

**Enantioselective Total Syntheses of Akuammiline Alkaloids
(+)-Strictamine, (-)-2(S)-Cathafoline, and (-)-Aspidophylline A**

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Garg, N. K. *et al.*
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Introduction

Short Biography

Professor Garg received his B.S. degree in 2000 from New York University, and his PhD in 2005 from the California Institute of Technology. After training as an NIH postdoctoral scholar at the University of California, Irvine, he joined the faculty at UCLA in 2007. In 2012, he was appointed as Vice Chair for Education. In 2013, Professor Garg was promoted to full Professor.

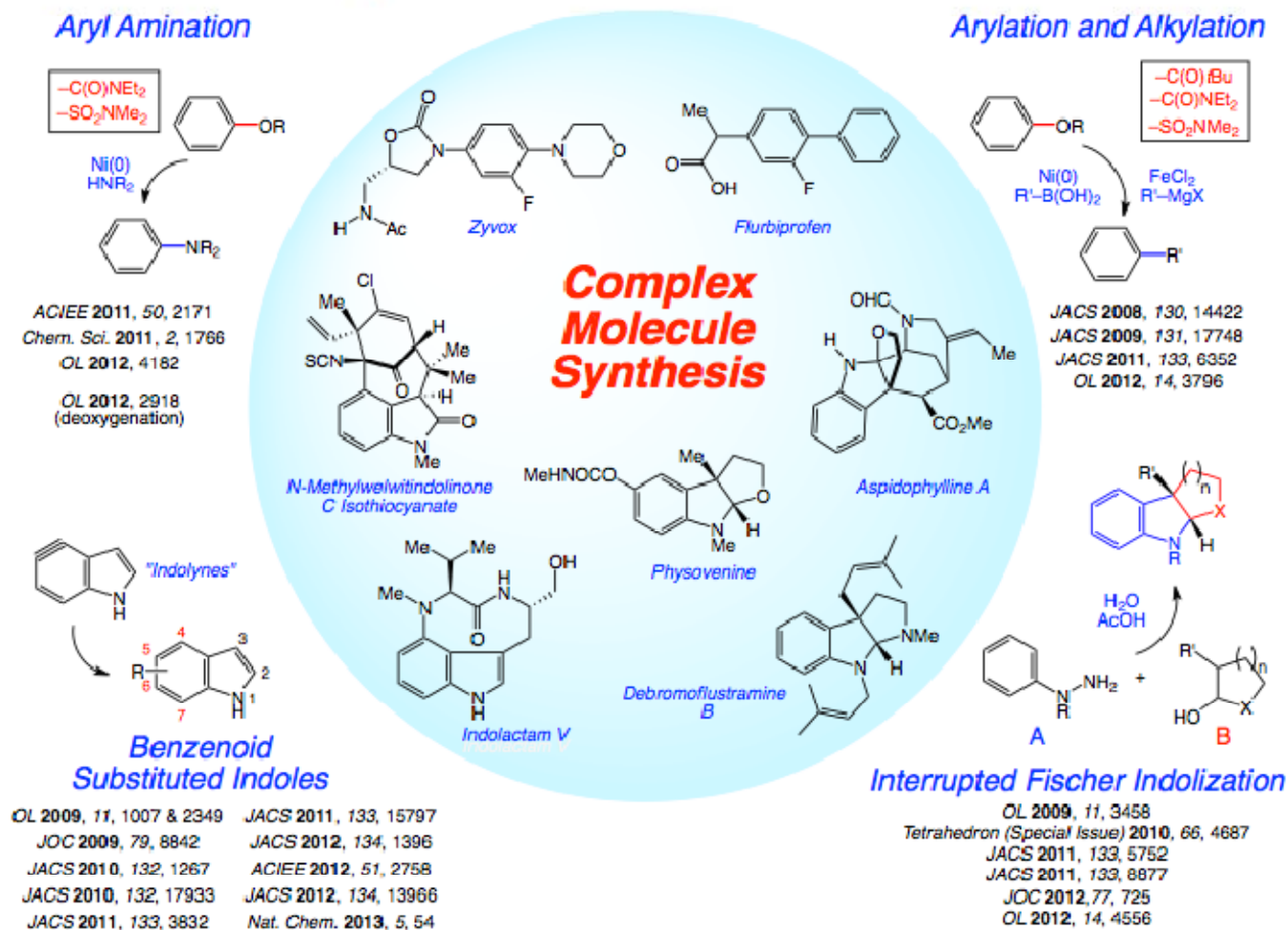


Garg, N. K.
University of California
Los Angeles

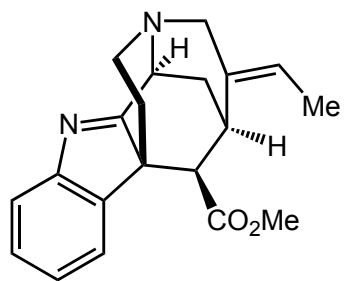
Introduction

Research Interest

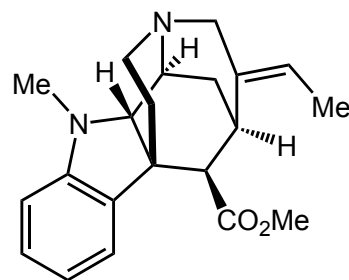
Garg Lab Research – UCLA – 2013



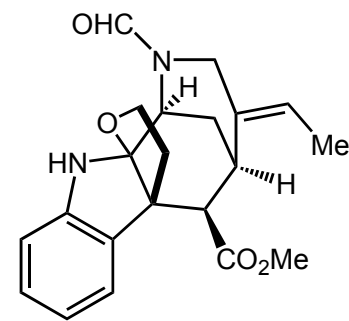
Introduction



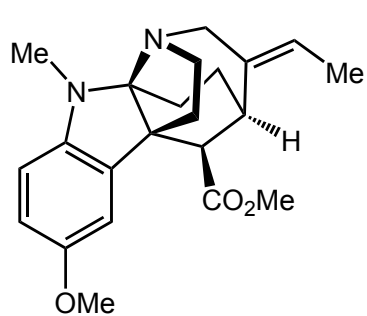
(+)-Strictamine (1)



