The Evolution of Cross-Coupling Reactions

Reporter: Bingtao Guan
Supervisor: Zhangjie Shi

2007.06.29
until the discovery and development of cross-coupling reactions starting in the 1970s, there were no simple, general direct methodologies known for C-C formation between unsaturated species …

--- Peter J. Stang

…total synthesis has benefited enormously from the palladium-catalyzed cross-coupling reactions…

--- K. C. Nicolaou

…somebodies in this field would win the Nobel Prize one day …

--- Anonymous
Reaction Nomenclature

The reaction of organometallic reagents with organic electrophiles in the presence of group 8–10 metal catalysts, notably Ni and Pd complexes.

This reaction is currently a popular method for a wide range of C-C, C-H, C-N, C-O, C-S, C-P, or C-M bond-forming processes.

\[ R-X + R'-m \xrightarrow{\text{catalyst } [M]} R-R' \]

- \( X = I, \text{Br, Cl, OTf, } \)
- \( F, \text{CN, OTs, } \)
- \( \text{OMs ... ... } \)
- \( m = \text{Li (Murahashi)} \)
- \( \text{Mg (Kumada-tamao, Corriu)} \)
- \( \text{B (Suzuki-Miyaura)} \)
- \( \text{Si (Tamao-Kumada, Hiyama-Hatanaka)} \)
- \( \text{Sn (Migita-Kosugi, Stille)} \)
- \( \text{Zn, Zr (Negishi)} \)
- \( \text{Al (Nozaki-Oshima, Negishi)} \)
- \( \text{Cu (Normant) ... ... } \)


The general catalytic cycle

**OPSS Lectures:**

**Oxidative Addition**

Reporter: Shiliang Tian
Supervisor: Prof. Zhangjie Shi

**The Mechanism of the Stille Reaction**

Reporter: Jing Liu (刘颖)
2005-12-30

\[
\begin{align*}
&M = \text{Fe, Co, Ni, Cu, Pd, Ru, Rh ... ...} \\
&m = \text{Li, Mg, B, Si, Sn, Zn, Zr, Al ... ...}
\end{align*}
\]
Contents

- Introduction

- The evolution of cross-coupling reactions

- The contributions from China

- Summary and outlook
The evolution of cross coupling reactions

• The organometallic reagents

• The organic electrophiles

• The catalysts

• Use of new technologies

What can be translated to the transition metal complex?
Fritz Ullmann
1875–1939

Phenol, aniline were almost the earliest nucleophilic reagents

During the first 70 years of the 20th century, aryl-aryl bond formation mostly relied on reductive coupling reactions.

The true breakthrough

[Ullmann reactions diagram]
Introduction of organometallic reagents

The confliction: reactivity and selectivity

Kumada-Corriu-Tamao Reaction

- Easily available
- Mild conditions
- Excellent reactivity
- Moisture sensitivity
- Poor tolerance

Corriu, J. P.; Masse, J. P. Chem. Commun. 1972, 144

\[
\text{PhCl} + \text{EtMgBr} \xrightarrow{\text{NiCl}_2(\text{dppe}) \text{Et}_2\text{O}, \text{reflux, 20h}} \text{PhEt} \quad 98\%
\]

\[
\text{Ph-Br} + \text{PhMgBr} \xrightarrow{\text{Ni(acac)}_2 \text{Et}_2\text{O, rt}} \text{PhPh} \quad 70\%
\]

\[
\text{Ph-Br} + \text{MeMgBr} \xrightarrow{\text{Pd(PPh}_3)_4 \text{benzene, rt}} \text{PhMe} \quad 100\%
\]
Functionalized Organomagnesium


![Image of Paul Knochel]


---

\[
\text{FG}^1 \quad \text{FG}^2 \\
\begin{array}{c}
\text{Br} \\
\text{CN} \\
\text{CO}_2 \text{Et} \\
\text{Br} \\
\text{H} \\
\text{CO}_2 \text{Me} \\
\text{CN} \\
\text{yield} = 62-95\%
\end{array}
\]

\[
\text{X} = \text{Cl, Br; } \text{FG}^1 = \text{CN, CO}_2 \text{Et, Br; } \text{FG}^2 = \text{H; CO}_2 \text{Me, CN; yield} = 62-95\%
\]

