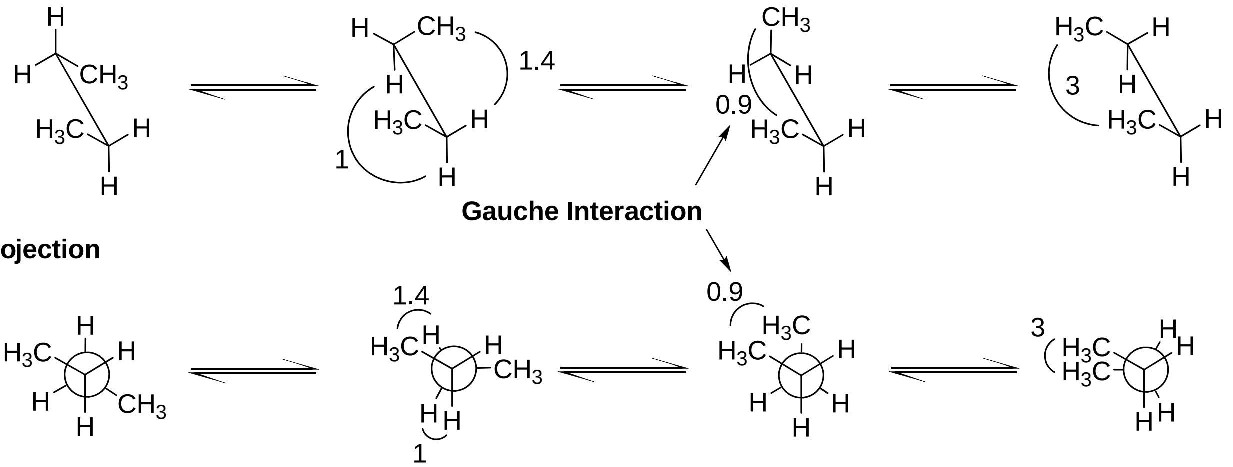
(Energy Values in Kcal/mol, M = Medium, L = Large)

2.1 Alkanes

Butane

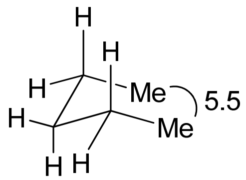


Sägebock Projection



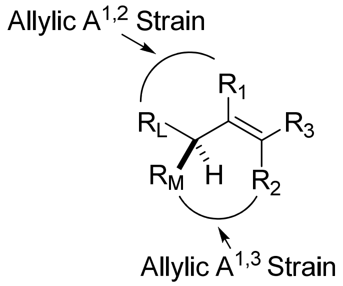
Relative Energy	**0**	**3.8**	**0.9**	**5**
	staggered antiperiplanar	eclipsed anticlinal	staggered synclinal *gauche* conformer	eclipsed synperiplanar

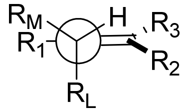
Special Interaction for Pentane:



Double Gauche Pentane or **Syn Pentane** Interaction

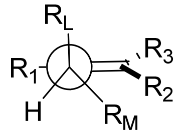
2.2 Alkenes: Allylic Strain





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

Favored for R_2 bigger R_1

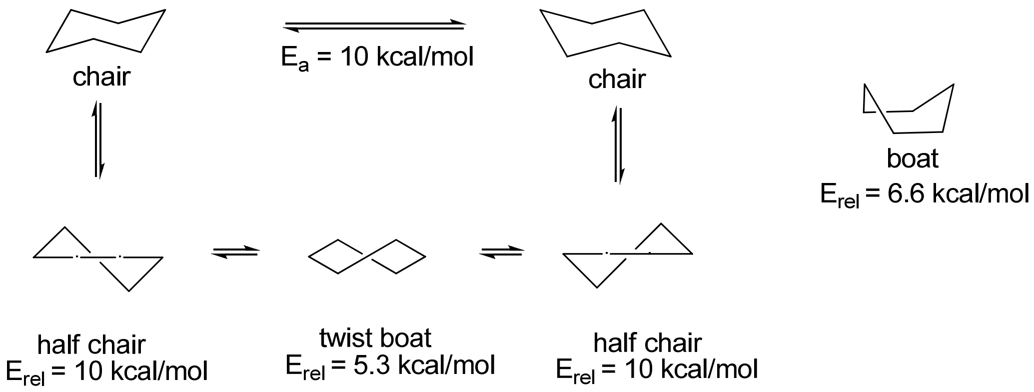


$A^{1,2}$ Minimized:
- R_L in free room ⊥ to DB
- H towards R_1

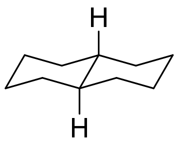
Favored for R_1 bigger R_2

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

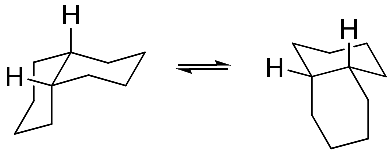
2.3 Cyclohexane



Special Case: Decalin



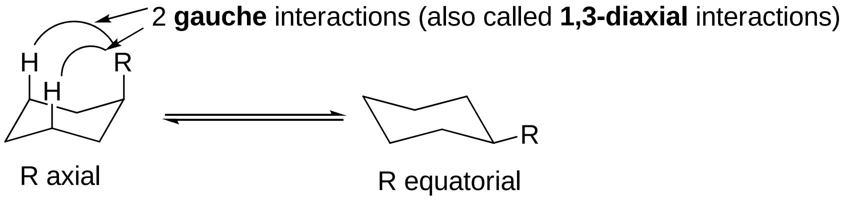
Trans decalin
Rigid



Cis decalin
Flexible

A Values

R	A value
CH_3	1.7
CH_2CH_3	1.7
$CH(CH_3)_2$	2.1
$C(CH_3)_3$	4.7
CN	0.2
C_6H_5	2.8
$Si(CH_3)_3$	2.5
OCH_3	0.6
Cl	0.6



A value (R) = - ΔG (axial-equatorial)

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

Important number to remember:

A Value CH_3: 1.7 Kcal/mol
1.4 Kcal = 10:1 mixture
21 Kcal = thermal energy at room temperature

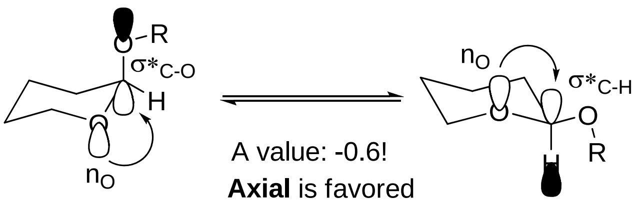
2.4 Stereoelectronic Effects: HOMO-LUMO interactions

Important Rules for HOMO-LUMO interactions

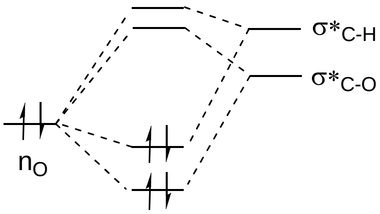
1) The nearest the energy of HOMO and LUMO, the strongest the interaction.
2) The absolute energy of orbitals is correlated to the electronegativity of the atoms/bonds
3) Stereoelectronics: a geometrical overlap of orbitals is necessary for interaction

Important examples:

Structural Anomeric Effect

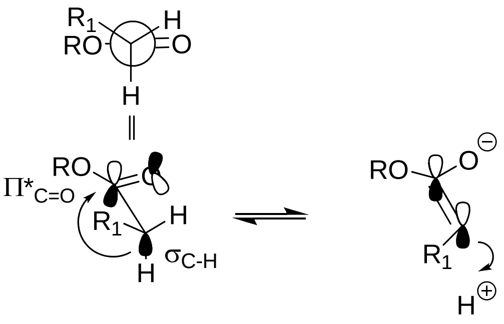


A value: -0.6!
Axial is favored



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

Enolate Formation



⟹ Hydrogen is acidic only ⊥ to C=O!

Microscopic Reversibility:

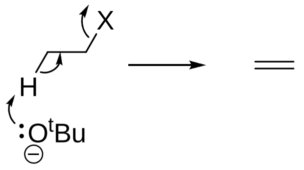
Protonation from Enolate is ⊥ to C=C!

Other examples seen in the lecture: Sn^2 substitution, elimination, conformation of esters, stabilization of carbocations

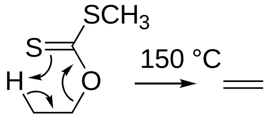
3. Alkenes

3.1 Synthesis of Alkenes

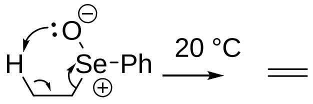
3.1.1 Elimination



E_2, trans elimination

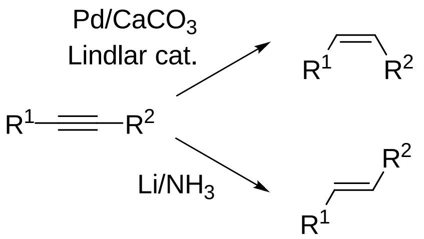


Chugaev syn elimination

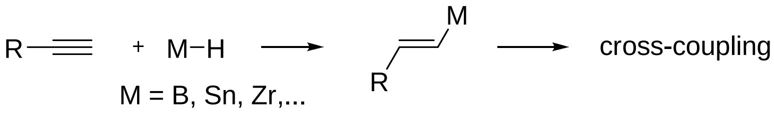


Selenoxide syn elimination

3.1.2 From Acetylenes



Reduction



Hydrometallation

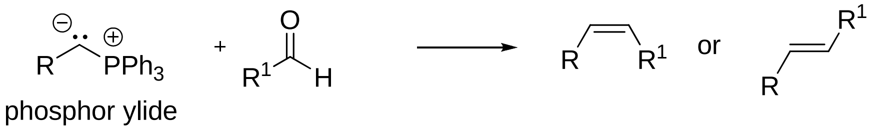
3.1.3 Olefin Metathesis (see inorganic chemistry lectures)

