

# Catalytic Enantioselective Aziridinations



MacMillan Group Meeting  
April 14, 2004  
Sandra Lee

## Key References:

General Reference: Sweeney, J. B. *Chem. Soc. Rev.* **2002**, *31*, 247.

Metal Catalyzed Aziridinations: Müller, P.; Fruit, C. *Chem. Rev.* **2003**, *103*, 2905.

Synthetic Applications: (1) McCoull, M.; Davis, F. A. *Synthesis* **2000**, *10*, 1347.  
(2) Zwanenburg, B.; ten Holte, P. *Top. Curr. Chem.* **2001**, *216*, 94.

## General Properties of Aziridines

### ■ How are they different from other secondary amines?

Weaker basicity than alkylamines but stronger than arylamines (aziridinium ion has a  $pK_a$  of 7.98)

Bond strain gives a higher barrier of inversion at N than in acyclic amines preventing racemization at RT.

most acyclic amines  $\sim 20 \text{ kJ mol}^{-1}$  for N-inversion

2-methylaziridines is  $\sim 70 \text{ kJ mol}^{-1}$

1-chloro-2 methyl aziridine (N-substitution with an EWG) is  $112 \text{ kJ mol}^{-1}$

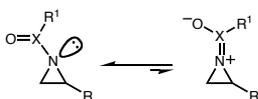
### ■ "Epoxides' ugly cousin?"

Epoxides and aziridines are both three-membered heterocycles with comparable Bæyer strain ( $111 \text{ kJ mol}^{-1}$ )

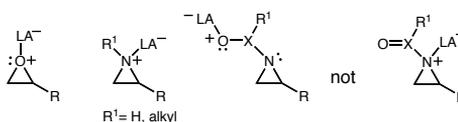
Difference lies in the additional valency and less electronegative heteroatom in aziridines make them less reactive in corresponding reactions for epoxides

### ■ Nature of the N-substituent

Activated aziridines refer to substitution with an EWG (e.g. acyl, carbamoyl, sulfonyl, sulfinyl, phosphoryl, phosphinyl), protonation, or addition of a Lewis acid to mask the N-H bond in simple aziridines.



ring strain prevents resonance interactions

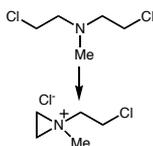


interaction with Lewis acid (LA) to non-bonded electron pairs

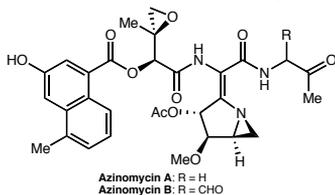
## Biologically Active Aziridines

- There are several classes of aziridine containing natural products that are potent and selective from the inherent specific alkylating ability of aziridines

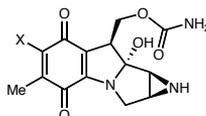
**Nitrogen Mustard**  
Similar to 'mustard gas' and acts by DNA alkylation



**Azinomycin**  
(extracted from *streptomyces grieseofuscus*)  
demonstrate anti-tumor activity that act by DNA crosslinking

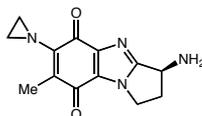


**Mistosanes**  
(extracted from *streptomyces verticillatus*)  
demonstrate anti-tumor and antibiotic activity that act by DNA alkylation



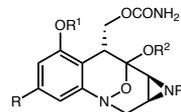
Mitomycin A: X = OMe, Y = Me, Z = H  
Mitomycin B: X = OMe, Y = H, Z = Me  
Mitomycin C: X = NH<sub>2</sub>, Y = Me, Z = H  
Porfiryomycin: X = NH<sub>2</sub>, Y = Me, Z = Me

**PBI**  
demonstrate anti-tumor activity by single strand DNA cleavage



PBI-A: R = OAc  
PBI-B: R = OCONH<sub>2</sub>  
PBI-C: R = H

**FR and FK Compounds**  
demonstrate anti-tumor activity by DNA cleavage



FR-900462: R = CHO, R<sup>1</sup> = R<sup>2</sup> = R<sup>3</sup> = H  
FR-66979: R = CH<sub>2</sub>OH, R<sup>1</sup> = R<sup>2</sup> = R<sup>3</sup> = H  
FR-70496: R = CHO, R<sup>1</sup> = Me, R<sup>2</sup> = H, R<sup>3</sup> = Ac  
FK-973: R = CHO, R<sup>1</sup> = R<sup>2</sup> = R<sup>3</sup> = Ac  
FK-317: R = CHO, R<sup>1</sup> = R<sup>2</sup> = R<sup>3</sup> = Ac

Sweeney, J. B. *Chem. Soc. Rev.* **2002**, 31, 247.

