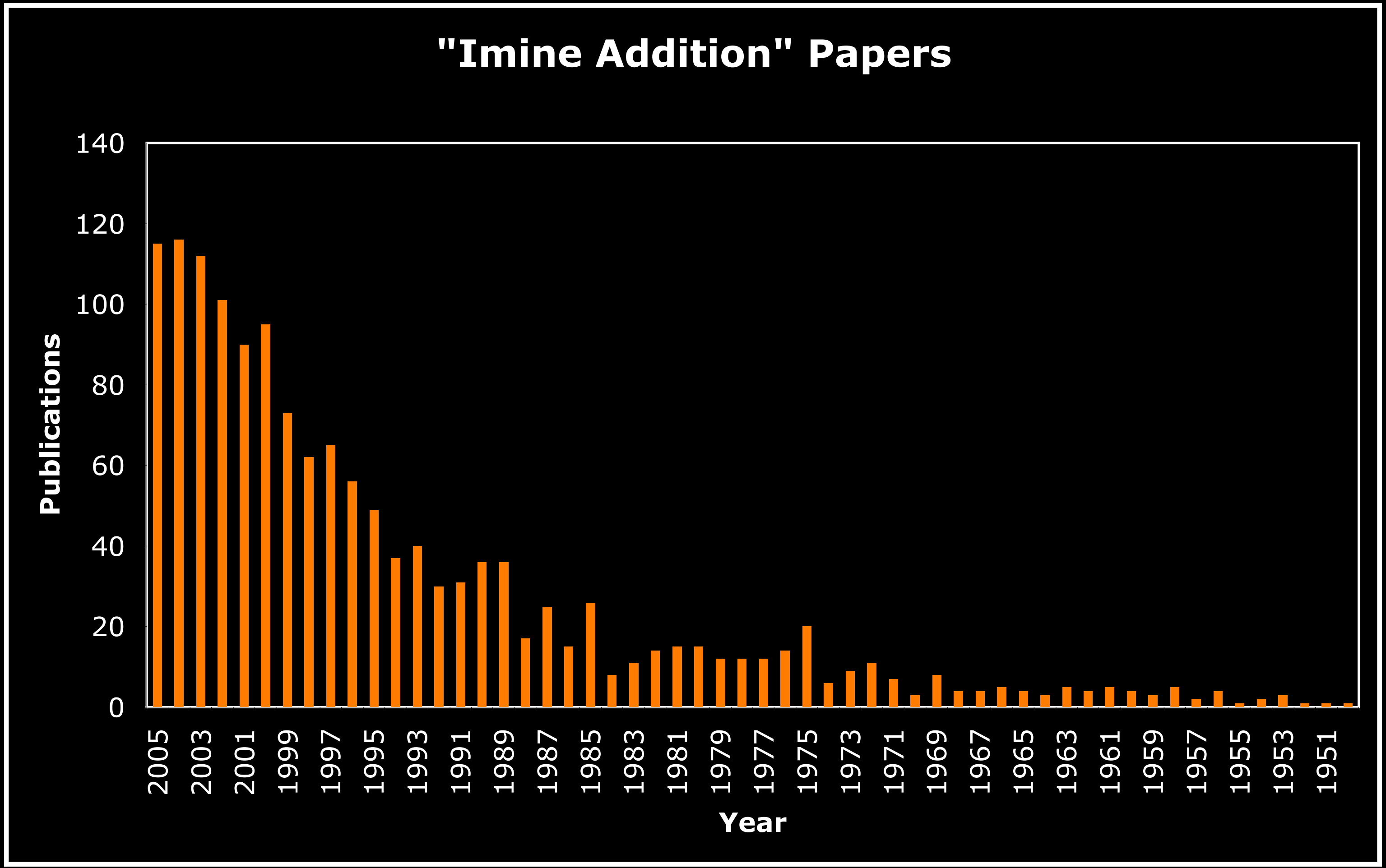
Applications of Imine additions: Hemigramicidin S and Polycyclic Azepine Investigations

Adam Hoye

Research Topic Seminar

April 22nd, 2006

Imine addition chemistry- statistics, general rxns,

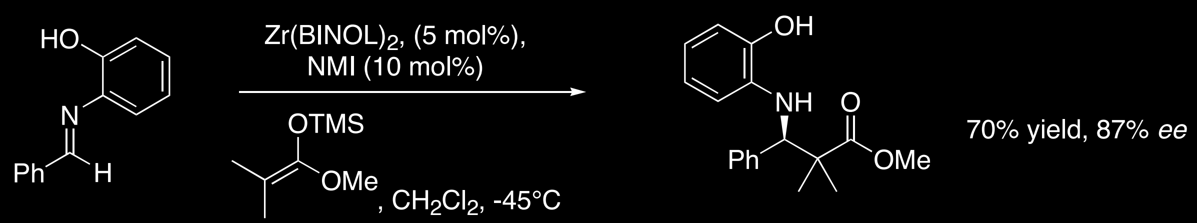


Imines as “the new carbonyl”

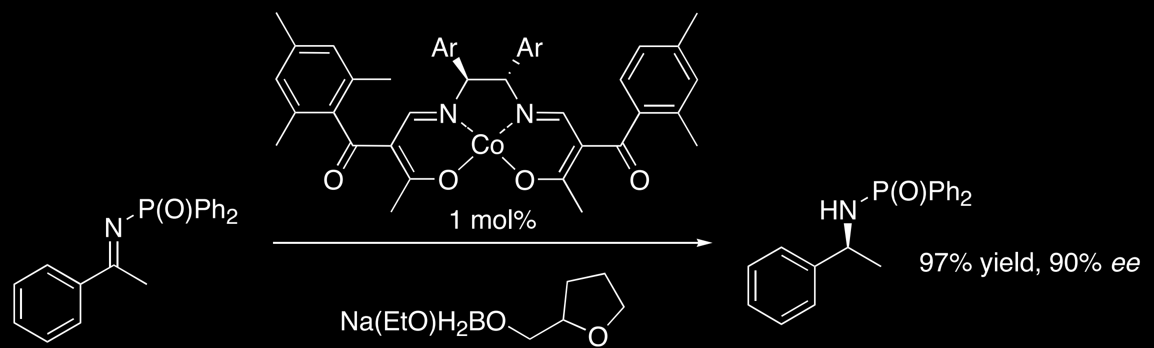
Source: SciFinder 2006

Selected Reactions of Imines

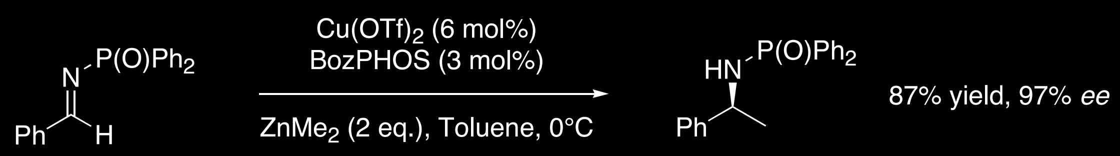
Kobayashi Asymmetric Mannich Reaction:



Mukaiyama Catalytic Reduction:

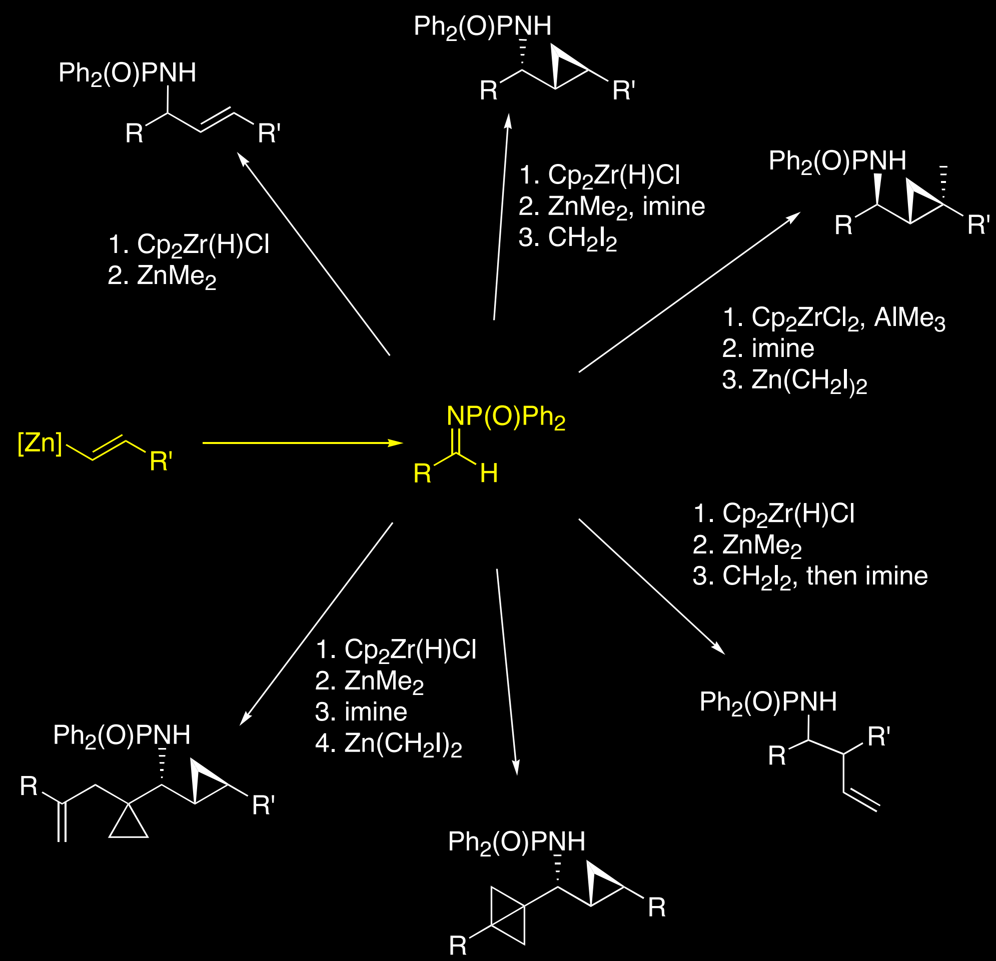


Charette Organozinc Addition:

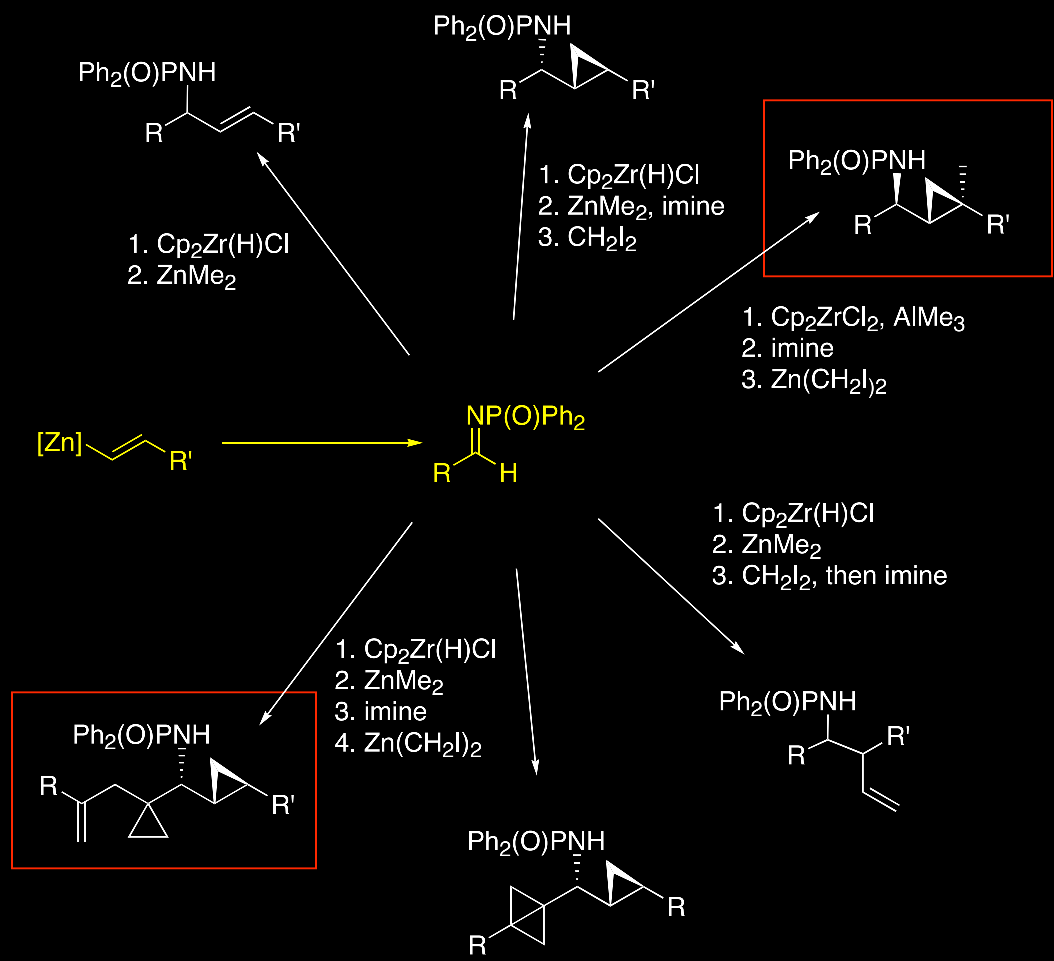


Kobayashi, S.; Ishitani, H,; *Chem. Rev.*, **1999**, *99*, 1069-1094
Charette, A. B. et al.; *Pure Appl. Chem.*, **2005**, *77*, 1259-1267

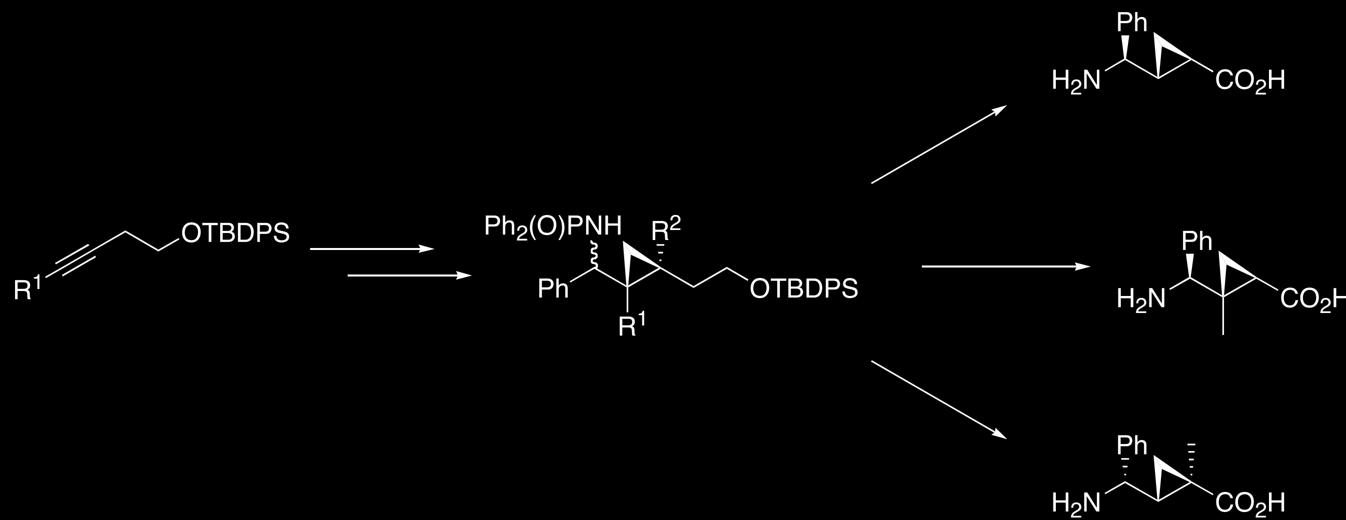
Imine methodology in the Wipf Group



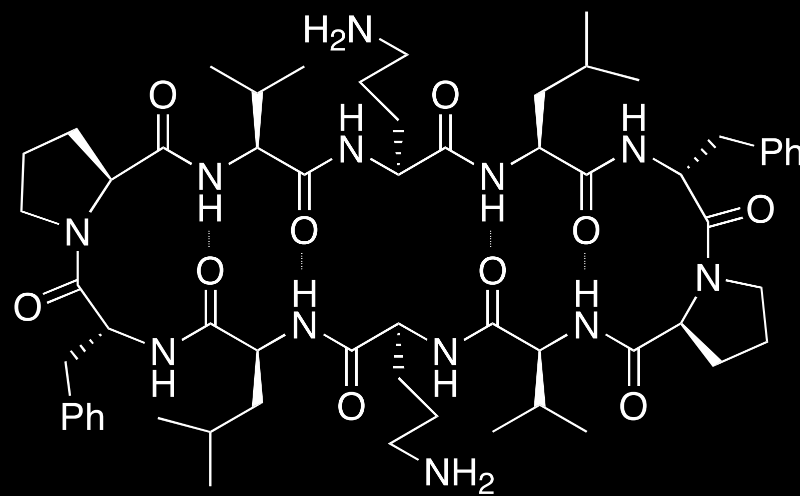
Imine methodology in the Wipf Group



Cyclopropyl amino acids



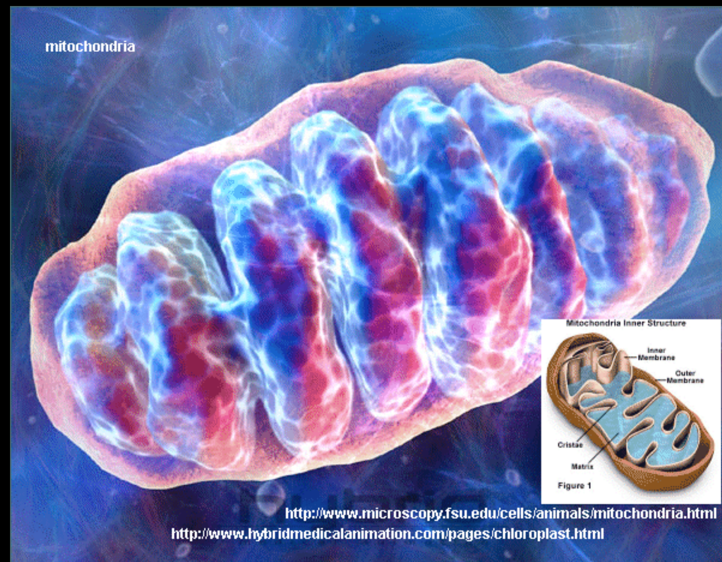
Gramicidin S



- Isolated (and used) in 1943 (USSR)
- Gramicidins A-D (linear) potent antibacterials, act via membrane insertion and aggregation, thus increasing cell permeability (high hemolytic activity)
-Rigid, symmetric β-strands connected by β-turns [(*cyclo*-^{D}Phe-Pro-Val-Orn-Leu)$_2$]
-Hydrophobic side chains (Val, Leu) on one face and polar residues (Orn) on the other, GS binds well to lipid bilayers
-No resistance to antibiotic activity has been found so far
-GS mitochondrial targeting

