Metal Catalyzed Outer Sphere Alkylations of Unactivated Olefins and Alkynes

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Organic Super-Group Meeting
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

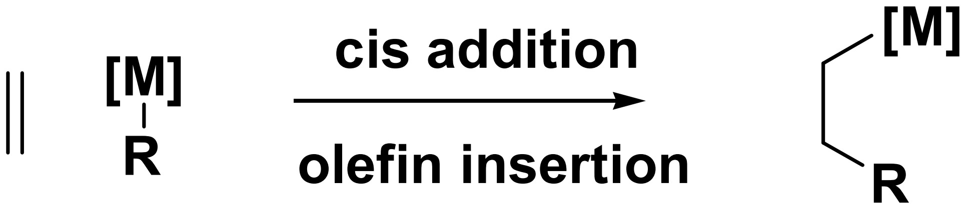
III. Catalytic Platinum Systems

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 in to an σ-alkyl-metal species. This is an “Inner Coordination Sphere” process.



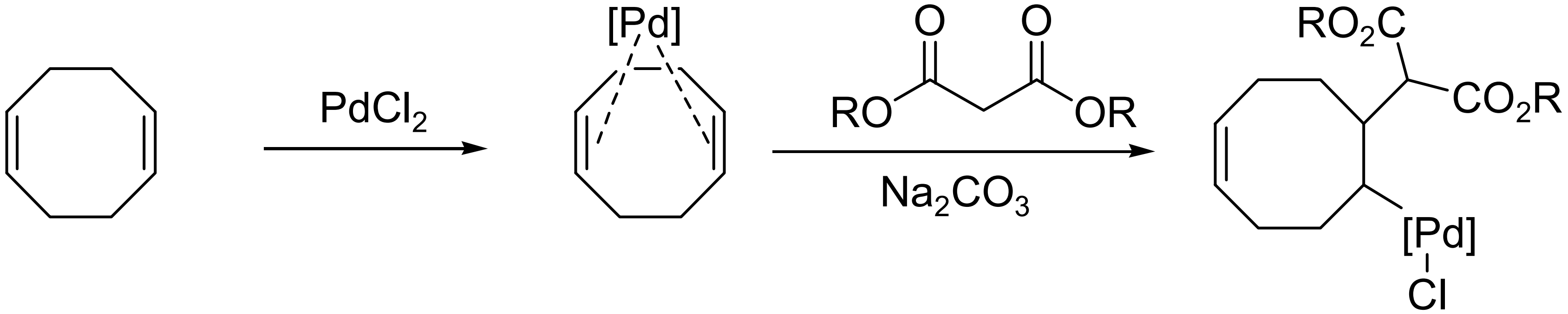
  - The alkyl-metal species could arise from:

  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

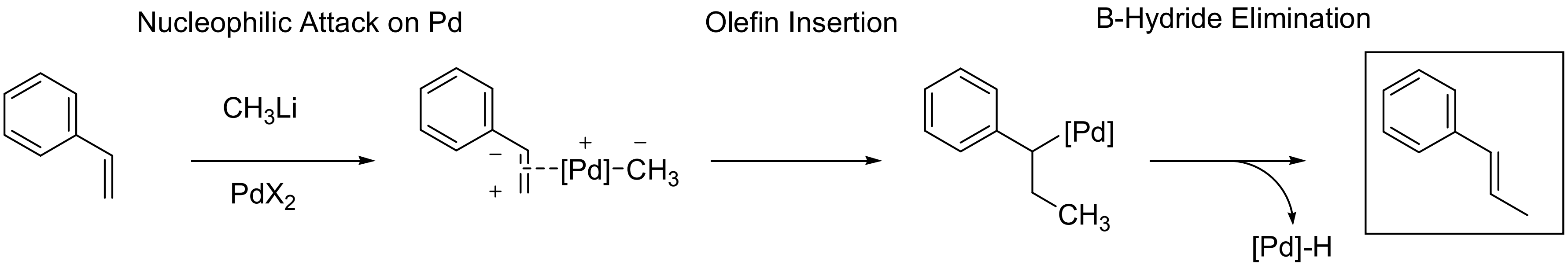
Tsuji, J. and Takahashi, H. *J. Am. Chem. Soc.* **1965**. 87(14), 3275-3276.



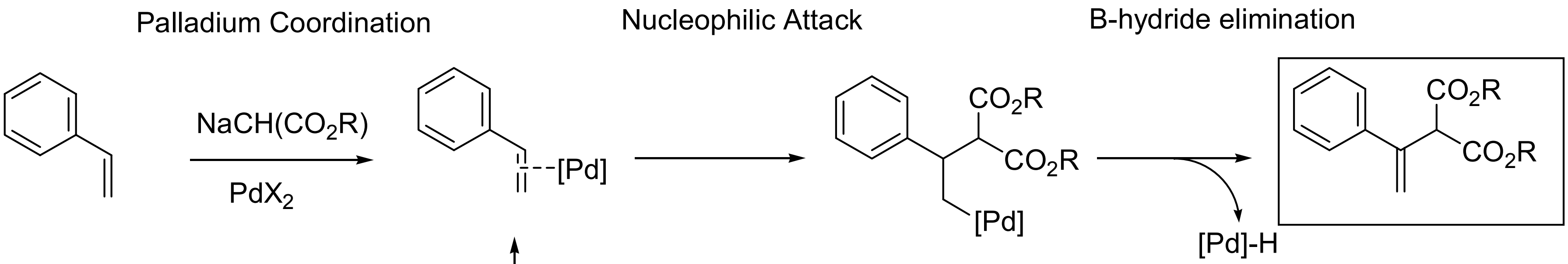
- Amino and Oxo-palladations (i.e. Wacker Process) were previously known and have since been much more widely studied.
- No distinction between cis and trans nucleophilic addition made.

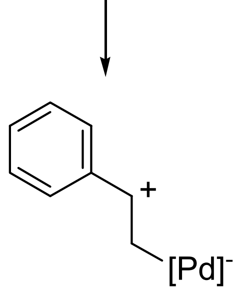
Carbopalladation on Styrene: Different Modes of Attack

Proposed different modes of attack based on different observed products with MeLi vs. Na-Malonate: Murahashi, S. et. al. *J. Org. Chem.* **1977**. 42 (17), 2870-2874.



Inner Sphere Mechanism

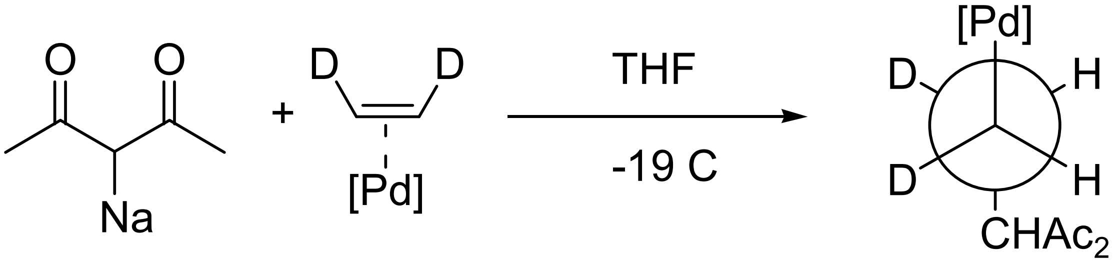




- Outer Sphere attack usually occurs at the more substituted carbon - more stabilization of + charge (In intermolecular processes).
- Stoichiometric in Pd

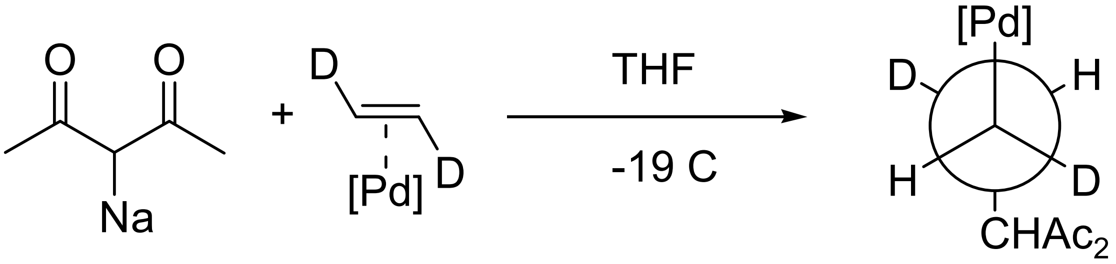
First Direct Evidence of Trans Addition

Kurosawa, H. et. al. *Tetrahedron Lett.* **1979**. 3, 255-256.



