

Enantioselective Total Synthesis of (–)-Hunterine A Enabled by a Desymmetrization/Rearrangement Strategy

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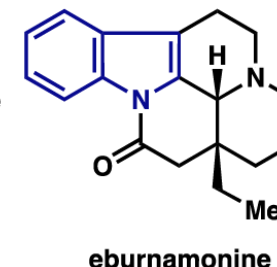
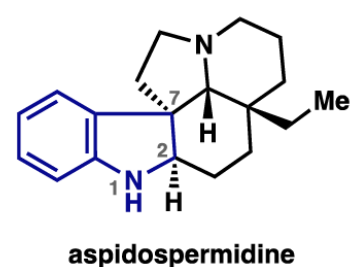


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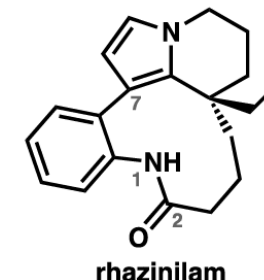
Introduction:

- A monoterpene indole alkaloid (MIA) isolated from *Hunteria zeylanica* (Apocynaceae) in 2019 by Zhang, Ye and co-workers
- Moderate cytotoxic activity against HepG2 liver cancer cell lines (35 μ M)
- Featuring a novel 6/7/6/6/5 pentacyclic ring system with an unprecedented azabicyclo[4.3.1]decane core, which presumably arose from bond cleavage and rearrangement of the indole unit

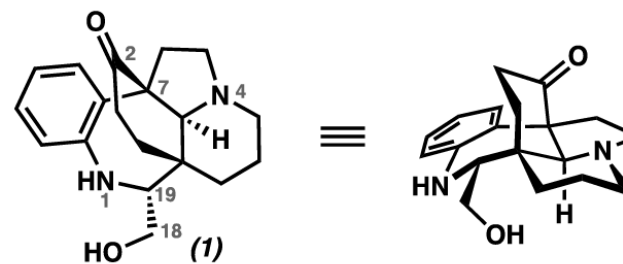
MIA: Conserved indole



MIA: C2–C7 indole cleavage

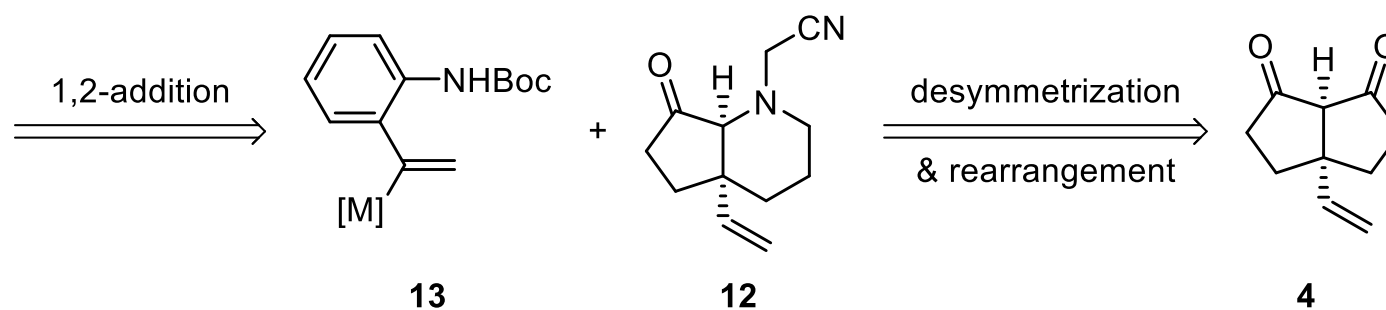
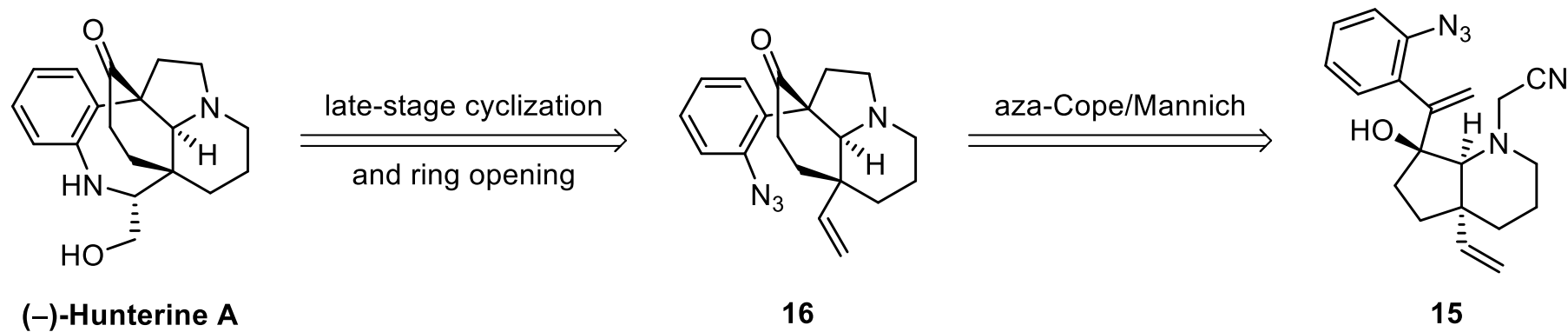


