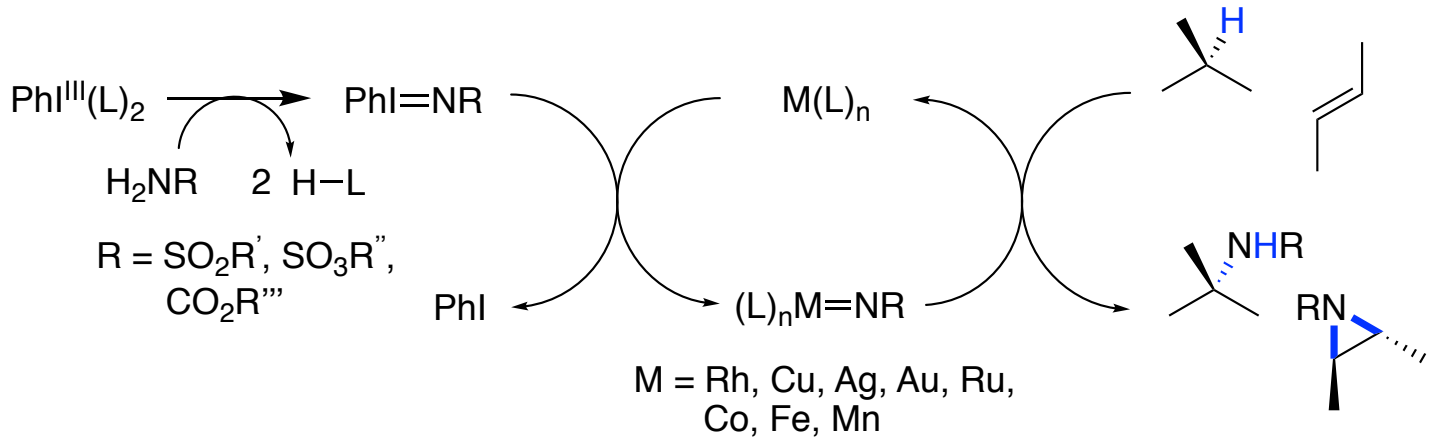
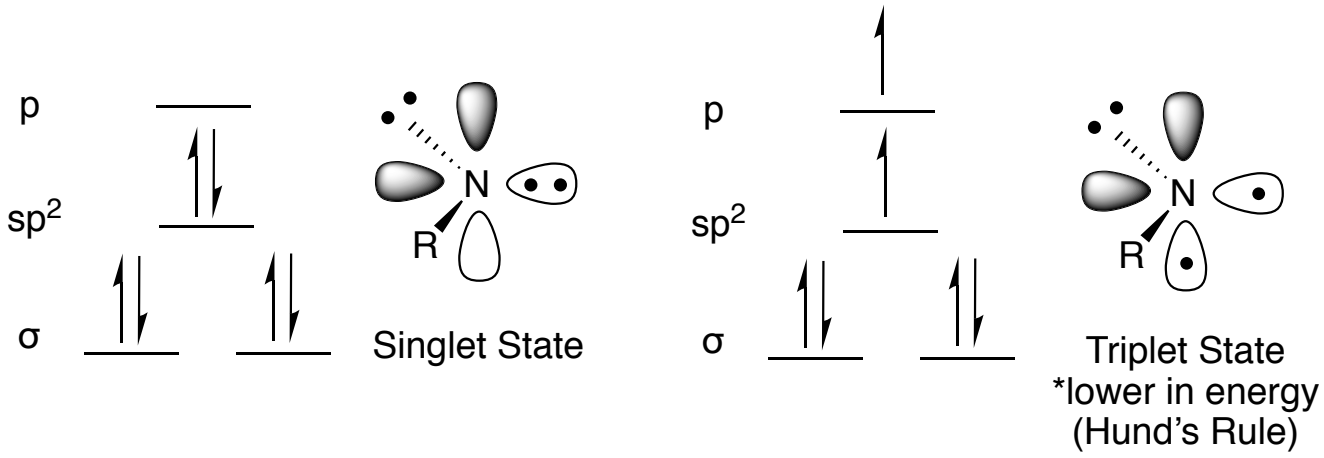
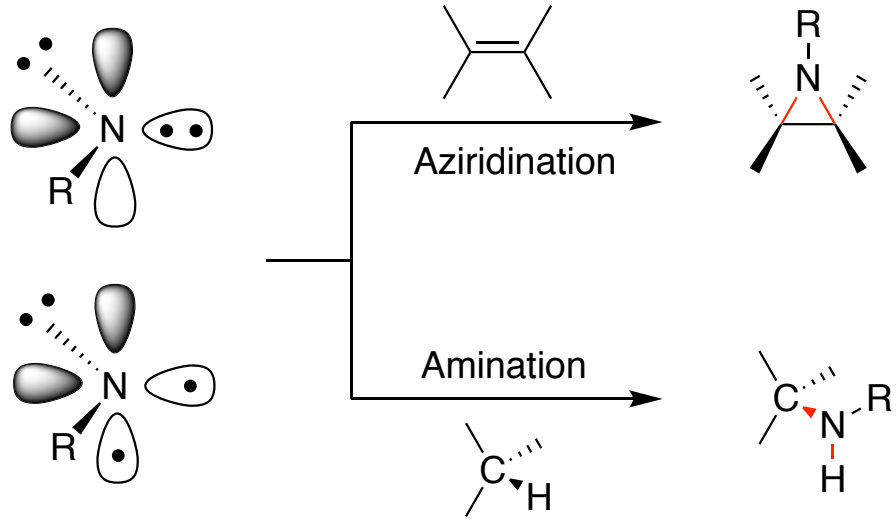
Iodine (III)-Mediated Transition Metal Nitrene Transfer: Stereoselective C-H Amination in Total Synthesis

Matt Nelli, 25 September 2017

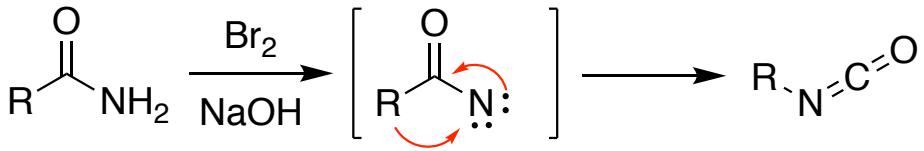


What is a Nitrene?

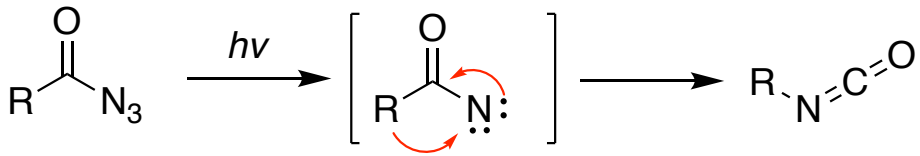


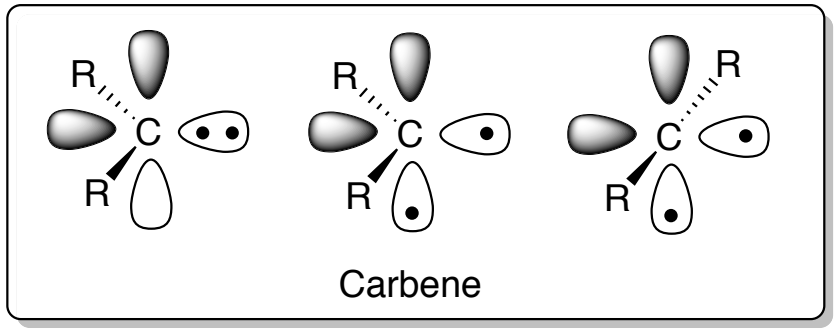


Hoffman Rearrangement



Curtius Rearrangement

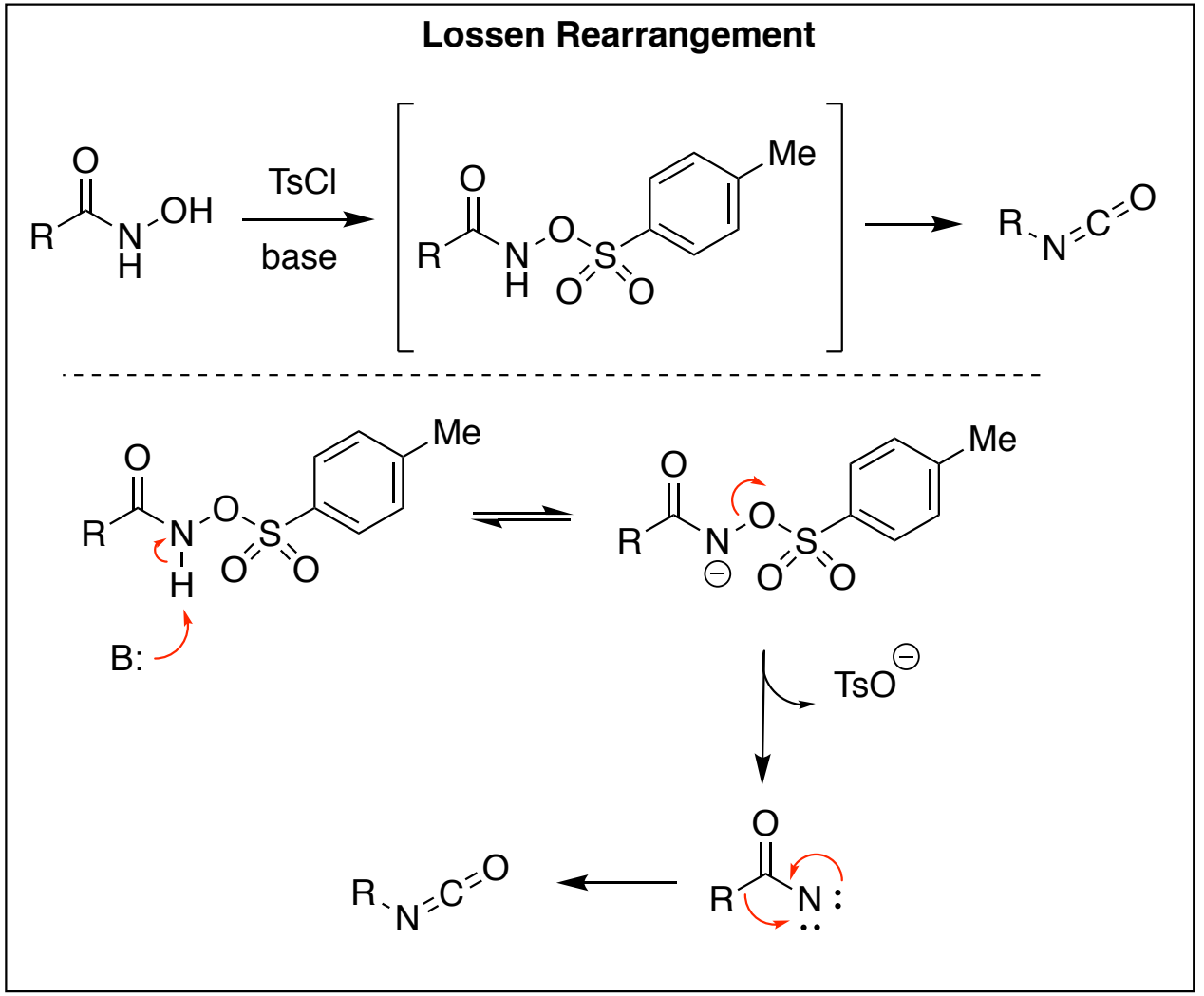




Darses; Rodrigues; Neuville; Mazurais; Dauban, *Chem. Commun.* **2017**, *53*, 493-508

First Mention of a Nitrene in the Literature

Johann Karl Wilhelm Ferdinand Tiemann
1848 – 1899

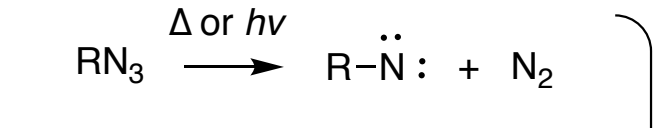


F. Tiemann, Ber. Dtsch. Chem. Ges. 1891, 24, 4162

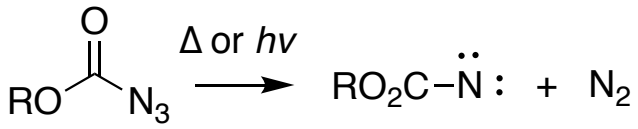
How is a Nitrene Generated?

Classical Synthesis of Nitrenes

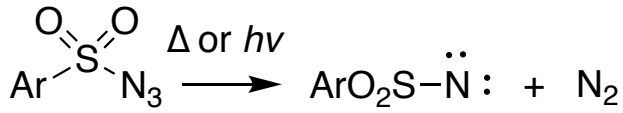
Smith, 1951 (Univ. of Michigan)
Smolinsky, 1960 (Bell Labs)



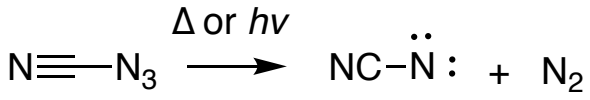
Lwowski, 1962 (Yale)



Breslow, 1964 (Hercules, Inc.)



