#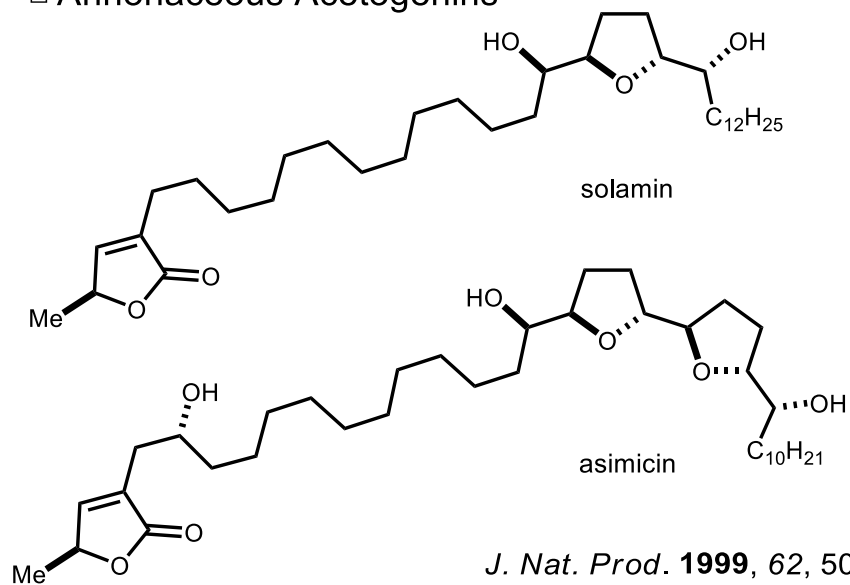 Library of Chiral Tetrahydrofuran, Tetrahydropyran, and Morpholine Diazides: Click and Other Applications for Scaffold Diversity

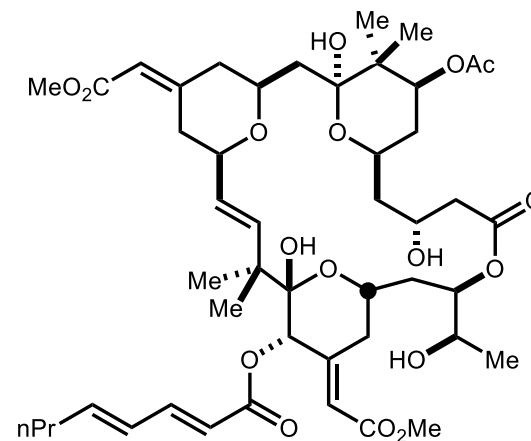Ki Bum Hong, Ph.D.
Wipf Group Research Topic Seminar
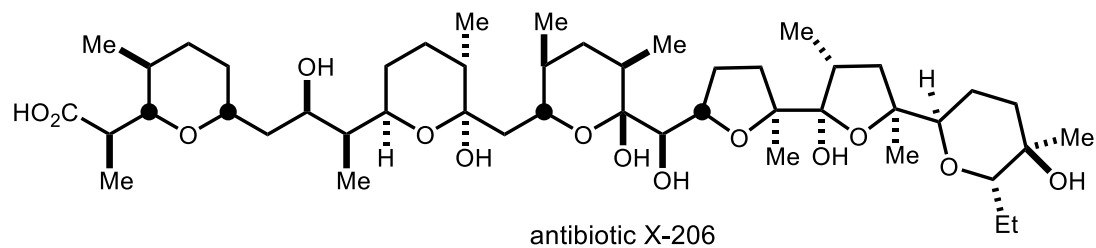Dec 18th, 2010

Naturally Occurring THF and THP Scaffolds

▢ Annonaceous Acetogenins

solamin

asimicin

J. Nat. Prod. **1999**, *62*, 504
J. Nat. Prod. **2008**, *71*, 1311

bryostatin 1

Nature, **2008**, *456*, 485
J. Am. Chem. Soc., **2002**, *124*, 13648
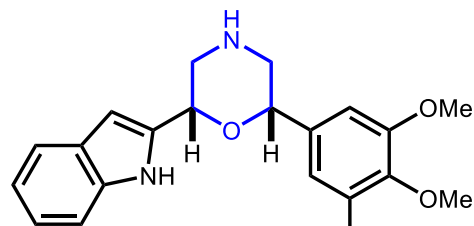*Angew. Chem. Int. Ed*. **2010**, *49*, 4580

antibiotic X-206

J. Am. Chem. Soc. **1988**, *110*, 2506
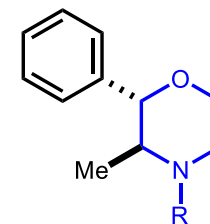
Biologically Active Morpholine Scaffolds
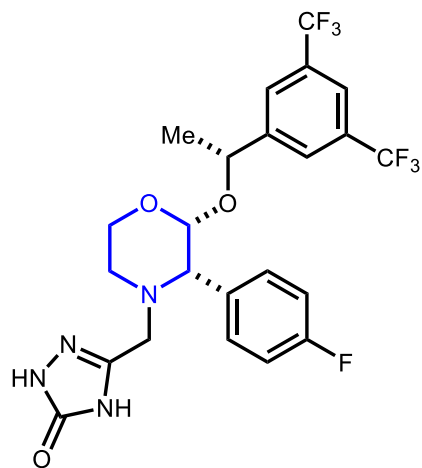
Merck NK$_1$ antagonist; aprepitant (Emend$^®$)
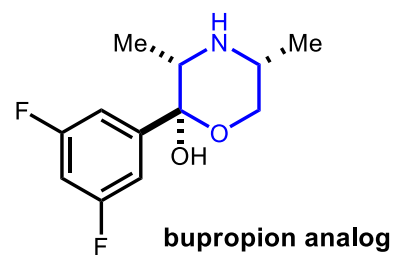
chenolin A
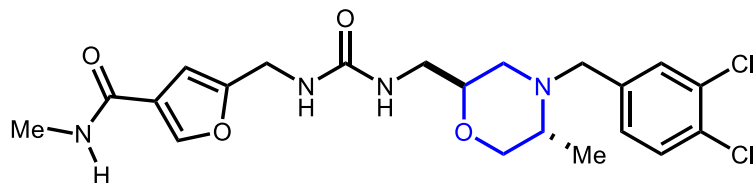
antimicrobial acivity
anti-inflammatory acitivty

