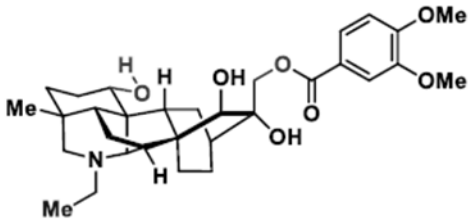
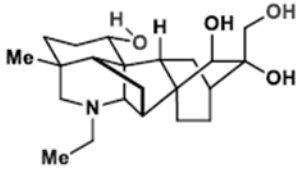
UNIVERSITÄT BERN

Syntheses of Denudatine Diterpenoid Alkaloids: Cochlearenine, N-Ethyl-1α-hydroxy-17-veratroyldictyzine, and Paniculamine

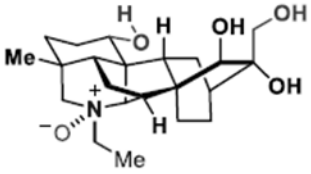
K. G. M. Kou, B. X. Li, J. C. Lee, G. M. Gallego, T.P. Lebold, A. G. DiPasquale, and R. Sarpong, *J. Am. Chem. Soc*. **2016**, *138*, 10830−10833



N-ethyl-1α-hydroxy-17-veratroyldictyzine



cochlearenine



paniculamine

Introduction

- First isolated from *Aconitum*, *Consolidum*, and *Delphinium* plants

- Interesting biological activity:
  - Used in traditional medicine (e.g., in China) for the treatment of pain and cardiovascular diseases
  - Modulate Na^+ and/or K^+ ion channels
  - May be subtype-specific: may allow specific targeting of particular ion channel isoforms implicated in channelopathies = minimized side effects
  - Cochlearenine: bradycardic effect at doses between 0.1 and 1 mg/mL

- 1200 known diterpenoid divided in 3 family C_{20}, C_{19},C_{18}

  → Belong to the C_{20} family: 20 contiguous carbon atoms

Introduction

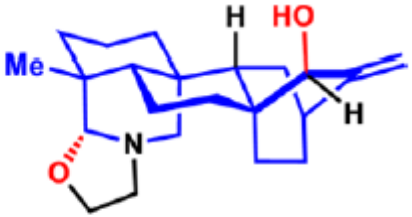
Synthesis of C_{20} diterpenoid alkaloids