## General Reactivities of Chiral Aziridines

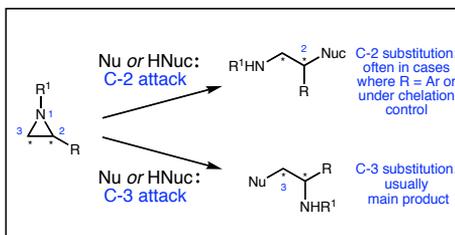
### Stereoselective Ring Openings

Hydrogenolysis: Pd(OH)<sub>2</sub>, H<sub>2</sub>

Reductive ring opening: SmI<sub>2</sub>

Hetero nucleophile ring opening: need activated system for N, S, or Br add'n

Carbon nucleophile ring opening: organocuprate add'n, MIRC



### Ring Expansions

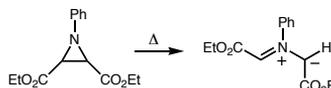
4-membered rings:  $\beta$ -lactams from aziridinecarboxamide

5-membered rings: imidazolines, oxazolines, and oxazolidinones

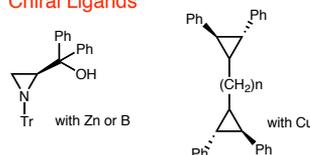
6-membered rings: aza-[2,3]-Wittig of vinyl aziridines

7-membered rings: aza-[3,3]-Claisen of vinylaziridines

### Azomethine Ylids

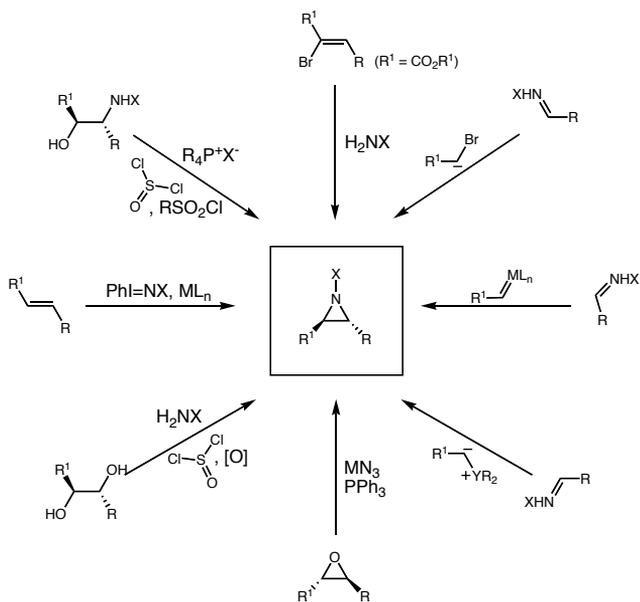


### Chiral Ligands



McCoull, M.; Davis, F. A. *Synthesis* **2000**, 10, 1347.

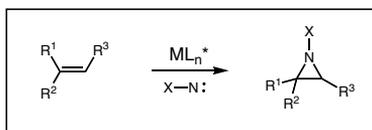
## Summary of Methods Used to Access Asymmetric Aziridines



Sweeney, J. B. *Chem. Soc. Rev.* **2002**, 31, 247.

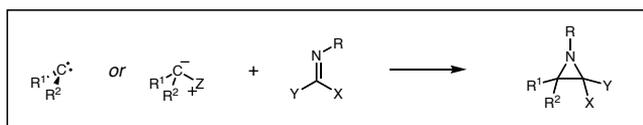
## Strategies for Accessing Asymmetric Aziridines