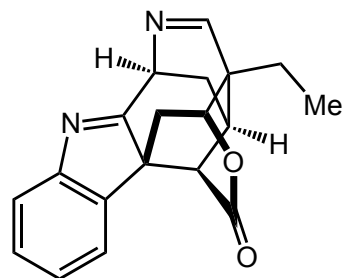
(-)-2(S)-Cathafoline (2)



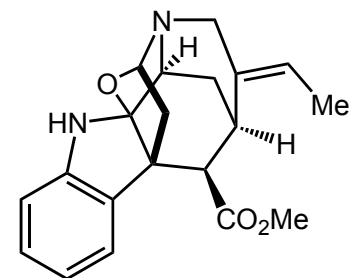
(-)-Aspidophylline A (3)



(-)-Vincorine (4)

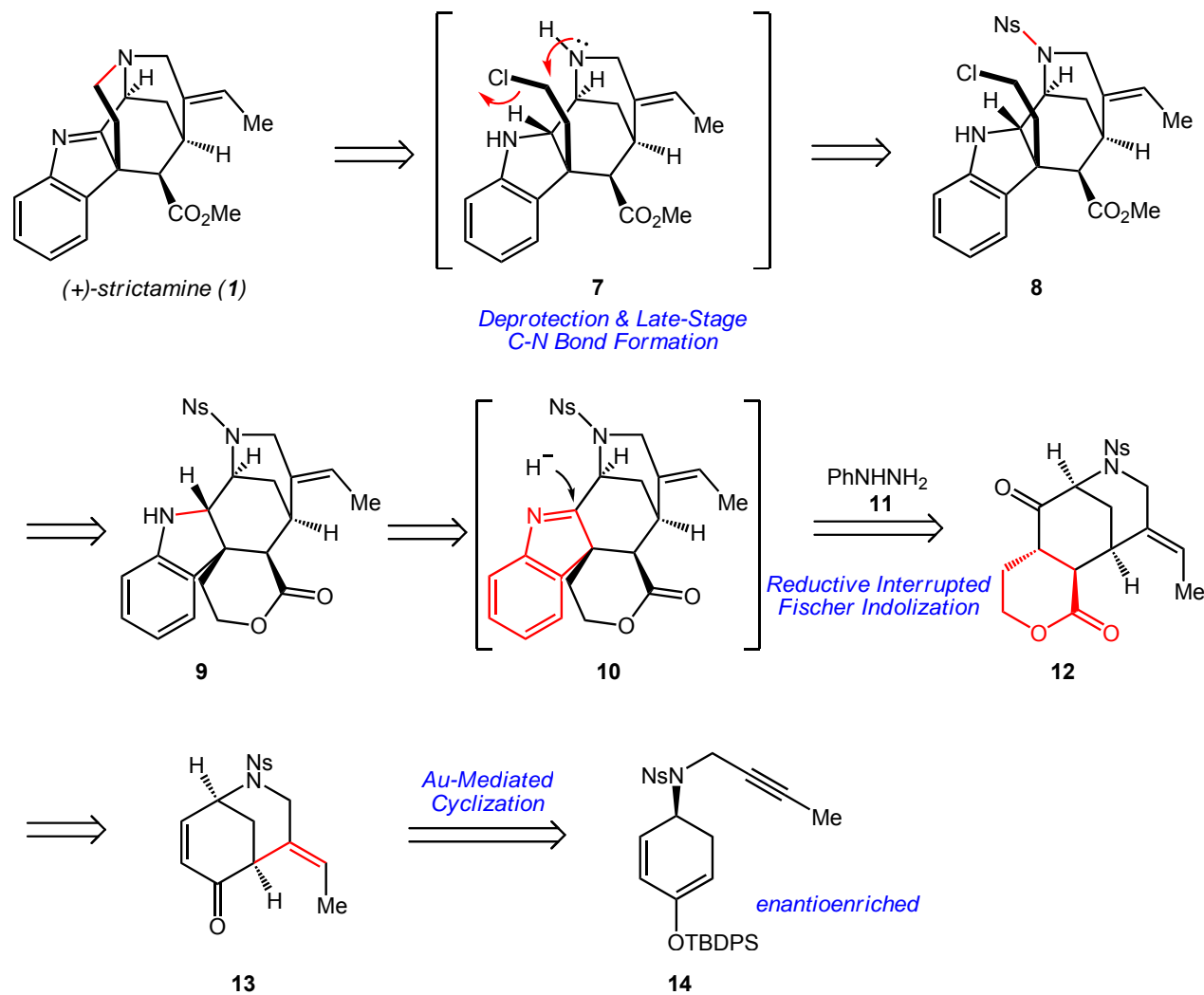


(+)-Scholarisine A (5)

