Stille-coupling

Comprehensive catalytic cycle and mechanistic factors

2014. 10. 11. M2 Hanada
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1. Introduction

Stille coupling (Migita-Kosugi-Stille coupling)

\[
\begin{align*}
R - X & \quad + \quad \text{R'} - \text{SnR''}_3 & \quad \xrightarrow{\text{PdLn}} & \quad \text{R} - \text{R'} & \quad + \quad \text{X} - \text{SnR''}_3 \\
(X = \text{halide, OTf})
\end{align*}
\]


Feature
- Organostannane
- Mild condition → Broad substrate scope, synthetic application

John Kenneth Stille (1930-1989)
He received B.A and M.A. degrees from the University of Arizona and received his Ph.D. from the University of Illinois, where he studied under Carl Marvel.
Stille began his independent career at the University of Iowa in 1957 before moving to Colorado State University in 1977.
Organostannane Feature

- **C — Sn**
  - (electronegativity) 2.55 1.96

- Air and moisture stable, tolerant of many functional groups.
  - Due to low polarity of the C-Sn bond
- Synthesized under mild condition
  - Highly toxic (and stannane byproduct is often inseparable.)

<table>
<thead>
<tr>
<th>High polarity bond</th>
<th>Similar polarity bond</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{C—Mg} )</td>
<td>( \text{C—Si} )</td>
</tr>
<tr>
<td>2.55 1.31</td>
<td>2.55 1.90</td>
</tr>
<tr>
<td>Grignard reagent</td>
<td>Hiyama coupling</td>
</tr>
<tr>
<td>Kumada coupling</td>
<td></td>
</tr>
</tbody>
</table>

| \( \text{C—Zn} \)  | \( \text{C—B} \) |
| 2.55 1.65          | 2.55 2.04          |
| Negishi coupling   | Suzuki coupling     |

Synthetic applications
Mild reaction condition and functional group tolerance
→ Applicable to the late stage of total synthesis

The last step of Ganbierol

Intermediate of Dynemicin A


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Original mechanistic proposal

1986 Stille

1 and 4 are only detectable Pd compound. ($^{31}$P NMR)

It is suggested that transmetalation is the rate-determining.
Stereochemistry of transmetalation

2-1. original mechanistic proposal

Retention? Inversion?

\[ \text{SnBu}_3 \text{H} \rightarrow \text{D} \quad \text{Cl} \quad \text{PhCH}_2 \text{Pd(PPh}_3)_2\text{Cl} \quad (4\text{mol}\%) \quad \rightarrow \quad \text{D} \text{H} \]  

HMPA, 65 °C  
> 65% inversion  


\[ \text{SnBu}_3 \text{HOBz} \rightarrow \text{OBz} \quad \text{Cl} \quad \text{Ph(PPh}_3)_2\text{Cl}_2, \text{CuCN} \quad \rightarrow \quad \text{OBz} \]  
toluene, 75 °C, 74%  
98% retention  

Additive effect?

LiCl effect is different depending on ligand.

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Prof. Pablo Espinet is founder (in 2007) and director of the Institute CINQUIMA (Center of Innovation in Chemistry and Advanced Materials). Research topics: molecular dynamics in solution, mechanism of the Stille reaction, other metal-catalyzed reactions (Negishi, Sonogashira), molecular materials.

Kinetics study of transmetalation by \(^{19}\)F NMR monitoring

\[
\begin{align*}
\text{Cl}_2\text{Cl} & \quad + \quad \text{R}^2\text{SnBu}_3 \\
\begin{array}{c}
\text{R}^2 = \text{vinyl (2a)} \\
\text{R}^2 = 4\text{-anisyl (2b)}
\end{array} & \quad \xrightarrow{3a, \text{cat}} \\
\text{Cl}_2\text{Cl} & \quad + \quad \text{R}^2 + \text{I}\text{SnBu}_3
\end{align*}
\]

Solvent = THF, temperature = 322.6 K

\[
\ln([1]_0 - [1]_1) = k_{\text{obs}} t
\]

The concentration of 1 is stoichiometrically linked to that of 2.

\[
k_{\text{obs}}^{-1} \text{ vs } [\text{AsPh}_3] \text{ and } k_{\text{obs}} \text{ vs } [3a] : \text{good linear dependence each}
\]

\[
\begin{align*}
r_{\text{obs}} &= k_{\text{obs}} \ [2a] = \\
&= \frac{a \ [3a]}{[\text{AsPh}_3] + b} \ [2a]
\end{align*}
\]

\[
a = (2.32 \pm 0.09) \times 10^{-5} \text{ s}^{-1} \quad b = (6.9 \pm 0.3) \times 10^{-4} \text{ mol L}^{-1}
\]
Dissociative pathway theory

Dissociative pathway:
Ligand dissociation occurs previous to transmetalation.

