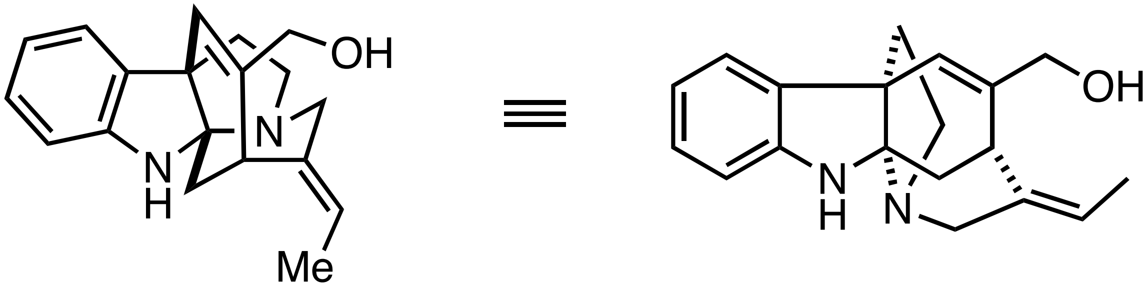
Nine-Step Enantioselective Total Synthesis of (+)-Minfiensine

Jones, S. B.; Simmons, B.; MacMillan, D. W. C.* *J. Am. Chem. Soc.* **2009**, ASAP. DOI: 10.1021/ja906472m



Kara George

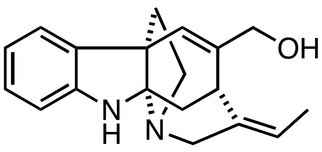
Wipf Group - Current Literature

September 12, 2009

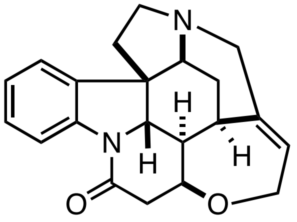
Strychnos Alkaloids

Biological Relevance: folk medicine, antimalarial, cytotoxic, antitumor

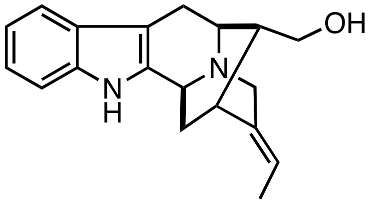
Synthetic Relevance: Excellent substrates for showcasing methodologies aimed at rapidly assembling polycyclic structures



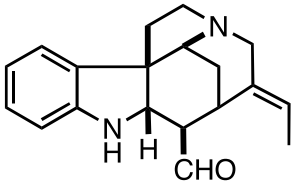
minfiensine



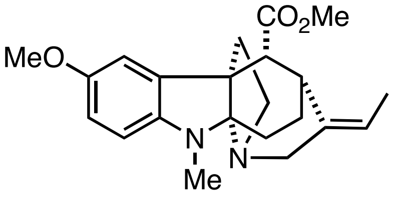
strychnine



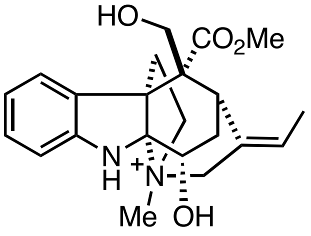
normacusine B



18-desoxy-Wieland-Gulmich aldehyde



vincorine



echitamine

Ramirez, A.; Garcia-Rubio, S. *Curr. Med. Chem.* **2003**, *10*, 1891.
Bonjoch, J.; Solé, D. *Chem. Rev.* **2000**, *100*, 3455.

History of Minfiensine

1989: Isolated from the African plant *Strychnos minfiensis* by Massiot and coworkers

2005: First total synthesis of (+)-minfiensine reported by Overman and coworkers

2008: Overman and coworkers publish a full paper including problems encountered in the 1st generation synthesis and a 2nd generation end play for the total synthesis of (+)-minfiensine

Qin and coworkers report a total synthesis of (±)-minfiensine

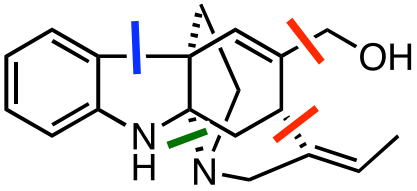
Padwa and coworkers report cycloaddition studies directed toward the tetracyclic core of minfiensine

2009: MacMillan and coworkers publish a nine-step total synthesis of (+)-minfiensine

Massiot, G.; Thépenier, P.; Jaquier, M.-J.; Le Men-Olivier, L.; Delaude, C. *Heterocycles* **1989**, *29*, 1435.
Dounay, A. B.; Overman, L. E.; Wrobleski, A. D. *J. Am. Chem. Soc.* **2005**, *127*, 10186.
Dounay, A. B.; Humphreys, P. G.; Overman, L. E.; Wrobleski, A. D. *J. Am. Chem. Soc.* **2008**, *130*, 5368.
Shen, L.; Zhang, M.; Wu, Y.; Qin, Y. *Angew. Chem. Int. Ed.* **2008**, *47*, 3618.
Bobeck, D. R.; France, S.; Leverett, C. A.; Sánchez-Cantalejo, F.; Padwa, A. *Tet. Lett.* **2009**, *50*, 3145.