3.1.4 From carbonyls

3.1.4.1 Aldol Condensation

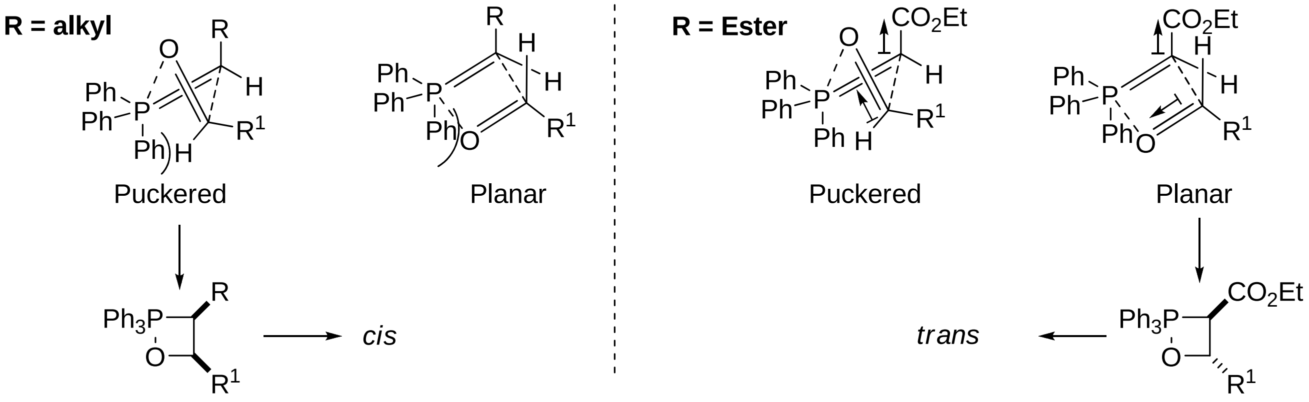
3.1.4.2 Wittig and Variations

Original Wittig



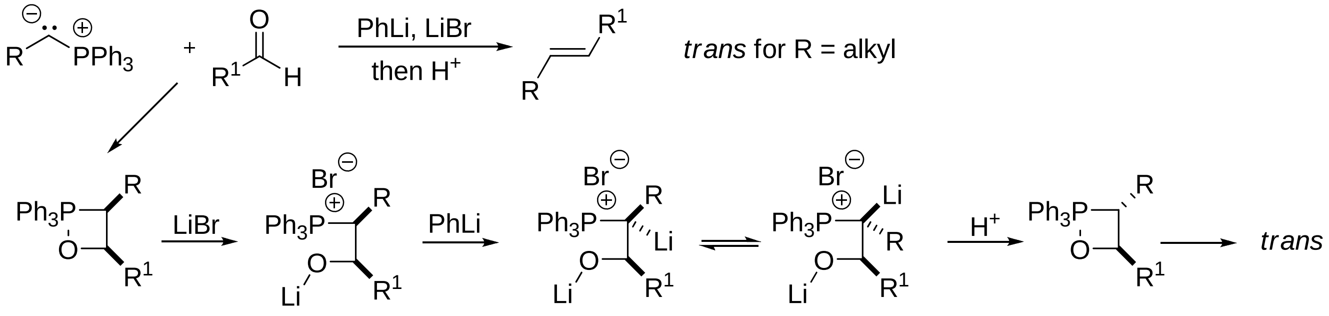
cis for R = alkyl
trans for R = CO_2R'

Mechanism



Two transition state are possible: puckered and planar. For alkyl groups, the reaction is controlled by sterics and the puckered TS is favored (less interactions with bulky Ph group). For esters, the reaction is controlled by electronics and the planar TS is favored (better Dipoles orientation).

Schlosser Variation

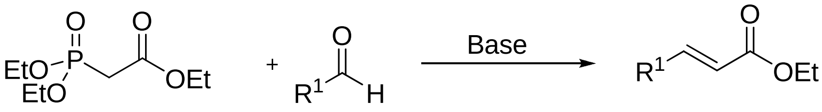


trans for R = alkyl

General problem with Wittig: Strong base is needed! It cannot be used for base-sensitive substrates.

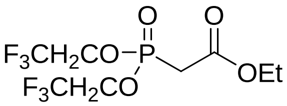
Milder Variations:

Horner-Wadsworth-Emmons (HWE)

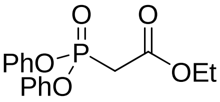


HWE is *trans* selective and weaker base can be used: very often used in total synthesis.

Cis-selective variations:



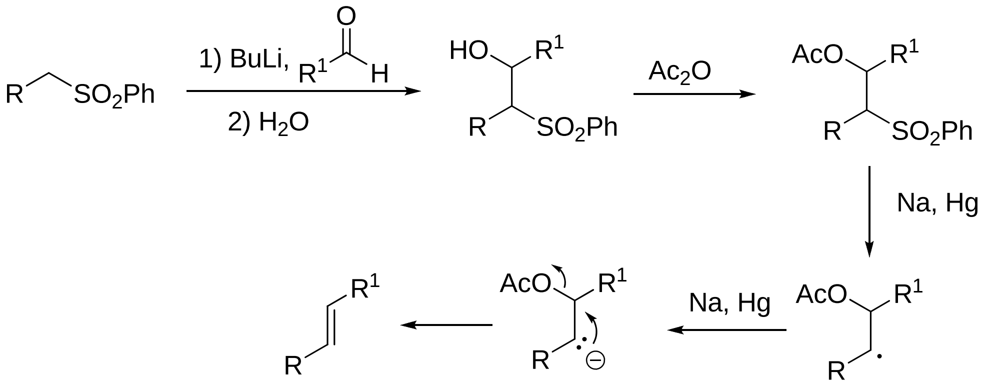
Still-Gennari



Ando

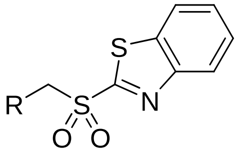
3.1.4.3 Julia and Variations

Julia-Lythgoe



Highly *trans* selective, but multi-steps

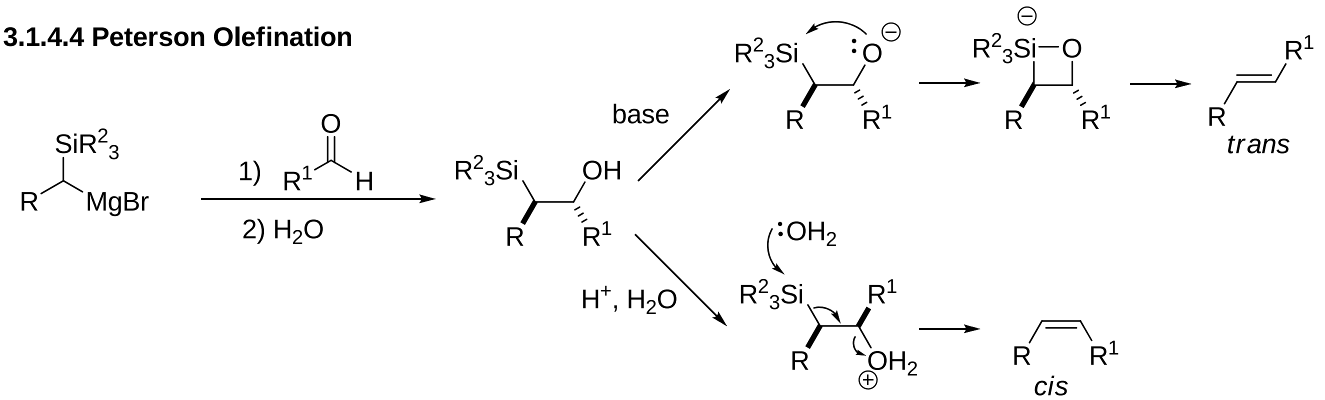
Julia-Kocienski



1 step only

Highly *trans* selective, milder than many Wittig methods

3.1.4.4 Peterson Olefination



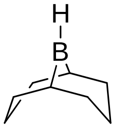
If high selectivity can be achieved in the first step, the Peterson protocol allows obtaining *trans* or *cis* olefins depending on the reaction conditions.

3.2 Hydroboration of Alkenes

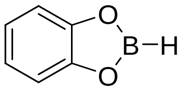
3.2.1 Important Boron Reagents and General Mechanism

BH_3

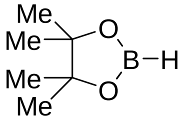
borane



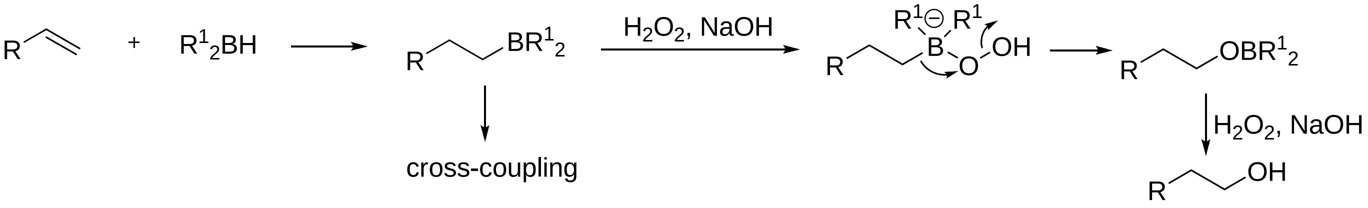
9-BBN



catechol borane

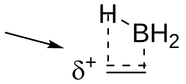


pinacol borane



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

Partial positive charge

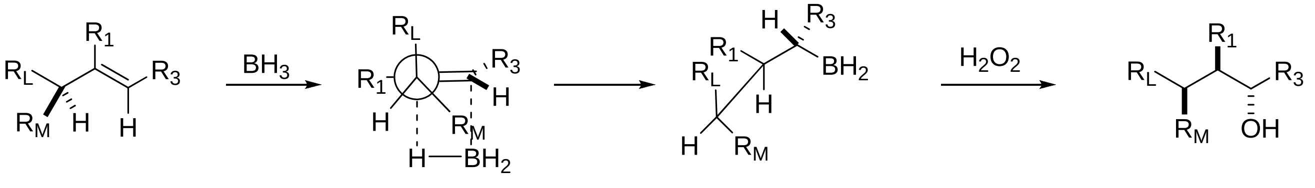


tertiary carbocation > secondary carbocation > primary carbocation

3.2.2 Control of Diastereoselectivity

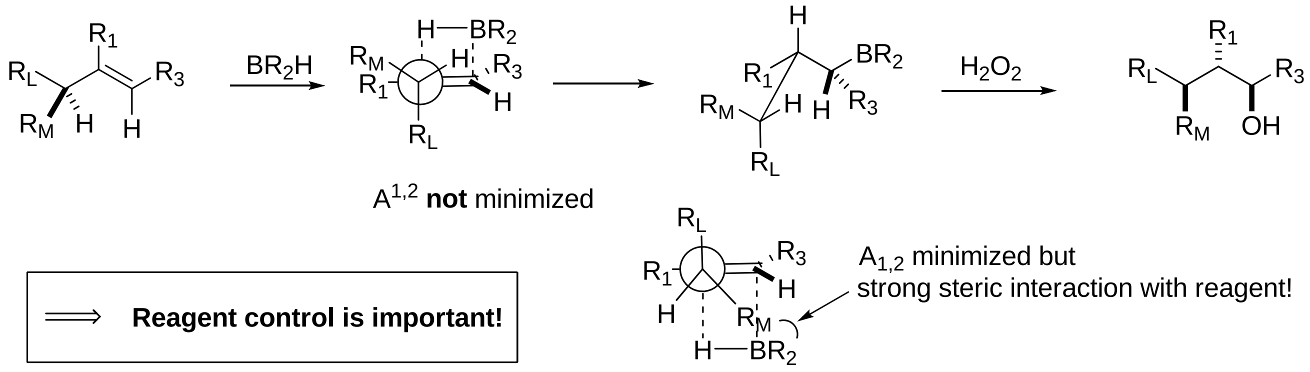
Hydroboration with BH_3: Minimize strongest Allylic strain, BH_3 comes opposite from R_L

A^{1,3} Minimized



A^{1,2} Minimized

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

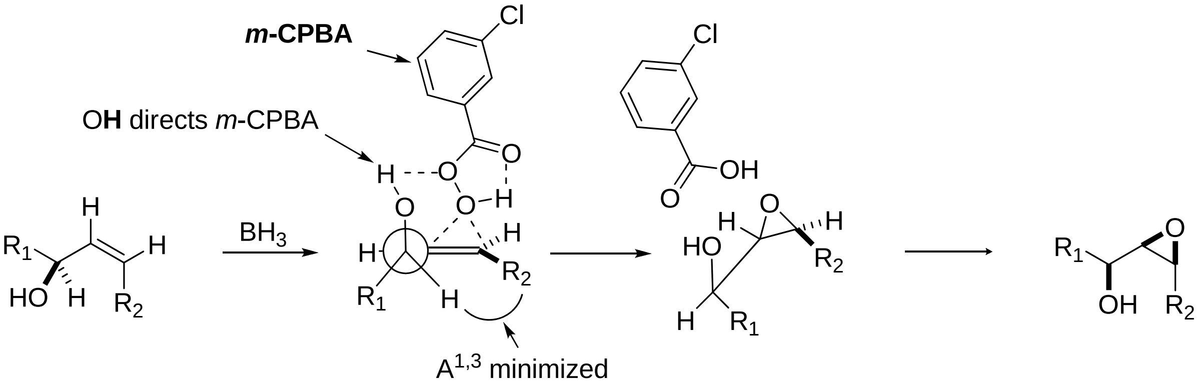


⟹ **Reagent control is important!**

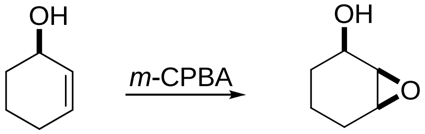
3.3 Alkene Oxidation

3.3.1 Epoxidation

3.3.1.1 Directed Epoxidation with *m*-CPBA



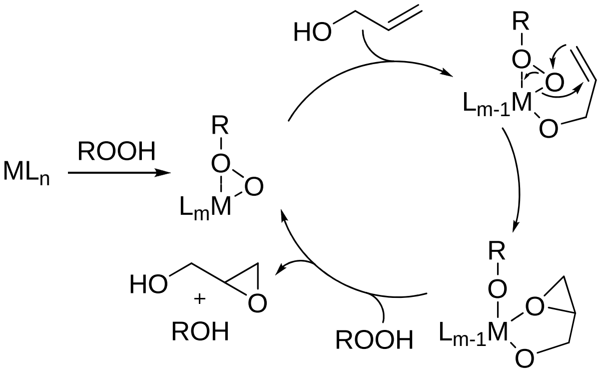
Prediction easy for cyclic substrates:



Directed reactions often allows for good selectivity in organic chemistry!

