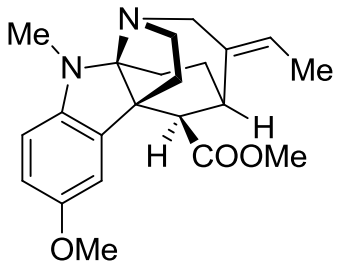


Nine-step enantioselective total synthesis of (-)-vincorine

Horning, B.D.; MacMillan, D.W.C *J. Am. Chem. Soc.* **2013**, *135*, 6442-6445.

Ioulia Gorokhovik – 23.05.2013

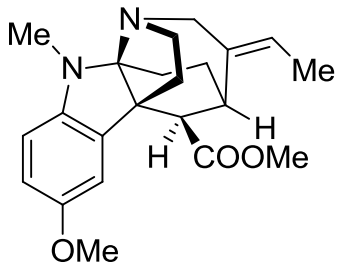
The akuammiline family

- Family isolated from plants in Southeast Asia and Africa

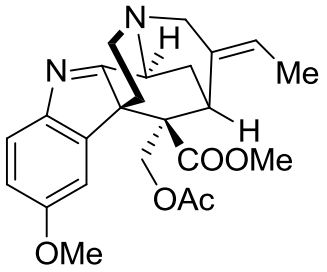
- Characterized by rigid polycyclic ring system with :
- Caged structure
- Quaternary center
- Indol(en)ine motif
- Numerous stereocenters

- Medical relevance :

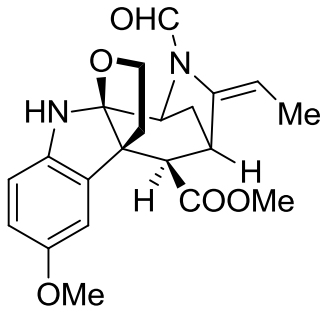
Anti-cancer properties



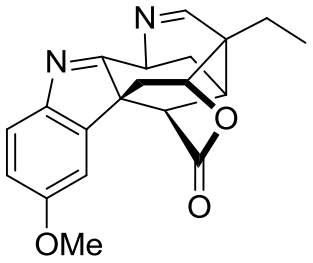
vincorine



akuammiline



aspidophylline



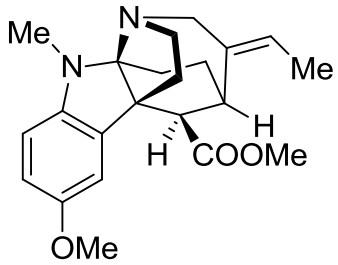
scholarisine

Boal, B.W. PhD dissertation, UC Los Angeles, **2012**.

(-)-Vincorine

- Vincorine extracted from *Vinca minor* (periwinkle)

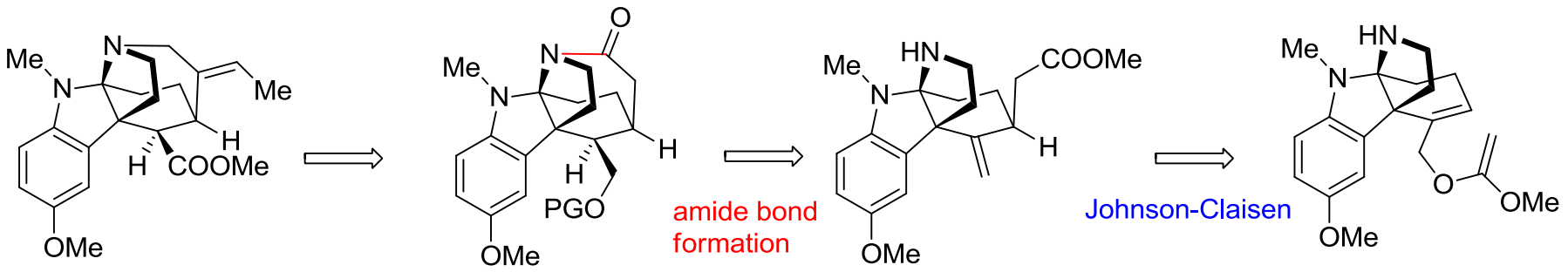
- Structural particularities :
  - Pyrroloindoline motif
  - 1 quaternary center
  - 3 other stereocenters



- Synthetic challenges :
  - Pentacyclic caged structure
  - Strained 7-membered ring
  - Enantioselective catalysis

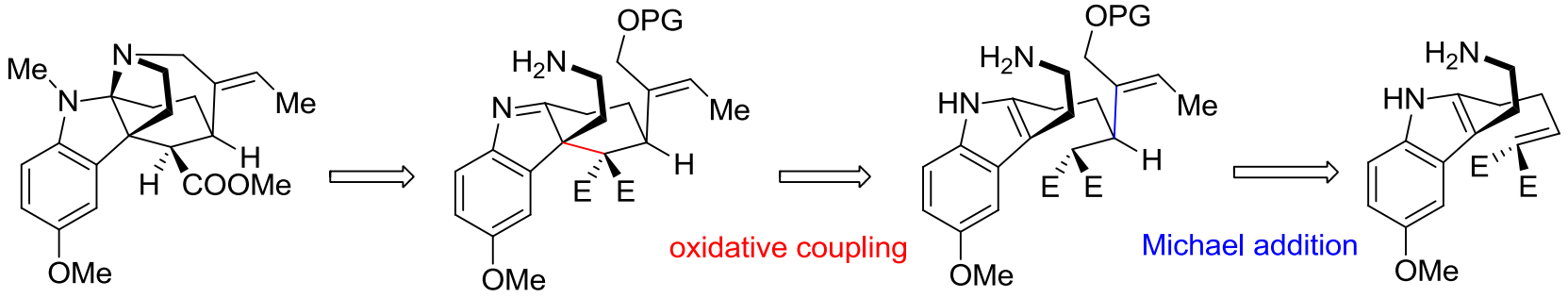
Previous syntheses

Qian et al., 2009 - 31 steps, 1% :