R = Me, phendimetrazine
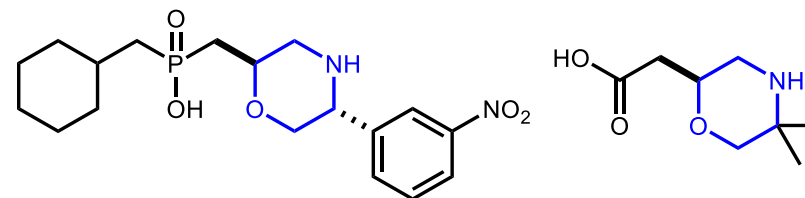R = H, phenmetrazine

appetitie suppressant
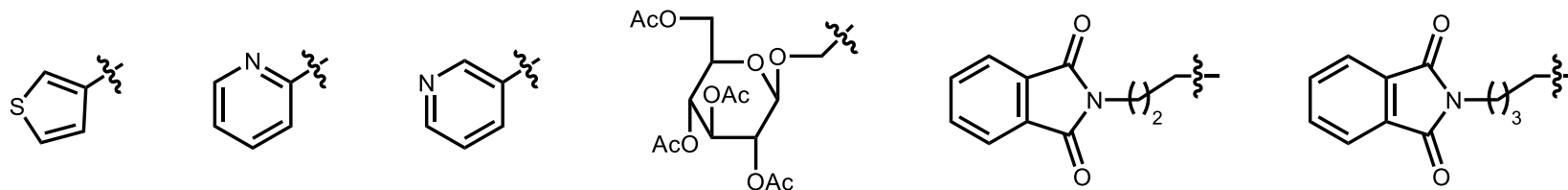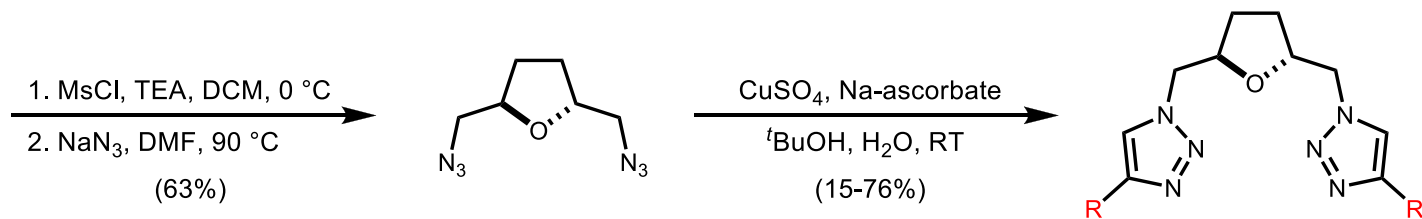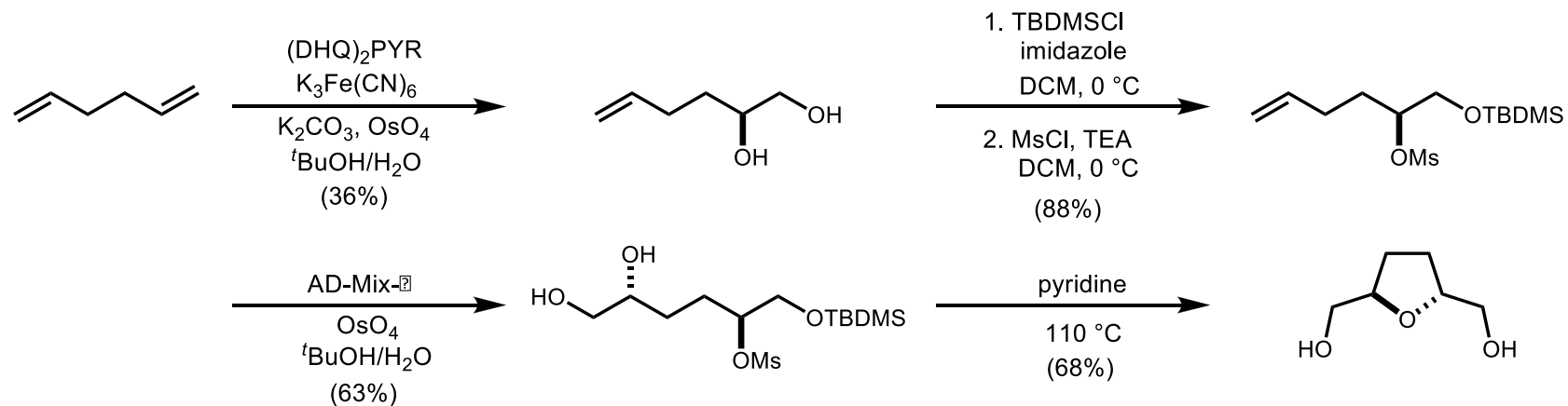
bupropion analog

CCR-3 antagonist; morpholinylmethylurea

anti-inflammatory

GABA$_B$ receptor antagonist

Synthesis **2004**, *5*, 641

Mono-Tetrahydrofuran Triazole Library: Click Chemistry

(DHQ)₂PYR : $(DHQ)_2PYR$, $K_3Fe(CN)_6$, K_2CO_3, OsO_4, $^tBuOH/H_2O$ (36%)

1. TBDMSCl, imidazole, DCM, 0 °C
2. MsCl, TEA, DCM, 0 °C (88%)

AD-Mix-β, OsO_4, $^tBuOH/H_2O$ (63%)

pyridine, 110 °C (68%)

1. MsCl, TEA, DCM, 0 °C
2. NaN₃, DMF, 90 °C (63%)

$CuSO_4$, Na-ascorbate, ^tBuOH, H_2O, RT (15-76%)

Mishra, J. K.; Wipf, P.; Sinha, S. C. *J. Comb. Chem.* **2010**, *12*, 609

Bis-Tetrahydrofuran Triazole Library: Click Chemistry

Reaction scheme, top row:

Starting diene → (DHQD)$_2$PHAL, K$_3$Fe(CN)$_6$, K$_2$CO$_3$, OsO$_4$, MeSO$_2$NH$_2$, ^{t}BuOH/H$_2$O (20%) → diol (OH, OH) → MsCl, TEA, DCM, 0 °C (99%) → bis-mesylate (OMs, OMs)

Second row:

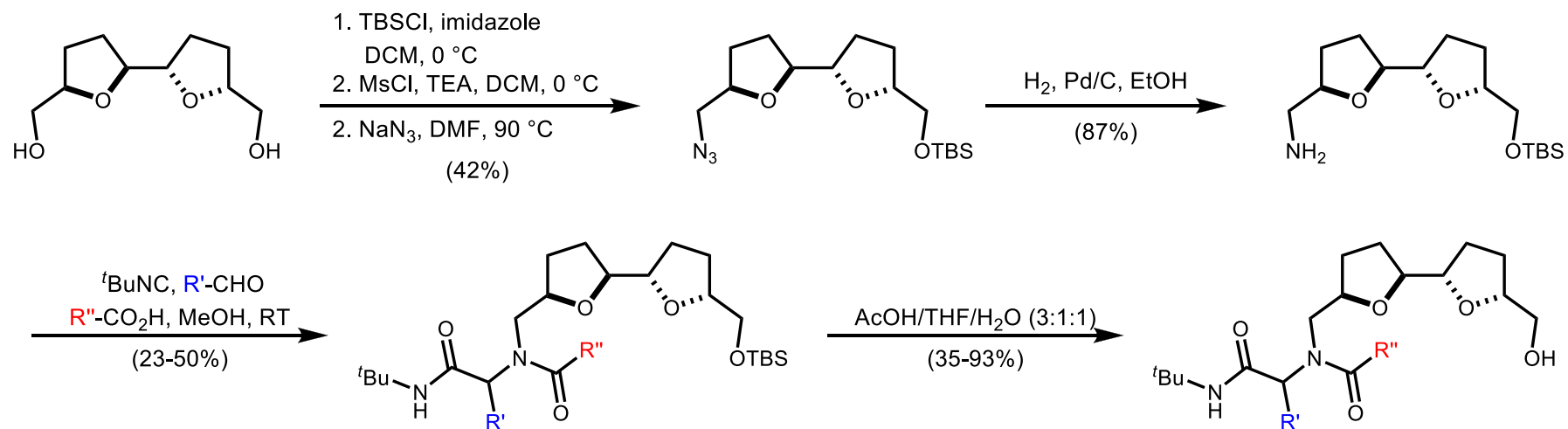(DHQD)$_2$PHAL, K$_3$Fe(CN)$_6$, K$_2$CO$_3$, OsO$_4$, ^{t}BuOH/H$_2$O (88%) → tetraol bis-mesylate (HO, OH, OMs, OMs, OH, OH) → pyridine, 110 °C (78%) → bis-THF diol (HO, OH)