Wadhwani, P.; Afonin, S.; Ieronimo, M.; Buerck, J.; Ulrich, A. S.; *J. Org. Chem.* **2006**, 71*, 55*
Wu, X.; Bu, X.; Wong, K. M.; Yan, W.; Guo, Z.; *Org. Lett.* **2003**, *5*, 1749

Mitochondria



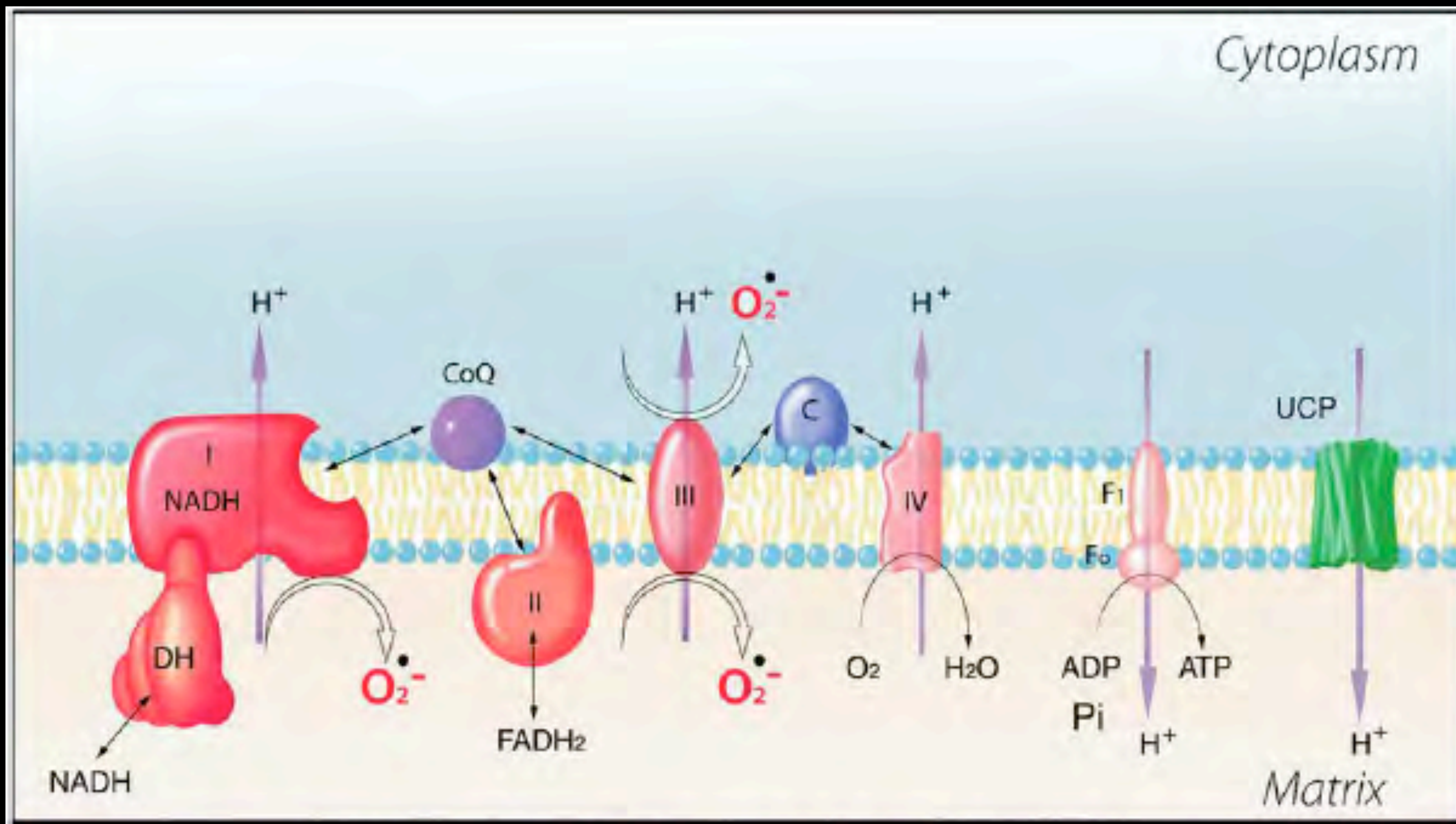
-Organelle membrane highly bacterial in type (high affinity for Gramicidins)

-Target of many cellular processes and proteins (“powerplant of cell”)

-Proficient inducer of apoptosis (programmed cell death)

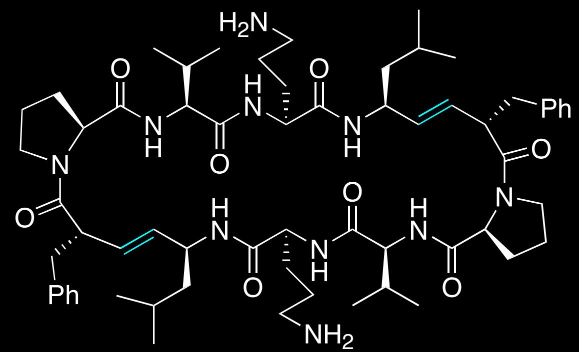
-Primary production of ATP

Reactive Oxygen Species (ROS) in ATP Production

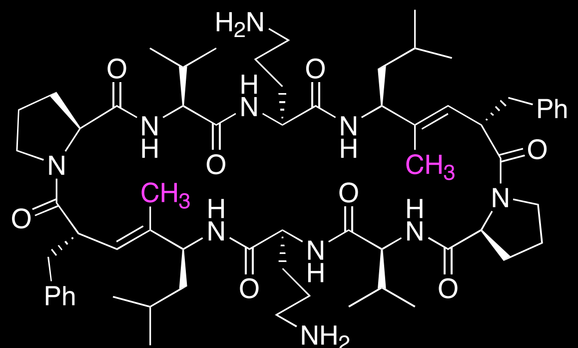


Superoxide dismutase traps ROS, but under conditions of high cellular stress, more ROS can be released, and damage to cells occurs.

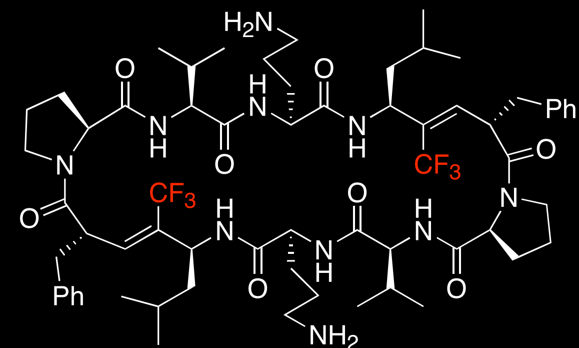
Gramicidin in our group- Jingbo Xiao



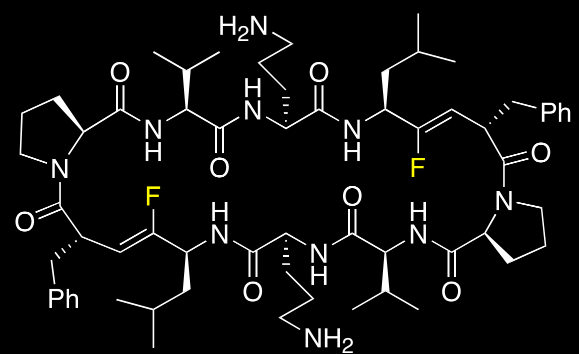
E-alkene Gramicidin S



$[CH_3]_2$GS



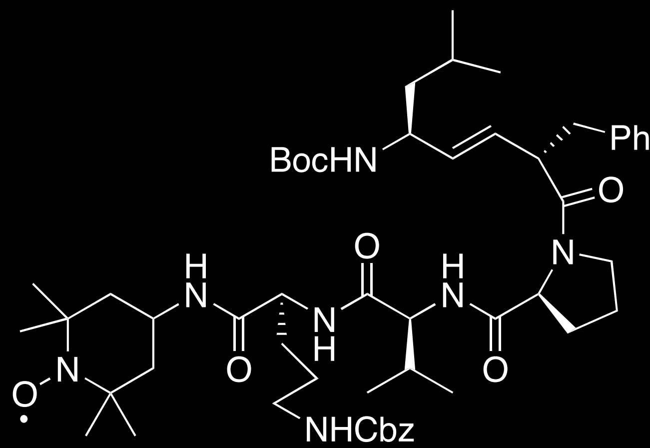
$[CF_3]_2$GS



$[F_2]$GS

Wipf, P.; Xiao, J.; Jiang, J.; Belikova, N. A.; Tyurin, V. A.; Fink, M. P.; Kagan, V. E.; *J. Am. Chem. Soc.* **2005**, *127*, 12460.
Xiao, J.; Westblum, B.; Wipf, P.; *J. Am. Chem. Soc.* **2005**, *127*, 5742.