vincorine

Ma et al., 2012 - 18 steps, 5% :



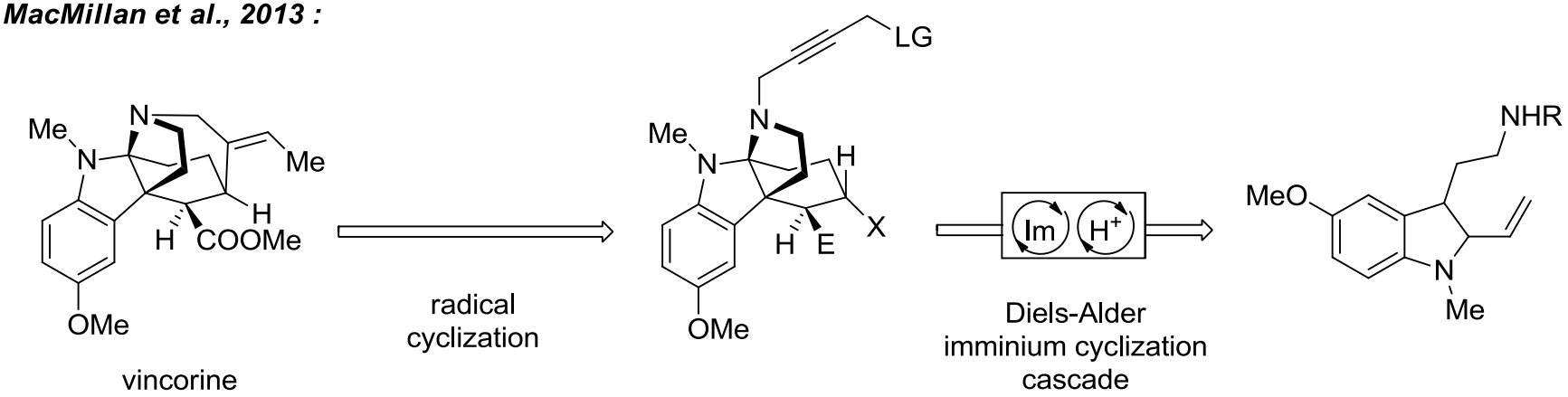
(-)-vincorine

For both syntheses, C-N bond formation forged 7-membered ring

Zhang, M.; Huang, X.; Shen, L.; Qin, Y. *J. Am. Chem. Soc.* **2009**, *131*, 6013-6020. Zi, W.; Xie, W.; Ma, D. *J. Am. Chem. Soc.* **2012**, *134*, 9126-9129.

MacMillan's strategy

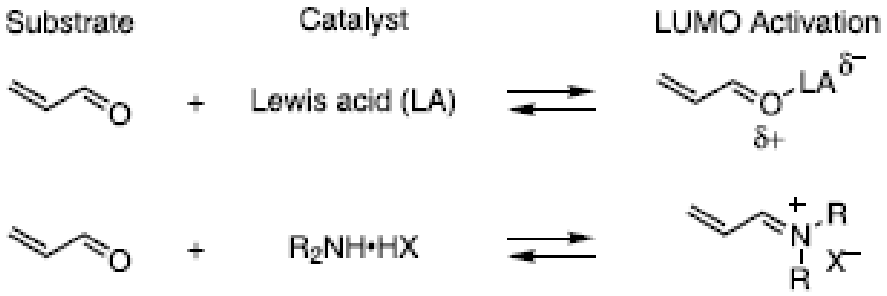
MacMillan et al., 2013 :



Would form the 7-membered ring and the methine with right stereochemistry in 1 step

