The Mechanism of the Stille Reaction


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Authors

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Prof. Antonio M. Echavarren, Institute of Chemical Research of Catalonia (ICIQ) Investigates, Spain, has been a NATO fellow at Colorado State University with Prof. J. K. Stille, new synthetic methods and the organometallic chemistry of late transition metals.
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Palladium Catalyzed Cross-coupling Reactions

Suzuki Reaction
Sonogashira Reaction
Hiyama Reaction
Kumada Reaction
Negishi Reaction
Heck Reaction

Stille Reaction

High selectivity
Broad Scope
High tolerance

Complex organic synthesis

I. Introduction
1976, C. Eaborn

\[ \text{Bu}_3\text{SnSnBu}_3 + \text{ArBr} \xrightarrow{\text{Pd(PPPh}_3\text{)}_4} \text{ArSnBu}_3 + \text{ArBr} + \text{Bu}_3\text{SnBr} \]

1977, M. Kosugi

\[ \text{RCOCI} + \text{CH}_2=\text{CHCH}_2\text{SnBu}_3 \xrightarrow{\text{RhCl(PPPh}_3\text{)}_3} \text{RCOCH}_2\text{CH}=\text{CH}_2 + \text{Bu}_3\text{SnCl} \]

\[ \text{RCOCI} + \text{R'}\text{SnBu}_3 \xrightarrow{\text{Pd(PPPh}_3\text{)}_4} \text{COR}^\prime + \text{Bu}_3\text{SnCl} \]

\[ \text{ArX} + \text{CH}_2=\text{CHCH}_2\text{SnBu}_3 \xrightarrow{\text{Pd(PPPh}_3\text{)}_4} \text{ArCH}_2\text{CH}=\text{CH}_2 + \text{Bu}_3\text{SnX} \]

1978–, J.K. Stille

\[ \text{RCOCI} + \text{R''SnS} \xrightarrow{\text{Pd(PPPh}_3\text{)}_4, \text{HMFA}} \text{RCOR}^\prime + \text{R'}\text{SnCl} \]

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Prof. John K. Stille

M. Kosugi, etc. Chem. Lett. 1977, 301 – 302; Chem. Lett. 1977, 1423–1424;
J. K. Stille etc. J. Am. Chem. Soc. 1978, 100, 3636–3638;

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Only observable Species

Inversion & retention

effects of additives: Cu(I), alkaline salt

s_{22}

influence of organic electrophile and solvent

Only observable Species

Rate determining?
2.1. Inversion versus Retention

C(sp^3)-X + PdL₄ : SN₂ reaction


Allyl halides: solvent, ligand

maleic anhydride

Pd(PPh₃)₄: inversion

2.2. cis Complexes in the Oxidative Addition

The oxidative addition step initially gives cis-complex. Usually the isomerization of the initial cis complex to thermodynamically favored trans isomer appears to be very fast relative to the transmetalation. Thus most time, the cis intermediate need not be considered.

2.3. Regioselectivity of the Oxidative Addition

2.4. The Role of Bidentate Ligands


2.5. Oxidative Addition with $[\text{Pd}_2(\text{dba})_3]$
2.6. The Role of Anionic Ligands

The partial or total saturation of the coordination shell of a zero valent palladium catalyst by halide ions should prevent its deactivation, e.g., by oligomerization.


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2.7. Cross-Coupling Reactions in the Presence of Bulky Phosphanes

- **Activation of Aryl Chlorides**, unactivated tosylates, triflates, bromides

**Bulky, chelating ligand**

13

12a R = Cy, R’ = H
12b R = Bu, R’ = H
12c R = Cy, R’ = Pr

**Monodentate Bulky ligands**

14

P(fBu)3

15

15a R = Cy
15b R = fBu

P(1-Ad)(fBu)2
**Alkyl Electrophiles**


**2.8. Palladacycles as Catalysts**

2.9. Heterocyclic Carbenes as Ligands


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3.1. The Transmetalation: A Ligand Substitution at Pd^{II}

**Associative**

![Chemical reaction diagram]

**Disassociative**

\(R\) = solvent molecule.

