Chem 634

Metal Mediated Substitution Chemistry

Reading: Heg Ch 1–2 (handout),
CS-B 7.1, 8.2–8.3, 11.3,
Grossman Ch 6
Announcements
Problem Set 1 due NOW.

Mary Beth Kramer Lectureship
101 Brown Laboratory
September 25, 2015, 4pm

Weaving Faculty Professional Development with Learning Space Affordances

Many institutions are making significant investments in learning spaces that will allow for innovative, student-centered and collaborative forms of teaching and learning. These approaches to teaching are supported by a broad body of literature. However, few current faculty were taught in environments like this themselves or have experience teaching in them. Faculty professional development through institutional units/centers exists in some form at most institutions. Traditional faculty development has been optimized for improving lecture-based teaching practices. As calls for reform in STEM education begin to coalesce around active-learning approaches, then, it is necessary for faculty development to also shift its focus. UMass has been in the process of providing faculty with professional development opportunities tailored to our team-based learning classrooms for the last 3 years. As faculty access to those spaces has expanded, our curriculum has responded to the needs of an audience interested in a broader view of active-learning. In this presentation, I will describe our evolving professional development approach tailored to active learning, faculty use of our active learning facilities, and current thinking on course and space design that undergirds our work. This is part of a larger multi-institution project through the Bay View Alliance in which we are exploring the overarching question of how PD-influenced instructional practices combine with learning space affordances to affect the learning experience of students.

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http://www.chem.umass.edu/faculty/weaver.html
Copper Promoted Substitution Chemistry

$S_N2$ –type Reactions:

\[
\text{Me} - \text{Br} \quad \text{H} \quad \text{Me} \quad \xrightarrow{\text{Ph}_2\text{CuLi}} \quad \text{Me} - \text{H} \quad \text{Ph} \quad \text{Me}
\]

$S_N2$ reaction

1° > 2° >> 3°

TfO~TsO~I > Br > Cl

- Mechanism not clear
- Review: Comp. Org Synth, Vol 3, Section 1.5
Copper Promoted Substitution Chemistry

Also sp\(^2\) systems:

\[
\begin{align*}
\text{TfO} & \quad \text{H} \quad \text{Me}_2\text{CuLi} \quad \text{Me} & \quad \text{H} & \quad \text{Bu} \quad \text{Bu} \quad \text{Bu} \quad \text{Bu} & \quad +10\% \text{ } E\text{-isomer}
\end{align*}
\]

- Also works with ArX
- But not used very often now...see later
Copper Promoted $S_{N2}'$ Chemistry

However, with PhMgBr + CuCN:

$\text{MeO}D\text{Me}$ isotopic label

BuMgBr
Cat. CuX

w/ 10% CuCl:
39%
61%

w/ 10% CuCN:
0%
100%

$\text{Me}D\text{Bu}$

$\text{Me}$

General $S_{N2}'$ mechanism:

Goering, JOC, 1986, 51, 2884
Reactions With Acid Chlorides

Recall:

\[
\text{R'OCl} \xrightarrow{\text{R'Li or R'MgX}} \text{R'O} \xrightarrow{\text{R'OH}} \text{R'OR'}
\]

cannot stop here, ketone more reactive

However:

\[
\text{R'OCl} \xrightarrow{\text{R'\text{2CuLi•LiX}}} \text{R'O} \xrightarrow{\text{clean}} \text{R'OR'}
\]
Palladium (and Nickel) Catalyzed Cross Coupling

\[
\begin{align*}
R-X + M-SnR_3 &\xrightarrow{LnPd(0) \text{ cat.}} R-R' \\
\text{aryl or vinyl} &\xrightarrow{C-C \text{ bond}} \\
\end{align*}
\]

X: TfO > I > Br > OTs ~ Cl

M = -SnR_3 (Stille reaction)
  -B(OR)_2 or B(OH)_2 w/ base (Suzuki reaction)*
  -SiR_3 (Hiyama reaction)
  -MgX (Kumada-Curriu reaction)
  -ZnBr (Negishi reaction)*

* = 2010 Nobel Prize
Basic Mechanism

- oxidative addition
- reductive elimination
- transmetallation
**Palladium and Nickel Sources**

**Palladium (0) Sources**

- \( \text{Pd}_2(\text{dba})_3 \)
- \( \text{Pd}(	ext{PPh}_3)_4 \)

Note: \( \text{dba} \) and \( \text{PPh}_3 \) are ligands.

