

# The Intramolecular Heck Reaction

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MacMillan Group Meeting  
July 14<sup>th</sup> 2004

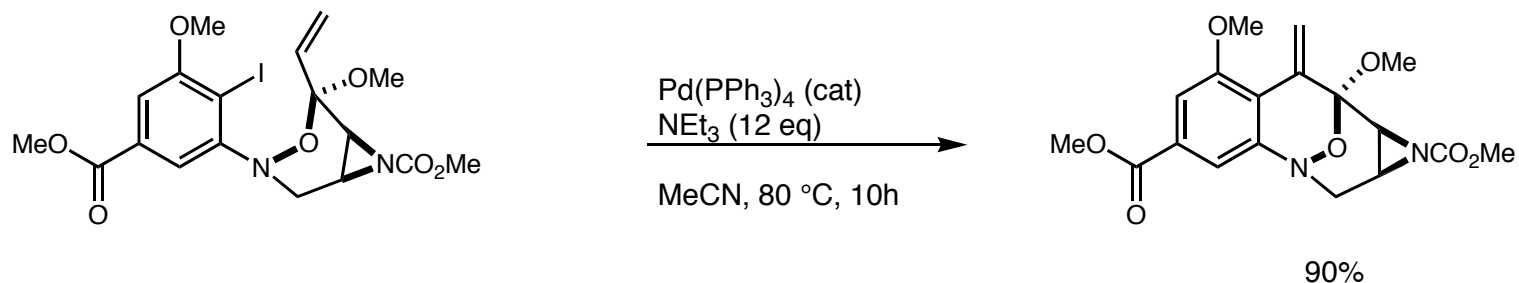
Beletskaya, I. P. *Chem. Rev.* **2000**, *100*, 3009

Overman, L. E. *Chem. Rev.* **2003**, *103*, 2945

Shibasaki, M. *Tetrahedron* **1997**, *53*, 7371

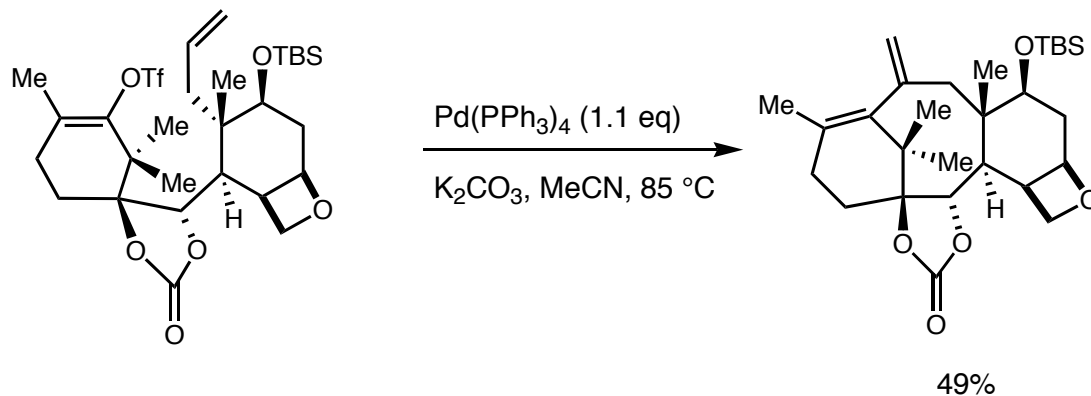
## Advantages of the Heck Reaction in C-C Bond Formation

- Palladium is extraordinarily tolerant of nearly all types of organic functionality and is highly chemoselective making its use feasible in highly functionalized or complex systems.



Danishefsky, S. J. *J. Am. Chem. Soc.* **1993**, 115, 6094

- Intramolecular Heck reaction can form very sterically hindered carbon-carbon bonds under reasonably mild conditions

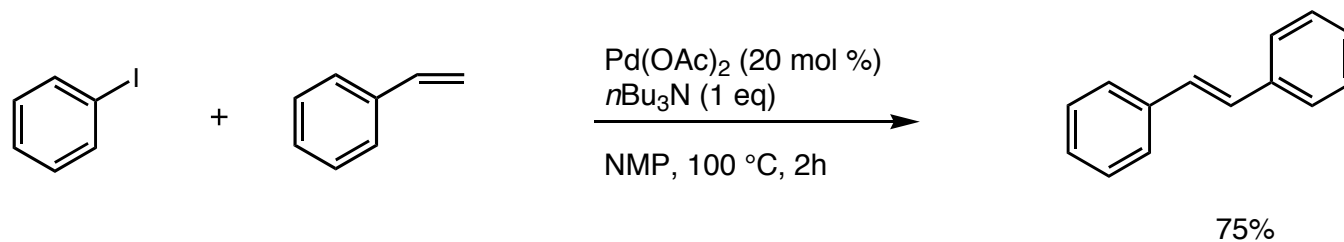


Danishefsky, S. J. *J. Am. Chem. Soc.* **1996**, 118, 2843

- Ability to form quaternary carbon stereocenters with high levels of asymmetric induction.....more on this to come

## Historical Perspective of the Heck Reaction

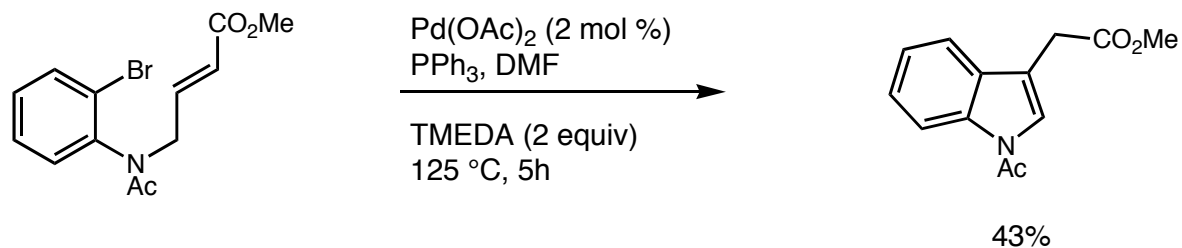
- The first intermolecular Heck reaction was reported by Heck in 1972



- Development of the general intermolecular reaction suffered due to poor regiocontrol of the addition and elimination steps for electronically neutral unsymmetrical olefins

Nolley, J.P.; Heck, R.F.; *Tetrahedron* **1972**, 37, 2320

- The first intramolecular Heck reaction was reported by Mori and Ban in 1977



Indole product formed as result of Pd-H isomerization of product olefin

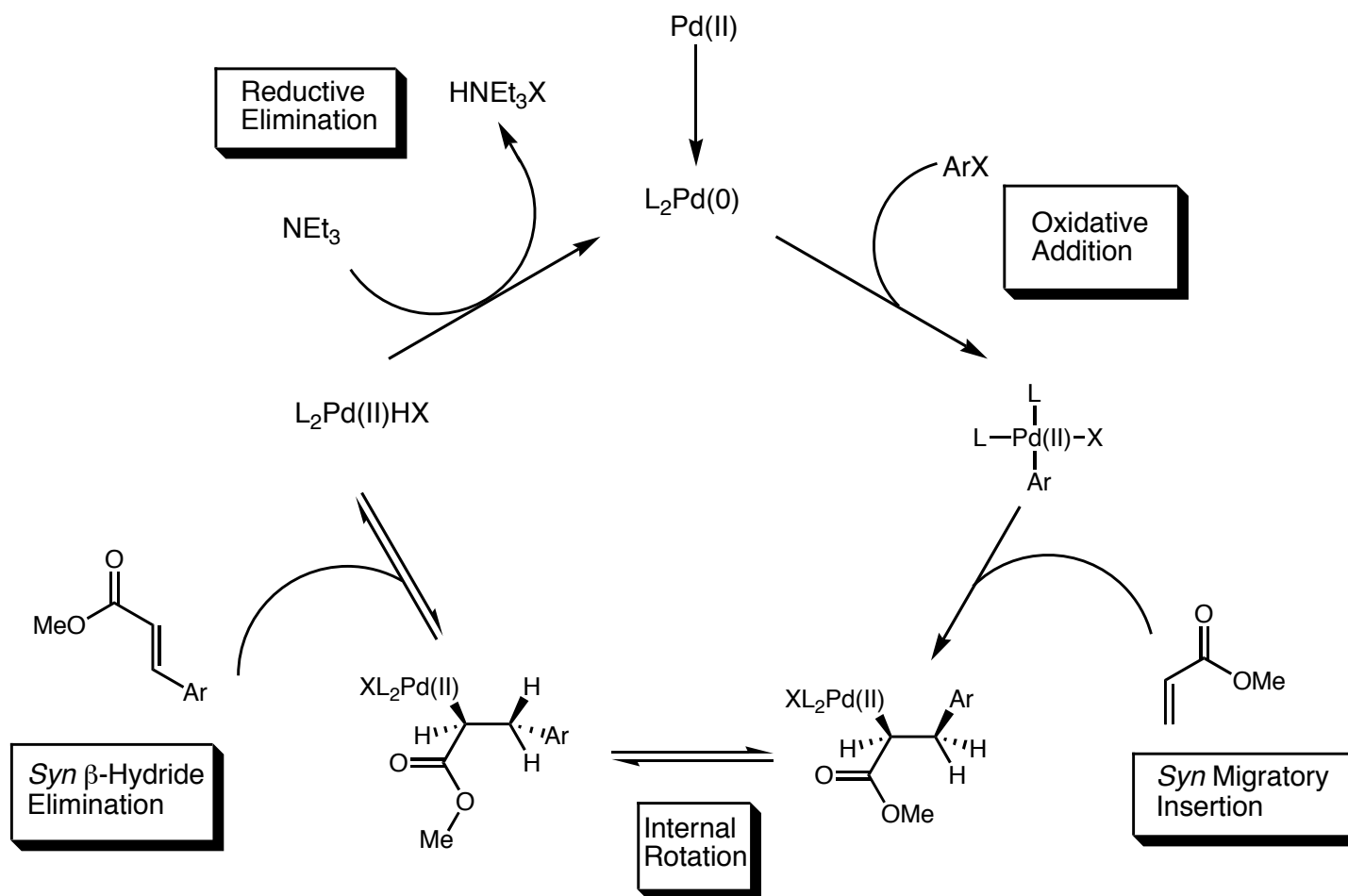
Mori, M.; Ban, K.; *Tetrahedron* **1977**, 12, 1037

## *Important Differences Between Inter- and Intramolecular Heck Reactions*

- In the intermolecular Heck reactions, only mono- and disubstituted olefins can participate, while in the intramolecular case tri- and tetrasubstituted olefins readily insert.
- The intramolecular Heck reaction is generally more efficient than the intermolecular version due to the elimination of entropic considerations
- Regiocontrol of olefin addition is difficult in the intermolecular process for electronically neutral olefins. However, the unimolecular process is governed generally by steric considerations giving highly regioselective couplings.
- Examples of asymmetric intermolecular Heck reactions are relatively recent, rare and not in any way general. Intramolecular asymmetric Heck reactions are known and well developed for a wide variety of substrates.