Starting from cheap achiral compounds
High complexity-generating step

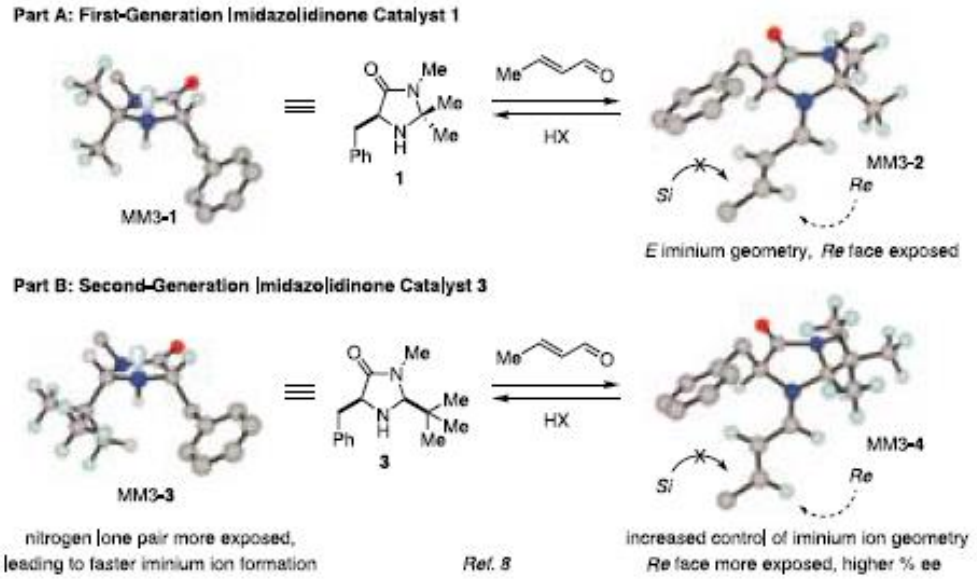
Imminium activation



Objectives of design :

- The iminium formation should be efficient and reversible.
- High levels of iminium geometry control
- Selective discrimination of the face of attack

- Based on the capacity of chiral amines to lower LUMO
- Reversible formation of iminium is mimicking Lewis acid-catalysis
- Used for Diels-Alder, Friedel-Crafts, Mukayama-Michael, cascade reactions…



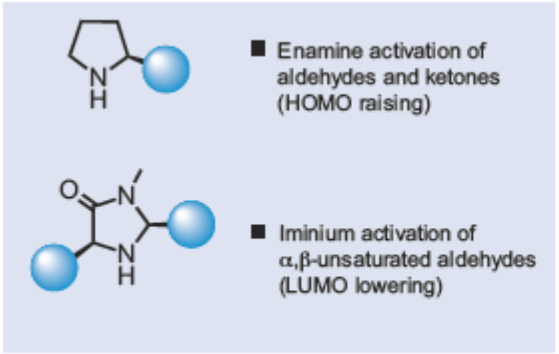
Lelais, G.; MacMillan, D.W.C. *Aldrichimica Acta*, **2006**, *39*, 79-87.

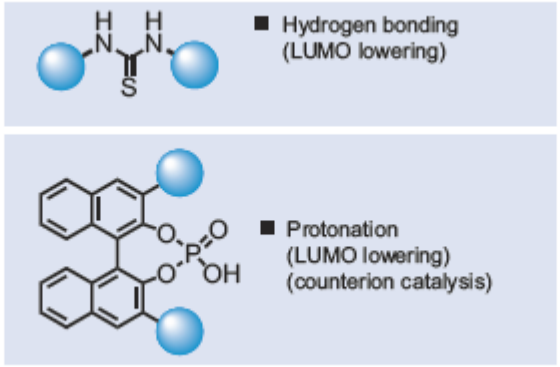
Organocatalytic cascades

Advantages of organocatalytic cascade reactions :

- Several reactions are carried out in 1 step
- Avoids protecting groups manipulation
- Rapid complexity generation
- Selectivities often good
- Good functional group tolerance
- Mild conditions

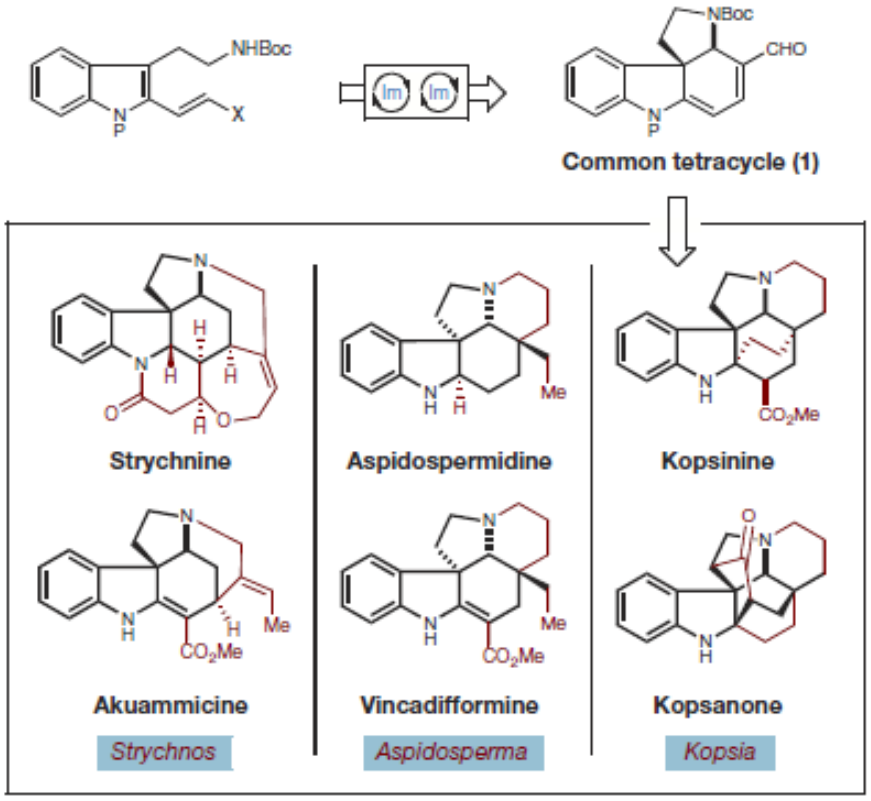
Organocalaysis allows different modes of activation combined on 1 catalyst





Grondal, C.; Jeanty, M.; Enders, D. *Nature Chemistry*, **2010**, *2*, 167-178.

