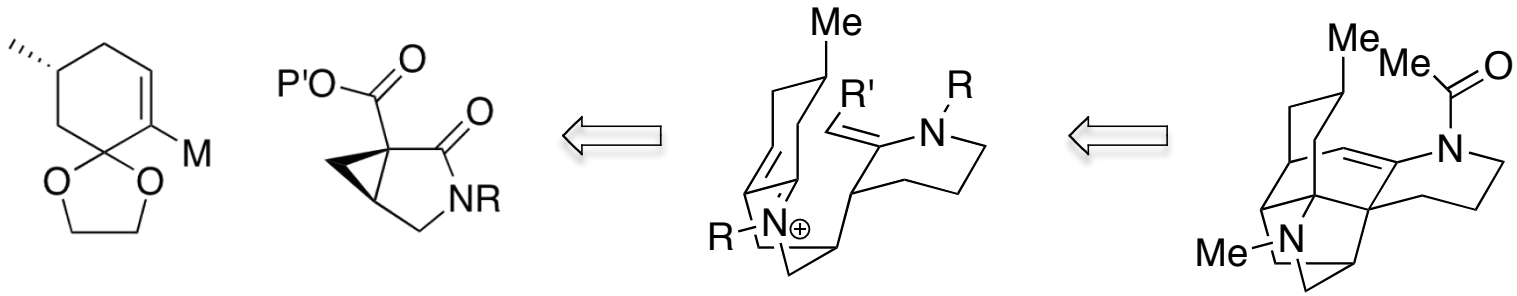
Total synthesis of (+)-Fastigiatine

Liau, B. B.; Shair. M. D.* *J. Am. Chem. Soc.,* **2010**. 132,
9594-9595. DOI: 10.1021/ja104575h



Yongzhao Yan
Wipf Group – Current literature
September 4, 2010

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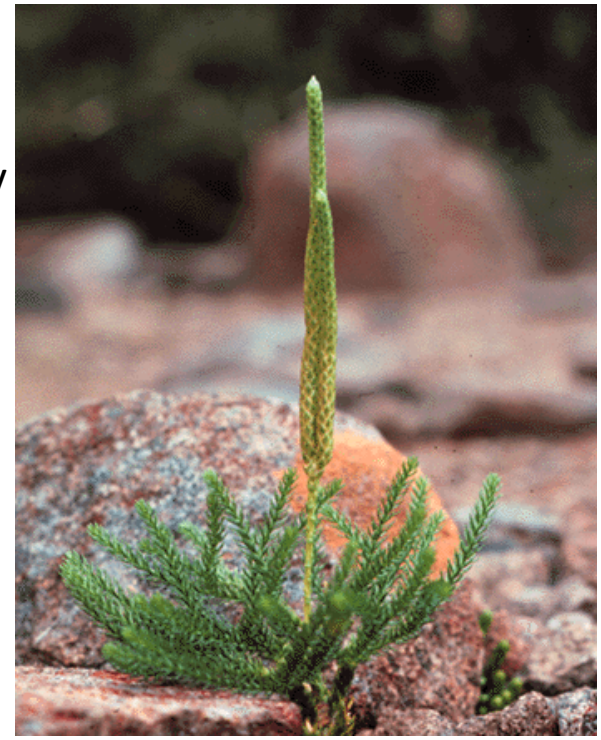
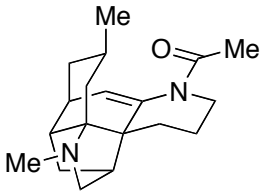
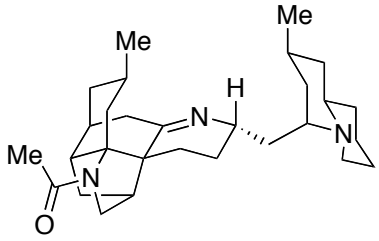
Background

- Isolated By Maclean in 1986 from *Lycopodium fastigiatum* **R. Br.** collected in New Zealand.
- Structure and relative configuration were resolved by X-ray and 2D NMR of the free base.
- Fused pentacyclic ring system of fastigiatine was found first time the Lycopodium family of alkaloid or elsewhere.
- Same core structure of Himeradine A.
- Himeradine A exhibited cytotoxicity against murine lymphoma L1210 cells (IC_{50}, 10 μg/mL) in vitro.





Fastigiatine



Himeradine A

Ma, X.; Gang, D. R,. *Nat. Prod. Rep.* **2004**, 21, 752–772.
Gerard, R.; Maclean, D., *Can. J. Chem.* **1986**, 64, 943 (1986).
Morita, H.; Hirasawa, H.; Kobayashi, J. *J. Org. Chem.* **2003**, 68, 4563-4566

