Catalytic Enantioselective Aziridinations

MacMillan Group Meeting
April 14, 2004
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Key References:

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 ~20 kJ mol^{-1} for N-inversion
    - 2-methylaziridines is ~70 kJ mol^{-1}
    - 1-chloro-2 methyl aziridine (N-substitution with an EWG) is 112 kJ mol^{-1}

■ "Epoxides' ugly cousin?"
  - Epoxides and aziridines are both three-membered heterocycles with comparable Bäeyer strain (111kJ 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.

Biologically Active Aziridines

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

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

Mitosanes
(extracted from *steptomyces verticillatus*)
Demonstrate anti-tumor and antibiotic activity that act by DNA alkylation

FR and FK Compounds
Demonstrate anti-tumor activity by DNA cleavage

Azomycin
(extracted from *steptomyces griesaeosorus*)
Demonstrate anti-tumor activity that act by DNA crosslinking

PBI
Demonstrate anti-tumor activity by single strand DNA cleavage


General Reactivities of Chiral Aziridines

- Stereoselective Ring Openings
  - Hydrogenolysis: Pd(OH)$_2$, H$_2$
  - Reductive ring opening: SnI$_2$
  - 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: β-lactams from aziridinocarboxamide
  - 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
  - C-2 substitution: often in cases where R = Ar or under chelation control

- Chiral Ligands
Summary of Methods Used to Access Asymmetric Aziridines


Strategies for Accessing Asymmetric Aziridines

- **Nitrene Transfer to Olefins**

  \[
  \begin{align*}
  &\text{R}^1\text{R}^2\text{R}^3 & \text{ML}_{n}^{+} & \xrightarrow{X \rightarrow N^{+}} & \text{X} \\
  &\text{R}^1\text{R}^2\text{R}^3 & \text{R}^1\text{R}^2\text{R}^3 & & \\
  &\text{M} = \text{Cu, Rh, Cu, Mn, Ru} \\
  \end{align*}
  \]

- **Carbene Addition to Imines**

  Metallocarbene Addition
  
  Lewis Acid Catalyzed Aziridination
  
  Chiral Sulfonium Ylides

Progress Towards Enantioselective Aziridination

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<td>Breslow and Gellman</td>
<td>Mansuy</td>
<td>Evans</td>
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<tr>
<td>Cu(I)/ TsN₃</td>
<td>Cu powder</td>
<td>Fe or Mn porphyrins</td>
<td>Catalytic Fe or Mn</td>
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<td>ethyl diazocacetate</td>
<td>or [Pb₂(OAc)₄] using TsN⁺</td>
<td>porphyrins</td>
<td>[bis(oxazoline)]Cu</td>
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<td>Catalytic Disilver(I)</td>
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<td>Rh(I) Complex</td>
<td>[bis(oxazoline)]Cu complex and diazocacetate</td>
<td>LA-VAPOL complex with diazocacetate</td>
<td>Ru(VI) and Ru(II)</td>
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<td>Dimine-Cu complex</td>
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<td>Sulfonium Ylide Addn</td>
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Strategies used are denoted by color:
- Blue: Michael addition to an olefin
- Red: Carbene addition to an imine


Cu-catalyzed Aziridinations: Evans and Jacobsen Complementary Methods

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

- Evans: Bis(oxazoline) Ligand System for Trans Olefins

- Jacobsen: D-i-mine Ligand System for Cis Olefins

**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 sulfonyle nitrene and additional oxygen coordination in the reactive intermediate

Quan, R. W.; Li, Z.; Jacobsen, E. N. JACS, 1996, 118, 8156.

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

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

- DFT calculations by Norrby and Andersson indicate that the ground state of the metalonitrene is in the triplet state (but energetically close to that of the singlet state by 0.1 kcal mol\(^{-1}\))

**Norrby’s Mechanistic Studies of the Cu-catalyzed Aziridination**

- **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-nilirenene (0th order in alkene)

  Observed 1st order reaction with 1st initial rate dependence on alkene concentration proportional to metal concentration

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


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

- **Masamune (1991)**
  - for styrene: 91 % yield
  - “not reproducible”

- **Kim (1999)**
  - for styrene: 88 % yield

- **Andersson (1998)**
  - for styrene, X = O, N-MeTol: 34 % yield
  - X = N-MeTol, 100 % yield

- **Scott (2002)**
  - for styrene: 91 % yield
  - 27 % yield

- **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 BF₃, TsCl, or TFAB) generates a manganese nitrido complex where to transfer the imido group to the olefin.
  Komatsu demonstrated that conjugated dienes underwent [2+1] addition to form alkenylaziridines (no [4+1] products were observed).
  Ho and Wong formed the free aziridine of styrene (36% yield, 81%ee) and trans-β-methyl styrene (20% yield, 91%ee).

