II. Special Topics

IIC. Organometallics

Boger Notes: p. 395 - 426 (Chapter XII)
Carey/Sundberg: B p. 477-546 (Chapter B 8)

A. Organometallic Mechanisms

Oxidation State: The oxidation state of a metal is defined as the charge left on the metal after all ligands have been removed in their natural, closed-shell configuration. This is a formalism and not a physical property!

d-Electron Configuration: position in the periodic table minus oxidation state.

18-Electron Rule: In mononuclear, diamagnetic complexes, the total number of electrons never exceeds 18 (noble gas configuration). The total number of electrons is equal to the sum of d-electrons plus those contributed by the ligands.
18 electrons = coordinatively saturated
< 18 electrons = coordinatively unsaturated.
For each Pd: Ox. state \( \text{Pd}^{2+} \), Cl\(^{-}\)

Bridging by lone pairs on Cl; each Cl acts as a 2-electron, mono negative ligands to one of the Pd's, and a 2-electron neutral donor ligand like PPh\(_3\) to the other

\[
d: 10 \ (4d^{10} \ 5s^0) - 2 = 8
\]

Electron count:

\[
\begin{align*}
\text{Cl}^2 & : 2e^- \\
\text{Cl} & : 2e^- \\
\text{Cl} & : 2e^- \\
\end{align*}
\]

\[
8e^- + d^8 = 16e^- \quad \text{unsaturated}
\]
Bonding considerations

*donation:*

\[
\begin{align*}
\text{vacant} & \quad \text{M} & \quad \rightarrow & \quad \pi \\
\text{dsp hybrid} & \quad \text{or} & \quad \sigma
\end{align*}
\]

*backdonation:*

\[
\begin{align*}
\text{filled} & \quad \text{d orbital} & \quad \rightarrow & \quad \pi^* 
\end{align*}
\]

for M-CO:

\[
\begin{align*}
\text{dsp}^n \text{ acceptor} & \quad \sigma-\text{donor}
\end{align*}
\]
Quantification of the Steric and Electronic Properties of Phosphorus Ligands


The steric and electronic properties of a tertiary phosphine ligand can dramatically influence the reactivity at the metal center and lead to marked changes in chemical reactivity. The steric bulk and electron-donor ability of a ligand are difficult properties to quantify, and indeed, the two properties are closely related. For example, as the steric bulk of the R groups in a tertiary phosphine of type PR₃ is increased, it is expected that the intervalence angles about the phosphorus atom will increase. Such a structural change would thereby reduce the s-character of the phosphorus lone pair orbital, making the ligand more Lewis basic. Therefore, it is often difficult to separate steric and electronic effects with respect to phosphorus donor ligands since the two factors are so intimately related.

Tolman suggested, using a geometrical parameter known as the cone angle, classifying phosphorus ligands according to size. For phosphines of type PR₃, the cone angle is defined as the apex of a cylindrical cone, centered 2.28 Å from the center of the phosphorus atom, which radiates out toward the R groups and just touches the van der Waals radii of the outermost atoms.

**The Tolman Cone Angle:**

In cases where the R groups contain internal degrees of freedom, the Tolman cone is taken to be the minimum angle which satisfies the condition that all of the R groups are completely contained within the geometrical construct.

For unsymmetrical phosphines or chelating diphosphines, the concept of cone angle is not as clear.
Tolman Cone Angle ($\theta$) for a Variety of Phosphines and Phosphites

<table>
<thead>
<tr>
<th>ligand</th>
<th>cone angle ($\theta$)</th>
<th>ligand</th>
<th>cone angle ($\theta$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PH$_3$</td>
<td>87°</td>
<td>P($\mu$-Tol)$_3$</td>
<td>145°</td>
</tr>
<tr>
<td>P(OMe)$_3$</td>
<td>107°</td>
<td>P($m$-Tol)$_3$</td>
<td>165°</td>
</tr>
<tr>
<td>PMe$_3$</td>
<td>118°</td>
<td>PCy$_3$</td>
<td>170°</td>
</tr>
<tr>
<td>P(OPh)$_3$</td>
<td>128°</td>
<td>P($O$-$t$-Bu)$_3$</td>
<td>172°</td>
</tr>
<tr>
<td>PEt$_3$</td>
<td>132°</td>
<td>P($t$-Bu)$_3$</td>
<td>182°</td>
</tr>
<tr>
<td>TFP</td>
<td>133°</td>
<td>P(C$_6$F$_5$)$_3$</td>
<td>184°</td>
</tr>
<tr>
<td>P(CF$_3$)$_3$</td>
<td>137°</td>
<td>P($\alpha$-Tol)$_3$</td>
<td>194°</td>
</tr>
<tr>
<td>PPh$_3$</td>
<td>145°</td>
<td>P(mesityl)$_3$</td>
<td>212°</td>
</tr>
</tbody>
</table>