---

\[
\begin{array}{c}
\text{FG}^1 \\
\text{FG}^2 \\
\text{MgX}
\end{array}
\]

\[
\text{FG} = \text{Br, CONR}^2, \text{CN, CO}_2 \text{Et} ...
\]

---

\[
\begin{array}{c}
\text{R}^1 \\
\text{R}^2
\end{array}
\]

\[
\begin{array}{c}
\text{FG}^1 \\
\text{FG}^2 \\
\text{MgX}
\end{array}
\]

\[
P\text{d(bda)}_2, \text{2 mol %} \\
P\text{dppf or P(t-Bu)}_3, \text{2 mol %} \\
\text{Toluene / THF} \\
\text{-20°C to -65°C, 6-12 h}
\]

\[
\text{R}^1 = \text{F, Cl, Br, NMe}_2, \text{CN, COOEt}...R^2 = \text{F, NH}_2, \text{OTPH, COOEt} ...
\]

\[
\text{L3} = \text{2'-(dicyclohexylphosphino)-N,N-dimethylbiphenyl-2-amine}
\]

---

**Negishi Reaction**

- **Good functional group compatibility**
- **Mild conditions**
- **Facility in preparation**
- **Water sensitive**
- **Zn waste**

\[
\text{R} = \text{alkyl or H, } X = \text{I or Br, } M = \text{Pd or Ni, Yield}=55-82\%
\]

\[
\text{R} - \text{ZnX} + \text{Ar} - X' \xrightarrow{\text{cat. Ni(PPh}_3)_4 \text{ or cat. Pd complex}} \text{R} - \text{Ar}
\]

\[
\text{R} = \text{Ar or ArCH}_2; \ X = \text{Br, Cl or Ar;} \ X' = \text{Br or I}; \text{Yield}=12-95\%
\]

\[
\text{R}^1 = \text{CH(CH}_2\text{)} \xrightarrow{\text{Cl(H)ZrCp}_2} \text{R}^1 \xrightarrow{\text{Ni(PPh}_3)_4} \text{Ar}
\]

\[
\text{Yield}=35-99\%
\]


Preparation of organozinc

**Insertion of Zinc**

\[
R - X + Zn \xrightarrow{\text{THF, 5-45°C}} R - Zn > 85%
\]

\(X = I, Br; R = \text{alkyl, aryl, benzyl, ally}\)

**Iodine-Zinc Exchange**

\[
R - I \xrightarrow{\text{cat CuI, Et}_2Zn} R_2Zn
\]

**Transmetalation**

\[
R - M \xrightarrow{ZnX_2} R - ZnX \\
M = \text{Cu, Li, Mg, B, Cd, Hg ... ...}
\]

\(FG = \text{CO}_2R, \text{enoate, CN, enone, halide, (RCO)}_2N, (\text{TMS})_2Si, RNH, NH_2, RCONH, (RO)_3Si, (RO)_2P(O), RS, RS(O), RSO_2, PhCOS ... ...\)


\[
\text{Ph} \xrightarrow{1) (-)-IpcBH}_2 \text{Zn}^{\text{iPr}}  \\
\text{Ph} \xrightarrow{2) Et}_2BH  \\
\text{Ph} \xrightarrow{3) iPr}_2Zn \xrightarrow{\text{Pd(db)})_2 \text{cat P(o-Tol)_3 cat BuCOCl}} \text{Bu}
\]

Boudier, A.; Flachsmann, F.; Knochel, P. *Synlett* **1998**, *1438*
Kosugi-Migita-Stille Reaction

John K. Stille

- **Neutral conditions**
- **Excellent compatibility**
- **Sn: toxicity, waste**
- **High cost**

“Radical” Twist Vs “Radical” Recovery


**Polymer-supported tin**  
Ar—Sn(CH₂CH₂C₆F₁₃)₃

**Fluorous tin**  
R—SnX₃

**Monoorganotin**

**Catalytic tin**

\[
\text{Bu₃SnH} \xrightarrow{\text{Pd(0)}} \text{Bu₃Sn—Pd—H} \\
\text{Bu₃SnX} \xrightarrow{\text{Bu₃Sn—Pd—H}} \text{Bu₃Sn—H} \\
\text{Bu₃SnX} \xrightarrow{\text{Bu₃Sn—H}} \text{Bu₃Sn—Bu₃Sn} \\
\]  