Anastassiou, 1965 (DuPont)



Synthetic Utility

-Insertion into alkyl and aryl C-H bonds
-Aziridination of alkenes

Drawbacks

-Harsh reaction conditions
-Free nitrene is highly reactive and has poor selectivity
-Only moderate yields

Smith & Brown, *JACS* **1951**, *73*, 2435. Smolinsky, *JACS* **1960**, *82*, 4717. Lwowski & Mattingly, *Tet. Lett.* **1962**, *3*, 277. Breslow *et. al.*, *Tet. Lett.* **1964**, *5*, 2905. Anastassiou *et. al.*, *JACS* **1965**, *87*, 2296. Kwart & Kahn, *JACS* **1967**, *89*, 1951

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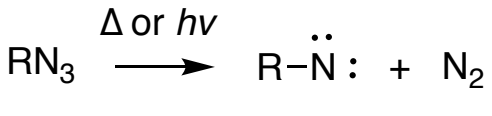

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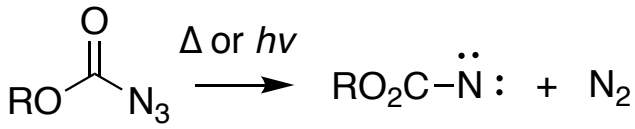

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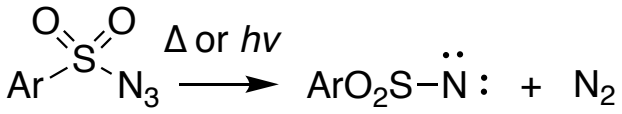

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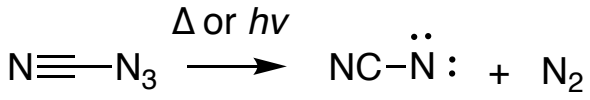
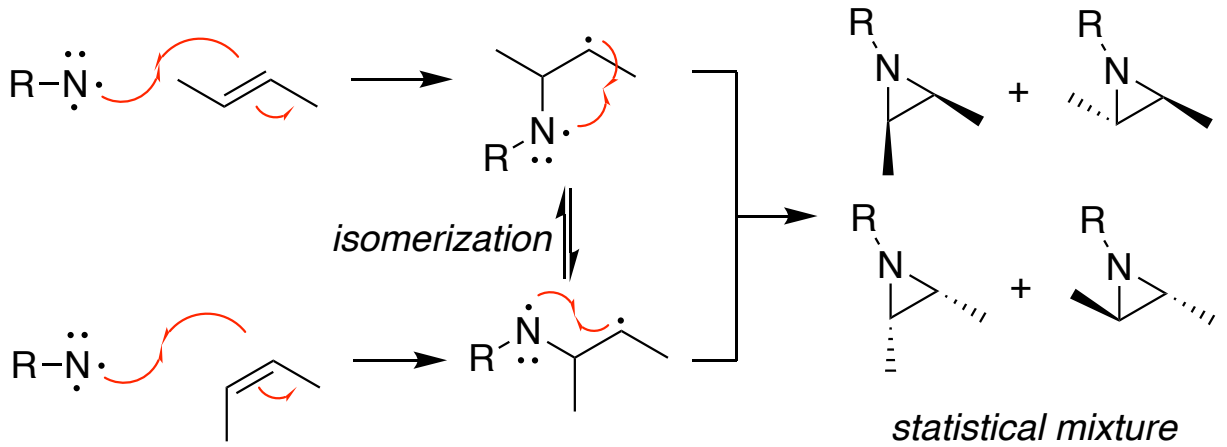
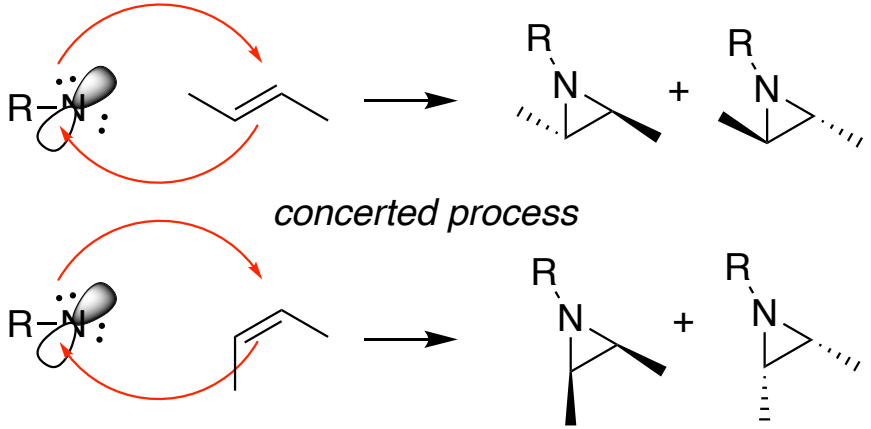


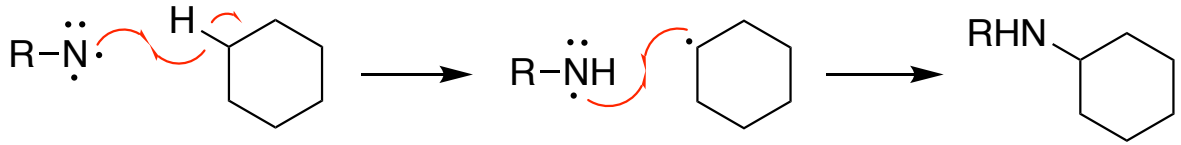
Triplet-Nitrene Aziridination Mechanism



Singlet-Nitrene Aziridination Mechanism



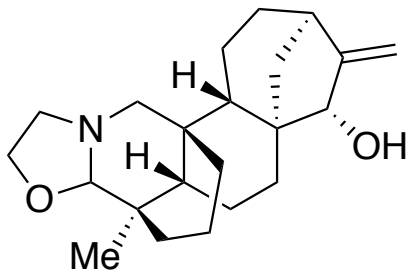
General C-H Insertion Mechanism



Smith & Brown, *JACS* **1951**, *73*, 2435; Smolinsky, *JACS* **1960**, *82*, 4717; Lwowski & Mattingly, *Tet. Lett.* **1962**, *3*, 277; Breslow *et. al.*, *Tet. Lett.* **1964**, *5*, 2905; Anastassiou *et. al.*, *JACS* **1965**, *87*, 2296.;Kwart & Kahn, *JACS* **1967**, *89*, 1951

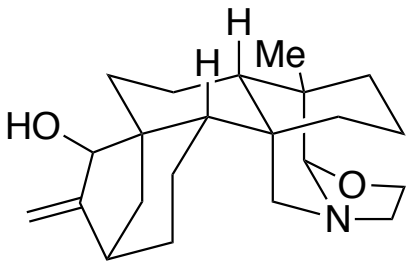
The First Nitrene C-H Insertion in Total Synthesis

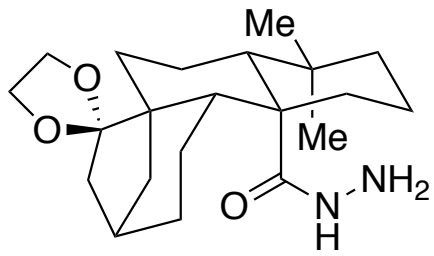
Masamune, 1964
(Mellon Institute)



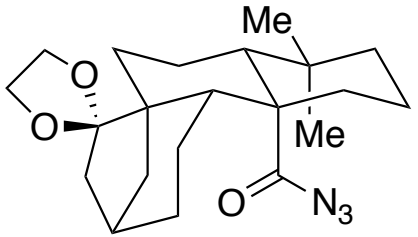
garryine

II

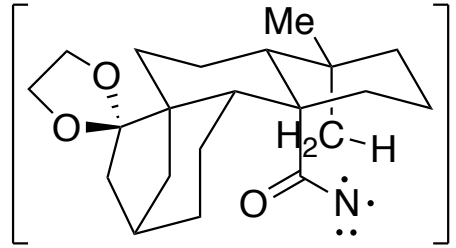


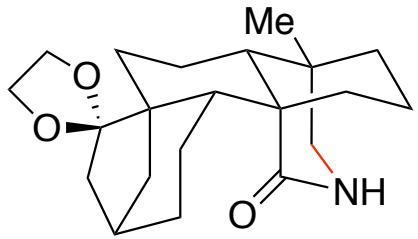


i. HNO_2

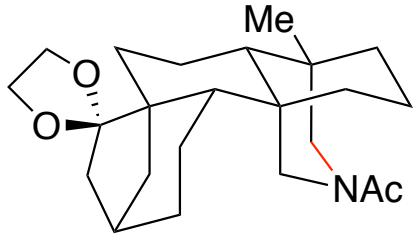


ii. *hv*, -15 °C





iii. LiAlH
iv. AcCl

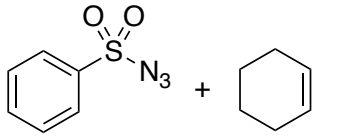


5% yield from
acyl hydrazine

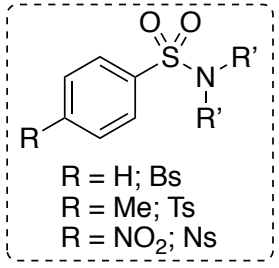
Metal-Catalyzed Nitrene Transfer

Kwart & Khan, 1967
(University of Delaware)

- Copper-catalyzed nitrene generation and transfer using phenyl sulfonyl azide
- Low yields and no selectivity between insertion or aziridination



*No consumption of phenyl sulfonyl azide without catalyst

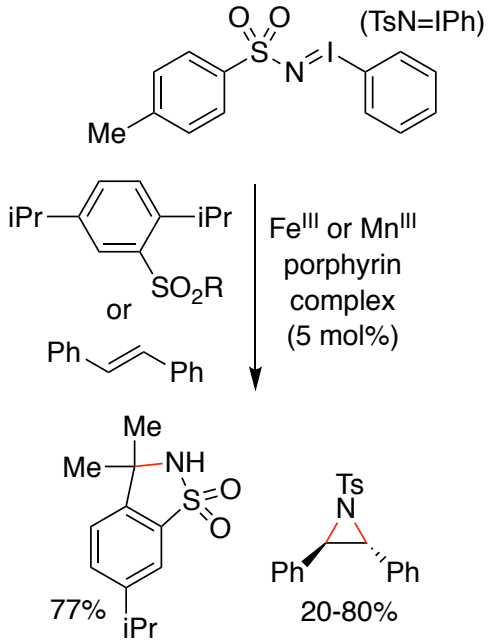


Breslow, 1983
(Columbia University)

- Nitrene insertion using sulfonyliminoiodinanes and iron or manganese porphyrin systems
- Only explored simple substrates, such as styrene and stilbene

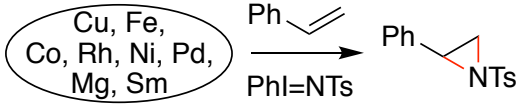
Mansuy, 1984
(l'École Normale Supérieure)

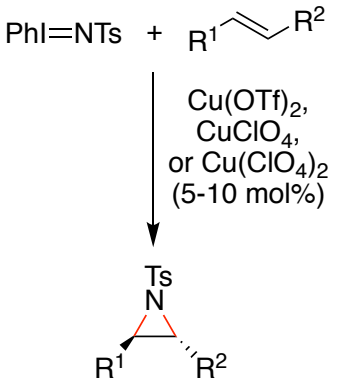
- Nitrene aziridination using sulfonyl-iminoiodinanes and iron or manganese porphyrin systems
- Only explored simple substrates, such as styrene and stilbene



Evans, 1994
(Harvard University)

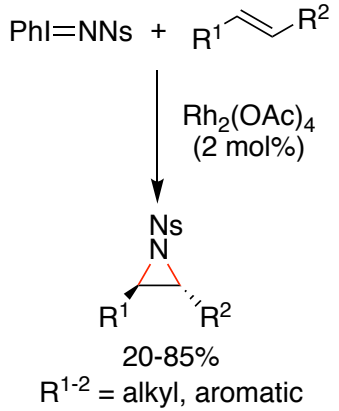
- Tested a large number of transition metals in nitrene transfer from sulfonyliminoiodinanes
- Explored efficiency of simple copper salts in catalyzing aziridination of olefins with a variety of substitution patterns





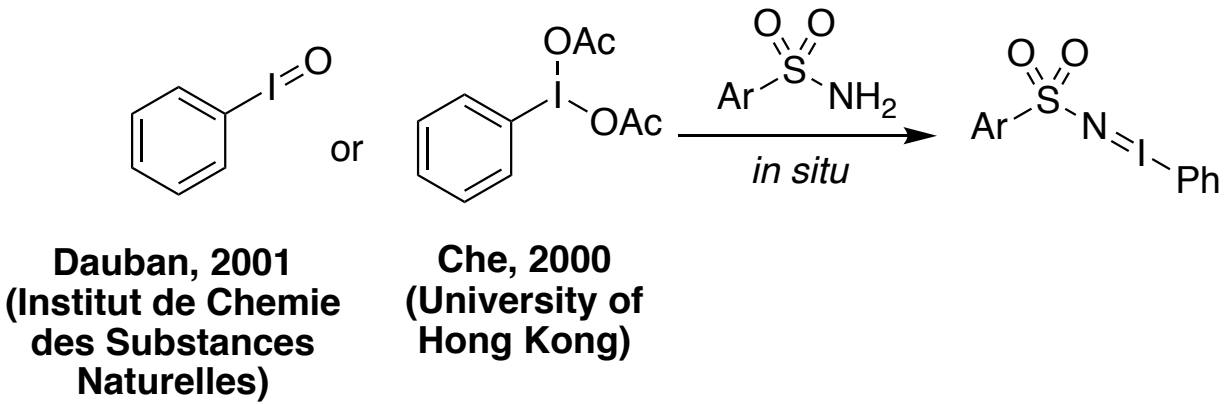
Müller, 1998
(University of Geneva)

