Total Syntheses of Phleghenrines A and C

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OL | Organic Letters

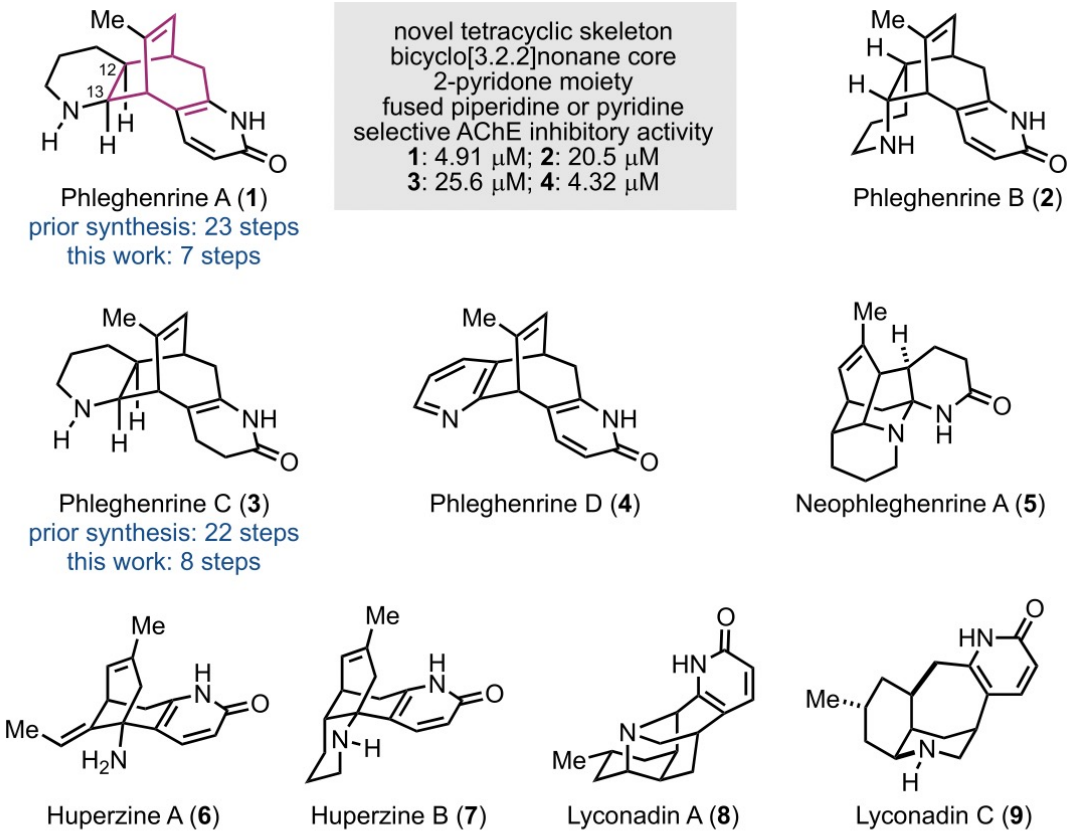

Figure 1. Phleghenrines and related alkaloids.

Phleghenrines have a distinct and complex tetracyclic skeleton featuring a bicyclo[3.2.2]nonene core.

Their novel chemical structures and potent acetylcholinesterase inhibition activity render them promising lead compounds for the drug discoveries in treatment of Alzheimer's disease and other related neurodegenerative disorders.

However, the low isolation yield (<0.0003%) is a major hurdle for their further biomedical development.

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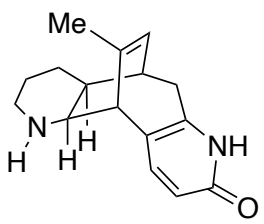
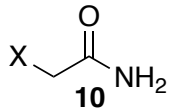
Retrosynthetic Analysis



Phleghenrine A **(1)**



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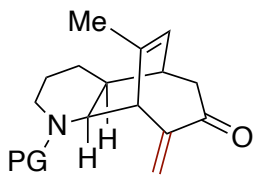
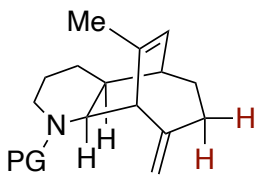
2-pyridone synthesis



