Total Synthesis of (+)-Yohimbine via an Enantioselective Organocatalytic Pictet–Spengler Reaction

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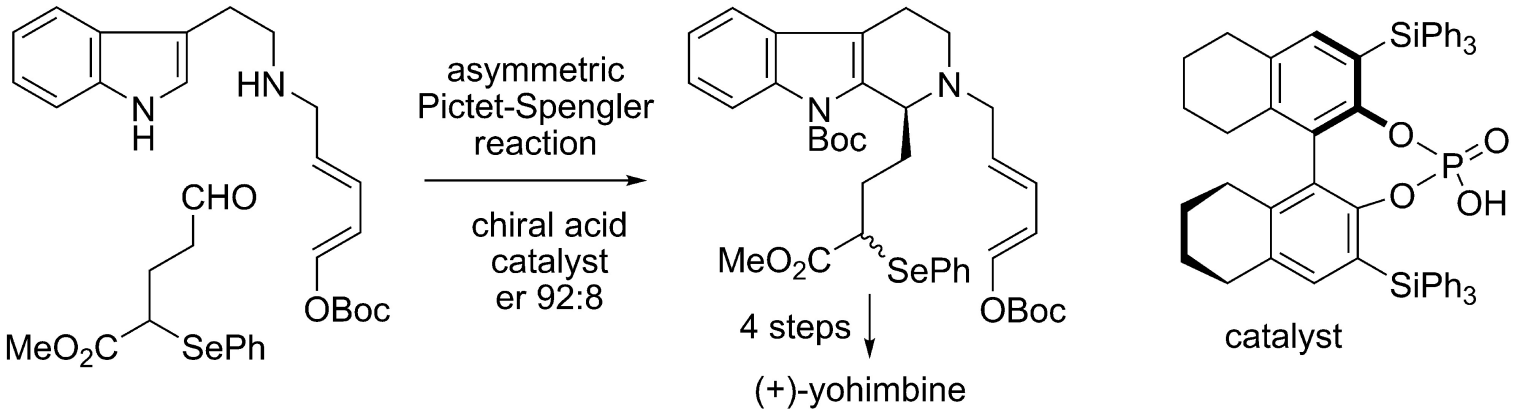
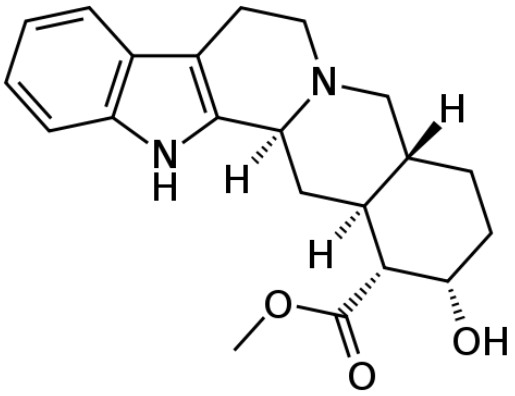


Liming Cao
Wipf Group Current Literature
11/26/2011

Indole alkaloids:(+)-Yohimbine

- the principal alkaloid found in the bark of evergreen *Pausinystalia yohimbe*, *Rubiaceae* family, with 31 other yohimbane alkaloids, mostly in South Africa

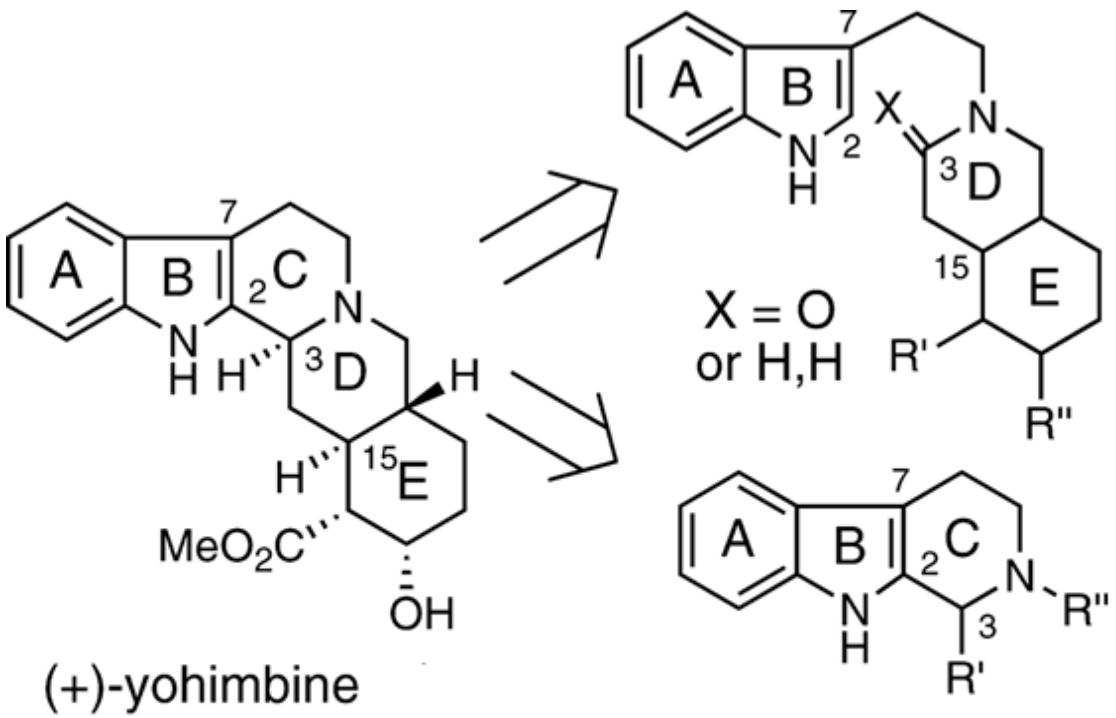
- well-known indole alkaloid in the medicinal history:
  - traditionally used as aphrodisiac
  - treatment of sexual dysfunction(HCl salt)
    - over-the-counter dietary supplement in herbal extract form
    - prescription medicine in pure form
  - remedy for type 2 diabetes in animal and human models carrying polymorphisms of the α_{2A}-adrenergic receptor gene



(+)-Yohimbine

Rosengren, A. H. et al. *Science*, **2010,** 327 (5962): 217–20
"Yohimbe: MedlinePlus Supplements", nlm.nih.gov. November 19, **2010.**
http://en.wikipedia.org/wiki/Yohimbine
http://nccam.nih.gov/health/yohimbe/

