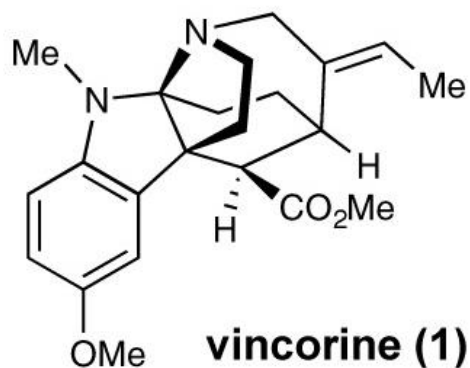


Nine-Step Enantioselective Total Synthesis of (-)-Vincorine

Benjamin D. Horning and David W. C. MacMillan
Merck Center for Catalysis at Princeton University
[dx.doi.org/10.1021/ja402933s](https://doi.org/10.1021/ja402933s)



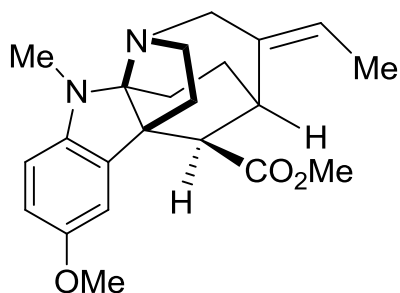
Joseph Salamoun

Wipf Group

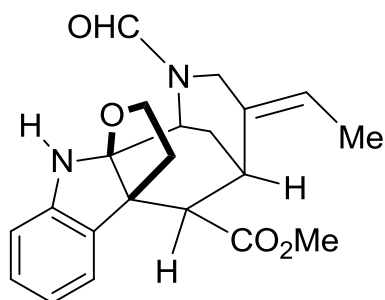
Current Lit. 05/11/13

Vincorine

- Isolated from *Alstonia vitiensis* in 1975.
- Indole alkaloids are of interest for cancer research and drug discovery.
- Belongs to the akuammiline alkaloid family.

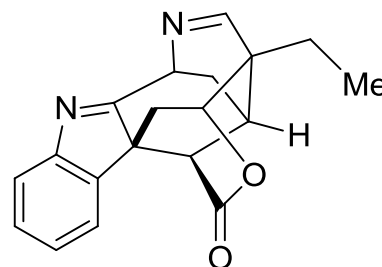


Vincorine



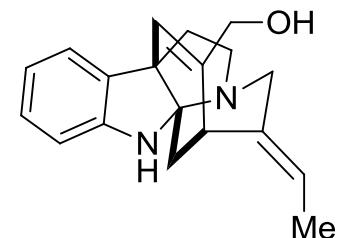
Aspidophylline A

See Liming's CL 06/18/11
for total synthesis.



Scholarisine A

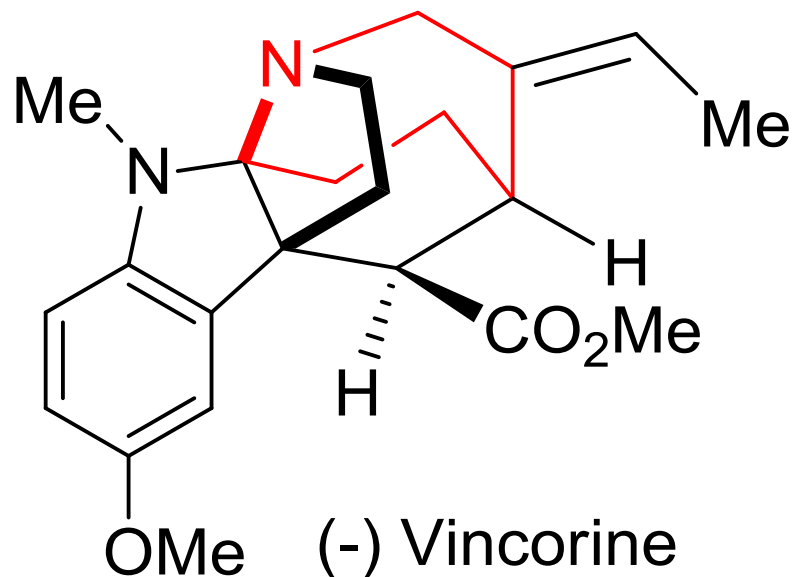
See Filip's CL 02/18/12
for total synthesis.