3.3.1.2 Directed Epoxidation with metal catalysts

General Mechanism

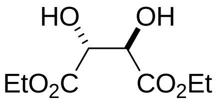


Often used MLn: $VO(acac)_2$, $Ti(OR)_4$

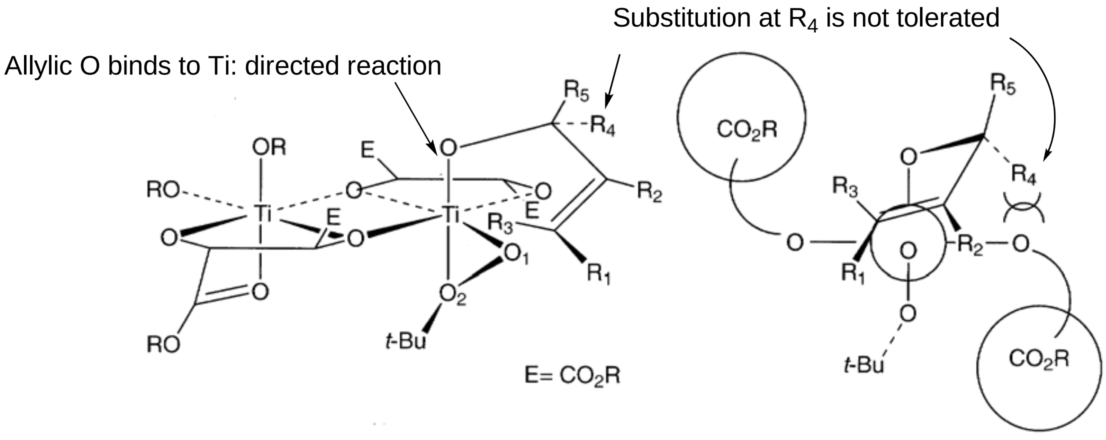
Catalytic Asymmetric Version: Sharpless Epoxidation

conditions: 5 mol% Ti(O^{i}Pr)$_4$, 5 mol% DET, ^{t}BuOOH, molecular sieves, CH$_2$Cl$_2$, -20 °C

DET = diethyltartrate



a cheap member of the chiral pool



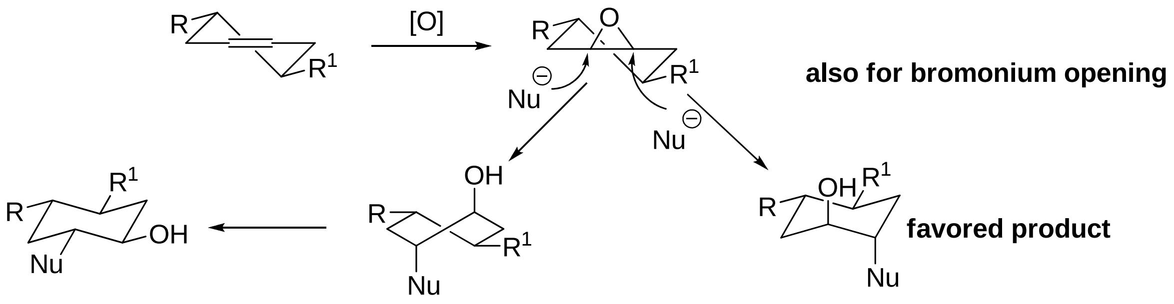
(The view down O^1-Ti bond axis)

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

> The Sharpless epoxidation is very often used for the synthesis of complex organic molecules!

3.3.1.3 Epoxide Opening and the Fürst-Plattner Rule



thermodynamically more stable

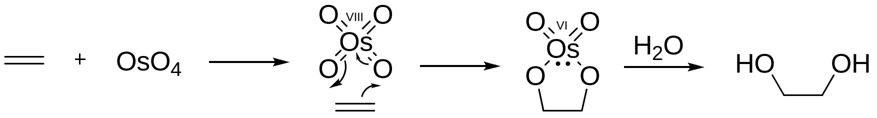
twist boat, high energy

directly to chair

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

3.3.2 Dihydroxylation

General Mechanism

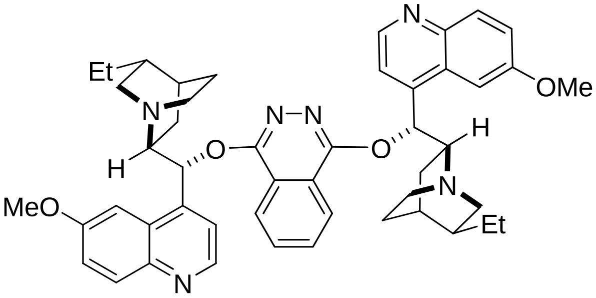


Problem with first method: Stoichiometric use of very toxic and expensive OsO_4

Sharpless Catalytic Asymmetric Dihydroxylation: Ad-mix

5 mol% $K_2OsO_4(OH)_4$ (catalyst)
$K_3Fe(CN)_6$ (stoichiometric oxidant)
cinchona-derived amines (chiral ligand)
Inorganic Base

sold as Ad-mix



$(DHQ)_2$-PHAL
example of chiral ligand

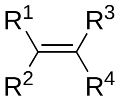
The Sharpless dihydroxylation is the most used method for the asymmetric synthesis of diols.

This reaction will be discussed in details in the couse catalytic asymmetric reactions in organic synthesis.

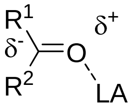
4. Addition to Carbonyl

4.1 General Concepts and Models

Comparison with Olefins



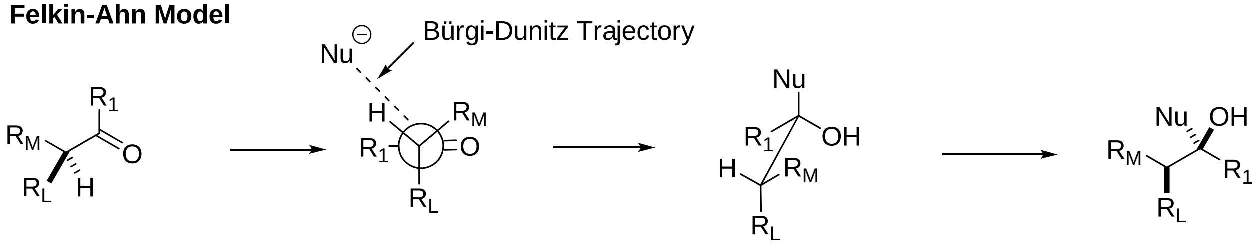
Olefins



Carbonyls

- Sterics is different: only lone pairs on O
- C=O bond is polarized: no issue of regiochemistry
- Further activation of carbonyls with Lewis Acis is easy and allow to modulate the reactivity

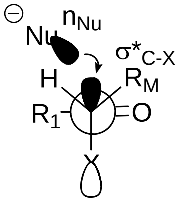
Felkin-Ahn Model



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

Polar Felkin-Ahn Rule

Electron-deficient groups behave as R_L



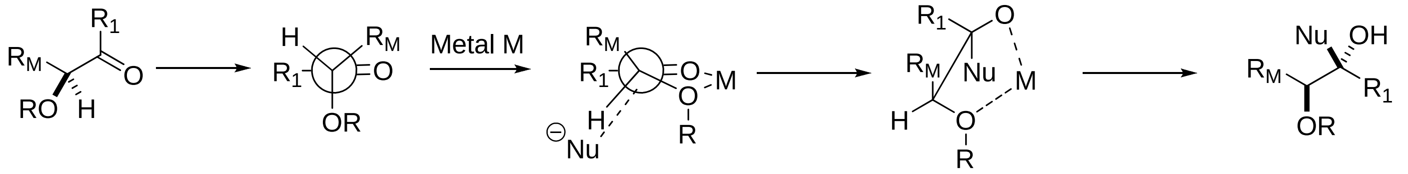
Favorable Interaction n_{Nu} to $\sigma^*_{C\text{-}X}$

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

4.2. Addition to Carbonyls not Following the Felkin Ahn Model

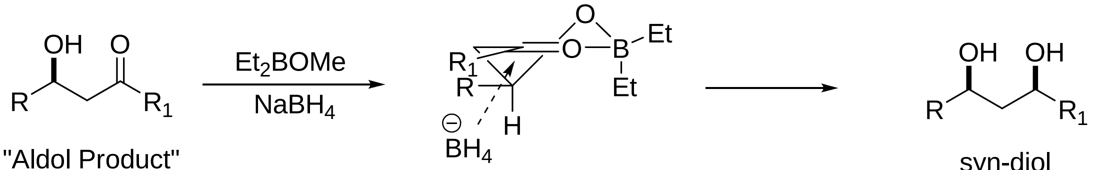
4.2.1. Chelate Control

1,2 Chelate control



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

1,3 Chelate control



"Aldol Product"

syn-diol

R equatorial
axial attack (see Fürst-Plattner rules)

Factors favoring chelation

- R group sterically not hindered:

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

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

- non-coordinating solvents:

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

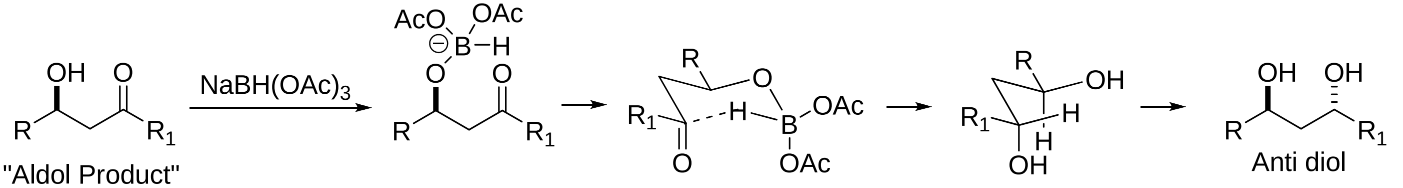
- Strong Lewis Acid, with more than one coordination site available

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.

