GDCh

Communications

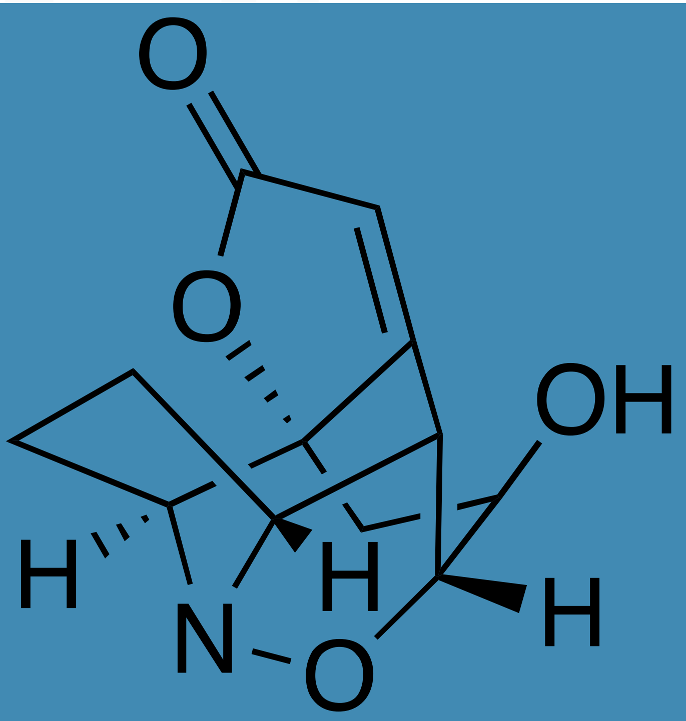
Angewandte
International Edition
Chemie

VIP Total Synthesis Very Important Paper

International Edition: DOI: 10.1002/anie.201706273
German Edition: DOI: 10.1002/ange.201706273

A Concise Enantioselective Total Synthesis of (−)-Virosaine A

*Jonathan M. E. Hughes and James L. Gleason**

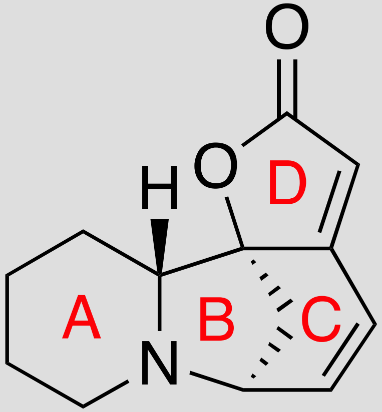


Angew. Chem. Int. Ed. **2017,** 56, 10830

(-)-VIROSAINE A

- From the family of Securinega alkaloids, known to treat eczema, allergic dermatitis and scald[1]

- Homogeneity relies on the tetracyclic backbone[2]

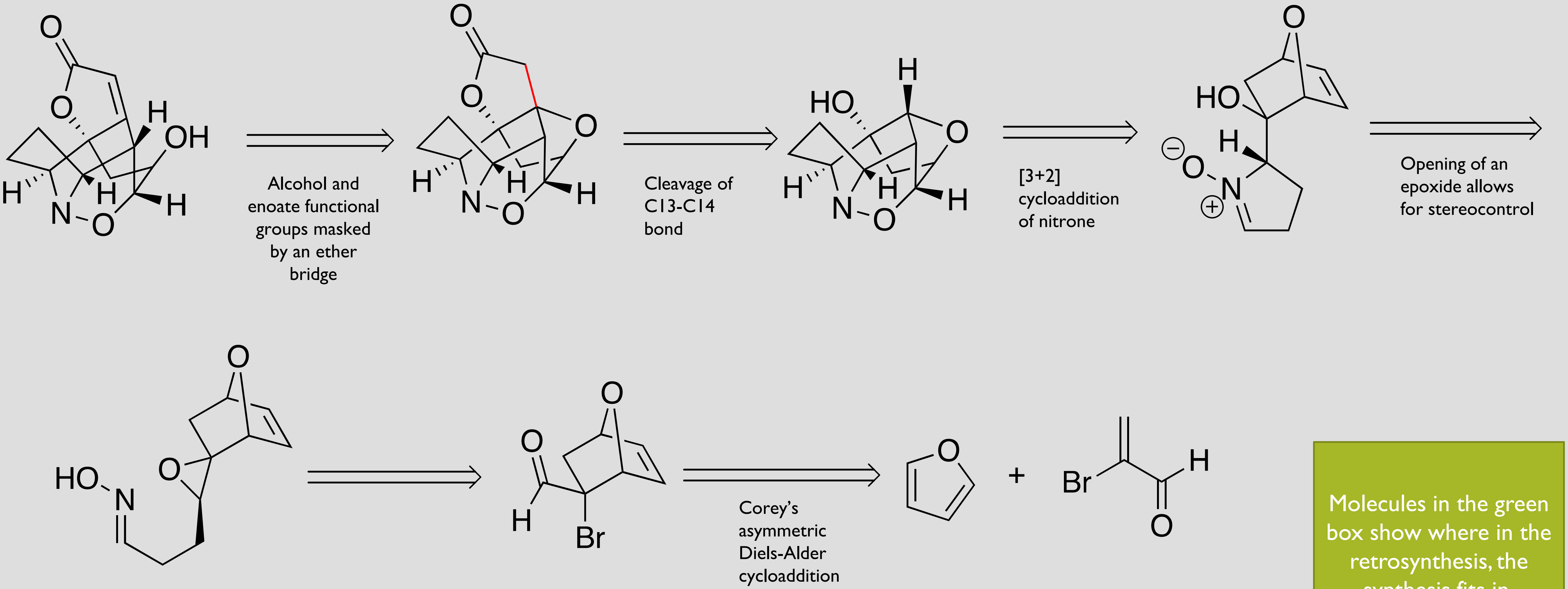


Securinine (isolated in 1956)

A- piperidine
B/C – azabicyclo [3.2.1] octane ring
D – butenolide

1. Angew. Chem. Int. Ed. **2017,** 56, 10830
2. Chirkin E, Atkatlian W, Poree F-H. In: Kno€lker H-J, ed. The Alkaloids. vol. 74. New York: Academic Press; 2015:1-120

APPROACH



Alcohol and enoate functional groups masked by an ether bridge

Cleavage of C13-C14 bond

[3+2] cycloaddition of nitrone

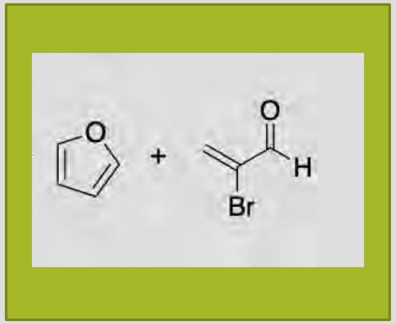
Opening of an epoxide allows for stereocontrol