Olefins, adventitious water, agostic bonds


3.2. Landmarks in the Study of the Transmetalation Mechanisms

![Chemical reaction diagram]

Course of the transmetalation of halo and triflate complexes with \(R^2SnBu_3\).

Based on the observed inverse dependence on the concentration of the ligand, Farina etc proposed the use of less coordinating ligands (AsPh\(_3\), P(furyl)\(_3\)) to facilitate the transmetalation step.

**Inversion**

\[
\text{H}^+ \text{C} - \text{SnBu}_3 \quad \text{BzO} \quad \text{PdCl(PPh}_3)_2 \quad \text{CuCN} (2 \text{ mol}%) \quad \text{tol.} \quad \text{75}^\circ \text{C}
\]


**Retention**

\[
\text{H}^+ \text{C} - \text{SnBu}_3 \quad \text{Ph} \quad \text{PdCl(PPh}_3)_2 \quad \text{HMPA,} \quad 65^\circ \text{C}
\]


**Inversion**

\[
\text{PdR}_1X(L-L) \quad \text{PdR}_1XL(S) \quad \text{PdR}_1X(LHagostic)
\]


3.3. Isolation of the Transmetalation Step


3.4. Proposals for Dissociative Mechanisms


J. F. Hartwig, etc. J. Am. Chem. Soc. 2004, 126, 5344-5345
3.5. The Cyclic Associative Transmetalation

**Noncoordinating solvents**

- Inverse order of retention


**Coordinating solvents**

- 4-coordinated

3.6. The Open Associative Transmetalation

In the presence of LiCl

oxidative addition

Pd(AsPh₃)₄

LiCl

THF

[PdCl₄(AsPh₃)₄]⁻

faster

More electron rich

ArOTf

[PdCl₄(AsPh₃)₄]⁻

Ar

Ph₃As-Pd-AsPh₃

Cl

faster

slower


The role of solvent

Conditions for \( S_n \) (open) transmetalation:

- polar, coordinating, nonbridging solvents
- nonbridging anionic ligands that are readily cleaved.

inversion

Open


retention

Cyclic


3.8. Enhancement of Stannane Nucleophilicity by Additives

**Fluoride additives**

**Hydroxide ions**

**Hydroxo ligand**

**Amine derivatives**

\[
\begin{align*}
\text{NMe}_2 & \quad \text{SnPh}_2 & \quad \text{Me} \\
\text{R} & \quad \text{Sn} \\
\end{align*}
\]


\[\begin{align*}
\text{N} & \quad \text{Sn} \\
\text{Me}_2 & \quad \text{SnR}_3 \\
\end{align*}\]

\[\text{[PdCl(HNCMe)_2]} \quad \text{PPPh}_3 \quad \text{THF, 50°C} \]

\[\begin{align*}
\text{R} = \text{Bu} & \quad 56 : 4 \\
\text{R} = \text{Me} & \quad 58 : 42 \\
\text{R} = \text{Ph} & \quad 45 : 55 \\
\end{align*}\]

\[\begin{align*}
\text{N} & \quad \text{Sn} \\
\text{Ar} & \quad \text{Pd} \\
\text{H}_2 & \quad \text{SnR}_3 \\
\end{align*}\]

\[\text{J. Yoshida, etc. J. Am. Chem. Soc. 2001, 123, 8773 – 8779.}\]

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\[\text{J. M. Brown, etc. Chem. Rev. 1988, 98, 1031 – 1046.}\]
4.1. The Effect of Bidentate Ligands

$[\text{PdRR}^\prime \text{L}]_2 \rightarrow [\text{PdRR}^\prime \text{L}]$


$n=1$, smallest bite angle

Electronic constraint

4.2. Coupling with Allylic Electrophiles: The Slow Reductive Elimination

Electron-poor olefins accelerate the reductive elimination of allylic arenes through the formation of complexes such as 82.

Catalytic allyl–aryl reductive coupling is more efficient than the stoichiometric one.

Under catalytic conditions, the allyl electrophile itself acts as the electron-withdrawing olefin.


4.3. Allyl–Benzyl Coupling

Mechanism

Y. Yamamoto, etc.

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5. Scrambling of Substituents and Homocoupling

Not affected by $\text{PPh}_3$


Inhibited by $\text{PPh}_3$


Exchange of organic groups between the Pd complex 87 and tetramethyltin.