Structure

- saturated (18 e-) complexes:
  - tetracoordinate: Ni(CO)$_4$, Pd(PPh$_3$)$_4$ are tetrahedral
  - pentacoordinate: Fe(CO)$_5$ is trigonal bipyramidal
  - hexacoordinate: Cr(CO)$_6$ is octahedral

- unsaturated complexes have high d$_x^2$-y$_2$;
  16e$^-$ prefers square planar
Basic reaction mechanisms

- **ligand substitution**: \( M-L + L' \rightarrow M-L' + L \)
can be associative, dissociative, or radical chain.

trans-effect: kinetic effect of a ligand on the role of substitution at the position trans to itself in a square or octahedral complex (ground-state weakening of bond).

\( L \rightarrow M \), repels negative charge to trans position.

- **oxidative addition**: 

  \[ [\text{Ph}_3\text{P}]_4\text{Pd} \xrightarrow{-L} [\text{Ph}_3\text{P}]_3\text{Pd} \quad 16 \text{ e}^- \xrightarrow{-L} [\text{Ph}_3\text{P}]_2\text{Pd} \quad 14 \text{ e}^- \xrightarrow{\text{Ph} \xrightarrow{\text{Br}}} \]

  strong \( \sigma \)-donor

  agostic (2\( e^- \)/3-center bond) interactions
- **reductive elimination**: the major way in which transition metals are used to make C,C- and C,H-bonds!

- **migratory insertion**: 

\[
\begin{align*}
\text{R} & \quad \text{Z} & \quad \text{Cp} \\
16e^- & & & \\
\text{CO} & & & \\
\text{Z} & \quad \text{Cp} & \quad \text{Cl} \\
18e^- & & & \\
\text{R} & \quad \text{Z} & \quad \text{Cp} & \quad \text{Cl} \\
16e^- & & & \\
\end{align*}
\]
- **β**-elimination/hydrometalation:

\[
\begin{align*}
\text{Dr. P. Wipf - Chem 2320} & \quad \begin{array}{c}
R \quad \text{R}
\end{array} \\
\text{4/10/2006} & \quad \begin{array}{c}
\text{4/10/2006}
\end{array}
\end{align*}
\]

\[
\begin{align*}
\text{β-elimination} & \quad \begin{array}{c}
\text{R}
\end{array} \\
\text{hydrometalation} & \quad \begin{array}{c}
\text{R}
\end{array}
\end{align*}
\]

- **olefin metathesis:**

\[
\begin{align*}
\text{Fischer carbene complex} & \quad \begin{array}{c}
\text{OMe}
\end{array} \\
\text{Δ, 80 °C} & \quad \begin{array}{c}
\text{Ph}
\end{array} \\
\text{EtO} & \quad \begin{array}{c}
\text{OMe}
\end{array} \\
\text{Ph} & \quad \begin{array}{c}
\text{OMe}
\end{array} \\
\text{EtO} & \quad \begin{array}{c}
\text{OMe}
\end{array} \\
\text{Ph} & \quad \begin{array}{c}
\text{OMe}
\end{array} \\
\text{EtO} & \quad \begin{array}{c}
\text{OMe}
\end{array}
\end{align*}
\]
Summary of Mechanisms:

- ligand substitution
- oxidative addition/reductive elimination
- migratory insertion/\(\beta\)-elimination (carbo-, hydrometalation)
- alkene metathesis
- transmetalation
B. The Synthetic & Mechanistic Chemistry of Cuprates

History & Structure of Cuprates

- In 1952, Gilman reported the *in situ* preparation of Me₂CuLi (*J. Org. Chem.* 1952, 17, 1630).

- House and others subsequently demonstrated that the chemistry of CuI-derived organometallics was distinctively different from their lithium- or magnesium-based precursors (House, H. O.; Respess, W. L.; Whitesides, G. M. *J. Org. Chem.* 1966, 31, 3138).

