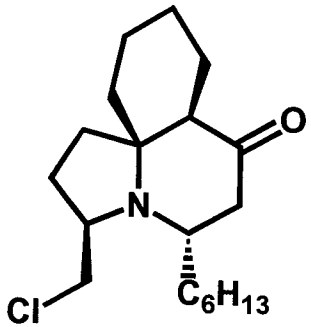
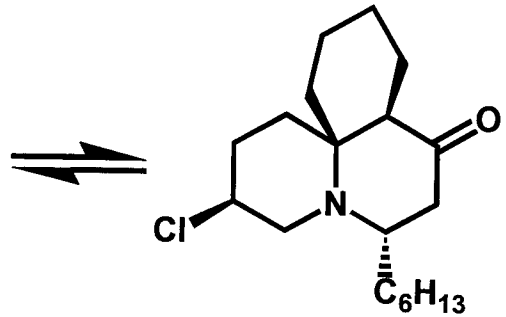
Yu Fan
02-18-03

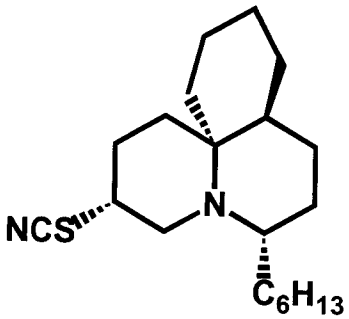
Total Syntheses of Cyclindricines, Fasicularin, and (+)-Lepadiformine



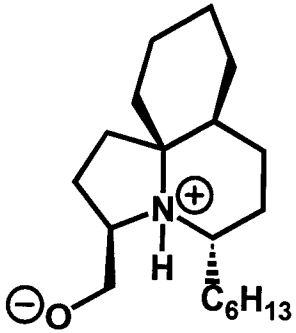
cyclindrine A



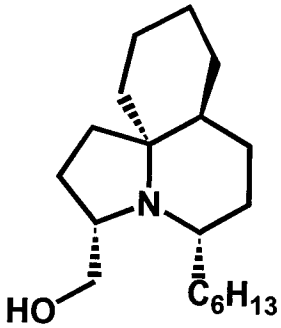
cyclindrine B



fascicularin



lepadiformine
(original structure)



lepadiformine
(revised structure)

Isolation and Structure of Cyclindricines

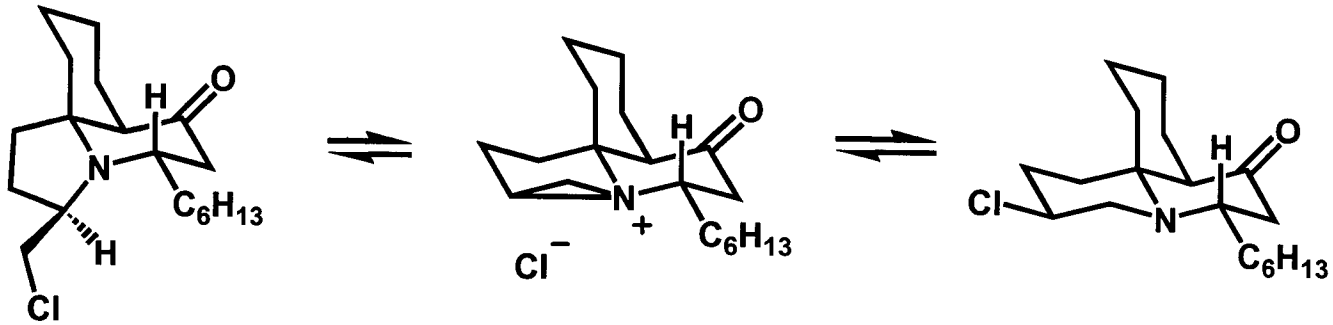
Blackman et al. Tetrahedron 1993, 49, 8645

isolated from the ascidian *Clavelina cylindrica* by HPLC in 0.039% and 0.034% yield

modest cytotoxic in brine shrimp larvae assay

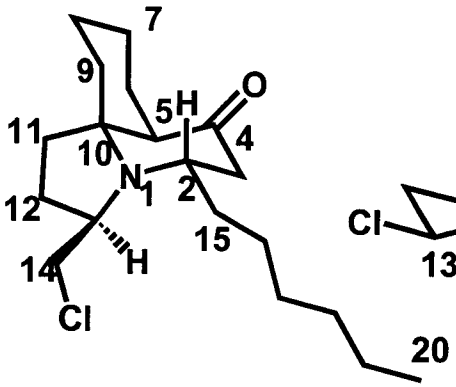
exists in equilibrium of 3 : 2 mixture in solution

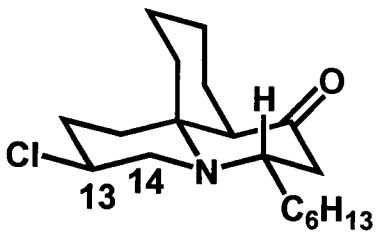
absolute configuration unknown

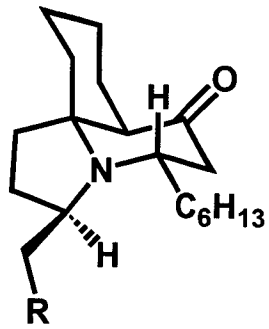


cyclindrine A

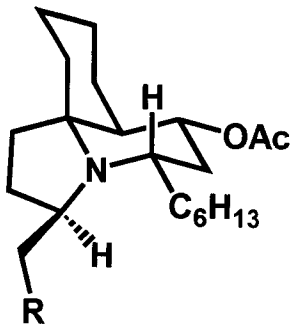
cyclindrine B







R = OH, OMe, OAc, SCN

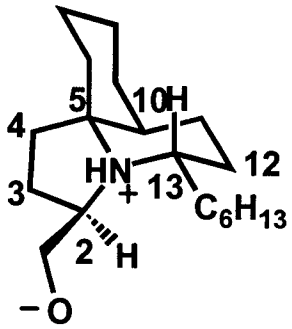


R = SCN, NCS

Isolation and Structure of Lepadiformine and Fasicularin

Biard et al. TL. 1994, 35, 2691-4

isolated from the ascidian *Clavelina lepadiformis* Muller by HPLC in 0.053% yield
modest cytotoxic against a few tumor cell lines IC_{50} 0.74 μg/mL to 9.20 μg/mL
proposed as zwiterionic form from the evidence below:



lepadiformine

^{13}C NMR

C2: 65.34
C5: 76.58
C13: 58.71

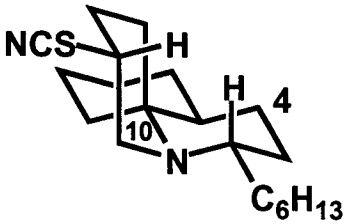
acidic proton
δ = 10 ppm
^{1}H-^{15}N HMQC
J = 75 Hz

FT-IR
sharp bands
2350 to 2700 cm^{-1}

failed to acylate or alkylate

Patil et al. TL. 1997, 38, 363-4

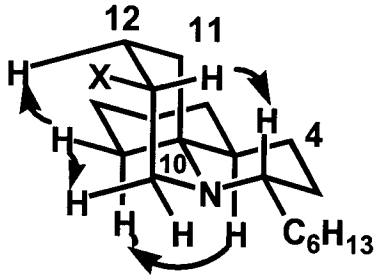
isolated from the ascidian *Nephteis fasicularis* in a DNA damaging assay
modest cytotoxic against Vero cell line IC_{50} 14.0 μg/mL



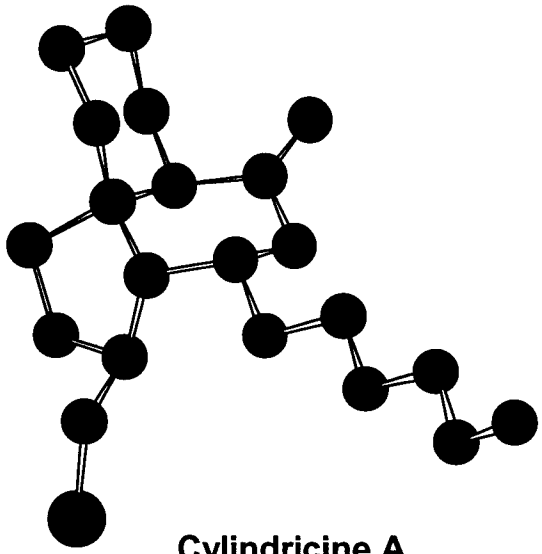
S-C≡N

~~N=C=S~~, IR 2152 cm-1
m/z 308, 276 for HCN, NCSH
^{13}C NMR 111.5 ppm
(isocyanate 129 ppm)

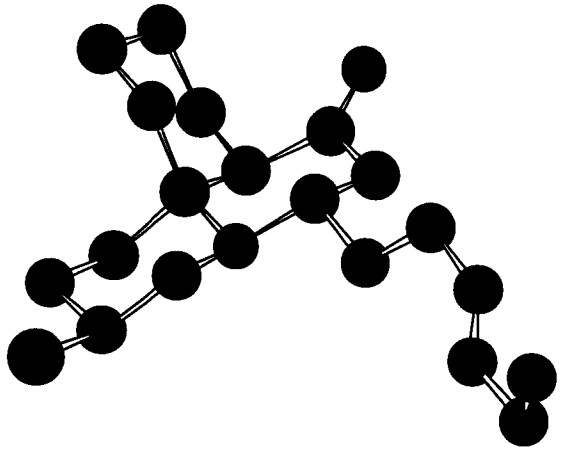
isothio



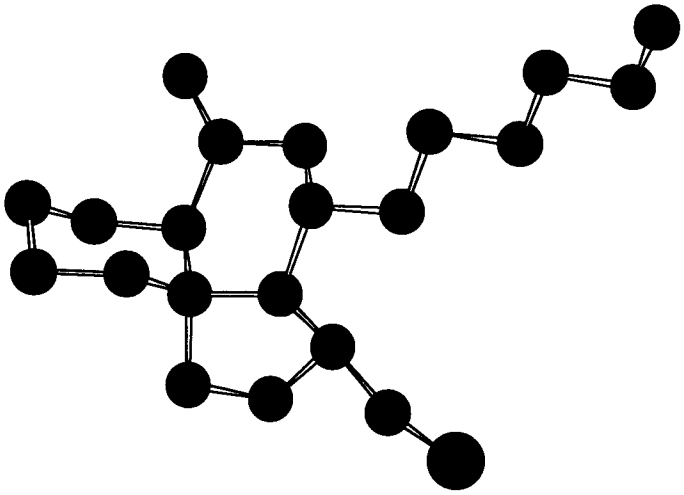
X-ray Structure of Cylindricines A and B

