

Reviews:

• General:

Brase, S.; de Meijere, A. In *Metal-catalyzed Cross-coupling Reactions*, Diederich, F., and Stang, P. J., Eds.; Wiley-VCH: New York, **1998**, pp. 99–166.

Cabri, W.; Candiani, I. *Acc. Chem. Res.* **1995**, *28*, 2–7.

de Meijere, A.; Meyer, F. E. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2379–2411.

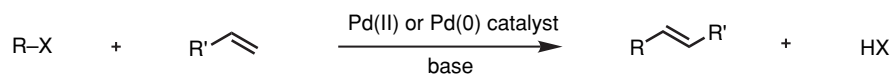
• Intramolecular:

Link, J. T.; Overman, L. E. In *Metal-catalyzed Cross-coupling Reactions*, Diederich, F., and Eds.; Wiley-VCH: New York, **1998**, pp. 231–269.

Gibson, S. E.; Middleton, R. J. *Contemp. Org. Synth.* **1996**, *3*, 447–471.

• Asymmetric:

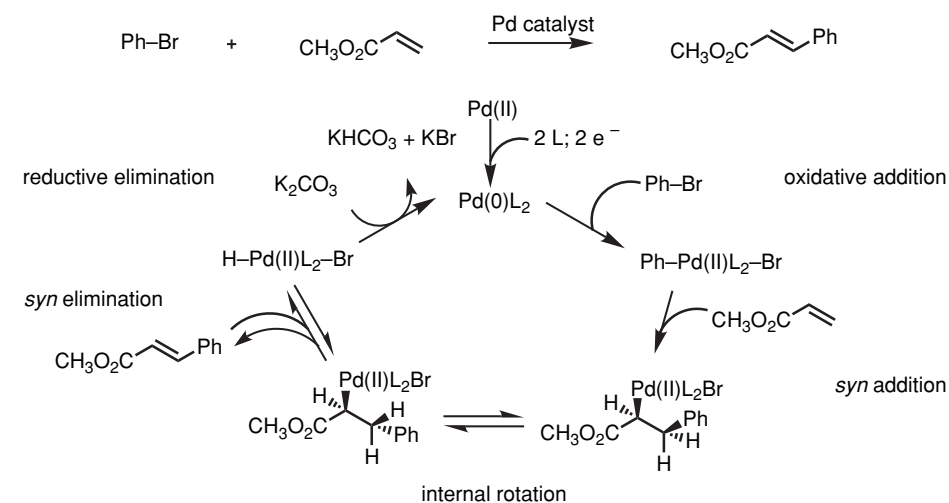
Shibasaki, M.; Boden, C. D. J.; Kojima, A. *Tetrahedron* **1997**, *53*, 7371–7393.

General transformation:

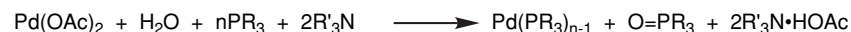
R = alkenyl, aryl, allyl, alkynyl, benzyl X = halide, triflate R' = alkyl, alkenyl, aryl, CO₂R, OR, SiR₃

Mechanism:

• Proposed mechanism involving neutral Pd:



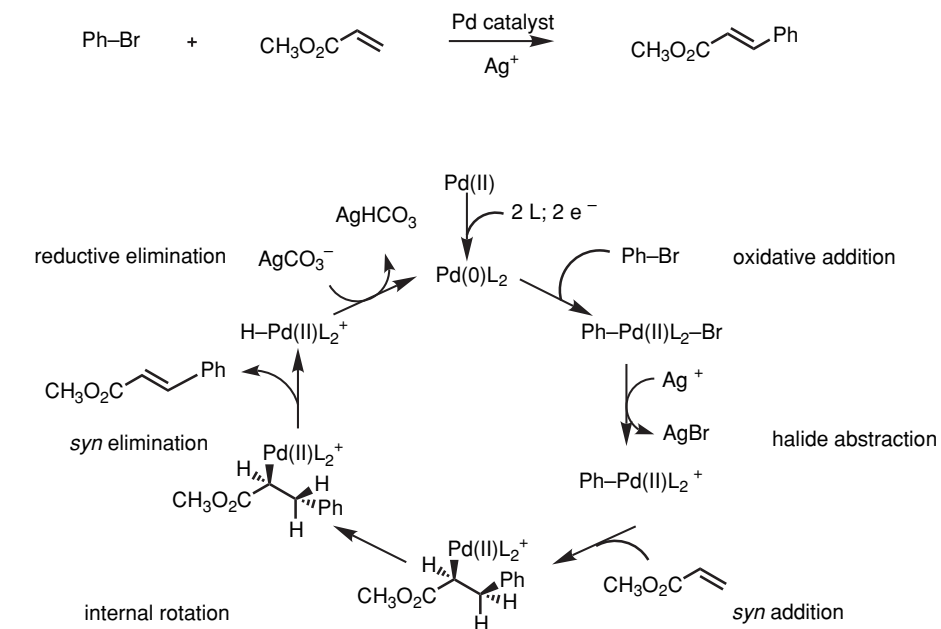
- Pd(II) is reduced to the catalytically active Pd(0) in situ, typically through the oxidation of a phosphine ligand.



Ozawa, F.; Kubo, A.; Hayashi, T. *Chemistry Lett.* **1992**, 2177–2180.

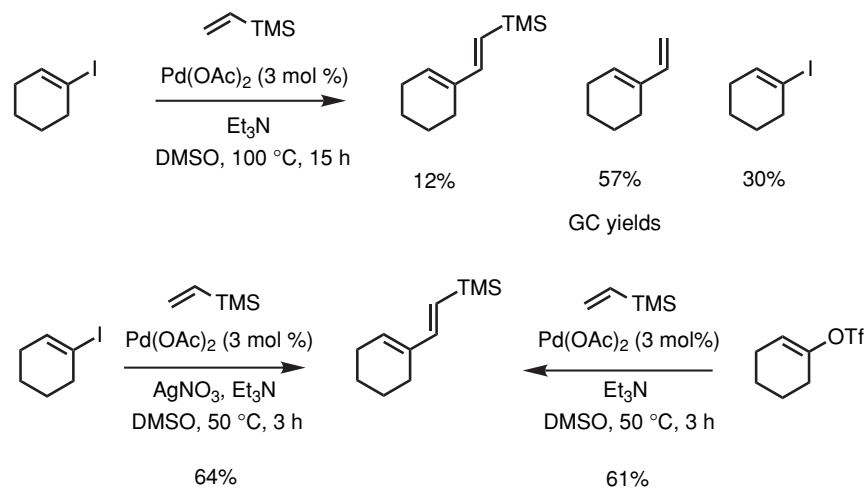
- Ag⁺ / Tl⁺ salts irreversibly abstract a halide ion from the Pd complex formed by oxidative addition. Reductive elimination from the cationic complex is probably irreversible.