General Strategies Employed in Previous Syntheses of Yohimbine and Related Alkaloids



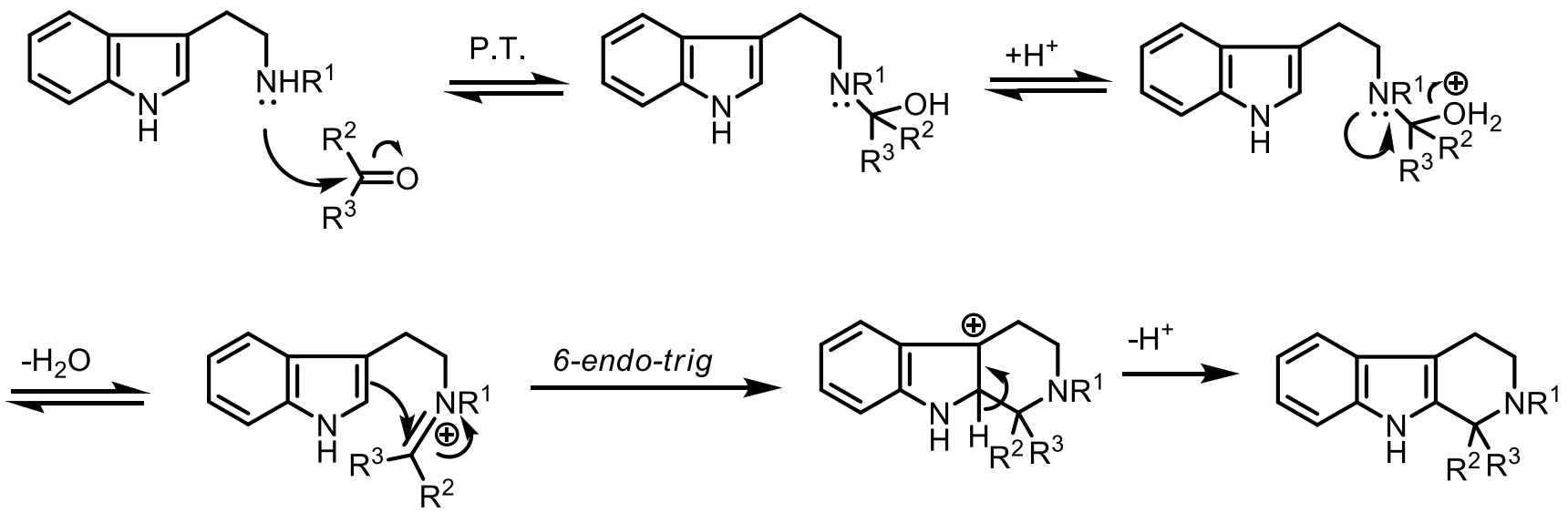
(+)-yohimbine

- generation of the DE-ring system, followed by cyclization to form the C ring
- difficult control of C(3) stereogenic center

- formation of the ABC-ring system, followed by annulation of DE rings
- lack of methods for:
  - praparation of enantioenriched ABC-rings --H8 BINOL PA catalyzed Pictet–Spengler Reaction
  - diastereoselective formation of DE-rings --IMDA

Mergott, D. J.et al. *Org. Lett*. **2008**, 10, 745– 748
Herleì, B. et al. *J. Org. Chem.* **2011**, 76, 8907−8912

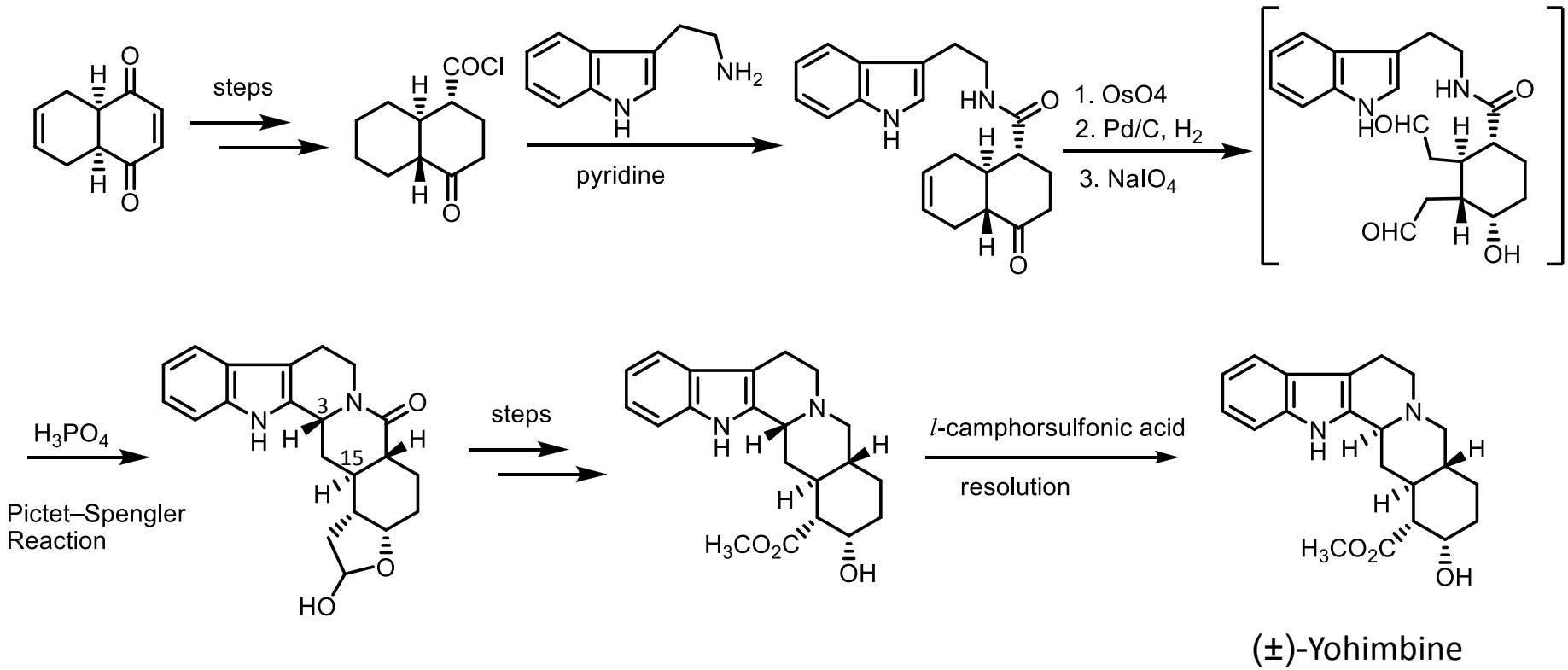
Pictet–Spengler Reaction



Kurti, L. et al. *Strategic Applications of Named Reactions in Organic Synthesis.* **2005**, 348.

