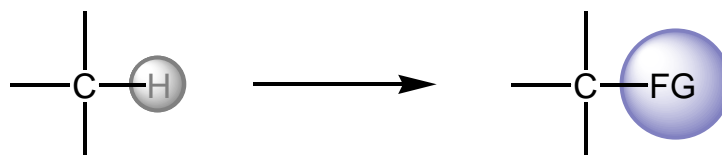


# C-H Activation in Natural Product Synthesis



## Reviews:

- Transition Metal: **Shilov, Shul'pin** *Chem. Rev.* **1997**, 97, 2879  
**Dyker** *ACIEE* **1999**, 38, 1698.
- Mechanism: **Bergman** *Acc. Chem. Res.* **1995**, 28, 154  
**Stahl, Labinger, Bercaw** *ACIEE* **1998**, 37, 2180
- Carbene-Induced: **Davies** *Chem. Rev.* **2003**, 103, 2861
- Stoichiometric: **Jones** *Top. Organomet. Chem.* **1999**, 3, 9.
- Catalytic: **Fujiwara** *Acc. Chem. Res.* **2001**, 34, 633.  
**Kakiuchi** *Top. Organomet. Chem.* **1999**, 3, 47.
- Synthesis: **Sames** *Science* **2006**, 312, 67

**Kristy Tran**  
**Leighton Group**  
**May 1, 2006**

# Mechanisms of C-H Activation

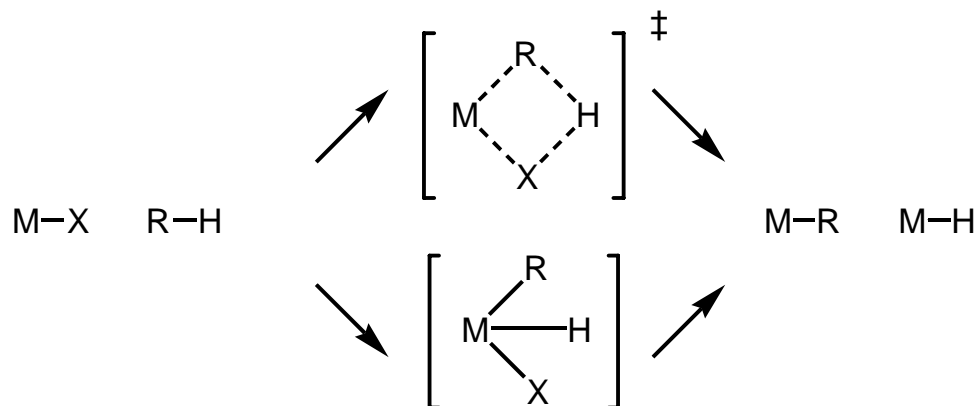
## Oxidative Addition



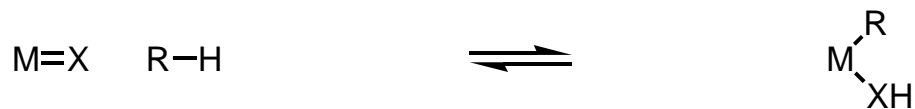
## Radical Process (Rare)



## Addition of Electrophilic Metal Center (Concerted or Oxidative Addition)

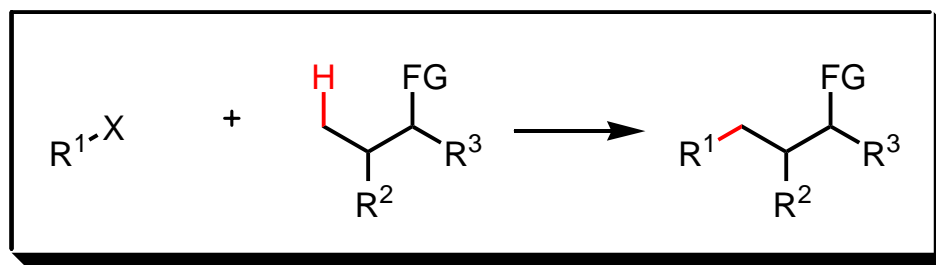
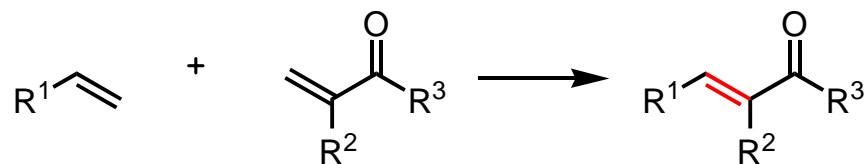
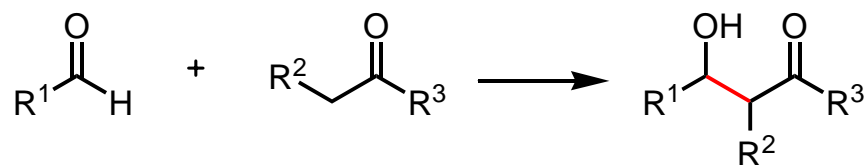


## Reversible Addition to an M=X Bond (Carbenoids)



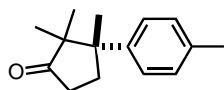
# Traditional vs C-H Activation

C-H activation offers *new disconnection strategies* which can rival traditional methods which requires manipulation of functional groups which are often relatively reactive and molecules which are unlike the target compound.



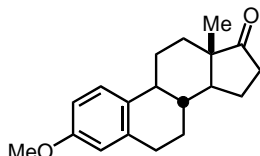
Simplifies synthetic approaches by using *topologically obvious assembly*

# C-H Activation in Natural Product Synthesis



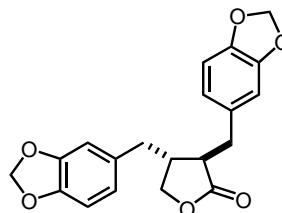
**(+)- $\alpha$ -Cuparenone**

Taber *JACS* **1985**, *107*, 196-9



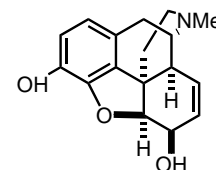
**(+)-Estrone methyl ester**

Taber *JOC* **1987**, *52*, 28



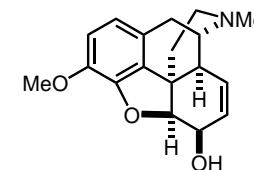
**(-)-Hinokinin**

Doyle *JOC* **1996**, *61*, 9146



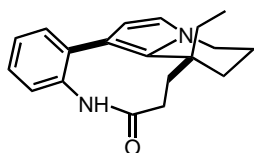
**(+)-morphine**

White *JOC* **1997**, *62*, 5250-1



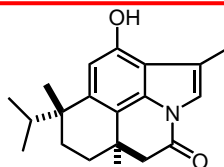
**(+)-Codeine**

White *JOC* **1999**, *64*, 7871-84



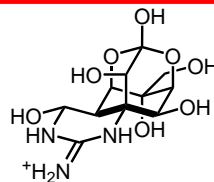
**Rhazinilam**

Sames *JACS* **2000**, *122*, 6321



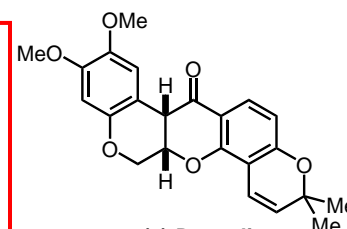
**Telocidin B4 Core**

Sames *JACS* **2002**, *124*, 11856



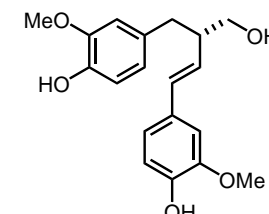
**Tetrodotoxin**

Du Bois *JACS*, **2003**, *125*, 11510



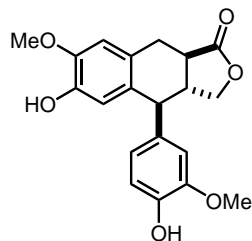
**(+)-Deguelin**

Sames *Org. Let.* **2003**, *5*, 4053-5



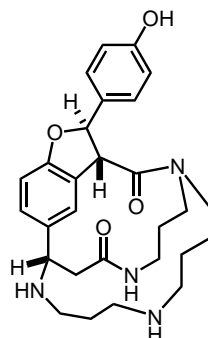
**(+)-Imperanene**

Davies *Tetrahedron: Asymm.* **2003**, *14*, 941



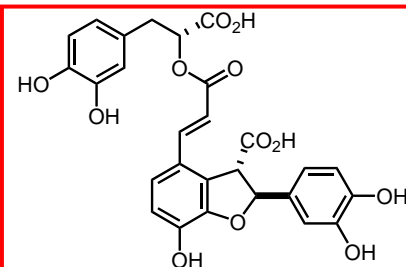
**(-)- $\alpha$ -Conidendrin**

Davies *Tetrahedron: Asymm.* **2003**, *14*, 941-9



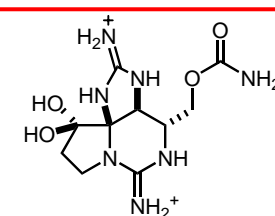
**(-)-Ephedradine A (Orantine)**

Fukuyama *JACS* **2003**, *125*, 8112-3



**(+)-Lithospermic Acid**

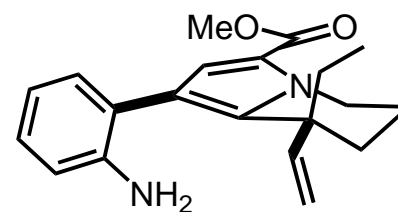
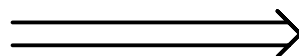
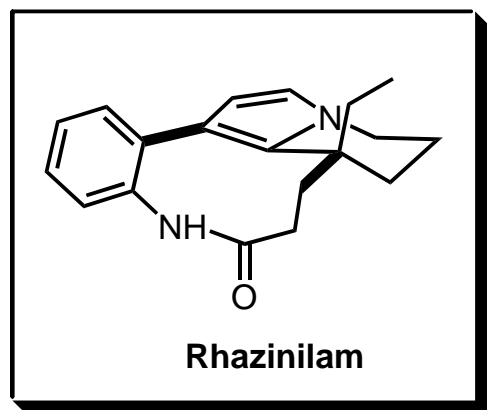
Bergman, Ellman *JACS*, **2005**, *127*, 13496



**(+)-Saxitoxin**

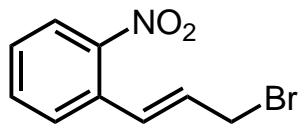
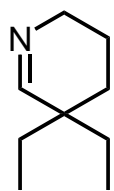
Du Bois *JACS* **2006**, *128*, 3926

# Rhazinilam - Retrosynthesis

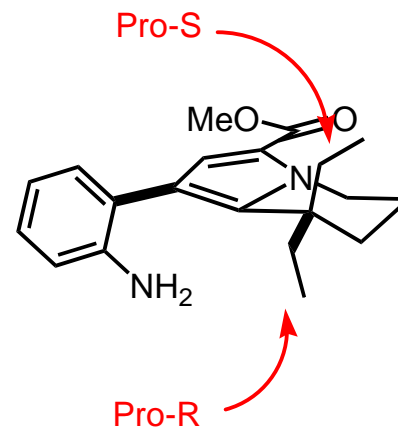


*Member of Aspidosperma class of alkaloids*  
*Antitumor properties*

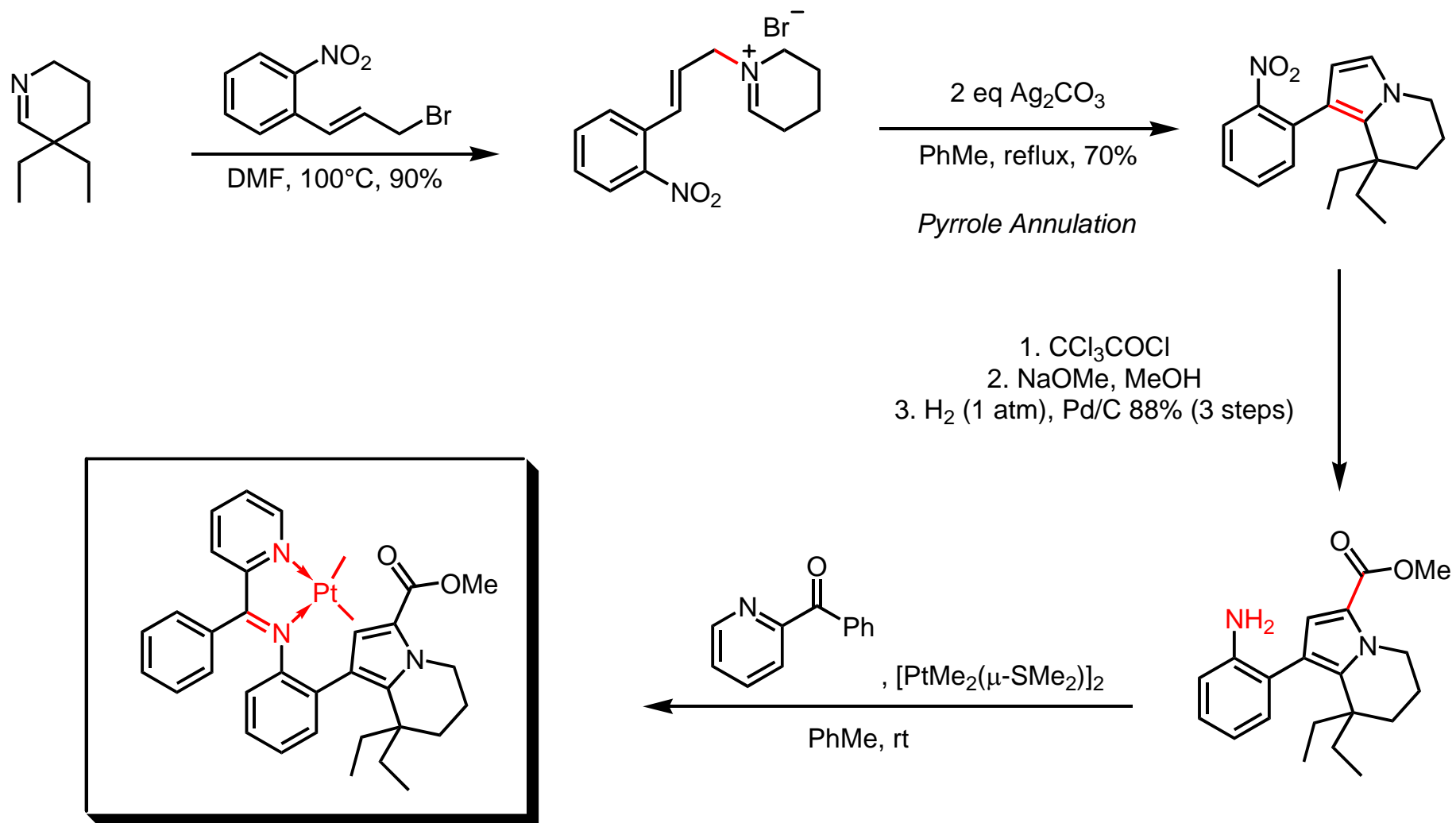
Selective dehydrogenation  
C-H bond activation