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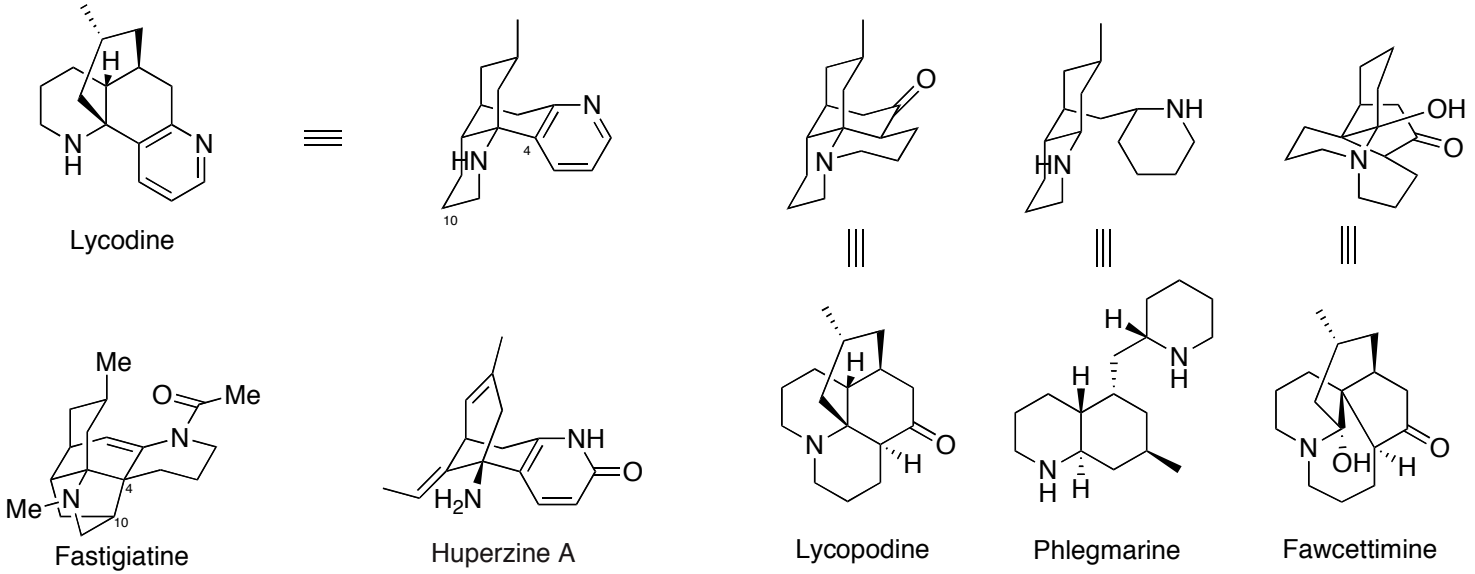
Lycopodium Alkaloids

- Over 200 lycopodium alkaloids have been identified.
- Members of this family are known to have cardiovascular and neuromuscular effects. Huperzine A is a potential treatment of Alzhelmer's Disease.
- Four major classes of lycopodium alkaloids.
- Fastigiatine has C4-C10 bond and five contiguous stereocenters including 2 vicinal quaternary carbons.



Ma, X.; Gang, D. R,. *Nat. Prod. Rep.* **2004**, 21, 752–772**.**

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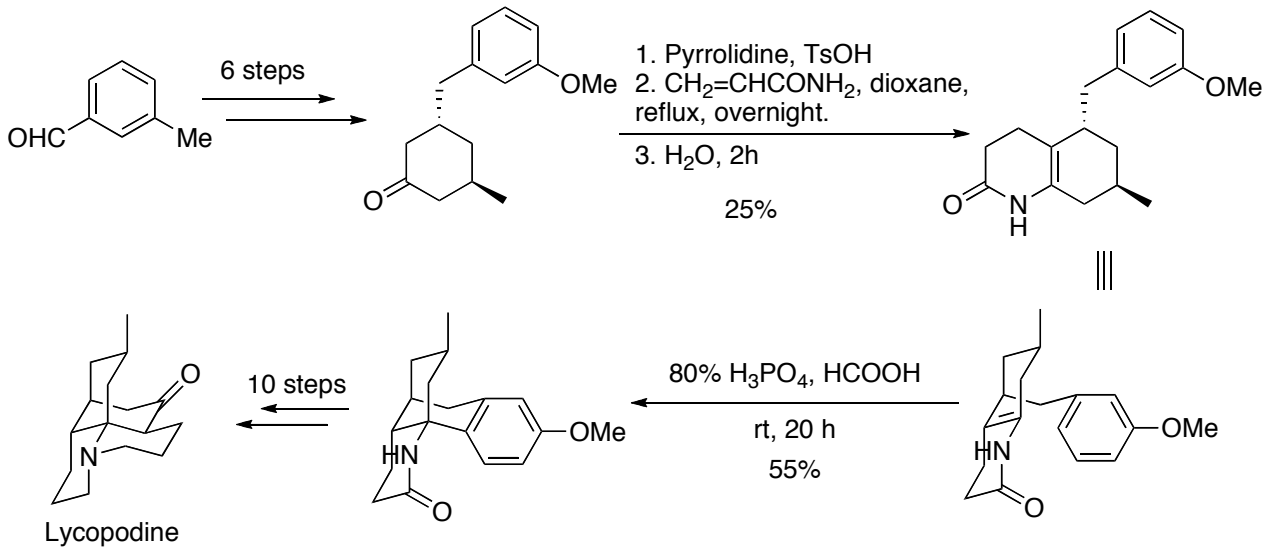
Stork's Synthetic Approaches (1968)



- 20 steps synthesis
- Use Pictet-Spengler cyclization to form the key fused tricyclic core.
- First total synthesis of *dl*-Lycopodine

Stork, G.; Kretchmer, R. A.; Schlessinger, R. H. *J. Am. Chem. Soc.* ***1968****, 90, 1647–1648.*