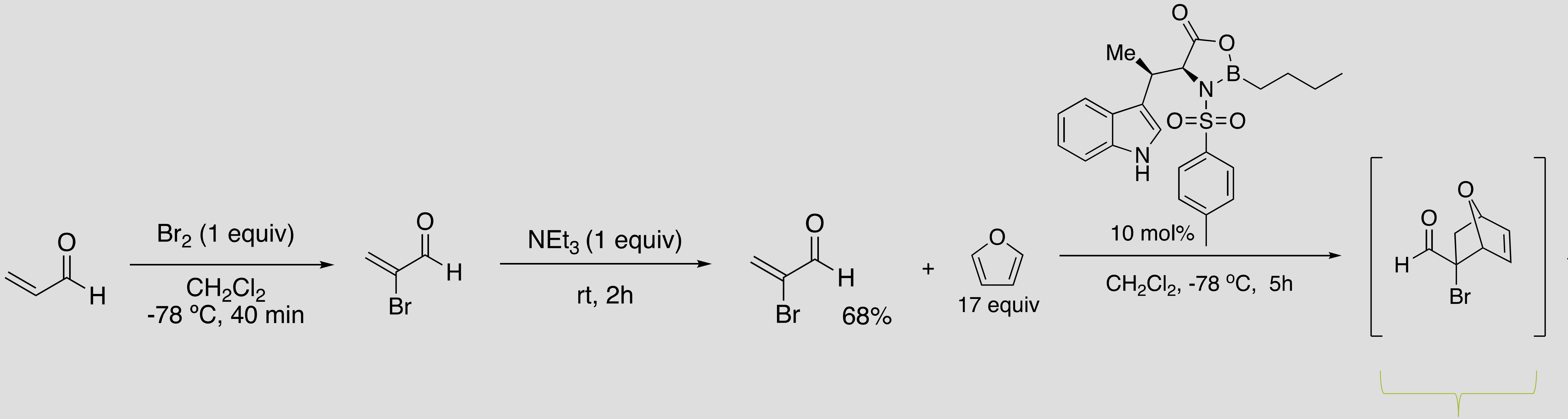
Corey's asymmetric Diels-Alder cycloaddition

Molecules in the green box show where in the retrosynthesis, the synthesis fits in.

1. Angew. Chem. Int. Ed. **2017,** 56, 10830

OXABOROLIDINONE-CATALYZED CYCLOADDITION



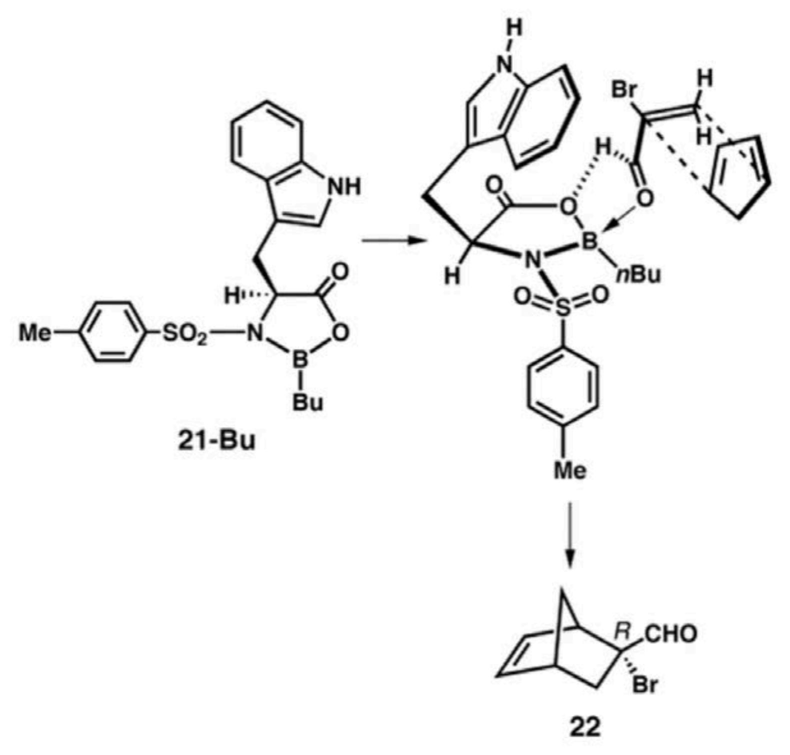


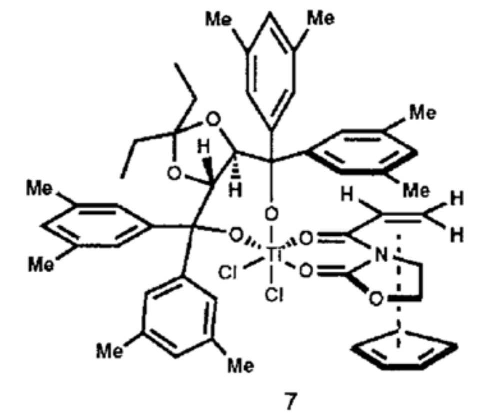
not stable enough to be isolated

Synthesis of the catalyst ….

Angew. Chem. Int. Ed. **2017,** 56, 10830
Org. Biomol. Chem. **2006**, *4*, 2119

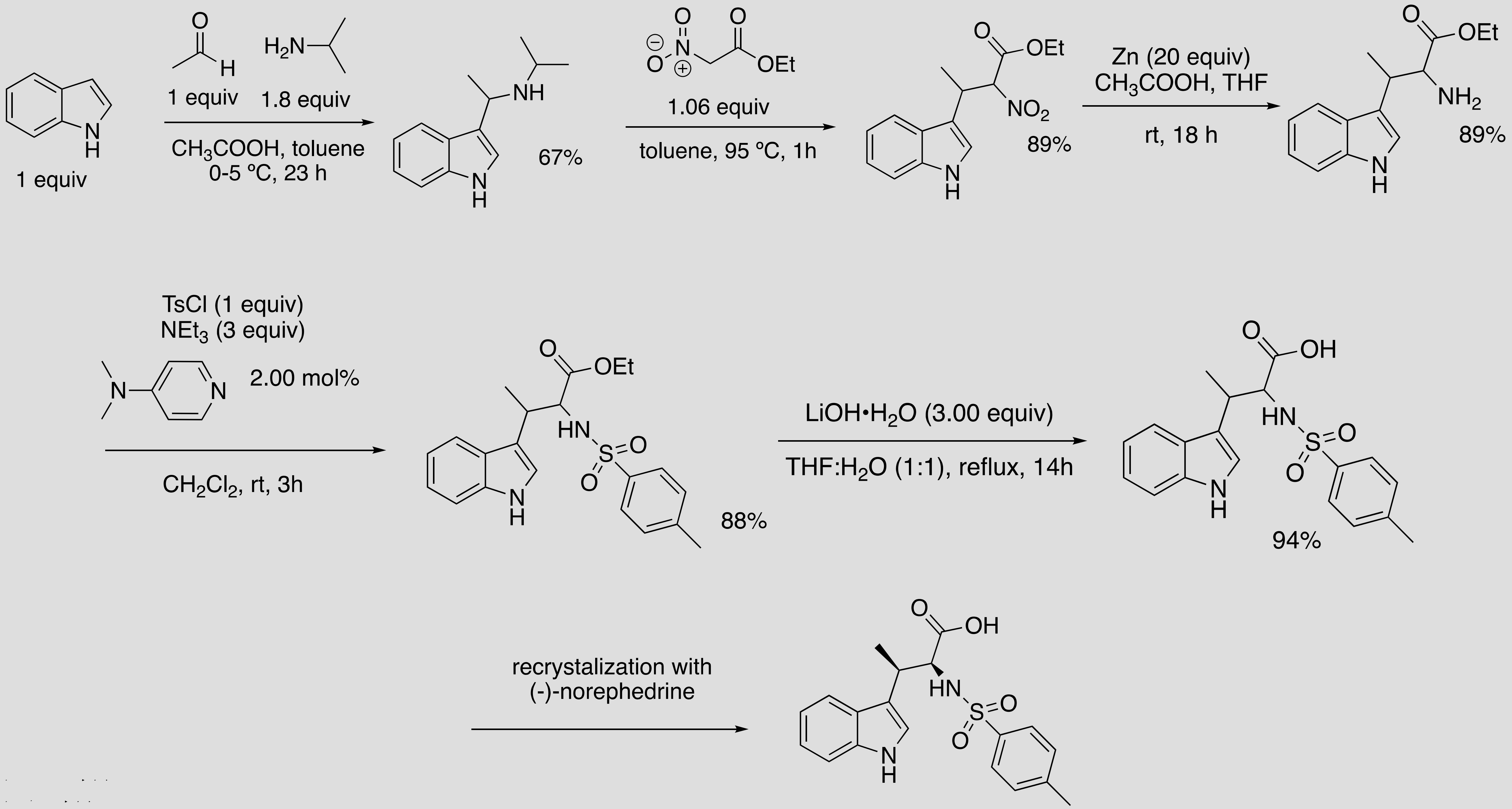
COREY'S ASYMMETRIC DIELS ALDER CYCLOADDITION[3]