(+)-Minfiensine

See Kara's CL 11/12/09
for total synthesis.

The Challenge

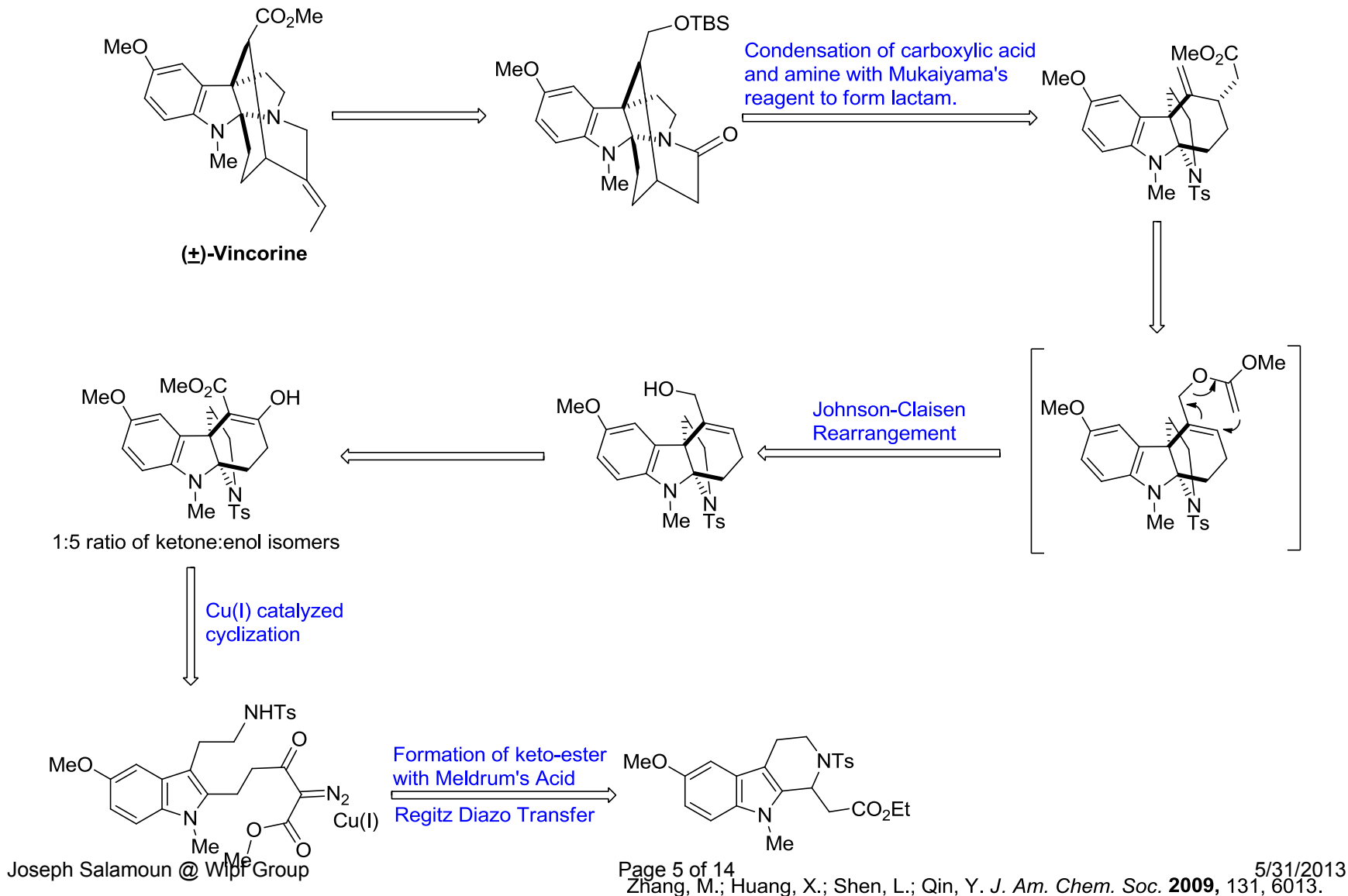


- Contains a pentacyclic caged structure.
- Installation of a strained seven-membered azepanyl ring system (red).
- Enantioselective synthesis.

