C-C Bond Formation - Organometallic Coupling Reactions
(McM 7th ed. 10.8, Lab ex 10)

Alkenes
(McM 7th ed. 11.8 – 11.9)

Dienes
(McM 7th ed. 14.1 – 14.3)
C-C Bond Formation - Organometallic Coupling Reactions
(McM 10.9, Lab ex 10)

Reagents often unstable
Difficult to make
Strong bases

No nu subst if C sp² or sp

pKa NH₃ 35

R =CH₂

pKa ca 25

CH₃

R =CH₂

pKa ca 44

pKa ca 60

Elimination
Grignard reagents and Organolithium reagents

R-H \xrightarrow{\text{Base}} R^-

\[ \text{R-X} \xrightarrow{\text{Mg}} \text{R-Mg-X} \]

R: \text{prim, sek, tert alkyl, alkenyl, aryl}

Nucleophile
Strong base

\[ \text{R-X} \xrightarrow{2 \text{Li}} \text{R-Li} + \text{LiX} \]

R: \text{prim, sek, tert alkyl, alkenyl, aryl}

Nucleophile
Strong base

\( \text{BuLi used a lot as strong base} \)

\[ \text{RMgX or RLi does not react well with alkyl halides in substitutions} \]
Organocuprates (McM 10.8)

2 $\text{R-Li} + \text{Cul} \rightarrow \text{R}_2\text{Cu} \quad \text{Li}^{\oplus} \quad + \quad \text{LiI}$

(R: alkyl, alkenyl, alkynyl, aryl)

Gilman reagent
Dialkylcuprate

$2 \text{R-MgX} + \text{Cul} \rightarrow \text{R}_2\text{CuMgX} + \text{IMgX}$

Participate in substitution with alkylhalides (Cl, Br, I)

Mech. see next slide
Also reaction with alkenyl halides and arylhalides (sp²) Not $S_N1$ or $S_N2$
Palladium catalyzed coupling reactions
(Lab ex. 10. McM 10.8, not McM 6th ed)

\[
R-X + R'\text{-Met} \xrightarrow{\text{cat. Pd(0)-complex}} R-R' + \text{Met-X}
\]

-aryl halide
-alkenyl halide
-alkynyl halide

- Met; (-MgX), -ZnX, -SnR₃, -B(OR)₂,

\[R': \text{alkynyl, alkenyl, aryl, alkyl}\]

\[\text{R’-Met:}\]
\[\text{R’ZnX - Negishi coupling}\]
\[-\text{Esp. good for } R' = \text{alkyl, } R'\text{ZnX generated in situ}\]

\[\text{R’SnBu}_3 / \text{R’SnMe}_3 - \text{Stille coupling}\]
\[-R' (\text{alkynyl}) \text{ aryl, alkenyl, organotin comp. tox } R’\text{SnBu}_3 / \text{R’SnMe}_3 \text{ stable}\]

\[\text{R’B(OH)}_2 / \text{R’B(OR)}_2 - \text{Suzuki coupling}\]
\[-R' (\text{alkynyl}) \text{ aryl, alkenyl, Green react. } R’\text{B(OH)}_2 / R’\text{B(OR)}_2 \text{ relatively stable}\]
\[\text{react. requires base}\]

\[\text{R’MgX - Kumada coupling}\]
\[\text{Less reactive, often Ni-cat. (less stable than Pd-cat)}\]
General mechanism

**Reductive elimination**
Pd reduced back to Pd(0)
C-C between aryls formed

**Oxidative addition**
[Pd(0) to Pd(II)]

**Met:**
-ZnX, -B(OH)$_2$, -SnR$_3$, (-MgX)

**Met-**

**Transmetallation**
(Ph transferred from Met to Pd, no redox)

**Alkenyl, aryl halides**
Pd complex from alkyl halides unstable

**N:**

- **Formed by Pd-cat coupling**

- Highly active against *Mycobacterium tuberculosis*

- Met: -ZnX, -B(OH)$_2$, -SnR$_3$, (-MgX)

- Alkenyl, aryl, alkyl react (depending on the metal used)
The Suzuki reaction
Special cases - No preformed R’Met

Coupling on alkynes - Sonogashira coupling

\[
R-X + R'\equiv H \xrightarrow{\text{cat. Pd(0)-complex}} \text{Base, CuX} R'\equiv R
\]

\[
\left( \text{Via } R'\equiv \text{Cu} \right)
\]

Coupling on alkenes - Heck coupling
(Somewhat diff. mech.)

\[
R-X + R'\equiv \xrightarrow{\text{cat. Pd(0)-complex}} \text{Base} R'\equiv R
\]
Why difficult to couple alkyl halides

H

| PdL₂ | ox. add |

L-Pd-L

X

β-hydride elimination

Trans metallation
C-C Bond Formation - Organometallic Coupling Reactions
(McM 7th ed. 10.8, Lab ex 10)