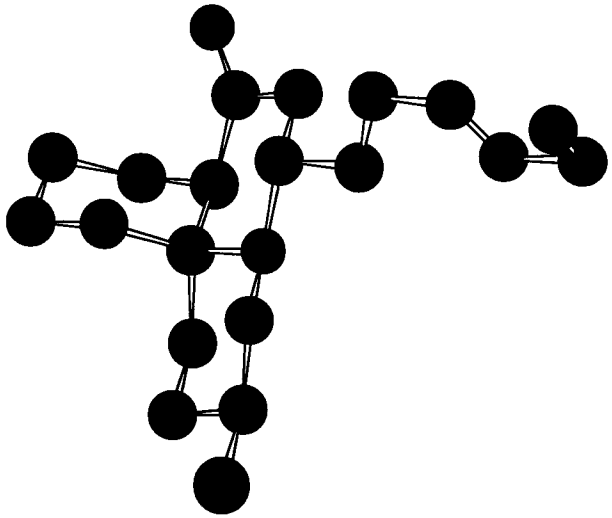


Cylindricine A

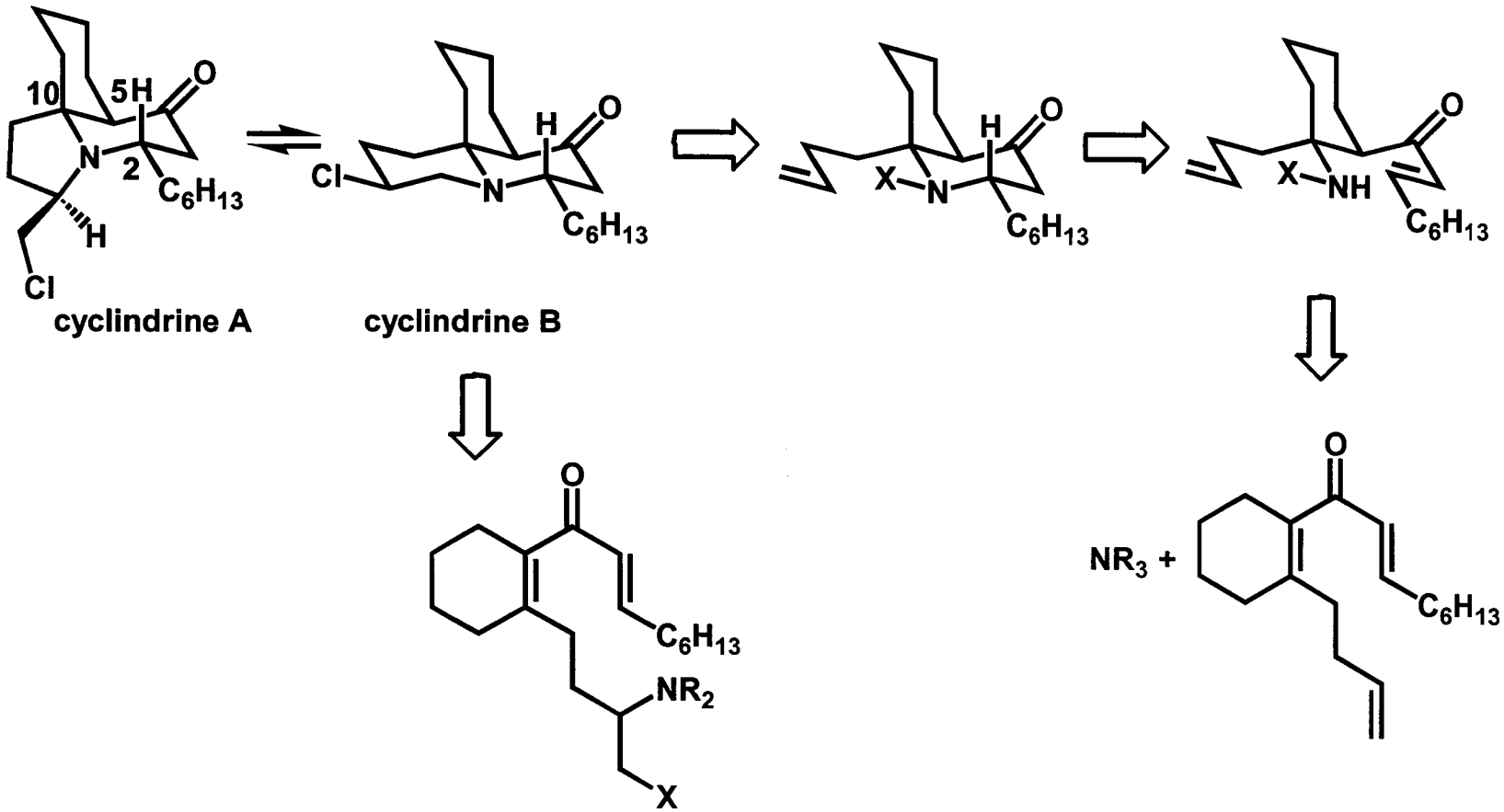


Cylindricine B



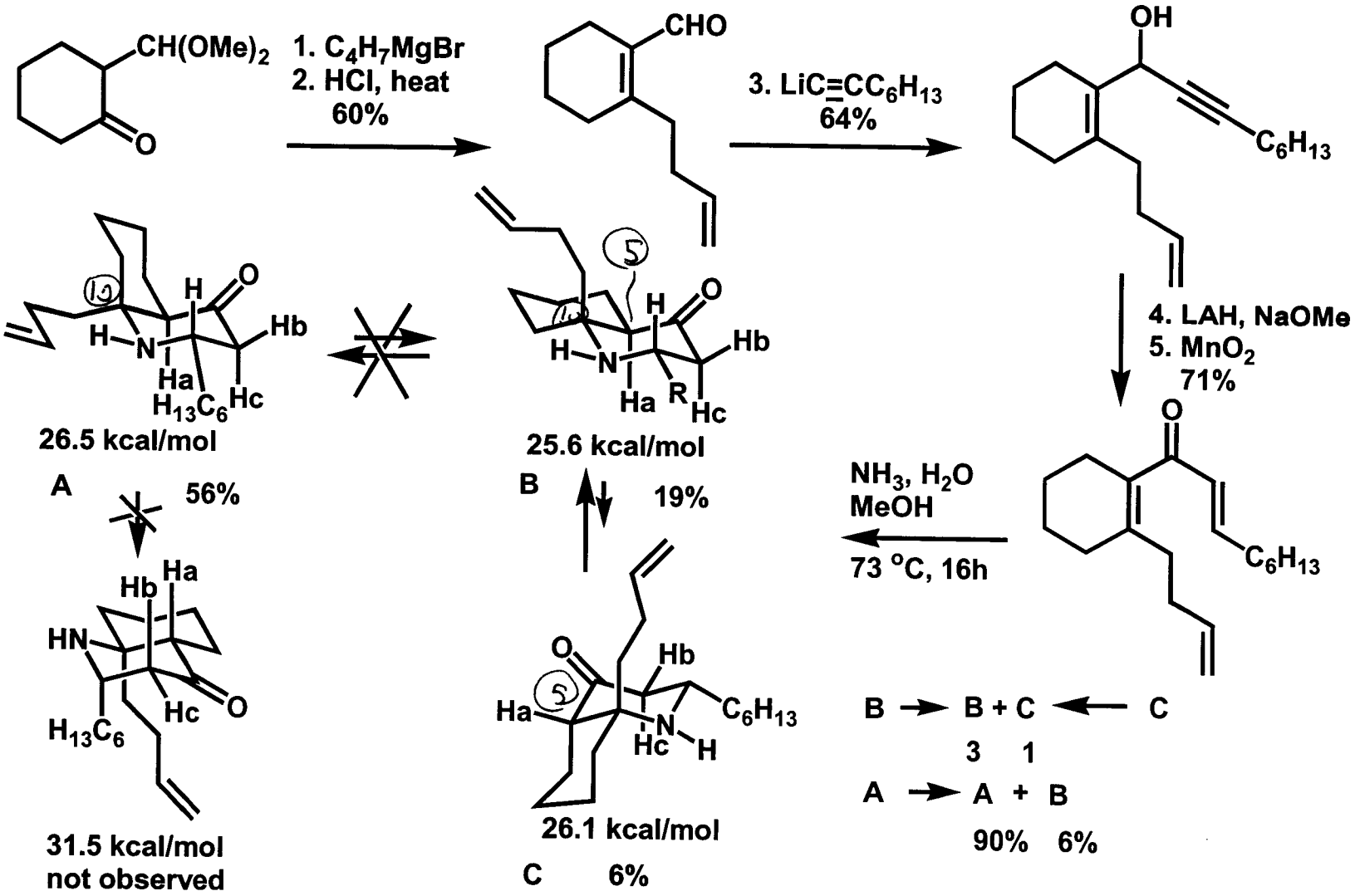


Syntheses of Cyclindricines by Double-Amino-Michael Reaction



the main issue to be addressed:
relative stereo-control at C2, C5, and C10

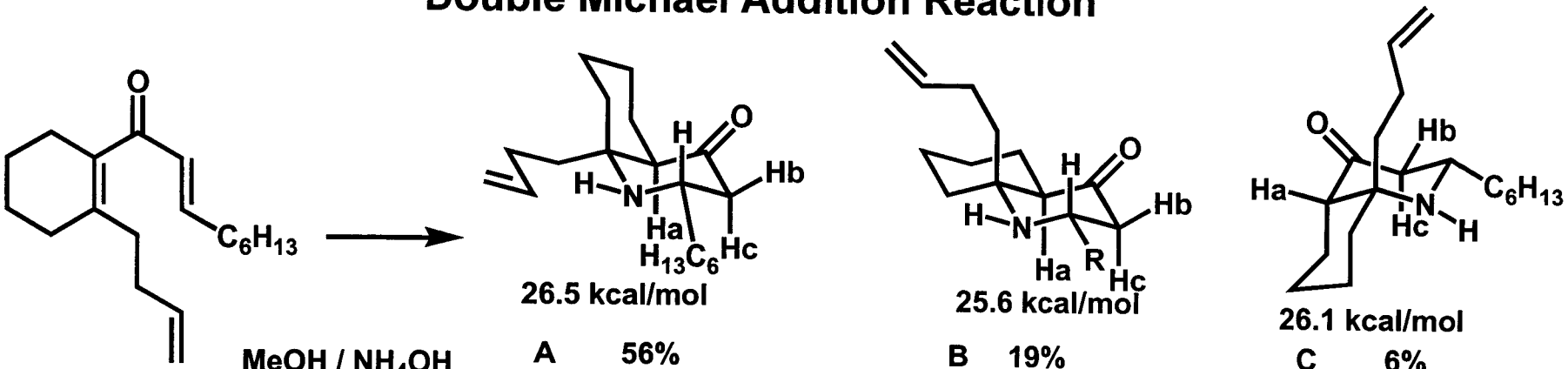
Snider's Syntheses of Cylindricines A, D and E



A, B ration is kinetically controlled, while B, C ratio is thermodynamically controlled.

Snider, B. S.; Liu, T. J. Or. Chem. 1997, 62, 5630.