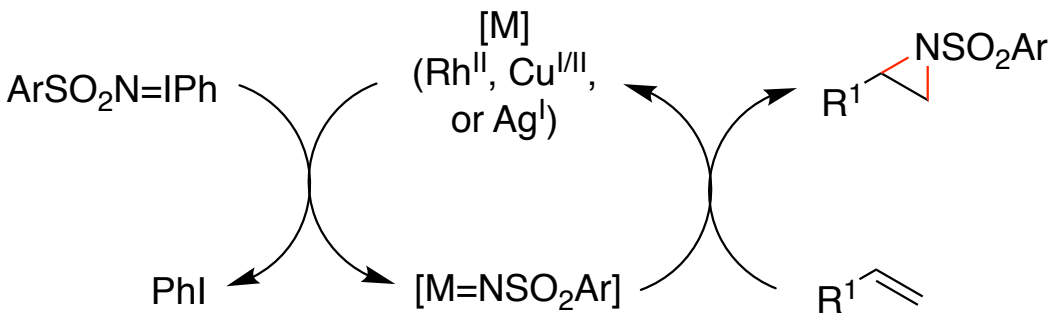
- Explored rhodium-catalyzed nitrene transfer from sulfonyliminoiodinanes to a greater extent than his contemporaries
- Only explored simple olefin substrates, such as stilbene albeit with some aryl substitution

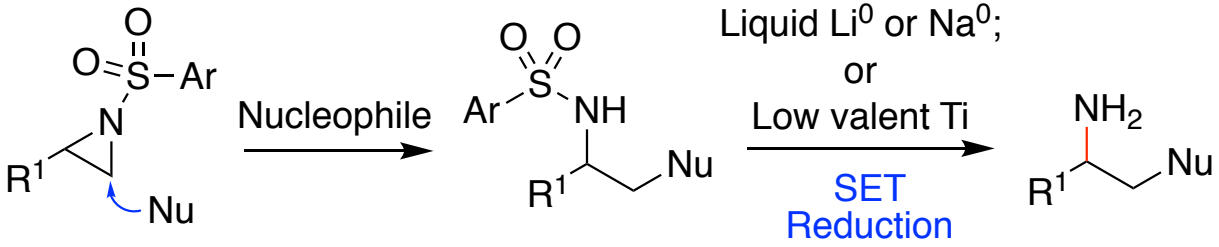


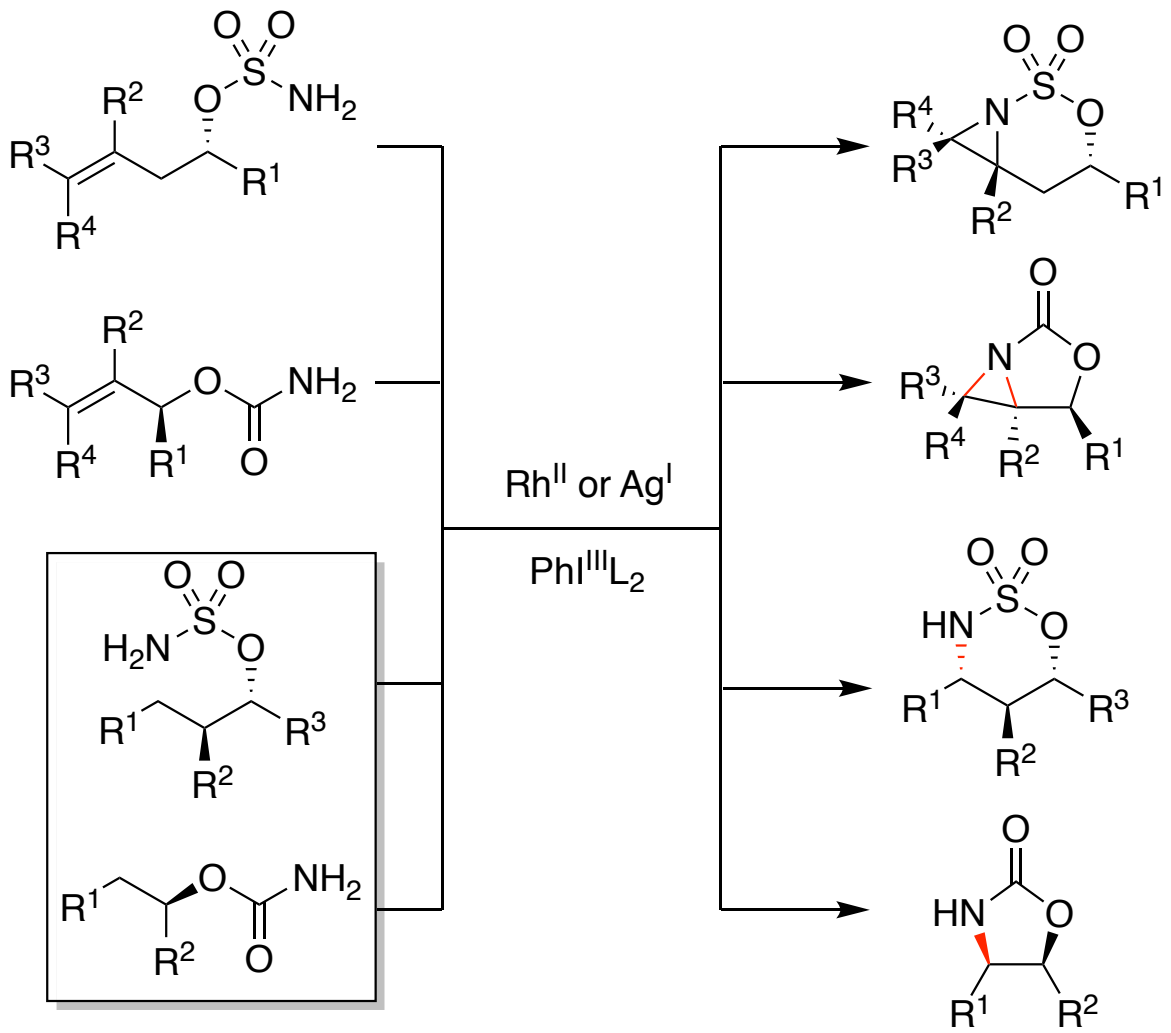
Kwart & Khan, *JACS* **1967**, *89*, 1951.;Breslow & Gellman, *JACS* **1983**, *105*, 6728.; Mansuy; Mahy; Dureault; Bedi' Battioni, *Chem. Commun.* **1984**, 1161.; Evans; Faul; Bilodeau, *JACS* **1994**, *116*, 2742.; Müller; Baud; Jacquier, *Tetrahedron* **1996**, *52*, 1543.

Synthetically Useful Nitrene Precursors





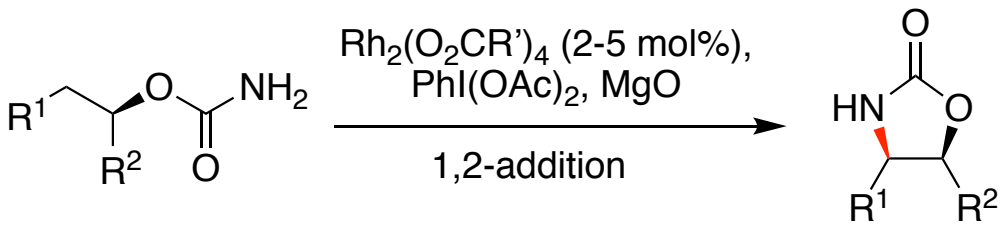




Yu; Huang; Zhou; Che, *Org. Lett.* **2000**, *2*, 2233.; Espino & Du Bois, *ACIE* **2001**, *40*, 598.; Dauban; Sanière; Tarrade; Dodd, *Synlett.* **2003**, *103*, 2905.

Stereospecific C-H Amination

Du Bois, 2001



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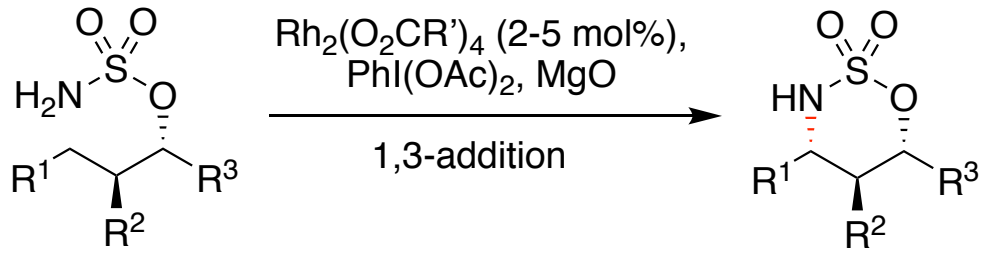

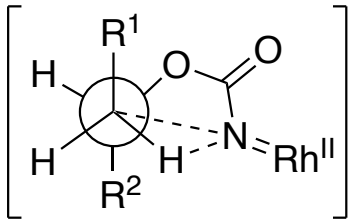

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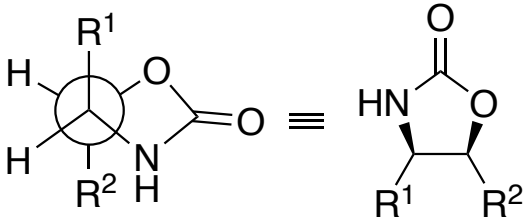
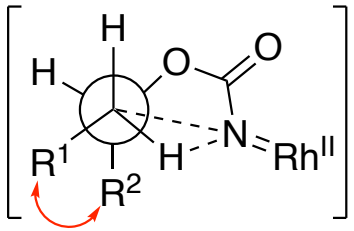
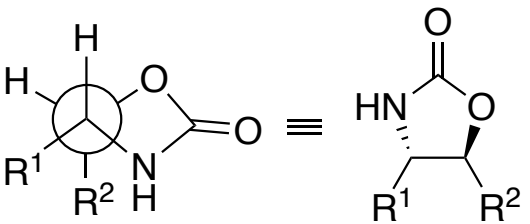


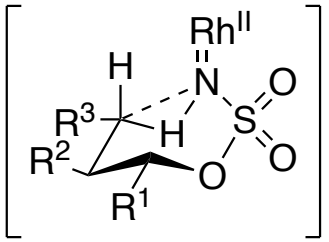
1,2-cis product



disfavored



1,2-trans product



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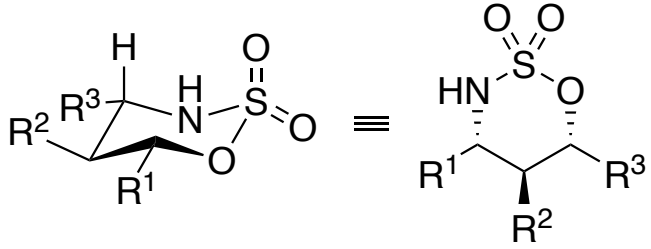
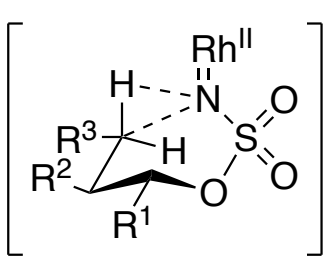


1,3-syn product



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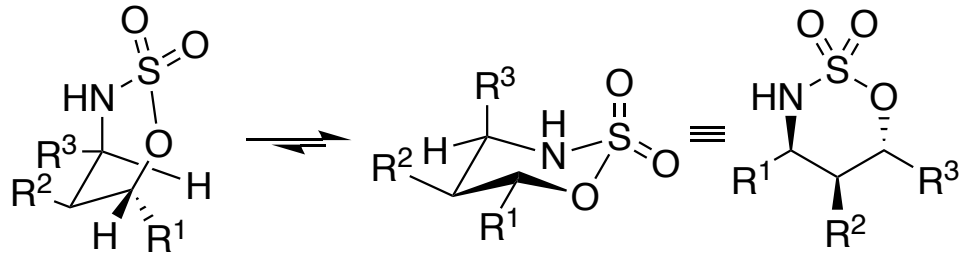
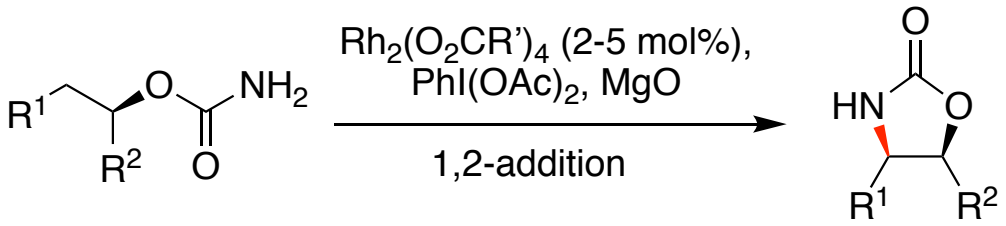


1,3-anti product

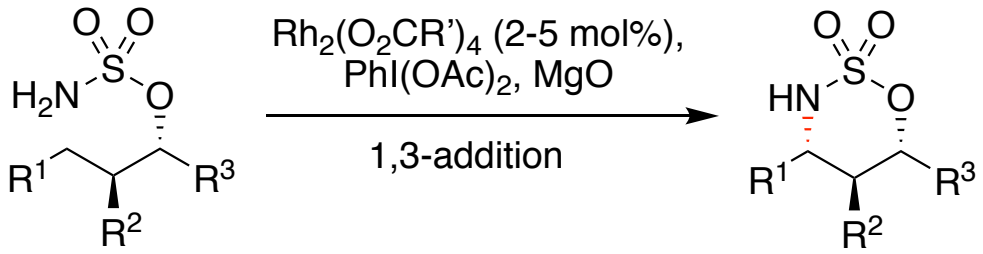
Wehn; Lee; Du Bois, *Org. Lett.* **2003**, *5(25)*, 4823-4826.; Espino & Du Bois, *ACIE* **2001**, *113*, 618-620.; Espino; Wehn; Chow; Du Bois, *JACS* **2001**, *123(28)*, 6935-6936.