### ■ Nitrene Transfer to Olefins



M = Cu, Rh, Cu, Mn, Ru

### ■ Carbene Addition to Imines



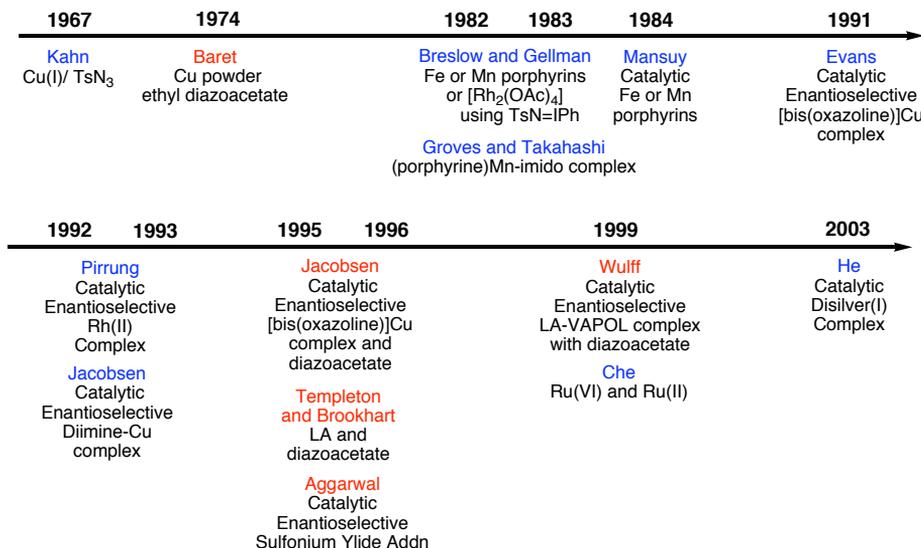
Metallo-carbene Addition

Lewis Acid Catalyzed Aziridination

Chiral Sulfonium Ylides

Müller, P.; Fruit, C. *Chem. Rev.* **2003**, 103, 2905.

## Progress Towards Enantioselective Aziridination



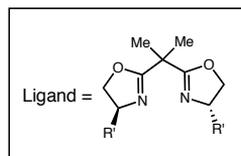
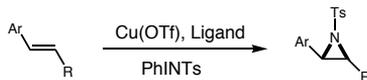
Strategies used are denoted by color  
 blue: nitrene add'n to an olefin  
 red: carbene add'n to an imine

Müller, P.; Fruit, C. *Chem. Rev.* **2003**, *103*, 2905.

### Cu-catalyzed Aziridinations: Evans and Jacobsen Complementary Methods

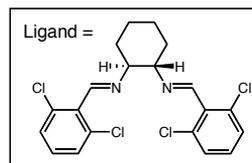
- Yields of aziridines are in the range of 25-95% using 5-10% catalyst and upto 5-fold excess of olefin over PhINTs

#### ■ Evans: Bis(oxazoline) Ligand System for Trans Olefins



olefin	ligand (R' =)	yield	ee
phenyl cinnamate	Ph	64%	97%
<i>trans</i> -methyl styrene	<i>t</i> -Bu	62%	70%
styrene	<i>t</i> -Bu	89%	63%

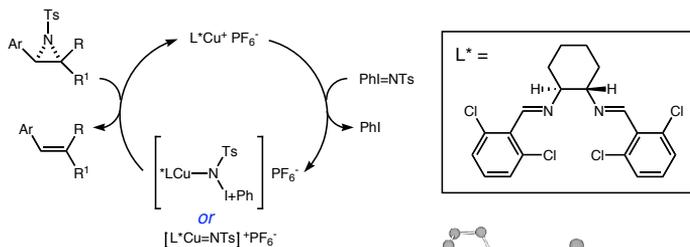
#### ■ Jacobsen: Di-imine Ligand System for Cis Olefins



olefin	yield	ee
Ar = Ph, R <sup>1</sup> = Me, R = OTBDPS	>95%	27%
<i>cis</i> -methyl styrene	79%	67%
styrene	79%	66%

Müller, P.; Fruit, C. *Chem. Rev.* **2003**, *103*, 2905.

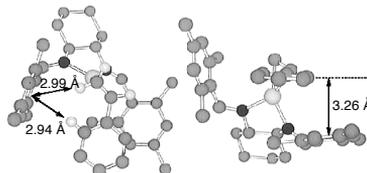
## Jacobsen's Proposed Mechanism of the (Diimine)copper-Catalyzed Aziridination



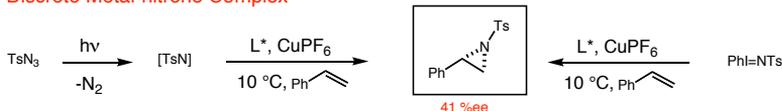
### Poor selectivity in non-aromatic alkenes

X-ray structure of  $L^*Cu$ -styrene complex shows that there are 2 non-bonded interactions

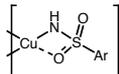
- 1) face-face interaction and
- 2) edge-face interaction of the arenes



