

# HONORS ORGANIC CHEMISTRY LAB

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Spring Semester 2014

Thursday 2:00 – 4:50

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# **Significance of Oxazolidinone**

Elliana and Kelsey

# Significance of Oxazolidinone

- Chiral Auxiliaries<sup>2</sup>
- Ligands for Metal Catalysts<sup>2</sup>
- Protecting Groups<sup>2</sup>
- Pharmaceutical Agents

# Pharmaceutical Agents

- Predominantly Antibacterial
- Bacterial Resistance to Antibiotics is Escalating<sup>1</sup>
  - Gram-positive bacteria: MRSA, Streptococci, Enterococci, MDRTB
  - Only rare instances of developed resistances have been reported
- Inhibition of Protein Synthesis<sup>1</sup>
  - Binds at P site at ribosomal 50S subunit
  - Prevents formation of 70S-initiation complex, therefore blocking translation

# Achieving Optimal Synthesis

- Areas for improved understanding/efficiency:
  1. What is the best way to get from amino alcohol to aziridine?
  2. Are regiochemistry and stereochemistry consistent and controllable?
  3. What various substituents will help or hinder the formation of an oxirane?

# References

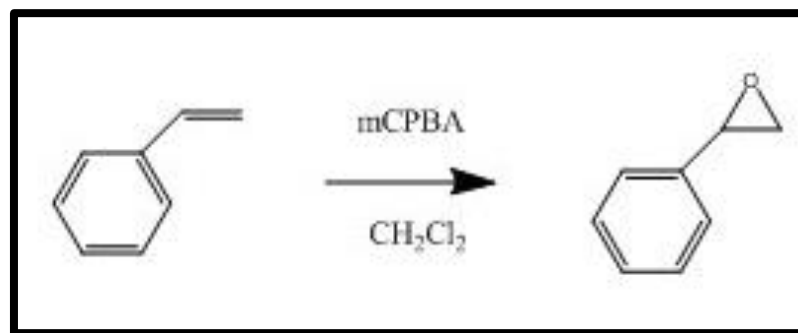
- 1- Neha, Pandit, Rajeev Singla, and Birenda Shrivastava. "Current Updates on Oxazolidinone and Its Significance." Current Updates on Oxazolidinone and Its Significance.
- 2- Wallace, Justin, Deborah Lieberman, Mathew Hancock, and Allan Pinhas. "Conversion of an Aziridine to an Oxazolidinone Using a Salt and Carbon Dioxide in Water." *Journal of Chemical Education*.

# **Overall Mechanism/ Reaction Scheme**

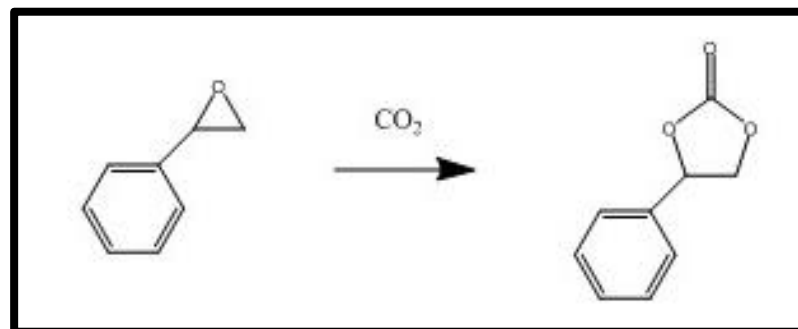
Catherine and Steven



# Alkene $\rightarrow$ Oxirane

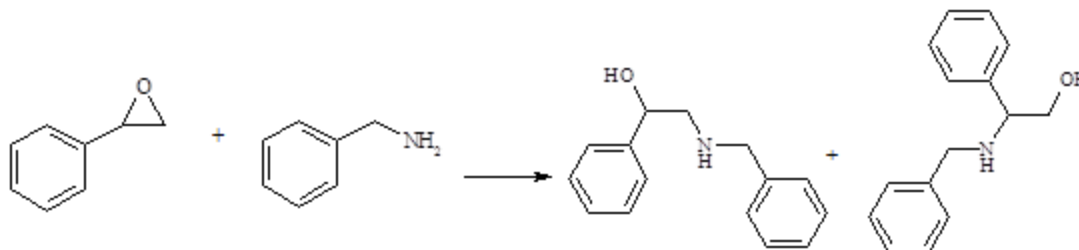


# Oxirane $\rightarrow$ Carbonate



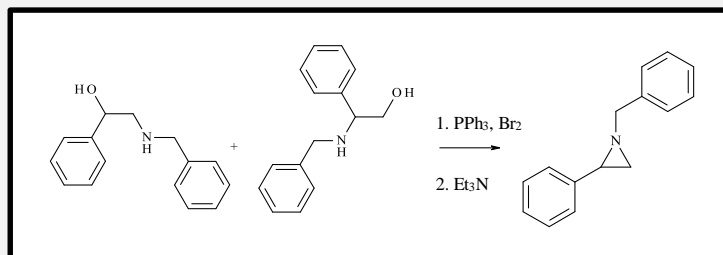
# Oxirane $\rightarrow$ Oxazolidinone

Step  
#1



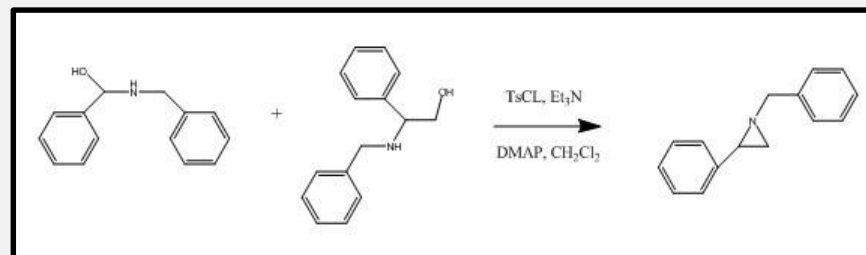
Step  
#2

Traditional

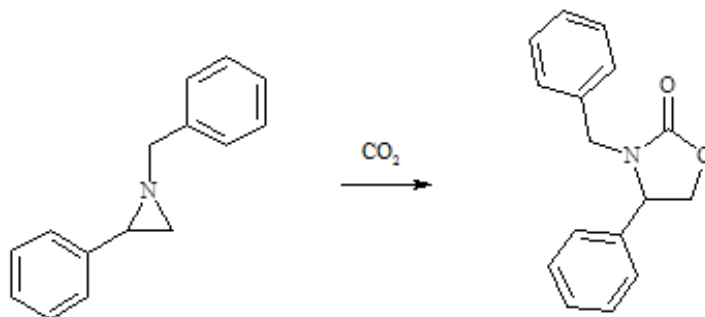


OR

Experimental



Step  
#3



# **Oxirane Synthesis with Substituted Alkenes and Subsequent Reactions**

Ayushi and Emily

# Oxirane Procedure

- Combine 1 g alkene with 20 mL dichloromethane and mCPBA (1.5 M excess)
- Reflux for 1 hour with heat and stirring
- Cool flask in ice bath
- In separatory funnel, extract the mCPBA byproduct into aqueous phase using 25 mL NaOH
  - Shake and vent vigorously
  - Extract twice
- Draw off lower organic layer over drying agent and dry using rotatory evaporator

# Amino Alcohol Procedure (Microscale )

- Combine 0.19 g triphenylphosphonium dibromide with 0.95 mL acetonitrile in round bottom flask
- Cool in ice bath for 10 minutes
- Add 0.1 g amino alcohol
- Dissolve 0.18 mL triethylamine in 0.26 mL acetonitrile and add dropwise to the reaction
- Stir reaction for 30-60 minutes
- Gravity filter off the triethylamine hydrobromide
- Dry using rotary evaporation
- Treat the residue with 5 mL of hexane
- Filter the solution to remove triphenylphosphine oxide
- Evaporate the solution to obtain Aziridine

# Cyclic Carbonate Procedure (Ball Mill)

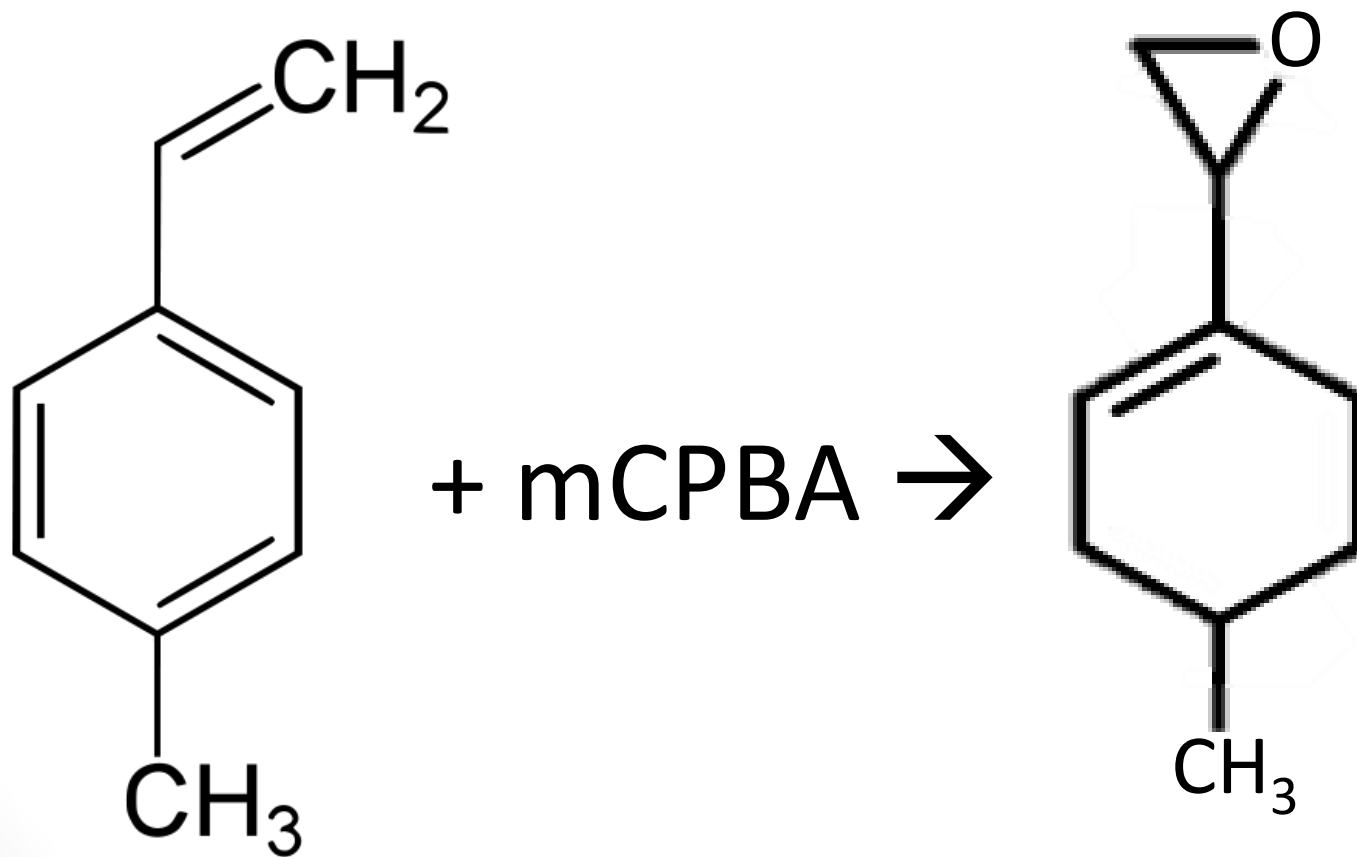
- Combine oxirane with silver pellet and dry ice in metal vial
- Tighten and react in High Speed Ball Mill for 24 hours

# **Oxirane Synthesis with Substituted Alkenes and Subsequent Reactions**

**4-methylstyrene**

Ayushi and Emily

# Oxirane Formation from 4-methylstyrene





# 2-(4-methylphenyl)oxirane

Print Date: 13 Feb 2014 16:25:39

## MS Data Review Active Chromatogram and Spectrum Plots - 2/13/2014 4:25 PM

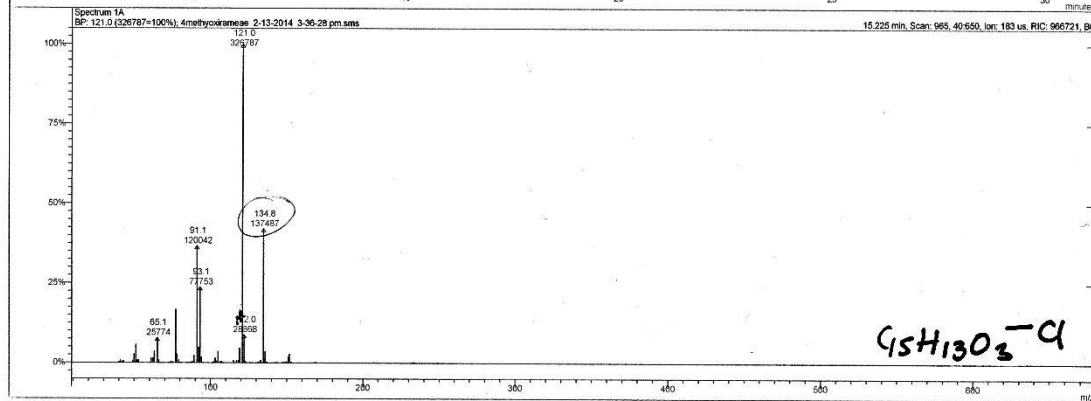
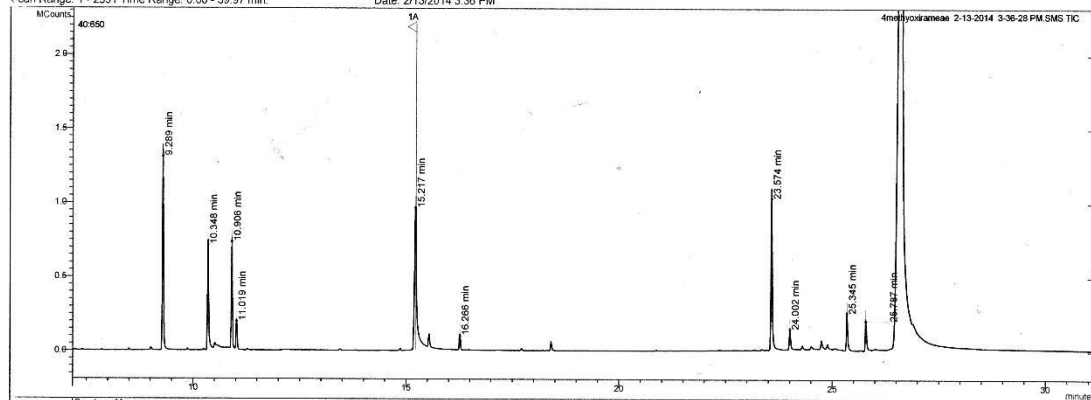
File: c:\varianw\data\4methyloxirameae 2-13-2014 3-36-28 pm.sms

Sample: 4methyloxirameae

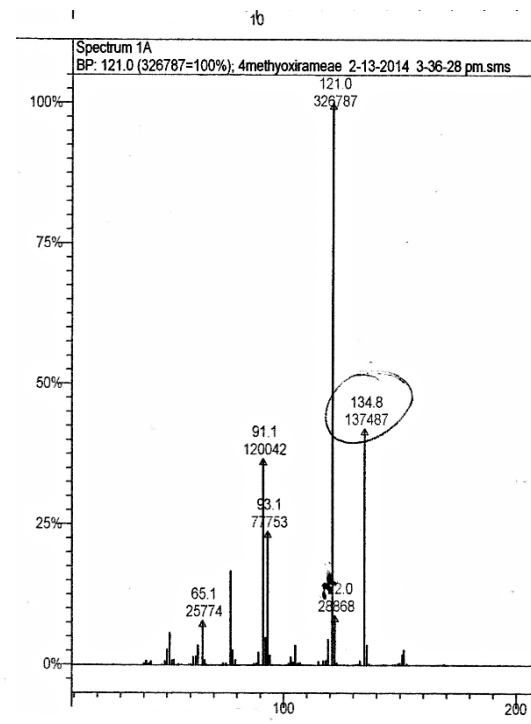
Operator: Honors

Date: 2/13/2014 3:36 PM

Scan Range: 1 - 2531 Time Range: 0.00 - 39.97 min.