Third row:

1. MsCl, TEA, DCM, 0 °C
2. NaN$_3$, DMF, 90 °C
(63%) → bis-THF diazide (N$_3$, N$_3$) → CuSO$_4$, Na-ascorbate, ^{t}BuOH, H$_2$O, RT (42–85%) → bis-triazole product (R, R)

R groups:

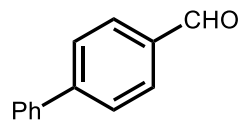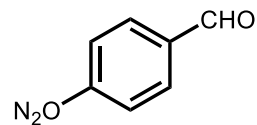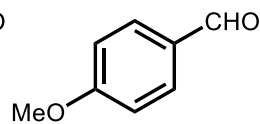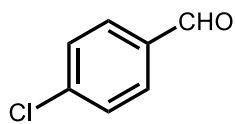Me—(chain), Cl—(chain), TBSO—(chain), cyclopentyl—(chain), cyclohexenyl—, phenethyl—, PhS—(chain)
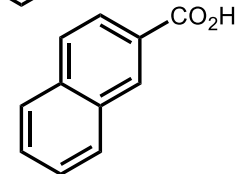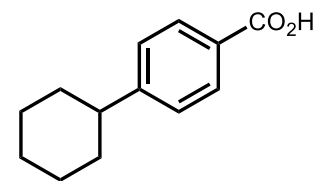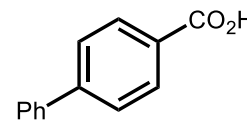
Wipf, P. *J. Comb. Chem.* **2010**, *12*, 609

Bis-Tetrahydrofuran Triazole Library: Ugi Chemistry

Reaction scheme:

Starting diol (HO...OH) →
1. TBSCl, imidazole, DCM, 0 °C
2. MsCl, TEA, DCM, 0 °C
2. NaN₃, DMF, 90 °C
(42%)
→ azide-OTBS compound (N₃...OTBS)

→ H₂, Pd/C, EtOH (87%) → amine-OTBS compound (NH₂...OTBS)

→ ᵗBuNC, R'-CHO, R''-CO₂H, MeOH, RT (23-50%) → Ugi product (ᵗBu-NH...OTBS)

→ AcOH/THF/H₂O (3:1:1) (35-93%) → Ugi product (ᵗBu-NH...OH)

- -

R'-CHO

4-chlorobenzaldehyde (Cl—C₆H₄—CHO)
4-methoxybenzaldehyde (MeO—C₆H₄—CHO)
4-nitrobenzaldehyde (N₂O—C₆H₄—CHO)
4-phenylbenzaldehyde (Ph—C₆H₄—CHO)

R''-CO₂H

4-iodobenzoic acid (I—C₆H₄—CO₂H)
4-phenylbenzoic acid (Ph—C₆H₄—CO₂H)
4-cyclohexylbenzoic acid
4-tert-butylbenzoic acid
4-phenylbenzoic acid (Ph—C₆H₄—CO₂H)
2-naphthoic acid

Wipf, P. *J. Comb. Chem.* **2010**, *12*, 609

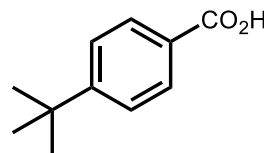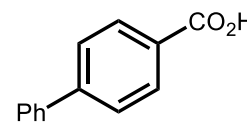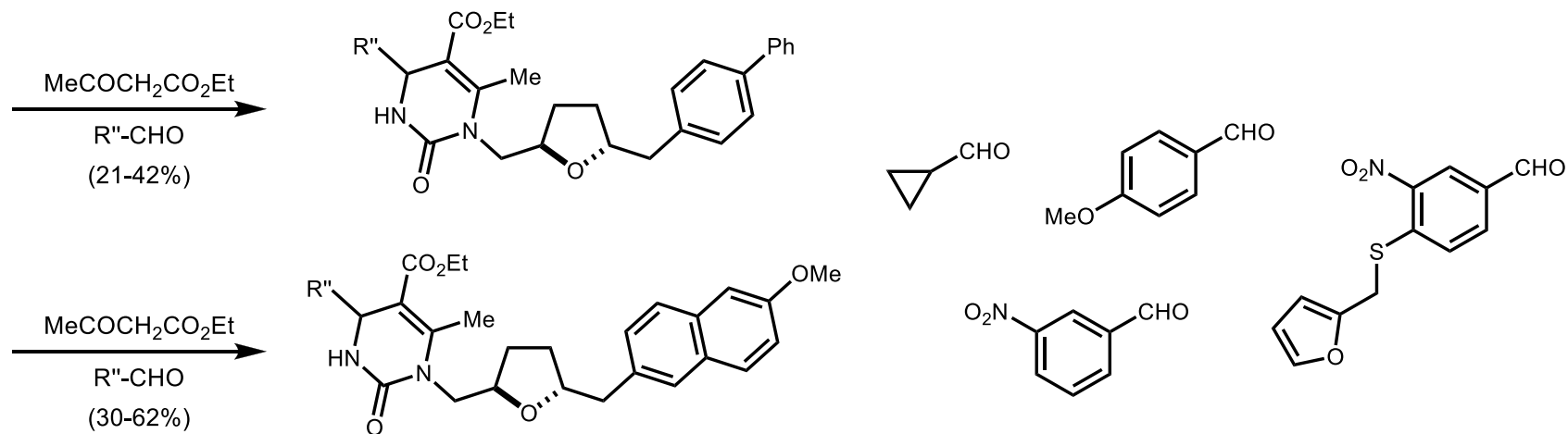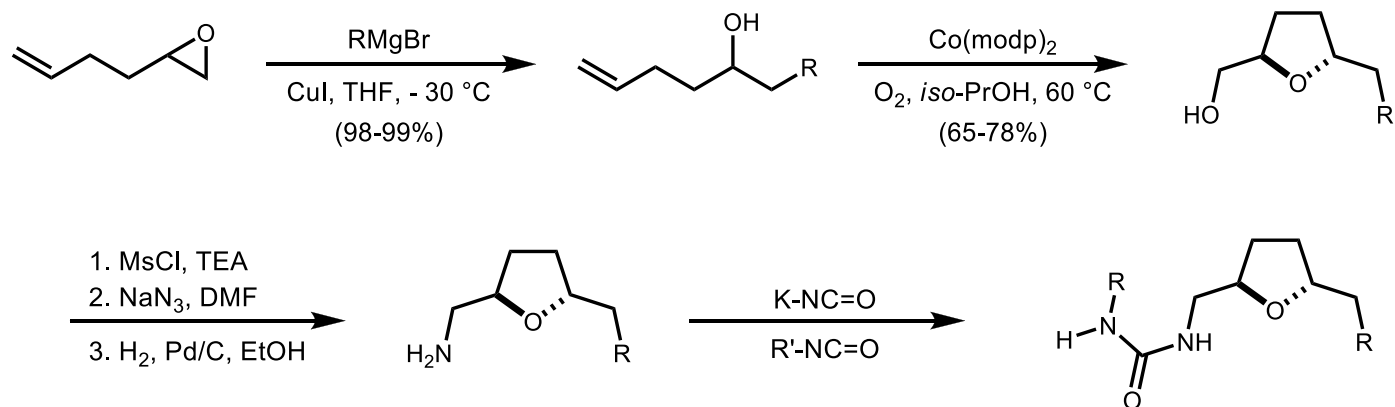## Mono-Tetrahydrofuran Methylamine Library: Biginelli Chemistry