- An example of a proposed mechanism involving cationic Pd:



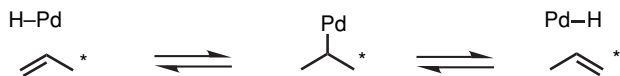
Abelman, M. M.; Oh, T.; Overman, L. E. *J. Org. Chem.* **1987**, *52*, 4133–4135.

- Reactions with vinyl or aryl triflates often parallel those of the corresponding halides in the presence of silver salts.

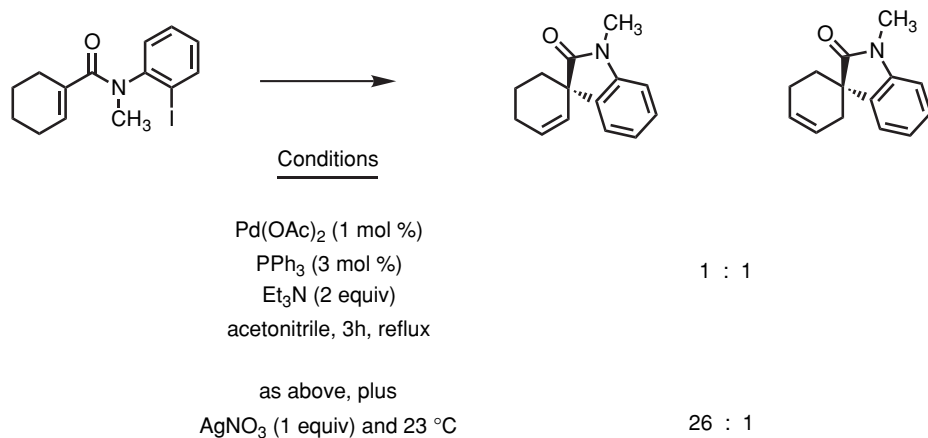


Karabelas, K.; Hallberg, A. *J. Org. Chem.* **1988**, *53*, 4909–4914.

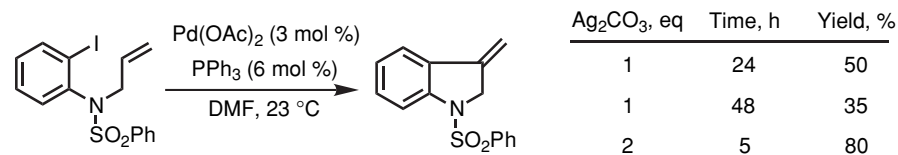
- Reversible β -hydride elimination can lead to alkene isomerization.



- Use of silver salts can minimize alkene isomerization.

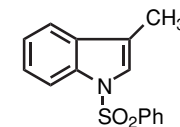


Abelman, M. M.; Oh, T.; Overman, L. E. *J. Org. Chem.* **1987**, *52*, 4133–4135.



Sakamoto, T.; Kondo, Y.; Uchiyama, M.; Yamanaka, H. *J. Chem. Soc. Perkin Trans. 1* **1993**, 1941–1942.

By-product:



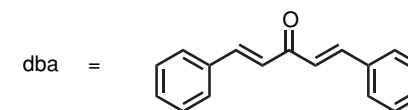
- With some ligands, experimental evidence points to a Pd(II)/Pd(IV) catalytic cycle, although the debate is ongoing.

Ohff, M.; Ohff, A.; van der Boom, M. E.; Milstein, D. *J. Am. Chem. Soc.* **1997**, *119*, 11687–11688.

Shaw, B. L.; Perera, S. D.; Staley, E. A. *J. Chem. Soc., Chem. Commun.* **1998**, 1361–1362.

Conditions:

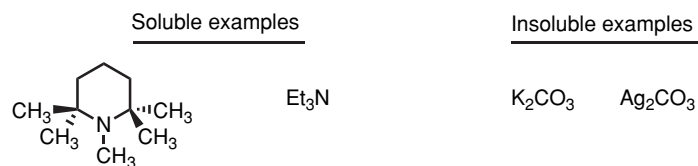
- Catalysts: Pd(OAc)₂ (most common) and Pd₂(dba)₃ (stable Pd(0) source; useful if substrate is sensitive to oxidation)



- Ligands: Phosphines (PR₃), used to prevent deposition of Pd(0) mirror.
- Solvents: Typically aprotic; a range of polarities.

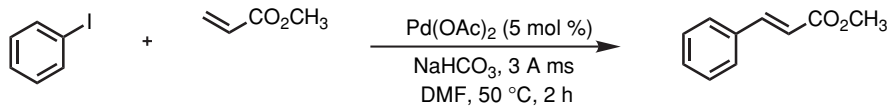
Solvent	toluene	THF	1,1-dichloroethane	DMF
Dielectric constant	2.4	7.6	10.5	38.3

- Bases: Both soluble and insoluble bases are used.



1,2,2,6,6-pentamethylpiperidine (PMP)

- Jeffery conditions: The combination of tetraalkylammonium salts (phase-transfer catalysts) and insoluble bases accelerates the rate to the extent that lower reaction temperatures are possible.



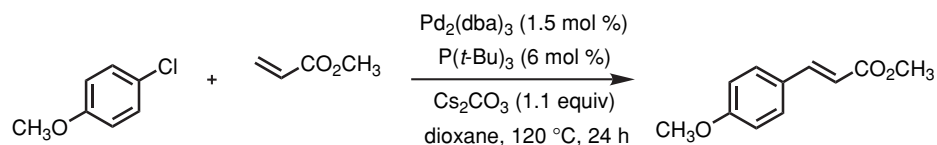
Equiv. of <i>n</i> -Bu ₄ NCl	GC Yield(%)
0	2
1	99

Jeffery, T. *Tetrahedron* **1996**, *52*, 10113–10130.

- One proposed explanation for this rate enhancement is based on the fact that palladium complexes can be stabilized by the coordination of halide ions; thus, the catalyst is less likely to decompose under the Heck reaction conditions.

Amatore, C.; Azzabi, M.; Jutand, A. *J. Am. Chem. Soc.* **1991**, *113*, 8375–8384.

- Conditions for the Heck coupling of aryl chlorides have been developed.

