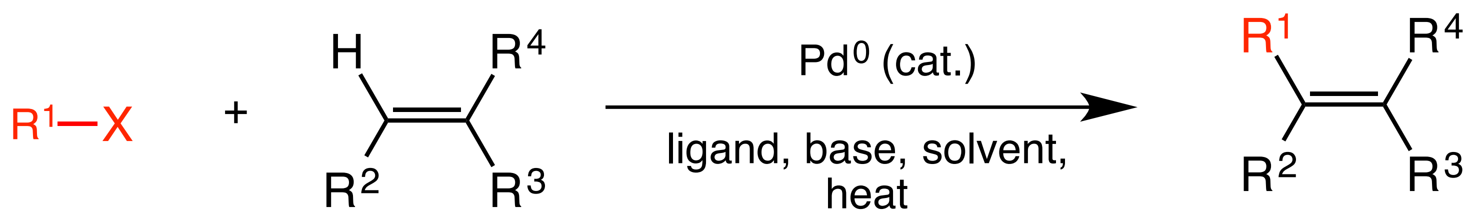
May Lab **Intramolecular Heck Reaction** *Po-An Chen* 9/8/2015



R^1 = aryl, benzyl, vinyl (alkenyl), alkyl (no β hydrogen), R^2, R^3, R^4 = alkyl, aryl, alkenyl;
X = Cl, Br, I, OTf, OTs, N_2^+; lignad = phosphines; base = 2º or 3º amine, KOAc, NaOAc, $NaHCO_3$

Reviews: (a) *Chem. Rev*. **2003**, *103*, 2945—2964
(b) *Pure & Appl. Chem*., **1994**, 1423—1430
(c) Kürti L., Czakó B., (2005) Strategic Applications of Named Reactions in Organic Synthesis: Background and Detailed Mechanisms

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Outline:

- Heck reaction
- Mechanism
- Scope and Limitations
- Experimental Conditions
- Applications


Professor Heck


Professor Overman


Professor Shibasaki

- Mizoroki-Heck reaction was named after Professor Tsutomu Mizoroki (1971) and Professor Richard F. Heck (1972).
- Heck awarded the 2010 Nobel Prize in Chemistry With Negishi and Suzuki for the palladium chemistry.
- Asymmertic Intramolecular Heck reaction was developed in 1989 by Shibasaki et al. and Overman et al independently.

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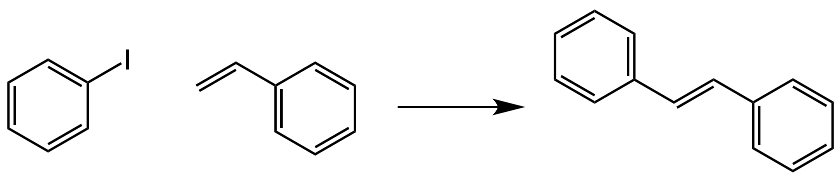
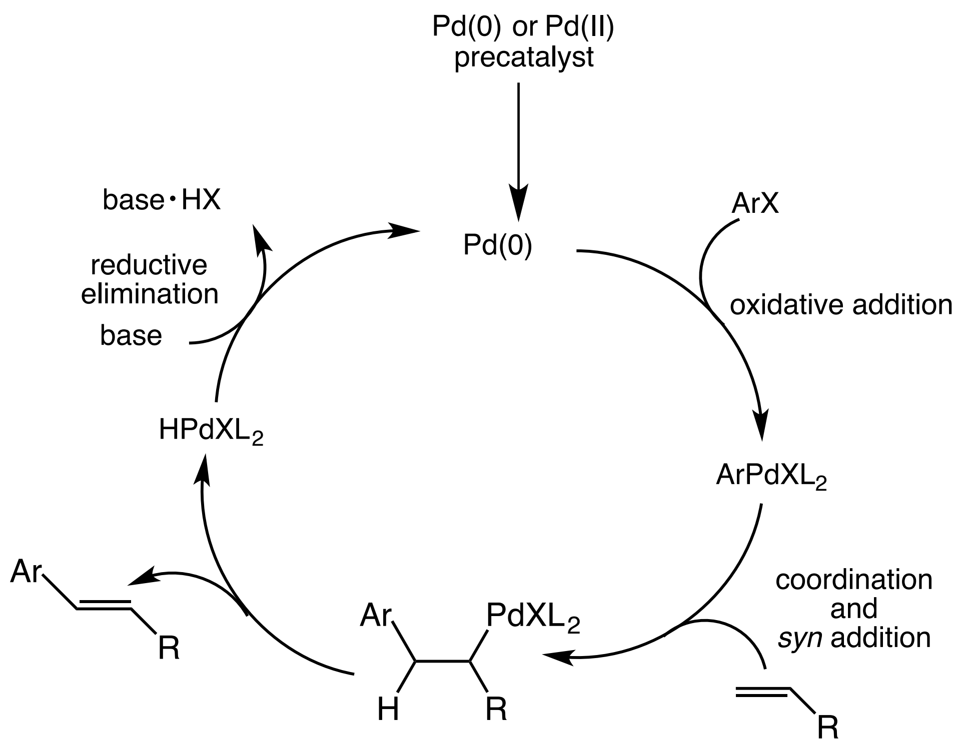
Intermolecular Heck reaction