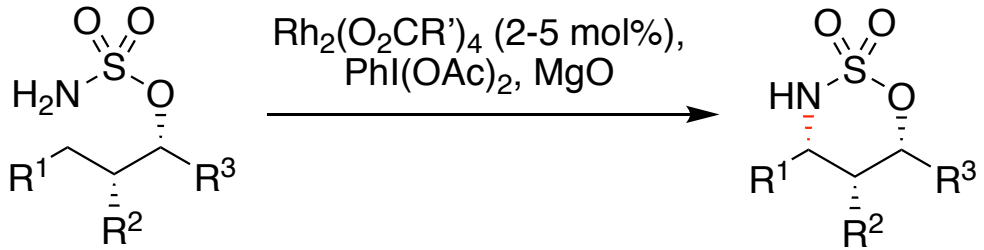
Stereospecific C-H Amination

Du Bois, 2001

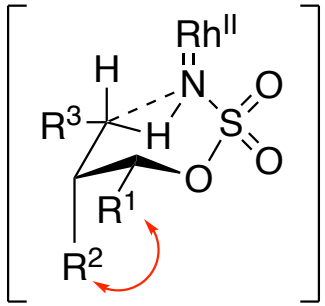


Du Bois, 2001





trace amounts



destabilizing gauche interaction

Wehn; Lee; Du Bois, *Org. Lett.* **2003**, *5(25)*, 4823-4826.; Espino & Du Bois, *ACIE* **2001**, *113*, 618-620.; Espino; Wehn; Chow; Du Bois, *JACS* **2001**, *123(28)*, 6935-6936.

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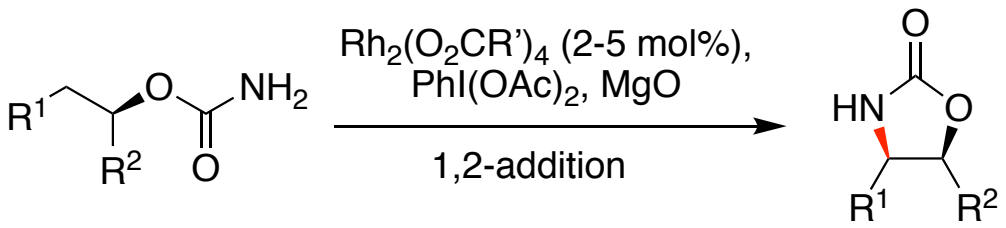
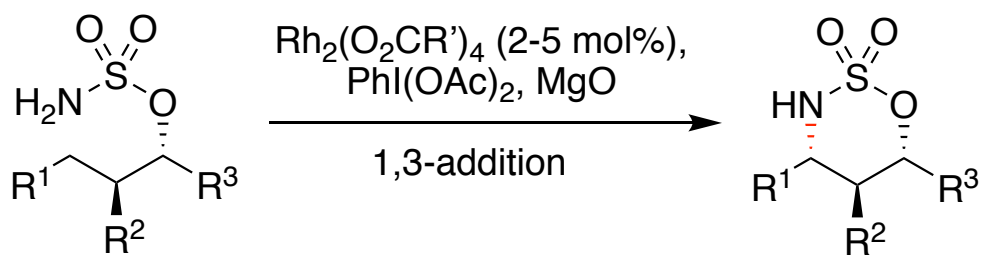
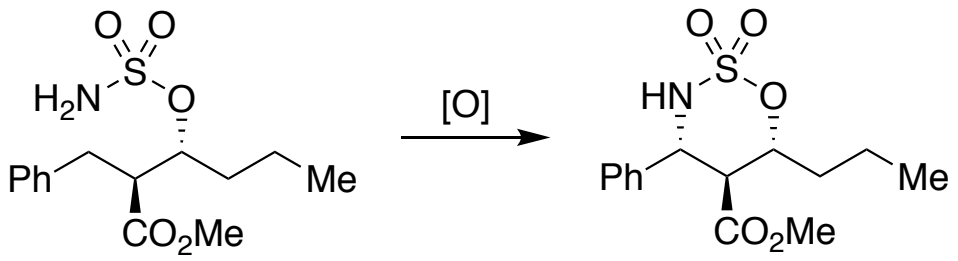
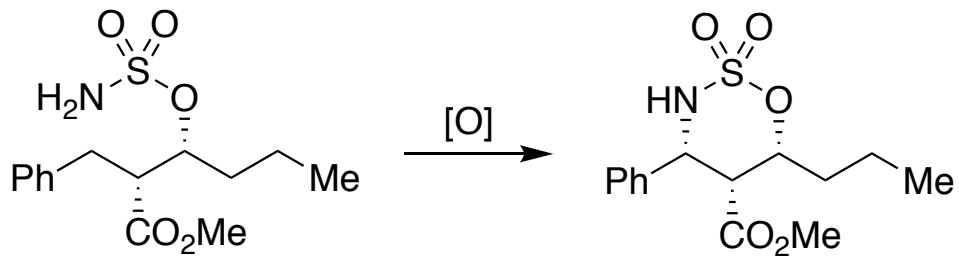


Du Bois, 2001





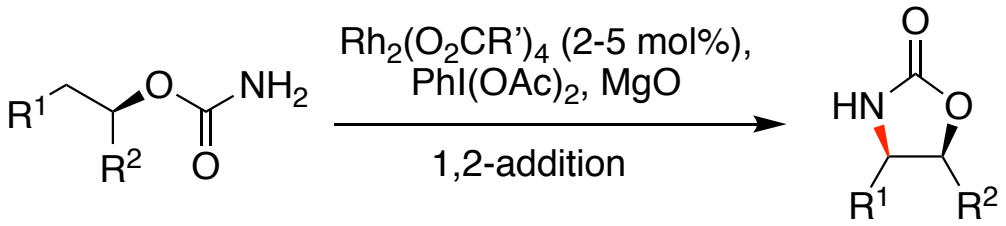
*Nitrene C-H insertions proceed well at 3° carbons, benzylic, and allylic positions



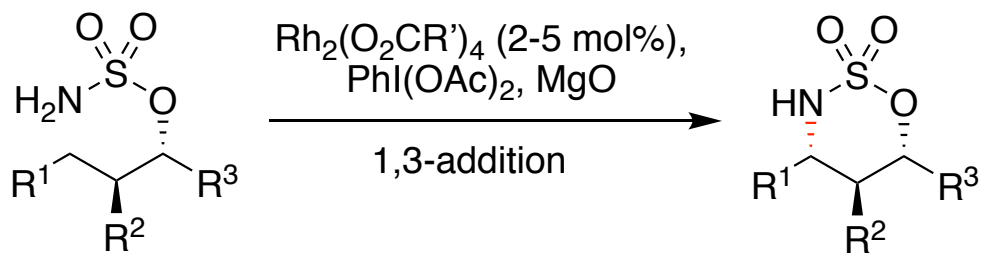
Wehn; Lee; Du Bois, *Org. Lett.* **2003**, *5(25)*, 4823-4826.; Espino & Du Bois, *ACIE* **2001**, *113*, 618-620.; Espino; Wehn; Chow; Du Bois, *JACS* **2001**, *123(28)*, 6935-6936.

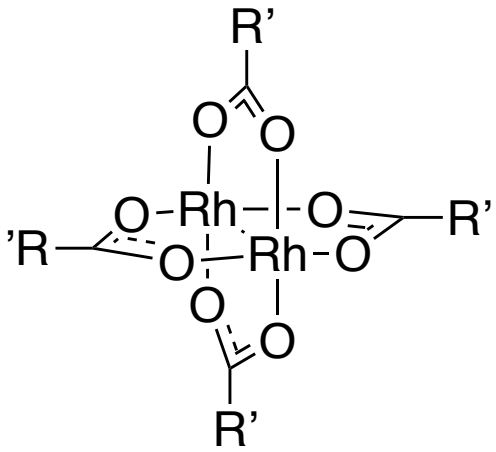
Stereospecific C-H Amination

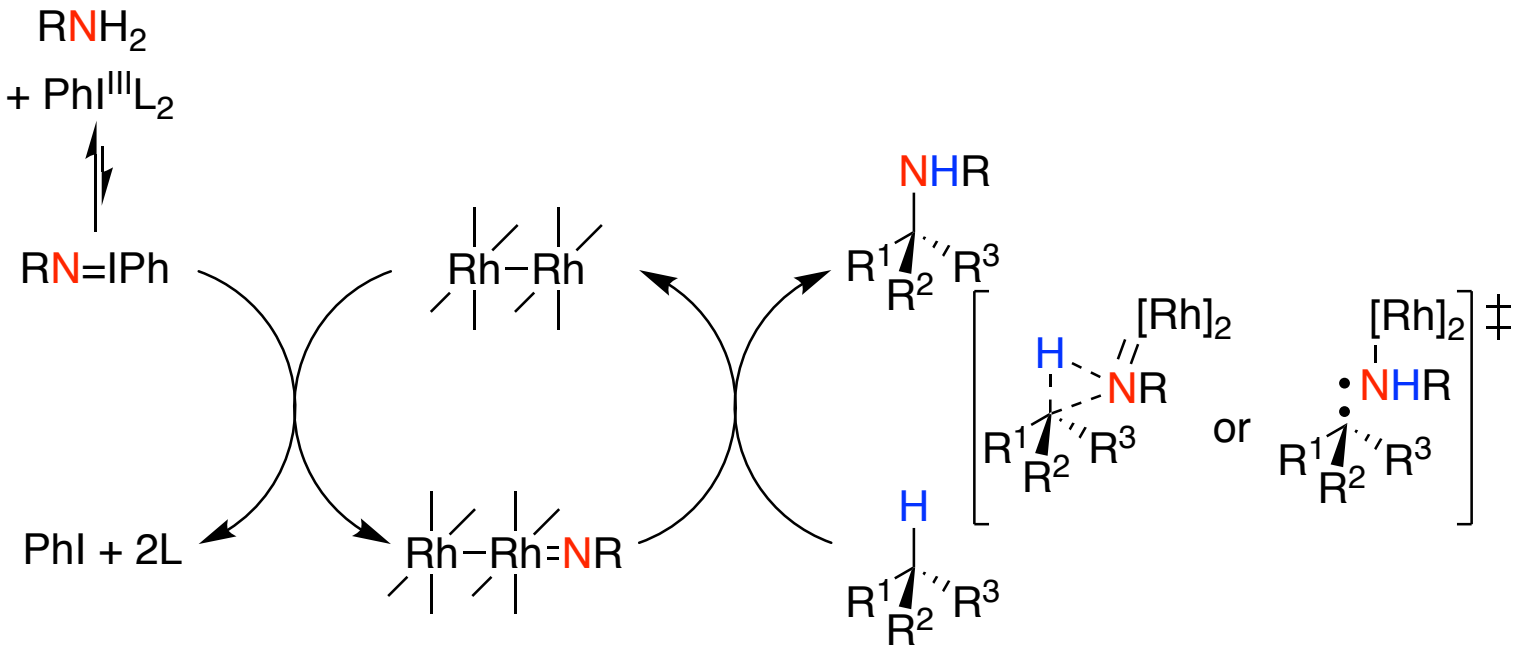
Du Bois, 2001



Du Bois, 2001



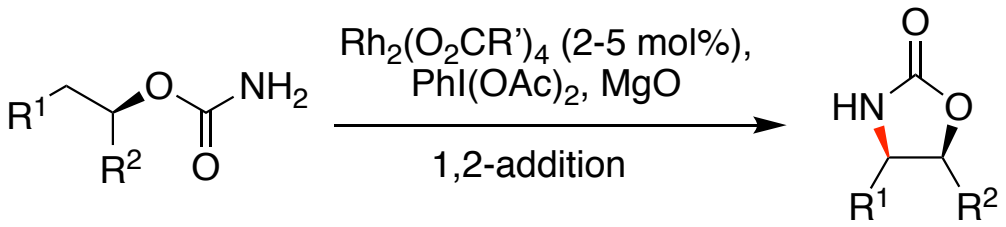




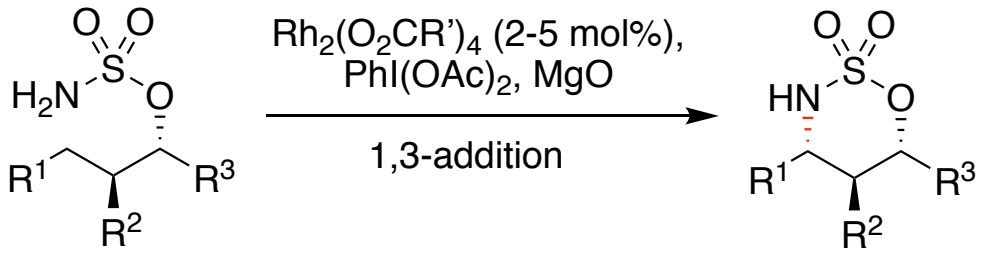
Wehn; Lee; Du Bois, *Org. Lett.* **2003**, *5(25)*, 4823-4826.; Espino & Du Bois, *ACIE* **2001**, *113*, 618-620.; Espino; Wehn; Chow; Du Bois, *JACS* **2001**, *123(28)*, 6935-6936.