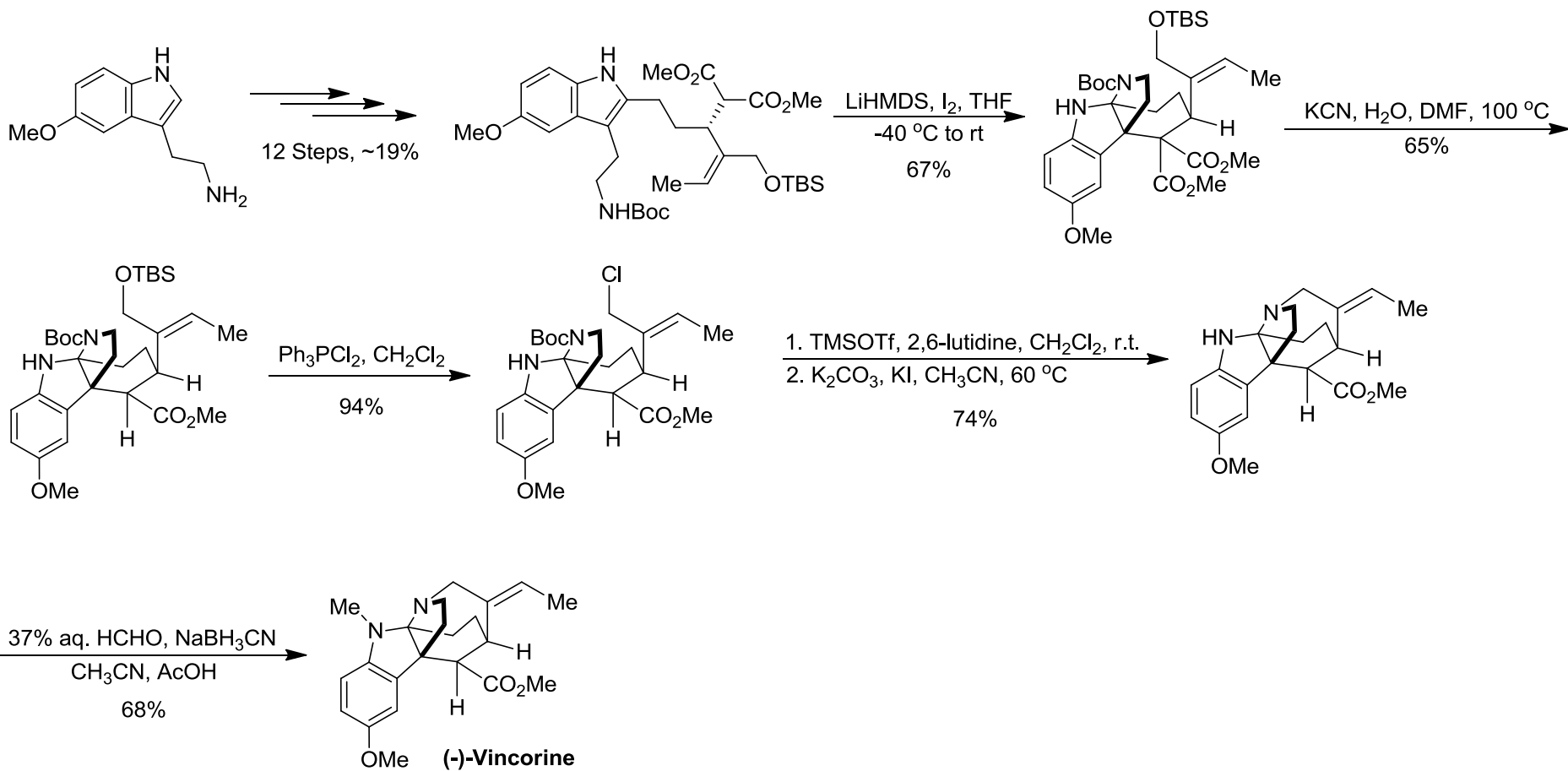
Previous Syntheses

- Total synthesis of Vincorine completed by:
 - Qin group, 31 steps, racemic, 1% overall yield
 - J. Am. Chem. Soc. 2009, 131, 6013-6020
 - Ma group, 18 steps, 5% overall yield
 - J. Am. Chem. Soc. 2012, 134, 9126-9129
 - MacMillan group, 9 steps, 9% overall yield
 - Title Paper, 2013