Previous Work

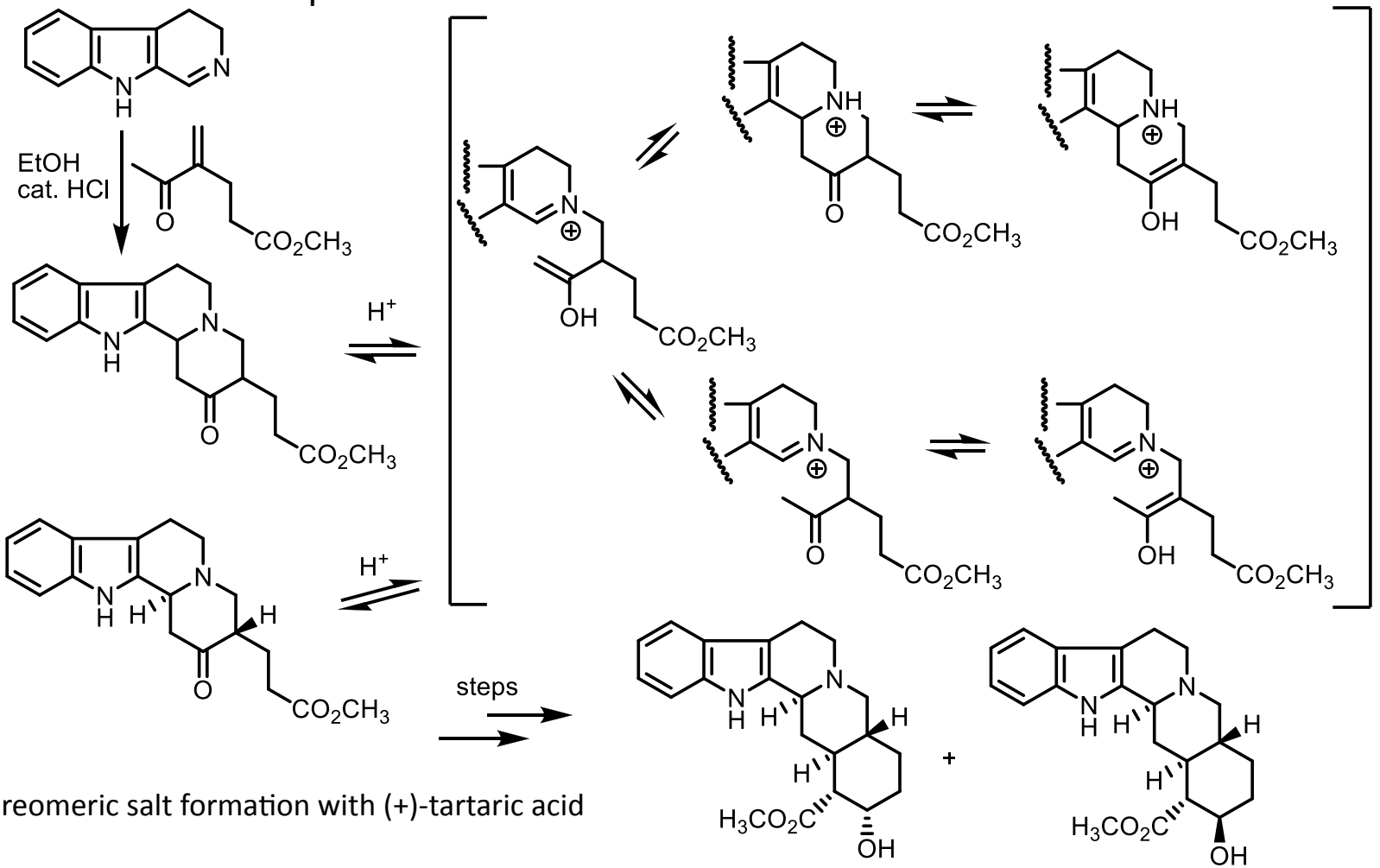
Tamelen and co-workers: the first total synthesis of the racemic compound



Tamelen, V. et al. *J. Am. Chem. Soc.* **1958**, *80*,5006.
Tamelen, V. et al. *J. Am. Chem. Soc.* **1969**, *91*,7315.

Previous Work

Szantay and co-workers: enantiopure form by a second-order asymmetric transformation step in the resolution of an intermediate