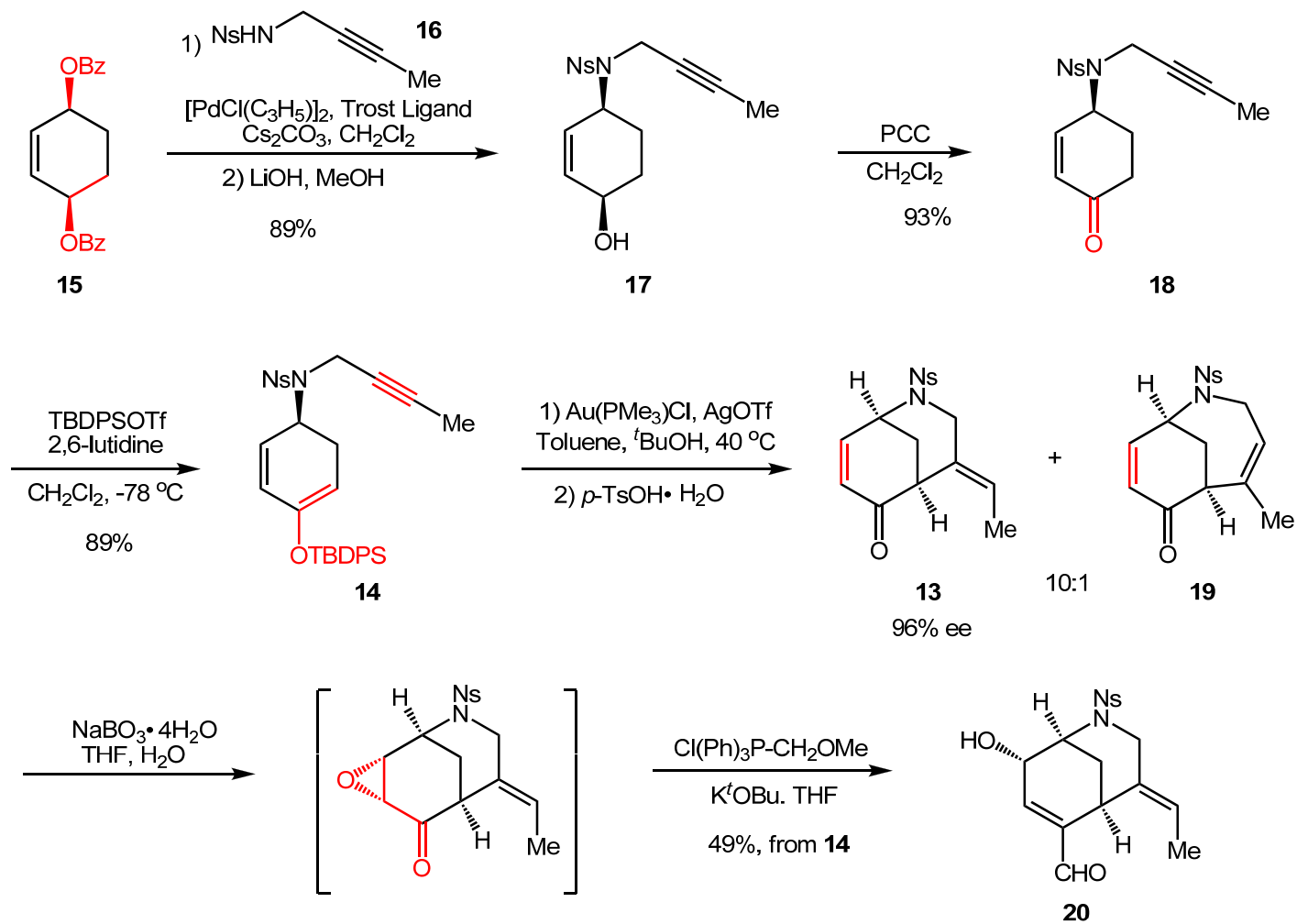


(-)-Picrinine (6)