J=4.2 Hz

$[Pd] = [Pd(n^5\text{-}C_5H_5)(PPh_3)]^+ClO_4^-$



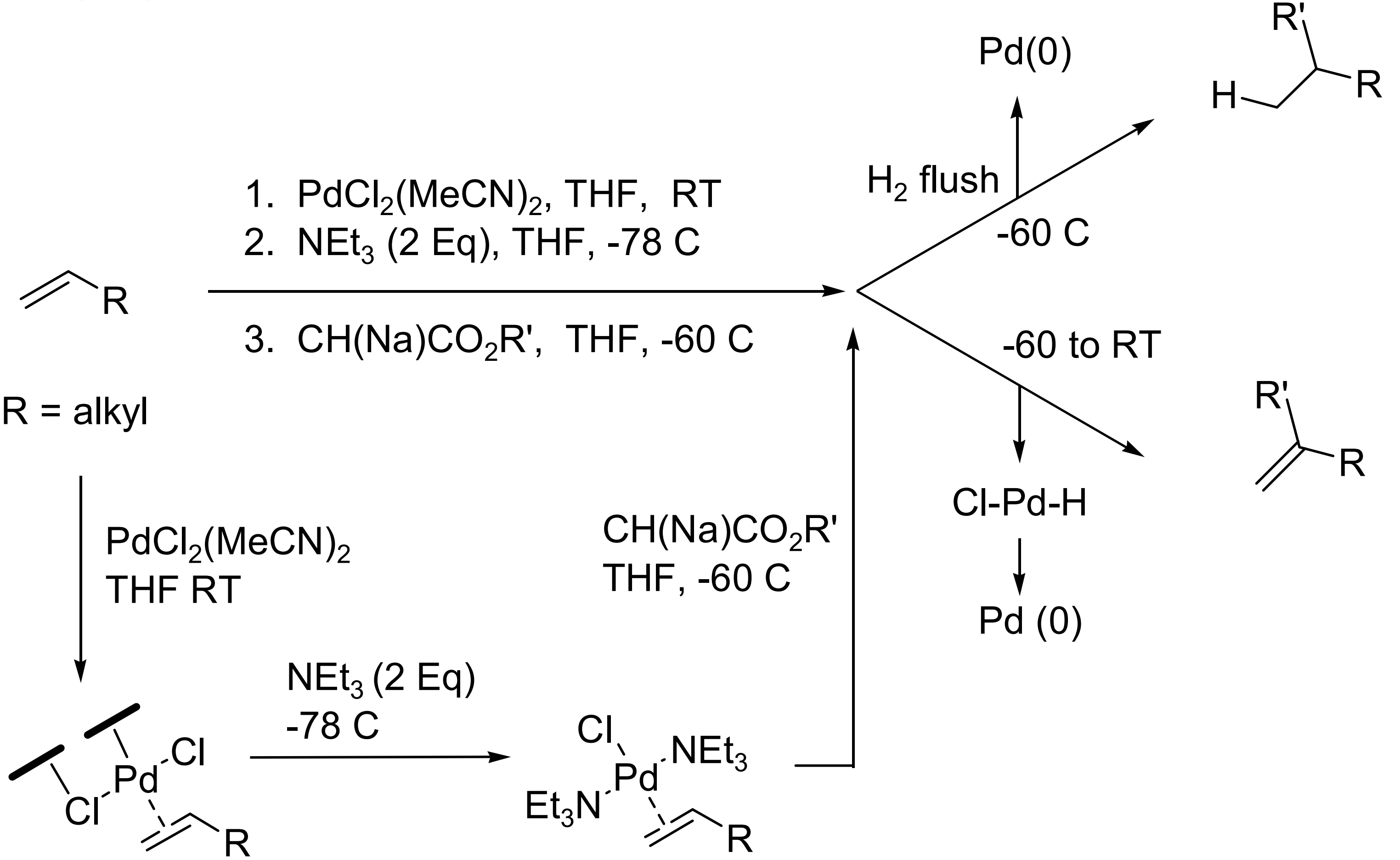
J=12.3 Hz

$[Pd] = [Pd(n^5\text{-}C_5H_5)(PPh_3)]^+ClO_4^-$

Palladium-Assisted Alkylation of Unactivated Olefins

Hegedus, L. S. et. al. *J. Am. Chem. Soc.* **1980**. 102, 4973-4979.

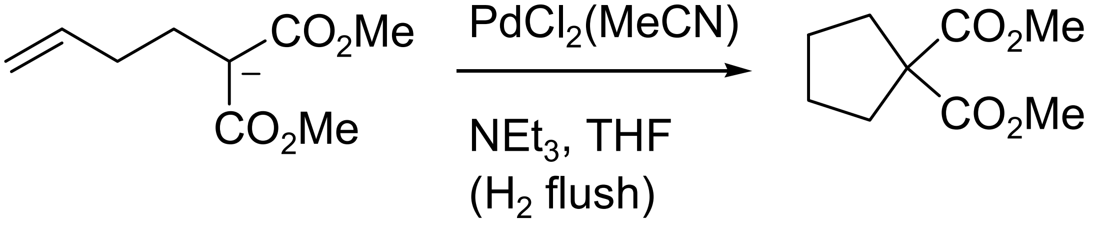
- Wanted general procedure for Outer Sphere carbopalladations on unactivated olefins – but reduction of Pd (II) was a problem.
- Overcame problem of nucleophilic reduction of Pd (II) by using NEt_3, in a step-wise, one pot procedure.



Palladium-Assisted Alkylation of Unactivated Olefins (Continued)

Hegedus, L. S. et. al. *J. Am. Chem. Soc.* **1980**. 102, 4973-4979.

- 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:

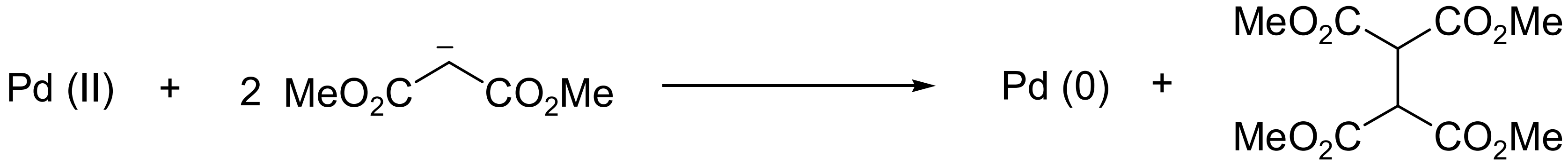


42% Yield

- In all cases the reaction is <u>stoichiometric in Palladium</u>.

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.
- <u>Problem</u>: Carbanions are very easily oxidized.
  - Reductive dimerization is a problem in carbopalladations:

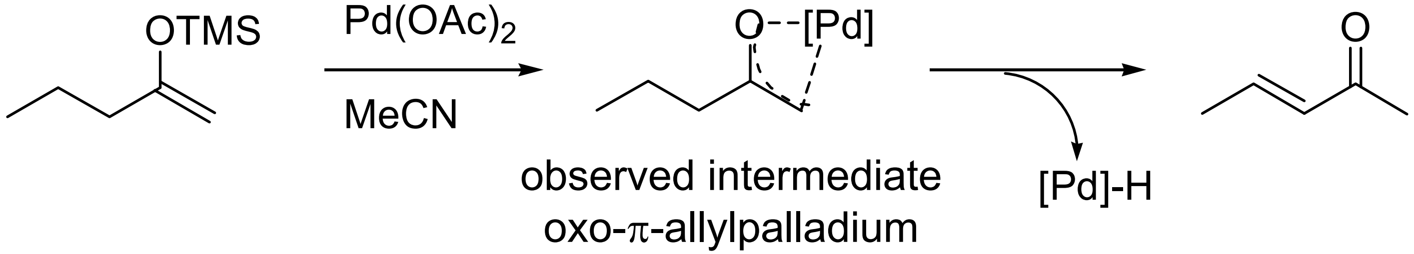


  - Therefore, any oxidant strong enough to oxidize the metal will probably oxidize the carbanion – preventing any desired reaction.