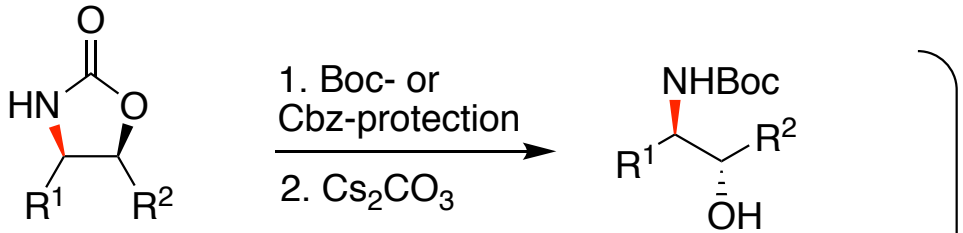
Stereospecific C-H Amination

Du Bois, 2001

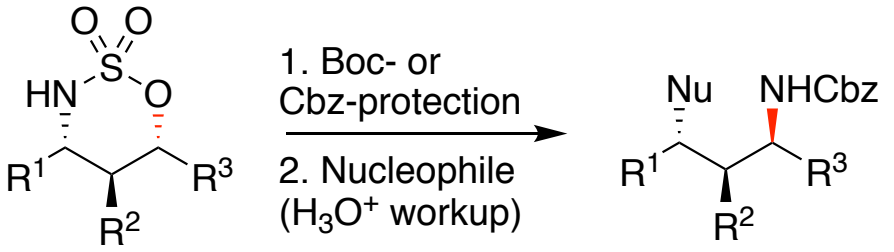


Du Bois, 2001





1,2-amino alcohols

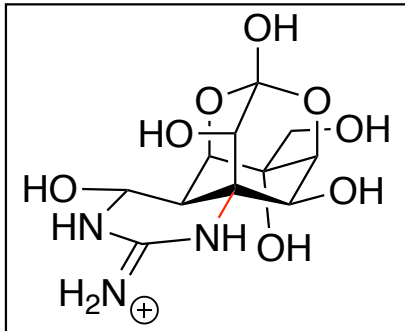


Nu = NR_2, SR, N_3, OR, etc.

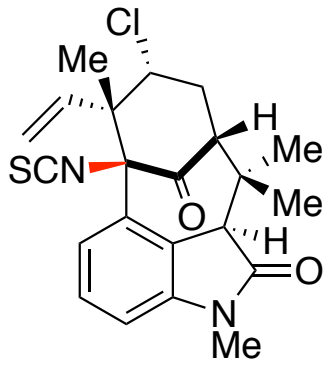
Valuable Synthetic Intermediates

Wehn; Lee; Du Bois, *Org. Lett.* **2003**, *5(25)*, 4823-4826.; Espino & Du Bois, *ACIE* **2001**, *113*, 618-620.; Espino; Wehn; Chow; Du Bois, *JACS* **2001**, *123(28)*, 6935-6936.

Natural Products Synthesized Using Nitrenes



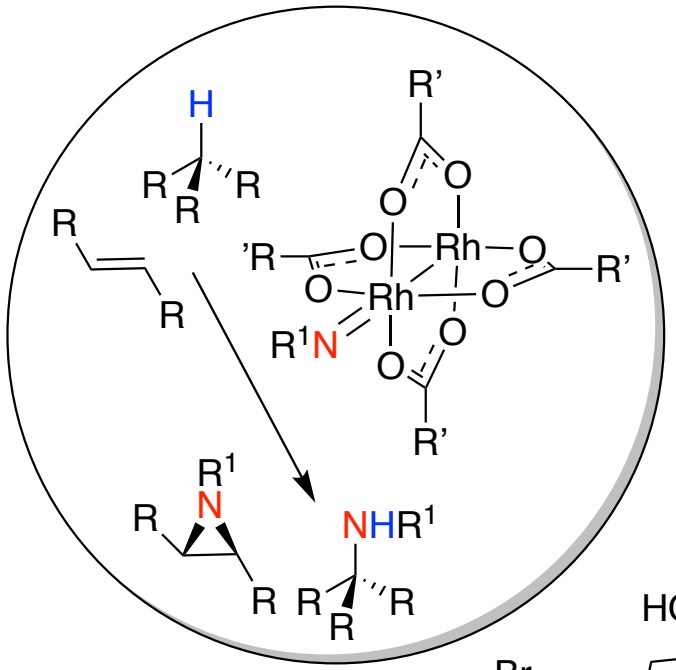
(-)-tetrodotoxin
Du Bois, 2003
(Stanford University)

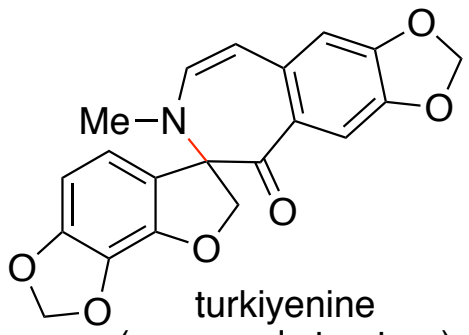


N-methylwelwitindolinone B isothiocyanate
Garg, 2014
(UCLA)

Carbamate-Derived

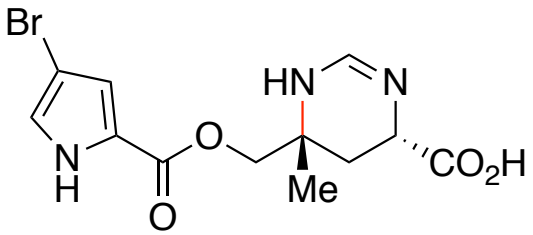
C-H Insertion



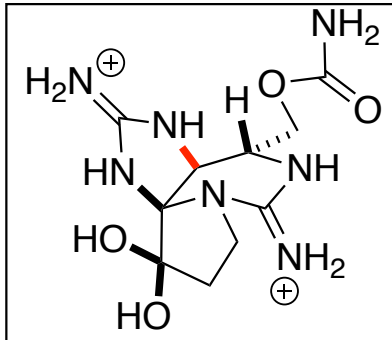


turkiyenine
(proposed structure)
Iwabuchi, 2016
(Tohoku University)

Aziridination

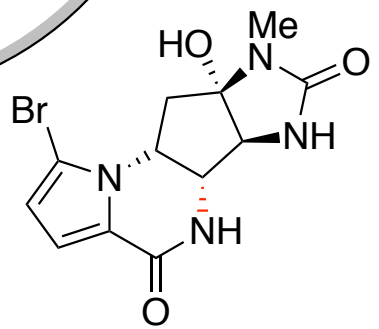


manzacidin A
Du Bois, 2002
(Stanford University)

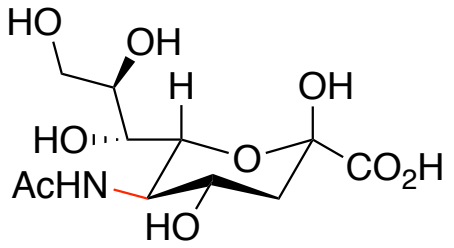


(+)-saxitoxin
Du Bois, 2006
(Stanford University)

Sulfamate Ester-Derived



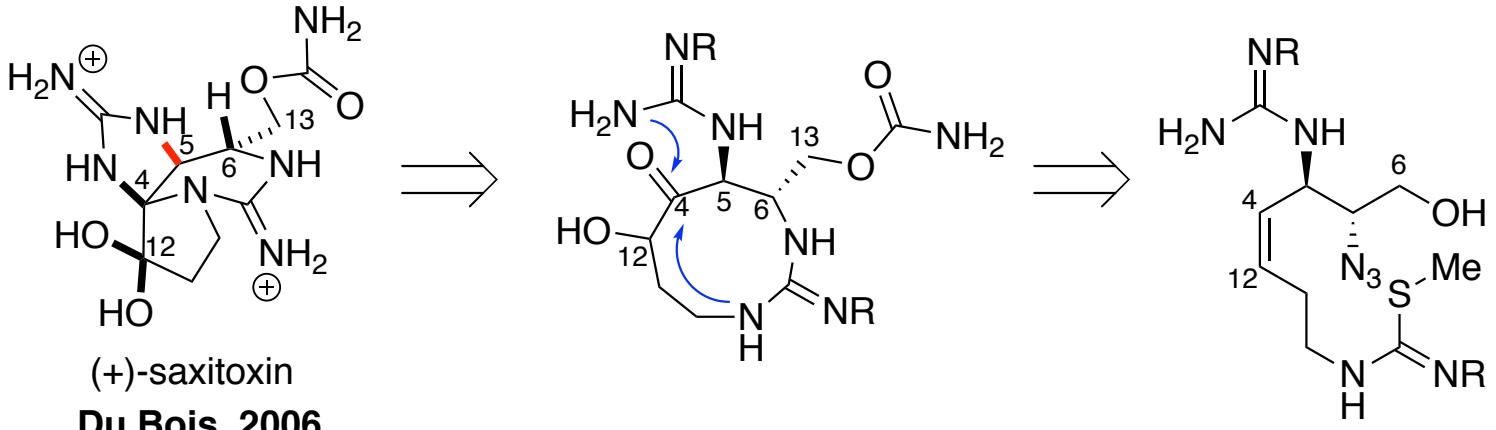
(-)-agelastatin A
Du Bois, 2009
(Stanford University)



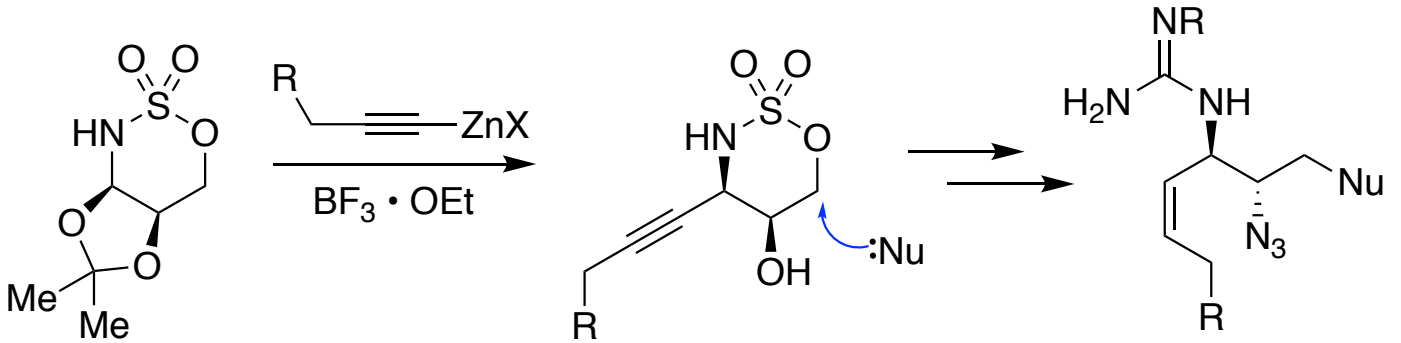
neu5Ac
Liu, 2011
(Nanyang Technological University)

Asymmetric Synthesis of (+)-Saxitoxin

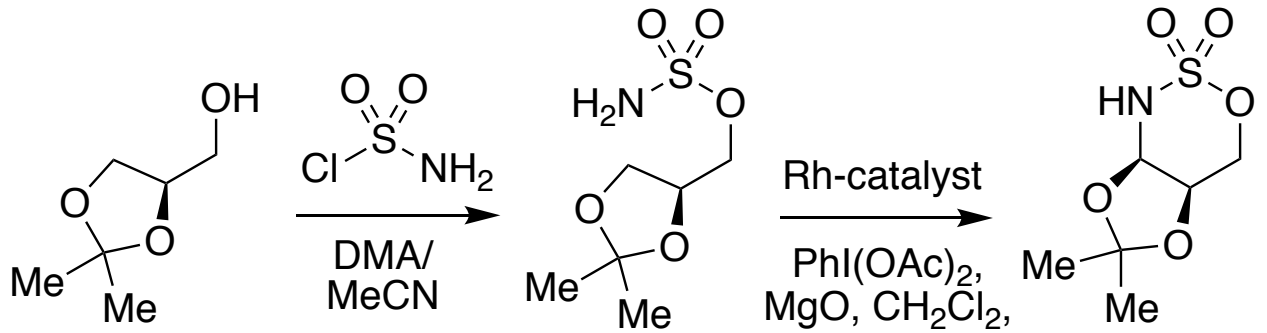
- Neurotoxin produced by cyanobacteria and dinoflagellates
- Selective Na_v channel inhibitor; binds directly to the pore of the channel
- Oral LD_{50} of 5.7 µg/kg and intravenous LD_{50} of 0.6µg/kg in humans; death occurs in 2-12 hours, usually from respiratory failure
- Isolated 1957 & structurally characterized in 1975



- Two racemic syntheses before Du Bois: Kishi, 1977 (Harvard) & Jacobi, 1984 (Dartmouth)
- Two asymmetric syntheses after Du Bois: Nagasawa, 2009 (Tokyo Univ.) & Looper, 2011 (Utah Univ.)



