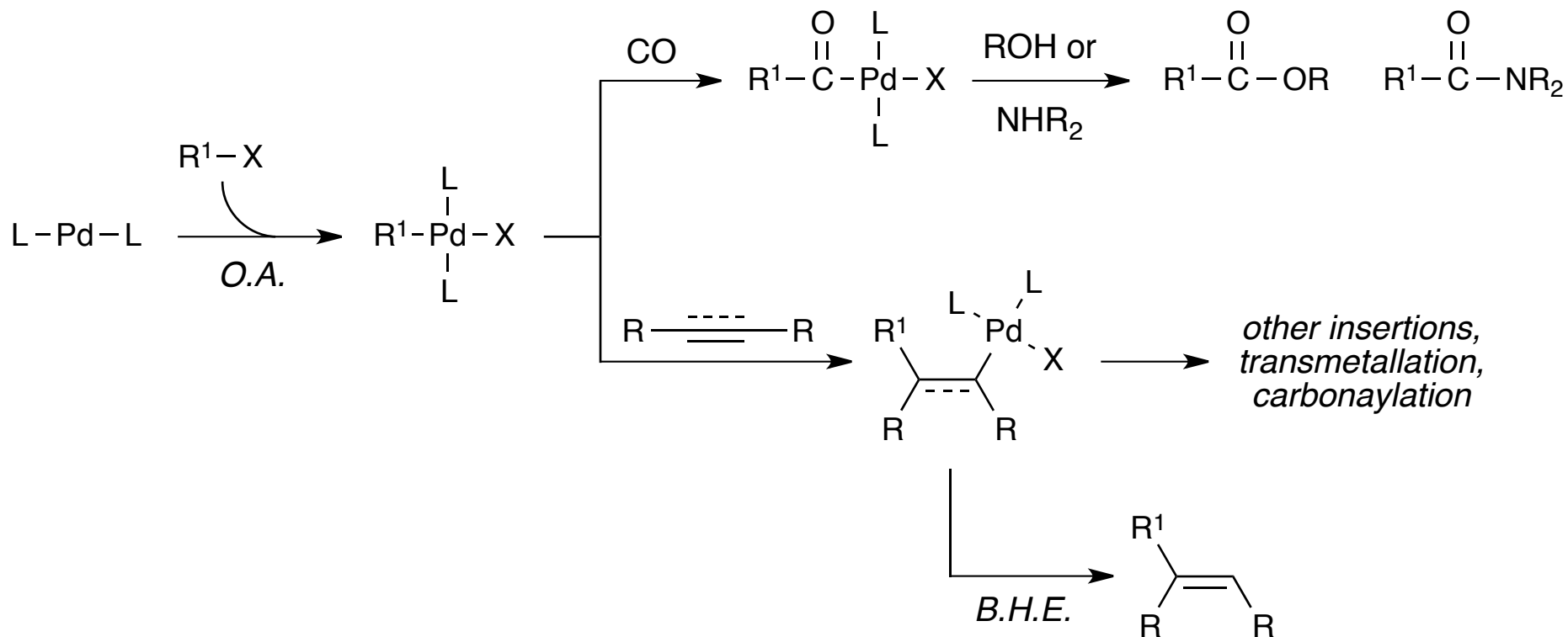


## Insertion Reactions

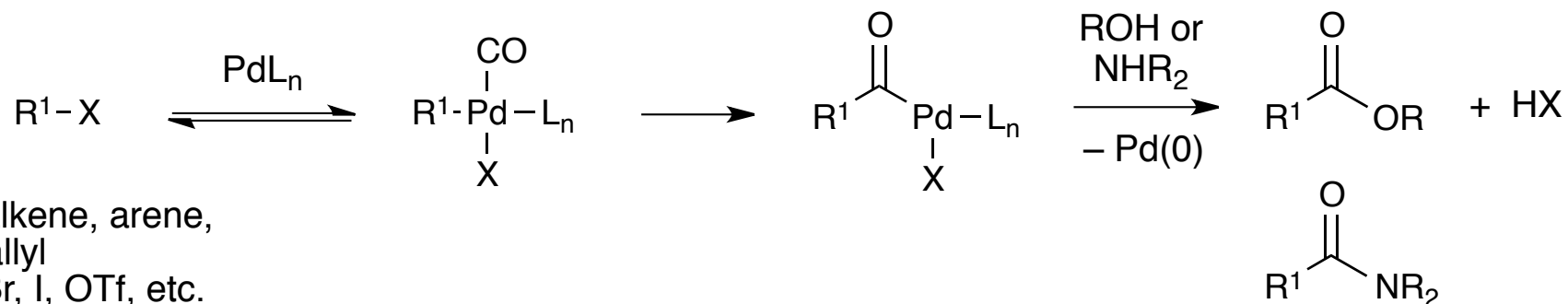
The Pd(II) species formed via oxidative addition can be engaged into other reactions not involving transmetallation. Migratory insertion reactions are very common. These can involve olefins, alkynes, and CO. Cascade reactions in which multiple insertion reactions take place are also possible. Depending on how the sequence is devised, the reaction can be terminated by either reductive elimination or  $\beta$ -hydride elimination.



## Carbonylation Reactions Of Carbon Electrophiles

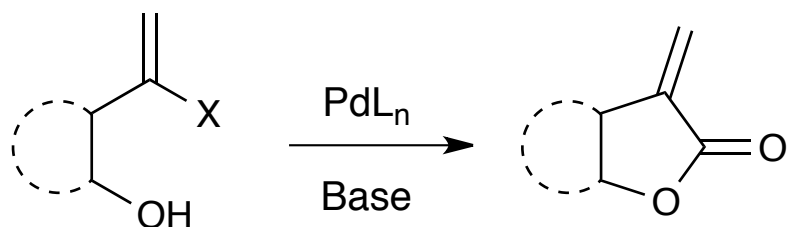
In contrast to acylrhodium intermediates, acylpalladium (and nickel) intermediates are reasonably stable at low pressures of CO (1 atm). They can also be formed directly from acid chlorides.

By running the carbonylation in the presence of an alcohol or amine, esters or amides can be formed.

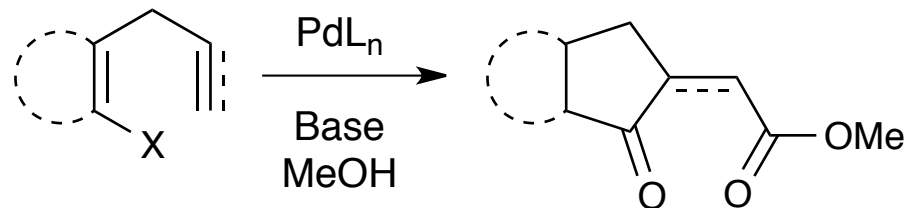


Alkenyl triflates are some of the more common substrates as they can be easily made from ketones.