Mac Millan's collective synthesis of natural products by organocascade catalysis



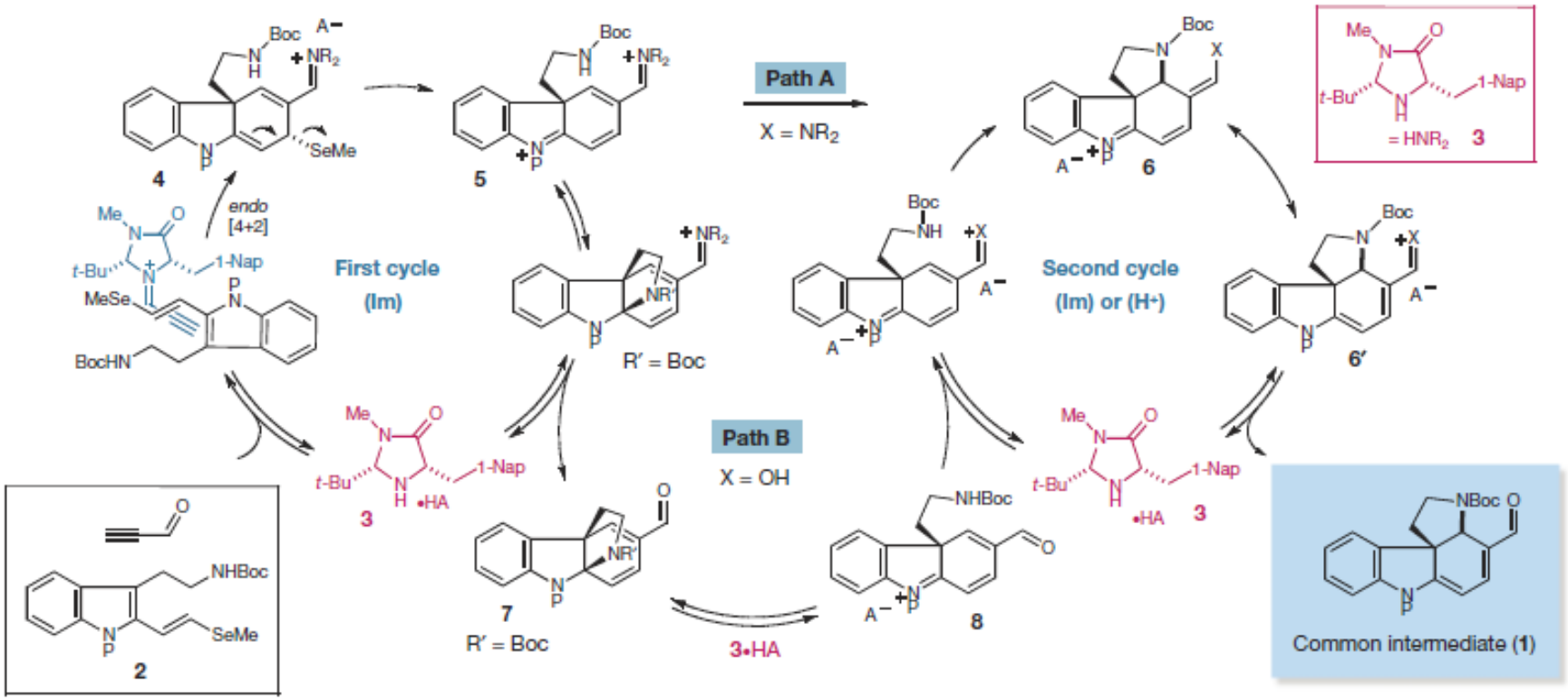
Collective synthesis :
Preparation of a common intermediate to structurally diverse natural products from different families.

Use of organocascade catalysis :
unprecedented levels of ease and efficiency.

In total, 34 steps for the 6 compounds
(76 steps in the previous syntheses)