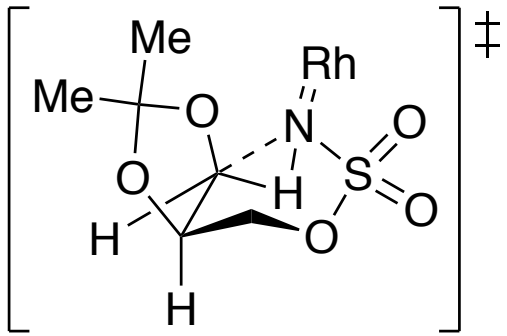
Preparing the Starting Material

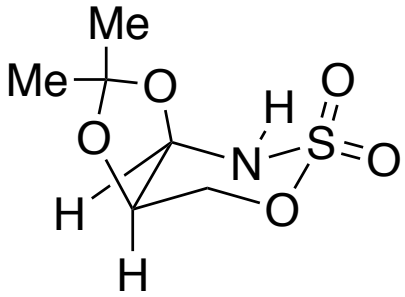


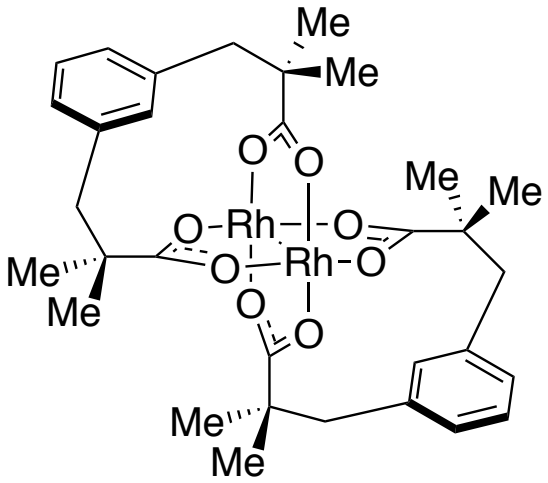
(R)-glycerol acetonide

$Rh_2(TPA)_4$	3 mol%	92%
$Rh_2(esp)_4$	0.3 mol%	76%

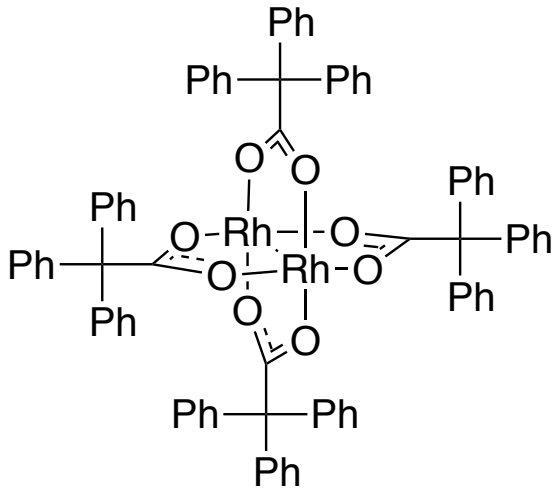
single diastereomer







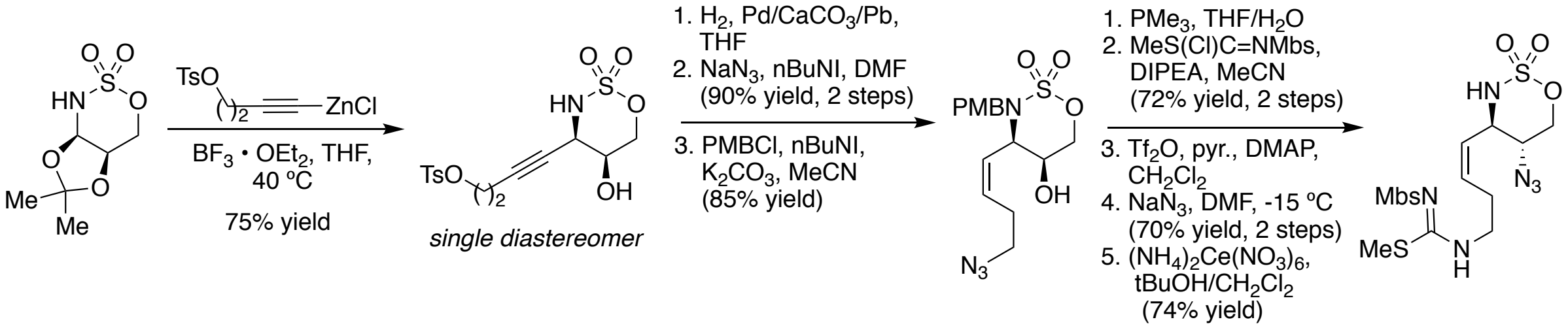
$Rh_2(esp)_4$

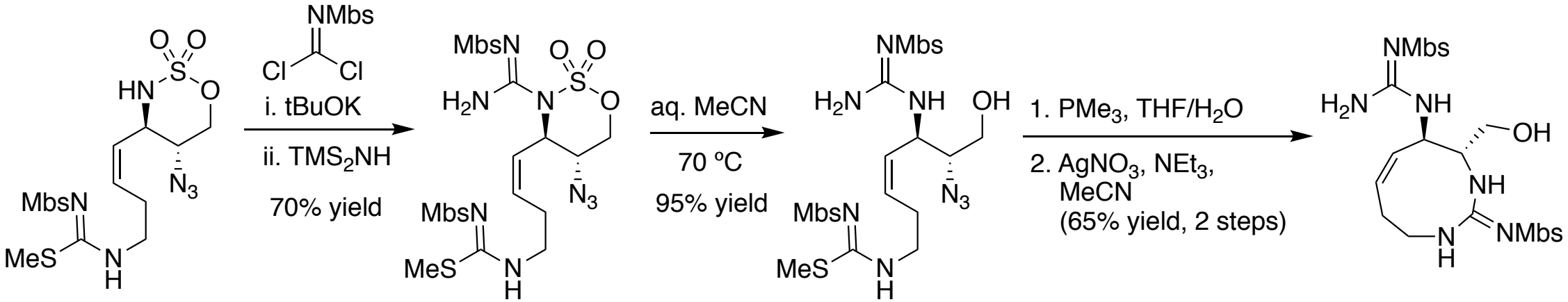


$Rh_2(TPA)_4$

Fleming & Du Bois, *JACS* **2006**, *128*, 3926-3927; Fleming; Fiori; Du Bois, *JACS* **2003**, *125*, 2028-2029

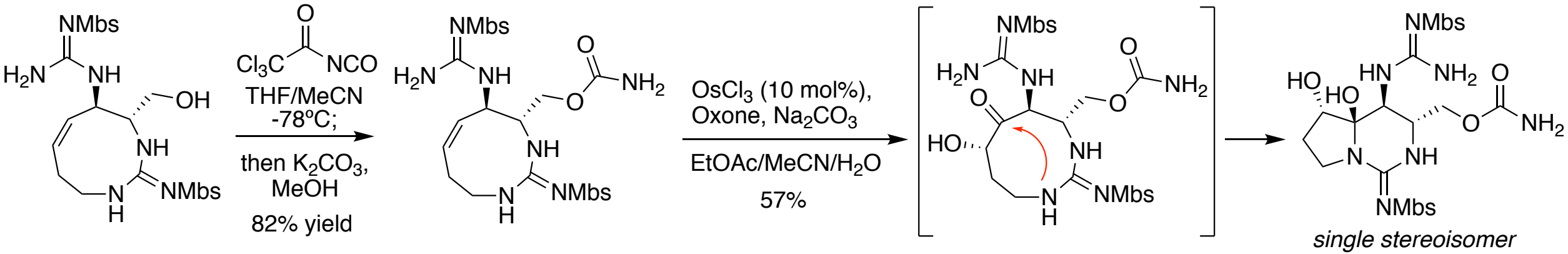
Steps to the 9-Membered Heterocycle

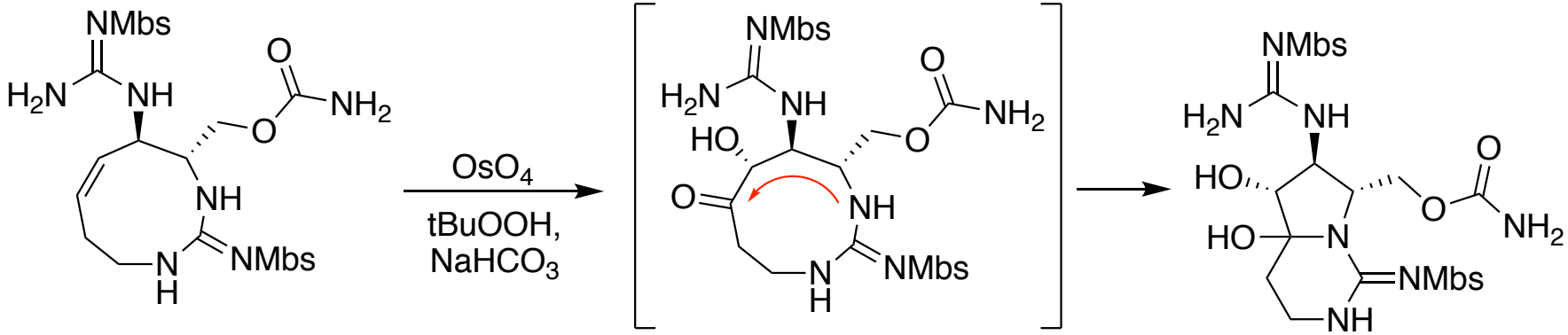




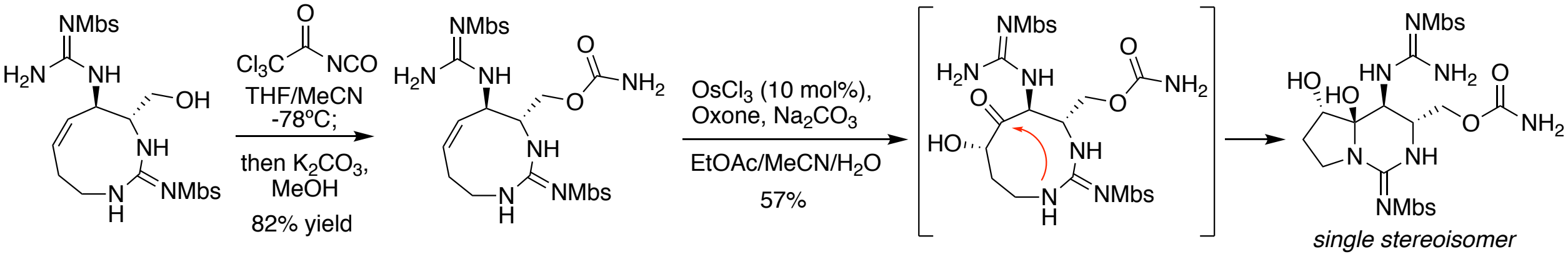
Fleming & Du Bois, *JACS* **2006**, *128*, 3926-3927; Fleming; Fiori; Du Bois, *JACS* **2003**, *125*, 2028-2029

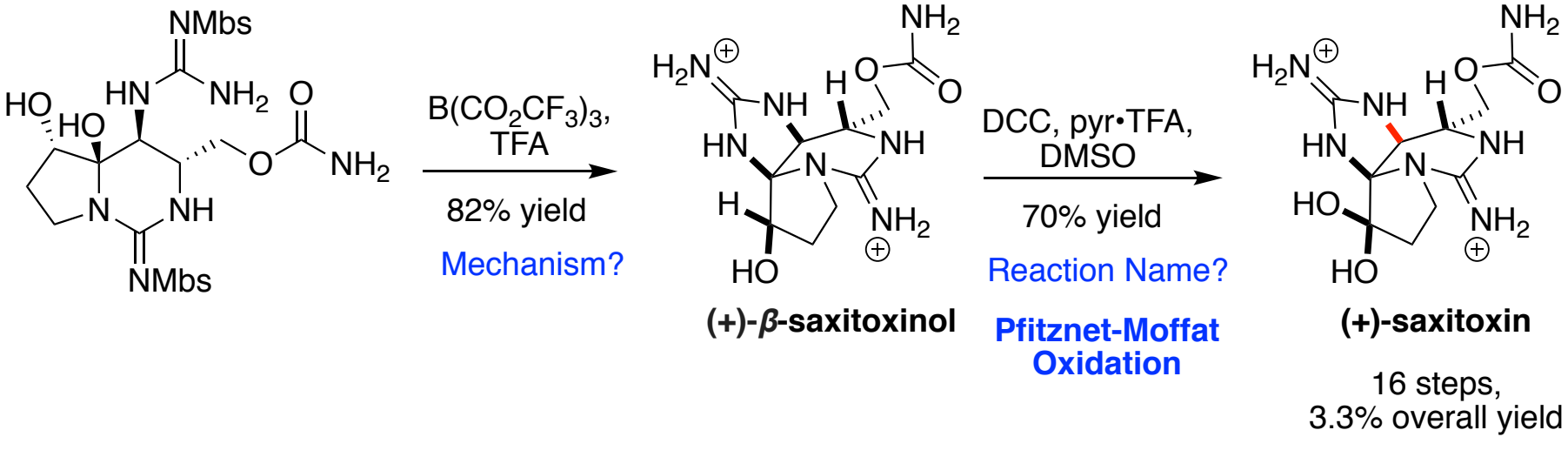
Formation of the Bicyclic Ring





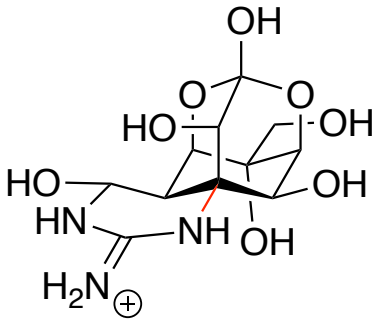
Finishing the Synthesis of (+)-Saxitoxin





