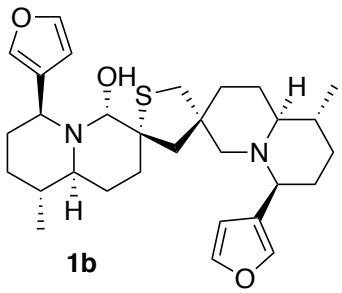
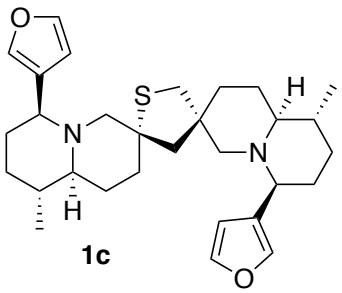
Total Synthesis of Unsymmetrically Oxidized Nuphar Thioalkaloids via Copper-Catalyzed Thiolane Assembly

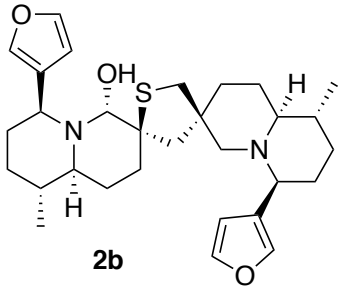
Lacharity, J. J.; Fournier, J.; Lu, P.; Mailyan, A. K.; Herrmann, A. T.; Zakarian, A. *J. Am. Chem. Soc.* **2017**, *139*, 13272–13275