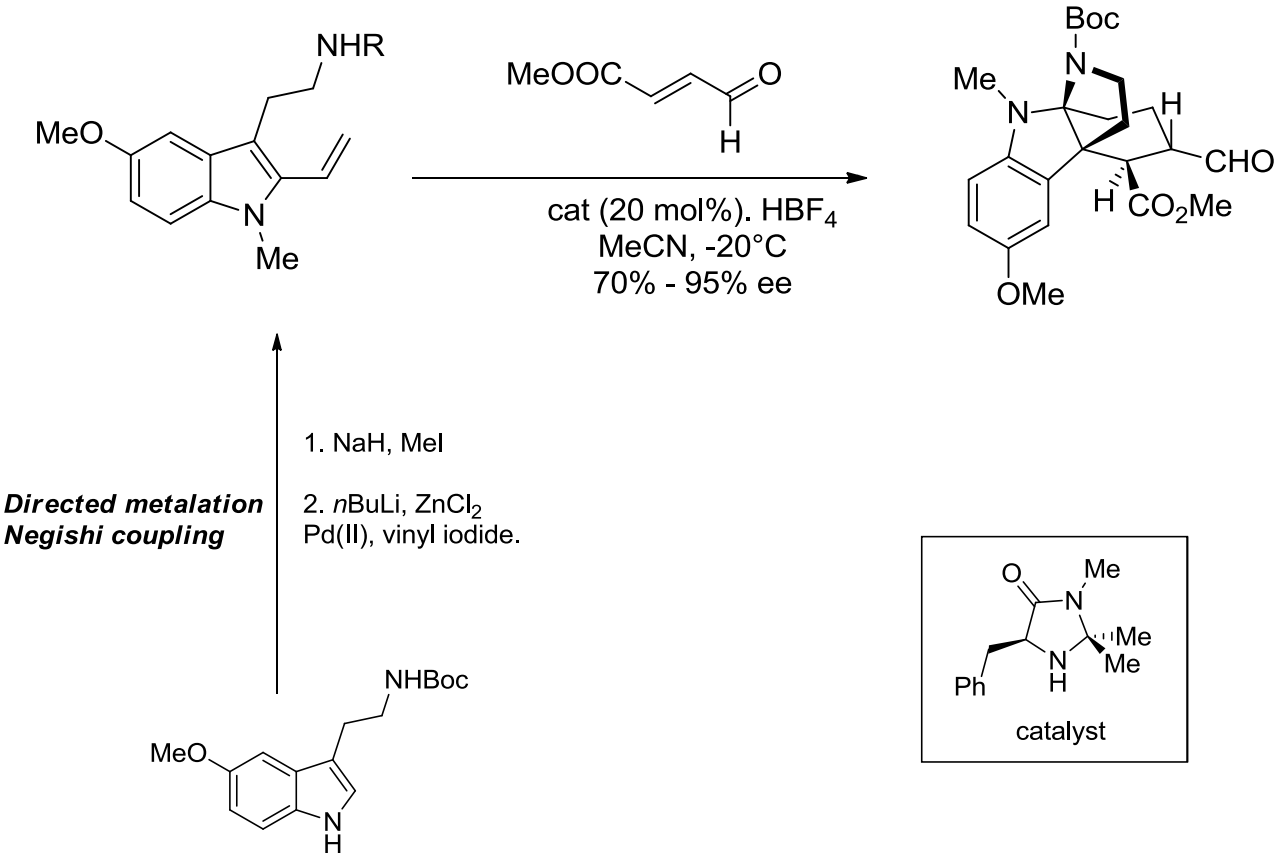
Jones, S.B.; Simmons, B.; Mastracchio, A.; MacMillan, D.W.C. *Nature*, **2011**, *475*, 183-188.

Mac Millan's collective synthesis of natural products by organocascade catalysis

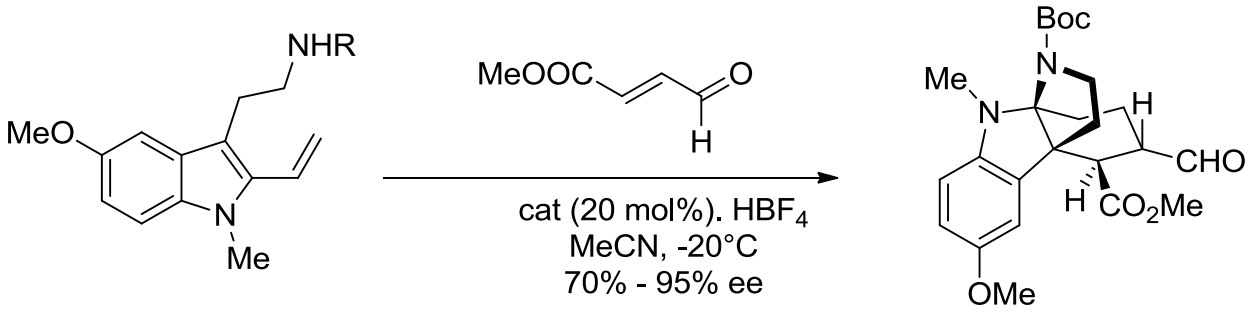


Jones, S.B.; Simmons, B.; Mastracchio, A.; MacMillan, D.W.C. *Nature*, **2011**, *475*, 183-188.