atisine

Pelletier, *Tetrahedron Lett*. **1963**

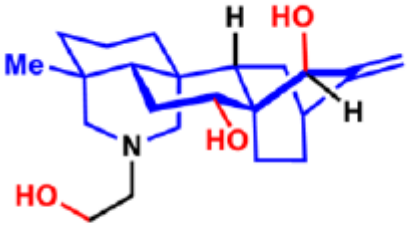
nominine

Masamune, *J. Am. Chem. Soc*. **1964**

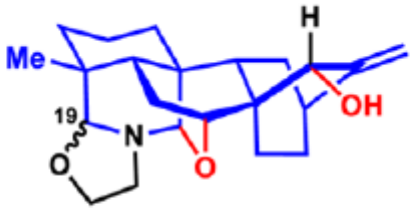


isoatisine

Baran, *J. Am. Chem. Soc.* **2014**

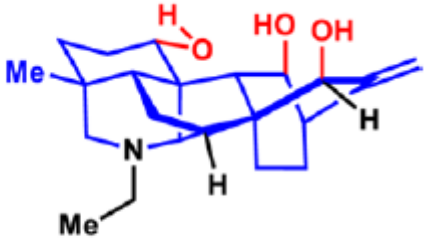


dihydroajaconine



spiramine C 19*S*
spiramine D 19*R*

Xu, *Angew. Chem., Int. Ed*. **2016**



lepenine

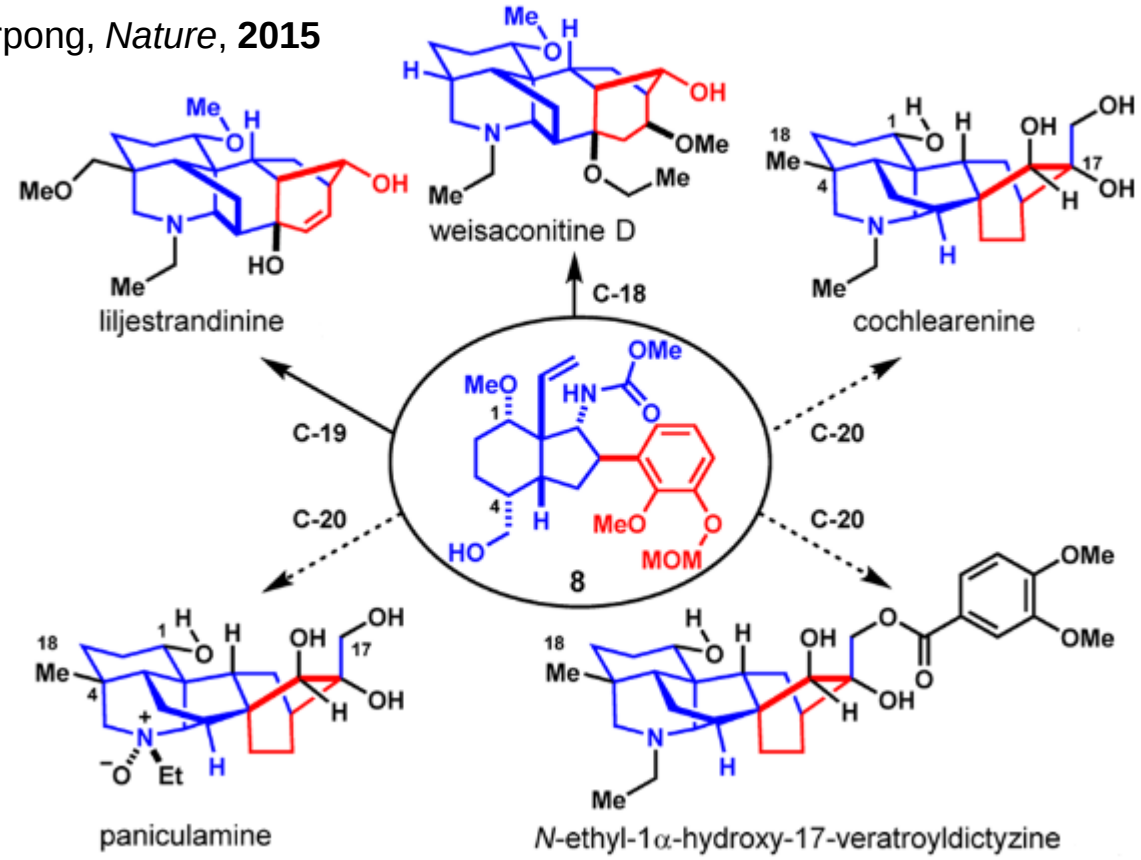
Fukuyama, *J. Am. Chem. Soc*. **2014**

Introduction

Synthesis of C_{20} C_{19} C_{18} metabolites

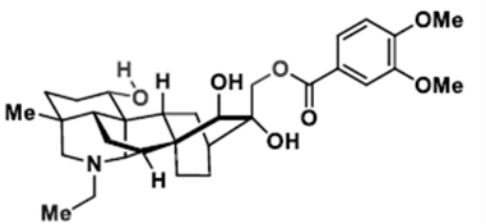
> Unified strategy: accessing $C_{20,}C_{19}$ C_{18} metabolites using one versatile intermediate

Sarpong, *Nature*, **2015**