134 g/mol



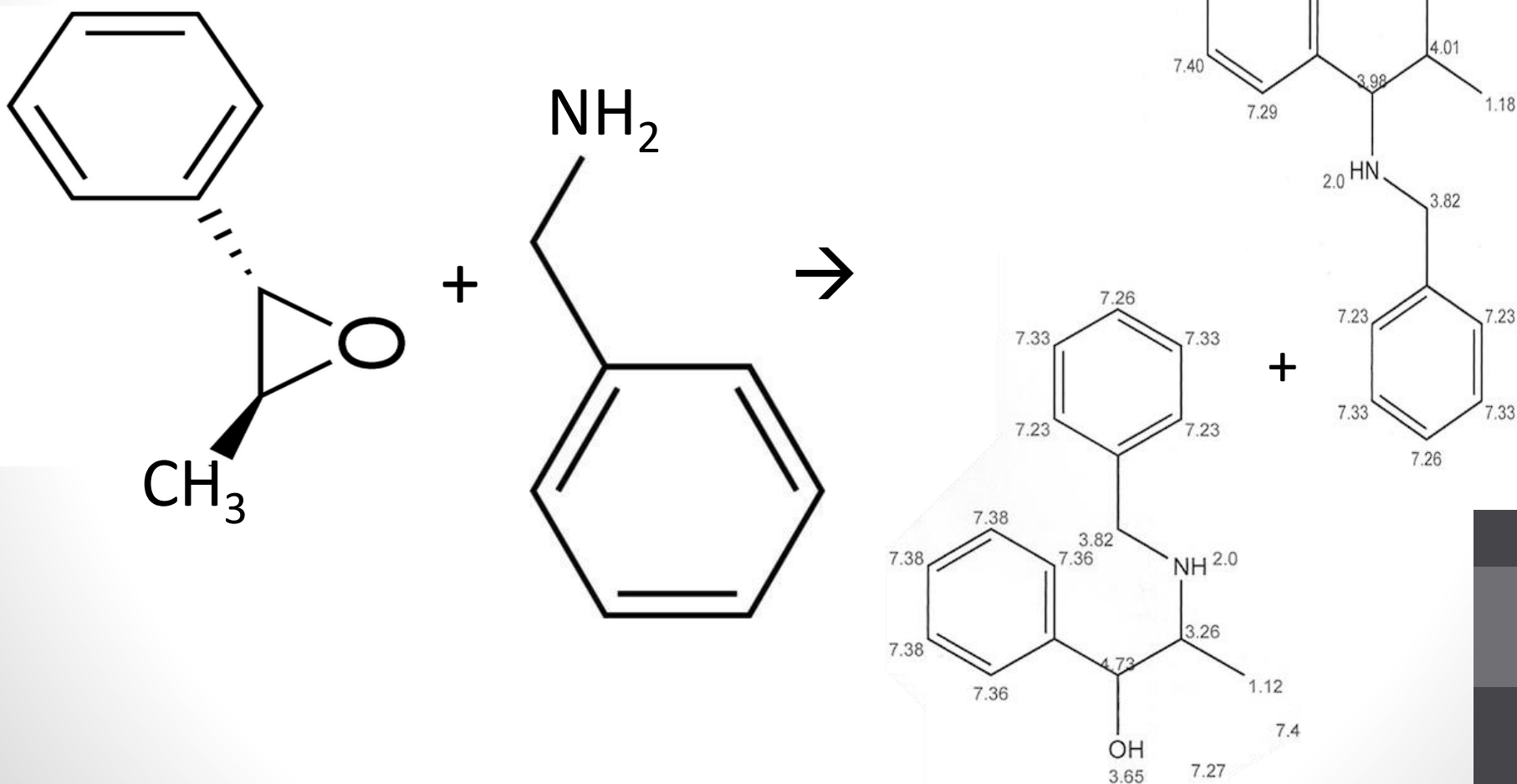
# Results

- Theoretical Yield: 2.26 g
- Actual Yield: 0.44 g
- Percent Yield: 19.6%

## Modifications to Original Procedure:

- Doubled initial starting material to 2 g
- Refluxed mixture for 24 hours (instead of 1 h)
- Stronger base (NaOH) for extraction

# Mechanism of Amino Alcohol from (1S, 2S)-(-)-1-Phenylpropylene Oxide

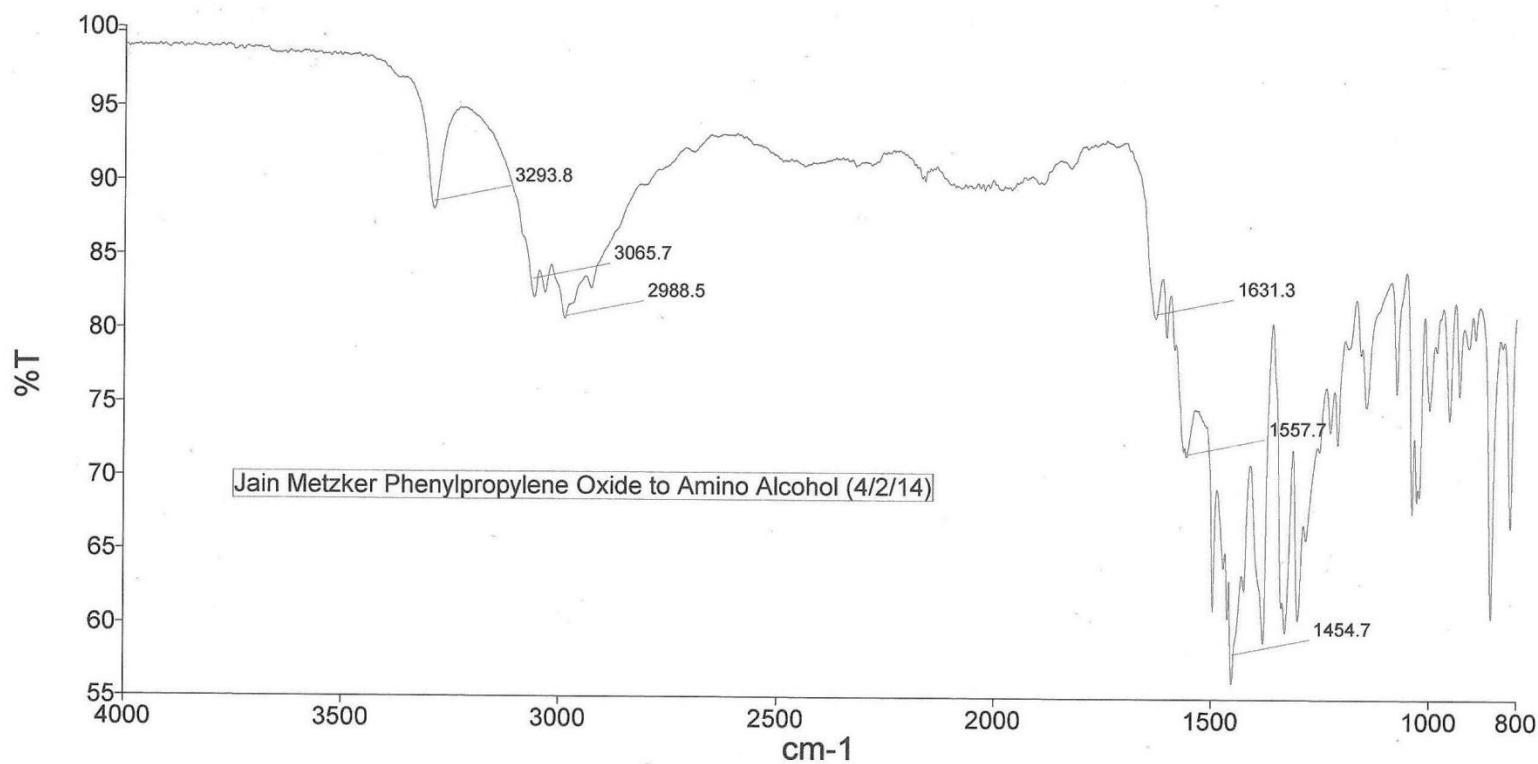


# Amino Alcohol

PerkinElmer Spectrum Express Version 1.01.00  
4/3/2014 2:58 PM

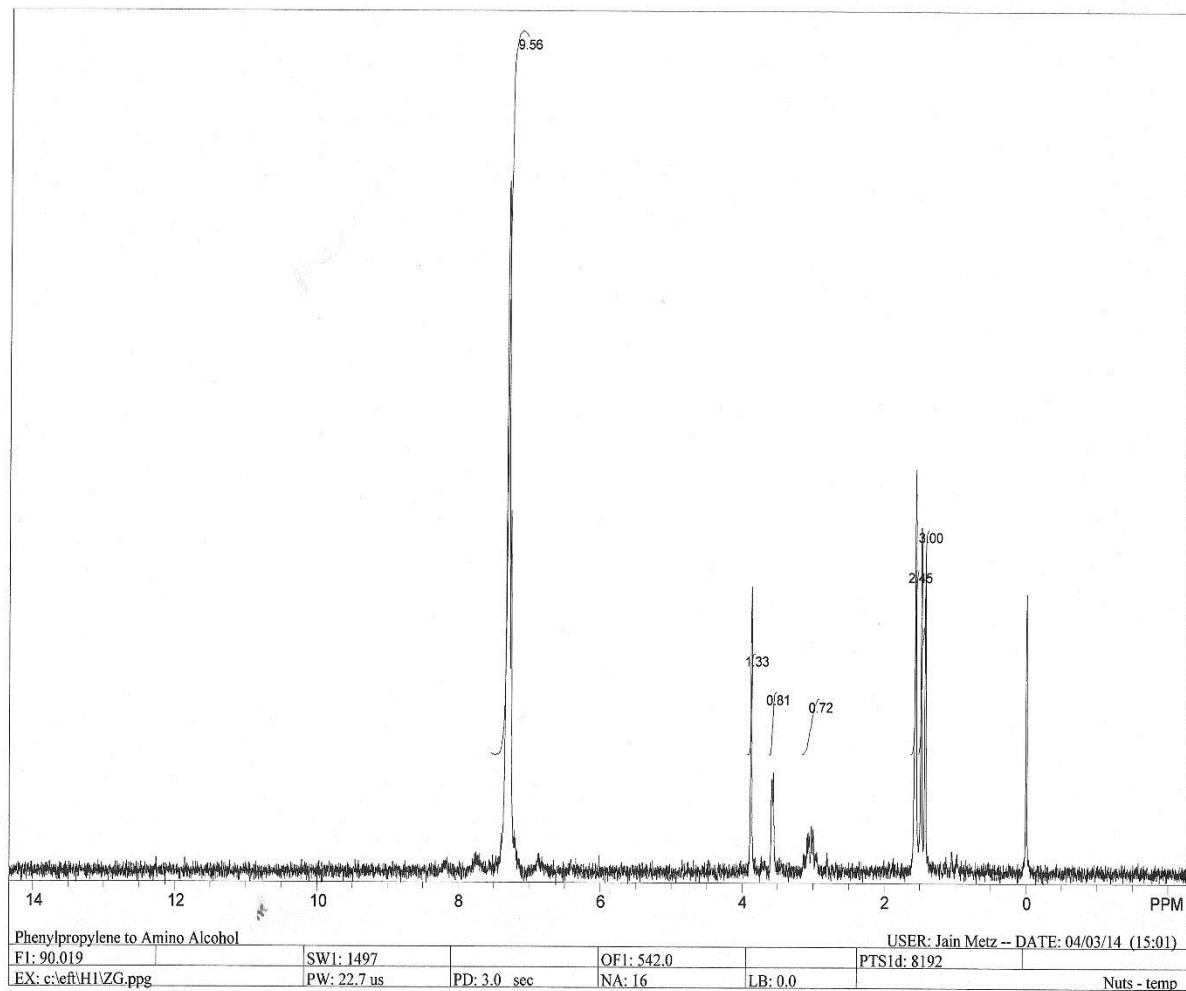
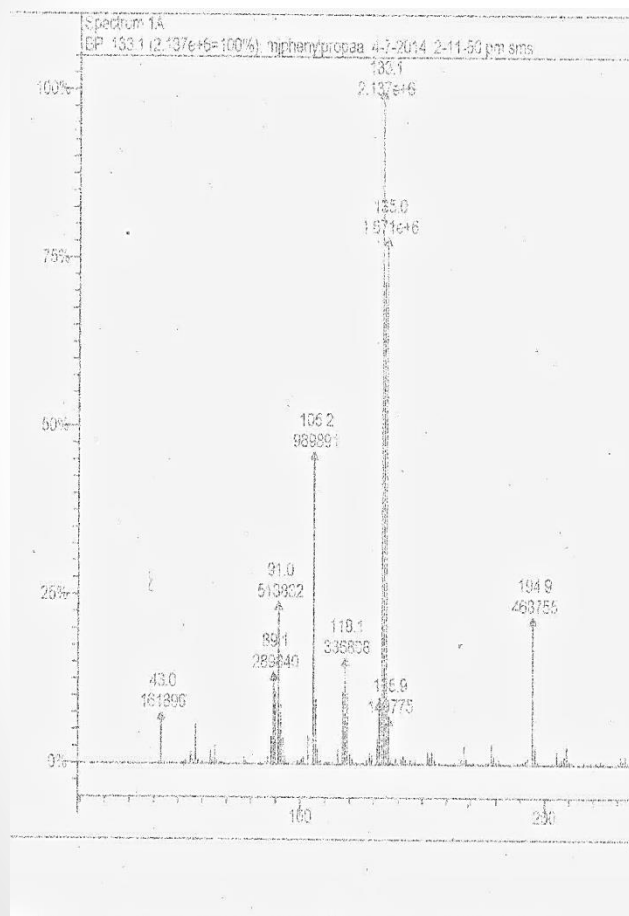
Analyst  
Date

Administrator  
Thursday, April 03, 2014 2:58 PM



Administrator 69 Sample 069 By Administrator date Thursday, April 03 2014

240 g/mol  
C<sub>16</sub>H<sub>18</sub>ON



# Results

- Theoretical Yield: 0.179 g
- Actual Yield: 0.0958 g
- Percent Yield: 53.5 %

## Modifications to Original Procedure

- Less starting material (.1 g phenylpropylene)
  - Adjusted all other reagent amounts accordingly

# Other Attempted Reactions

- Amino alcohol → Aziridine
  - Insignificant product obtained
- Oxirane → Cyclic Carbonate
- Combined oxirane with dry CO<sub>2</sub> in high speed ball mill
- IR did not show carbonyl group

# **Oxirane Synthesis with Substituted Alkenes and Subsequent Reactions**

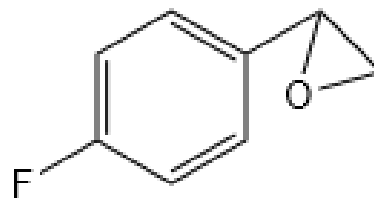
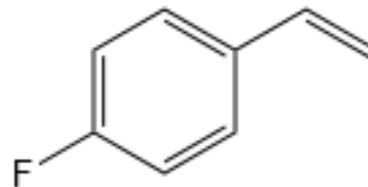
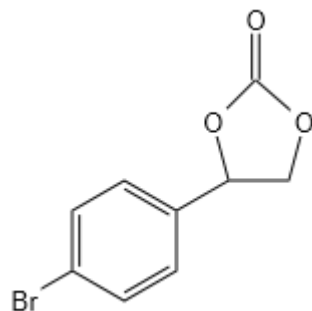
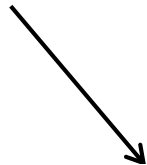
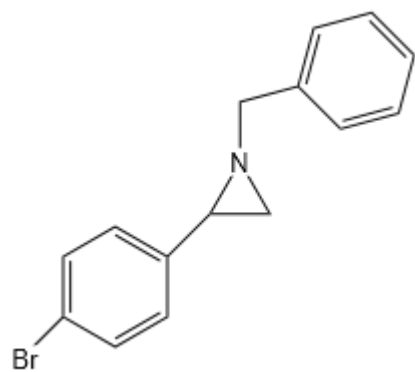
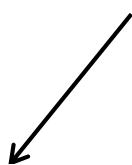
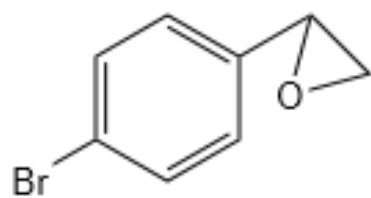
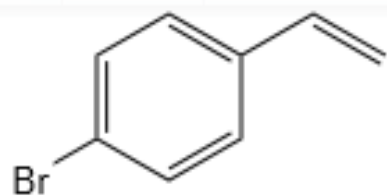
**4-bromostyrene and 4-fluorostyrene**

Bridgette and Brooke



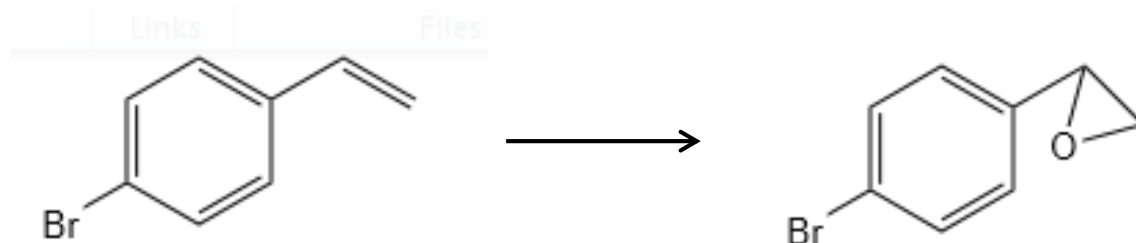
Links

Files



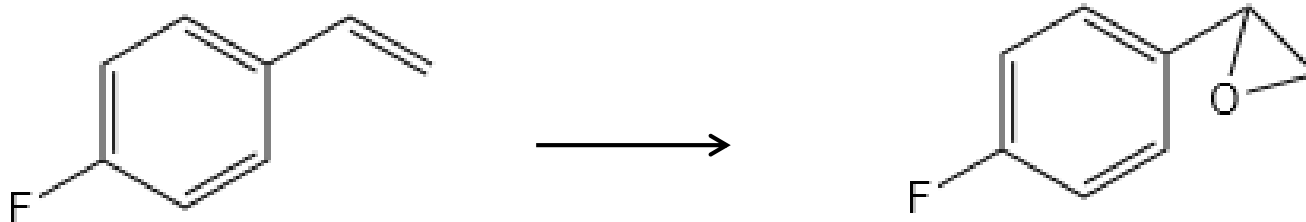
# 4-bromostyrene to 4-bromostyrene oxide