Experimental consistence
- Excess ligand retards the reaction.
- Modest donicity (AsPh₃) ligand is effective. (than PPh₃)
- The first-order dependence on stannane
  (Slow transmetalation from C)

3-2. Kinetic transmetalation analysis

Experimental inconsistency of the dissociative pathway

If: Late dissociation (rate-determining)

\[ r_{\text{obs}} = k_{\text{obs}} [2a] = \frac{k_2' K_{\text{dis}} [3a]_{\text{total}}}{K_{\text{dis}} + [\text{AsPh}_3] [2a]} \]

\[ \approx k_1' [3a] \quad ([\text{AsPh}_3] \approx 0) \]

If: Fast dissociation

\[ r_{\text{obs}} = k_{\text{obs}} [2a] = \frac{k_2' K_{\text{dis}} [3a]_{\text{total}}}{K_{\text{dis}} + [\text{AsPh}_3]} \]

\[ k_2' = 1.8 \times 10^{-1} \text{ s}^{-1} \quad K_{\text{dis}} = 1.3 \times 10^{-4} \text{ mol L}^{-1} \]

\[ K_{\text{dis}} = k_1'/k_{1.'} \]

\[ k_1' = 1.8 \times 10^{-1} \text{ s}^{-1} \quad k_{1.'} = 1.3 \times 10^{-4} \text{ mol L}^{-1} \]

Experimental result

Inconsistent

→ zeroth order with respect to [2a]

→ 12% of 3a should be dissociated as C, but it was not detected.

3-2. Kinetic transmetalation analysis

**Associative (cyclic) transmetalation**

Cyclic pathway equation

\[
\frac{d[IV]}{dt} = k_1[2a][3a] - k_{-1}[IV][AsPh_3] - k_2[IV] = 0
\]

\[
[IV] = \frac{k_1[2a][3a]}{k_{-1}[AsPh_3] + k_2}
\]

\[
\frac{r_{obs}}{k_1} = k_2[IV]
\]

\[
r_{obs} = k_{obs}[2a] = \frac{k_1k_2[3a]}{k_{-1}[AsPh_3] + k_2}[2a]
\]

\[
k_1 = 0.034 \text{ mol}\text{-}1 \text{ L s}^{-1}
\]

\[
k_2/k_{-1} = 6.9 \times 10^{-4} \text{ mol L}^{-1}
\]

Experimental result

\[
r_{obs} = k_{obs}[2a] = \frac{a[3a]}{[AsPh_3] + b}[2a]
\]

\[
a = (2.32 \pm 0.09) \times 10^{-5} \text{ s}^{-1} \quad b = (6.9 \pm 0.3) \times 10^{-4} \text{ mol L}^{-1}
\]

(trans-[PdR_1R_2L] was not observed, so cis addition was proposed.)

Triflate: (1) Solvent coordinating

Neutral intermediate: Previously proposed solvent coordinating intermediate

\[
\begin{align*}
R \dot{\text{Pd}} - X & \quad \text{(S)} \quad \text{(S)} \\
\text{L} & \quad \text{L} & \quad \text{L} & \quad \text{L} \\
\end{align*}
\]


Cationic intermediates were characterized by Espinet et al.

\[
\begin{align*}
\text{CDCl}_3, \text{CH}_2\text{Cl}_2, \text{PhCl} : \text{non-coordinating}
\end{align*}
\]

\[
\begin{align*}
\text{THF: coordinating}
\end{align*}
\]

In polar coordinating solvents, solvent coordinating complex is stable even though X is halide.
(NMP (less coordinative than HMPA) is able to displace triflate and PPh$_3$ trans to R, but cannot displace halides trans to R or PPh$_3$ cis to R)
$S_E^2$ open pathway: reasonable mechanism for inversion

First stille proposed intermediate

Espinet et al. proposed intermediate

- Associative pathway
- HMPA coordinated intermediate
- The bridging ability of HMPA is poor.

Cyclic:
$X = \text{Halide}$
Stereochemistry: retention
Solvent: non-coordinating

Open:
$X = \text{Halide, or } -\text{OTf}$
Stereochemistry: inversion
Solvent: coordinating
(non-coordinating(-OTf))
Triflate : (2) Role of LiCl

LiCl effect is different depending on ligand.

Oxidative addition speed

AsPh₃ is less coordinating ligand than PPh₃. Thus, it is supposed effective.

PPh₃:
Oxidative addition is fast.