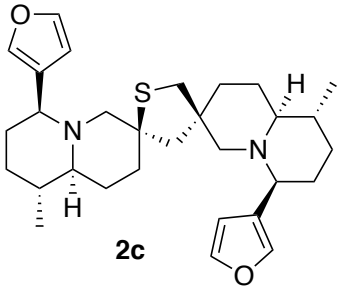
1b



1c



2b

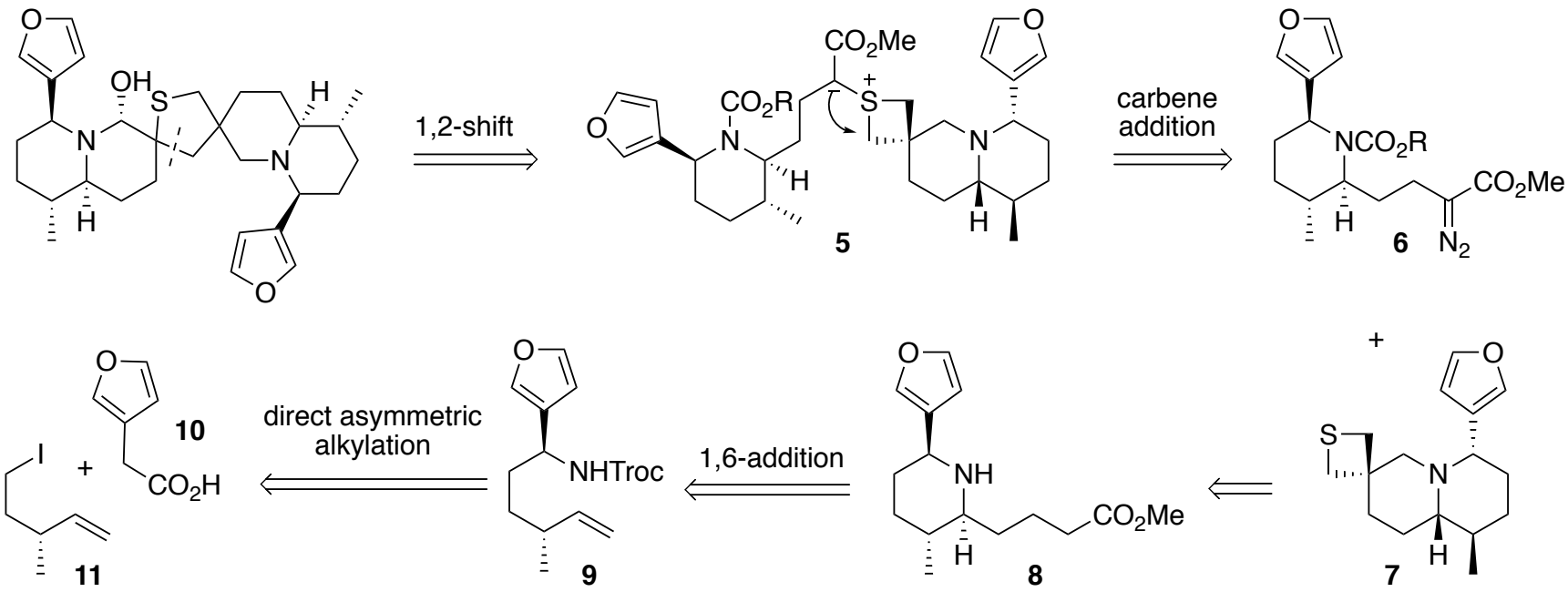


2c

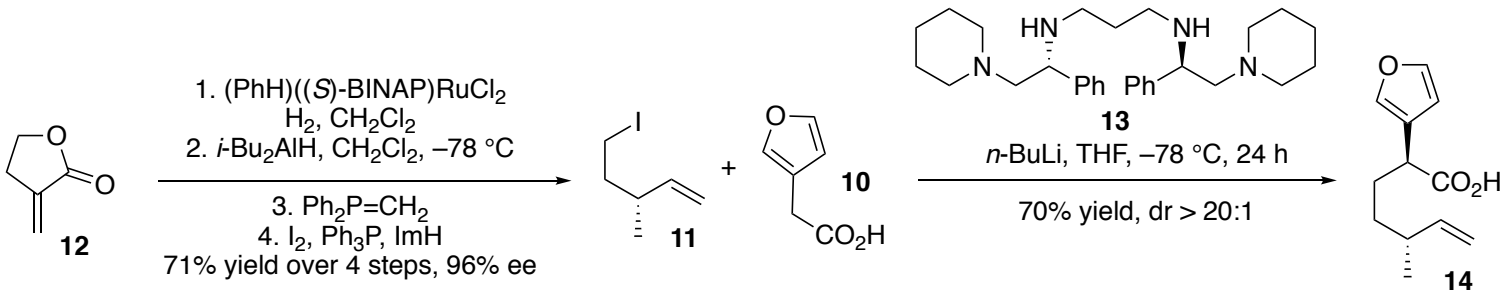
- Isolated from *Nuphar lutea* (yellow water lily) by Achmatowicz in 1964[1].
- Some of the variants of this class of alkaloids, including 1b and 2b, showed some cytotoxic activity.
- Synthetic strategy: stereodivergent synthesis of two fragments to be coupled through a metallocarbene insertion into the thietane C–S bond to form the central spirothiolane ring system.

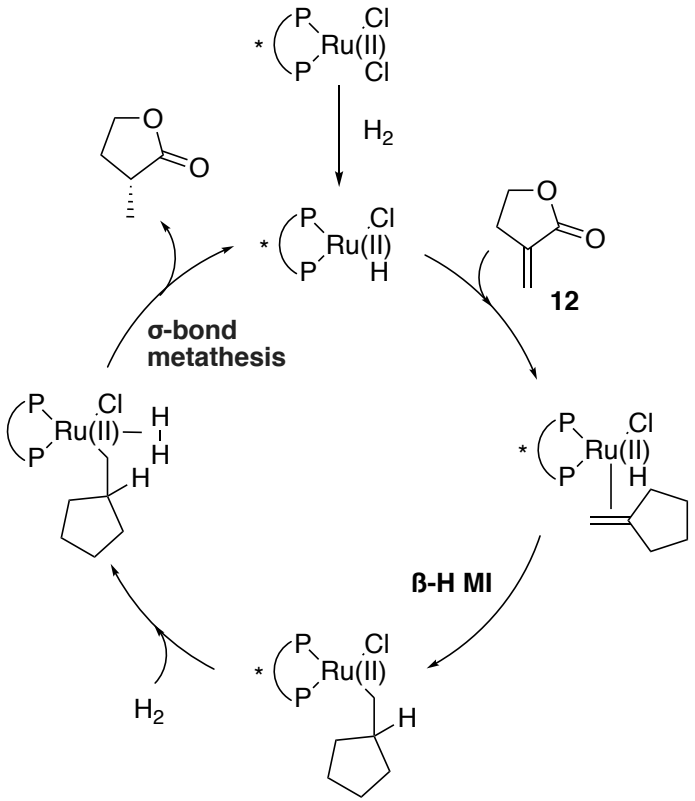
1. Achmatowicz, O.; Bellen, Z. *Tetrahedron Lett.* **1962,** *3*, 1121.