- First attempt- Followed “Generic Procedure for Oxirane Synthesis from Alkenes”
  - MS showed oxirane, but traces of starting material and mCPBA present
- Second attempt – Modifications: Five times more starting material, performed five additional extractions of mCPBA into the aqueous phase with 0.1 M NaOH solution and shook very vigorously, didn't cool reaction mixture in ice bath or use drying agent.
  - MS showed a pure oxirane product with the molecular of 199 g/mol



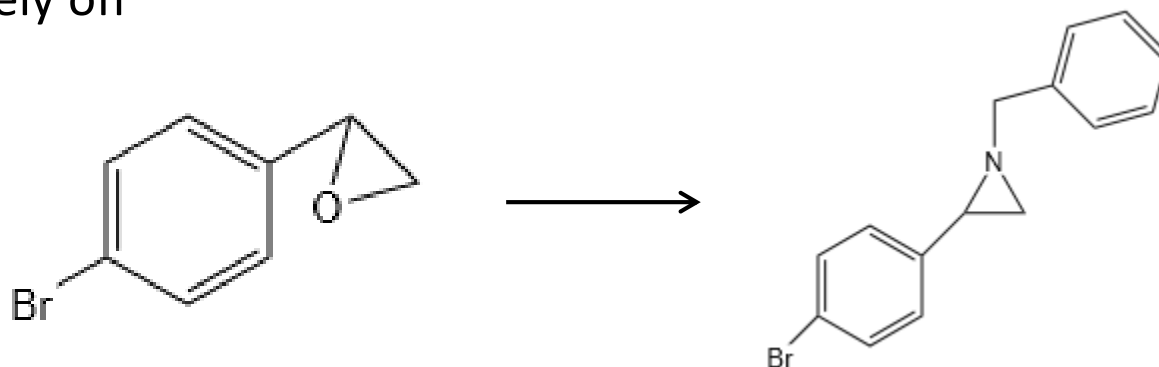
# 4-fluorostyrene to 4-fluorostyrene oxide

- First and only attempt – followed our modified procedure with the additional extractions of mCPBA
  - MS showed mostly starting material



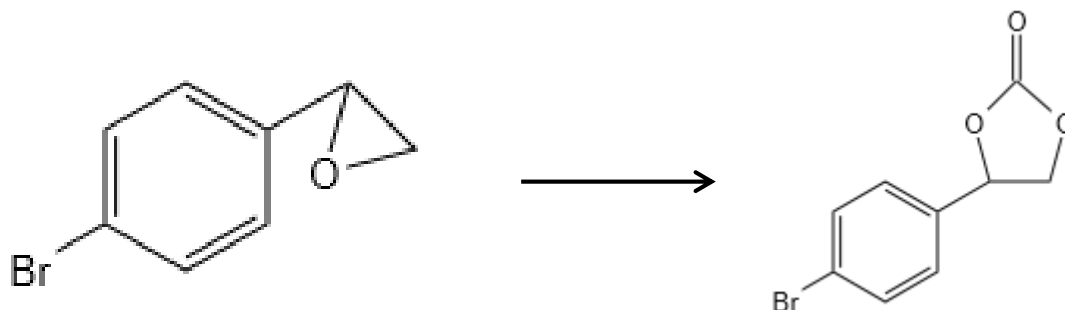
# 4-bromostyrene oxide to aziridine

- First attempt – started with 0.2 g of 4-bromostyrene oxide and followed “Organometallics” Paper for Aziridine synthesis
  - Unsuccessful – molecular weight of desired aziridine compound was extremely off
- Second attempt- started with 1.0 g of new 4-bromostyrene oxide material that was more pure and followed “Organometallics” Paper for Aziridine synthesis
  - Unsuccessful – molecular weight of desired aziridine compound was extremely off



# 4-bromostyrene oxide to cyclic carbonate compound

- First attempt – Used first oxirane and dry ice CO<sub>2</sub> in ball mill for approximately 24 hours
  - IR did not show carbonyl group
- Second attempt – Used the second oxirane (more pure) and dry ice CO<sub>2</sub> in ball mill for approximately 24 hours
  - IR did not show carbonyl group

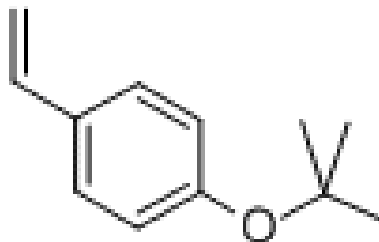


# Oxirane Synthesis with Substituted Alkenes and Subsequent Reactions

**4-*tert*-butoxystyrene**

Elliana and Kelsey

# Assessment of Starting Material



Compound	4- <i>tert</i> -Butoxystyrene
Molecular Weight	176.25 g/mol
Melting Point	-38 °C
Boiling Point	72-73 °C 0.1 mm Hg
Density	0.936 g/mL at 25 °C

## Hypothesis:

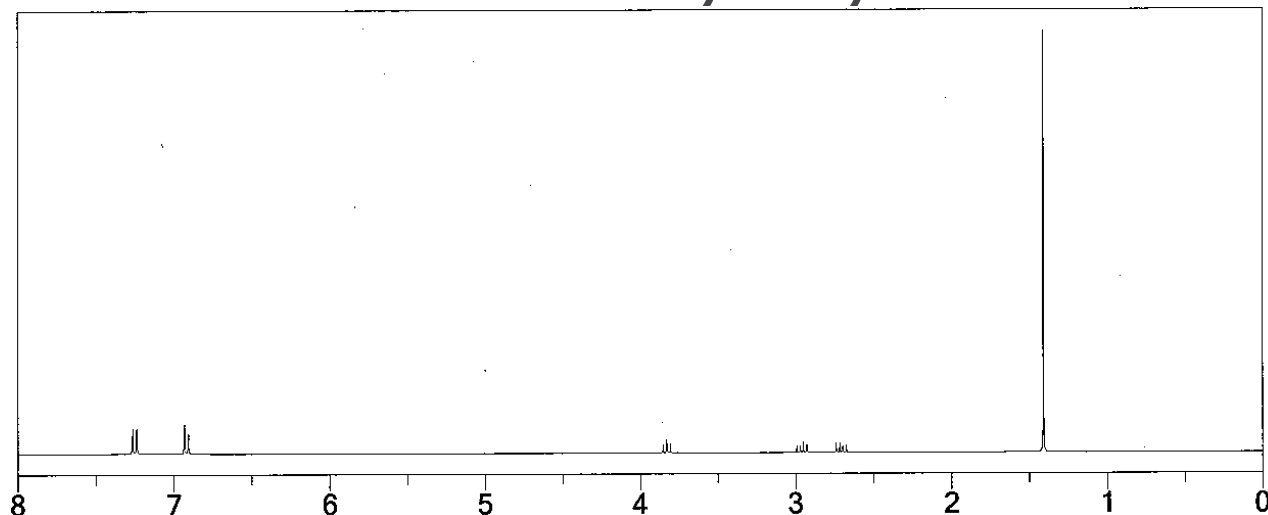
- Due to the electron donating effect of the *tert*-butoxy substituent, it will be possible to synthesize 4-*tert*-butoxystyrene oxide from 4-*tert*-butoxystyrene.
- As such, it will be possible to synthesize aziridine and oxazolidinone from the resulting oxirane product.

# Synthesis of Oxirane

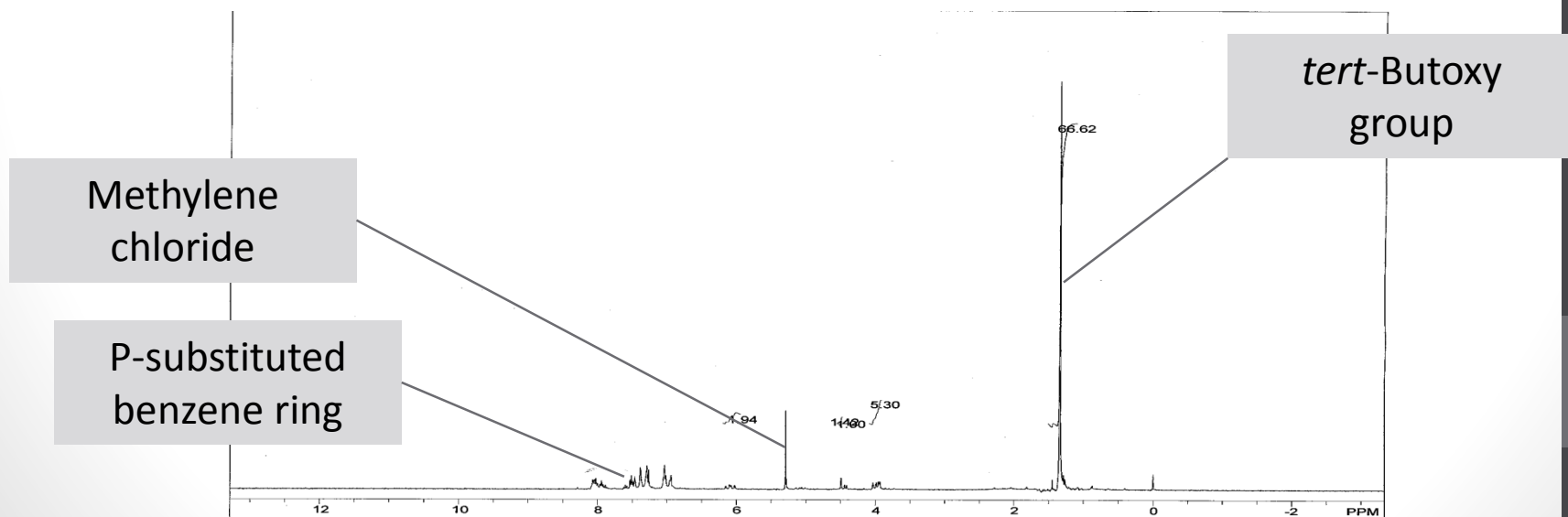
- **First Attempt:** Starting Material Present
  - GCMS was inconclusive, contained no M peak
  - NMR confirmation of 4-*tert*-Butoxystyrene
- **Second Attempt:** Marginal Success
  - Modification to Procedure: reflux for extra hour
  - GCMS inconclusive; no yields obtained
  - NMR justifies continuation of synthesis of oxazolidinone



# NMR 4-*tert*-Butoxystyrene Oxide



Estimated NMR via ChemNMR (above)



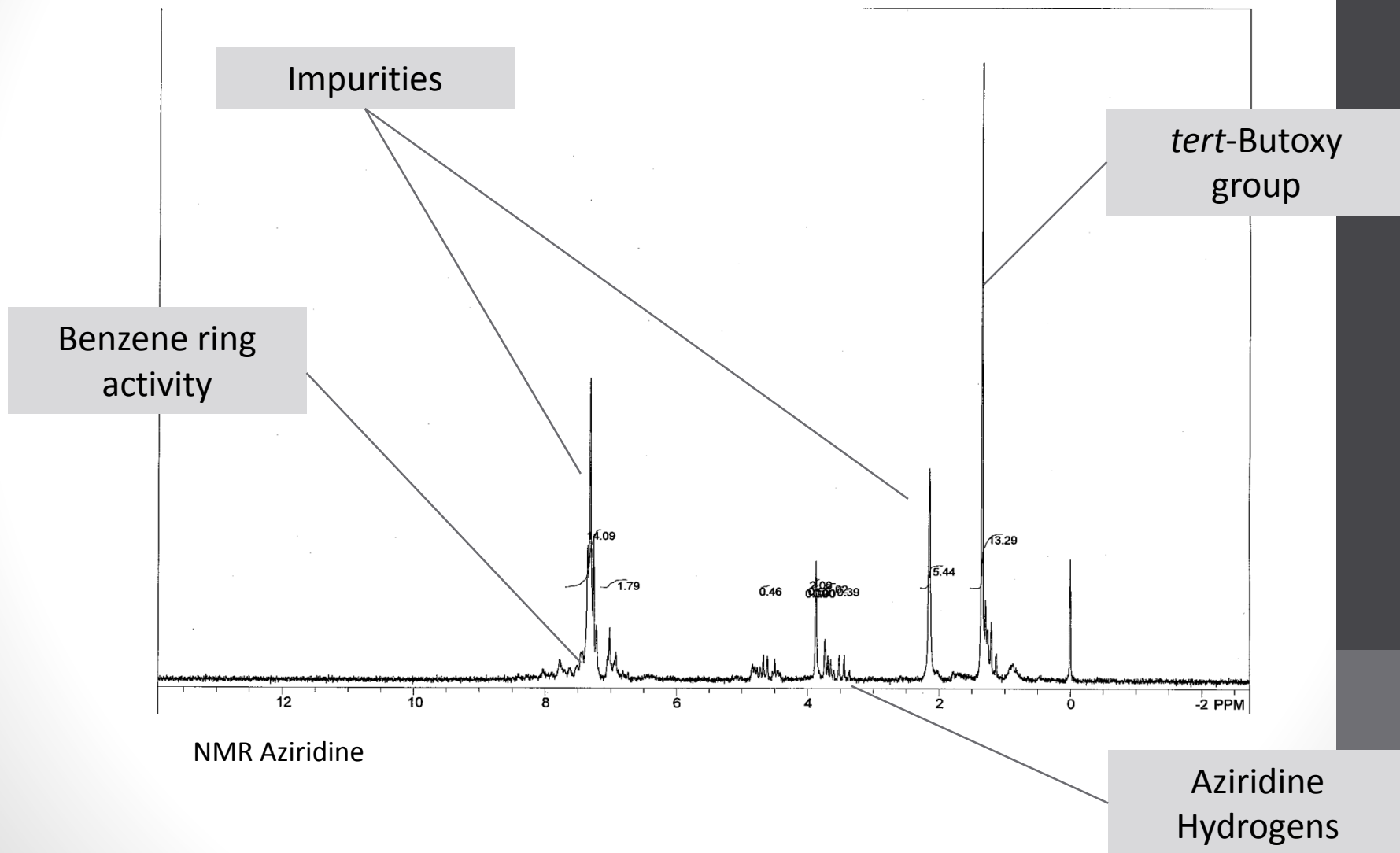
Real NMR (above)

# Synthesis of Aziridine

- Notable Observations:
  - Product was insoluble in hexane
    - Ether substituted for hexane
  - Evident impurities
    - Crystals of triphenylphosphine oxide in product material; soluble in ether
  - GCMS inconclusive; no yield obtained
    - Largely due to compounding impurities
    - No solvent found to remove impurities
- NMR provides some justification for the continuation of synthesis of oxazolidinone

# NMR Aziridine

from 4-*t*Butoxystyrene Oxide



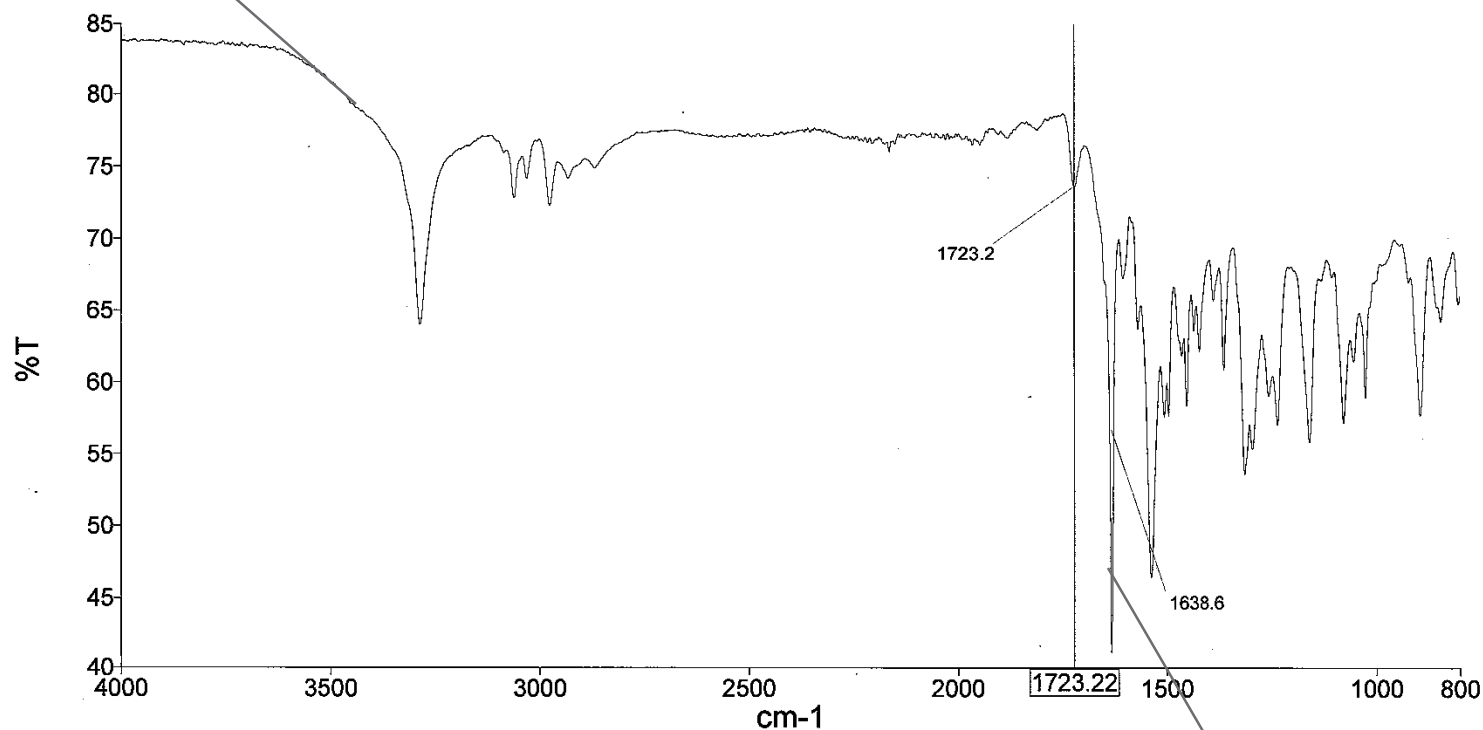
# Synthesis of Oxazolidinone

- Inconclusive evidence of product
  - Carbonyl peak observed
  - GCMS inconclusive; no M peak observed
- Reasoning
  - Accumulation of impurities confounds spectral data