AsPh₃:
Oxidative addition is slow.
Difference between ligands

### Table 2. Organopalladium(II) Species Formed upon the Oxidative Addition of $C_6F_5$–OTf (1) to $[PdL_4]^a$

<table>
<thead>
<tr>
<th>entry</th>
<th>L</th>
<th>solvent</th>
<th>additive $^b$</th>
<th>complex(es) $^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PPh$_3$</td>
<td>PhCl</td>
<td>none</td>
<td>trans-[$PdR$(OTf)L$_2$] $^+$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>[PdRL$_3$] $^+$</td>
</tr>
<tr>
<td>2</td>
<td>PPh$_3$</td>
<td>PhCl</td>
<td>LiCl</td>
<td>trans-[$PdR$(OTf)L$_2$] $^+$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>[PdRL$_3$] $^+$</td>
</tr>
<tr>
<td>3</td>
<td>PPh$_3$</td>
<td>THF</td>
<td>none</td>
<td>trans-[$PdRCI$L$_2$] $^+$</td>
</tr>
<tr>
<td>4</td>
<td>PPh$_3$</td>
<td>THF</td>
<td>LiCl</td>
<td>trans-[$PdRCI$L$_2$] $^+$</td>
</tr>
<tr>
<td>5</td>
<td>AsPh$_3$</td>
<td>PhCl</td>
<td>none</td>
<td>none $^+$</td>
</tr>
<tr>
<td>6</td>
<td>AsPh$_3$</td>
<td>PhCl</td>
<td>LiCl</td>
<td>none $^+$</td>
</tr>
<tr>
<td>7</td>
<td>AsPh$_3$</td>
<td>THF</td>
<td>LiCl</td>
<td>none $^+$</td>
</tr>
<tr>
<td>8</td>
<td>AsPh$_3$</td>
<td>THF</td>
<td>LiCl</td>
<td>trans-[$PdRCI$L$_2$] $^+$</td>
</tr>
</tbody>
</table>

$^a$ After 30 min at 20 °C; [I] = 0.2 mol L$^{-1}$, [PdL$_4$] = 0.01 mol L$^{-1}$.  
$^b$ [LiCl] = 0.2 mol L$^{-1}$.  
$^c$ R = $C_6F_5$.

**PPh$_3$:** Oxidative addition is **fast**.

**AsPh$_3$:** Oxidative addition is **slow**.

### Table 1. Coupling Reactions between $C_6F_5$–OTf (1) and Sn(CH=CH)$_2$Bu$_3$ (2) Catalyzed by $[PdL_4]$: Conversion to $C_6F_5$–CH=CH$_2$ (3a)$^a$

<table>
<thead>
<tr>
<th>entry</th>
<th>L</th>
<th>solvent</th>
<th>additive $^b$</th>
<th>conversion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>10 h</td>
</tr>
<tr>
<td>1</td>
<td>PPh$_3$</td>
<td>PhCl</td>
<td>none</td>
<td>86</td>
</tr>
<tr>
<td>2</td>
<td>PPh$_3$</td>
<td>PhCl</td>
<td>LiCl</td>
<td>92</td>
</tr>
<tr>
<td>3</td>
<td>PPh$_3$</td>
<td>THF</td>
<td>none</td>
<td>65</td>
</tr>
<tr>
<td>4</td>
<td>PPh$_3$</td>
<td>THF</td>
<td>LiCl</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>AsPh$_3$</td>
<td>PhCl</td>
<td>none</td>
<td>6</td>
</tr>
<tr>
<td>6</td>
<td>AsPh$_3$</td>
<td>PhCl</td>
<td>LiCl</td>
<td>5</td>
</tr>
<tr>
<td>7</td>
<td>AsPh$_3$</td>
<td>THF</td>
<td>none</td>
<td>13</td>
</tr>
<tr>
<td>8</td>
<td>AsPh$_3$</td>
<td>THF</td>
<td>LiCl</td>
<td>79</td>
</tr>
</tbody>
</table>

$^a$ At 50 °C; [I] = [2] = 0.2 mol L$^{-1}$, [PdL$_4$] = 0.01 mol L$^{-1}$.  
$^b$ [LiCl] = 0.2 mol L$^{-1}$.  

**PPh$_3$ in THF:** LiCl **retards** the reaction.  
**AsPh$_3$ in THF:** LiCl **accelerates** the reaction.

Mechanistic explanation

$L = \text{PPh}_3$ (rds is transmetalation.)

$\text{fast}$

$\text{Pf} - \text{OTf} \quad \xrightarrow{[\text{PdL}_4]} \quad \text{Pf-Pd} - \text{OTf} + 2 \text{L} \quad 1$

Fast transmetalation

$\text{PF-Pd} - \text{THF (TfO)} \quad \xleftrightarrow{} \quad \text{PF-Pd} - \text{L (TfO)}$

$\text{7a.OTf} \quad \xrightarrow{- \text{LiOTf}} \quad \text{LiCl} \quad \text{5a.OTf}

Slow transmetalation = Retarded

$L = \text{AsPh}_3$ (rds is oxidative addition.)

$\text{slow}$

$\text{PF} - \text{OTf} \quad \xrightarrow{[\text{PdL}_4]} \quad \text{Pf-Pd} - \text{OTf} + 2 \text{L} \quad 4a$

accelerate

$\text{PF-Pd} - \text{THF (TfO)} \quad \xleftrightarrow{} \quad \text{PF-Pd} - \text{L (TfO)}$

$\text{7a.OTf} \quad \xrightarrow{- \text{LiOTf}} \quad \text{LiCl} \quad \text{5a.OTf}$

LiCl is effective in only slow oxidative addition reaction.
(In some reactions, other effect is also suggested.)

