Metal Catalyzed Outer Sphere Alkylationsof Unactivated Olefins and Alkynes

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Literature Presentation

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Outline

I. Background
   • Introduction to Carbometallation
   • “Inner Sphere” vs. “Outer Sphere”
   • Review of Seminal Work

II. Catalytic Palladium Systems

III. Catalytic Platinum Systems

IV. Catalytic Gold Systems
I. Background:

Carbometallation is the formal addition of a metal and a carbon atom across a double bond.

- Cis addition would involve olefin insertion into an \( \sigma \)-alkyl-metal species. This is an “Inner Coordination Sphere” process.

\[
\text{cis addition} \\
\text{olefin insertion}
\]

- The alkyl-metal species could arise from:
  1. Oxidative addition of the metal to an electrophile.
  2. Transmetallation of a nucleophile to the metal.
  3. Direct nucleophilic attack on the palladium.

- Trans addition would involve an “Outer Coordination Sphere” nucleophilic attack on the metal-olefin coordination complex.
First Example: Carbopalladation of an Olefin


- Amino and Oxo-palladations (i.e. Wacker Process) were previously known and have since been much more widely studied.
- No distinction between cis and trans nucleophilic addition made.
Carbopalladation on Styrene: Different Modes of Attack


- **Outer Sphere attack** usually occurs at the more substituted carbon - more stabilization of + charge (in intermolecular processes).
- **Stoichiometric** in Pd
First Direct Evidence of Trans Addition


\[
\text{[Pd]} = [\text{Pd}(n^5-\text{C}_5\text{H}_5)(\text{PPh}_3)]^{+}\text{ClO}_4^{-}
\]

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\]

\[
\text{O} \quad \text{O} \quad \text{Na} \quad \text{[Pd]} \quad \text{THF} \quad -19 \, ^\circ \text{C}
\]

J=4.2 Hz

\[
\text{O} \quad \text{O} \quad \text{Na} \quad \text{[Pd]} \quad \text{THF} \quad -19 \, ^\circ \text{C}
\]

J=12.3 Hz
Palladium-Assisted Alkylation of Unactivated Olefins


- Wanted general procedure for Outer Sphere carbopalladations on unactivated olefins – but reduction of Pd (II) was a problem.
- Overcame problem of nucleophilic reduction of Pd (II) by using NEt₃, in a step-wise, one pot procedure.

\[ \text{H}_{-}\text{H} \]

\[ \text{PdCl}_2(\text{MeCN})_2, \text{THF, RT} \]

\[ \text{NEt}_3 (2 \text{ Eq}), \text{THF, -78 C} \]

\[ \text{CH(Na)CO}_2\text{R'}, \text{THF, -60 C} \]

\[ \text{H}_2 \text{ flush} \]

\[ -60 \text{ C} \]

\[ -60 \text{ to RT} \]

\[ \text{Cl-Pd-H} \]

\[ \text{Pd (0)} \]

1. \[ \text{PdCl}_2(\text{MeCN})_2, \text{THF, RT} \]
2. \[ \text{NEt}_3 (2 \text{ Eq}), \text{THF, -78 C} \]
3. \[ \text{CH(Na)CO}_2\text{R'}, \text{THF, -60 C} \]
Palladium-Assisted Alkylation of Unactivated Olefins (Continued)


- Worked well on a variety of terminal olefins.
  - Internal alkenes gave only traces of reaction.
- Worked with a variety of malonates.
- Without triethylamine, reductive dimerization predominates.
- Using HMPA as an additive the reaction works on a variety of un-stabilized nucleophiles: Enolates of ketones and esters.
  - Un-stabilized nucleophiles are usually ineffective because they attack the palladium first – Inner Sphere.
- First Intramolecular case:

  \[
  \text{CO}_2\text{Me} \quad \text{CO}_2\text{Me} \\
  \text{CO}_2\text{Me} \\
  \text{CO}_2\text{Me} \\
  \text{PdCl}_2(\text{MeCN}) \\
  \text{NEt}_3, \text{THF} \\
  (\text{H}_2 \text{ flush}) \\
  \text{42% Yield}
  \]

- In all cases the reaction is *stoichiometric in Palladium*. 

\[
\text{CO}_2\text{Me} \\
\text{CO}_2\text{Me} \\
\text{CO}_2\text{Me} \\
\text{CO}_2\text{Me} \\
\text{CO}_2\text{Me} \\
\text{42% Yield}
\]
Problems with Catalysis

• Since the process is a formal reduction of the metal (Pd (II) to Pd (0) – re-oxidation of the metal is necessary.