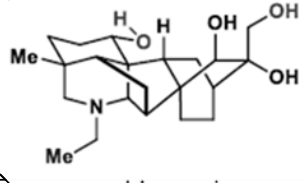
Introduction

Retrosynthetic Analysis



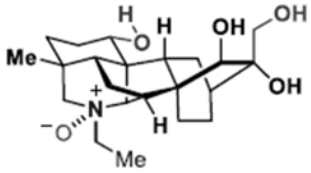
N-ethyl-1α-hydroxy-17-veratroyldictyzine

Esterification



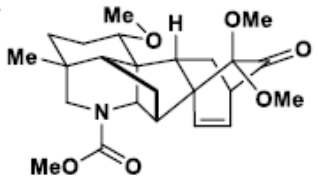
cochlearenine

Oxidation

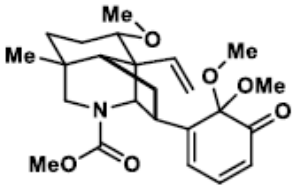


paniculamine

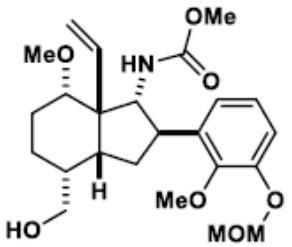
"Functionnal groups manipulation"



Methylation
Piperidine formation
Oxidative dearomatization

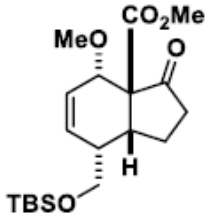


Intramolecular Diels-Alder

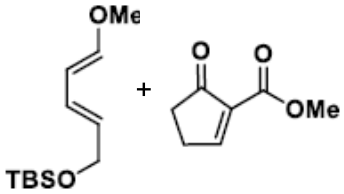


Common intermediate

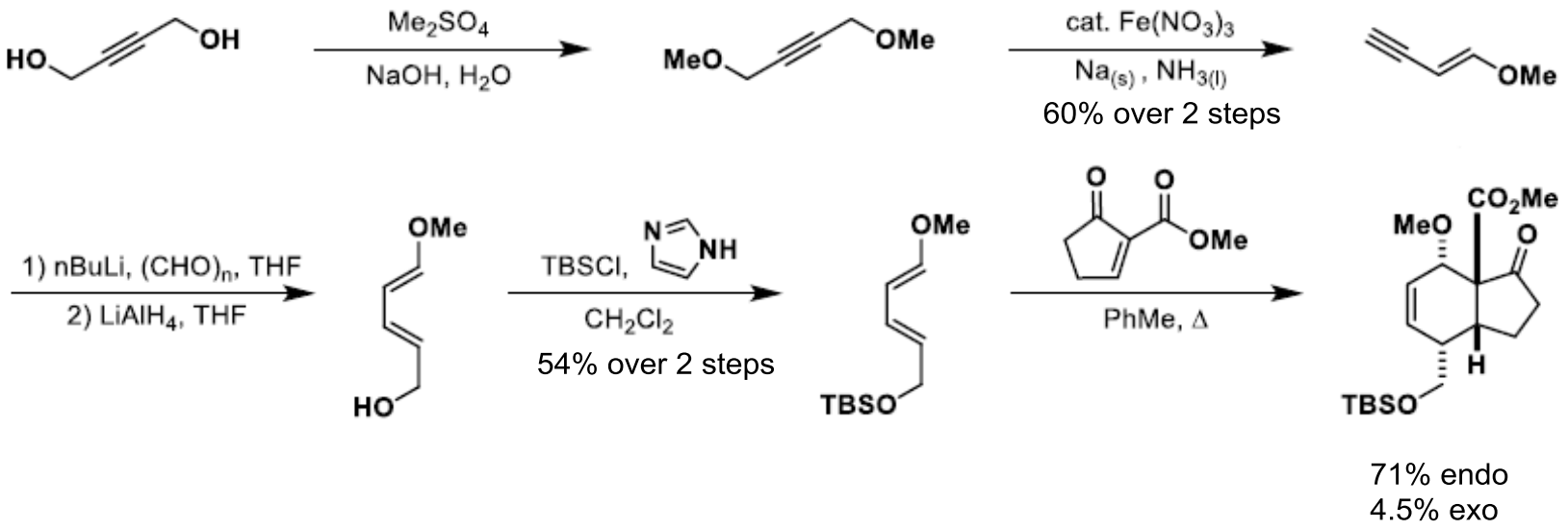
Hydrogenation
Olefination
Conjugate addition