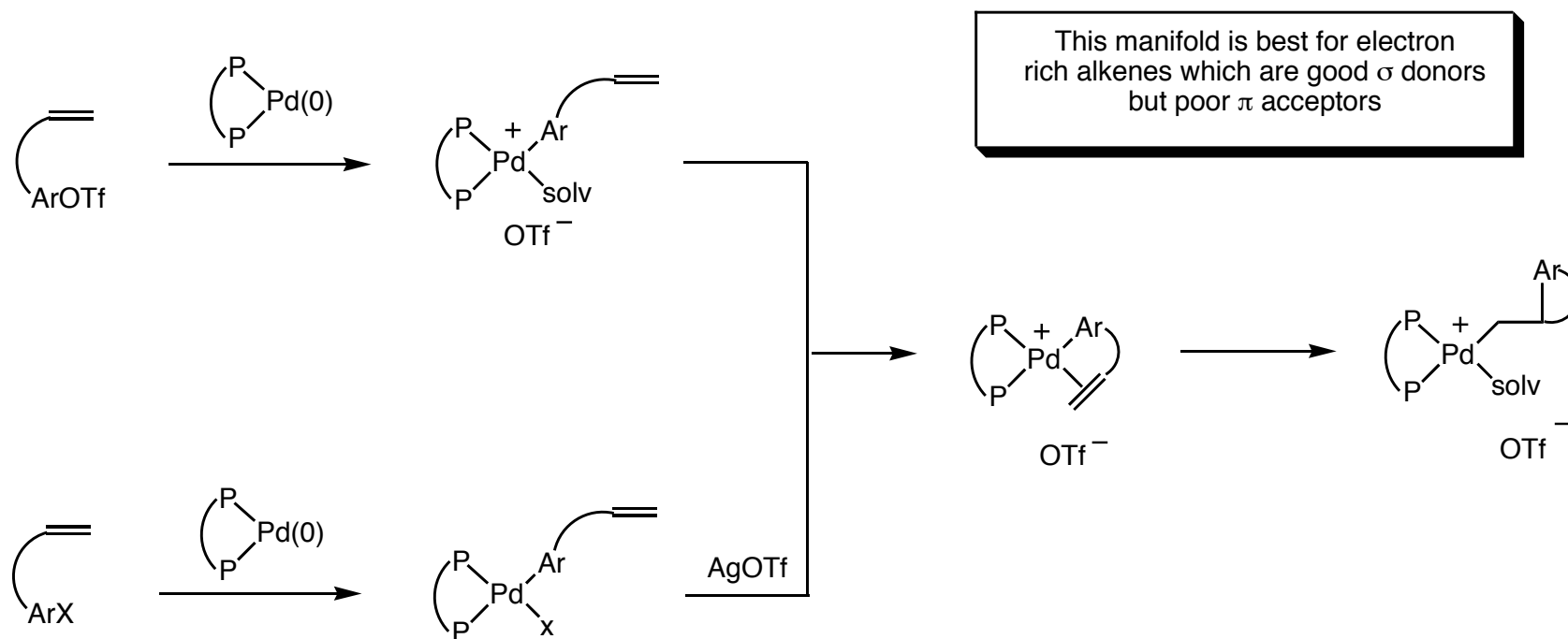
## General Catalysis of the Heck Reaction

- Cycle is catalytic in palladium with the addition of stoichiometric base to scavenge HX



## Cationic Manifold for Intramolecular Heck Reactions

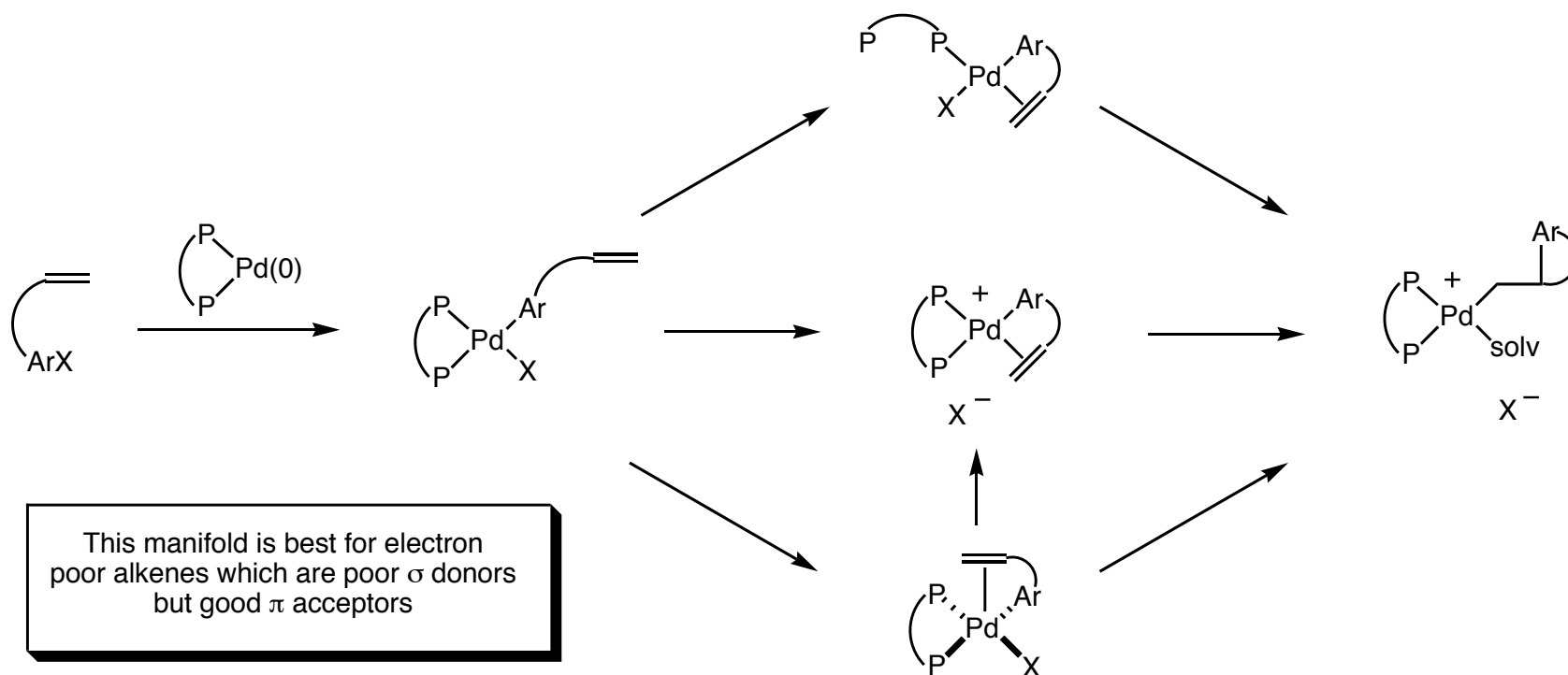
- All aryl triflates react via the cationic pathway
- Aryl halides can enter the cationic manifold by the addition of stoichiometric Ag salts.



- The triflate counterion is considered to be completely dissociated from the metal center, creating a coordinative unsaturation that can accommodate the olefin while both phosphines remain bound. This has important implications for asymmetric catalysis....

## Neutral Manifold for Intramolecular Heck Reactions

- All aryl halides react via the neutral pathway in the absence of silver or thallium salts
- Aryl triflates can enter the neutral manifold by the addition of stoichiometric halide salts.

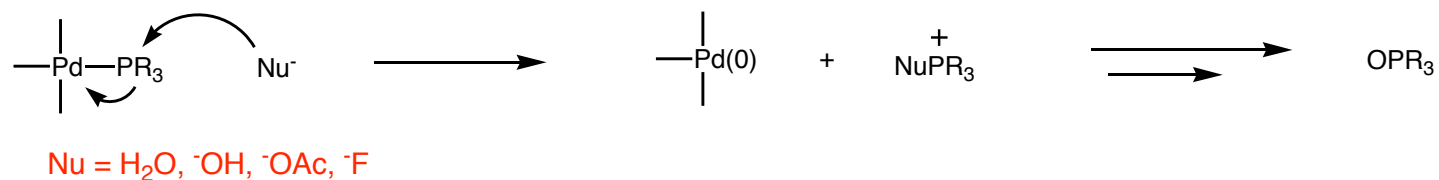


- Dissociation of one of the bidentate phosphate arms drastically reduces the ability for the ligand to transmit chirality to the cyclized product.

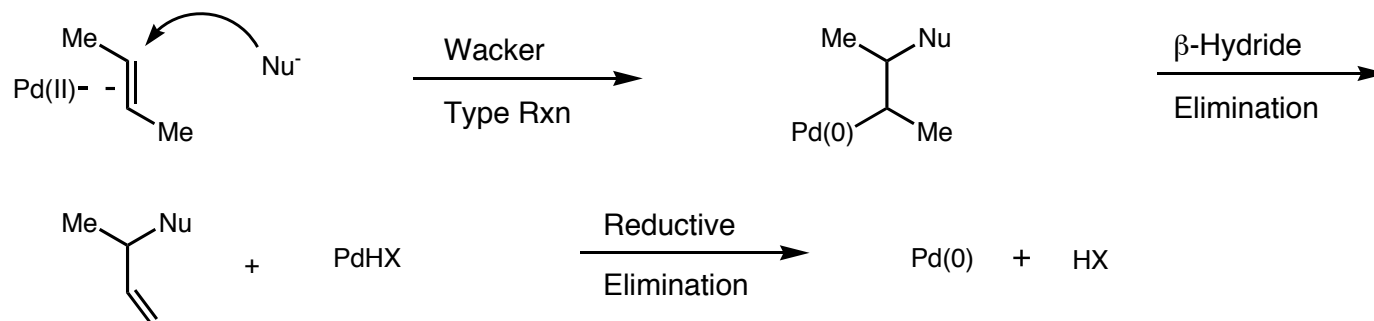
## Preactivation of Palladium Salts Produces Catalytically Active Species