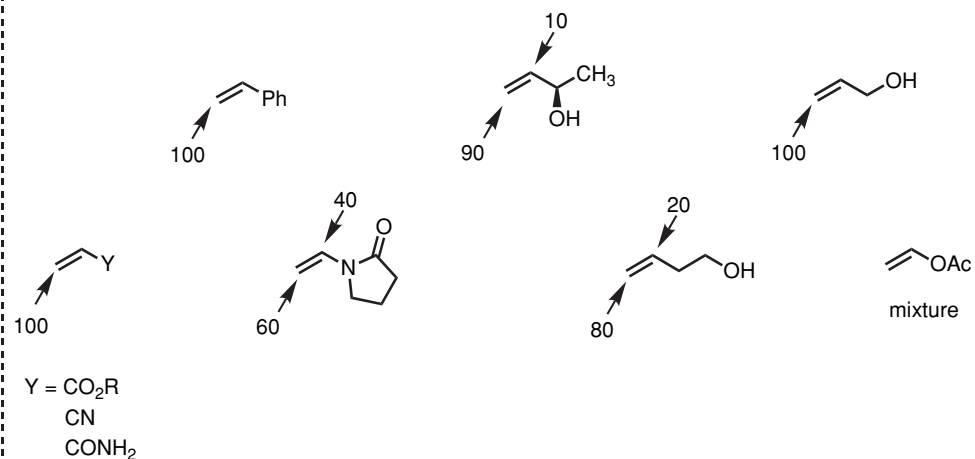


82%

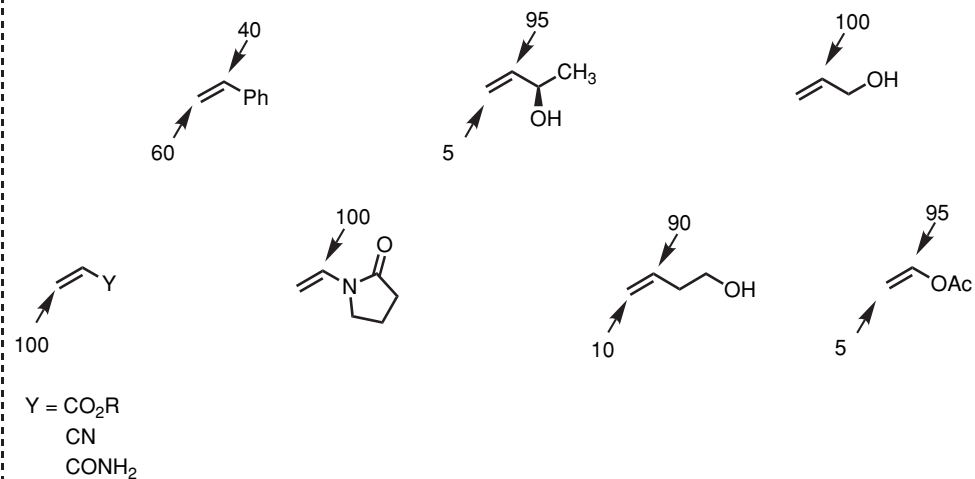
Littke, A. F.; Fu, G. C. *J. Org. Chem.* **1999**, *64*, 10–11.

Regiochemistry of addition:

- Neutral Pd complexes: regiochemistry is governed by sterics; position of Ar attachment:



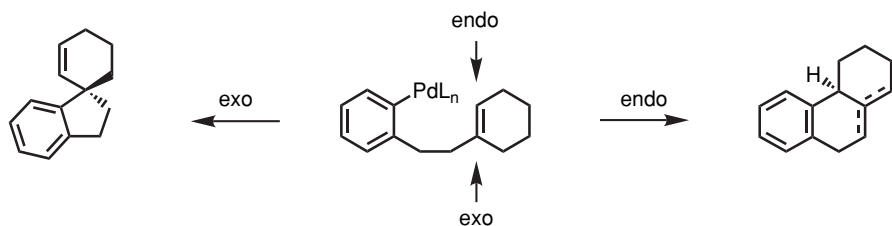
- Cationic Pd complexes: regiochemistry is affected by electronics. The cationic Pd complex increases the polarization of the alkene favoring transfer of the vinyl or aryl group to the site of least electron density.



Cabri, W.; Candiani, I. *Acc. Chem. Res.* **1995**, *28*, 2–7.

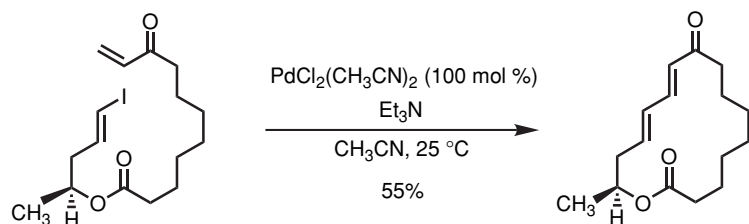
Cabri, W.; Candiani, I.; Bedeschi, A.; Penco, S.; Santi, R. *J. Org. Chem.* **1992**, *57*, 1481–1486.

- A major issue in intramolecular Heck reactions is the mode of ring closure, i.e., *exo* versus *endo*.



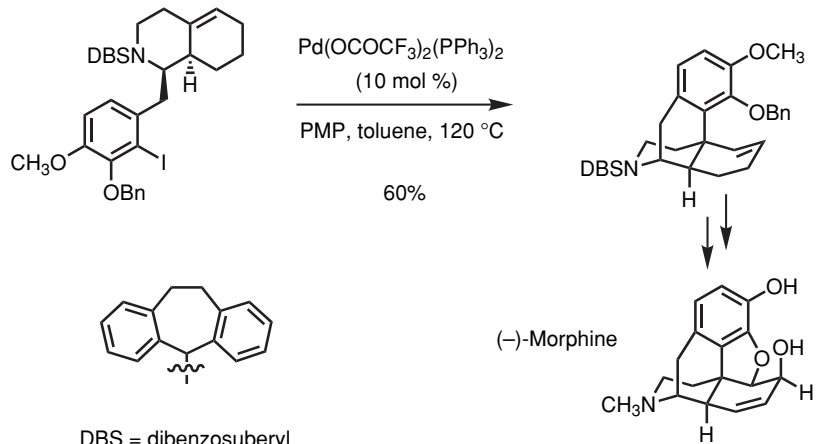
- For large rings, conformational effects can be minimal. If a neutral Pd complex is used, sterics enforce *endo* selectivity.

- The Heck reaction is useful for macrocyclization.