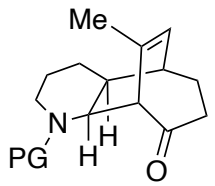
11

allylic C-H oxidation



12

FGI

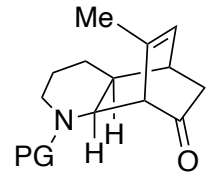


13

bicyclo[3,2,2]nonene
difficult to synthesize

1C deletion

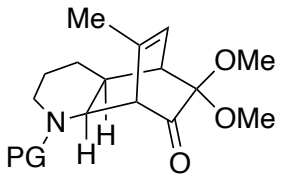
1C insertion



14

bicyclo[2,2,2]octene
Diels-Alder reaction

FGA



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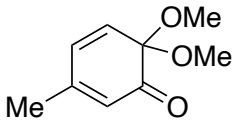
Diels-Alder



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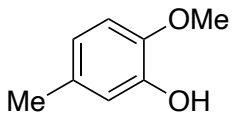
oxidative dearomtization



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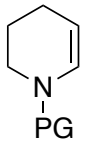

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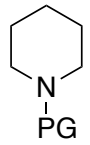
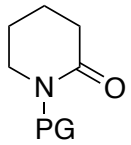


19

or



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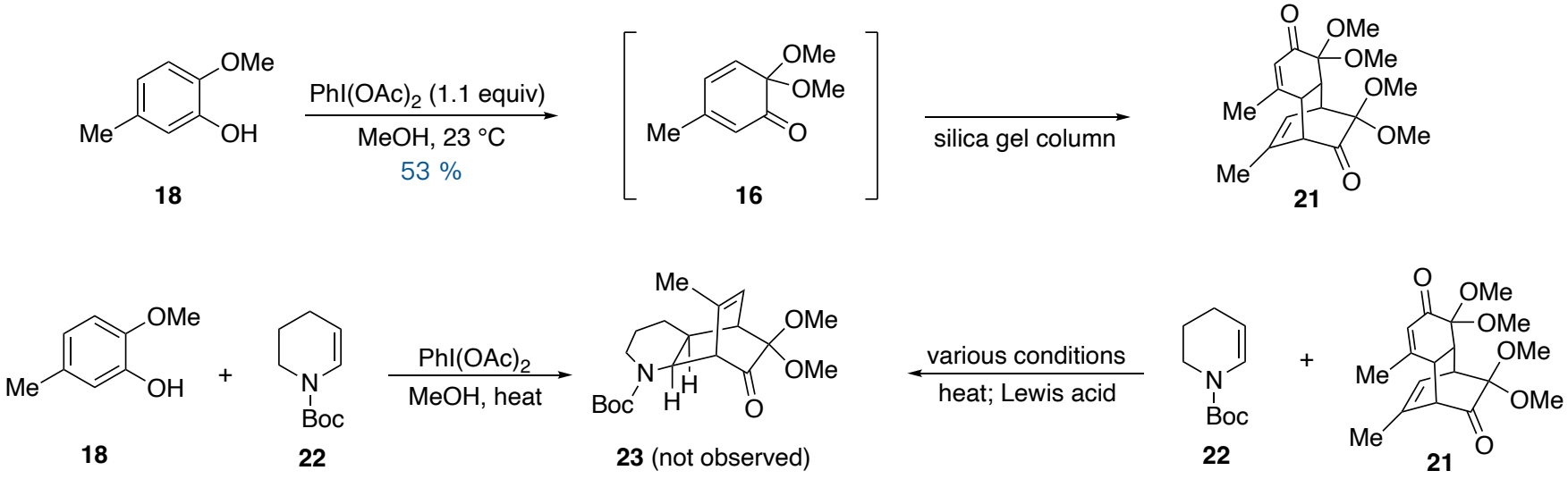
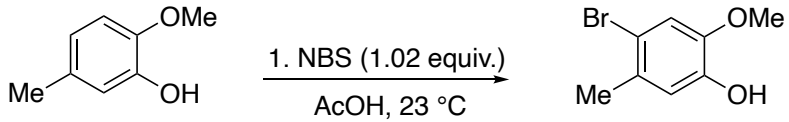
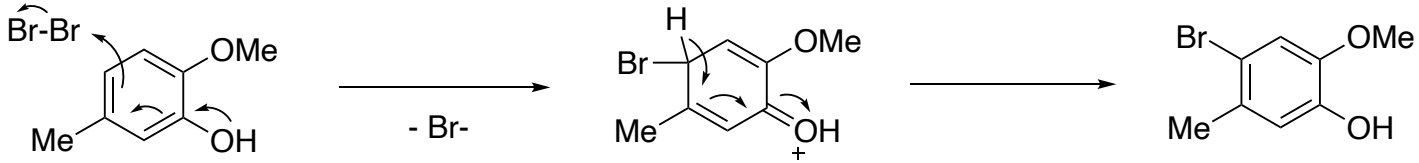
Attempted Dearomatization and Diels-Alder reaction