### Discrete Metal-nitrene Complex



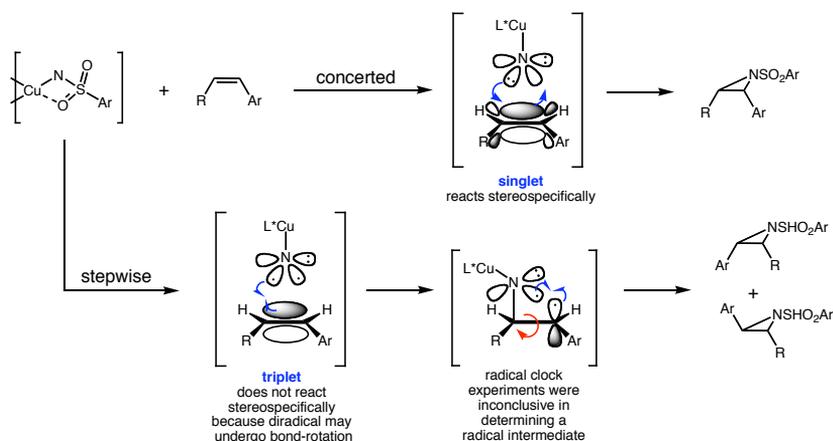
DFT studies support a copper-bound sulfonyl nitrene and additional oxygen coordination in the reactive intermediate



Li, Z.; Quan, R. W.; Jacobsen, E. N. *JACS* **1995**, *117*, 5889.  
 Quan, R. W.; Li, Z.; Jacobsen, E. N. *JACS* **1996**, *118*, 8156.

## Nitrene Transfer from in the Cu-catalyzed Asymmetric Aziridination

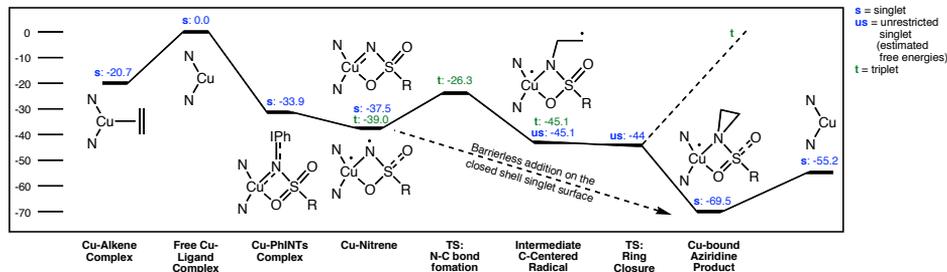
- Stereospecific aziridination may occur via a singlet metallonitrene complex and nonspecific aziridination through the triplet state metallonitrene complex



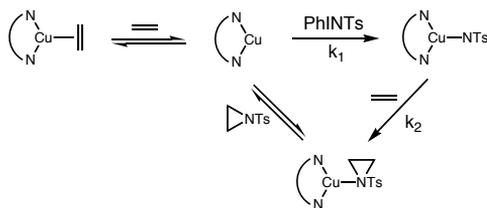
- DFT calculations by Norrby and Andersson indicate that the ground state of the metallonitrene is in the triplet state (but energetically close to that of the singlet state by 0.1 kcal mol<sup>-1</sup>)

## Norby's Mechanistic Studies of the Cu-catalyzed Azirdination

### Potential free energy surface of a model system (BSIII/298K)



### Kinetic Studies



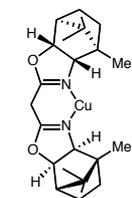
Computational studies indicate the rate-determining step to be the formation of the Cu-nitrene (0<sup>th</sup> order in alkene)

Observed 1<sup>st</sup> order reaction with initial rate dependence on alkene concentration proportional to metal concentration

Müller examined electronic substituent effects on substituted styrenes and observed a  $\rho$ -value -0.49 (vs  $\sigma^+$ ), which is in the range for concerted carbene transfer to olefins

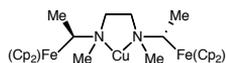
Andersson, P. G.; Norrby, P.-O. *JACS* **2000**, *122*, 8013.  
 Müller, P. *Can. J. Chem.* **1998**, *76*, 738.