- Structural information on organocopper derivatives is scarce. Mixing MeLi-MeCu in different stoichiometric ratios provides an equilibrium mixture of Me₂CuLi, Me₃Cu₂Li, and Me₃CuLi₂. The latter reagent is supposed to be more stereoselective and more reactive than Me₂CuLi (Ashby, E. C. et al. *J. Am. Chem. Soc.* 1977, 99, 5312; *J. Org. Chem.* 1977, 42, 2805).
Structure of Cuprates - The Controversy Begins....

- In 1981, Lipshutz proposed the formation of “higher-order mixed cyanocuprates” (H.O. cuprates) by the addition of 2 equiv of an organolithium reagent to 1 equiv of copper cyanide.
- These $\text{Me}_2\text{Cu}($CN$)$Li$_2$ reagents were assumed to be dianionic salts with the cyano group bound to copper (Lipshutz et al. *J. Am. Chem. Soc.* 1981, 103, 7672).
- Furthermore, it was claimed that H.O. cuprates are more reactive than lower order Gilman cuprates and be more stable due to backbonding from the filled d-orbital on copper to the empty $\pi^*$-orbital on the nitrile (Lipshutz et al. *Synthesis* 1987, 325; *J. Org. Chem.* 1983, 48, 546).

Structure of HO (?) Cuprates

- Whether or not the cyanide ligand is bound to copper has been a controversial topic (Bertz, S. H. *J. Am. Chem. Soc.* 1991, 113, 5470).
- The Bertz proposal has the cyano group coordinated as lithium cyanide to a Gilman-like species. In the presence of HMPA, some free LiCN is indeed detected (Cabezas, J. A.; Oehlschlager, A. C. *J. Am. Chem. Soc.* 1997, 119, 3878; no trace of LiCN is found if the cuprate is prepared in THF only).
- Also, EXAFS and XANES studies have shown that the addition of cyanide to dimethylcuprate does not cause a significant change at the copper center (Barnhart, T. M.; Huang, H.; Penner-Hahn, J. E. *J. Org. Chem.* 1995, 60, 4310).
- However, addition of methyl $E$-cinnamate led to changes attributed to a cuprate-enoate $\pi$-complex.
Structure of Cuprates


- A solid state structure, however, stresses the separation of [Ar₂Cu]⁻ and [Li₂CN]⁺ units (Kronenburg, C. M. P.; Jastrzebski, J. T. B. H., "A model structure for the resting state of cyanocuprate reagents R₂Cu(CN)Li₂. The x-ray crystal structure of [Ar₂Cu(CN)Li₂(THF)₄]⁺." J. Am. Chem. Soc. 1998, 120, 9688).

Structure of Cyano Cuprates

Proposed solution structure for Me₂CuLi-LiCN

X-ray structure for Ar₂CuLi-LiCN
Conjugate Additions

The formation of a $\pi$-complex appears to be followed by $\sigma$-complex formation and reductive elimination. The reductive elimination is rate-determining (Frantz, D. E.; Singleton, D. A.; Snyder, J. P., "$^{13}$C Kinetic isotope effects for the addition of lithium dibutylcuprate to cyclohexenone. Reductive elimination is rate-determining." J. Am. Chem. Soc. 1997, 119, 3383).

Conjugate Additions - To Be or Not To Be A Radical
Conjugate Additions

- **Caveat**: The mechanism of cuprate additions depends on cuprate structure, substrate, solvent, additives (e.g. TMS-Cl), and the specific reaction conditions.


- Effect of substrates:

  \[
  \begin{align*}
  \text{C} & > \text{C} \text{OR} \quad \text{CN} \quad \gg \quad \text{C} \text{O}^{-} \quad \text{RO} \quad \text{C} \text{O} \text{R}
  \end{align*}
  \]

  - Unsaturated esters are less reactive than enones.
  - \(\beta,\beta\)-Disubstitution slows reaction.
Evidence for ionic mechanism


Evidence for radical anion mechanism


- Half-life of intermediate radical anion is very short.
- Subsequent coupling with cuprate reagent (after α-transfer) is faster than other radical reactions in some cases.
- However, competitive single electron reductions with cuprates have been observed and they may be used to effect reductive elimination reactions analogous to dissolving metal or Zn reductions.
Mixed Organocuprates - Enter the Dummies