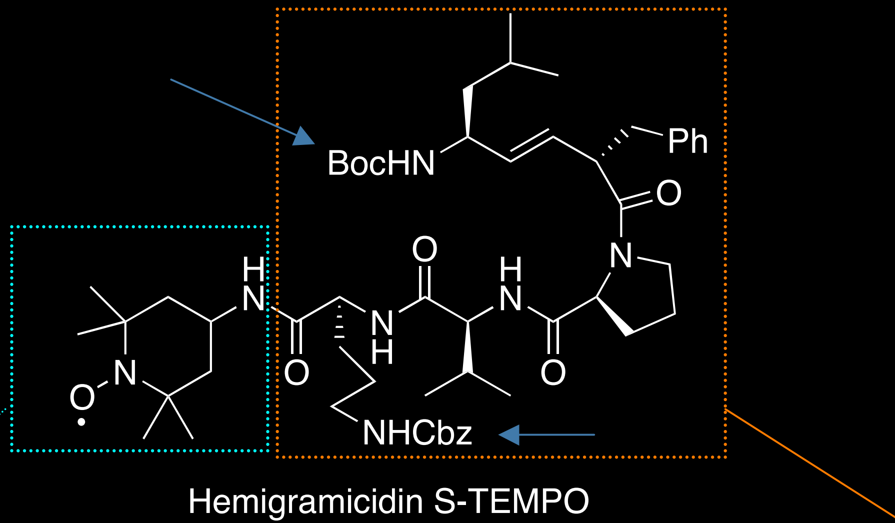
Hemigramicidin



Hemigramicidin S-TEMPO

Wipf, P.; Xiao, J.; Jiang, J.; Belikova, N. A.; Tyurin, V. A.; Fink, M. P.; Kagan, V. E.; *J. Am. Chem. Soc.* **2005**, *127*, 12460.

Hemigramicidin



Hemigramicidin S-TEMPO

ROS scavenger moiety of superoxide dismutase

β-turn mimic motif, bacterial membrane active

- Acetylated amino fucntions reduce hemolytic activity

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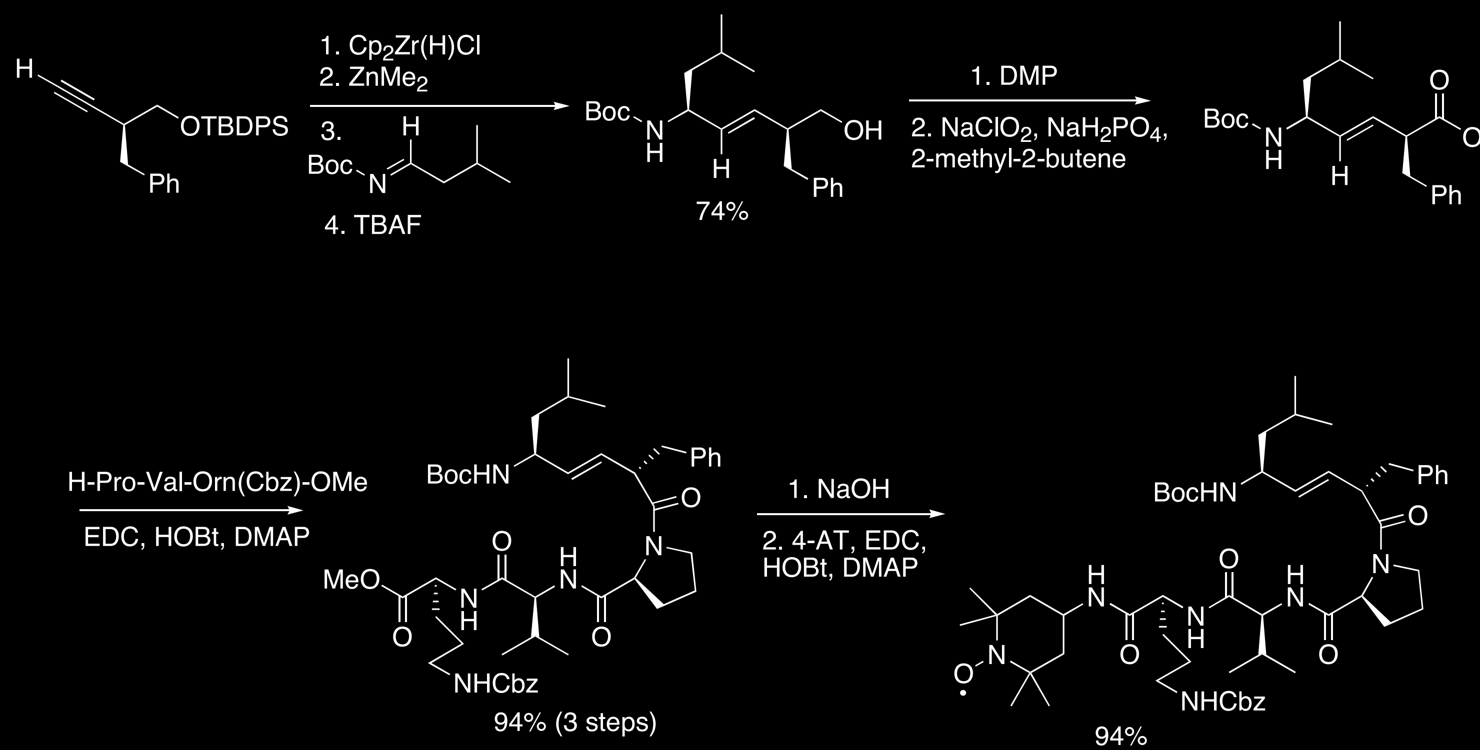
Hemigramicidin Synthesis



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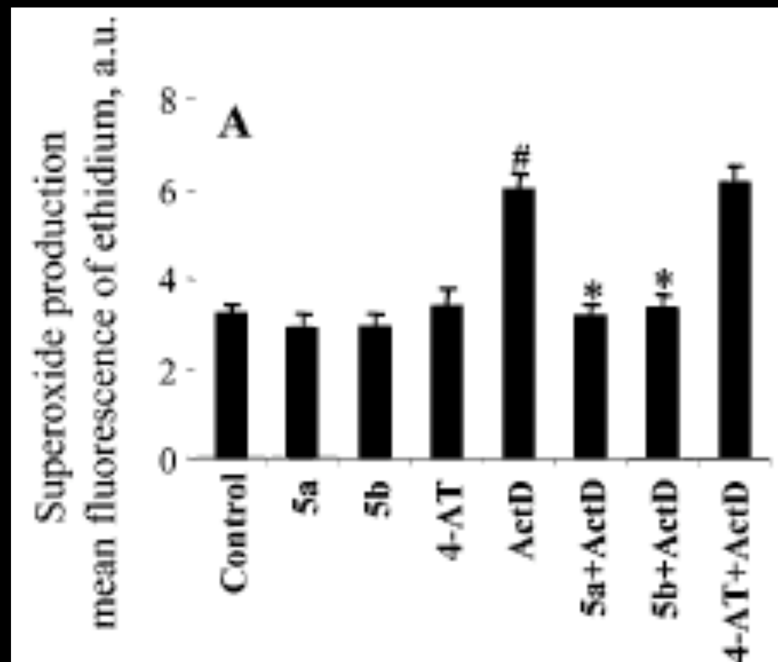
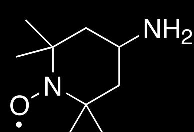
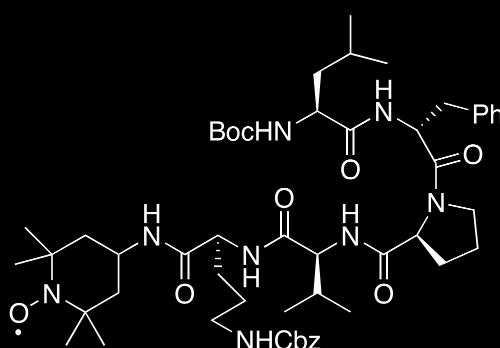
Biological Studies *in vitro*

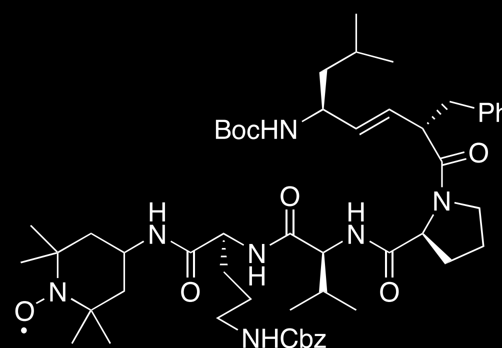




4-AT



5a



5b

Wipf, P.; Xiao, J.; Jiang, J.; Belikova, N. A.; Tyurin, V. A.; Fink, M. P.; Kagan, V. E.; *J. Am. Chem. Soc.* **2005**, *127*, 12460.

Biological Studies *in vivo*

- Hemorrhagic shock leads to cellular hypoxia, under which mitochondria leak electrons, leading to the formation of ROS ($O_2^{\bullet -}$).

Macias, C. A.; Chiao, J. W.; Xiao, J.; Arora, D. S.; Tyurina, Y. Y.; Delude, R. L.; Wipf, P.; Kagan, V. E.; Fink, M. P.; *In Press*, **2006**.