Palladium-Promoted Alkylation of Olefins by Silyl Enol Ethers

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

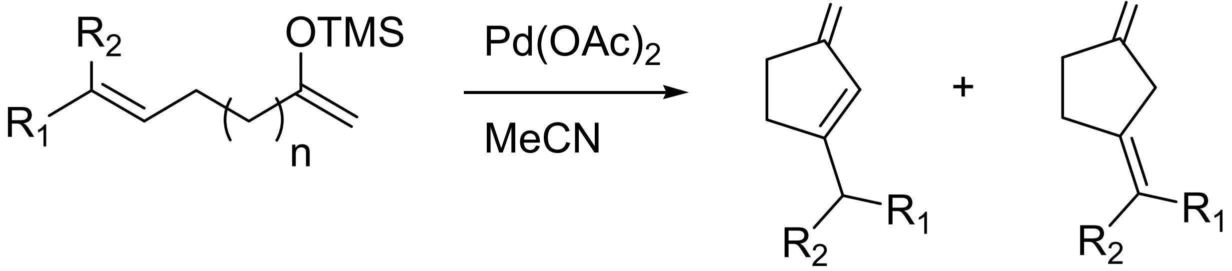
Ito, Y., Aoyama, H., Hirao, T. Mochizuki, A., and Saegusa, T. *J. Org. Chem.* **1978**. 43(5), 1011-1013.



observed intermediate
oxo-π-allylpalladium

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

Ito, Y., Aoyama, H., Hirao, T. Mochizuki, A., and Saegusa, T. *J. Am. Chem. Soc.* **1979**. 101(2), 494-496.

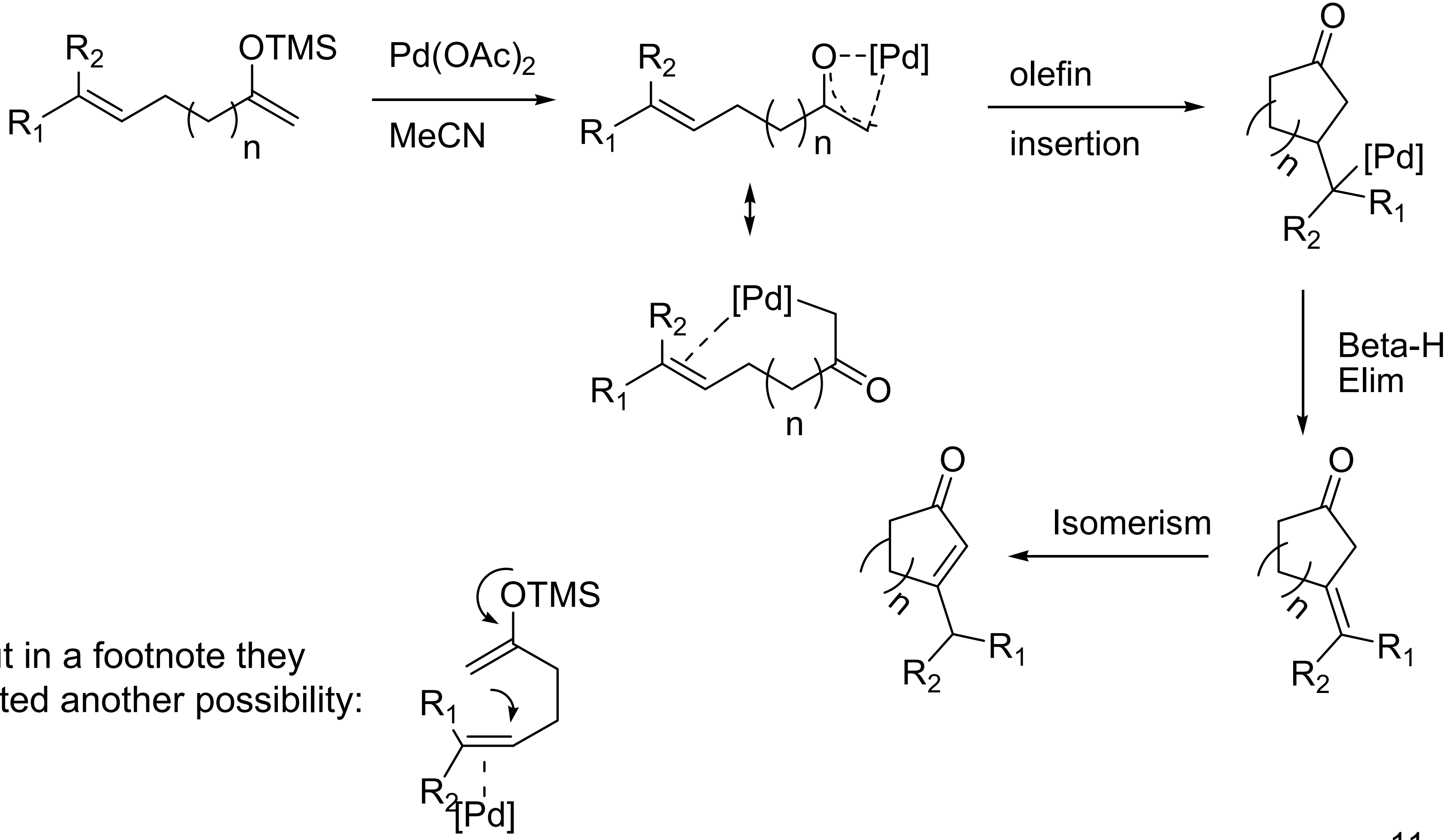


- Works on a variety of substrates.
- Since silyl enol ethers don’t get oxidized by Pd (II), they could get some weak catalysis (0.5 Molar Equiv) using a benzoquinone re-oxidant – but yields suffered.

Palladium-Promoted Alkylation of Olefins by Silyl Enol Ethers

Ito, Y., Aoyama, H., Hirao, T. Mochizuki, A., and Saegusa, T. *J. Am. Chem. Soc.* **1979**. 101(2), 494-496.

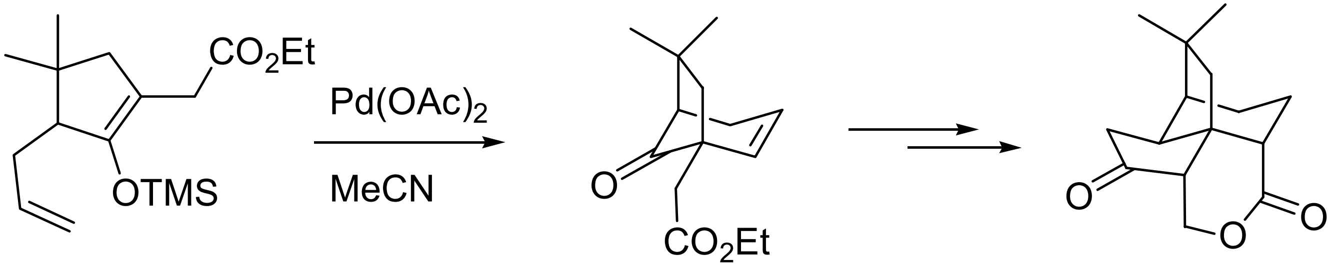
By analogy they proposed this “Inner Sphere” mechanism:



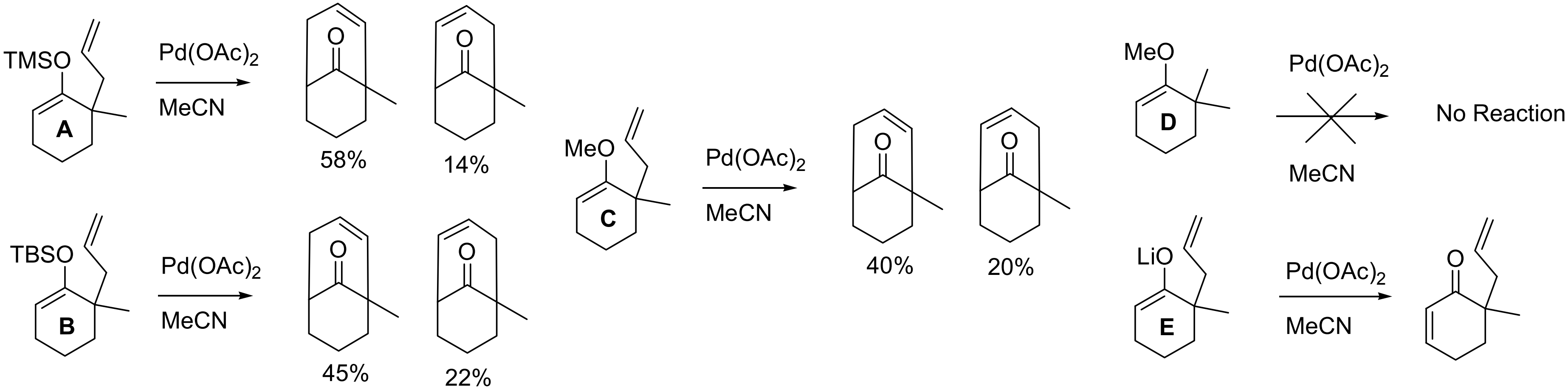
But in a footnote they noted another possibility:

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.