**Palladium (II) Sources (Reduced In Situ)**

- \( \text{Pd(OAc)}_2 \)
- \( \text{Pd(Cl)}_2 \)
- \( (\text{MeCN})_2\text{PdCl}_2 \)

**Nickel Sources**

- \( \text{Ni(COD)}_2 \)
- \( \text{NiX}_2 \) (\( X=\text{Cl}, \text{Br}, \text{I} \))
- 1,5-COD:
Ligands

Ar−X

X = TfO, I, Sometimes Br (easy oxidative addition)

PPh₃

Ph₂P–PPh₂
dppe

Fe

PPh₂

dppf

X = Br

X = Cl

Pt-Bu₃, PCy₃, NHC’s

P(o-tol)₃

R'

PR'₂

R= Cy, t-Bu

Ligand is the most important part of the catalyst for controlling reactivity.
Active Catalysts for Oxidative Addition

Larger more electron-rich ligands favor lower coordination numbers required for ArCl

- Note: the need for low valent Pd(0) explains why Pd$_2$(dba)$_3$ and Pd(PPh$_3$)$_4$ can be problematic.
- Also, this trend explains why metal:ligand ratio can be very important to reactivity.
Sonogashira Reaction

\[ \text{Ar}-X \xrightarrow{\text{R} \equiv} \text{Ar} \equiv \text{R} \]

\text{Pd(0) cat, CuI cat, Et}_3\text{N}
Formation of Copper Acetylide

\[ \text{R} = \text{Cu(I)} = \text{Cu(III)} \]

\[ \text{R} = \text{Cu(I)} \]

\[ \text{R} = \text{Cu(III)} \]

\[ \text{R} = \text{Cu} \]

\[ \text{pka} \sim 20 \]

\[ \text{pka}^* \sim 9 \]
Mechanism

**Reductive Elimination**

Ar—C≡C—R

**Oxidative Addition**

LₙPd(0) → Ar—C≡C—LₙPd

**Transmetalation**

CuX → Cu—C≡C—R

**Reductive Elimination**

R—C≡C—H

**Oxidative Addition**

Ar—X → LₙPd(0)
Hartwig-Buchwald Enolate Arylation

\[ \text{Ar-X} \xrightarrow{\text{RO}} \text{Ar} \]

\[ \text{L}_n\text{Pd}(0) \text{ cat NaOtBu} \]

\[ \text{Ar} \xrightarrow{\text{L}_n\text{Pd}(0)} \text{CO}_2\text{R} \]

\[ \text{Ar} \xrightarrow{\text{X}} \text{L}_n\text{Pd}^{\text{II}} \]

\[ \text{NaX} \xrightarrow{\text{tBuONa}} \text{R'} \xrightarrow{\text{OR}} \text{R'} \]

\[ \text{H} \]
**Buchwald-Hartwig Amination**

\[
\begin{align*}
\text{Ar} - X & \xrightarrow{HNR_2, L_nPd(0), \text{base}} \text{Ar} - NR_2 \\
X &= \text{Br, Cl, OTf}
\end{align*}
\]

Similar cross couplings with ROH, F-, etc. These are challenging due to RE.

Buchwald: *ACIE*, **2008**, 47, 6338
Buchwald-Hartwig Amination

\[
\text{Ar–X} \xrightarrow{\text{HNR}_2, L_nPd(0), \text{base}} \text{Ar–NR}_2
\]

X=Br, Cl, OTf

Consider pK_a’s:

- typical bases: K_3PO_4 or tBuONa
  - pK_a': 8    17
  - vs. HNR_2
  - pKa: 35
Buchwald-Hartwig Amination

- Reductive Elimination Difficult
- Typical Ligands:

\[ \text{L}_{\text{nPd}(0)} \]

\[ \text{Ar}-\text{NR}_2 \quad \text{L}_{\text{nPd}(0)} \quad \text{Ar}-\text{X} \]

\[ \text{L}_{\text{1Pd}^{\text{II}}-\text{X}} \]

\[ \text{BHX} \]

\[ \text{BrettPhos} \]

\[ \text{X-Phos} \]

\[ \text{tBu-X-Phos} \]

\[ \text{R}_3\text{NH}^+ \text{ like (pka } \sim \text{ 9)} \]
Heck Reaction

- Alkenes as nucleophiles.
- Achieves the arylation or vinylation of an alkene.