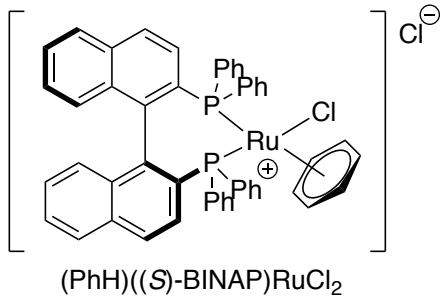
Retrosynthesis



Forward Synthesis







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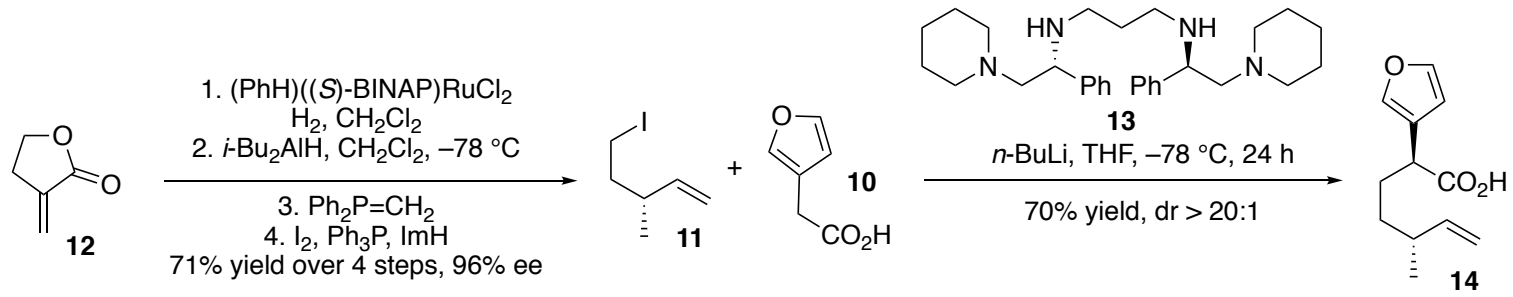
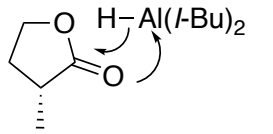
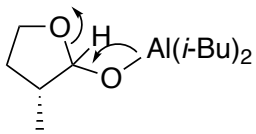
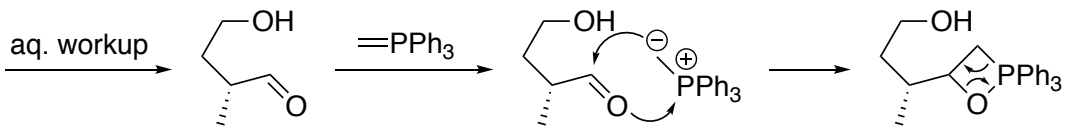