- Phosphines, amines and olefins can all act as reductants

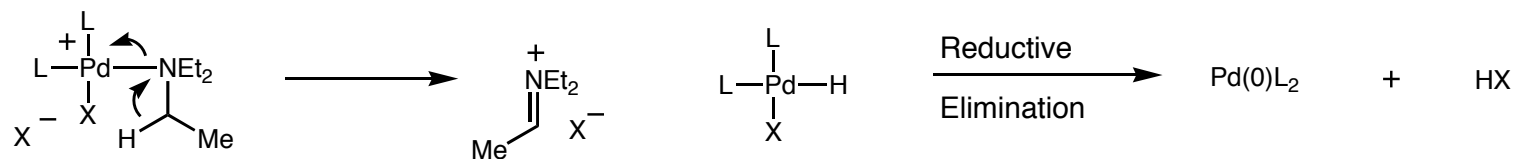
### Phosphines



### Olefins



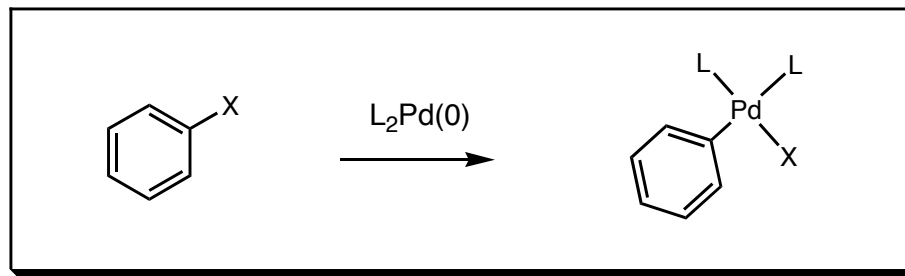
### Amines



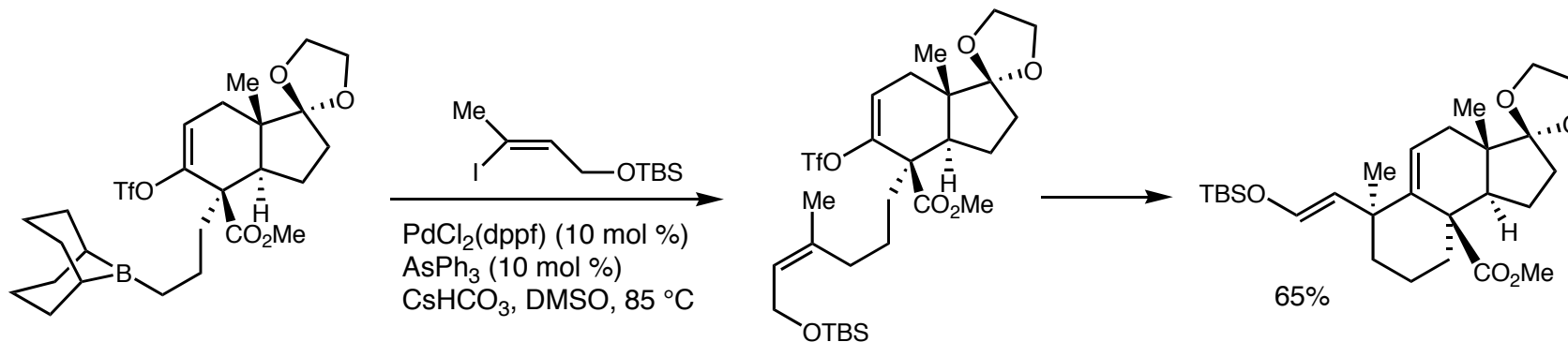
- Amines and olefins have no effect on the rate of reduction when phosphine is present



## Oxidative Addition

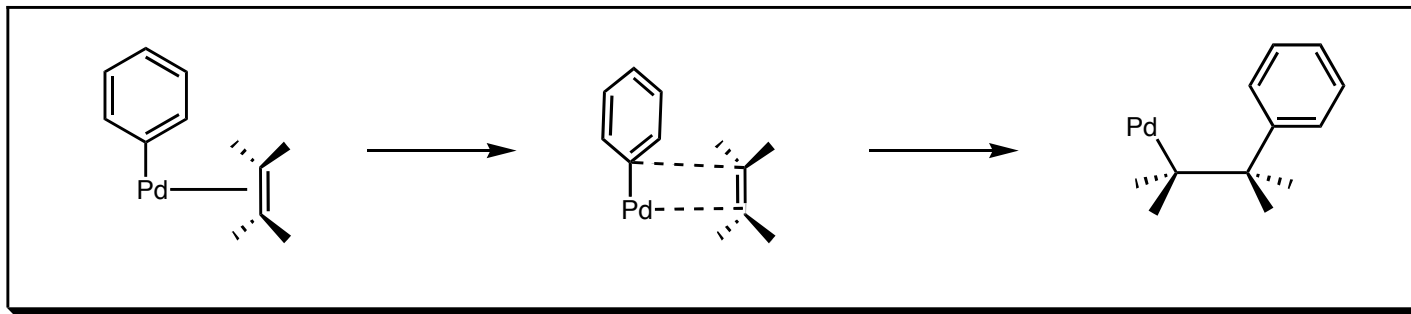


- The 14 electron complex L<sub>2</sub>Pd(0) is the catalytically active species.
- Rate of insertion: I > OTf > Br >> Cl
- Phosphines aid in solubilizing the metallic palladium, keeping it in the catalytic cycle.
- Addition initially gives the d<sup>8</sup> square planar compound in which the arene and the halogen are cis to one another.
- Rate differentials allow for interesting tandem reactions



## Migratory Insertion

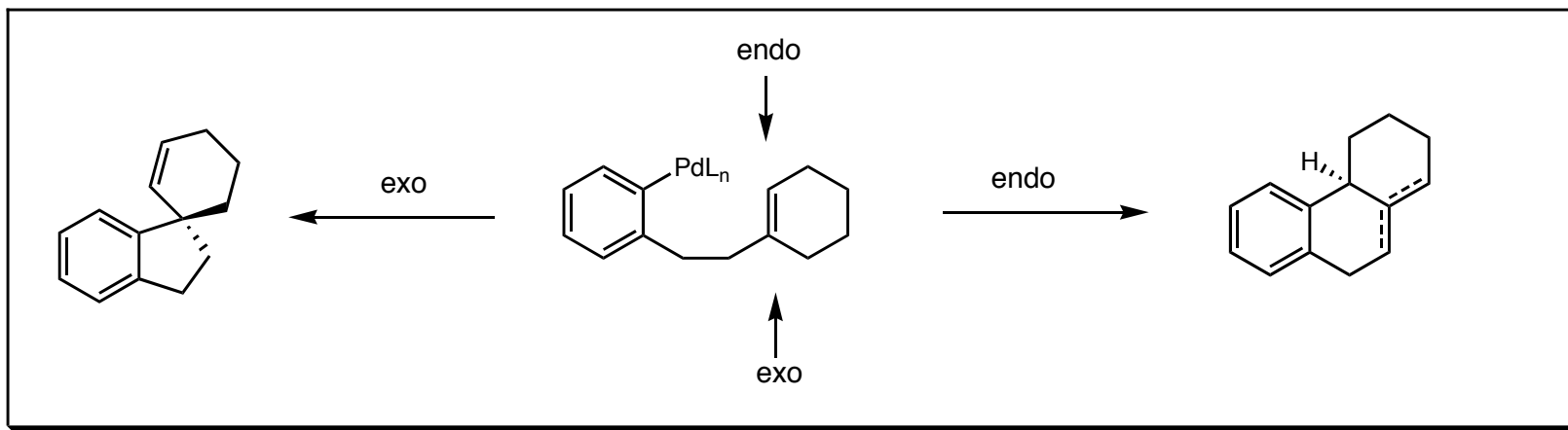
- Migratory insertion is a basic organometallic transformation and is the carbon-carbon bond forming step in the Heck reaction



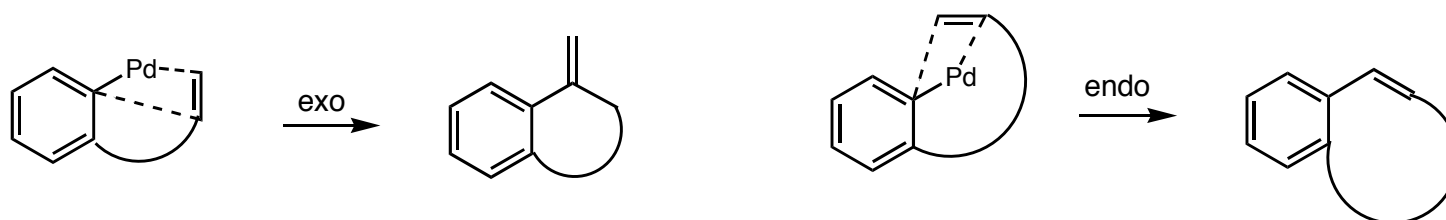
- The reaction is considered to be a concerted process
- The elimination of entropic factors in the intramolecular Heck allows insertion into trisubstituted and tetrasubstituted olefins, which is not possible in the bimolecular process
- The regiochemistry of the intermolecular Heck insertion step is highly sensitive to the electronics of the substrate, the reaction manifold, and steric congestion. As a result regioselectivity can be poor for certain classes of substrates
- Does the intramolecular Heck suffer from the same lack of regiochemical control?

## Regioselectivity in the Intramolecular Heck Reaction

- Ring closure is highly exo selective for 5,6, and 7 membered rings



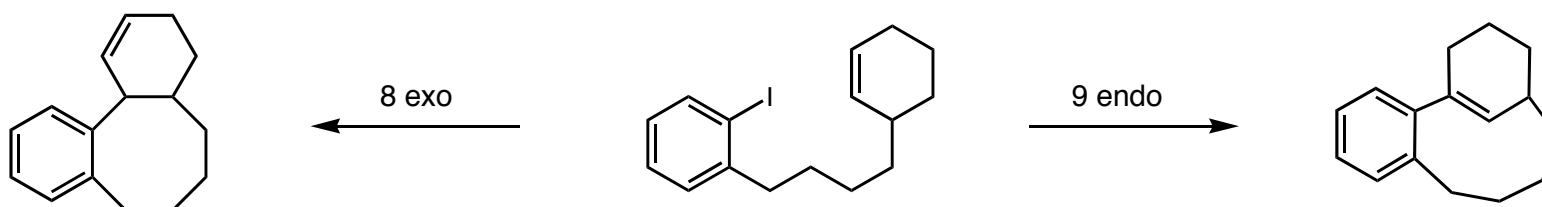
- Transition state to give exo products in reactions forming small rings is much lower in energy than the endo TS due to the length of the tether. Much longer and more flexible chains are needed to adopt the proper conformation for endo insertion.