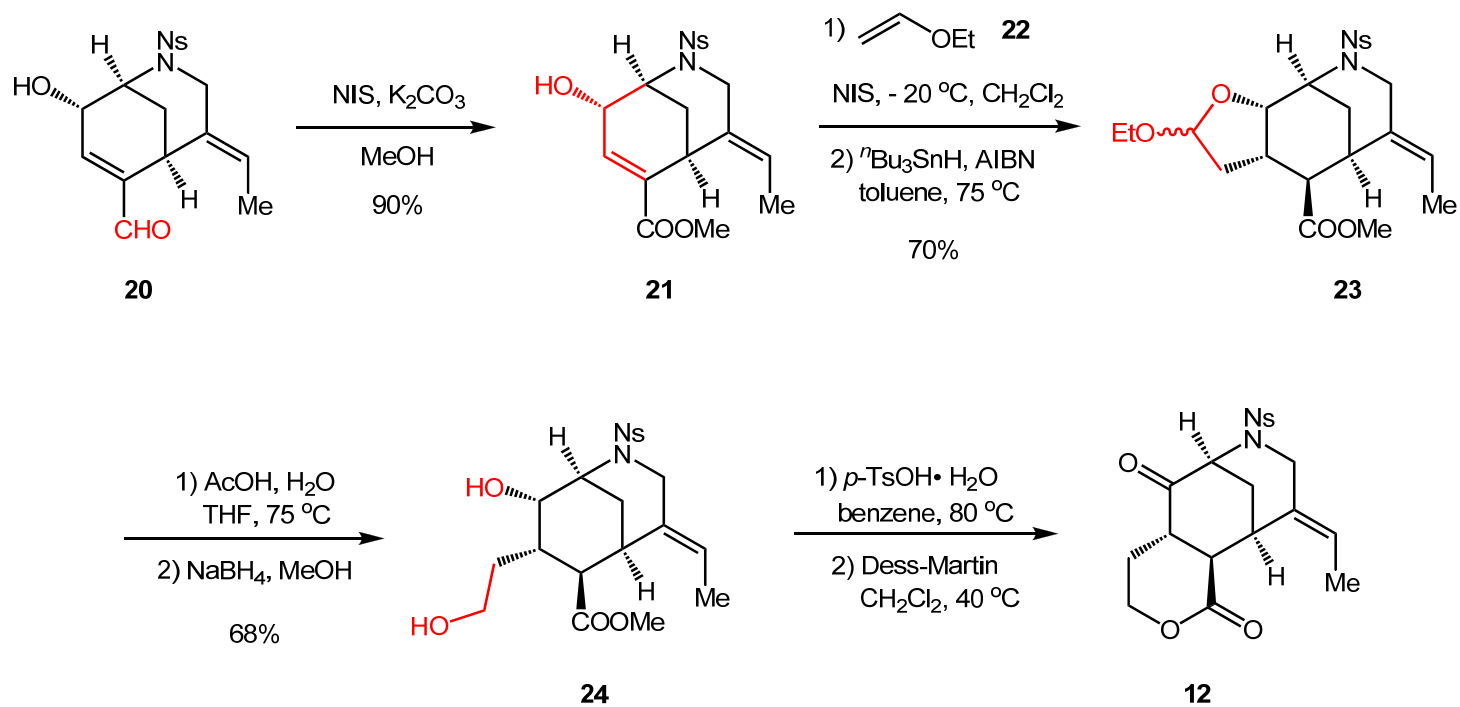
Retrosynthesis of (+)-Strictamine



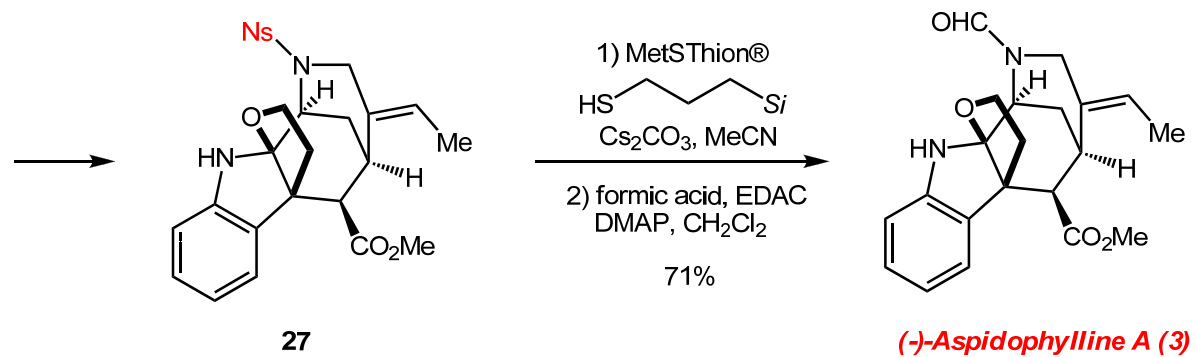
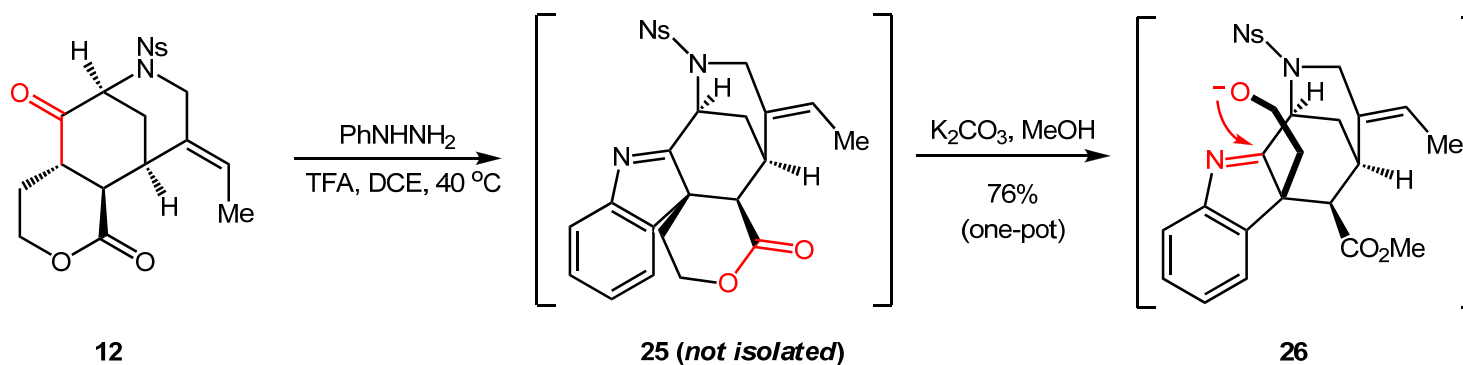
Enantioselective Total Synthesis of (-)-Aspidophylline A



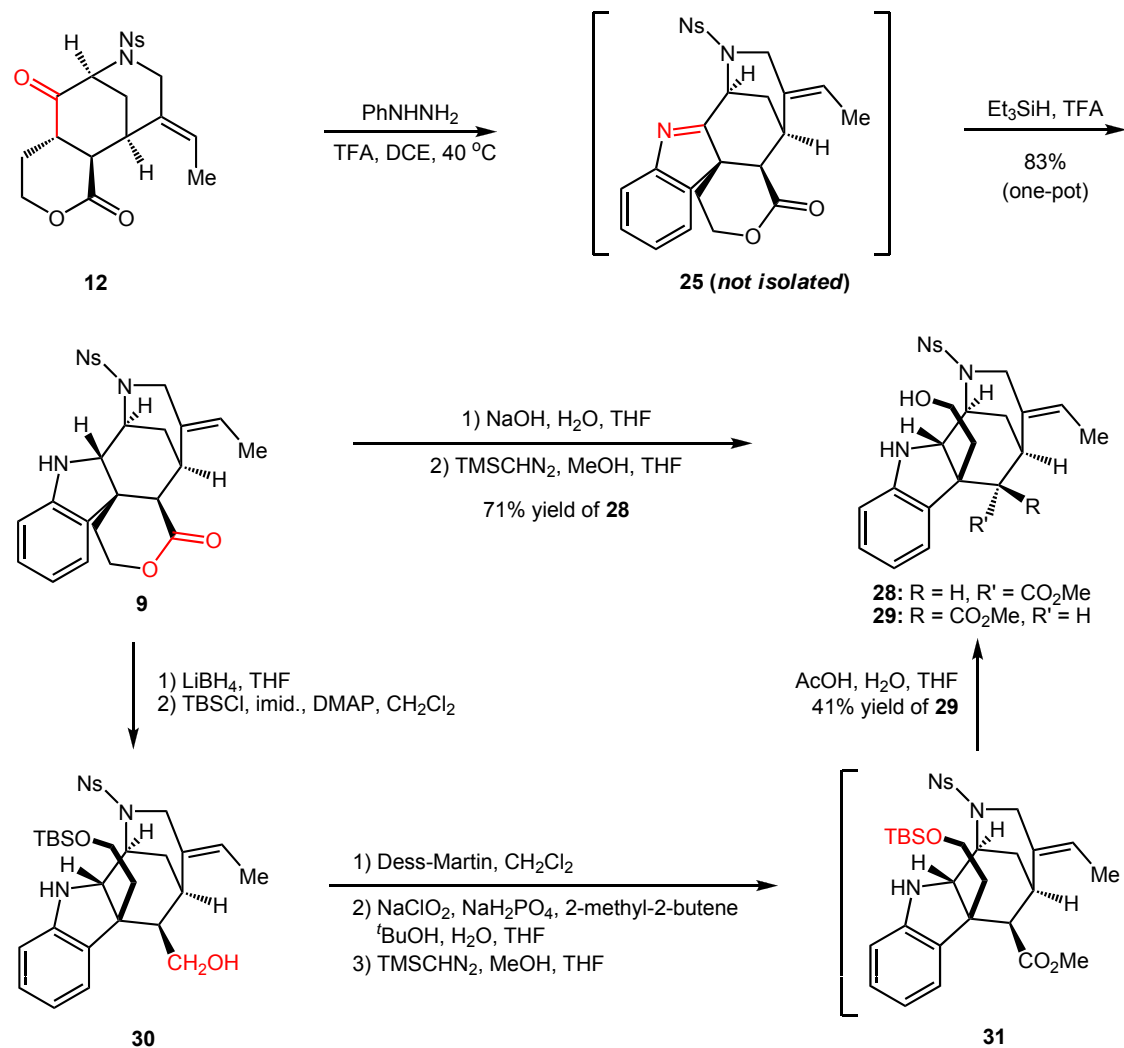
Enantioselective Total Synthesis of (-)-Aspidophylline A