Application of Azides: Scaffold Diveristy

Hemetsberger, H. *Monatsh. Chem.* **1972**, *103*, 194
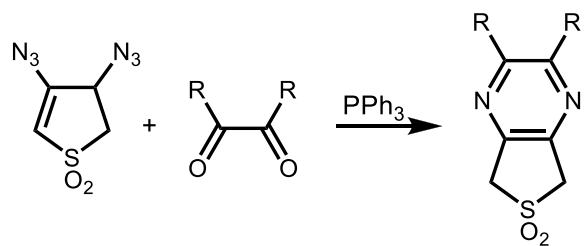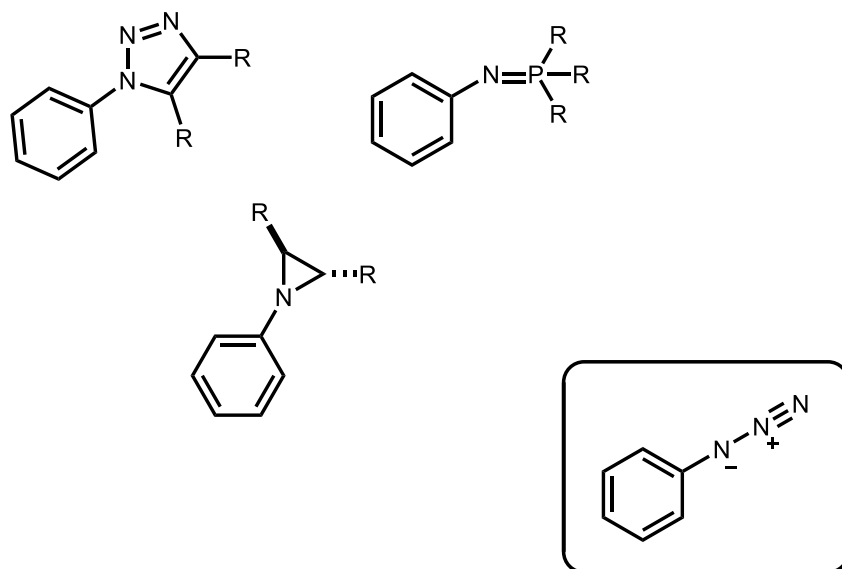
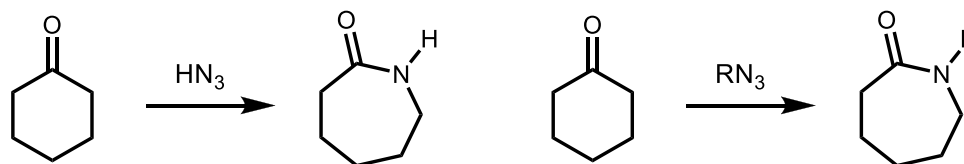Ko, C. -W. *Molecules.* **1996**, *1*, 93
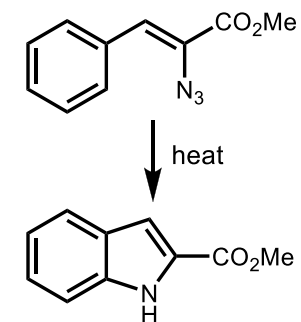
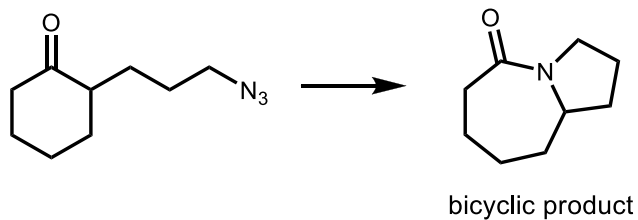Sundberg, R. J. *J. Org. Chem.* **1972**, *37*, 719

Reactions of Organic Azide: Schmidt

⬚ Generalized Schmidt Reaction Mechanism
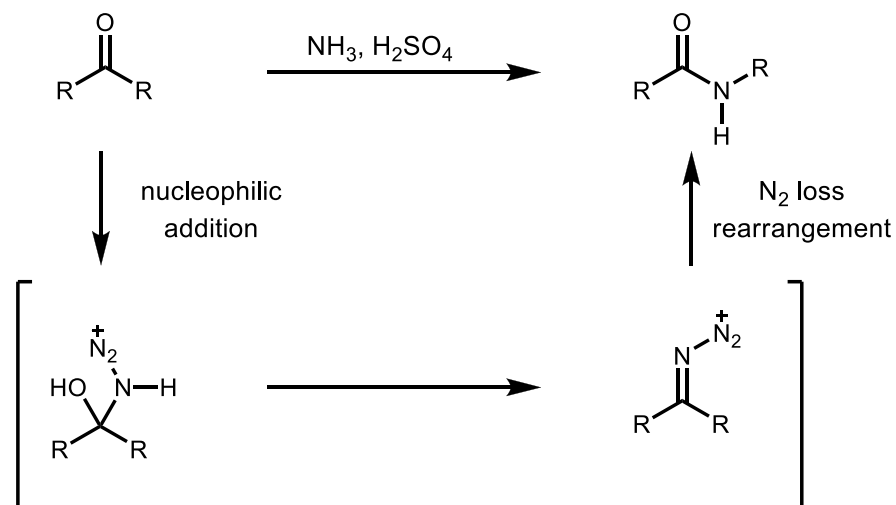
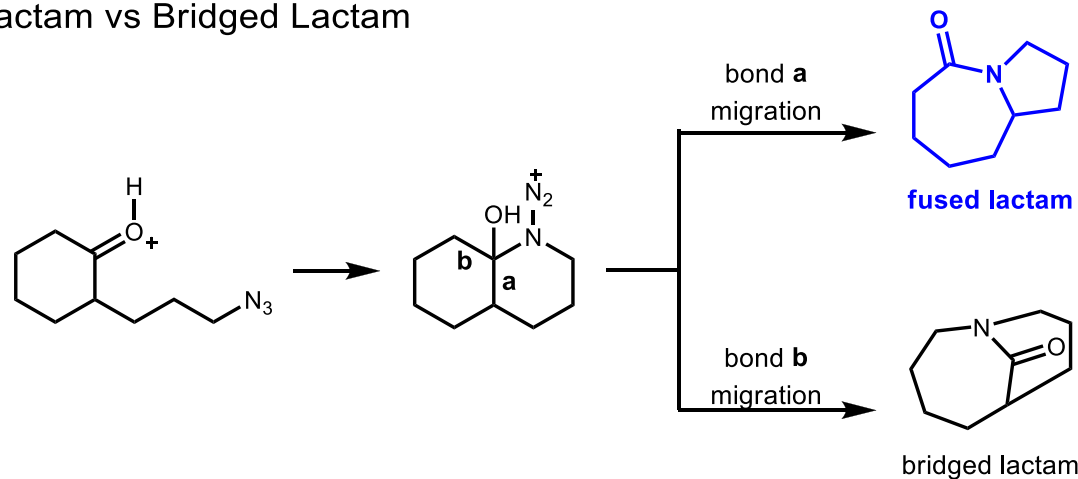⬚ Hydrazoic Acid vs Alkyl Azide Insertion