B. M. Novak, etc. J. Am. Chem. Soc. 1997, 119, 12441-12453
6.1. Reactions via Palladium Carbenes

Sterically hindered alkenyl stannanes

\[
\begin{align*}
\text{R}^1 & \quad \text{Pd} \quad \text{L} \quad \text{X} \\
\text{Bu}_3\text{Sn} & \quad \text{SnBu}_3 \\
\text{R}^2 & \quad \text{SnBu}_3 \\
\text{R}^1 & \quad \text{Pd} \quad \text{L} \\
\text{R}^2 & \quad \text{PdL}_2
\end{align*}
\]

N. J. Taylor, etc. J. Am. Chem. Soc. 2003, 125, 12700-12701
6.2. Reactions Initiated by the Oxidative Addition of Stannanes

oxidative addition of the organotin reagent to a Pd<sup>0</sup> complex.

E. Shirakawa, T. Hiyama, etc. Organometallics 2000, 19, 5671 – 5678;

6.3. A New Catalytic Cycle Based on Pd$^{II}$/Pd$^{IV}$?

Few evidence


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7. Copper Effects

In nonpolar solvents

Fig. 2. Inhibition by added L of the coupling of C\textsubscript{6}F\textsubscript{5}Cl\textsubscript{3} with Bu\textsubscript{3}SnCH\textsubscript{2}CH\textsubscript{3} catalyzed by trans-Pd[C\textsubscript{6}F\textsubscript{5}Cl\textsubscript{3}]L\textsubscript{1\texttext{\textsubscript{2}}} 2, represented as k\textsubscript{obs}/k\textsubscript{0}.

Cul is to mitigate the "autoretardation" by free L of the rate-determining associative transmetalation. The effect is strong for PPh\textsubscript{3} and weak for AsPh\textsubscript{3} for two reasons: 1) The autoretardation is much more effective for L=PPh\textsubscript{3} (Figure 2), and 2) Cul is a more effective scavenger of PPh\textsubscript{3} than of AsPh\textsubscript{3}.

P. Espinet, etc. Organometallics 2003, 22, 1305 – 1309.

In polar solvents

Sn/Cu transmetalation,


regioselectivity

\[
\begin{array}{c}
\text{entry} & \text{Conditions} & \text{102/103} \\
1 & \text{toluene, 100°C} & 100:0 \\
2 & \text{toluene, 100°C, } \text{CuI (1 equiv)} & 100:0 \\
3 & \text{DMF, 50°C} & 100:0 \\
4 & \text{DMF, 50°C, CuI (1 equiv)} & 39:70 \\
\end{array}
\]


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Transmetalation:
- Solvent, reagents, catalyst
- Nucleophilicity:
  - Solvent, additives
  - Sterically demanding ligands
  - Organotin compounds (Stille coupling)
  - Fluoride-activated silanes (Hiyama coupling) (Suzuki coupling)
  - Other nucleophilic organometallic compounds

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- All my labmates
Thank You &
Happy New
Year !!!

\[ \text{C(sp}^2\text{-}X) \]

\[ \text{J. K. Stille, etc, Acc. Chem. Res. 1977, 10, 434 – 442.} \]
Vinyl Halides: retention

Pt, isolated

Aryl Halides

2. electron transfer
3. a three-center mechanism involving direct attack of the metal at the aryl-halogen bond
$[\text{Pd}]$ stands for either 2 or 3; $R^1: \text{C}_6\text{Cl}_2\text{F}_3$; $L: \text{PPh}_3$; $p-r$: pseudorotation.

**Transphobia:** The destabilizing interaction between Pairs of ligands in Pd$^\text{II}$ complexes.


The rearrangement is irreversible, does not involve a free phosphonium cation, and does not require phosphine dissociation.


The "T"-shaped geometry of a d₈ complex represents a minimum energy configuration, and reductive elimination as well as cis-trans isomerization of the "T"-shaped complexes proceeds through a "Y"-shaped saddle point.

Figure 2. Total energy change along the hypothetical path for reductive amination of 11a (2) and 13a (3).


Organometallics 2000, 19, 1458-1460