Pyrrole Annulation



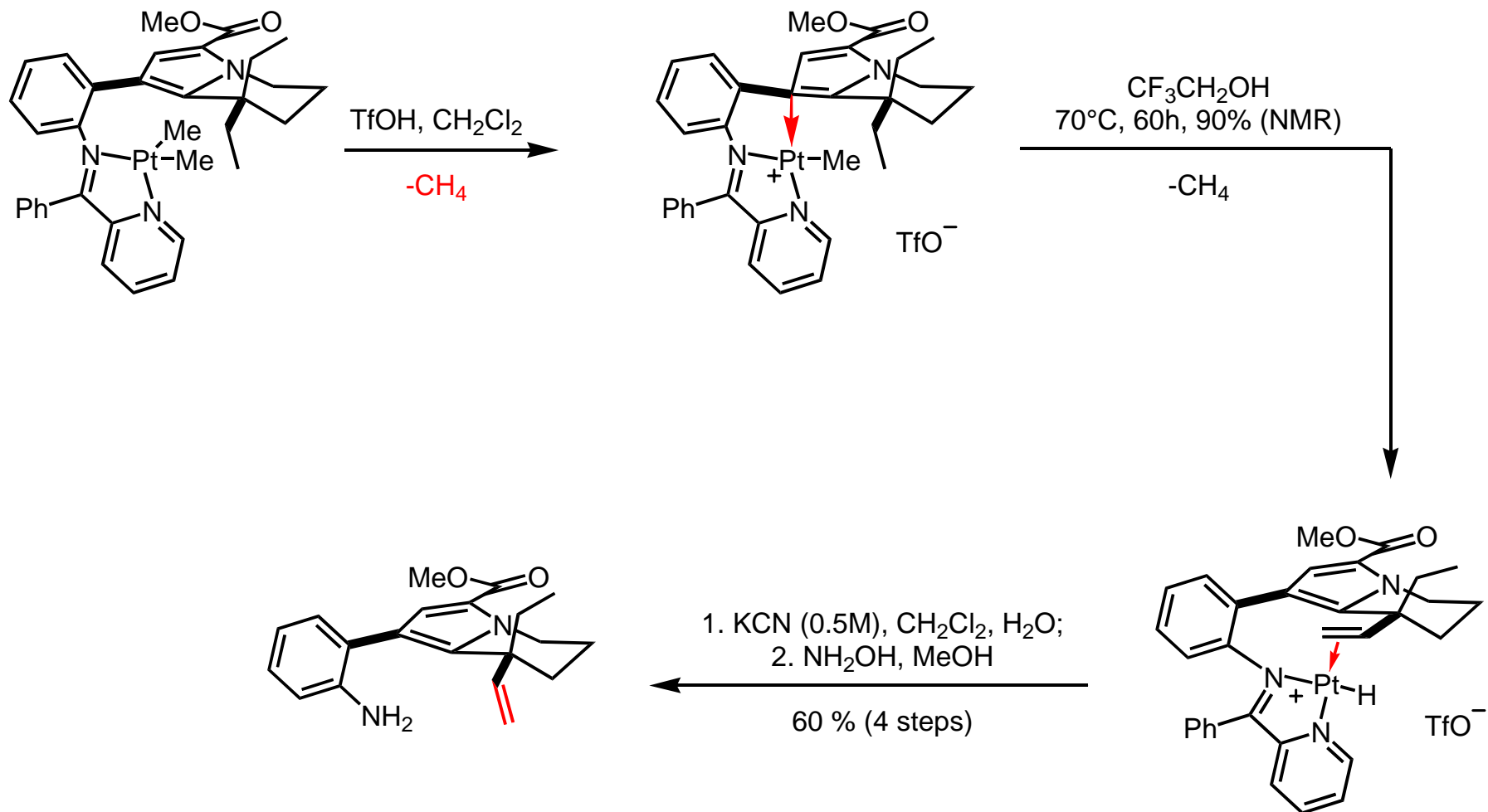
# Racemic Synthesis of C-H Activation Precursor



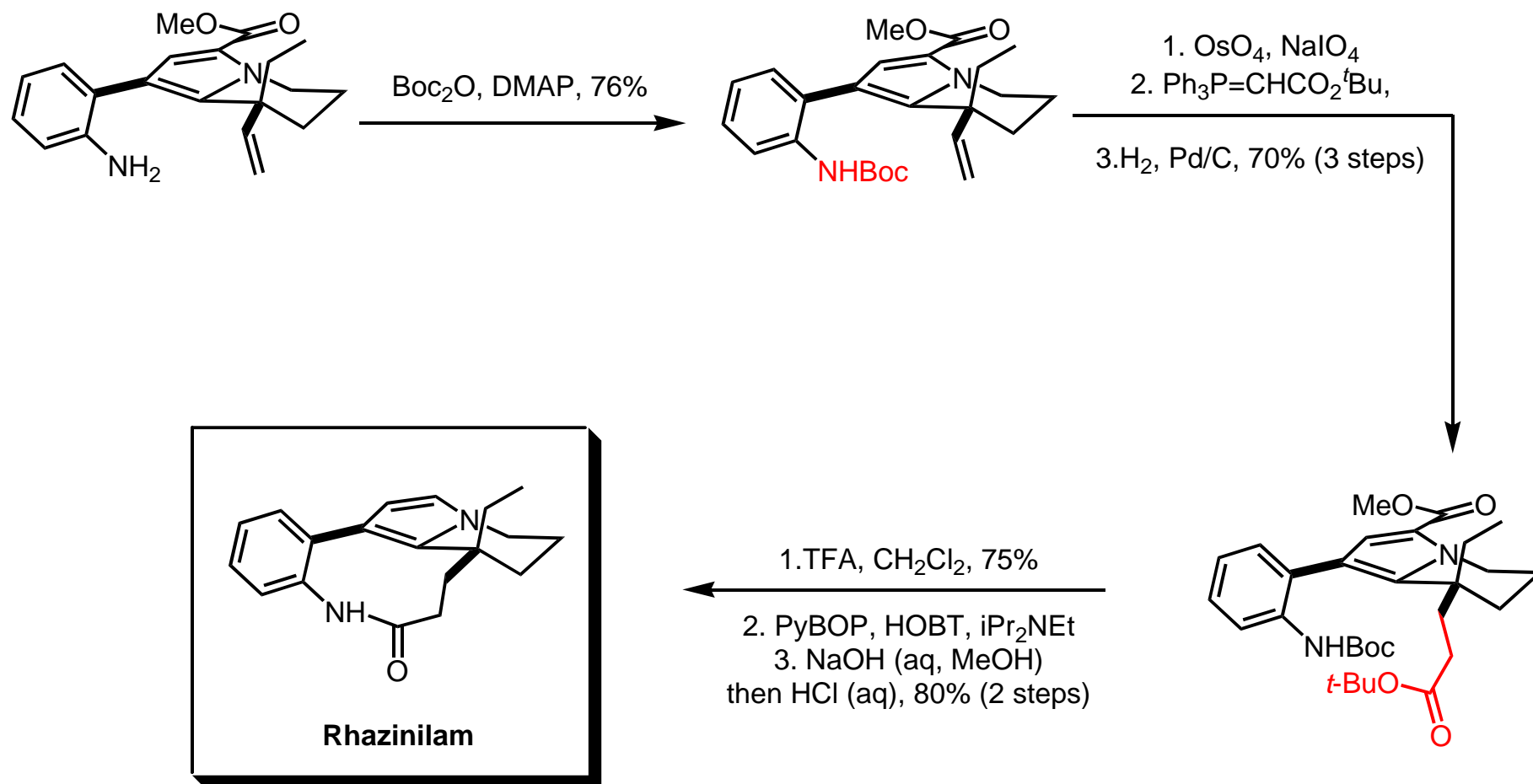
Johnson, J. A.; Sames, D., *J. Am. Chem. Soc.* **2000**, 122, 6321-2.

Grigg, R.; Myers, P.; Somasunderam, A.; Sridharan, V. *Tetrahedron* **1992**, 48, 9735

# Selective C-H Bond Activation



# Endgame of Razinilam



HOBT = 1-hydroxybenzotriazole hydrate (used in peptide synthesis to suppress racemization)

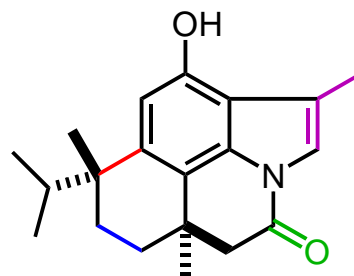
PyBOP = Benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate

Johnson, J. A.; Sames, D., *J. Am. Chem. Soc.* **2000**, *122*, 6321-2.

# Teleocidin B4 Core

Friedel-Crafts (racemic)