Double Michael Addition Reaction



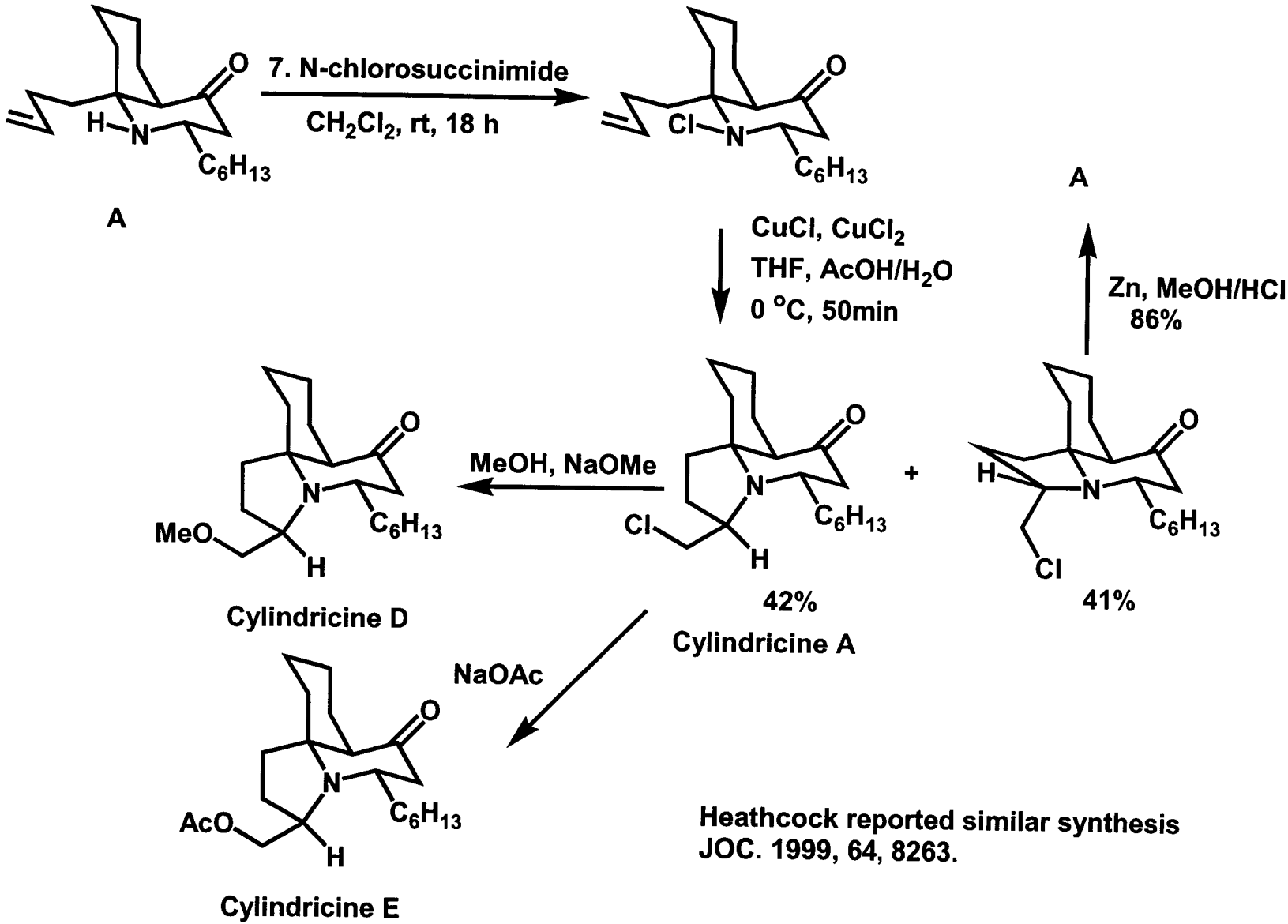
	A	B	C
$MeOH / NH_4OH$ 3 / 1	56%	19%	6%
$MeOH / NH_4Cl / NH_4OH$ 1 / 13	47%	34%	5%
$MeOH / NH_4Cl / NH_4OH$ 1.3 / 1	20%	26%	9%

A possible rationale:

The first attack on monosubstituted enone, then the stability of two rotamers in different medium determines A / B ratio; Retro-Michael is very slow presumably due to the steric hinderince around Ha.

more stable in low pH medium

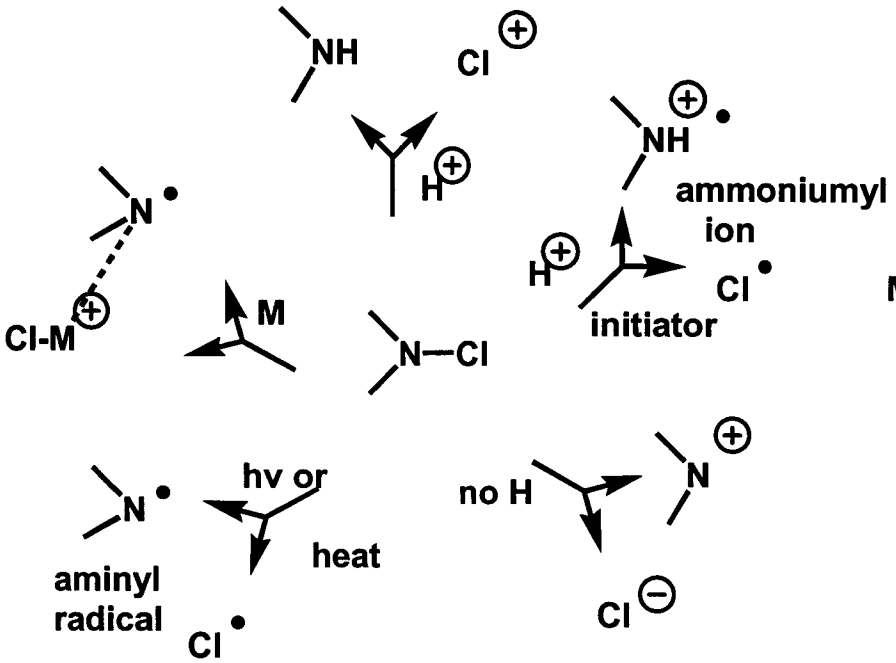
Snider's Syntheses



Heathcock reported similar synthesis
JOC. 1999, 64, 8263.

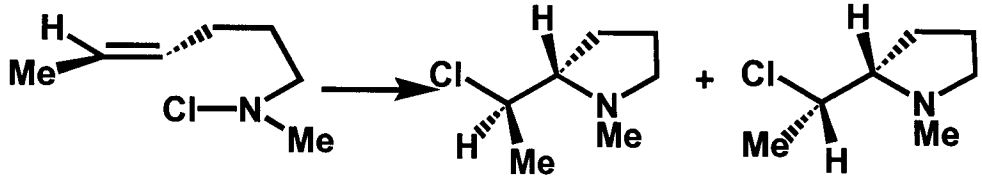
Metal Mediated Olefin Cyclization with *N*-Chloroamine

review on chemistry of N-chloroamine:
Stella, L. ACIEE, 1983, 22, 337

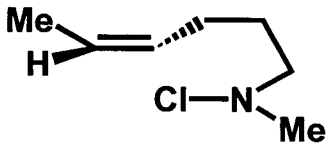


review on intramolecular
olefin cyclization/functionalization
Cardillo, G. Orena, M. Tetrahedron 1990, 46, 3321

highly stereoselective radical cyclization:

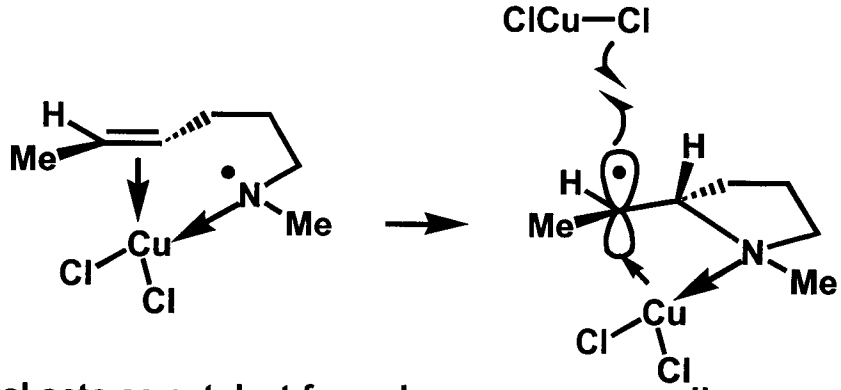


	yield		
$CuCl\text{-}CuCl_2$	80%	100	0
$FeCl_2$	78%	100	0



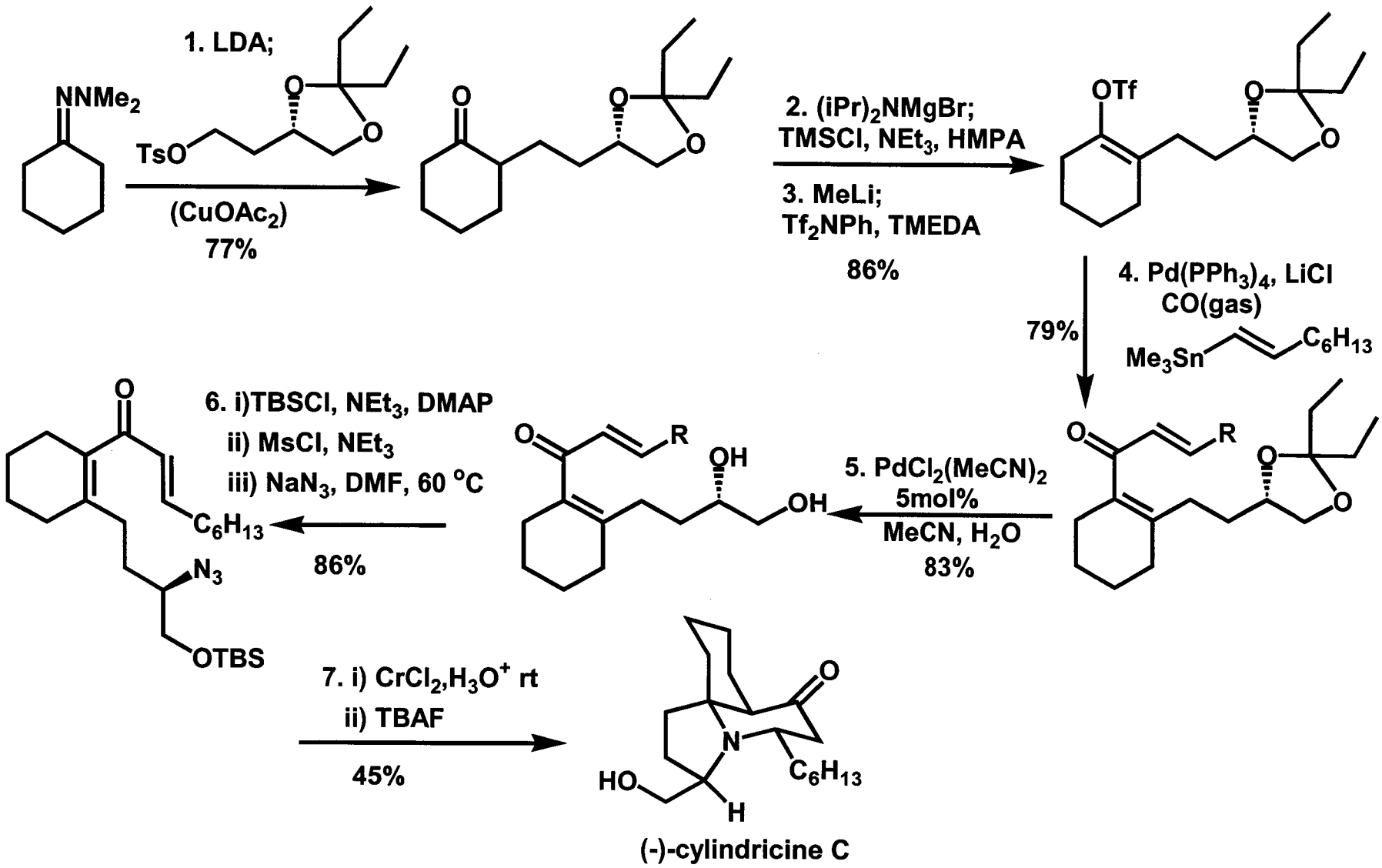
$CuCl\text{-}CuCl_2$	79%	9	91
$FeCl_2$	76%	0	100