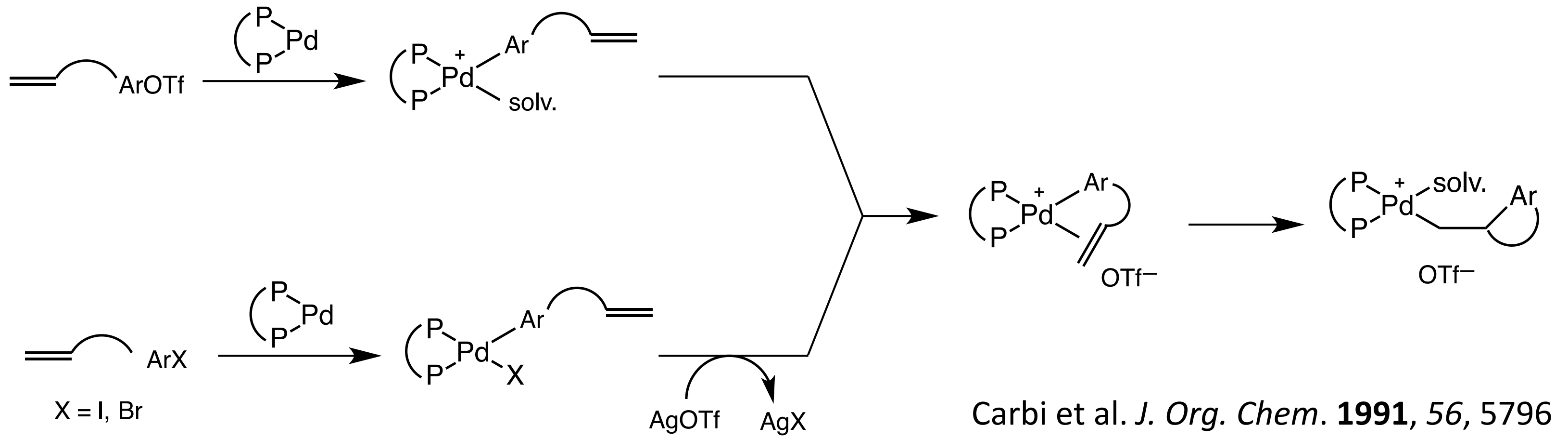


Intramolecular Heck reaction

General Mechanism

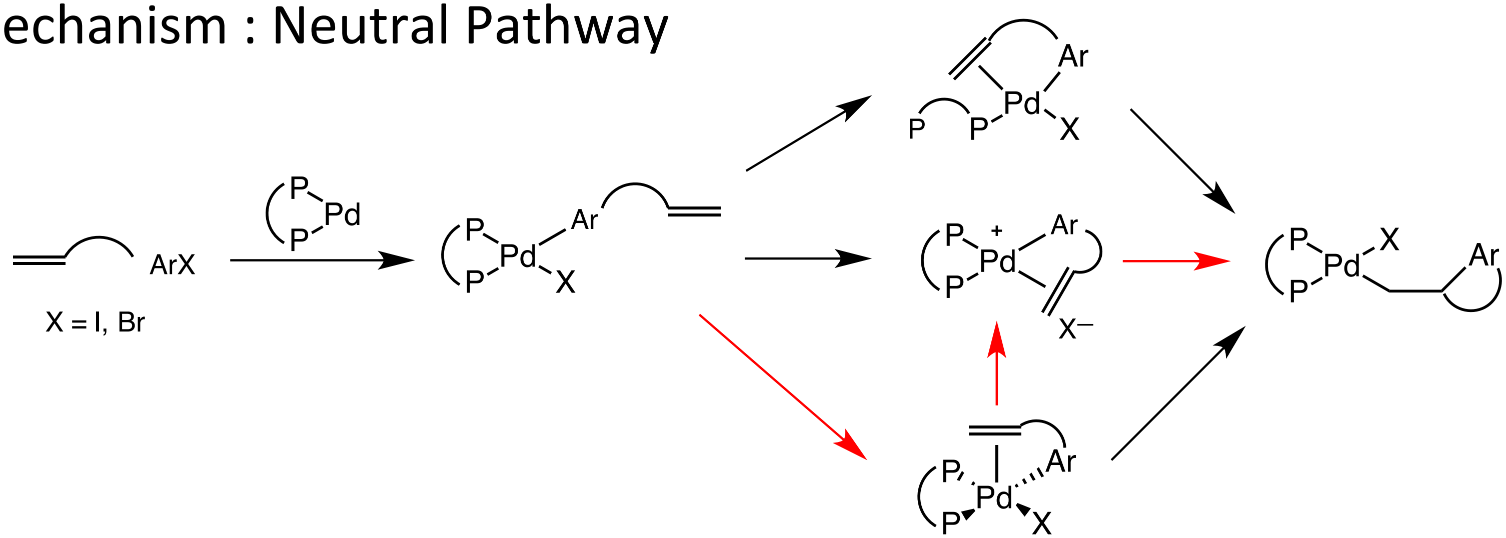


Mechanism : Cationic Pathway



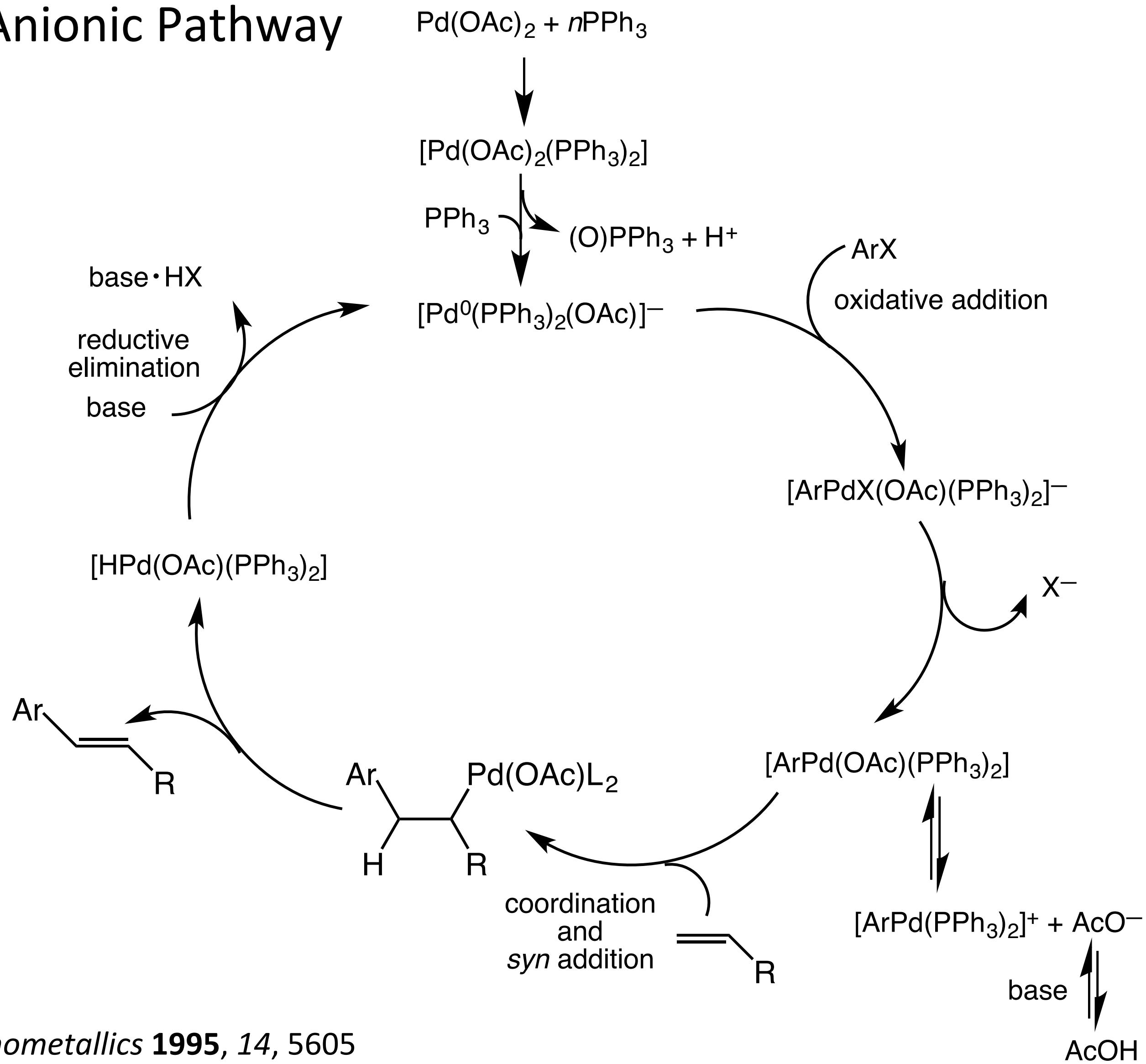
Carbi et al. *J. Org. Chem*. **1991**, *56*, 5796
Hayashi et al. *J. Am. Chem. Soc*. **1991**, *113*, 1417

Mechanism : Neutral Pathway



Norton et al. *J. Am. Chem. Soc.* **1984**, *106*, 5505
Hoffmann et al. *J. Am. Chem. Soc.* **1978**, *100*, 2079