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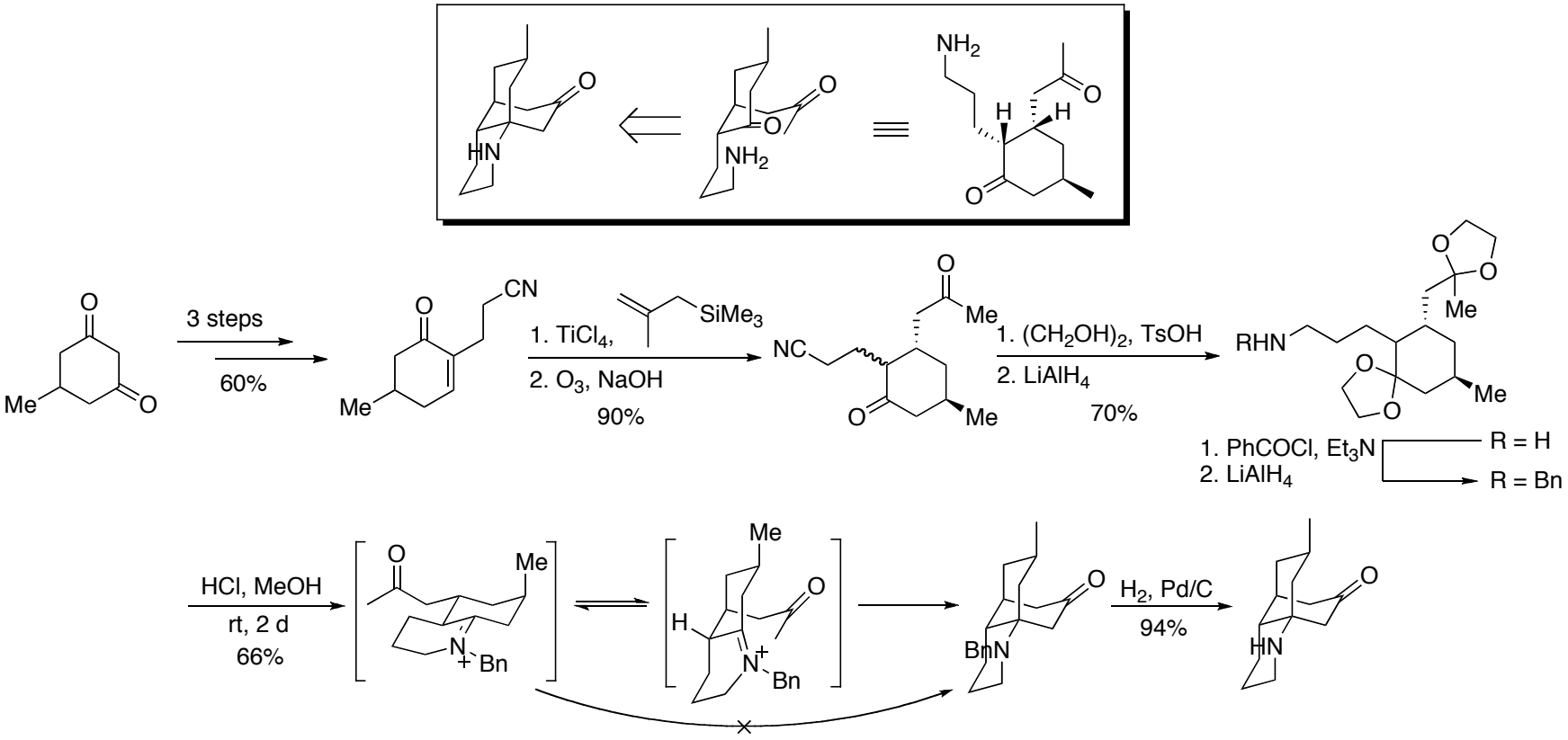
Heathcock's Synthetic Approaches (1980's)



- Use intramolecular Mannich condensation to form the key fused tricyclic core along with the quaternary stereocenter.

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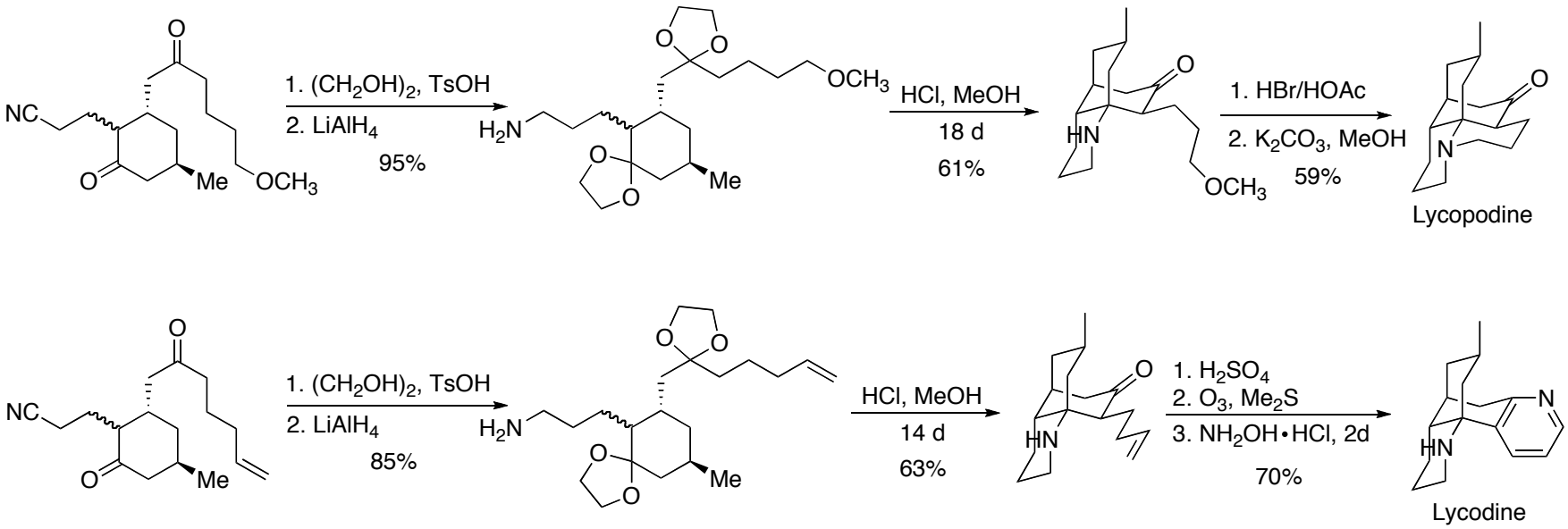
Heathcock's Synthetic Approaches (cont'd)



- Racemic synthesis of Lycopodine (13 steps, 16.6% overall yield)
- Racemic synthesis of Lycodine (11 steps, 13.2% overall yield)

Heathcock, C. H.; Kleinman, E. F.; Binkley, E. S. *J. Am. Chem. Soc.* ***1982****, 104, 1054–1068.*