Alkenylation of phenol

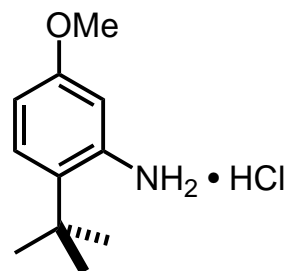


Alkenylation of unactivated alkyl

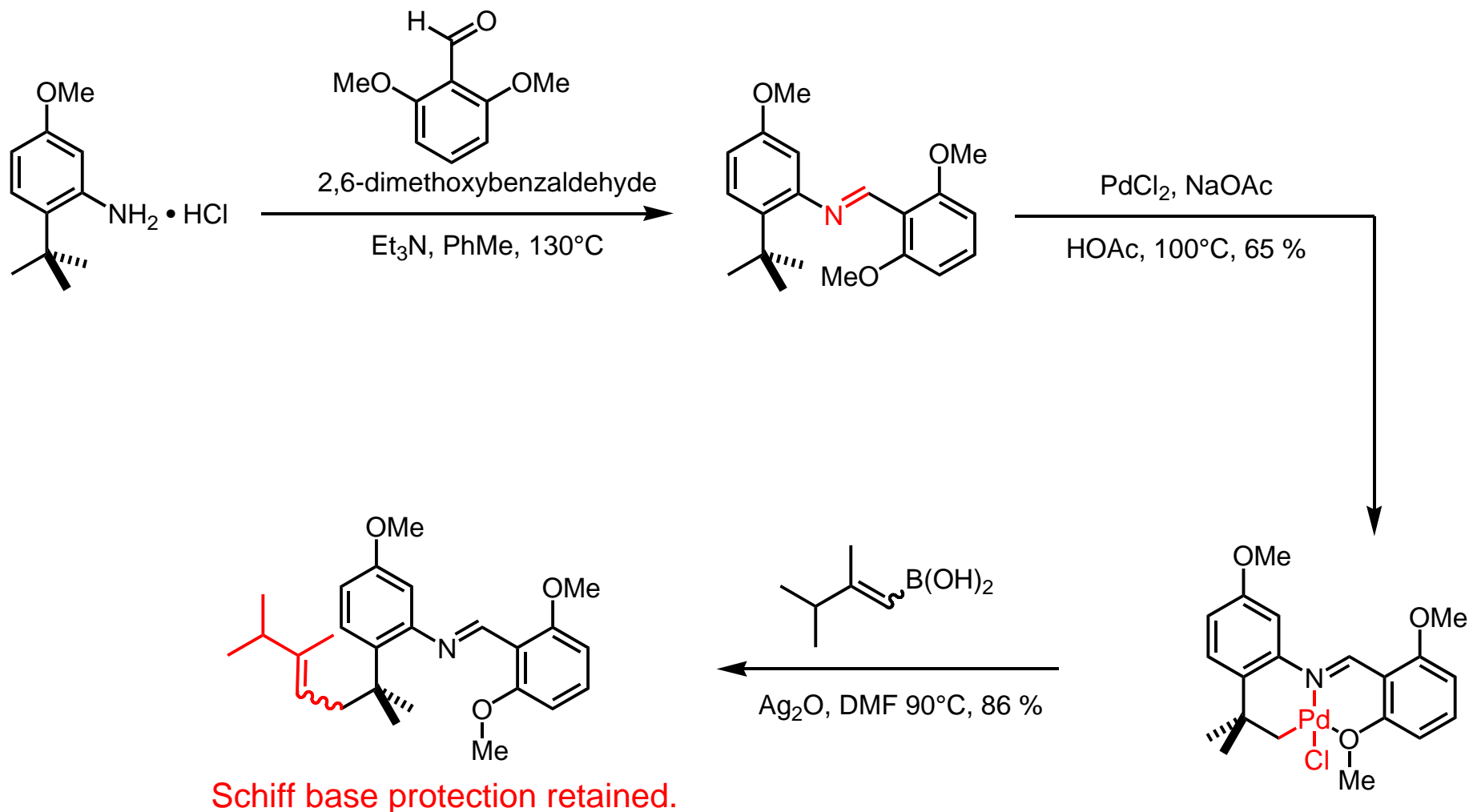
Carbonylation of unactivated alkyl

Teleocidin B4 Core

*Two tandem cycles of  
directed C-H bond  
functionalizations*



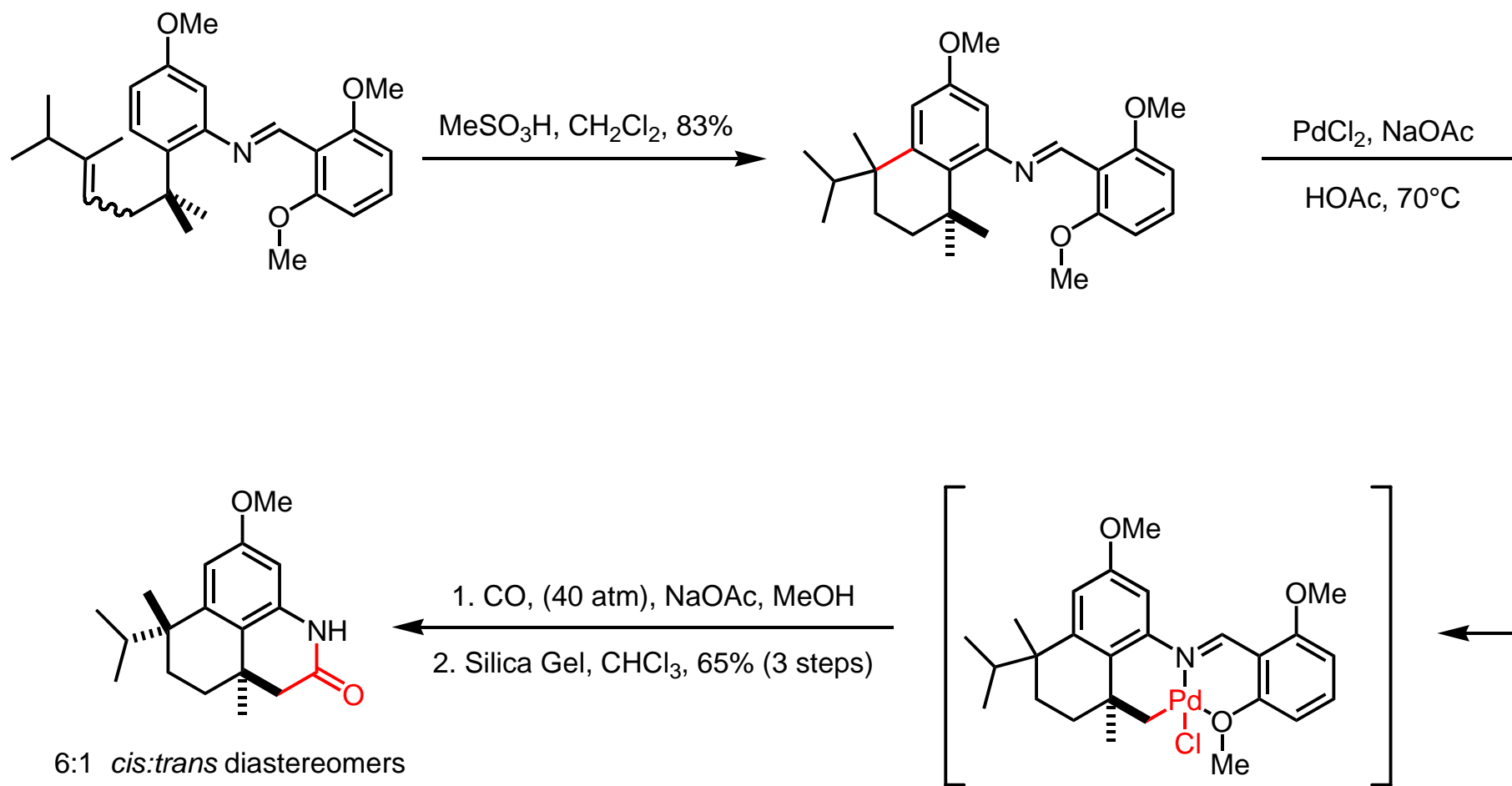
# Alkenylation of Unactivated Alkane



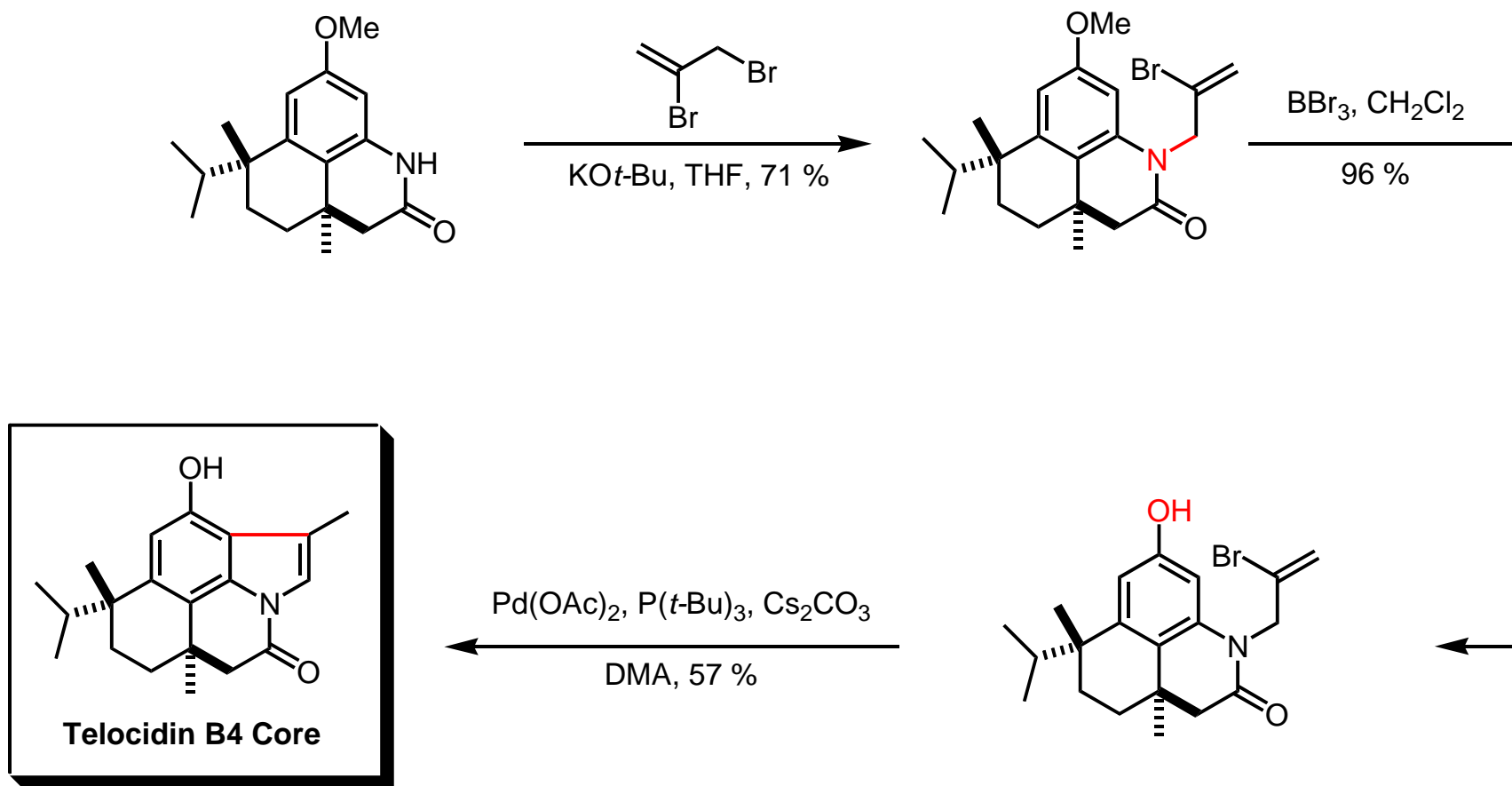
Schiff base protection retained.

In position for second cycle of C-H activation/ C-C bond formation without interruption

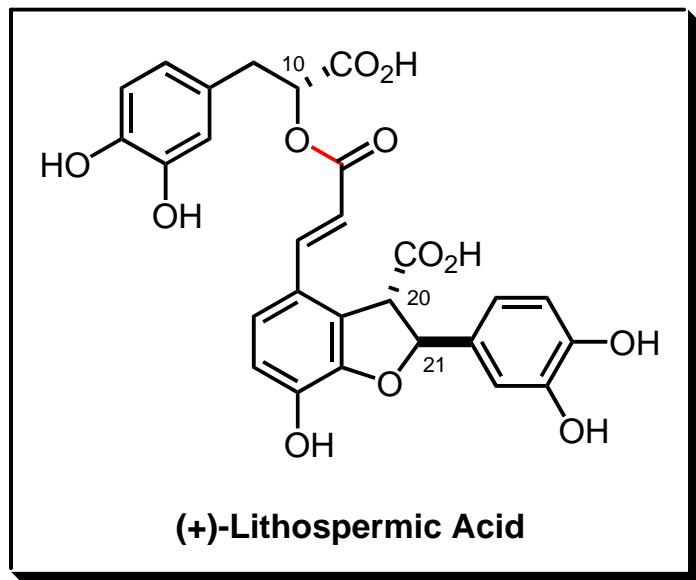
# Carbonylation of Unactivated Alkane



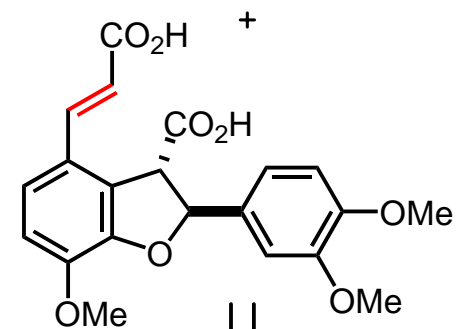
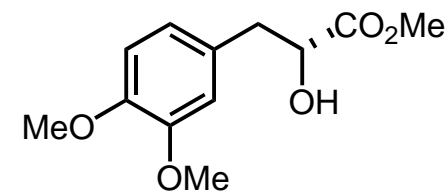
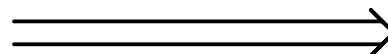
# Completion of Teleocidin B4 Core



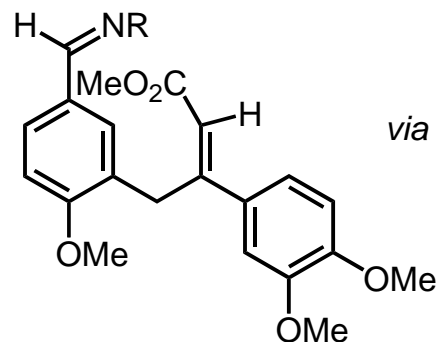
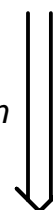
# (+)-Lithospermic Acid



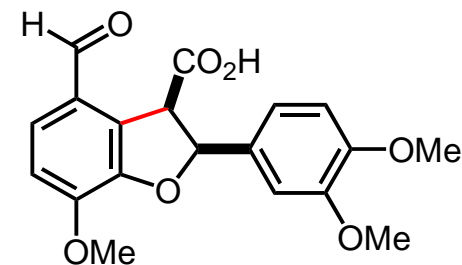
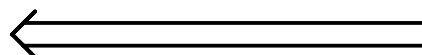
*Global Deprotection  
and Esterification*



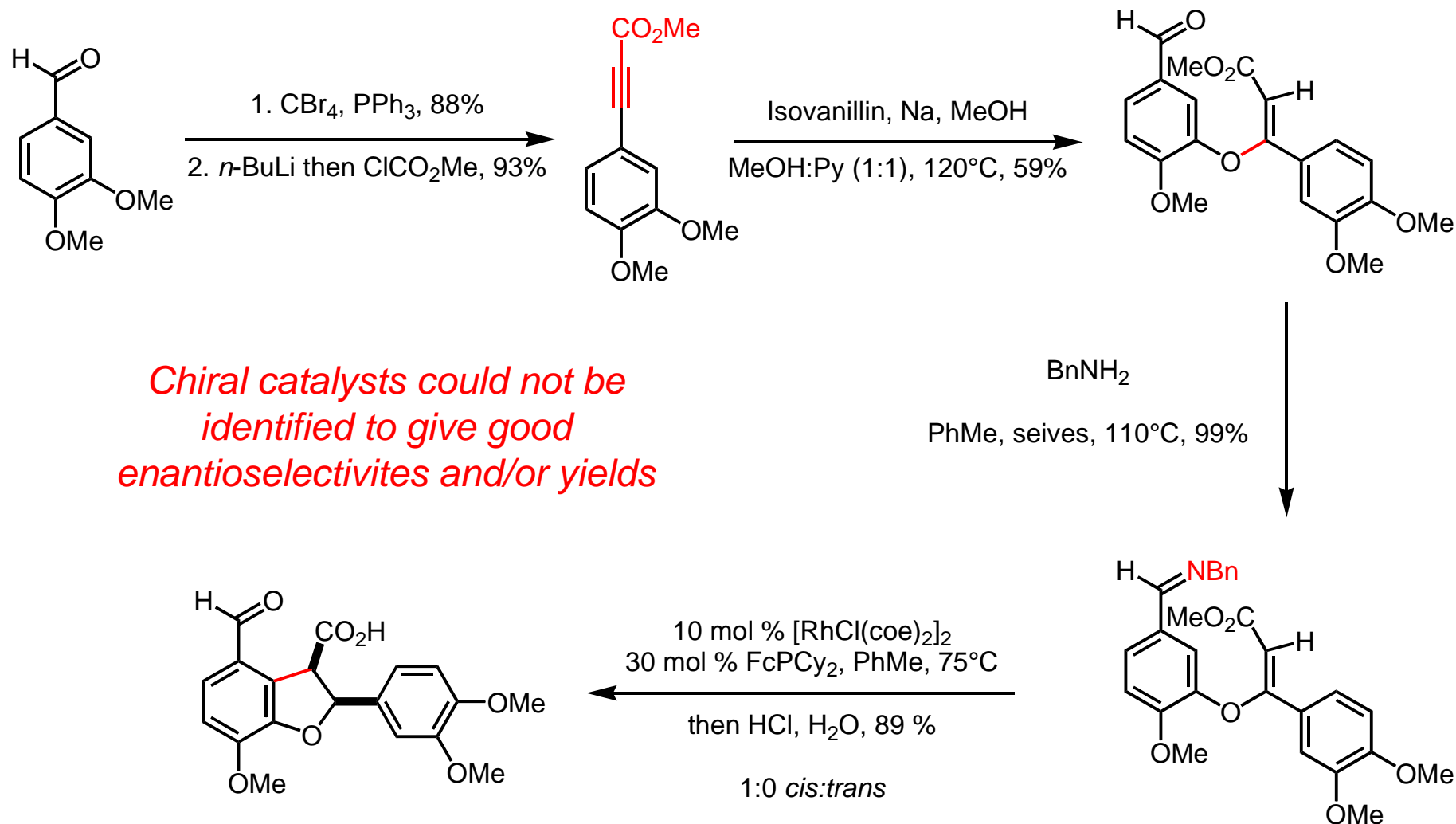
*Knovenagel Condensation  
& C20 Epimerization*



*Intramolecular Asymmetric Alkylation  
via catalytic Rh Catalyzed C-H Bond Activation*



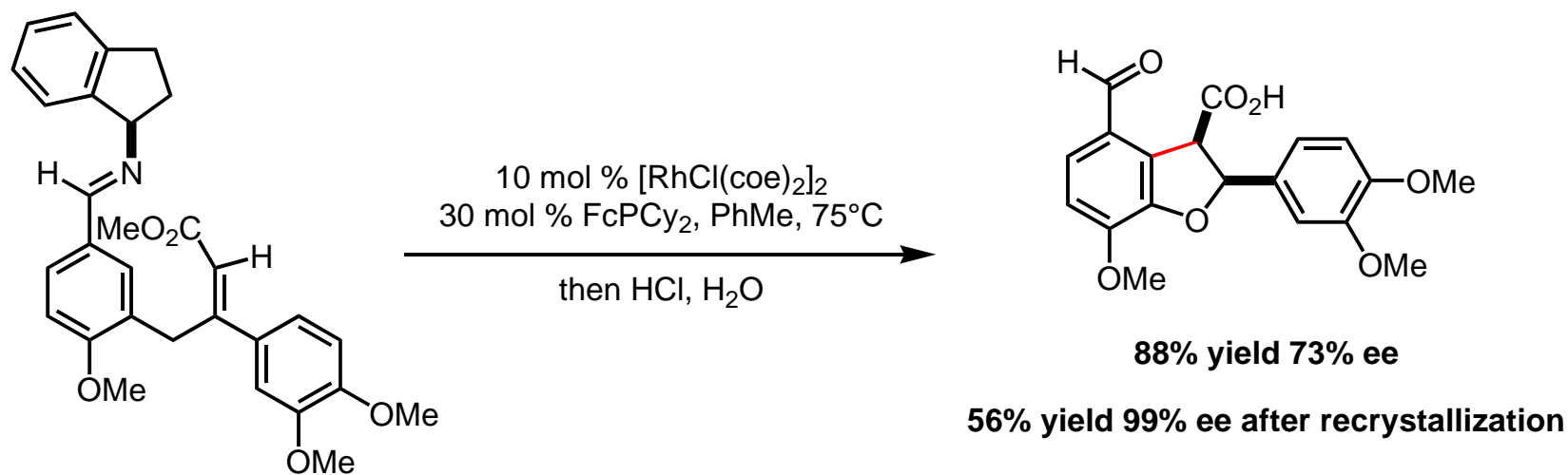
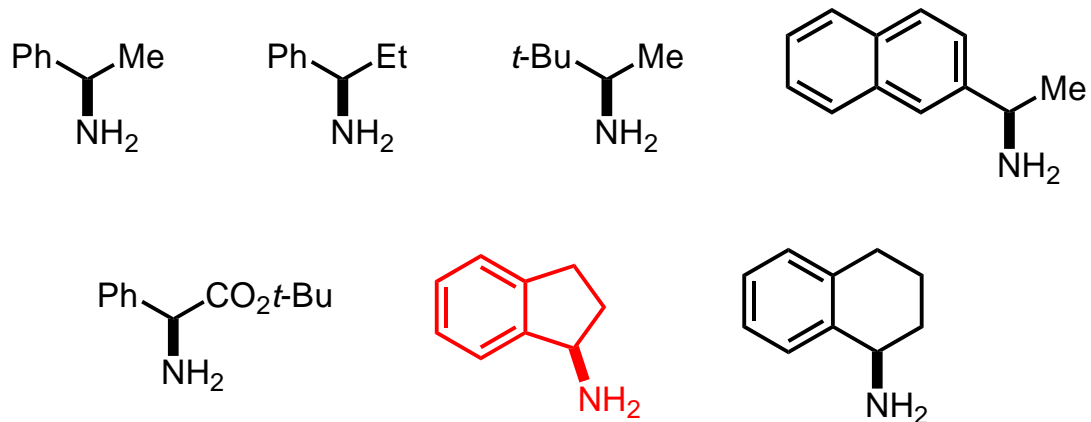
# Racemic Intramolecular Alkylation