Additive study: copper effect

Copper effect: $\text{Cu(I)}$ salt accelerate the reaction

\[
\begin{align*}
\text{I} & \xrightarrow{\text{Pd}2\text{dba}, \text{dioxane}} \text{SnBu}_3 \\
& \xrightarrow{\text{CuI}, 50 \, ^\circ\text{C}, \text{ligand}} \\
\end{align*}
\]

In the absence of CuI

\[
\begin{array}{cccccccc}
0 & 50 & 100 & 150 & 200 & 250 & 300 & 350 & 400 \\
\text{time (min)} & & & & & & & & \\
\end{array}
\]

Figure 1. Kinetics of the coupling between iodobenzene ($C_0 = 0.139 \, \text{M}$) and vinyltributyltin ($C_0 = 0.139 \, \text{M}$), catalyzed by Pd$_2$dba$_3$ (5% mol Pd) and triphenylphosphate (20% ligand) in dioxane at 50 $^\circ\text{C}$. $k_{\text{obs}}$: $2.66 \times 10^{-6} \, \text{min}^{-1}$ ($r^2 = 0.994$).

Scheme 1

\[
\begin{align*}
\text{Pd} & \xrightarrow{k_1} \text{Pd} + [\text{S}] \\
& \xrightarrow{k_{-1}} \text{Pd} + \text{L} \\
& \xrightarrow{k_2} \text{SnBu}_3 \\
\end{align*}
\]

$K = k_1/k_{-1}$

$S = \text{Solvent}$

$k_{\text{obs}} = k_1 [\text{Pd}] [\text{stannane}] / [\text{L}] + K$

basicity, i.e., (pentafluorophenyl)diphenylphosphine (comparable in denticity to the more popular triflylphosphine, TFP), and finally a “soft” highly dissociating ligand such as AsPh$_3$. Different ratios of Pd to ligand and Cu to Pd were explored. Concentrations of 1 and 2 were estimated

In the presence of CuI

Figure 2. Kinetics of the coupling between iodobenzene ($C_0 = 0.139 \, \text{M}$) and vinyltributyltin ($C_0 = 0.139 \, \text{M}$), catalyzed by Pd$_2$dba$_3$ (5% mol Pd) and triphenylphosphate (20% ligand) in the presence of 15% CuI in dioxane at 50 $^\circ\text{C}$. $k_{\text{obs}}$: $3.90 \times 10^{-3} \, \text{min}^{-1}$ ($r^2 = 1.00$).

Table 1. Effect of Added CuI on the Rate of the Palladium-Catalyzed Coupling between Iodobenzene and Vinyltributyltin in Dioxane at 50 $^\circ\text{C}$ (Eq 1)$^a$

<table>
<thead>
<tr>
<th>entry</th>
<th>ligand</th>
<th>Pd:L:CuI molar ratio</th>
<th>$10^6 k_{\text{obs}}$ (min$^{-1}$)</th>
<th>HPLC yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PPh$_3$</td>
<td>1:4:0</td>
<td>2.66 [0.35]</td>
<td>85</td>
</tr>
<tr>
<td>2</td>
<td>PPh$_3$</td>
<td>1:4:1</td>
<td>13.5 [1.1]</td>
<td>91</td>
</tr>
<tr>
<td>3</td>
<td>PPh$_3$</td>
<td>1:4:2</td>
<td>303 [31]</td>
<td>&gt;95</td>
</tr>
<tr>
<td>4</td>
<td>PPh$_3$</td>
<td>1:4:3</td>
<td>590 [37]</td>
<td>78</td>
</tr>
<tr>
<td>5</td>
<td>PPh$_3$</td>
<td>1:4:4</td>
<td>523 [49]</td>
<td>45</td>
</tr>
<tr>
<td>6</td>
<td>PPh$_3$</td>
<td>1:4:2 ($\text{CuBr}_2$)</td>
<td>260 [12]</td>
<td>90</td>
</tr>
<tr>
<td>7</td>
<td>PPh$_3$</td>
<td>1:2:0</td>
<td>170 [61]</td>
<td>91</td>
</tr>
<tr>
<td>8</td>
<td>PPh$_3$</td>
<td>1:2:2</td>
<td>547 [44]</td>
<td>56</td>
</tr>
<tr>
<td>9</td>
<td>PPh$_3$</td>
<td>1:4:2 + LiI (200%)</td>
<td>64.5 [9.8]</td>
<td>71</td>
</tr>
<tr>
<td>10</td>
<td>PPh$_3$</td>
<td>1:4:0 + LiI (200%)</td>
<td>1.70 [0.18]</td>
<td>nd</td>
</tr>
<tr>
<td>11</td>
<td>PPh$_3$</td>
<td>1:6:0</td>
<td>1.19 [0.08]</td>
<td>nd</td>
</tr>
<tr>
<td>12</td>
<td>PPh$_3$</td>
<td>1:6:2</td>
<td>5.89 [1.1]</td>
<td>nd</td>
</tr>
<tr>
<td>13</td>
<td>PPh$_3$</td>
<td>1:6:4</td>
<td>271 [77]</td>
<td>74</td>
</tr>
<tr>
<td>14</td>
<td>F$_6$C$_6$-PPh$_2$</td>
<td>1:4:0</td>
<td>185 [11]</td>
<td>&gt;95</td>
</tr>
<tr>
<td>15</td>
<td>F$_6$C$_6$-PPh$_2$</td>
<td>1:4:1</td>
<td>367 [38]</td>
<td>&gt;95</td>
</tr>
<tr>
<td>16</td>
<td>F$_6$C$_6$-PPh$_2$</td>
<td>1:4:2</td>
<td>401 [39]</td>
<td>&gt;95</td>
</tr>
</tbody>
</table>