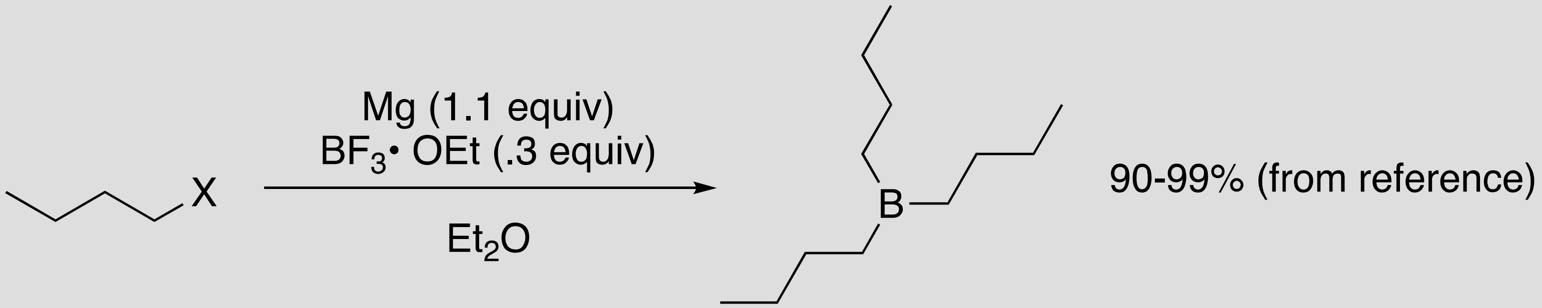


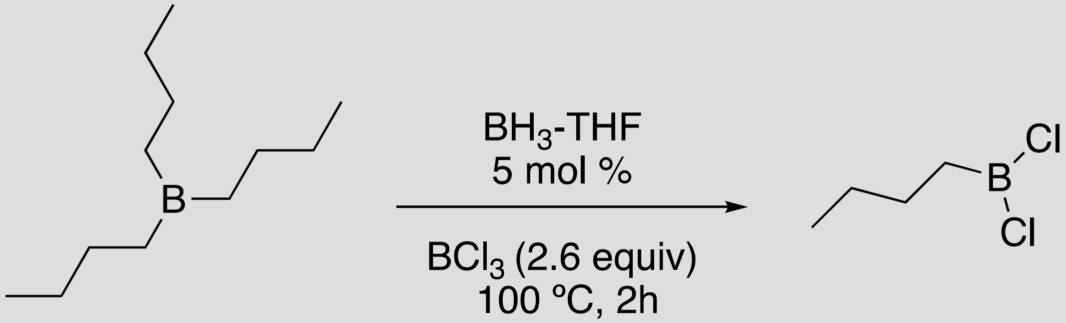


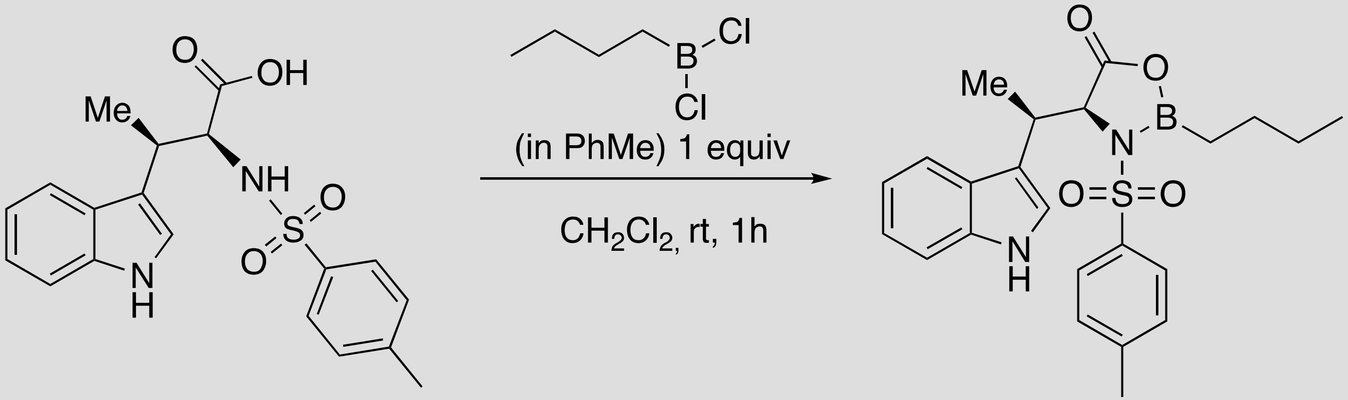
- Oxazaborolidnes were originally used for enantioselective reduction of ketones
- Pi-electron rich aromatic rings were known to channel Diels alder reactions along a stereochemical pathway
- Led to the study of their potential role in enantioselective Diels alder cycloadditions

3. Angew. Chem. Int. Ed. **2002, 41**, 1650
Tet. Lett. **1991**, 32, 6289-6292.


1 equiv
1 equiv
1.8 equiv
CH3COOH, toluene
0-5 ºC, 23 h
67%
1.06 equiv
toluene, 95 ºC, 1h
89%
Zn (20 equiv)
CH3COOH, THF
rt, 18 h
89%
TsCl (1 equiv)
NEt3 (3 equiv)
2.00 mol%
CH2Cl2, rt, 3h
88%
LiOH•H2O (3.00 equiv)
THF:H2O (1:1), reflux, 14h
94%
recrystalization with
(-)-norephedrine