4.2.2. Directed Reduction



"Aldol Product"

Anti diol

- Chair transition state
- All R groups equatorial

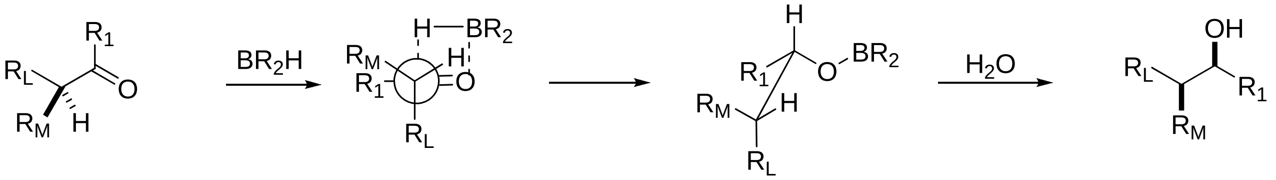
chelate conditions give syn!

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

Use of chelate conditions or directed reductions allow to acces both syn and anti diols from aldol synthons, and are also essential methods for the selective synthesis of polyols polyketide natural products.

4.2.3 Reagents Binding to Carbonyl during Addition

Borane Reduction



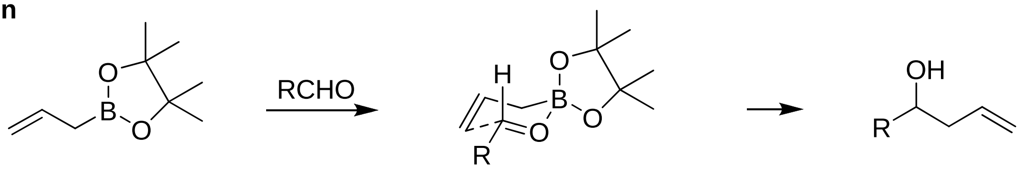
- R_L is ⊥ to C=O
- BR_2 bind to O during reduction
- Minimize BR_2-Substrate interaction ⇒ Smallest Substituent towards BR_2 (H)

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

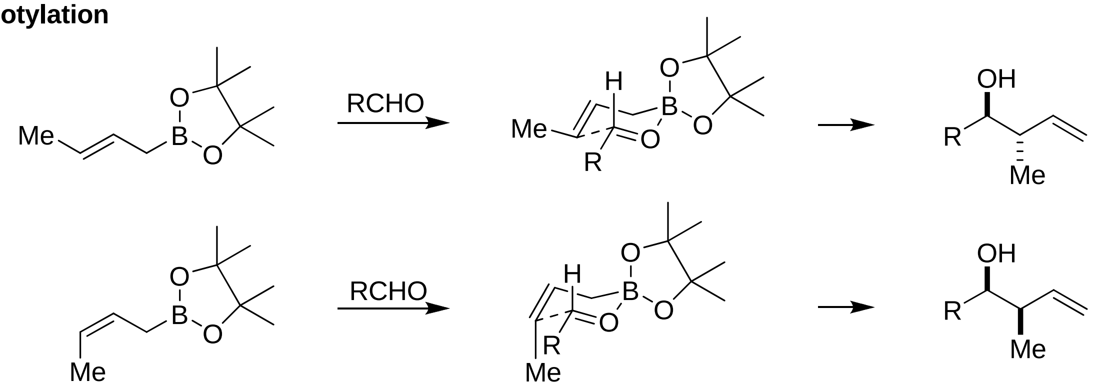
Allylation, **Aldol Reactions via Chair Transitions States**

4.3 Allylation of Carbonyls

Allylation



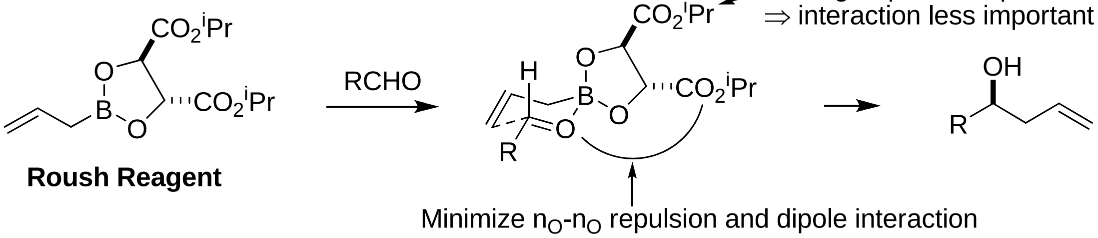
Crotylation



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

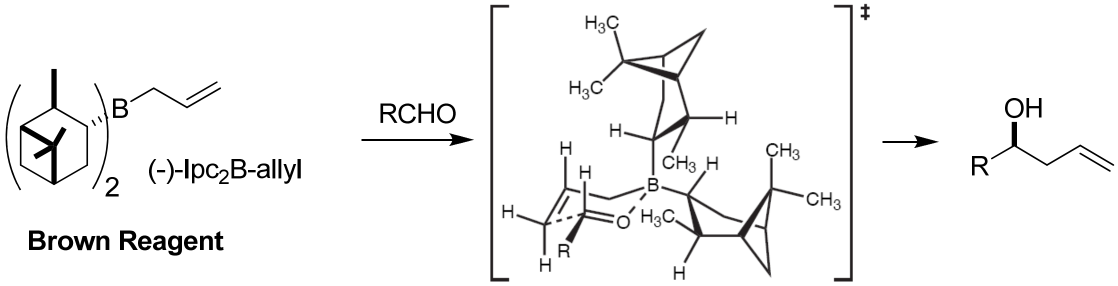
Chiral Reagents For Allylation Reactions

Ester group in axial position further away
⇒ interaction less important



Roush Reagent

Minimize n_O-n_O repulsion and dipole interaction

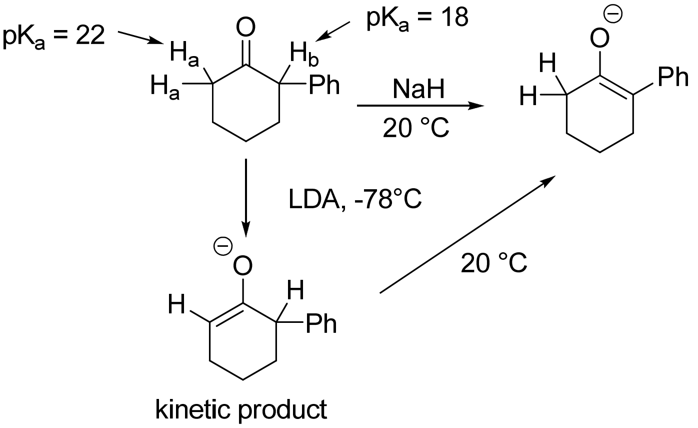


Brown Ipc reagent is very reliable and often used in total synthesis.

5. Enolate Generation and Reactivity

5.1 Selective Generation of Enolates

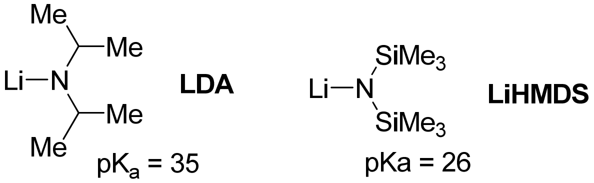
Kinetic vs thermodynamic control



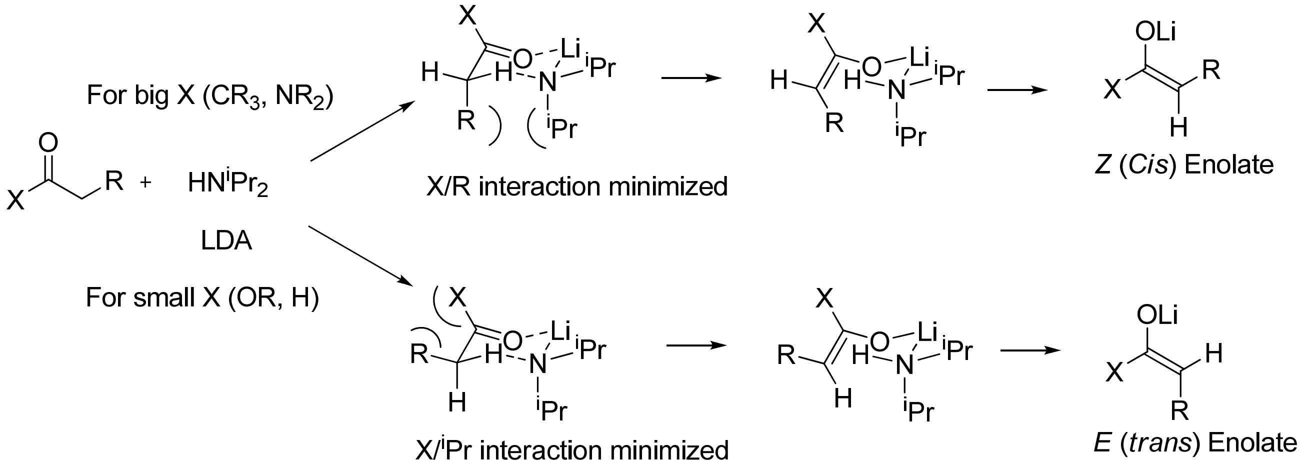
H_a is less sterically hindered, faster to deprotonate and leads to the kinetic product with bulky base at low temperature.

Deprotonation of Hb leads to the more stable conjugated double bond, the thermodynamic product, at higher temperature.

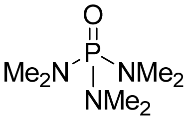
Important bases for kinetic deprotonation:



Deprotonation with LDA: *cis* vs *trans* selectivity

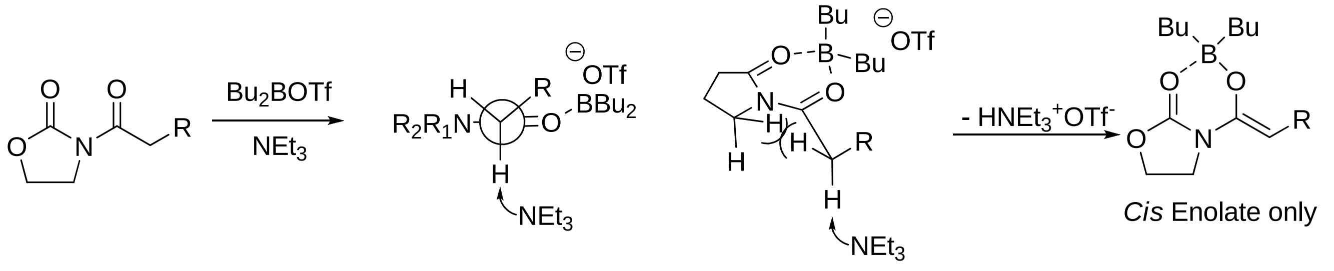


exception for esters: Adding HMPA leads to *Z* (*Cis*) Enolate



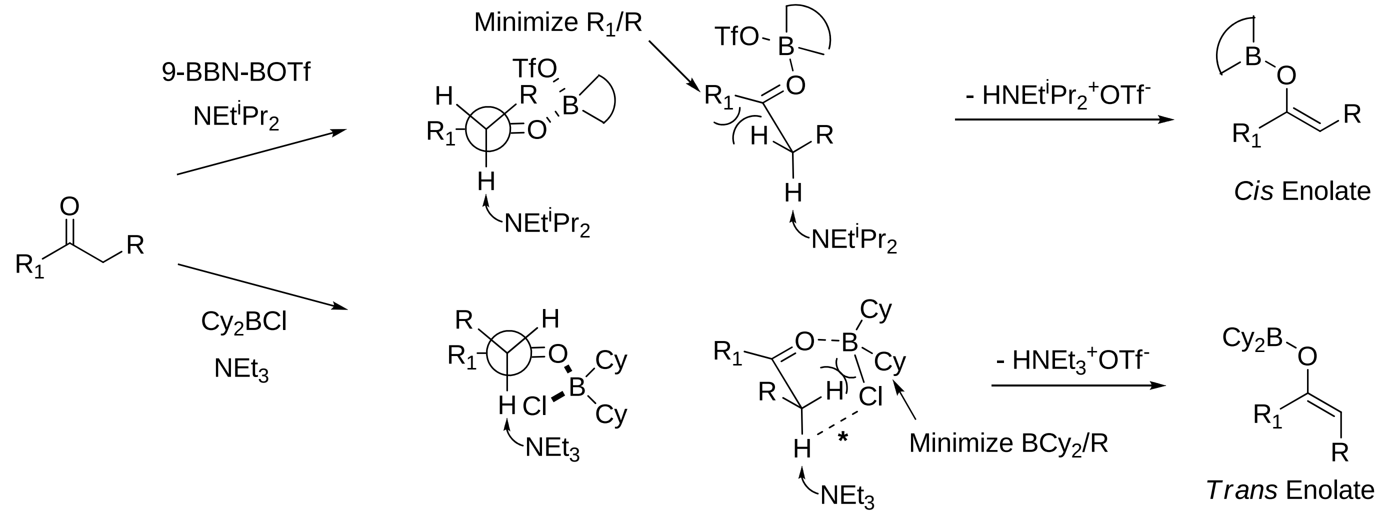
HMPA: good ligand for lithium ⇒ Cyclic transition state is partially disrupted