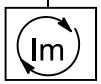
The synthesis

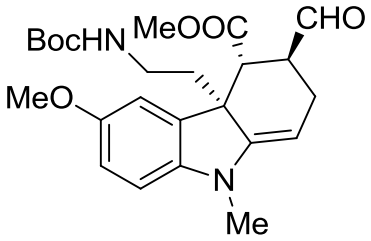


The synthesis

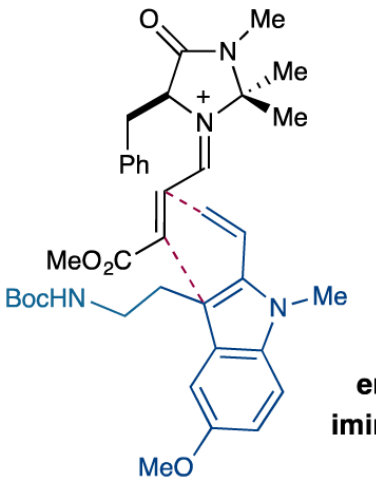


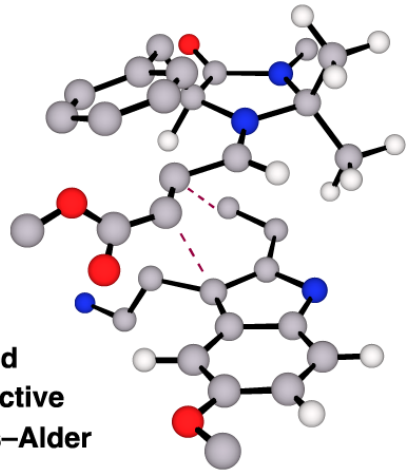
Diels Alder reaction





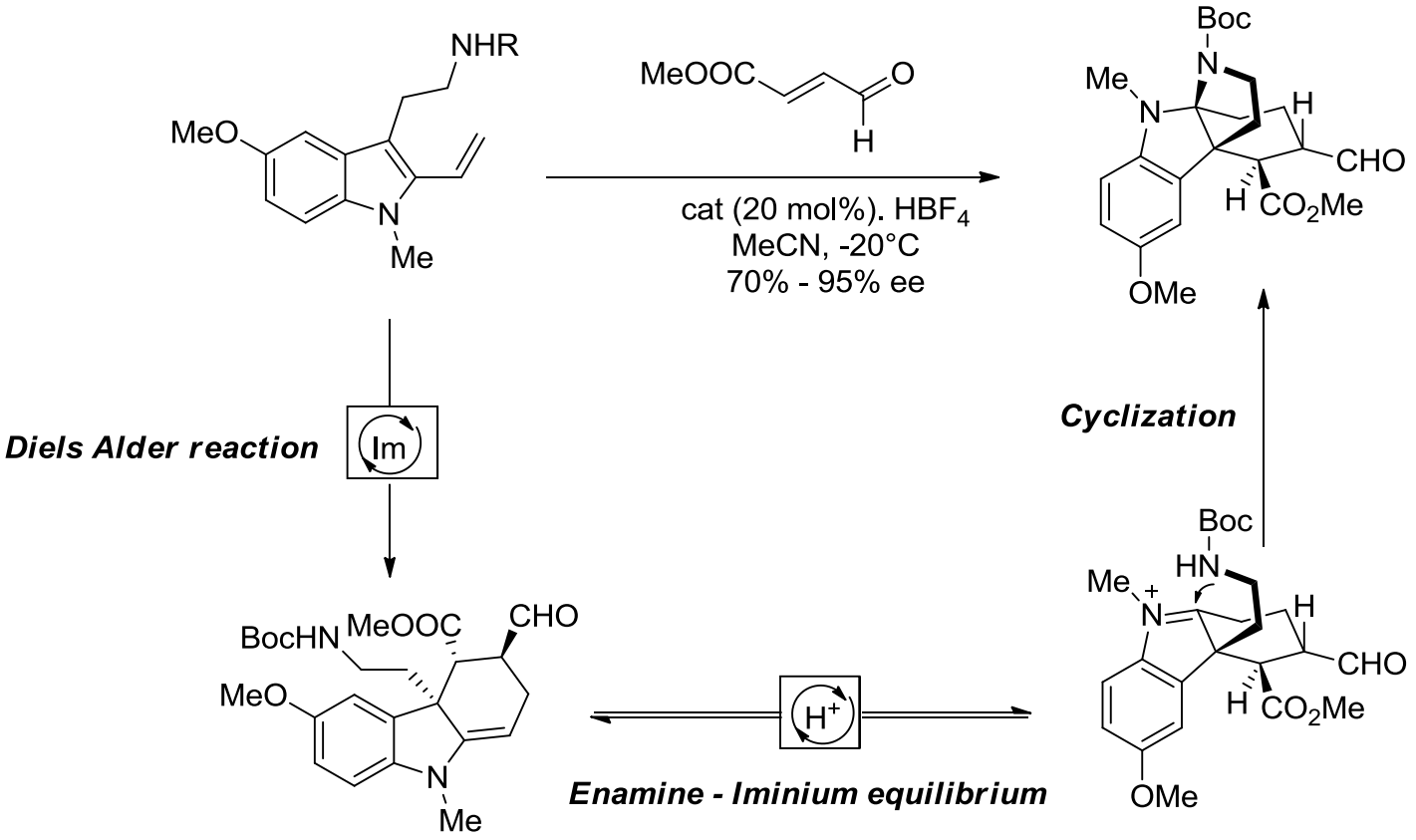
(TS–A) Proposed Asymmetric Diels–Alder Transition State