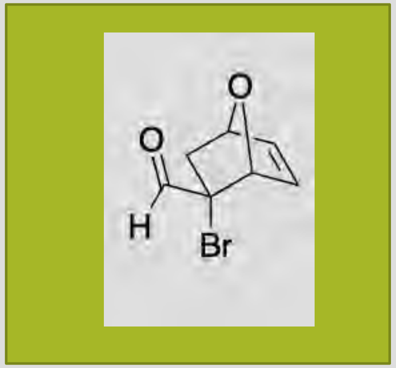


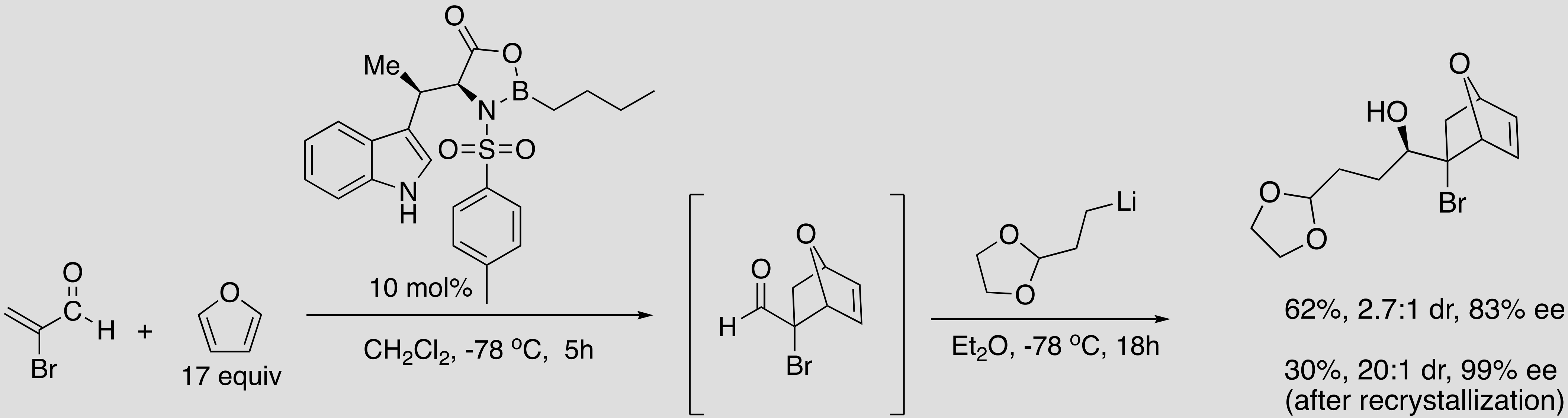




Brown, H. C.; Racherla, U. S. *J. Org. Chem.* **1986**, *51,* 427.
Brown, H. C.; Levy, A. B. *J. Organomet. Chem.* **1972**, *44*, 233.
Angew. Chem. Int. Ed. **2017,** 56, 10830

TRAPPING OF THE OXABICYCLE





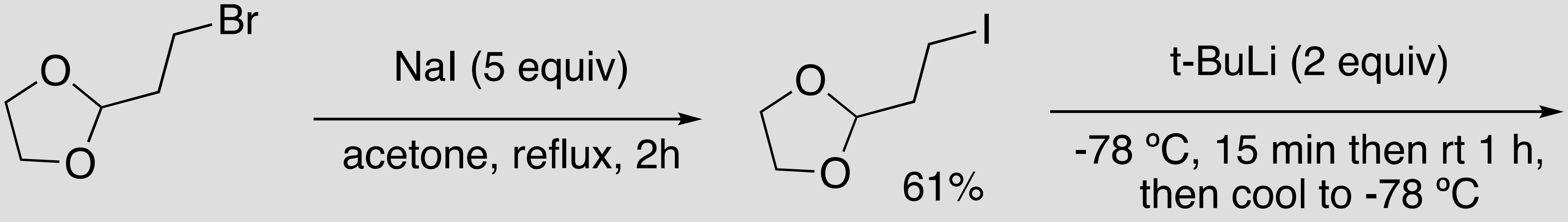
62%, 2.7:1 dr, 83% ee

30%, 20:1 dr, 99% ee
(after recrystallization)

Synthesis of the
organolithium reagent ….

Org. Lett. **2014,** 16, 2854

SYNTHESIS OF ORGANOLITHIUM REAGENT



NaI (5 equiv)

acetone, reflux, 2h

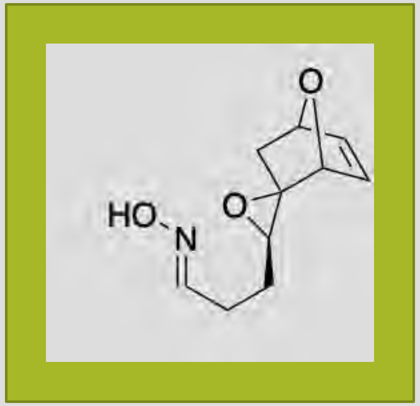
61%

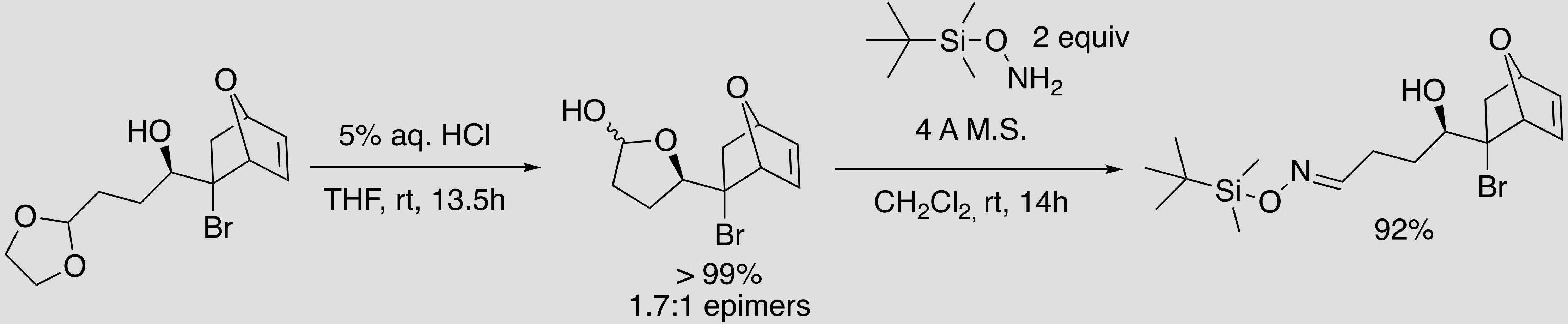
t-BuLi (2 equiv)