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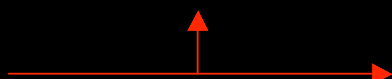
~55% of blood removed
(60 min)



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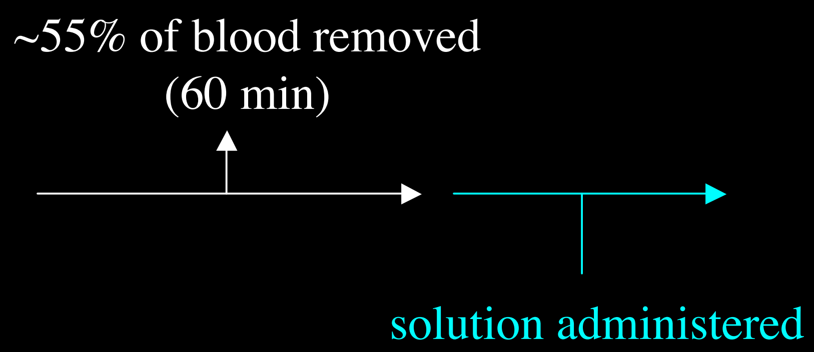

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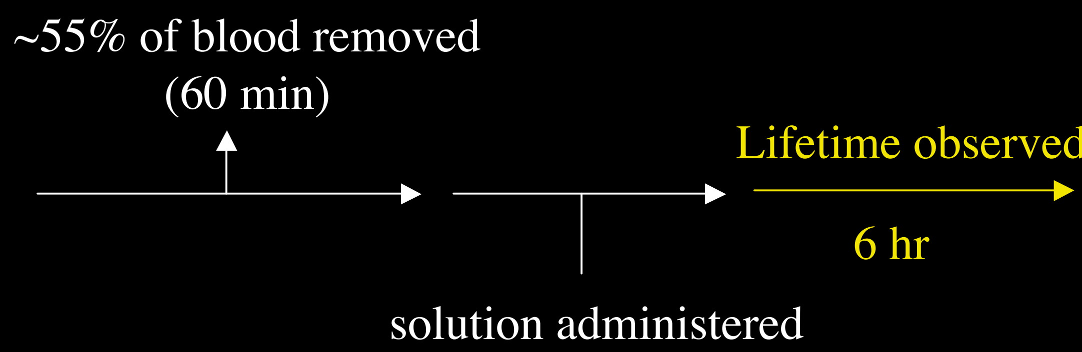

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- Hemorrhagic shock leads to cellular hypoxia, under which mitochondria leak electrons, leading to the formation of ROS (O_2•$^-$).

~55% of blood removed
(60 min)

solution administered

Lifetime observed

6 hr

KCl
euthanization

Macias, C. A.; Chiao, J. W.; Xiao, J.; Arora, D. S.; Tyurina, Y. Y.; Delude, R. L.; Wipf, P.; Kagan, V. E.; Fink, M. P.; *In Press*, **2006**.

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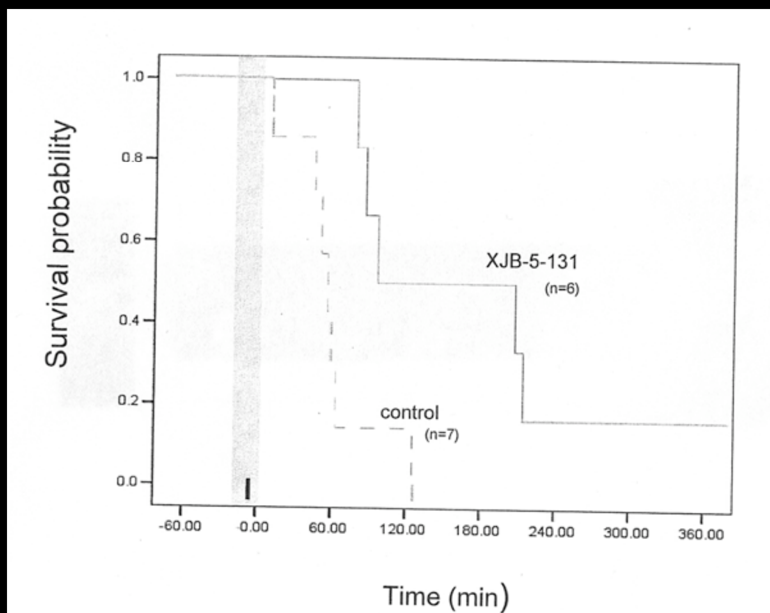
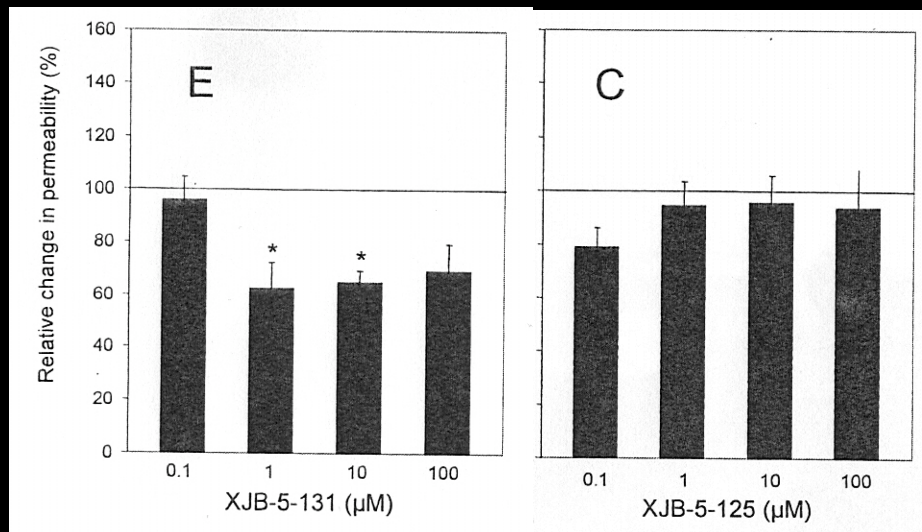


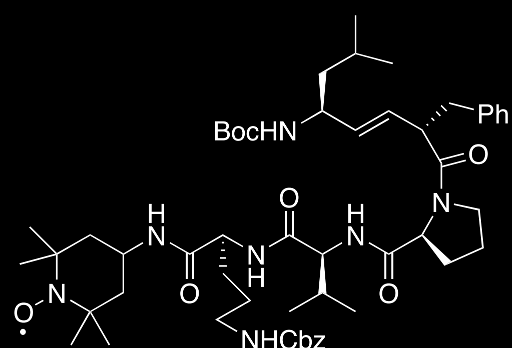
<u>Control</u>: 1 rat after 60 min

<u>XJB-5-131</u>: 6 rats after 60 min, 3 at 180 min, 1 at 6 hr!!

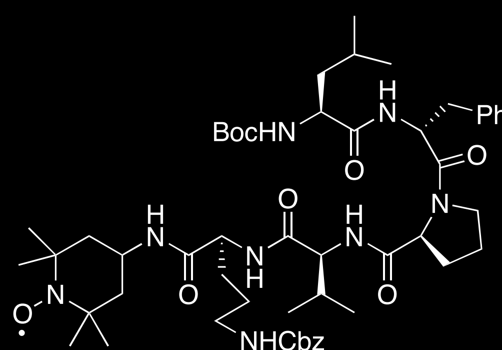
Macias, C. A.; Chiao, J. W.; Xiao, J.; Arora, D. S.; Tyurina, Y. Y.; Delude, R. L.; Wipf, P.; Kagan, V. E.; Fink, M. P.; *In Press*, **2006**.

Why Incorporate Peptide Isosteres?





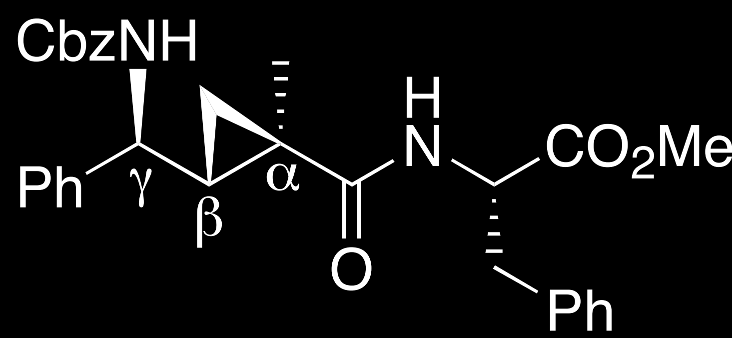
XJB-5-131



XJB-5-125

Even slight, seemingly innocuous changes in structure can have drastic biological consequences!