Overman’s Approach to (+)-Minfiensine

1st Generation:



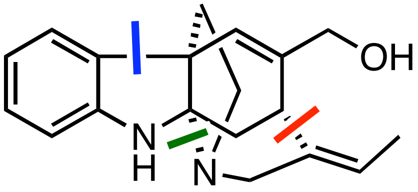
Catalytic Assymetric Heck

**Heck Cyclization-
Carbonylation Sequence**

Iminium Ion Cyclization

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

2nd Generation:



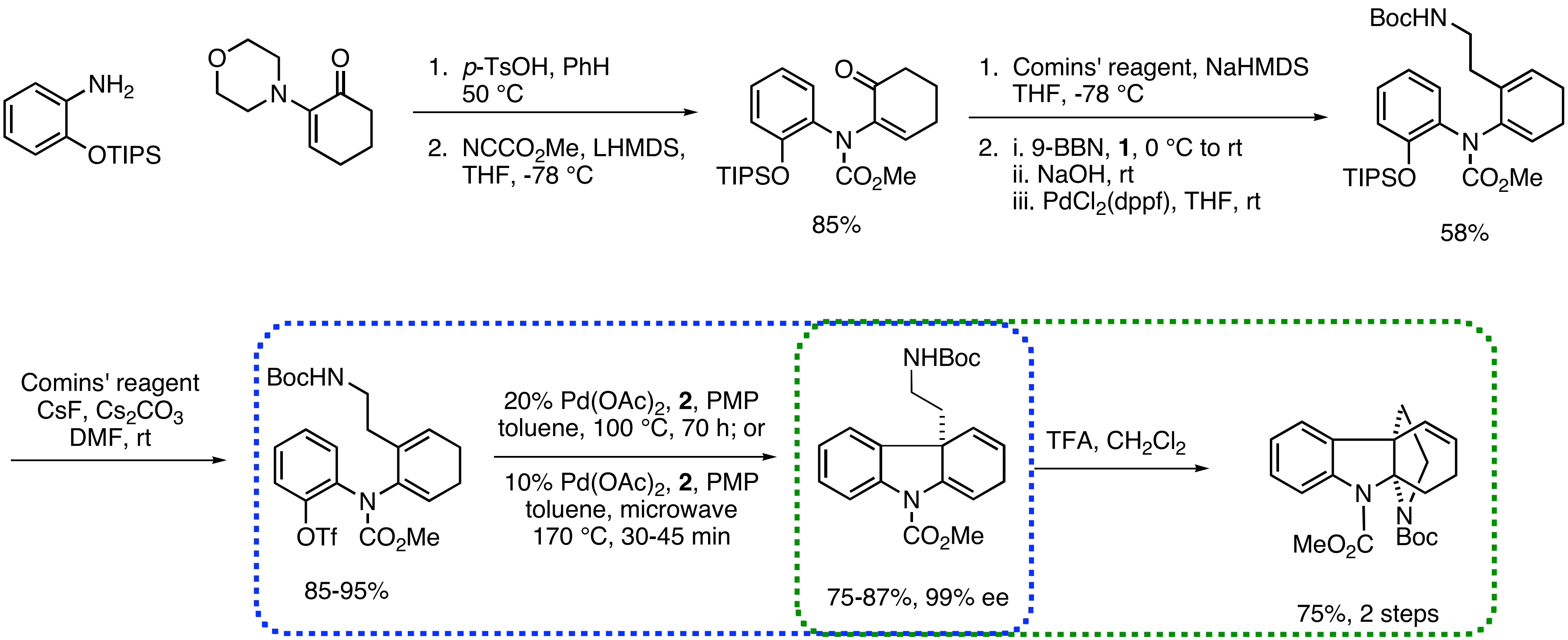
Catalytic Assymetric Heck

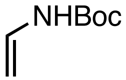
**Pd-catalyzed intramolecular
enolate/vinyl iodide coupling**

Iminium Ion Cyclization

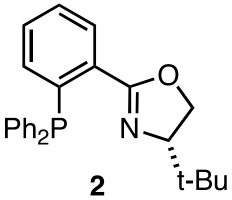
Dounay, A. B.; Humphreys, P. G.; Overman, L. E.; Wrobleski, A. D. *J. Am. Chem. Soc*. 2008, 130, 5368.