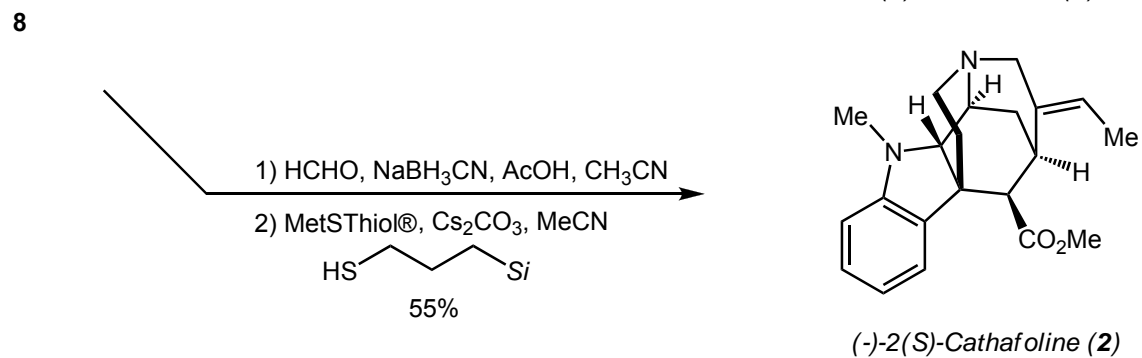
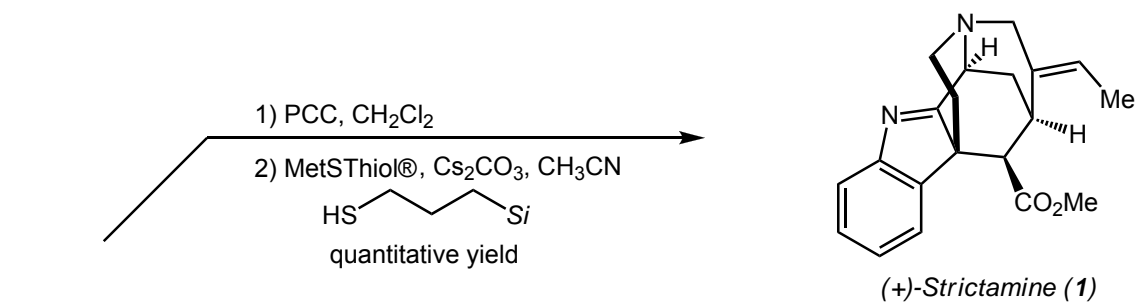
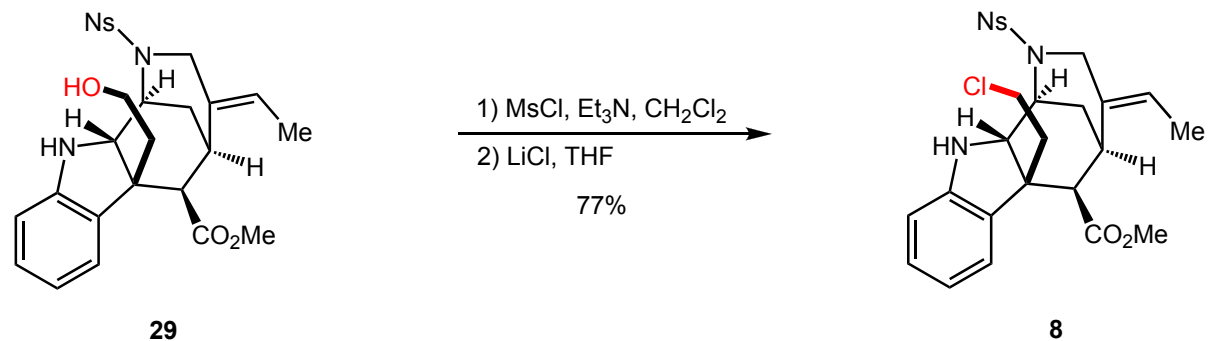
Enantioselective Total Synthesis of (-)-Aspidophylline A



Enantioselective Total Synthesis of (+)-Strictamine, (-)-2(S)-Cathafoline



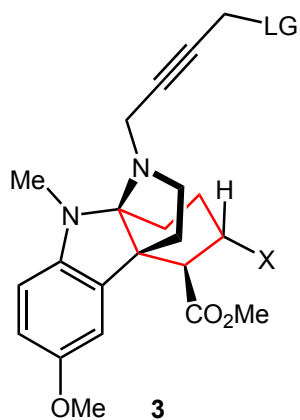
Enantioselective Total Synthesis of (+)-Strictamine, (-)-2(S)-Cathafoline