α-Methyl-α,β-Cyclopropyl-γ-Amino Acids



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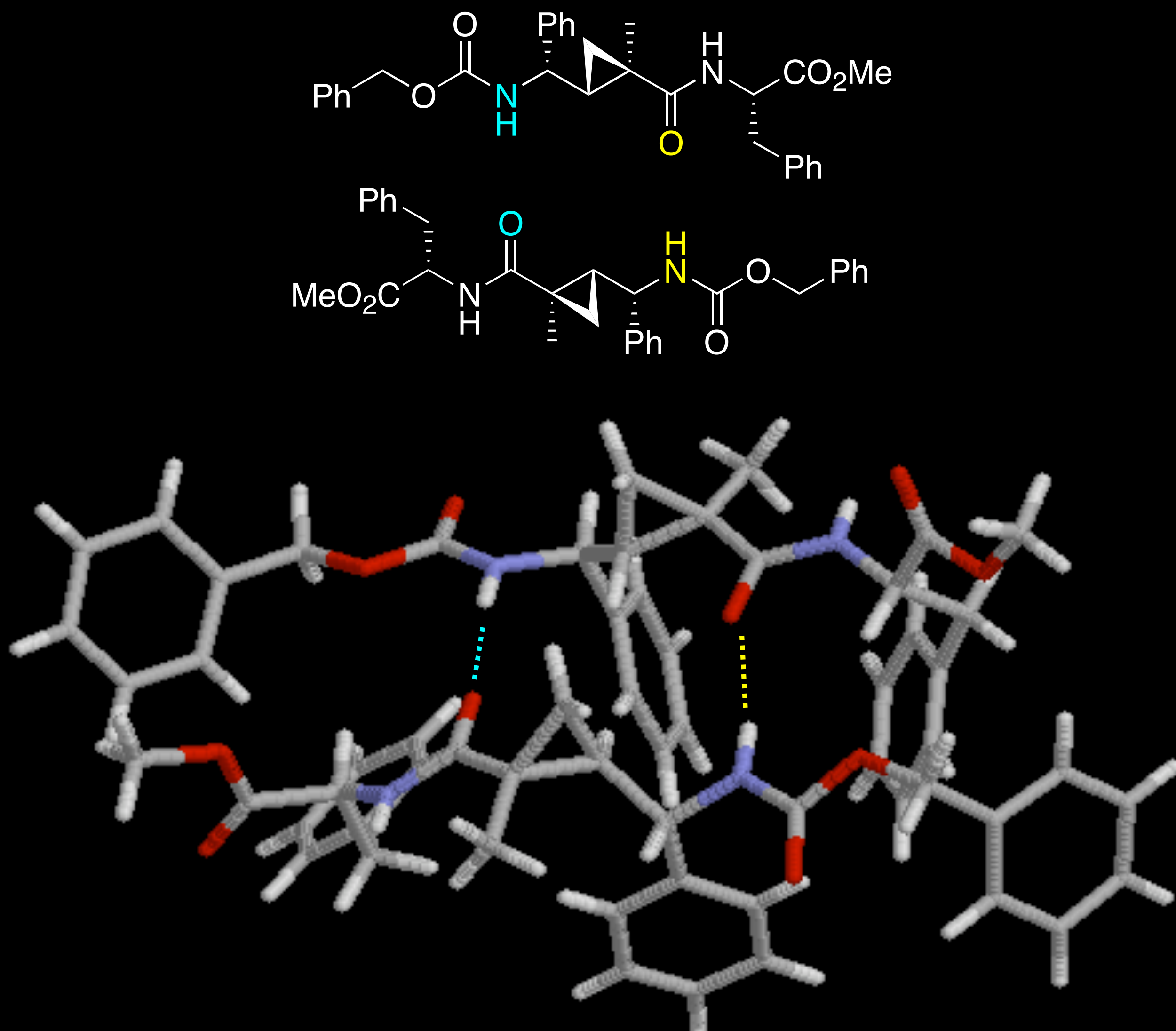
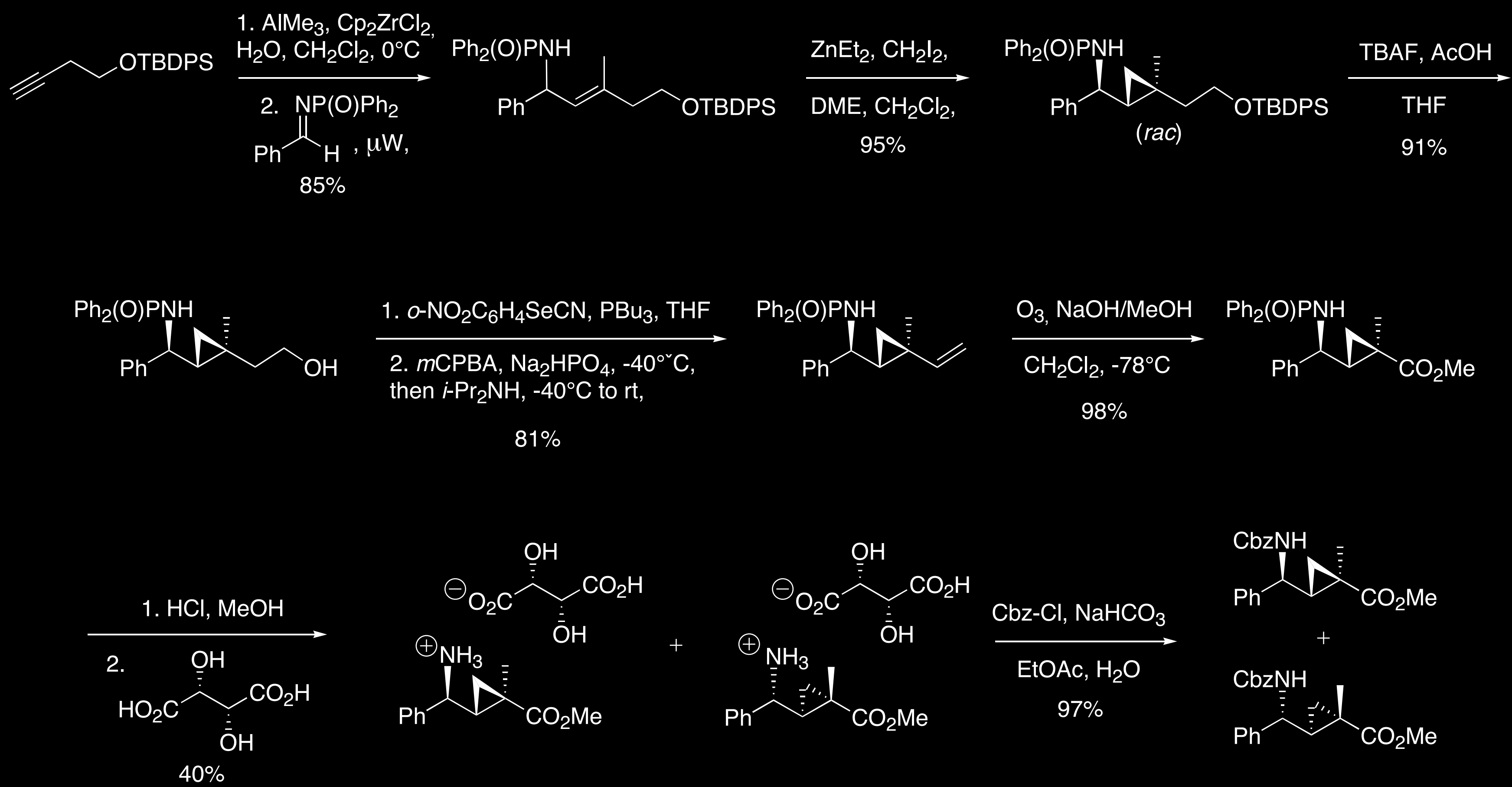


Wipf, P.; Stephenson, C. R. J.; *Org*. *Lett*. **2005**, *7*, 1137.

Cyclopropyl Amino Acid Synthesis



Wipf, P.; Stephenson, C. R. J.; *Org. Lett.* **2005**, *7*, 1137.

Interesting ROS Statistic

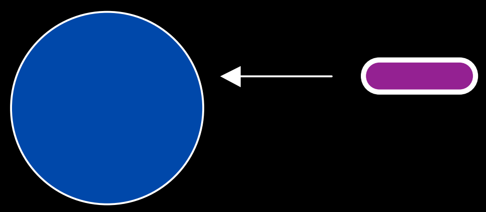
"Under normal metabolic conditions, each cell in our body is exposed to about 10^{10} molecules of superoxide each day. For a person weighing 150 pounds, this amounts to about 4 pounds of superoxide per year!"

http://lpi.oregonstate.edu/f-w97/reactive.html

An Aside- Theory of Aging

Mitochondria, Oxidants, and Aging. Balaban, R. S.; Nemoto, S.; Finkel, T.; *Cell,* **2005**, *120*, 483-495.

- Many believe the seeds of aging can be traced back to a chance encounter around *2 billion years ago* between a host cell and an invading bacterium



Theory of Aging

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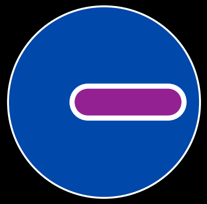
-In this case an agreement between host and invader formed (and has remained intact to this day).



Theory of Aging

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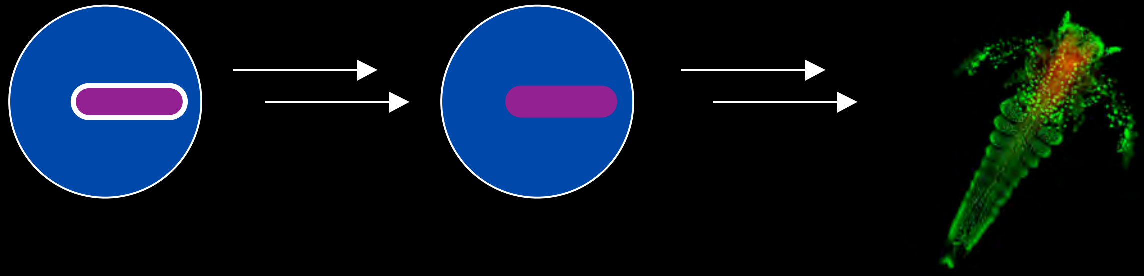
- Many believe the seeds of aging can be traced back to a chance encounter around *2 billion years ago* between a host cell and an invading bacterium

-In this case an agreement between host and invader formed (and has remained intact to this day).

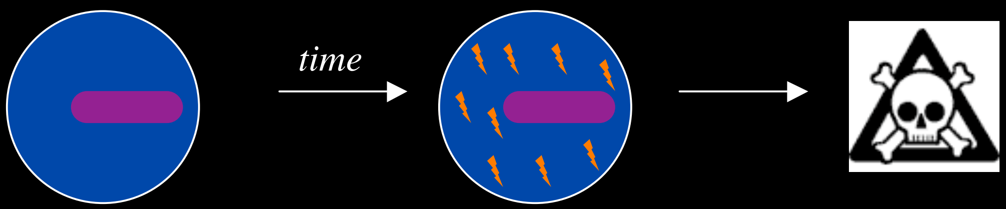
-At first roles were independent, then gradually responsibility shifted (cell- maintenance, bacterium- energy production), until specialization led to (eventually) the formation of muscles, etc.