- **Manganese(III) Porphyrin-based Catalysis with TsN=IPh**
  [Diagram of catalysts: Marchon (1999), Katsuki (1996), Che (1997)]

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

- Yield and level of asymmetric level induction in aziridination is lower than in epoxidation.
  [Diagram of epoxidation and aziridination]

- 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 π-orbital of the oncoming olefin and dx-py orbital of the nitrene metal bond.

**References:**
**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) Dimine Complex**
  Limited substrate scope only for cyclic substrates and reaction is proven to be better suited to amidation than aziridination.

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**Rhodium(II)-Catalyzed Aziridinations**

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

- **Rh is less efficient at trapping nitrene than Cu, using Pirrung's catalyst, TsN=Ph gives a 55 ee% in the aziridination of styrene and TsN₂ gives a 17 % ee**

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

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Cha, C.-M.; et al. JACS 1999, 121, 9120.

Catalytic Disilver(I) Aziridination of Olefin

- A promising new unique di-nuclear silver catalyst

\[
\begin{align*}
\text{R}^1 & \quad \text{R}^2 \\
\text{Ph} & \quad \text{NTs} \\
\text{Ag-catalyst (2 mol\%)}
\end{align*}
\]

<table>
<thead>
<tr>
<th>olefin</th>
<th>yield</th>
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<tr>
<td>styrene</td>
<td>91%</td>
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<tr>
<td>trans-methyl styrene</td>
<td>95%</td>
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<tr>
<td>R^1 = alkyl, R^2 = H</td>
<td>66 - 71%</td>
</tr>
<tr>
<td>R^1, R^2 = Ph (trans)</td>
<td>88%</td>
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<tr>
<td>R^1, R^2 = Ph (cis)</td>
<td>86%</td>
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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 enantioselctive aziridination of imines was by Jacobsen (1995)

- Jørgensen (1999) has shown that tosyl aziridines can be generated using TMS-diazomethane with CuL^*

\[
\begin{align*}
\text{PhN} & \quad + \quad \text{HCOEt} \\
\text{L}^* \quad \text{CuPhF}_2(\text{MeCN})_2 \quad \text{Ph} \\
\text{mechanism:}
\end{align*}
\]

30 %yield (44 %ee) + 7 %yield (36 %ee)

Optically active aziridines

Azomethine Ylide

\[
\begin{align*}
\text{RCOEt} & \quad \text{L}^* \quad \text{CuPhF}_2(\text{MeCN})_2 \\
\text{L}^* \quad \text{CuPhF}_2(\text{MeCN})_2 \\
\text{Ph} & \quad \text{Ph}
\end{align*}
\]

Leads to racemic aziridine products

**Lewis-Acid Catalyzed Aziridination of Imines**

- Brookhart and Templeton (1996) used BF₃, AlCl₃, and TiCl₄ with yields of 42 - 93 % yield. A wide range of LAHs have been used in aziridinations of imines.
- Wulff (1999) had a breakthrough using (S)-VAPOL and BH₃ to generated '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 carbeneoid reactions (diethyl fumarate and maleate) were not observed.

**Aziridination of Imines via Chiral Sulfonium Ylides**

- Aggarwal (1996): *in situ* generation of a carbene via diazo decomposition of a stable tosylhydrazone with [Rh₂(OAc)]₄ or [Cu(acac)]₄. 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.

**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-Ts 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 phosphonyl groups).
  - Smaller groups on N leads to increased trans selectivity (alkoxy carbonyl groups).

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

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**Conclusion and Future Directions**

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

  \[
  \text{H}_2\text{SO}_4 \xrightarrow{\text{<250 °C}} \text{N} = \text{C} \xrightarrow{\text{KOH}} \text{N} = \text{C} \text{O} \]

- 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-, 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 (Aggarwal and Wulff) an higher reactivity (Du Bois and He) that show better substrate scope.