Retrosynthesis of (-)-Vincorine

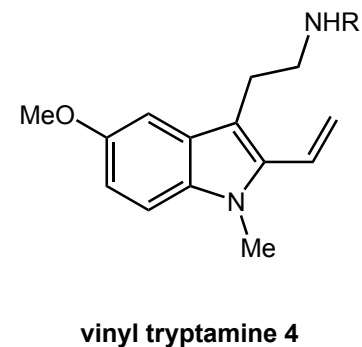


radical
cyclization



Im H^+

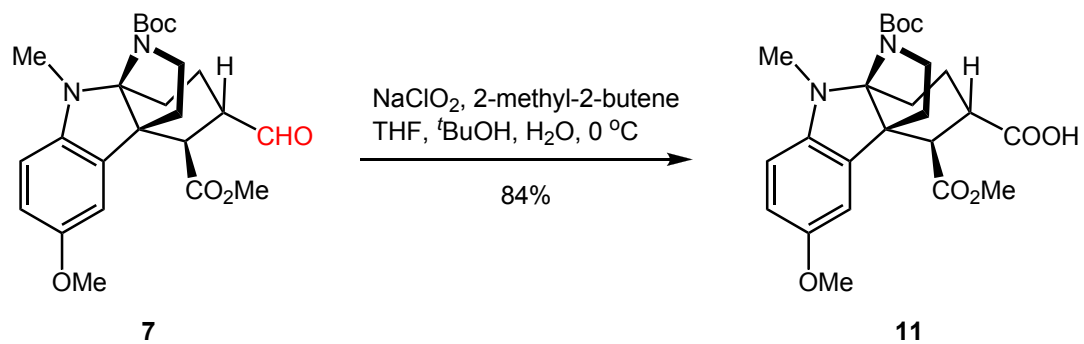
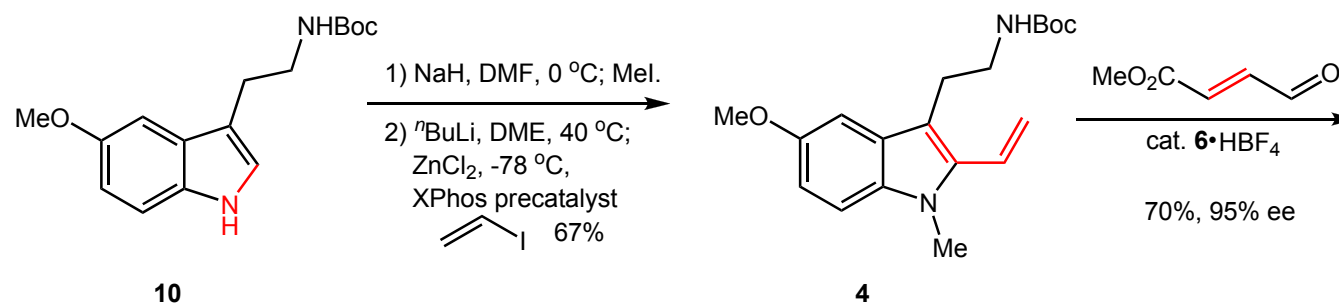
Diels-Alder
iminium cyclization
cascade



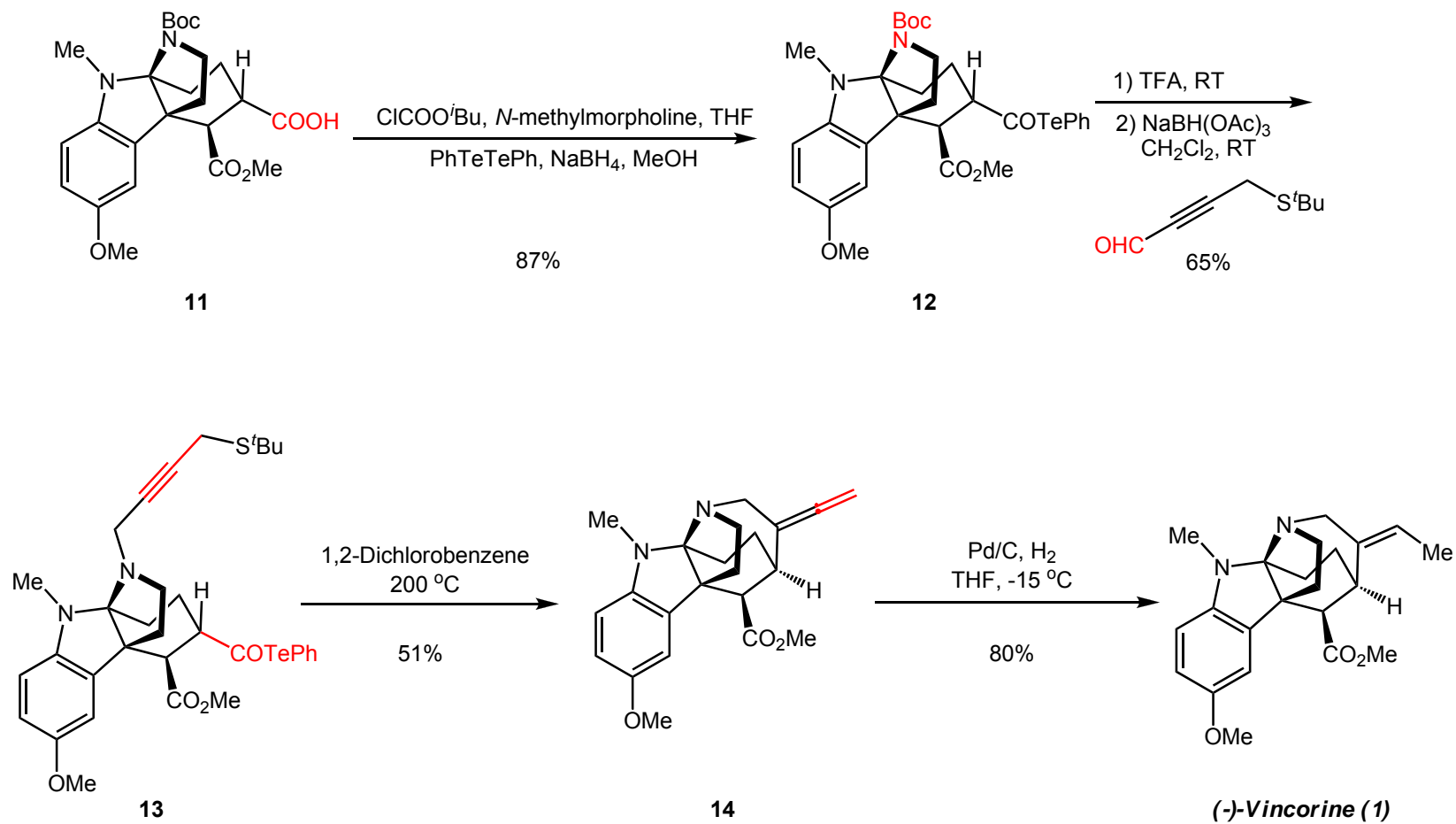
Synthetic Challenges

- 1) pentacyclic caged structure
- 2) strained 7-membered ring
- 3) enantioselective catalysis