- Historically, the Heck Reaction preceded all other palladium-catalyzed cross-couplings.
- 2010 Nobel Prize
- Also called the Mizoroki–Heck reaction. Mizoroki published similar findings just prior to Heck’s work.
Mechanism

Base·HX → LnPd(0) → Ar–X

oxidative addition

LnPd(0) + Base → LnPdII

β-Hydride elimination

Ar = R

alkene binding

migratory insertion
Notes on the Heck Reaction

Intermolecular (alkene and halide on different molecules):

- Somewhat limited scope.
- Normally limited to CH\(_2\)CH\(_2\), mono- and di-substituted alkenes.
- Tri- and tetra-sub. alkenes are too poor of ligands to engage Pd(II) intermediate.
  Electron-rich alkenes generally better than electron-poor.
- Regioselectivity is often poor.

Intramolecular (alkene and halide tethered together):

- Much better scope.
- Can form carbocycles and heterocycles of all types.
- Mono-, di-, tri- and tetra-substituted, electron-rich and electron-poor alkenes all work.
Example of Intramolecular Heck Reaction

\[
\begin{align*}
\text{N} & \quad \text{O} \\
\text{Me} & \quad \text{I} \\
\text{Pd(OAc)}_2 & \quad \text{cat.} \\
\text{PPh}_3, \text{Et}_3\text{N} & \quad \rightarrow \\
\text{Me} & \quad \text{O} \\
\end{align*}
\]
Stereospecificity

\[
\text{cis-migratory insertion} \\
\text{cis-}\beta\text{-Hydride elimination}
\]
Exo Cyclization Preferred

- exo strongly preferred
- 5-exo, 6-exo very easy to accomplish
- difficult to form small rings (3-exo, 4-exo, etc)

Via:

exo-cyclization PREFERRED

endo-cyclization NOT
Asymmetric Intramolecular Heck Reaction

\[
\begin{align*}
\text{MeO} & \quad \text{I} & \quad \text{O} & \quad \text{OSiR}_3 \\
\text{Me} & \quad \text{Me} & \quad \text{Me}
\end{align*}
\]

\[
Pd(OAc)_2 \quad \text{(S)-Binap}
\]

\[
\begin{align*}
\text{MeO} & \quad \text{Me} & \quad \text{OSiR}_3 \\
\text{Me} & \quad \text{Me} & \quad \text{Me}
\end{align*}
\]

84% yield
95% ee (97.5:2.5)

Binap:

Chiral
Can be resolved

Overman, JACS, 1998, 120, 6500

Shibisaki has also contributed to this area
**Heck Carbonylation**

\[
\text{Ph}^X \xrightarrow{\text{CO, Nuc, } L_n\text{Pd}(0), \text{base}} \text{Ph}^\text{Nuc}
\]

- \( X = I, \text{OTf} \quad L = \text{PPh}_3, \text{etc.} \)
- \( X = \text{Br} \quad L = \text{Xantphos} \)
- \( X = \text{Cl} \quad L = \text{PCy}_2\text{PCy}_2 \)

**Nuc =**

- \( \text{H}_2\text{O} \)
- \( \text{ROH} \)
- \( \text{H}_2\text{NR} \)
- \( \text{HNR}_2 \)
- \( \text{Bu}_3\text{SnH} \)

**Product =**

- \( \text{Ph}^\text{OH} \)
- \( \text{Ph}^\text{OR} \)
- \( \text{Ph}^\text{NHR} \)
- \( \text{Ph}^\text{NR}_2 \)
- \( \text{Ph}^\text{H} \)
Mechanism
Reductive Elimination Details

Transmetallation:

\[ L_nPd^{II}X_{Ar} \xrightarrow{\text{Nuc-H}} L_nPd^{II}O_{Ar} \xrightarrow{\text{R.E.}} Nuc \rightarrow NucAr \]

Or:

Addition-Elimination:

Both mechanisms are known.
Cross Coupling With Alkyl Groups

\[
\text{Dec-Br + 9-BBN → } \text{Dec-hex} + \text{hex} \quad \text{85%} \\
\text{9-BBN:} \quad \text{B} \quad \text{N}
\]

Limited to 1° electrophiles with Pd.

Fu, 
JACS, 2001, 123, 10099
Fu, ACIE, 2002, 41, 945 (RCI, ROTs)
2° Alkyl Halides

\[ \text{R-Br} + \text{BrZn-R'} \xrightarrow{\text{NiBr}_2 \cdot \text{diglyme} \text{ (S)-pybox}} \text{R-R'} \]

82%, 91% ee

Fu, *JACS*, 2003, 125, 14726

\[ \text{Cl} + \text{BrZn-R'} \xrightarrow{\text{NiBr}_2 \cdot \text{diglyme} \text{ (S)-pybox}} \]

82%, 91% ee

racemic!

