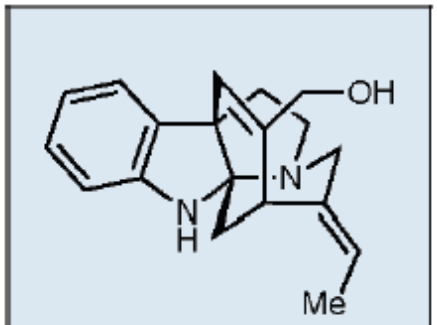
Nine-Step Enantioselective Total Synthesis of (+)-Minfiensine



minfiensine (1)

Spencer B. Jones, Bryon Simmons, and David W. C. MacMillan*

Merck Center for Catalysis at Princeton University, Princeton, New Jersey 08544

J. Am. Chem. Soc. **2009**, *131*, 13606–13607

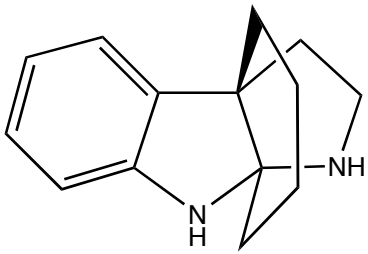
Anil Kumar Gupta

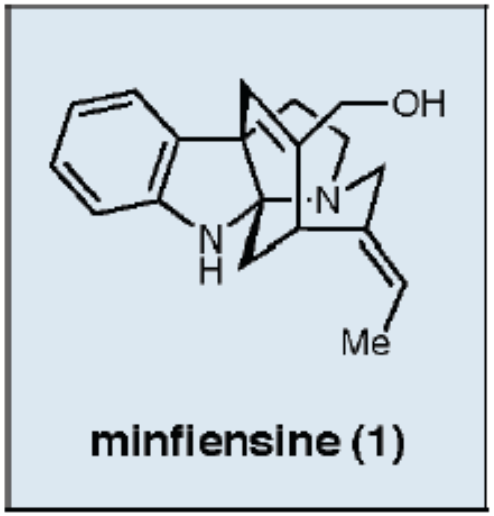
Literature Presentation

04/02/2010

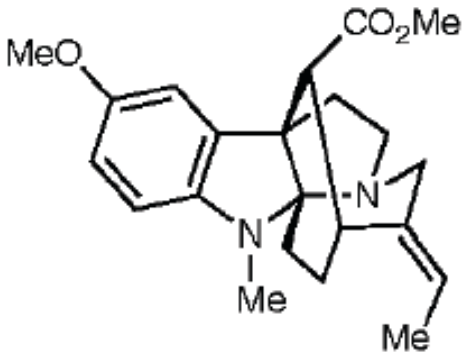
Isolation and Structural Features

- Isolation product from *Strychnos minfiensis*
- 1,2,3,4-tetrahydro-9a,4a-(iminoethano)-9*H-carbazole moiety*
- A tetracyclic core

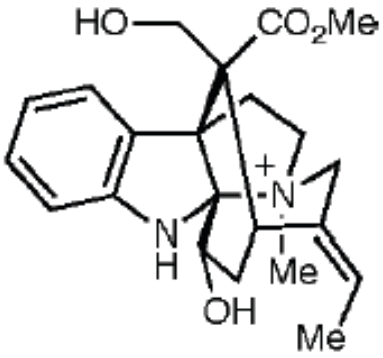




minfiensine (1)



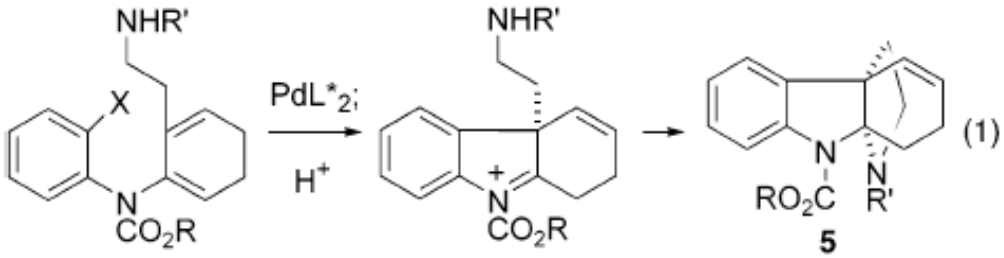
vincorine (2)



echitamine (3)