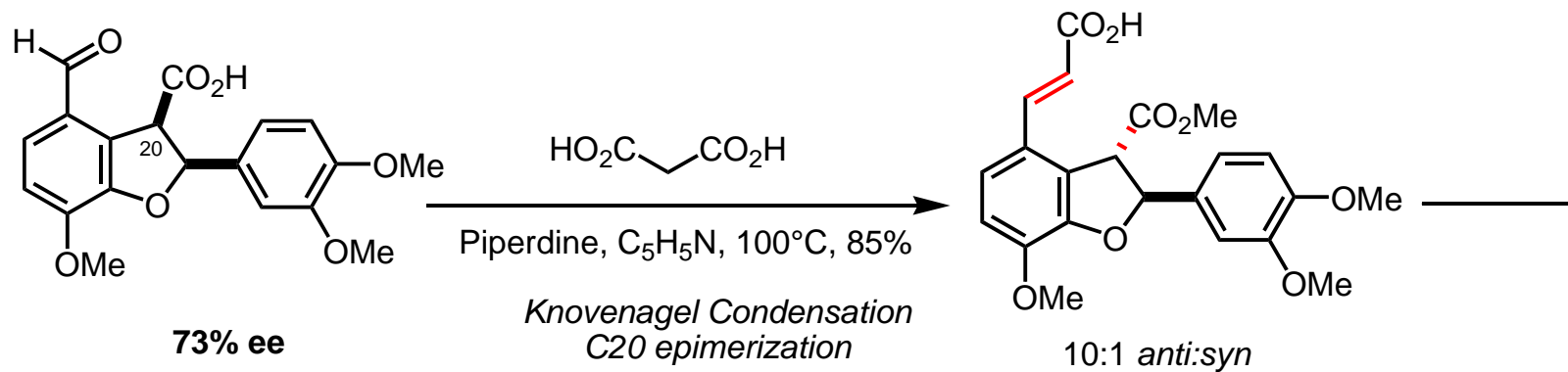
coe = cyclooctene; Fc-ferrocenyl

O'Malley, S.J.; Tan, K.L.; Watzke, A.; Bergman, R.G.; Ellman, J.A. *J. Am. Chem. Soc.* **2005**, *127*, 13496.

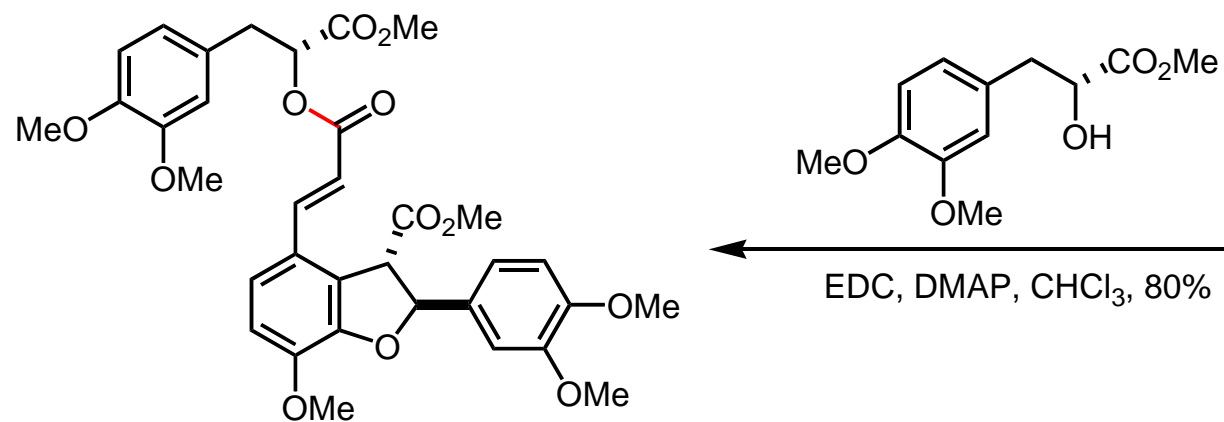
# Chiral Amine Auxillaries



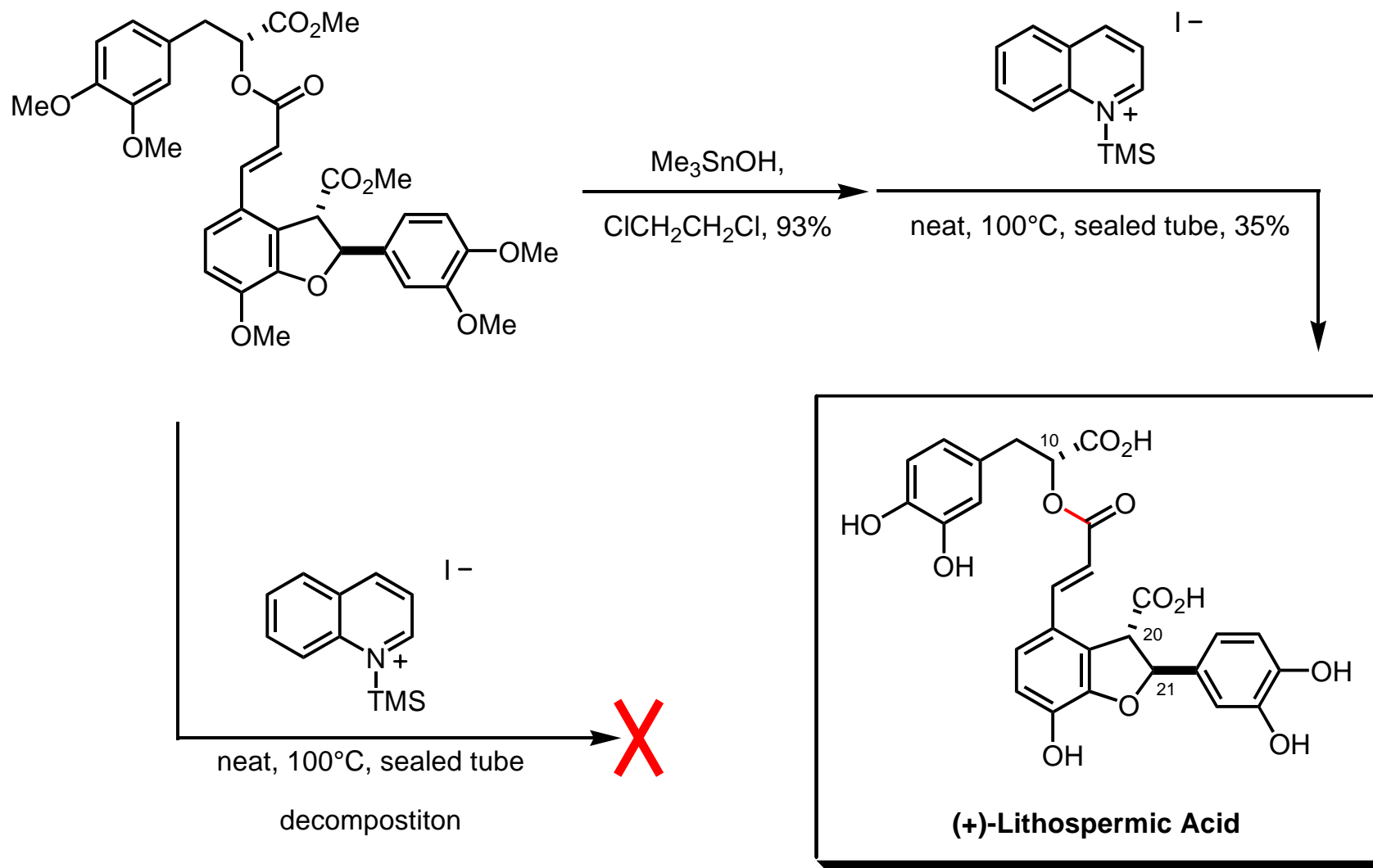
# Heptamethyl Lithospermic Acid



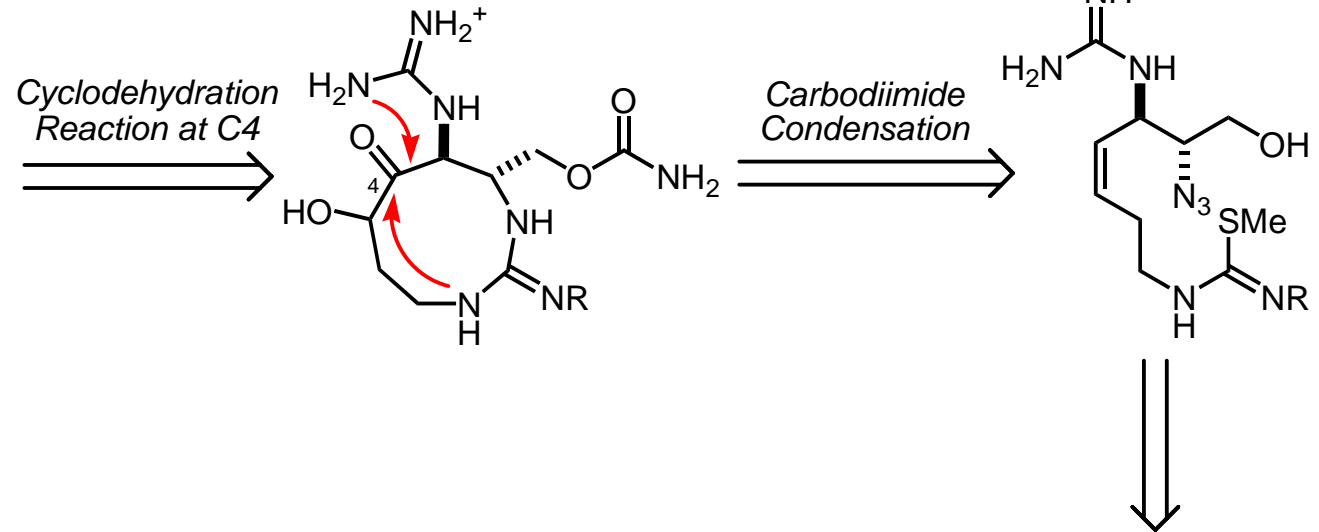
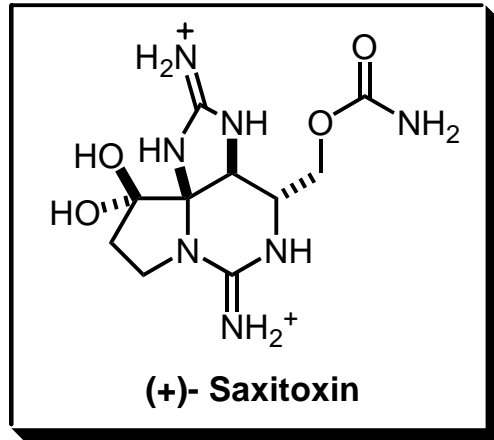
99% ee after recrystallization



# Global Deprotection and Lithospermic Acid



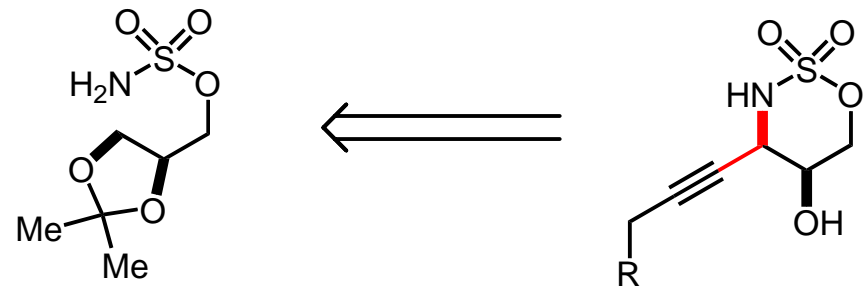
# Saxitoxin



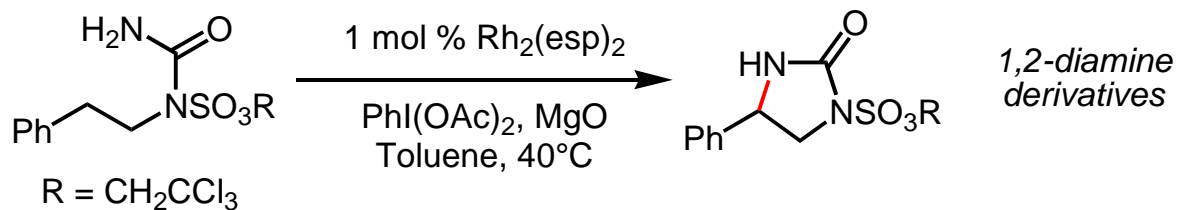
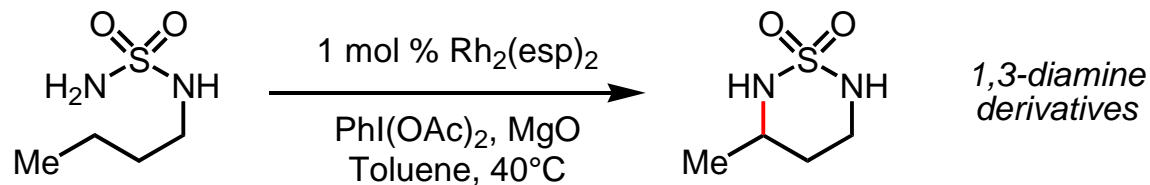
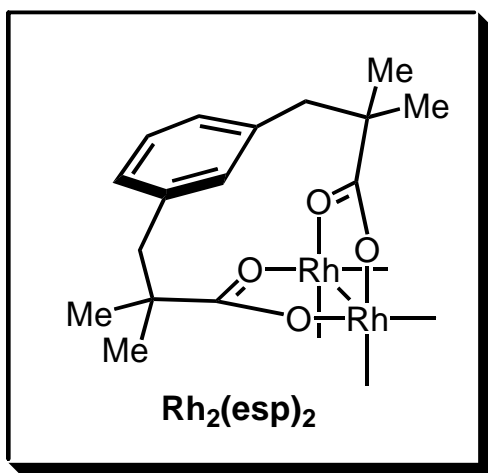
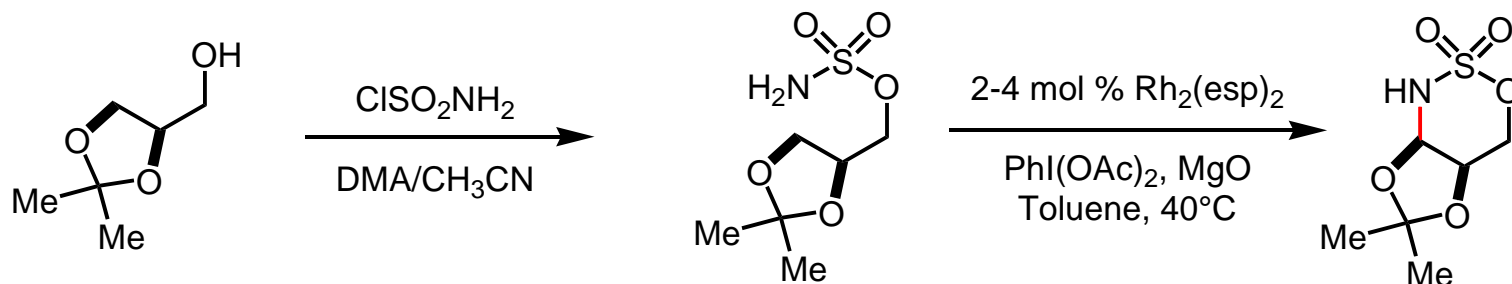
Chemical Weapon  
Designation: TZ