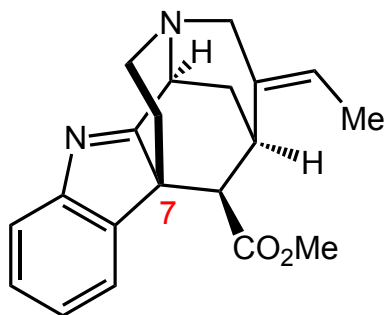
Enantioselective Total Synthesis of (-)-Vincorine



Enantioselective Total Synthesis of (-)-Vincorine



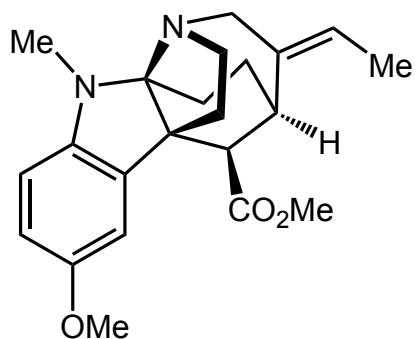
Summary



(+)-Strictamine

- 1) [3.3.1]-azabicyclic core:
gold-mediated cyclization
- 2) introduction of the key C7 quaternary stereocenter:
reductive interrupted Fischer indolization reaction
- 3) 27 steps and 0.9% overall yield

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(-)-Vincorine

- 1) tetracyclic alkaloid core:
stereoselective organocatalytic Diels-Alder,
iminium cyclization cascade sequence
- 2) seven-membered azepanyl ring system:
single electron-mediated cyclization
- 3) 9 steps and 9% overall yield

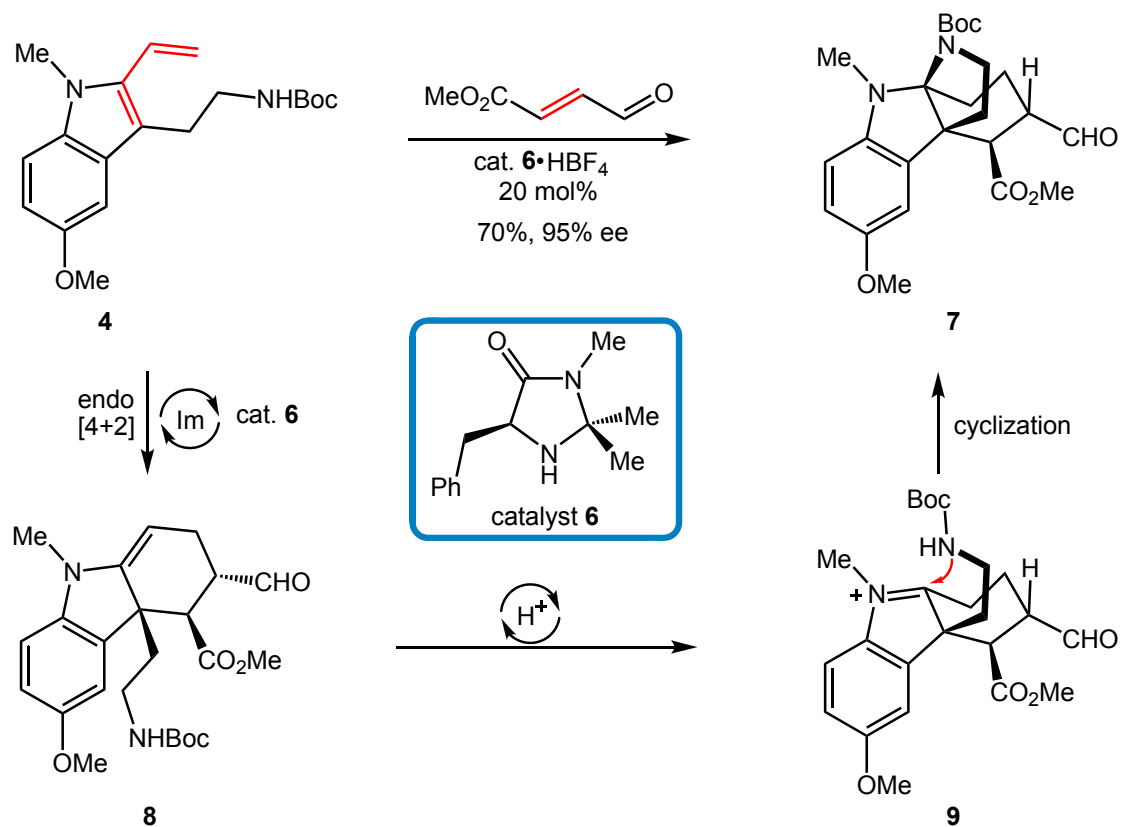
MacMillan, D. W. C. *et al. J. Am. Chem. Soc.* **2013**, 135, 6442.

The akuammiline alkaloids are a family of bioactive natural products that have been studied for over a century. To date, over 30 akuammilines have been isolated, examples of which are shown in Figure 1 (1–6). These natural products can be divided into four structural subclasses, with completed total syntheses recently reported in three of these categories. Aspidophylline A (3), an example of the furoindoline-containing subclass, has been accessed synthetically by our group and the laboratories of Zhu and Ma. In addition, our laboratory has completed the total synthesis of picrinine (6), a C5-oxidized akuammiline. With regard to the skeletally rearranged akuammilines, breakthroughs include total syntheses of vincorine (4) by Qin, Ma, and MacMillan, and total syntheses of scholarisine A (5) by Smith and Snyder.