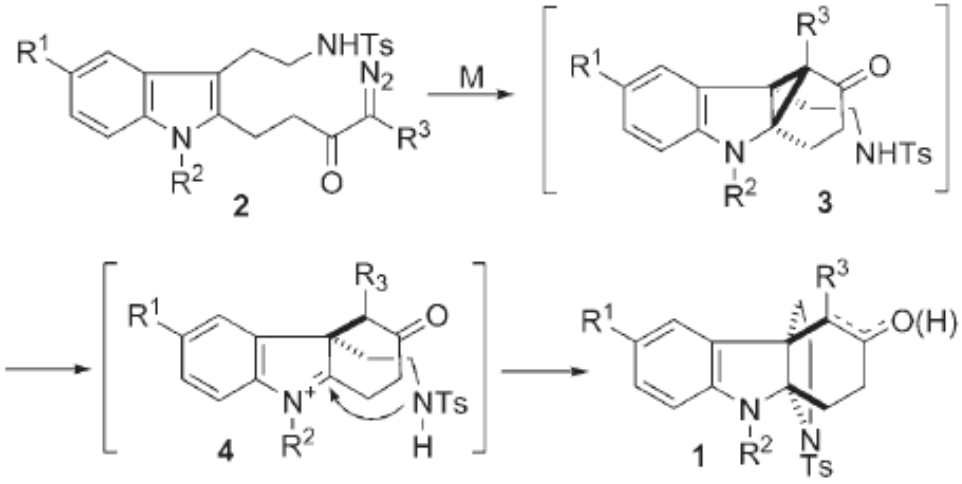
Previous Approaches

Asymmetric Heck-Iminium Ion Cyclization



Dounay, A. B.; Overman, L. E.; Wrobleski, A. D. *J. Am. Chem. Soc*. **2005***, 127*, 10186-10187.