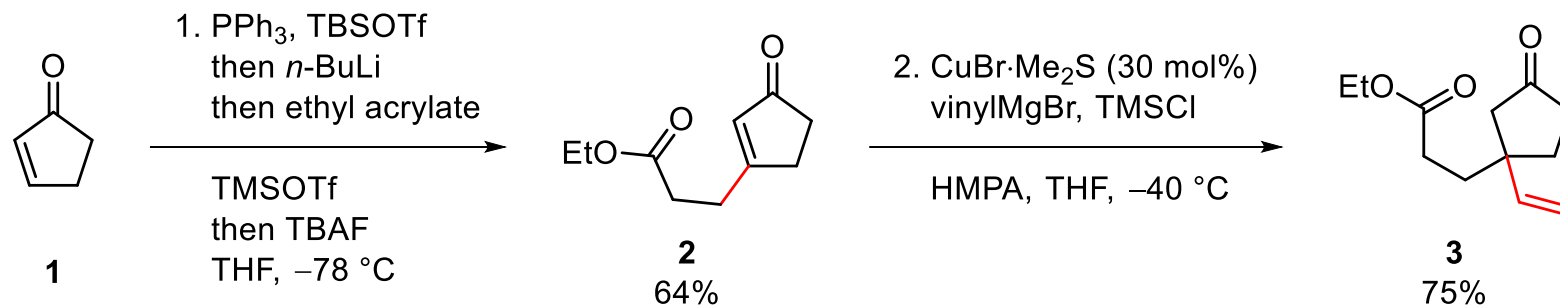
(–)-Hunterine A: Rearranged MIA, N1–C2 indole cleavage



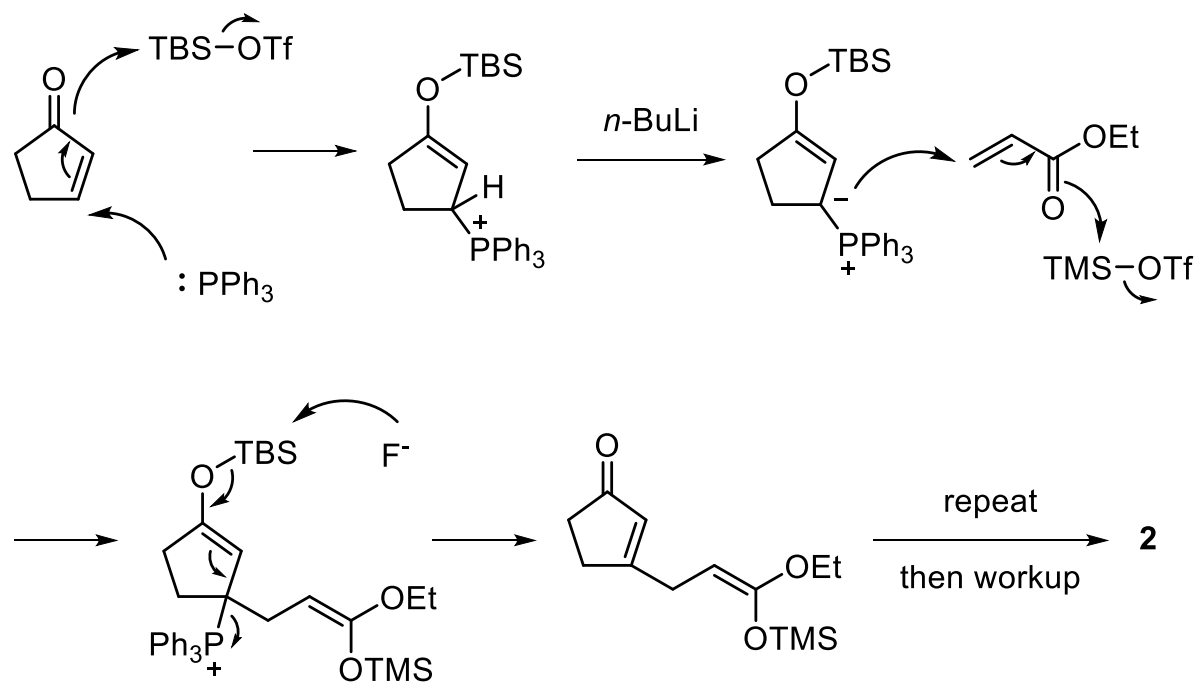
- MIA with cleaved N1–C2 indole bond
- 6/7/6/6/5 pentacyclic skeleton
- azabicyclo[4.3.1]decane core
- cytotoxic against HepG2 cell lines
- no prior syntheses