Diels Alder



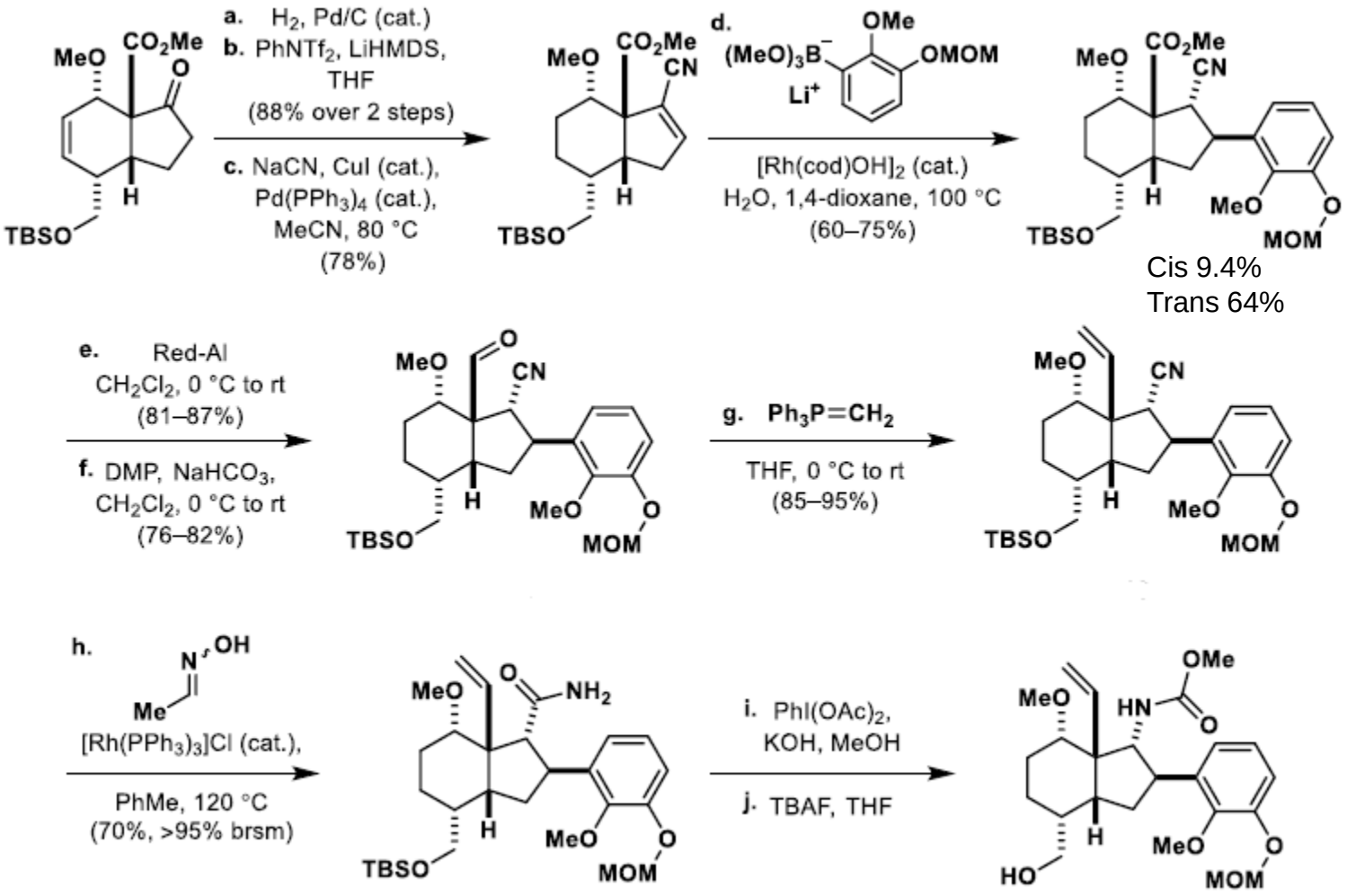
Synthesis of Common Intermediate



Prabhakaran, J., Lhermitte, H., Das, J., Sasi-Kumar, T. K. & Grierson, D. S. *Synlett,* **2000,** 5, 658–662