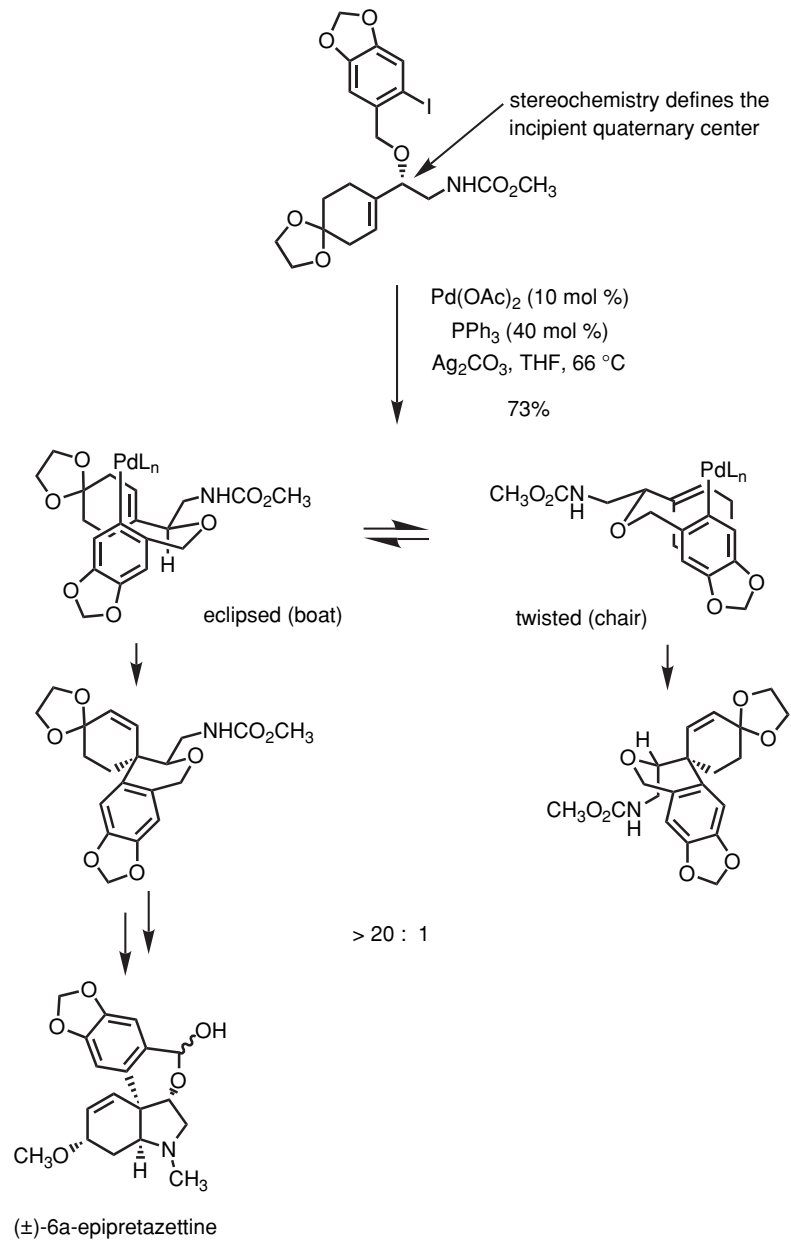
Ziegler, F. E.; Chakraborty, U. R.; Weisenfeld, R. B. *Tetrahedron* **1981**, *37*, 4035–4040.

- Five-, six-, and seven-membered ring closures (the most efficient Heck ring closures) give predominantly *exo* products.



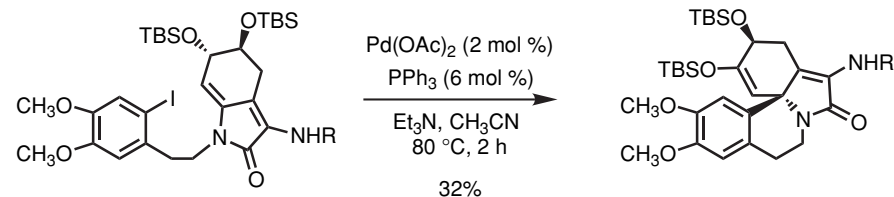
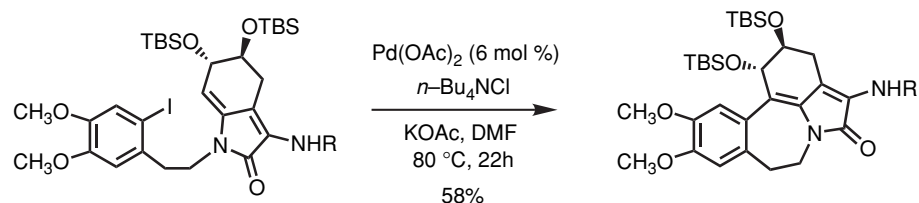
Hong, C. Y.; Kado, N.; Overman, L. E. *J. Am. Chem. Soc.* **1993**, *115*, 11028–11029.

- Conformational effects are more important when forming smaller rings. The eclipsed orientation is preferred for the reaction, even if this means the rest of the molecule must adopt a less than ideal conformation.



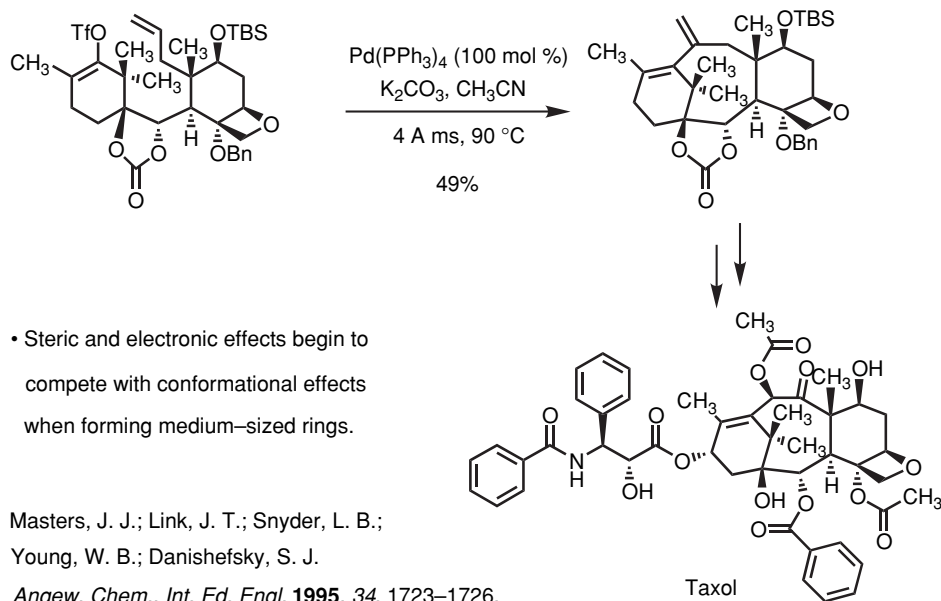
Overman, L. E. *Pure & Appl. Chem.* **1994**, *66*, 1423–1430.