Asymmetric Synthesis of (-)-Tetrodotoxin

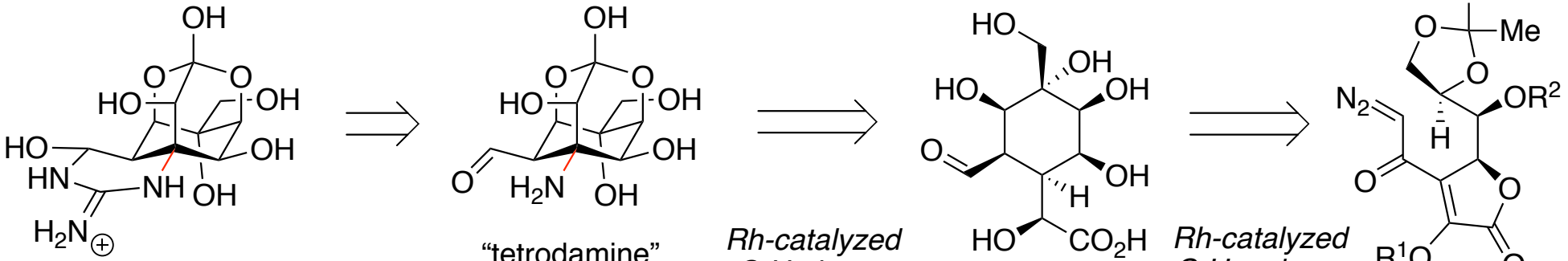
- Potent neurotoxin produced by symbiotic bacteria found in certain marine animals, like pufferfish
- Selective Na_v inhibitor; binds directly to the pore of the channel
- LD_{50} for humans is unknown, but is estimated to be between 5-8 µg/kg ; death occurs in 2-12 hours, normally by respiratory failure
- Structure elucidated in 1964 and confirmed in 1970 by X-ray crystallography



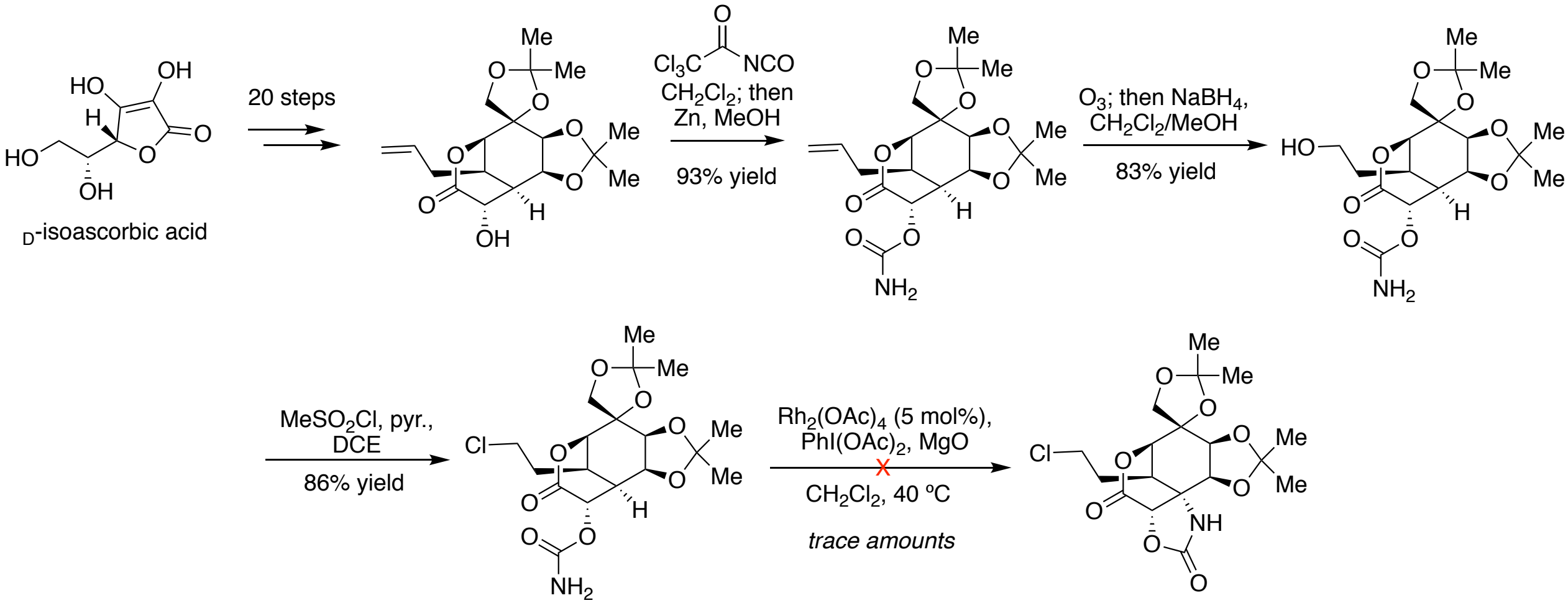
(-)-tetrodotoxin

Du Bois, 2003
(Stanford University)

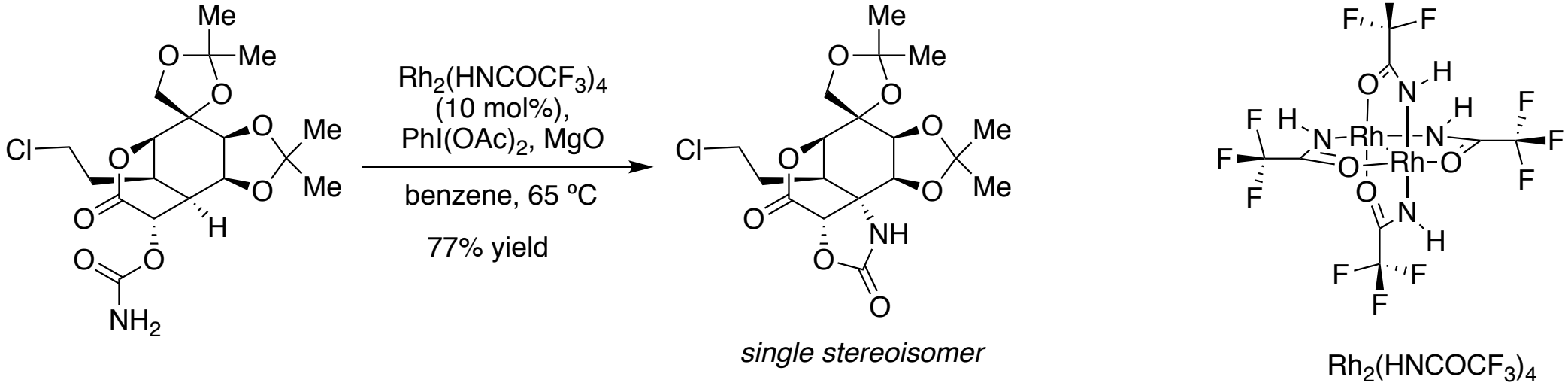
- One racemic synthesis before Du Bois: Kishi, 1972 (Nagoya Univ.)
- One asymmetric synthesis at the same time as Du Bois: Isobe, 2003 (Nagoya Univ.)