## Other Ligand Systems Developed for Cu-catalyzed Asymmetric Aziridinations



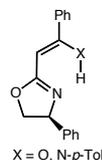
Masamune (1991)

for styrene:  
 91 %yield  
 88 %ee  
 \*not reproduced\*



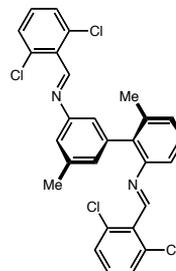
Kim (1999)

for styrene:  
 88 %yield  
 74 %ee



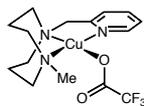
Andersson (1998)

for styrene:  
 X = O: 90% yield, 24 %ee  
 X = N-p-Tol: 100% yield, 15 %ee



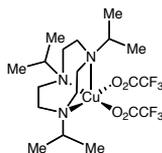
Scott (2002)

for styrene:  
 91 %yield  
 27 %ee



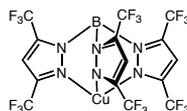
Halfen (2001)

for styrene:  
 99 %yield



Halfen (1999)

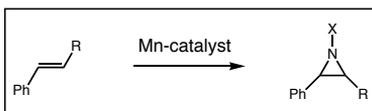
for styrene:  
 99 %yield



Dias and Lovely (2002)

for styrene:  
 99 %yield

## Manganese-Catalyzed Aziridinations

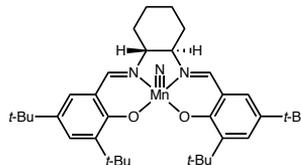


### Nitridomanganese(V) Complexes

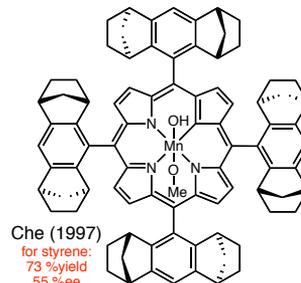
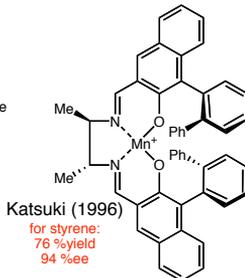
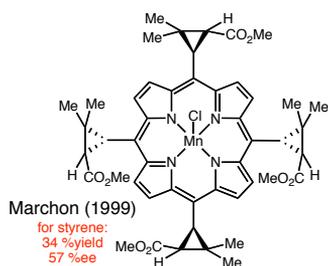
Activation (by  $\text{BF}_3$ ,  $\text{TsCl}$ , or  $\text{TFAA}$ ) generates a manganese nitrido complex where to transfer the imido group to the olefin

Komatsu demonstrated that conjugated dienes underwent [2+1] add'n to form alkenylaziridines (no [4+1] products were observed)

Ho and Wong formed the free aziridine of styrene (36 %yield, 81 %ee) and *trans*- $\beta$ -methyl styrene (20 % yield, 91 %ee).



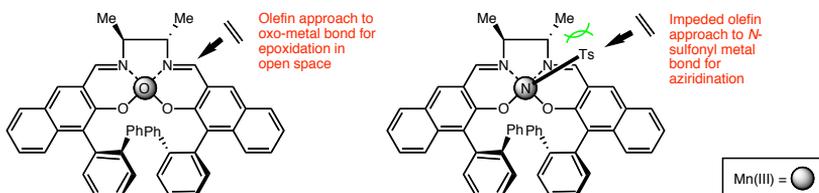
### Manganese(III) Porphyrin-based Catalysis with $\text{TsN}=\text{I}^{\text{Ph}}$



Müller, P.; Fruit, C. *Chem. Rev.* **2003**, *103*, 2905.

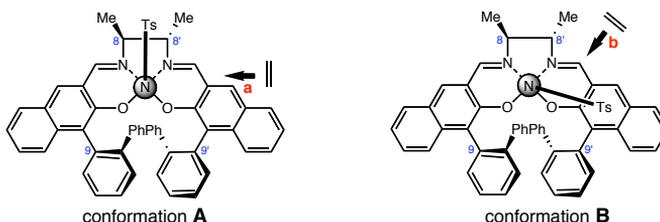
## Origins of Diastereoselectivity and Enantioselectivity in Mn-Catalyzed Aziridinations

- Yield and level of asymmetric level induction in aziridination is lower than in epoxidation



- Enantioselectivity is considered to be steric repulsion of the C8 or C9' substituent, the *N*-sulfonyl group and the olefinic substituent

Conformation **A** and **B** allow for olefin approach to maximize the  $\pi$ -orbital of the oncoming olefin and  $d\pi\text{-}\pi^*$  orbital of the nitrene metal bond



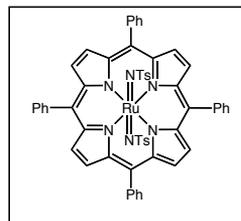
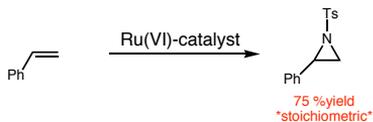
Katsuki, T.; etal. *Synlett* **1993**, 469.