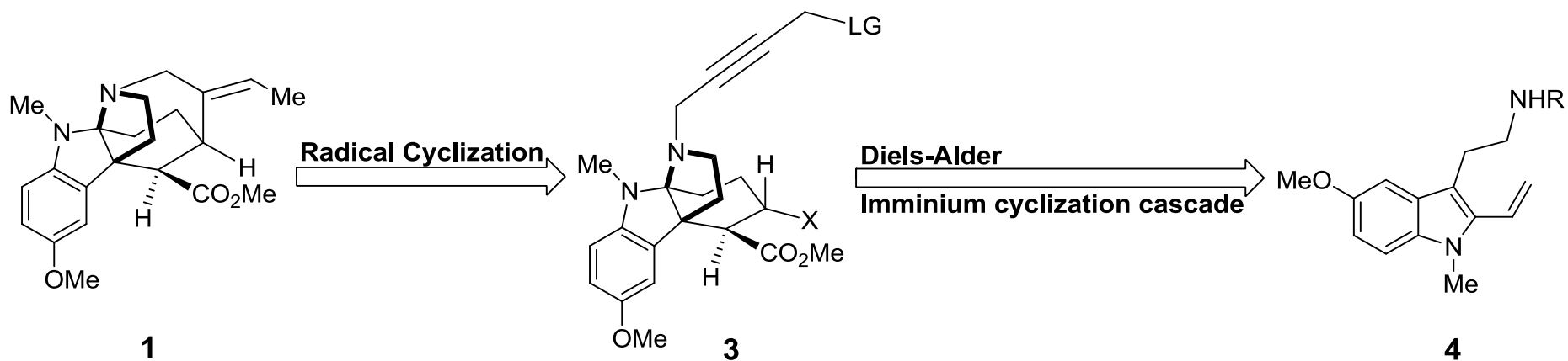
Key Steps from Qin Group



Key Steps from Ma Group

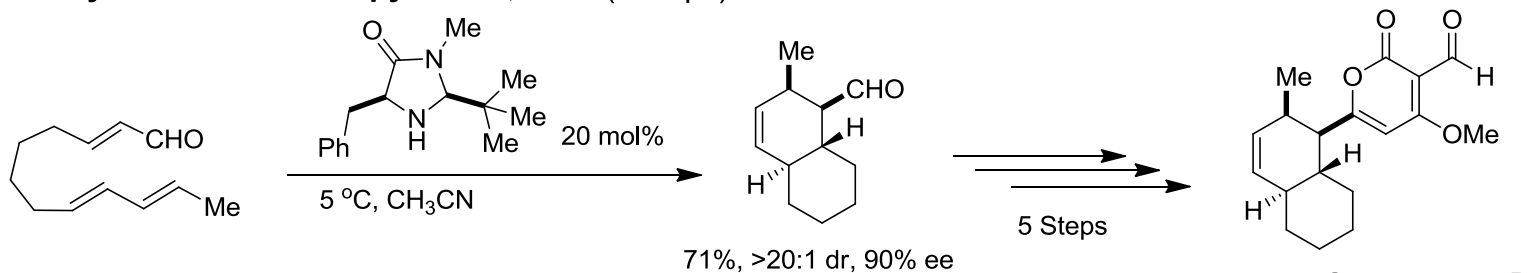


MacMillan's Strategy



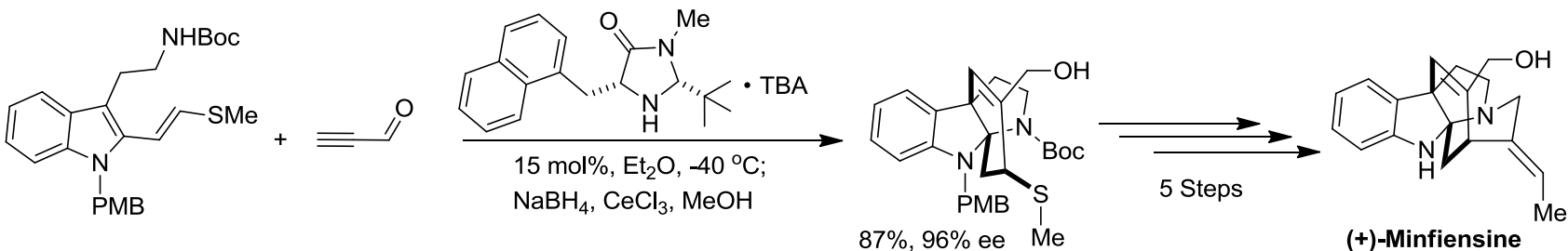
MacMillan's Earlier Methodology

Total Synthesis of Solanapyrone D, 2005 (9 steps)



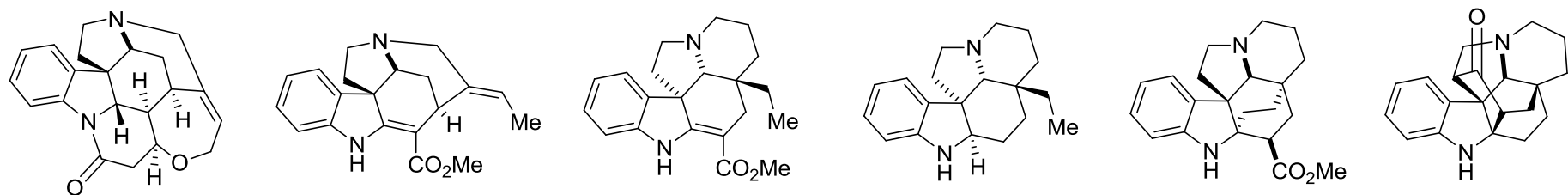
Wilson, R. M.; Jen, W.S.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, 127, 11616.

Total Synthesis of Minfiensine, 2009 (9 steps, 21% overall yield)



Jones, S. B.; Simmons, B; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2009**, 131, 13606.

Total Synthesis of Six Natural Products, 2011



(-)-Strychnine, 12 steps, 6.4% overall yield. **(-)-Akuammicine**, 10 steps, 10% overall yield. **(+)-Vincadifformine**, 11 steps, 8.9% overall yield. **(+)-Aspidospermidine**, 9 steps, 24% overall yield. **(-)-Kopsinine**, 9 steps, 14% overall yield. **(-)-Kopsanone**, 11 steps, 10% overall yield.