• **Problem:** Carbanions are very easily oxidized.
  – Reductive dimerization is a problem in carbopalladations:

\[
\text{Pd (II)} + 2 \text{MeO}_2\text{C} = \text{CO}_2\text{Me} \rightarrow \text{Pd (0)} + \text{MeO}_2\text{C} - \text{CO}_2\text{Me} + \text{MeO}_2\text{C} - \text{CO}_2\text{Me}
\]

  – Therefore, any oxidant strong enough to oxidize the metal will probably oxidize the carbanion – preventing any desired reaction.
Palladium-Promoted Alkylation of Olefins by Silyl Enol Ethers

- Silyl enol ethers transmetallate to Pd (II), β-H Elimination gives α,β-unsaturation:

\[
\text{OTMS} \quad \text{Pd(OAc)}_2 \quad \text{MeCN} \quad \text{observed intermediate} \quad \text{oxo-π-allylpalladium} \quad [\text{Pd}-\text{H}]
\]

- When an olefin is present, a formal insertion product is recovered:

\[
\text{R}_1 \quad \text{R}_2 \quad \text{OTMS} \quad \text{Pd(OAc)}_2 \quad \text{MeCN} \quad \text{R}_2 \quad \text{R}_1
\]

- Works on a variety of substrates.
- Since silyl enol ethers don’t get oxidized by Pd (II), they could get some weak catalysis (0.5 Molar Equiv) using a benzoquinone re-oxidant – but yields suffered.
Palladium-Promoted Alkylation of Olefins by Silyl Enol Ethers


By analogy they proposed this “Inner Sphere” mechanism:

But in a footnote they noted another possibility:
Palladium-Promoted Alkylation of Olefins by Silyl Enol Ethers

During the synthesis of (+/-)-Quadrone, the mechanism of this cyclization was explored: Kende, A. S. et al. *J. Am. Chem. Soc.* 1982. 104, 1784-1785.

Product distributions in a model system are consistent an Outer Sphere process:

- If desilylation is first step: A and B and E should give same distribution, and C should not react (because it doesn’t form an enone in D).
- Cyclization and enone formation does not proceed through same intermediate.
- Evidence supports an Outer Sphere mechanism.
Pt (II) Additions to Ethylene


- Addition is irreversible.
- Also works with inorganic nucleophiles (NO$_2^-$, N$_3^-$, NCO$^-$).
- Heating to 50 °C gives β-hydride elimination.
- Treatment of product with acids results in the facile cleavage of the Pt-C bond, regenerating Pt (II).
Summary – Up to ~2001

• “Outer Sphere” carbopalladations are stoichiometric in palladium.
• Pd/amine and Pt/amine complexes are the only known promoters.
• The products of carbopalladations (alkyl-palladium complexes) undergo $\beta$-hydride elimination above -20 ºC.
• The carbopalladation products can be quenched with H$_2$ by simply flushing the system below -20 ºC.
• Stabilized and non-stabilized carbon nucleophiles work well.
• Using silyl enol ethers as the nucleophile allows weak catalysis (50 mol%), but technical problems with the system limit its utility.
• One isolated example of a Pt (II) cationic complex adding to ethylene. No other late TM system is known.
• Hegedus: “[The process] is unlikely to find extensive use in synthesis”

II. First Example of TM (Pd) Catalysis - Hydroalkylation


Looking at carbopalladations to get cyclopentanones:

\[
\begin{align*}
\text{expected} & \quad \text{PdCl}_2(\text{MeCN})_2 \text{ (1 Eq)} \\
\text{PdCl}_2(\text{MeCN})_2 \text{ (5%)} & \quad \text{Dioxane, 25 C}
\end{align*}
\]

- Surprising results: No net oxidation and endo ring closure.

If no net oxidation, then Pd (II) would not be reduced and catalysis is possible:

\[
\begin{align*}
\text{expected} & \quad \text{PdCl}_2(\text{MeCN})_2 (1 \text{ Eq}) \\
\text{PdCl}_2(\text{MeCN})_2 (5\%) & \quad \text{Dioxane, 25 C}
\end{align*}
\]

- Mono terminal substitution on olefin is well tolerated.
- \(\alpha\)-substitution is tolerated.
Mechanistic Investigation


2 possible mechanisms: “Outer” vs. “Inner” Sphere

Results are consistent with an outer coordination sphere mechanism.
Mechanistic Investigation (Continued)


Other labeling experiments:

- Palladium migration around the ring must occur.
Plausible mechanism with palladium migration:

Mechanistic Investigation (Continued)

Extension to Non-Stabilized Enolates


Early Investigations:

\[
\begin{align*}
\text{PdCl}_2(\text{MeCN})_2 (10\%) & \quad \longrightarrow \\
\text{TMSCl} & \\
\text{CuCl}_2 (1 \text{ eq}) & \quad \text{sealed tube}
\end{align*}
\]

- TMSCl to generate silyl enol ether \textit{in situ}.
- CuCl\textsubscript{2} to stabilized oxidation state of Pd.