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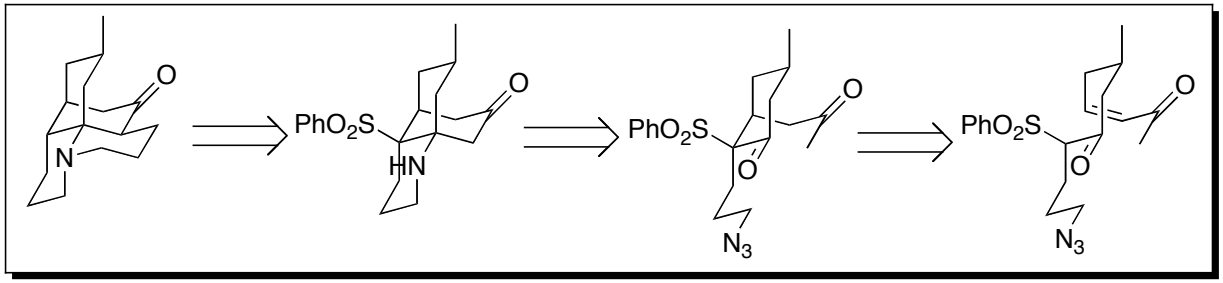
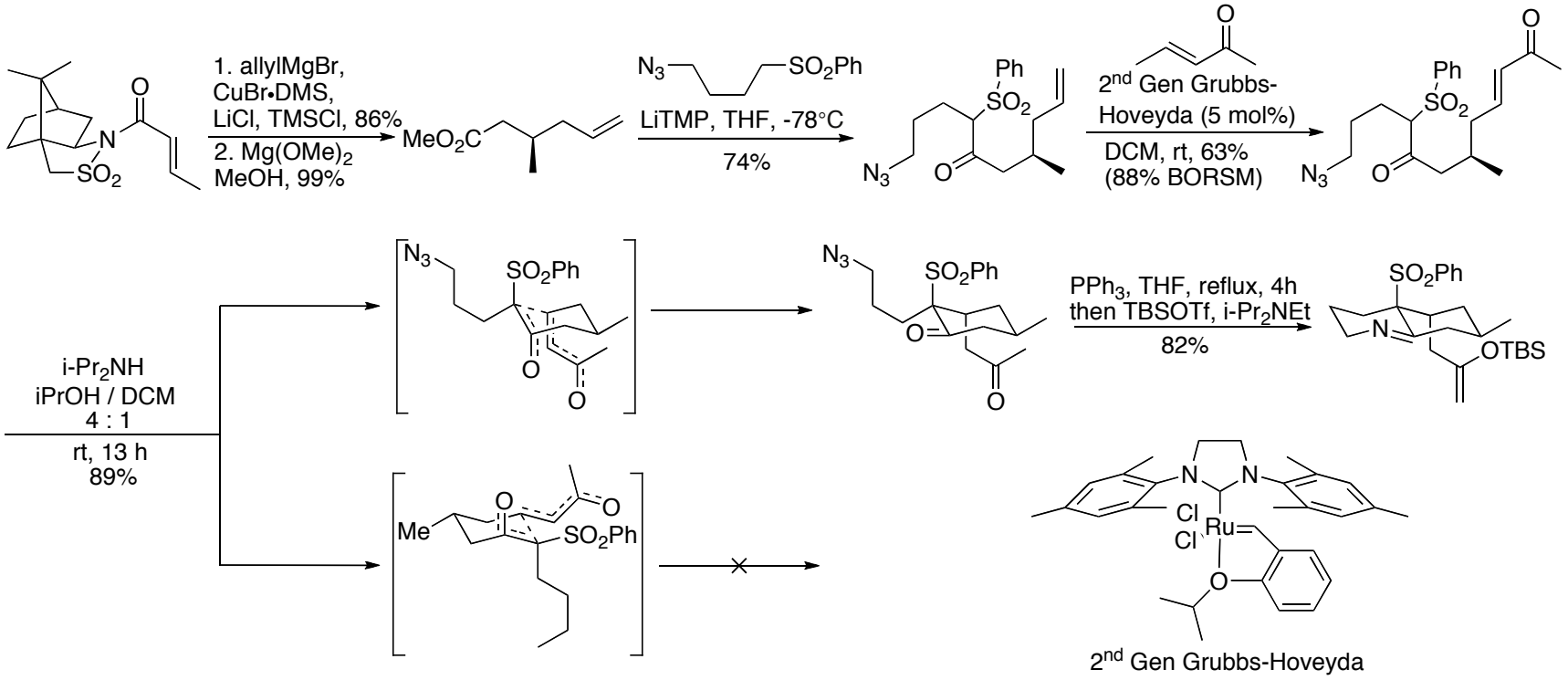
Carter's Synthetic Approaches (2008)