- Variation of reaction conditions can greatly influence *exo* versus *endo* selectivity in small rings.



- The authors' rationale for these results is that under the Jeffery conditions, the coordination sphere of palladium is relatively smaller, and thus the metal can be accommodated at the more substituted alkene site during migratory insertion.

Rigby, J. H.; Hughes, R. C.; Heeg, M. J. *J. Am. Chem. Soc.* **1995**, *117*, 7834–7835.



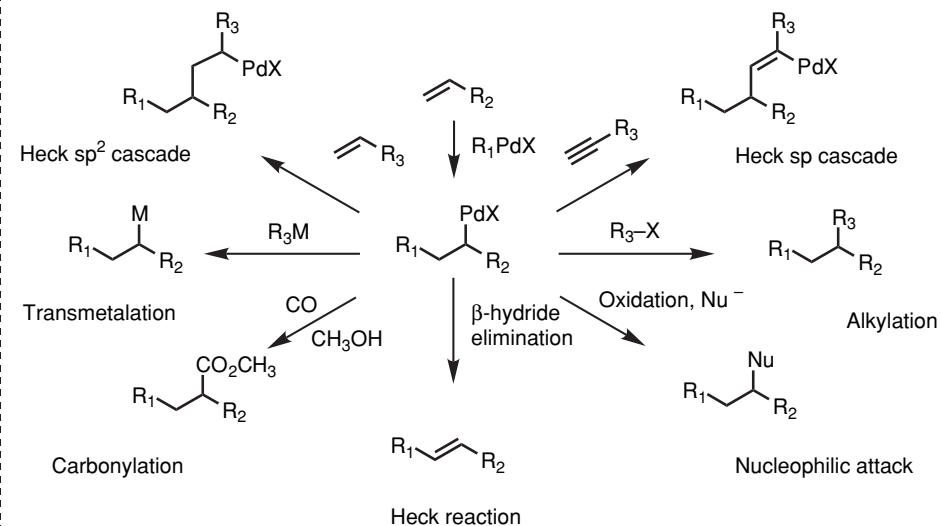
- Steric and electronic effects begin to compete with conformational effects when forming medium-sized rings.

Masters, J. J.; Link, J. T.; Snyder, L. B.; Young, W. B.; Danishefsky, S. J.

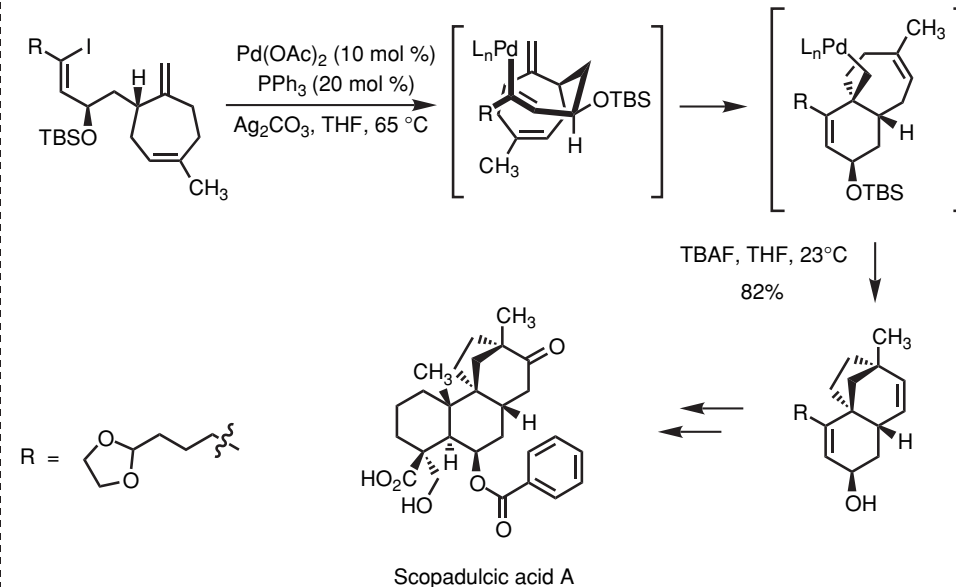
Angew. Chem., Int. Ed. Engl. **1995**, *34*, 1723–1726.

Tandem Reaction:

- Additional reaction pathways become available when the initial Pd–C species does not (or can not) decompose via β -hydride elimination.



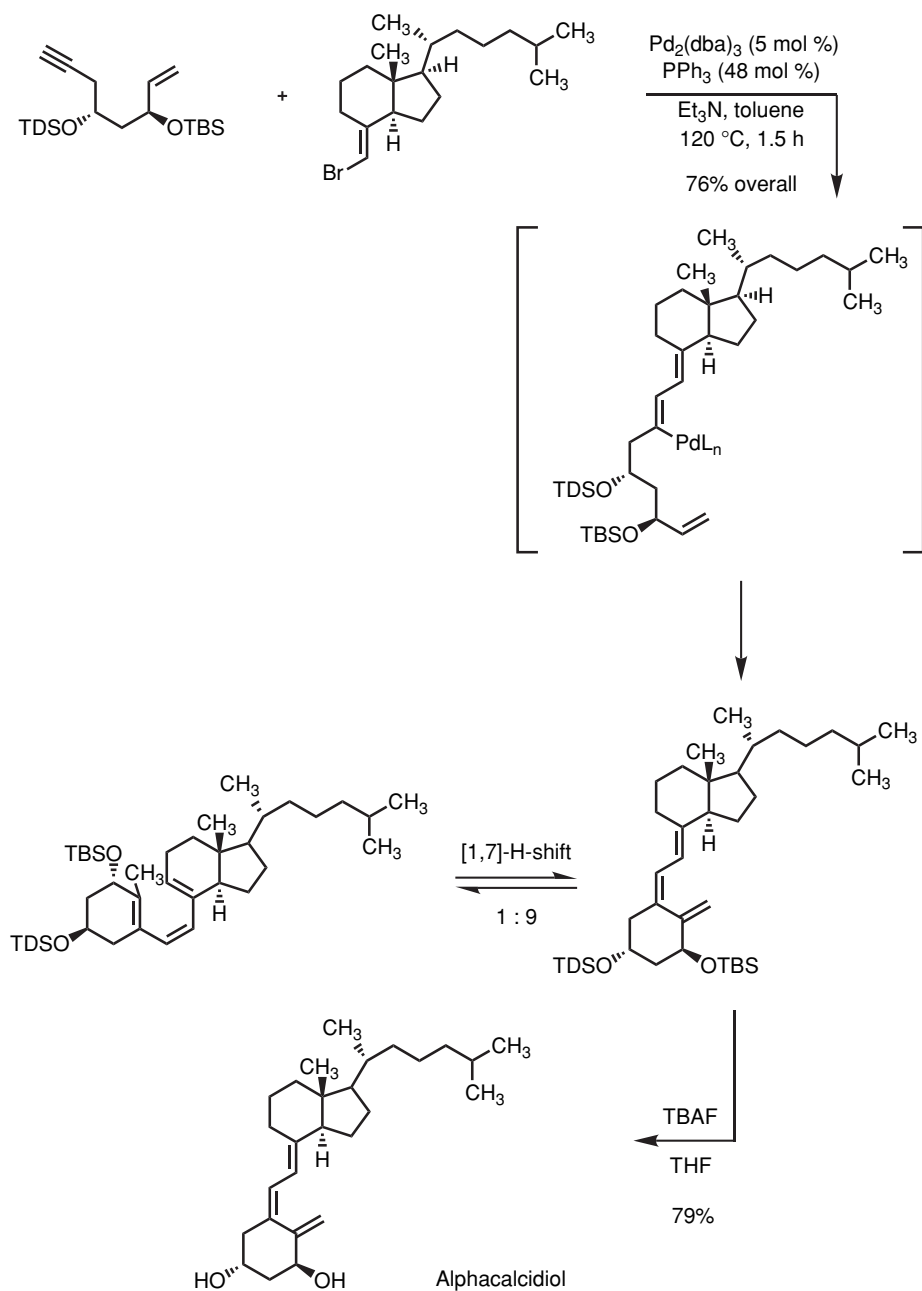
- Tandem Heck reactions:



Kucera, D. J.; O'Connor, S. J.; Overman, L. E. *J. Org. Chem.* **1993**, *58*, 5304–5306.

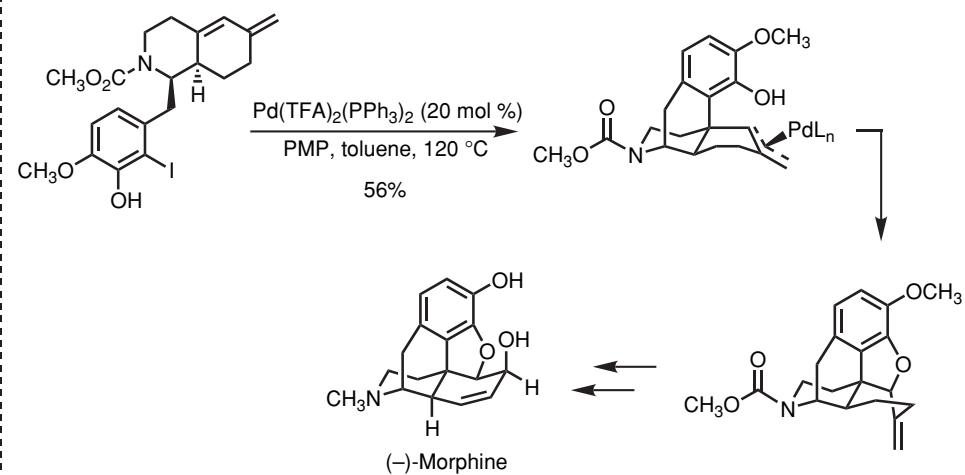
Fox, M. E.; Li, C.; Marino, J. P.; Overman, L. E. *J. Am. Chem. Soc.* **1999**, *121*, 5467–5480.

• Tandem Heck reaction, intermolecular



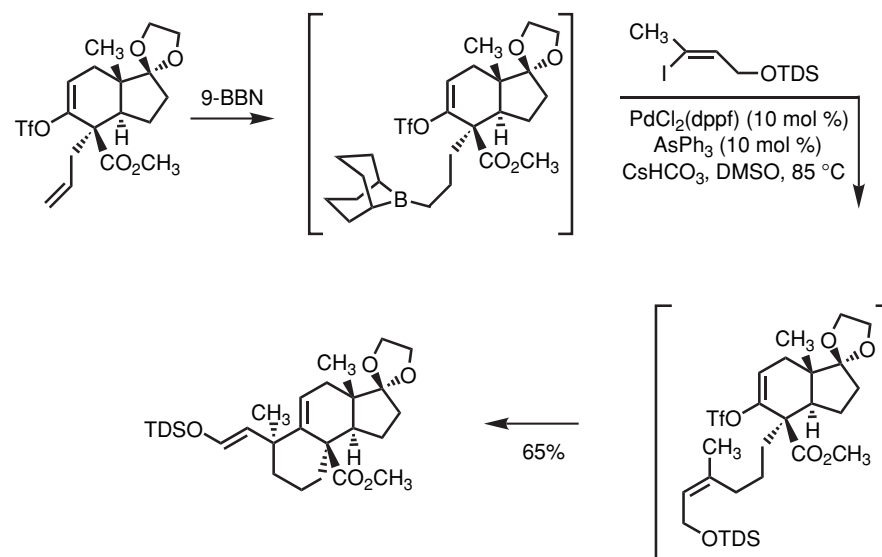
Trost, B. M.; Dumas, J.; Villa, M. J. *Am. Chem. Soc.* **1992**, *114*, 9836–9845.

• Tandem Heck/ π -allylpalladium reactions



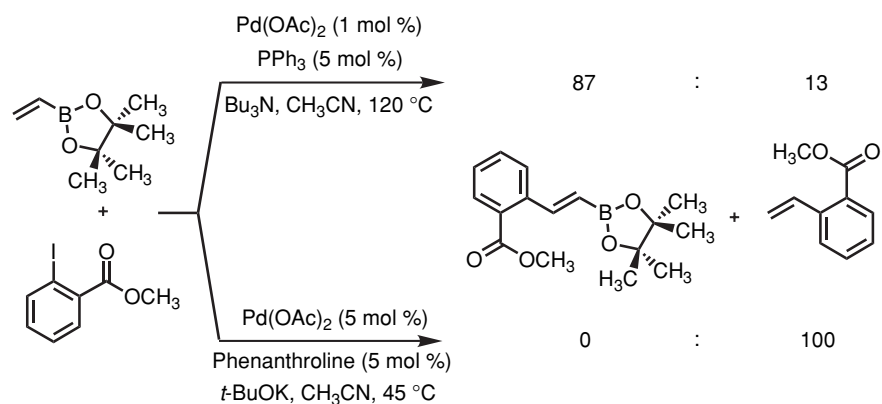
Hong, C. Y.; Overman, L. E. *Tetrahedron Lett.* **1994**, *35*, 3453–3456.