Stella et al. TL. 1981, 22, 61



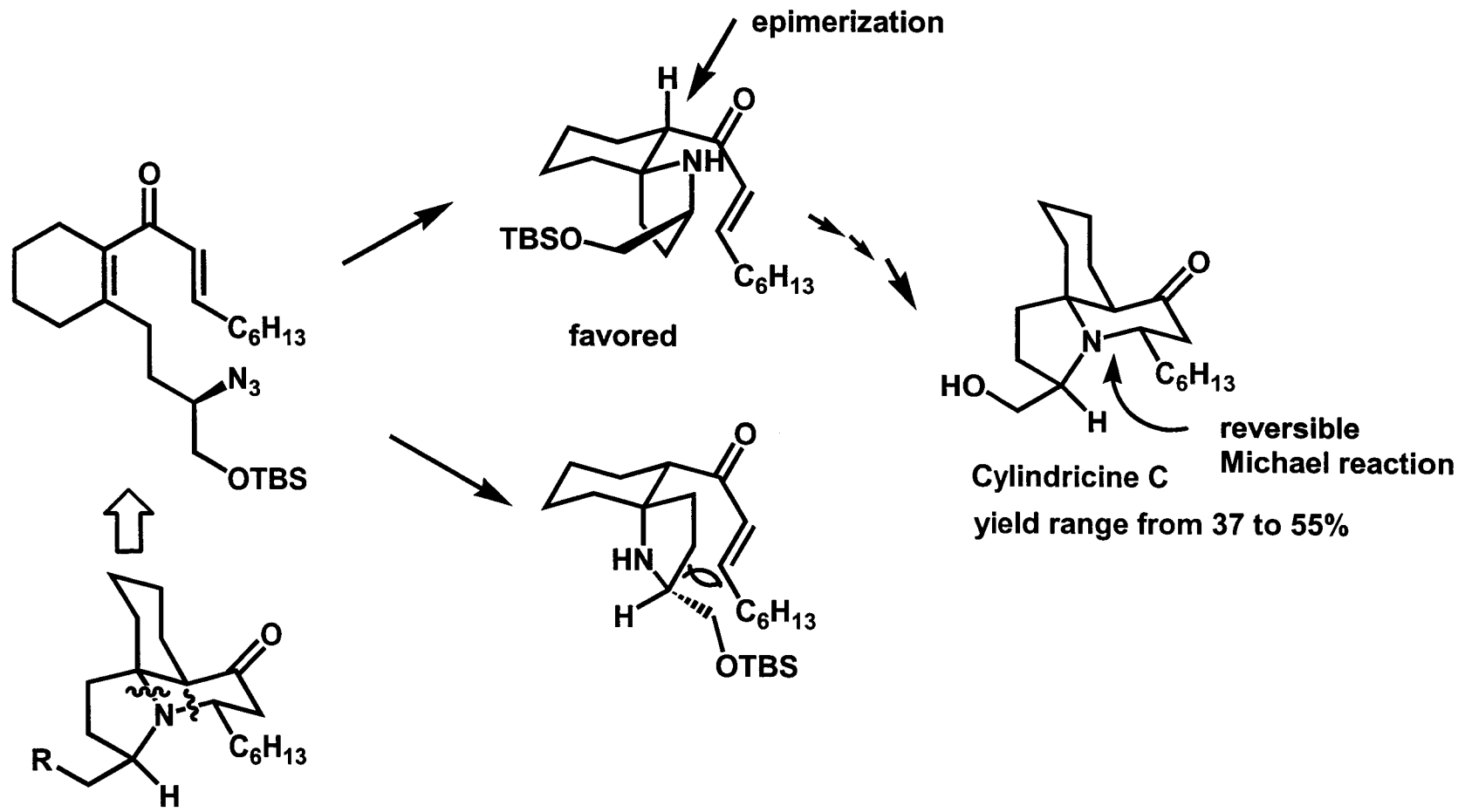
Metal acts as catalyst for redox process as well as organization center.

Molander's Enantioselective Synthesis of (-)-Cylindricine C



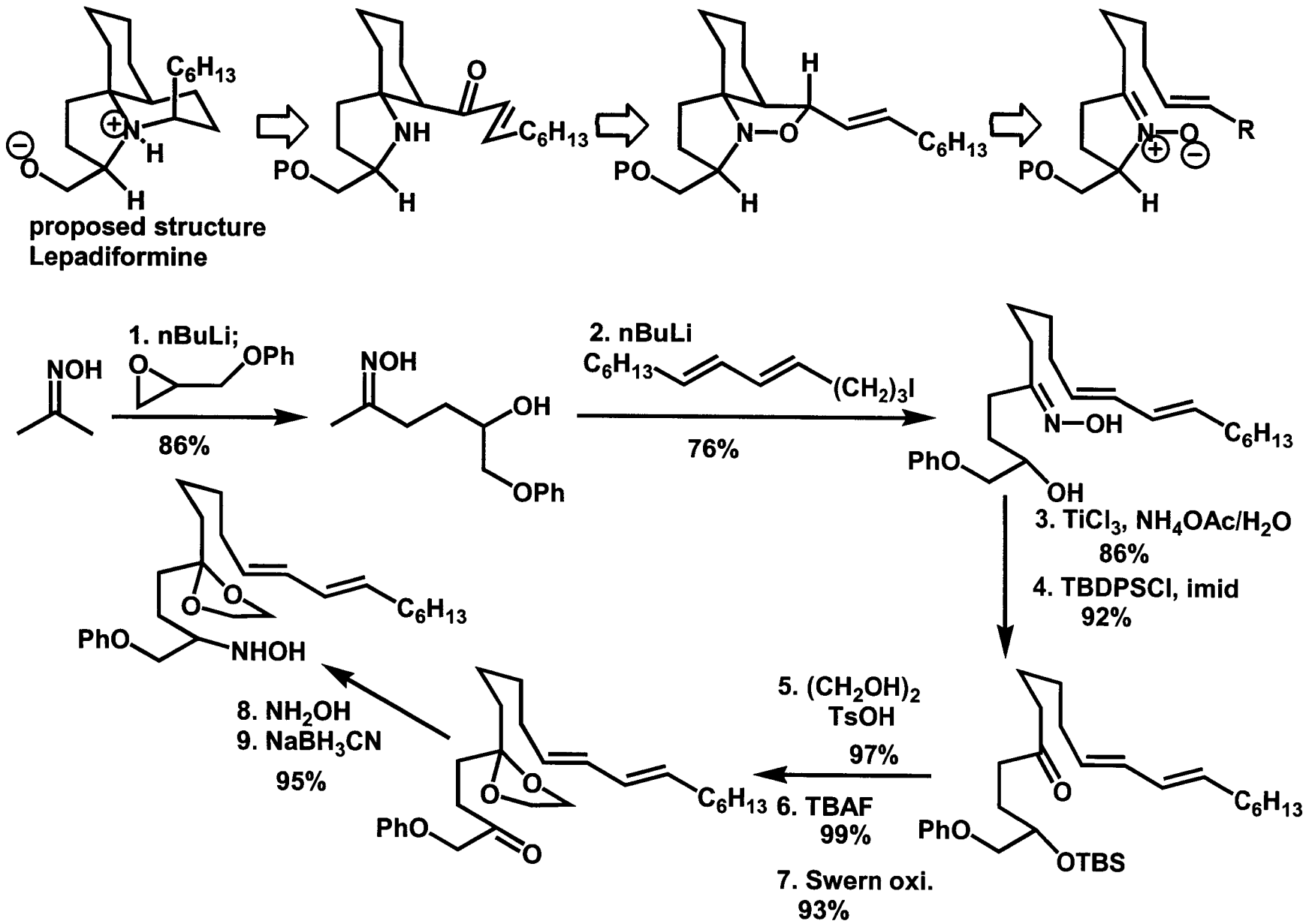
Molander et al. JOC, 1999, 64, 5183.