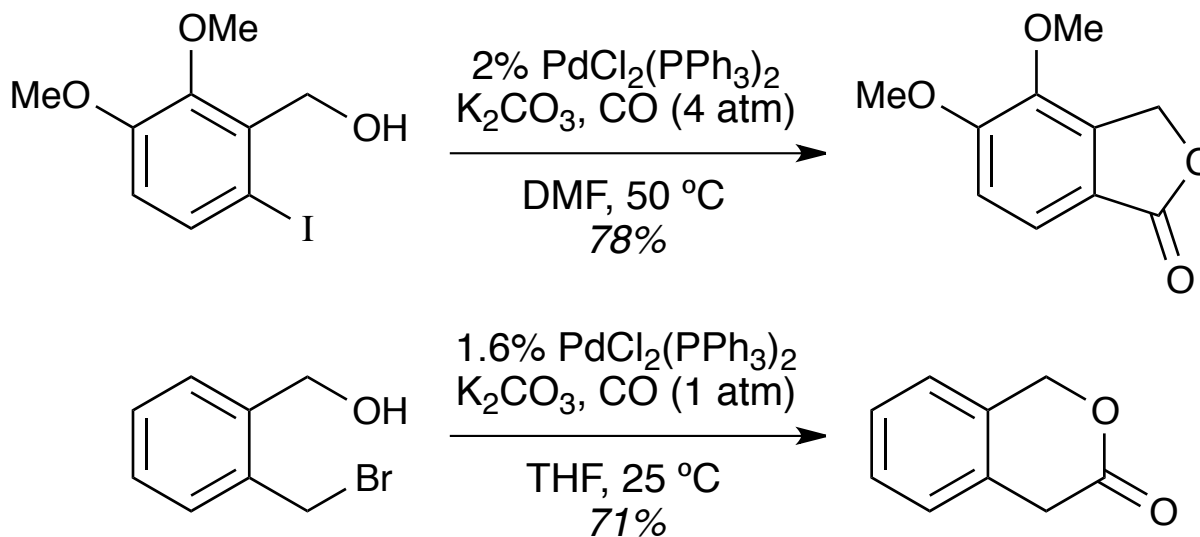
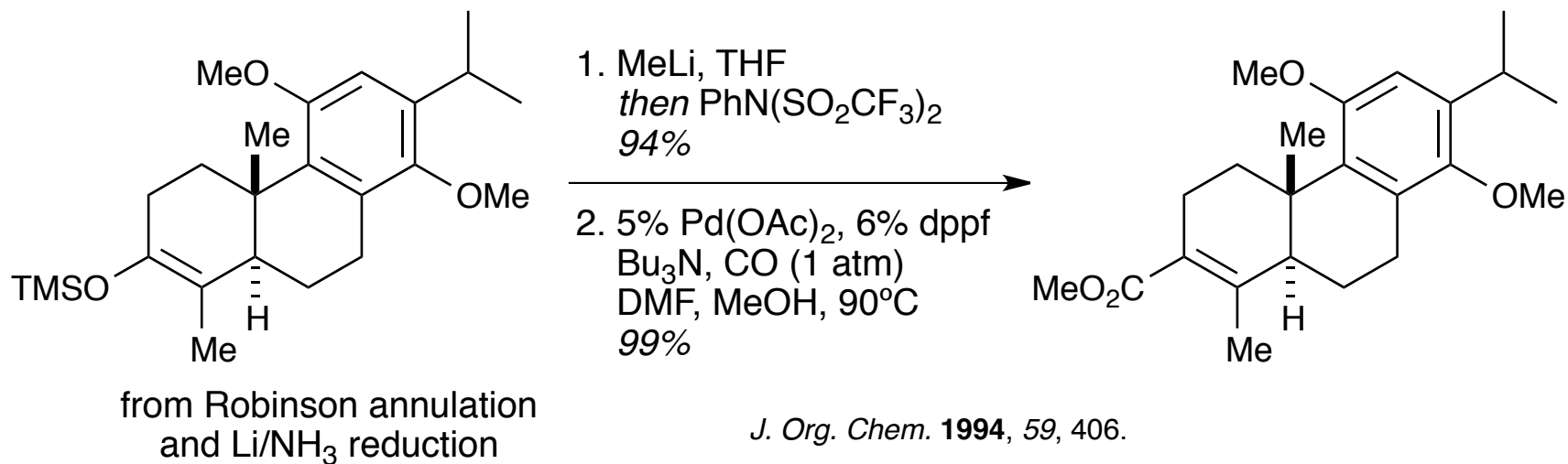
Final trapping can also be intramolecular



Acyl metal intermediate can undergo insertions by alkenes/alkynes

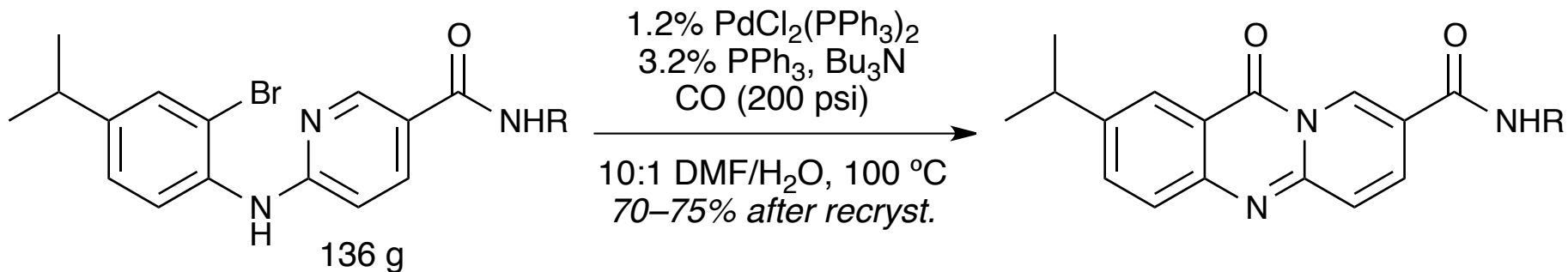


## Carbonylation Reactions



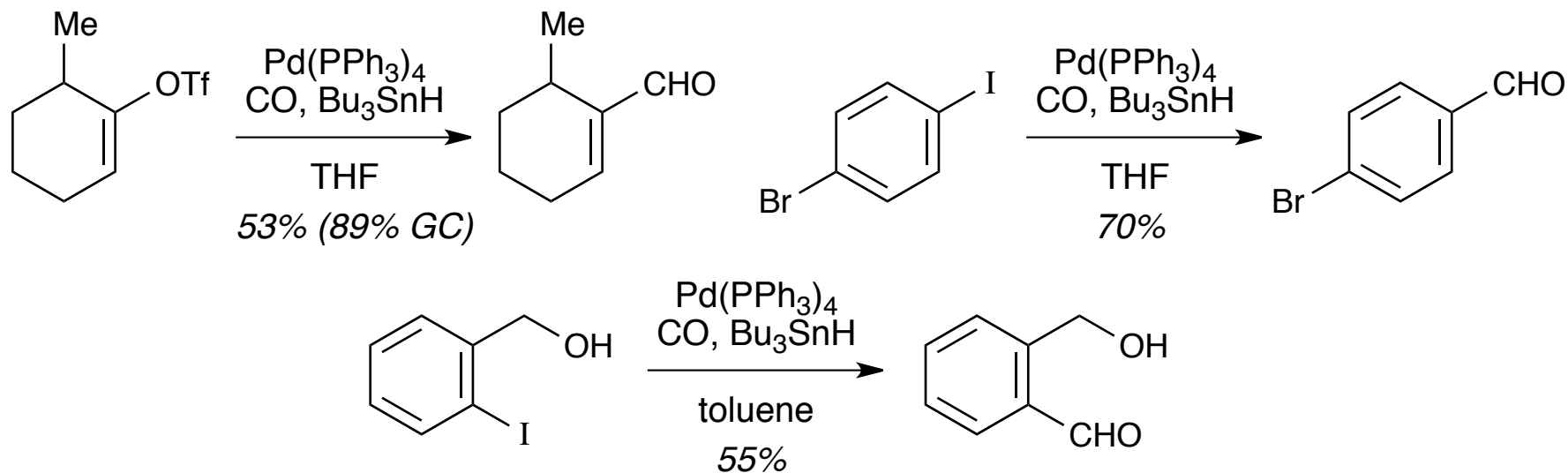
*J. Am. Chem. Soc.* **1980**, 102, 4193.