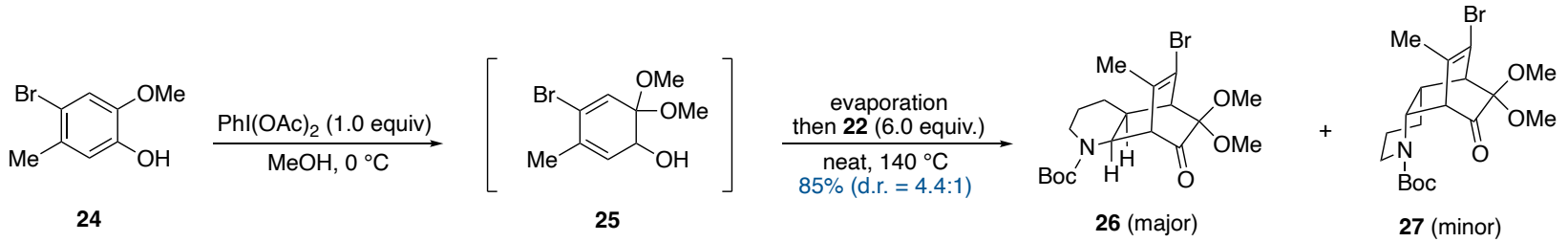




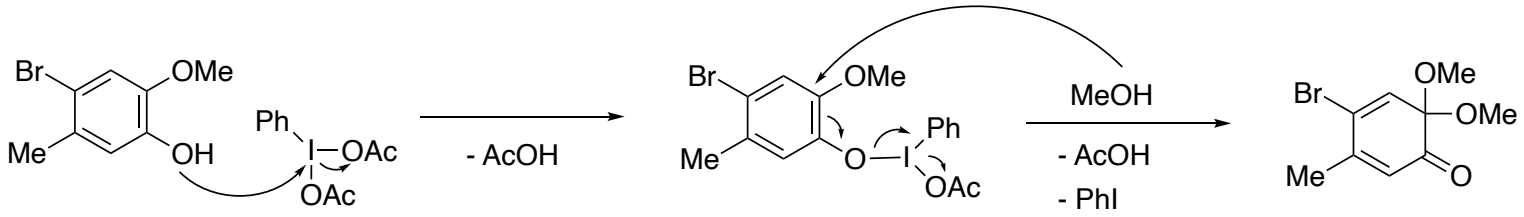
18 **24**

Bromination of phenols and electrophilic aromatic substitution

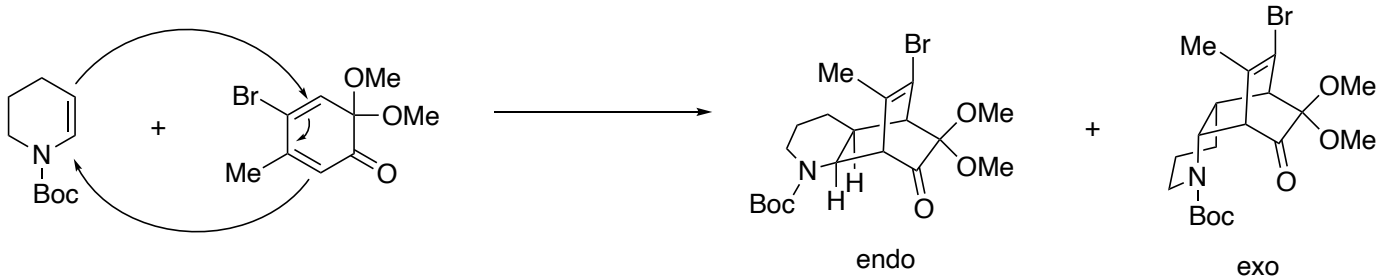