• Tandem Suzuki/Heck reactions



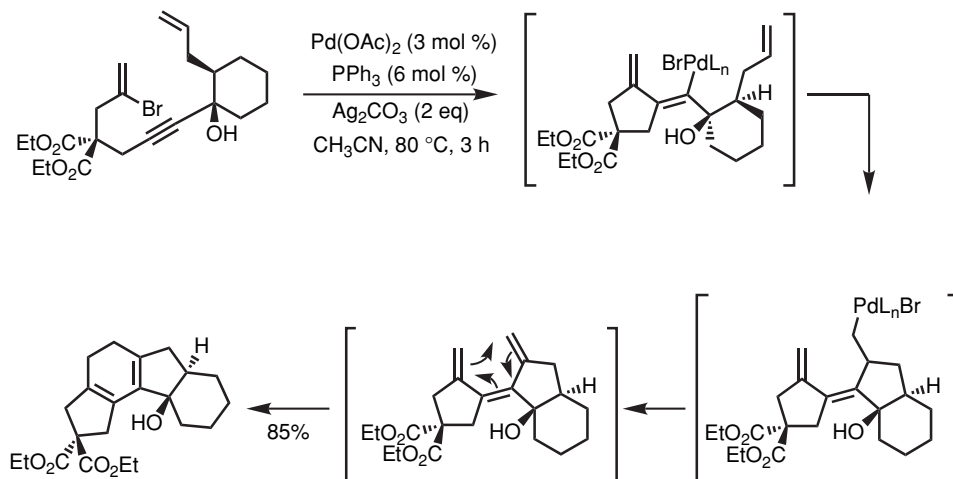
Kojima, A.; Honzawa, S.; Boden, C. D. J.; Shibasaki, M. *Tetrahedron Lett.* **1997**, *38*, 3455–3458.

- The ease of reaction (Heck versus Suzuki) is highly dependent upon the reaction conditions:



Hunt, A. R.; Stewart, S. K.; Whiting, A. *Tetrahedron Lett.*, **1993**, 34, 3599–3602.

- Tandem Heck/ 6π -electrocyclization reactions:



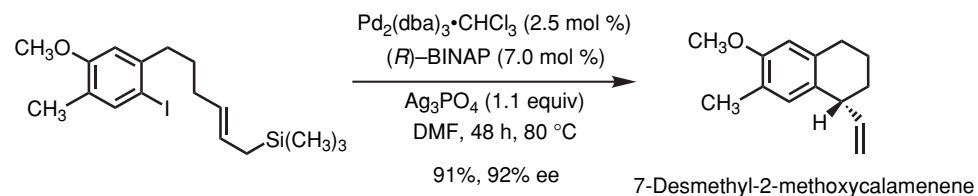
Henniges, H.; Meyer, F. E.; Schick, U.; Funke, F.; Parsons, P. J.; de Meijere, A. *Tetrahedron* **1996**, 52, 11545–11578.

Enantioselective Heck Reactions:

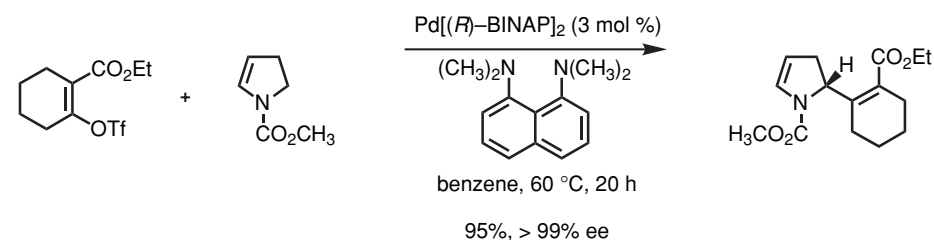
- Typical yields = 50–80%

- Typical ee's = 80–95%

- Formation of tertiary stereocenters:

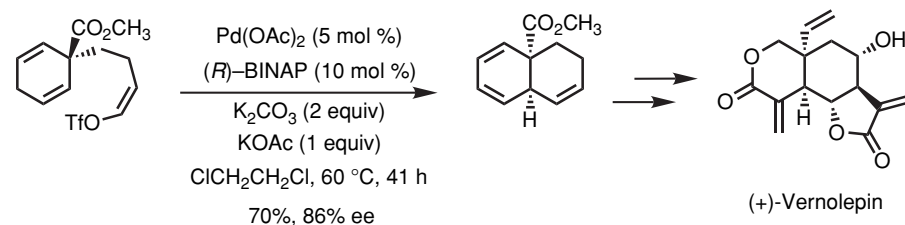


Tietze, L. F.; Raschke, T. *Synlett* **1995**, 597–598.

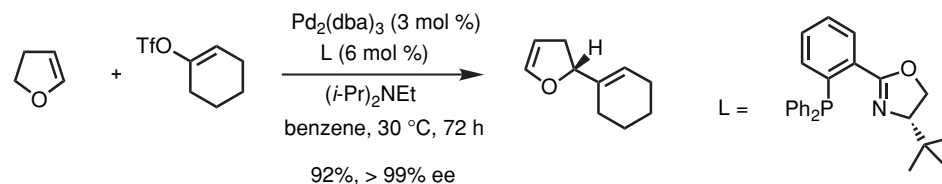


- Note that the alkene within the initially formed pyrrolidine has migrated under the reaction conditions.

Ozawa, F.; Kobatake, Y.; Hayashi, T. *Tetrahedron Lett.* **1993**, 34, 2505–2508.



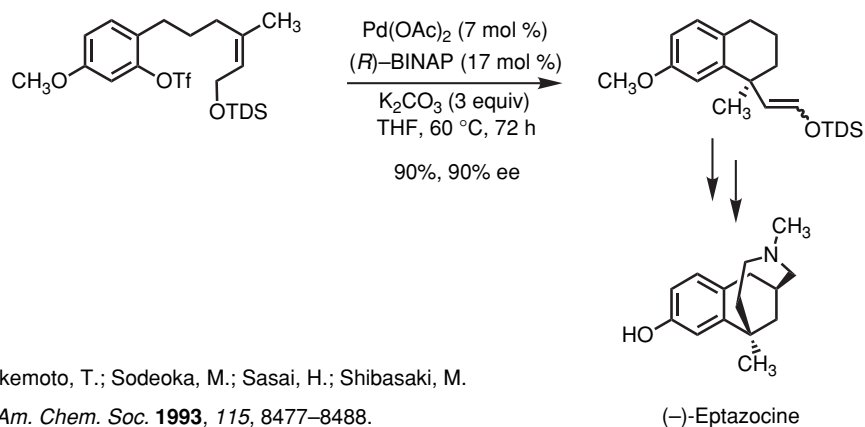
Ohari, K.; Kondo, K.; Sodeoka, M.; Shibasaki, M. *J. Am. Chem. Soc.* **1994**, 116, 11737–11748.