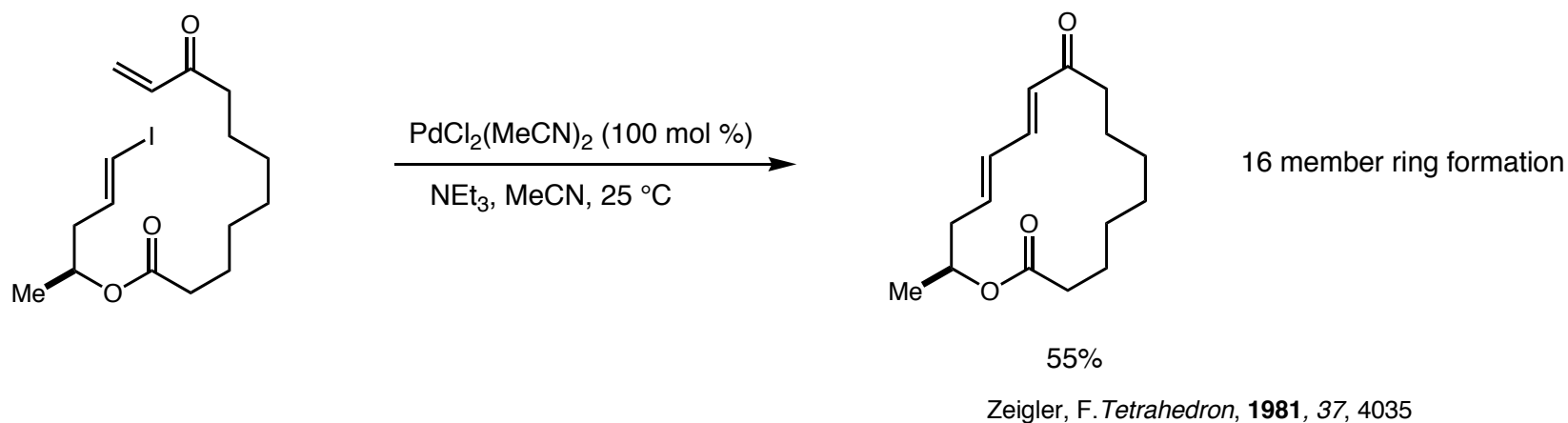
- Exo closure also ensures that the bulky palladium complex ends up on the less hindered carbon.
- Endo products obtained in small ring closure usually arise from an exo closure-isomerization mechanism where the intermediate  $\text{Pd-H}$  adds back into an olefin in the product molecule. This can often be avoided by the addition of silver salts.

## Large Rings Give Predominantly Endo Closure

- This rationale is validated by a mix of exo and endo products in the closure of medium rings (8-12)



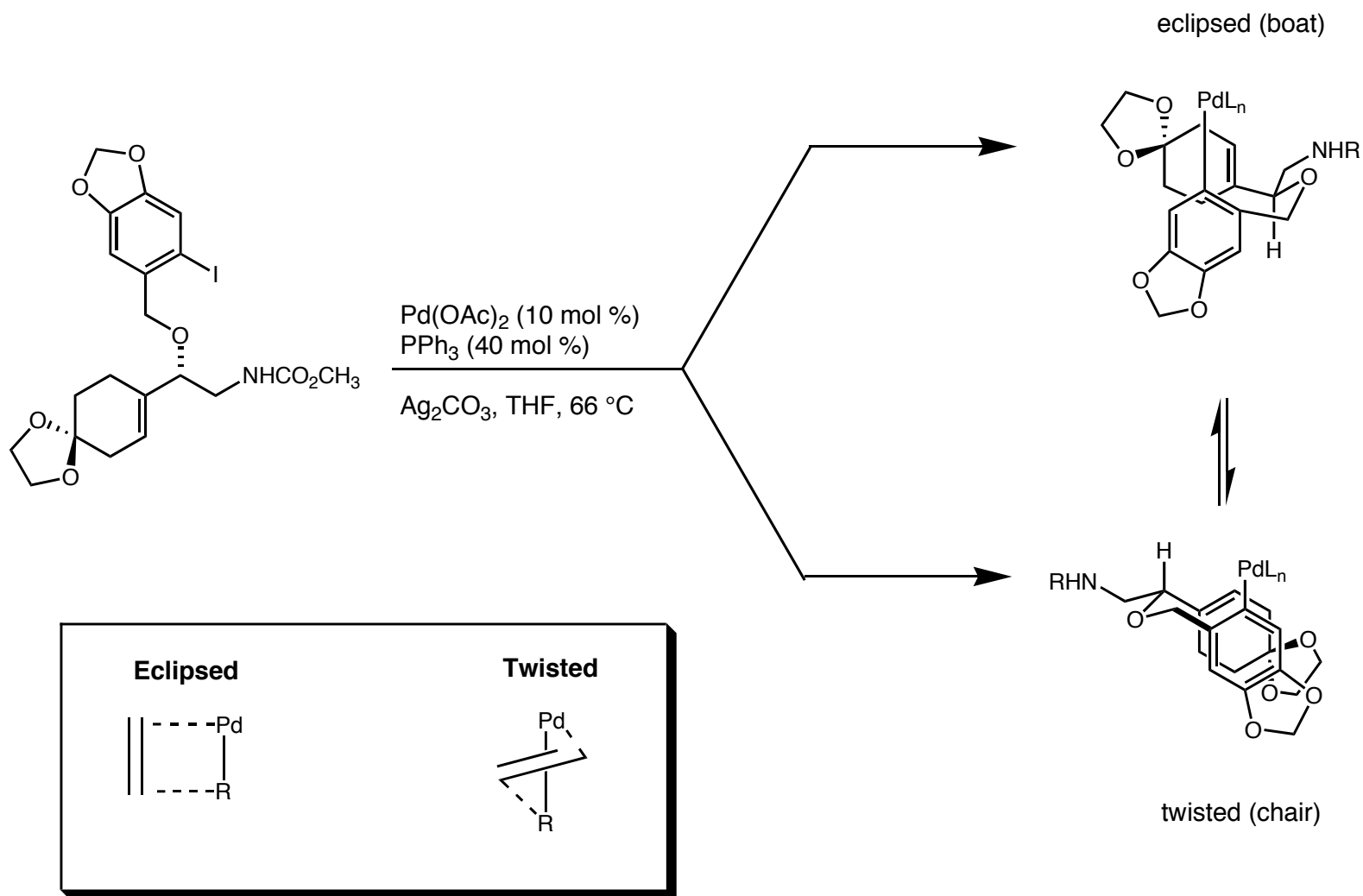
- For large ring formation (13 and greater) the Heck reactions becomes endo selective and can be used as a macrocyclization strategy



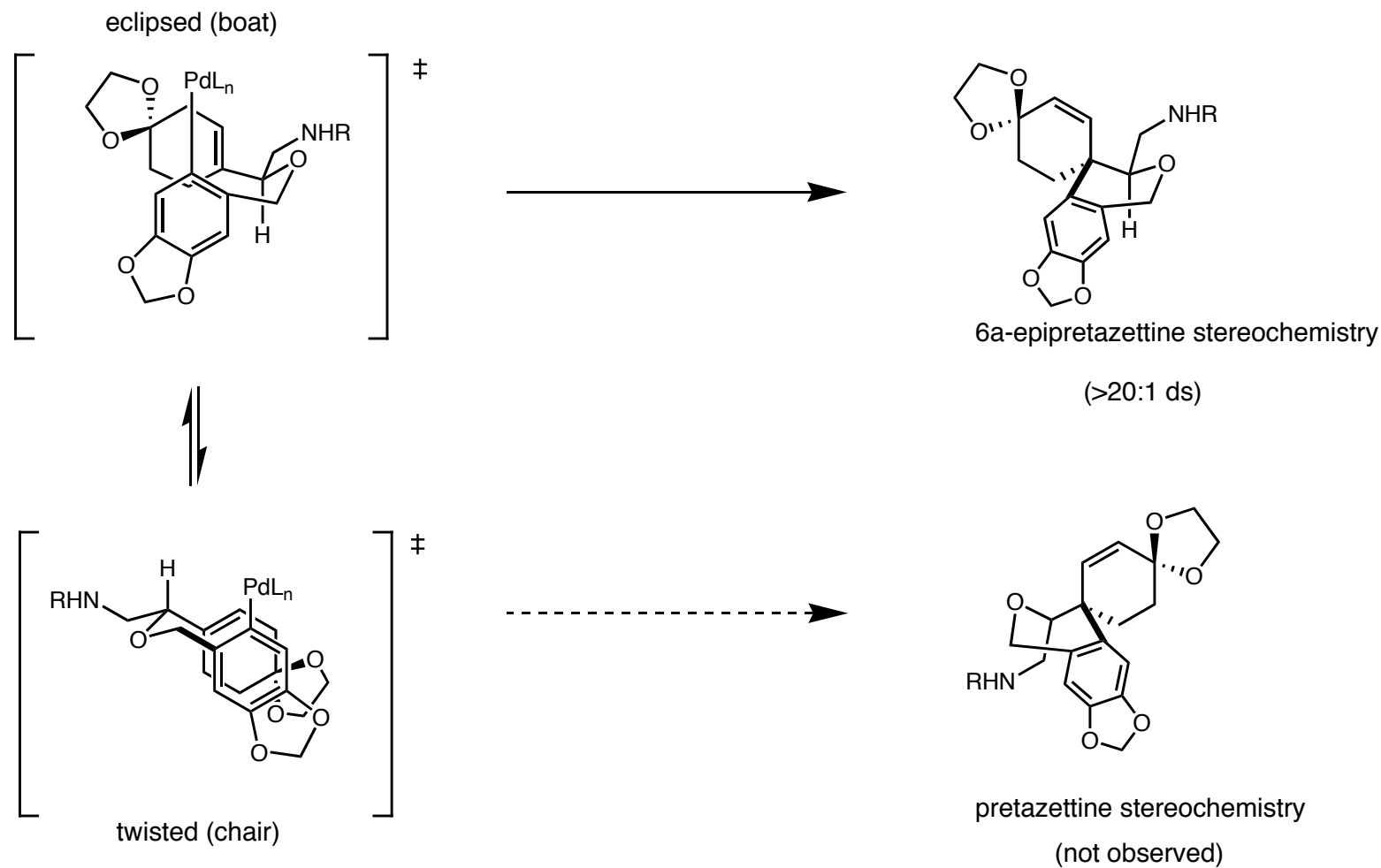
- What is the actual transition state orientation between the olefin and the alkyl palladium in the intramolecular Heck reaction?

## Probing the Transition State of the Migratory Insertion Step

- Setting the side chain in a pseudo-equatorial position gives rise to two different molecular conformations with different orientations of the olefin and aryl-Pd bond.