## Ruthenium-Catalyzed Aziridinations

### Ruthenium(VI) Porphyrin Complex

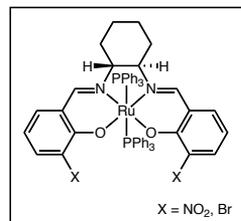
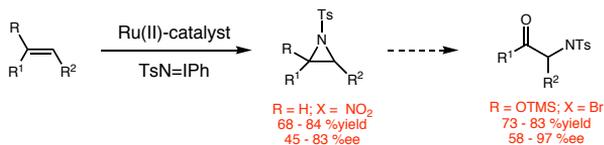
Ruthenium counterparts of Mn-porphyrin aziridinating reagents have only been isolated and characterized recently

Mechanism is assumed to be via a stepwise via a radical intermediate and thus is not stereospecific



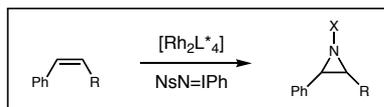
### Ruthenium(II) Diimine Complex

Limited substrate scope only for cyclic substrates and reaction is proven to be better suited to amidation than aziridination



Che, C.-M.; et al. *JACS* **1999**, *121*, 9120.  
Che, C.-M.; et al. *Chem. Commun.* **2002**, 124.

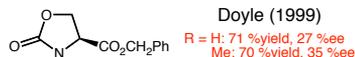
## Rhodium(II)-Catalyzed Aziridinations



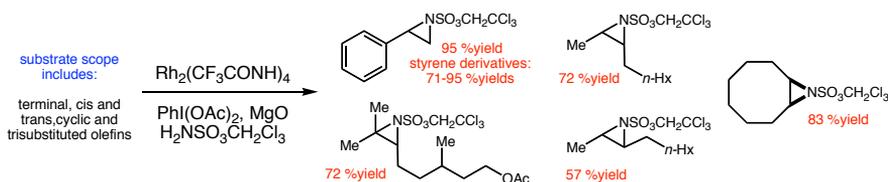
- Issues of competing C-H insertion reactions and electron-rich olefins can often give ring opened/ cycloaddition products (ie. pyrrolidines)



- Rh is less efficient at trapping nitrene than Cu, using Pirring's catalyst, TsNI=Ph gives a 55 ee% in the aziridination of styrene and TsN<sub>3</sub> gives a 17 %ee



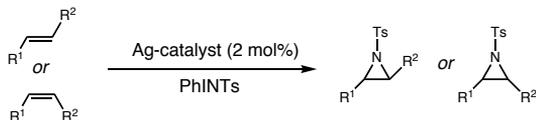
- Guthikonda and Du Bois are able to aziridinate alkyl and aryl substituted olefins using an *in situ* derived phenyliodine and trichloroethylsulfamate



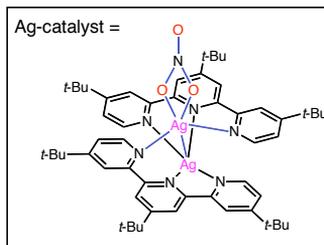
Müller, P.; Fruit, C. *Chem. Rev.* **2003**, *103*, 2905.  
Guthikonda, K.; Du Bois, J. *JACS* **2002**, *124*, 13672.

## Catalytic Disilver(I) Aziridination of Olefin

- A promising new unique di-nuclear silver catalyst



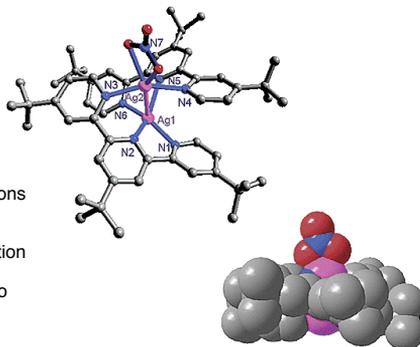
olefin	yield
styrene	91%
<i>trans</i> -methyl styrene	89%
R <sup>1</sup> = alkyl, R <sup>2</sup> = H	66 - 71%
R <sup>1</sup> , R <sup>2</sup> = Ph ( <i>trans</i> )	88%
R <sup>1</sup> , R <sup>2</sup> = Ph ( <i>cis</i> )	86%



Each of the silver ions of the dinuclear complex is a 5-coordinate and stabilized two bridging tridentate terpyridine ligands