Marx, J. N., Cox, J. H. & Norman, L. R. *J. Org. Chem.* **1972,** 37, 4489–4491

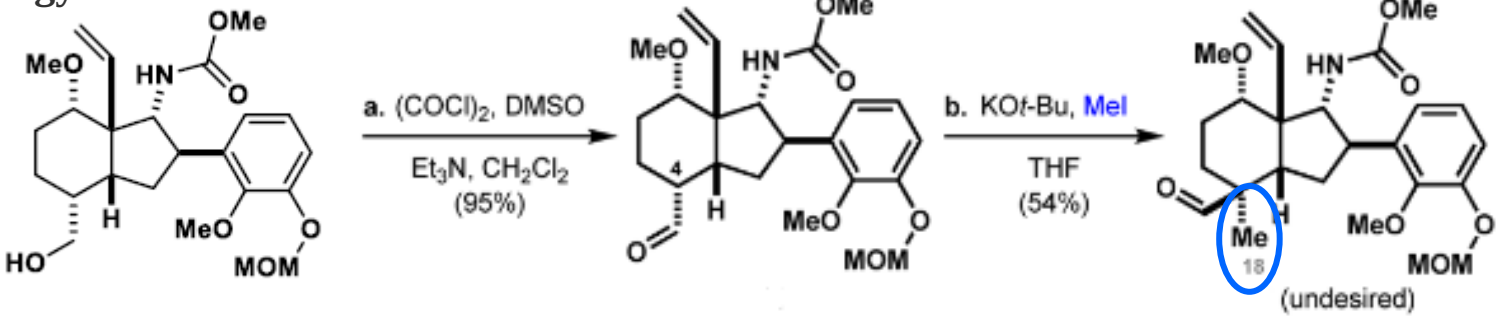
Synthesis of Common Intermediate



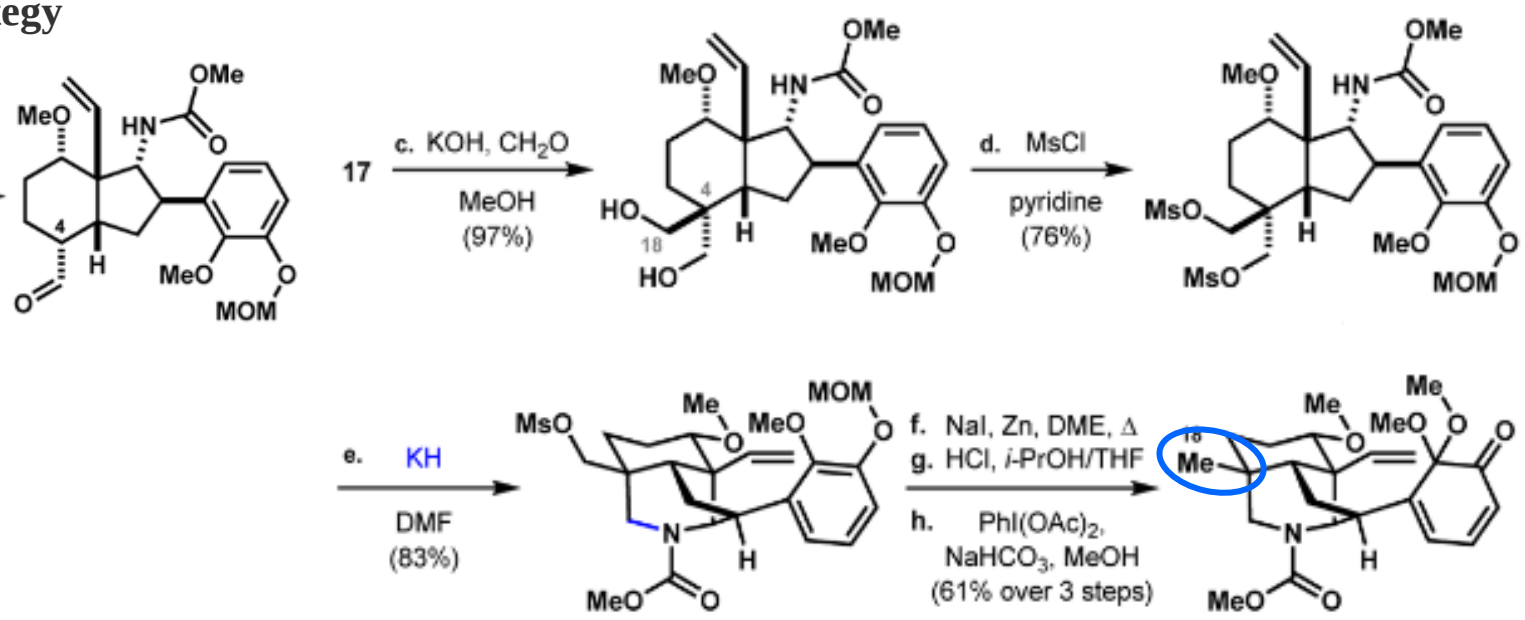
Bandyopadhyaya, A. K. *et al*. *Bioorg. Med. Chem. Lett.* **20**, 6680–6684 (2010)