Overmann's Route to the Carbazole Core





1

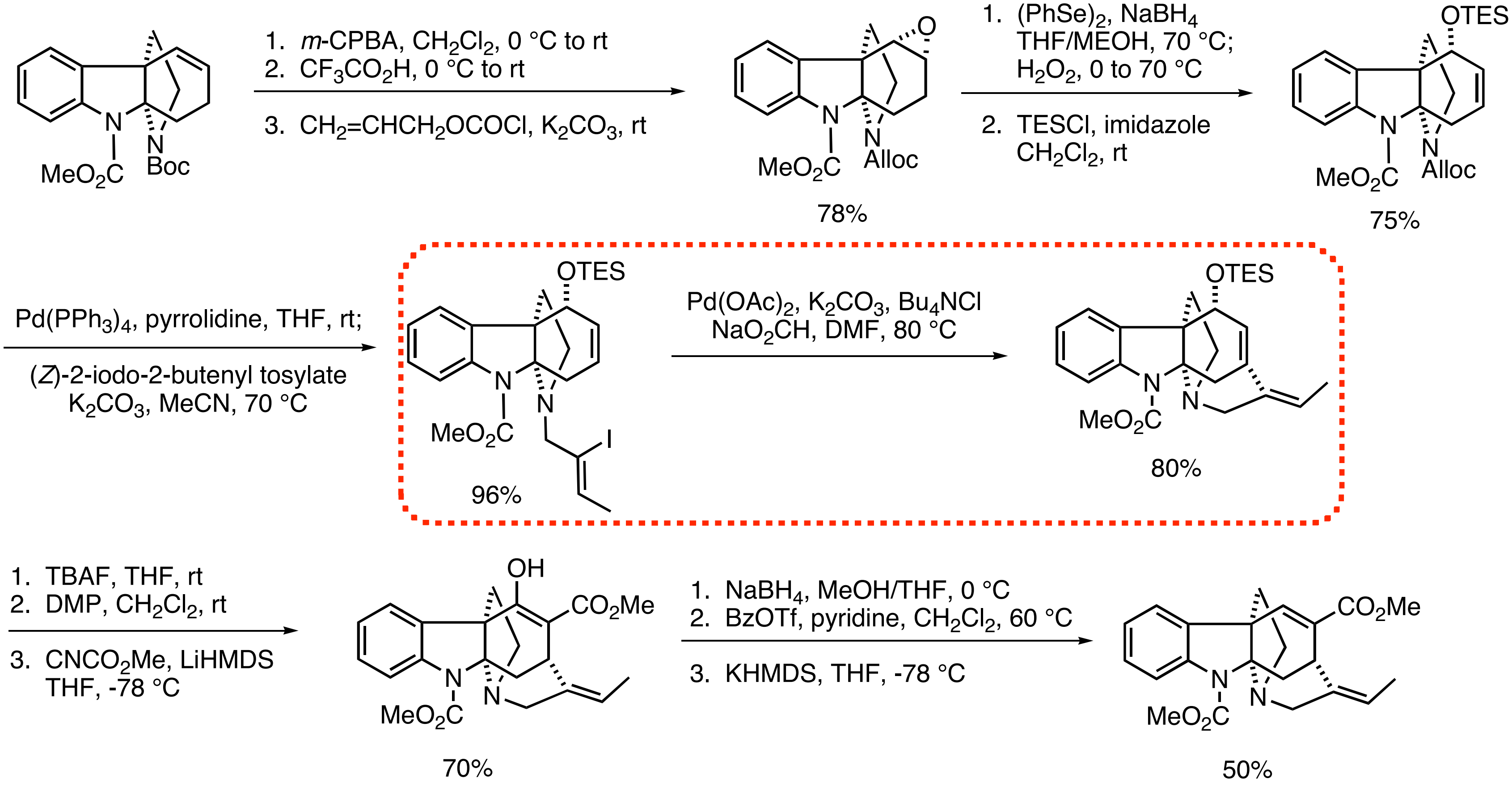


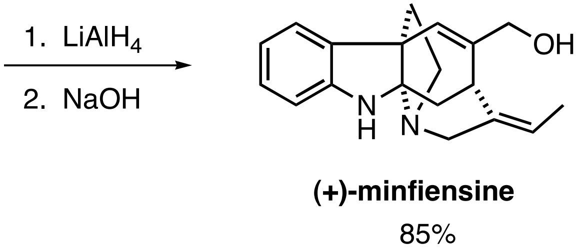
2

Features:

- Catalytic asymmetric Heck-iminium ion cyclization sequence provides access to the carbazole framework in an enantioselective fashion