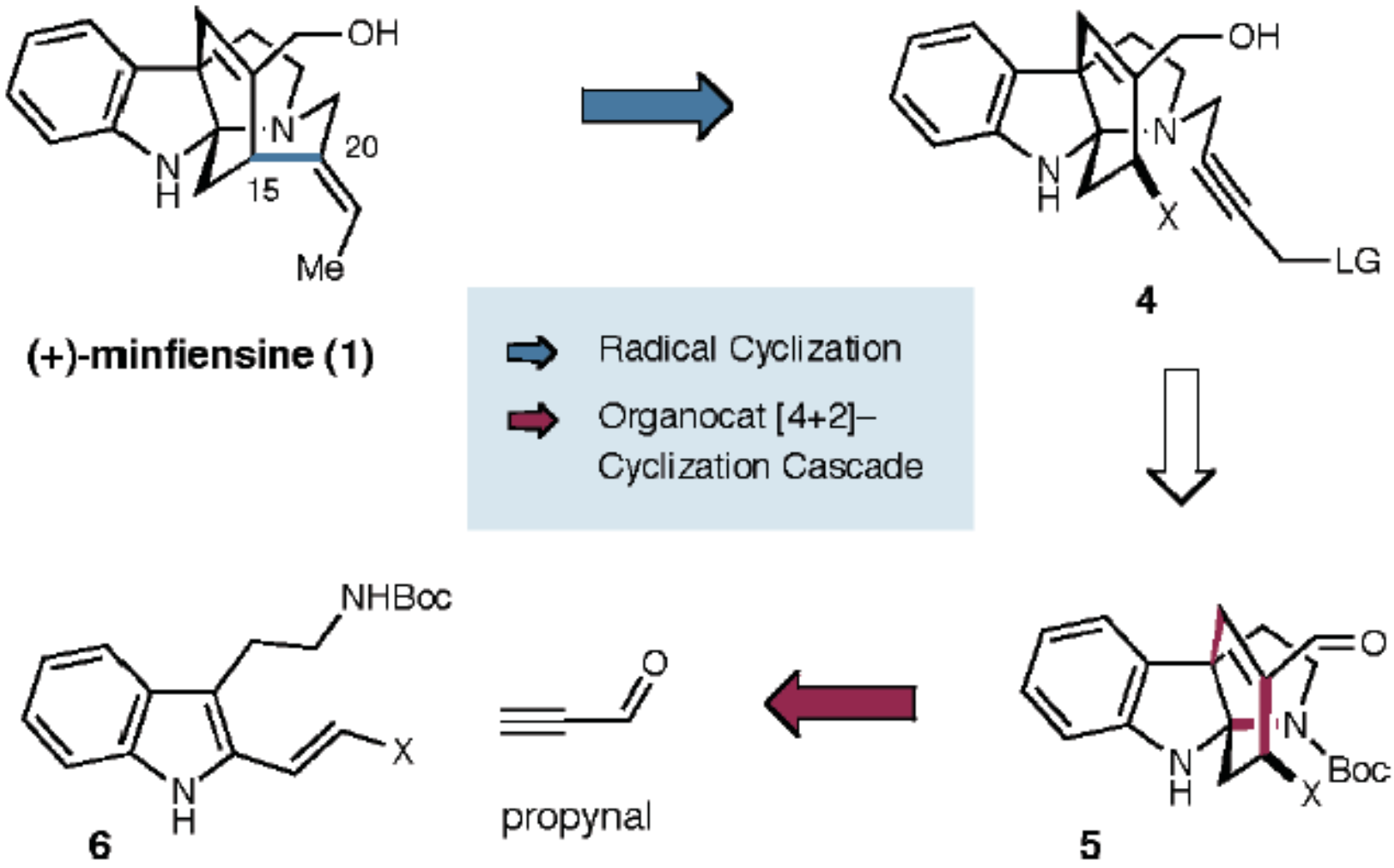
Three-step one-pot cascade reaction



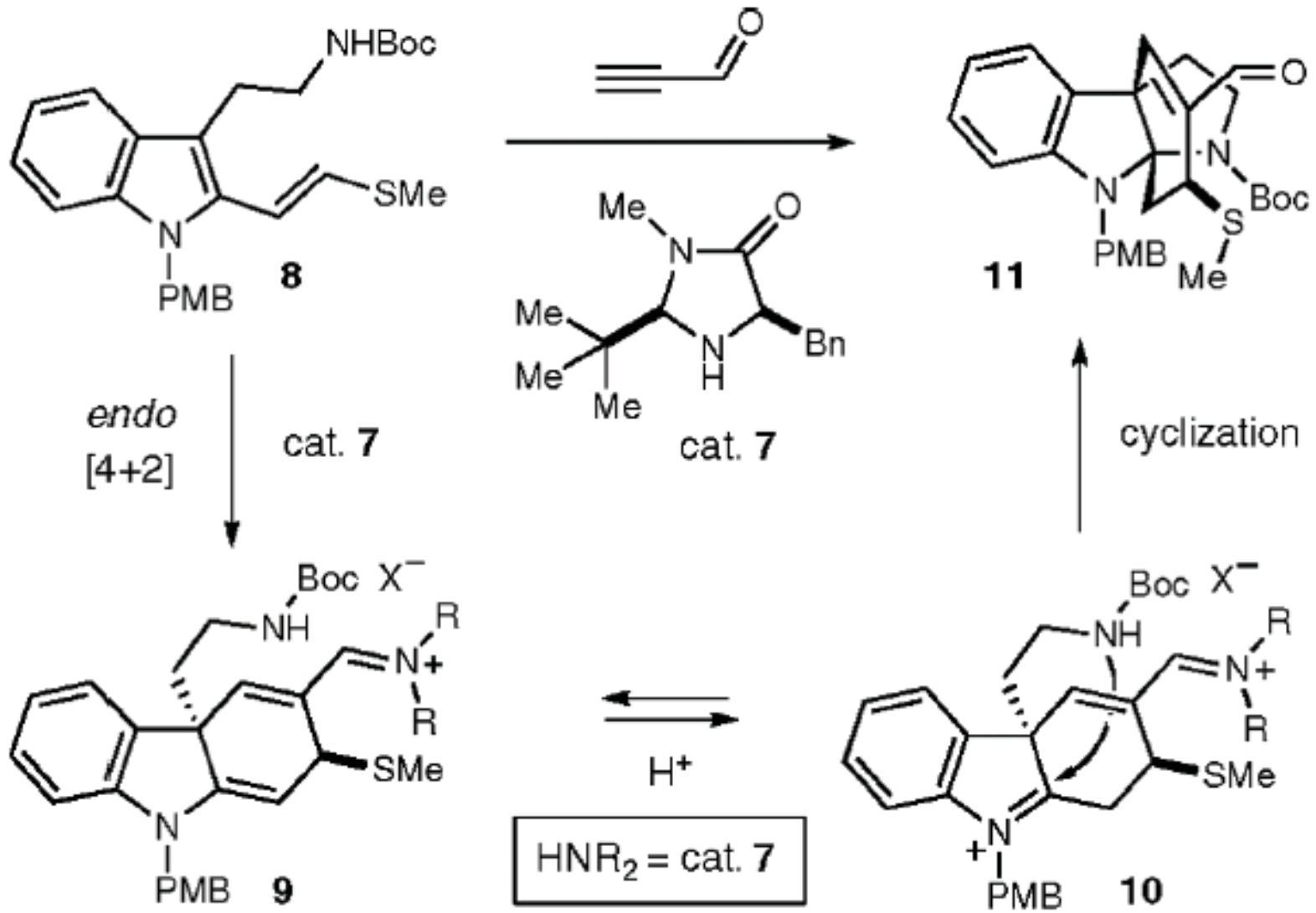
Scheme 1. Three-step one-pot cascade reaction for the assembly of tetracyclic skeleton **1**. Ts = *p*-toluenesulfonyl.