Retro-synthetic route

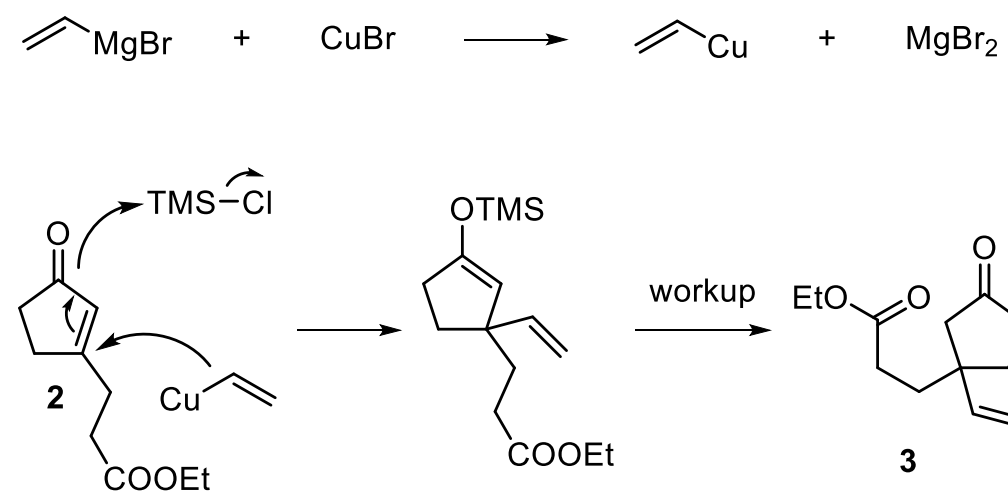


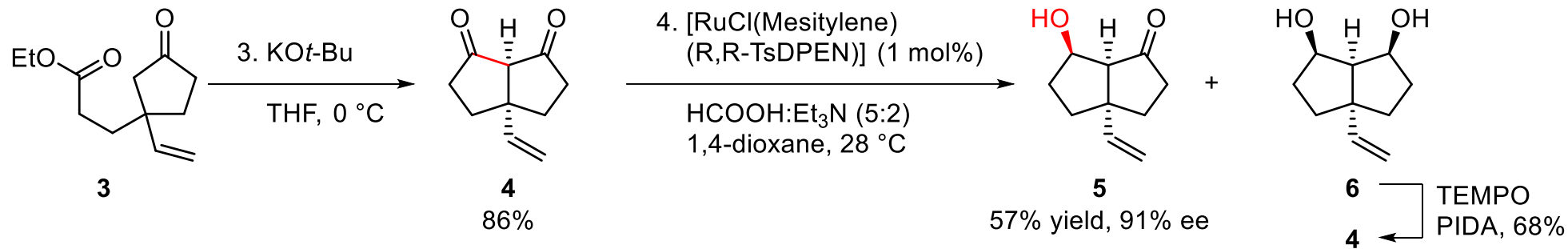


Ylide formation and addition to ethyl acrylate:

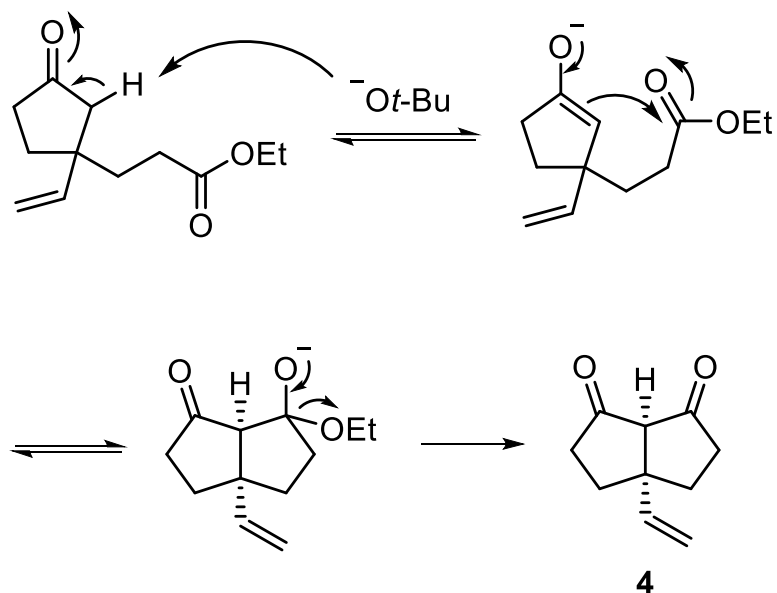


Cu-catalyzed 1,4-addition:

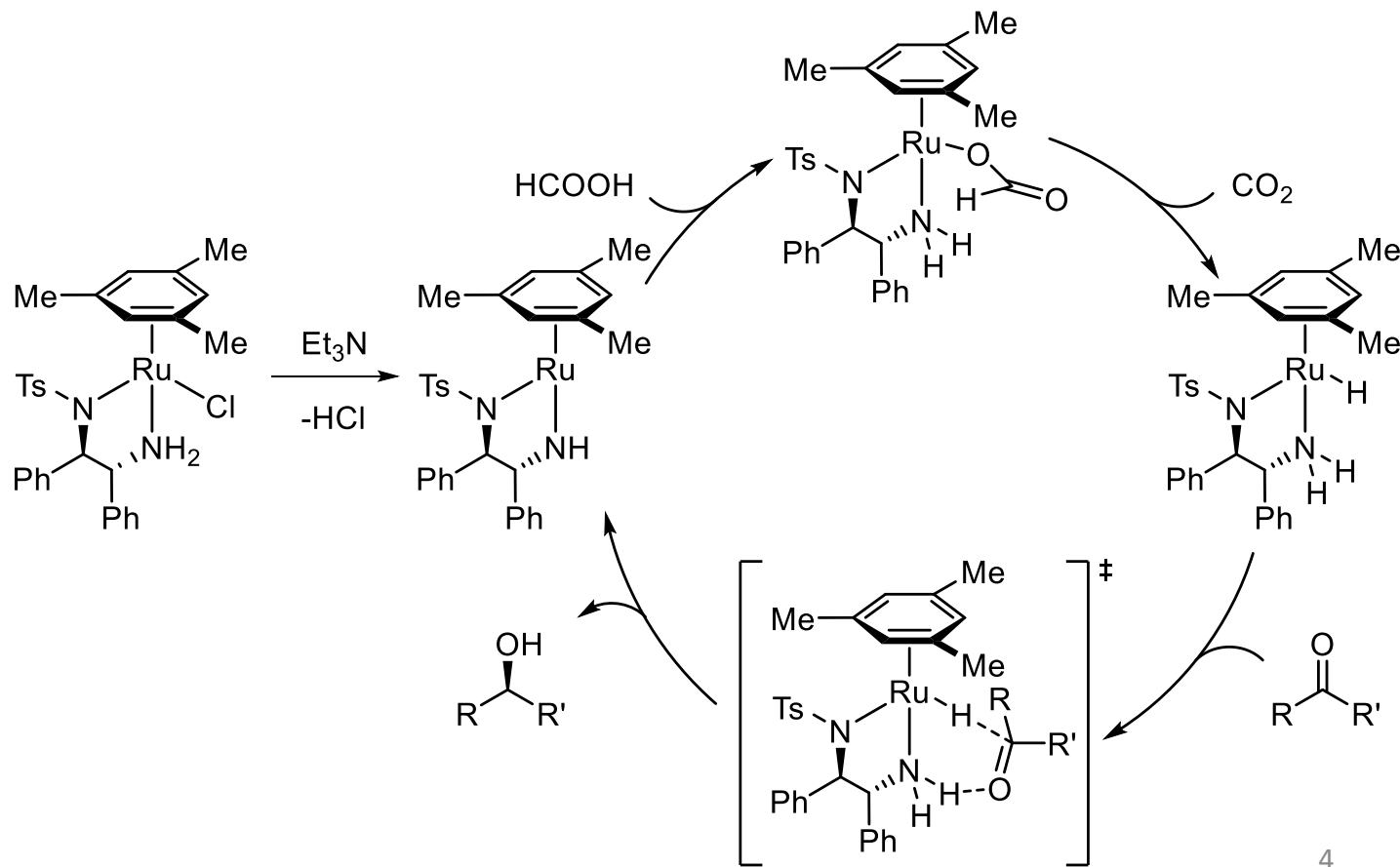


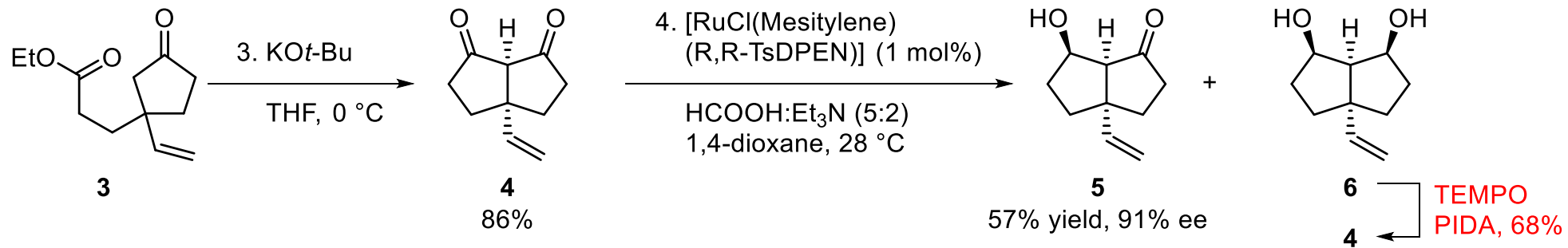


Intramolecular Claisen condensation:

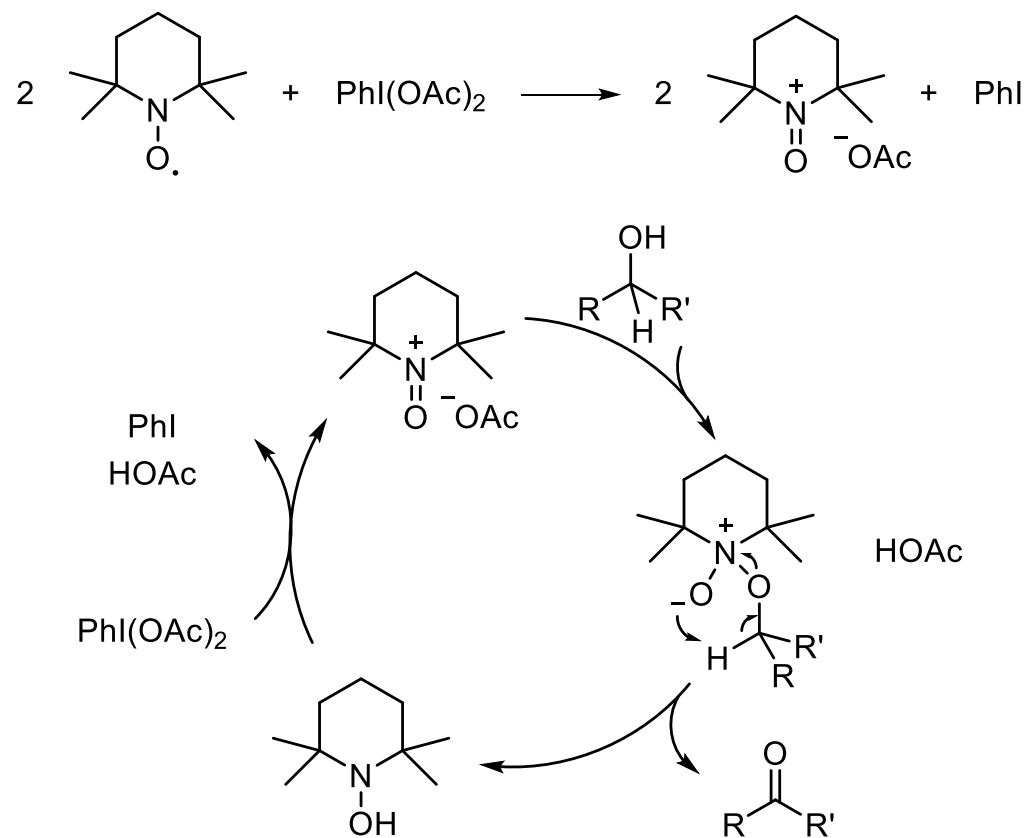


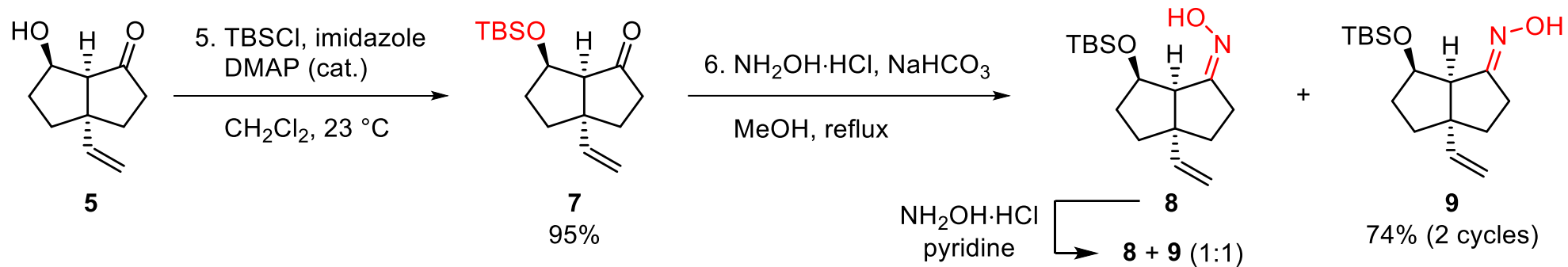
Desymmetrize via Noyori's transfer hydrogenation:



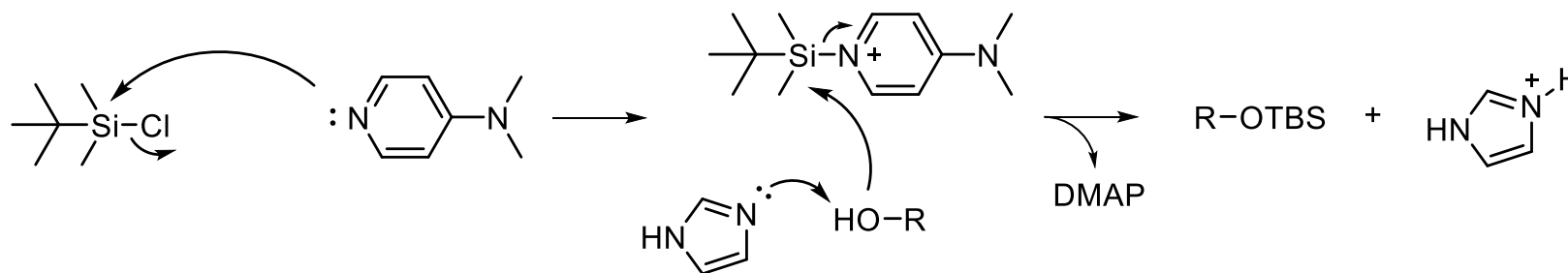


Oxidation of alcohol with TEMPO:

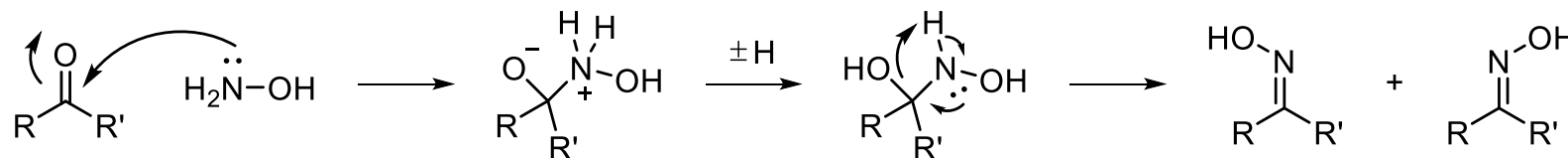


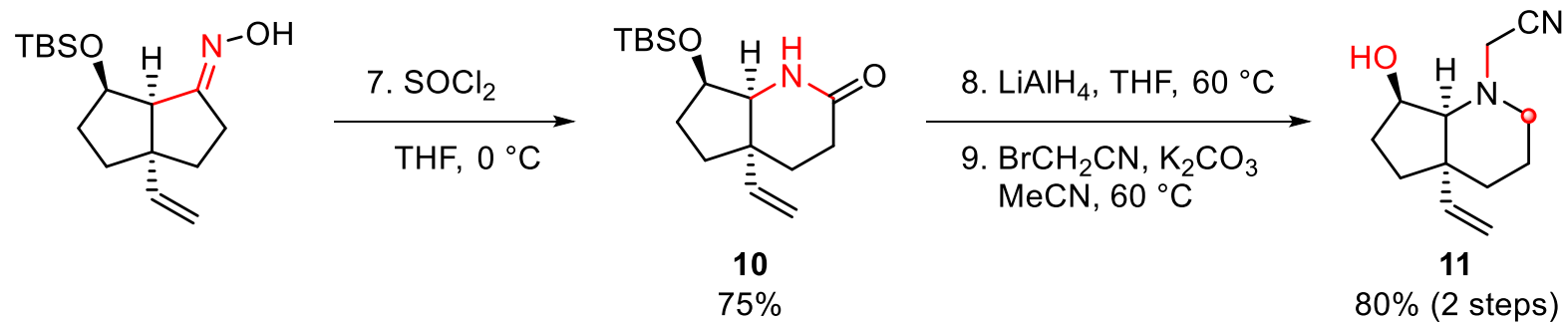


Silylation:

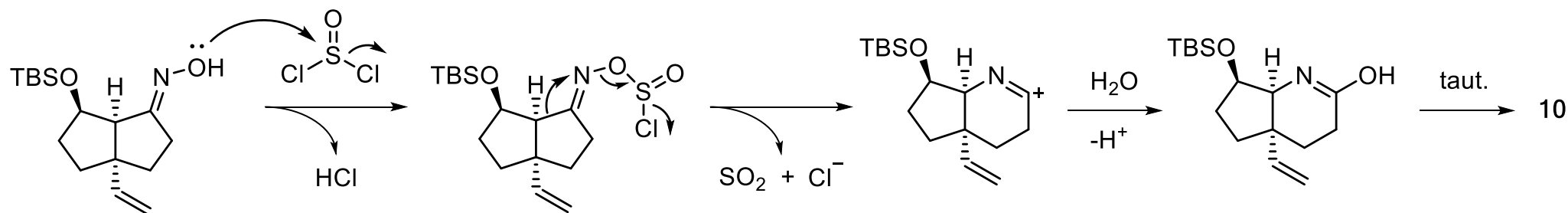


Condensation of hydroxylamine:

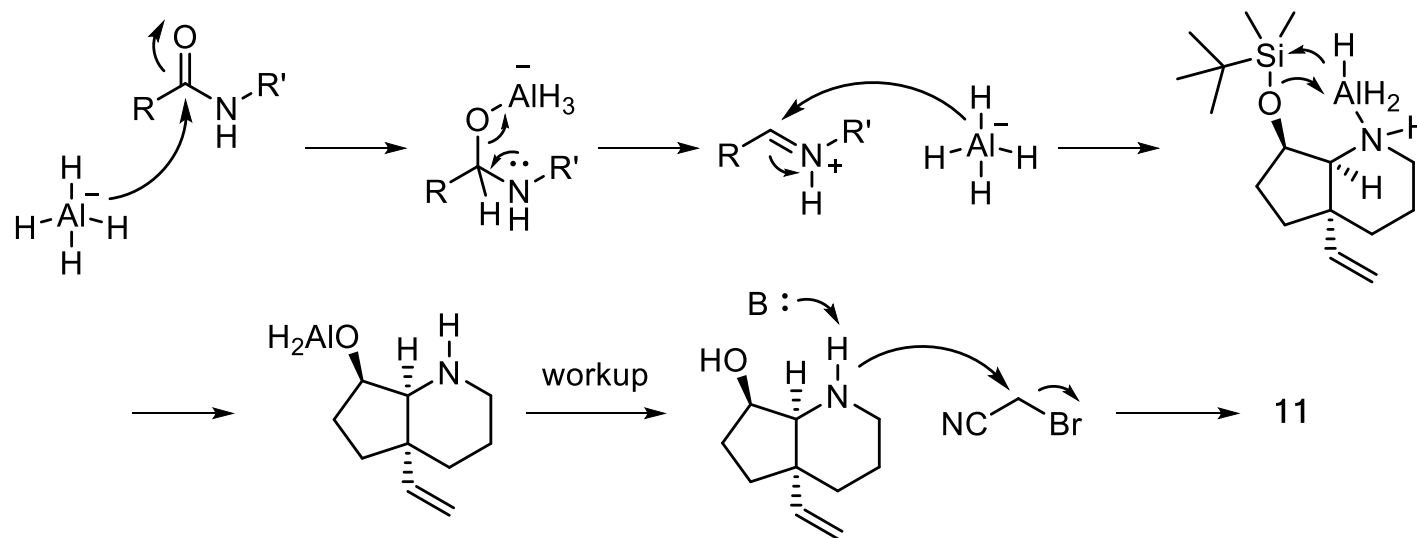


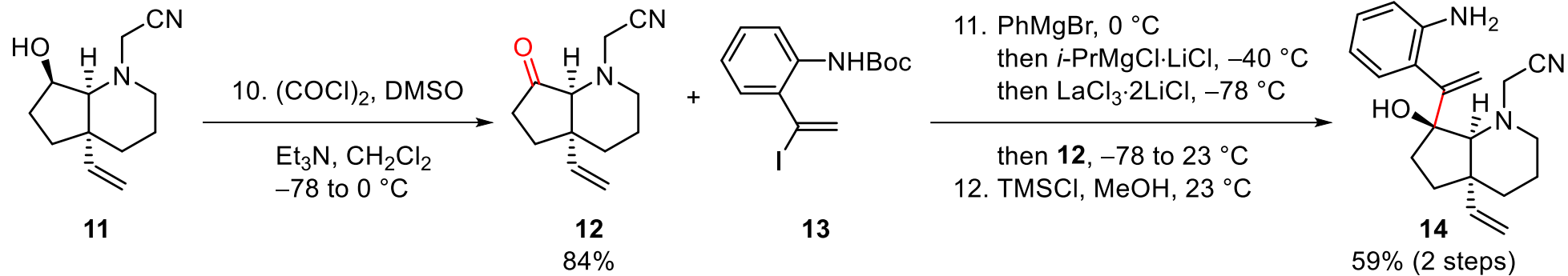


Beckmann rearrangement:

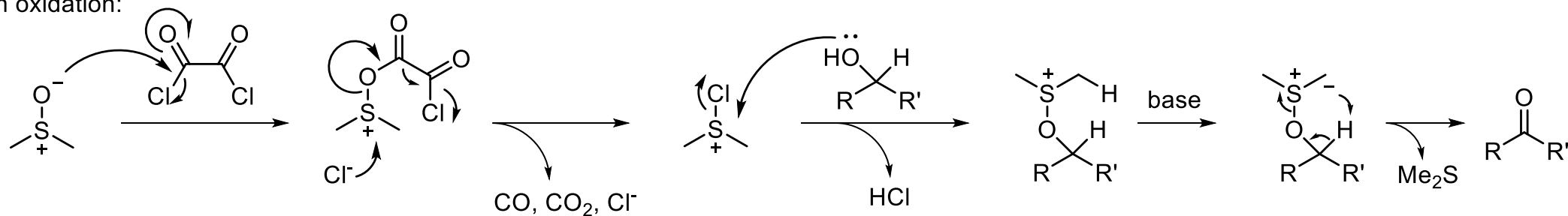


Reduction of amide with LAH and simultaneous desilylation:

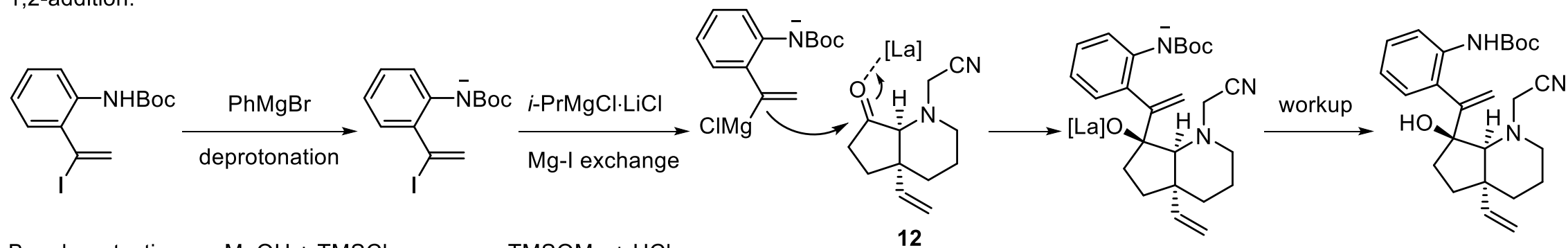




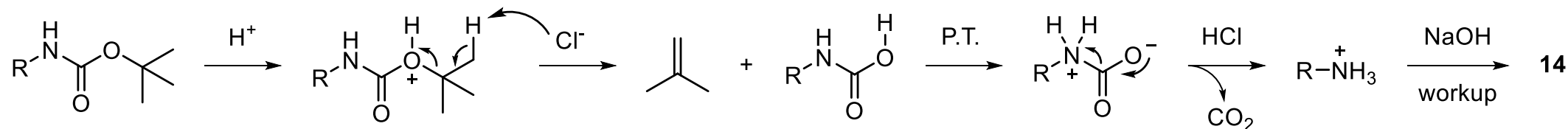
Swern oxidation:

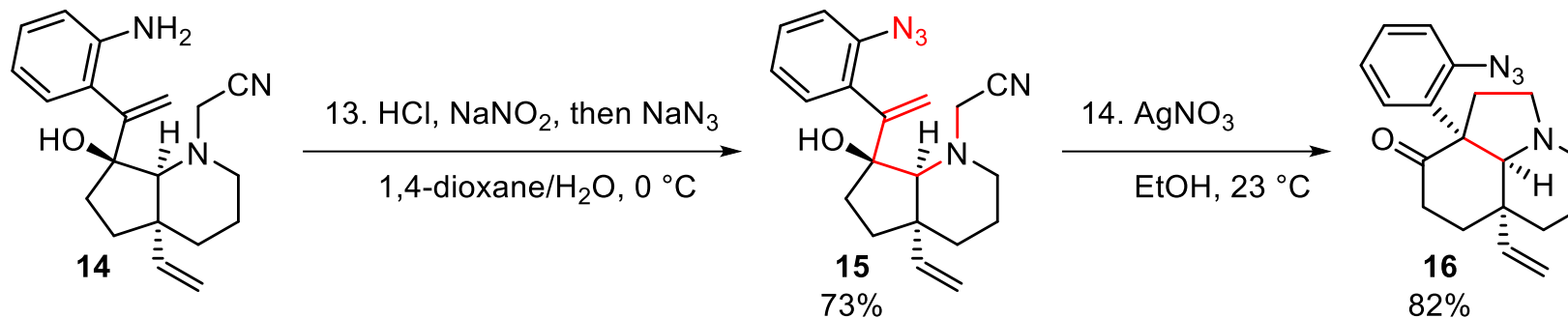


1,2-addition:

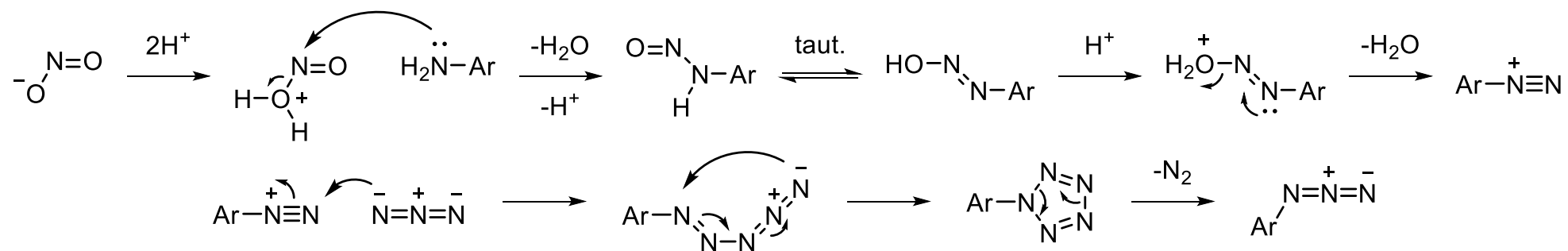


Boc deprotection: $\text{MeOH} + \text{TMSCl} \longrightarrow \text{TMSOMe} + \text{HCl}$