Molander's Rationale for Observed Stereoselectivity



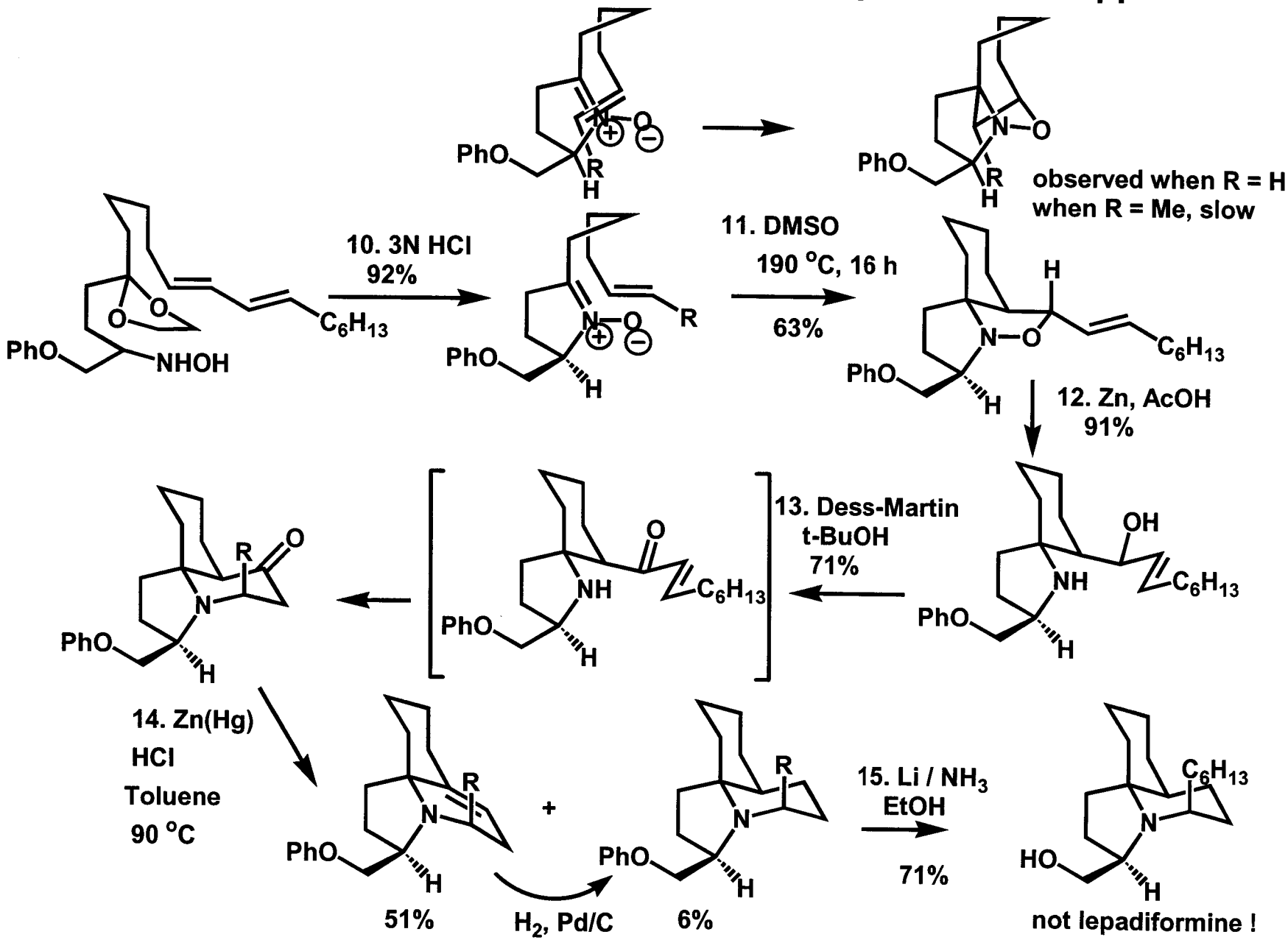
Tandem reaction is efficient in terms of creating complexity, but ...

Weinreb's Intramolecular Nitro/olefin Dipolar Cycloaddition Approach



Weinreb et al. JOC. 1999, 64, 686

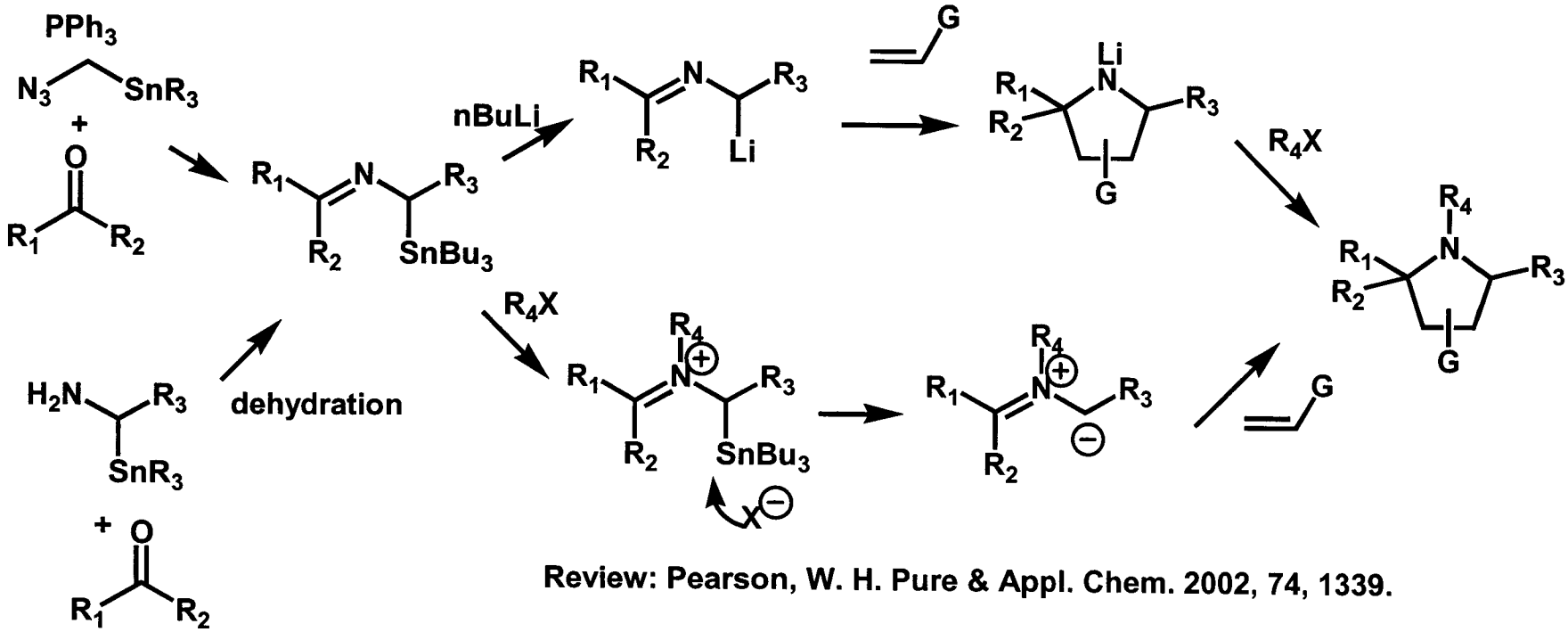
Weinreb's Intramolecular Nitro/olefin Dipolar Cycloaddition Approach



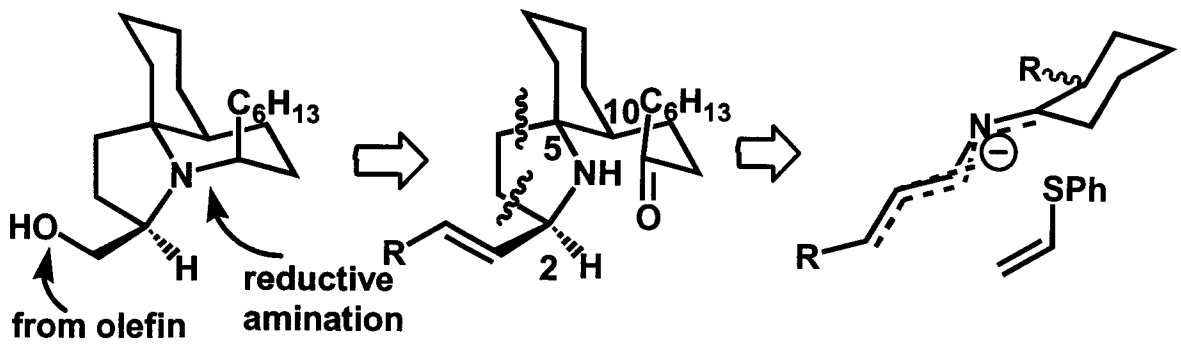
Weinreb et al. JOC. 1999, 64, 4865

Pearson's 2-Azaallylanion Cycloaddition Approach to Lepadiformine

tin-lithium exchange for the generation of non-stablized 2-azaally anion

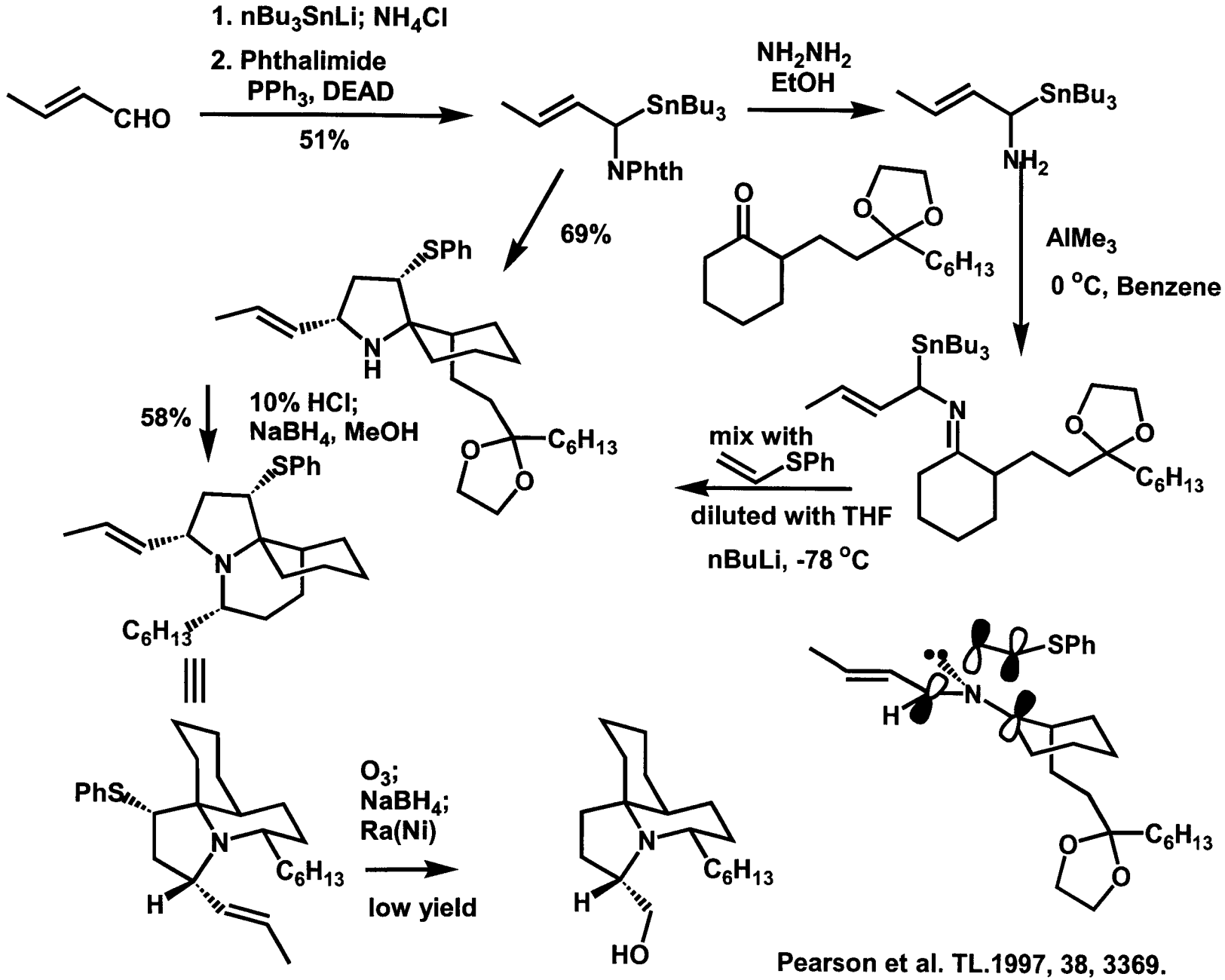


Review: Pearson, W. H. Pure & Appl. Chem. 2002, 74, 1339.