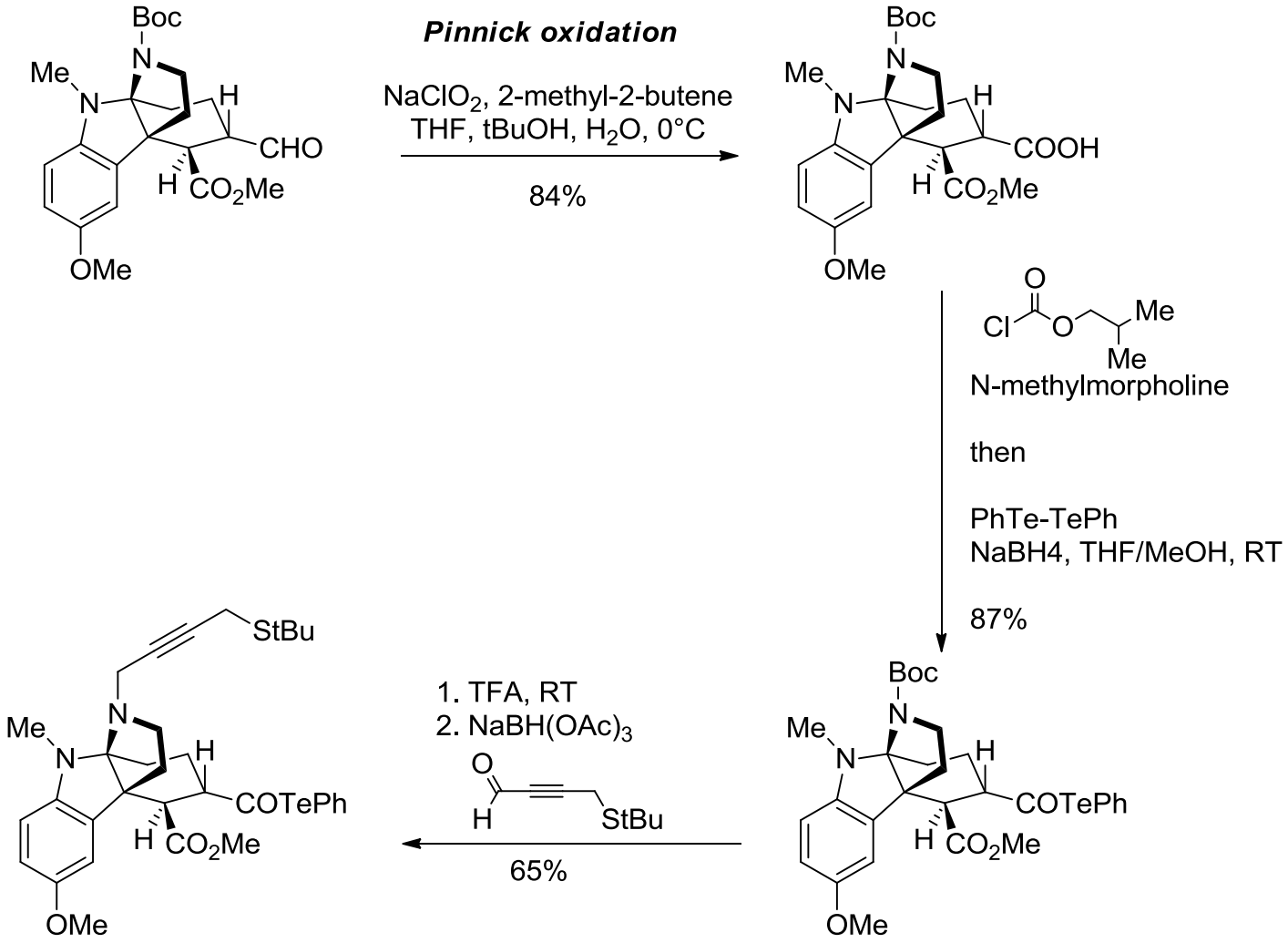
***endo*- and enantioselective iminium Diels–Alder**

The synthesis



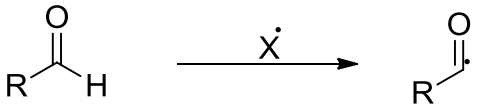
Generation of 1 quaternary center, 3 other centers, 2 cycles – 70% yield, 95% ee.

The synthesis



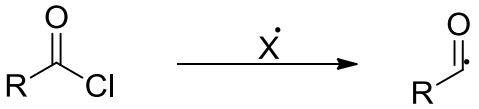
Acyl radicals precursors RCO-X

From aldehydes



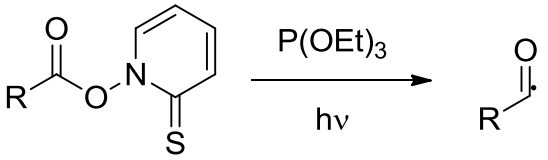
Poor chain transfer step.
Aldehyde needed in high concentrations.
Often not very efficient

From acyl chlorides



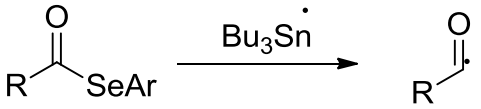
Many side products.
Parasit non radical reactions

From acids



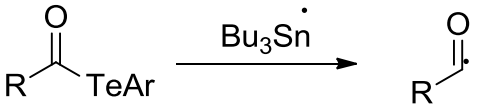
Via *O*-acyl thiohydroxamates

From acyl selenides



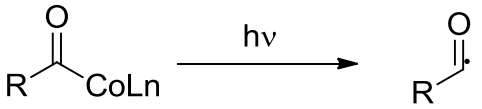
Most convenient method.
React readily but are quite stable.

From acyl tellurides



Analogous to selenides.