Shen, L.; Zhang, M.; Wu, Y.; Qin, Y. *Angew. Chem. Int. Ed.* **2008***, 47,* 3618-3621.

Scheme 1. Retrosynthetic Approach to Minfiensine Pentacycle



Scheme 2. Enantioselective Catalytic Cascade Sequence to Core



Proposed Transition State

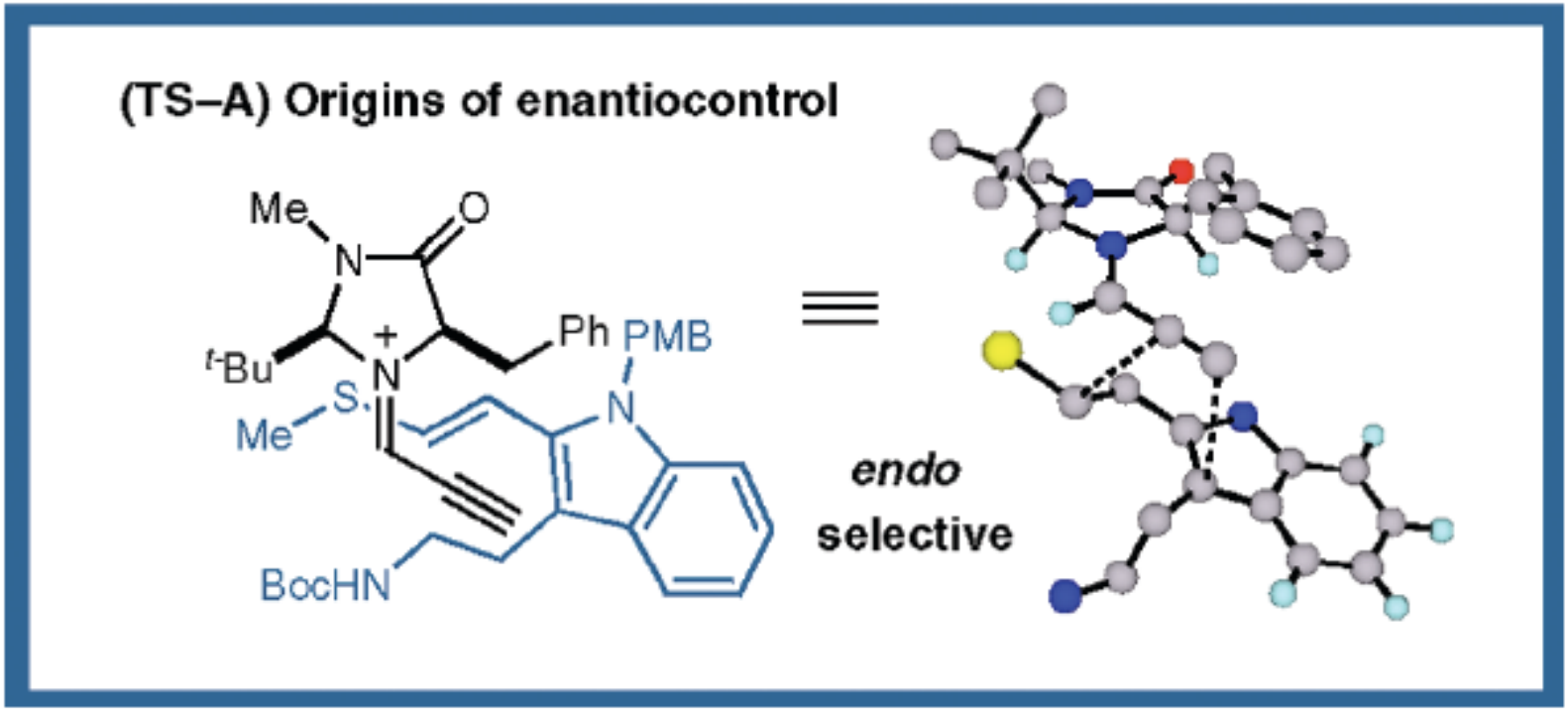
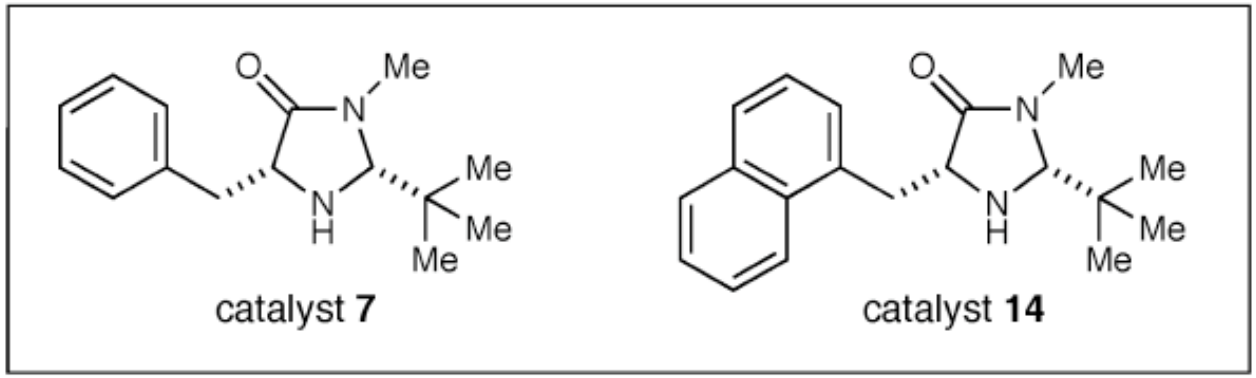
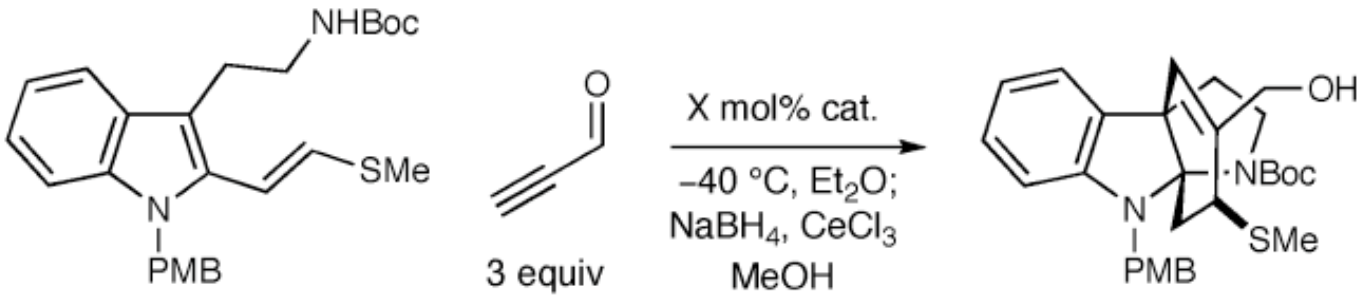