Deprotonation of Imides with Bu_2BOTf and NEt_3 (soft enolization)



Very strong $A^{1,3}$ with Imides!

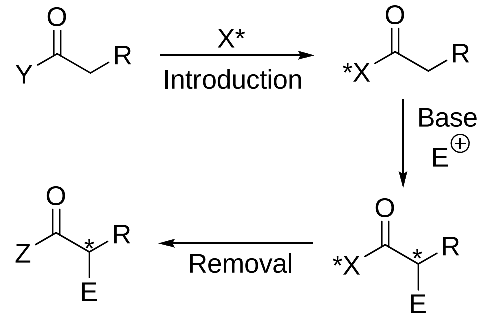
Deprotonation of Ketones



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

5.2 Chiral Auxiliary and Enolate Alkylation

5.2.1 General Concept



The chiral auxiliary X* should be:

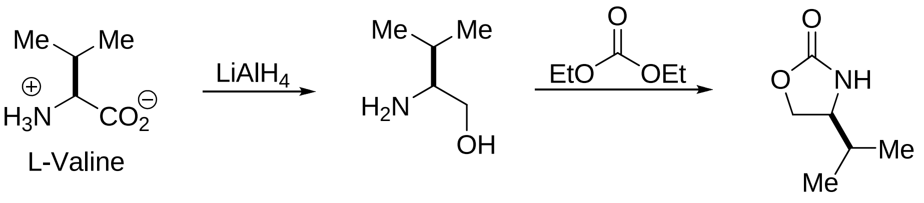
- easy to introduce and remove
- able to create an efficient asymmetric induction
- cheap and recoverable

Disadvantage: multi-step protocol

Advantage: chiral auxiliary is bound covalently: good asymmetric induction and separation of diastereomers possible

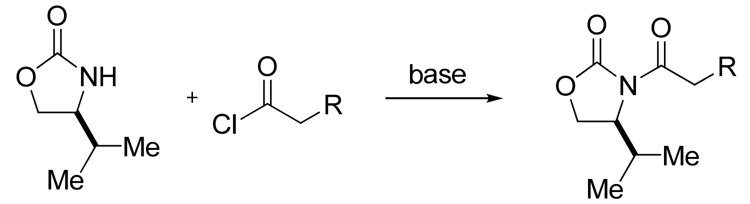
5.2.2 Evans Oxazolidinone Auxiliary

Synthesis: easy from cheap natural amino acid

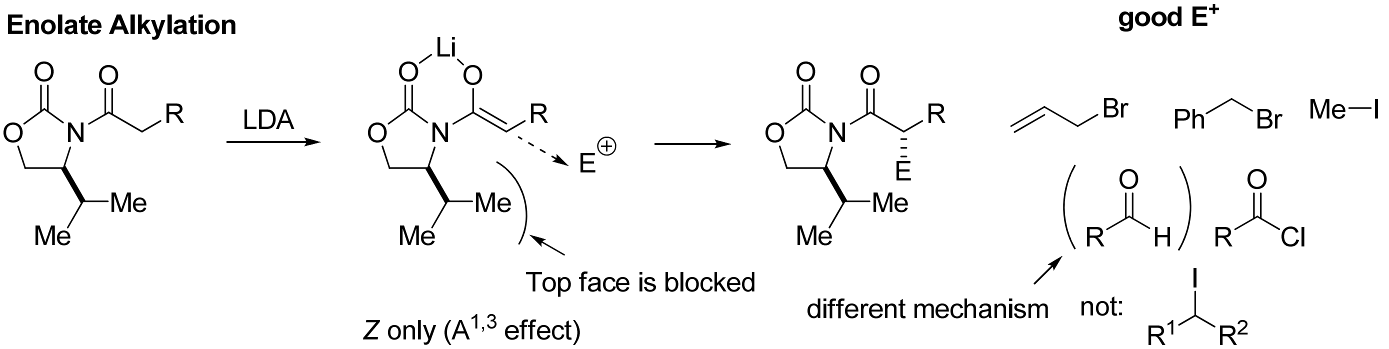


Oxazolidinone

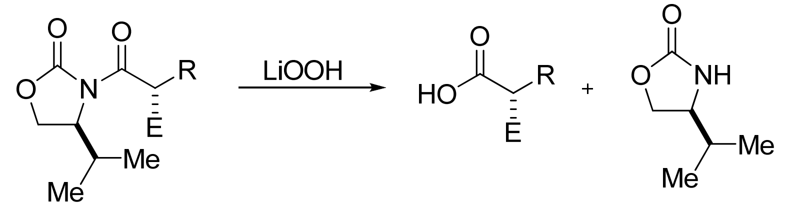
Auxiliary Introduction



Enolate Alkylation

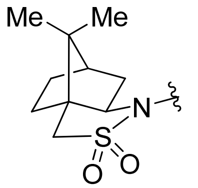


Auxiliary Removal



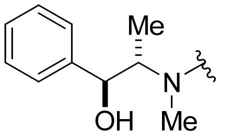
Many other alternatives possible (see lecture target synthesis)

5.2.3 Other Auxiliaries



Oppolzer Sultam

From Camphor

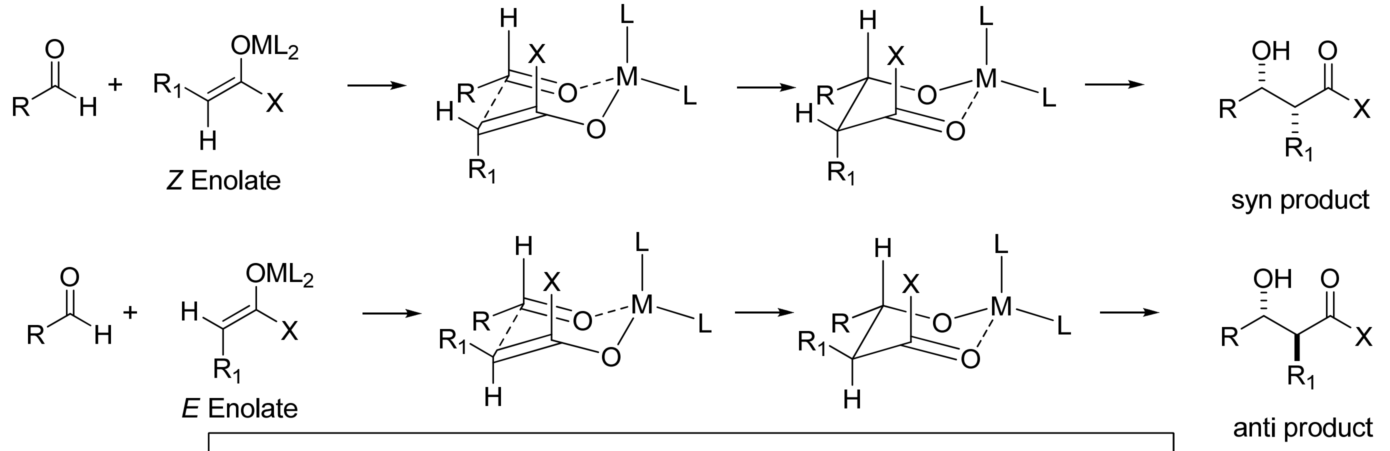


Myers Pseudoephedrin auxiliary

Myers auxiliary is often used for alkylation reaction in synthesis, as the enolate formed are more reactive then the ones from Evans' auxiliary

6. Aldol Reaction

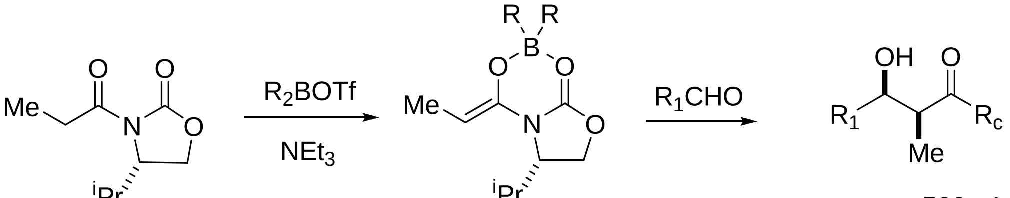
6.1 Zimmermann-Traxler Transition State



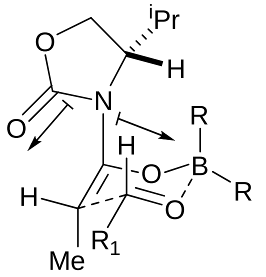
- Chair transition state (Zimmerman-Traxler)
- R group of aldehyde equatorial
- Geometry of double bond transfered to stereocenter: *cis* to syn, *trans* to anti

6.2 Aldol Reactions using Evans' Auxiliary

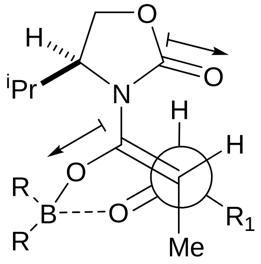
Evans Syn Aldol:



up to 500 : 1



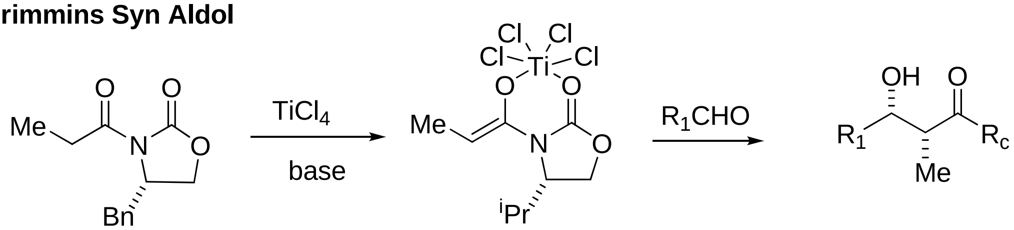
- Chair Transition State
- Minimized Dipoles
- Aldehyde comes opposite from ^{i}Pr

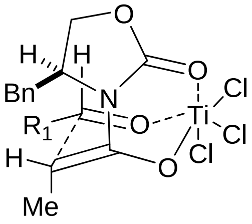


Newman view from the left

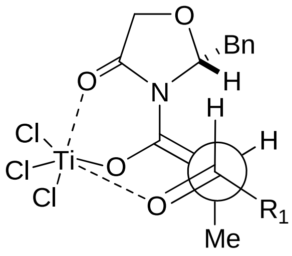
Important: In order to activate the aldehyde for addition, B has to bind to the aldehyde. As B has only two free binding sites, the oxazolidinone carbonyl is now free and rotates to minimize dipole interactions.