**Copper Effects**

\[
\text{R—Pd—I} + \text{L} \xrightarrow{\text{Cul}} \text{CuLₙ} + \text{L} \\
\text{Sn—R} \xrightarrow{\text{Cu—I}} \text{Cu—R} \\
\]

**Fluoride anion**

\[
\text{R'—Sn—NR₂} \xrightarrow{\text{F—}} \text{R'—Sn—NR₂} \\
\text{R₃SnCl} \xrightarrow{\text{F—}} \text{R₃SnF} \\
\]

Tamejiro Hiyama

- **Low toxicity**
- **Easy preparation**
- **Amount of activator**


Denmark, S. E.; Choi, J. Y. J. Am. Chem. Soc. 1999, 121, 5821

Denmark, S. E.; Wehrli, D.; Choi, J. Y. Org. Lett. 2000, 2, 2491

**Suzuki-Miyaura Reaction**


- **Commercial availability**
- **Stability to heat, oxygen, water**
- **Excellent flexibility**
- **Easy separation**
Development of the organoboron reagents

Over 450 boronic acids available commercially
Difficult to purify

Decrease in atom economy

Air-sensitive

Protected Boronic acid

Survive many reactions:
Metal-halogen exchange, Dihydroxylation, cycloadditions, Wittig reactions, Oxidation and Epoxidation ...

Arylation of carbonyl compounds and nitriles

Challenges:
- Electronic effects
- Temperature
- Uncatalyzed condensation
- $\beta$-Hydrogen elimination
- The structures of intermediate

Proper Base and Ligands

Amination

Kosugi, M.; Kameyama, M.; Migita, T. *Chem. Lett.* **1983**, *927*

**John F. Hartwig**


**Stephen L. Buchwald**

Etheration and Thiation

\[ RO^- + X= Br, I; n= 1, 2, 3 \]

\[ R= CN, CHO, C(O)Ph \]

\[ \text{lower nucleophilicity} \]

Organohalide had contributed most to cross coupling reactions, however…
The evolution of cross coupling reactions

• The organometallic reagents
• The organic electrophiles
• The catalysts

Use of new technologies

What can be activated and used in the reaction?
The low reactivity of chlorides

\[ \text{BDE: } I: 65 \text{ kcal mol}^{-1} \quad \text{Br: 81 kcal mol}^{-1} \quad \text{Cl: 96 kcal mol}^{-1} \]

Ph-X BDE:  
- I: 65 kcal mol\(^{-1}\)  
- Br: 81 kcal mol\(^{-1}\)  
- Cl: 96 kcal mol\(^{-1}\)
Activated aryl chlorides

Traditional palladium catalysts are effective.

Unactivated aryl chlorides

The key is the choice of ligand ……

Activation of fluoride and arylnitrile

**Ph-X BDE:** Cl: 96 kcal mol\(^{-1}\)  F: 126 kcal mol\(^{-1}\)  CN: 132 kcal mol\(^{-1}\)

C-O activation


C-N activation

The first example of catalytic C-C bond formation via the cleavage of aryl C-N bonds in anilines...


**Carbonic acid derivatives**

Acyl halides  
Aldehydes  
Acid anhydrides  
Thioesters  
Esters

**Tsuji–Trost reaction**


**Formula and Reactions**

\[
\begin{align*}
R & \quad \text{Acyl halides} \\
\text{Aldehydes} & \quad \text{Stille, Suzuki, Negishi} \\
\text{Acid anhydrides} & \quad \text{Hiyama, Heck couplings} \\
\text{Thioesters} & \\
\text{Esters} & \\
\end{align*}
\]

Trost, B. M.; Crawley, M. L. Chem. Rev. **2003**, *103*, 2921  
Cross-Coupling Reactions with Alkyl Halides

Two problematic steps:

Slow oxidative addition

Rapid β-hydride elimination

The design of new, more active catalyst systems and the development of suitable reaction conditions is of great significance … …

The evolution of cross coupling reactions

- The organometallic reagents
- The organic electrophiles
- The catalysts
- Use of new technologies

What activate the substrates and drive the catalytic cycle?
The transition metals

<table>
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<th>IVB</th>
<th>VB</th>
<th>VIB</th>
<th>VIIB</th>
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<td>W</td>
<td>Re</td>
<td>Os</td>
<td>Ir</td>
<td>Pt</td>
</tr>
</tbody>
</table>

1970                      75                     80                    85                   90
1972                      79                     88                    85                   90
1971                      82                     85                    88                   90

Cu Ni Pd Fe, Co

Cu
Low cost
Low toxicity
Harsh conditions

Ni
Low cost
Good reactivity
Toxicity

Pd
Mild condition
High TON
High cost

Fe, Co
Very Low cost
Innocuity
Environmental benign
The role of the ligands

The ligand can change the steric bulk around the metal center, the electronic properties of the metal, and enforce the bite angle preferred by the ligand (for diphosphines).

**Oxidative addition:**
Aromatic nucleophilic substitution
*Electron-rich ligand* increases the nucleophilicity of Pd specie.
The bulky ligand facilitates the generation of “true” catalyst.

**Reductive elimination:**
Electron-withdrawing and sterically demanding ligands facilitates the reductive elimination.
For bulky ligands, the steric properties dominate over the electronic properties.
Typical ligands

\[ t{-}\text{Bu}P{-}t{-}\text{Bu} \quad \text{Cy}P{-}\text{Cy} \quad \text{P}(t{-}\text{Bu})_2 \quad \text{P}(\text{t-Bu})_2 \]

\[ n = 1, 2, 3, \ldots \]

\[ \text{PPh}_2 \quad \text{DPPF} \quad \text{DTPF} \quad \text{D}^*\text{BPF} \]

\[ \text{PCy}_2 \quad \text{R} = \text{t-Bu} \quad \text{R'} = \text{H} \quad \text{R'} = \text{NMe}_2 \quad \text{R'} = \text{iPr} \quad \text{R'} = \text{Et} \quad \text{R'} = \text{Me} \quad \text{R'} = \text{OMe} \]

\[ \text{R} = \text{t-Bu} \quad \text{R'} = \text{H} \quad \text{R'} = \text{NMe}_2 \quad \text{R'} = \text{iPr} \quad \text{R'} = \text{Et} \quad \text{R'} = \text{Me} \quad \text{R'} = \text{OMe} \]

\[ \text{R} = \text{t-Pr} \quad \text{R} = \text{OMe} \]

\[ \text{R} = \text{aryl, t-Bu, iPr, Ad} \ldots \]

\[ \ldots \ldots \]

Examples

- Ar
- Cl
- F
- O
- CN

- P(tBu)_3
- PCy_3, P(t-Bu)_2Me
- Ni
- Pd

- C-N
- C-O
- C-S

- Fe
- CyPF-tBu
The evolution of cross coupling reactions

- The organometallic reagents
- The organic electrophiles
- The catalysts
- Use of new technologies
New technologies

• Non-conventional solvents:
  Water, ionic liquids, supercritical carbon dioxide and fluorous carbons, solvent free …

• Solid-Phase-Supported Cross-Coupling Reactions.

• Microwave-Assisted Cross-Coupling Reactions.

• … …

Kabalka, G. W.; Pagni, R. M.; Hair, C. M. Org. Lett. 1999, 1, 1423

And the reference
Contents

• Introduction

• The evolution of cross-coupling reactions

• The contributions from China

• Outlook and Summary
The contributions from China

Start late. Increased rapidly.
Contents

- Introduction
- The evolution of cross-coupling reactions
- The contributions from China
- Summary and Outlook
Summary and Outlook

\[
R - A + R' - B \xrightarrow{\text{catalyst } [M]} R - R'
\]

**Ullmann reaction**
A = X, B = X, or
R = H, R' = R''N, O, S

**Cross coupling reactions**
A = X, B = Mg, B, Si, Sn ...
X = Br, I
R' = C -, N -, O -, S -
X = Cl, F, CN, O, N
R = allkyl

**Decarboxylative cross Coupling**
A = COOH

**Direct arylation**
A or B or both = H

**Conditions**
- Harsh Conditions
- Conventional Conditions
- New Technologies

- Broader! Greener! More efficient!
My special discovery!