- $\text{R(X)}\text{Cu}^-$ ($\text{X}=$alkynyl, CN, NR$_2$, SMe, PR$_3$ a. o.) in which the $\text{X}^-$ group acts as a nontransferable ("dummy") ligand provided a breakthrough for the synthetic use of cuprates. Seemingly a paradox, cyano and alkynyl groups have low energy of activation for 1,2-migration as a consequence of participation of the $\pi$-orbitals in the transfer step. A long accepted hypothesis for the dummy ligand effect of these groups was that they form a strong Cu-$\text{X}$ bond. However, it has been shown that the transfer selectivity is controlled by the metal-coordination ability of the $\text{X}$ group in the polymetallic cluster rather than the Cu-$\text{X}$ bond strength.
In addition to Gilman and Cyanocuprate reagents, Yamamoto-type cuprates (Yamamoto, Y. Angew. Chem., Int. Ed. Engl. 1986, 25, 947) and cuprate/TMS-Cl mixtures have interesting reactivity. Organocopper compounds can also be obtained via transmetalation (Kharasch-Grignard; Wipf, P., "Transmetalation reactions in organocopper chemistry," Synthesis 1993, 537-557):

- \( \text{RLi, CuI, } R_3P \) (1:1:2)
- \((\text{COD})\text{RCuMgX}\)
- \(\text{RCu(SPh)Li, } \text{RCu(OBu)Li, } \text{RCu(NMe_2)Li}\)
- \(\text{RCu(SPh)Li}\)
- \(\text{RCu(CEC' Bu)Li and RCu(CN)Li}\)
- \(\text{RCu(CN)Li}\)
- \(\text{RCu(C=CP)Li}\)
- \(\text{RCu(C=CC(OMe)Me_2)Li}\)

**Other Cuprates**

- In addition to Gilman and Cyanocuprate reagents, Yamamoto-type cuprates (Yamamoto, Y. Angew. Chem., Int. Ed. Engl. 1986, 25, 947) and cuprate/TMS-Cl mixtures have interesting reactivity. Organocopper compounds can also be obtained via transmetalation (Kharasch-Grignard; Wipf, P., "Transmetalation reactions in organocopper chemistry." Synthesis 1993, 537-557):
Mechanism of TMSCl-accelerated additions of cuprates to enones

- Several conflicting theories have been proposed to explain this effect. Corey and Boaz suggested that TMS-Cl accelerates the conjugate addition by the silylation of a d,π*-complex to produce the silyl enol ether of a Cu(III)-adduct and thus make the process irreversible (e.g., 2→7).

- Kuwajima, in contrast, suggested that TMS-Cl acted as a Lewis acid to activate the enone (e.g., 1→5), and Lipshutz presented NMR evidence that the chloride acts as a Lewis base and associates with the lithium cation of cuprate dimers (e.g., 1→6). Snyder and Bertz suggested that the chloride coordinates with copper to stabilize formation of the Cu(III) intermediate 7 (X=Cl).
The measurement of kinetic isotope effects is consistent with a rate-limiting silylation of the intermediate $\pi$-complex. These data support the Corey proposal, have no bearing on the push-pull proposal by Lipshutz, but do not support any importance for TMS-Cl coordination of the initial enone or a formal Cu(III) intermediate. Also, the basic mechanism appears to be the different in THF or Et$_2$O, and it is known that TMSCl has less effect on additions to enones in the latter where the rate-limiting step is reductive elimination.

However, TMS-Cl does have a large impact on additions to $\alpha,\beta$-unsaturated esters, amides, and nitriles in ether, and this might also go hand in hand with a change in the rate-limiting step.

- TMS-Cl trapping is also useful in the regiospecific generation of enolates.

Stereochemistry of Conjugate Additions: Cyclic Substrates

2,3-diastereoselectivity

condition dependent:
cis preferred, but isomerization to trans is facile.

3,4-diastereoselectivity

3-substituted enones

R1, R trans: cis

<table>
<thead>
<tr>
<th>R1</th>
<th>R</th>
<th>trans: cis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>Me</td>
<td>72:28</td>
</tr>
<tr>
<td>Et</td>
<td>Me</td>
<td>78:22</td>
</tr>
<tr>
<td>Pr</td>
<td>Me</td>
<td>88:12</td>
</tr>
<tr>
<td>Ph</td>
<td>Me</td>
<td>96:4</td>
</tr>
<tr>
<td></td>
<td>(87:13)</td>
<td></td>
</tr>
</tbody>
</table>

Et | Ph | 89:11      |
| Pr | Me | 89:11      |
| Ph | Et | 92:8       |

2,3-Diastereoselection determined by protonation of enolate

pseudo equatorial

pseudo axial

axial protonation, chair-like transition state, cis to C3 R-substituent.