From acyl cobalt



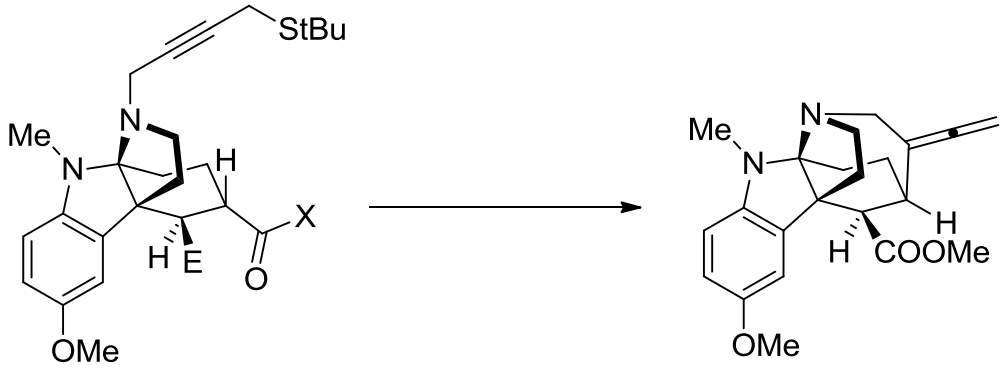
Possible reaction of acyl radical with ligand. Moderate to good yields.

From diverse thioesters: various methods but often lack of reactivity

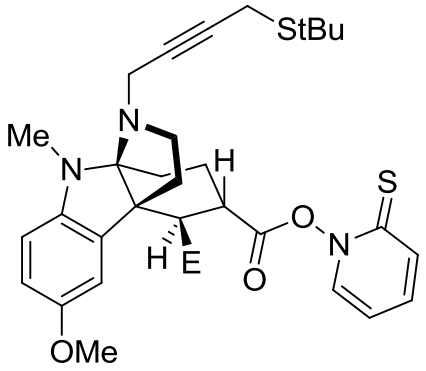
+ other less common methods

Chen, C.; Crich, D.; Papadatos, A . *J. Am. Chem. Soc.* **1992**, *114*, 8313-8314. Crich, D.; Chen, C.; Hwang, J-T.; Yuan, H.; Papadatos, A.; Walter, R. I. *J. Am. Chem. Soc.* **1994**, *116*, 8937-8951. Chatgilialoglu, C.; Drich, D.; Komatsu, M.; Ryu, I. *Chem. Rev.* **1999**, *99*, 1991-2070.

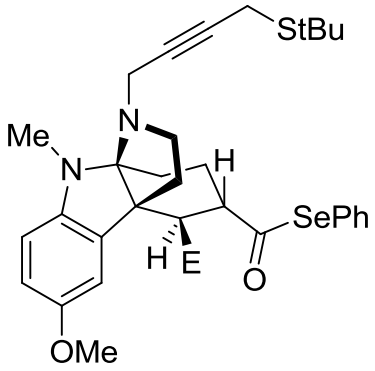
The synthesis



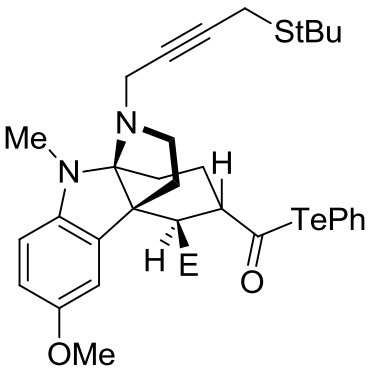
Formation of the 7-membered ring (complicated)



Barton ester
120°C : 18%
thiopyridyl byproduct by radical recombination

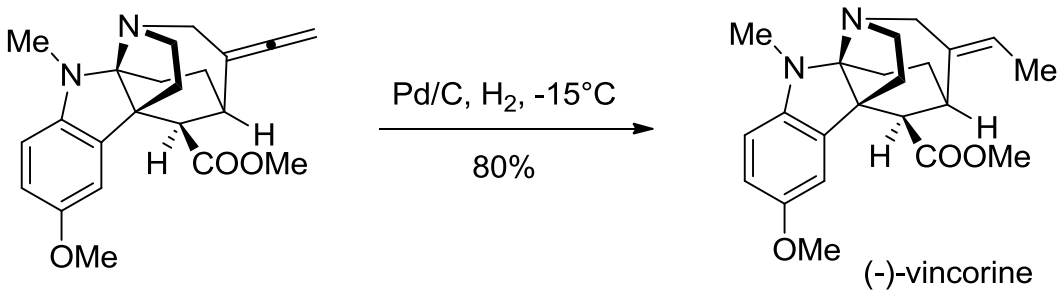


Acyl selenide
Bu_6Sn_2 - 120°C - $h\nu$: 17%
decomposition under reaction conditions



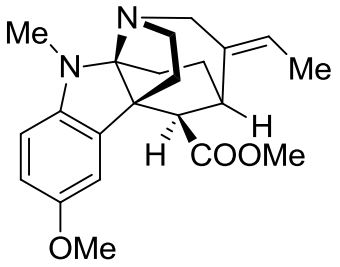
Acyl telluride
120°C : 8%
160°C : 31%
200°C : 51%

The synthesis



Conclusion

- Synthesis of (-)-vincorine in 9 steps and 9% yield.



Previous ones : Qian 31 steps, 1% overall yield

Ma 18 steps, 5% overall yield

- Key steps :
  - Organocatalytic Diels-Alder/amine cyclization cascade
  - 7-*exo*-dig radical cyclization using an acyl telluride

- Synthesis of analogs ongoing