⬚ Intramolecular Schmidt Reaction

bicyclic product

Regiochemical Possibilities for Intramolecular Schmidt Reaction

◇ Fused Lactam vs Bridged Lactam

bond **a** migration → **fused lactam**

bond **b** migration → bridged lactam

Aube, J. *J. Am. Chem. Soc*. **1995**, *117*, 10449

◇ Reactive Conformations leading to Fused and Bridged Lactams

A:B=**57**:17 — **A**

A:**B**=10:**65** — **B**
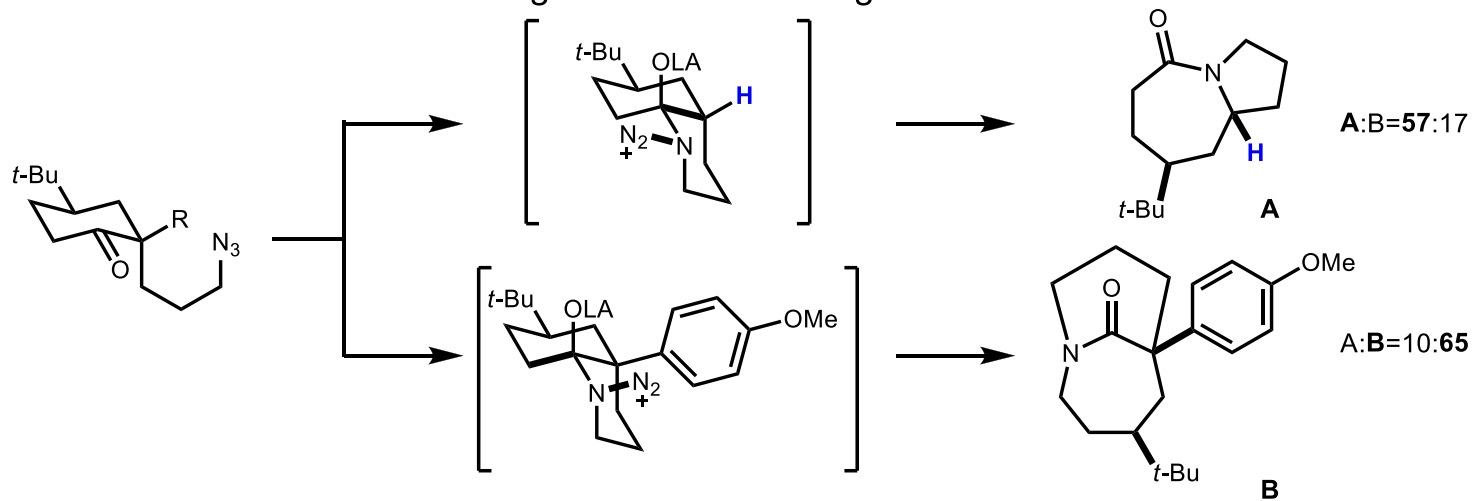
Aube, J. *J. Am. Chem. Soc*. **2005**, *127*, 4552

Competition: Schmidt Reaction vs Mannich Reaction

☐ Schmidt vs Mannich Pathways in Intermolecular Reaction

acids

TfOH, DCM: 30%

TiCl$_4$, DCM: 80%

+ n-HexN$_3$

+ BnN$_3$

TfOH, DCM

(79%)
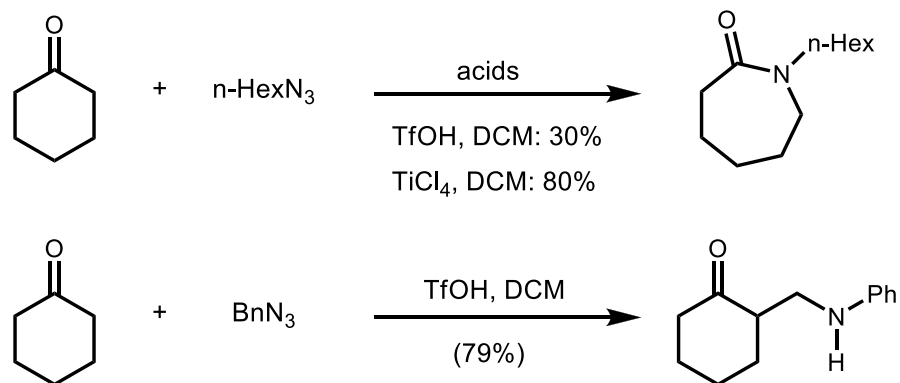
Aube, J. *J. Org. Chem*. **1992**, *57*, 1635
Aube, J. *J. Am. Chem. Soc*. **2000**, *122*, 7226

☐ Schmidt vs Mannich Pathways in Intramolecular Reaction

TfOH

(60%)

TfOH

(55%)
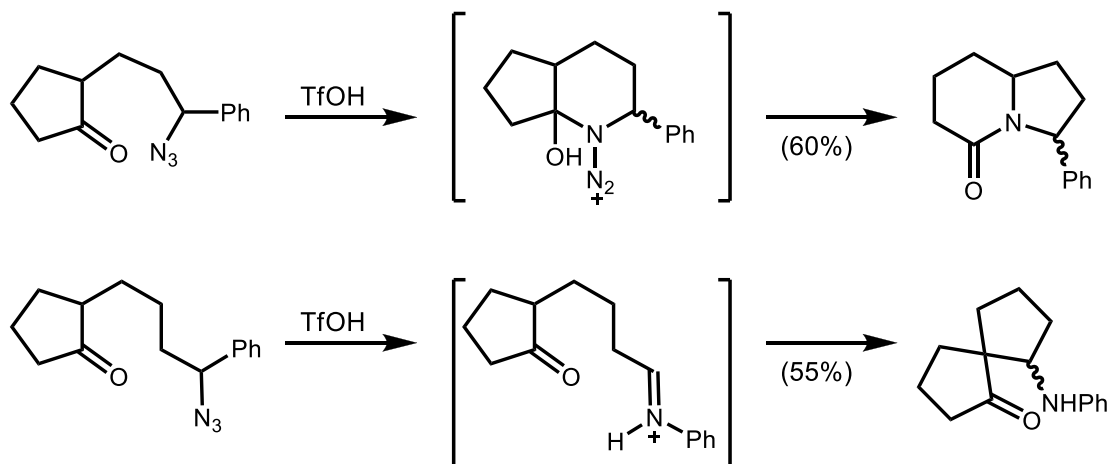
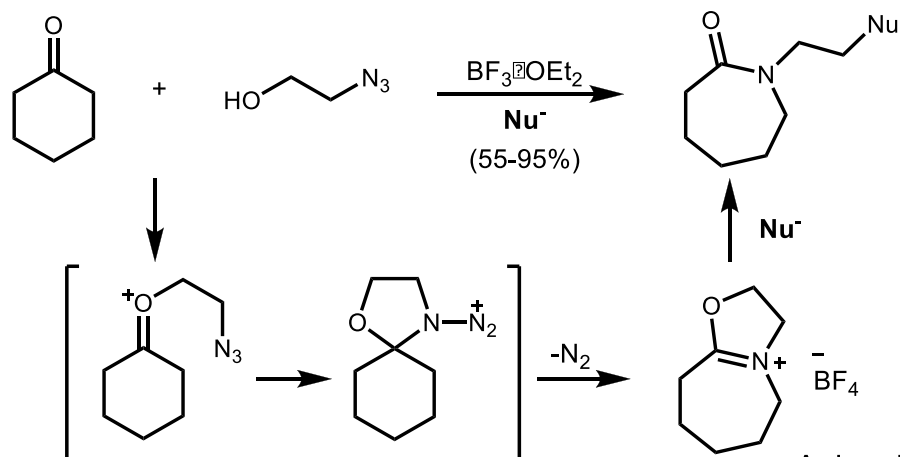Aube, J. *J. Org. Chem*. **2001**, *66*, 886