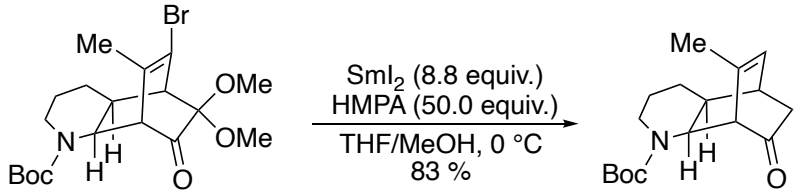


Oxidative dearomatization



Diels−Alder reaction

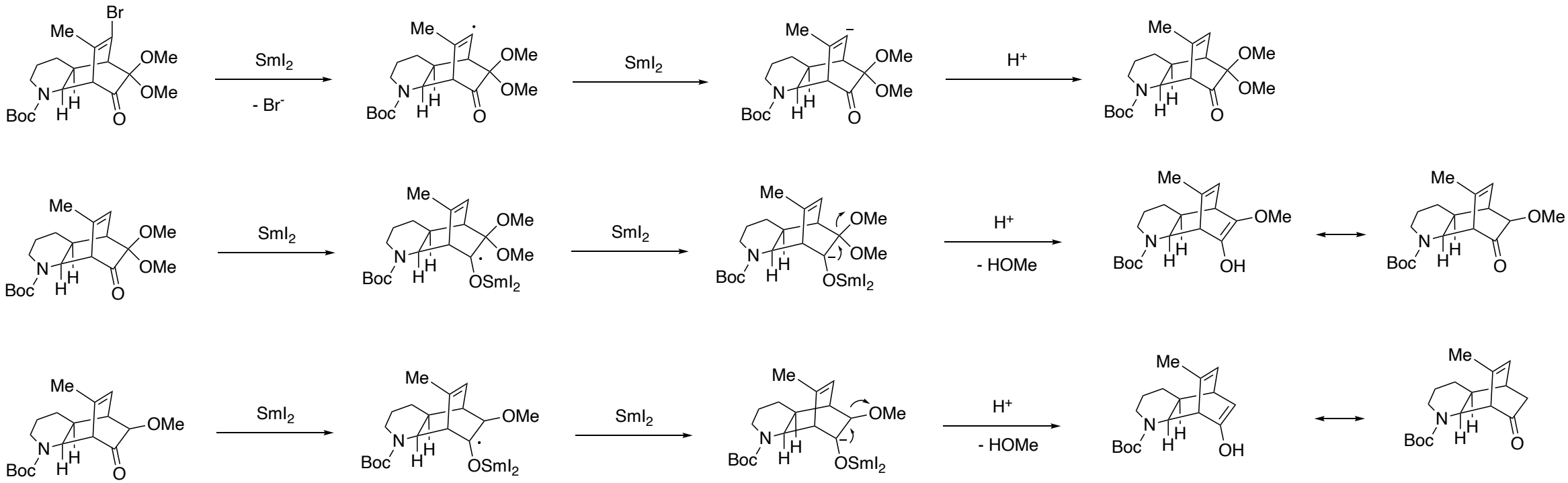


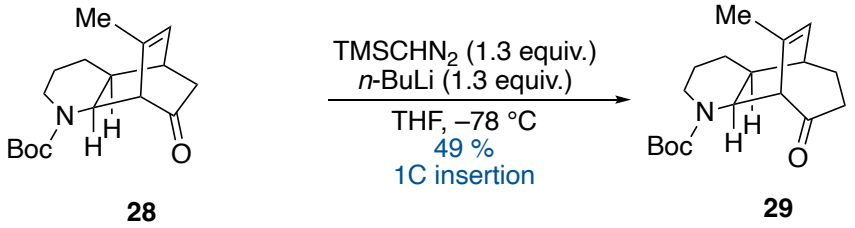


26 (major)