## Carbonylation Reactions



*J. Org. Chem.* **1987**, *52*, 2469.

Performing the carbonylation at higher pressures (3<sup>+</sup> atm) in the presence of Bu<sub>3</sub>SnH or slow addition of the tin hydride will form the aldehyde.



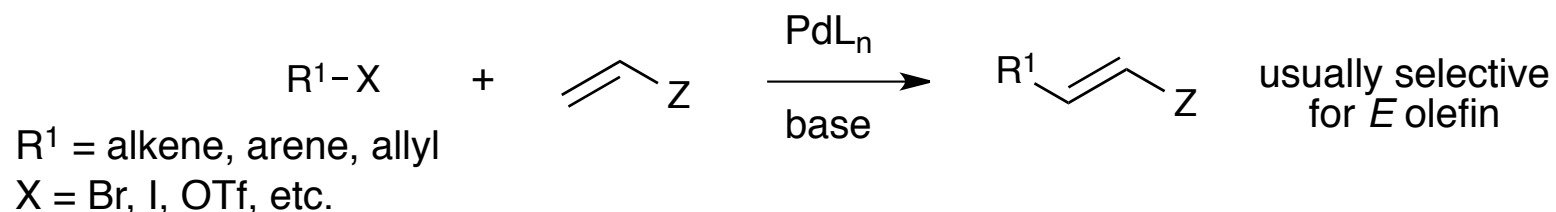
*J. Am. Chem. Soc.* **1986**, *108*, 452.

# Heck Reactions

*Bull. Chem. Soc. Jpn* **1971**, *44*, 581.; *J. Org. Chem.* **1972**, *37*, 2320.

In general terms, the Heck (or Mizoroki-Heck) reaction involves an oxidative addition followed by insertion into an alkene. The reaction is terminated by a  $\beta$ -hydride elimination to "regenerate" the olefin.

In principle any halide or pseudohalide electrophile can be used, except those with  $\beta$ -hydrides.



Phosphines required with aryl bromides, but hinder reactions with iodides. Typically amines bases are used. Originally, high reaction temps were required. The insertion step is thought to be the difficult step.

So-called "Jeffery conditions" have become quite popular as they allow lower reaction temperatures to be used. These conditions involve ligandless Pd(OAc)<sub>2</sub> with polar solvents (e.g., DMF, NMP) and tetraalkylammonium salts (usually Bu<sub>4</sub>NCl or Bu<sub>4</sub>NBr), often with carbonate bases. There is evidence that Pd nanoparticles are formed and are stabilized by the anions (*Angew. Chem. Int. Ed.* **2000**, *39*, 165.). Chloride anions also help promote oxidative addition processes (*J. Am. Chem. Soc.* **1991**, *113*, 8375.).

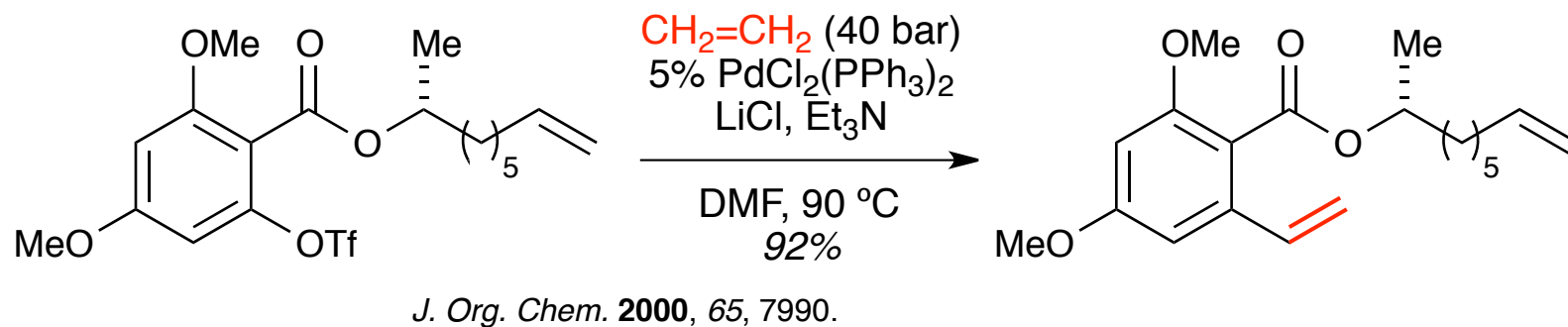
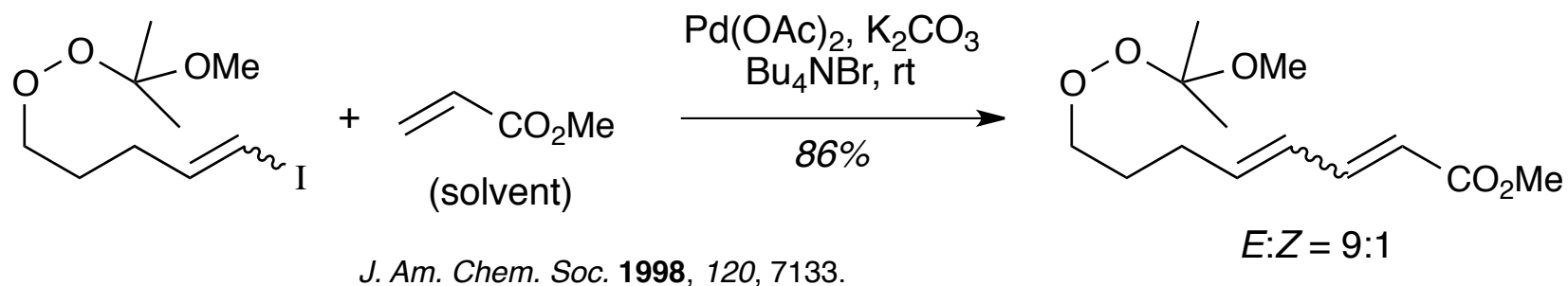
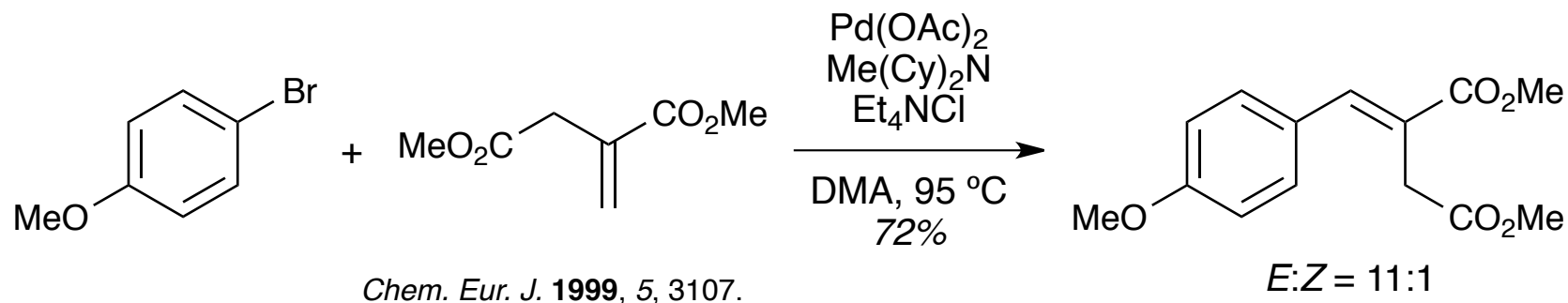
Jeffery conditions: *Chem. Commun.* **1984**, 1287.; *Tetrahedron Lett.* **1985**, *26*, 2667.; *Tetrahedron Lett.* **1988**, *29*, 905.; *Synthesis* **1987**, 70.; *Tetrahedron* **1996**, *52*, 10113.