Toxic, paralytic agent

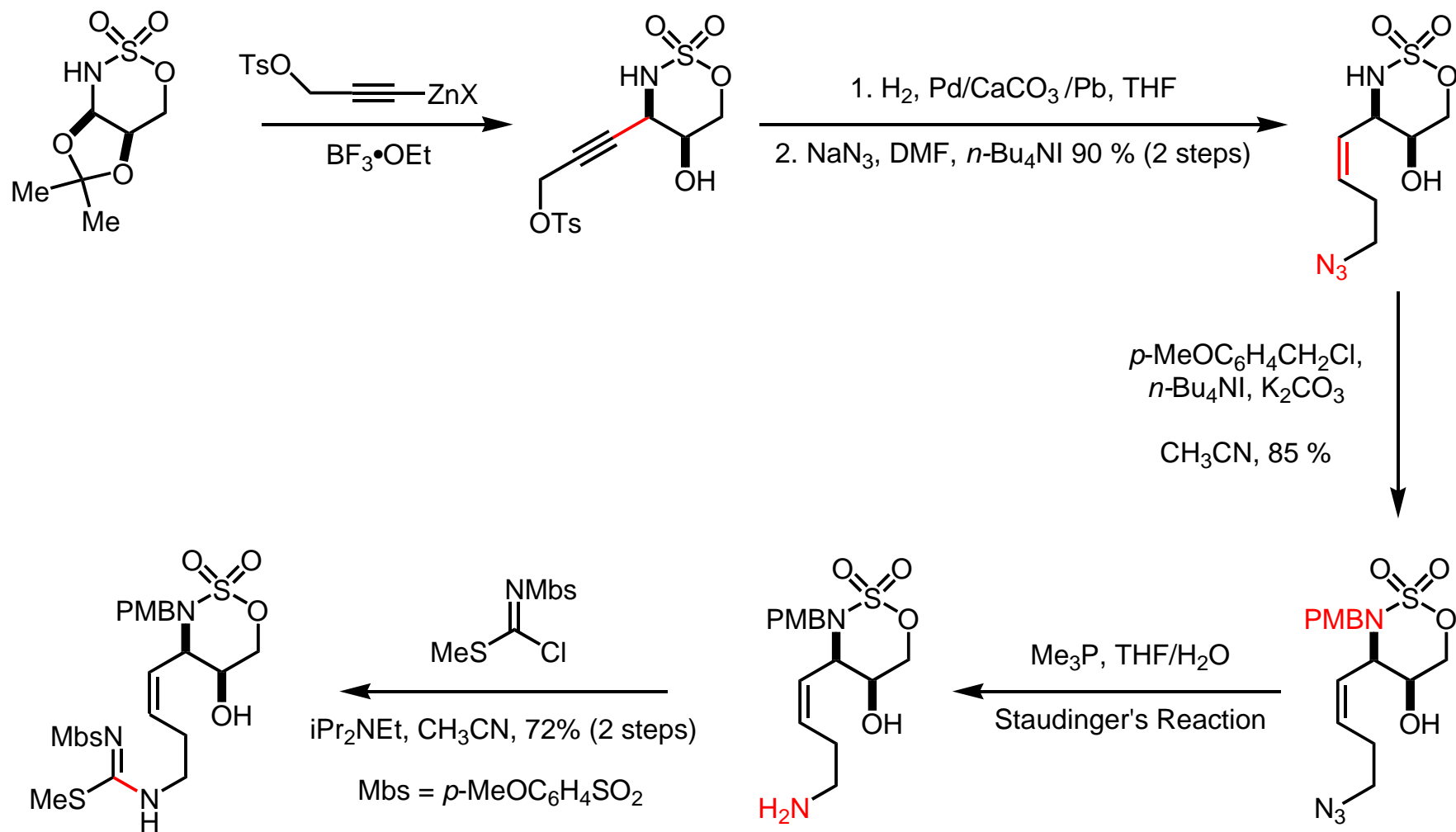
Selective voltage gated  
Na<sup>+</sup> channel blocker



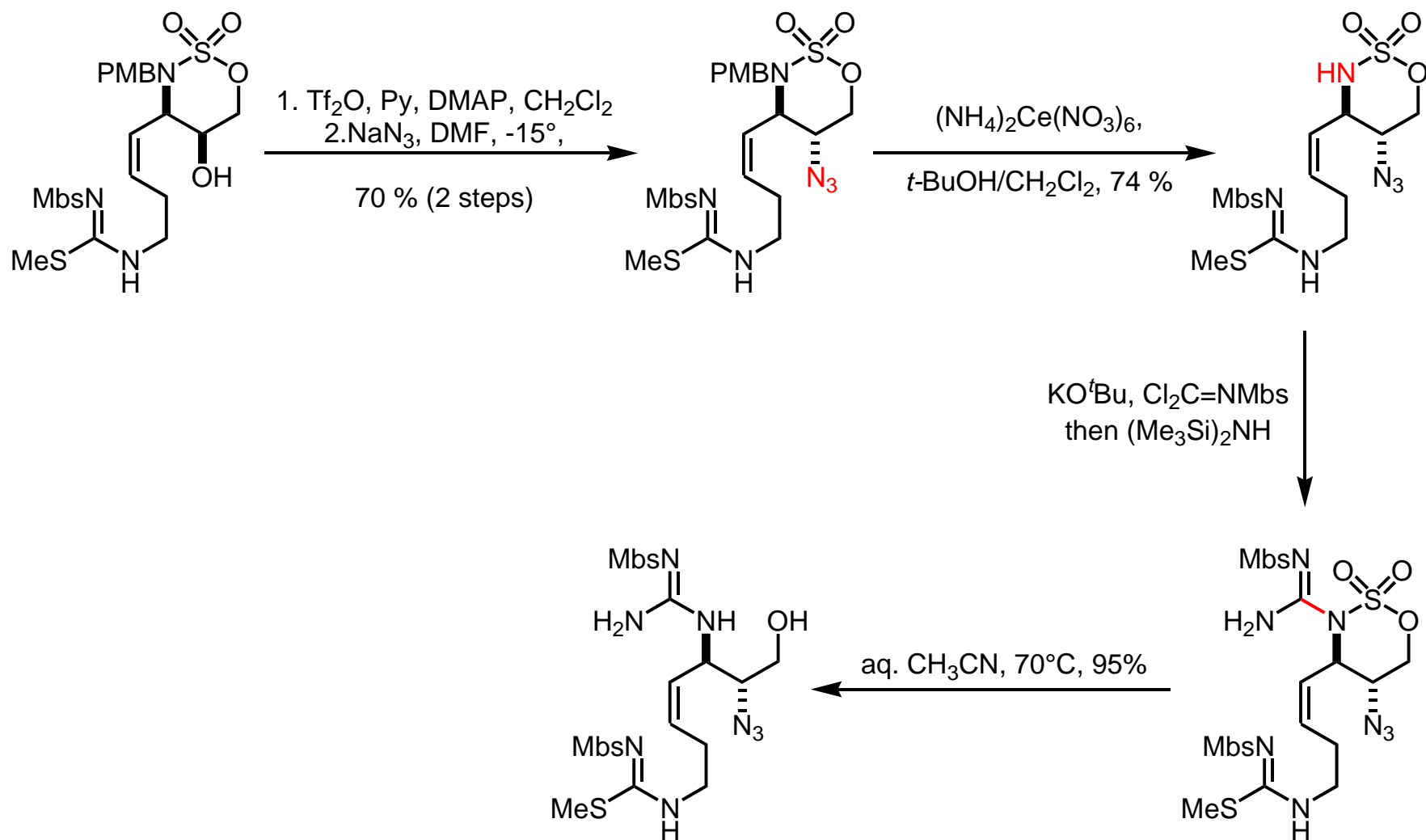
# Rh-catalyzed Sulfamate Insertion



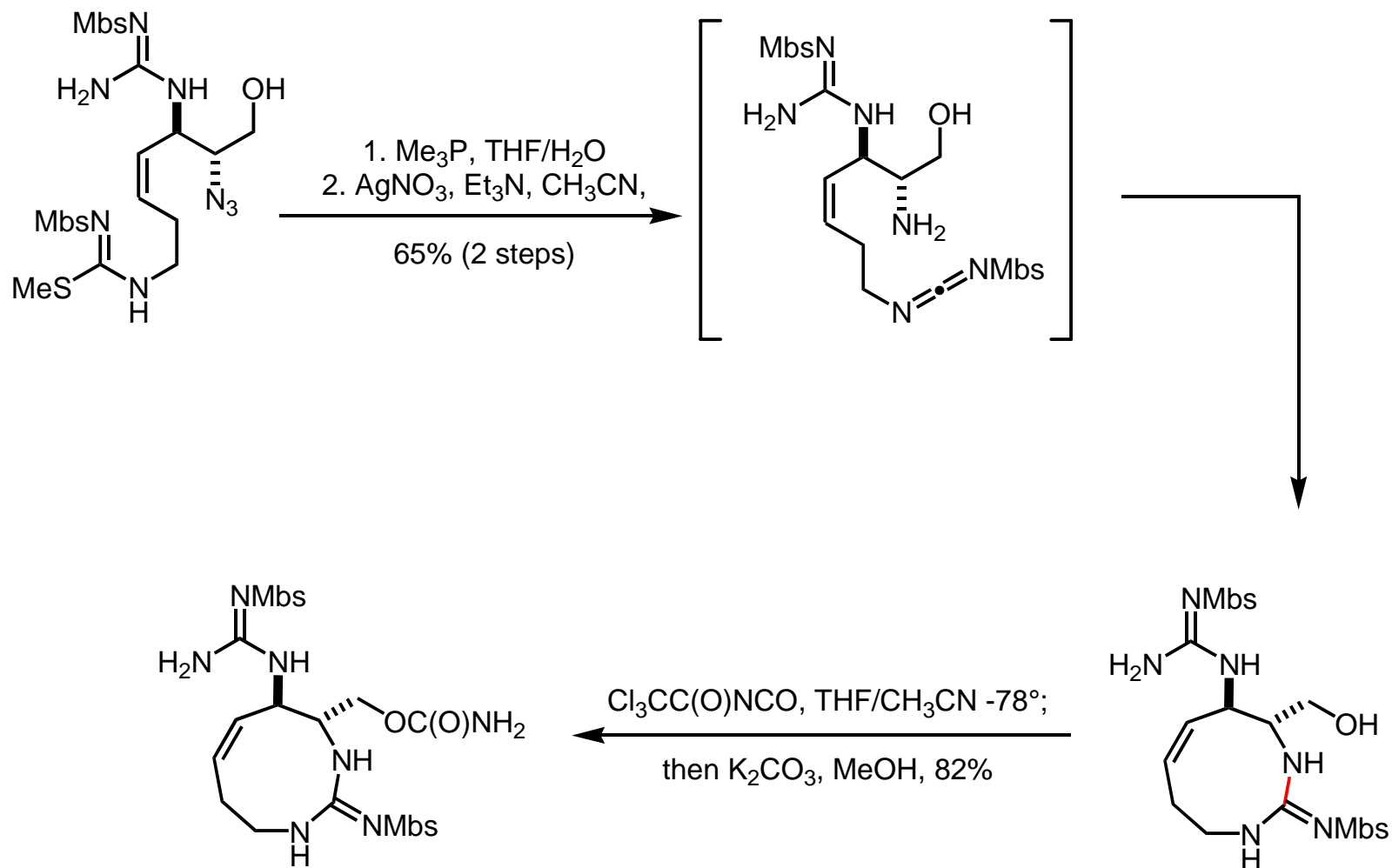
# N,O-Acetals as Latent Iminium Ions Equivalents