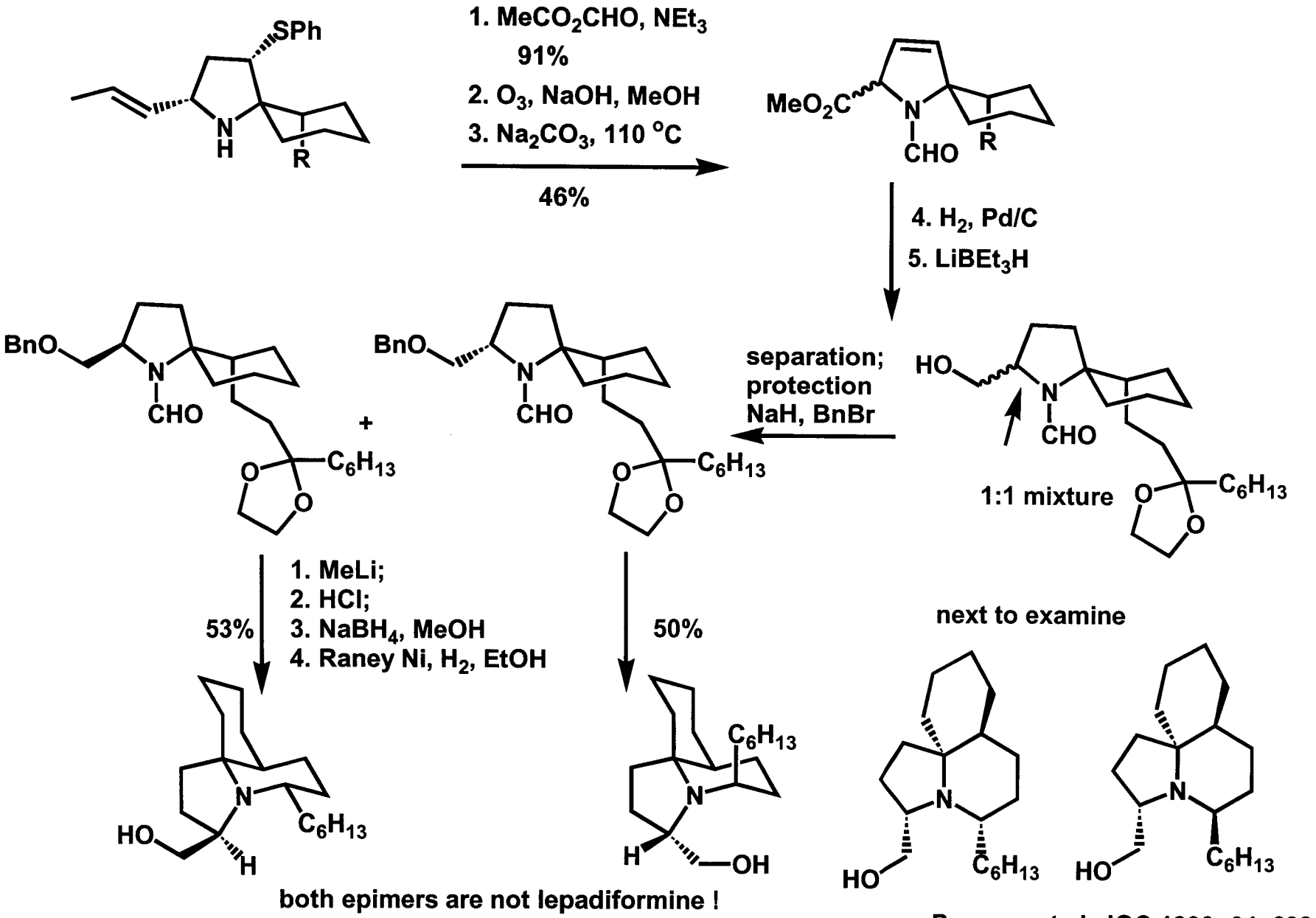
How to establish desired stereochemistry at C2, C5, and C10...?

Pearson's 2-Azaallylanion Cycloaddition Approach to Lepadiformine



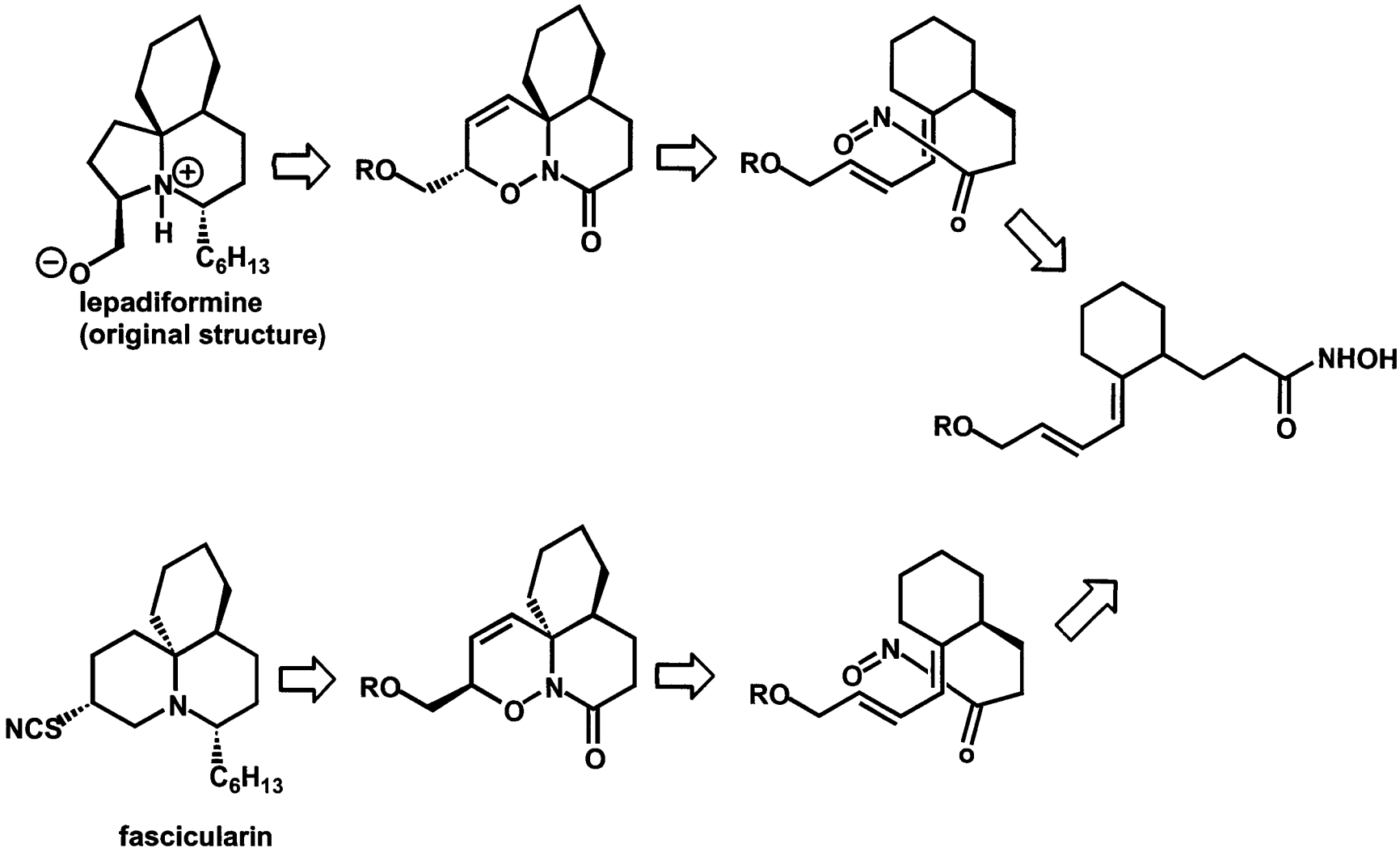
Pearson et al. TL.1997, 38, 3369.

Epimerization to Other Stereoisomers



Pearson et al. JOC.1999, 64, 688

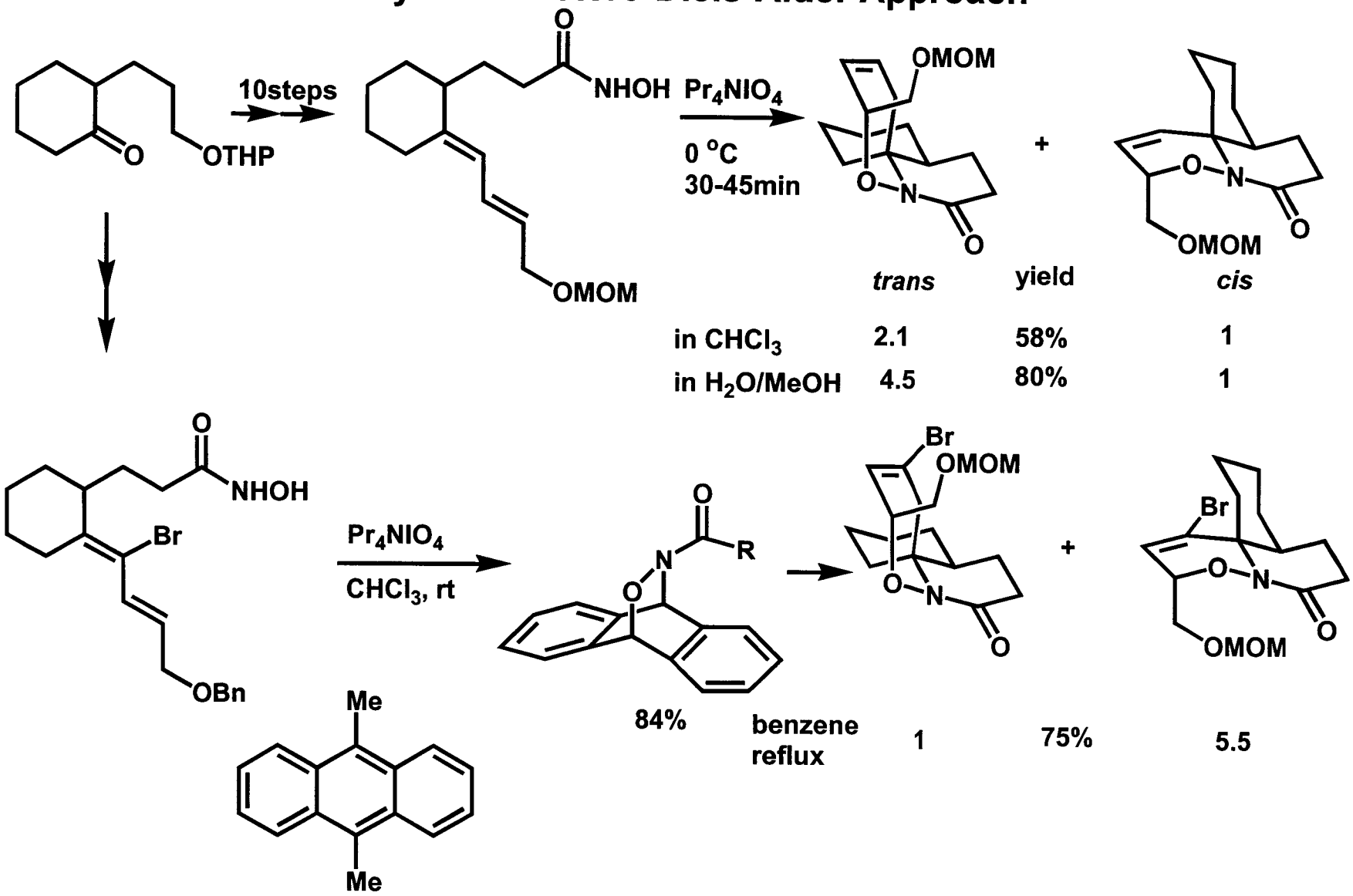
Kibayashi's Hetero-Diels-Alder Approach



This approach has an intrinsic drawback: too linear!!