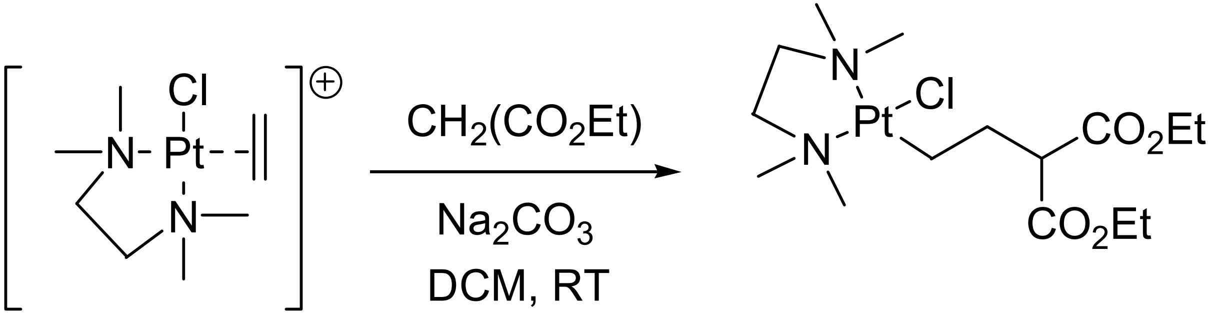
Product distributions in a model system are consistent an Outer Sphere process:



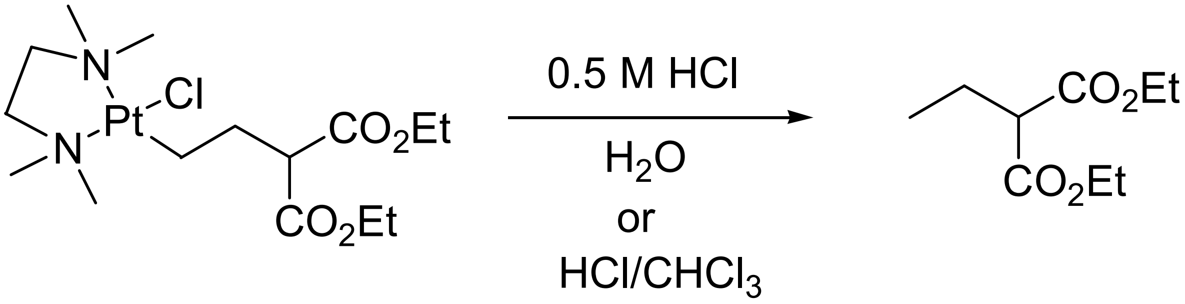
- If desilylation is first step: **A** and **B** and **E** should give same distribution, and **C** should not react (because it doesn't form an enone in **D**).
- Cyclization and enone formation does not proceed through same intermediate.
- Evidence supports an Outer Sphere mechanism.

Pt (II) Additions to Ethylene

Fanizzi, F. P et. al. *J. Chem. Soc. Dalton Trans.* **1992**. 309-312.



- Addition is irreversible.
- Also works with inorganic nucleophiles (NO_2^-, N_3^-, NCO^-).
- Heating to 50 ºC 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

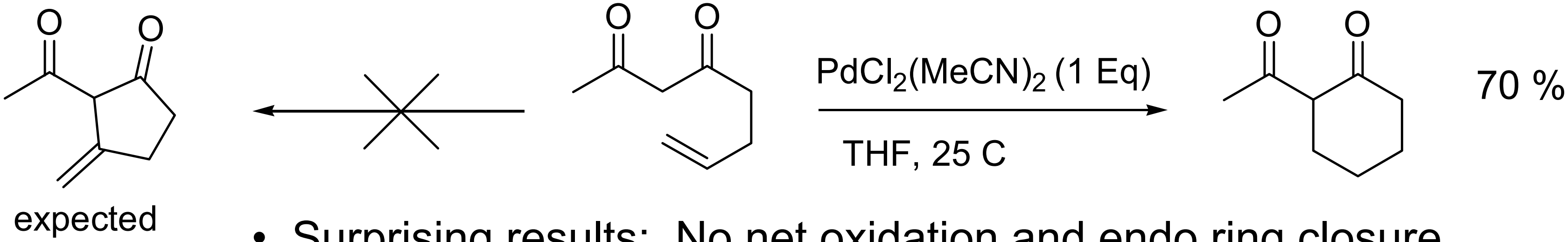
- "Outer Sphere" carbopalladations are stoichiometric in palladium.
- Pd/amine and Pt/amine complexes are the only known promoters.
- The products of carbopalladations (alkyl-palladium complexes) undergo β-hydride elimination above -20 ºC.
- The carbopalladation products can be quenched with H_2 by simply 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"

Hegedus, L. S. Transition Metals in the Synthesis of Complex Organic Molecules. **1999**.
University Science Books, Sausalito, California.

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

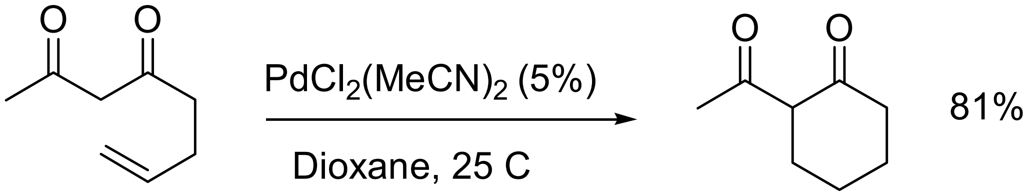
Pei, T. and Widenhoefer, R. A. *J. Am. Chem. Soc.* **2001**. 123, 11290-11291.

Looking at carbopalladations to get cyclopentanones:



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

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

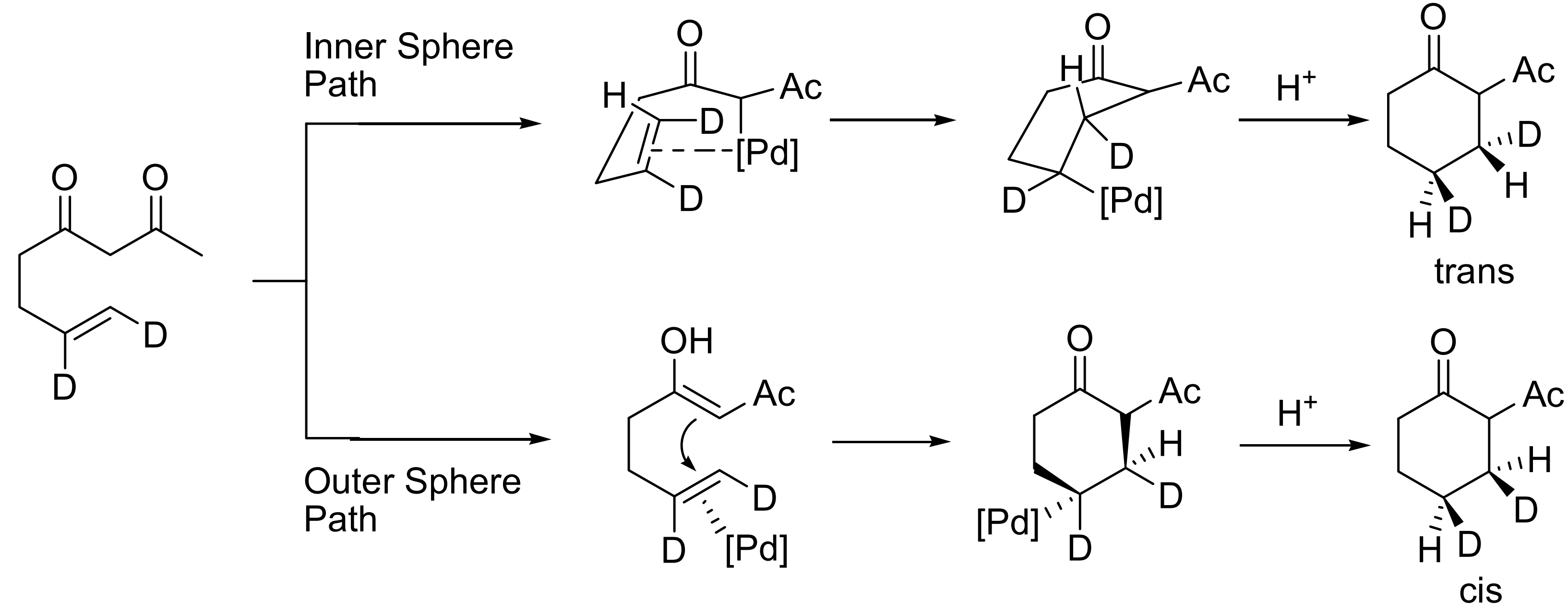


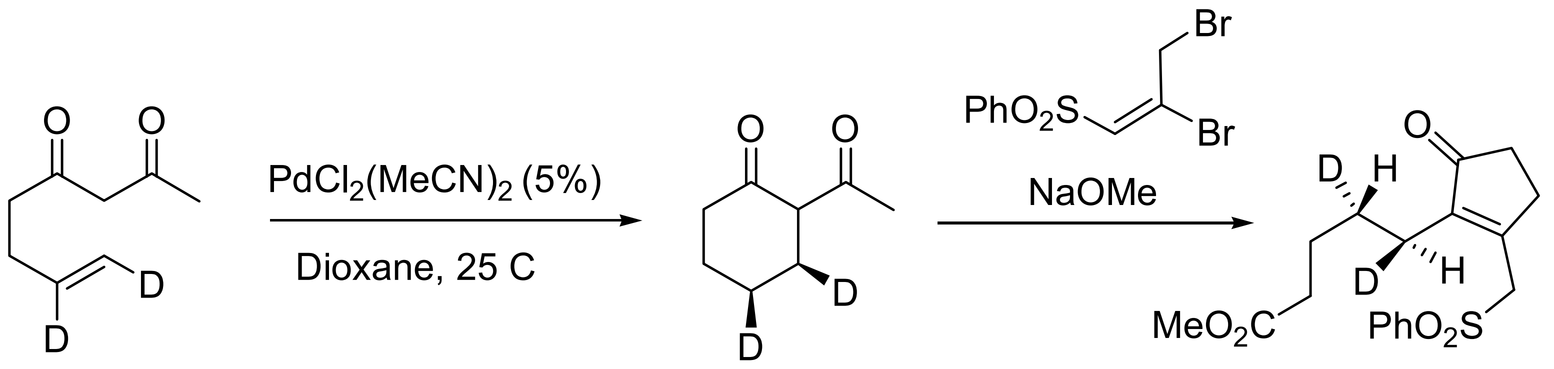
- Mono terminal substitution on olefin is well tolerated.
- α-substitution is tolerated.
- β-keto esters give lower yields. But using TMSCl as an additive gives comparable yields (Pei. T and Widenhoefer, R. A. *Chem. Comm.* **2002**. 650-651.)

Mechanistic Investigation

Qian, H. and Widenhoefer, R. A. *J. Am. Chem. Soc.* **2003**. 125, 2056-2057.

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



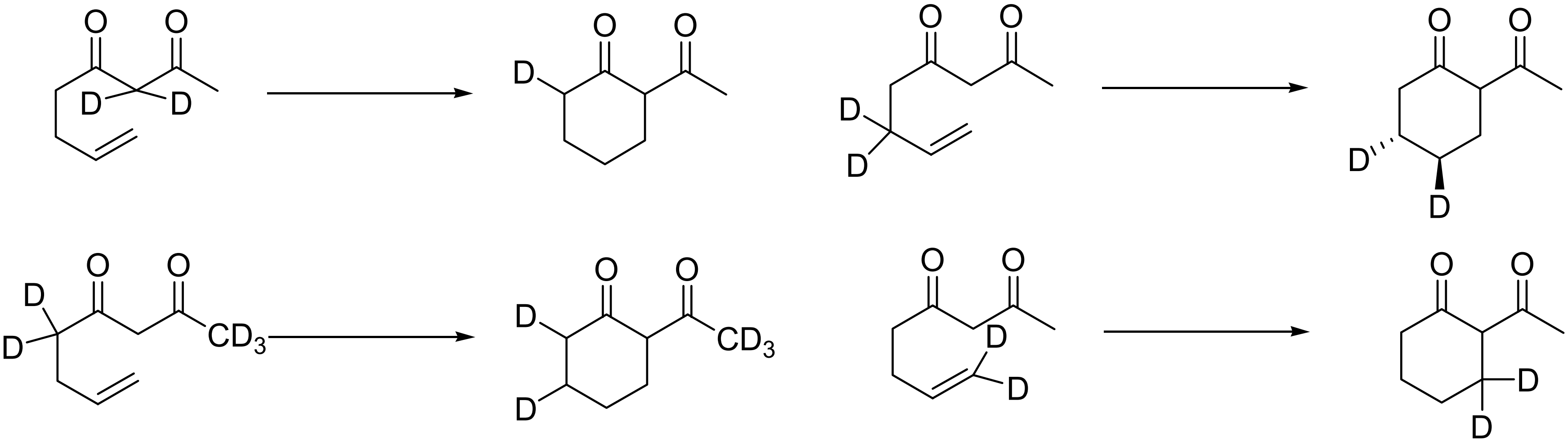


Results are consistent with an outer coordination sphere mechanism.

Mechanistic Investigation (Continued)

Qian, H. and Widenhoefer, R. A. *J. Am. Chem. Soc.* **2003**. 125, 2056-2057.

Other labeling experiments:

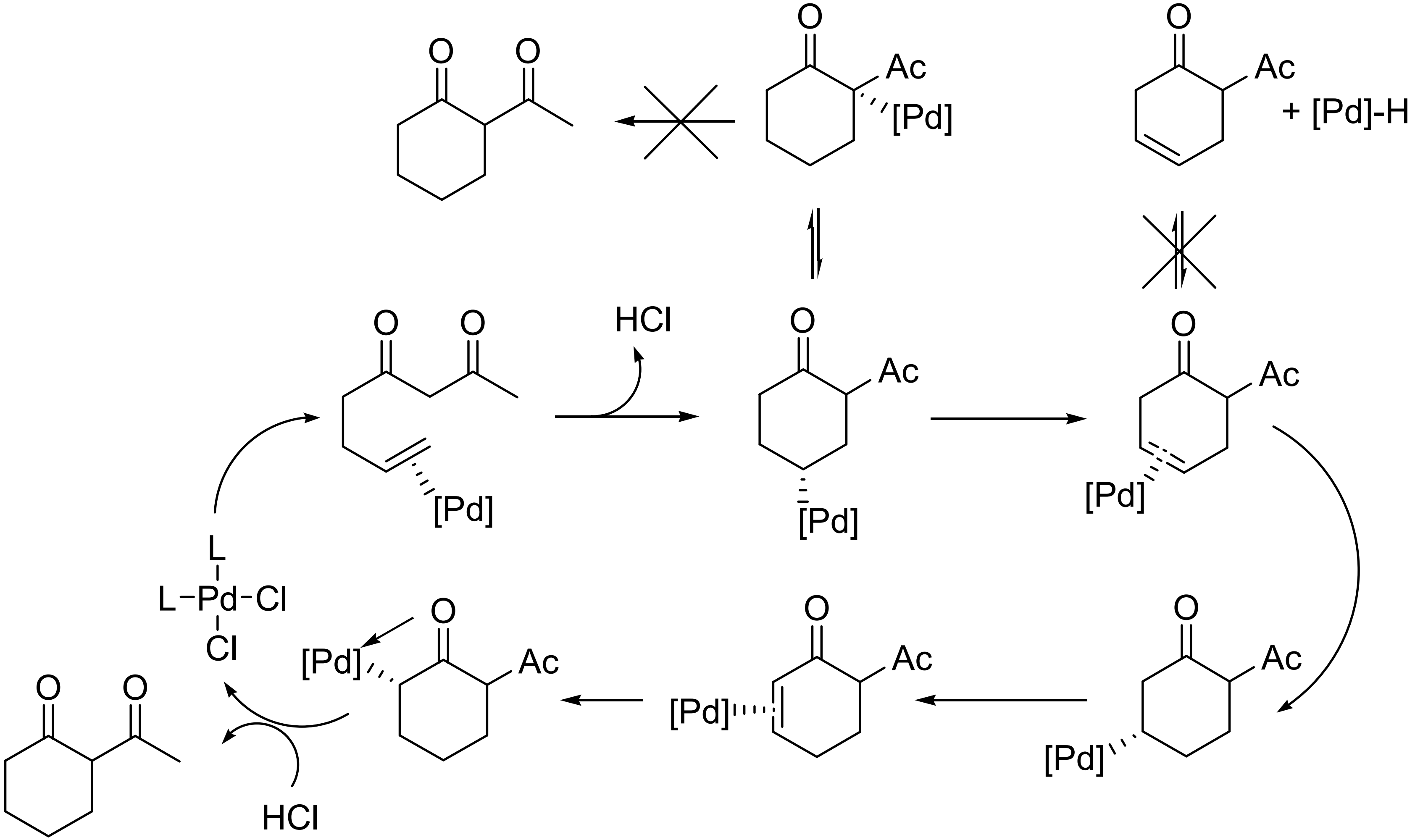


- Palladium migration around the ring must occur.