-78 ºC, 15 min then rt 1 h,
then cool to -78 ºC

Org. Lett. **2011**, *13*, 4850
J. Organomet. Chem. **1967**, *9*, 165

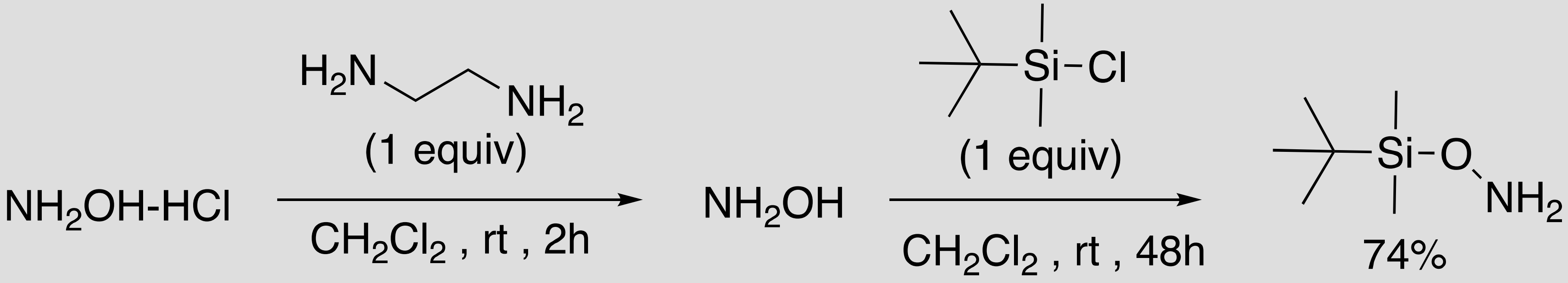
AFTER TRAPPING OF THE OXABICYCLE



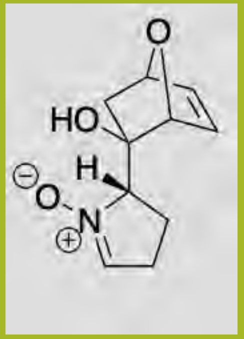


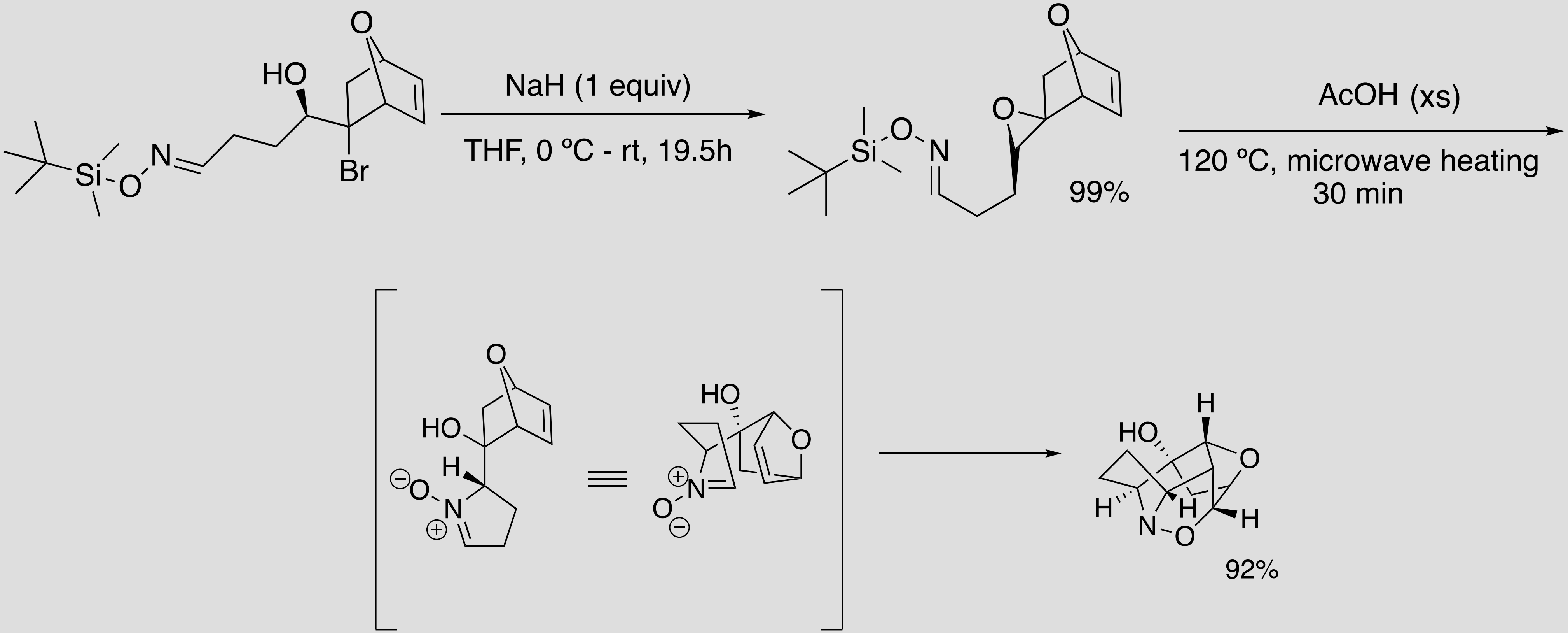
Synthesis of TBSONH$_2$….