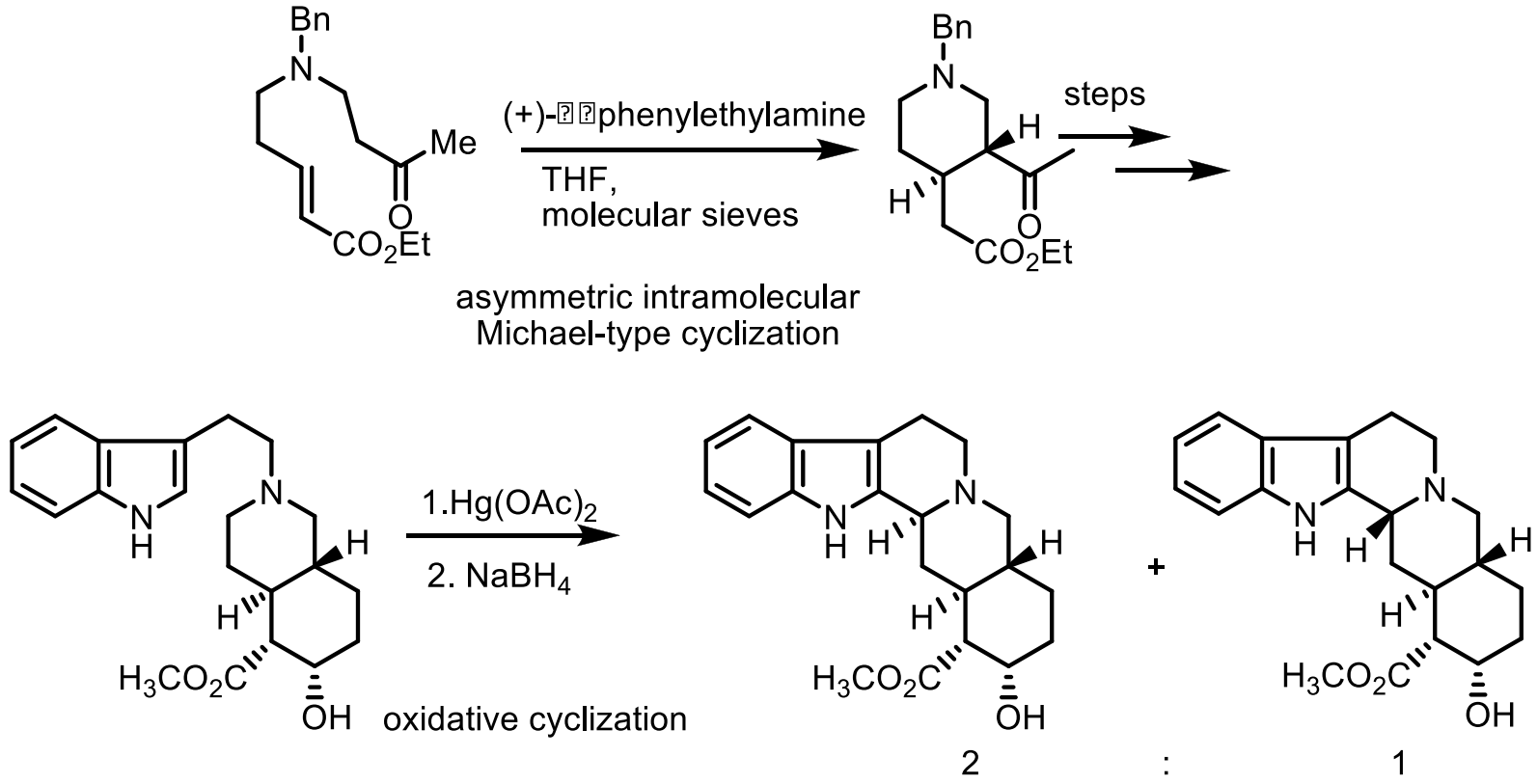


Diastereomeric salt formation with (+)-tartaric acid

Blaskó, G. et al. *Liebigs Ann. Chem.* **1986,** 655.
Cs. Szantay, L. et al, *J. Org. Chem.* **1967,** *32*, 423.

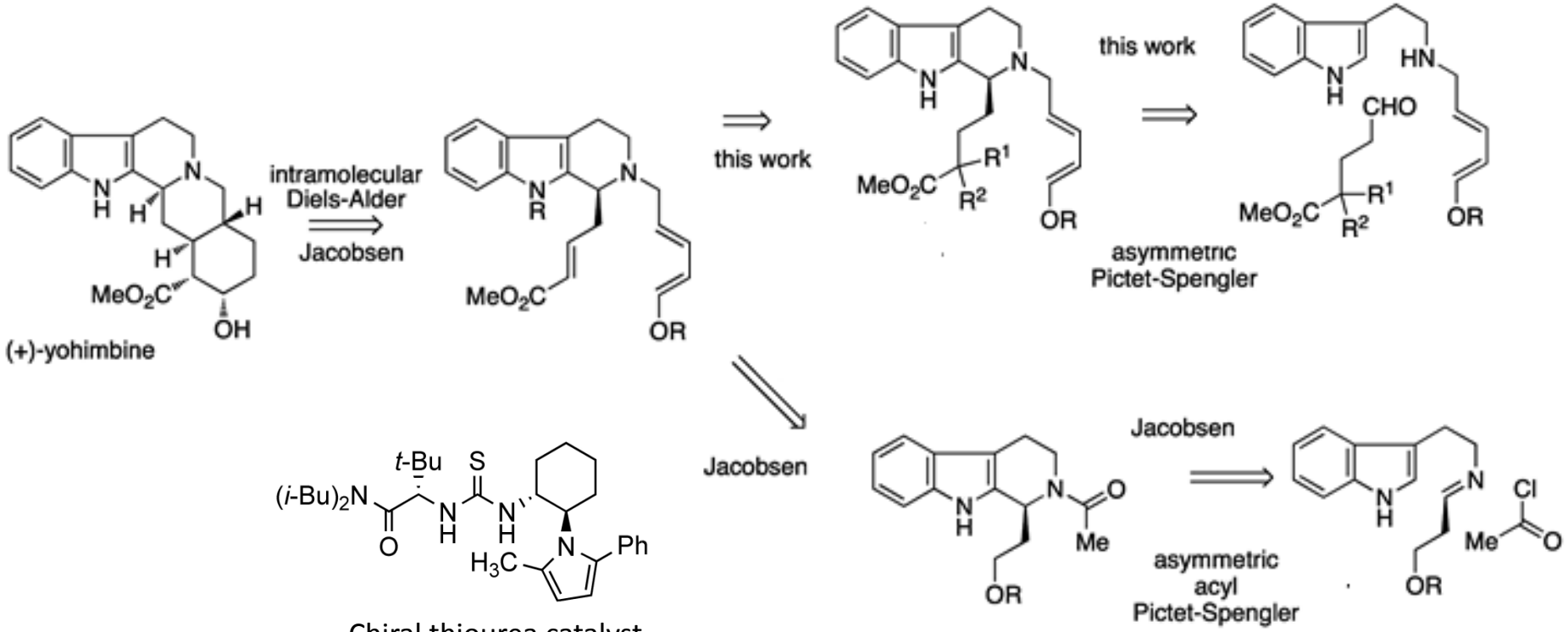
Previous Work

Momose and co-workers: the first asymmetric synthesis of (+)-yohimbine



Hirai, Y, et al. *Tetrahedron Lett.* **1990,** *31,* 4755.
N. Aimi, E. et al. *Tetrahedron,* **1973**.*29*.2015.