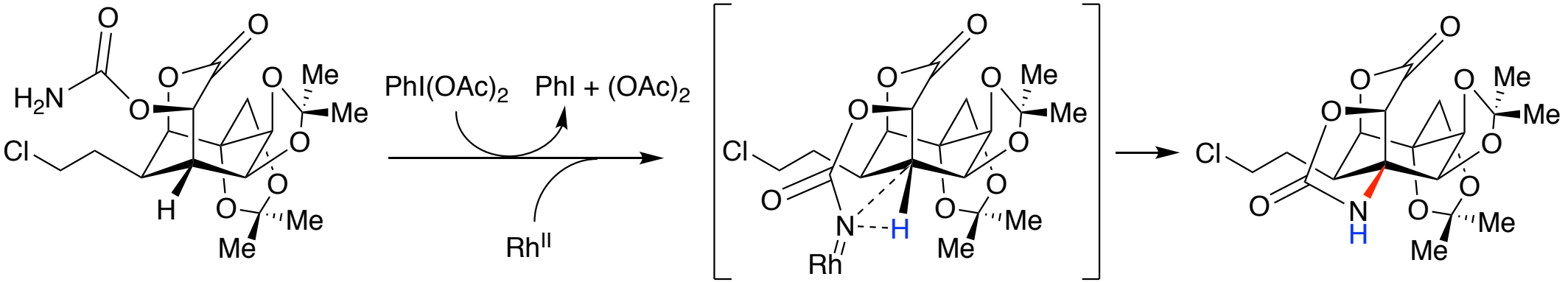


Preparing the Carbamate Intermediate

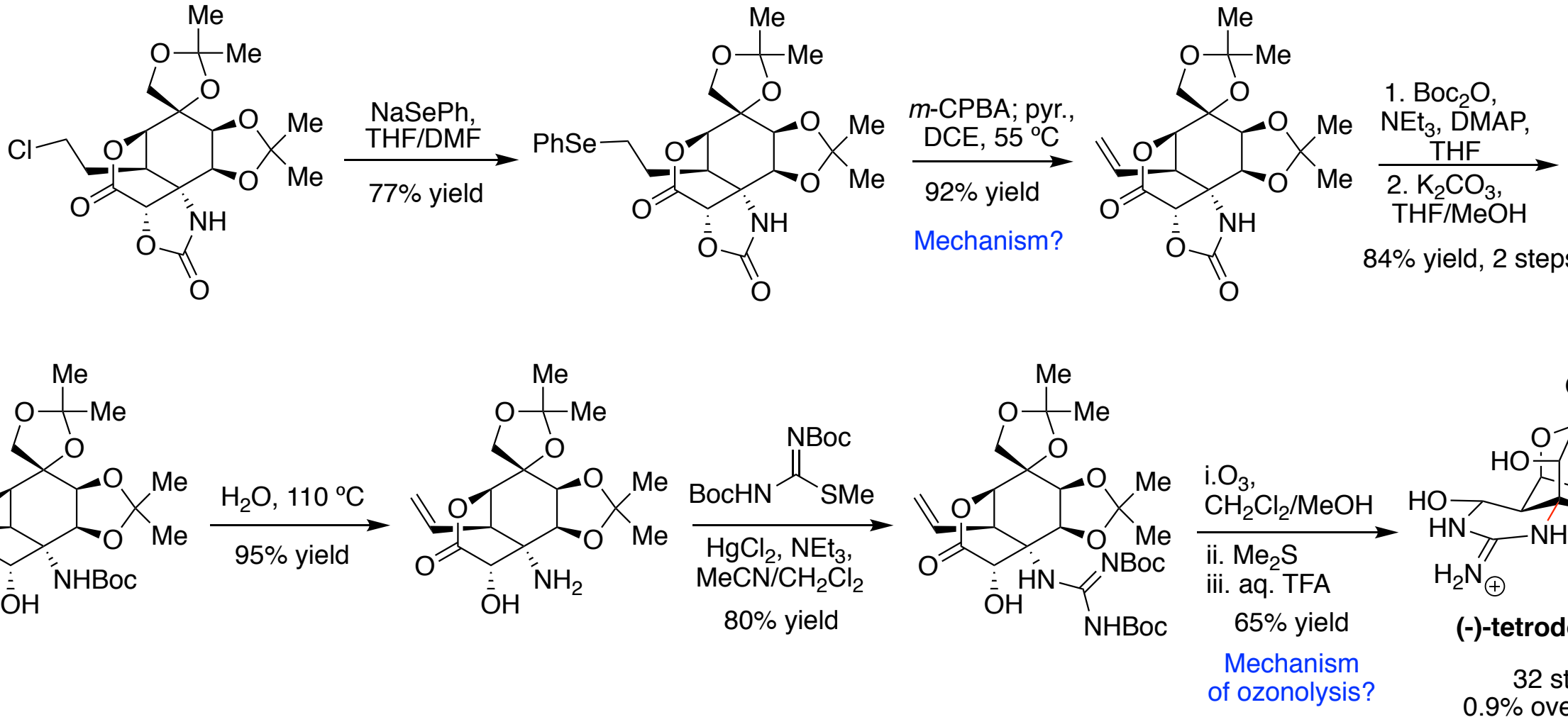


Stereospecific Nitrene Insertion

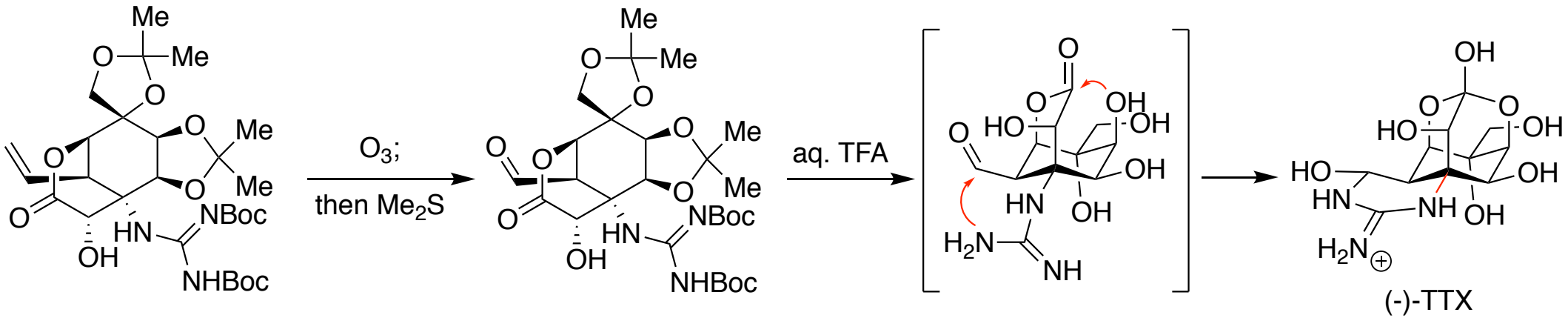




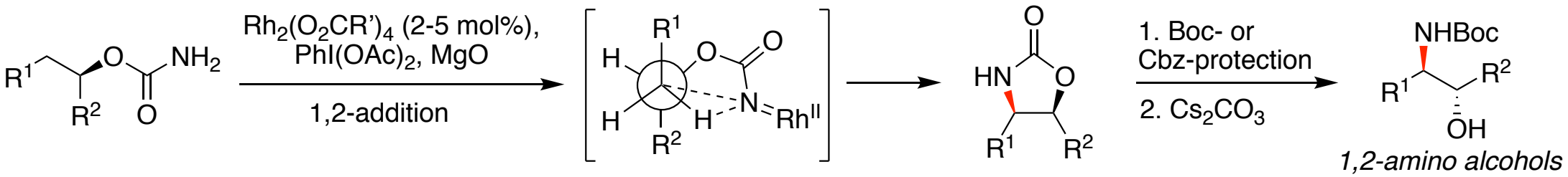
Finishing the Synthesis of (-)-Tetrodotoxin

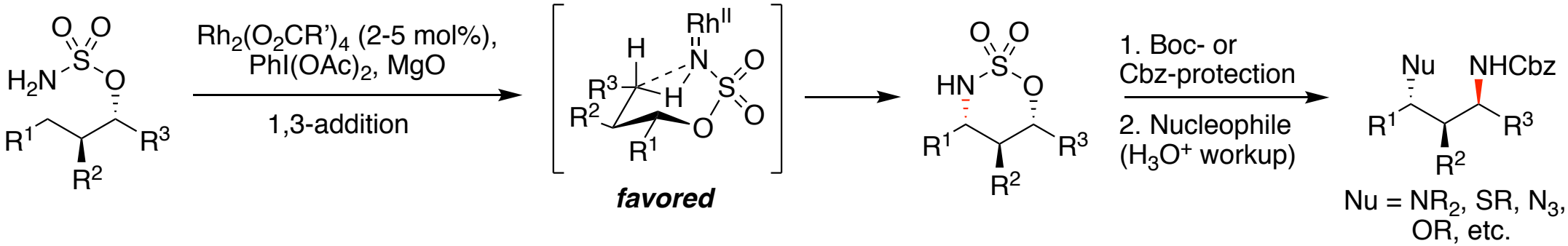


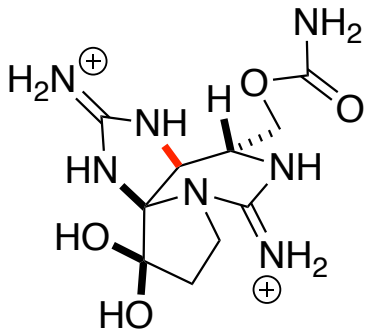
Mechanism of the Last Step



Summary

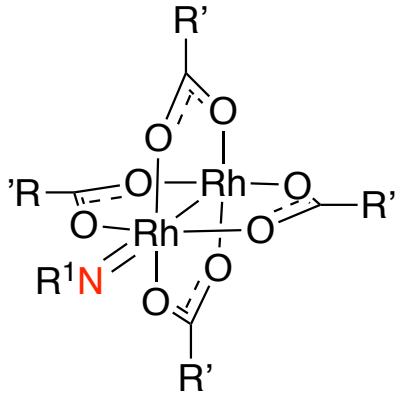


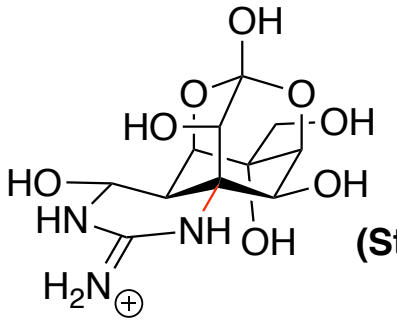




(+)-saxitoxin

Du Bois, 2006
(Stanford University)

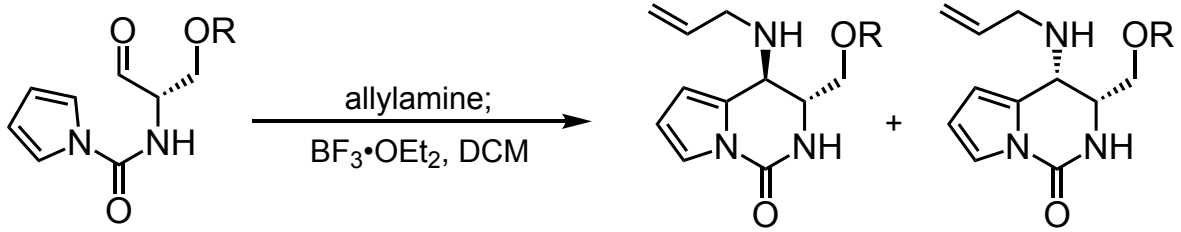




(-)-tetrodotoxin

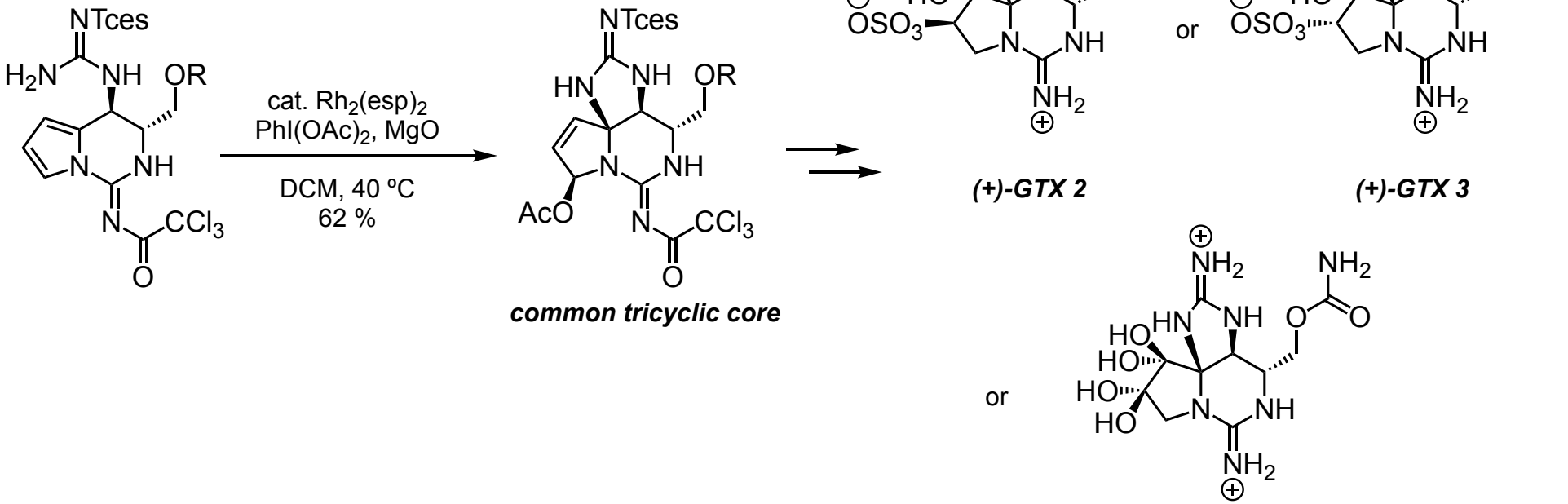
Du Bois, 2003
(Stanford University)

1. Provide mechanisms for each part and explain the preference for the trans diastereomer.
(Mulcahy et al. *J. Am. Chem. Soc.* **2016**, *138*, 5994-6001.)



Name?

>20:1 preference for trans



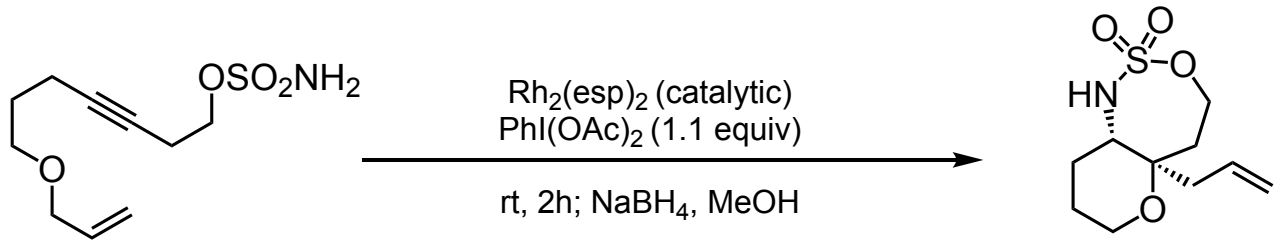
common tricyclic core

(+)-GTX 2

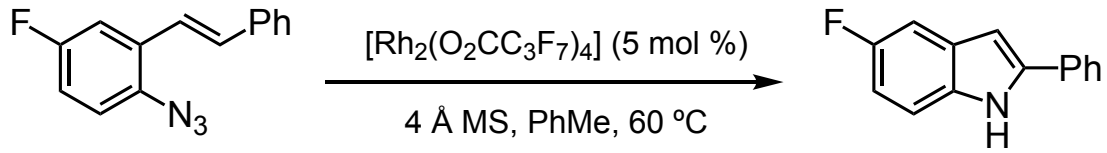
(+)-GTX 3

(+)-11,11-dhSTX

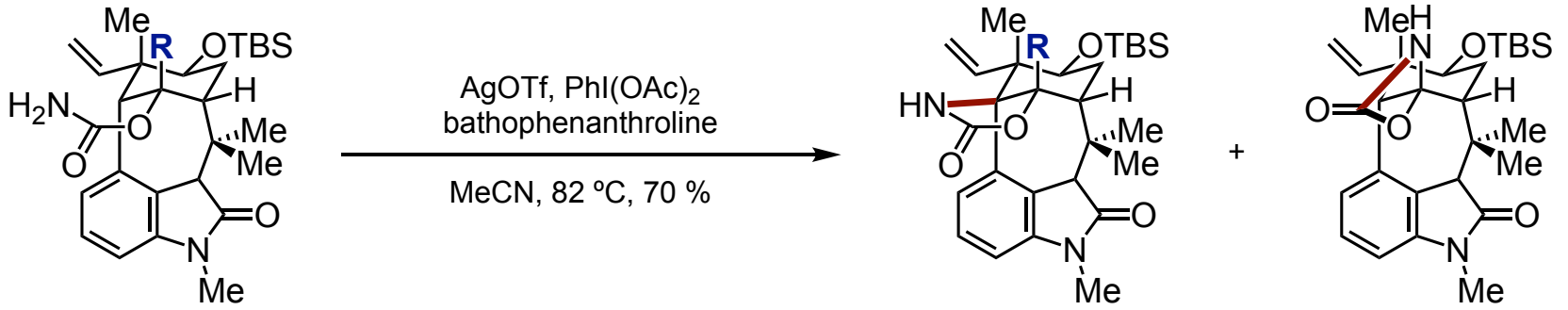
2. Provide a mechanism for the following transformation (Thornton and Blakey, *J. Am. Chem. Soc.* **2008**, *130*, 5020).



3. Mechanism? (*Angew. Chem. Int. Ed.* **2008**, *47*, 5056).



4. The following reaction was used in Garg's synthesis of N-methylwelwitindolinone D. What is the mechanism? Explain the observed selectivity for the two insertion products when R=H vs D. (*Angew. Chem. Int. Ed.* **2013**, *52*, 12422).



R=H	**44%**	**37%**
R=D	**70%**	**30%**