Table 1. Organocatalytic Diels–Alder-Cascade Cyclization Studies



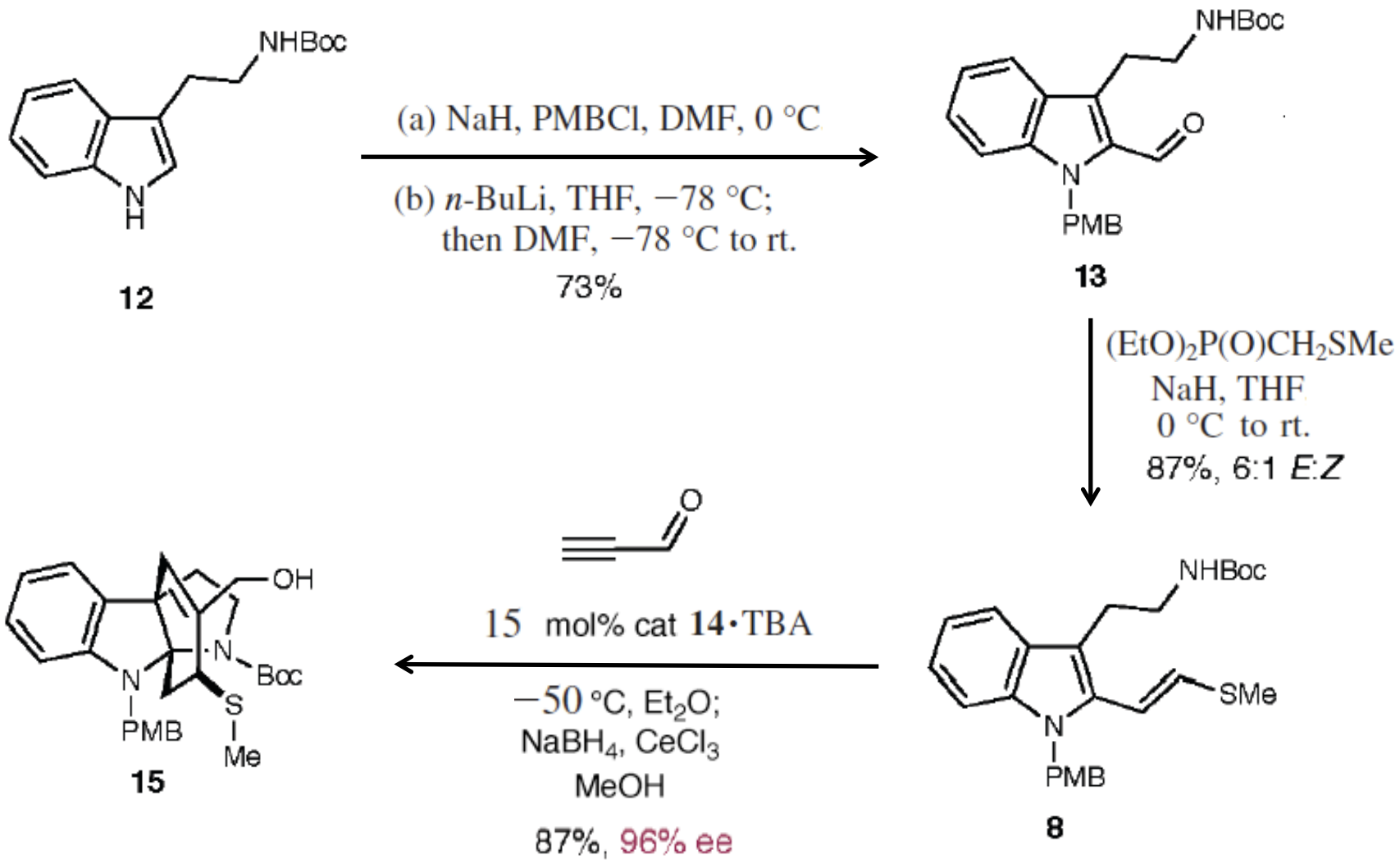


8 **15**

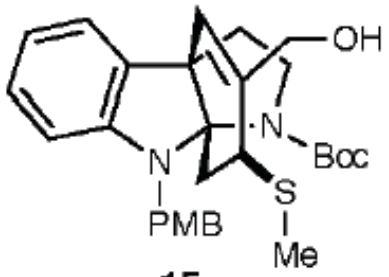
entry	catalyst · HA	mol %	time (h)	% yield[a]	% ee[b]
1	**7**·TFA	20	12	84	75
2	**7**·TBA	20	12	81	88
3[c]	**14**·TBA	15	24	87[d]	96
4	**14**·TBA	10	48	83	94
5	**14**·TBA	5	72	80	94

[a] Yield determined by ^{1}H NMR with internal standard. [b] Enantiomeric excess determined by chiral SFC analysis. [c] At −50 °C. [d] Isolated yield.

Forward Synthesis



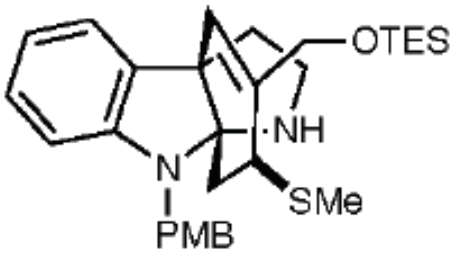
Forward Synthesis



15