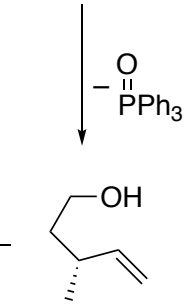
Lactone Reduction



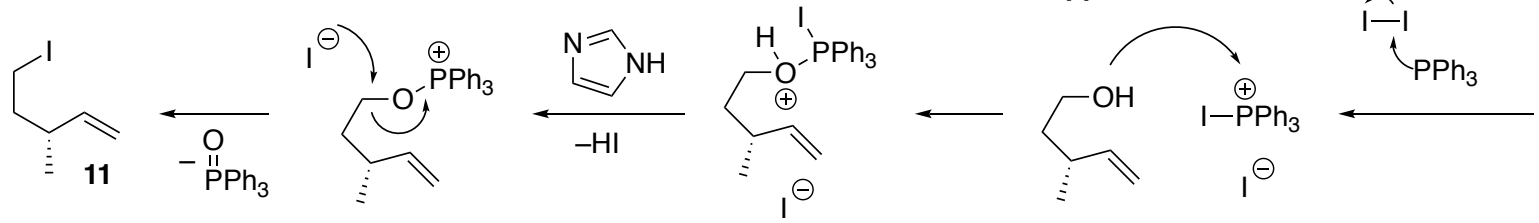


Wittig Homologation

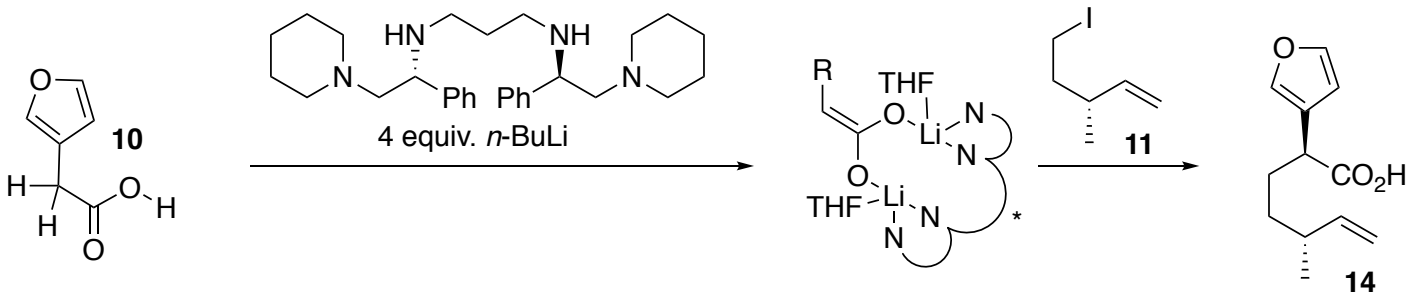


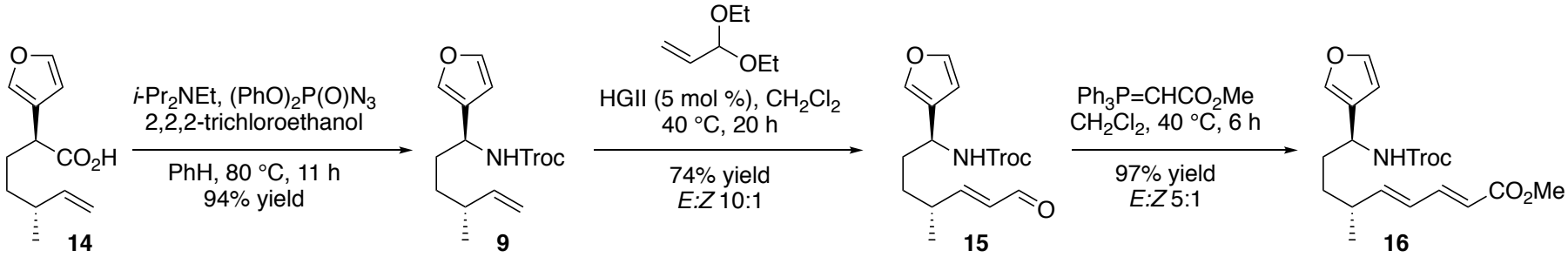


Appel Reaction

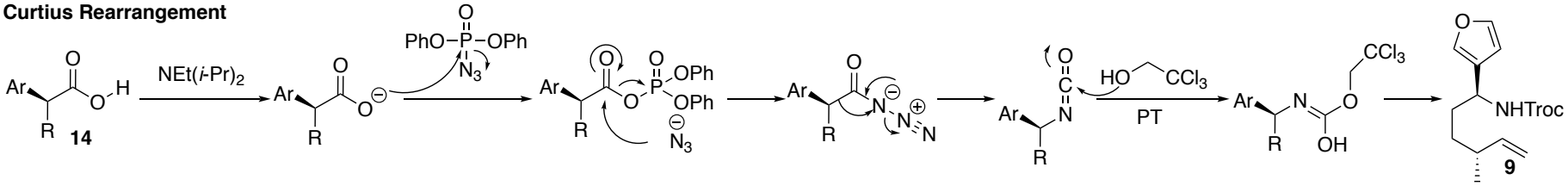


Asymmetric Alkylation

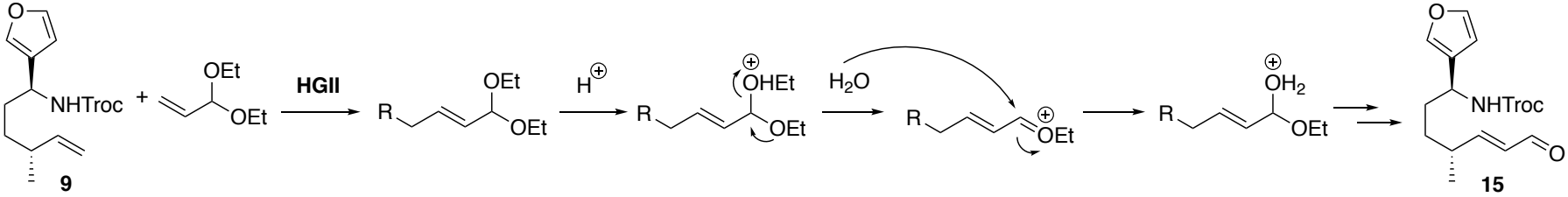