28

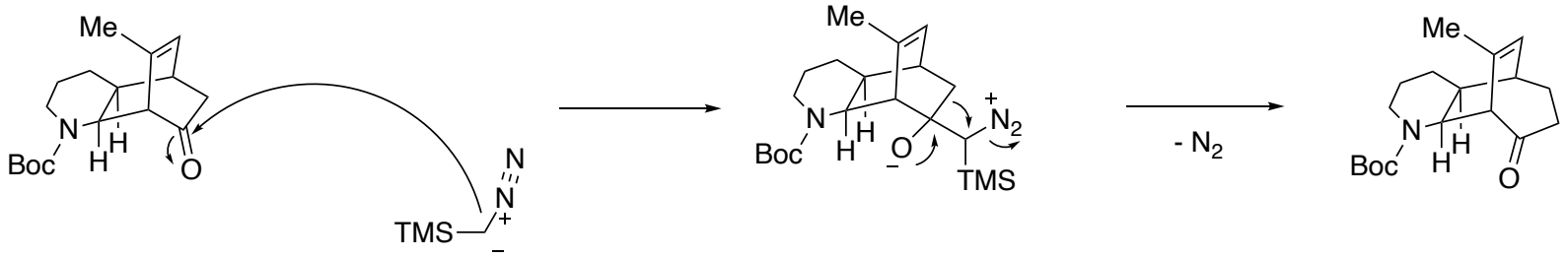
SmI_2 reduction

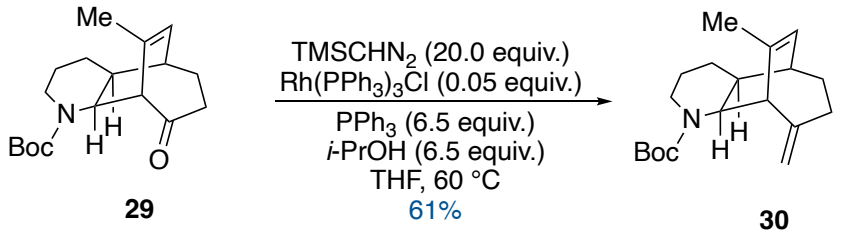




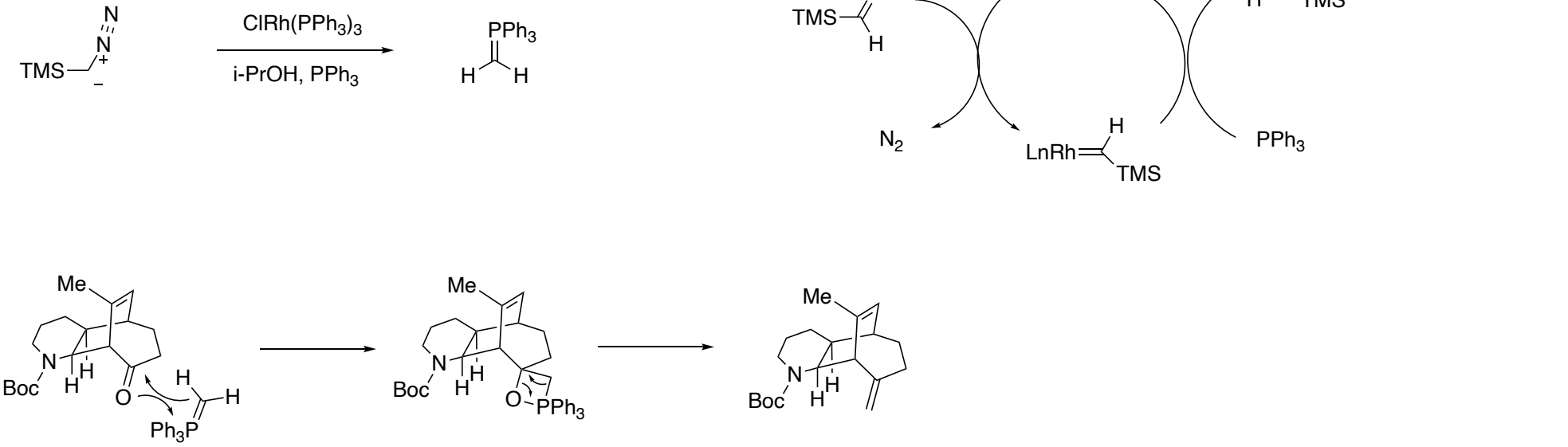
28 **29**

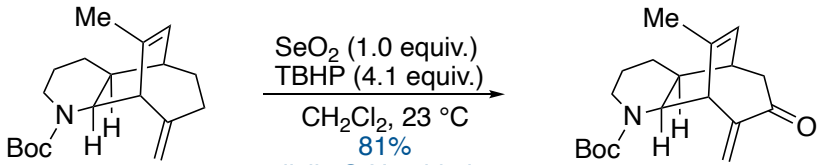
Büchner−Curtius− Schlotterbeck one-carbon insertion