X-ray structure of the catalyst shows two terminal positions (one weakly bound by a nitrate anion)

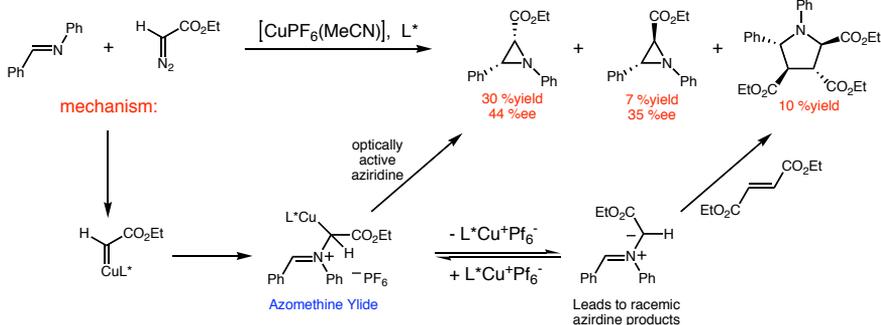
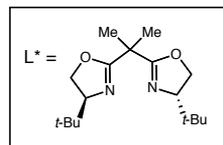
Reactivity is assumed to be from electronic communication between the silver ions (Ag-Ag distance is 2.842 Å) with an assumed transient Ag=NTs group coordinated to the active aziridinating agent



Cui, Y.; He, C. *JACS* **2003**, *125*, 16202.

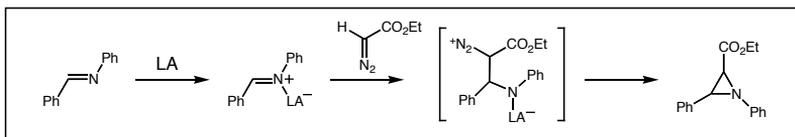
## Aziridination via Metallocarbene Addition to Imines

- Initial aziridinations with diazoacetates (with Rh(II), Mn(III), Cu(I)) were plagued by poor yields and racemic products (due to the formation of intermediary ylides)
- First enantioselective aziridination of imines was by Jacobsen (1995)
- Jørgensen (1999) has shown that tosyl aziridines can be generated using TMS-diazomethane with CuL\*

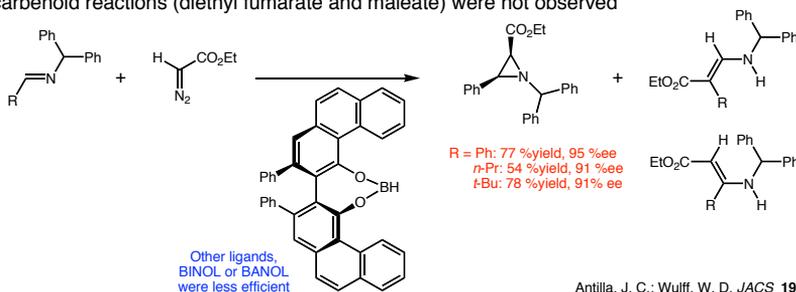


Hansen, K. B.; Finney, N. S.; Jacobsen, E. N. *ACIE* **1995**, *34*, 676.  
 Juhl, K.; Hazell, R. G.; Jørgensen, K. A. *J. Chem. Soc., Perkins Trans.* **1999**, 2293.

## Lewis-Acid Catalyzed Aziridination of Imines

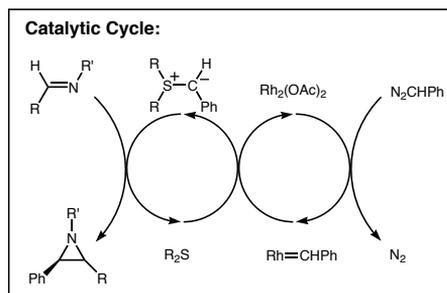
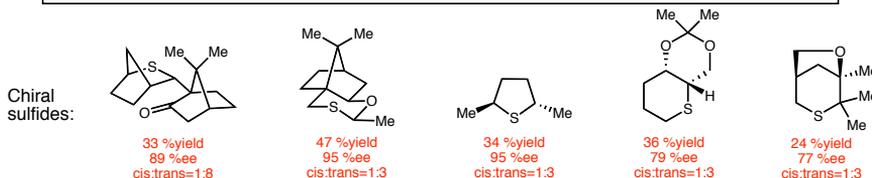
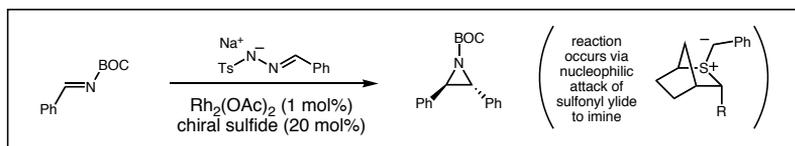