Mechanistic Investigation (Continued)

Qian, H. and Widenhoefer, R. A. *J. Am. Chem. Soc.* **2003**. 125, 2056-2057.

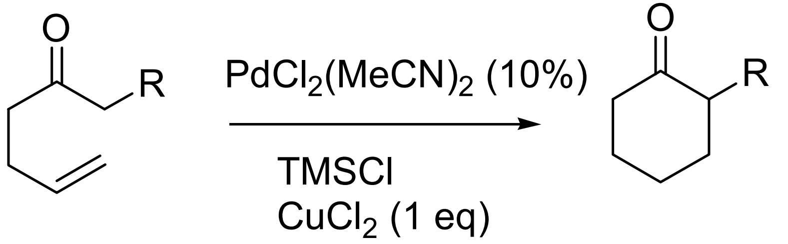
Plausible mechanism with palladium migration:



Extension to Non-Stabilized Enolates

Wang, X., Pei, t., Han, X. and Widenhoefer, R. A. *Org. Lett.* **2003**. 5 (15), 2699-2701.

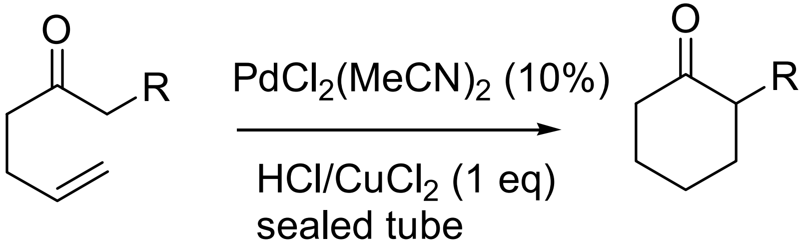
Early Investigations:



- TMSCl to generate silyl enol ether *in situ*.
- $CuCl_2$ to stabilized oxidation state of Pd.

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

Optimized conditions:

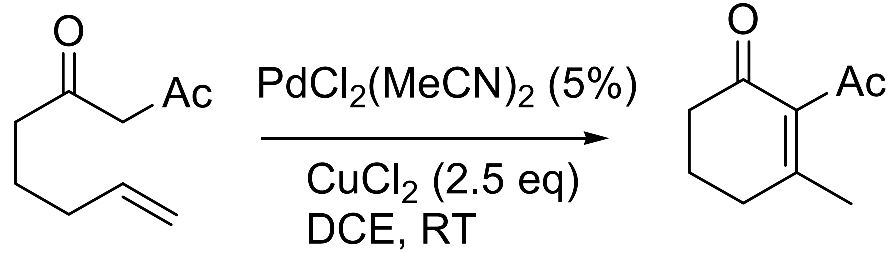


- Worked on a variety of aryl and alkyl R groups.
- Disubstitution to make quaternary centers also tolerated.

First Pd Catalyzed Oxidative Alkylation of Olefins

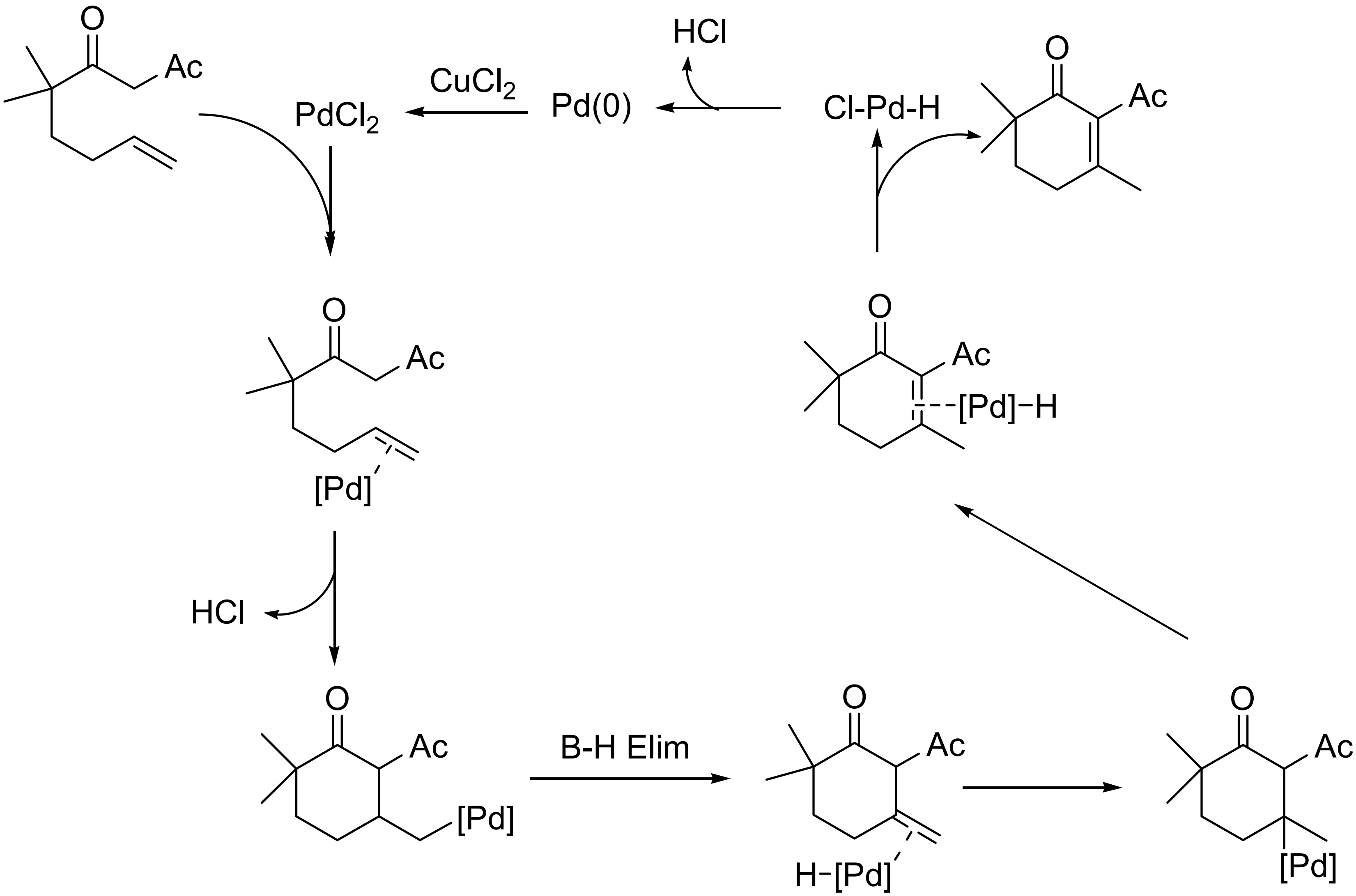
Pei. T. Wang, X., and Widenhoefer, R. A. *J. Am. Chem. Soc.* **2002**. 125(3), 648-649

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



- $CuCl_2$ is a stoichiometric re-oxidant.
- Reaction can be catalytic in $CuCl_2$ (10%) with O_2 atmosphere.

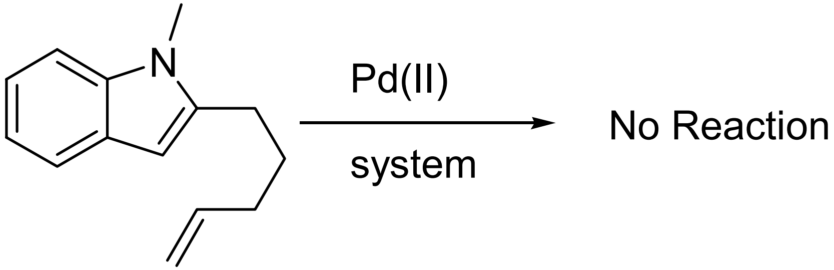
Proposed Mechanism:



III. Pt (II) Alkylation of Olefins with Indoles

Liu, C., Han, X., Wang, X., Widenhoefer, R. A. *J. Am. Chem. Soc.* **2004**. 3700-3701.