In summary, we have completed the first total syntheses of two akuammiline natural products that possess a methanoquinolizidine core. Our asymmetric approach to **1** and **2** features a gold-mediated cyclization to assemble the [3.3.1]-azabicyclic core of the natural products, a reductive interrupted Fischer indolization reaction to introduce the key C7 quaternary stereocenter and access late-stage compounds, and a series of carefully executed late-stage transformations to complete the total syntheses. Moreover, we have also completed the first enantioselective total synthesis of aspidophylline A (**3**). These studies constitute new achievements in the popular area of akuammiline alkaloid synthesis, and provide many lessons that should impact future endeavors in the synthesis of complex molecules.

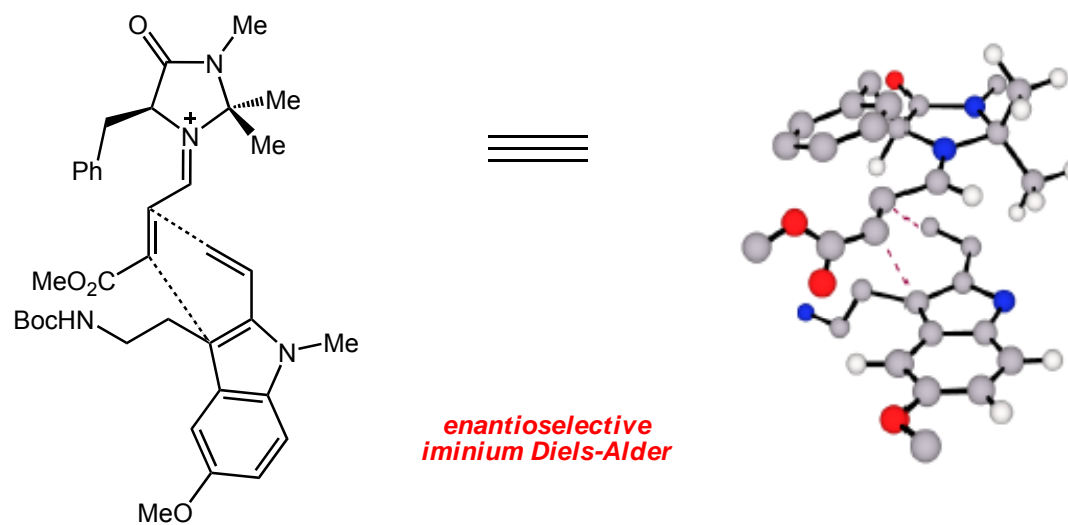
Enantioselective Total Synthesis of (-)-Vincorine

Enantioselective Organocatalytic Cascade Sequence



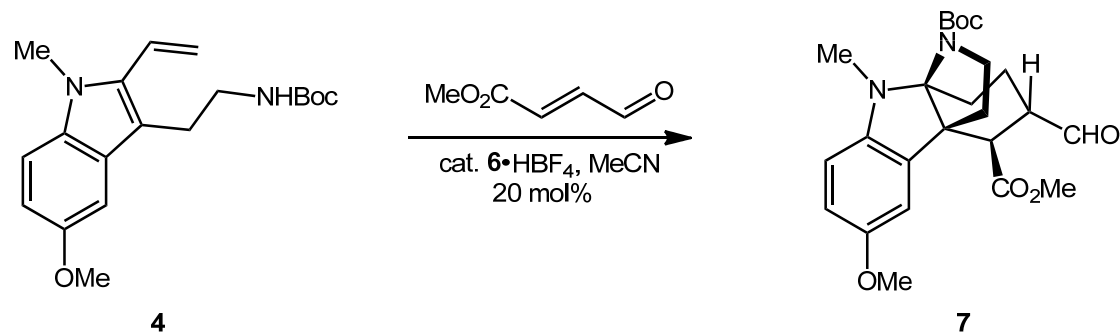
Enantioselective Total Synthesis of (-)-Vincorine

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



Enantioselective Total Synthesis of (-)-Vincorine

Organocatalytic Diels-Alder/Cyclization Cascade



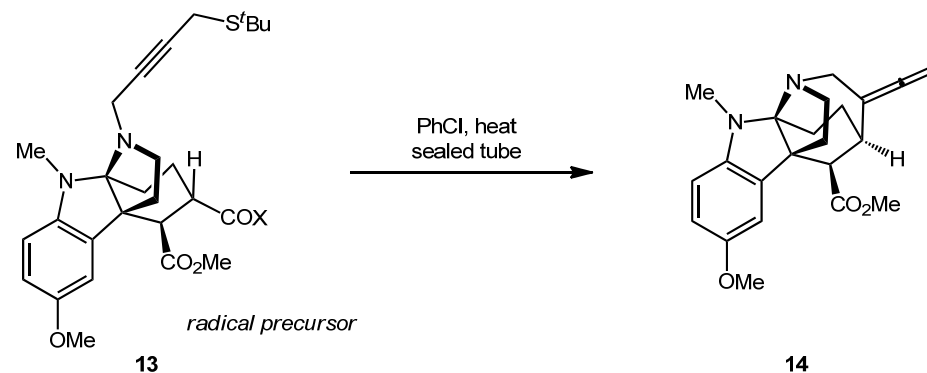
entry	HX	T (°C)	t (h)	yield (%) ^a	ee (%) ^b
1	HClO ₄	0	4	38	88
2	HCl	0	4	25	73
3	HBf ₄	0	4	71	93
4	HBf ₄	-10	6	75	94
5 ^c	HBf ₄	-10	6	62	94
6	HBf ₄	-20	6	73 (70) ^d	95

^a Yield based on SFC analysis relative to an internal standard; ^b Determined by SFC analysis; ^c Reaction run with 5% v/v water; ^d Isolated yield.



Enantioselective Total Synthesis of (-)-Vincorine

Evaluation of Radical Cyclization Substrates



entry	COX	conditions	conc. (mM)	conv. (%)	yield (%) ^a
1		120 °C, 1 h	4	100	18
2		120 °C, 3 h Bu ₆ Sn ₆ , hv	4	38	17
3		120 °C, 5 h Bu ₆ Sn ₆ , hv	4	85	17
4		120 °C, 12 h	6	100	8
5		160 °C, 12 h	6	100	31
6 ^b		200 °C, 10 h	6	100	51 ^c

^a Yield based on ¹H NMR analysis; ^b 1,2-Dichlorobenzene used as solvent. ^c Isolated yield.