- Brookhart and Templeton (1996) used  $\text{BF}_3$ ,  $\text{AlCl}_3$ , and  $\text{TiCl}_4$  with yields of 42 - 93 % yield. A wide range of LAs have been used in aziridinations of imines
- Wulff (1999) had a breakthrough using (S)-VAPOL and  $\text{BH}_3$  to generate 'vaulted' an axially chiral boron complex. Previous attempts of testing chiral ligands with zinc triflates and various lanthanide triflates had yielded low ee's
- Enamines formation was the main side product, however, typical secondary products for carbenoid reactions (diethyl fumarate and maleate) were not observed



Antilla, J. C.; Wulff, W. D. *JACS* **1999**, *121*, 5099.  
 Antilla, J. C.; Wulff, W. D. *ACIE* **2000**, *39*, 4518.

## Aziridination of Imines via Chiral Sulfonium Ylides



- Aggarwal (1996): *in situ* generation of a carbene via diazo decomposition of a stable tosylhydrazone with  $[\text{Rh}_2(\text{OAc})_4]$  or  $[\text{Cu}(\text{acac})_2]$ , its association to a chiral sulfide, and transfer to an imine

- A range of imine N-substitution (tosyl, SES, Dpp, and carbamoyl) are amenable to this procedure

Aggarwal, V. K. *Synlett* **1998**, 329.

Aggarwal, A. K.; Thompson, A.; Jones, R. V. H.; Standen, M. C. H. *JOC* **1996**, *61*, 8368.

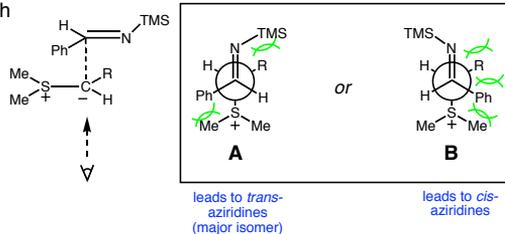
## Origin of Diastereoselectivity and Enantioselectivity in Sulfonium Ylide Aziridination

- Energy difference between the *syn*- and *anti*- betaines is under kinetic control  
Calculations suggest that the sulfur ylide reacts in an "end-on" approach to the *N*-T's imine to give rise to transition states **A** and **B**.

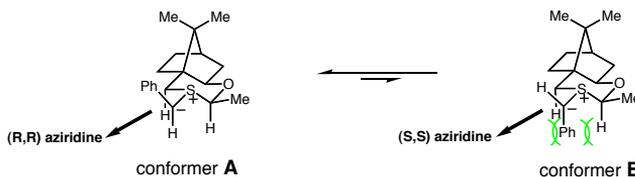
- Observed diastereoselectivity varies with *N*-substitution:

Larger bulky groups on *N* leads to reduced *trans* selectivity (sulfonyl or phoshylnyl groups)

Smaller groups on *N* leads to increased *trans* selectivity (alkoxycarbonyl groups)



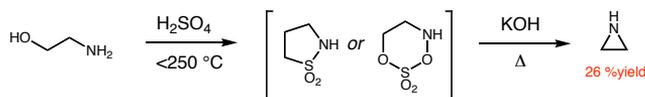
- Conformer **A** reacts is favored over conformer **B** which has unfavorable 1,3-diaxial interactions (attack opposite the methyl group) and electronic (a combination of the anomeric effect and Ciepak effect) control.



Aggarwal, V. K., et al. *J. Chem. Soc. Perkin Trans. 1*, 2001, 1635.

## Conclusion and Future Directions

- From the first synthesis of an aziridine by Gabriel (1888) was a two step process from an amino alcohol



- Single step methods for accessing aziridines from prochiral substrates has been through metal catalyzed aziridinations that utilize two general strategies: *nitrene addition into olefins* or *carbene addition into imines*
- Developed catalytic systems (Cu-, Rh-, Mn-, Rh-, Ru-based catalysts) have attained good enantioselectivities but have not been readily translatable to other substrates

Movement is towards newer catalyst systems that have higher enantioselectivities (Agarwal and Wulff) an higher reactivity (Du Bois and He) that show better substrate scope.