Synthetic Strategies toward (+)-Yohimbine

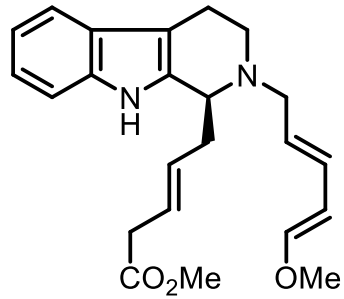


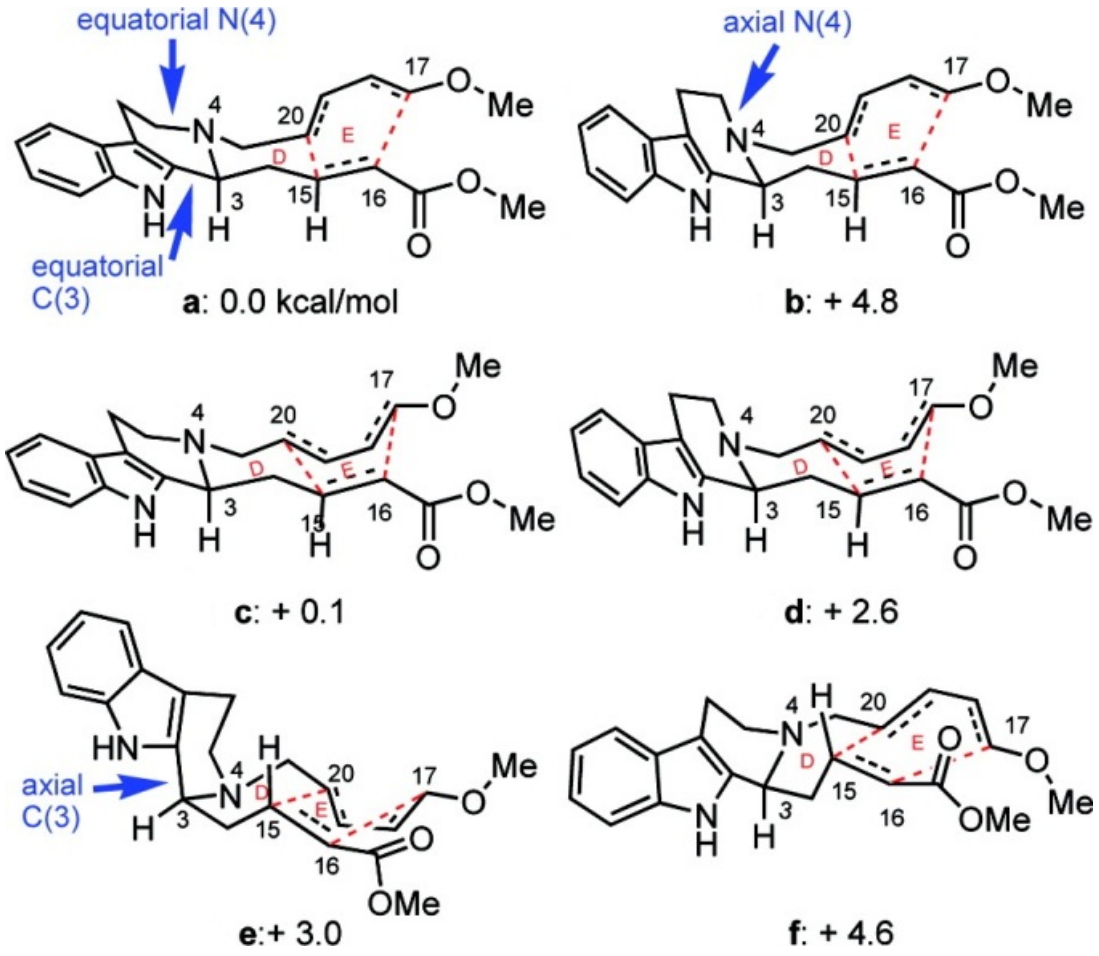
Chiral thiourea catalyst

First catalytic enantioselective total synthesis of (+)-yohimbine

Herlé, B. et al. *J. Org. Chem*. **2011**, *76*, 8907.
Mergott, D. J. et al. *Org. Lett*. **2008,** *10*, 745.

Relative energies of IMDA transition structures



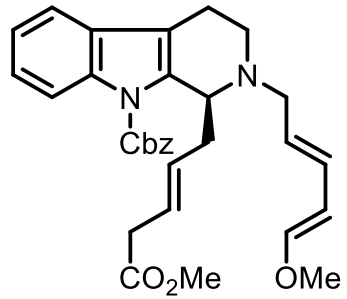


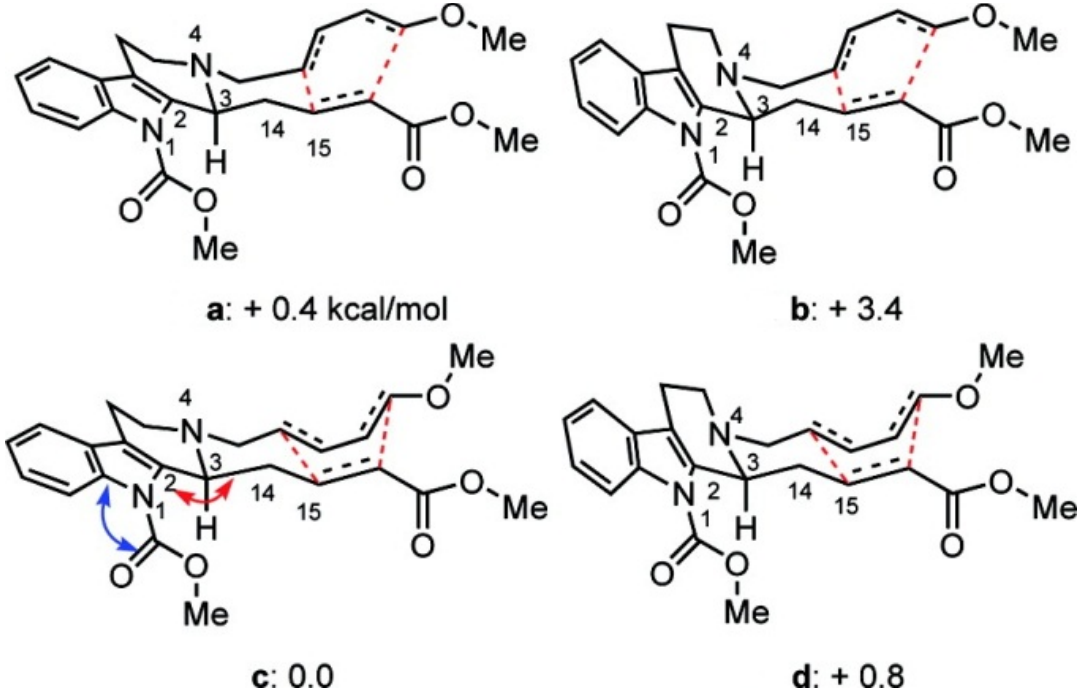
- D-ring: chairlike over boatlike (a-e vs f).
- C3 substituent: equatorial over axial (a vs e).
  - High dienophile facial selectivity, C3-C15 cis.
- N4 substituent: equatorial over axial (a,c vs b,d).
- Negligible endo/exo preference with equatorial N4 subtituent (c vs a).
- Significant endo preference with axial N4 substituent (d vs b).
  - Model not good