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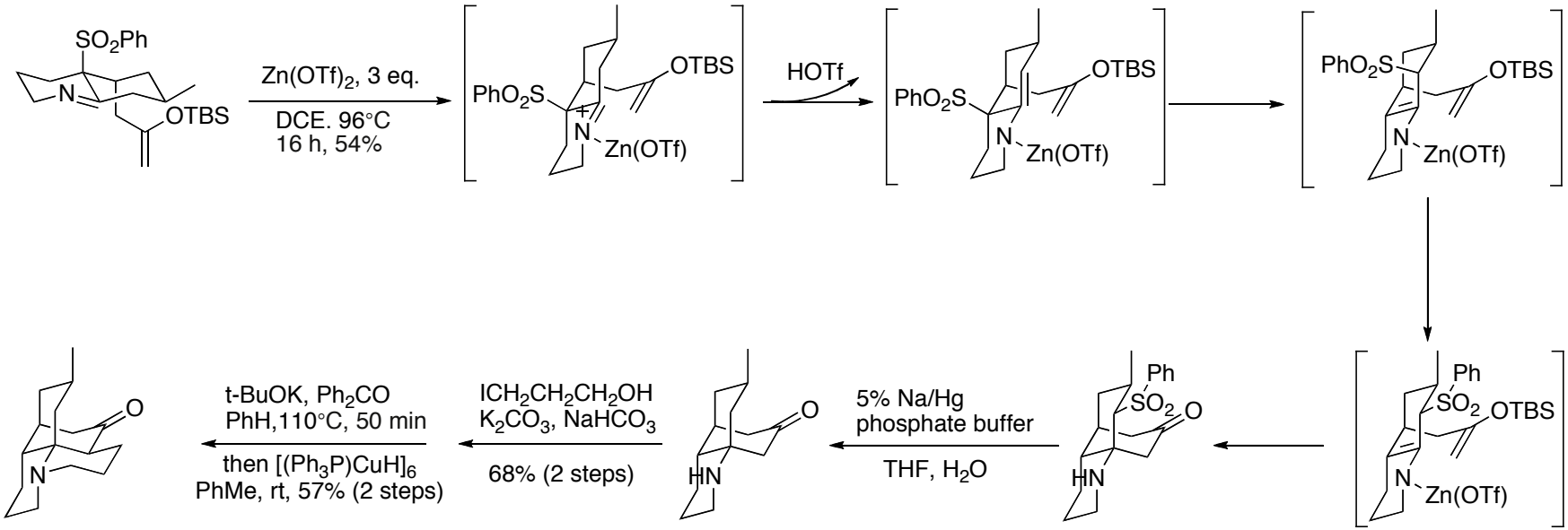
Carter's Synthetic Approaches (2008)



- Use Micheal addition and Mannich Reaction to construct the key tricyclic core.
- First enantioselective synthesis of lycopodine.
- 11 steps, 6% yield.

Yang, H,; Carter, R. G.; Zakharov, L. N. *J. Am. Chem. Soc.,* ***2008****, 230, 9238-9239*

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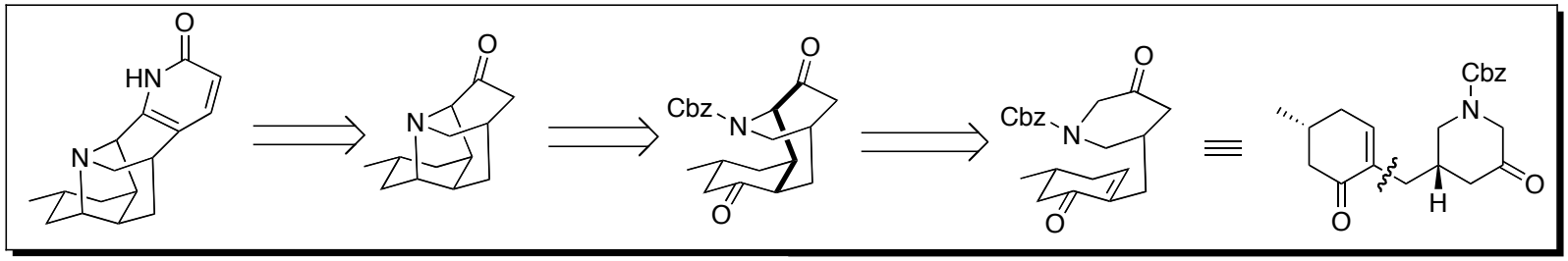
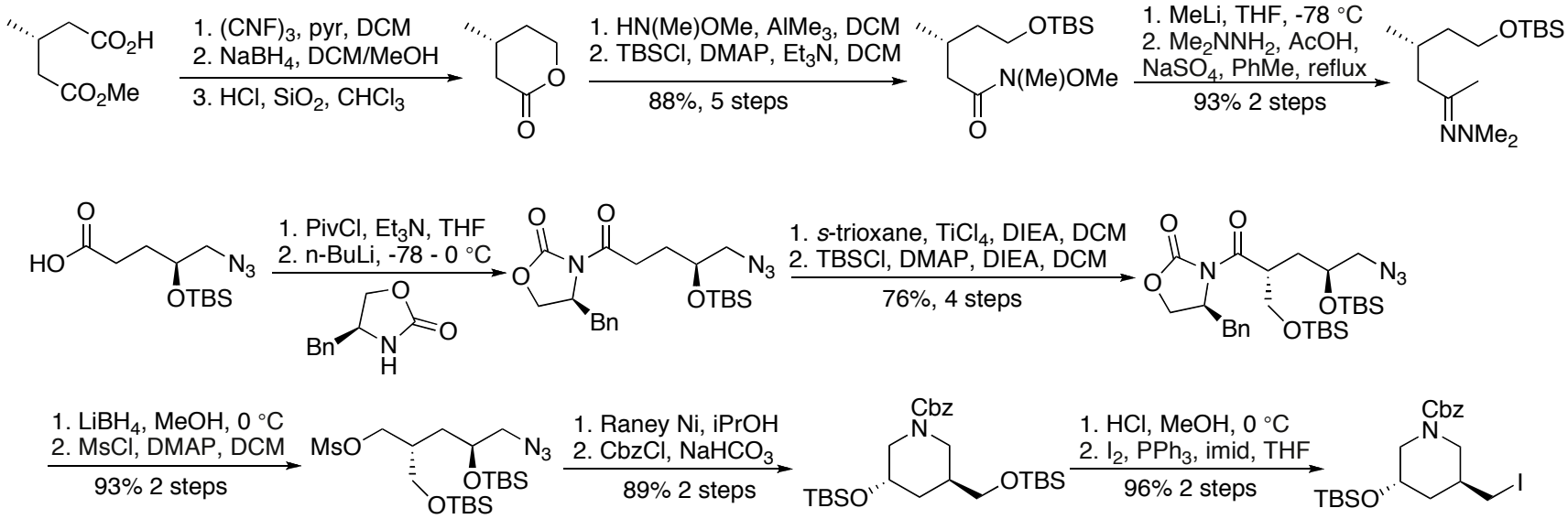
A. B. Smith's Synthetic Approaches (2008)