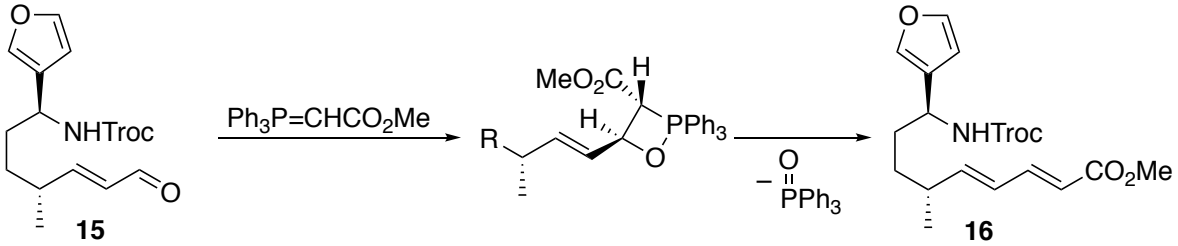
Curtius Rearrangement

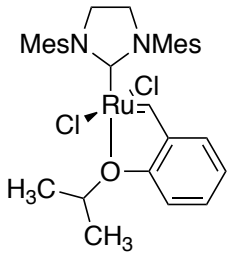


Cross Metathesis

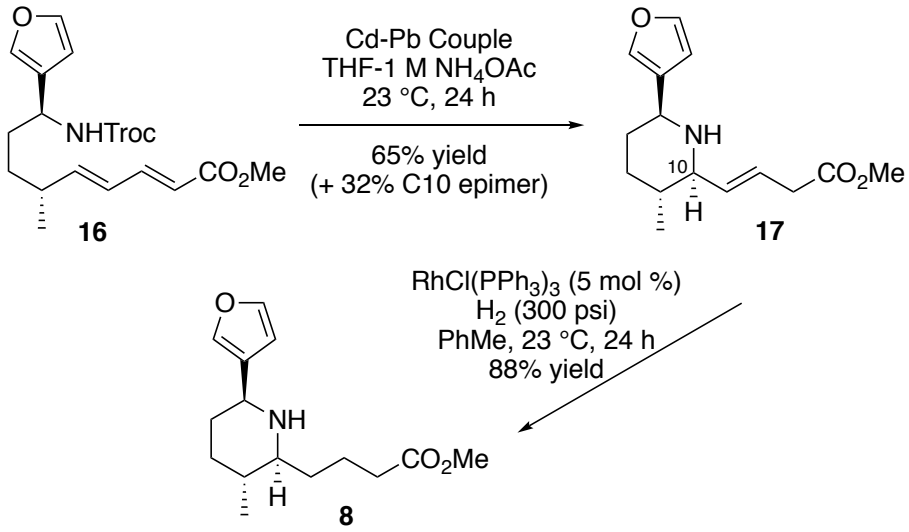


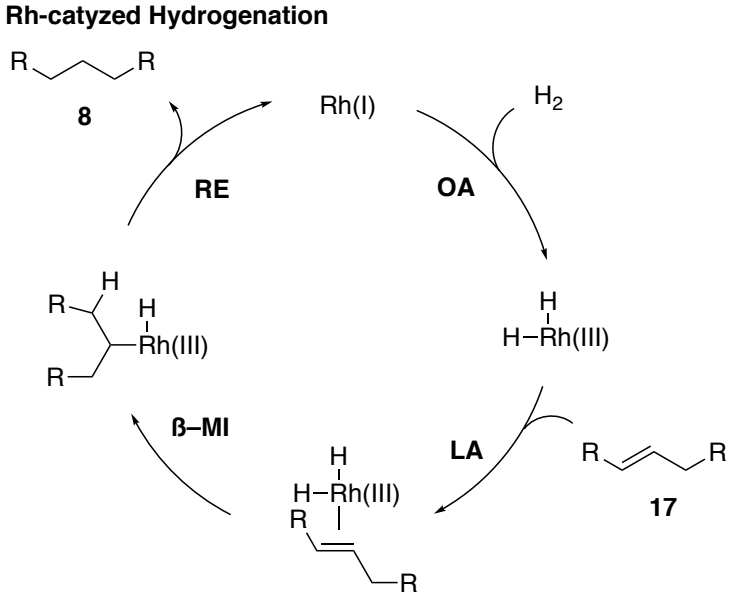
Wittig Reaction

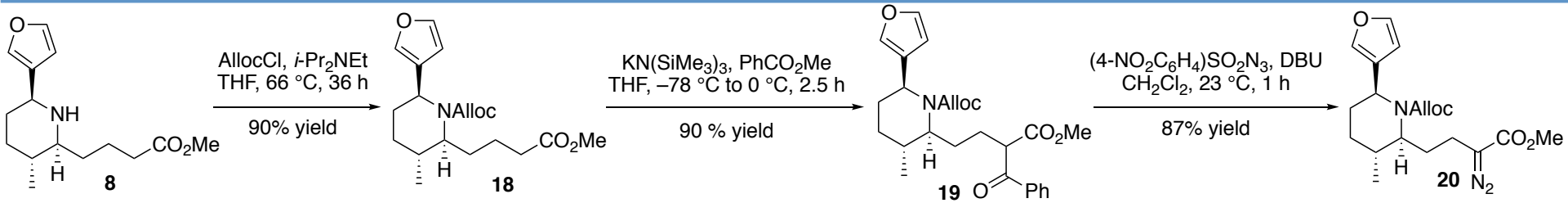




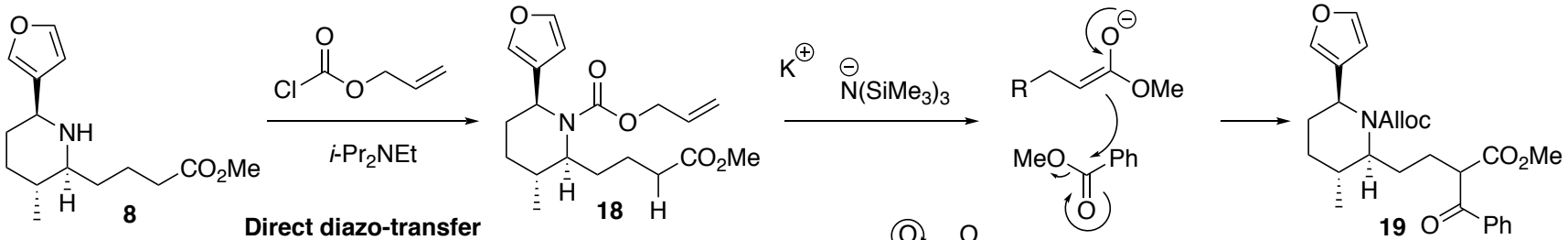
Hoveyda Grubbs Catalyst Second Generation (HGII)