Synthesis of Piperidine Derivative

- **1st strategy**



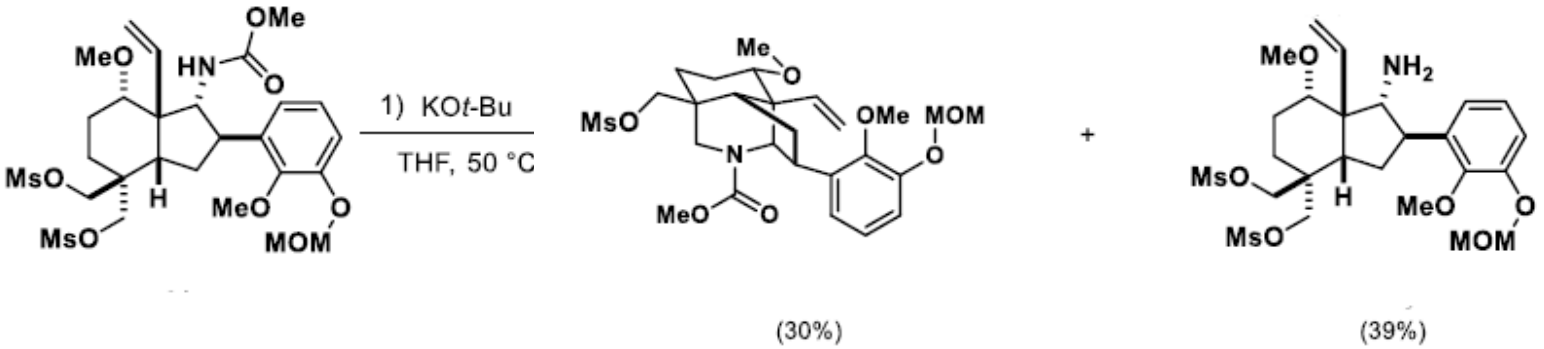
- **2nd strategy**



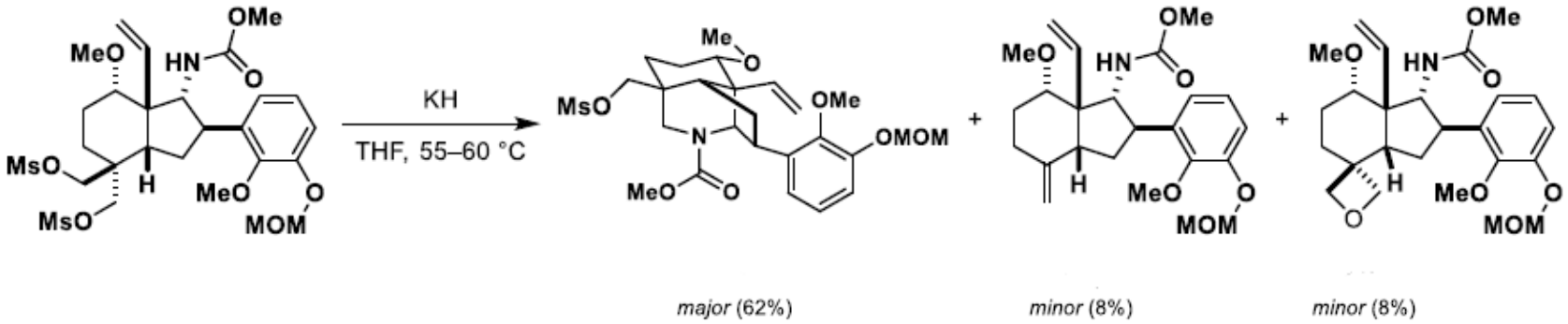
Synthesis of Piperidine Derivative

Optimization of Piperidine Ring Formatiom

- KOtBu as base instead of KH



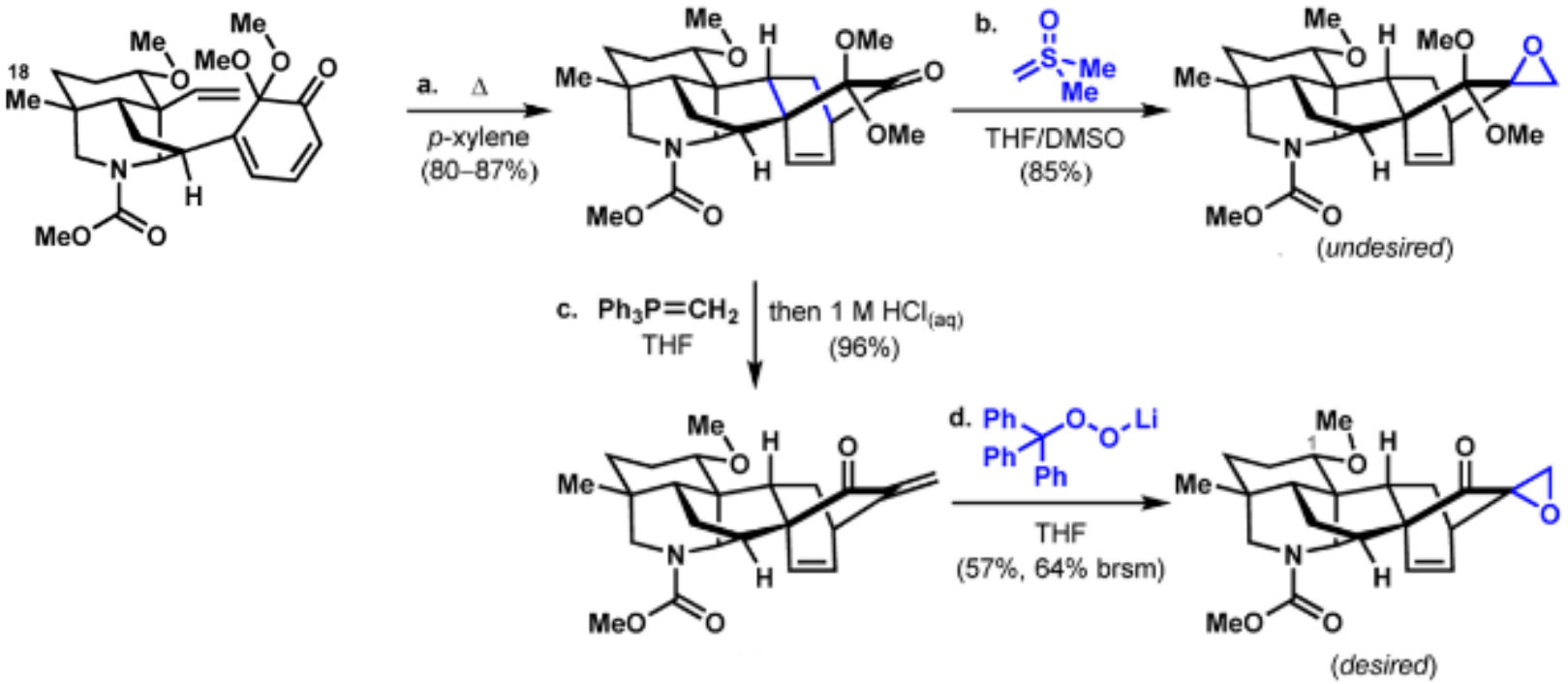
- THF as solvent instead of DMF



Tom, N. J.; Simon, W. M.; Frost, H. N.; Ewing, M. *Tetrahedron Lett.* ***2004,*** *45,* 905.