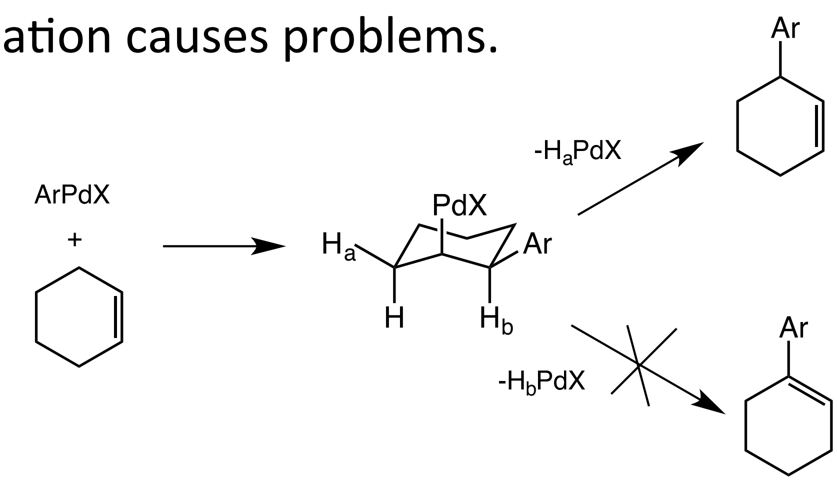
Mechanism : Anionic Pathway



Amatore et al. *Organometallics* **1995**, *14*, 5605
Organometallics **2001**, *20*, 3241

Scope and Limitations:

- 5-*exo* and 6-*exo* cyclizations favored.
- Dehalogenation product as byproduct.
- Reaction rate is strongly influenced by the degree of substitution of the olefin.
- The order of halide: I > Br ~ OTf > Cl.
- β hydride elimination causes problems.