…but not the end of the story!

-The eubacteria (mitochondria) did not immediately kill the host, but it may not have entered into the symbiotic agreement with full disclosure…

-The continuous production of ROS from ATP production pathway slowly but assuredly kills the host cell (oxidative damage)- the bacterium fulfillls its purpose!



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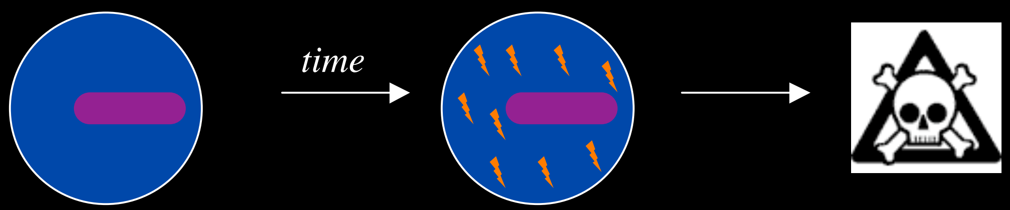


-Mitochondrial DNA employs a variant genetic code from the Proteobacteria family

Is the Mitocondrion…

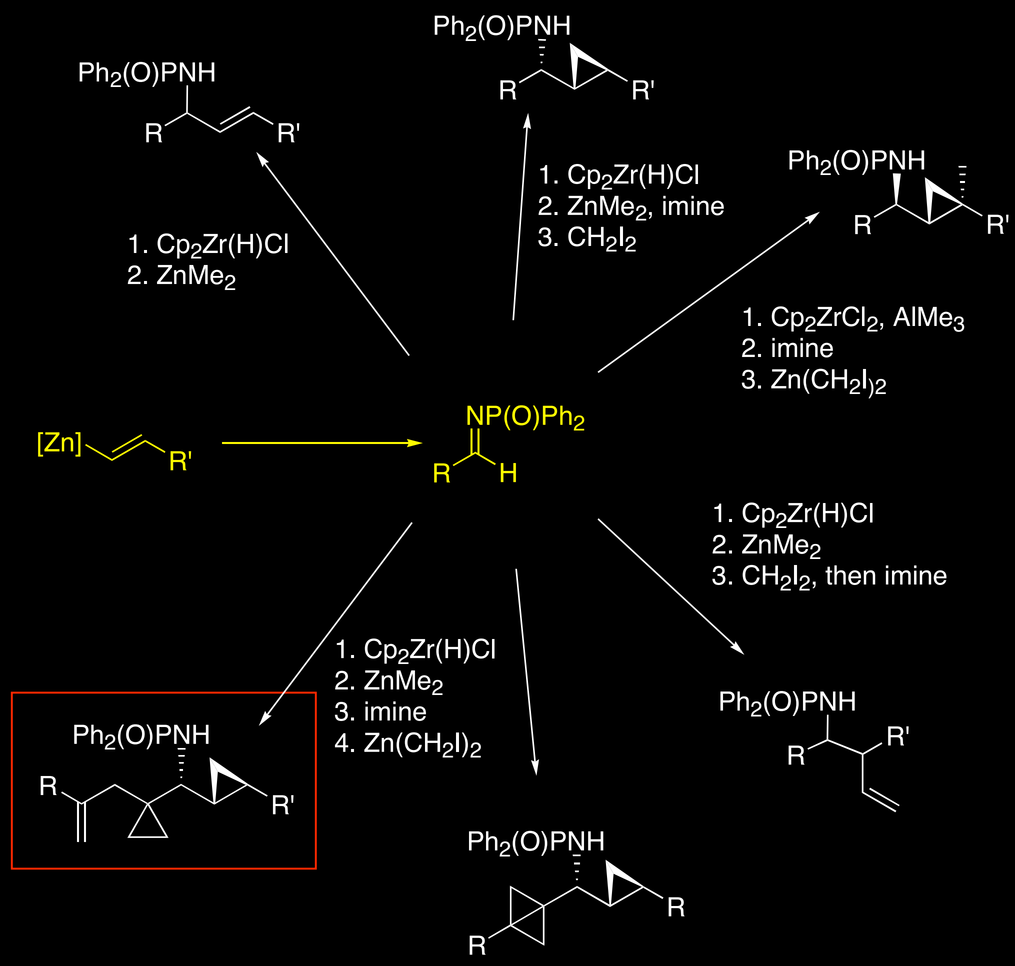
…like the Trojan horse?

…like Romeo and Juliet?

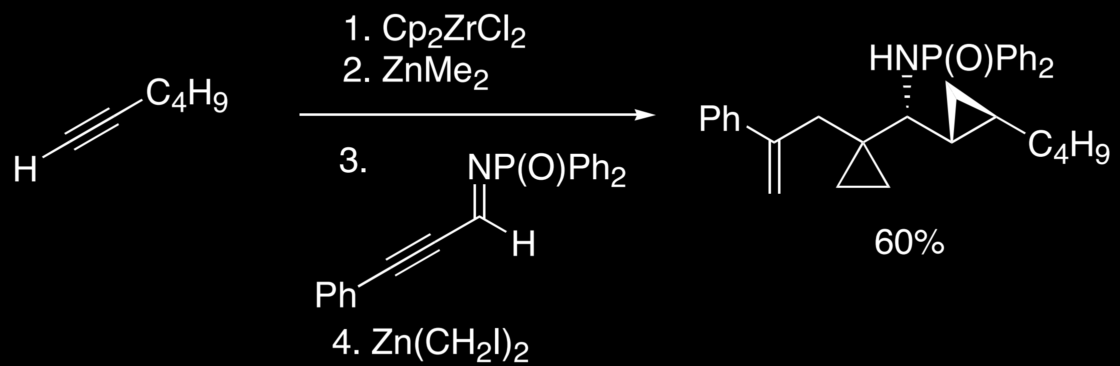
Is the Mitocondrion…

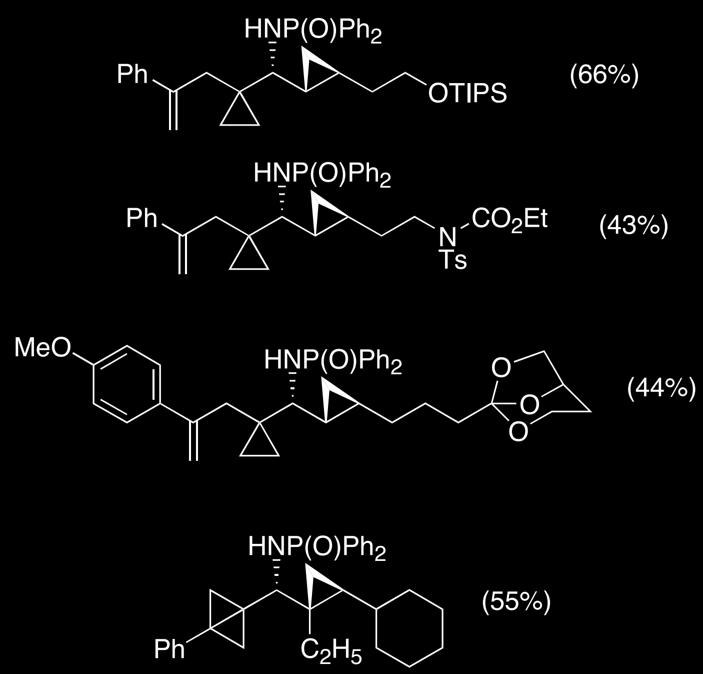
…does it matter???