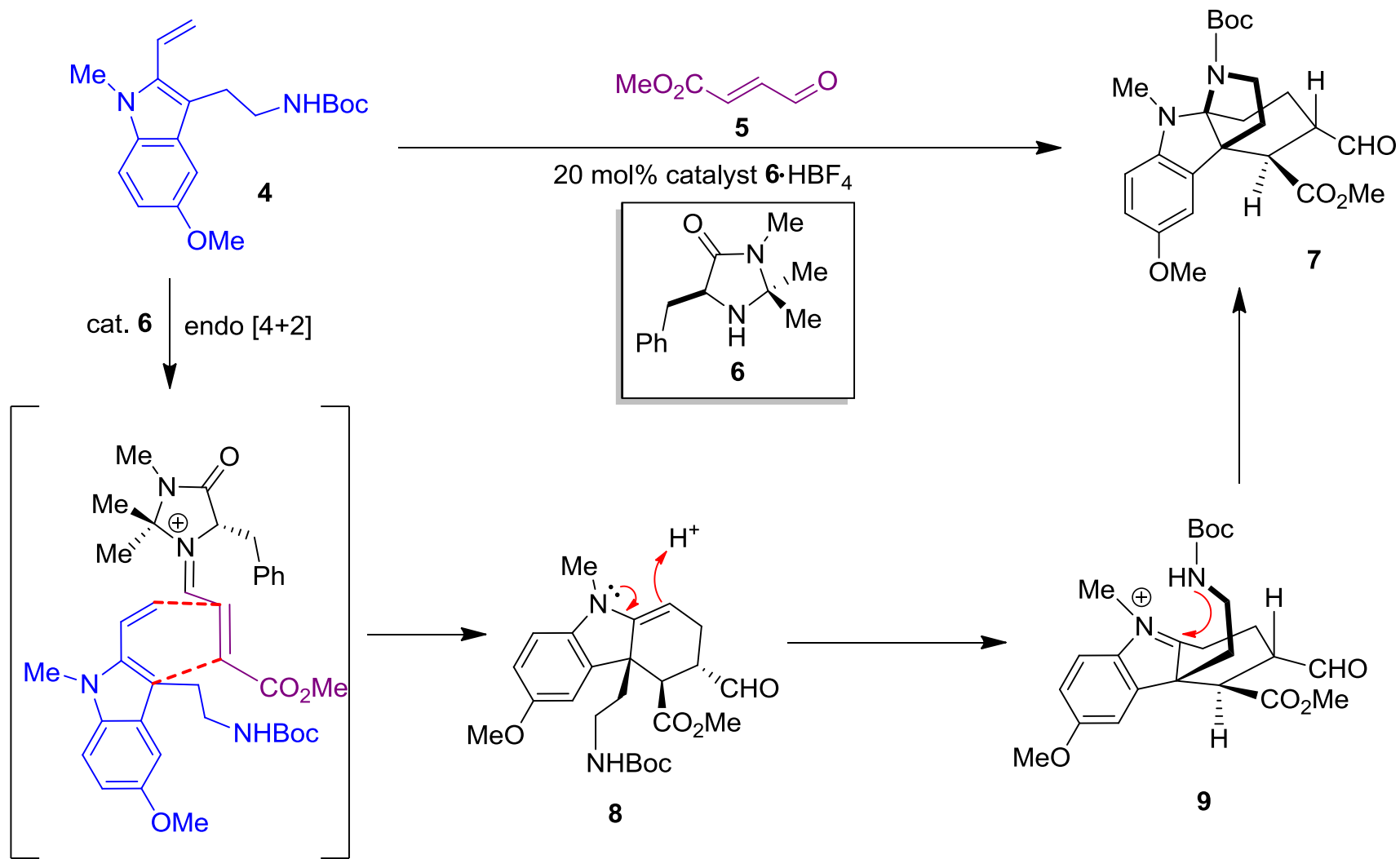
Joseph Salamoun @ Wipf Group

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