Kinetic study of copper effect

Characterized by $^{19}$F NMR.

**Table 2. Determination of the Copper Effect in Couplings of C$_6$Cl$_2$F$_3$I (1) with R$^2$SnBu$_3$ (2a,b) Catalyzed by trans-[Pd(C$_6$Cl$_2$F$_3$)IL$_2$] (3, 4)$^a$**

<table>
<thead>
<tr>
<th>R$^2$</th>
<th>L</th>
<th>$k^0_{\text{obs}}/10^{-5}$ s$^{-1}$</th>
<th>$k'_{\text{obs}}/10^{-5}$ s$^{-1}$</th>
<th>$k''_{\text{obs}}/10^{-5}$ s$^{-1}$</th>
<th>$(k''<em>{\text{obs}} - k'</em>{\text{obs}})/(k^0_{\text{obs}} - k'_{\text{obs}})$</th>
</tr>
</thead>
<tbody>
<tr>
<td>vinyl</td>
<td>AsPh$_3$</td>
<td>$33.7 \pm 0.4$</td>
<td>$1.12 \pm 0.03$</td>
<td>$1.60 \pm 0.03$</td>
<td>$0.015 \pm 0.001$</td>
</tr>
<tr>
<td>vinyl</td>
<td>PPh$_3$</td>
<td>$0.99 \pm 0.04$</td>
<td>$\approx 0$</td>
<td>$0.311 \pm 0.005$</td>
<td>$0.314 \pm 0.014$</td>
</tr>
<tr>
<td>aryl</td>
<td>AsPh$_3$</td>
<td>$1.94 \pm 0.02$</td>
<td>$0.118 \pm 0.02$</td>
<td>$0.122 \pm 0.02$</td>
<td>$0.002 \pm 0.016$</td>
</tr>
<tr>
<td>aryl</td>
<td>PPh$_3$</td>
<td>$0.054 \pm 0.002$</td>
<td>$\approx 0$</td>
<td>$0.016 \pm 0.002$</td>
<td>$0.30 \pm 0.04$</td>
</tr>
</tbody>
</table>

$^a$ [I]$_0$ = [2]$_0$ = (2.000 ± 0.017) × 10$^{-1}$ mol L$^{-1}$, [3] or [4] = (1.00 ± 0.03) × 10$^{-2}$ mol L$^{-1}$, THF, 322.6 K. See definition of $k^0_{\text{obs}}$, $k'_{\text{obs}}$, and $k''_{\text{obs}}$ in the text.

$k^0_{\text{obs}} \rightarrow$ Pd only  
$k'_{\text{obs}} \rightarrow$ Pd : L : Cu = 1 : 2 : 0

$k''_{\text{obs}} \rightarrow$ Pd : L : Cu = 1 : 2 : 2

$(k''_{\text{obs}} - k'_{\text{obs}})/(k^0_{\text{obs}} - k'_{\text{obs}}) \rightarrow$ the fraction of autoretardation compensated by Cul

Evaluation of the copper effect

<table>
<thead>
<tr>
<th>R²</th>
<th>L</th>
<th>(k^0_{\text{obs}}/10^{-5} \text{s}^{-1})</th>
<th>(k'_{\text{obs}}/10^{-5} \text{s}^{-1})</th>
<th>(k''_{\text{obs}}/10^{-5} \text{s}^{-1})</th>
<th>((k''<em>{\text{obs}} - k'</em>{\text{obs}})/(k^0_{\text{obs}} - k'_{\text{obs}}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>vinyl</td>
<td>AsPh₃</td>
<td>33.7 ± 0.4</td>
<td>1.12 ± 0.03</td>
<td>1.60 ± 0.03</td>
<td>0.015 ± 0.001</td>
</tr>
<tr>
<td>vinyl</td>
<td>PPh₃</td>
<td>0.99 ± 0.04</td>
<td>≈0</td>
<td>0.311 ± 0.005</td>
<td>0.314 ± 0.014</td>
</tr>
<tr>
<td>aryl</td>
<td>AsPh₃</td>
<td>1.94 ± 0.02</td>
<td>0.118 ± 0.02</td>
<td>0.122 ± 0.02</td>
<td>0.002 ± 0.016</td>
</tr>
<tr>
<td>aryl</td>
<td>PPh₃</td>
<td>0.054 ± 0.002</td>
<td>≈0</td>
<td>0.016 ± 0.002</td>
<td>0.30 ± 0.04</td>
</tr>
</tbody>
</table>