Overman's 1st Generation End Play

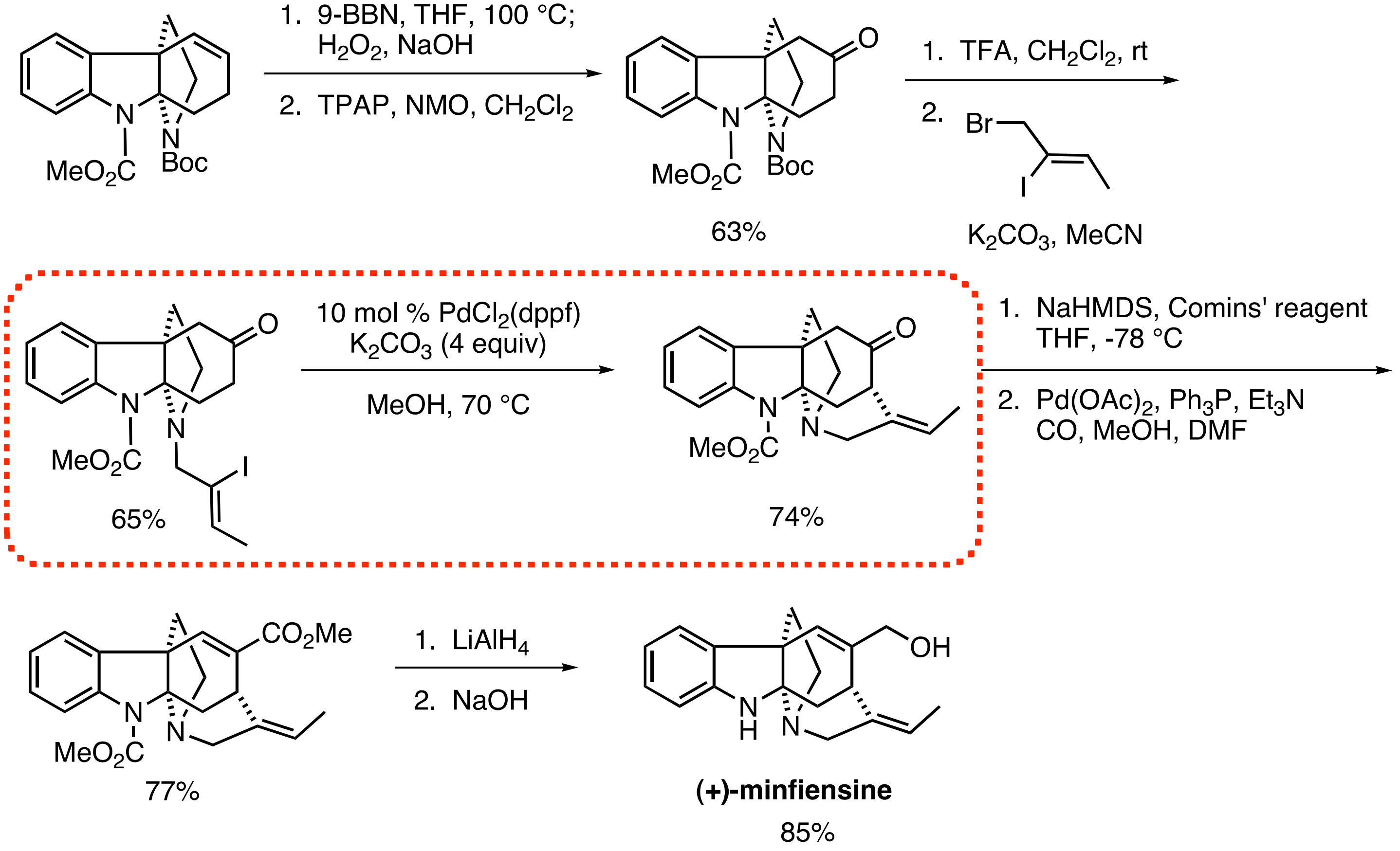




Features:

- Heck cyclization-carbonylation sequence to generate the fifth ring of (+)-minfiensine
- 13.4% yield and 16 steps from cat. asymmetric Heck
- 4.1% overall yield and 22 total steps

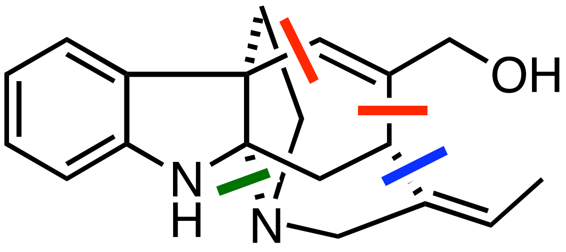
Overman’s 2nd Generation End Play



Features:

- Intramolecular Pd-catalyzed ketone enolate vinyl iodide coupling to construct the final ring of (+)-minfiensine
- 19.7% yield and 9 steps from cat. asymmetric Heck
- 6.5% overall yield and 15 total steps