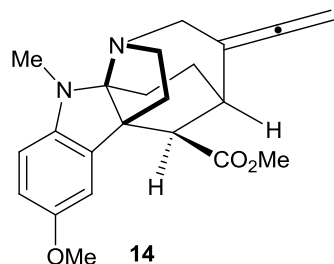
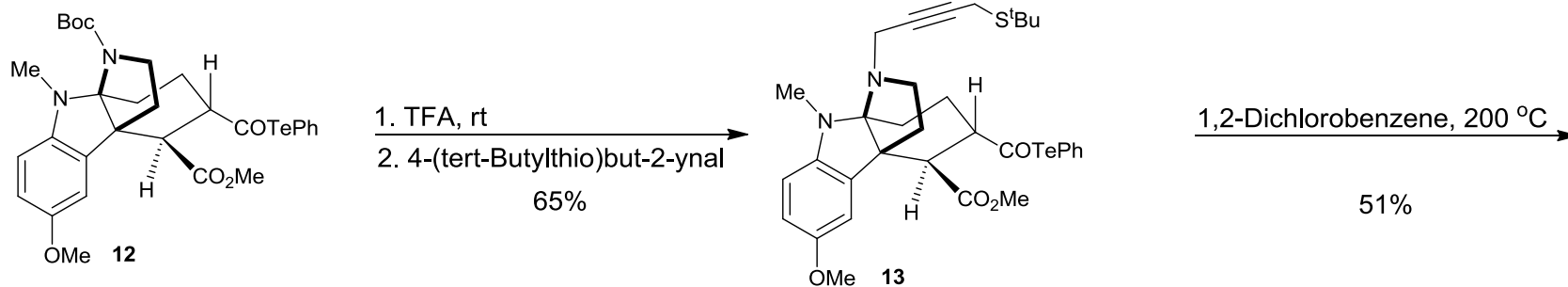
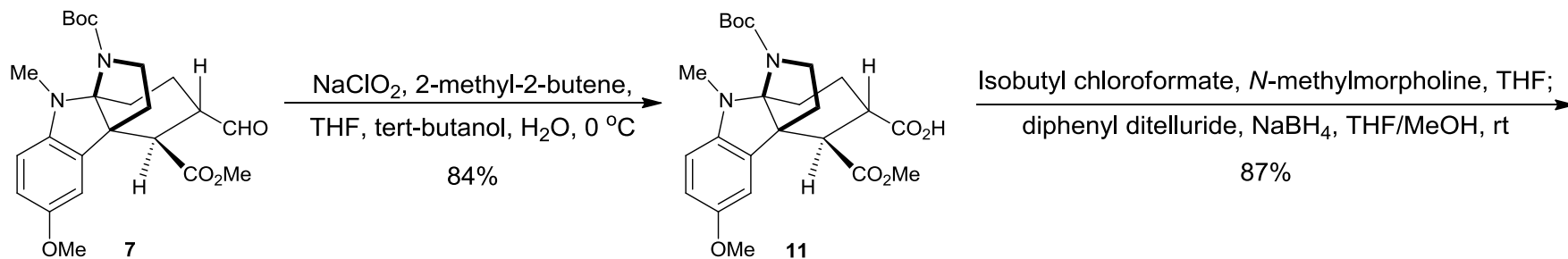
5/31/2013