\(a \ [1]_0 = [2]_0 = (2.000 ± 0.017) \times 10^{-1} \text{mol L}^{-1}, [3] \text{ or } [4] = (1.00 ± 0.03) \times 10^{-2} \text{mol L}^{-1}, \text{THF, 322.6 K. See definition of } k^0_{\text{obs}}, k'_{\text{obs}}, \text{ and } k''_{\text{obs}} \text{ in the text.}

No new Pd species were observed by \(^{19}\text{F NMR.}\)

→ Cul did not react with Pd complex directly nor promote the dissociation of the ligand.

\((k''_{\text{obs}} - k'_{\text{obs}})/(k^0_{\text{obs}} - k'_{\text{obs}}) \to \text{the fraction of autoretardation compensated by Cul}

Cul compensates 30% autoretardation for PPh₃, and 1% for AsPh₃. (R² = aryl)

In the presence of Cul

\([\text{AsPh₃}]_{\text{free}} = 1.5 \times 10^{-2} \text{mol L}^{-1} \to \text{Cul captured 25% released AsPh₃.}\)

\([\text{PPh₃}]_{\text{free}} = 2.1 \times 10^{-4} \text{mol L}^{-1} \to \text{Cul captured 99% released PPh₃.}\)

Copper salt is more effective scavenger when the ligand is PPh₃.

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   2-1. Original mechanistic proposal
   2-2. Opposite two results
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   3-1. Dual pathway
   3-2. Kinetic transmatalation analysis
   3-3. Triflate (1) solvent effect
   3-4. Short summary
   3-5. Triflate (2) LiCl
   3-6. Additive study : Copper effect
4. Summary
5. Perspective
   5-1. Future direction of this field
   5-2. What to overcome
Summary

Dual pathway catalytic cycle
- Open pathway → inversion products
- Cyclic pathway → retention ones.

- Coordinative solvent gives open pathway products.

- Rate-determining step: usually transmetalation, but in some cases it is oxidative addition.
  (ex. X = OTf, L = AsPh₃)

- LiCl: effective only slow oxidative addition (ex. X = OTf, L = AsPh₃)
- CuI: scavenger of free ligand (for especially PPh₃ rather than AsPh₃)
Index

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0. The author suggests that this dual reaction pathways might be found in reactions like Suzuki-Miyaura coupling. (Due to similarity of the polarity of boron compound)

1. Furture direction of this field
   - New cocatalyst - Development of the current reaction paradigm
   - Giving to an explain to some phenomenon (selectivity etc.)
   - Changing from Palladium to another metal

2. What Stille coupling (or other reaction) should overcome next?
New cocatalyst: Gold

Table 2: Palladium-catalyzed cross-coupling of $p$-CF$_3$C$_6$H$_4$I (1) with various ArSn($n$Bu)$_3$ compounds using $L=\text{AsPh}_3$, and added LiCl in both the absence and presence of a gold cocatalyst.$^{[a]}$

<table>
<thead>
<tr>
<th>Entry</th>
<th>Au cat.</th>
<th>Product</th>
<th>$t$ [h]</th>
<th>Yield [%]</th>
<th>Other products (Yield [%])</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>yes</td>
<td>[C$_6$H$_4$CF$_3$]</td>
<td>5</td>
<td>83</td>
<td>2(7), 3(10)</td>
</tr>
<tr>
<td>2</td>
<td>–</td>
<td>[C$_6$H$_4$CF$_3$]</td>
<td>5</td>
<td>68</td>
<td>1(22), 2(5), 3(5)</td>
</tr>
<tr>
<td>3</td>
<td>yes</td>
<td>[C$_6$H$_4$CF$_3$]</td>
<td>6</td>
<td>89</td>
<td>2(8), 3(3)</td>
</tr>
<tr>
<td>4</td>
<td>–</td>
<td>[C$_6$H$_4$CF$_3$]</td>
<td>6</td>
<td>4</td>
<td>1(80), 2(3), 3(12)</td>
</tr>
<tr>
<td>5</td>
<td>yes</td>
<td>[C$_6$H$_4$CF$_3$]</td>
<td>24</td>
<td>84</td>
<td>1(&lt;1), 2(8), 3(6)</td>
</tr>
<tr>
<td>6</td>
<td>–</td>
<td>[C$_6$H$_4$CF$_3$]</td>
<td>24</td>
<td>&lt;1</td>
<td>1(85), 2(3), 3(10)</td>
</tr>
<tr>
<td>7</td>
<td>yes</td>
<td>[C$_6$H$_4$CF$_3$]</td>
<td>24</td>
<td>90</td>
<td>2(4), 3(6)</td>
</tr>
<tr>
<td>8</td>
<td>–</td>
<td>[C$_6$H$_4$CF$_3$]</td>
<td>24</td>
<td>0</td>
<td>1(81), 2(5), 3(11)</td>
</tr>
<tr>
<td>9</td>
<td>yes</td>
<td>[C$_6$H$_4$CF$_3$]</td>
<td>48</td>
<td>64</td>
<td>1(1), 2(19), 3(1)</td>
</tr>
<tr>
<td>10</td>
<td>–</td>
<td>[C$_6$H$_4$CF$_3$]</td>
<td>48</td>
<td>0</td>
<td>1(19), 2(38), 3(29)</td>
</tr>
<tr>
<td>11</td>
<td>yes</td>
<td>[C$_6$H$_4$CF$_3$]</td>
<td>48</td>
<td>0</td>
<td>1(22), 2(36), 4(42)</td>
</tr>
<tr>
<td>12</td>
<td>–</td>
<td>[C$_6$H$_4$CF$_3$]</td>
<td>48</td>
<td>0</td>
<td>1(90), 2(2), 4(2)</td>
</tr>
</tbody>
</table>

