

## DMITRI MENDELEYEV (1834 – 1907)

The Russian chemist, Dmitri Mendeleev, was the first to observe that if elements were listed in order of atomic mass, they showed regular [periodical] repeating properties. He formulated his discovery in a periodic table of elements, now regarded as the backbone of modern chemistry.

The crowning achievement of Mendeleev's periodic table lay in his prophecy of then, undiscovered elements. In 1869, the year he published his periodic classification, the elements gallium, germanium and scandium were unknown. Mendeleev left spaces for them in his table and even predicted their atomic masses and other chemical properties. Six years later, gallium was discovered and his predictions were found to be accurate. Other discoveries followed and their chemical behaviour matched that predicted by Mendeleev.

This remarkable man, the youngest in a family of 17 children, has left the scientific community with a classification system so powerful that it became the cornerstone in chemistry teaching and the prediction of new elements ever since. In 1955, element 101 was named after him: Md, Mendelevium.

# π-Acid Catalyzed C-H Alkylation

Part of the C-H Activation seminar series

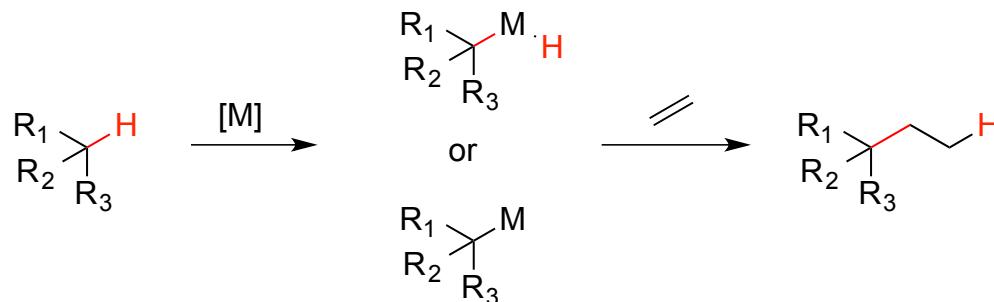
John Thompson

Dong Group - Literature Review

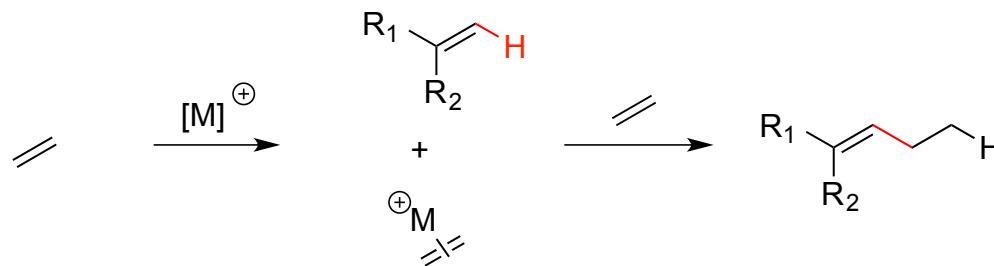
February 18<sup>th</sup>, 2015

# Alkylation pathways for olefins with metals

- Activation of C-H bond ( $sp^2$  and  $sp^3$ )

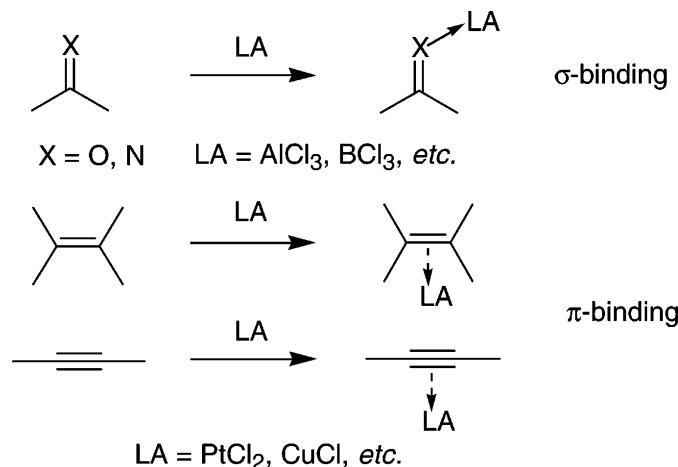


- Activation of olefin for alkylation



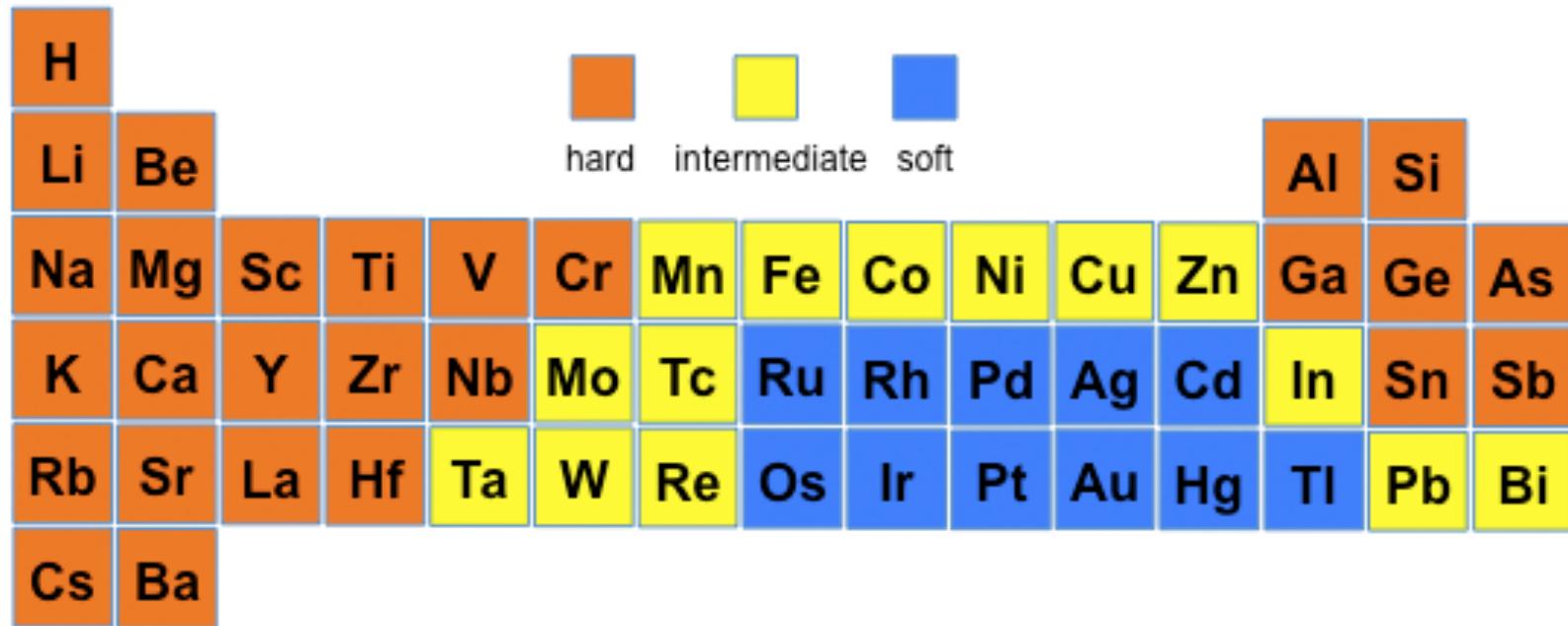
# Lewis acid activation

- The fundamental role of a Lewis-acid catalyst lies in the activation of the C=X bond; where (X = O, NR, CR<sub>2</sub>), thereby decreasing the LUMO energy and promoting nucleophilic addition to the C=X bond.



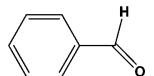
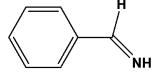
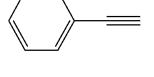
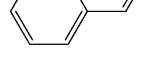
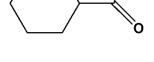
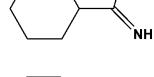
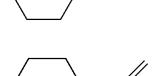
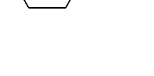
- Classic Lewis acids** (i.e. BCl<sub>3</sub>, AlCl<sub>3</sub>, etc.) make strong σ-complexes with carbonyl and imine groups
  - Used in Friedel-Crafts, Diels-Alder, and other electrophilic reactions
- Transition metal Lewis acids** can be bifunctional
  - Activating olefins through π-binding or (and) make the σ-complexes with heteroatoms

## Choosing your metal



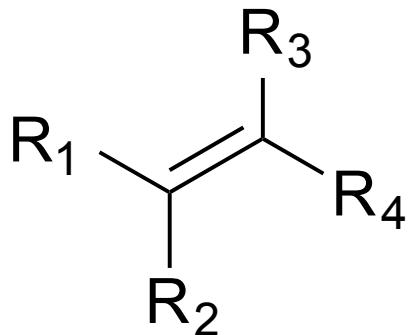
# Heats of formation for generated LA-olefin complexes

TABLE 1. Computed Heats of Formation (B3LYP/SDD, kcal mol<sup>-1</sup>)<sup>a</sup> and Their Selected Ratios (Shown in Bold) of the Substrates 1–8 with Representative Lewis Acids

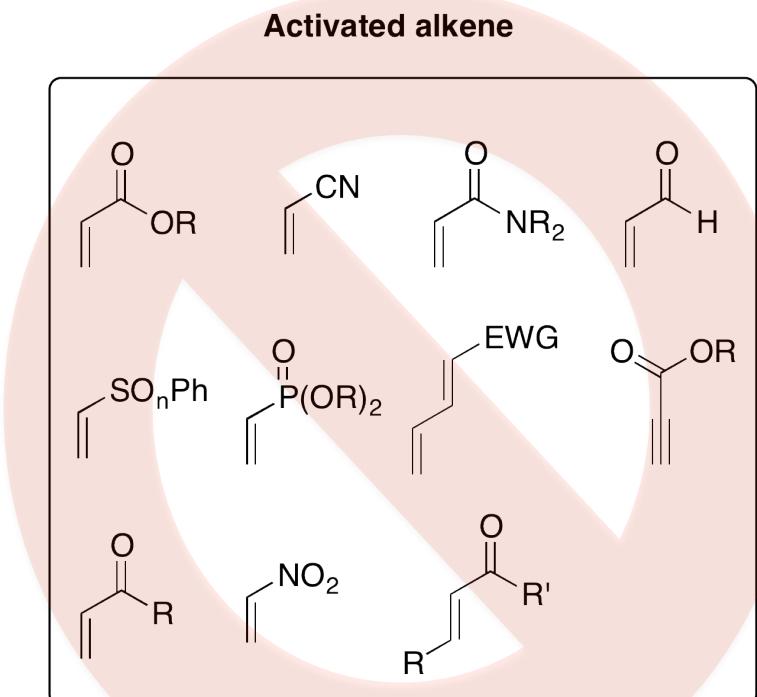
Lewis Acid	BCl <sub>3</sub>	MgCl <sub>2</sub>	AlCl <sub>3</sub>	CuCl	CuCl <sub>2</sub>	AgCl	AuCl	AuCl <sub>3</sub>	PtCl <sub>2</sub>
 1	18.9	34.5	40.7	37.4	25.4	26.4	33.1	35.9	46.9
 2	42.1	44.2	55.1	51.8	41.2	39.6	53.6	60.3	71.5
 3	0.9	15.2	19.1	33.1	14.3	22.6	34.7	32.5	49.4
 4	0.4	15.7	19.2	33.6	18.1	24.4	37.5	36.8	53.9
 5	17.2	33.1	38.7	36.6	23.9	26.0	32.7	35.1	38.9
 6	42.6	44.4	55.4	52.2	41.9	40.4	54.3	61.1	72.4
 7	1.3	18.7	18.4	35.3	16.1	25.2	36.2	30.9	49.5
 8	8.8	25.6	26.4	43.6	25.2	34.7	48.1	43.2	68.8

# What type of olefins are we looking for

- mono- to tetra- substituted olefins



- Simple alkyl or styrene type olefins
  - Styrene olefins are somewhat “activated” (Suffer from polymerizations)
- Avoid 1,4-type Michael acceptors



# Overview

---

- **Hydroalkylation of pronucleophiles**

- 1,3-Diene alkylation
- Intramolecular olefin alkylation
- Intermolecular olefin alkylation



**Ross Widenhoefer**  
Duke University  
~20 years

- **Hydroalkylation of electron rich arenes**

- Electron rich benzene rings
- Electron rich heterocycles



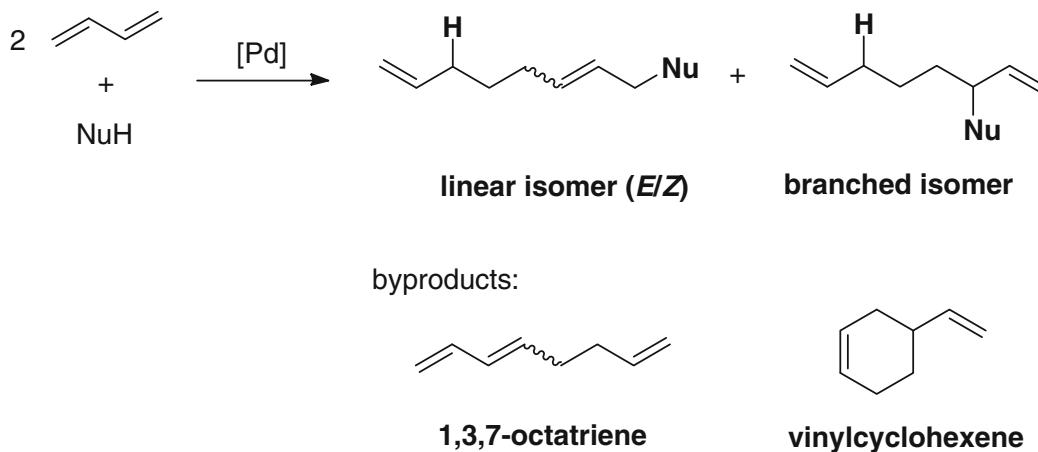
**Chi-Ming Che**  
University of Hong Kong  
~25 years



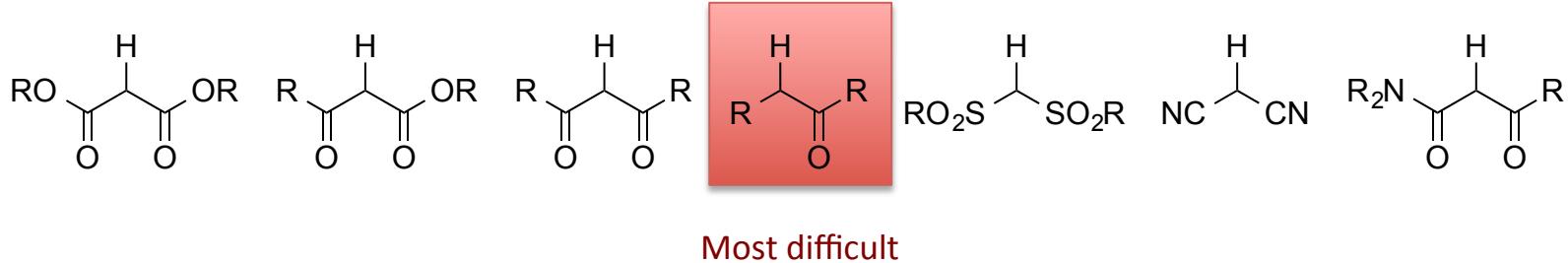
**Chao-Jun Li**  
McGill University  
~20 years

# Pronucleophile alkylation of 1,3-dienes

- Palladium catalyzed **telomerization** of dienes – discovered in 1967 by Smutny
    - Dimerization of butadiene (or even trimerization)
    - Similar to allylic substitution pathways – alleviates use of bases and leaving groups

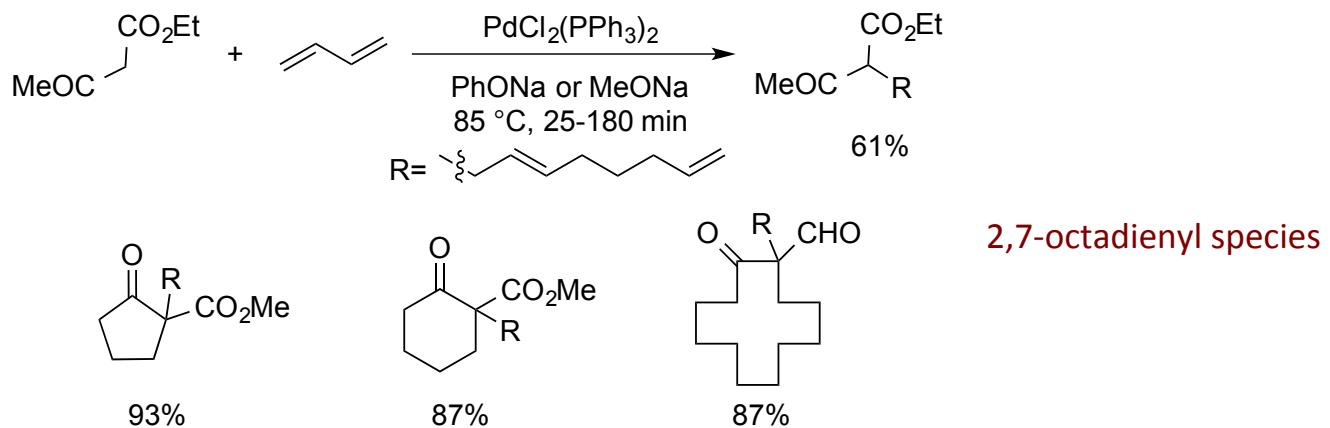


- C-C bond formed from activated methylene species with electron-withdrawing groups, or ***pronucleophiles***