Macmillan’s Approach to (+)-Minfiensine



Organocatalytic Diels-Alder Cyclization

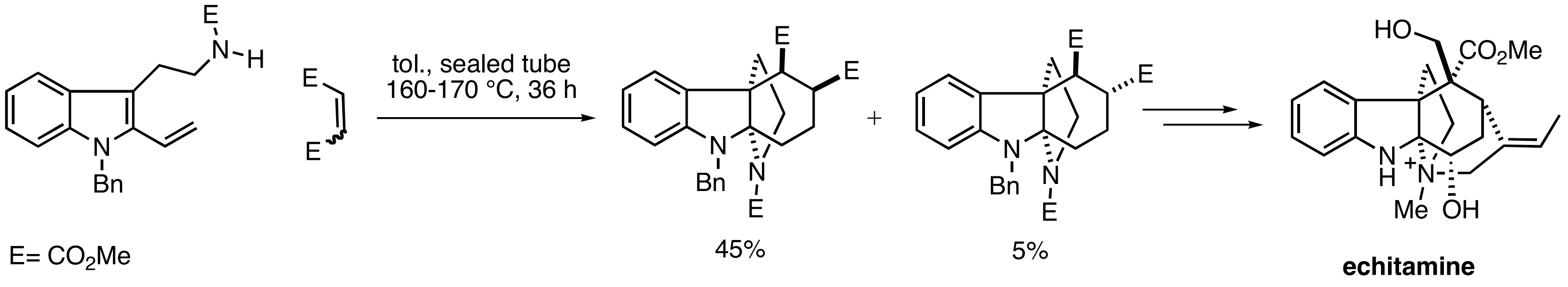
Radical Cyclization

Amine Cyclization

Jones, S. B.; Simmons, B.; MacMillan, D. W. C.* *J. Am. Chem. Soc.* **2009**, ASAP. DOI: 10.1021/ja906472m

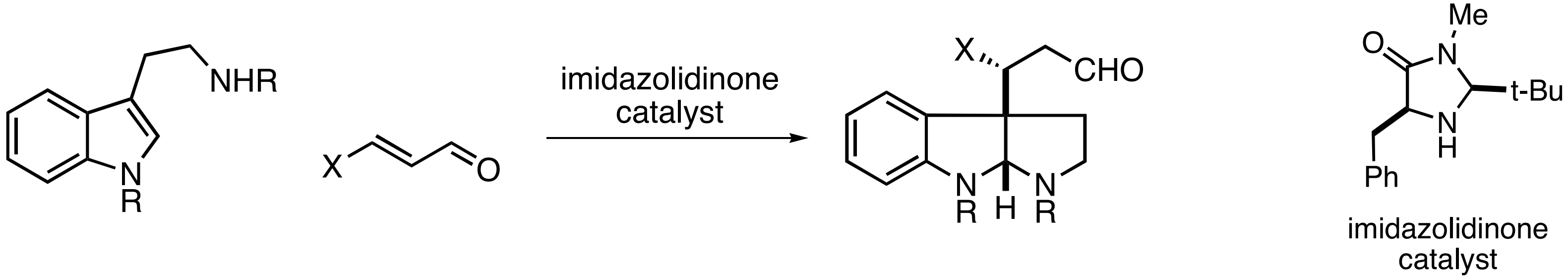
Precedence for Cyclization Cascade Sequence

Diels-Alder/amine cyclization sequence to access the echitamine ring system



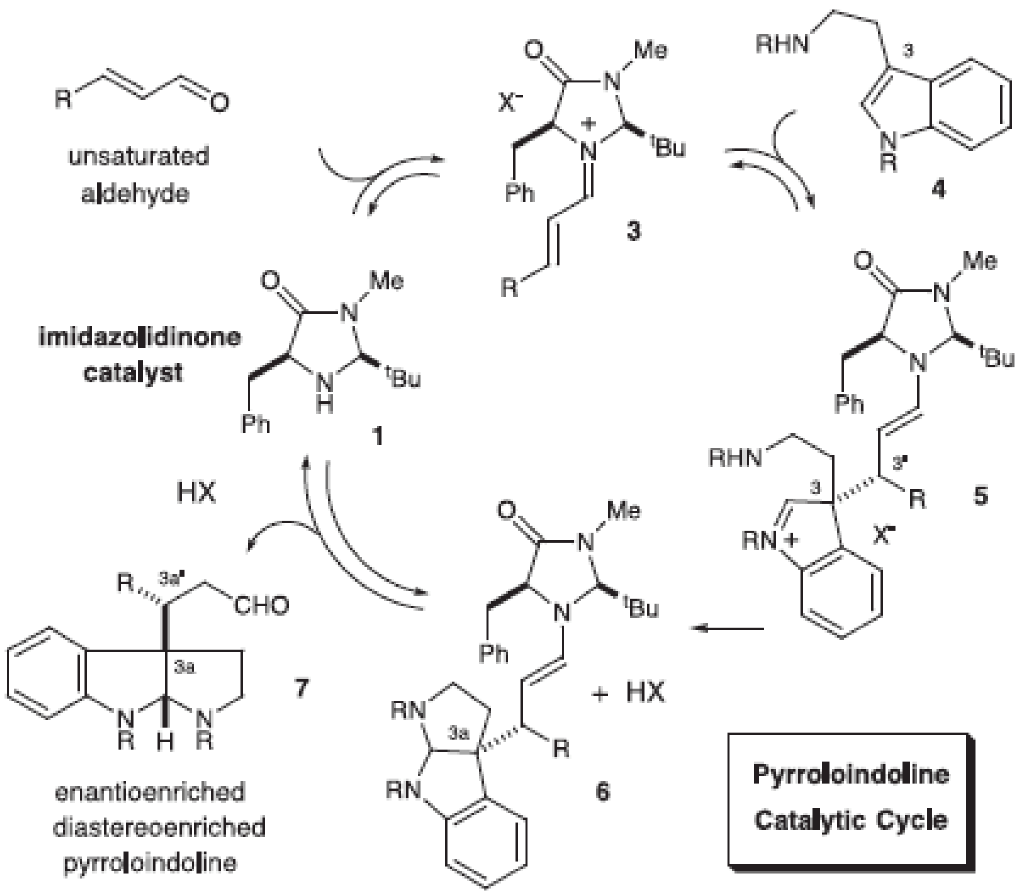
Lévy, J.; Sapi, J.; Laronze, J. Y.; Royer, D.; Toupet, L. *Synlett* **1992**, 601.