[a] Reaction conditions: MeCN, 80°C, $[p$-CF$_3$C$_6$H$_4$I]$=0.10$ m, $[\text{ArSn}-(n$Bu)$_3]=0.11$ m, $[\text{AsPh}_3]=4.07\times10^{-3}$ m, $[\text{LiCl}]=\text{saturated solution}$. Pd catalyst: $[\text{PdCl}_2(\text{AsPh}_3)_2]=2\times10^{-3}$ m, Au catalyst: $[\text{AuCl}(\text{AsPh}_3)_3]=2\times10^{-3}$ m. The reactions were monitored until total conversion of the starting $p$-CF$_3$C$_6$H$_4$I was observed, or for the time indicated. Yields were determined by peak integration of the $^{19}$F NMR spectra, and are average of two runs.

Gold cocatalyst improves the yield even in some reaction which doesn’t proceed at all without gold.

Giving explanation to some phenomena

- Regiocontrolled oxidative addition with CuI

\[
\begin{align*}
\text{SnBu}_3 & \quad \text{Pd(PPh}_3\text{)}_4 \\
& \quad (5 \text{ mol\%}) \\
& \quad \text{conditions} \\
& \quad L = \text{PPh}_3 \\
\end{align*}
\]

\[
\begin{array}{c|c|c}
\text{entry} & \text{conditions} & \text{ratio (5:6)}^{12} \\
\hline
1 & \text{toluene/100 °C} & 100:0 \\
2 & \text{toluene/CuI(1.0 equiv)/100 °C} & 100:0 \\
3 & \text{DMF/50 °C} & 100:0 \\
4 & \text{DMF/CuI(1.0 equiv)/50 °C} & 30:70 \\
\end{array}
\]

\[
\text{Cu transmetalation possibility}
\]

\[
\text{SnBu}_3 \quad \text{Cul} \quad \text{Bu}_3\text{SnI} \quad (+ \text{SM} + \text{Bu}_3\text{SnOH})
\]

※Only in polar solvents

33


Changing from Pd to another metal

- CuTC

\[ \text{R} - \text{I} + \text{R'} - \text{SnBu}_3 \xrightarrow{1.5 \text{ equiv CuTC}} \text{NMP} \xrightarrow{\text{R"RCuX}} \text{R} - \text{R'} \]

\[ \text{CuTC} = \text{Cu-O} \]


Wang, M; Lin, Z.; Organometallics 2010, 29, 3077.

Total Synthesis of Formamicinone

What Stille coupling (or other reaction) should overcome? (just my view)

✗Sn toxicity – high toxicity, stoichiometric amount

Possible answer
1. Reducing Sn → catalytic amount of tin?

2. Some other metals replace tin?
   (cf: C-H sililation, C-H borylation)

Or others?

Thank you for your kind attention.
Table 1
Vinyltri
tin (Pd:L)