Jones, S. B.; Simmons, B; Mastracchio, A.; MacMillan, D. W. C. *Nature* **2011**, 475, 183.

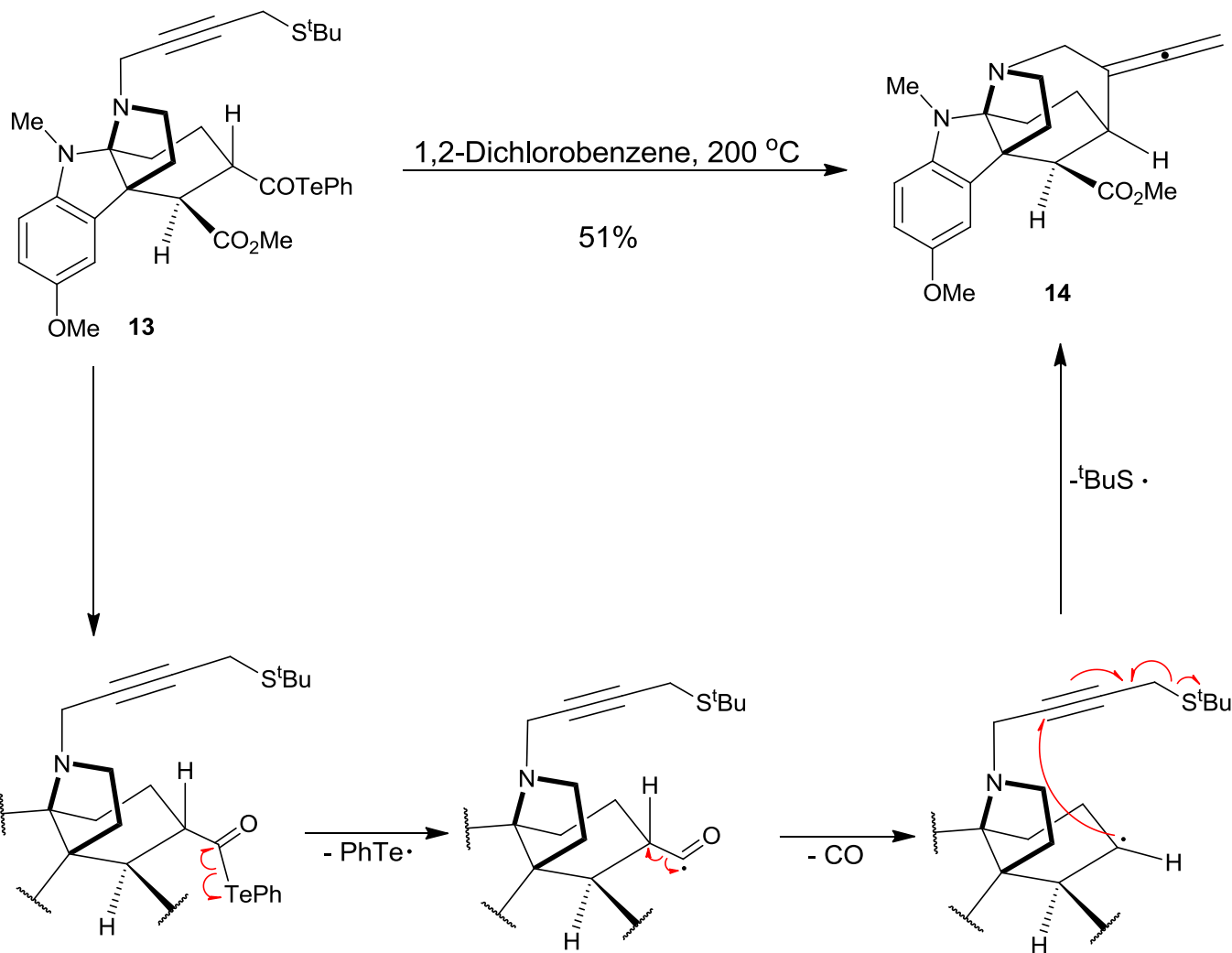
Enantioselective Organocatalytic Cascade