Beshore, D. C.;Smith, A. B., III. *J. Am. Chem. Soc.* ***2007****, 129, 4148–4149.*
Beshore,D. C.; Smith, A. B., III. J. Am. Chem. Soc. ***2008****, 130, 13778–13789.*

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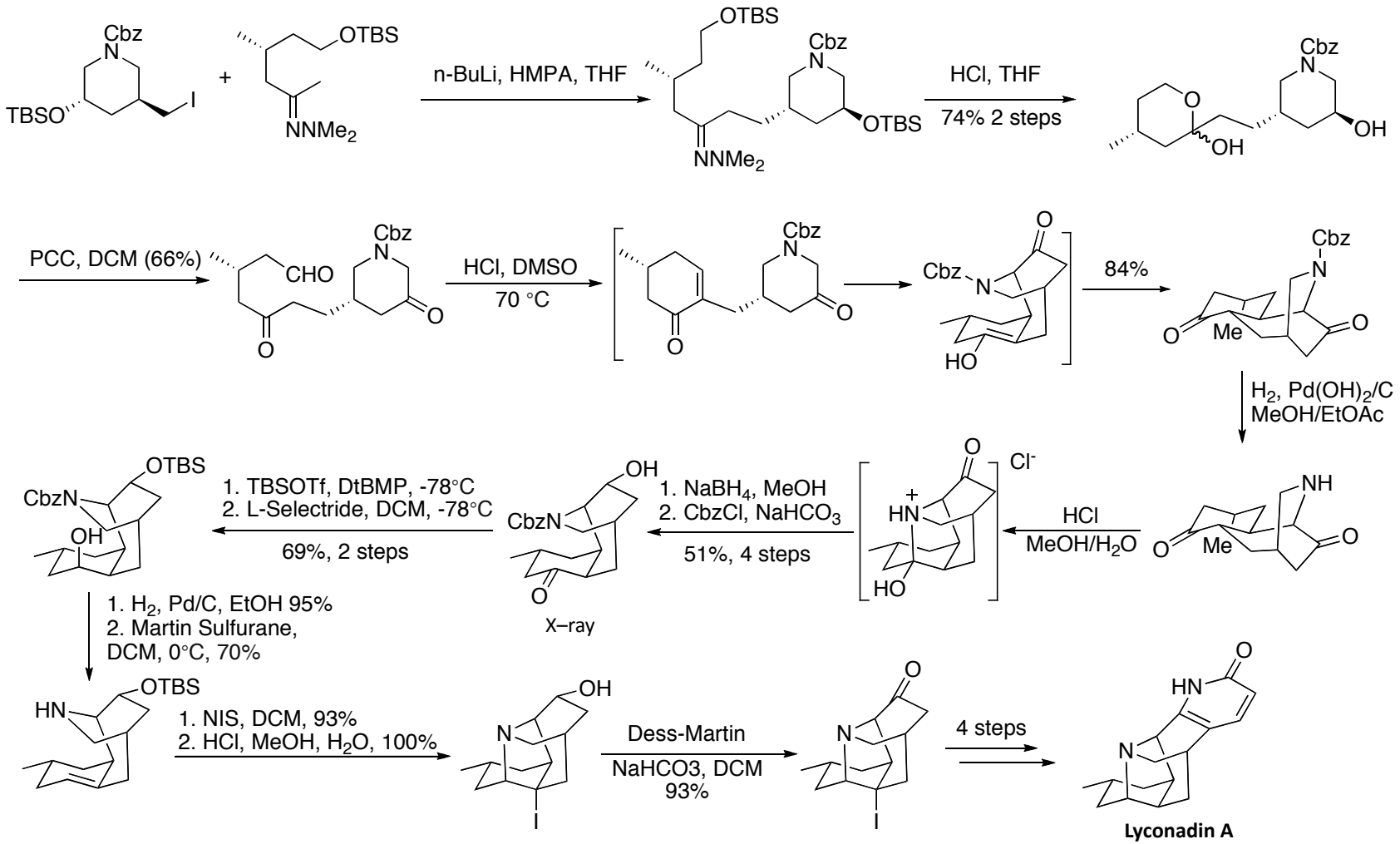
A. B. Smith's Synthetic Approaches (2008)



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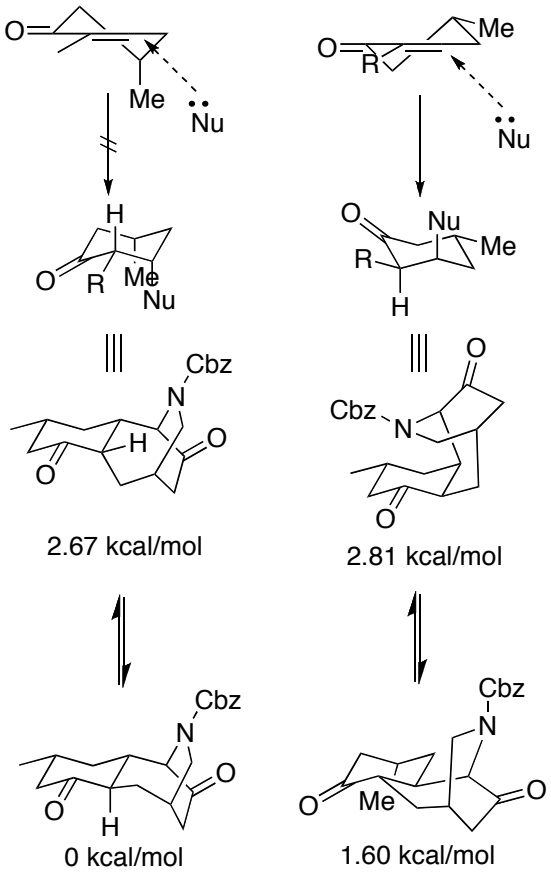
A. B. Smith's Synthetic Approaches (2008)



- First total synthesis of lyconadin A
- Use 7 endo-trig cyclization to form two key tertiary stereocenter.
- Wrong stereocenter at C 12 but isomerized to form the correct configuration.
- Fail to form a anti-Bredt iminium ion
- Application of 5-*endo* aminoiodo olefin cyclization is used to form the tetracyclic structure.