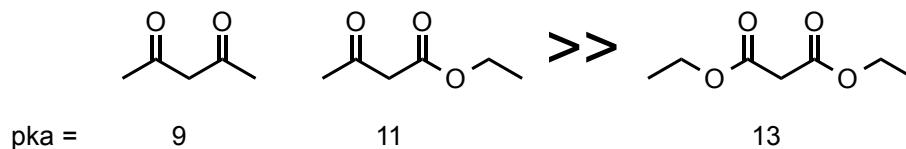


# First alkylation with 1,3-butadiene

- Hata group in 1971 disclosed first activated methylene alkylation
  - PdCl<sub>2</sub> salts were effective catalysts, with Pd(0) species also showing reactivity without the basic additive – but lower yields



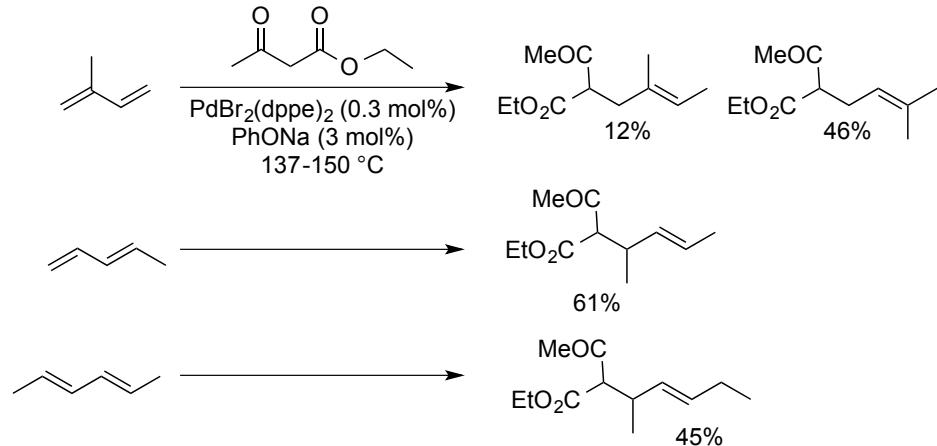
- Reactivity trend



- Importantly, **no O-alkylation observed**
- Pt(II) salts also worked, but not efficiently
- Without PPh<sub>3</sub> → phenol would add into the telomer
- Authors believed a Pd(0)-PPh<sub>3</sub> species was active catalyst

# Expansion of this chemistry

- Bidentate ligands inhibit dimerization of dienes
- Substituted dienes only afford 1:1 adduct formation

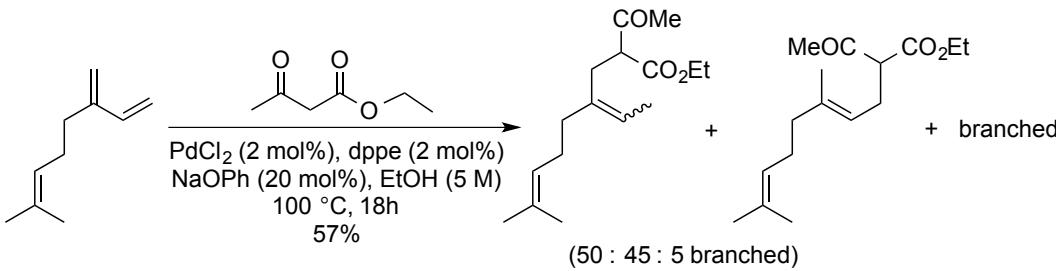


Internal substitution = linear product

Terminal substitution = branched

Hata. *Bull. Chem. Soc. Jap.* **1972**, 45, 1183

- Years later, expanded additions to more important dienes

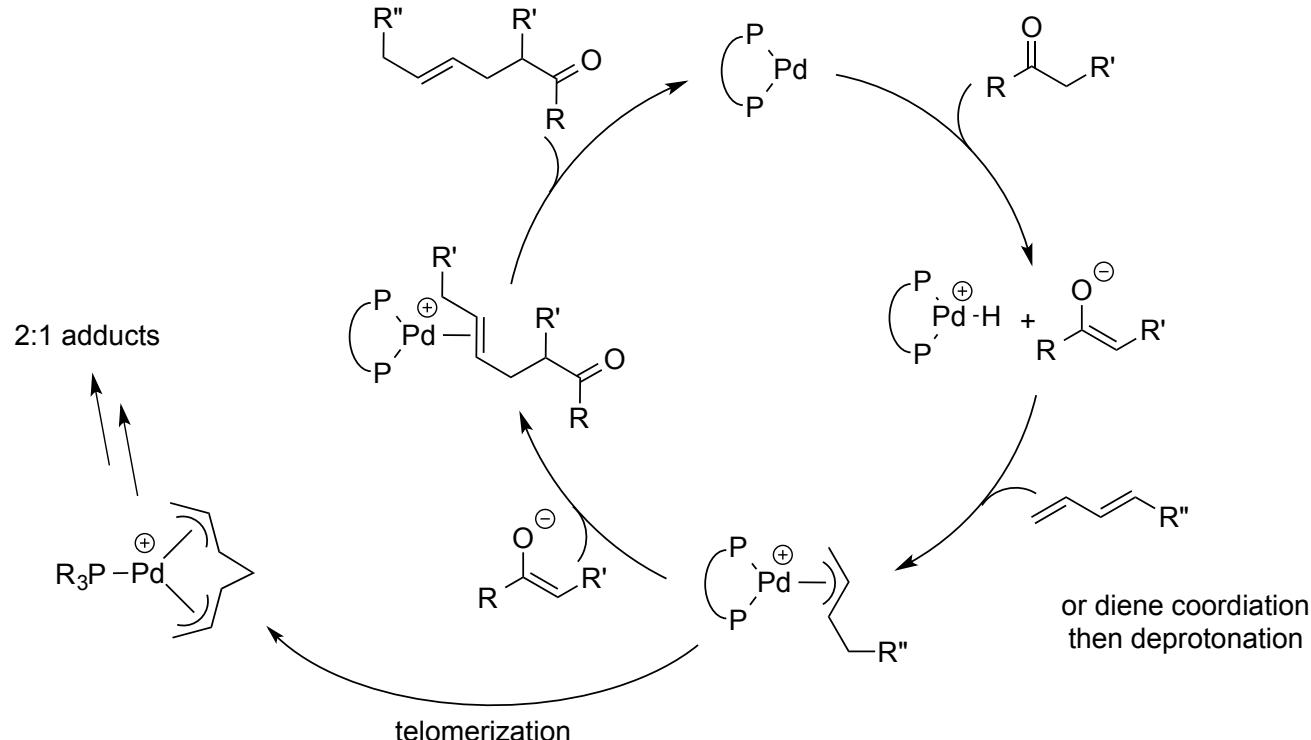


Switching to Ni(II) lead to branched products selectively

Baker. *Tet. Lett.* **1978**, 38, 3575

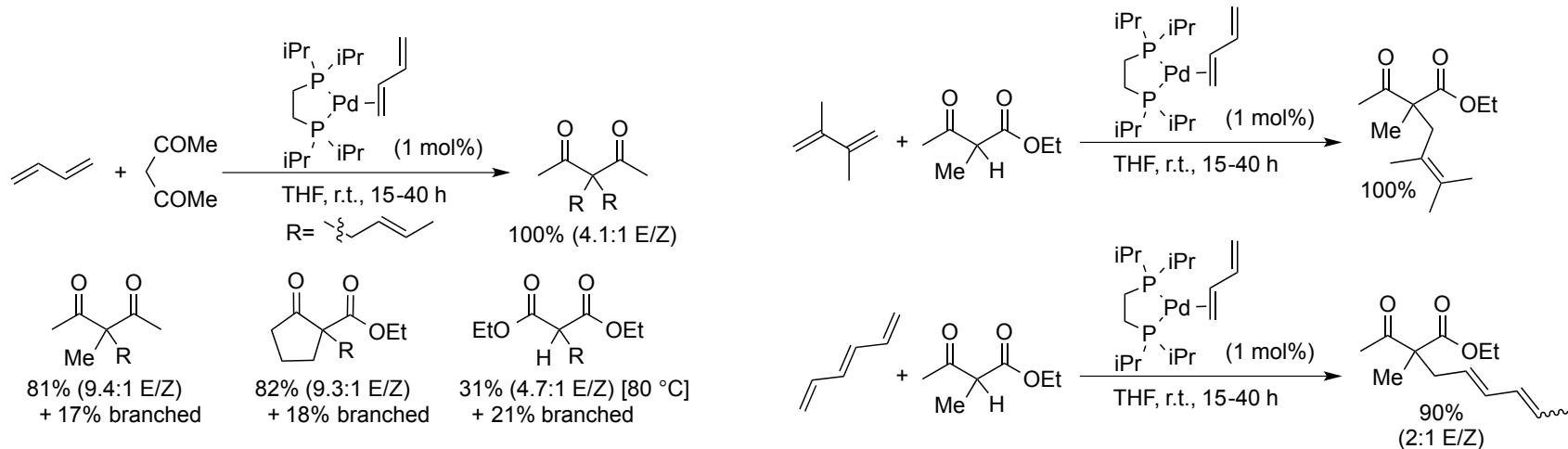
# Mechanistic Analysis

- Electron rich palladium(0) deprotonates acidic C-H bond of the pronucleophile
- Without bulky bidentate ligands, the telomerization reaction can occur
- *Not a carbometallation reaction!*



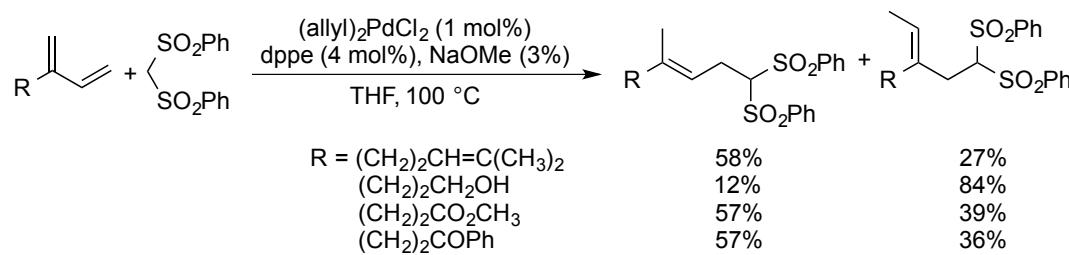
# Improving diene alkylation

- Modifying the basicity and bidenticity of the palladium(0)-ligands eliminated the usage of alkoxides.



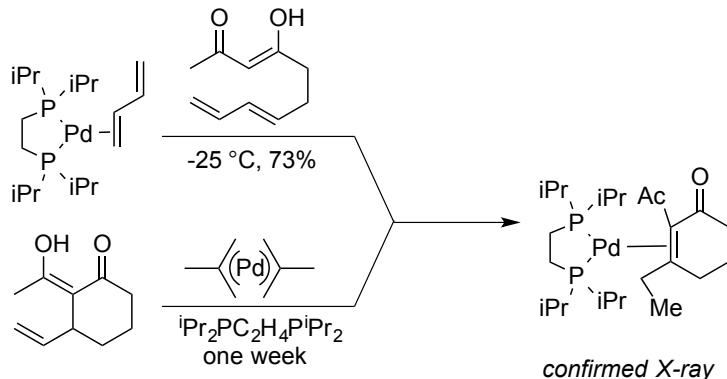
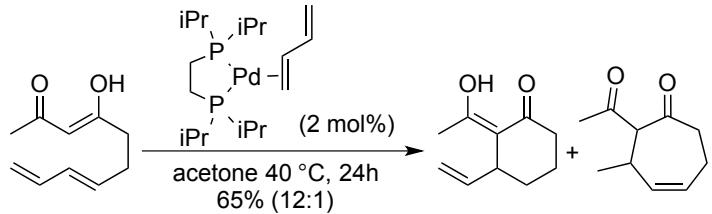
Jolly. *Synthesis* 1990, 1990, 771

- Trost used simpler dppe to achieve alkylation with more detailed substrate scope



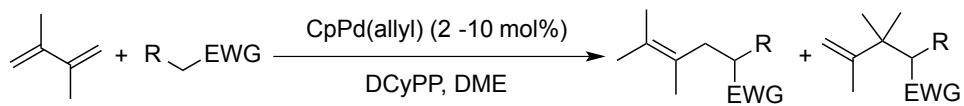
Trost. *Tet. Lett.* 1992, 33, 1831

# Most recent 1,3-diene alkylations

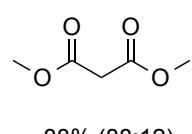
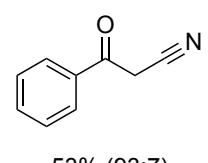
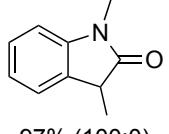
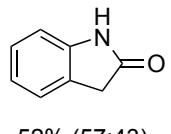
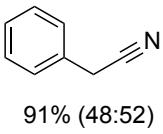
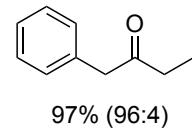
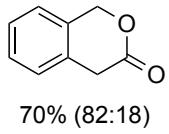
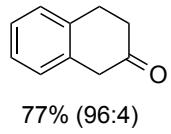


Jolly. *J. Organomet. Chem.* **1995**, 486, 163

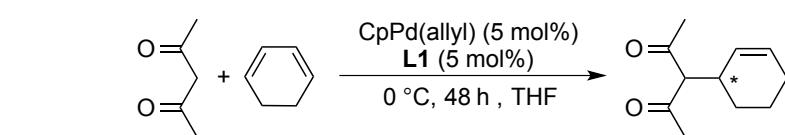
- Hartwig greatly expanded the field



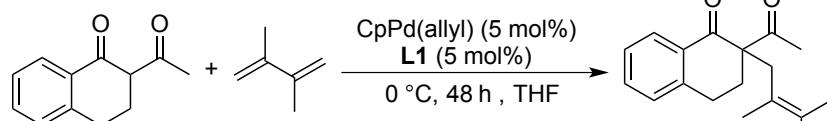
## Nucleophiles



DCyPP =  $Cy_2P\text{---}CH_2\text{---}PCy_2$



71% yield  
81% ee



97% yield  
57% ee

$L1 = \begin{array}{c} \text{---}P\text{Bu}_2 \\ | \\ \text{---}C_5\text{H}_5\text{---Fe---C}_5\text{H}_5\text{---}P\text{Ph}_2 \end{array}$

Hartwig. *JOC* **2004**, 69, 7552

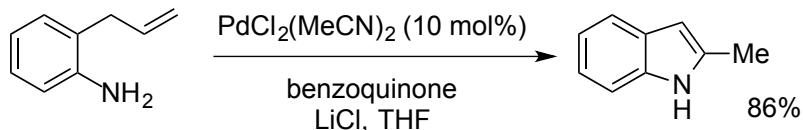
# Overview

---

- **Hydroalkylation of pronucleophiles**
  - 1,3-Diene alkylation
  - Intramolecular olefin alkylation
  - Intermolecular olefin alkylation
  
- **Hydroalkylation of electron rich arenes**
  - Electron rich benzene rings
  - Electron rich heterocycles

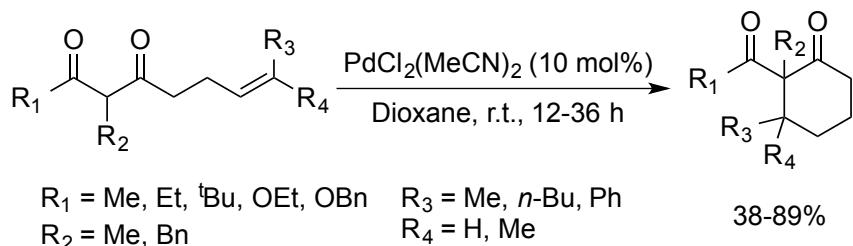
# Intramolecular olefin alkylations

- Pioneered by Widenhoefer of Duke University
- Analogous transformation to the Michael reaction, except no preactivation required
- Major issue with this chemistry = **avoiding over oxidation**



Murahashi. *Acc. Chem. Res.* **1990**, 23, 49

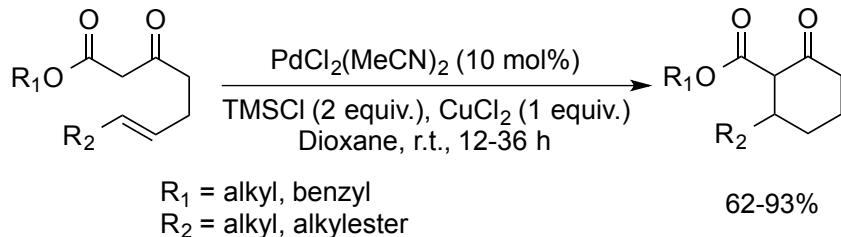
- PdCl<sub>2</sub> salts were found to catalyze diketone alkylations without oxidants at room temp!