# IR of Oxazolidinone

from 4-*t*Butoxystyrene Oxide

N-H stretch:  
3500-3100



IR of product Oxazolidinone (above)

C=O for Amide:  
1690-1640

# Synthesis of Cyclic Carbonate

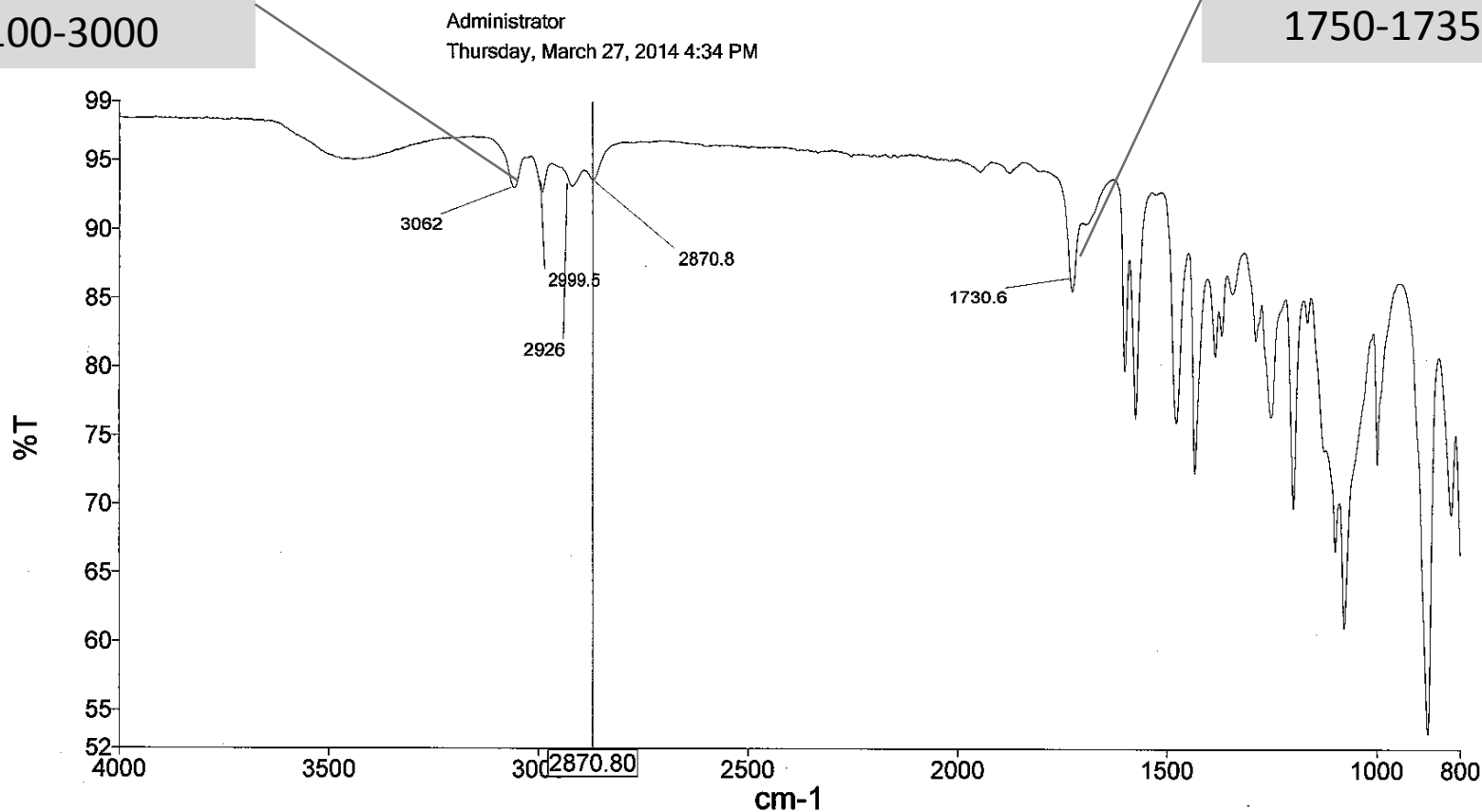
- Synthesis with 4-*tert*-butoxystyrene oxide
  - No definitive evidence of carbonyl peak
  - GCMS data inconclusive; compounding impurities
  - No conclusive evidence that cyclic carbonate may be synthesized from this oxirane
- Synthesis with 3-chlorostyrene oxide
  - Definitive carbonyl peak observed
  - Conclusive evidence that cyclic carbonate may be synthesized from this oxirane

# IR of Cyclic Carbonate

from 4-*t*Butoxystyrene Oxide

C=C-H for Alkene:  
3100-3000

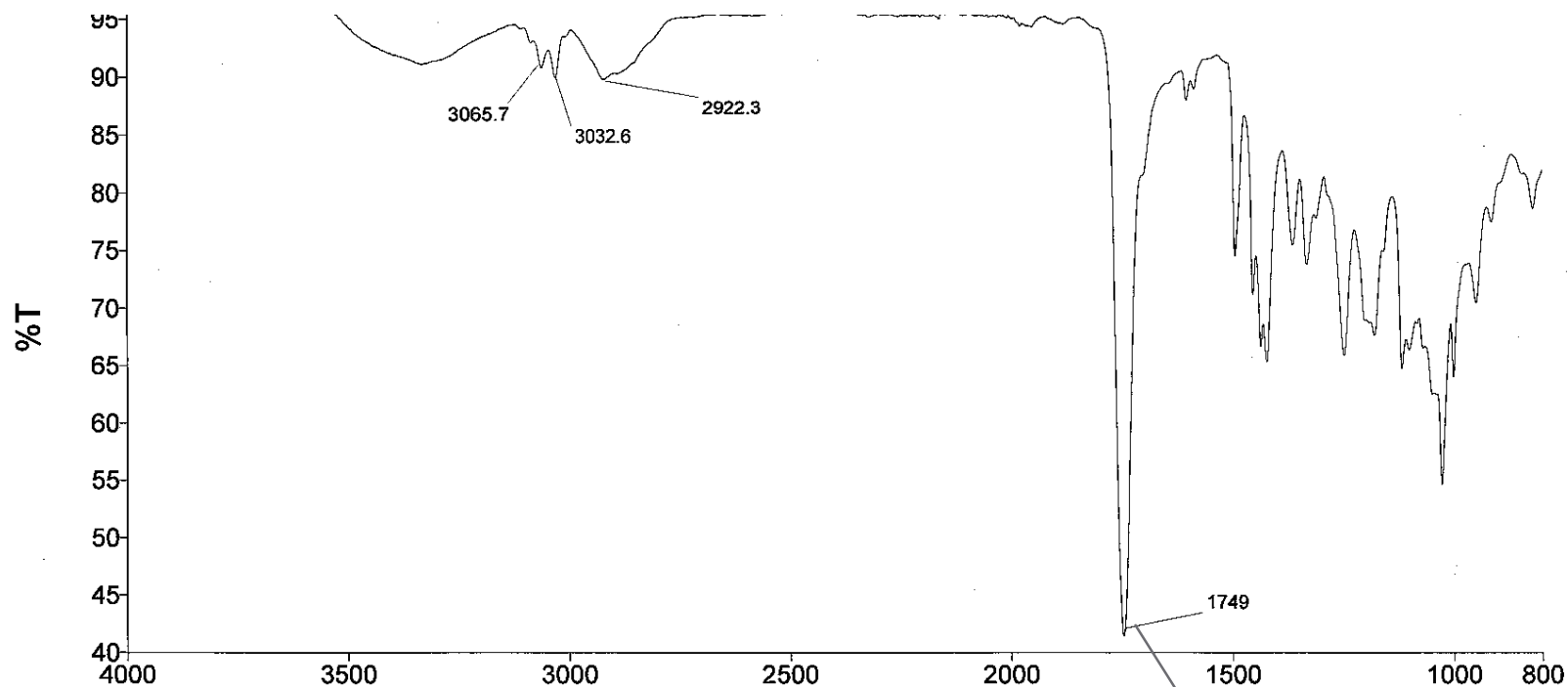
C=O for Ester:  
1750-1735



IR of Cyclic Carbonate 4-*t*Butoxystyrene Oxide (above)

# IR of Cyclic Carbonate

from 3-chlorostyrene oxide



IR of cyclic carbonate from 3-chlorostyrene oxide

C=O for Ester:  
1750-1735



# Limitations

- Definitive evidence for the synthesis of aziridine and oxazolidinone was unattainable due to impurities
- Lack of definitive success may be attributable to the steric hindrance and chemical behavior of the *tert*-butoxy group
- Experimental procedures must be perfected in order to obtain usable product for synthesis of oxazolidinone or cyclic carbonate

# Preliminary Conclusions

- 4-*tert*-Butoxystyrene oxide was synthesized from 4-*tert*-butoxystyrene with limited success
- It was not possible to synthesize pure aziridine and oxazolidinone from the resulting oxirane product.

# **Oxirane Synthesis with Substituted Alkenes and Subsequent Reactions**

**alpha-methylstyrene**

Catherine and Steven

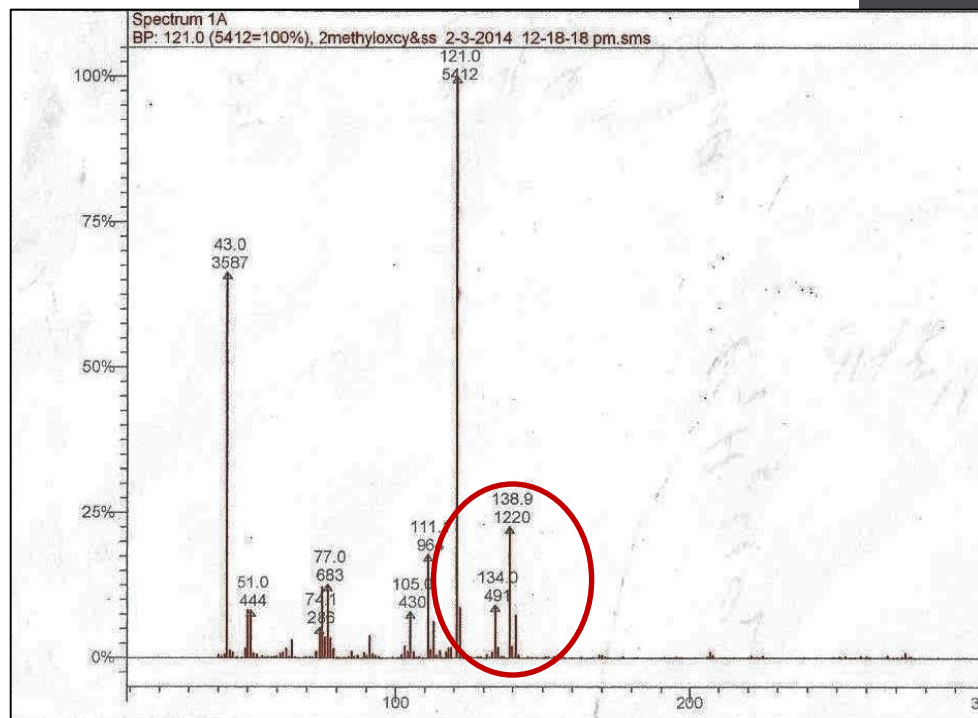
# First Attempt - Oxirane

## Method

- Traditional procedure

## Results

- 6% yield of 2-methyl-2-phenyloxirane



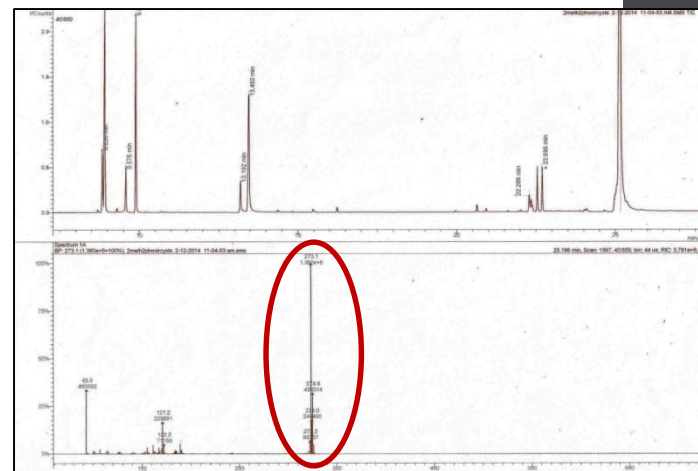
# Second Attempt - Oxirane

## Method

- 3x Starting material

## Results

- **Mass Spec**
  - small fraction of oxirane present (134.8)
  - Unknown compound at ~25mins (273/274)



# Third Attempt - Oxirane

## Method

- Re-refluxed the product from the last attempt in parallel with starting our third attempt
- Increased reflux time from 1hr to 2hrs
- Continued with 3x starting material

## Results

- **Mass Spec** – Peak at 273
- **NMR** of sample and starting material
  - No starting material was present
- **IR** – Carbonyl present  $1725\text{ cm}^{-1}$  (mCPBA present)

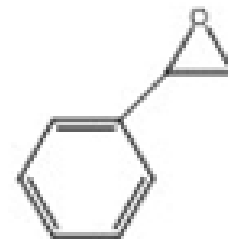
# Fourth Attempt - Oxirane

## Method

- Separation technique refined
  - Shook more vigorously
  - **Mass Spec** → 25min peak of 273
- Tried separating product again with a stronger base (6M NaOH)
- Also did a separation of mCPBA and dichloromethane only (6M NaOH)

## Results

- Stronger base removed mCPBA from mixtures (no 25 minute peak)
- Finally made our oxirane! (14.1% yield)



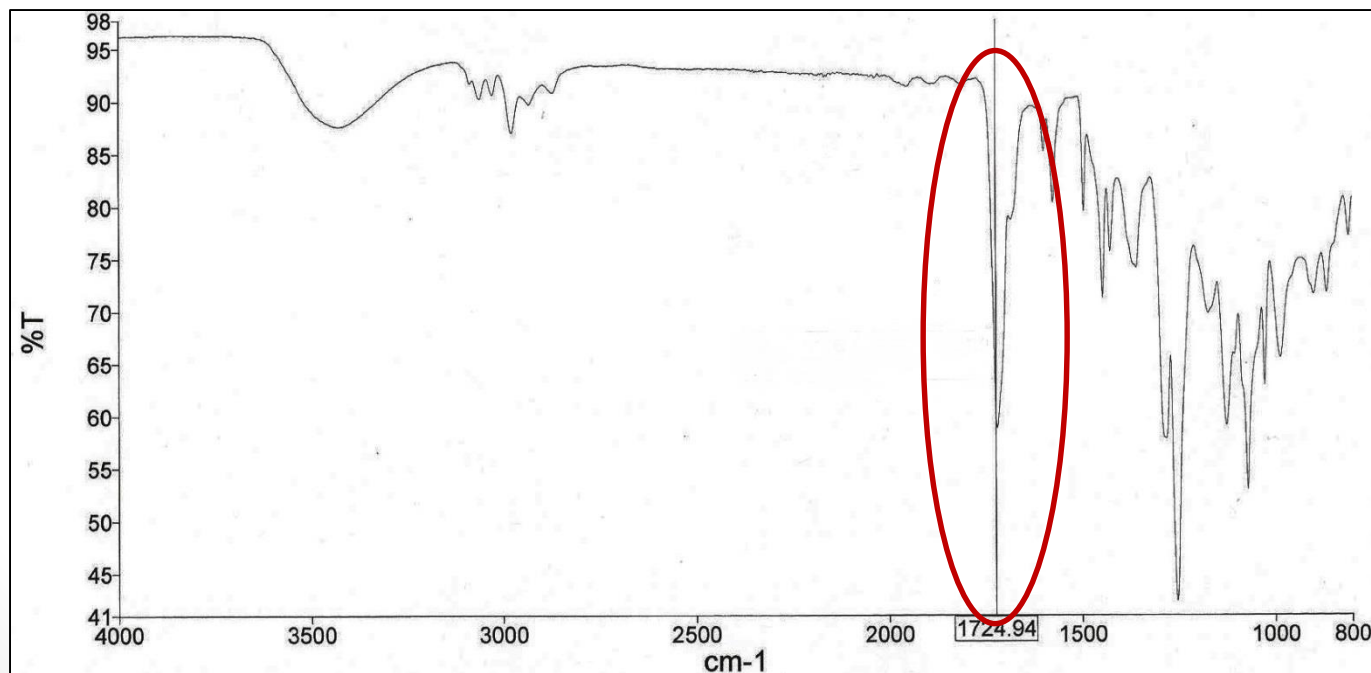
# Next Steps

## Formation of Carbonate

- Performed high speed ball mill procedure
- **IR**– carbonyl group present

## Formation of Amino Alcohol

- General procedure using benzylamine and boiling hexane
- **MS** – no amino alcohol