<table>
<thead>
<tr>
<th>entry</th>
<th>ligand</th>
<th>rel rate (b)</th>
<th>θ (c)</th>
<th>ν (d)</th>
<th>yield (e)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PPh₃</td>
<td>1.0 (0.38)</td>
<td>145</td>
<td>2068.9</td>
<td>15.2</td>
</tr>
<tr>
<td>2</td>
<td>MePPh₂</td>
<td>&lt;0.07</td>
<td>136</td>
<td>2067.0</td>
<td>&lt;2</td>
</tr>
<tr>
<td>3</td>
<td>P(CH₂CH₂CN)₃</td>
<td>&lt;0.07</td>
<td>132</td>
<td>2078.0</td>
<td>&lt;2</td>
</tr>
<tr>
<td>4</td>
<td>(4-MeOC₆H₄)₃P</td>
<td>&lt;0.07</td>
<td>145</td>
<td>2066.1</td>
<td>&lt;2</td>
</tr>
<tr>
<td>5</td>
<td>[2,4,6-(MeO)₃C₆H₆]₃P</td>
<td>&lt;0.07</td>
<td>184</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>(4-FC₆H₄)₃P</td>
<td>0.60 (0.08)</td>
<td>145</td>
<td>2071.3</td>
<td>10.7</td>
</tr>
<tr>
<td>7</td>
<td>(4-ClC₆H₄)₃P</td>
<td>0.71 (0.10)</td>
<td>145</td>
<td>2072.8</td>
<td>nd</td>
</tr>
<tr>
<td>8</td>
<td>(2-MeC₆H₄)₃P</td>
<td>35.2 (2.4)</td>
<td>194</td>
<td>2066.6</td>
<td>19</td>
</tr>
<tr>
<td>9</td>
<td>(2-furyl)₃P</td>
<td>105 (2.4)</td>
<td>145</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>(2-tienyl)₃P</td>
<td>4.8 (0.5)</td>
<td></td>
<td></td>
<td>68.6</td>
</tr>
<tr>
<td>11</td>
<td>Ph₂PC₆F₅</td>
<td>24.3 (0.7)</td>
<td>158</td>
<td>2074.8</td>
<td>&gt;95</td>
</tr>
<tr>
<td>12</td>
<td>PhP(C₆H₅)₂</td>
<td>950 (4.1)</td>
<td>184</td>
<td>2078.5</td>
<td>58.3f</td>
</tr>
<tr>
<td>13</td>
<td>P(C₆F₅)₃</td>
<td>g</td>
<td>184</td>
<td>2090.9</td>
<td>13.2</td>
</tr>
<tr>
<td>14</td>
<td>P(OPh)₃</td>
<td>95.2 (9.1)</td>
<td>130</td>
<td>2083.5</td>
<td>88f</td>
</tr>
<tr>
<td>15</td>
<td>P(OiPr)₃</td>
<td>42.8 (5.3)</td>
<td>131</td>
<td>2075.9</td>
<td>25f</td>
</tr>
<tr>
<td>16</td>
<td>AsPh₃</td>
<td>1100 (95)</td>
<td>142</td>
<td></td>
<td>&gt;95</td>
</tr>
<tr>
<td>17</td>
<td>SbPh₃</td>
<td>13.2 (1.5)</td>
<td>142</td>
<td></td>
<td>56.4</td>
</tr>
</tbody>
</table>

* 0.16 M PhI and stannane, 3.2 mM Pd, 12.8 mM ligand.  
  For PPh₃ first-order rate constant was 4.6 \times 10^{-5} \text{ min}^{-1}; each rate is the average of two or three determinations.  
  The figure in parentheses is the standard deviation.  
  Cone angle; see ref 17.  
  IR frequency of Ni(CO)₃L complex; see ref 17.  
  HPLC yield after 72 h.  
  Catalyst decomposed.  
  Catalyst apparently still active in all other cases.  
  Indicated conversion and catalyst decomposition were instantaneous (<2 min).
Figure 1. $^{19}$F NMR (282 MHz, $F^3$ region) spectra sequence (intervals in hours) of the coupling of C$_6$Cl$_2$F$_3$I (1, 0.2 mol L$^{-1}$) with (CH$_2$=CH)SnBu$_3$ (2a, 0.2 mol L$^{-1}$) catalyzed by trans-[Pd(C$_6$Cl$_2$F$_3$I)(AsPh$_3$)$_2$] (3a, 0.01 mol L$^{-1}$) and AsPh$_3$ (0.02 mol L$^{-1}$), in THF at 322.6 K. The product is C$_6$Cl$_2$F$_3$(CH=CHI) (4a).

Figure 2. Retarding effect of the addition of AsPh$_3$ on the coupling of C$_6$Cl$_2$F$_3$I (1, 0.2 mol L$^{-1}$) and (CH$_2$=CH)SnBu$_3$ (2a, 0.2 mol L$^{-1}$) catalyzed by trans-[Pd(C$_6$Cl$_2$F$_3$I)(AsPh$_3$)$_2$] (3a, 0.01 mol L$^{-1}$) in THF at 322.6 K.

Figure 3. 

\[
\text{Cl} \quad \text{F} \quad \text{L} \quad \text{Pd} \quad \text{X} \quad \text{S} \\
\begin{array}{cc}
\text{Cl} & \text{F} \\
\text{L} & \text{Pd} \\
\text{Cl} & \text{F} \\
\end{array}
\]

L$^{-1}$ and (Cl
Cl$_2$F$_3$I)(AsPh
L$^{-1}$); (b) wi

$F_{ortho} \delta = -86.9$, t

L = PPh$_3$
S = HMPA

\[
\text{Cl} \quad \text{F} \quad \text{L} \quad \text{Pd} \quad \text{S} \quad \text{X} \\
\begin{array}{cc}
\text{Cl} & \text{F} \\
\text{L} & \text{Pd} \\
\text{Cl} & \text{F} \\
\end{array}
\]

$F_{ortho} \delta = -85.8$, d

L$^{-1}$ and (Cl
Cl$_2$F$_3$I)(AsPh
L$^{-1}$); (b) wi

$F_{ortho} \delta = -88.1$, d