Destabilizing 1,3-diaxial interaction developing.

this is preferred

axial protonation, chair-like transition state, trans to C3 R-substituent.

most stable product observed

readily epimerizes to more stable product.
Face-selective Addition Reaction to a Heterocycle


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Stereochemistry of Conjugate Additions: Bicyclic Enones
3-Component Conjugate Addition - Enolate Trapping


### Allylic Displacements

- **OAc**
  - 2 eq Me₂CuLi, 0 °C
  - Et₂O, 10 min
  - 99%
  - Ph
  - 96 : 4

- **OAc**
  - 2 eq Me₂CuLi, 0 °C
  - Et₂O, 10 min
  - 96%
  - Ph
  - 96 : 4

- **OAc**
  - 2.7 eq Me(CN)₂CuLi, 20 °C, Et₂O, 20 h
  - 76%
  - Ph
  - 49 : 51

- **OAr**
  - Pent₂Zn, -10 °C, 2.5 h
  - 1.2 eq CuCN(LiCl)₂
  - THF/NMP 2:1
  - (Ar = C₆F₅)
  - 98% ee
  - 83%, 90% ee
  - Pent
  - 9%
Epoxide Openings

\[
\begin{align*}
\text{reagent:} & \quad \text{Et}_2\text{O, 13 h} \\
\text{3 eq MeMgBr, 34 °C} & \quad 5\% \quad 5\% \quad 7\% \quad 15\% \quad 63\% (X = \text{Br}) \\
\text{3 eq MeMgCl, 34 °C} & \quad 45\% \quad 22\% \quad 1\% \quad 0\% \quad 31\% (X = \text{Cl}) \\
\text{3 eq MeLi, LiBr, 34 °C} & \quad 90\% \quad 0\% \quad 1\% \quad 0\% \quad 0\% \\
\text{2 eq } \text{Me}_2\text{CuLi, 0 °C (14 h)} & \quad 88\% \quad 0\% \quad 1\% \quad 0\% \quad 0\%
\end{align*}
\]

\[
\begin{align*}
\text{reagent:} & \quad \text{Ph, 20 °C, THF, 4 h} \\
\text{Me}_2\text{Cu(CN)Li}_2 & \quad 68 : 32 (93\% \text{ yield}) \\
\text{MeLi} & \quad 71 : 29 (\text{trace}) \\
\text{Me}_2\text{ZnL}_2 & \quad 51 : 49 (93\% \text{ yield}) \\
\text{Et}_2\text{Al, additive} & \quad \text{0 °C, PhMe, 3 h} \\
\text{none} & \quad 33 : 67 (75\% \text{ yield}) \\
\text{5\% PPh}_3 & \quad 2 : 98 (95\% \text{ yield})
\end{align*}
\]

Reduction Pathways

\[
\begin{align*}
\text{OLi} & \quad \text{H}_2\text{CO} \quad \text{Me} \quad \text{OCH}_3 \\
\text{H}_2\text{CO} \quad \text{Me} \quad \text{OCH}_3 & \quad \text{OLi} \\
\text{R}_2\text{CuLi} & \quad \text{X = Cl reduction} \\
\text{R}_2\text{CuLi} & \quad \text{X = OCH}_3 \quad \text{conjugate addition}
\end{align*}
\]
Synthetic Examples

Conjugate Reduction

- Moritani, Y.; Appella, D. H.; Jurkauskas, V.; Buchwald, S. L., “Synthesis of β-alkyl cyclopentanones in high enantiomeric excess via copper-catalyzed asymmetric conjugate reduction.” J. Am. Chem. Soc. 2000, 122, 6797-6798. The pioneering work by Stryker, Lipshutz and Hiyama demonstrated that achiral phosphine-copper hydrides such as [(Ph₃P)CuH]₆ reduce enones via 1,4-reduction. In this work, chiral cyclopentanones were obtained from polymethylhydrosiloxane (PMHS), CuCl, NaOt-Bu, and chiral bis-phosphines.
- Cyclohexenones and cycloheptenones are also reduced with good ee’s, but 1,2-reduction competes to some extent.

\[
\begin{align*}
\text{Ketone} & \quad \rightarrow \quad \text{Ketone} \\
\text{(S)-p-tol-BINAP, CuCl} & \quad (5\text{mol\% each}) \\
\text{NaO}t\text{-Bu, PMHS, 0 °C} & \quad 84\%; 98\% \text{ ee}
\end{align*}
\]

Applications in Natural Product Synthesis

- 1,2-Shift of Copper-Ate Complexes