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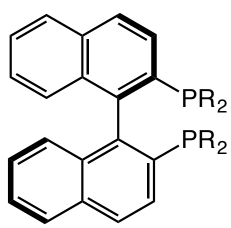
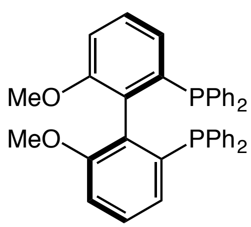
Experimental Conditions:

- Precatalysts
  $Pd(OAc)_2$, $Pd_2(dba)_3$, $Pd(PPh_3)_4$ … etc

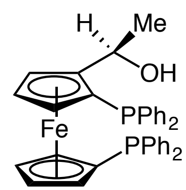
- Ligands
  PPh_3, P(*o*-tol)$_3$, dppe, dppp,



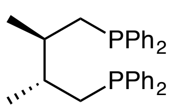
(*R*)-(+)-BINAP R = Ph
(*R*)-Tol-BINAP R = *p*-tolyl



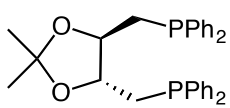
(*R*)-MeO-BIPHEP



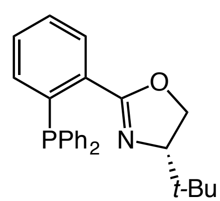
(−)-(*R*,*S*)-BPPFOH



(*R*,*R*)-CHIRAPHOS



(*R*,*R*)-DIOP



Pfaltz phosphinooxazoline

Amatore et al. *J. Am. Chem. Soc.* **1997**, *119*, 5176

- Additives
  Ag(I): Ag_2CO_3, Ag_3PO_4, and Ag-exchanged zeolite
  Tl(I): Tl_2CO_3, TlOAc, and $TlNO_3$. (toxicity)

- Bases:
  A stoichiometric amount of base is needed.
  Inorganic base: K_2CO_3, $CaCO_3$...etc.
  Organic base: Et_3N, *i*-Pr_2NEt, PMP…etc.

- Solvent and Temperature :
  Degassed solvent is critical because phosphines usually oxidized to phosphine oxides.
  From r.t. to over 100 ^{o}C.

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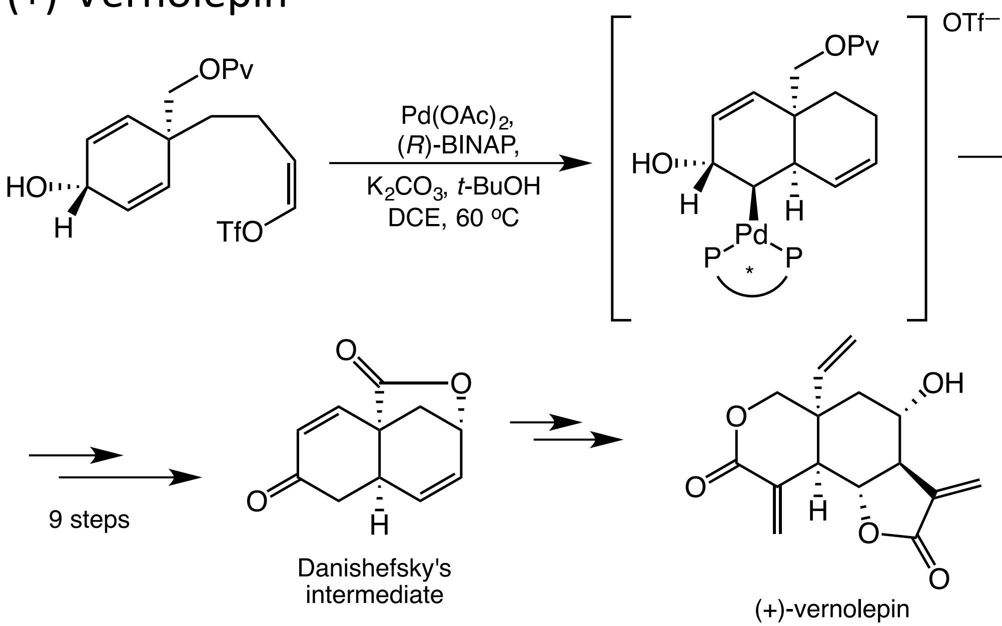
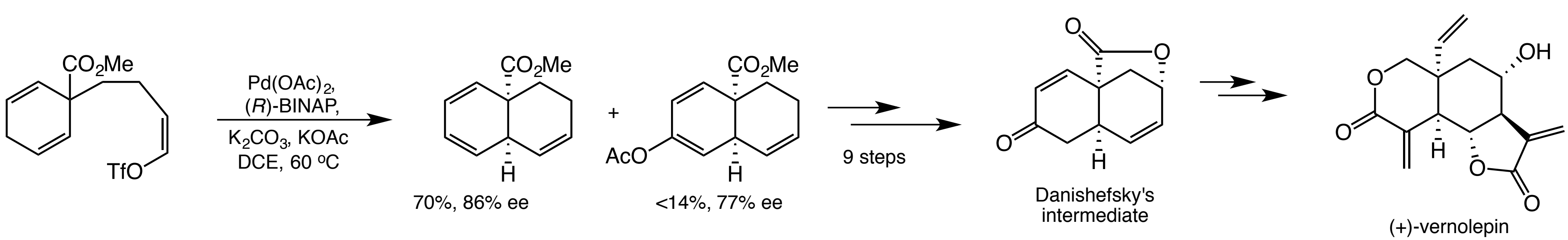
Formation of Tertiary centers:

(+)-Vernolepin



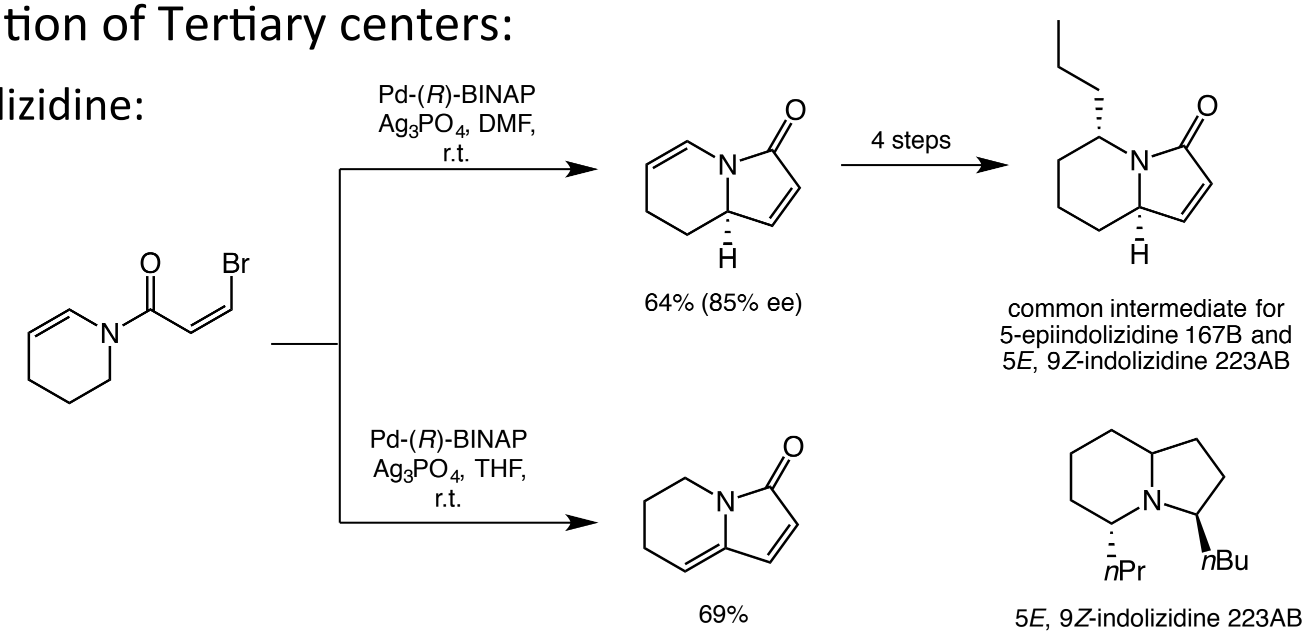
Shibasaki et al. *Tetrahedron Lett.* **1993**, 4219
Danishefsky et al. *J. Am. Chem. Soc.* **1977**, *99*, 6066



Shibasaki et al. *J. Am. Chem. Soc.* **1994**, *116*, 11737

Formation of Tertiary centers:

Indolizidine:



Sulikowski et al. *Tetrahedron Lett.* **2001**, *42*, 6621
Yoda et al. *Tetrahedron Lett.* **2001**, *42*, 2509
Hart et al. *J. Org. Chem*. **1982**, *47*, 4403

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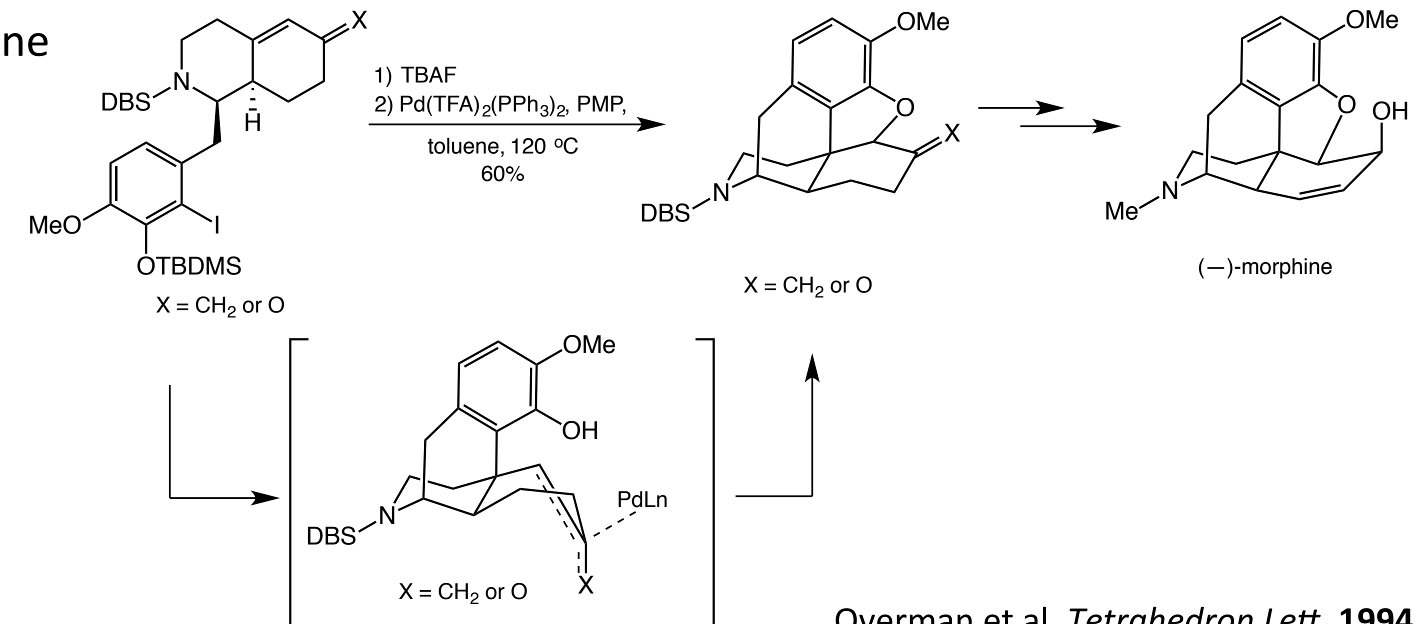
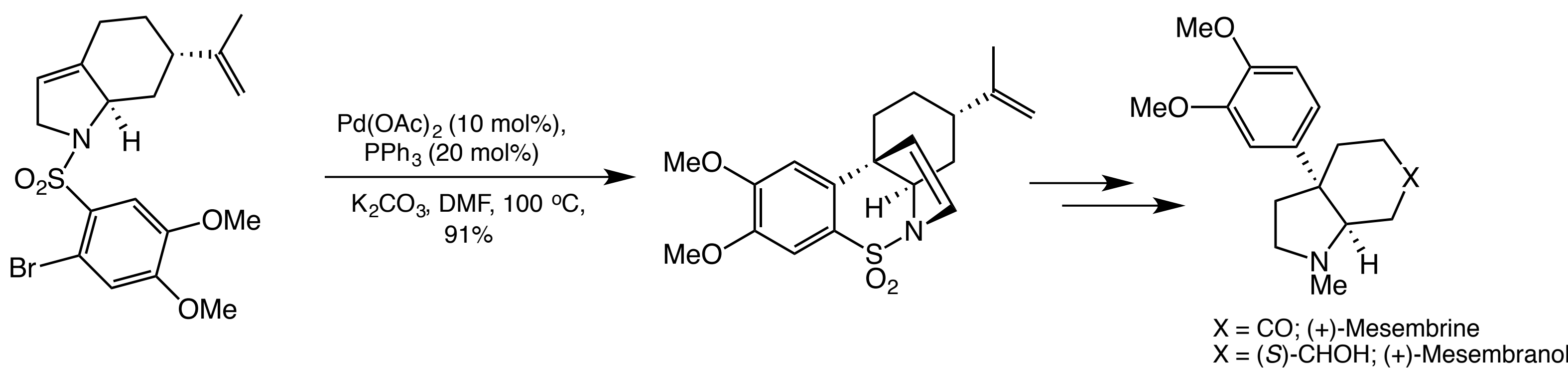
Formation of Quaternary centers:

(—)-morphine



Overman et al. *Tetrahedron Lett*. **1994**, *35*, 3453

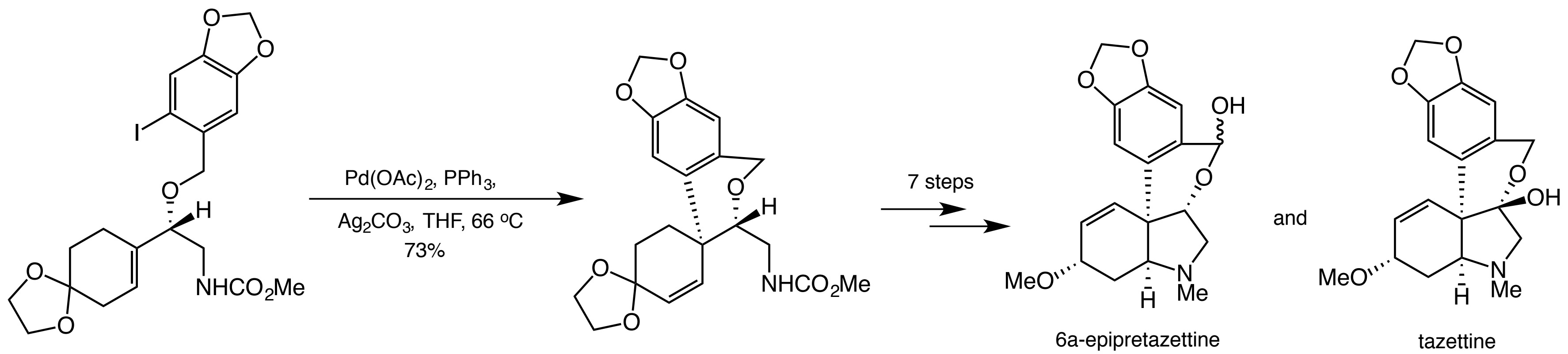
(+)-Mesembrine and (+)-Mesembranol

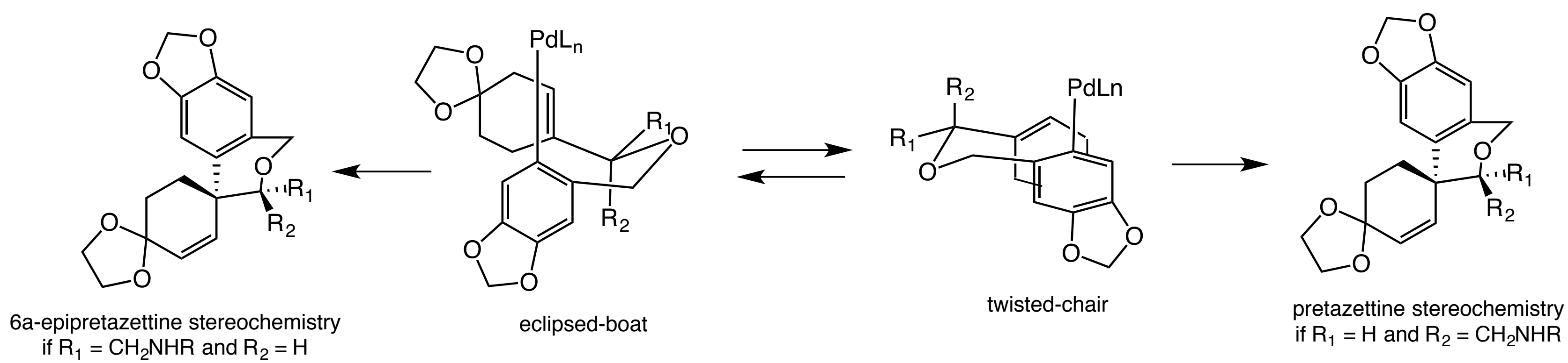


Evans et al. *J. Org. Chem.* **2013**, *78*, 3410

Formation of Quaternary centers:

6a-epipretazettine and tazettine

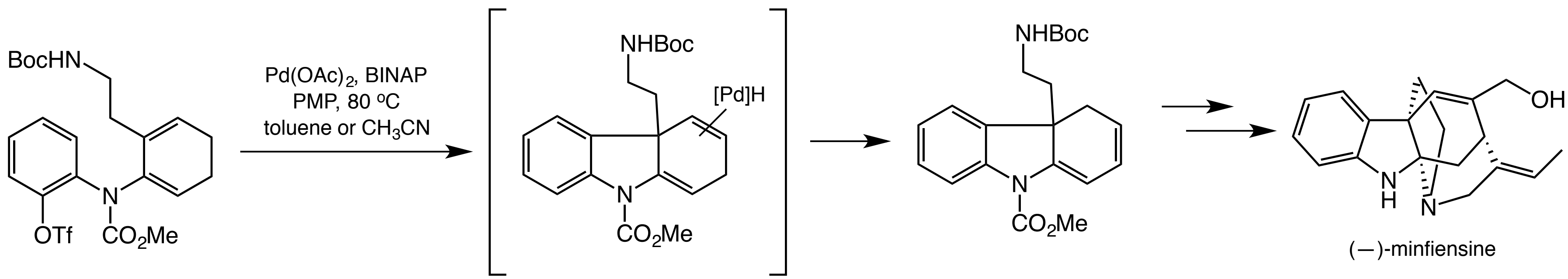




Overman et al. *J. Am. Chem. Soc*. **1990**, *112*, 6959

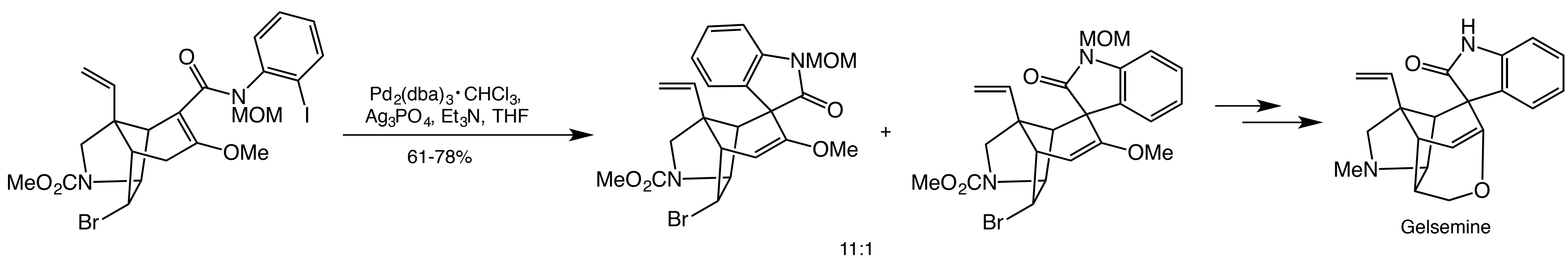
Formation of Quaternary centers:

(—)-minfiensine



Overman et al. *J. Am. Chem. Soc.* **2008**, *130*, 5368

(±)-Gelsemine (spiro ring)



Overman et al. *J. Am. Chem. Soc.* **2005**, *127*, 18054

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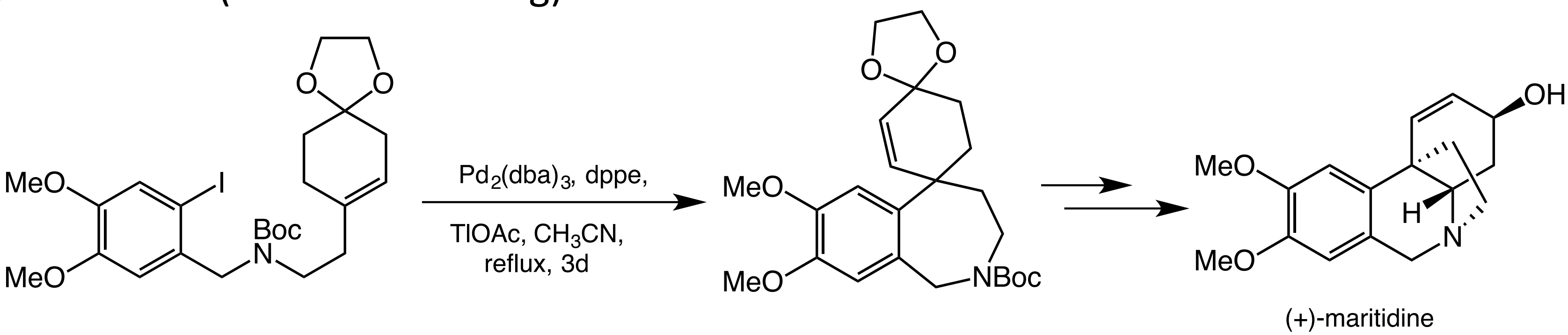
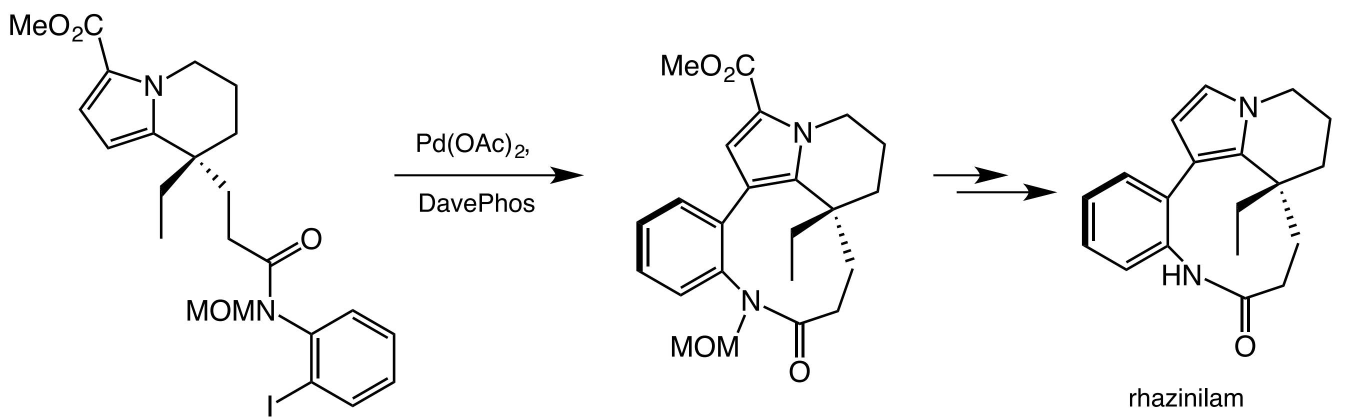
Formation of Quaternary centers:

(+)-maritidine (7-membered ring)



Guillou et al. *Org. Lett.* **2003**, *5*, 1845

(±)-rhazinilam (9-membered ring)



Trauner et al. *Org. Lett*. **2005**, *7*, 5207

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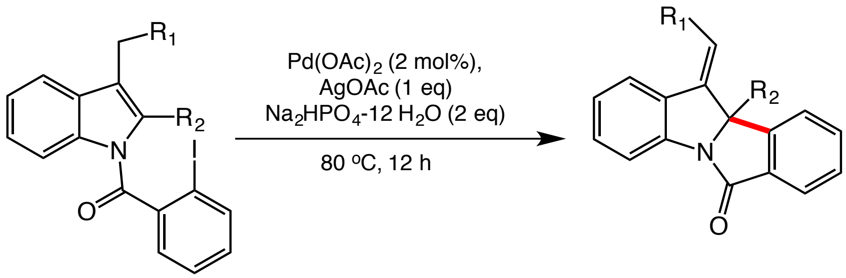
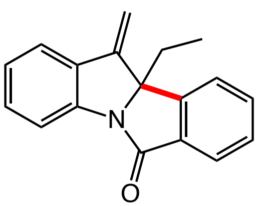
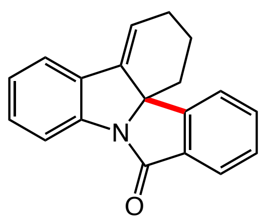
Formation of Quaternary centers:

Indoline system

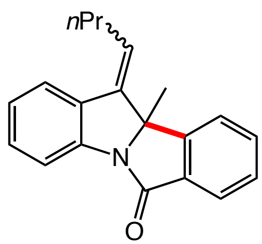




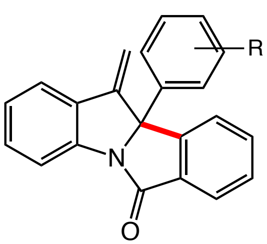
65%



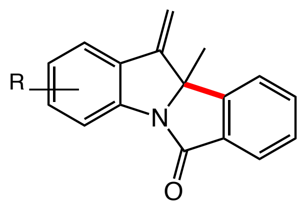
50%



90%



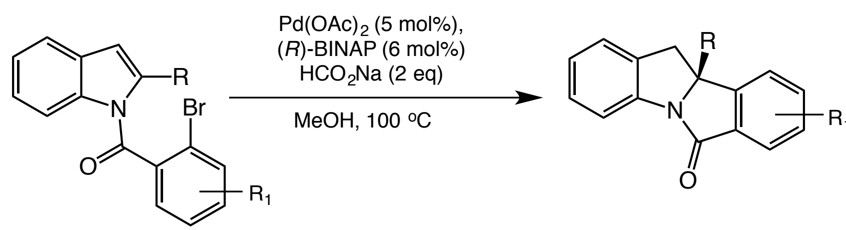
R = OCH_3, CH_3, F, Cl, Br, or H
> 90%

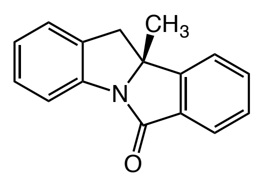


R = *m*-OMe, F, CF_3, Br, *i*Pr
> 80%

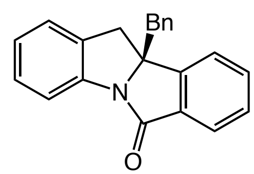
Wu et al. *Org. Lett.*, **2012**, *14*, 2066

Dearomatization and Reductive Heck Reaction

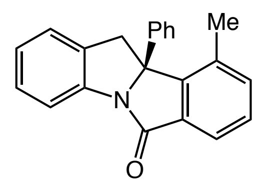




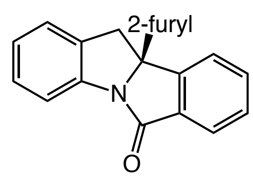
85%, 97% ee



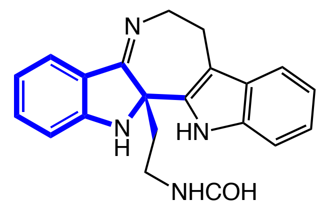
78%, 97% ee



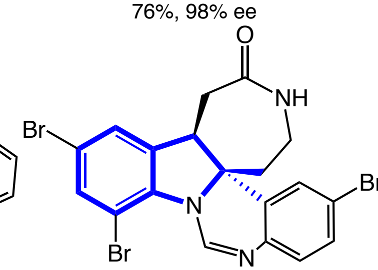
76%, 98% ee



67% 98% ee



Trigonoliimine C



Hinckdentine A

Jia et al. *J. Am. Chem. Soc.* **2015**, *137*, 4936