Wide range of olefins can be employed: cyclic and acyclic, electron-deficient (esters, amides, ketones, nitriles, aldehydes), unactivated, electron-rich (enol ethers).

The insertion proceeds with *syn*-addition of R group and metal. BHE is a *cis* process as well.

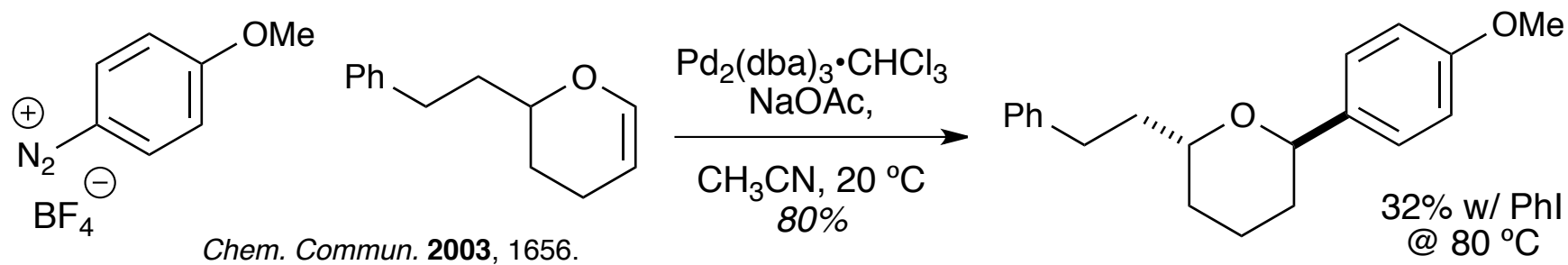
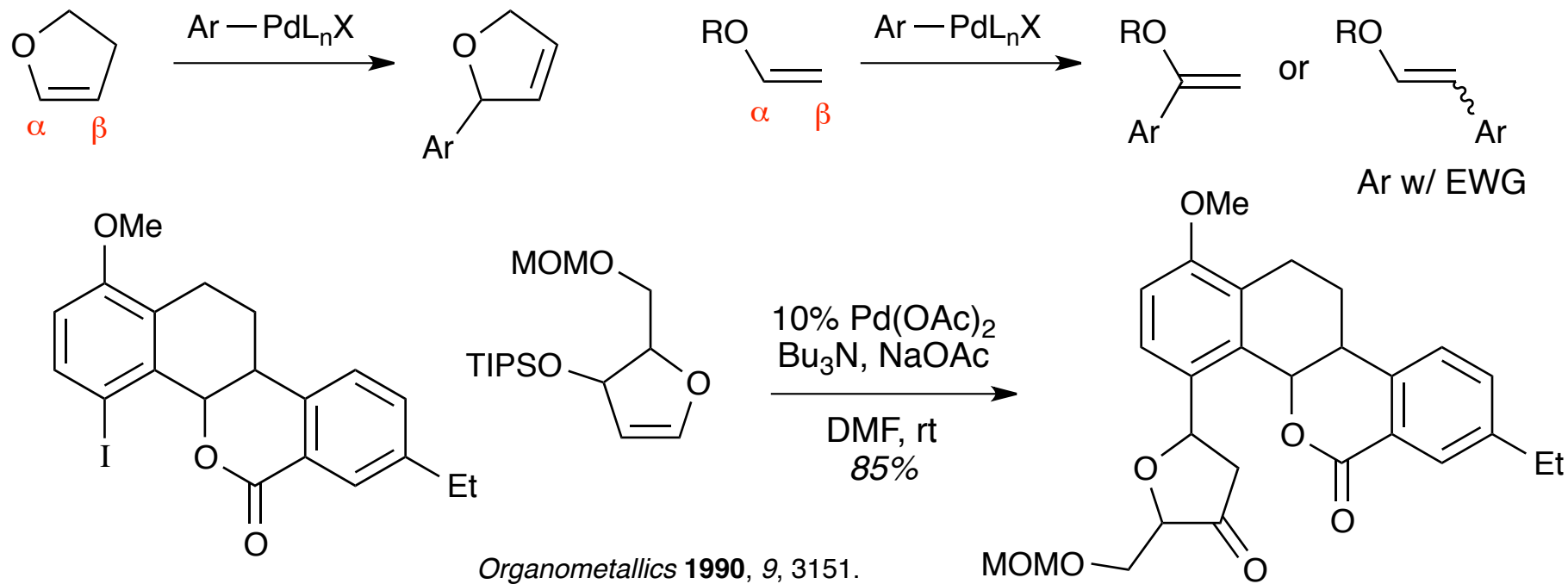
# Heck Reactions

Electron-poor and unactivated are sterically controlled and place R-group on less-substituted position.



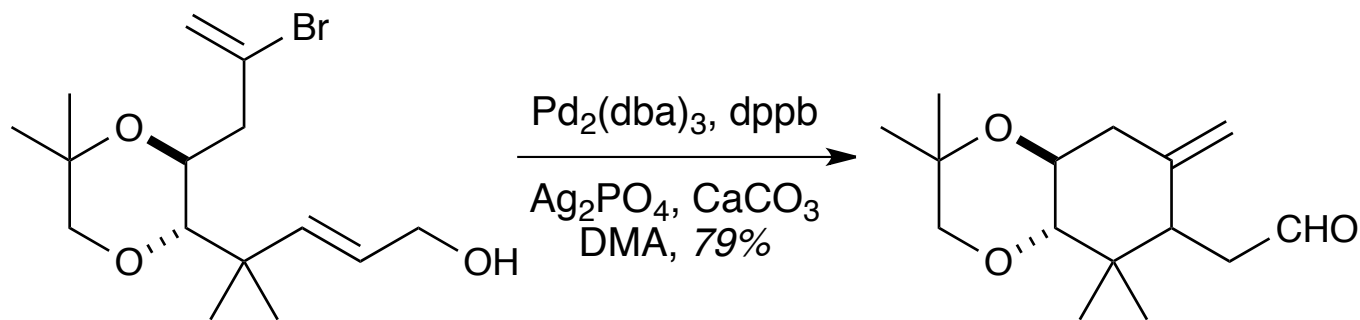
# Heck Reactions

Regioselectivity of electron-rich olefins is more complex. With cyclic systems,  $\alpha$ -arylation is observed. Mixtures with acyclic enol ethers. Bidentate phosphines and electron-rich halides favor  $\alpha$ -arylation. Electron-poor halides favor  $\beta$ -arylation. (*J. Org. Chem.* **1987**, *52*, 3529.)