SYNTHESIS OF TBSONH$_2$

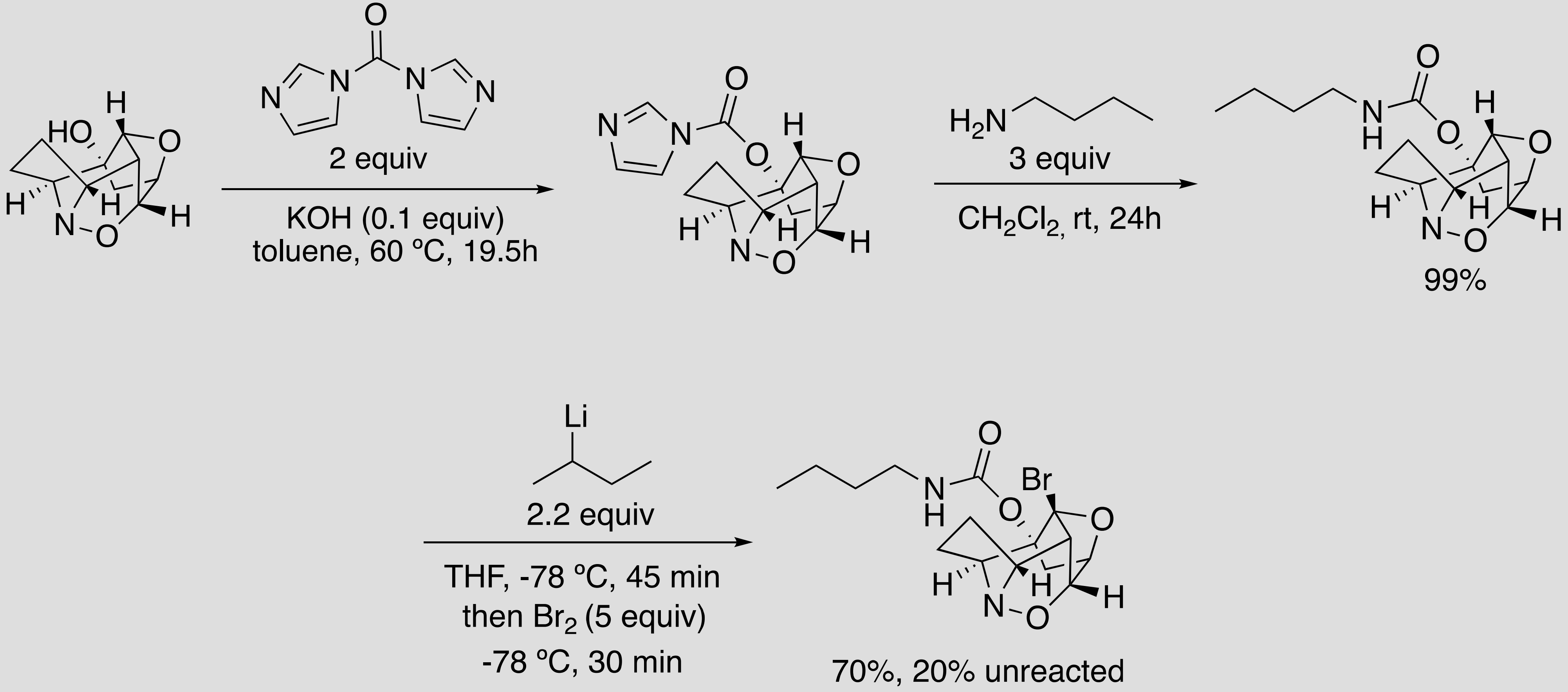


FORMATION OF CAGED BACKBONE

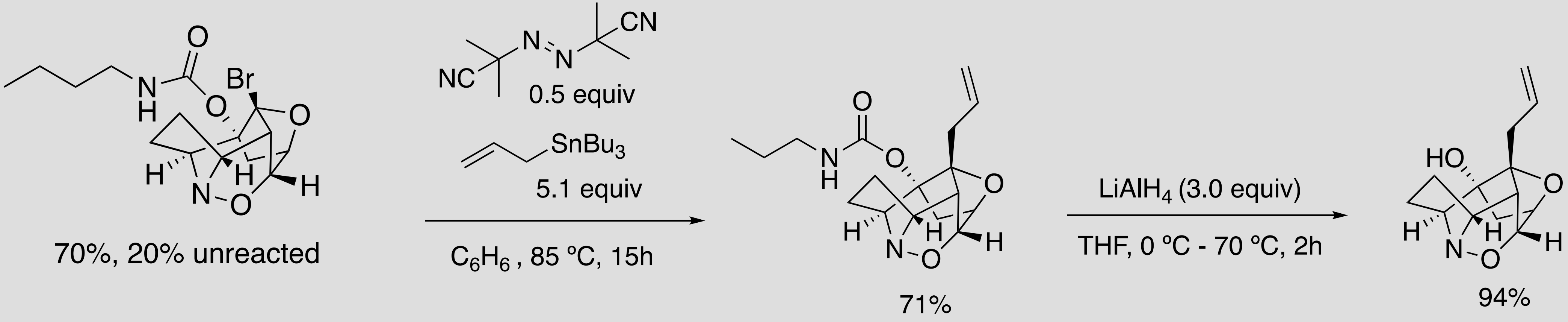




FINAL SYNTHESIS

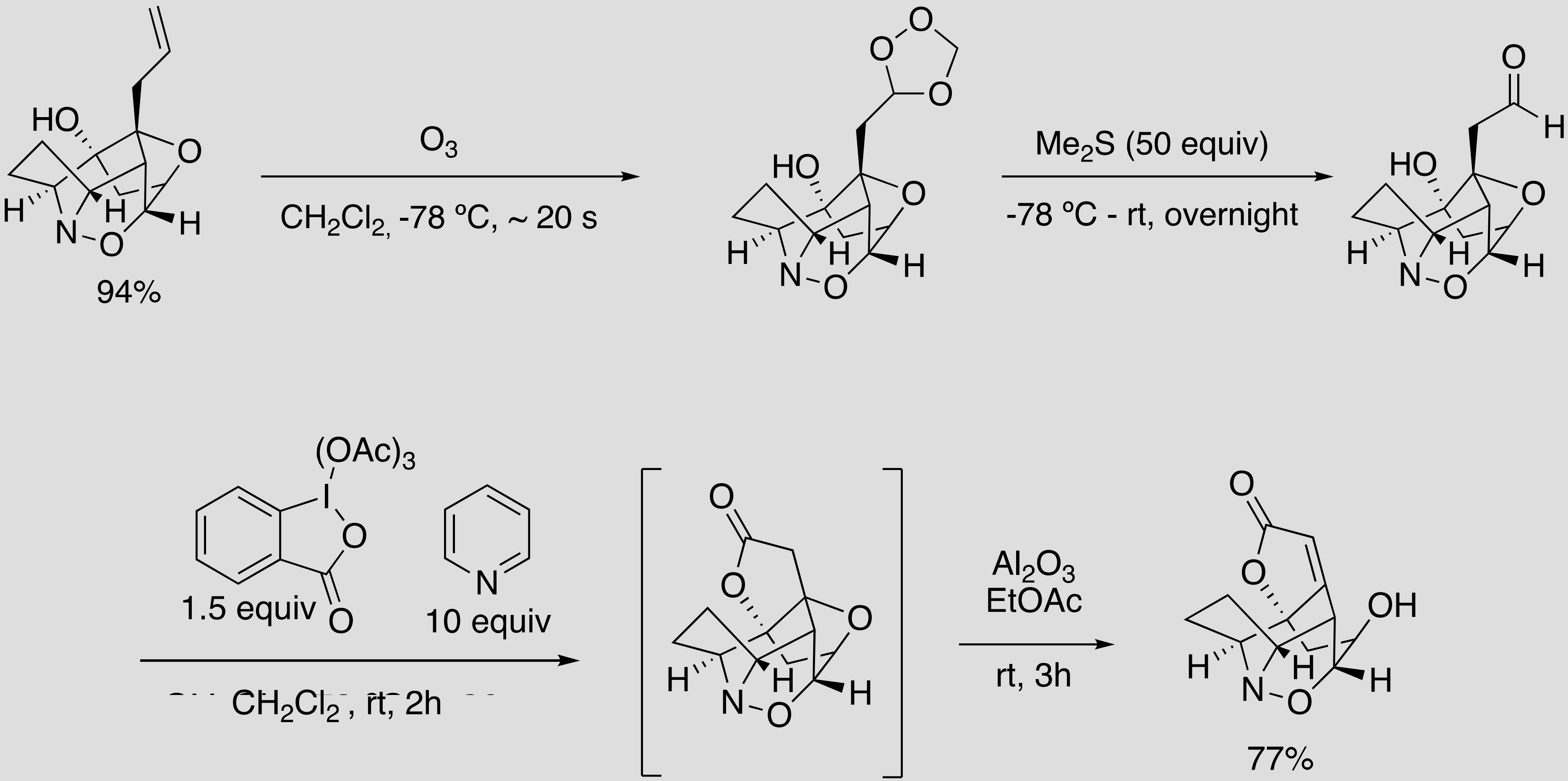


FINAL SYNTHESIS, CONT'D



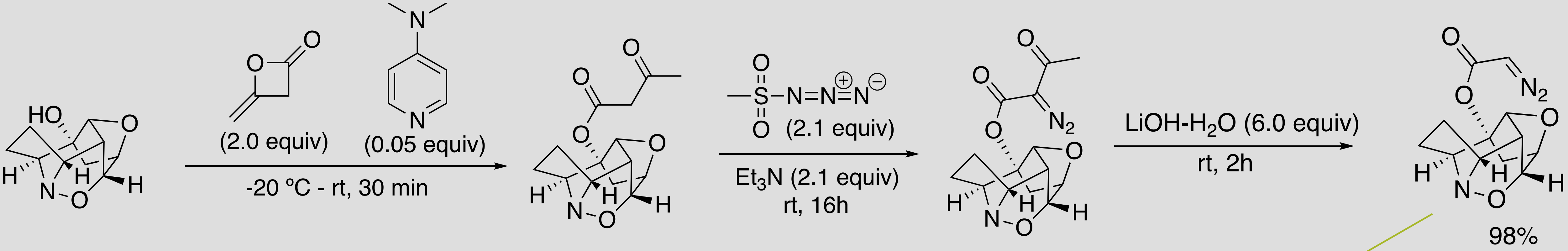
"Keck conditions"