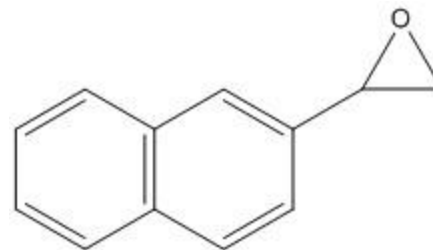
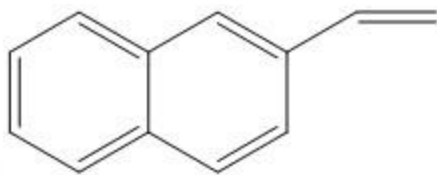
# **Oxirane Synthesis with Substituted Alkenes and Subsequent Reactions**

**2-vinylnaphthalene**

Manoj and Patrick

# Synthesis of Oxirane

- Started with 2-vinylnaphthalene
- Procedure:
  - Dissolved alkene in dichloromethane
  - Added mCPBA, heated for 1 hour
  - Carried out Base Extractions
  - Finally used roto-vap machine

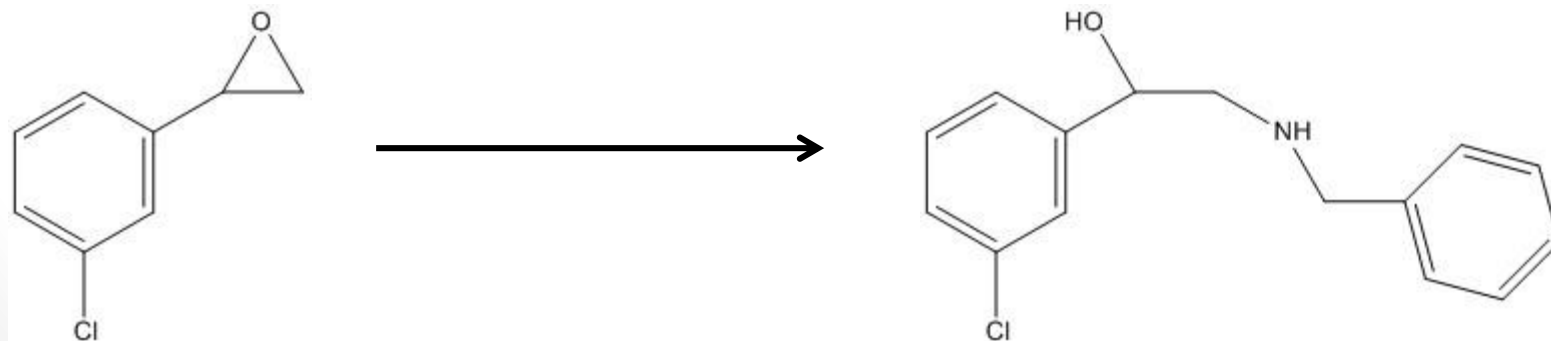


# Results

- First attempt: no oxirane acquired, temperature fluctuated during heating process of 1 hour
- Second attempt: very little oxirane acquired, temperature was controlled and reaction proceeded for 2 hours
  - We attempted a another base extraction followed by a water extraction to eliminate any mCPBA by-product
  - Water extraction resulted in “pink-smoothie” solution

# Synthesis of Amino Alcohol

- Started with 3-chlorostyreneoxide
- Procedure:
  - Combined equimolar amounts of oxirane and benzyl amine and let solution mix for ~1 week
  - Added boiling hexane and filtered solution
  - Used roto-vap machine and identified compound



# Results

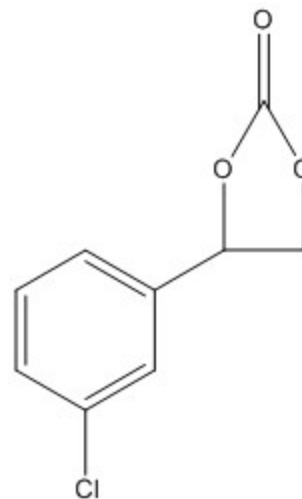
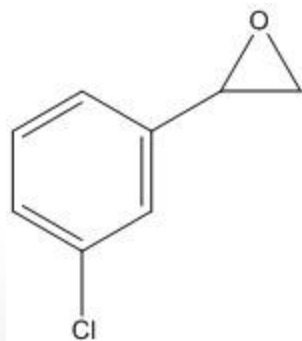
- First Attempt: we had a viscous yellow solution which required a large amount of hexane, product potentially left on filter paper
  - Rinsed out of paper with dichloromethane and repeated procedure
  - This resulted in an orange colored solution
  - GCMS identified product as not being an Amino Alcohol

# Results (cont.)

- Second Attempt: Used smaller reaction container to ensure proper mixing of reactants
  - Used Ether to filter instead of hexane
  - GCMS identified product as not being an Amino Alcohol
  - GCMS data was identical to the product when hexane was used to filter

# Synthesis of Carbonate

- Started with 3-chlorostyreneoxide
- Procedure:
  - Combined oxirane and dry ice ( $\text{CO}_2$ ) in ball mill tube
  - Ran ball mill for ~16 hours
  - Identified product using IR



# Results

- First Attempt: no product, ran reaction again
- Second Attempt: dilute product resulted but dilute carboxylate was present in IR
  - Dissolved product in ether and filtered using Pasteur pipette
  - Took IR again, dilute carboxylate still present



# Future Experimentation for all Oxirane Procedures

- Using alkenes with different functional groups to produce an oxirane – procedures may be unique for starting materials
- Using different conditions and reagents when synthesizing amino alcohol and carbonate
- Using different conditions to improve oxirane yield (i.e. heating period, new solvents)
- Clean up aziridine
  - Methodology for removing excess benzylamine from amino alcohol (vacuum pump? Need to ask Dr. L)
  - New solvents (similar to ether but cannot dissolve triphenylphosphine oxide)

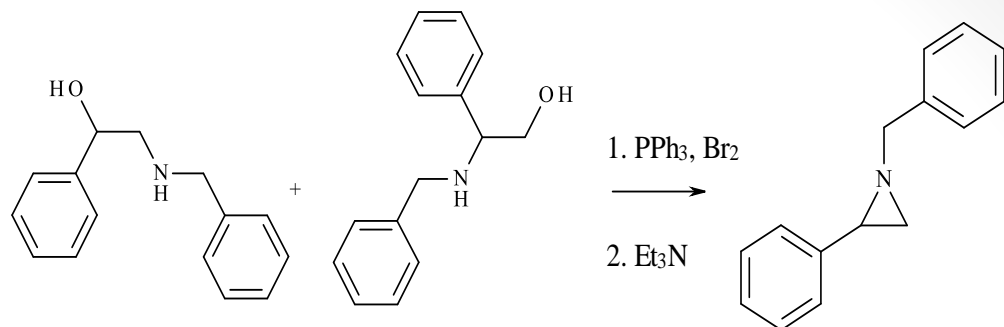
# **Aziridine Synthesis – standard preparation versus new method**

Charles and Gail

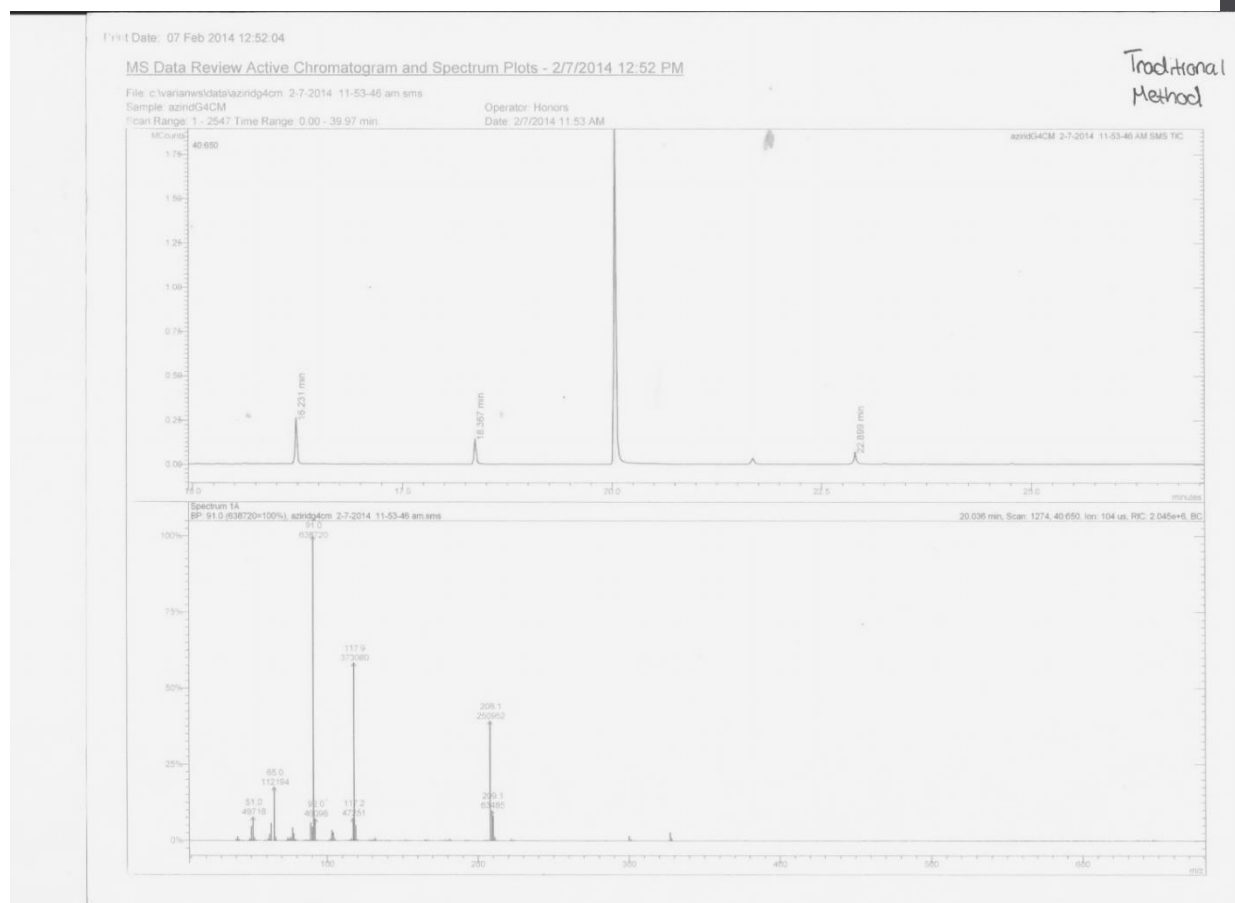
# Goals

- Conversion of amino alcohol to aziridine
- Standard preparation vs. new method
  - Which is more efficient?
  - Which protocol is easier to follow?
  - Which has a larger yield?

# First Steps

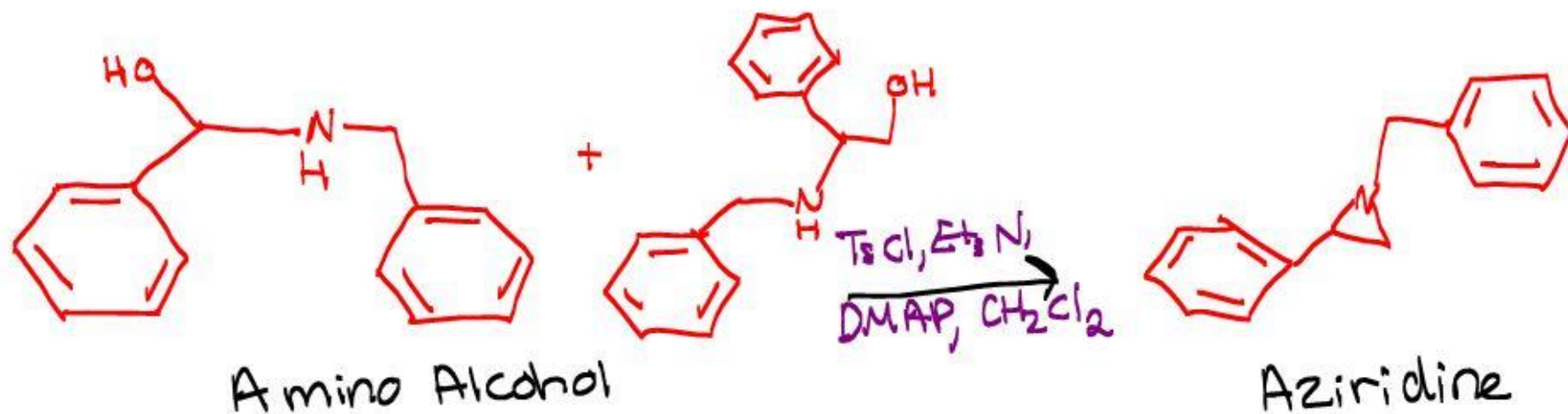


- Make aziridine using the triphenylphosphine dibromide intermediate
- Success!



# New Aziridine Method

- One pot method from Vicario et al. using Amino Alcohol, DMAP, TsCl, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub> and saturated NH<sub>4</sub>Cl



# New Aziridine Method cont.

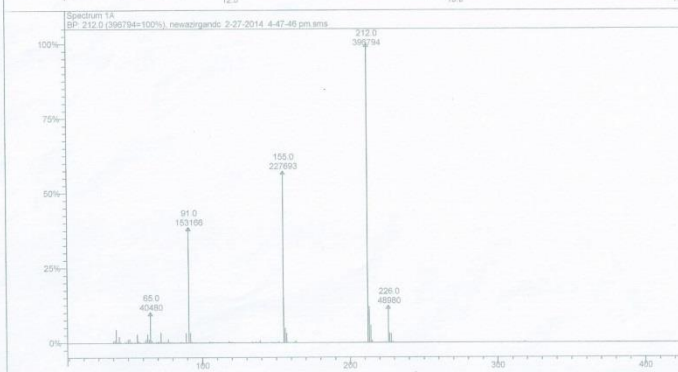
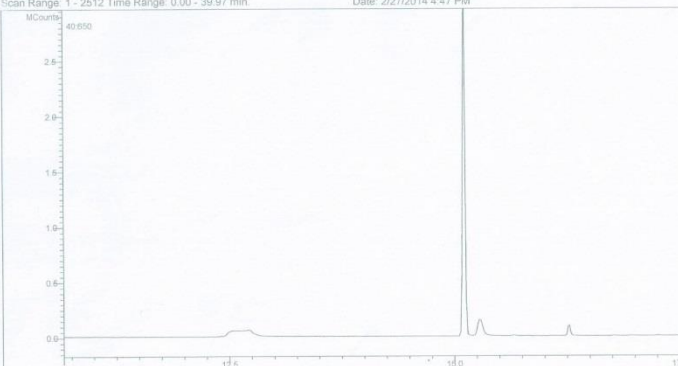
- 1<sup>st</sup> run- stirred reaction for 1 day
- 2<sup>nd</sup> run- stirred for 1 week
- Tried to purify part of the product using microscale column

Print Date: 27 Feb 2014 17:44:41

## MS Data Review Active Chromatogram and Spectrum Plots - 2/27/2014 5:44 PM

File: c:\varian\ms\data\newazirgandc 2-27-2014 4-47-46 pm.sms  
Sample: newazirgandc  
Scan Range: 1 - 2512 Time Range: 0.00 - 39.97 min