Enatioselective organocatalytic construction of pyrroloindolines



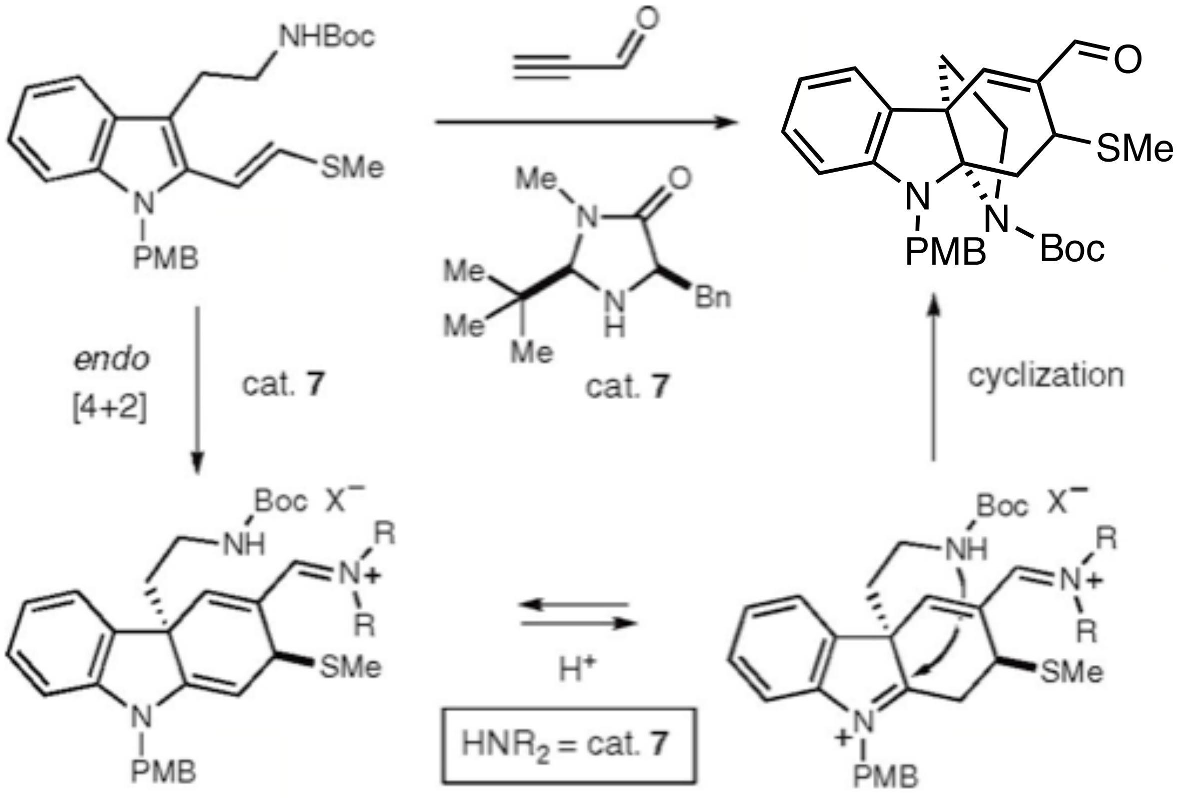
Austin, J. F.; Kim, S.-G.; Sinz, C. S.; Xiao, W.-J.; MacMillan, D. W. C. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, 101, 5482.

Enatioselective Organocatalytic Construction of Pyrroloindolines: Catalytic Cycle