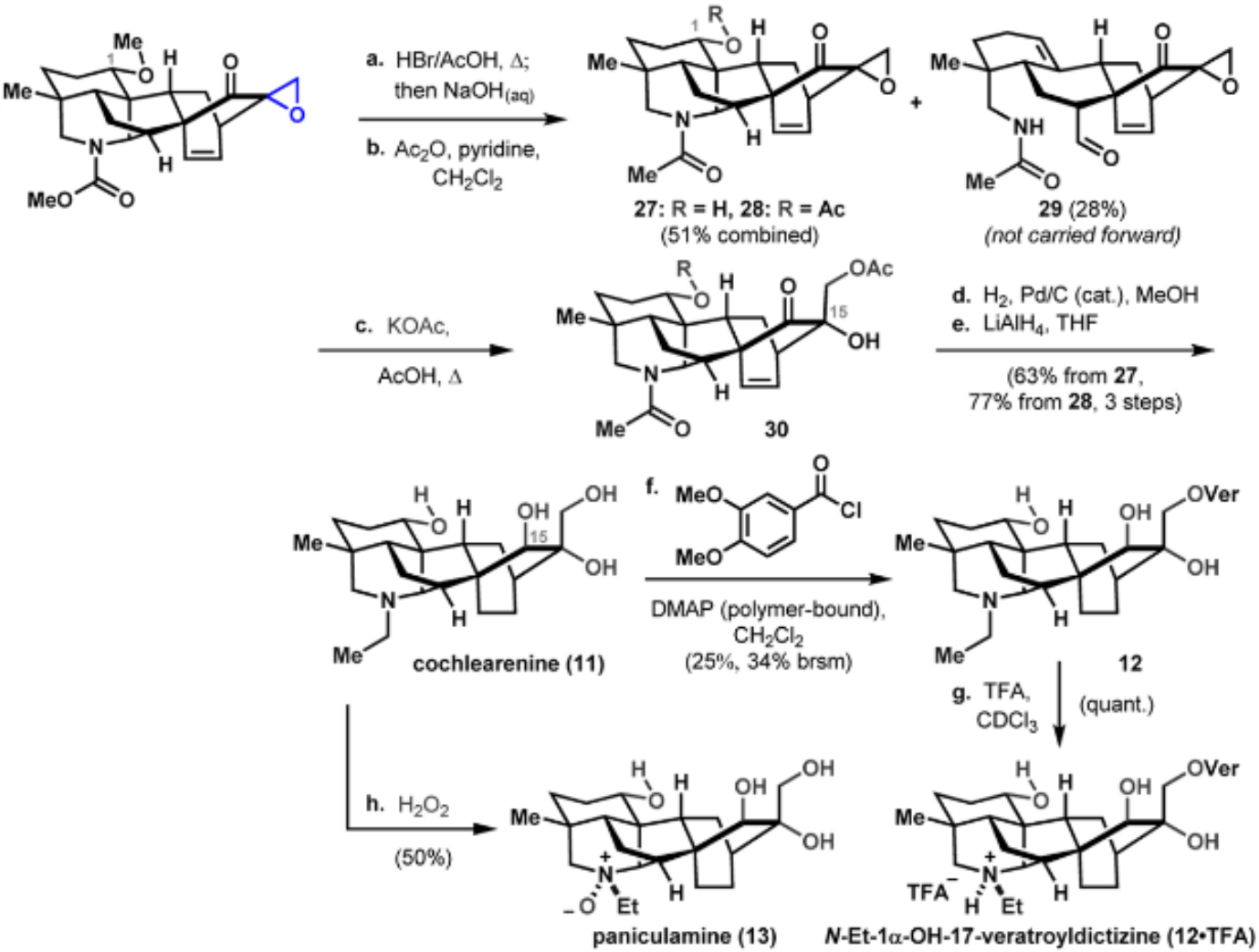
Synthesis of Epoxide

Additional Carbon Atom



Weitz, E.; Scheffer, A.*Ber. Dtsch. Chem. Ges. B* **1921**, *54*, 2975

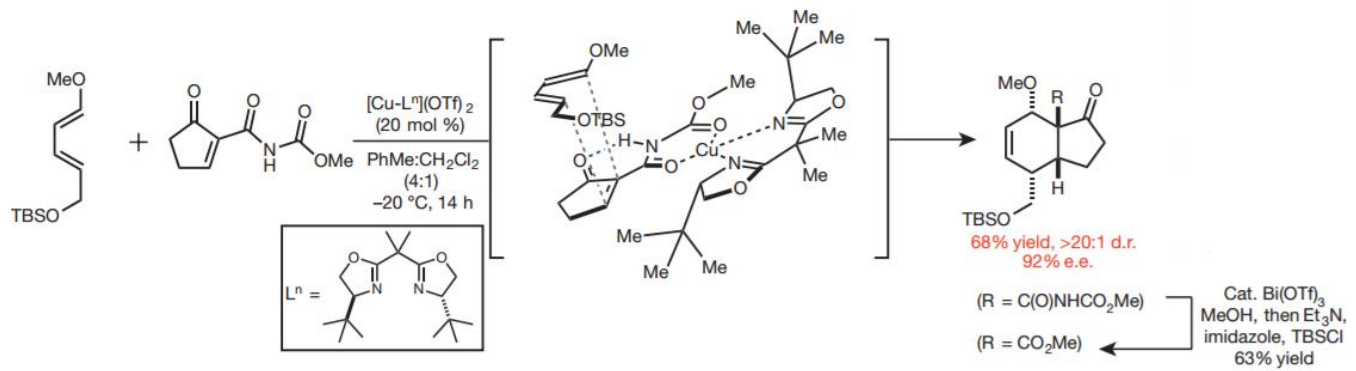
End Game



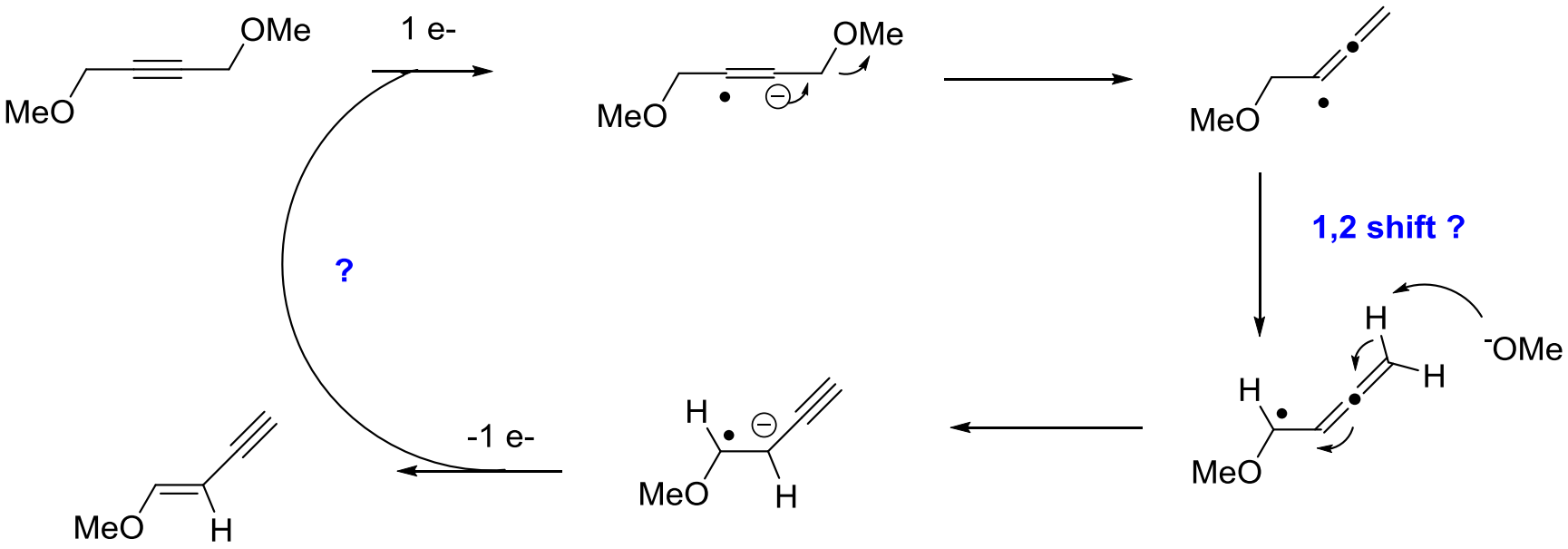
Tang, P.; Chen, Q.-F.; Wang, L.; Chen, Q.-H.; Jian, X.-X.; Wang, F.-P.*Tetrahedron*, **2012**, *68*, 5668-5676