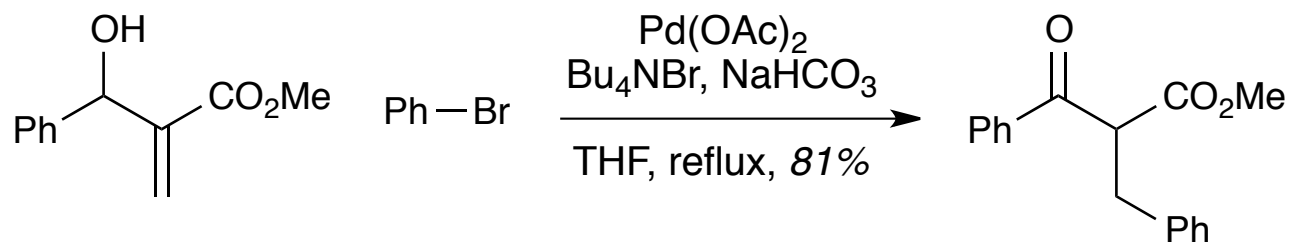


# Heck Reactions

Use of allylic alcohols gives aldehyde or ketone via  $\beta$ -hydride elimination toward alcohol.



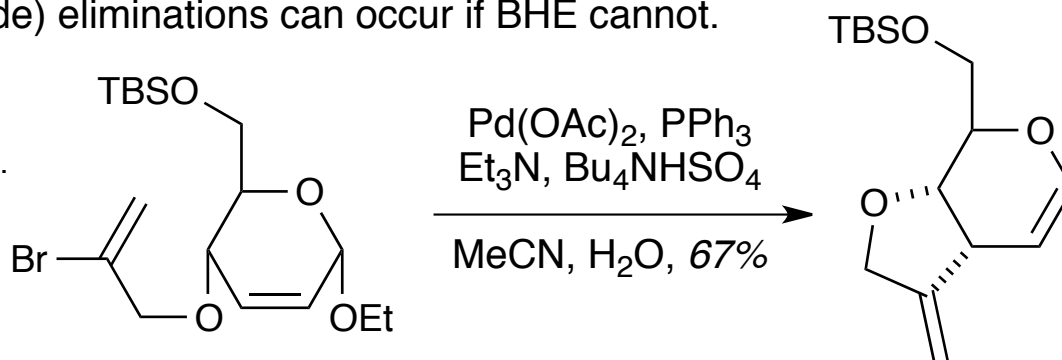
*Angew. Chem. Int. Ed.* **1999**, *38*, 3662.



*Tetrahedron* **1998**, *54*, 4943.

$\beta$ -alkoxide (or hydroxide) eliminations can occur if BHE cannot.

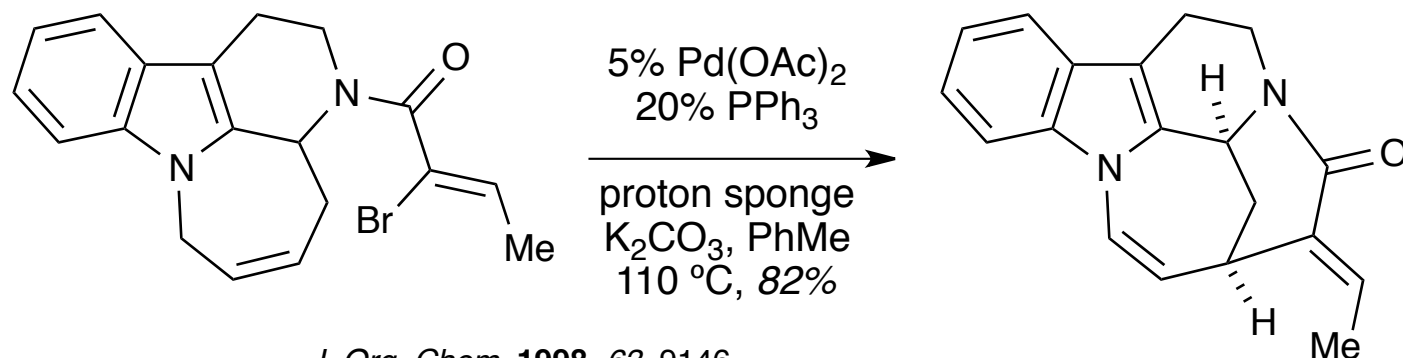
*J. Org. Chem.* **1997**, *62*, 1341.



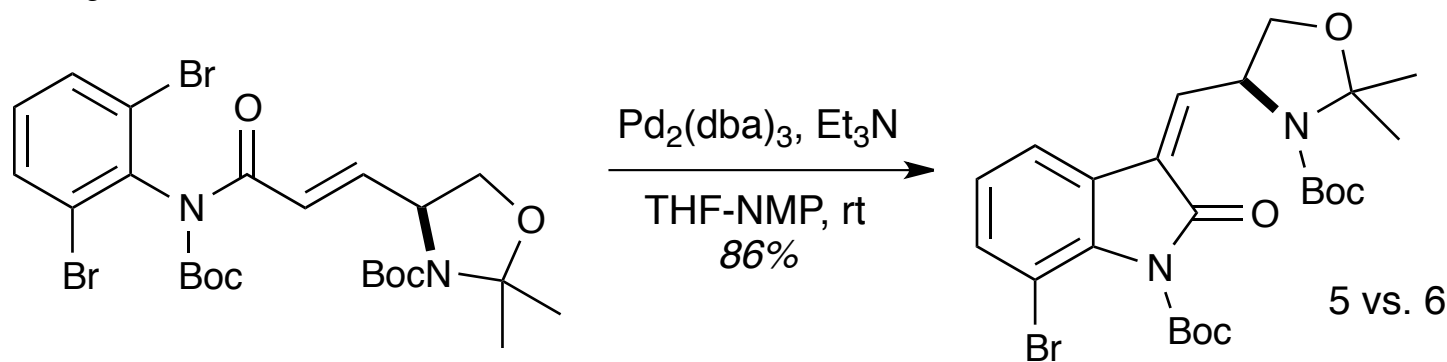


# Heck Reactions

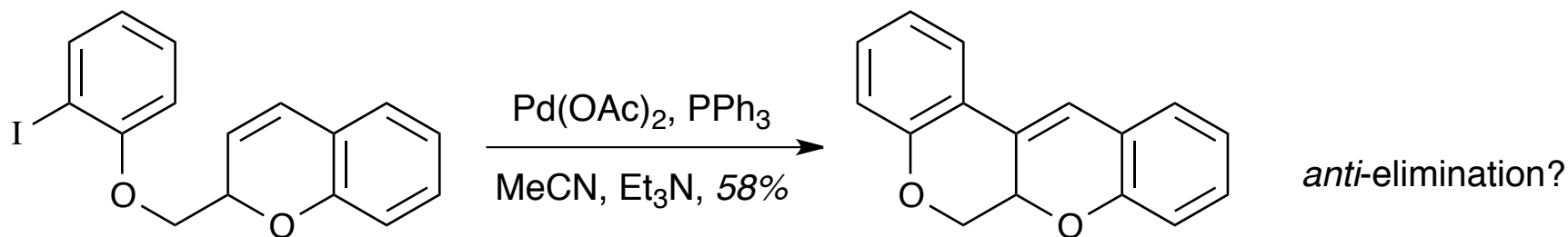
Intramolecular Heck reactions work especially well and many examples exist. Regioselectivity is usually high, but mode of addition (exo vs endo) is less predictable. In general, 5-exo and 6-eso are favored.