Reactivity: Boyer Reaction and Schmidt Reaction

◻ Early Examples of Boyer Reaction: 2-Oxazoline Synthesis
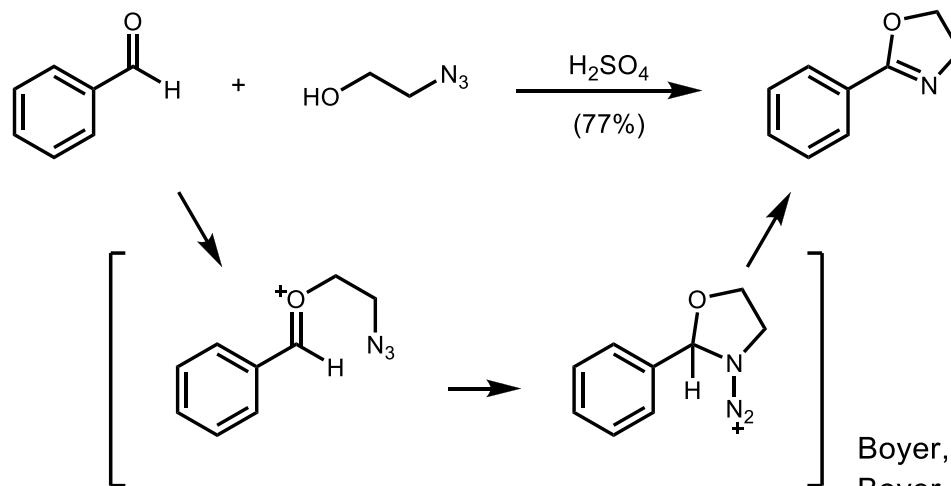
Boyer, J. H. *J. Am. Chem. Soc*. **1955**, *77*, 951
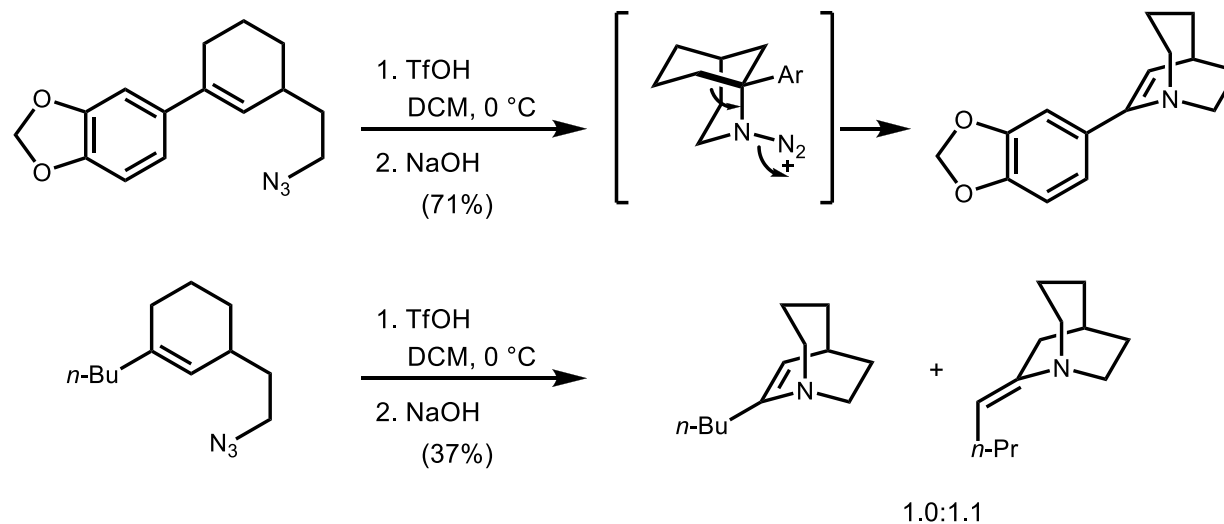Boyer, J. H. *J. Am. Chem. Soc*. **1956**, *78*, 325

◻ Schmidt Reaction of Hydroxyalkyl Azides with Ketone

Aube, J. *J. Org. Chem*. **1996**, *61*, 10
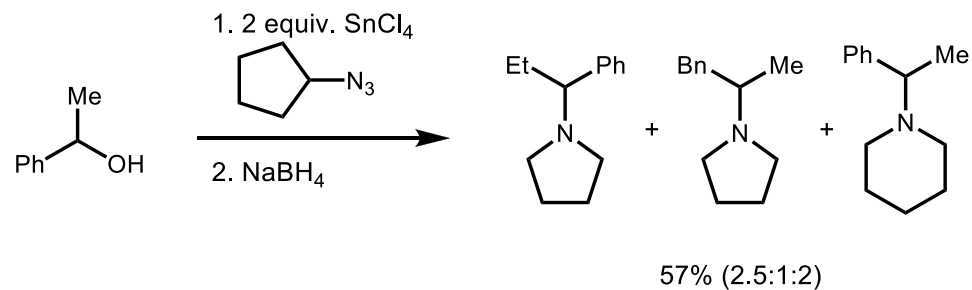Aube, J. *J. Org. Chem*. **2008**, *73*, 201

Schmidt Reaction with Carbocation

☐ Pearson: Intramolecular Case

1. TfOH
   DCM, 0 °C

2. NaOH
   (71%)

1. TfOH
   DCM, 0 °C

2. NaOH
   (37%)

n-Bu

n-Pr

1.0:1.1

☐ Pearson: Intermolecular Case

Pearson, W. H. *J. Am. Chem. Soc.* **1993**, *115*, 10183

1. 2 equiv. SnCl$_4$

2. NaBH$_4$

Et   Ph   Bn   Me   Ph   Me

57% (2.5:1:2)
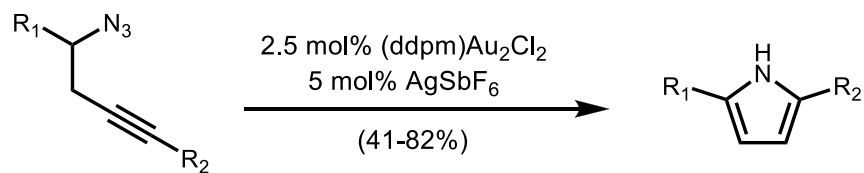
Pearson, W. H. *J. Org. Chem.* **1995**, *60*, 4960