FINAL SYNTHESIS, CONT'D



FAILED APPROACHES

Approach 1 – carbene C-H insertion of an α-diazoacetate



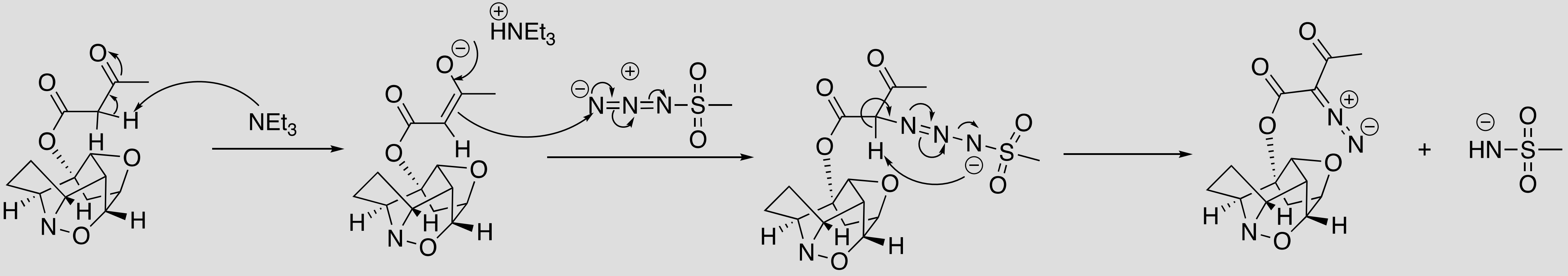
Under a range of carbene generating conditions (Rh^{2+} , Cu^{2+}, hν) products no clean products could be generated

Org. Lett. **2011,** 13, 3620
Angew. Chem. Int. Ed. **2017,** 56, 10830
Chem. Rev. **2010**, 110, 2, 704-724.

Regitz Diazo Transfer ……

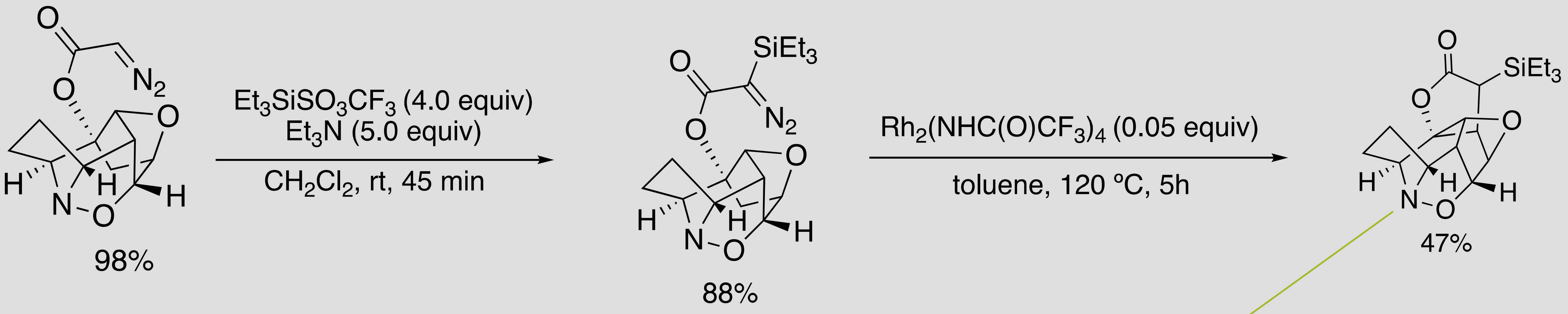
REGITZ DIAZO TRANSFER

This reaction was first reported in 1967 by Regitz, hence the name. The reaction involves a base-promoted transfer of a diazo group from an azide (most commonly tosylazide), onto a methyl or methylene carbon with neighboring electron withdrawing groups.



Wang, Z. *Comprehensive Organic Name Reactions and Reagents*; J. Wiley & Sons: Hoboken, NJ, 2010.