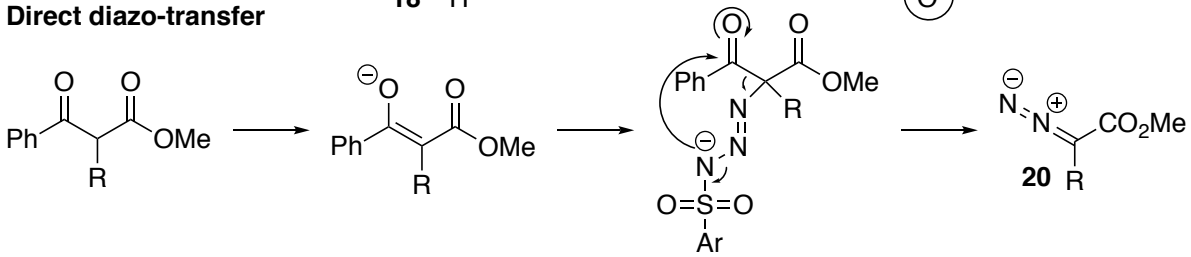


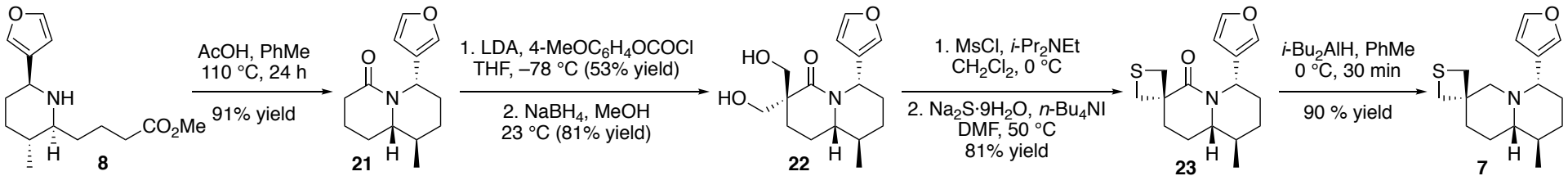


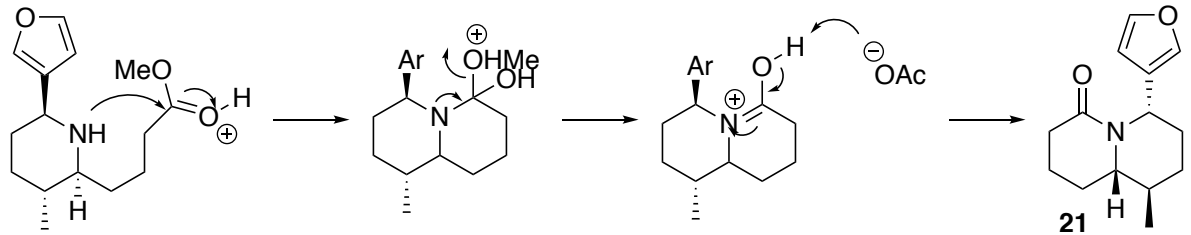
Alloc-protection and acylation

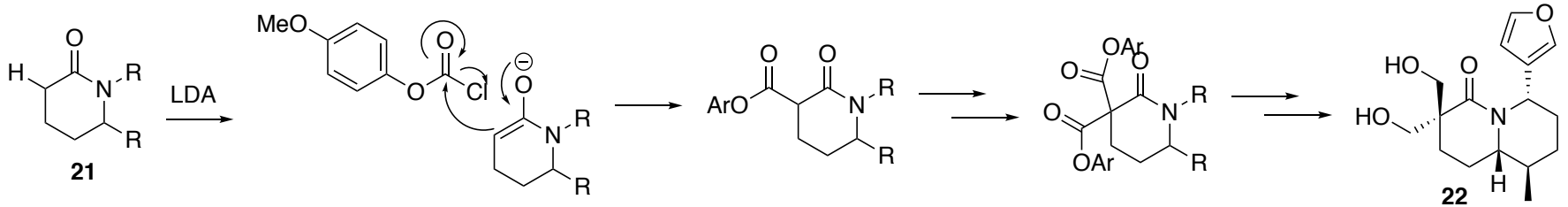


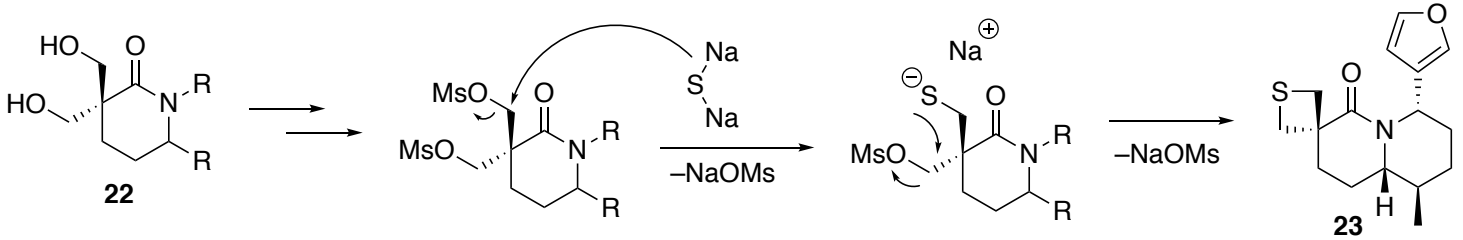
Direct diazo-transfer

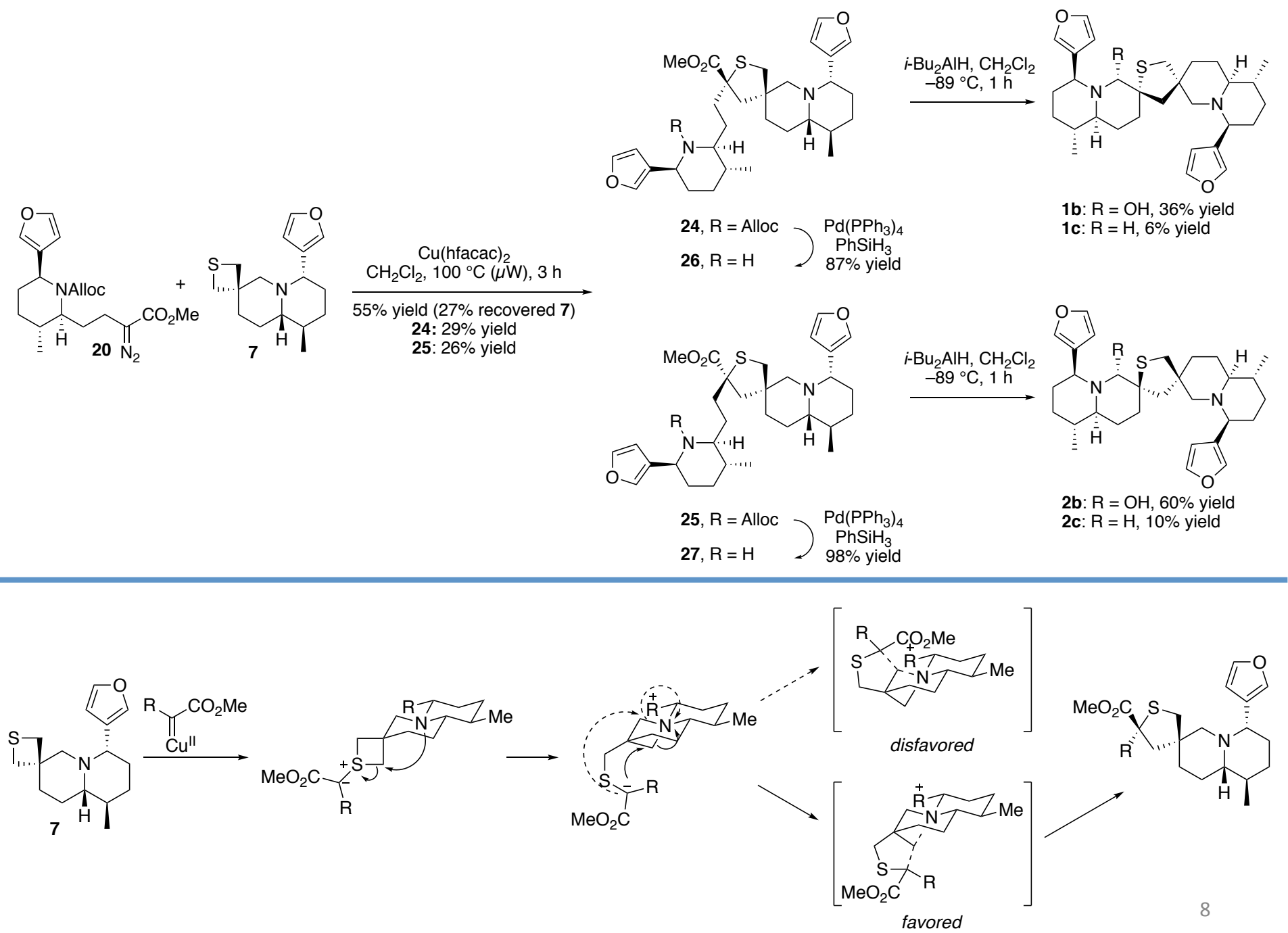



AcOH, PhMe
110 °C, 24 h
91% yield