Metal-Mediated Schmidt Reaction

☐ Hg(OTf)$_2$-Promoted Schmidt Reaction with NaBH$_4$ Workup

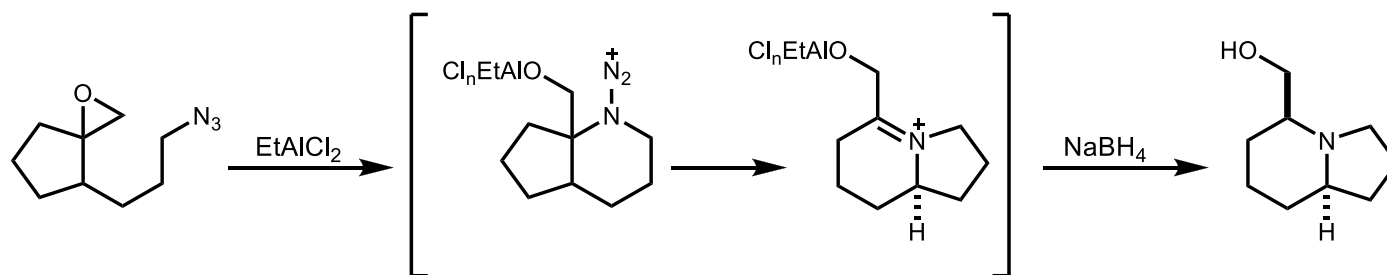Pearson, W. H. *J. Org. Chem.* **2000**, *65*, 8326
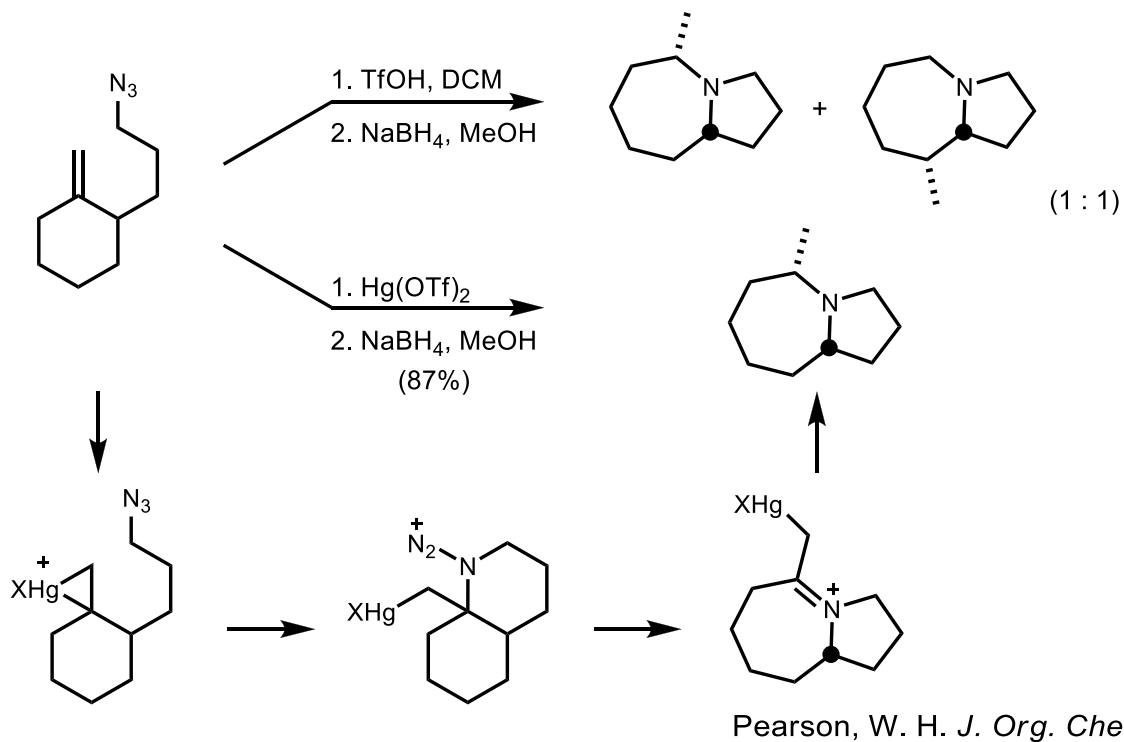
☐ Au(I)-Promoted Acetylenic Schmidt Reaction

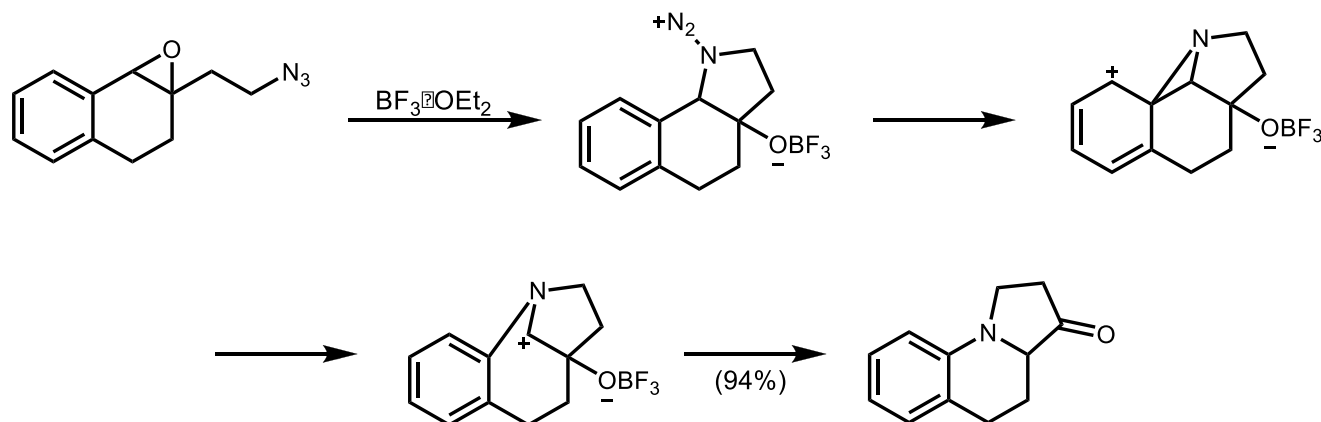Toste, D. F. *J. Am. Chem. Soc.* **2005**, *127*, 11260