- *Endo* selective alkylation
- Trisubstituted olefins were poor substrates

Widenhoefer. *JACS* **2001**, 123, 11290

- Less acidic substrates required stoichiometric TMSCl and CuCl<sub>2</sub> oxidants

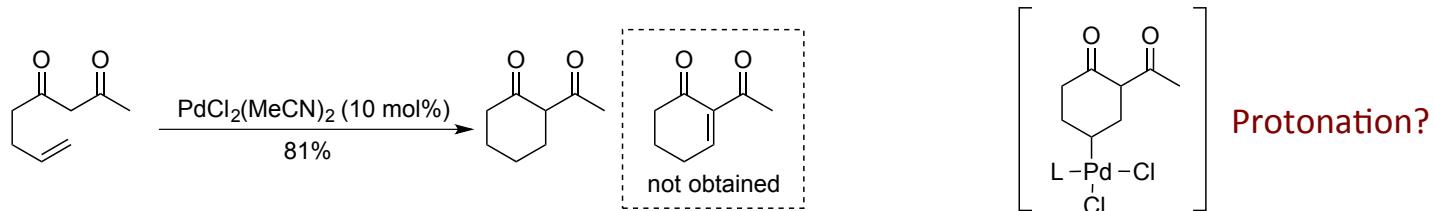


- TMSCl proposed to increase enol tautomer
- CuCl<sub>2</sub> prevents catalyst decomposition

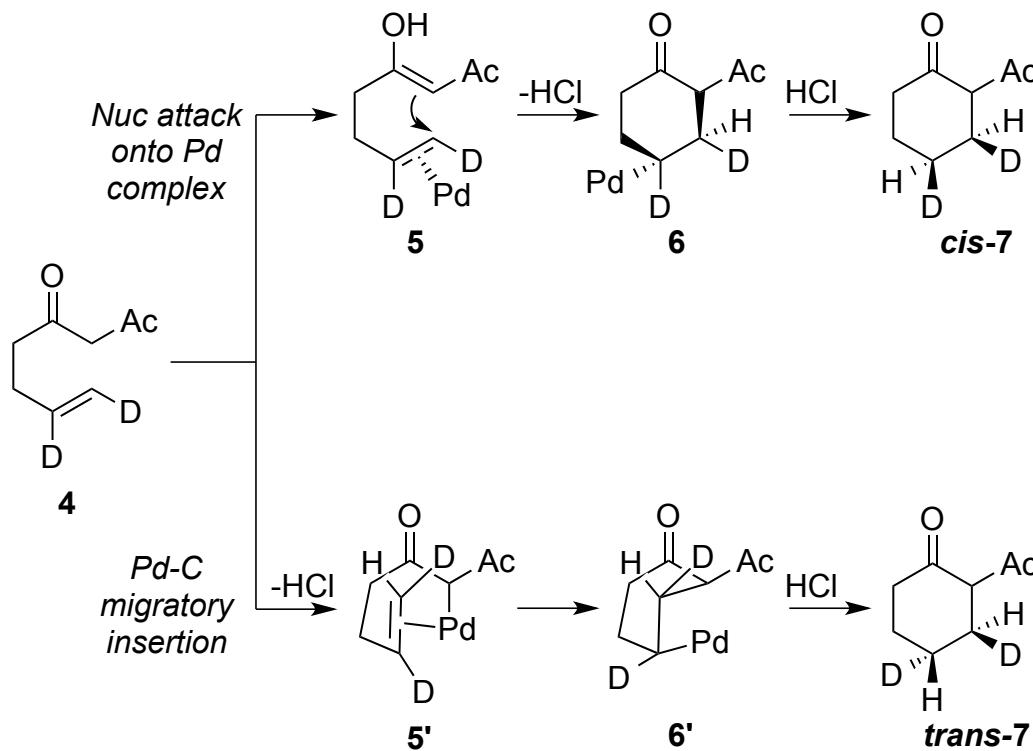
Widenhoefer. *Chem Commun* **2002**, 650

# Mechanism study

- So why did Pd(II) not get reduced to Pd(0) under these conditions?

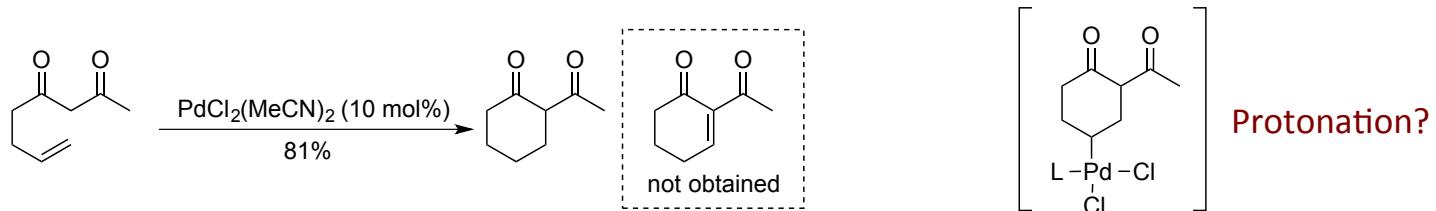


- Utilized deuterium studies

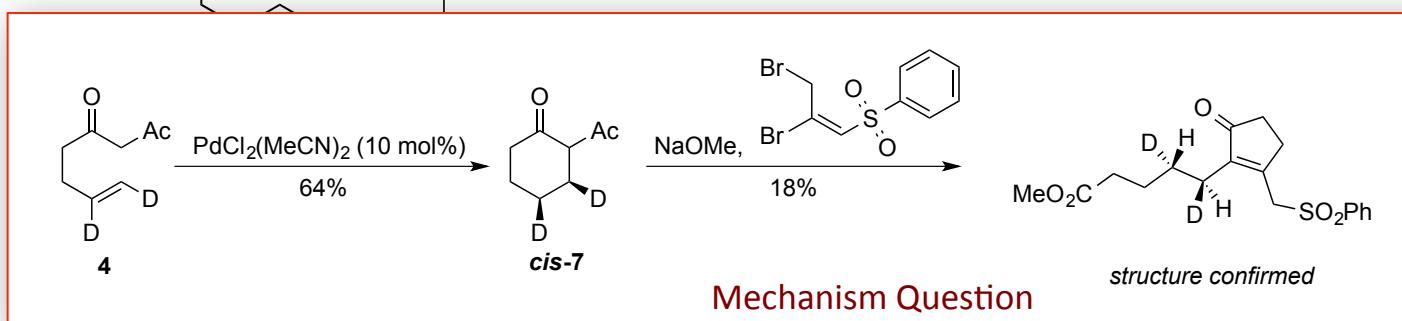
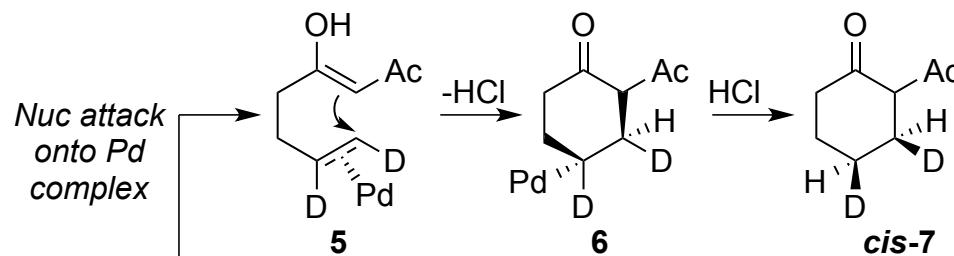


# Mechanism study

- So why did Pd(II) not get reduced to Pd(0) under these conditions?



- Utilized deuterium studies



Mechanism Question

5'

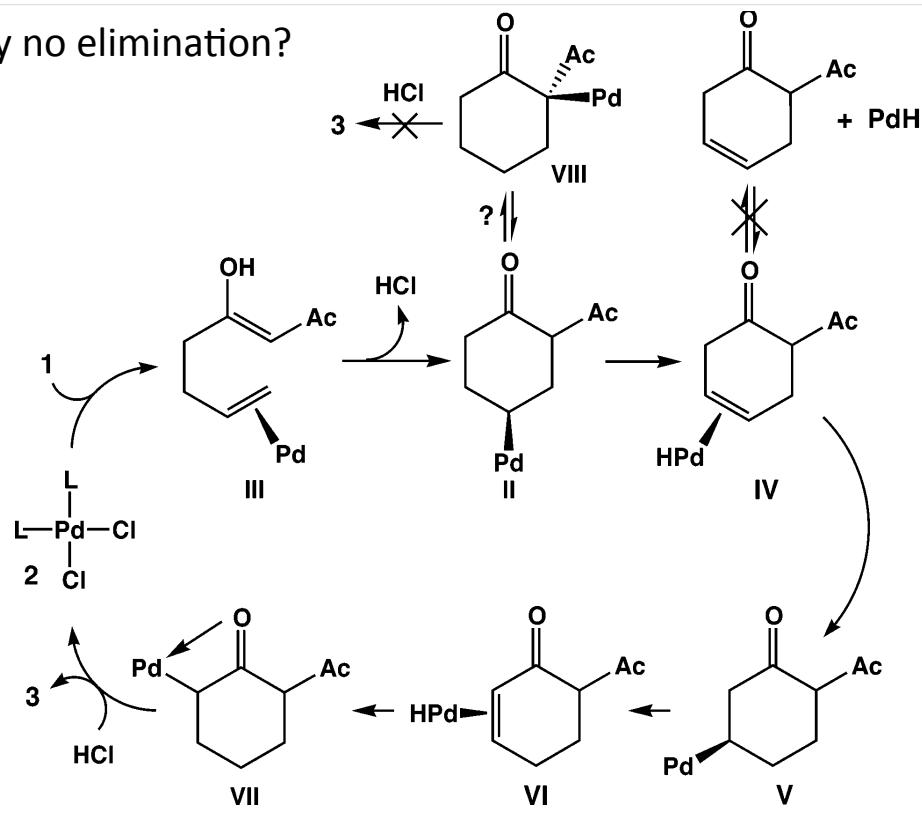
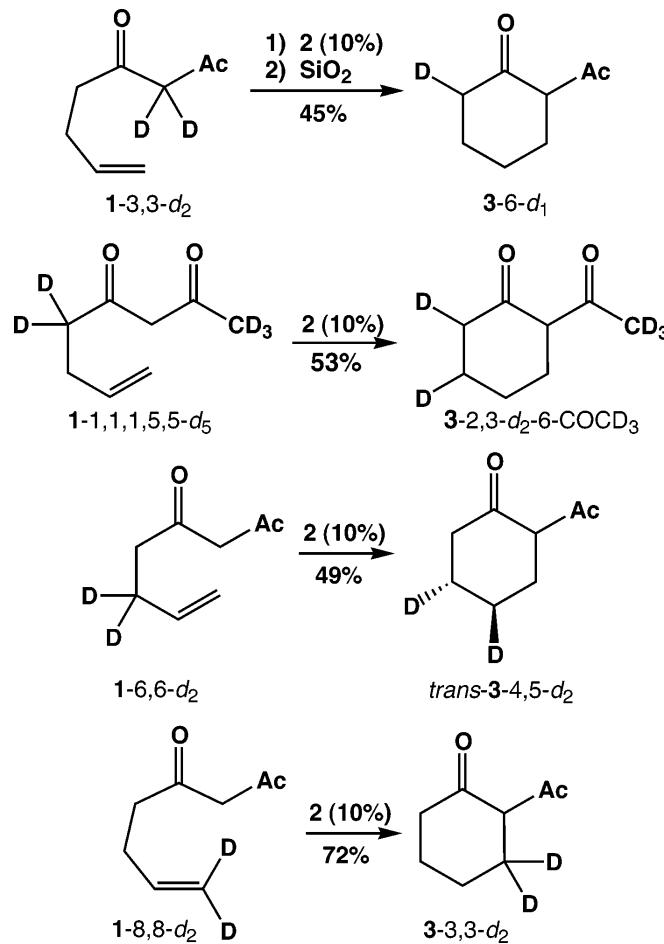
6'

trans-7

Widenhoefer. JACS 2003, 125, 2056

# Mechanism study continued

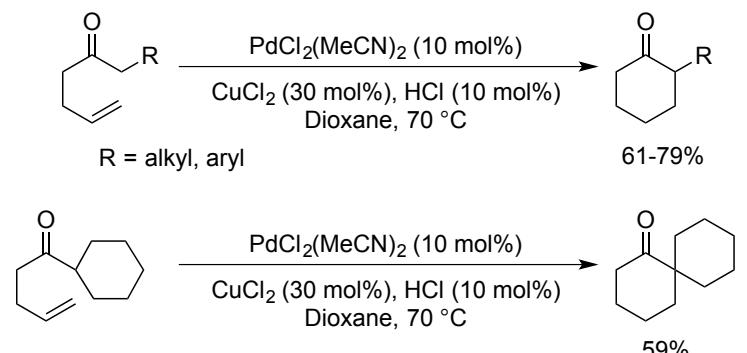
- How does the protonolysis work? – Why no elimination?



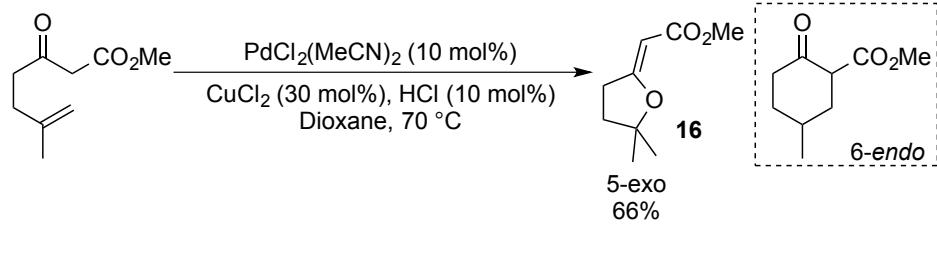
- Reaction fails to form 5-membered rings
    - Highly endo selective
  - Authors propose highly restricted enolic attack
    - 6-*endo* actually then is kinetically favored

# Deeper investigations

- Original work with TMSCl additives increased yields presumably due to the silyl enol ether
  - NMR studies showed that TMSCl was hydrolyzed forming HCl in the reaction

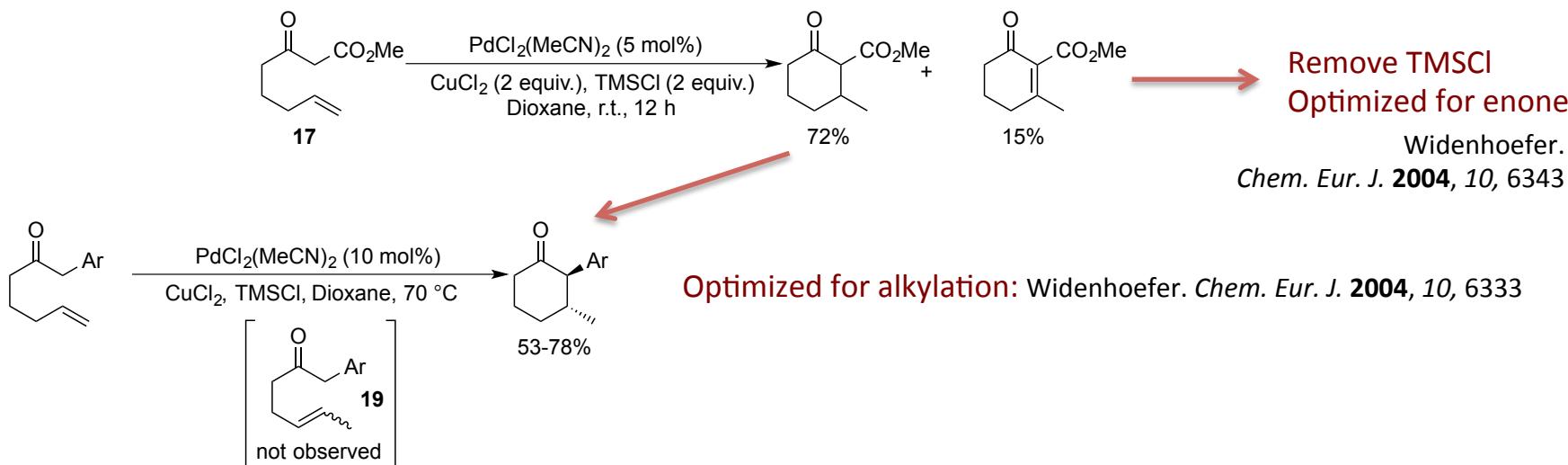


- Substitute the internal olefin position?