The general catalytic cycle

Learn from the catalyst!

The way to success

Preivation

R → R' Reductive Elimination

R → X Oxidative Addition

Transmetalation

X → R Find a target

Try different ways

R' → R Success

M = Fe, Co, Ni, Cu, Pd, Ru, Rh ...

m = Li, Mg, B, Si, Sn, Zn, Zr, Al ...

M = You, I, We ...

m = Every road leads to Rome.

[R] [R']

R → X

M

m → X

m → R'

[R] [R']

X → R

M

X → m

m → R'

[M] = Fe, Co, Ni, Cu, Pd, Ru, Rh ...

m = Li, Mg, B, Si, Sn, Zn, Zr, Al ...

[M] = You, I, We ...

m = Every road leads to Rome.

Learn from the catalyst!
Acknowledgement

• Prof. Shi

• All professors and students in Institute of the Organic Chemistry.

• All members in our lab.

• My family and my friends.
1.1.1 Cross Coupling reactions principles

```
\begin{align*}
\text{L-Pd-L} & \xrightarrow{-2 \text{ L}} \text{L-Pd-L} \quad \text{18 e} & \quad \text{L-Pd-} \quad \text{14 e} & \quad \text{L-Pd-} \quad \text{12 e} & \quad \text{Pd}_n\text{L}_m \quad \text{Pd black} \\
\text{Ar-X} & \quad \text{very slow} & \quad \text{slow} & \quad \text{FAST} & \quad \text{FAST} & \quad \text{very slow}
\end{align*}
```

Oxidative Addition to LnPd(X)Ar

- low coordination at palladium is favored by bulky ligands
- low coordination at palladium is favored by high reaction temperature
• Optimum Ligand Search

\[
\text{t-Bu}_3\text{P} - \text{Pd} - \text{Pt-Bu}_3 \quad \rightarrow \quad \text{t-Bu}_3\text{P} - \text{Pd} - \square
\]

14 e

catalytically highly active species

carbene ligands

ca. 50 kcal/mol

leads to more robust catalyst

cyclopalladate ligands

\[
\text{D} = \text{N, P, O}
\]

12 e

ca. 36 kcal/mol

chelate effect
Electronic Effects

Steric Effects

The ligand cone angle $\theta$

Bond dissociation energies:

I: 65 kcalmol$^{-1}$
Br: 81 kcalmol$^{-1}$
Cl: 96 kcalmol$^{-1}$
F: 126 kcalmol$^{-1}$

I: 51 kcalmol$^{-1}$
Br: 66 kcalmol$^{-1}$
Cl: 82 kcalmol$^{-1}$
F: 122 kcalmol$^{-1}$

I: 57 kcalmol$^{-1}$
Br: 70 kcalmol$^{-1}$
Cl: 84 kcalmol$^{-1}$
F: 110 kcalmol$^{-1}$
The reaction shown in the image is a palladium-catalyzed coupling reaction. The general scheme is:

\[
\text{MeO-Cl} + \text{RSH} + \text{NaOtfBu} \xrightarrow{\text{Pd (OAc)}_2 / L (0.1 \text{ mol } \%)} \text{MeO-S-R} \xrightarrow{\text{DME / 110 } ^\circ \text{C}}
\]

The diagram includes a conversion chart with data points for each ligand (1-12) showing the percentage of coupling with 1-octanethiol and thiophenol. The ligands are labeled with their respective structures and names:

1. CyPF-fBu
2. CyPFCy (R = Cy)
3. CyPFPh (R = Ph)
4. PPFCy (R = Cy)
5. PPF-fBu (R = fBu)
6. PPFCy (R = Cy)
7. BINAP (R = Ph)
8. tol-BINAP (R = 4-Me-C_6H_4)
9. DPEphos
10. Xantphos
11. DPPF (R = Ph)
12. DIPPF (R = iPr)