Alkenes - Synthesis by elimination react.
(McM 7th ed. 11.8 – 11.9)

Dienes
(McM 7th ed. 14.1 – 14.3)
Elimination reactions - Repetition

E2: mechanism

\[
\text{B} : \quad \begin{array}{c}
\text{R'} \\
\text{R'} \\
\text{R} \\
\text{H} \\
\text{R} \\
\text{X}
\end{array} \xrightarrow{\text{R'}} \quad \begin{array}{c}
\text{R'} \\
\text{R'} \\
\text{R} \\
\text{H} \\
\text{R} \\
\text{X}
\end{array} \quad + \text{BH} + \text{X} \quad \text{• One step} \quad \text{• 2. order} \quad \text{• Stereospecific}
\]

E1: mechanism

\[
\text{H} \quad \begin{array}{c}
\text{R'} \\
\text{R'} \\
\text{R} \\
\text{X}
\end{array} \xrightarrow{\text{R'}} \quad \begin{array}{c}
\text{R'} \\
\text{R'} \\
\text{R} \\
\text{X}
\end{array} + \text{BH} + \text{X} \quad \text{• Two steps} \quad \text{• 1. order} \quad \text{• 1. step rate limiting} \quad \text{• 1.step = 1. step in S_N1} \quad \text{• Not stereospecific}
\]

Elimination in competition with substitution
E2 and stereochemistry (McM 11.9)

Reactant
Anti Periplanar conformation

Anti transition state

Alkene

cannot react E2
Deuterium Isotope Effect (McM 11.8)
(Kinetic Isotope Effect)

• Important in elucidation of reaction mechanisms
• Cleavage of C-H and C-D requires different amount of energy

Hookes Law, Stretching frequencies, IR

\[ \nu = \frac{1}{2\pi c} \sqrt{\frac{f(m_1 + m_2)}{m_1 m_2}} \]

\( \nu \) C-H: ca 3000 cm\(^{-1}\)
\( \nu \) C-D: ca 2200 cm\(^{-1}\)

Relationship between stretching frequency (\( \nu \)) and zero-point energy (\( E^0 \))
\( E^0 = \frac{1}{2} h \nu \)
\( E^0 \) C-H 18 kJ/mol
\( E^0 \) C-D 13 kJ/mol
Higher activation energy for cleavage of C-D
Cleavage of C-H will be faster
Mechanistic Information from Deuterium Isotope Effect

E2 C-H broken in rate limiting step

Same prod. no info from regio / stereosel.

Fastest if E2, C-H more easily broken
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(McM 7th ed. 14.1 – 14.3)
Dienes (McM 14.1-3)

\[
\text{C} = \text{C} - (\text{CH}_2)_n - \text{C} = \text{C}
\]

- \( n > 1 \): Isolated diene
- \( n = 1 \): Skipped diene
- \( n: 1,2,3... \): Non conjugated diene

\[
\text{C} = \text{C} - \text{C} = \text{C} - \text{C}
\]

Conjugated diene

\[
\text{C} = \text{C} = \text{C}
\]

Cumulated diene (allene)

- Molecular orbitals
- Addition react.

See also cycloadditions (Diels Alder etc)
chapter 30 - lecture 4 & 5
Conjugated dienes

\[
\begin{align*}
\text{147 Å} & \quad \Delta H^\circ_{\text{hydrog}} - 253 \text{ kJ/mol} \\
\text{153 Å} & \quad \Delta H^\circ_{\text{hydrog}} - 236 \text{ kJ/mol}
\end{align*}
\]

Less energy difference - *conjugated* diene more stable
Molecular orbitals of $\text{H}_2$ (cf fig 1.17) - $\sigma$-bond

Molecular orbitals of $\pi$-bond (cf fig. 1.18)
Molecular orbitals of H\(_2\) (cf fig 1.17) - σ-bond

- Energy
- H 1s orbital
- H-H Binding MO (filled)
- H-H Antbinding MO (unfilled)

Molecular orbitals of π-bond (cf fig. 1.18)

- Energy
- 2 p orbitals
- Node
- π Bonding MO
- π Antibonding MO

MO 1,3-butadiene

- cf fig 14.2
- delvis dobbeltbind. karakter

π Molecular orbitals

- Energy
- 4 p orbitals
- 2 nodes
- 3 nodes
- 1 node
- 0 nodes
- Antibonding MO
- Bonding MO
- LUMO
- HOMO

Energy absorb
UV spectra

- \( h\nu \)
- 1 e⁻
- 4 π electron
- in 2 bonding orbitals (ground state)
Long conjugated systems - colored compounds

\[ \beta\text{-Carotene} \]
Electrophilic addition to conjugated dienes

Termodyn prod: High activation barrier, most stable prod.
Vigorous cond. (high temp), reversible

Kinetic prod: Low activation barrier, less stable prod.
Mils cond, (low temp,) irreversible