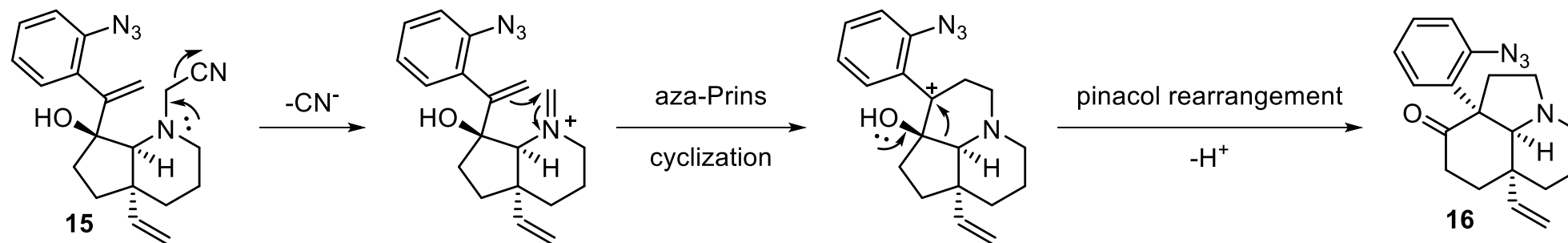


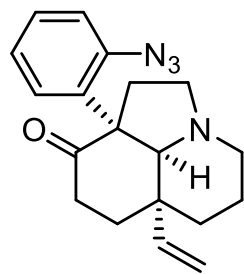


Transformation of aniline to azide via diazonium salts:



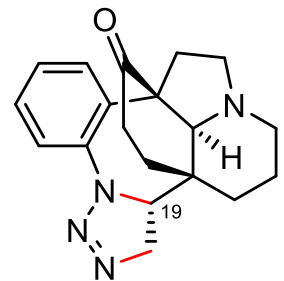
aza-Cope/Mannich reaction:





16
82%

15. heptane, 23 °C

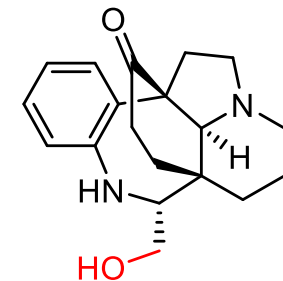


17

80% combined yield, 2.5:1 dr at C19

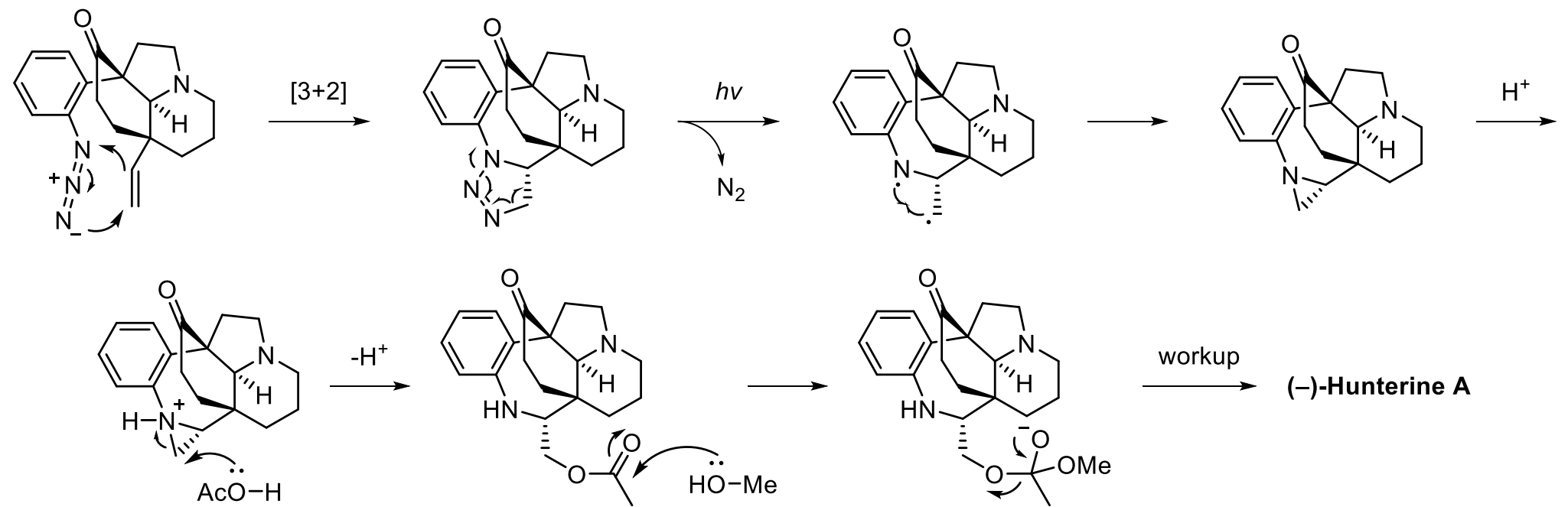
16. $h\nu$ (350 nm), C_6H_6 , 23 °C
then AcOH

17. K_2CO_3 , MeOH, 23 °C



(-)-Hunterine A
54% (2 steps)

Azide-alkene dipolar cycloaddition and subsequent aziridine formation/ring opening:



Thanks for your attention!