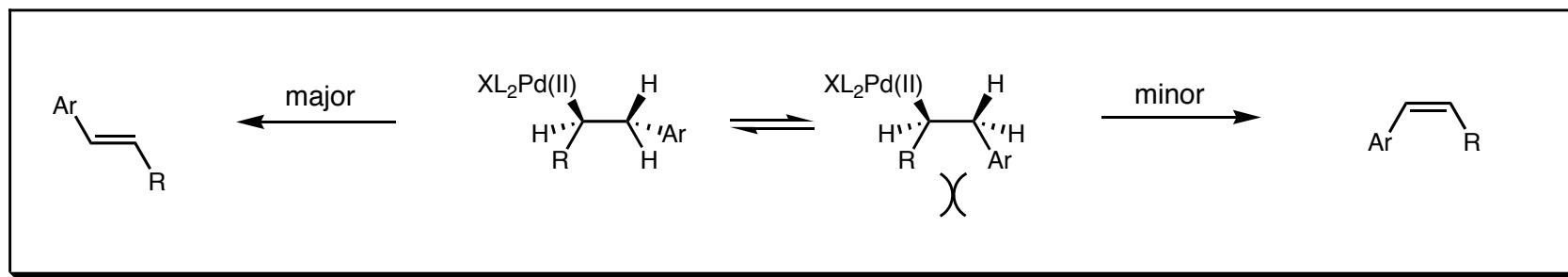
## Probing the Migratory Insertion Transition State: Synthesis of Amaryllidaceae Alkaloids



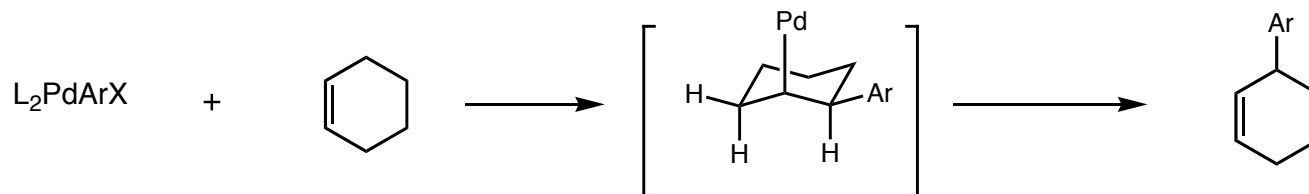
■ The disfavored boat ground state conformer has a much lower barrier to insertion than its counterpart, allowing the reaction to proceed with nearly complete diastereoselectivity

## $\beta$ -Hydride Elimination: General Considerations

- The hydride and the palladium must be *syn* coplanar for elimination to occur

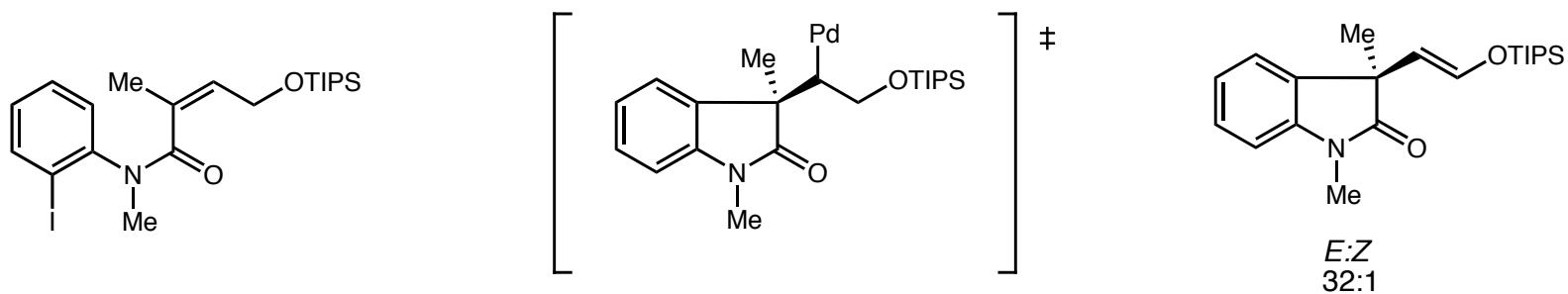


- The olefin isomer product ratio is kinetically controlled. *Trans* geometries are favored due to eclipsing interactions in the transition state that gives the *syn* isomer.
- Regiocontrol control of elimination for unsymmetrical, acyclic alkenes with several sets of  $\beta$ -protons is problematic
- This problem is avoided in additions to cyclic systems



## $\beta$ -Hydride Elimination: Intramolecular Possibilities

■ In the intramolecular Heck addition across tri- and tetrasubstituted olefins leads to the formation of quaternary carbon centers. Thus elimination must occur away from the newly formed carbon-carbon bond



■ If there are no protons oriented properly to eliminate, the alkyl Pd species persists and can participate in subsequent reactions

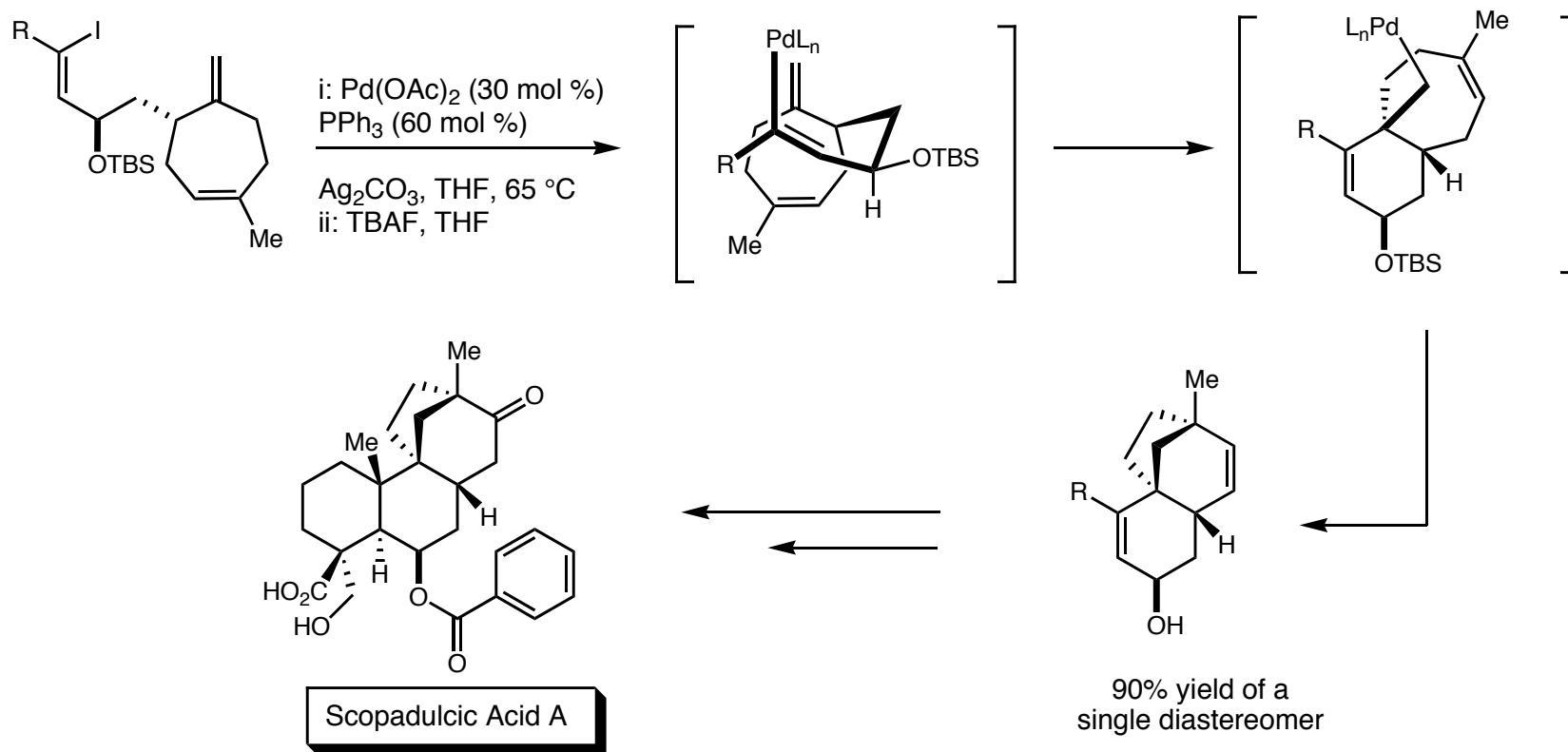
■ The potential to participate in tandem reactions unlocks the true synthetic power of the Heck reaction



## Intramolecular Heck in Tandem Reactions

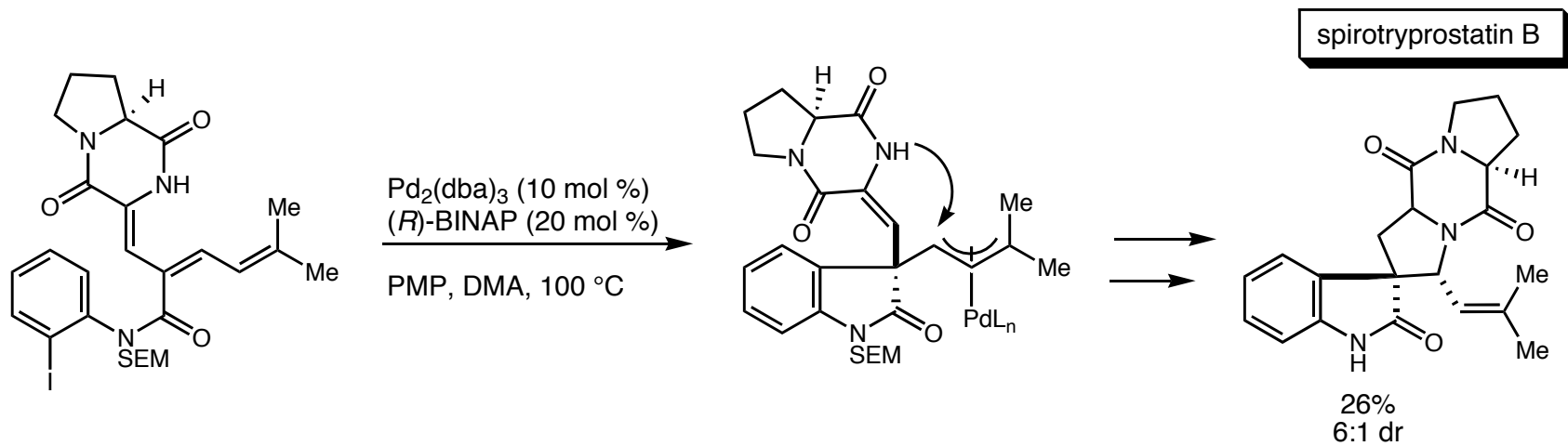
■ If there are no available  $\beta$ -hydrogens to eliminate, the alkyl palladium species can participate in sequential reactions, allowing for the amazingly rapid production of molecular complexity.