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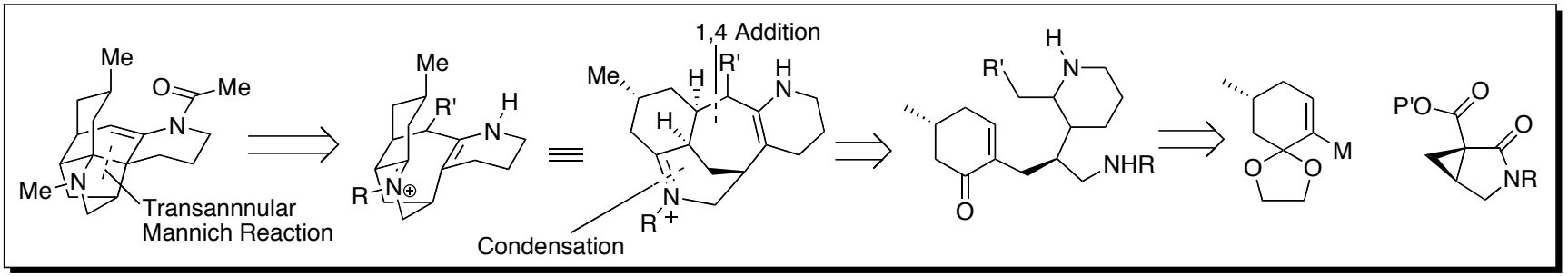
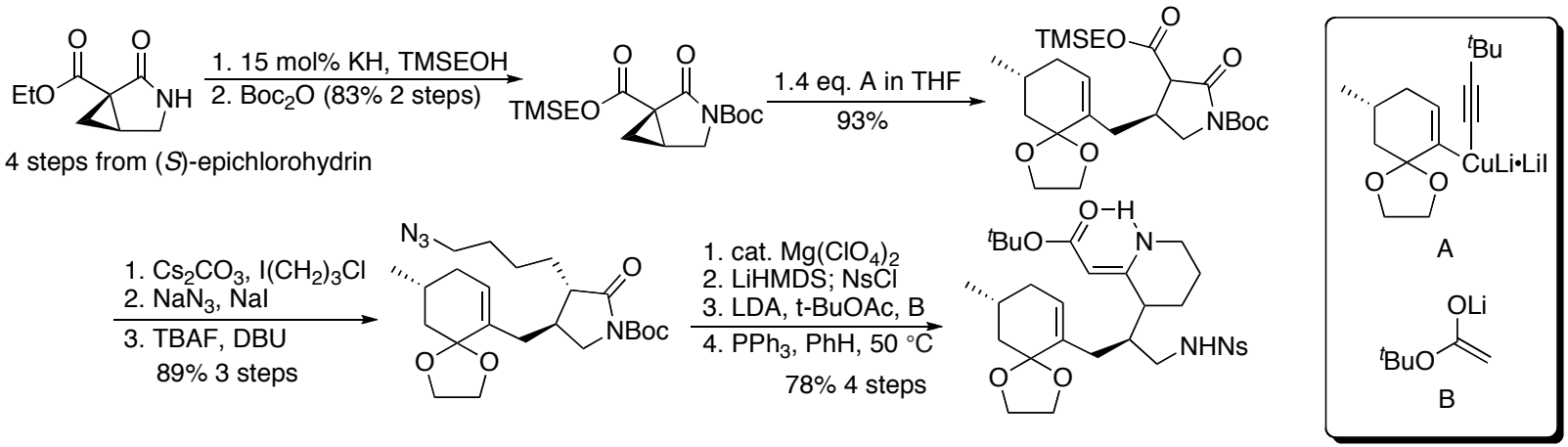
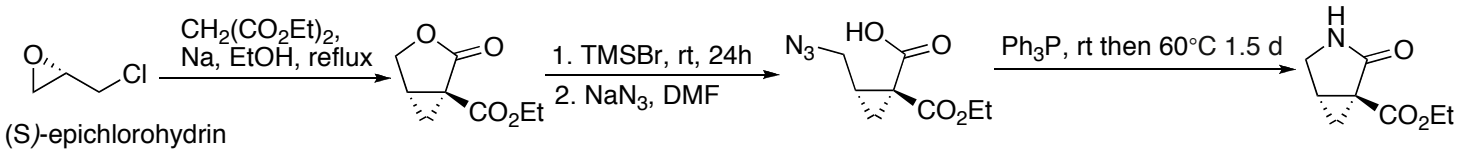
Total Synthesis of (+)-Fastigiatine