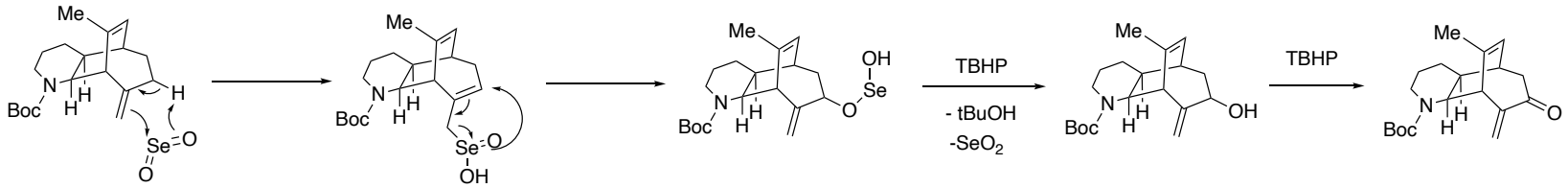
Wittig one-carbon homologation using the Lebel modification



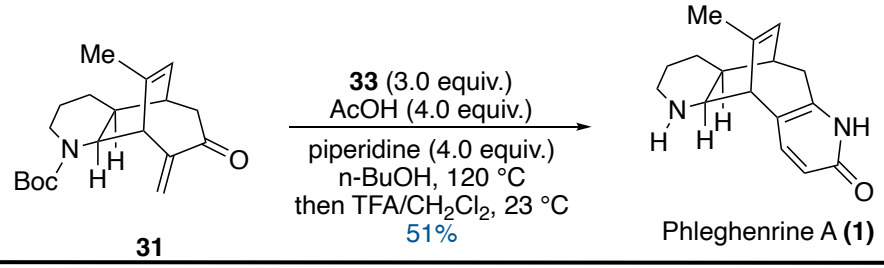


30 **31**

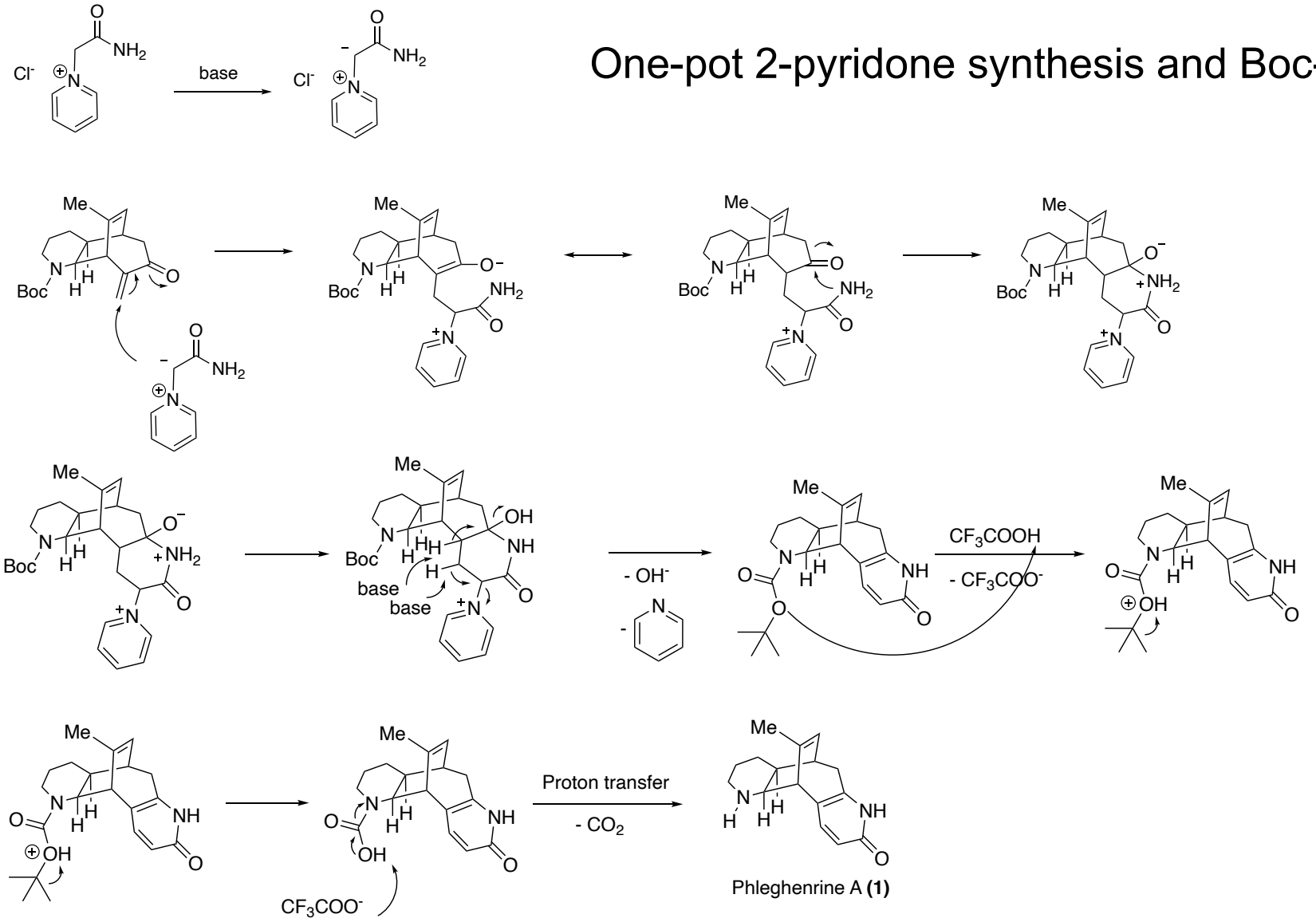
Allylic C-H oxidation

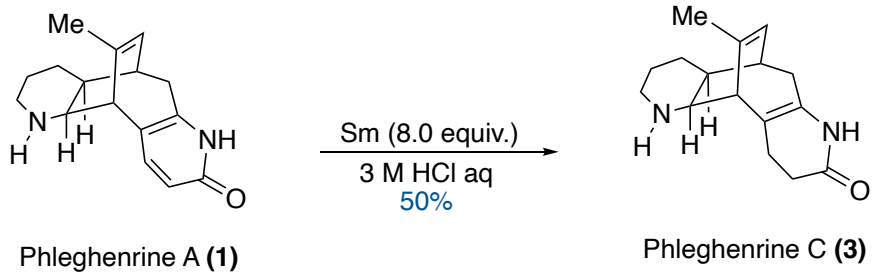