Operator: Honors  
Date: 2/27/2014 4:47 PM

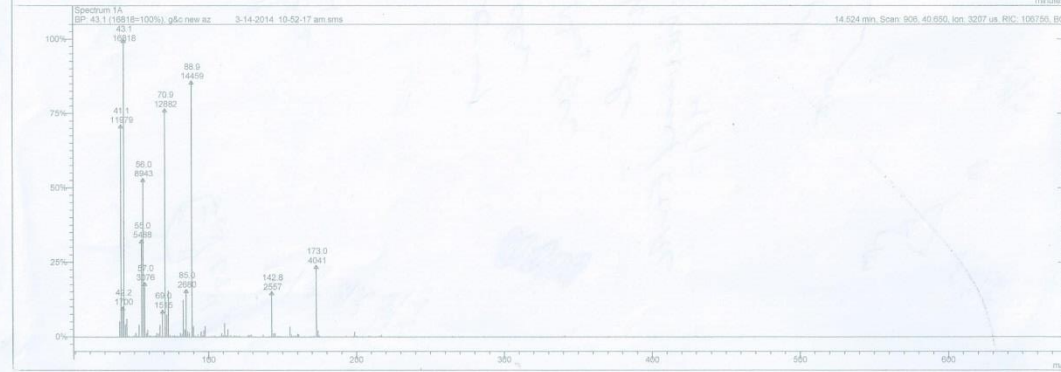
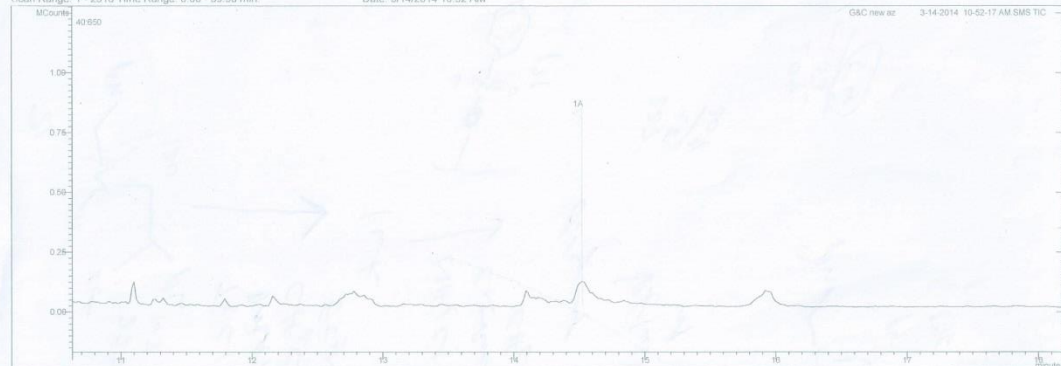


Print Date: 14 Mar 2014 11:37:44

## MS Data Review Active Chromatogram and Spectrum Plots - 3/14/2014 11:37 AM

File: c:\varian\ms\data\g5c new az 3-14-2014 10-52-17 am.sms  
Sample: G5C new az  
Scan Range: 1 - 2516 Time Range: 0.00 - 39.98 min

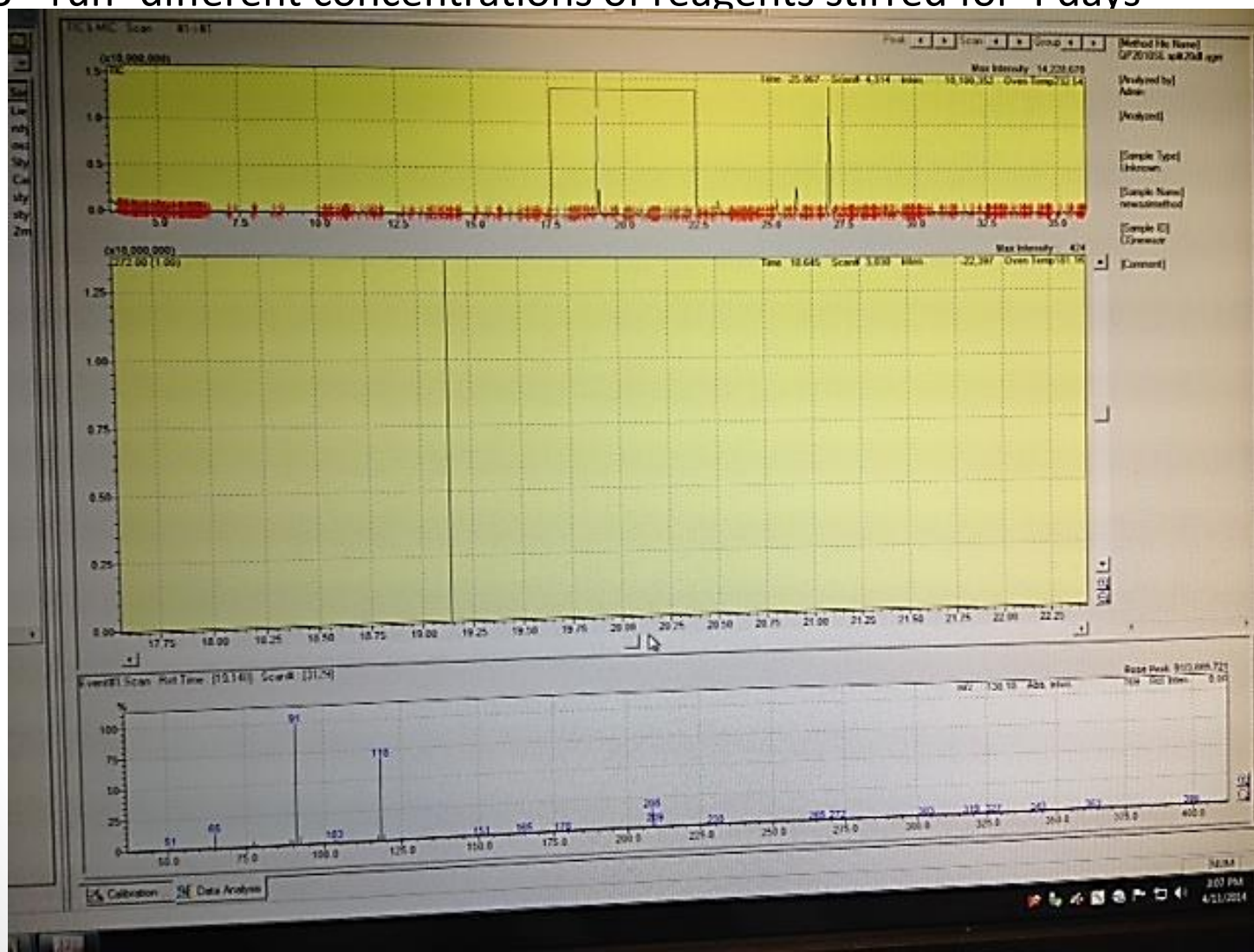
Operator: Honors  
Date: 3/14/2014 10:52 AM



Post Column Mass spec  
Of Fraction 5 of 5 columns  
Column 2

# New Aziridine Method Cont.

- 3<sup>rd</sup> run- different concentrations of reagents stirred for 4 days





# Conclusion

- Aziridine!
- Work on finding out what is coming out later on mass spec and purify sample!