Reaction of Alkyl Azides with Epoxides

☐ Epoxide-Initiated Electrophilic Cyclization of Azides

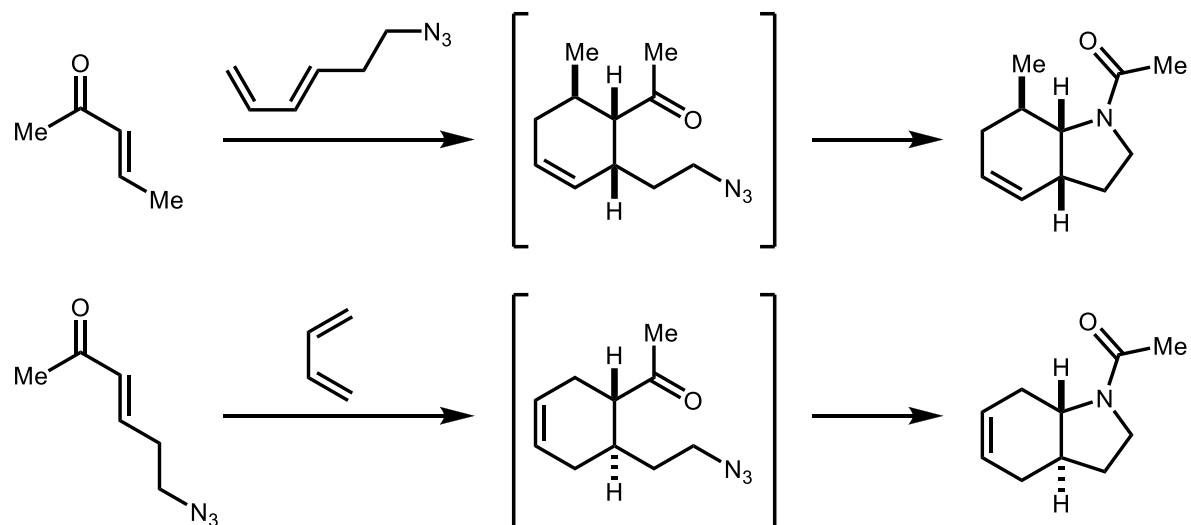Baskaran, S. *Org. Lett*. **2003**, *5*, 583

☐ Amination of Arenes Using Aryl Epoxyazides

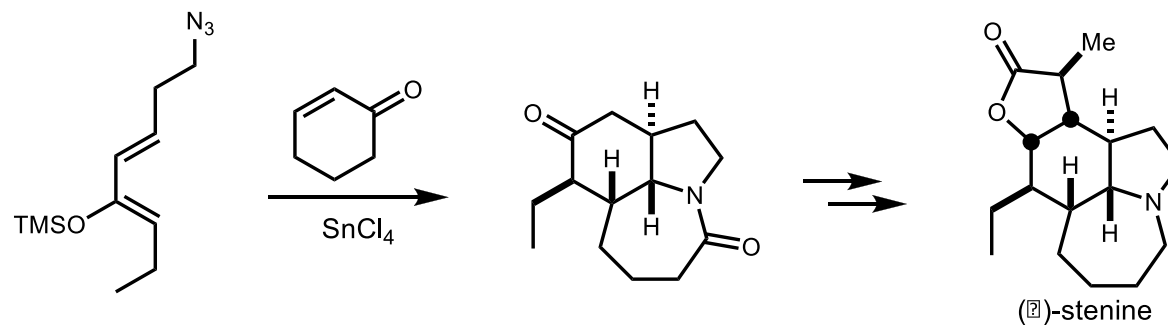Murphy, J. A. *Org. Lett*. **2003**, *5*, 3655

Domino Diels-Alder/Schmidt Reactions

▣ Domino Azido-Schmidt Ring Expansion with DA Reaction
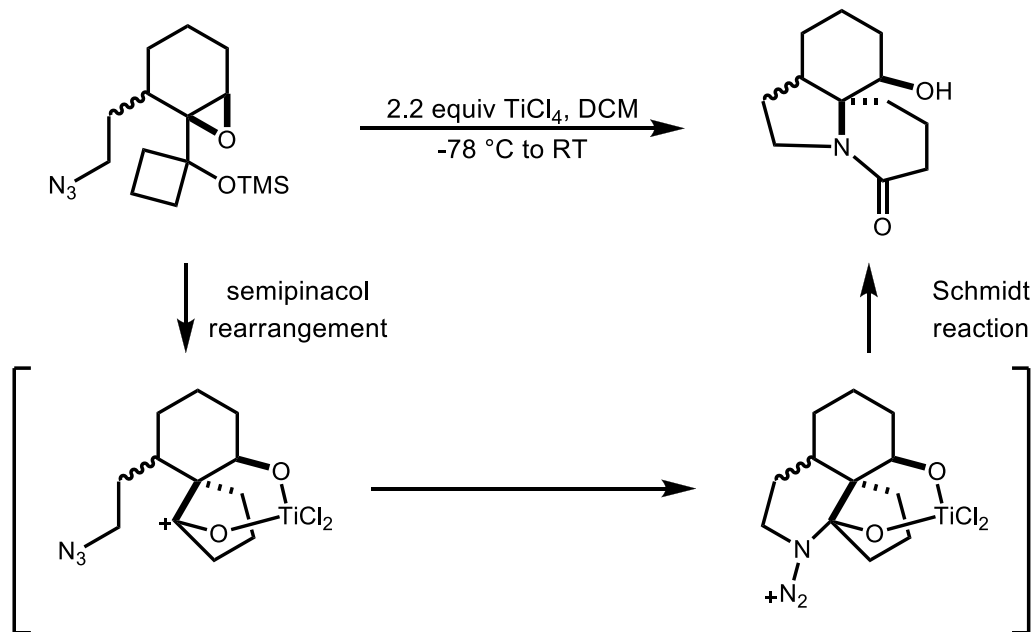

Aube, J. *Org. Lett*. **2004**, *6*, 4993

▣ Synthesis of the Stemona Alkaloid
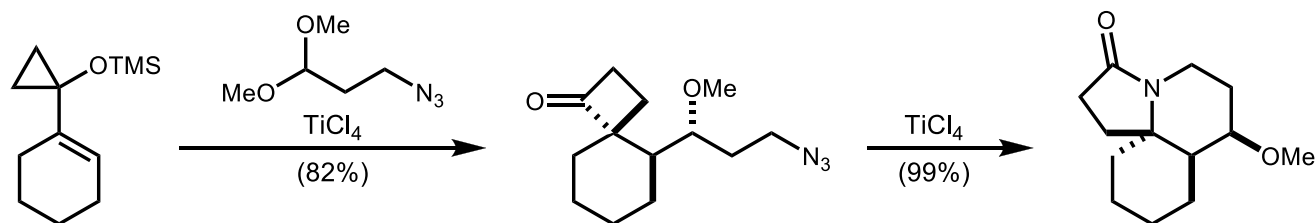

(▣)-stenine

Aube, J. *J. Am. Chem. Soc*. **2005**, *127*, 15712

Tandem Semipinacol/Schmidt and Prins/Schmidt Rearrangements

 Tandem Semipinacol/Schmidt Rearrangement

2.2 equiv TiCl$_4$, DCM
-78 °C to RT

semipinacol
rearrangement

Schmidt
reaction

Tu, Y. Q. *Org. Lett*. **2006**, *8*, 5271

 Tandem Prins/Schmidt Reaction

TiCl$_4$
(82%)

TiCl$_4$
(99%)

Aube, J. *Org. Lett*. **2010**, *12*, 1244