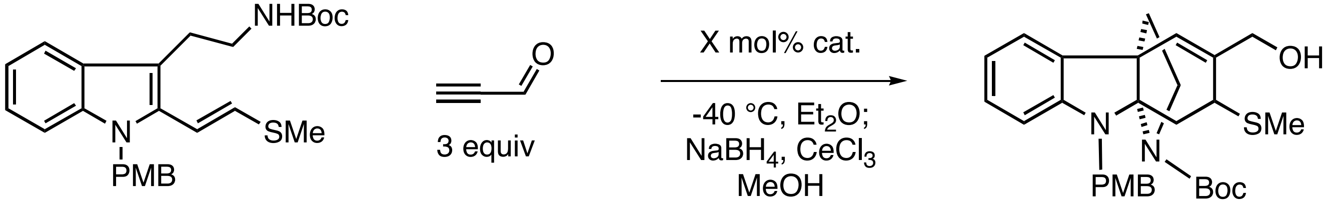


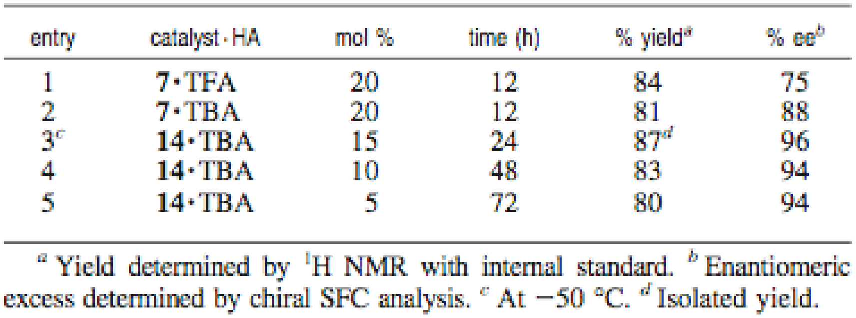
Austin, J. F.; Kim, S.-G.; Sinz, C. S.; Xiao, W.-J.; MacMillan, D. W. C. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, 101, 5482.

Enantioselective Catalytic Cascade Sequence to Access the Tetracyclic Carbazole Framework of (+)-Minfiensine



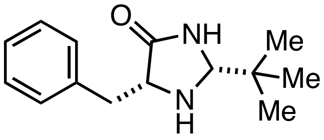
Organocatalytic Diels-Alder Cyclization Cascade Studies



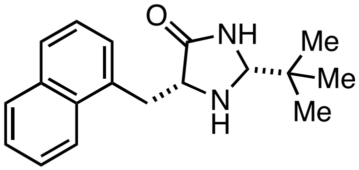


entry	catalyst·HA	mol %	time (h)	% yield[a]	% ee[b]
1	**7**·TFA	20	12	84	75
2	**7**·TBA	20	12	81	88
3[c]	**14**·TBA	15	24	87[d]	96
4	**14**·TBA	10	48	83	94
5	**14**·TBA	5	72	80	94

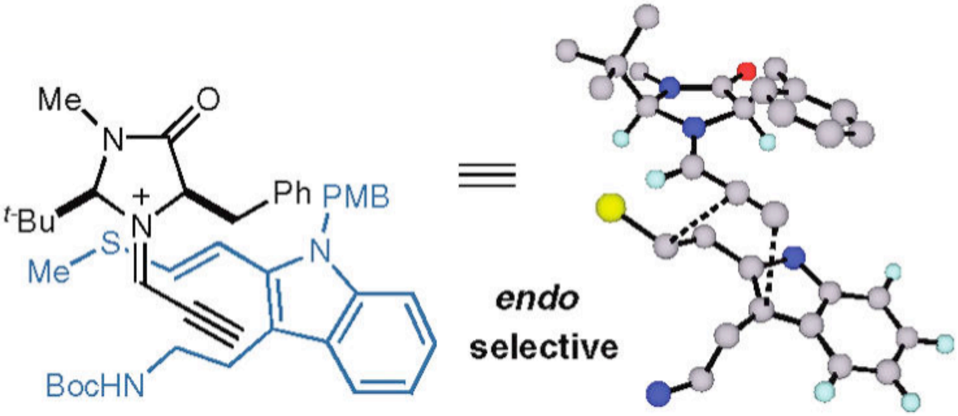
[a] Yield determined by ^{1}H NMR with internal standard. [b] Enantiomeric excess determined by chiral SFC analysis. [c] At −50 °C. [d] Isolated yield.