Loiseleur, O.; Hayashi, M.; Schmees, N.; Pfaltz, A. *Synthesis* **1997**, 1338–1345.

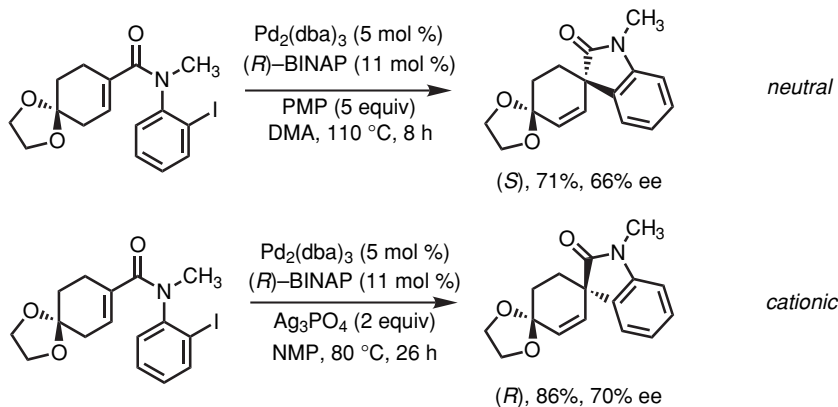
Andrew Haidle

• Formation of quaternary stereocenters:

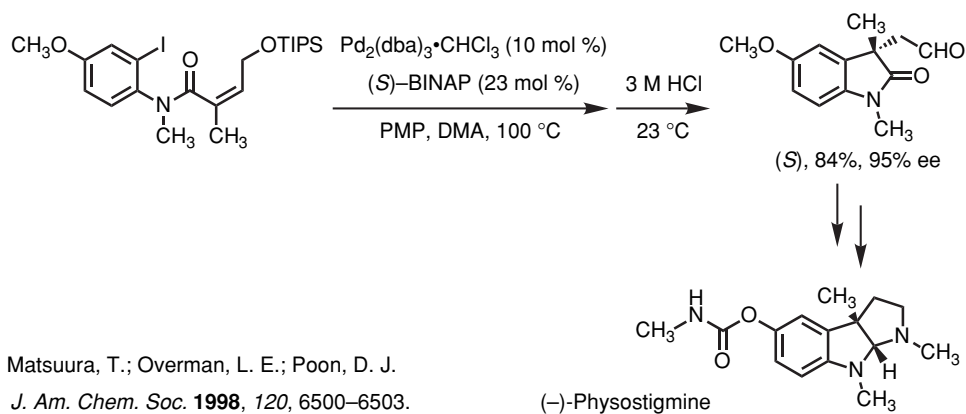


Takemoto, T.; Sodeoka, M.; Sasai, H.; Shibasaki, M.
J. Am. Chem. Soc. **1993**, *115*, 8477–8488.

• The choice of base influences whether the Pd complex is neutral or cationic; this in turn can influence the stereochemical outcome.

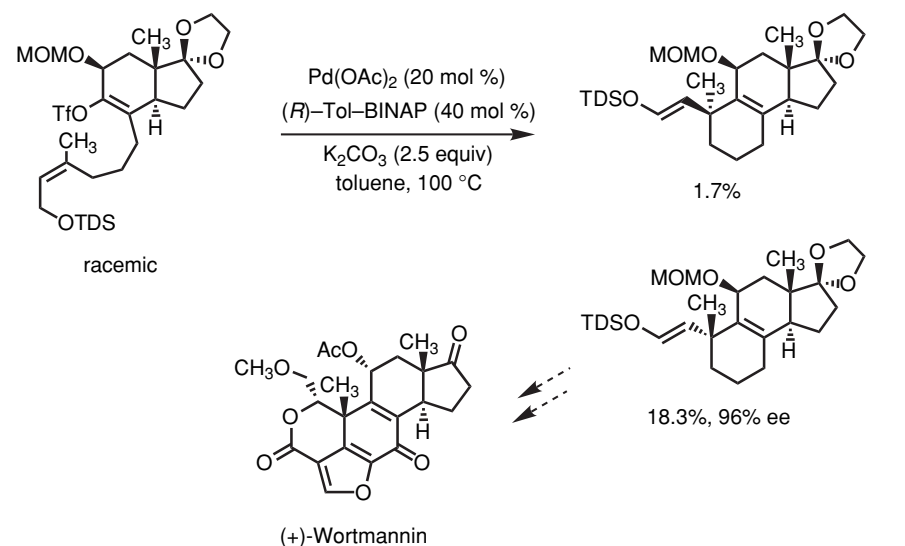


Ashimori, A.; Bachand, B.; Overman, L. E.; Poon, D. J. *J. Am. Chem. Soc.* **1998**, *120*, 6477–6487.



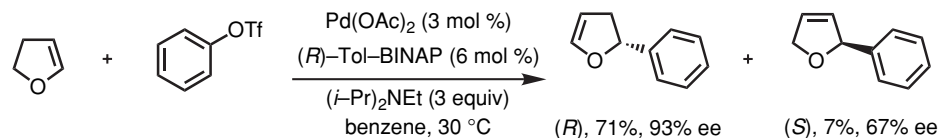
Matsuura, T.; Overman, L. E.; Poon, D. J.
J. Am. Chem. Soc. **1998**, *120*, 6500–6503.

• Kinetic Resolution:

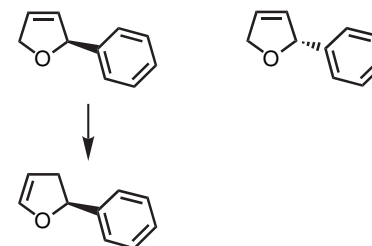


• The enantiomer of the major product not observed. Instead, a complex mixture of products was formed.

Honzawa, S.; Mizutani, T.; Shibasaki, M. *Tetrahedron Lett.* **1999**, *40*, 311–314.



• Initial products are 2,3 dihydrofurans:



• Only the (R) isomer can isomerize due to the asymmetric environment of the ligand.

Ozawa, F.; Kubo, F.; Matsumoto, Y.; Hayashi, T.; Nishioka, E.; Yanagi, K.; Moriguchi, K.

Organometallics **1993**, *12*, 4188–4196.