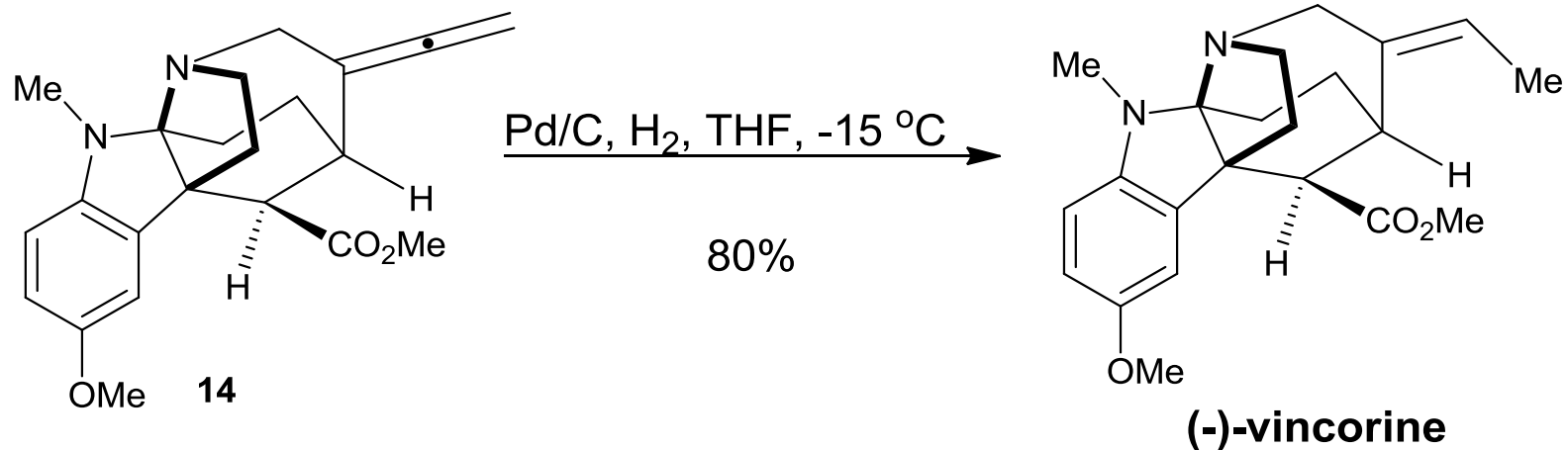
MacMillan's Synthesis Cont'd



Mechanism of Single-Electron Mediated Cyclization



MacMillan's Synthesis Cont'd



Conclusions

- 9 step, 9% overall yield, enantioselective synthesis.
- Stereoselective organocatalyzed Diels-Alder, iminium cyclization cascade sequence builds the tetracyclic core structure in one step.
- Seven member azepanyl ring constructed by single electron-mediated cyclization.