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

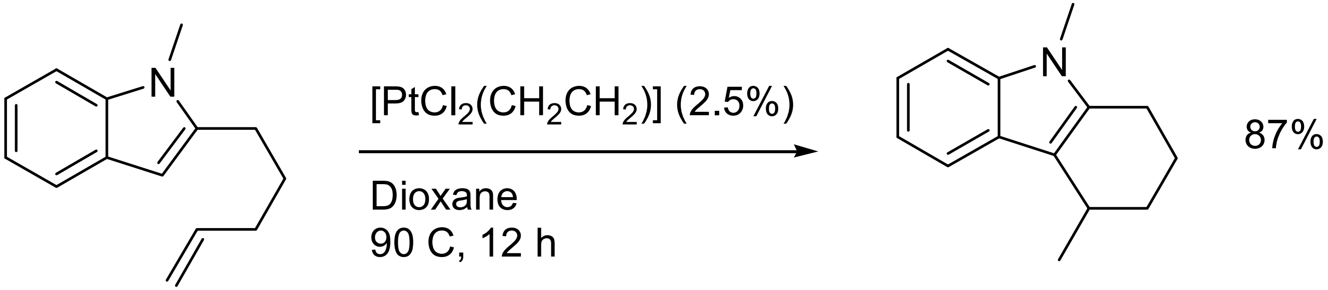


As we saw earlier:

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

Fanizzi, F. P et. al. *J. Chem. Soc. Dalton Trans.* **1992**. 309-312.

Using a simple Pt (II) catalyst:



Pt (II) Alkylation of Olefins with Indoles

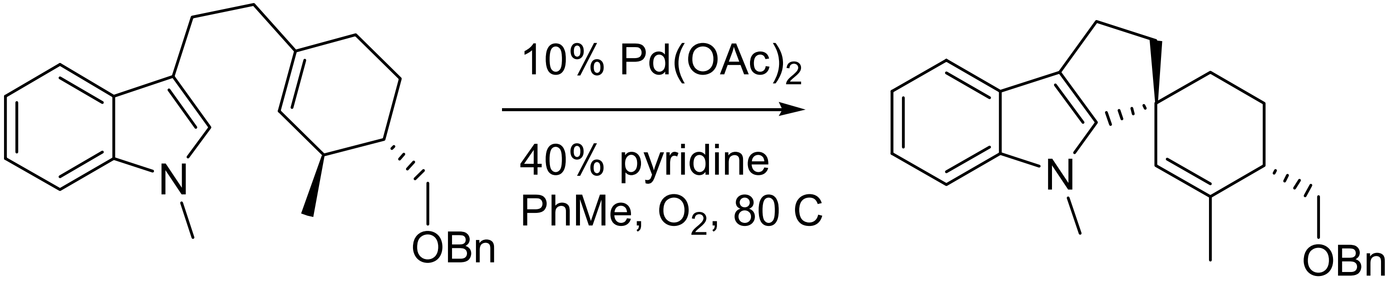
Liu, C., Han, X., Wang, X., Widenhoefer, R. A. *J. Am. Chem. Soc.* **2004**. 3700-3701.

Optimized system: $PtCl_2$, 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?

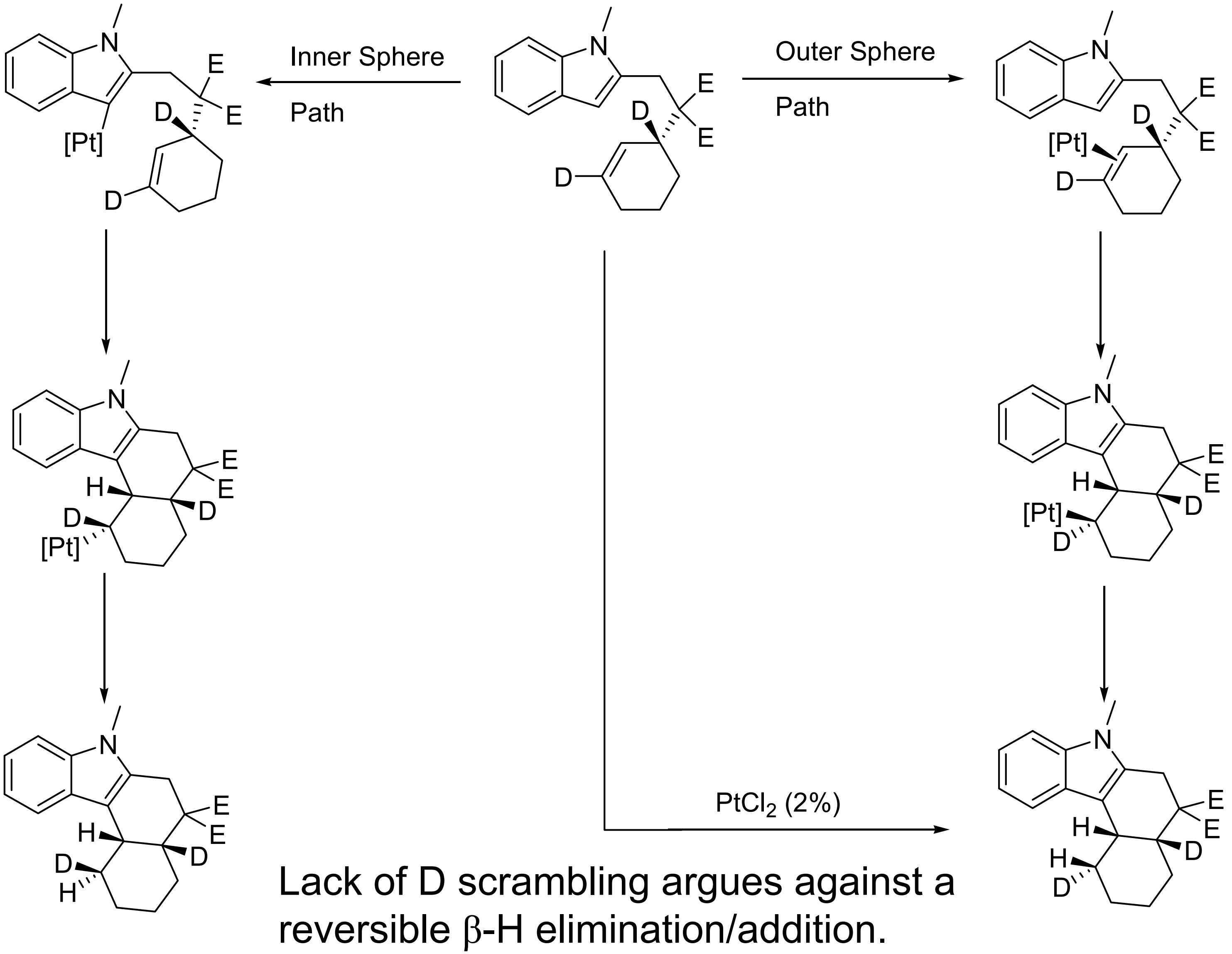
- Stoltz has reported a C-H activation/olefin insertion mechanism (Inner Sphere) for this related system: Ferreira, E. M. and Stoltz, B. *J. Am. Chem. Soc.* **2003**. 125(32), 9578-9579.



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. *J. Am. Chem. Soc.* **2004**. 3700-3701.

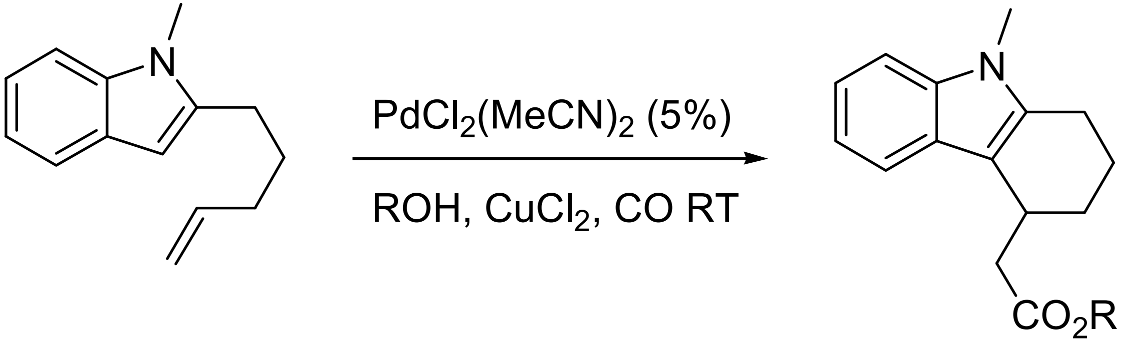


Lack of D scrambling argues against a reversible β-H elimination/addition.