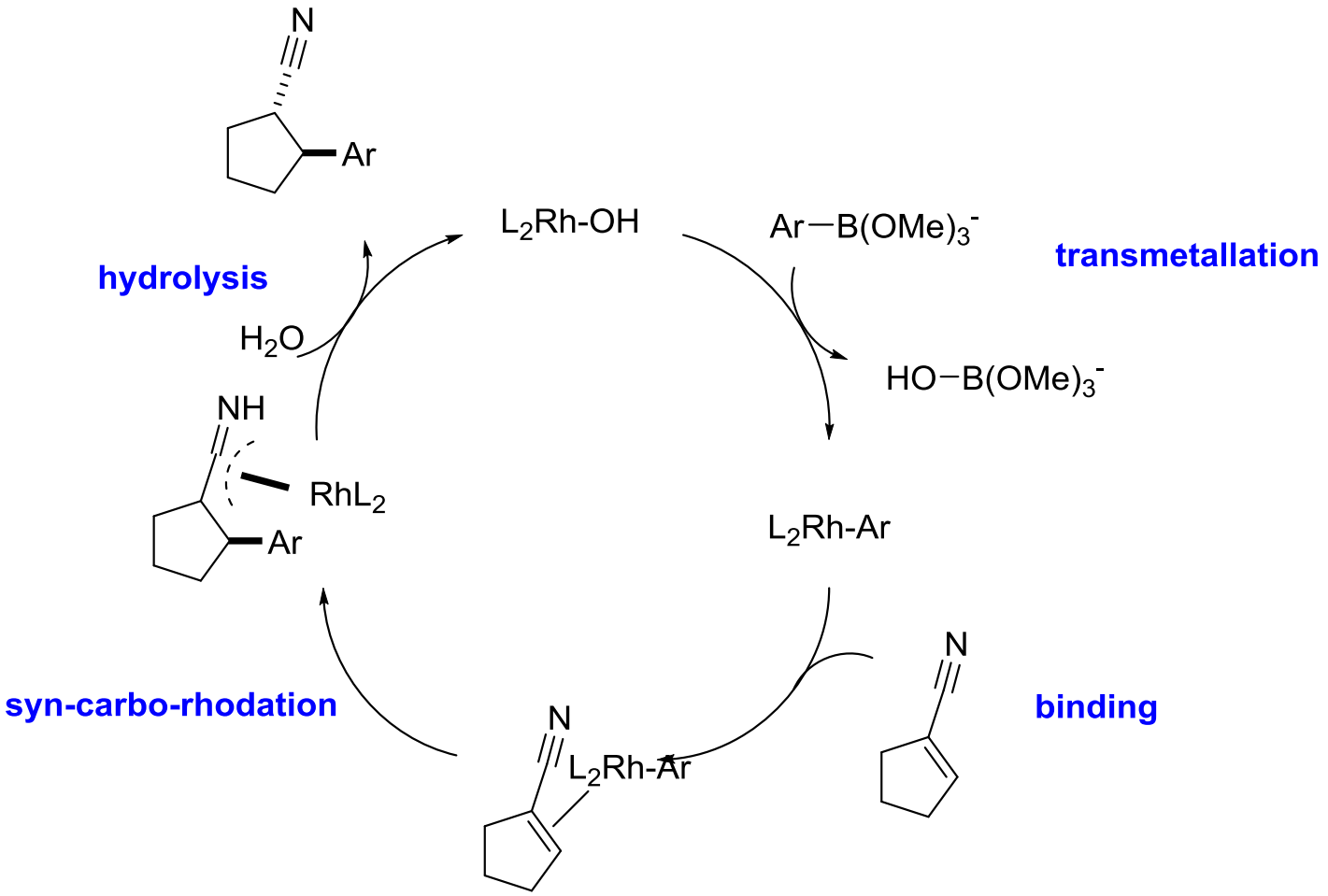
Conclusion

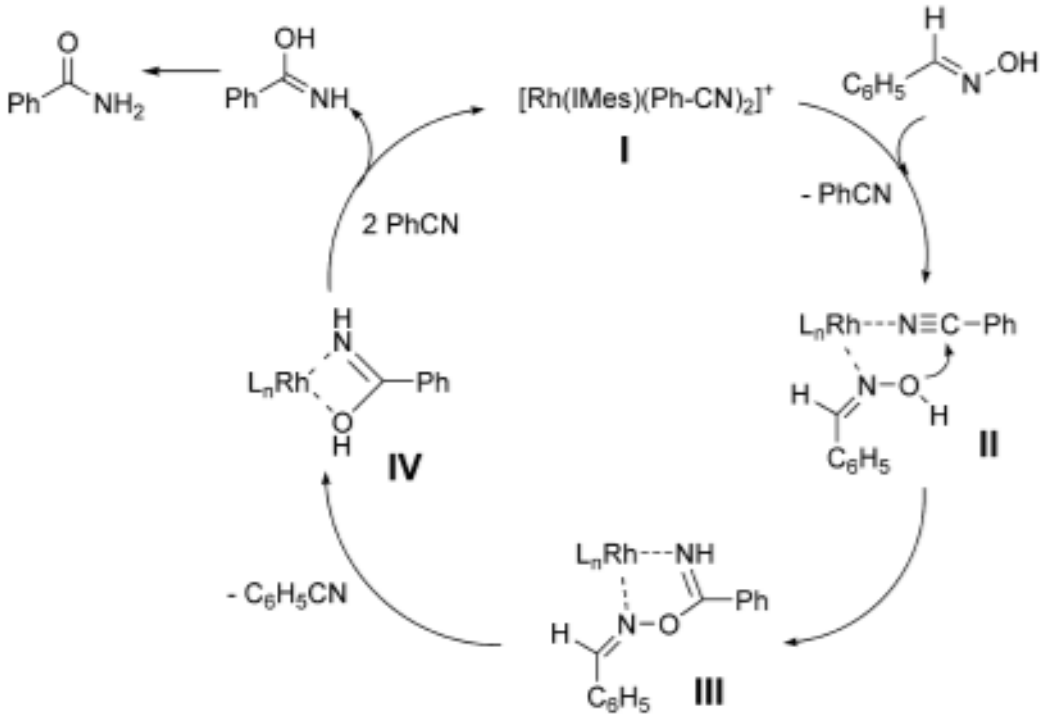
- First total synthesis of in racemic form of cochlearenine , Nethyl-1α-hydroxy-17-veratroyldictyzine, and paniculamine
- 25, 26 and 26 steps respectively
- Keys steps
  - stereoselective installation of the C18
  - methyl group via dimesylate ,
  - optimal conditions for the piperidine ring formation
  - demethylation of the 1-methoxy group under acidic conditions
- Common intermediate can be prepared in 30 g scale and enantioselectively

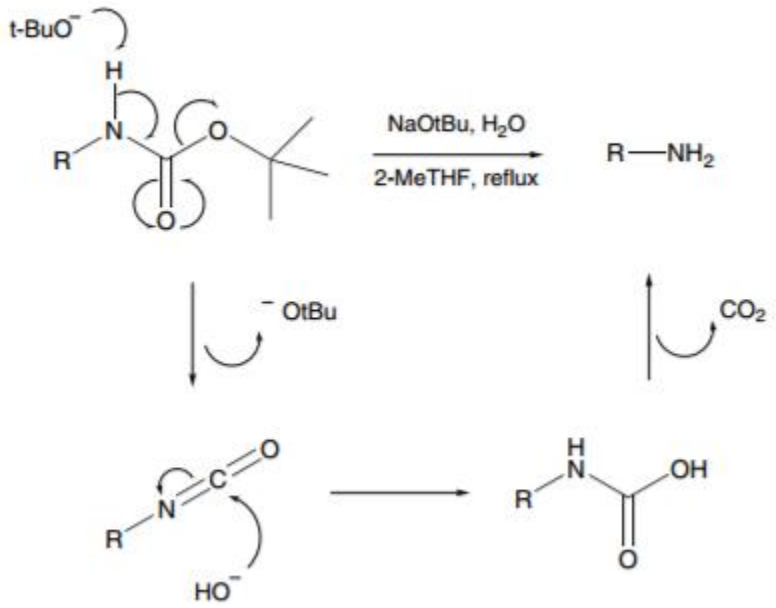


Thank you for your attention!


OMe
MeO
1 e-
OMe
MeO
MeO
1,2 shift ?
H
H
H
-OMe
MeO
?
-1 e-
H
MeO
H
MeO
H


N
Ar
L2Rh-OH
Ar—B(OMe)3-
transmetallation
hydrolysis
H2O
HO—B(OMe)3-
NH
RhL2
Ar
L2Rh-Ar
N
binding
syn-carbo-rhodation
N
L2Rh-Ar


[Rh(IMes)(Ph-CN)2]+
I
- PhCN
II
III
- C6H5CN
IV
2 PhCN


t-BuO⁻
H
N
R
O
O
NaOtBu, H2O
2-MeTHF, reflux
R—NH2
⁻ OtBu
CO2
O
C
N
R
HO⁻
H
N
OH
R
O