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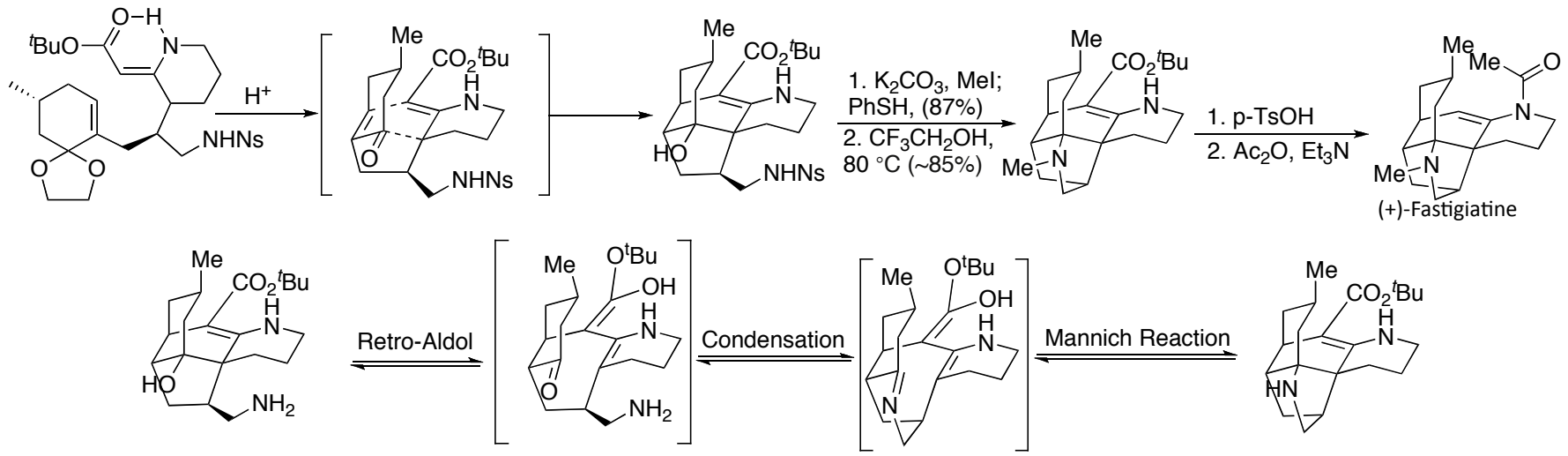
Total Synthesis of (+)-Fastigiatine



- First total synthesis of (+)-fastigiatine
- 15 steps, 30% yield from cyclopropane precursor.
- Use cyclopropane opening, formal [3+3] cycloaddition reaction and Mannich reaction to construct the core of (+)-fastigiatine and (-)-himeradine

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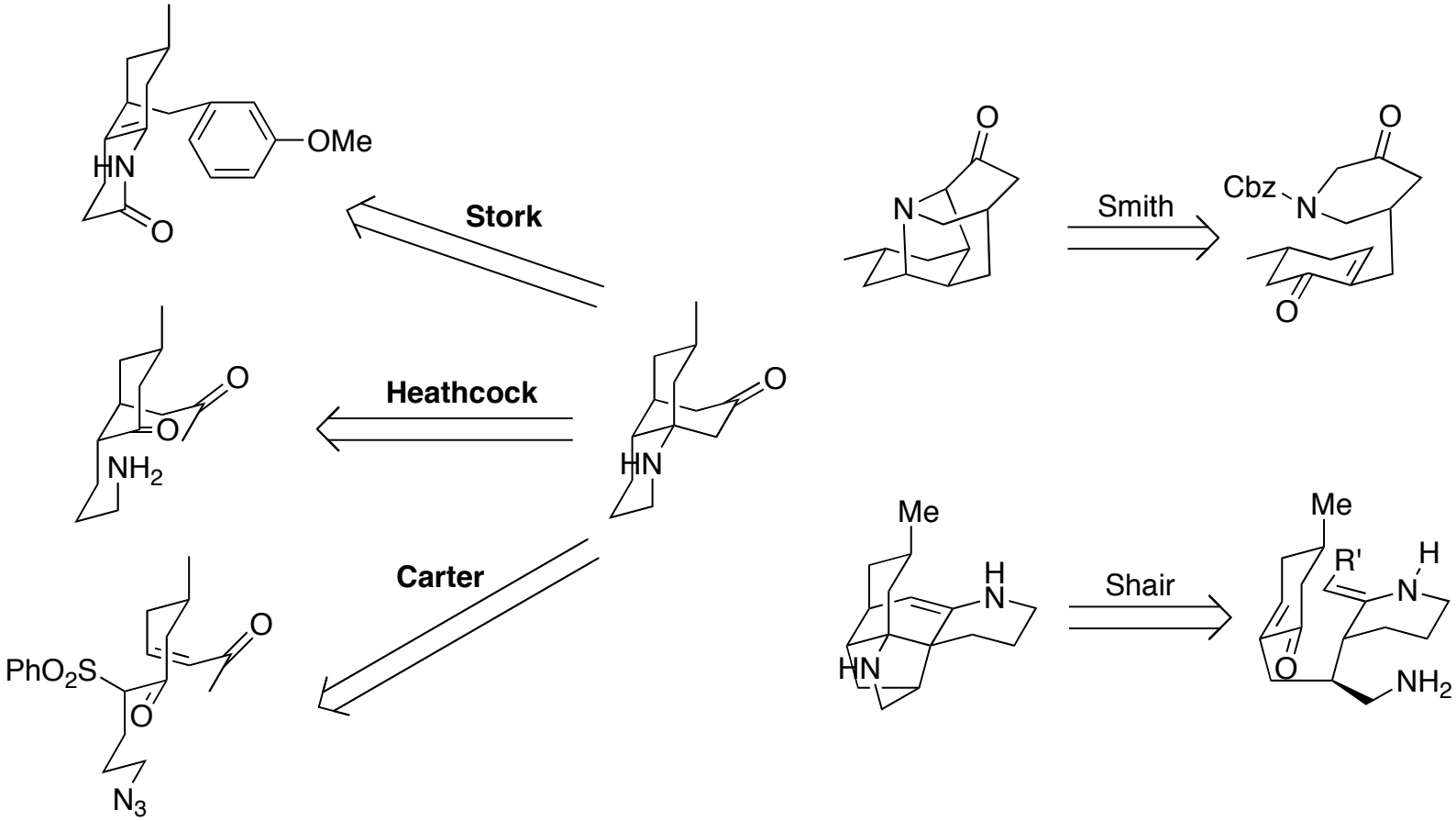
Summary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HN
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Stork
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Smith
Cbz
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O
Heathcock
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NH2
HN
O
Carter
PhO2S
O
O
N3
Me
H
N
HN
Shair
Me
R'
H
N
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NH2