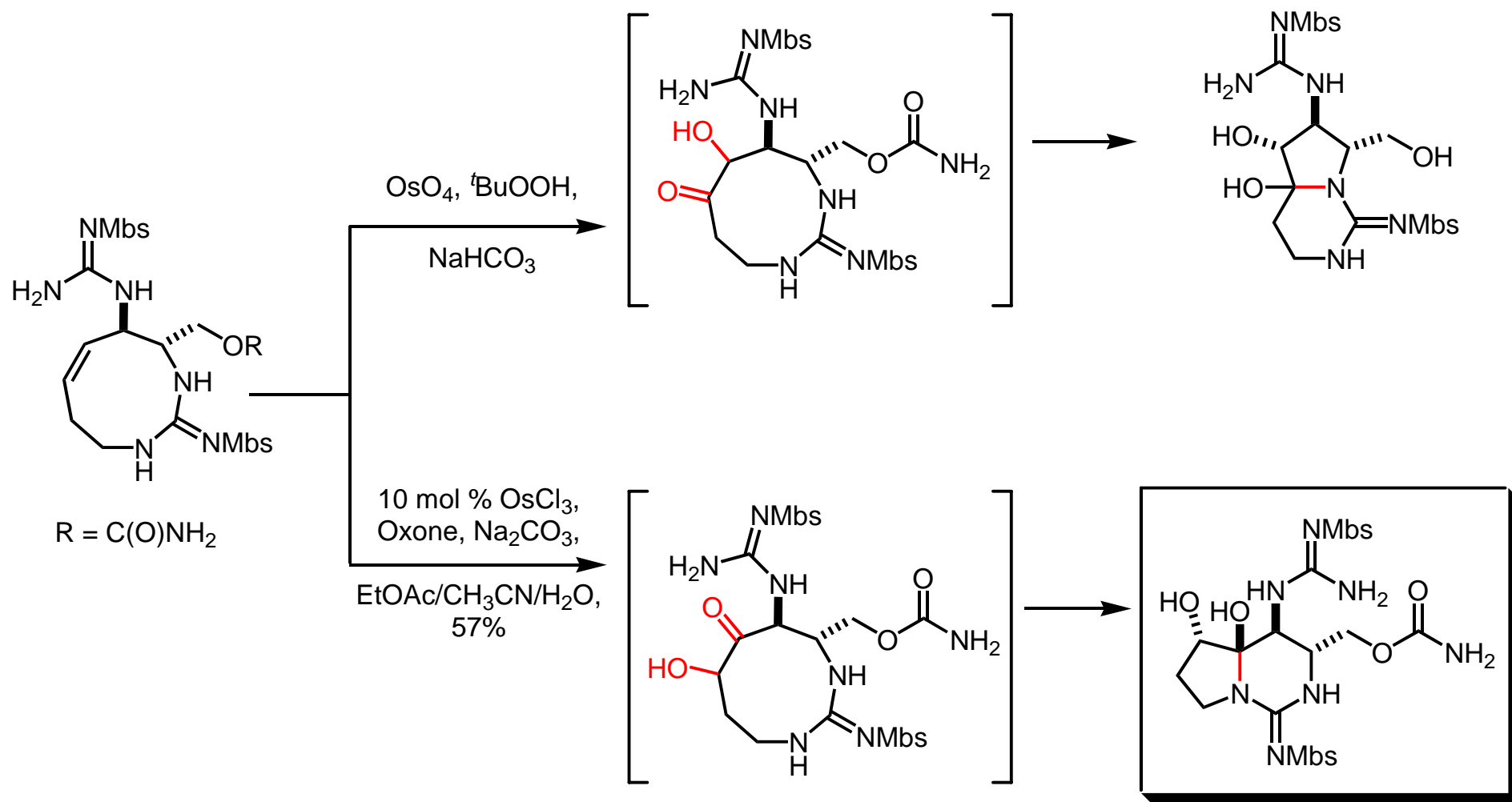
# Synthesis of Acyclic Core of Saxitoxin



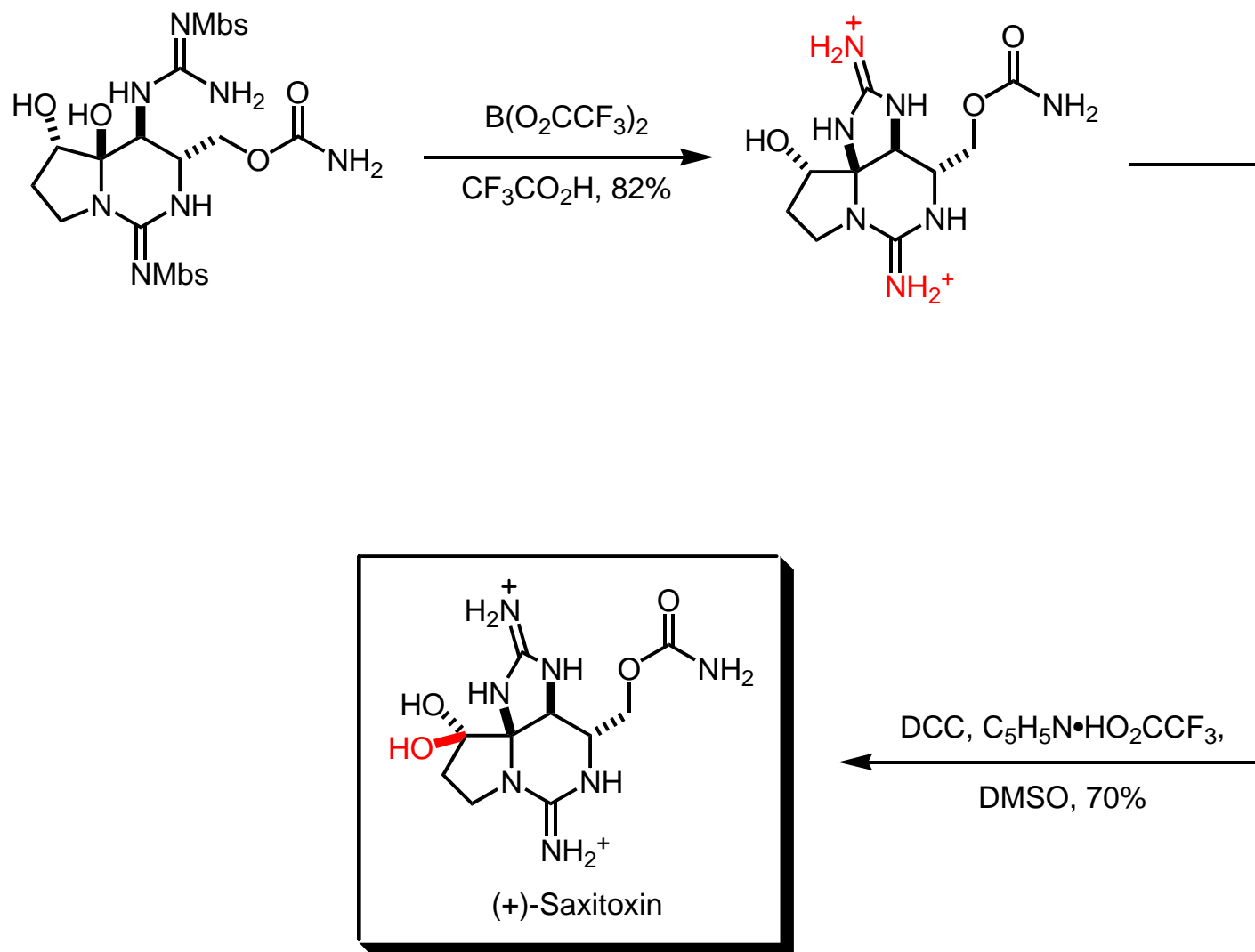
# Carbodiimide Condensation



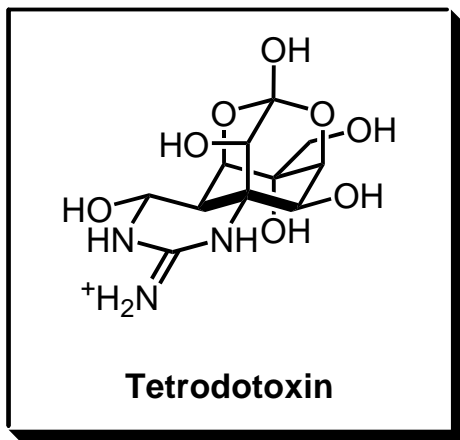
# Alkene Ketohydroxylation & Cyclodehydration



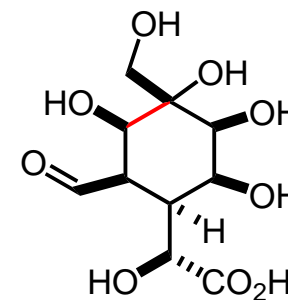
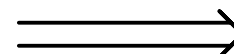
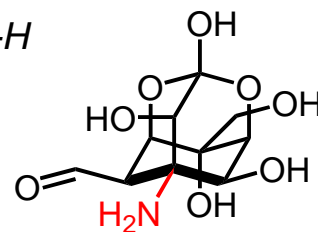
# Synthesis of (+)-Saxitoxin



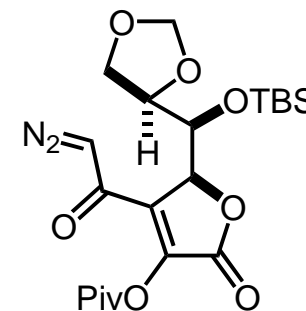
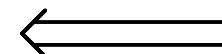
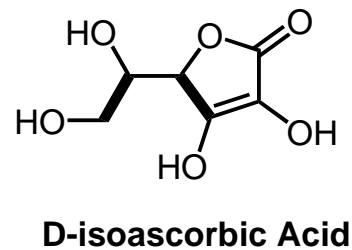
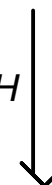
# Tetrodotoxin



*Rh-nitrene C-H  
Amination*



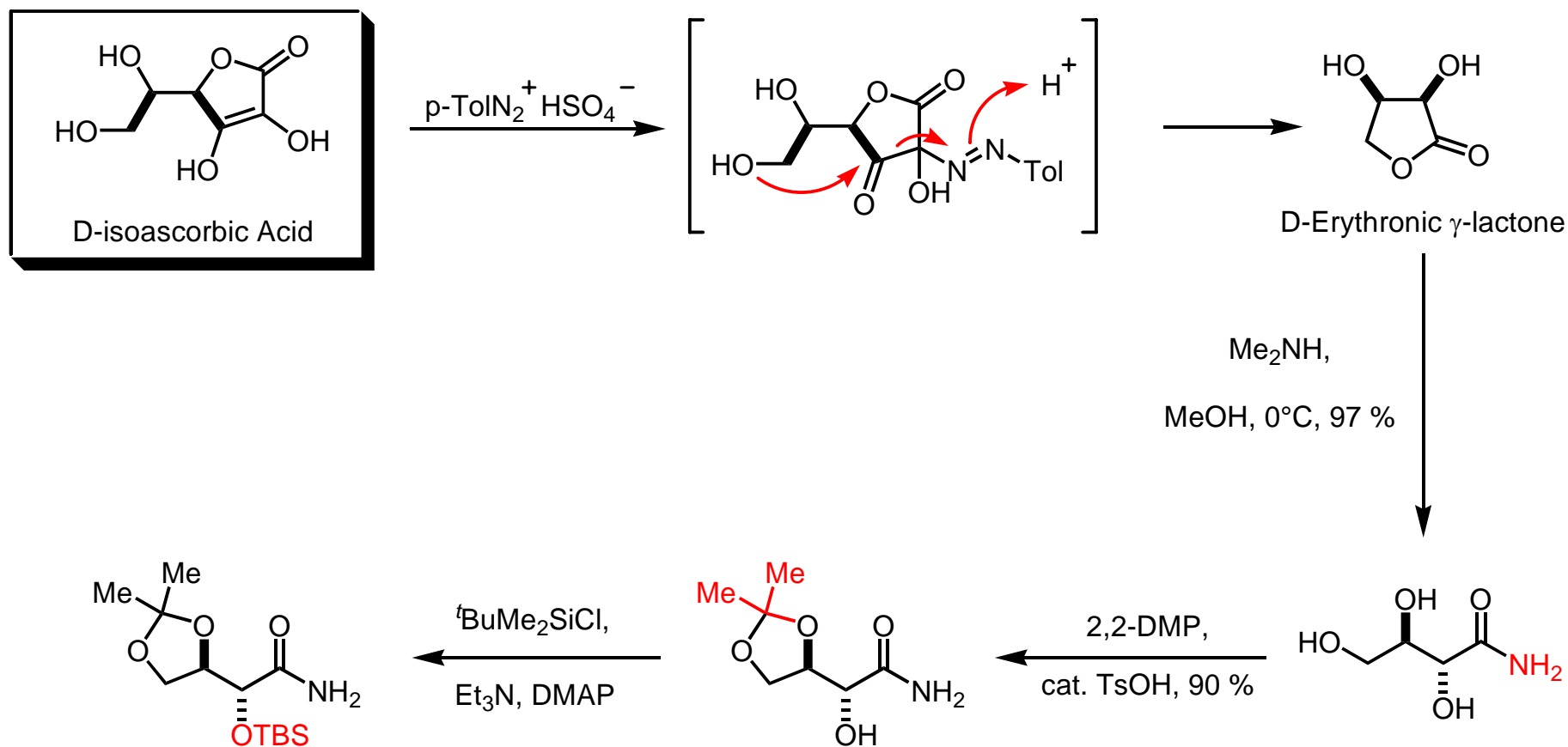
*Rh-carbene C-H  
Alkylation*



Guanidium poison from the  
Japanese fugu

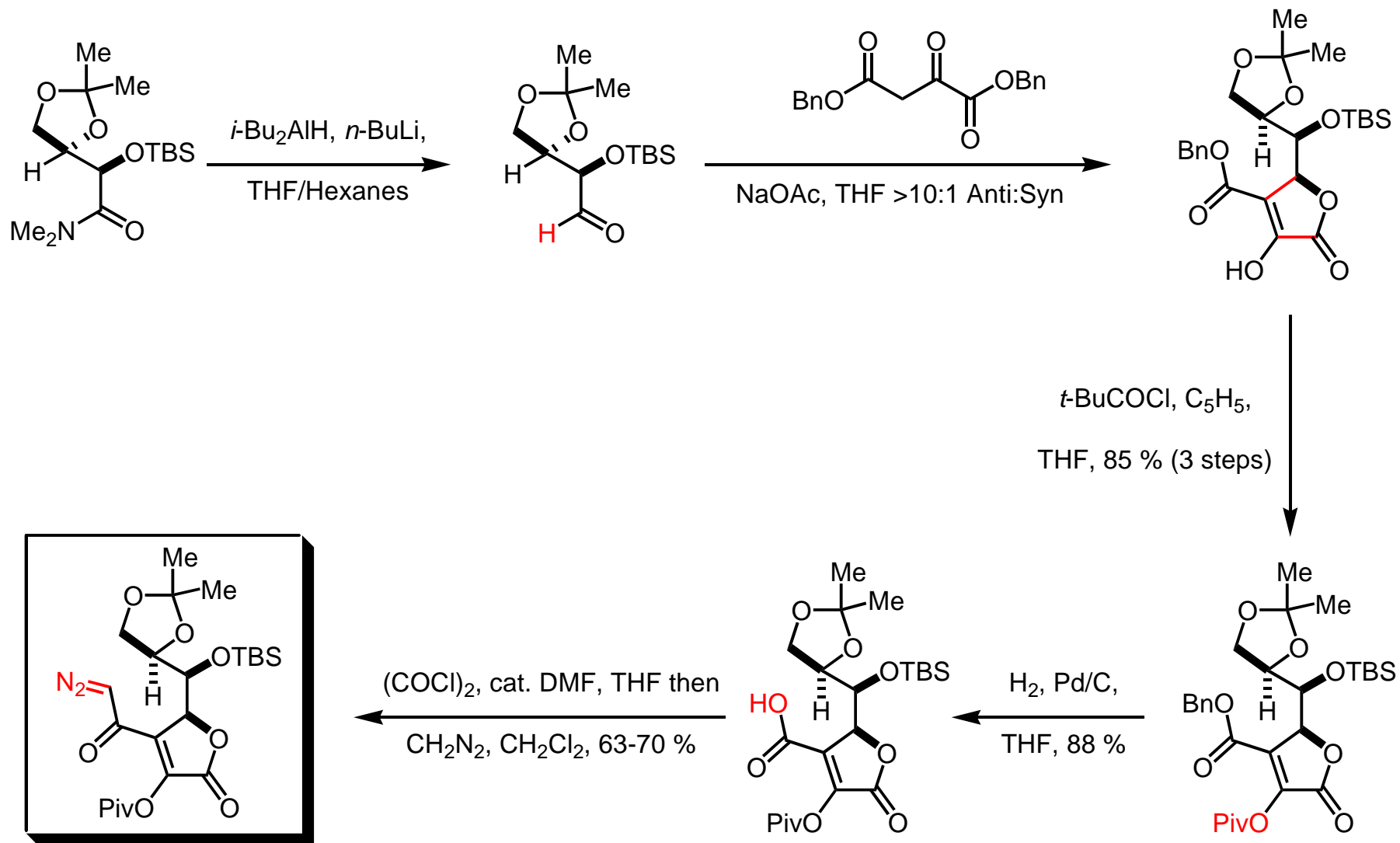
Selective voltage gated  
 $Na^+$  channel blocker