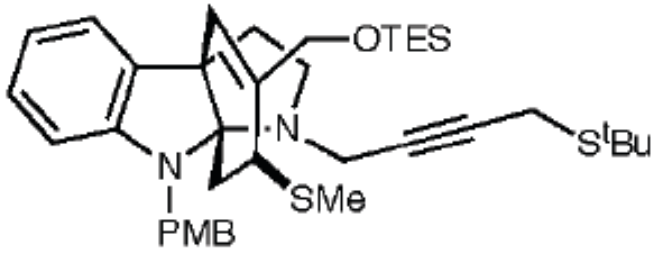
TESOTf, MeCN, 0 °C

84%



16

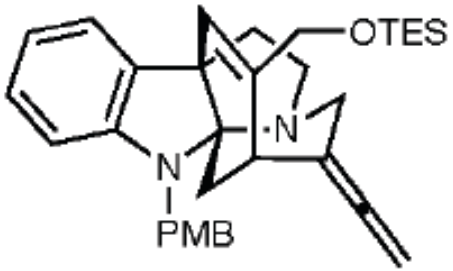
4-(*tert*-Butylthio)but-2-ynal
$NaBH(OAc)_3$,
CH_2Cl_2, rt.
96%



18

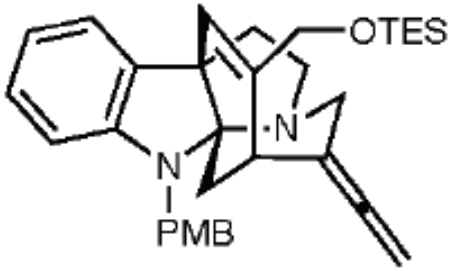
3 equiv *t*-Bu_3SnH

0.3 equiv AIBN,
toluene, 110 °C.
61%



19

Forward Synthesis



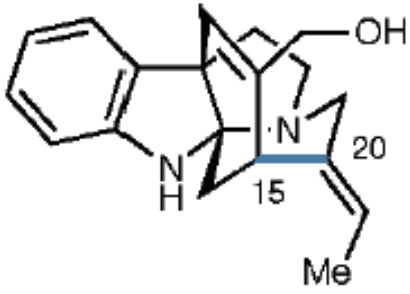
19

(h) Pd/C, H_2, THF, −15 °C;

(i) PhSH, TFA, rt.

90%

>20:1 *E*:*Z*



(+)-minfiensine (1)

- 9 steps synthesis
- 21 % overall yield from commercial materials
- A new cascade organocatalysis sequence
- 6-*exo*-dig radical cyclization