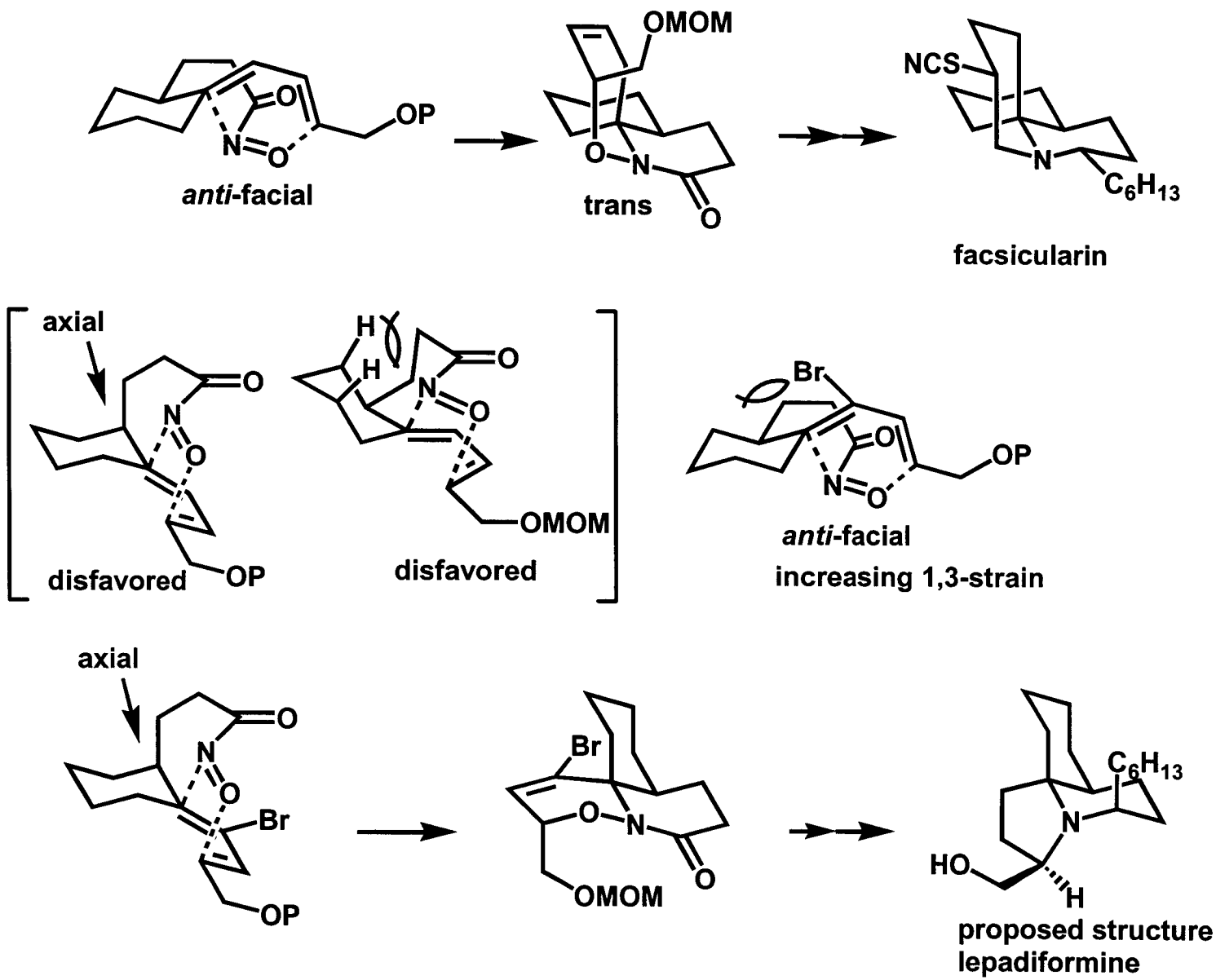
Kibayashi et al. TL. 2000, 41, 1205.
Kibayashi et al. JACS. 2000, 122, 4583.

Kibayashi's Hetero-Diels-Alder Approach

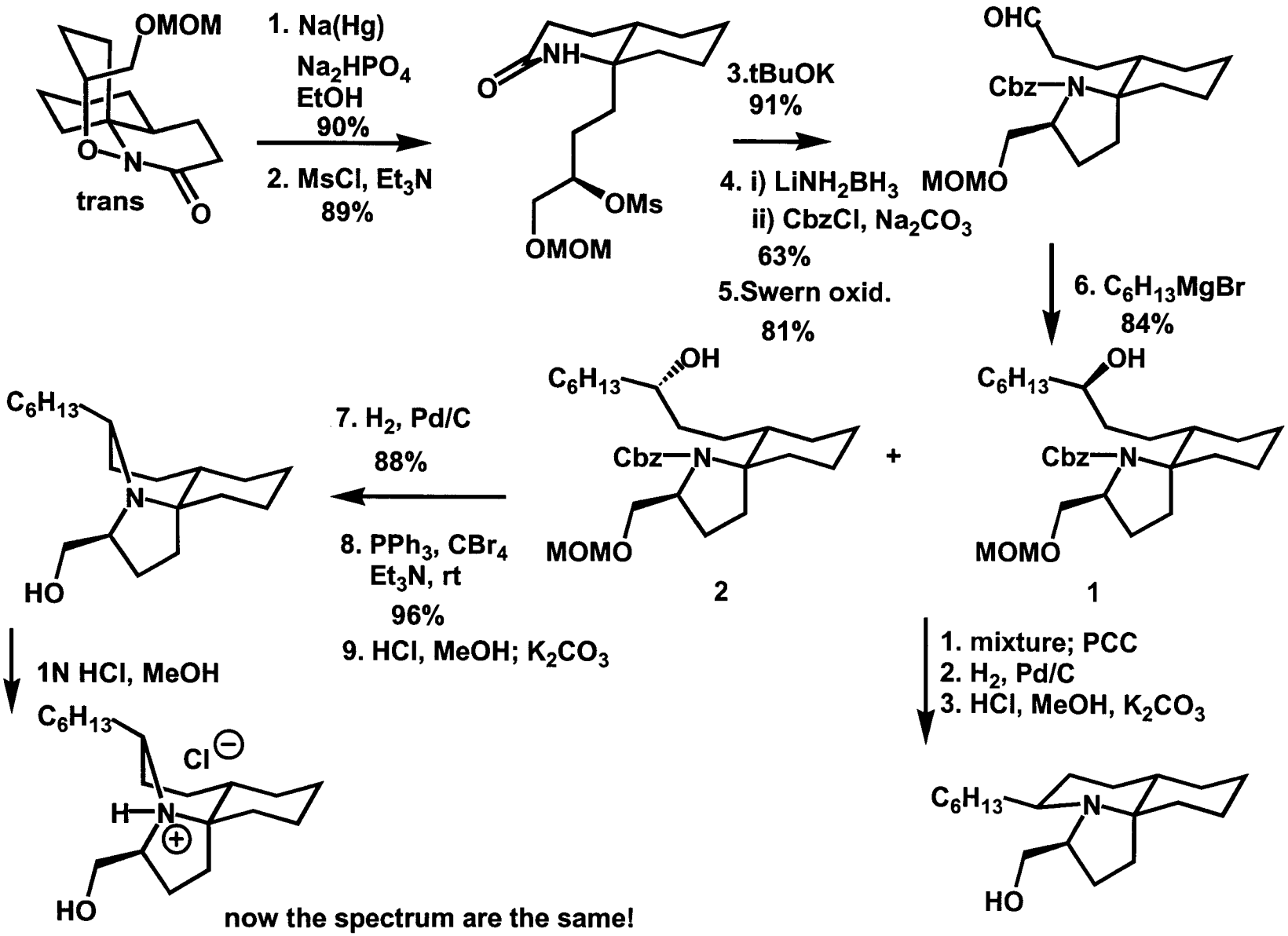


Kibayashi et al. TL. 2000, 41, 1205.
Kibayashi et al. JACS. 2000, 122, 4583.