Fu, *JACS*, 2005, 127, 10482

(S)-pybox:

\[ \text{\begin{array}{c}
| O & N \\
\hline
i-Pr & N & i-Pr
\end{array}} \]
Iron Catalysis

\[
\text{Cl} \quad \text{OMe} \quad + \quad \text{HexMgBr} \quad \xrightarrow{\text{Fe(acac)}_3} \quad \text{Hex} \quad \text{OMe}
\]

\[
\text{ArMgBr} \quad + \quad \text{Me} - \text{Me} \quad + \quad \text{Me} - \text{Me} \quad \xrightarrow{\text{FeCl}_3 \quad \text{tmeda, -78°C}} \quad \text{Me} \quad \text{Me} \quad \text{Ar} \quad + \quad \text{less than 20%} \quad \text{CH}_2=\text{CH}_2
\]

Furstner, *ACIE*, 2002, 3856 (Fe^2-)

Nakamura, *JACS*, 2004, 126, 3686

Ullman/Goldberg Coupling

Good for weakly basic N-nuc (amide, heterocyclic, etc.)
Limited to ArI and some ArBr.

**π-Allyl Chemistry**

Tsuji-Trost

\[
\begin{align*}
\text{X} & \quad \text{L}_n\text{Pd}(0) \quad \text{PdL}_n\text{X} \quad \text{Pd-X} \\
\text{η}^1 & \quad \text{η}^3 \\
X &= \text{Cl, Br, OAc, OC(O)R, OP(O)R}_2, \text{etc}
\end{align*}
\]
π-Allyl Chemistry

Backside attack
If the metal π-allyl can isomerize to the terminal position, this provides a pathway for racemization.
Substitution Reaction with π-Allyl Electrophiles

Type 1: Non-basic Nucleophiles (pKₐ’ < 25, DMSO)

\[
\text{nuc}^- = \text{RO} \xrightarrow{\text{LₙPd(0)}} \text{Pd}^{II}X_L_n \xrightarrow{\text{nuc}^-} \text{Me} \xrightarrow{\text{nuc}^-} \text{Me} \xrightarrow{\text{nuc}^-} \text{Me} \xrightarrow{\text{nuc}^-} \text{note: less sub. side of π-allyl}
\]

\[
\text{nuc}^- = \text{RO-} \xrightarrow{\text{ONa}} \text{OMe}
\]

- amines
- PhO-
- \( \text{R} \overset{\text{NO}}{\xrightarrow{\text{2}}} \text{NO}_2 \)
- etc.

double backside displacement = net retention
Substitution Reaction with $\pi$-Allyl Electrophiles

Type 2: Transmetallation

Transmetallation occurs with: $R_3\text{SnR}$, $RB(OH)_2$, etc.

Net inversion observed
Asymmetric Variant

Trost modular Ligand: "TML"

BzO\[\overset{\text{meso}}{\text{O}}\]OBz + Me\[\overset{\text{PhO}_2\text{S}^-}{\text{NO}_2}\] \rightarrow \text{(allyl)PdCl}_2, L^* \rightarrow \text{Bz} = \overset{\text{\text{O}}}{\text{\text{O}}}

\[\left[\overset{\text{L}^*\text{XPd}}{\overset{\text{O}}{\overset{\text{\text{O}}}{\text{Bz}}}}\right] \rightarrow \overset{\text{Me}}{\text{O}_2\text{N}}\overset{\text{\text{O}}}{\text{\text{O}}}

>90% ee


Lloyd-Jones, *JACS*, **2009**, 131, 9945
stereoselectivity in AAA reaction
Other Metal π-Allyl Chemistry

Mo π-allyl

X-ray and NMR

Double Retention at more hindered side

Trost, JACS, 1987, 109, 1469
Lloyd-Jones, JACS, 2004, 126, 702
Other Metal π-Allyl Chemistry

Mo π-allyl

Trost, OL, 2007, 9, 861
Rhodium and Iridium π-Allyl Chemistry

\[
\text{Me} \quad \text{HO} \\
\text{[Ir(cod)Cl]_2, L^*} \\
\text{Me} \quad \text{O} \\
87\%, 95\% \text{ ee}
\]

Hartwig, *JACS*, 2003, 125, 3426