*J. Org. Chem.* **1998**, *63*, 9146.



*Org. Lett.* **2001**, *3*, 2863.



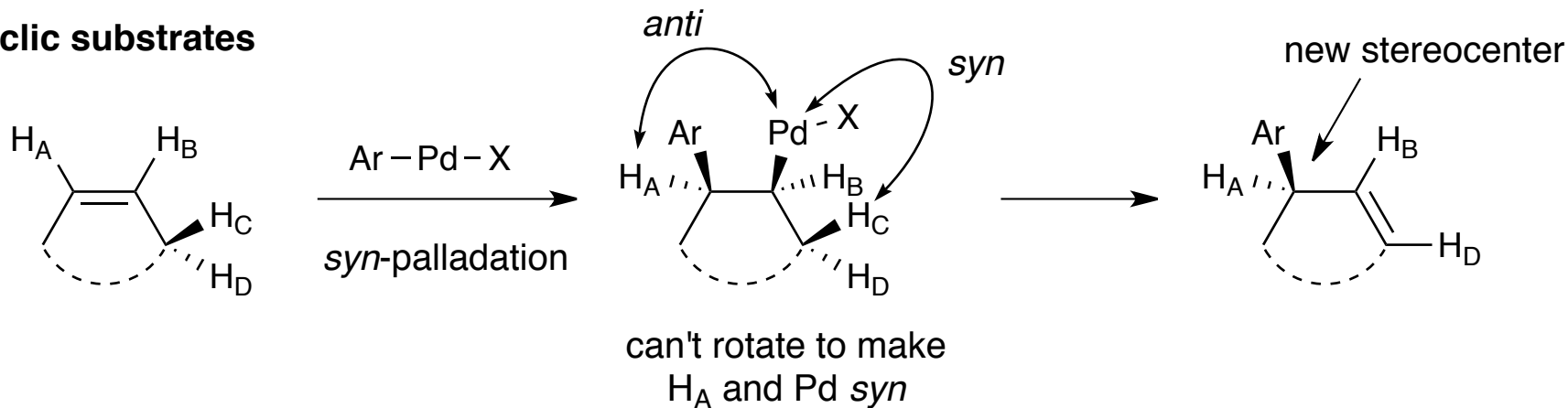
*J. Chem. Soc., Perkin Trans. 1* **1992**, 539.

*anti-elimination?*

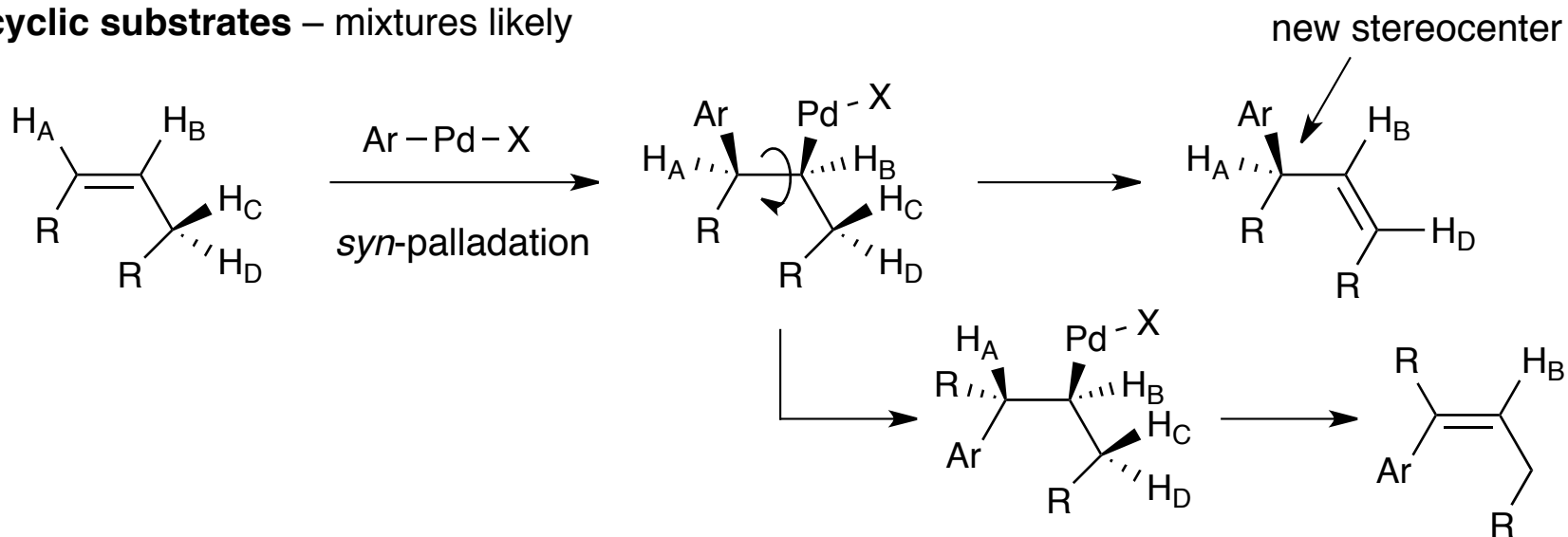
# Asymmetric Heck Reactions

Many olefins are prochiral. By including chiral ligands, Heck reactions can, in principle, be used to generate stereocenters. In order for this to occur, the  $\beta$ -hydride elimination must occur away from the newly formed stereocenter. This restricts substrates to cyclic olefins or the formation of quaternary stereocenters.