1. LDA, 4-MeOC6H4OCOCl
THF, –78 °C (53% yield)
2. NaBH4, MeOH
23 °C (81% yield)
1. MsCl, i-Pr2NEt
CH2Cl2, 0 °C
2. Na2S·9H2O, n-Bu4NI
DMF, 50 °C
81% yield
i-Bu2AlH, PhMe
0 °C, 30 min
90 % yield
8
21
22
23
7

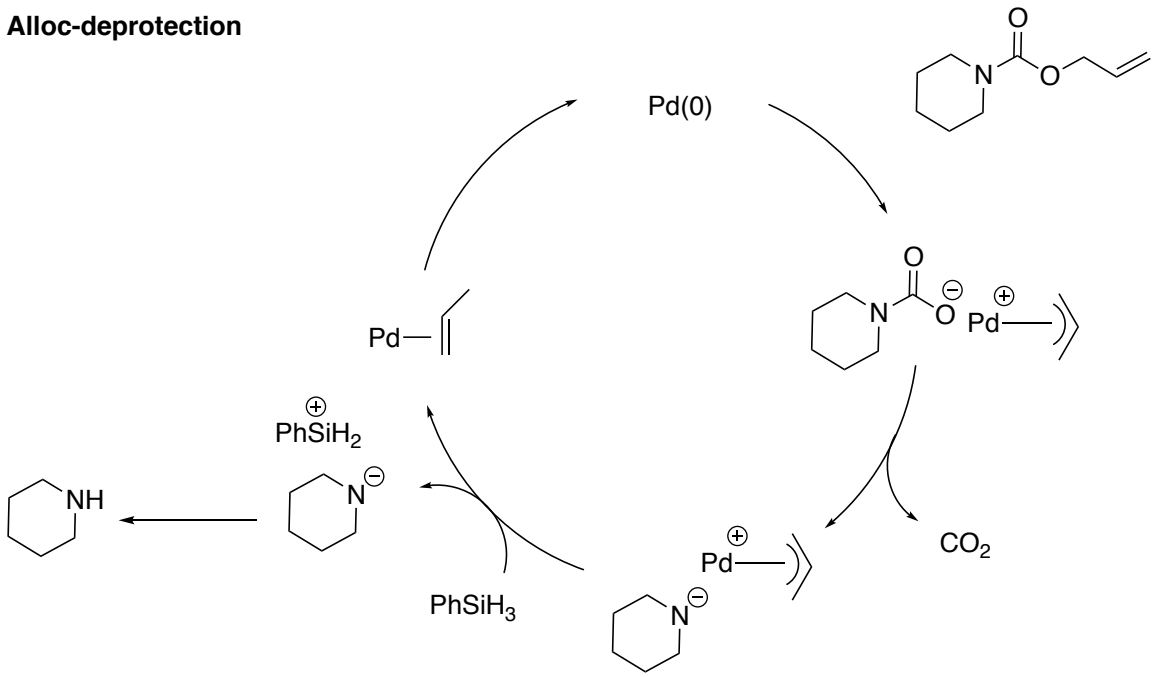

MeO
Ar
OHMe
OH
OAc
21


LDA
MeO
ArO
OAr
21
22


MsO
Na
–NaOMs
–NaOMs
22
23


NAlloc
CO2Me
N2
20
7
Cu(hfacac)2
CH2Cl2, 100 °C (μW), 3 h
55% yield (27% recovered 7)
24: 29% yield
25: 26% yield
MeO2C
24, R = Alloc
26, R = H
Pd(PPh3)4
PhSiH3
87% yield
i-Bu2AlH, CH2Cl2
–89 °C, 1 h
1b: R = OH, 36% yield
1c: R = H, 6% yield
25, R = Alloc
27, R = H
98% yield
2b: R = OH, 60% yield
2c: R = H, 10% yield
Cu^II
disfavored
favored

Alloc-deprotection



Lactamization-Reduction