catalyst 7

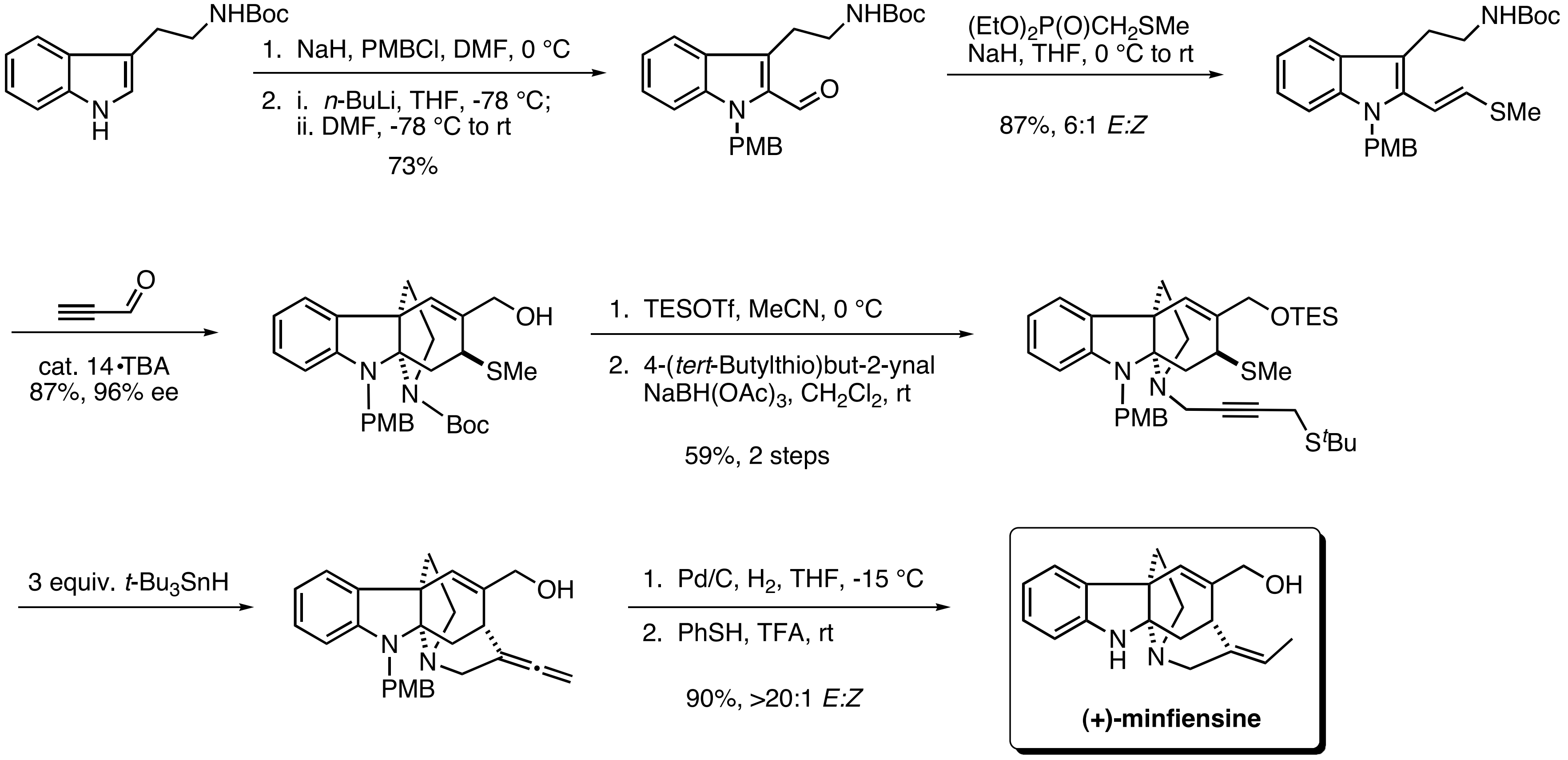


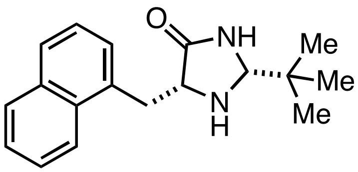
catalyst 14



endo **selective**

Nine-Step Total Synthesis of (+)-Minfiensine





catalyst 14

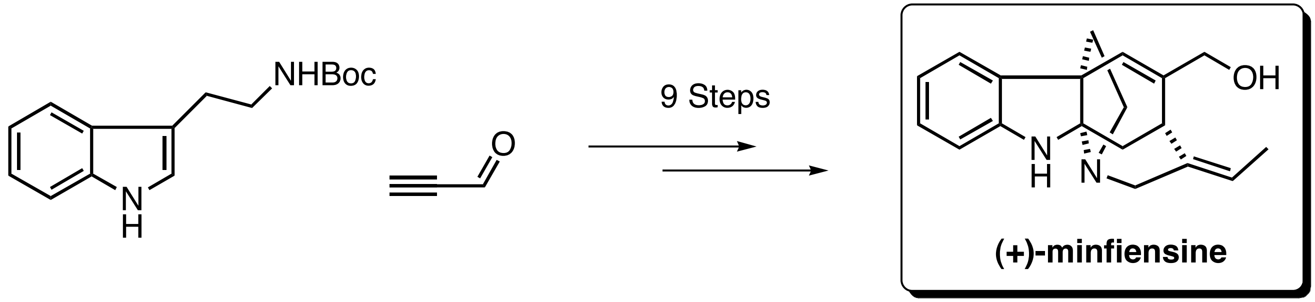
Conclusions and Future Directions

- MacMillan and coworkers were able to synthesize (+)-minfiensine in only 9 steps and 21% overall yield from commercial materials
    - 53% yield and 5 steps from the tetracyclic intermediate

- Access to the tetracyclic carbazole framework was achieved rapidly and enantioselectively by a new organocatalytic Diels-Alder/amine cyclization sequence

- The final ring system of (+)-minfiensine was accomplished via a 6-exo-dig radical cyclization

- Application of this methodology could be utilized to access the tetracyclic carbazole moiety of related alkaloids



(+)-minfiensine