FAILED APPROACHES CONT'D

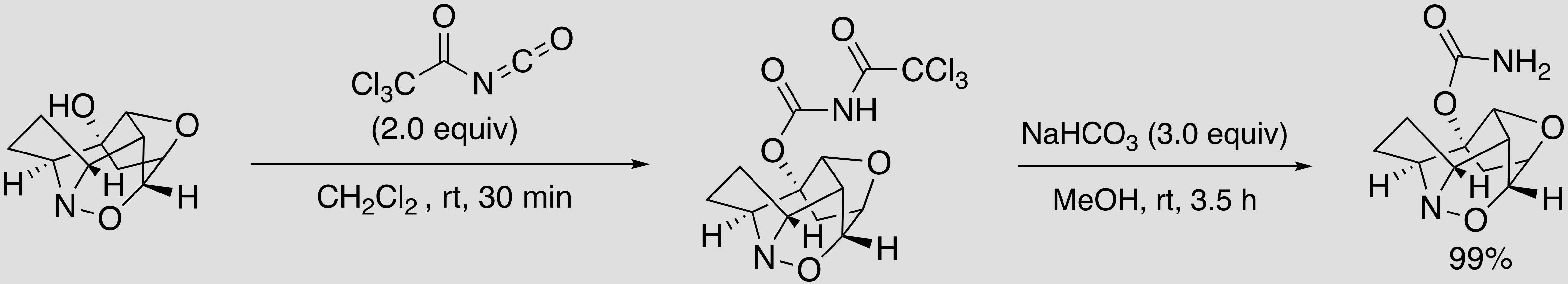


α-silyl diazoacetates have been shown to attenuate C-H insertion reactivity

Angew. Chem. Int. Ed. **2017,** 56, 10830

FAILED APPROACHES CONT’D

Approach 2 – Nitrene C-H insertion



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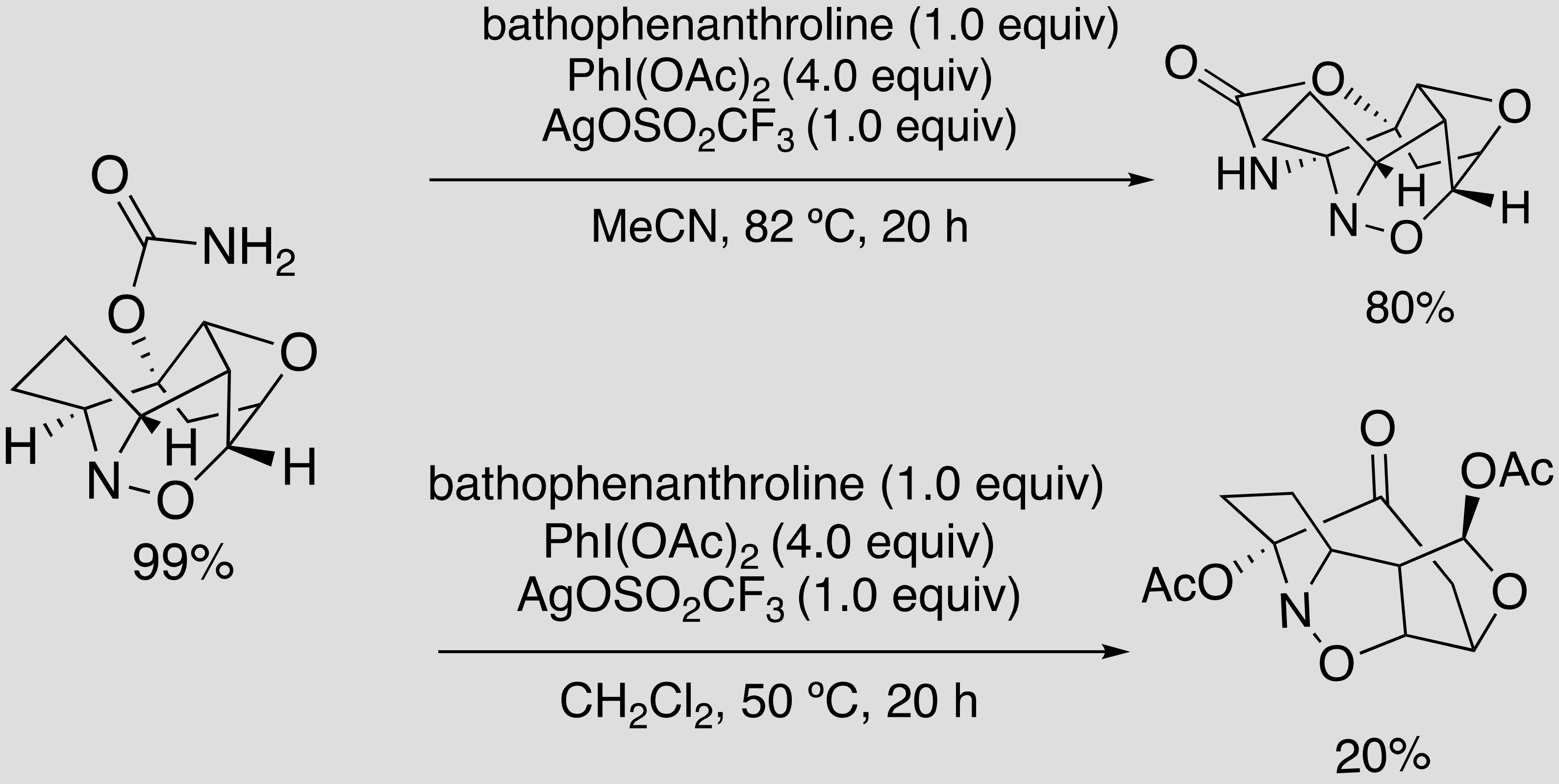
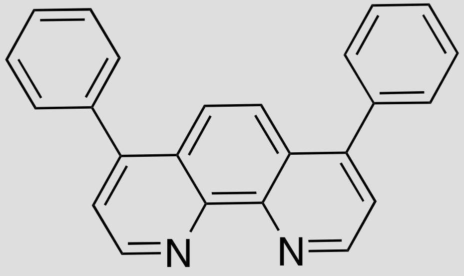
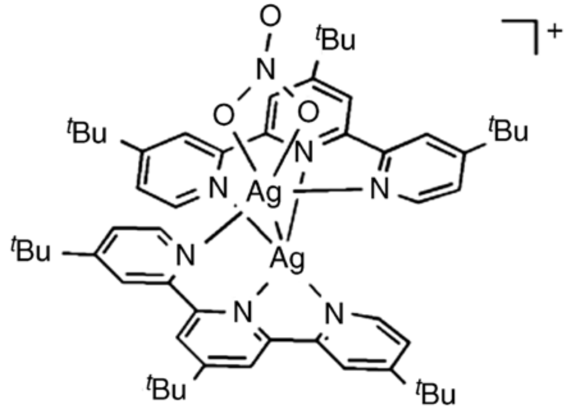
FAILED APPROACHES CONT'D





bathophenanthroline



[Ag$_2$(^{t}Bu$_3$tpy)$_3$(NO$_3$)](NO$_3$)

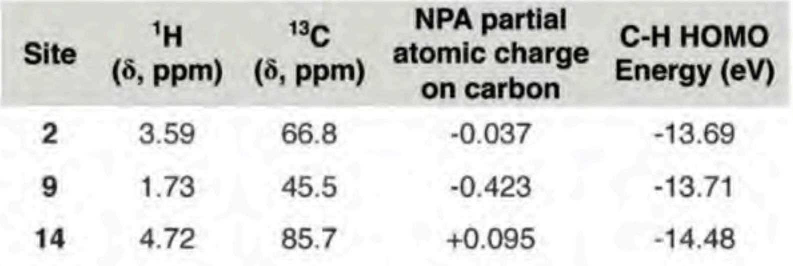
Angew. Chem. Int. Ed. **2007, 4**6, 5184

Harmata, M.; Wender, P. A. *Silver in organic chemistry*; J. Wiley & Sons: Hoboken, NJ, 2010.

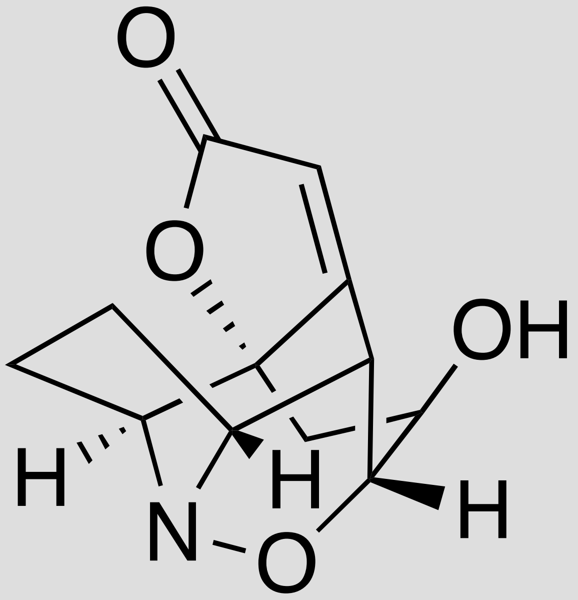
FAILED APPROACHES CONT’D

Explanation for lack of C14 reactivity

1. Steric and stereo electronic properties
   - inability of the oxygen lone pair to donate into the C14-H14 σ^* orbital resulting in inductive deactivation by oxygen



Site	^{1}H (δ, ppm)	^{13}C (δ, ppm)	NPA partial atomic charge on carbon	C-H HOMO Energy (eV)
2	3.59	66.8	-0.037	-13.69
9	1.73	45.5	-0.423	-13.71
14	4.72	85.7	+0.095	-14.48



LONGEST LINEAR SEQUENCE 17 STEPS

OVERALL YIELD 9%

THANK YOU TO THE GLEASON GROUP

FOR MAKING THIS MOLECULE