NMR analysis of the reaction showed no \textit{in situ} formation of enol ether – concluded that HCl promotes reaction (formed from residual moisture and TMSCl).

Optimized conditions:

\[
\begin{align*}
\text{PdCl}_2(\text{MeCN})_2 (10\%) & \quad \longrightarrow \\
\text{HCl/CuCl}_2 (1 \text{ eq}) & \quad \text{sealed tube}
\end{align*}
\]

- Worked on a variety of aryl and alkyl R groups.
- Dissubstitution to make quaternary centers also tolerated.
First Pd Catalyzed Oxidative Alkylation of Olefins


- Initial investigations with the previous system gave only hydroalkylation.
- But, extending the chain by one methylene gave the desired conversion.

\[ \text{CuCl}_2 \text{ is a stoichiometric re-oxidant.} \]

\[ \text{Reaction can be catalytic in CuCl}_2 (10\%) \text{ with O}_2 \text{ atmosphere.} \]
Proposed Mechanism:
III. Pt (II) Alkylation of Olefins with Indoles


Extension of Pd (II) system to indole carbon nucleophiles?

As we saw earlier:

- Cationic Pt (II) complexes are highly reactive toward outer sphere attack.
- Pt (II) alkyl metal complexes are highly reactive toward protonolysis.


Using a simple Pt (II) catalyst:

\[
\text{[PtCl}_2(\text{CH}_2\text{CH}_2)] \text{ (2.5%)} \rightarrow \text{87%}
\]

Dioxane
90 C, 12 h
Pt (II) Alkylation of Olefins with Indoles

Liu, C., Han, X., Wang, X., Widenhoefer, R. A.  

**Optimized system:** PtCl₂, Dioxane, 60 °C, 18-24 h.

- Works on a variety of indoles.
- Also found that asymmetric alkylation was possible (69% e.e.) with a Pt (II)-BIPHEP complex.

Is this actually an Outer Sphere process?

- Stoltz has reported a C-H activation/olefin insertion mechanism (Inner Sphere) for this related system: Ferreira, E. M. and Stoltz, B.  

Stereochemistry results from a syn addition/syn β-H elim pathway.
Pt (II) Alkylation of Olefins with Indoles

Liu, C., Han, X., Wang, X., Widenhoefer, R. A.  

Lack of D scrambling argues against a reversible β-H elimination/addition.
Pd (II) Alkylation of Olefins with Indoles


Palladium system undergoes the same alkylation but protonation does not occur – the resulting alkyl-Pd species must be quenched with CO/alcohol.

\[
\text{N} \quad \text{PdCl}_2(\text{MeCN})_2 (5\%) \quad \text{ROH, CuCl}_2, \text{CO RT} \quad \text{N}
\]

- Mechanism studies once again show an outer-sphere alkylation process followed by syn-CO insertion.
- Pt (II) system does not undergo CO insertion.

System also works on 3-alkyl indoles. 6-endo cyclization suggests similar outer sphere mechanism (direct contrast to Stoltz systems):
IV. Gold (I) Catalyzed Conia-Ene Reaction


Conia-Ene Reaction:

Au (I) catalyzed version:

- 80-95% yield on a variety of terminal alkynyl β-keto ester substrates.
- Good d.r. observed with 3 and 4 substitutions.
- Low catalyst loading, short reaction times and “open-flask” conditions.

Is the mechanism consistent with an inner or outer sphere mechanism?
Gold (I) Catalyzed Conia-Ene Reaction (Continued)


2 possible mechanisms:

Deuterium label study:

Supports an Outer Sphere mechanism
Another Gold (I) Catalyzed Carbocyclization


Au (I) also catalyzes the 5-endo-dig cyclization of δ-alkynes:

- Works on a variety of β-keto esters and alkynes.
- The reaction even tolerates terminal halo substitution on the alkyne.
- By analogy to the previous system, they proposed an outer-coordination sphere mechanism involving initial gold coordination to the alkyne.
- Once again this reaction is substrate specific.
Summary

• Carbopalladations are an effective C-C bond forming reaction.
• Outer Sphere (trans) processes have seen limited use in synthesis.
  • Inherent problem of carbon nucleophiles reducing Pd (II).
  • Prior to 2001, all reactions where stoichiometric in Pd.
• The past 3 years have seen a revival of Outer Sphere carbopalladation chemistry.
  • First catalytic system: Hydroalkylations using Pd (II).
  • Oxidative alkylations were developed and made catalytic using a stoichiometric CuCl₂ re-oxidant.
  • Pt (II) and Au (I) systems have expanded the scope of substrates and nucleophiles.
  • All the systems remain highly substrate specific.
  • The search continues for a general system for efficient catalysis over a range of substrates.