■ Tandem Heck reaction: Creation of two rings and two quaternary centers in a single step

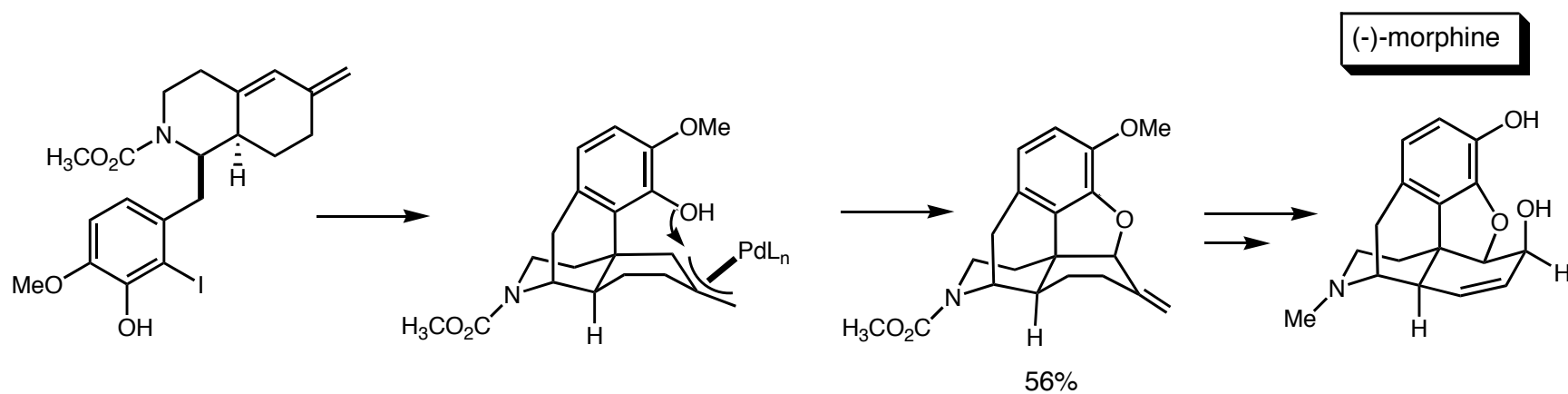


## Tandem Heck - $\pi$ Allyl Reactions

- Heck reactions on conjugated dienes create electrophilic  $\pi$  allyl complexes that are susceptible to nucleophilic attack



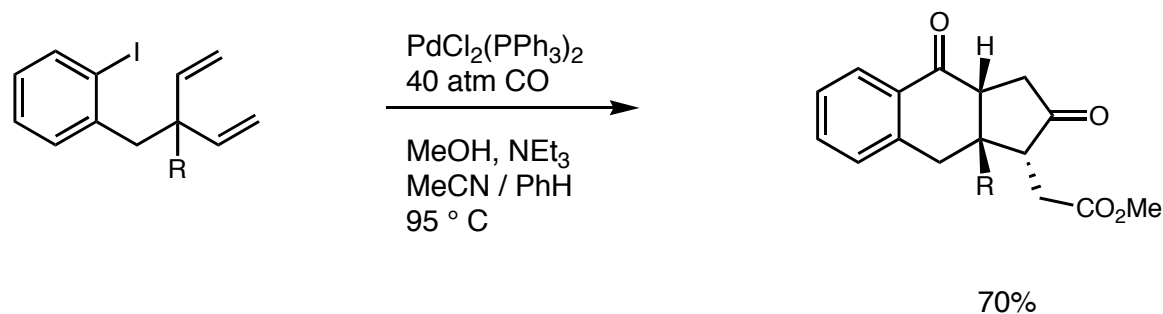
Overman, L.E. *ACIEE*, **2000**, 39, 4596



Overman, L.E. *Tetrahedron Lett.* **1994**, 35, 3453

## Reactions with Carbon Monoxide and Alkynes

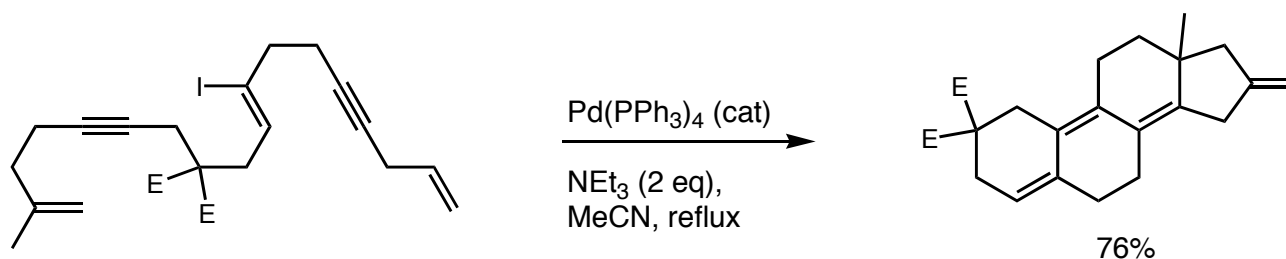
### Tandem Heck-Carbonylation Sequences



High CO pressure makes final carbonylation faster than  $\beta$ -hydride elimination

As a general rule  $\sigma$ -alkylpalladium complexes insert CO more rapidly than they insert alkenes while  $\sigma$ -acylpalladium complexes add alkenes more rapidly than they add CO

### Tandem Heck Reactions with Alkynes



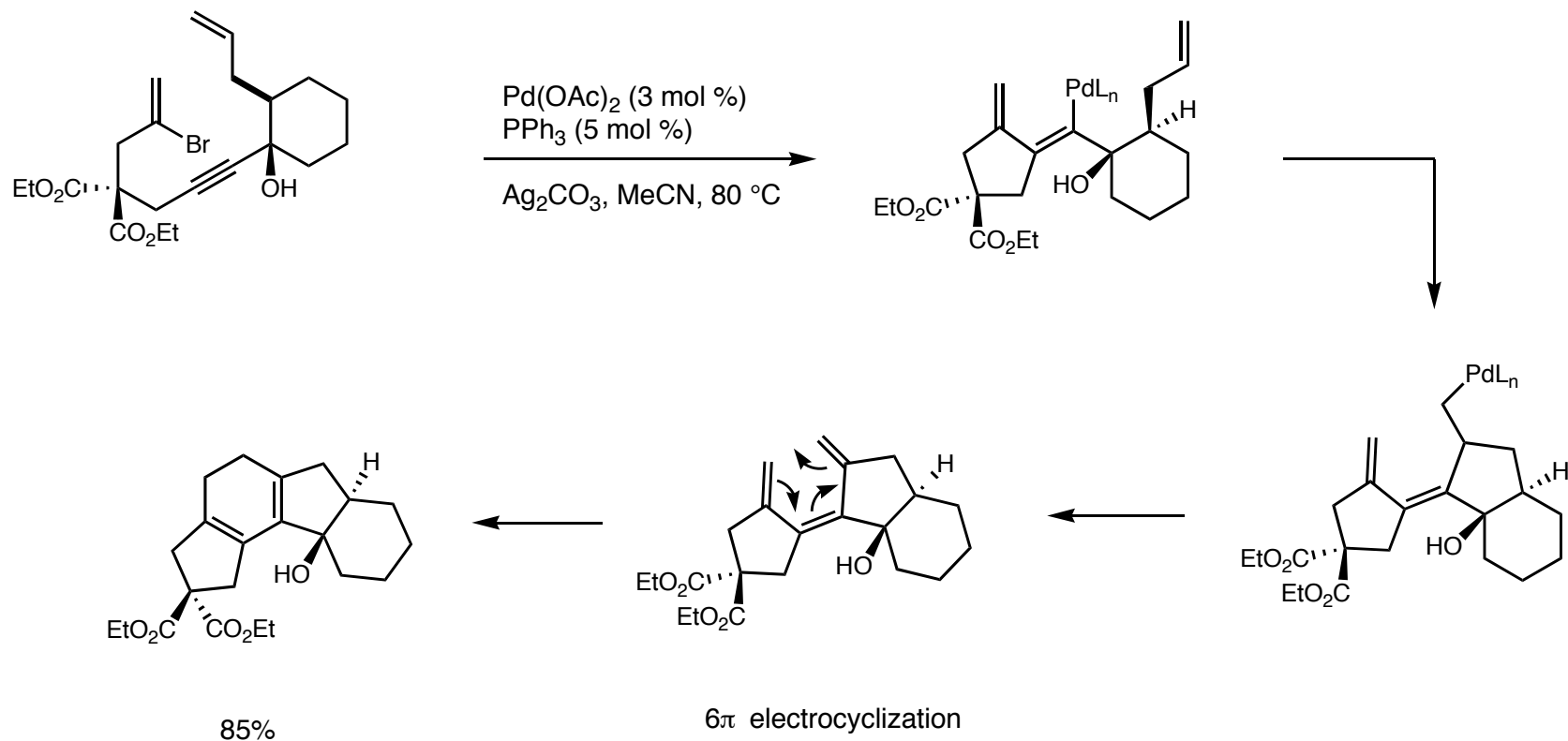
Alkynes insert more rapidly than alkenes

Negishi, E. *ACIEE*, **1996**, 35, 2125

Negishi, E. *Chem Rev.*, **1996**, 96, 365

## Heck of a Lot of Tandem Reactions

### ■ Tandem Heck-Electrocyclization



■ These examples show the generality and utility of palladium catalyzed tandem reactions to accomplish strategic carbon-carbon bond formation in complex organic molecules

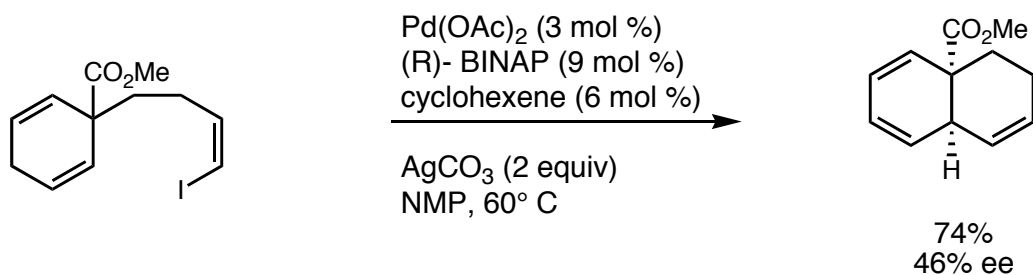
## *Considerations for an Asymmetric Intramolecular Heck Reaction*

- The asymmetric variant came more than a decade after the first reported reaction. Most likely due to the fact that most people did not think of the Heck reaction as a way to create  $sp^3$  centers
- Progress was also likely slowed by Heck's assertion in 1982 that bidentate phosphines were horrible ligands for the intermolecular Heck reaction.
- Initial strategies focused on the desymmetrization of prochiral dienes, but as the technology advanced more difficult substrate classes were investigated whereby the metal could discriminate between prochiral faces of a single olefin
- Investigation showed that partitioning the reactions toward the cationic manifold was essential to get high levels of asymmetric induction. This due to the fact that under cationic conditions, both phosphines remain bound to the metal at all times.