Pd (II) Alkylation of Olefins with Indoles

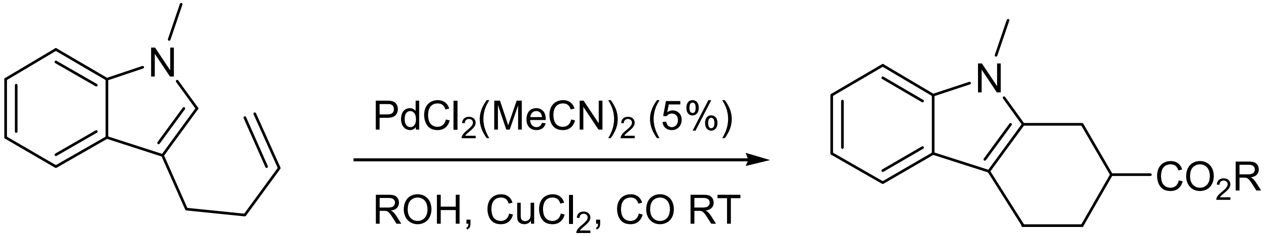
Liu, C. and Widenhoefer, R. A. *J. Am. Chem. Soc.* **2004**. 10250-10251.

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



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

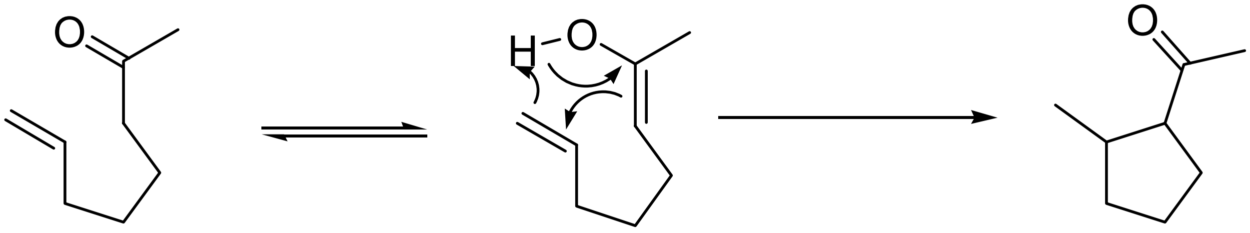
System also works on 3-alkyl indoles. 6-endo cyclization suggests similar outer sphere mechanism (direct contrast to Stoltz systems):



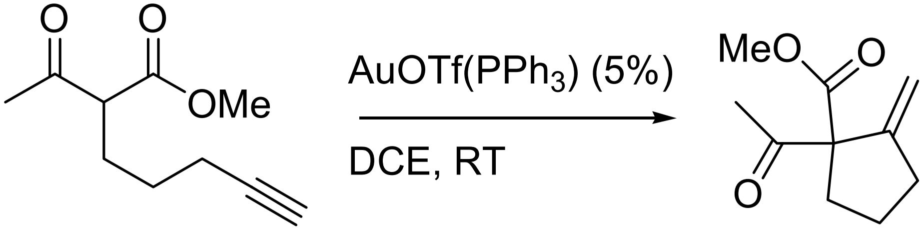
IV. Gold (I) Catalyzed Conia-Ene Reaction

Kennedy-Smith, J. J., Staben, S. T., and Toste, F. D. *J. Am. Chem. Soc.* **2004**. 126(14), 4526-4527.

Conia-Ene Reaction:



Au (I) catalyzed version:



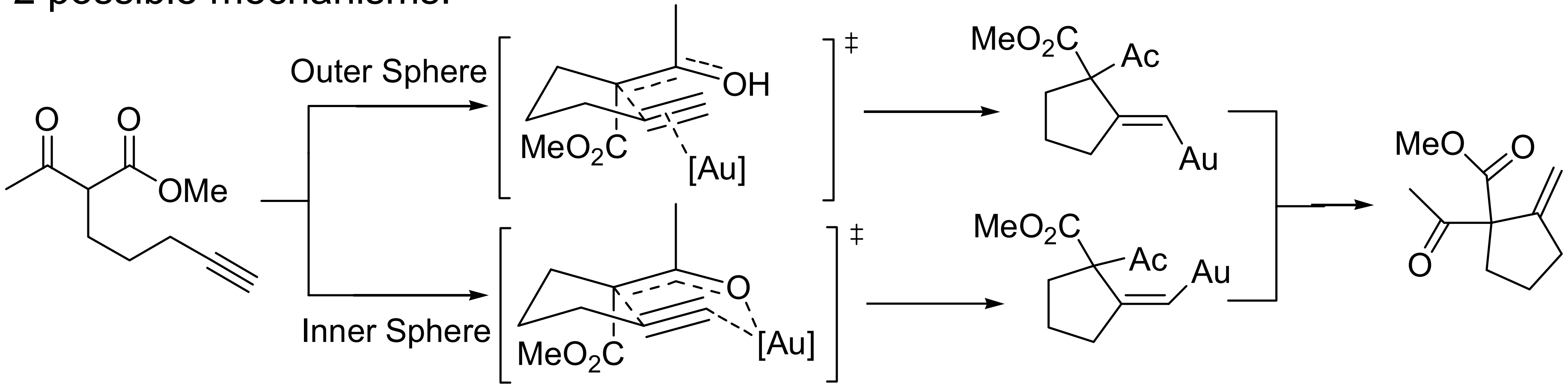
- 80-95% yield on a variety of terminal alkynyl β-keto ester substrates.
- Good d.r. observed with 3 and 4 substitutions.
- Low catalyst loading, short reaction times and “open-flask” conditions.

Is the mechanism consistent with an inner or outer sphere mechanism?

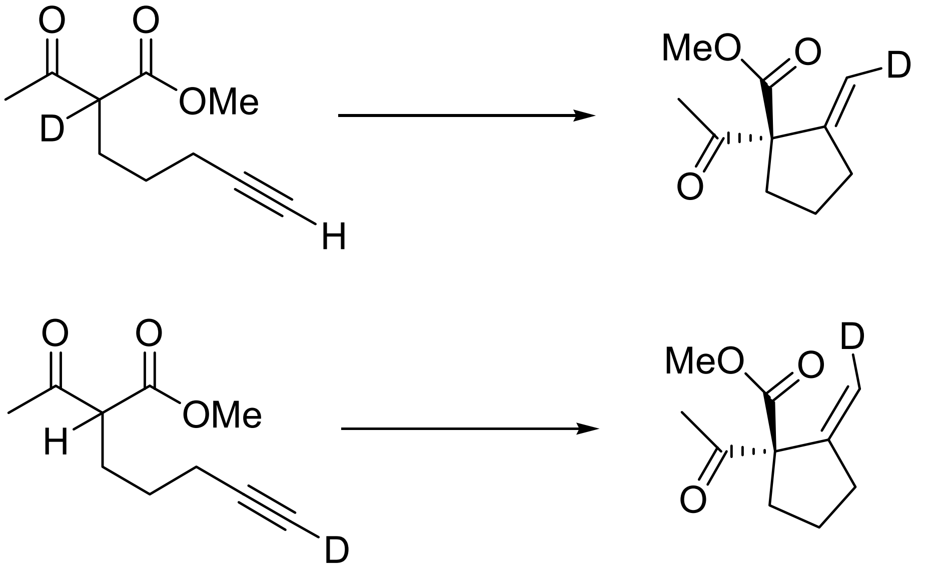
Gold (I) Catalyzed Conia-Ene Reaction (Continued)

Kennedy-Smith, J. J., Staben, S. T., and Toste, F. D. *J. Am. Chem. Soc.* **2004**. 126(14), 4526-4527.

2 possible mechanisms:



Deuterium label study:

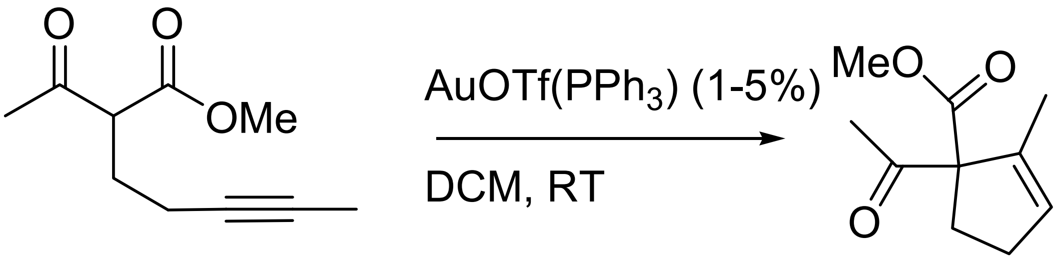


Supports an Outer Sphere mechanism

Another Gold (I) Catalyzed Carbocyclization

Staben, S. T., Kennedy-Smith, J. J., and Toste, D. *Angew. Chem. Int. Ed.* **2004**. 5350-5352.

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 a 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 $CuCl_2$ 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.