- B3LYP/6-311+G-(d,p)//B3LYP/6-31G(d) level of density functional theory
- **c** and **d** lead to a cycloadduct with the relative configuration of (+)-yohimbine

Mergott, D. J. et al. *Org. Lett*. **2008,** *10,* 745.

Relative energies of IMDA transition structures



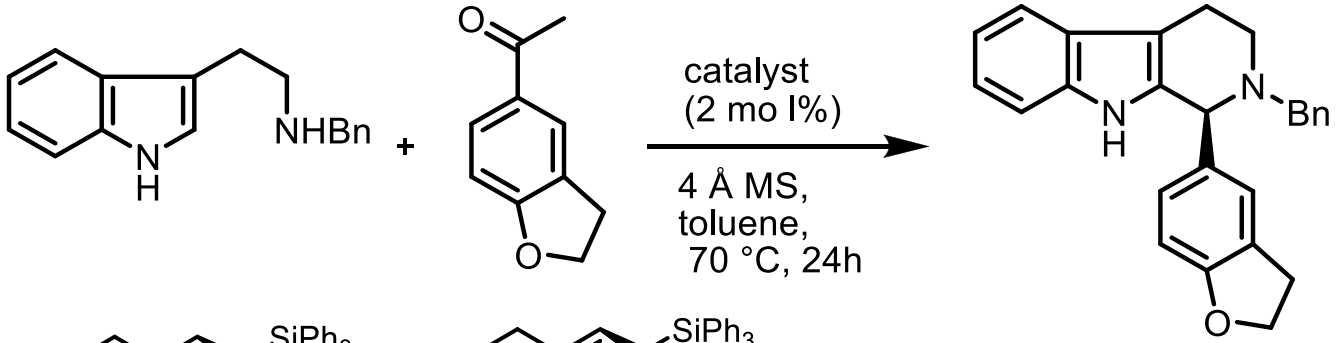


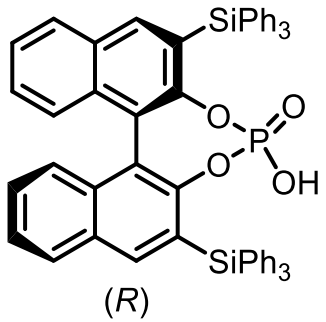
- N4 substituent: equatorial over axial (a,c vs b,d).
- Small endo preference with equatorial N4 subtituent (c vs a).
- Significant endo preference with axial N4 substituent (d vs b).
- Axial N4 substituent TS more accessible
  - Carbamate C=O coplanar with indole, repulsive nonbonding interactions
  - A basis for high diastereoselectivity

- **c** and **d** lead to a cycloadduct with the relative configuration of (+)-yohimbine

Mergott, D. J. et al. *Org. Lett*. **2008,** *10,* 745

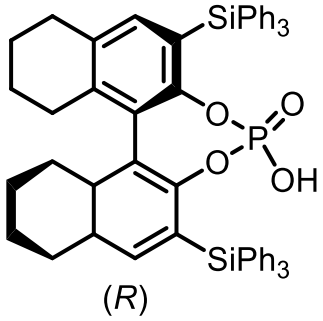
Previous Work





(*R*)

a



(*R*)

b

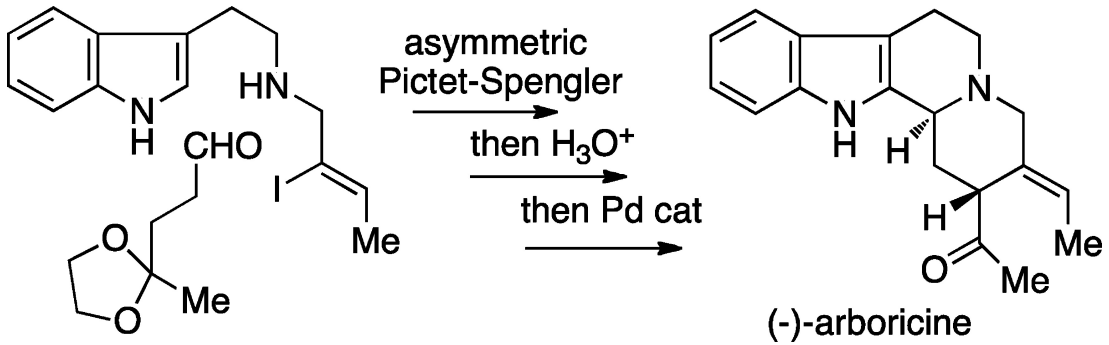
:

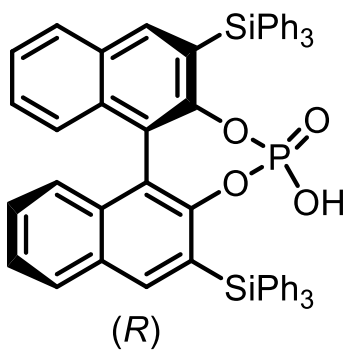
entry	catalyst	Conversion(%)[a]	ee(%)[b]
1	a	100	85
2	b	90	78

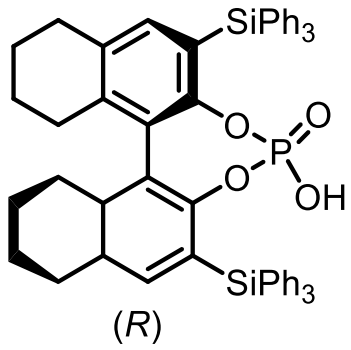
a. Determined by 1H NMR spectroscopy. b. Determined by HPLC on a chiral column (Chiralcel OD).