Crimmins Syn Aldol



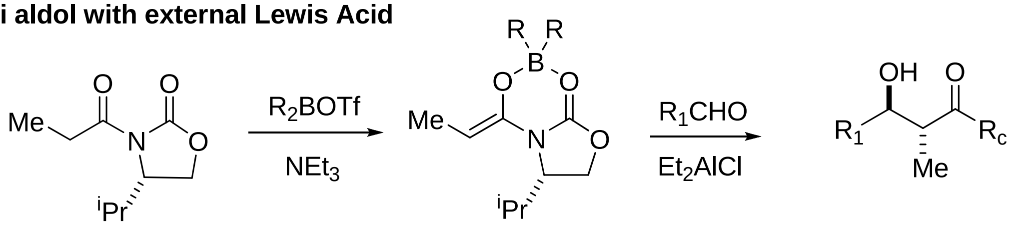


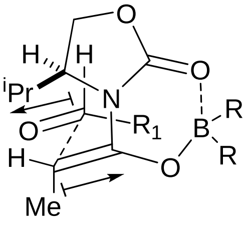
- Chair Transition State
- All Carbonyl bound to Ti
- Aldehyde comes opposite from Bn



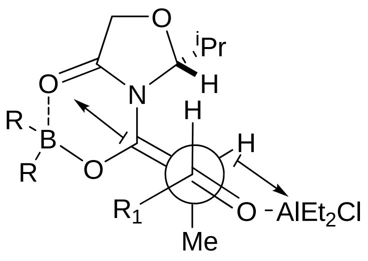
Newman view from the back

Anti aldol with external Lewis Acid



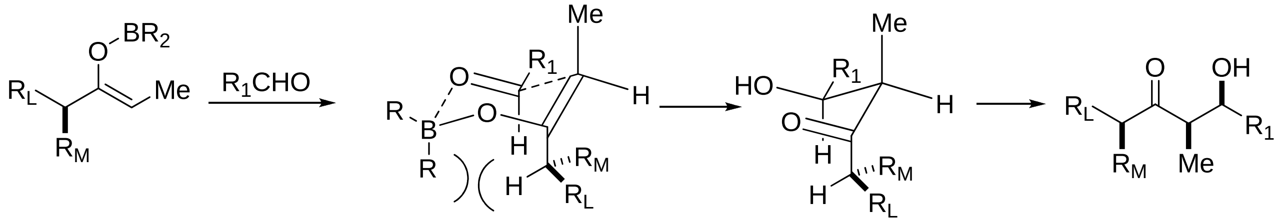


- Free transition state (no chair)
- B chelates the auxiliary
- Minimized dipoles and steric: carbonyl antiperiplanar to enolate
- Aldehyde comes opposite from ^{i}Pr
- R_1 group away from auxiliary

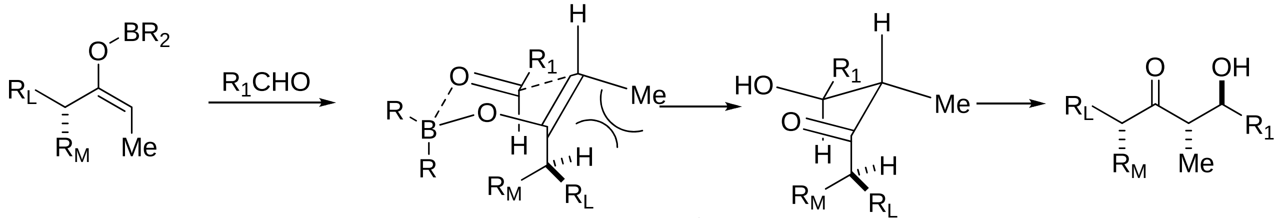


Newman view from the back

6.3 Ketone (Paterson) Aldol



Minimized steric



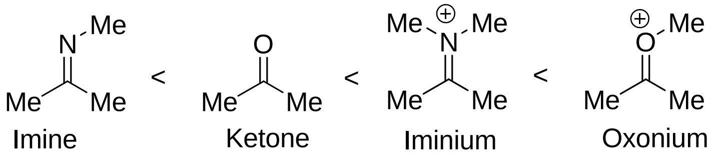
Minimized $A^{1,3}$

- 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

7. Reaction of Imines and Conjugated Systems (Mannich and Michael Reactions)

7.1 Chemistry of Imines

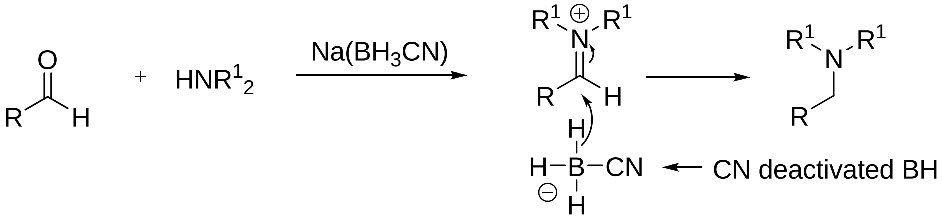
Comparison of Reactivity as Electrophile



δ^+on C	+ 0.33	+ 0.51	+ 0.54	+ 0.63

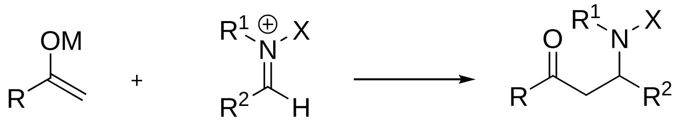
Imine are less reactive as electrophile then carbonyl compounds, but they are easy to activate as iminium

Reductive Amination



Because of the electron-withdrawing CN group, $Na(BH_3CN)$ is not able to reduce carbonyls, but it is strong enough to reduce the more reactive iminium.

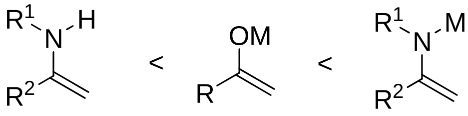
Mannich Reaction = Imine equivalent of aldol reaction



β-amino ketone

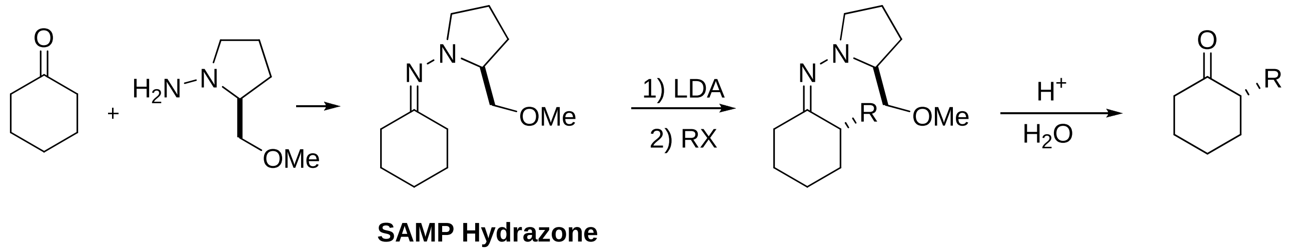
7.2 Chemistry of Enamine and Metalloenamine

Comparaison of Nucleophilicity

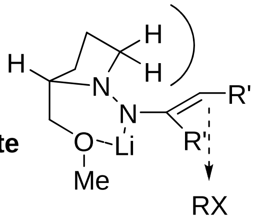


Enamine are easily formed from iminium, but less nucleophilic than enolate. Metalloenamine are very reactive.

Enders SAMP Chiral Auxiliary for Ketone

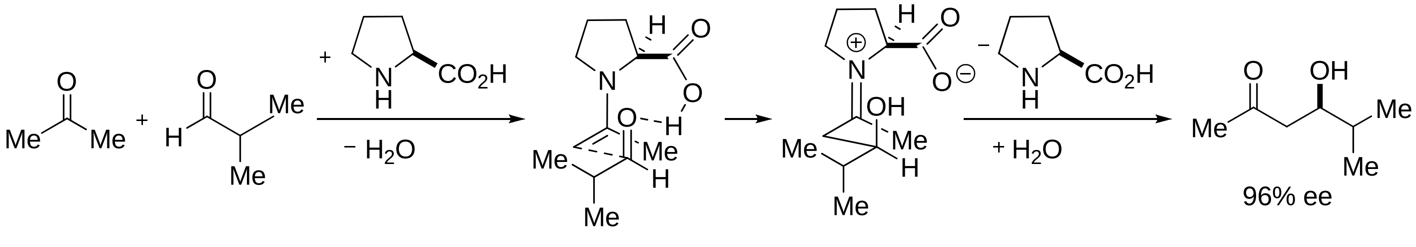


Transition State



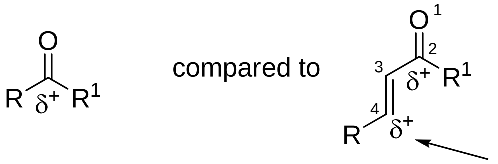
- A highly reactive Li enamine is formed
- The Li metal is bound opposite to the enamine double bond to minimize steric interactions with the electrophile
- The electrophile comes opposite to the pyrrolidine ring

Proline Catalyzed Aldol: via enamine intermediates



7.3 Conjugate Addition and the Vinylogous Principle (Michael Addition)

Vinylogous Principle



Regioselectivity

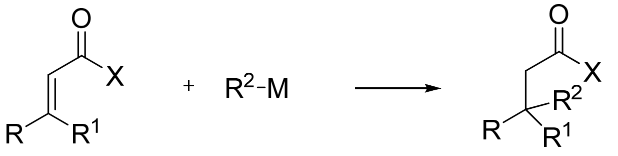
1,2 -Addition favored for hard nucleophile (Grignard)

1,4 (Michael) Addition favored for soft nucleophile (Cuprate)

Electronic properties are "transmitted" by double bond = vinylogous principle

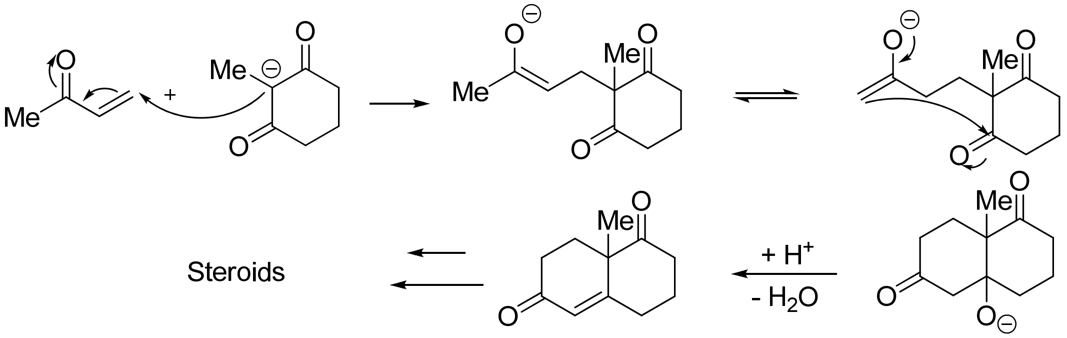
Important Applications of Michael Addition

Synthesis of (all-carbon) quaternary centers



quaternary centers are generally difficult to synthesize!