Alder ene like 4+2 addition [2,3]-sigmatropic shift



One-pot 2-pyridone synthesis and Boc-deprotection

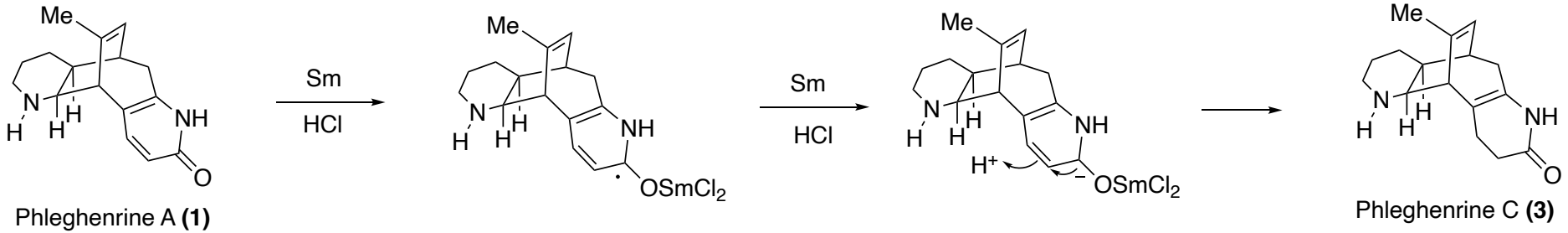




Phleghenrine A **(1)**

Phleghenrine C **(3)**

Partial reduction



Phleghenrine A **(1)**

Phleghenrine C **(3)**

Thanks!