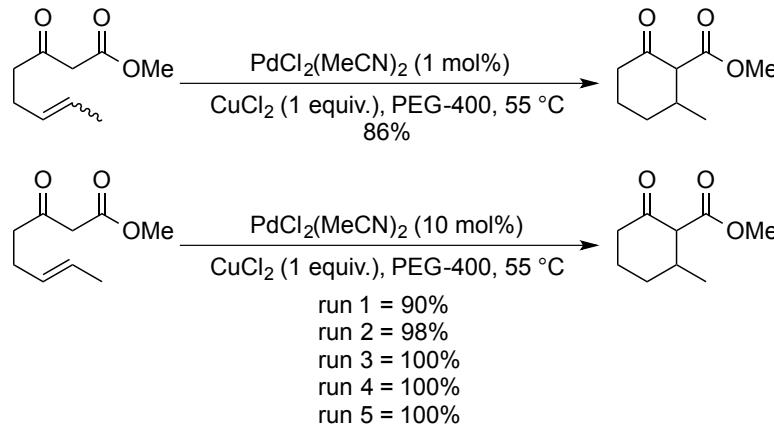
Widenhoefer. *Chem. Eur. J.* **2004**, *10*, 6343

- Extend alkene position?



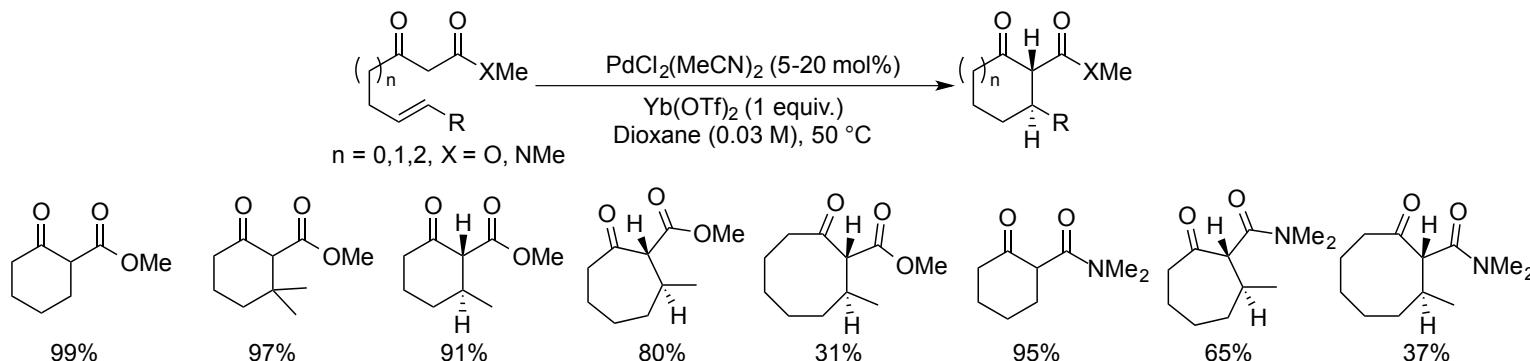
# Alkylation practicality

- PEG-400 [poly(ethylene glycol-400)] – used as a solvent (non volatile or mixing)
  - Acidic and improves stability of catalyst → recyclable



Yang. JOC 2005, 70, 5347

- Lewis acid additives could replace HCl to promote enol formation

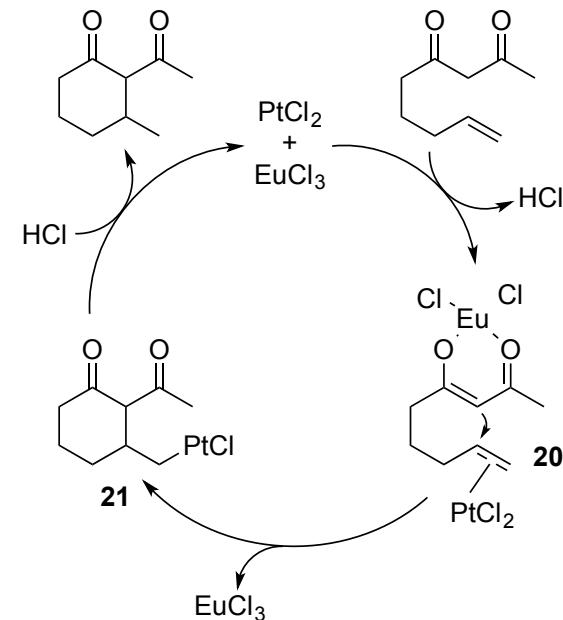
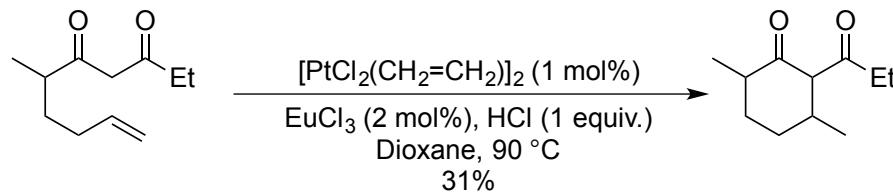
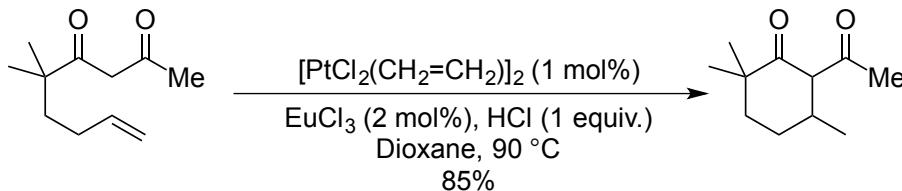


- Could reduce LA loadings to catalytic, but slower reactions
- First formation of larger rings!

Yang. Org. Lett. 2003, 5, 2869

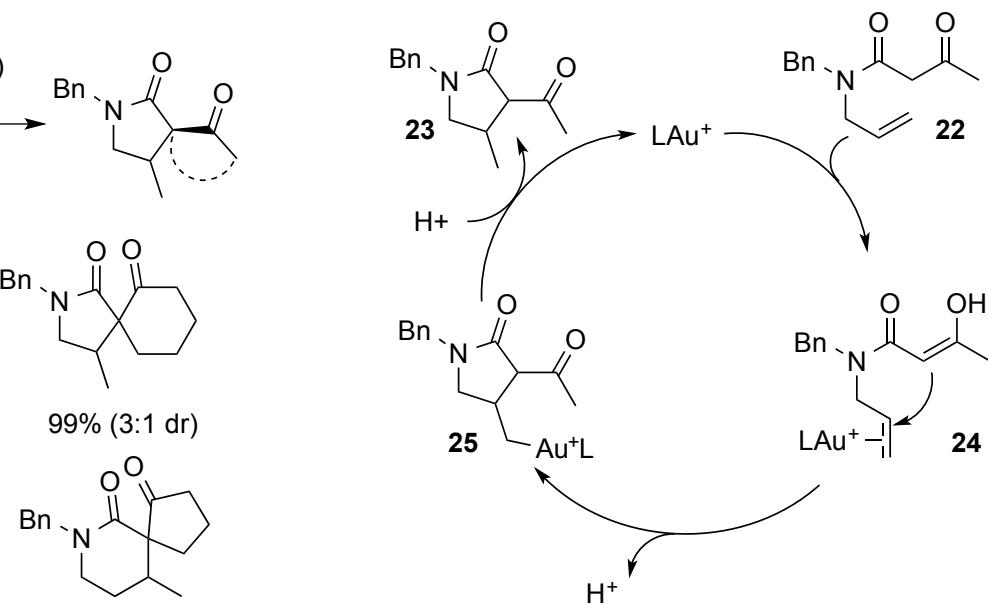
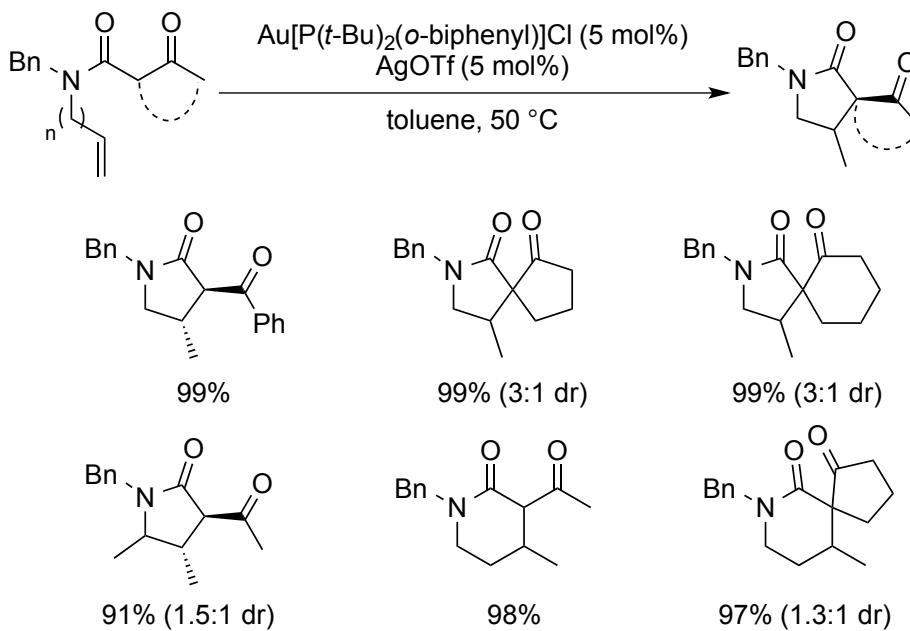
# Pt catalysis

- Alkyl Pt(II) complexes are less receptive towards  $\beta$ -hydride elimination pathways
  - Combined with LA additive, reaction was highly effective

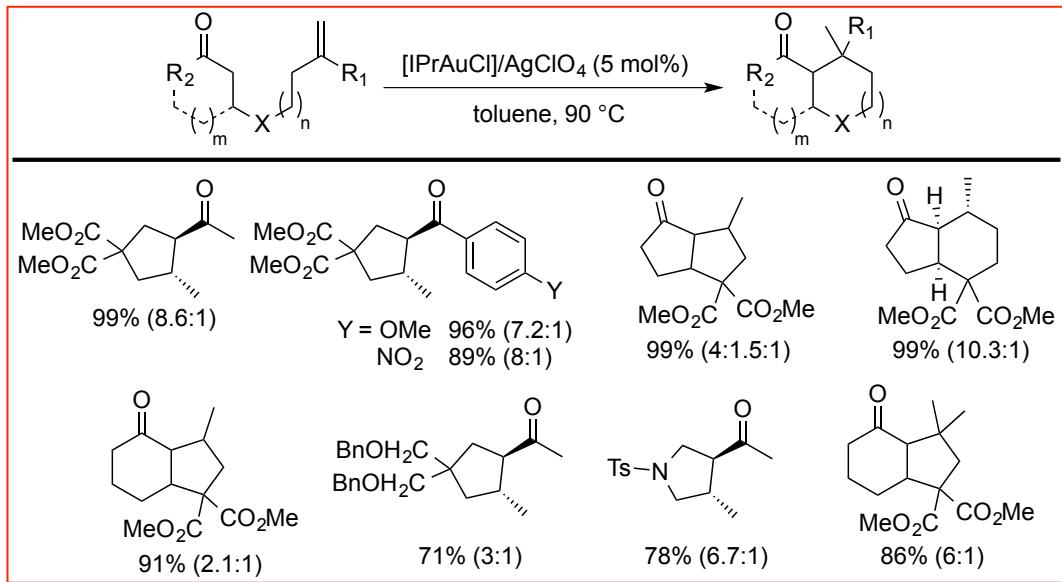


# Gold Catalysis

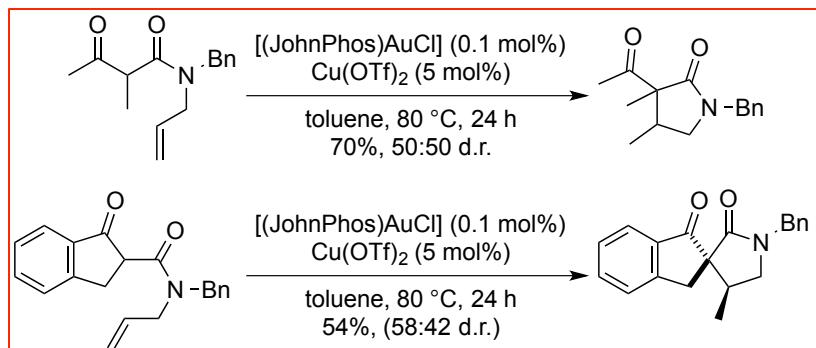
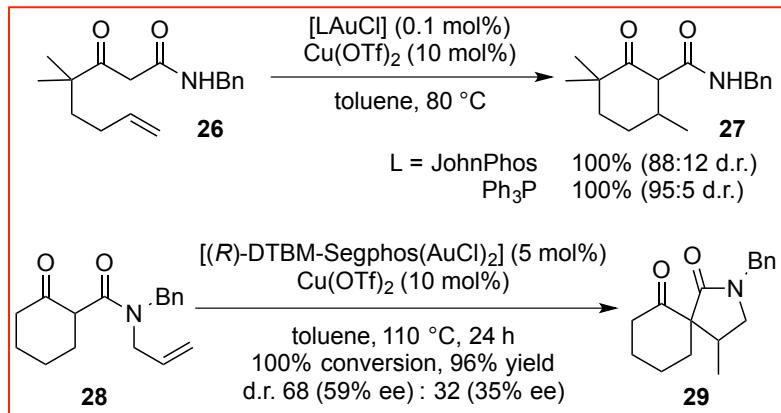
- Chi-Ming Che enters the game towards the synthesis of biologically relevant molecules
  - First gold catalysis in this field with unactivated olefins
  - $\text{Au}(\text{PPh}_3)\text{Cl}/\text{AgOTf}$  results in 87% yield
- All *exo-trig cyclizations*, no *endo*!
- 5g scale – 90% yield / or with water as solvent for 94% yield



# Gold becomes the top choice



Che. Angew. Chem. Int. Ed. 2011, 50, 4937



Gandon. Angew. Chem. Int. Ed. 2013, 52, 5848

Gandon. Che. Eur. J. 2014, 20, 5439

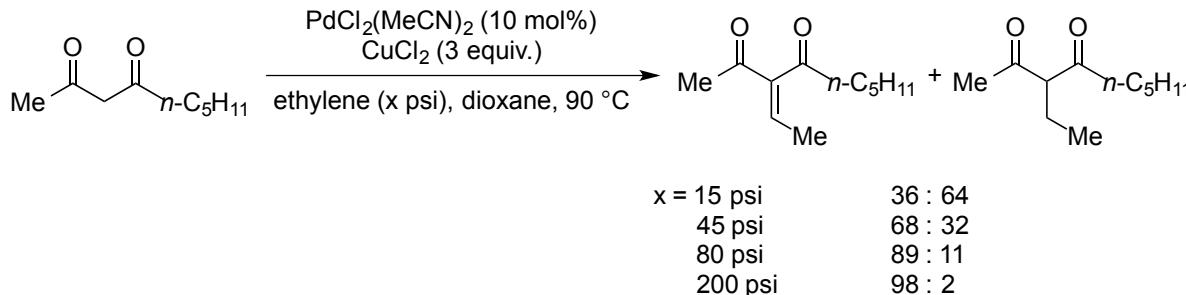
# Overview

---

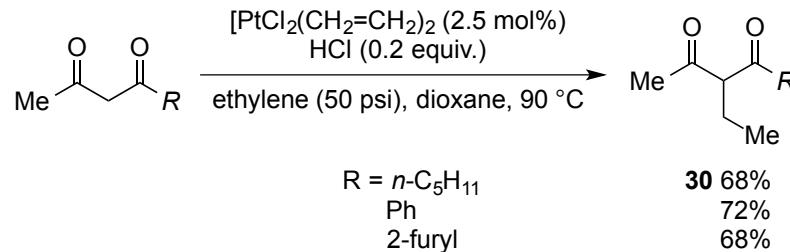
- **Hydroalkylation of pronucleophiles**
  - 1,3-Diene alkylation
  - Intramolecular olefin alkylation
  - **Intermolecular olefin alkylation**
  
- **Hydroalkylation of electron rich arenes**
  - Electron rich benzene rings
  - Electron rich heterocycles

# Intermolecular olefin alkylation

- More uncommon and difficult than **intramolecular** counterpart
- First discovery was with ethylene gas from Widenhoefer



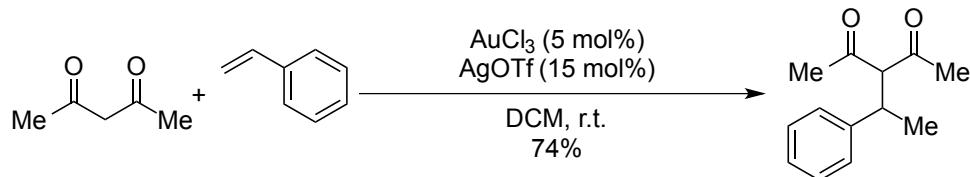
- Used previous conditions for intramolecular cyclizations
- Increasing ethylene leads to oxidized product
  - Ethylene association favored over protonolysis pathway