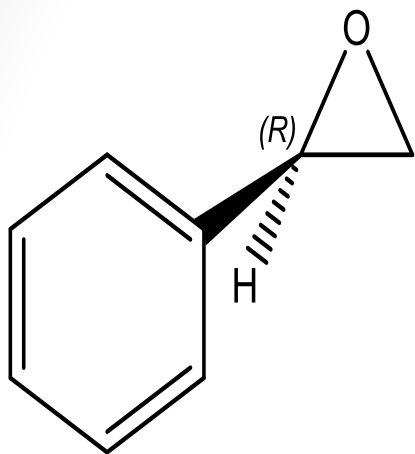


# Oxazolidinone Chirality

Alex, Cory and Evan

# **Stereochemical Mechanism**

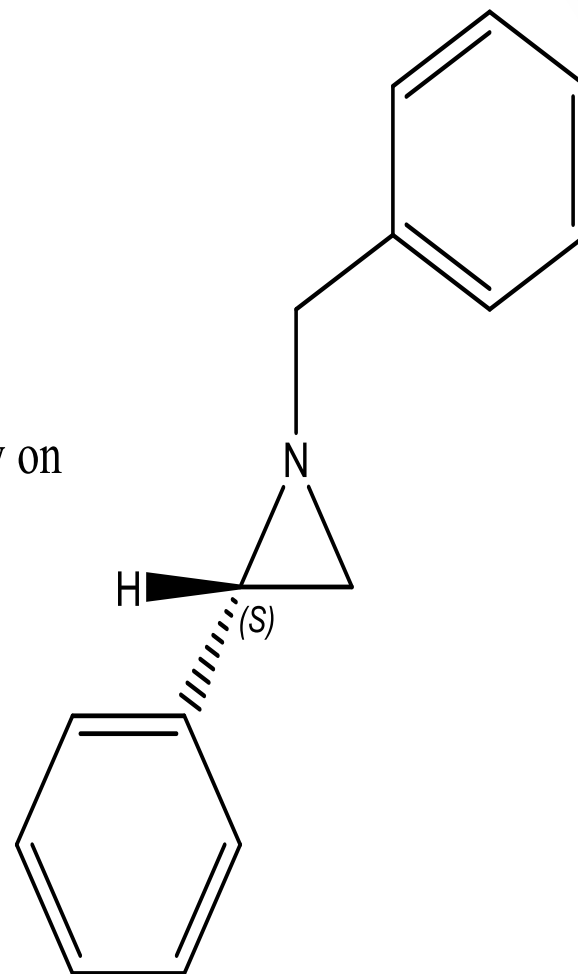
## Formation of Oxazolidinone

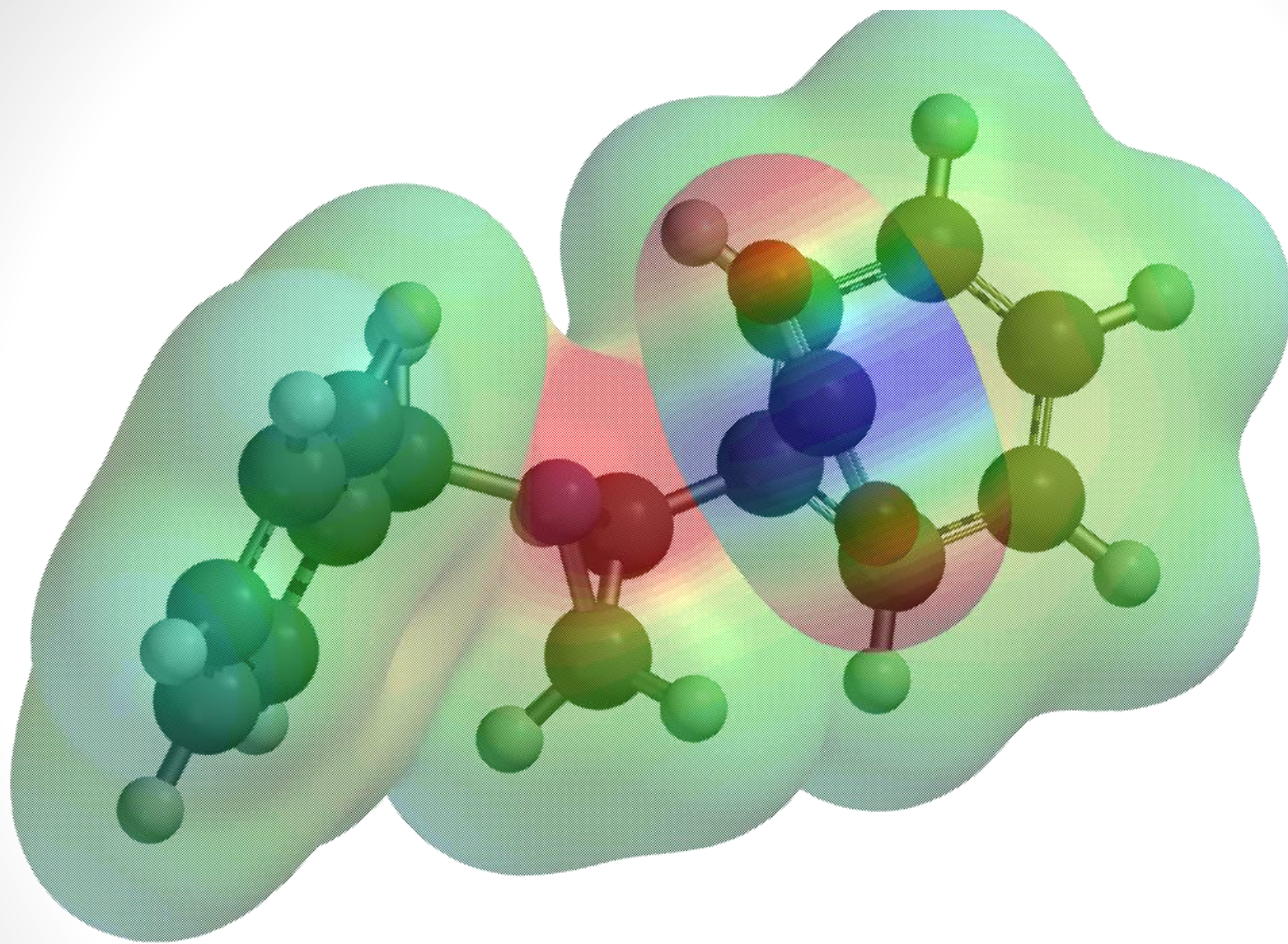


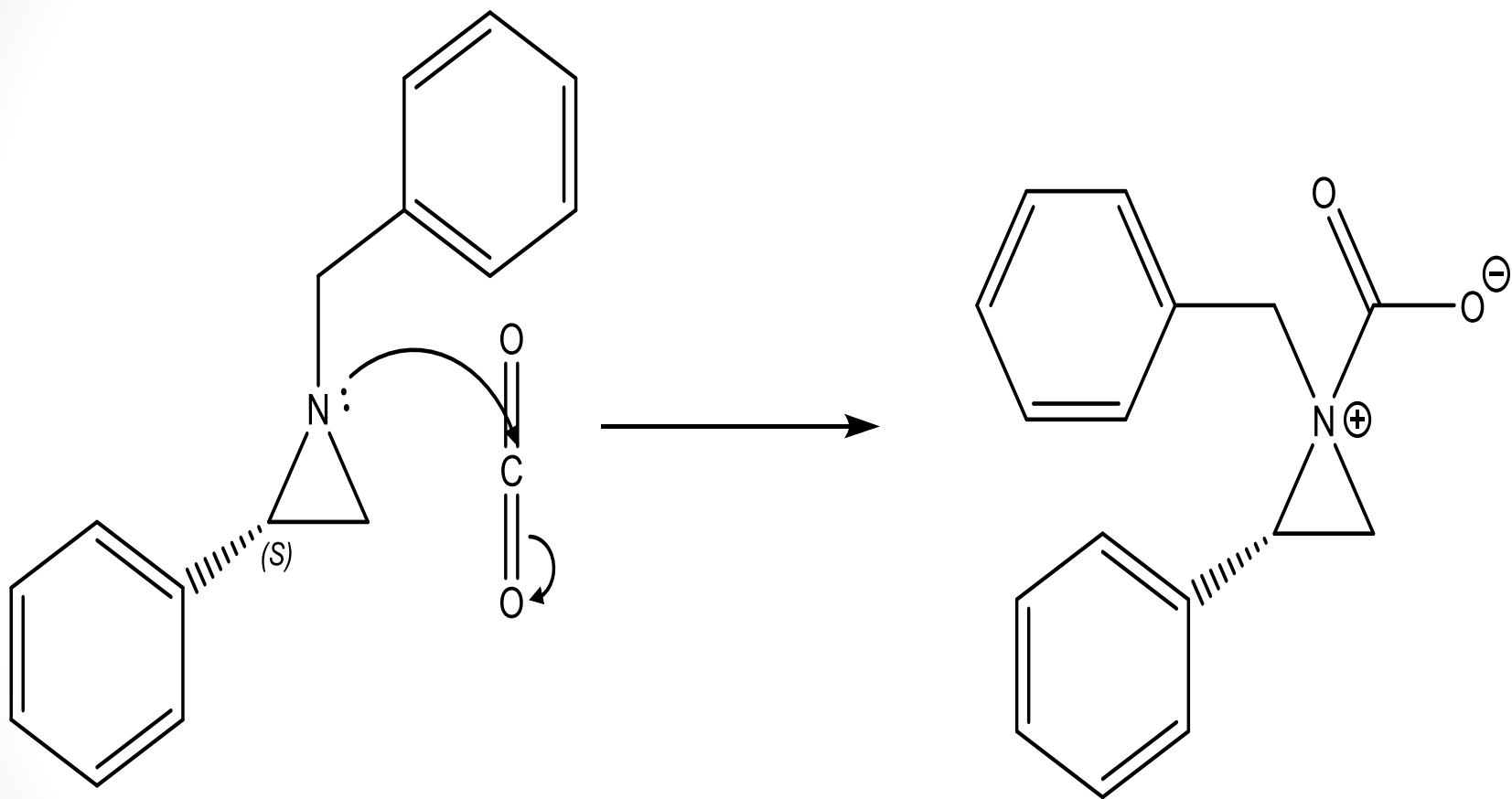
R - Styrene Oxide

Aziridine Synthesis  
Proceeds via 2 Methods

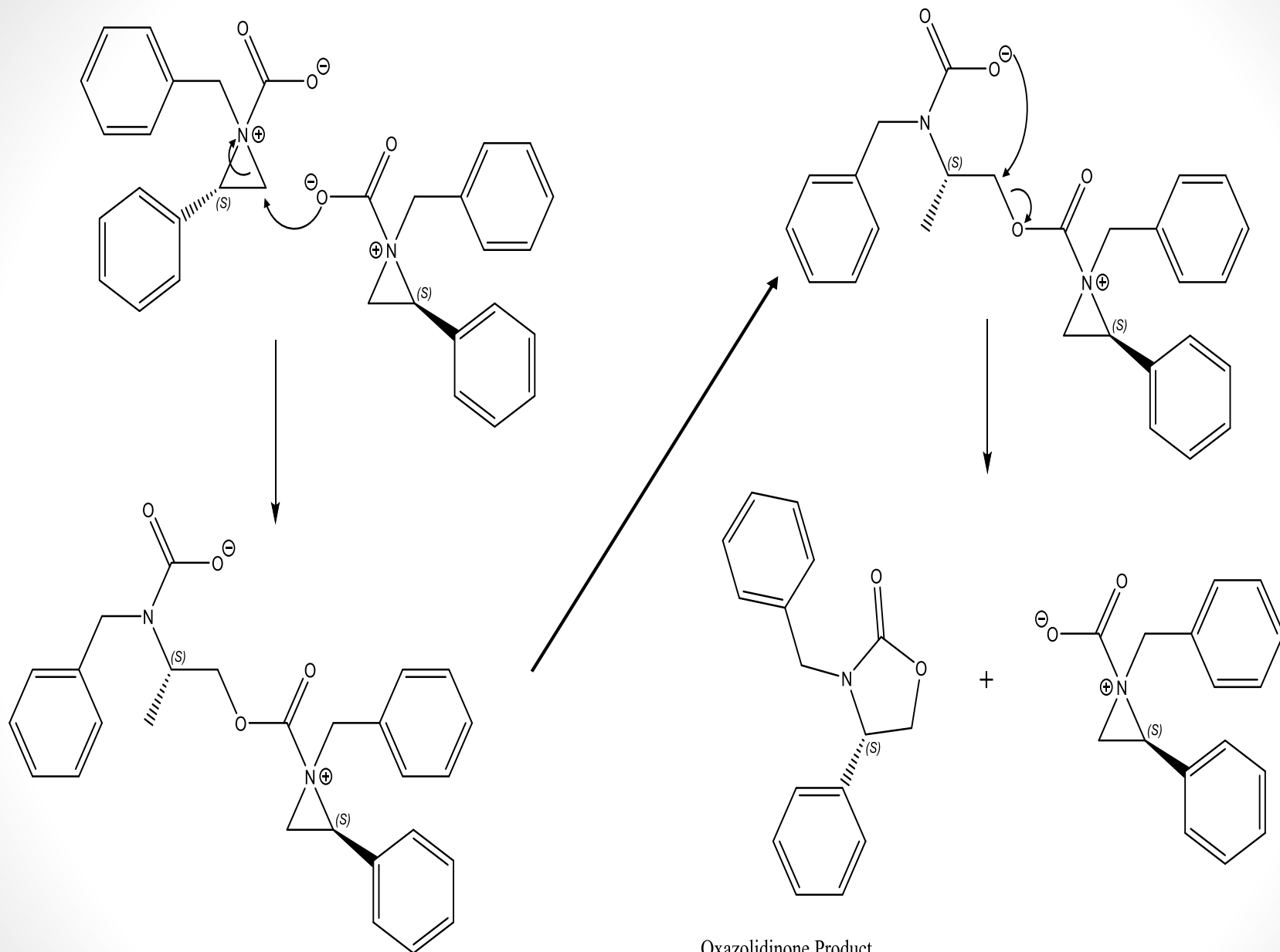
—————→  
Both methods result in net  
*inversion* of stereochemistry on  
the chiral carbon







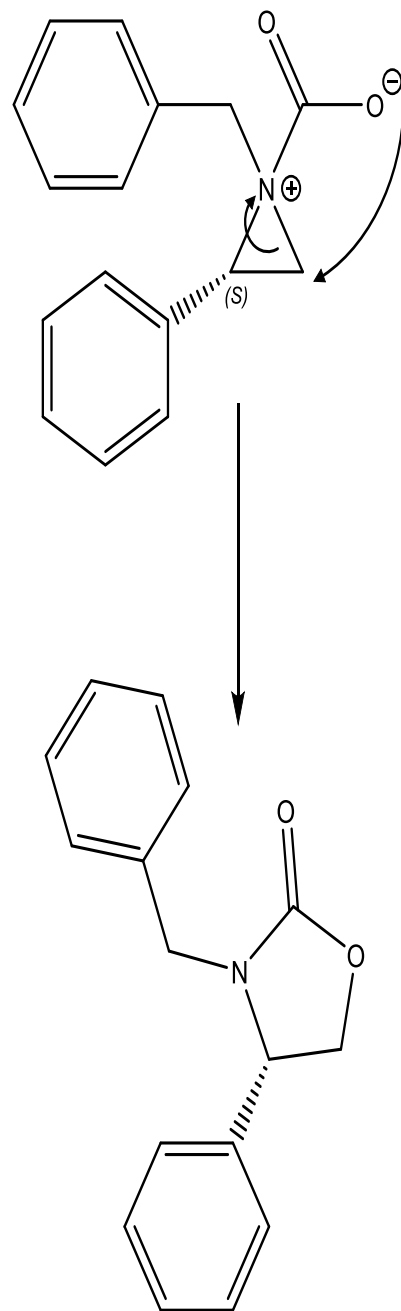
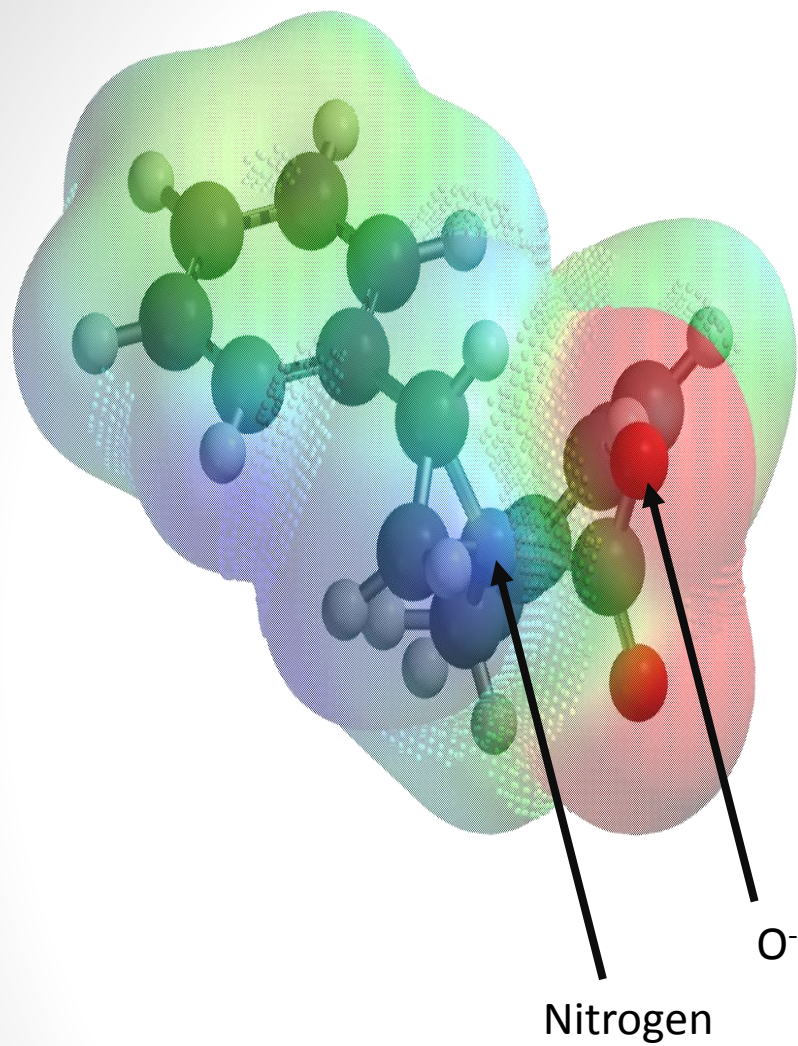
# **Mechanism One**



Oxazolidinone Product  
Retention of Stereochemistry of Aziridine  
Net Inversion of Stereochemistry from (R)-Styrene Oxide

# **Mechanism Two**





# Initial Approach

- Polarimeter
- NMR Shift Reagents
- Recrystallization

# GC-MS of Racemic Oxazolidinone

Print Date: 21 Feb 2014 13:20:26

## MS Data Review Active Chromatogram and Spectrum Plots - 2/21/2014 1:20 PM

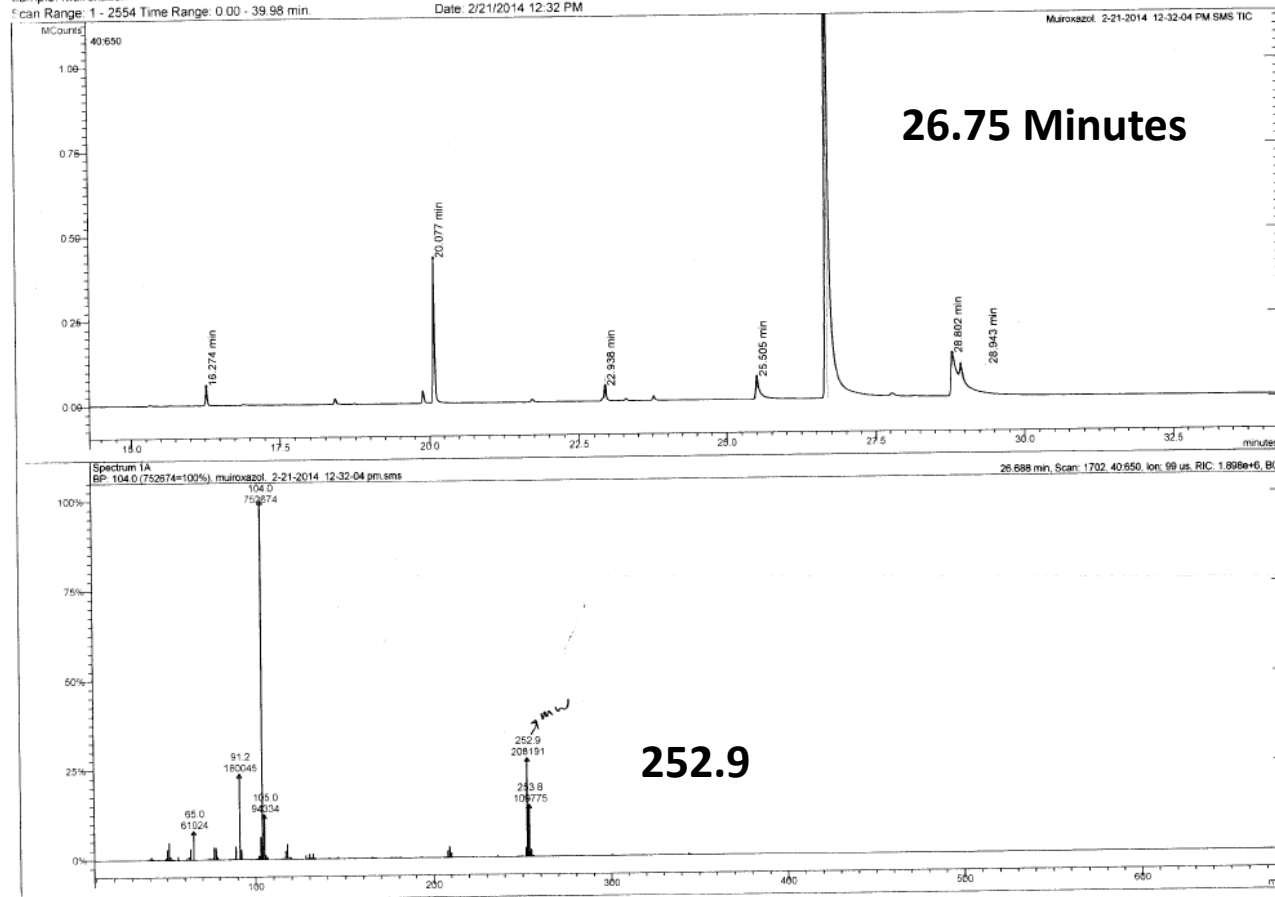
File: c:\varian\ms\data\muioxazol. 2-21-2014 12:32:04 pm.sms

Sample: Muioxazol

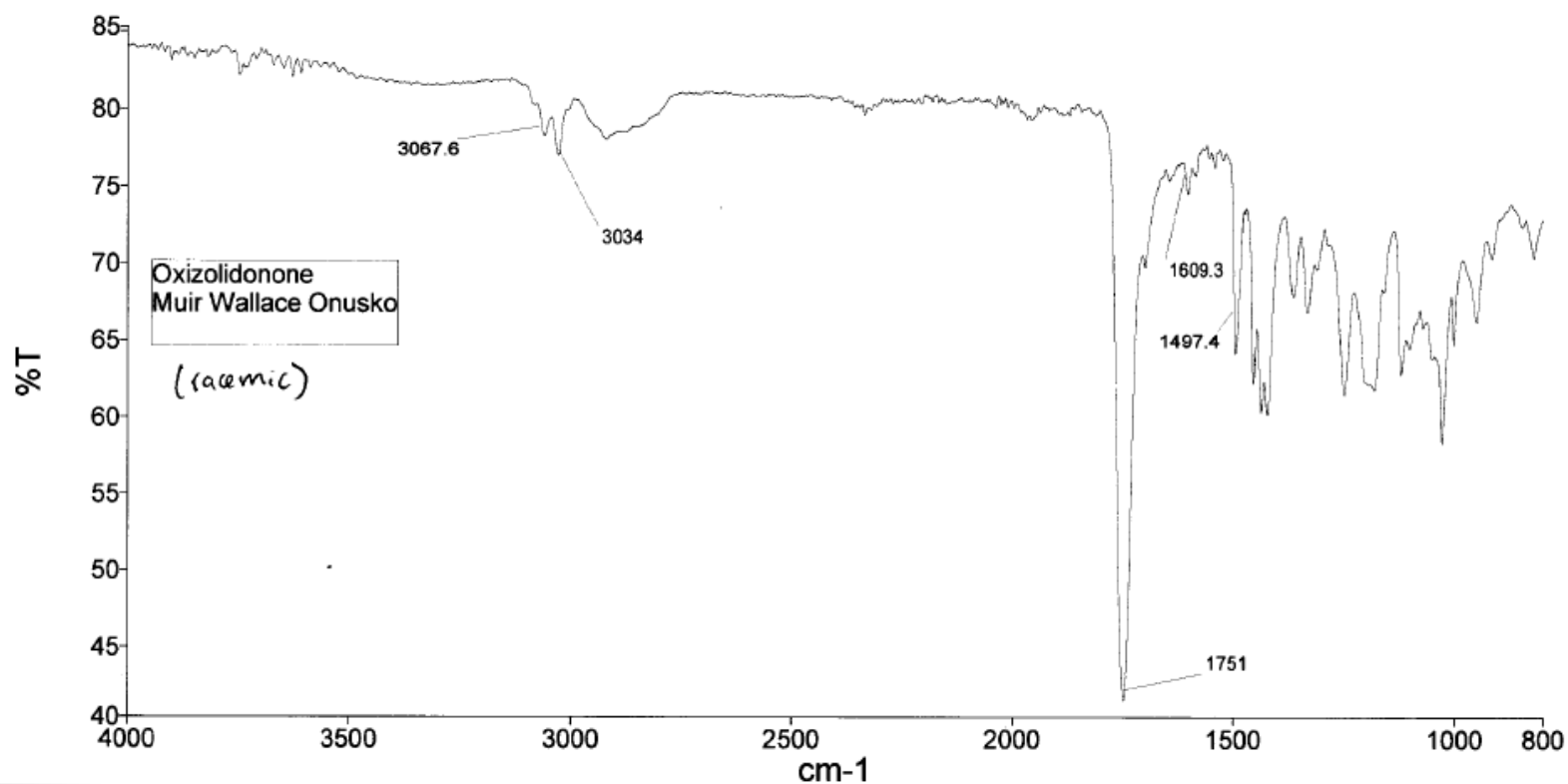
Operator: Honors

Scan Range: 1 - 2554 Time Range: 0.00 - 39.98 min.