# Synthesis of Rh-Carbene Precursor

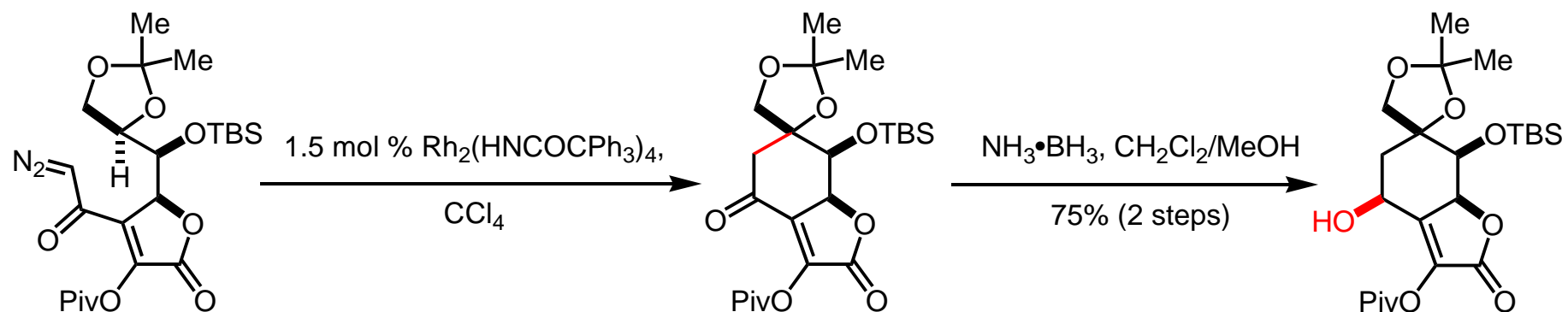


Hinman, A.; Du Bois, J. *J. Am. Chem. Soc.* **2003**, *125*, 11510.  
Carrira, E. M.; Dubois, J. *J. Am. Chem. Soc.* **1994**, *117*, 8106.  
Cohen et al. *J. Am. Chem. Soc.* **1983**, *105*, 3661.

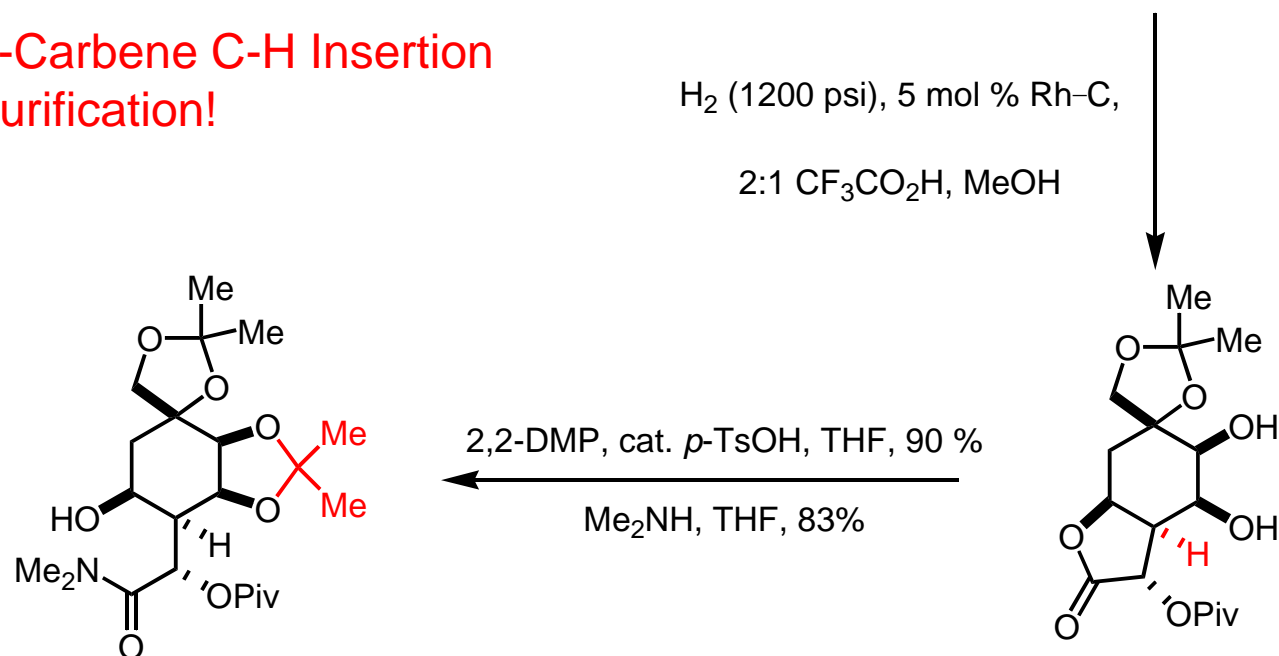
# Synthesis of Rh-Carbene Precursor – Cont.



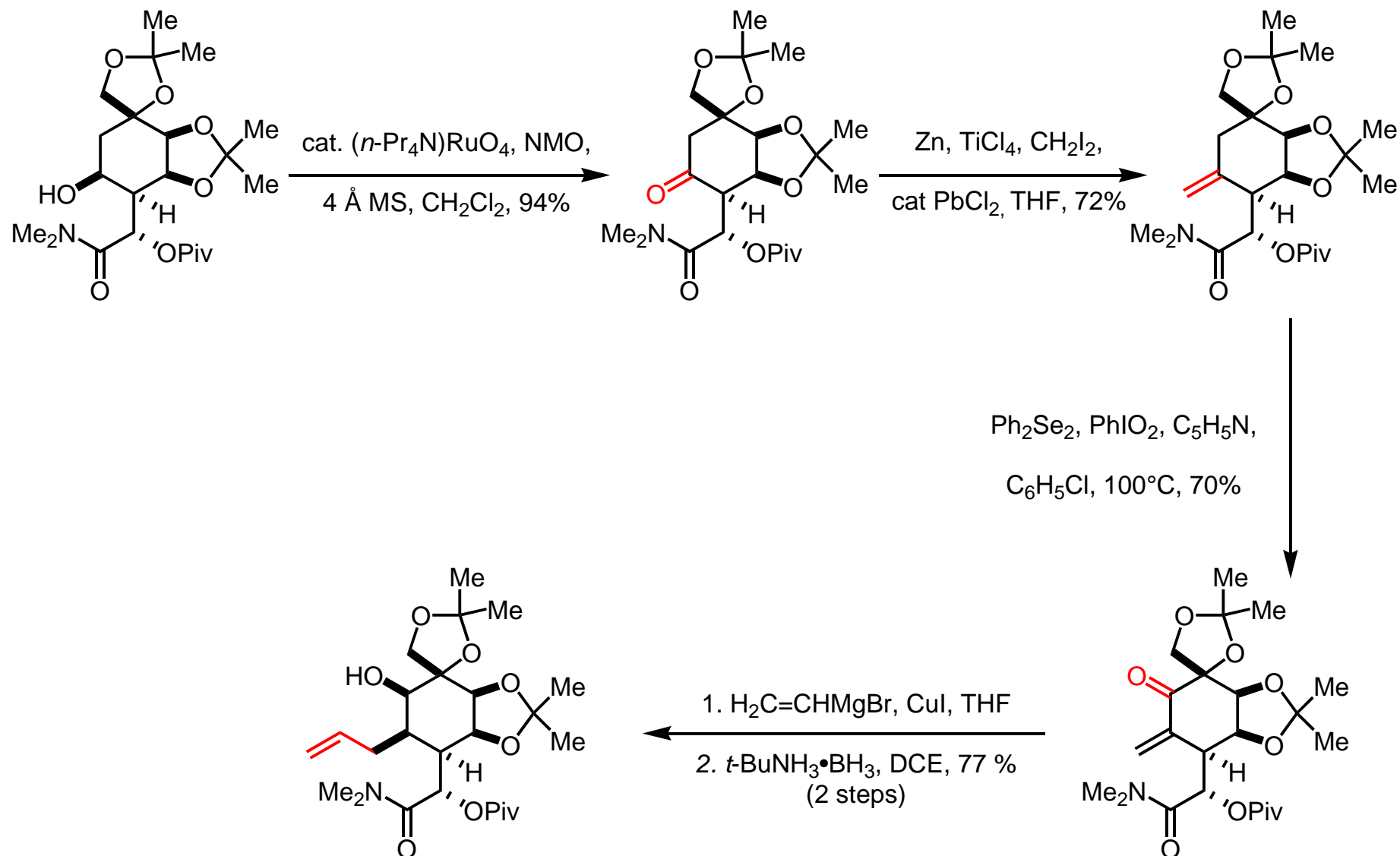
# Stereospecific Rh-Carbene C-H Insertion



Stereospecific Rh-Carbene C-H Insertion  
No purification!



# Formation of Bridge C5 Lactone

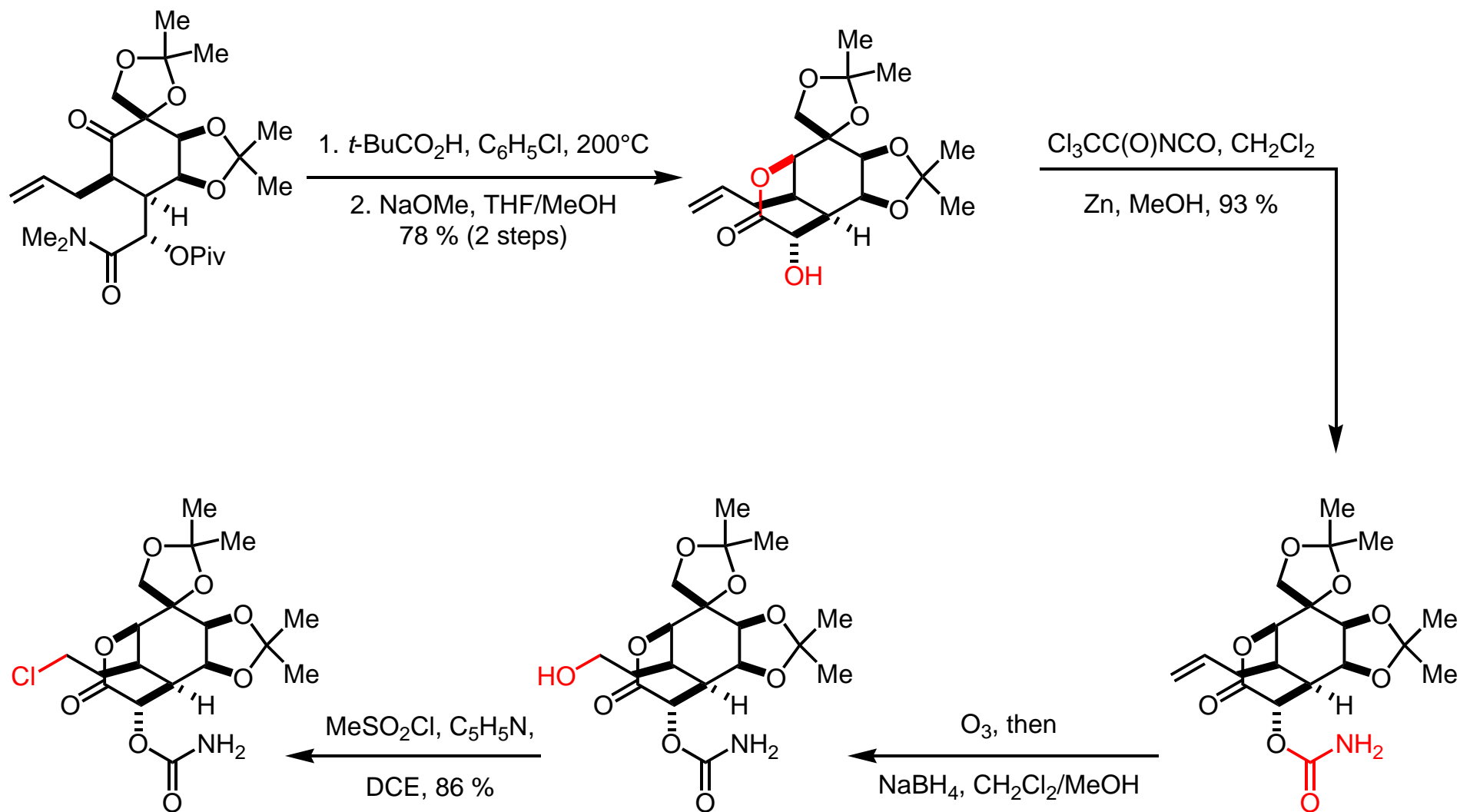


Hinman, A.; Du Bois, J. *J. Am. Chem. Soc.* **2003**, *125*, 11510.