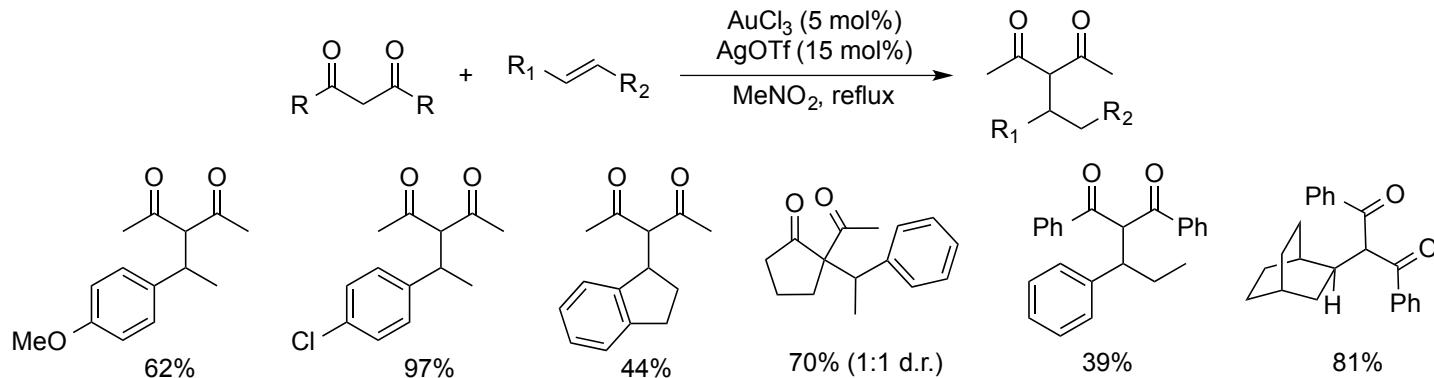
➤ *Pt(II) species utilized to slow down  $\beta$ -Hydride elimination*

# Moving back to Gold

- First alkylation with [activated] olefins by gold catalysis was accomplished by Li



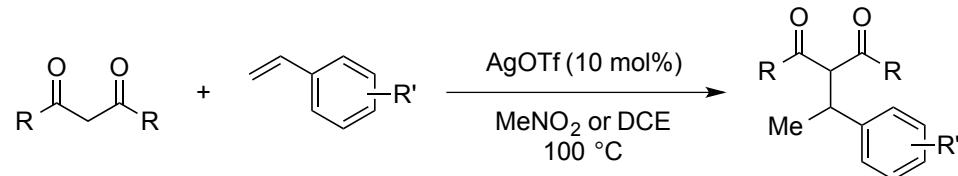
- *Regioselective Markovnikov product*
- *Styrene used in excess due to dimerization issue*



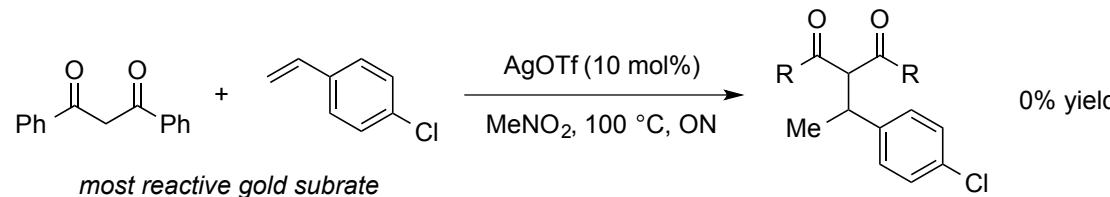
- *Ligands stabilizing gold reduced yields*
- *Electron rich olefins reduce yields*

# All this use of silver additives.....

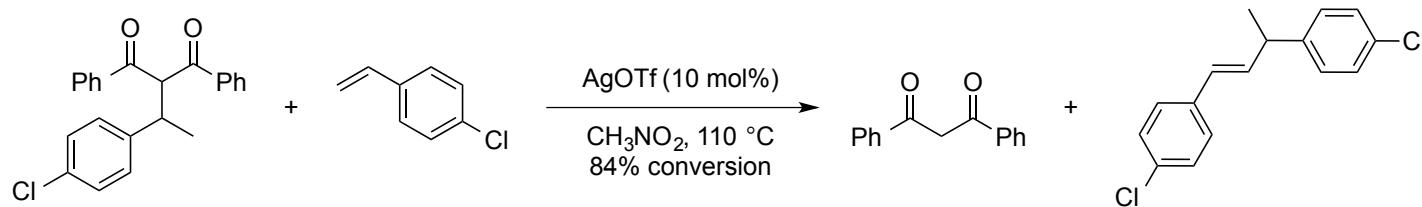
- First alkylation with olefins (activated) by silver catalysis was accomplished by Li
  - Only works with higher temps and OTf counter-anion



- Substrate scope was equivalent to previous report, with slightly diminished yields
- Highlight of this paper:



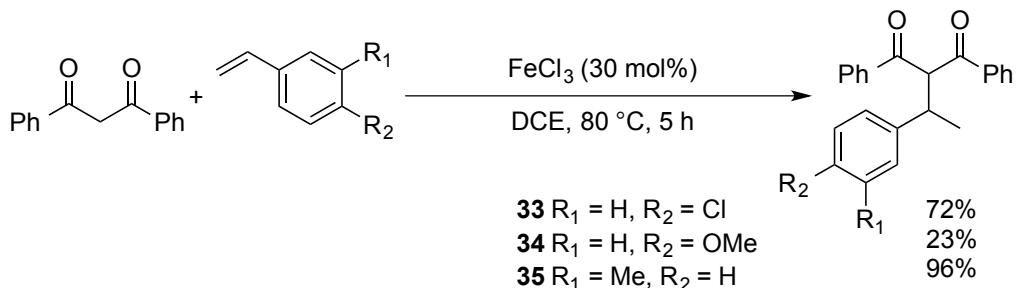
reaction time:	conversion (%):
1	11
3	50
4	60
7	40
11	27



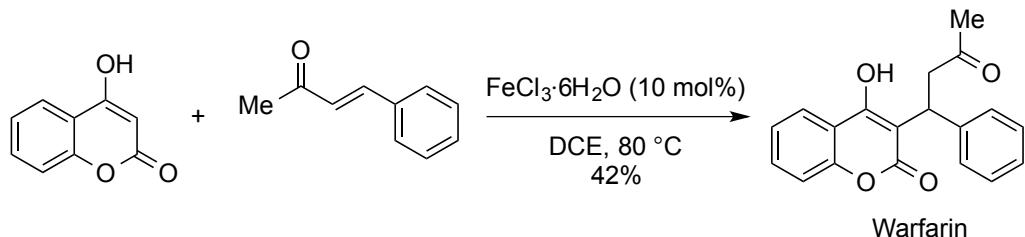
➤ C-C bond formation is reversible with silver-catalyzed C-C bond cleavage

Li. JOC 2005, 70, 5752

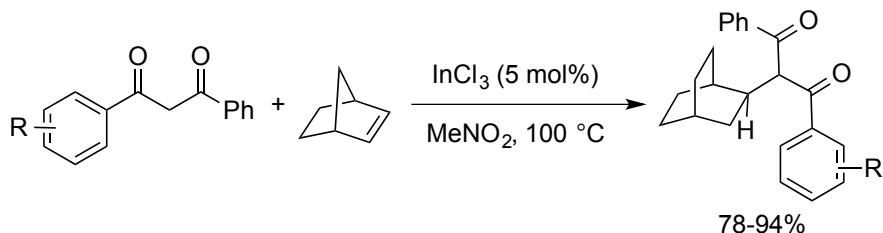
# More abundant earth metals



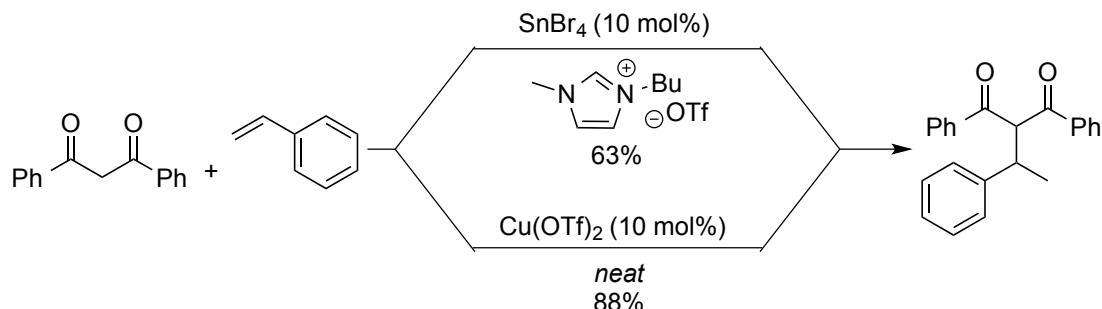
Duan and Wu. *Tet. Lett.* **2007**, *48*, 5157



Beller. *Chem. Asian. J.* **2007**, *2*, 909



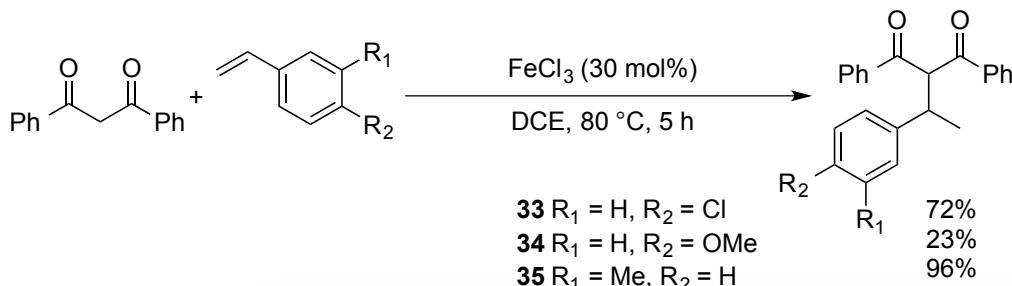
Yuan. *Synlett* **2007**, *20*, 3219



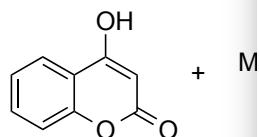
Li. *J. Mol. Catal. A: Chem.* **2008**, *279*, 218

➤ Gets rid of hazardous DCM solvent

# More abundant earth metals



Duan and Wu. *Tet. Lett.* **2007**, *48*, 5157

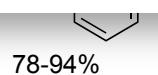
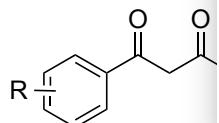


Unsolved Problems for Intermolecular Alkylation:

2007, *2*, 909

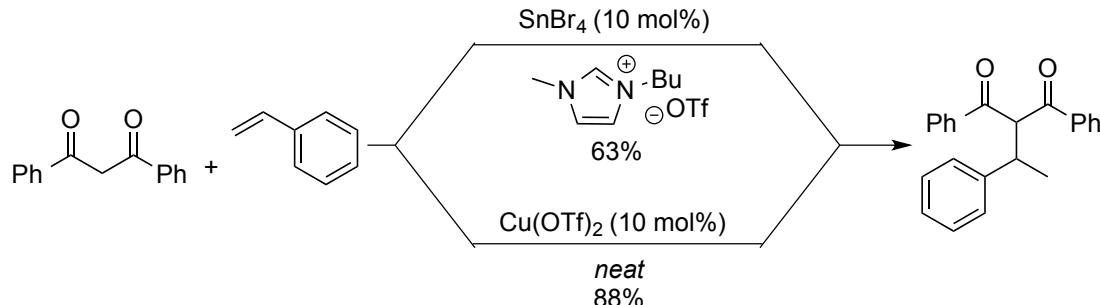
*Monoketo compounds still unattainable*

*Simple linear unactivated olefins have not yet been used*



78-94%

3219



*Li. J. Mol. Catal. A: Chem.* **2008**, *279*, 218

➤ Gets rid of hazardous DCM solvent

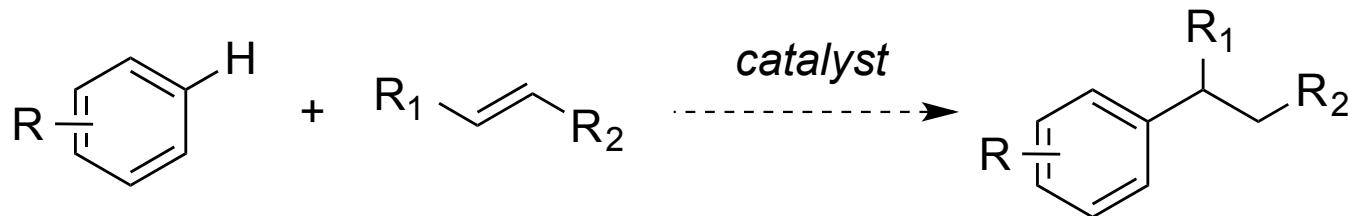
# Overview

---

- **Hydroalkylation of pronucleophiles**
  - 1,3-Diene alkylation
  - Intramolecular olefin alkylation
  - Intermolecular olefin alkylation
- **Hydroalkylation of electron rich arenes**
  - Electron rich benzene rings
  - Electron rich heterocycles

# Alkylation of electron rich benzenes

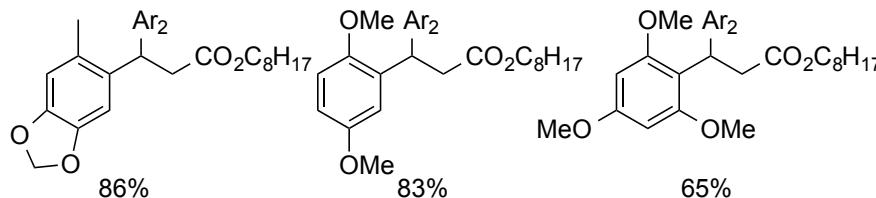
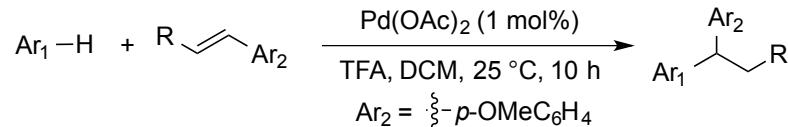
- Mild/selective alternative towards Friedel-Crafts reactions



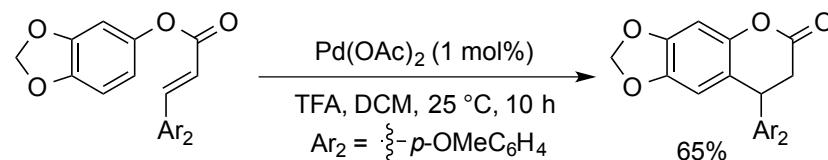
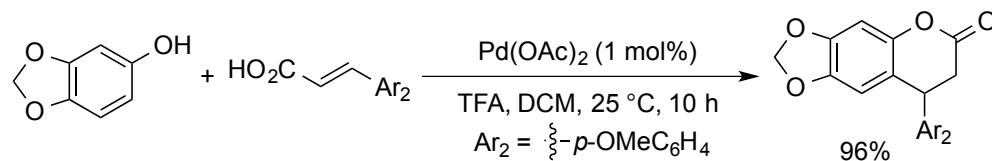
- Need really electron deficient metal species to activate olefins for weaker nucleophiles
- Major limitation → product formed is highly susceptible towards β-hydride elimination

# Alkylation of electron rich benzenes

- Utilized very electrophilic Pd(II) or Pt(II) cationic species (Pt was less reactive)
  - Main scope of this transformation is for alkynes

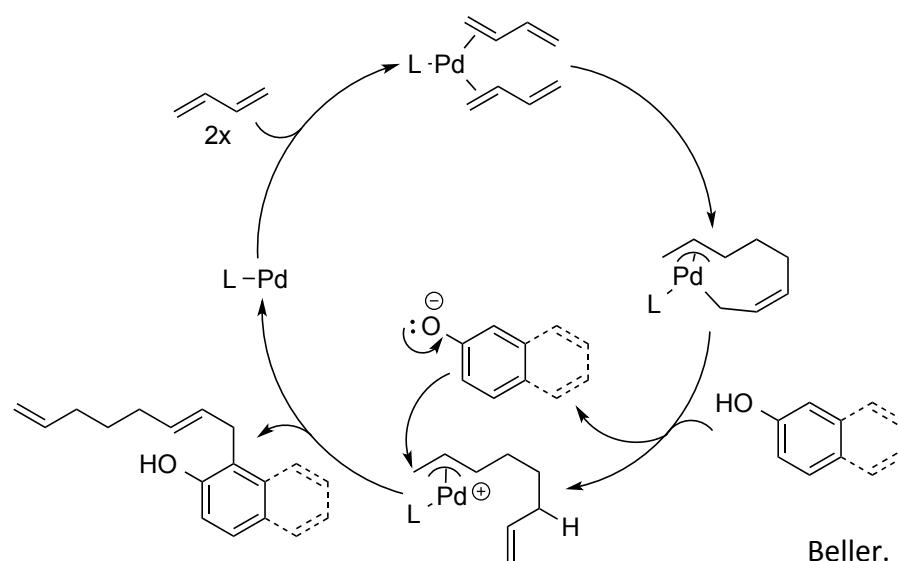
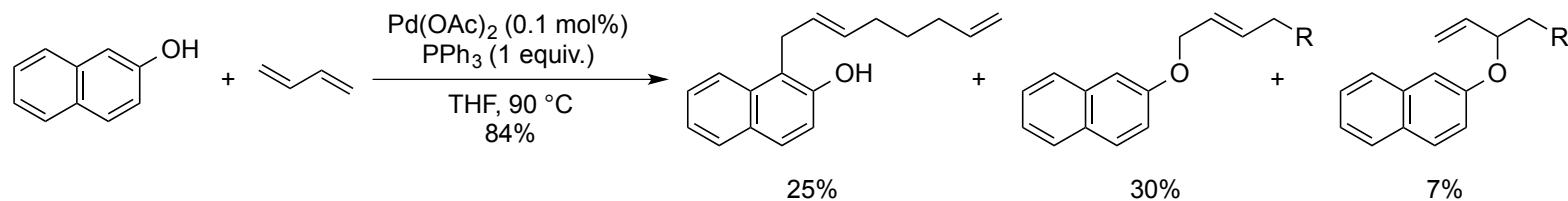