Date: 2/21/2014 12:32 PM



# IR of Racemic Oxazolidinone



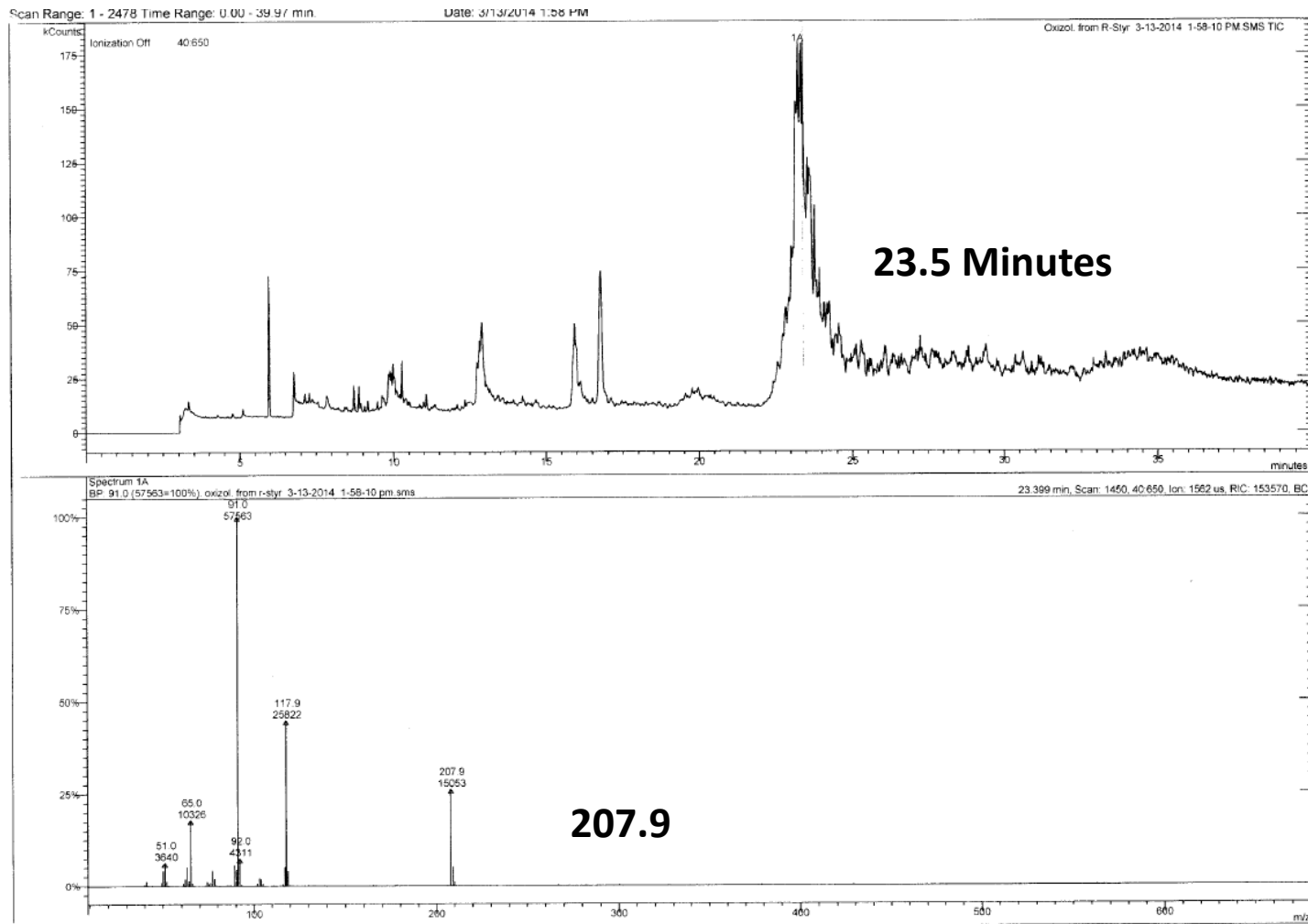
# Polarimeter Reading

- Produced what we thought to be oxazolidinone from R-styrene oxide, and took a polarimeter reading
- $\alpha = [0.03^\circ]$  (4 readings)
- $L = 1 \text{ dm}$
- $C = [0.002 \text{ g} / 6.8 \text{ mL}]$  (in Diethyl Ether)
- $\alpha_{\text{ether}} = [0.00^\circ]$  (4 readings)
- $\text{Specific Rotation} = \frac{\alpha}{L * C} = 102^\circ$

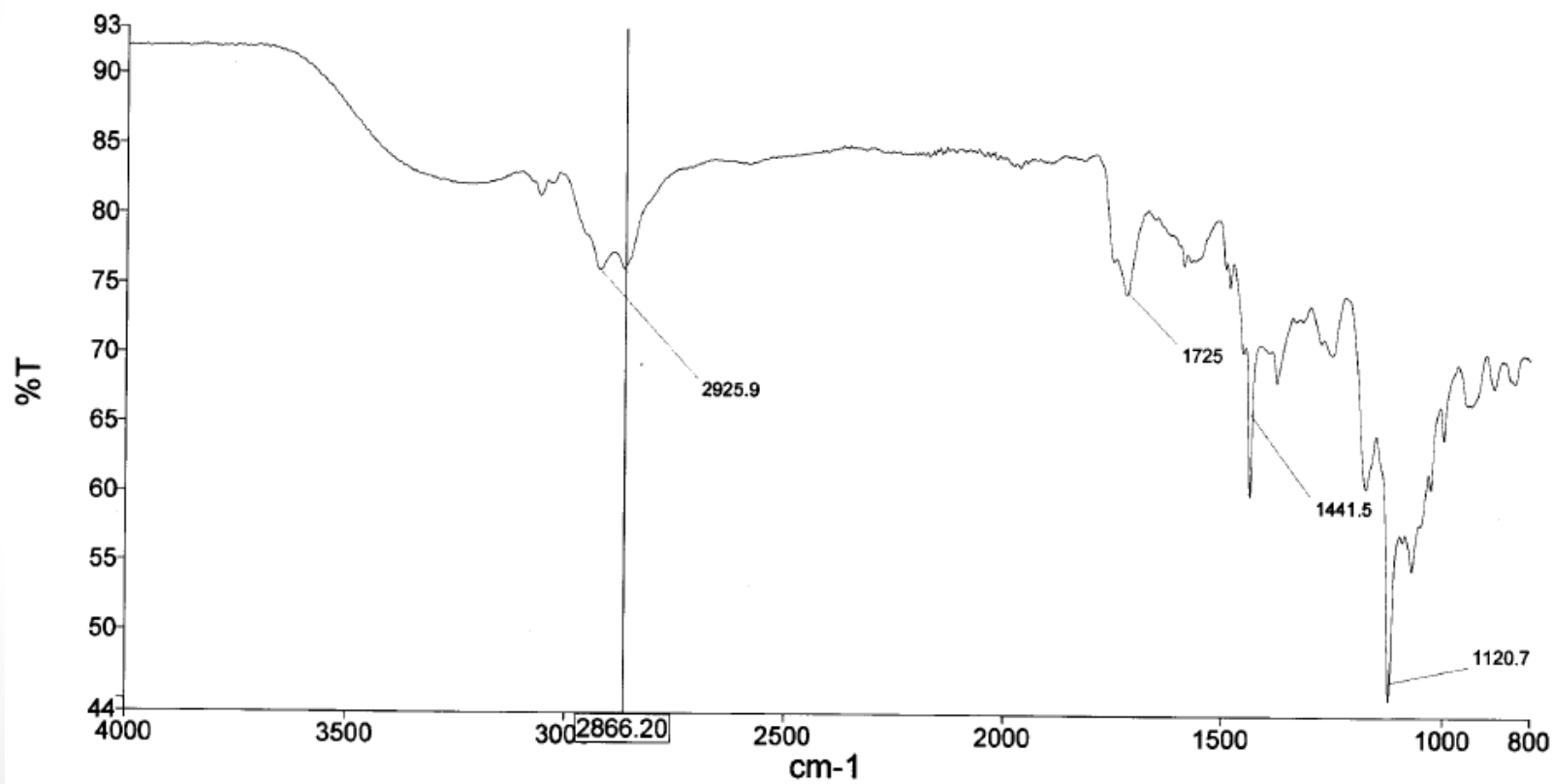
# Testing Polarimeter Material

- The material was not pure enough to make a conclusion.
- As the GS-MS report and the IR show, there was likely a majority of aziridine in the sample, and results were inconclusive with respect to oxazolidinone.
- It could be possible that this is the specific rotation of aziridine from R-styrene oxide.

# GC-MS



# IR Peaks

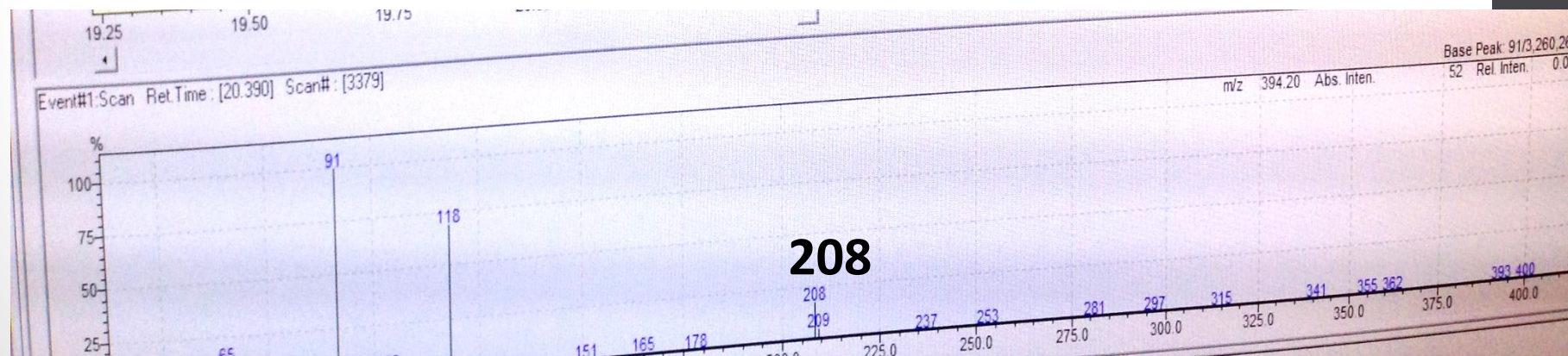
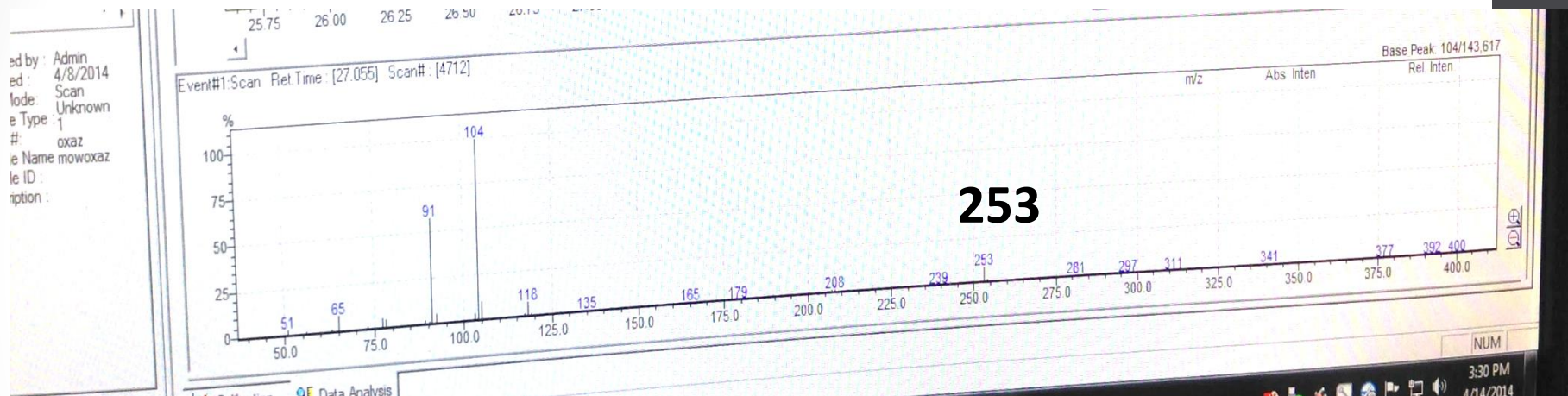
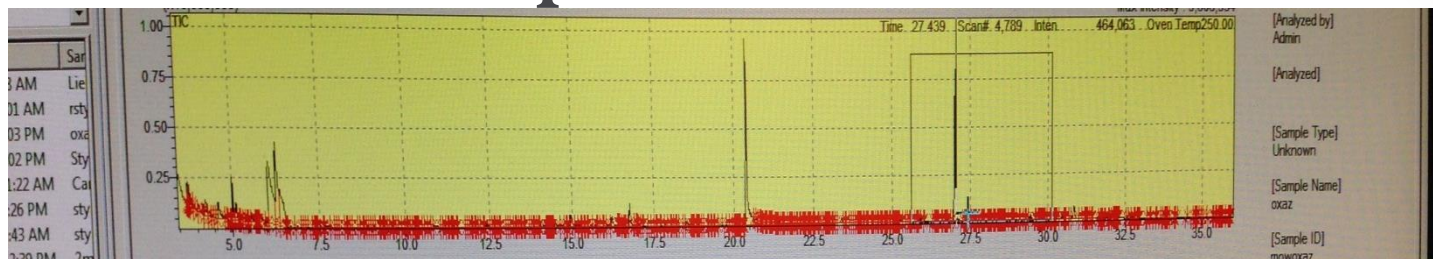




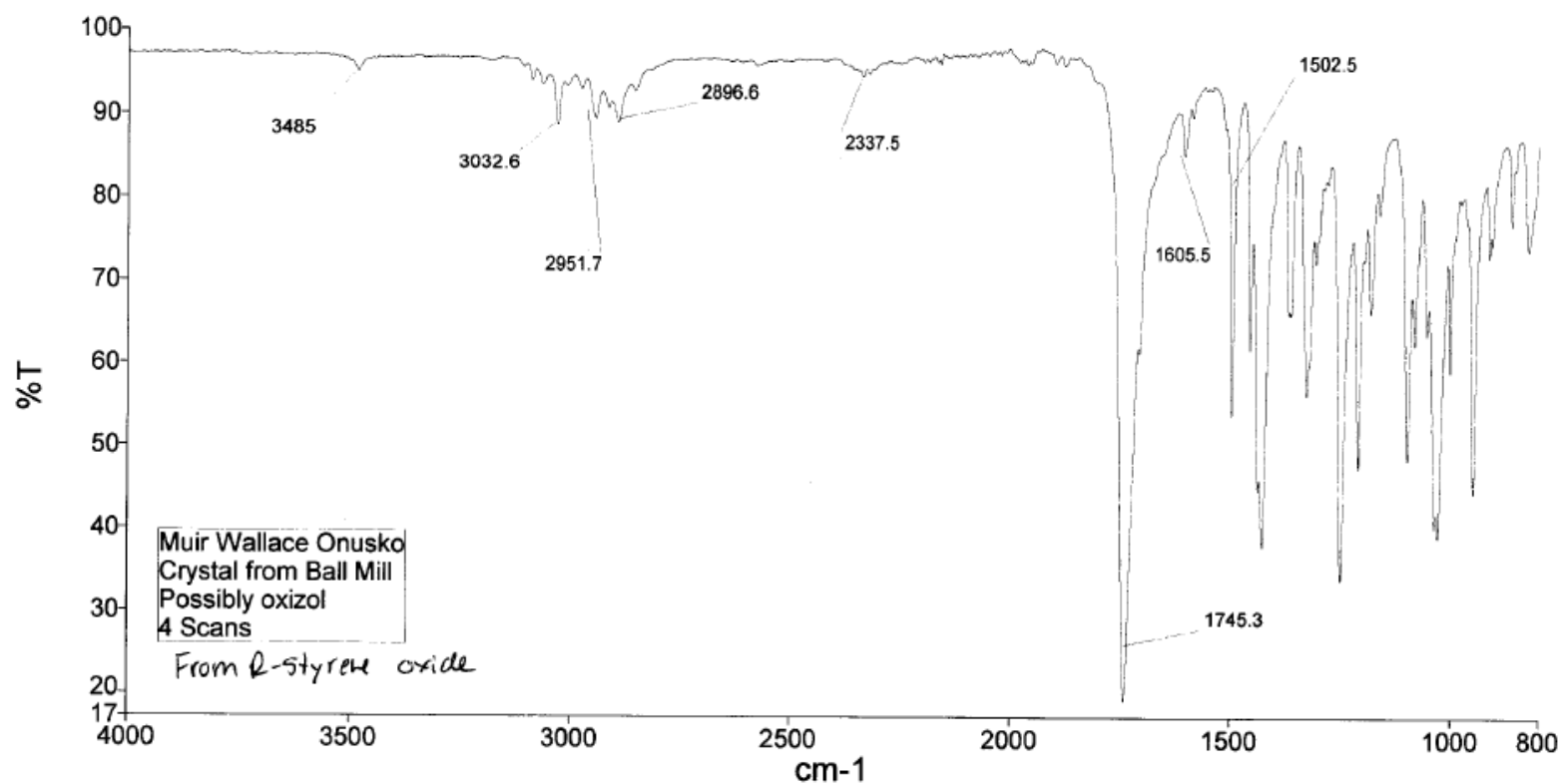
# Crystal

- Ran sample in ball mill two more times with additional R-styrene oxide.
- White, semi-transparent crystal had formed on the milling balls around the normal yellow oil.
- Unknown black material also formed.
- Both samples sent to crystallography lab.

# GC – MS of Sample



# IR of Sample



# Recrystallization

- Crystal is likely oxazolidinone, and the oil is likely aziridine.
- Crystal product was insoluble in isopropyl alcohol, while yellow oil was soluble.
- Recrystallization of s-styrene oxide product produced a similar white crystal, although crystal was too soft to be removed.

# Conclusions

- Very likely that crystalline oxazolidinone can be produced.
- Three sessions in the ball mill is ideal for producing oxazolidinone.
- No differences between oxazolidinone produced from R- and S-styrene oxide.
- Isopropyl alcohol may be useful solvent for recrystallization of oxazolidinone.

# Further Steps

- Continue with the recrystallization of Oxazolidinone and aziridine.
- Obtain results from crystallography lab.
- Repeat procedure to obtain more crystals and fine-tune the recrystallization process.

# Summary of Conclusions

Bridgette and Brooke

- Successful oxirane synthesis from various substituted alkenes with procedural modifications
- Marginal success in synthesis of cyclic carbonate compounds from substituted oxiranes made in laboratory
- Limited success in synthesis of aziridine and oxazolidinone from substituted oxiranes made in laboratory
- Successful synthesis of aziridine with “new method”
  - Need further analysis of abnormality in MS and purification
- Successful synthesis of oxazolidinone with no difference in R- and S-styrene oxide starting material
- Probable success in synthesis of crystalline oxazolidinone