Sewgobind, N. V. Et al. *J. Org. Chem.* **2008**, *73*, 6405

Previous Work

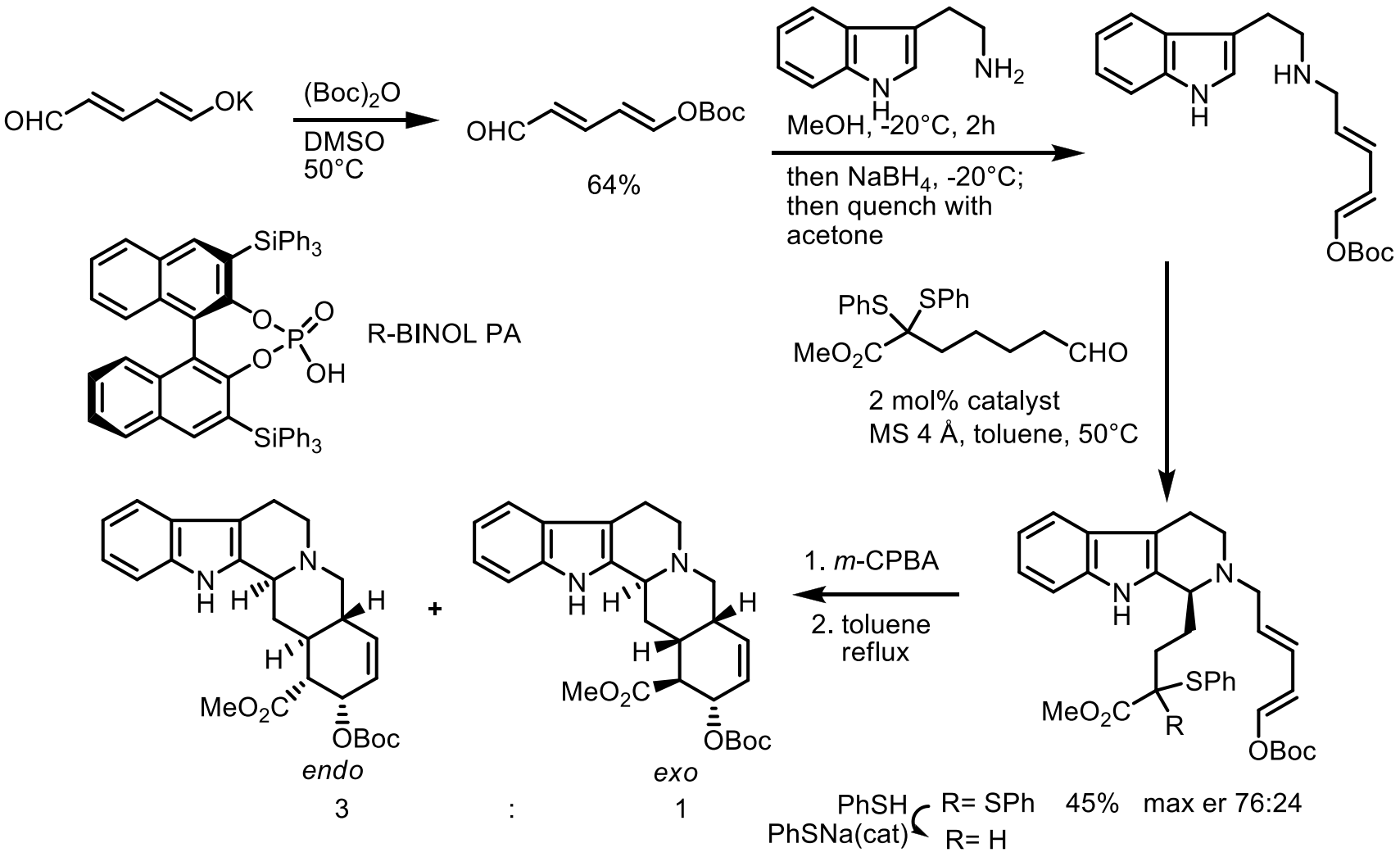






Wanner, M. J. et al. *Org. Lett*. **2009**, *11*, 2579.
Herlé, B. et al. *J. Org. Chem*. **2011**, *76*, 8907.