- Phenols allowed for bicyclic formation – with esterification occurring before or after alkylation



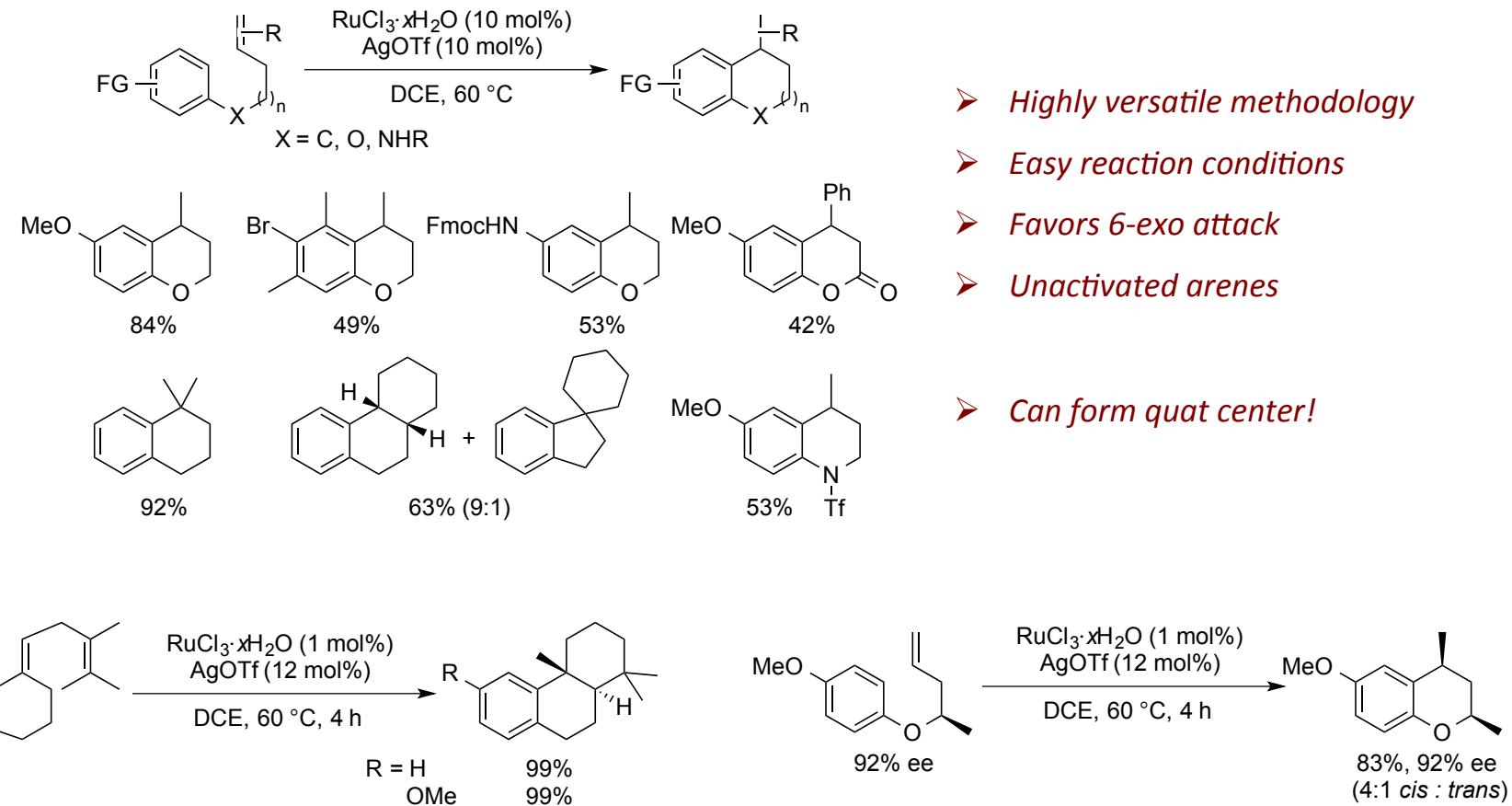
# Phenolic alkylations through telomerization

- Earlier report in the late 1960s only saw *O*-alkylation with phenols with Pd(II) catalysis
- Beller tried conditions from telomerization reaction with methanol



# Intramolecular hydroarylation

- Sames group is the first to utilize ruthenium in this field
  - Other metals screened promoted olefin isomerization

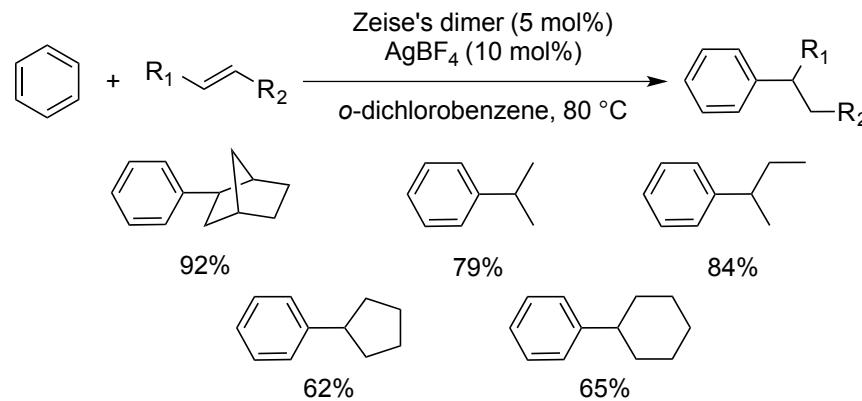


Promotes polyene cyclizations

Substrate chirality can promote stereoselectivity

# More general arene alkylation procedure

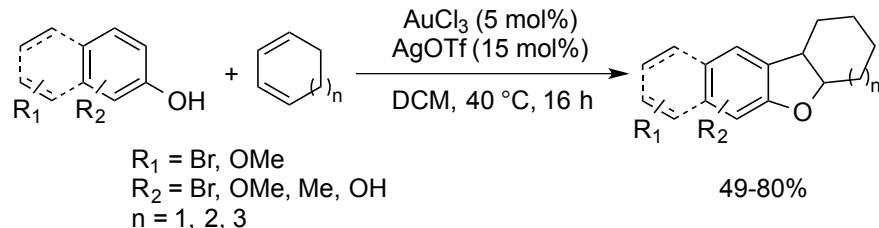
- Don Tilley's group did in-depth Pt catalyst examinations
  - Original goal was to make a Pt(IV) species
- They did discover that Pt(II) salts with Ag additives could promote this transformation
  - AgOTf and AgBF<sub>4</sub> were necessary



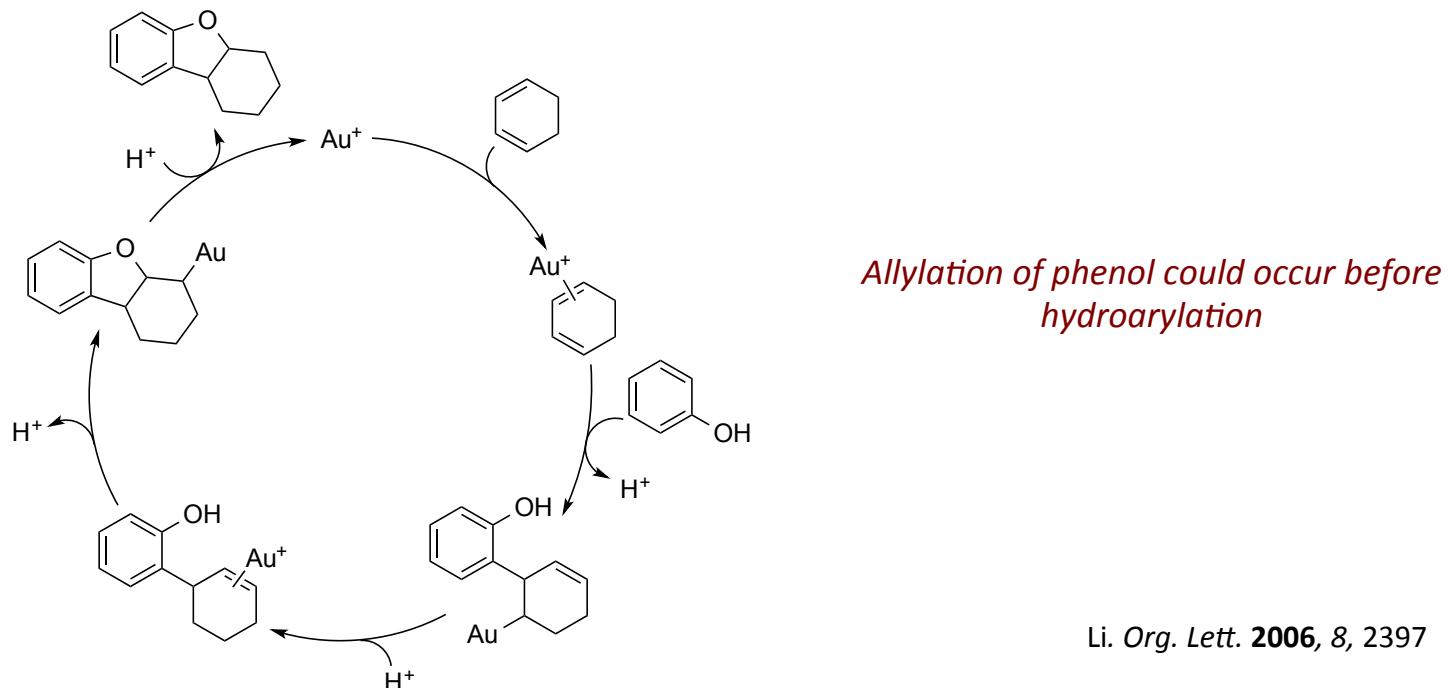
- HOTf could catalyze this reaction separately, but they ruled out its involvement in this process

# Annulation reaction of phenols

- Used catalytic system discovered for 1,3-diketone alkylations

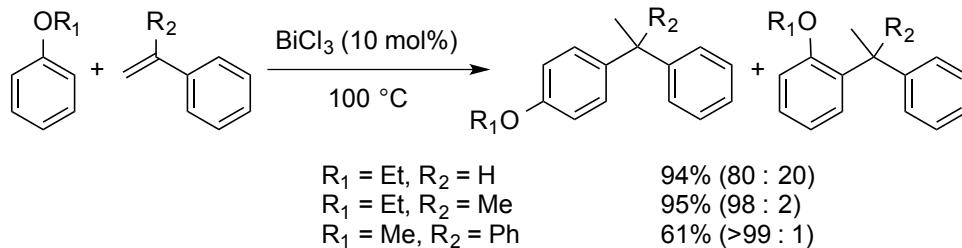


- EWGs or increasing tether size lowers reaction yield
- Analines did not participate in this reaction

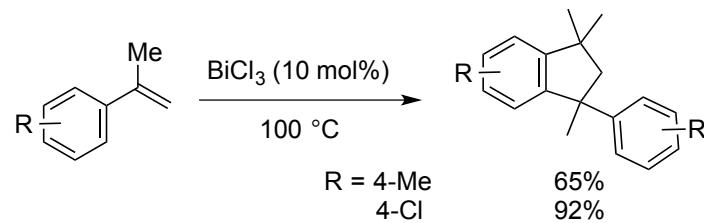


# Bismuth catalysis

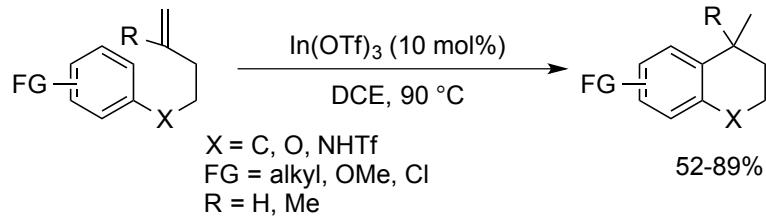
- Bi(III) salts are bench stable, inexpensive, and nontoxic
- Was very effective for neat reaction conditions



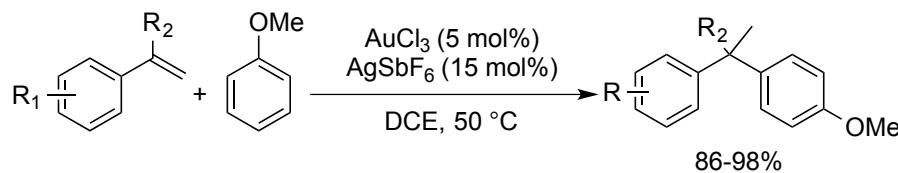
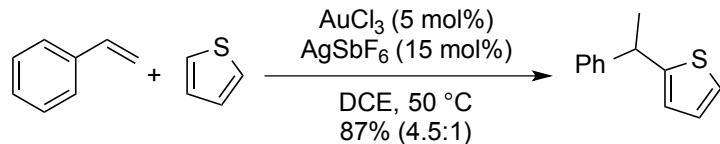
- Was very successful cyclic dimer formation of unactivated styrenes
  - Trisubstituted olefins were not compatible



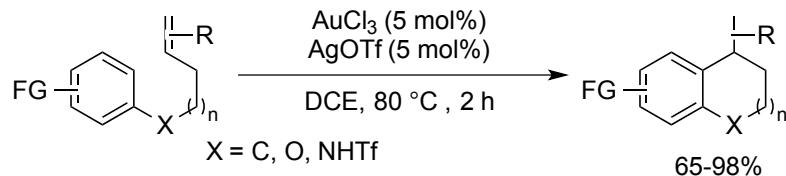
# Other lewis acid systems



Tan. *Tet. Lett.* **2010**, 51, 4466



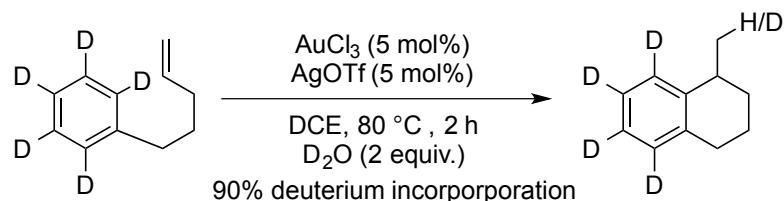
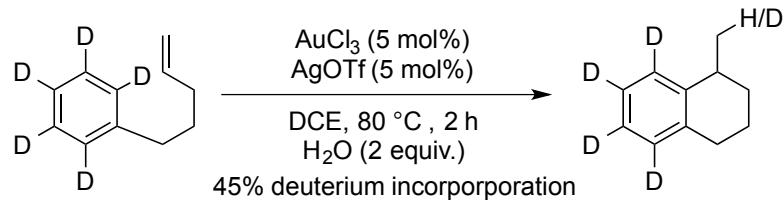
Che. *J. Organomet. Chem.* **2009**, 694, 494



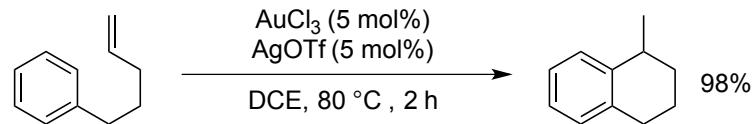
Weghe. *Tet. Lett.* **2011**, 52, 3509

# Some mechanistic analysis

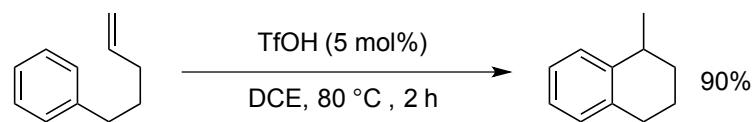
- Protonolysis was presumed the limiting step



- Question that remains for these systems, is it Bronstead acid catalysis?