Imine methodology in the Wipf Group



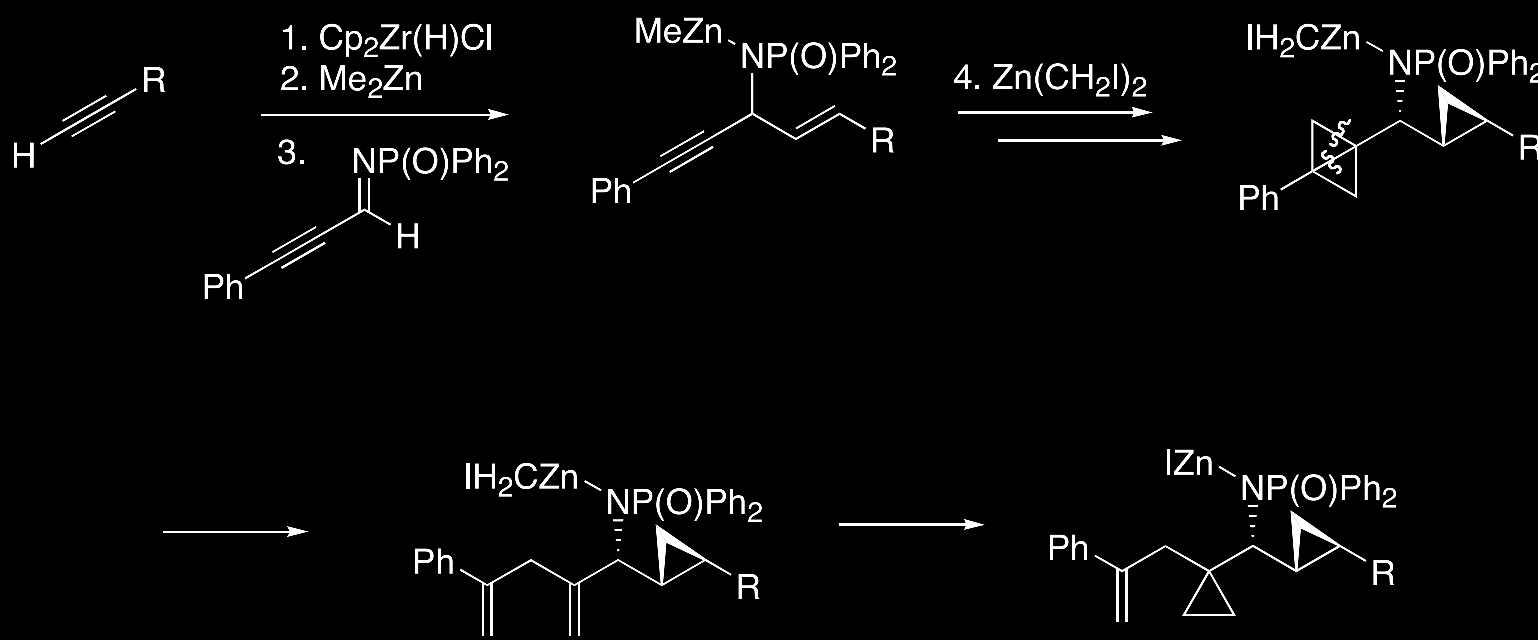
Alkynylimine Addition





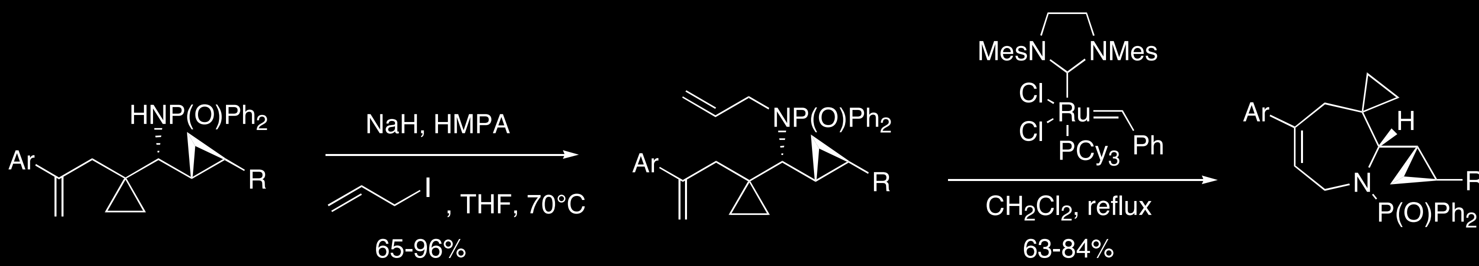
Wipf, P.; Stephenson, C. R. J.; Okumura, K.; *J. Am. Chem. Soc.*, **2003**, *125*, 14694-14695

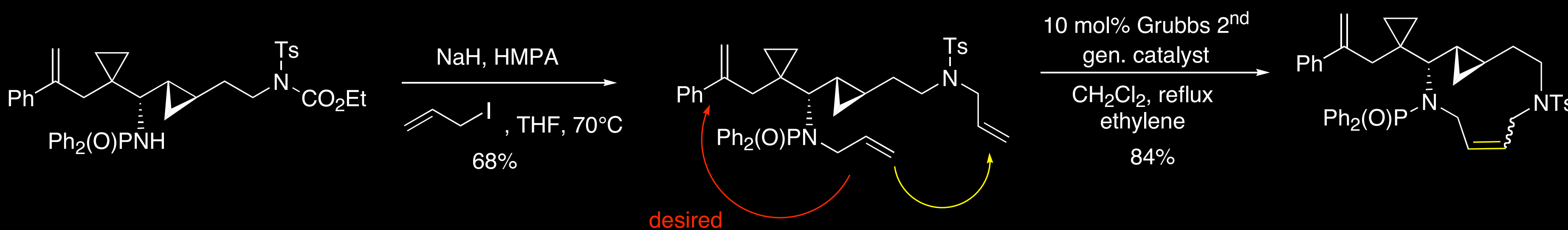
Proposed Mechanism



10 C-C bonds formed, 2 C-C bonds broken!

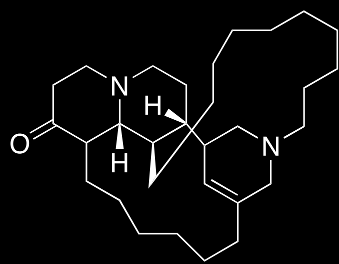
Azaspirocycles (Unexpected result)



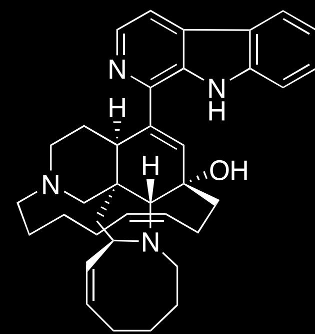


Wipf, P.; Stephenson, C. R. J.; Walczak, M. A. A.; *Org. Lett.*, **2004**, *6*, 3009-30012

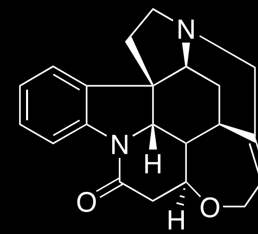
Macrocyclic Azepines in Natural Products



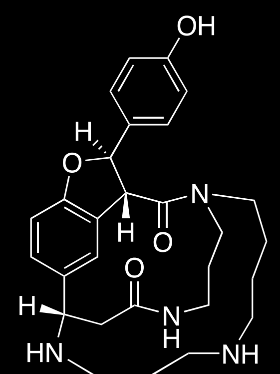
Saraine A



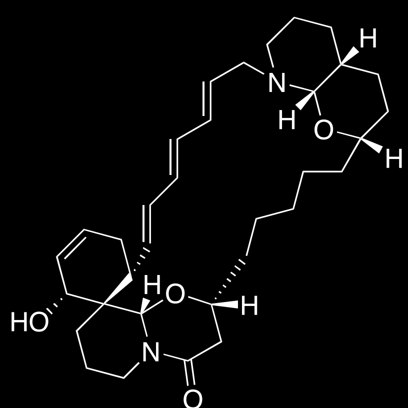
Manzamine A



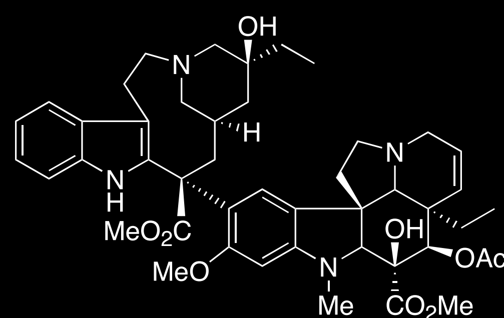
(-)-Strychnine



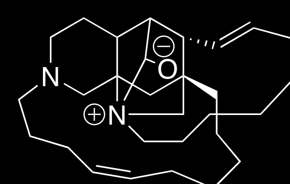
(-)-Ephedradine A



Upenamide

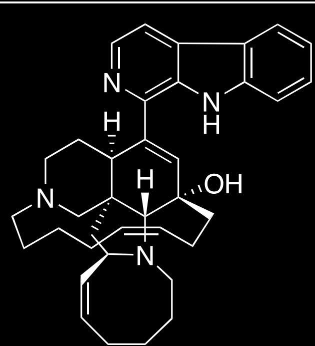


(+)-Vinblastine

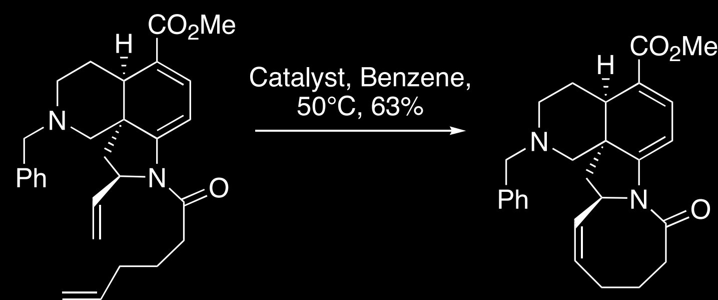


Misenine

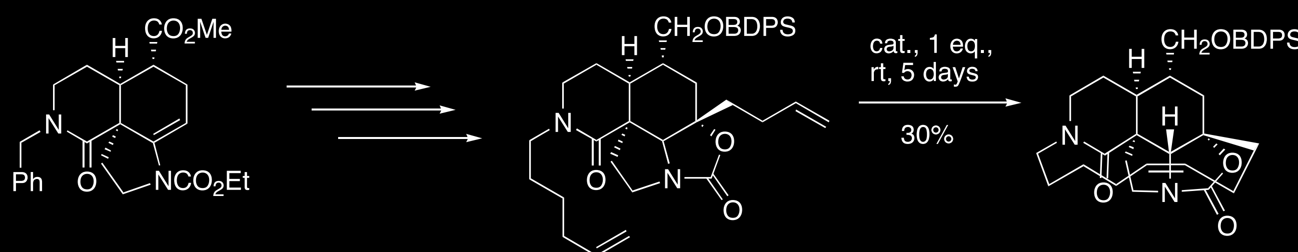
Metathesis-Based Synthetic routes



Manzamine A



Martin; *Tet*. *Lett*., **1994**, *35*, 691



Pandit; *Tet*. *Lett*., **1994**, *35*, 3191

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