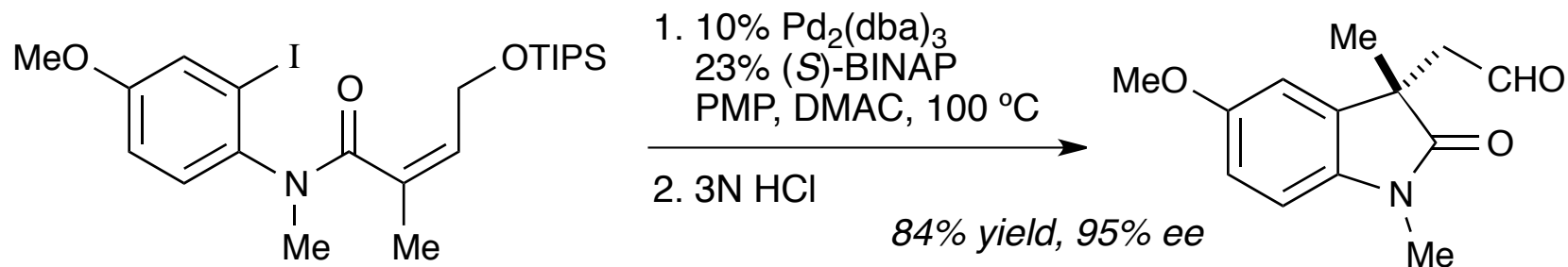
## cyclic substrates



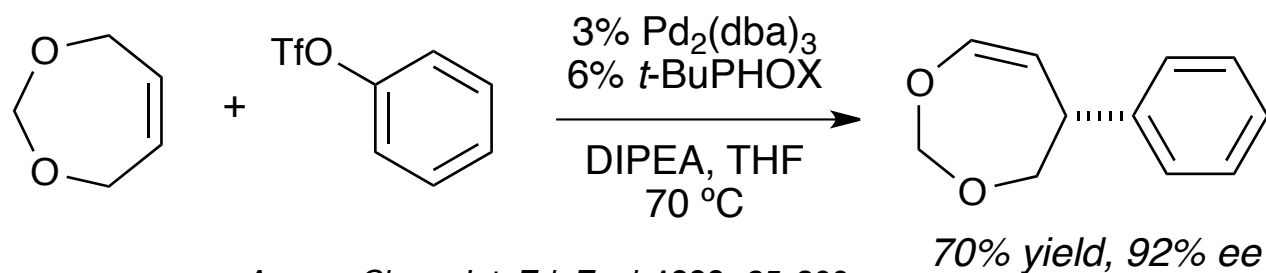
## acyclic substrates – mixtures likely



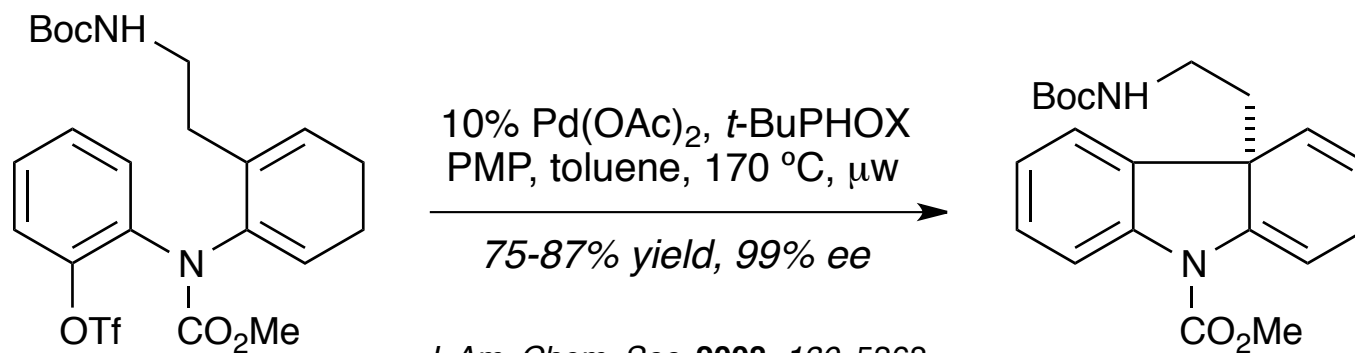
# Asymmetric Heck Reactions



*J. Org. Chem.* **1993**, *58*, 6949.



*Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 200.

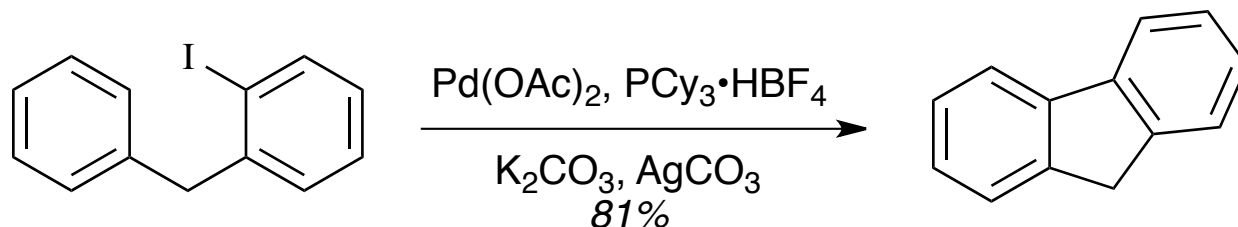


*J. Am. Chem. Soc.* **2008**, *130*, 5368.

## "Aromatic" Heck Reactions

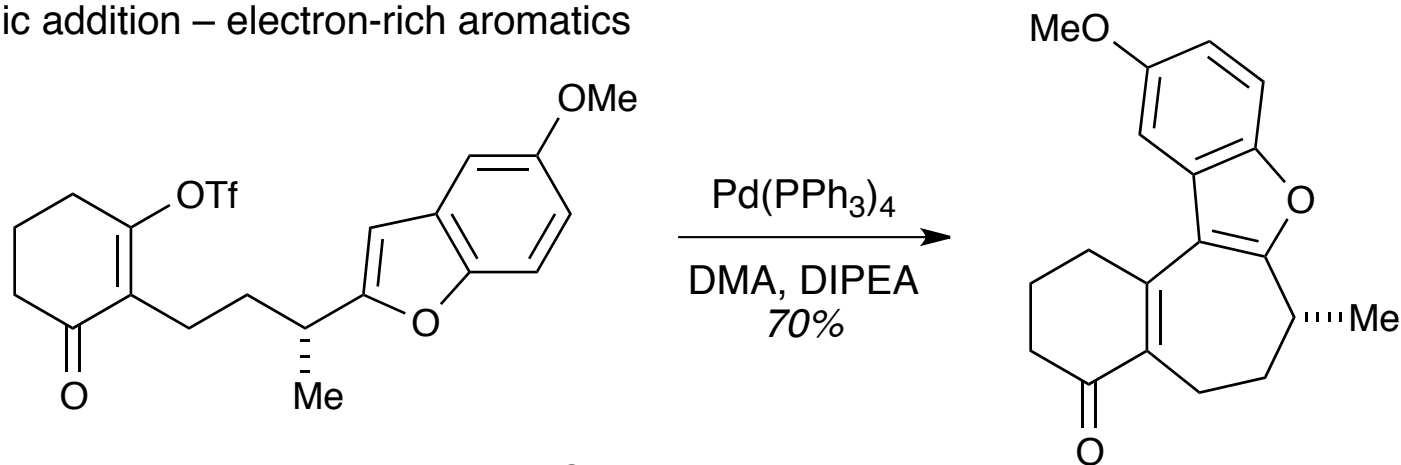
"Insertions" can also occur with electron-rich (or neutral) aromatic groups. Two mechanisms are possible, likely due to electronics of aromatic partner. Calculations have supported both.

"metathesis" mechanism – neutral aromatics



*J. Am. Chem. Soc.* **2006**, *128*, 581.