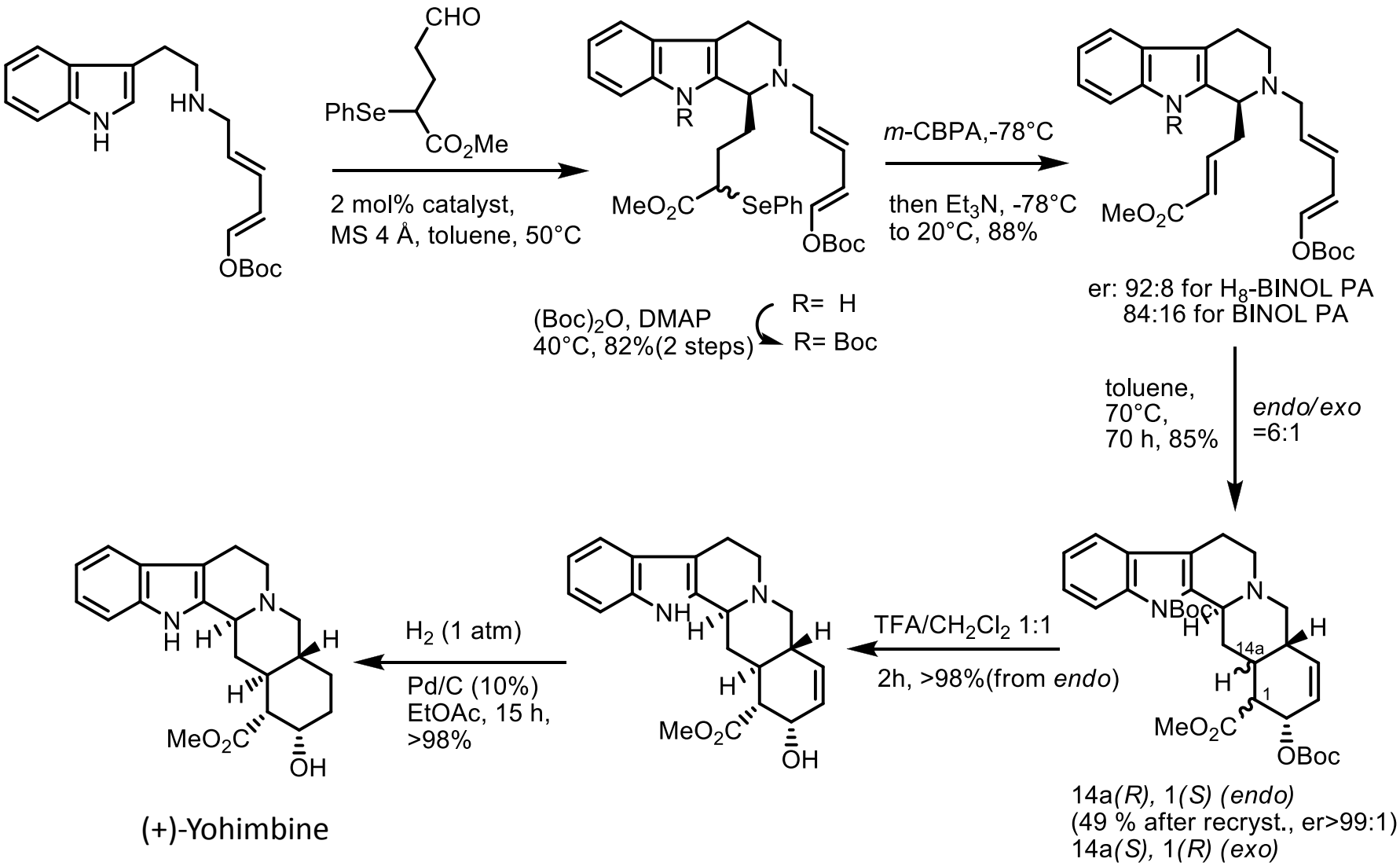
Total Synthesis of (+)-Yohimbine



The selectivities and overall yield leave much to be desired.

Herlé, B. et al. *J. Org. Chem*. **2011**, *76*, 8907.

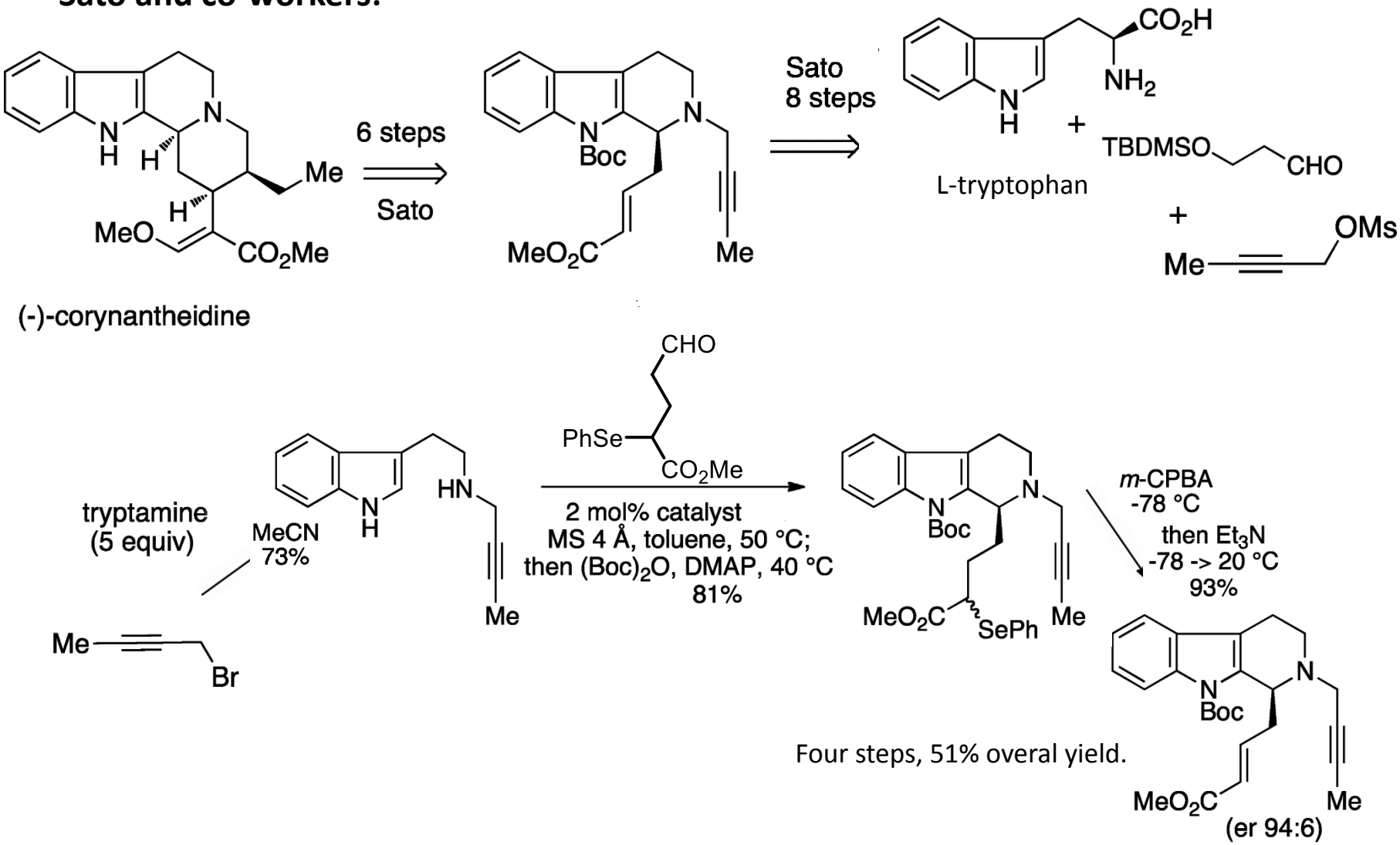
Total Synthesis of (+)-Yohimbine



Herlé, B. et al. *J. Org. Chem*. **2011**, *76*, 8907.

Other applicatons

Sato and co-workers:



Herlé, B. et al. *J. Org. Chem*. **2011**, *76*, 8907.

Conclusion

- Key steps include:
  - The enantioselective organocatalytic Pictet−Spengler reaction
  - Intramolecular Diels-Alder reaction

- Total synthesis involved nine steps from tryptamine (only six pots) and gave an overall yield of 16%.

- It also worked well for for *N*-alkyltryptamines as was proven in the key chirality introducing step of the total syntheses of arboricine and corynantheidine.