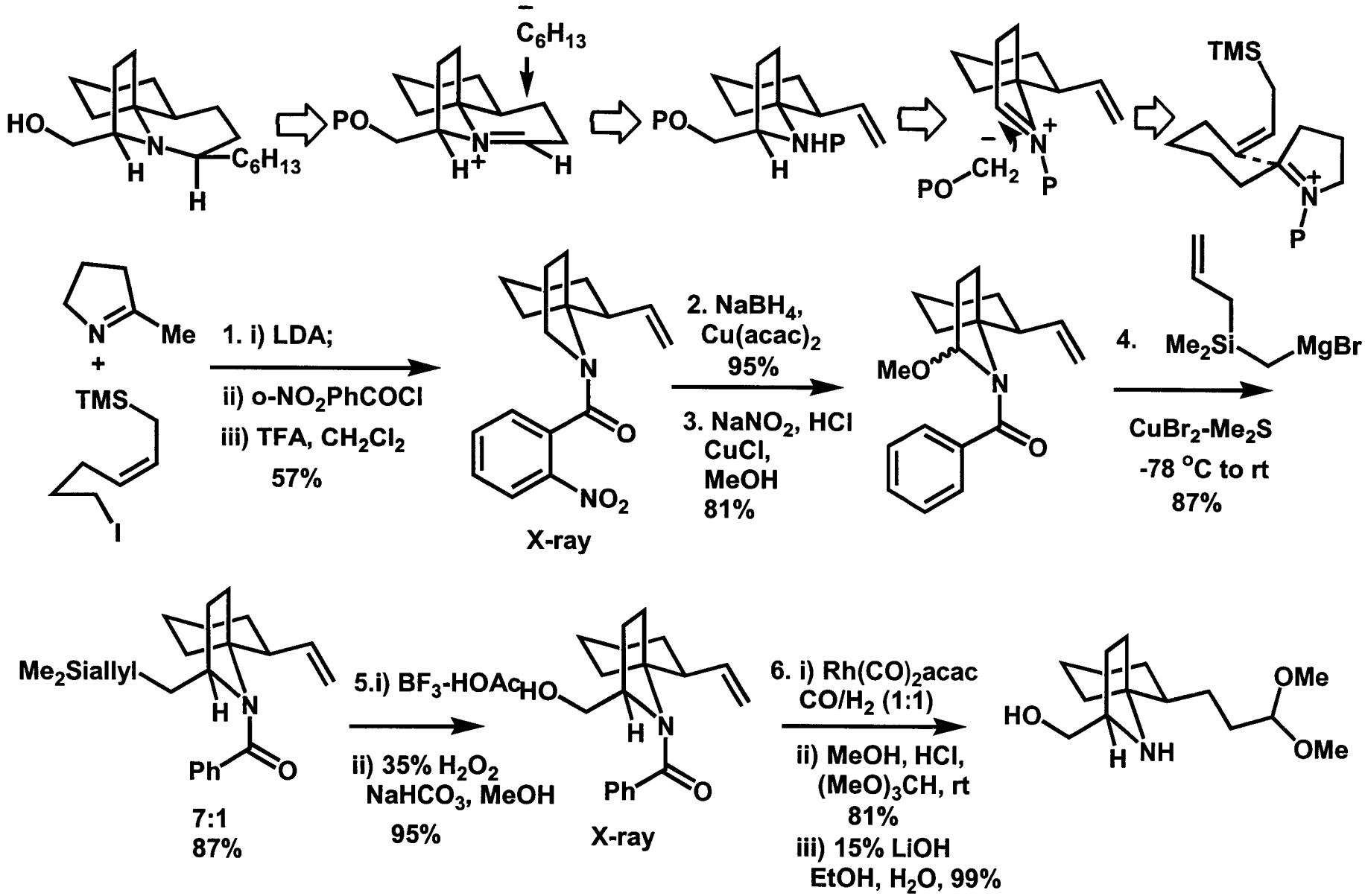
Rationale for Stereo-selectivity



Kibayashi's Synthesis of Lepadiformine

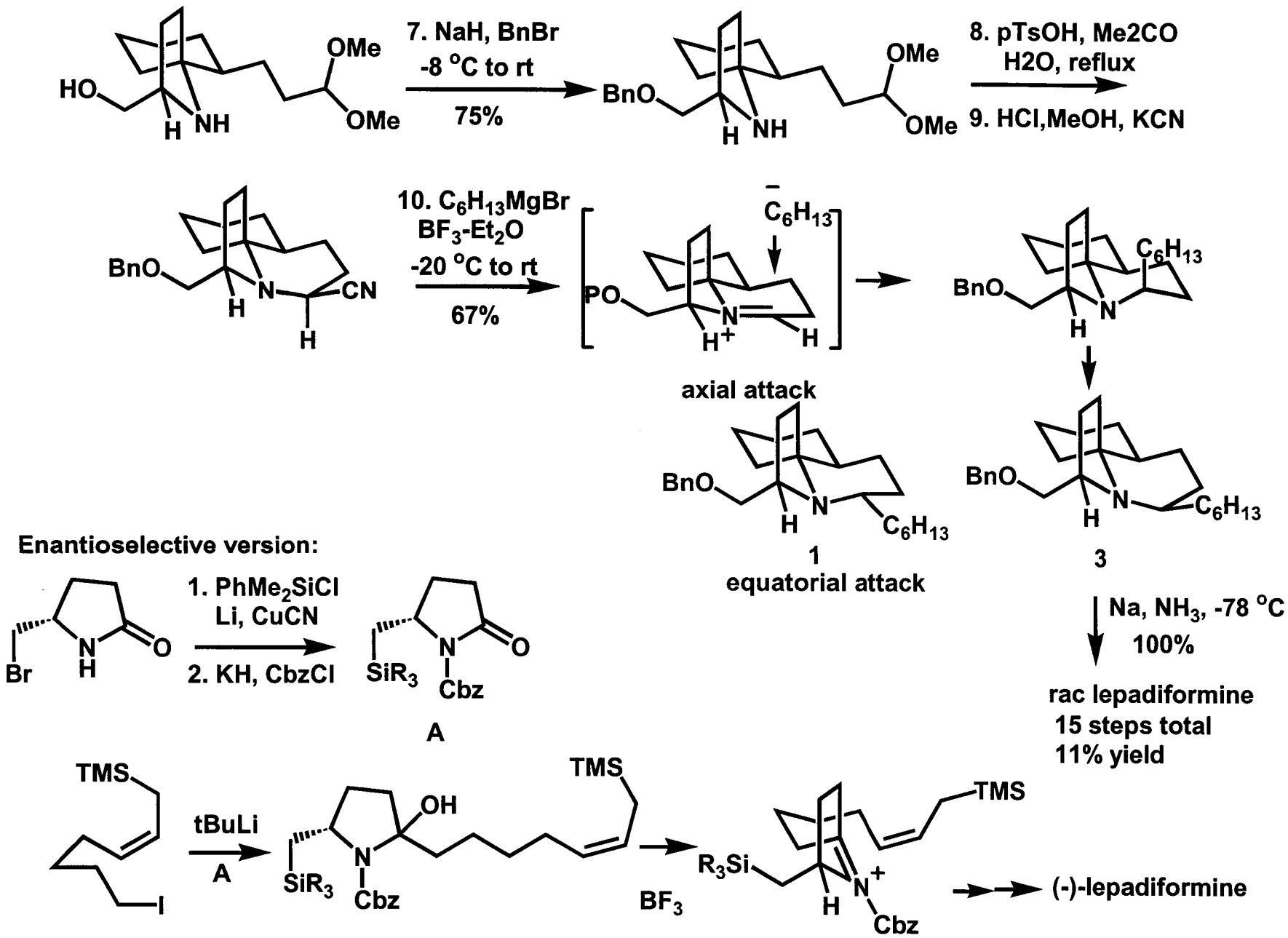


Weinreb's Synthesis of Lepadiformine

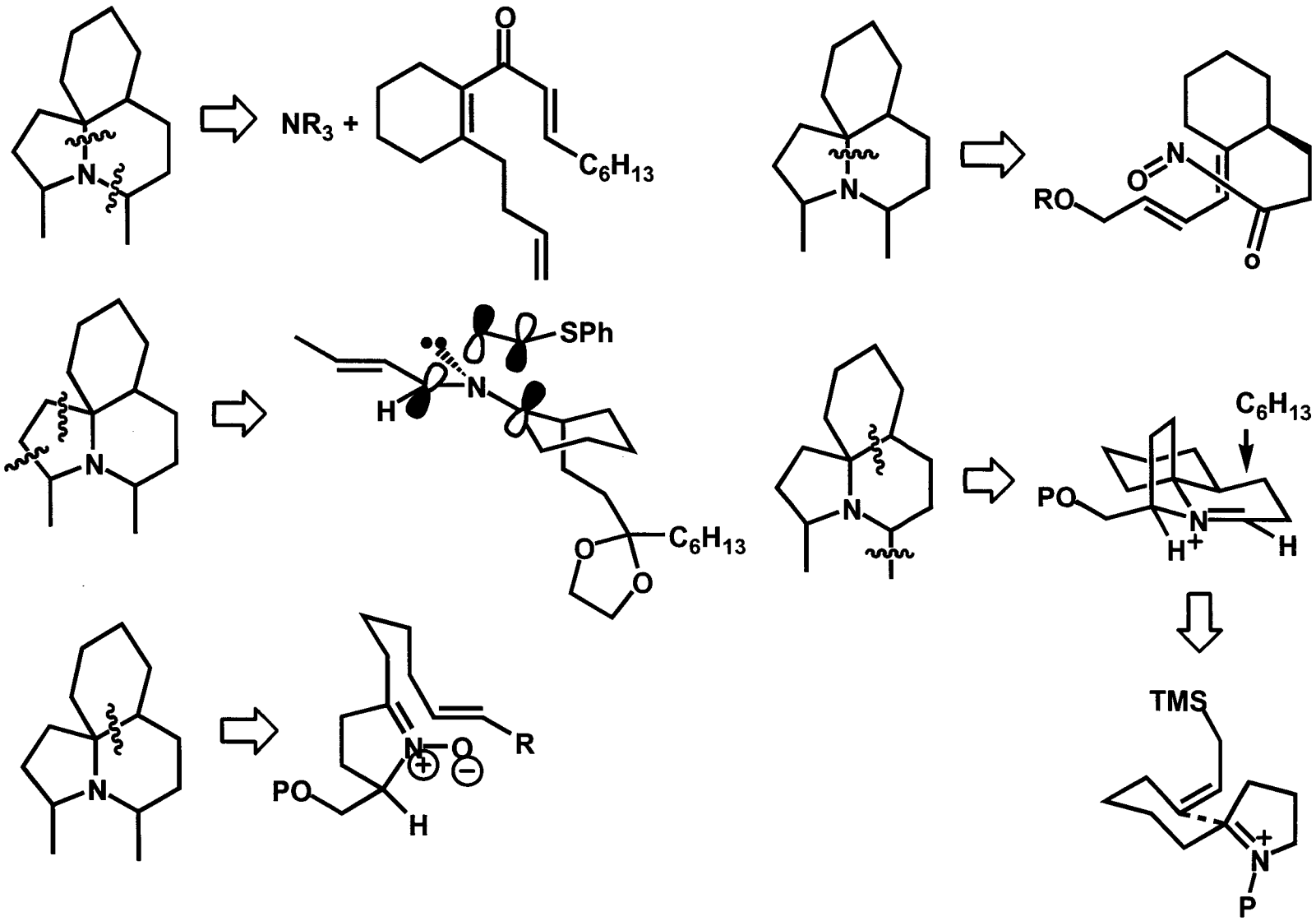


Weinreb et al. Org. Lett. 2001, 3, 3507.
Weinreb et al. JOC. 2002, 67, 4337.

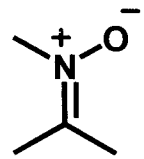
Weinreb's Synthesis of Lepadiformine



Summary



Do you know their names?

		prefix			prefix
—CN	cyanide	cyano-	—NO		nitroso-
—NC	isocyanide	isocyano-	—C≡N⁺—O⁻	nitrile oxide	
—OCN	cyanate	cyanato-	—C=NOH	oxime	hydroxyimino-
—NCO	isocyanate	isocyanato-		nitrone	
—SCN	thiocyanate	thiocyanato-			
—NCS	isothiocyanate	isothiocyanato-	$—NHNH_2$	hydrazine	
—SeCN	selenocyanate	selenocyanato-	—NHN=C<	hydrazone	hydrazono-
—NCSe	isoselenocyanate	isoselenocyanato-			