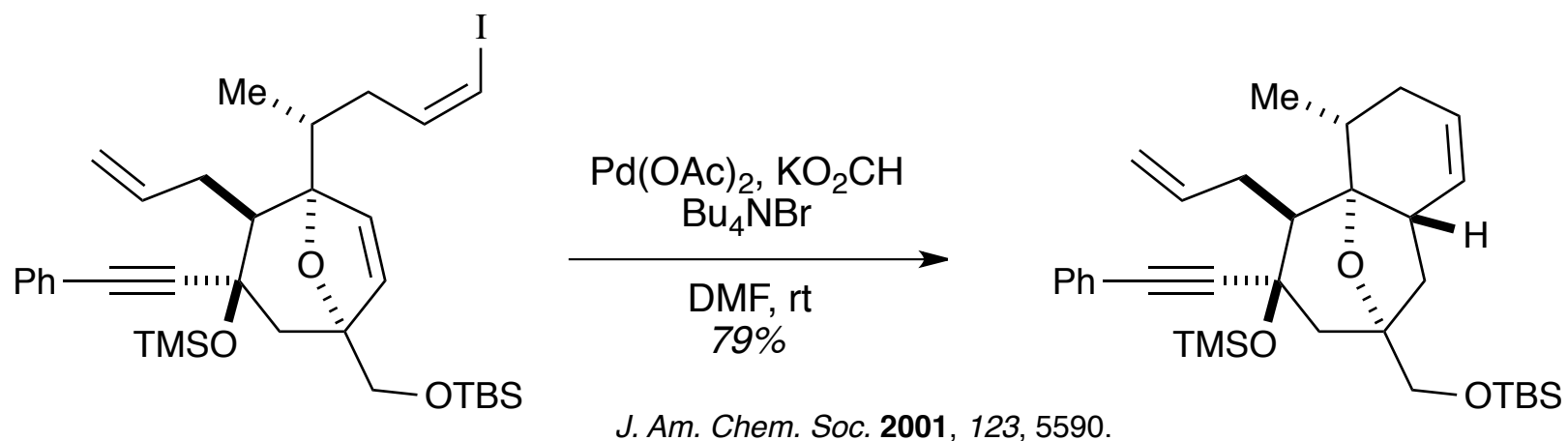
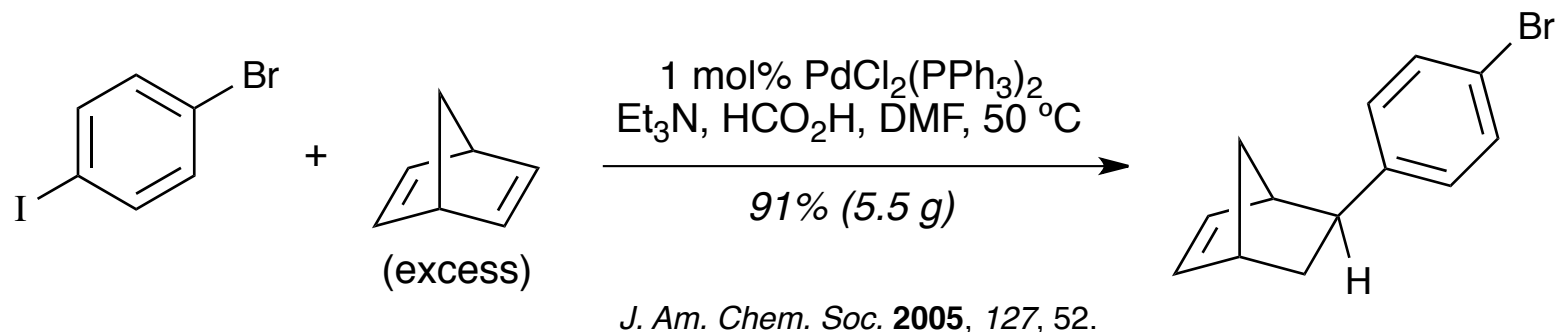
electrophilic addition – electron-rich aromatics



*Angew. Chem. Int. Ed.* **2002**, *41*, 1569.

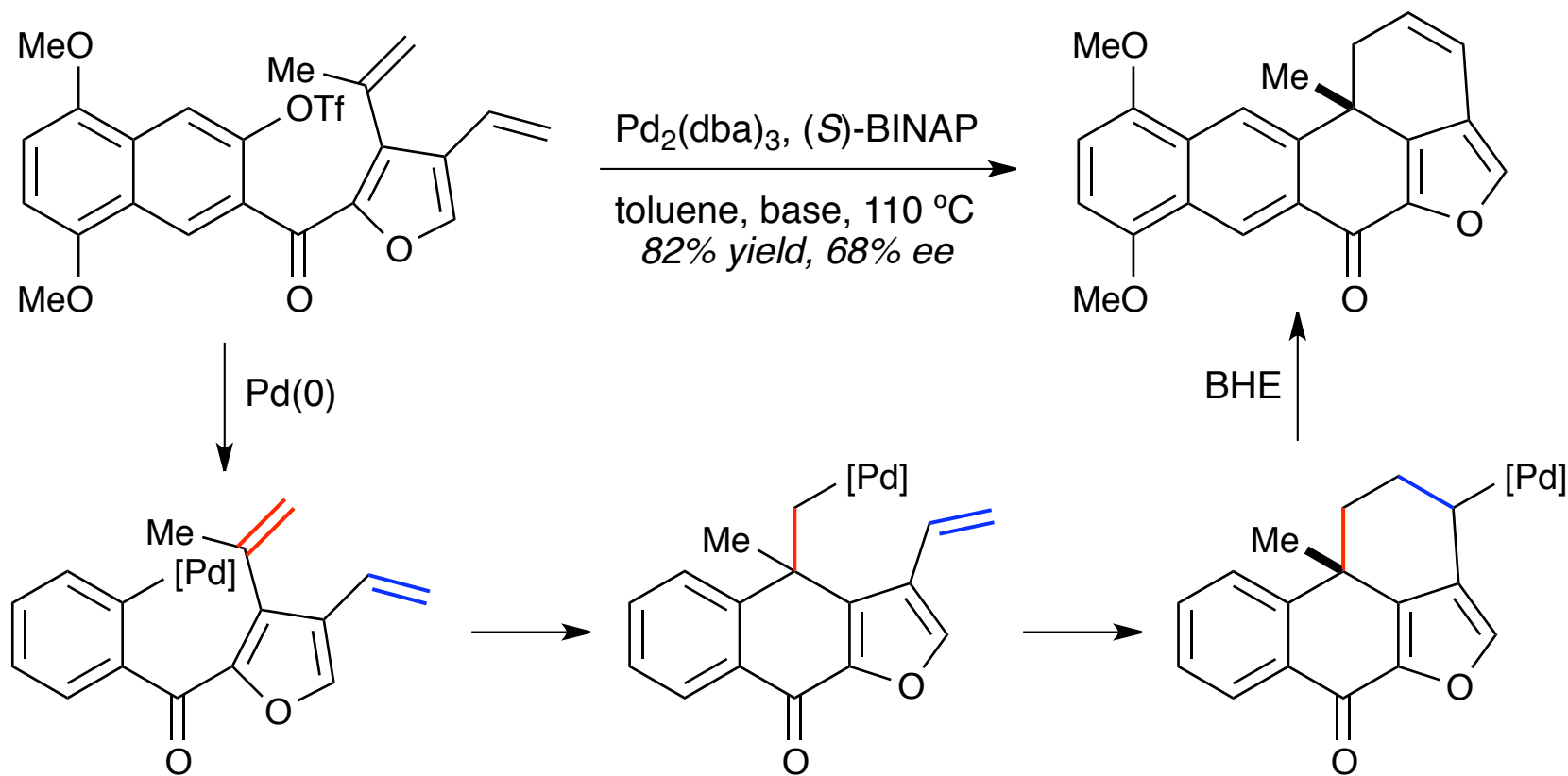
## Reductive Heck Reactions

If the insertion is set up such that  $\beta$ -hydride elimination is not possible, the  $\sigma$ -alkyl palladium intermediate can be intercepted by other processes. If carried out in the presence of formic acid or ammonium formate, a "reductive Heck" reaction will take place. This is most common with bicyclic olefins.



## Cascade Reactions

Cascade reactions are also possible. In these cases, several alkene/alkyne insertions take place with a polyunsaturated substrate. Excellent strategy for constructing polycyclic products. Incorporating CO is also possible, but high pressures required to suppress  $\beta$ -hydride elimination.



# Cascade Reactions