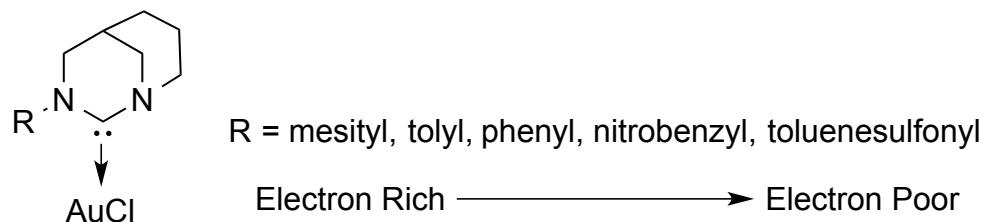


*Could the combination of  $\text{AuCl}_3$  and  $\text{AgOTf}$  simply generate TfOH?*

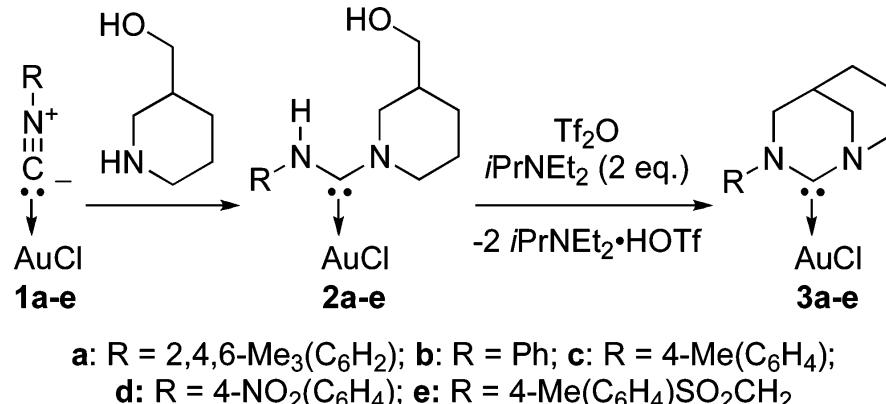


# Getting unique in this catalysis

- Goal: overcome the inability of Friedel-Crafts incapability with analines
- Anti-Bredt electrophilic carbenes
  - Found use in hydroaminations of alkynes and allenes



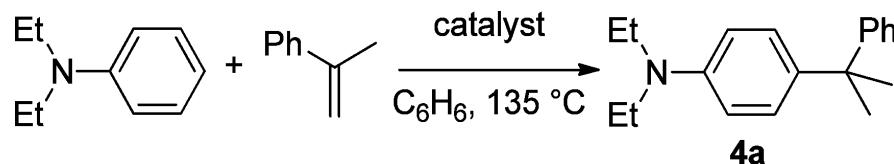
- Synthesis of ligand is built in coordination sphere of metal



# Getting unique in this catalysis

- Goal: overcome the inability of Friedel-Crafts incapability with analines

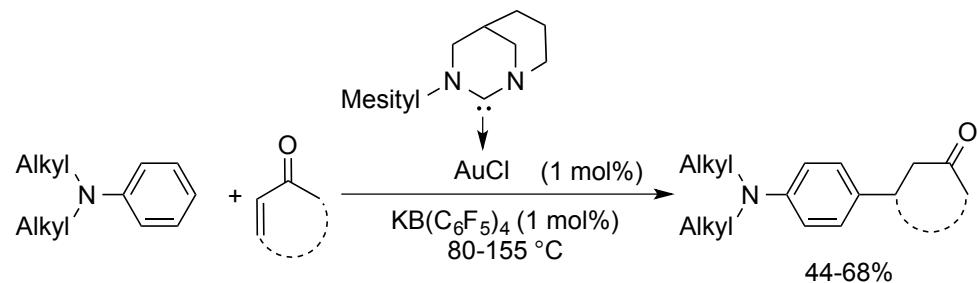
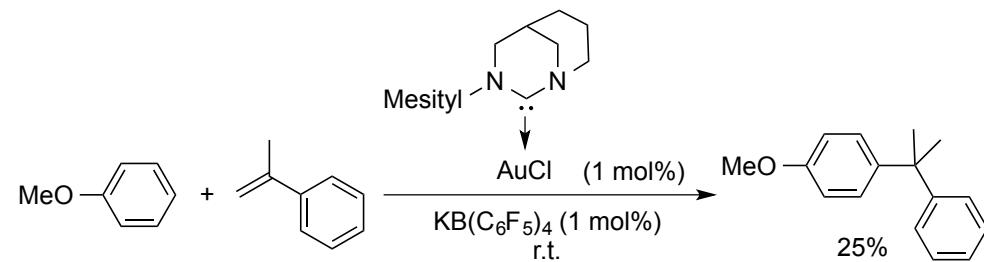
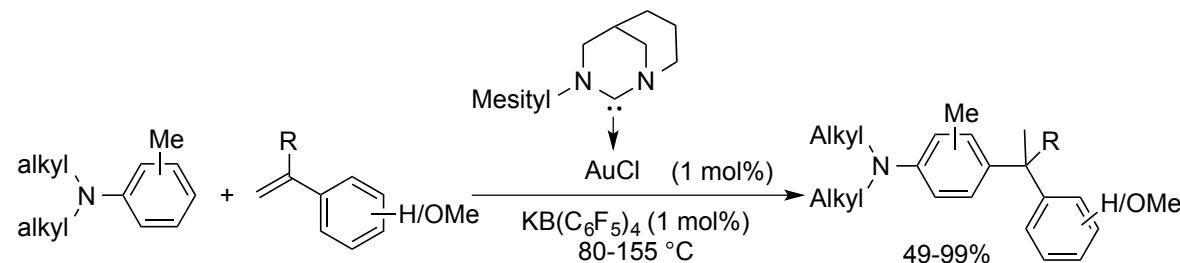
**Table 1. Hydroarylation of  $\alpha$ -Methylstyrene with  $N,N$ -Diethylaniline<sup>a</sup>**



entry	catalytic system	conversion (%)
1	[ <b>3a</b> + KB(C <sub>6</sub> F <sub>5</sub> ) <sub>4</sub> ] (5 mol %)	97
2	[ <b>3b</b> + KB(C <sub>6</sub> F <sub>5</sub> ) <sub>4</sub> ] (5 mol %)	98
3	[ <b>3c</b> + KB(C <sub>6</sub> F <sub>5</sub> ) <sub>4</sub> ] (5 mol %)	89
4	[ <b>3d</b> + KB(C <sub>6</sub> F <sub>5</sub> ) <sub>4</sub> ] (5 mol %)	69
5	[ <b>3e</b> + KB(C <sub>6</sub> F <sub>5</sub> ) <sub>4</sub> ] (5 mol %)	38
6	<b>3a</b> (5 mol %)	0
7	[ <b>3a</b> + AgOSO <sub>2</sub> CF <sub>3</sub> ] (5 mol %)	12
8	[AuCl <sub>3</sub> + 3 AgSbF <sub>6</sub> ] (5 mol %)	10
9	FeCl <sub>3</sub> (10 mol %)	3
10	BiCl <sub>3</sub> (10 mol %)	4

<sup>a</sup>After 24 h; determined by GC.

# Getting unique in this catalysis



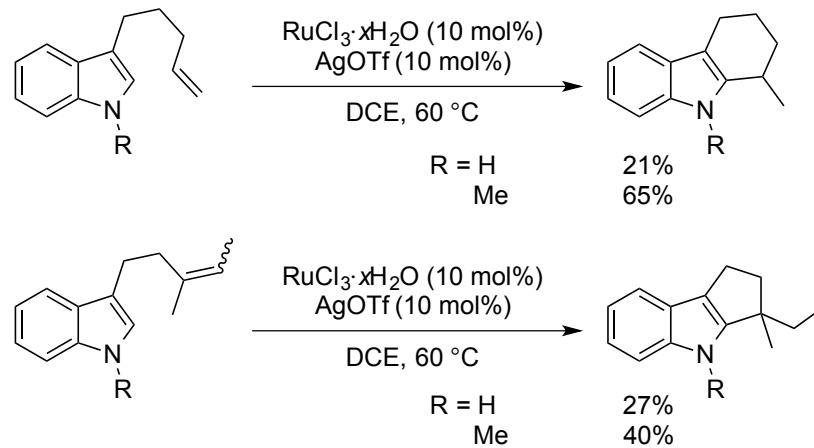
# Overview

---

- **Hydroalkylation of pronucleophiles**
  - 1,3-Diene alkylation
  - Intramolecular olefin alkylation
  - Intermolecular olefin alkylation
- **Hydroalkylation of electron rich arenes**
  - Electron rich benzene rings
  - **Electron rich heterocycles**

# Electron rich heterocycles

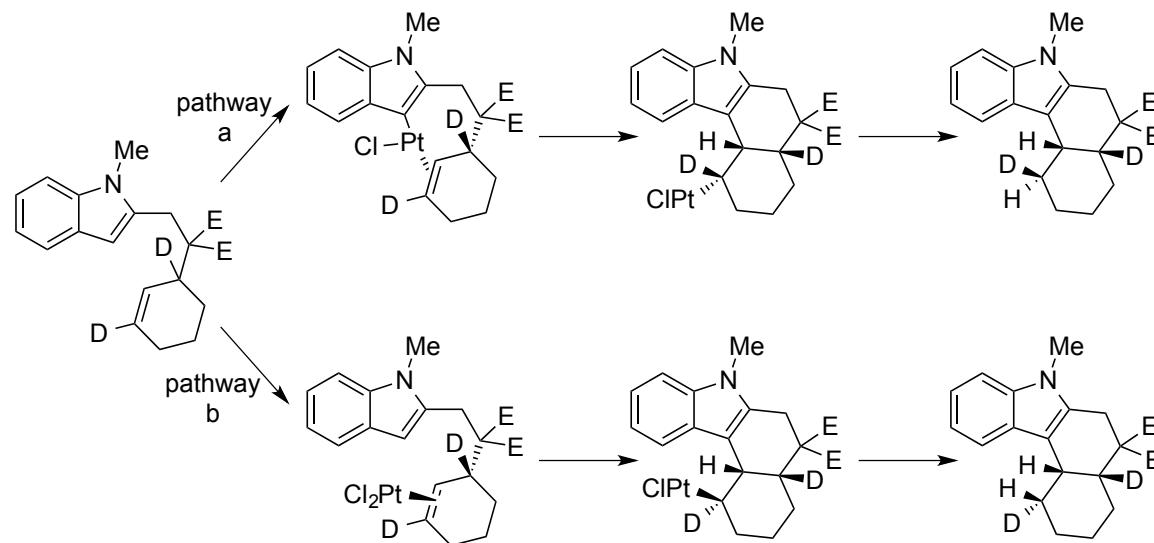
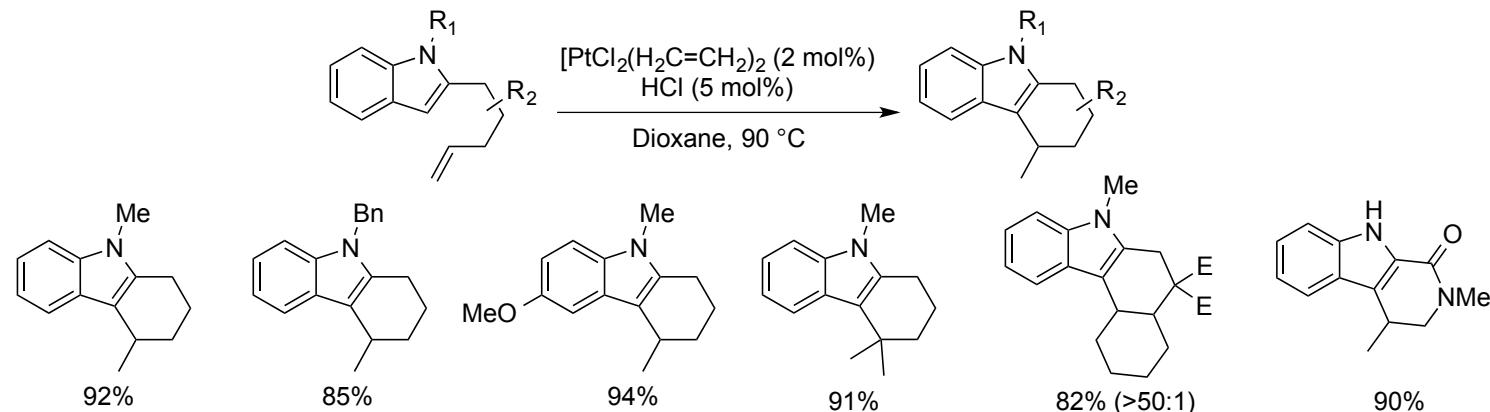
- Focus lies mainly on indole systems
- First report by Sames in 2004 in previously discussed paper (only 2 examples)



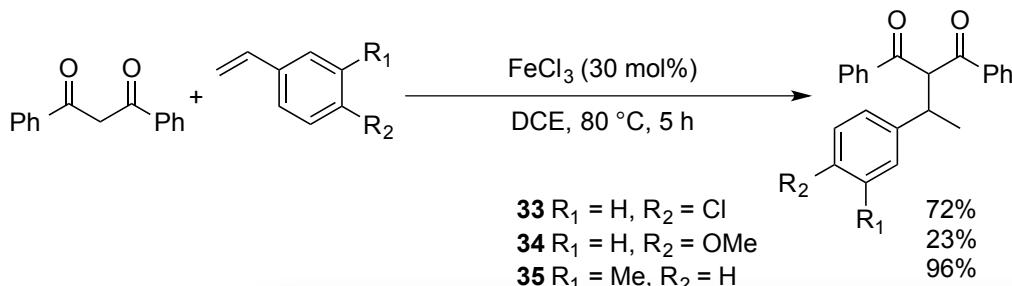
- Actually a very unique example, where alkylation takes place at the less nucleophilic C(2) position

# Alkylation at the C3 position of indoles

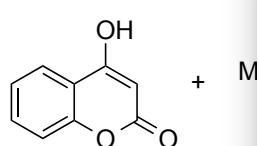
- C3 alkylation of indoles is most widely seen in the literature



# More abundant earth metals



Duan and Wu. *Tet. Lett.* **2007**, *48*, 5157

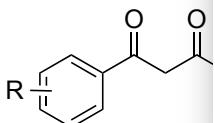


Unsolved Problems for Intermolecular Alkylation:

2007, *2*, 909

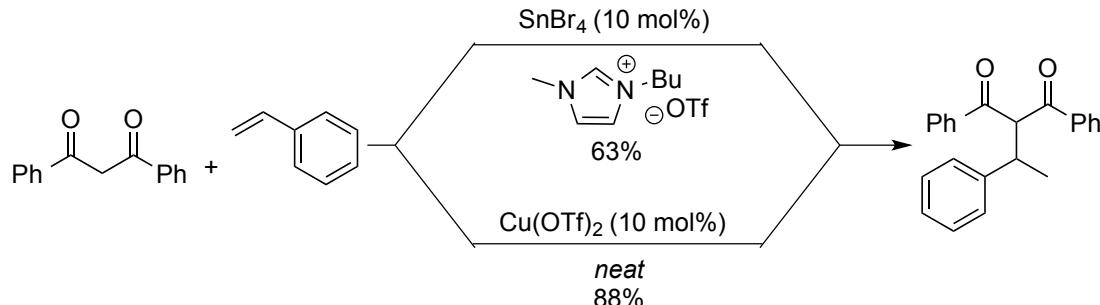
*Monoketo compounds still unattainable*

*Simple linear unactivated olefins have not yet been used*



78-94%

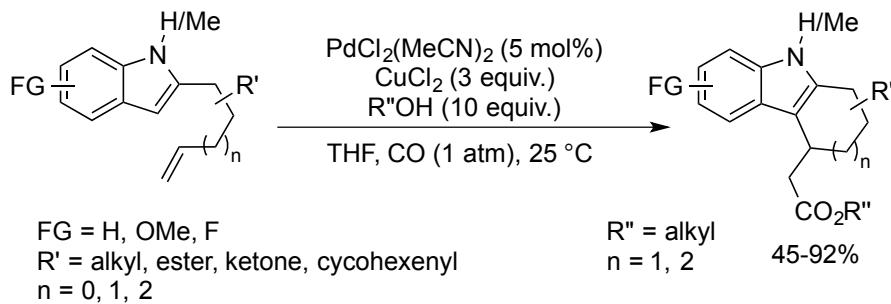
3219



*Li. J. Mol. Catal. A: Chem.* **2008**, *279*, 218

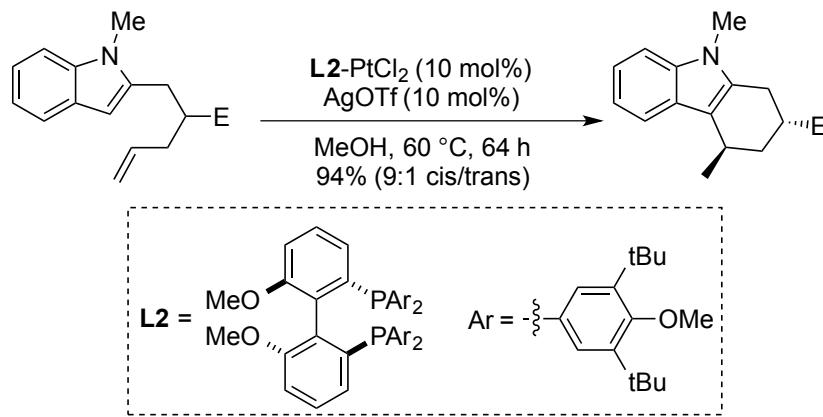
➤ Gets rid of hazardous DCM solvent

# Widenhoefer's contribution



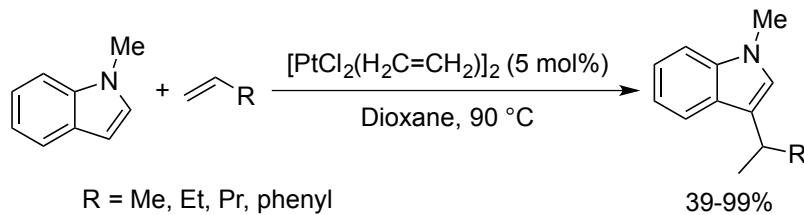
Tandem cyclization/carboalkoxylation

Widenhoefer. *JACS* **2004**, *126*, 10250



Assymmetric alkylation

Widenhoefer. *Org. Lett.* **2006**, *8*, 3801

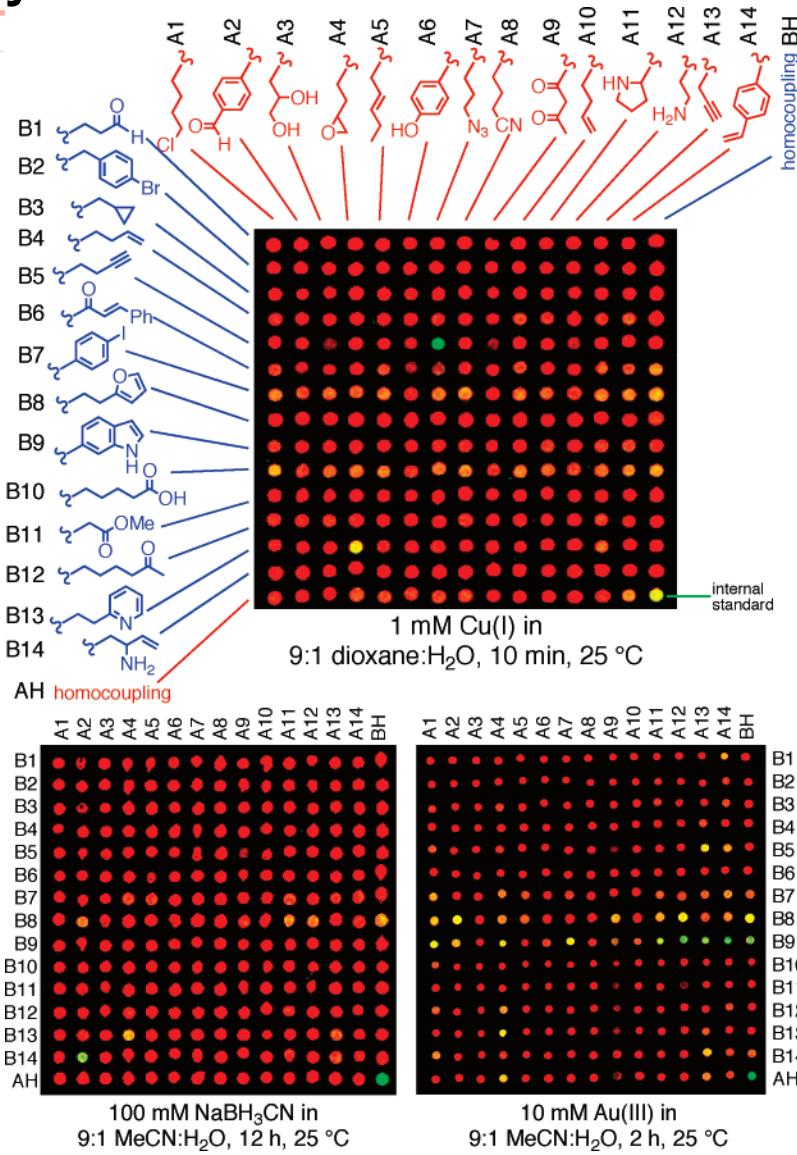
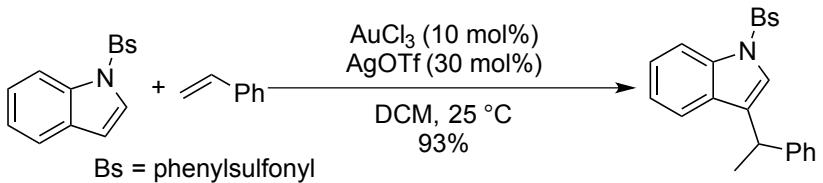


First intramolecular addition

Widenhoefer. *Chem. Commun.* **2006**, 3717

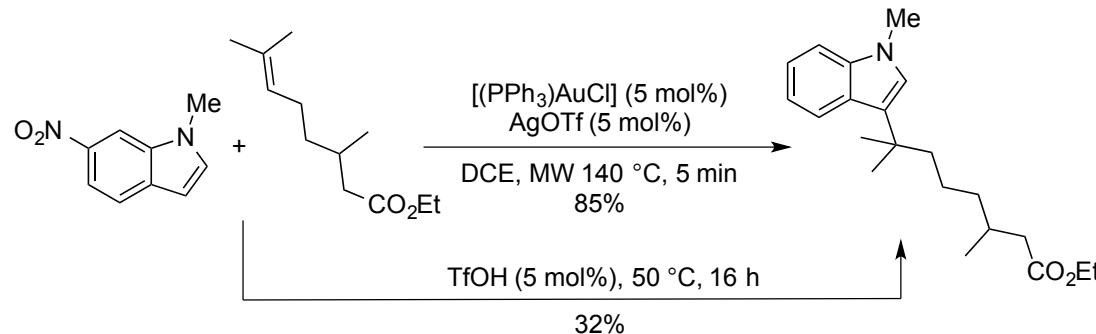
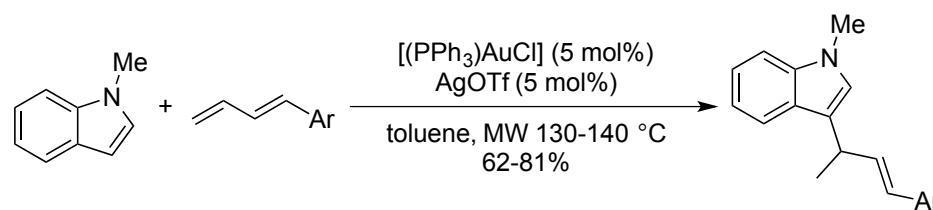
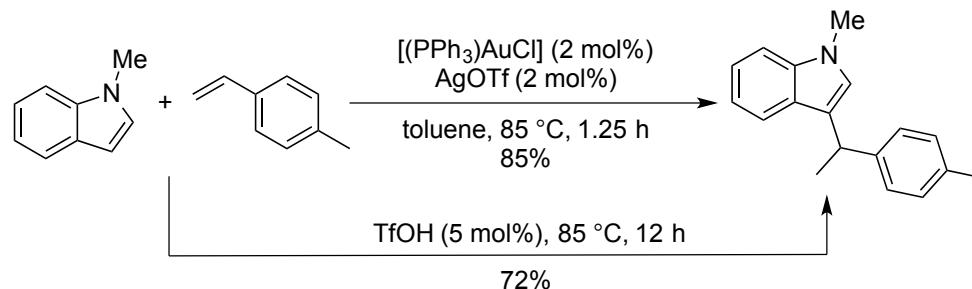
# Gold discovery for indole alkylation

- An interesting side story, group working on reaction discovery from high-throughput screening of large collection of substrates – only looking for new bond formations
- Main focus in this group was with DNA hybridization reactions, but also wanted to test this on small molecule bond-forming reactions
- System works for evaluating > 50,000 potential new reactions
- Screened various metals (i.e. Cu, Pd, Au, etc)



# Other Au catalysis for this alkylation

- Che in the same year followed up with more analysis of this reaction and scope



# Future of this field

---

## Alkylations of pronucleophiles

- Simple olefin alkylations of pronucleophiles is very rare and could be exploited
- Alkylations of simple ketones or weakly acidic C-H bonds is still open for exploration

## Alkylations of arenes

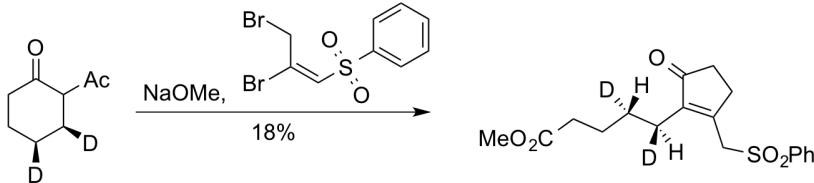
- Trend is moving away from very expensive metals
- Functionalization of electron deficient arenes through this methodology is difficult
- With rise of Bronstead acid catalysts, this field must work to differentiate themselves with asymmetric transformations or with more diverse substrates

# Questions

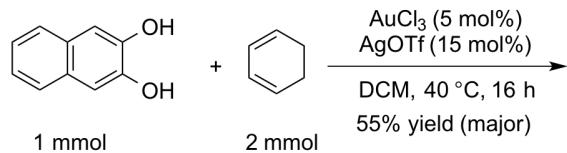
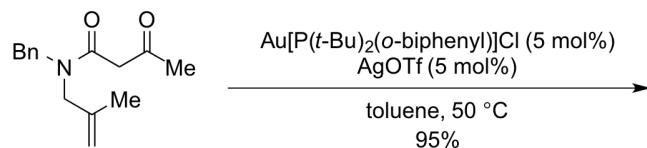
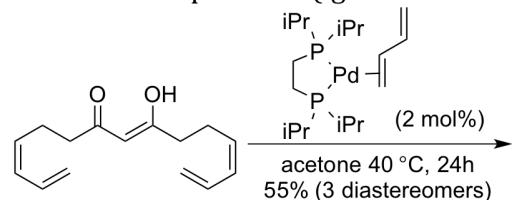
---



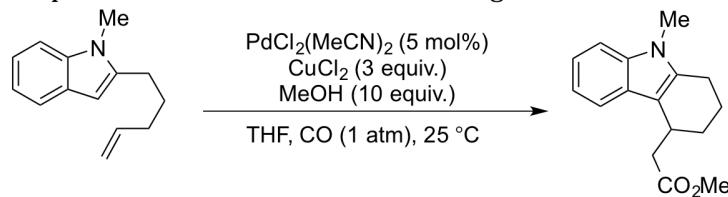
1. Propose a mechanism for the following transformation.



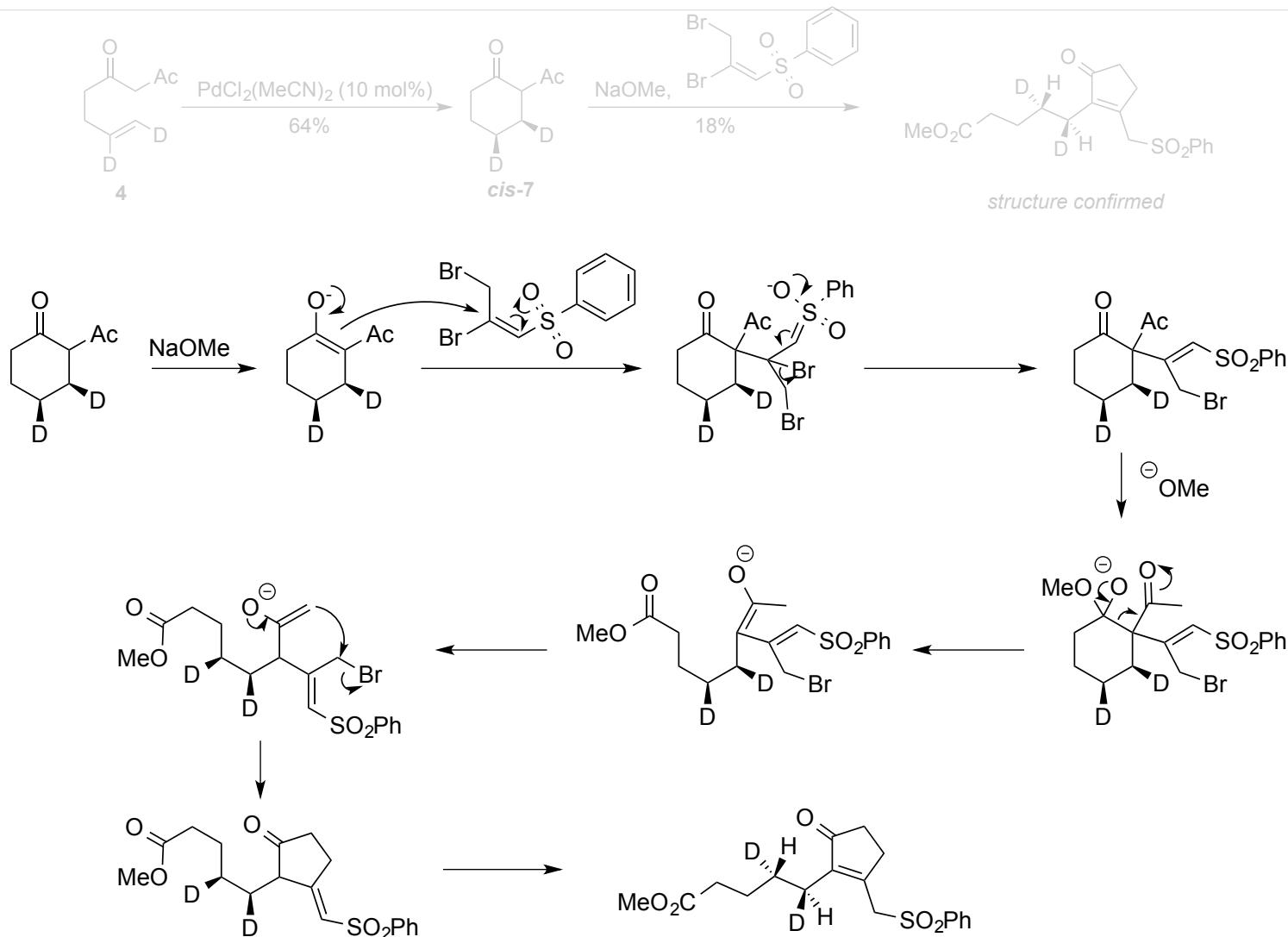
2. Predict the products (ignore stereochem & other isomers).



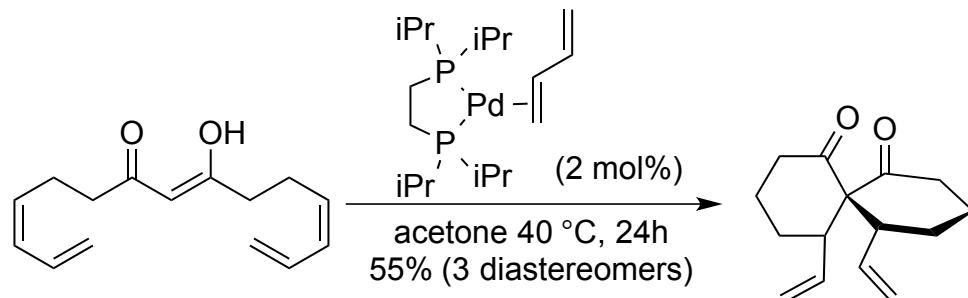
3. Propose a mechanism for the following transformation.



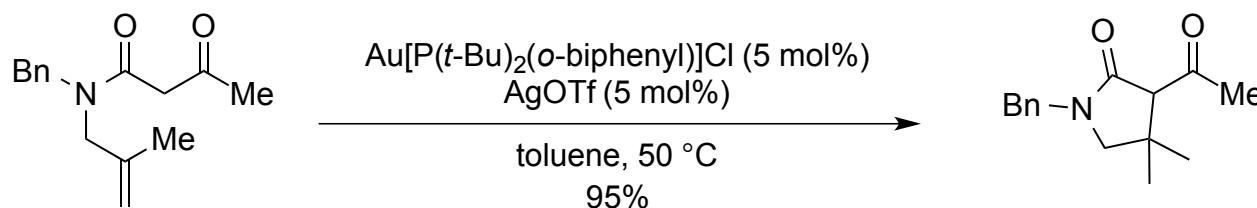
# Question 1



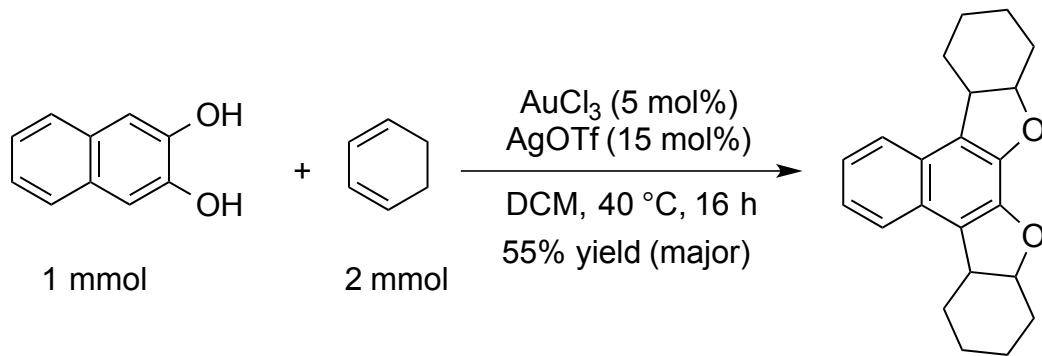
## Question 2



Jolly. *J. Organomet. Chem.* **1995**, 486, 163



Che. *JACS* **2007**, 129, 5828



Li. *Org. Lett.* **2006**, 8, 2397

# Question 3