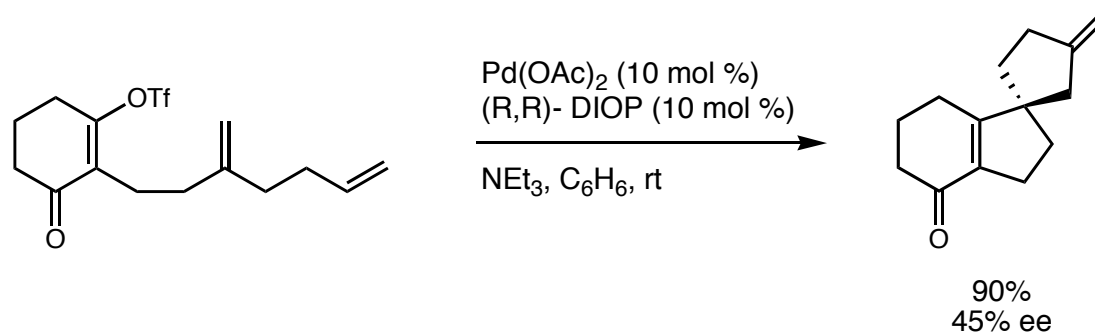
## Asymmetry in the Intramolecular Heck: First Reports

- In 1989 Shibasaki and Overman independently report the first asymmetric intramolecular Heck reactions

Shibasaki creates a tertiary carbon stereocenter and desymmetrizes a quaternary center in the formation of a *cis* decalin



Overman reports first use of the intramolecular Heck in the creation of asymmetric quaternary centers

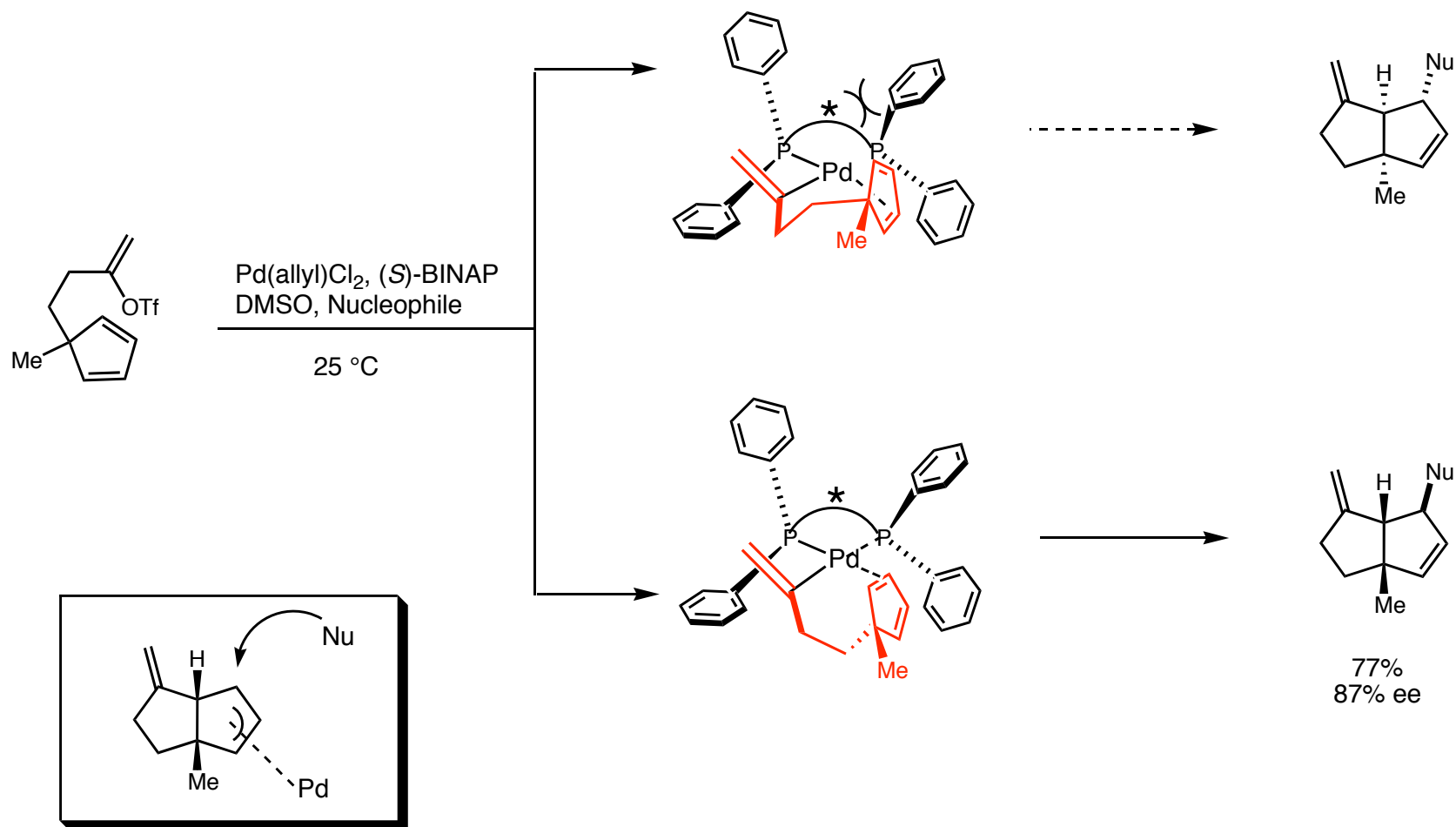


Shibasaki, M. *J. Org. Chem.* **1989**, *54*, 4738

Overman, L. E. *J. Org. Chem.* **1989**, *54*, 5846

## Asymmetry in the Intramolecular Heck: Desymmetrization

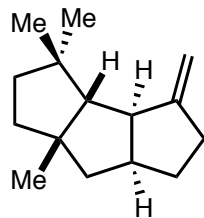
- Bulky BINAP ligand directs the approach of the prochiral diene



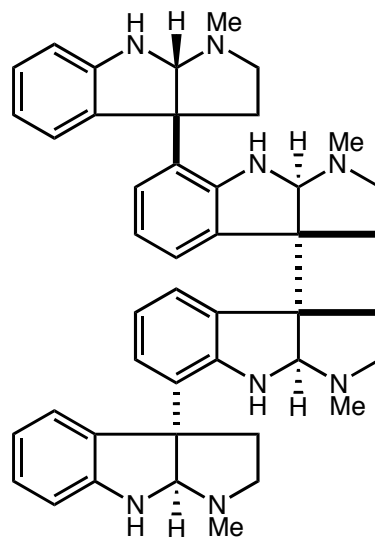
- $\pi$  allyl intermediate can be trapped with a variety of nucleophiles

## Asymmetric Heck Reactions in Natural Products Synthesis

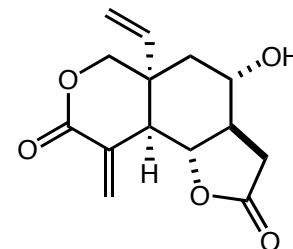
- These are a handful of representative natural products synthesized utilizing the asymmetric Heck Reaction



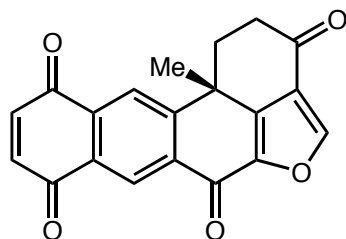
(-)-capnellene  
Shibasaki 1996



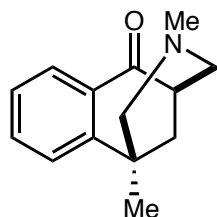
quadrigemine C  
Overman 2002



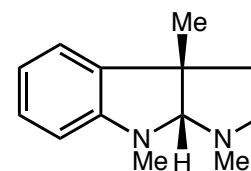
(+)-vernolepin  
Shibasaki 1994



xestoquinone  
Keay 1999



(-)-epatozocine  
Shibasaki 1993



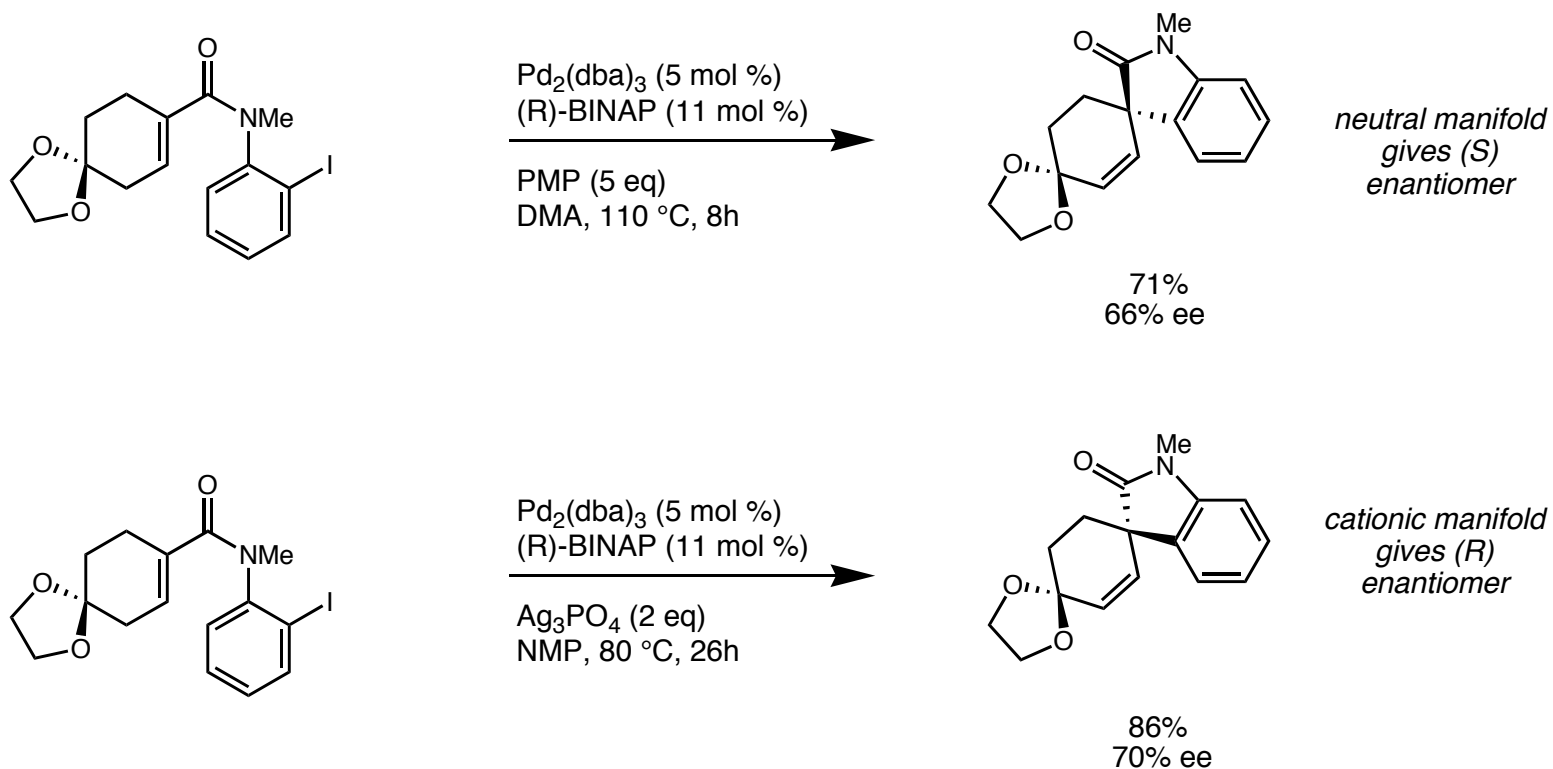
(-)-physostigmine  
Overman 1998

- The diversity of these molecules shows the generality of the Heck reaction in solving many types of synthetic problems



## What the Heck? Asymmetric Reactions Using Neutral Conditions

- Overman reports cyclization gives either enantiomer of product from the same enantiomer of BINAP by changing the base:

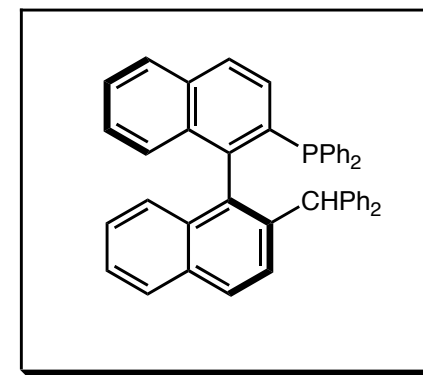
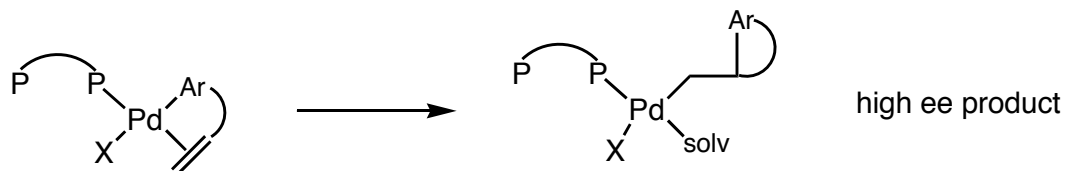


- This is the first report neutral manifold Heck reactions giving high levels of asymmetric induction:

## Mechanistic Exploration of Anomalous Asymmetry

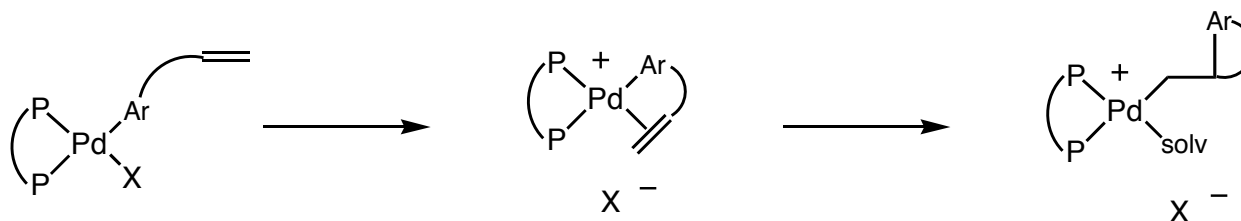
### Overman investigated three possibilities:

1. A monodentate BINAP may be able to produce these unusually high enantioselectivities



Result: BINAP derivatives only capable of monodentate binding gave poor enantioselectivity for the *opposite* enantiomer previously observed. This explanation was thus discounted

2. Under reaction conditions the halide could be ionized, allowing entrance into the cationic reaction manifold

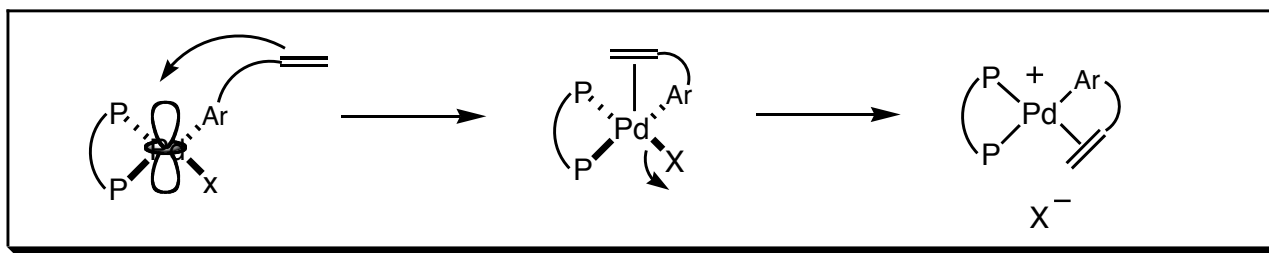


Result: Sense of enantioinduction should be the same as in the cationic reaction since the intermediates are the same, yet the opposite enantiomer is observed, eliminating this as a possible explanation

■ What the Heck is going on? The third possibility proved to be the only one to fit the data...

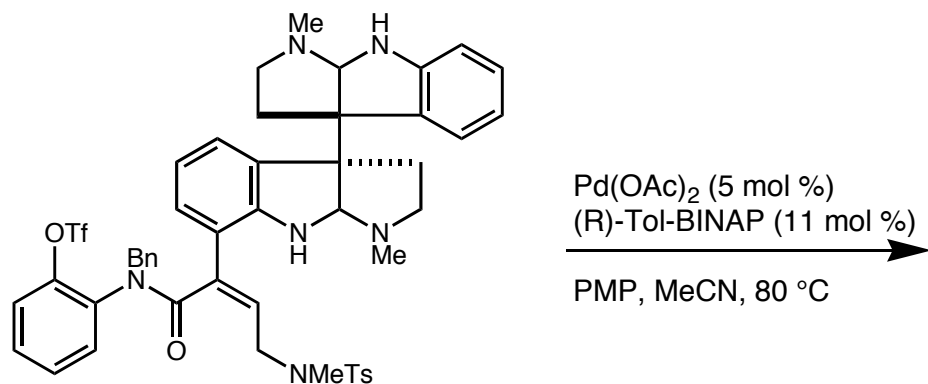
## Mechanistic Rationale Suggests a Novel Mode of Chiral Induction

### 3. Axial coordination of the olefin to the square planar complex could be enantiodiscriminating



- Pd(II) is a  $d^8$  ion that prefers to exist in square planar geometries. The ligand exchange chemistry is dominated by axial coordination into the  $dz^2$ -like MO followed by pseudorotation and ligand dissociation, giving a new square planar complex.
- For this particular class of substrate Overman postulated that both phosphines remain bound as the olefin binds and the complex kicks out the halide ion. Olefin binding becomes the enantiodetermining step, as the olefin is directed by the ligand differently in an axial approach than it would be in a side on approach.
- Theoretical calculation show that insertion into the olefin from the pentacoordinate intermediate to be energetically prohibitive.
- This type of induction is in no way general and is a peculiar characteristic of this specific substrate class, but it show that there are "secret doors" between reaction manifolds that allow for unforeseen results.

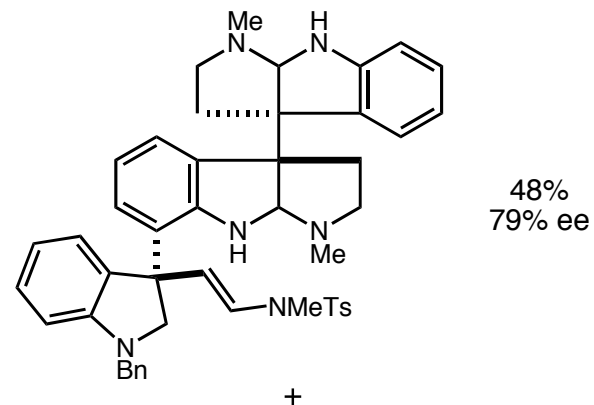
## Resolution of Racemates Gives Access to Hodgkinsine Derivatives



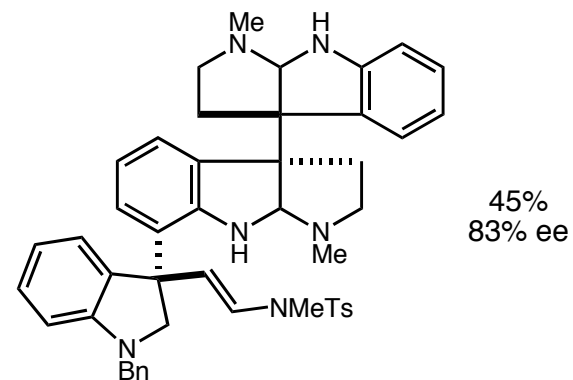
racemic

Reaction had little to no inherent diastereoselectivity when achiral phosphines were used

Hodgkinsine stereochemistry

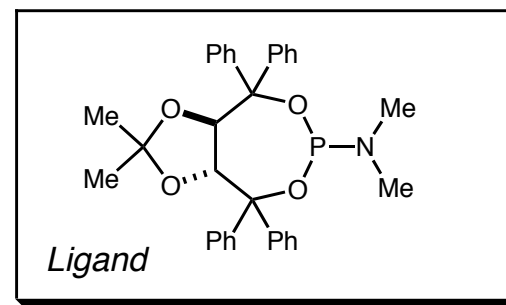
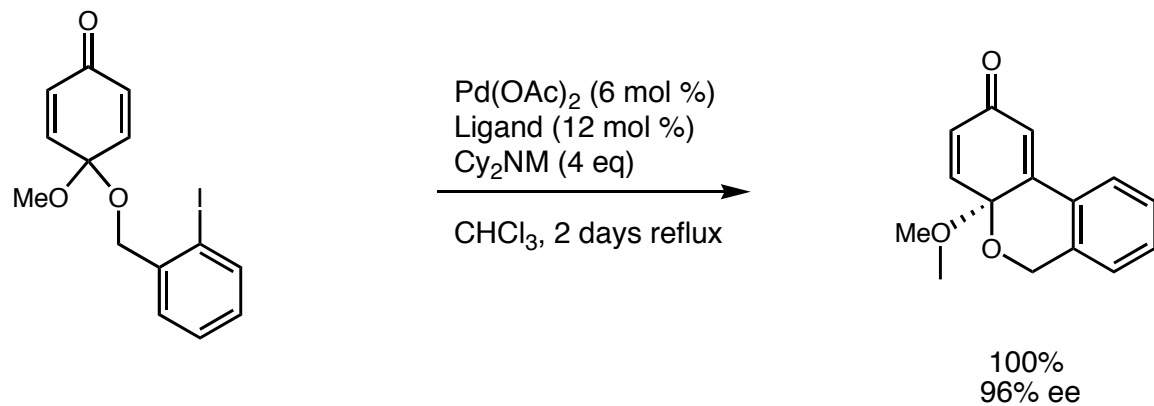


Hodgkinsine B stereochemistry



- This is the first report of an asymmetric intramolecular Heck reaction for resolution of racemates

## Asymmetry From Monodentate Ligands



- Feringa's TADDOL phosphoramidite ligand shows that bidentate ligands are not essential for chiral induction
- Silver or thallium salts were not needed to obtain high ee's, indicating a neutral-type reaction manifold
- Use of BINAP gave poor yield and little to no enantioselectivity

## *Conclusions, Limitations, and Future Directions*

- The intramolecular Heck reaction is an incredibly powerful method for the construction of polycyclic structures and quaternary carbon stereocenters
- The incredible functional group tolerance of palladium make Heck reactions possible on even the most sensitive of substrates
- Extensive optimization studies are often required to develop optimal conditions for every new substrate
- Reactions are easily poisoned by molecular oxygen
- Introduction of new recoverable ligands that will broaden substrate scope amenable to asymmetric catalysis
- Further investigation of tandem reactions involving the intramolecular Heck and application in complex molecule synthesis
- Finding milder reaction conditions that also allow for lower catalyst loadings