Robinson annulation



Wieland-Miescher
Diketone

The asymmetric variation of this method is possible with proline as a catalyst (Hajos-Parrish-Eder-Sauer-Wiechert Reaction)

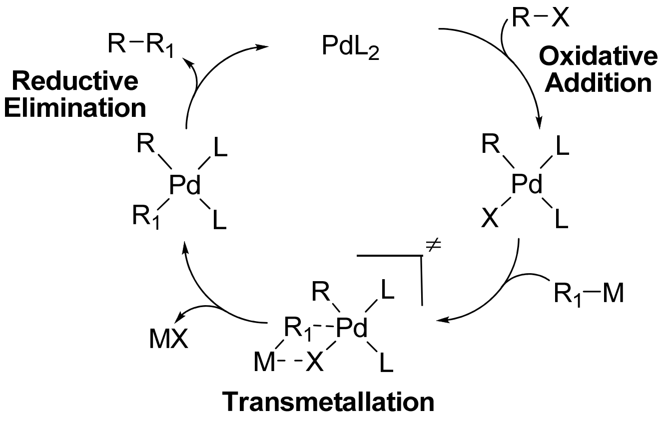
8. Cross Coupling Reactions

Cross Coupling reactions are very often used in medicinal chemistry and synthesis nowadays!

8.1 Organometallic-RX Cross Coupling

$$R{-}X \quad + \quad R_1{-}M \xrightarrow{\text{catalyst}} R{-}R_1$$

catalyst: most often Pd, but also Ni, Fe



M = BX_2: **Suzuki**
M = SnR_3: **Stille**
M = ZnX: **Negishi**
M = MgX: **Kumada**
special: R_1-M = $R_2{-}C{\equiv}C{-}CuX$: **Sonogashira**

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

Comparison of Organometallic Reagents

Reactivity: $BX_2 < SnR_3 < ZnX < MgX$

Stability: $BX_2 > SnR_3 > ZnX > MgX$

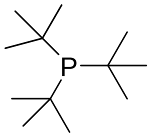
Boronic acid derivatives are the most stable, but they need activation with nucleophile (OH^-) to react!

Recent efforts to accelerate oxidative addition (important to use cheaper Cl reagents)

Oxidative addition is faster for:

Electron-rich ligands (more electrons)
mono-coordinated Pd intermediates (more place)

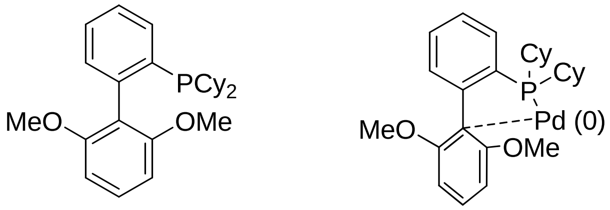
Important recently introduced ligands:



Tri-*tert*-butyl phosphine

Fu, MIT

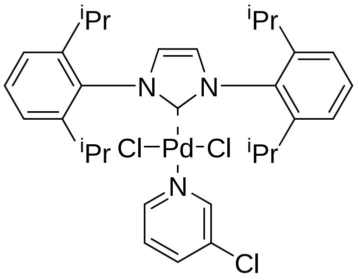
Steric bulk to promote mono-coordination



Biarylphosphine

Buchwald, MIT

Pd-Aryl interaction to promote mono-coordination

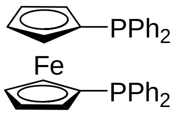


N-Heterocyclic Carbenes (NHC)

more electron-rich than phosphines

here: commercially available PEPPSI ligand (Aldrich)

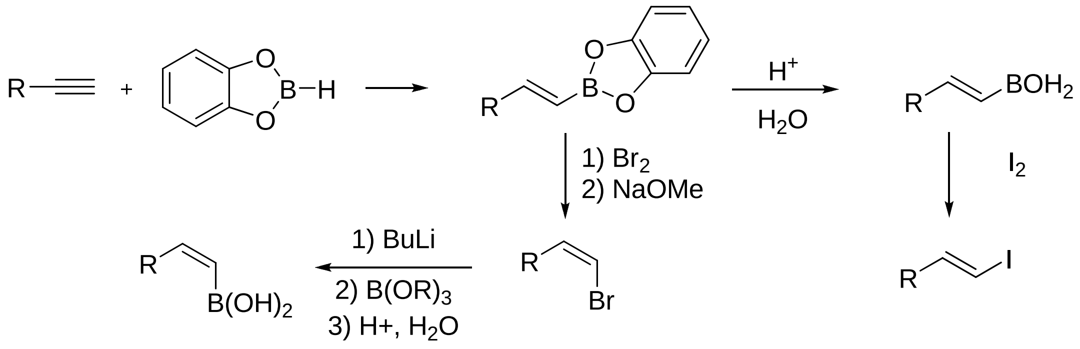
Special for Suzuki with alkyl-boronic acid derivatibes



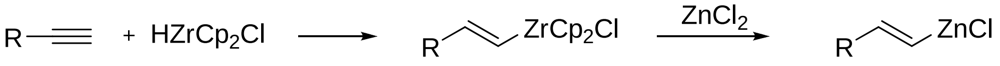
dppf (Di(bisphenylphosphino)ferrocene)

Bidentate ligand good to prevent β-hydride elimination

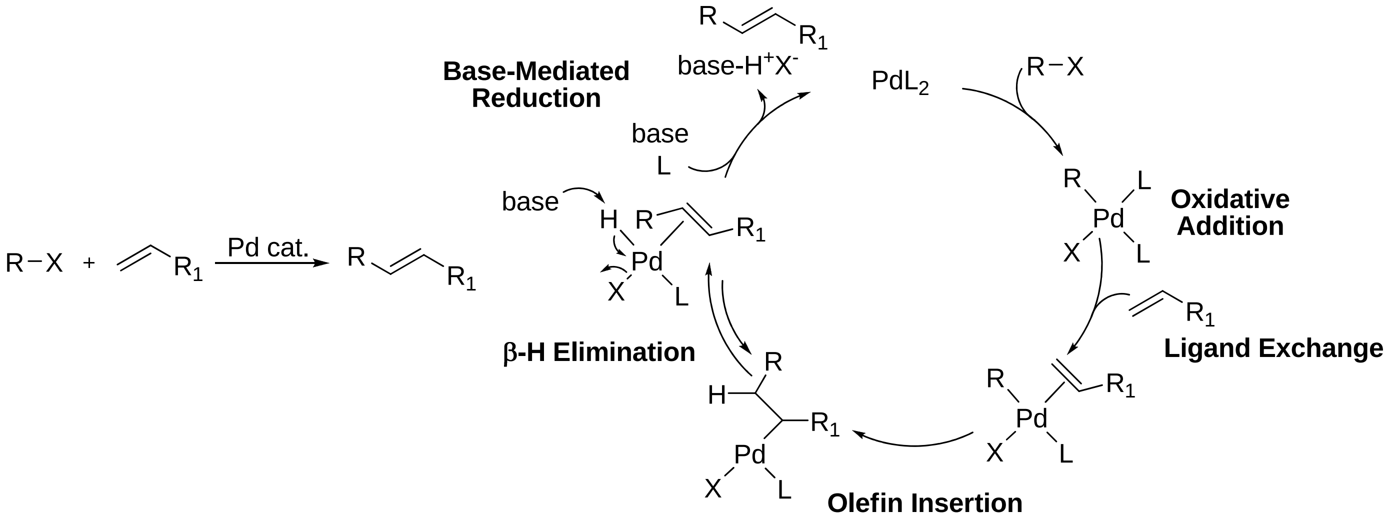
Building blocks for the synthesis of all diene isomers via Suzuki coupling



Hydrozirconation-Transmetallation for the synthesis of Organozinc reagents:



8.2 Heck Coupling

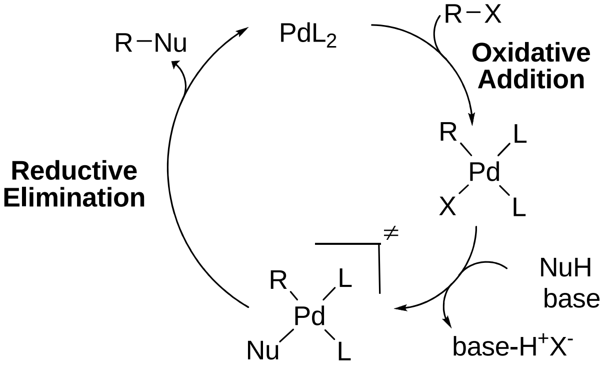


The β-H elimination step is reversible, which can lead to isomerization of the double bond!

8.3 C-Heteroatom Coupling

$$\mathrm{NuH} + \mathrm{R-X} \xrightarrow[\text{Base}]{\text{Pd cat.}} \mathrm{R-Nu}$$

Nu = R^1R^2N, RO, RS



Especially the amination (**Buchwald-Hartwig Amination**) is important for pharma

8.4 Future Progress and Current Topic of Research: Olefin and CH Functionalization

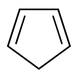
9. Cycloadditions

9.1 Diels-Alder Cycloaddition

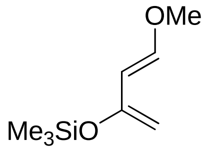
9.1.1 General Aspects

Mechanism, endo and ortho rules: see supplementary material

Important Dienes

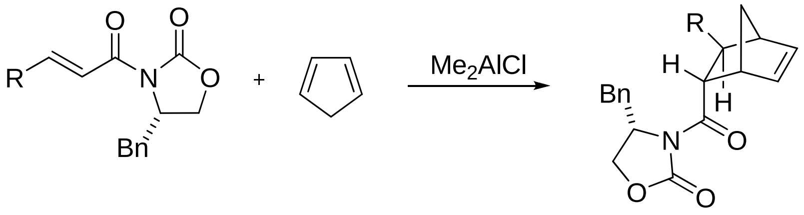


cyclopentadiene



Danishefsky diene

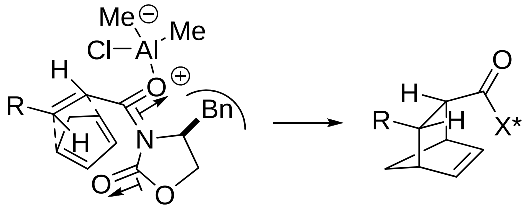
9.1.2 Diastereoselective Diels-Alder Reactions with Evans' Auxiliary



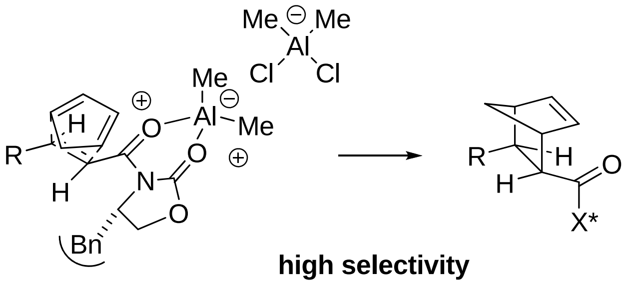
2 Different models depending of stoichiometry of Lewis Acid:

1 Eq. Me_2AlCl: no chelate

2 Eq. Me_2AlCl: chelate



low selectivity

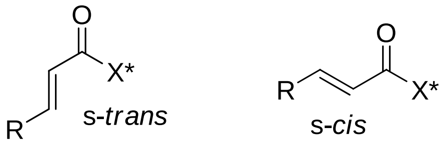


high selectivity

- Endo transition state
- Minimize dipole with oxazolidinone
- L. A. binds O opposite to bulky Bn group
- Dienophile in s-*trans* conformation to prevent interaction with L. A.
- Diene comes opposite to bulky Bn

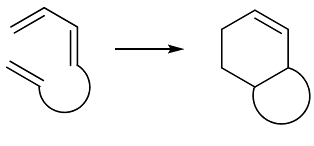
- Endo transition state
- Abstraction of Cl by second L. A. allows chelation
- Dienophile in s-*cis* conformation to prevent interaction with bulky Bn
- Diene comes opposite to bulky Bn

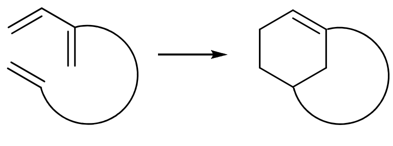
In this case, different mechanisms lead to the same product, because two key structural elements are changing: chelation vs dipole control and s-*cis* vs s-*trans* conformation of dienophile



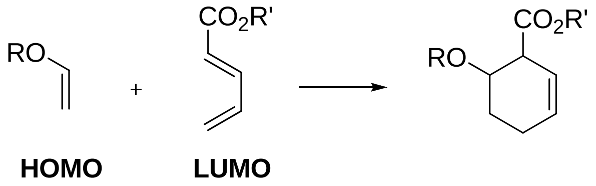
9.1.3 Special Diels-Alder Reactions

Intramolecular Diels-Alder Reactions

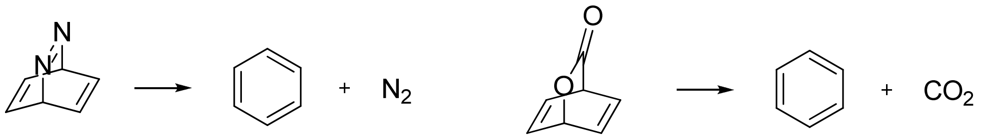




Inverse Electron-Demand Diels-Alder Reactions



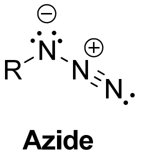
Retro Diels-Alder Reactions



Retro Diels-Alder reaction is particularly good if the products are very stable (aromatic compounds) and/or stable gases that escape the reaction mixture (N_2, CO_2)

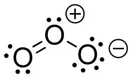
9.2 [3+2] Cycloaddition Reactions (1,3-Dipolar Cycloadditions)

Important 1,3-dipoles

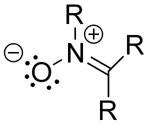


Azide

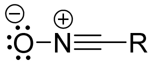
Diazo



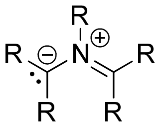
Ozone



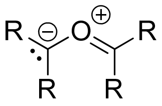
Nitrone



Nitrile Oxide

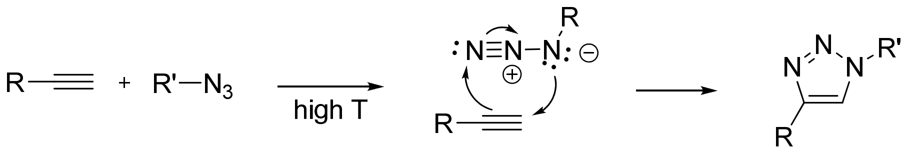


azomethine ylide



carbonyl ylide

Huisgen Cycloaddition of Azide and Acetylene



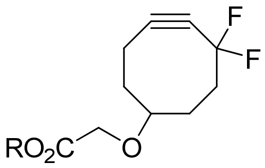
Triazole

Sharpless: At room temperature with Cu catalyst = example of Click Chemistry

Click chemistry: ideally: easy reaction for the addition of compounds, without waste generation, with high tolerance towards impurities and functional group, at room temperature and physiological conditions

Very interesting properties of this reaction: it can be performed in the presence of virtually any other functional group and azide, and to a lesser extent acetylenes, are absent in biomolecules: this reaction is ideally suited for the synthesis of bioconjugates.

Bertozzi trick: use strained alkynes in rings to promote reaction at room temperature without catalyst in living cell!

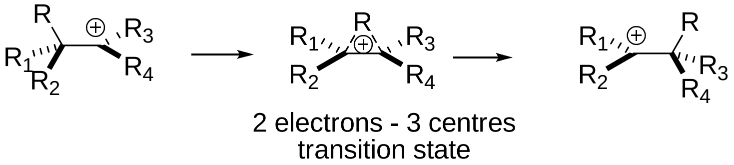


10. Rearrangements

10.1 Rearrangement via Reactive Intermediates

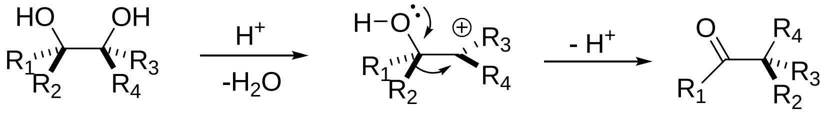
10.1.1 Cationic Intermediates

1,2-Alkyl Shift: Wagner-Meerwein Rearrangement

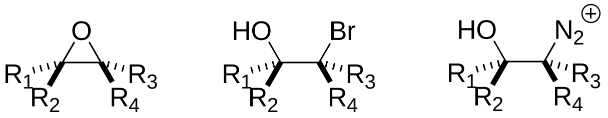


The group which stabilizes the best the cation is migrating

Pinacol Rearrangement

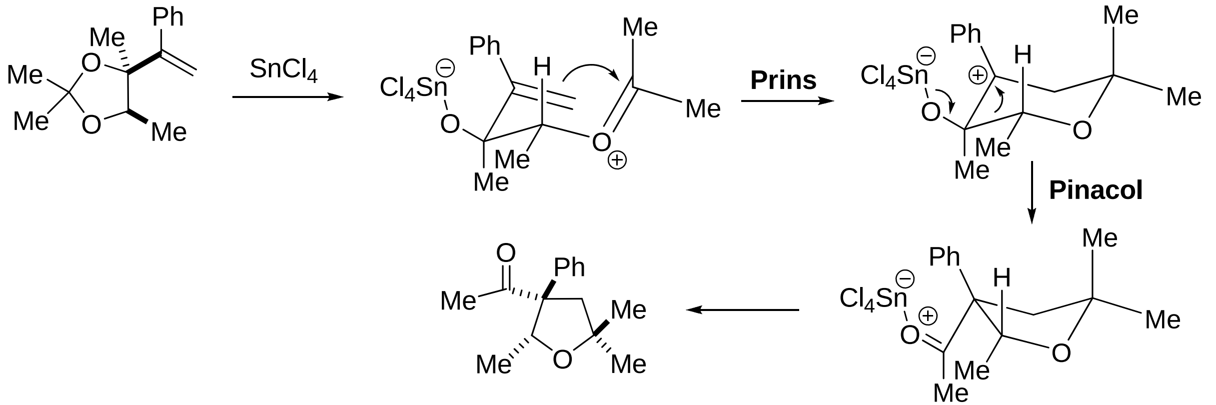


Same Starting from:



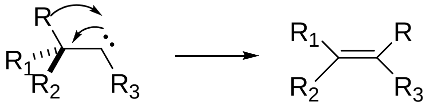
Semi-Pinacol Rearrangements

Prins-Pinacol:

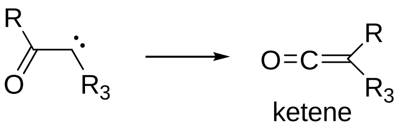


10.1.2 Carbene and Nitrene Intermediates

carbene

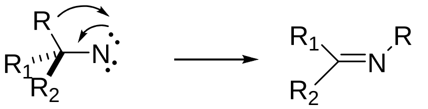


important special case:

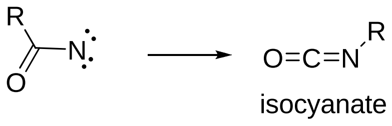


Name Reactions: Fritsch-Buttenberg-Wiechell, Arndt-Einstert, Wolff.

nitrene



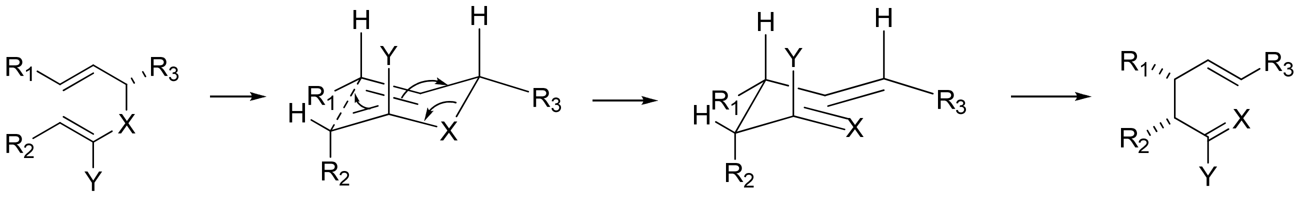
important special case:



Name Reactions: Curtius, Hofmann, Lossen, Schmidt

10.2 [3,3] Sigmatropic Rearrangements

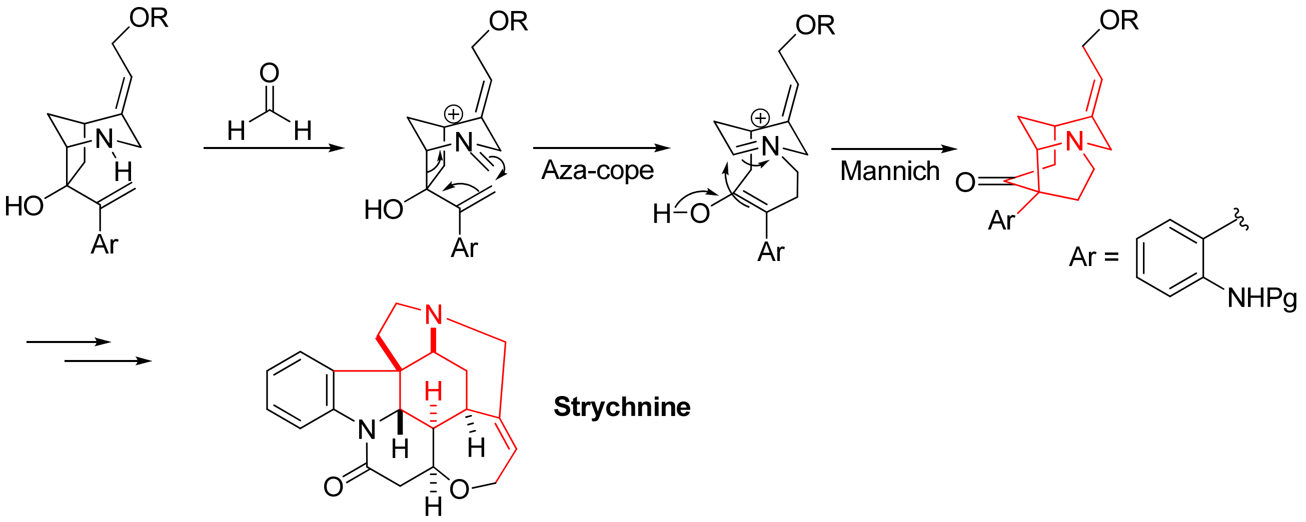
10.2.1 General Mechanism



- 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, $OSiR_3$)

10.2.2 Overman's Aza-Cope Mannich approach towards Strychnine



Strychnine