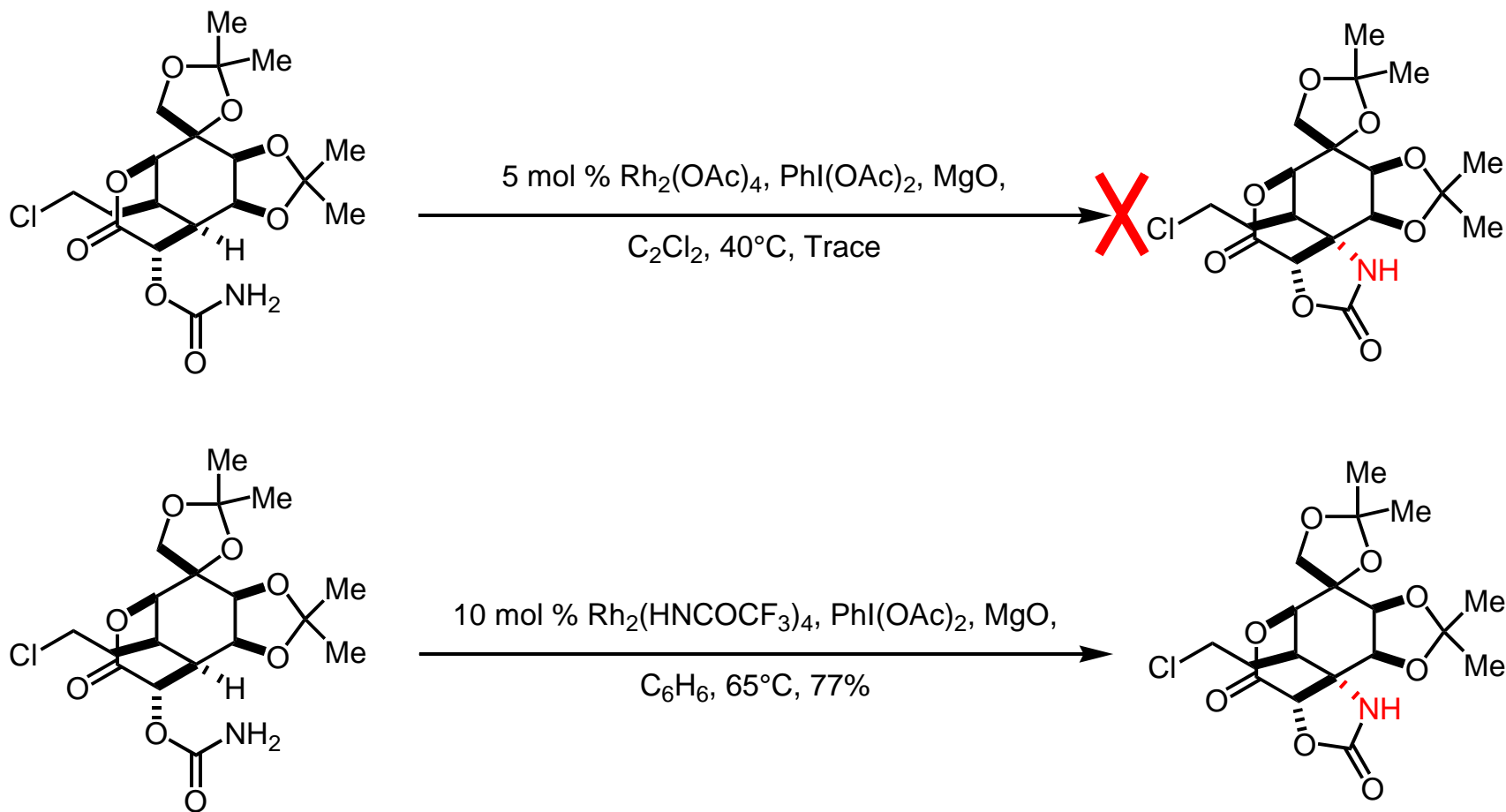
Olfination: Takai, *J. Org. Chem.* **1994**, *59*, 2668

Allylic Oxidation: Barton, Crich *Tetrahedron* **1985**, *41*, 4359

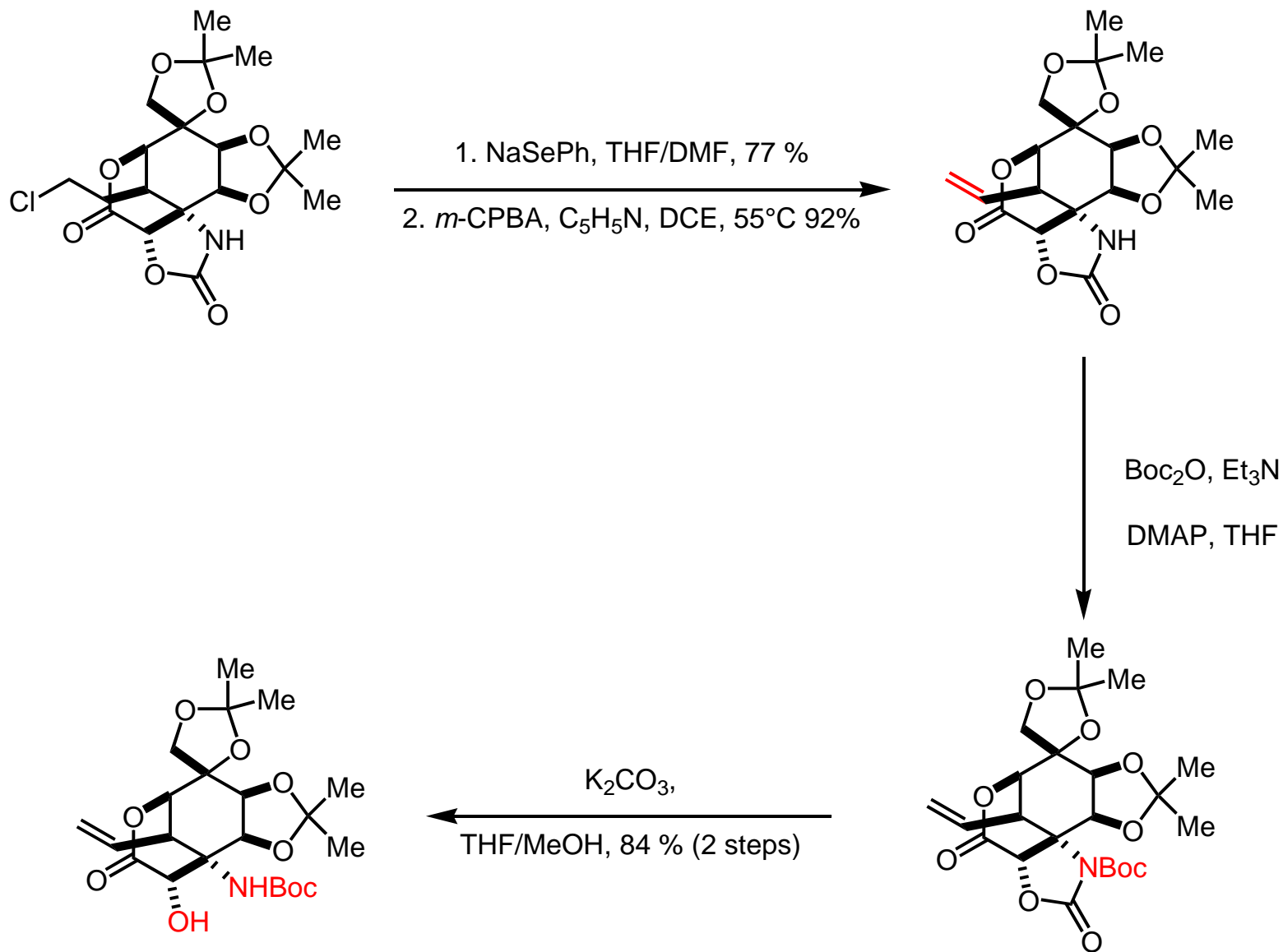
# Formation of Bridge C5 Lactone– Cont.



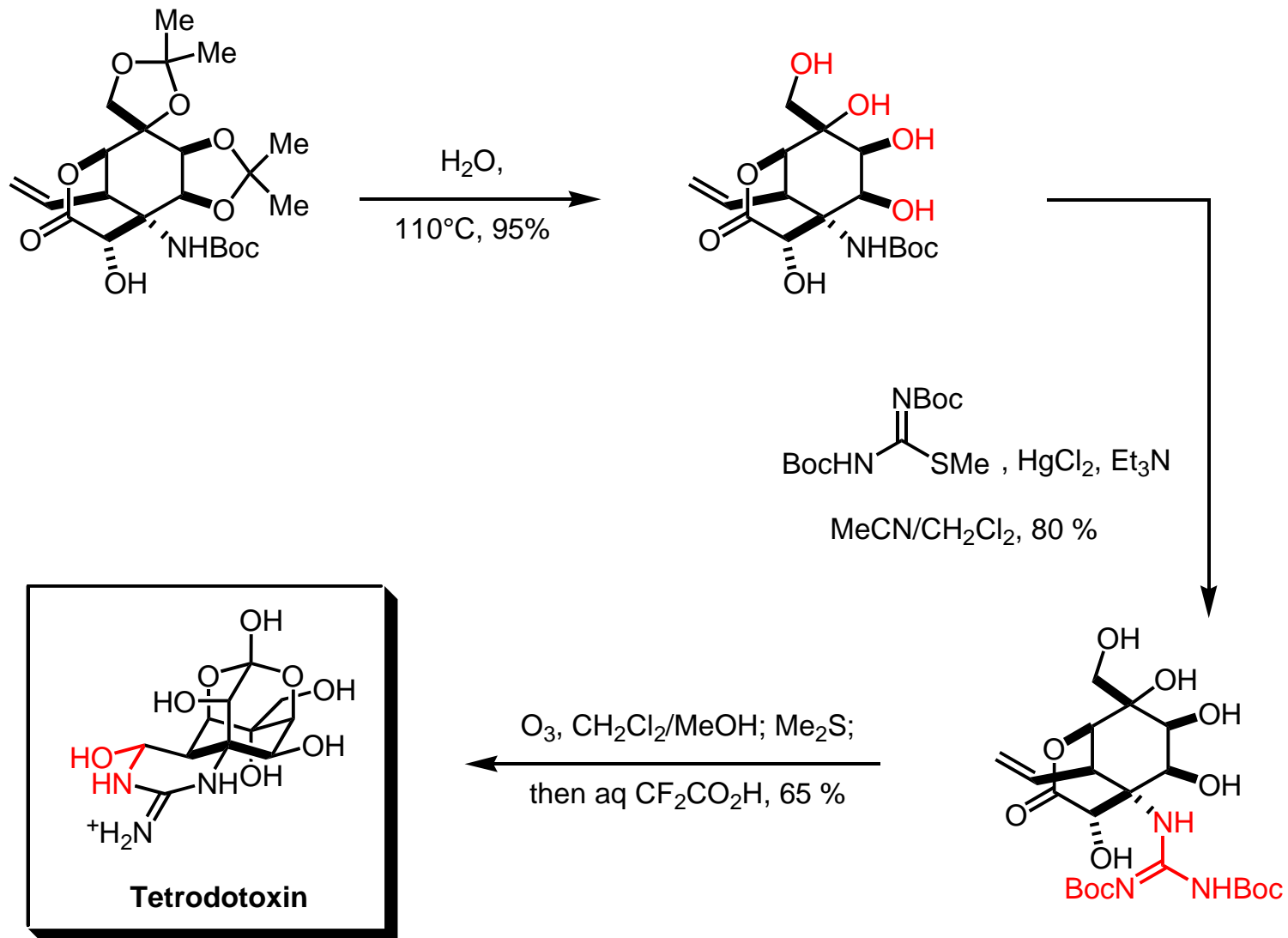
# Late Stage Stereospecific Rh-nitrene C-H Insertion



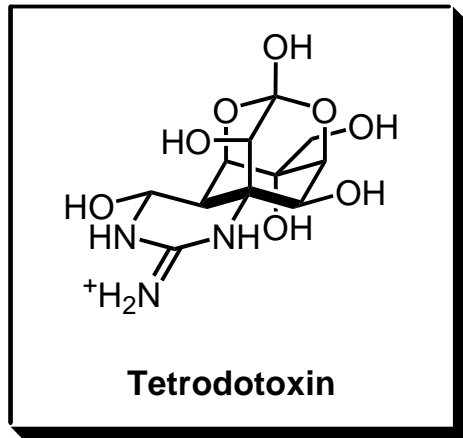
# Endgame



# Synthesis of Tetrodotoxin



# Tetrodotoxin



*"It's bungee jumping for the indoorsy type; really, who cares what it tastes like as long as you live to tell the tale." –Lonely Planet*

Last night he and I ate fugu,  
Today I help carry his coffin.

*"I want to eat fugu, but I  
don't want to die"*

*I cannot see her tonight.  
I have to give her up  
So I will eat fugu.  
--Yosa Buson (Japanese Poet)*

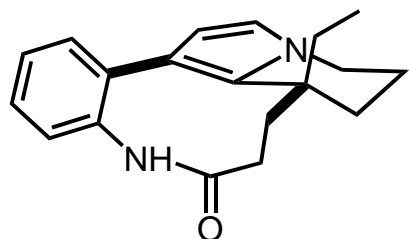
***...enough neurotoxin remains to produce a mellow, tingling glow – a flush and a drug rush. Remember, tetrodotoxin is 160,000 times more potent than cocaine. Eating fugu is an ancient and hallowed Japanese tradition, but it's also a rush. No wonder the stuff is so popular.***

*--[http://www.asiaandaway.com/travel\\_destinations/japan/tokyo/fugu-vooodoo\\_61](http://www.asiaandaway.com/travel_destinations/japan/tokyo/fugu-vooodoo_61)*

# Summary

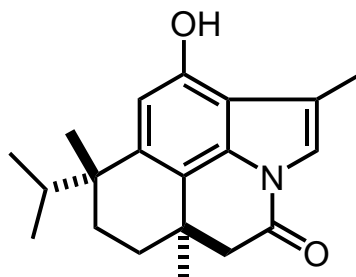
- Selective C-H bond activation (Rhazinlam and Teleocidin B4) but often *stoichiometric* in metal.
- *Catalytic* and *Enantioselective* C-H Activation (Lithospermic Acid) but with limited selectivity.
- *Functional group* tolerance (Tetrodotoxin and Saxitoxin)
- CH Activation process allows for new strategies in synthetic methods

# And they lived happily ever after...



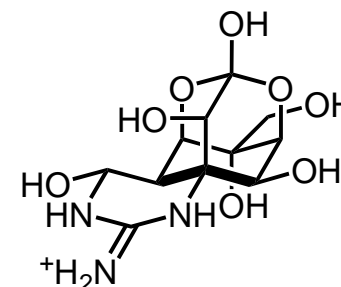
**Rhazinilam**

Sames *JACS* **2000**, *122*, 6321



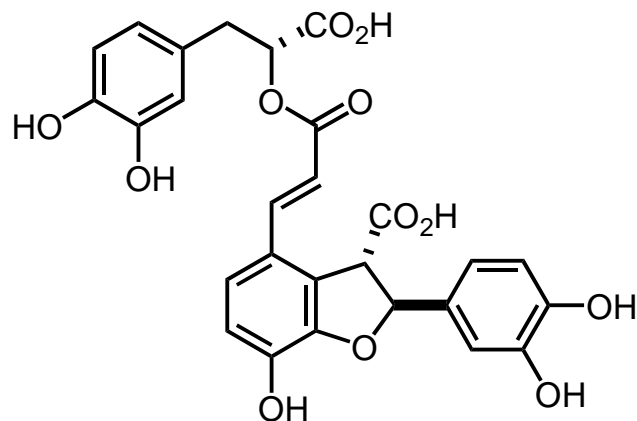
**Telocidin B4 Core**

Sames *JACS* **2002**, *124*, 11856



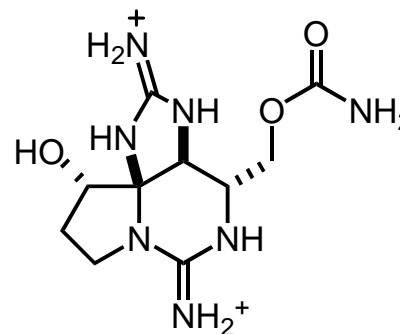
**Tetrodotoxin**

Du Bois *JACS*, **2003**, *125*, 11510



**(+)-Lithospermic Acid**

Bergman, Ellman *JACS*, **2005**, *127*, 13496



**(+)-Saxitoxin**

Du Bois *JACS* **2006**, *128*, 3926