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[2]
- Ligands for Metal Catalysts[2]
- Protecting Groups[2]
- Pharmaceutical Agents

Pharmaceutical Agents

- Predominantly Antibacterial
- Bacterial Resistance to Antibiotics is Escalating[1]
  - Gram-positive bacteria: MRSA, Streptococci, Enterococci, MDRTB
  - Only rare instances of developed resistances have been reported
- Inhibition of Protein Synthesis[1]
  - 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?

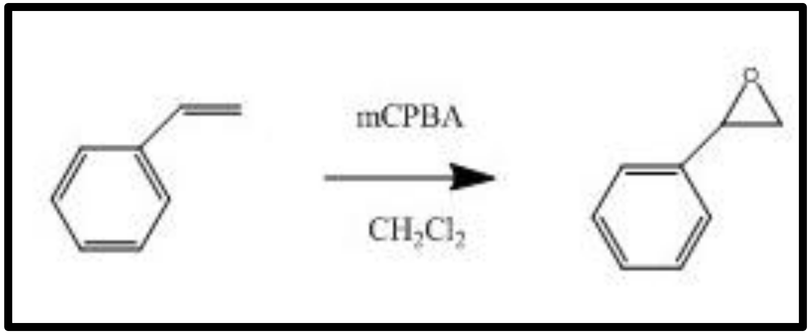
References

- 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*.

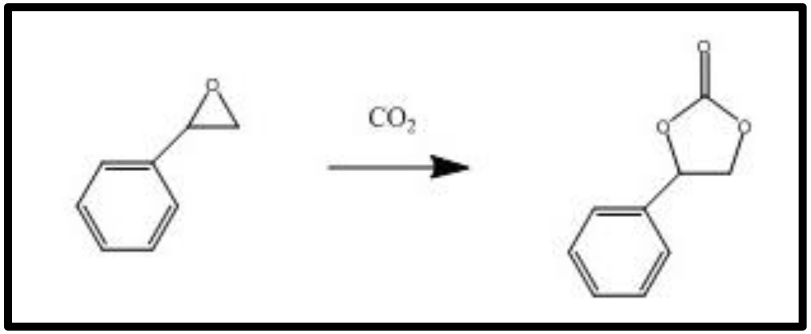
Overall Mechanism/ Reaction Scheme

Catherine and Steven

Alkene → Oxirane

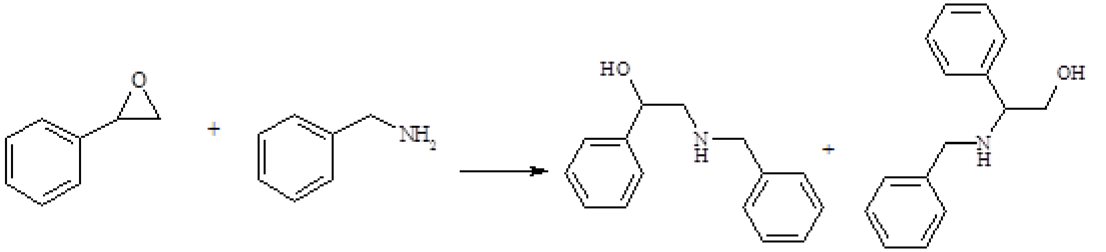


Oxirane → Carbonate



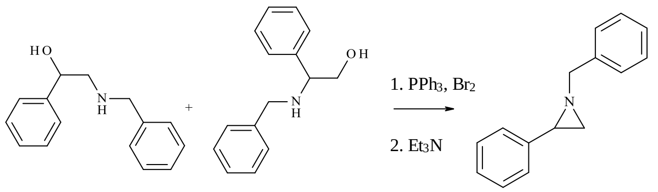
Oxirane → Oxazolidinone

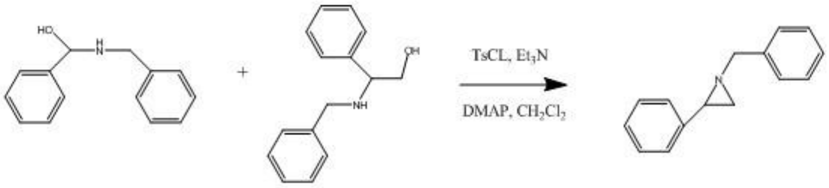
Step #1



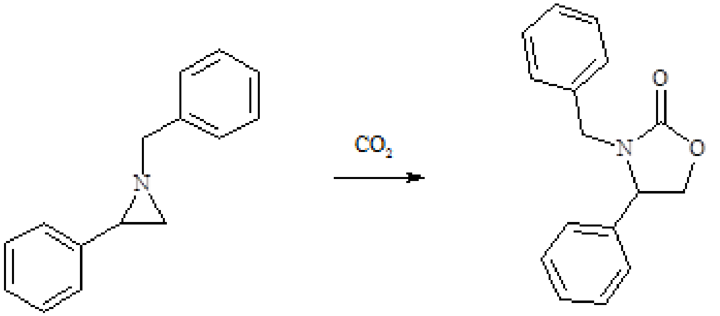
Step #2

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)

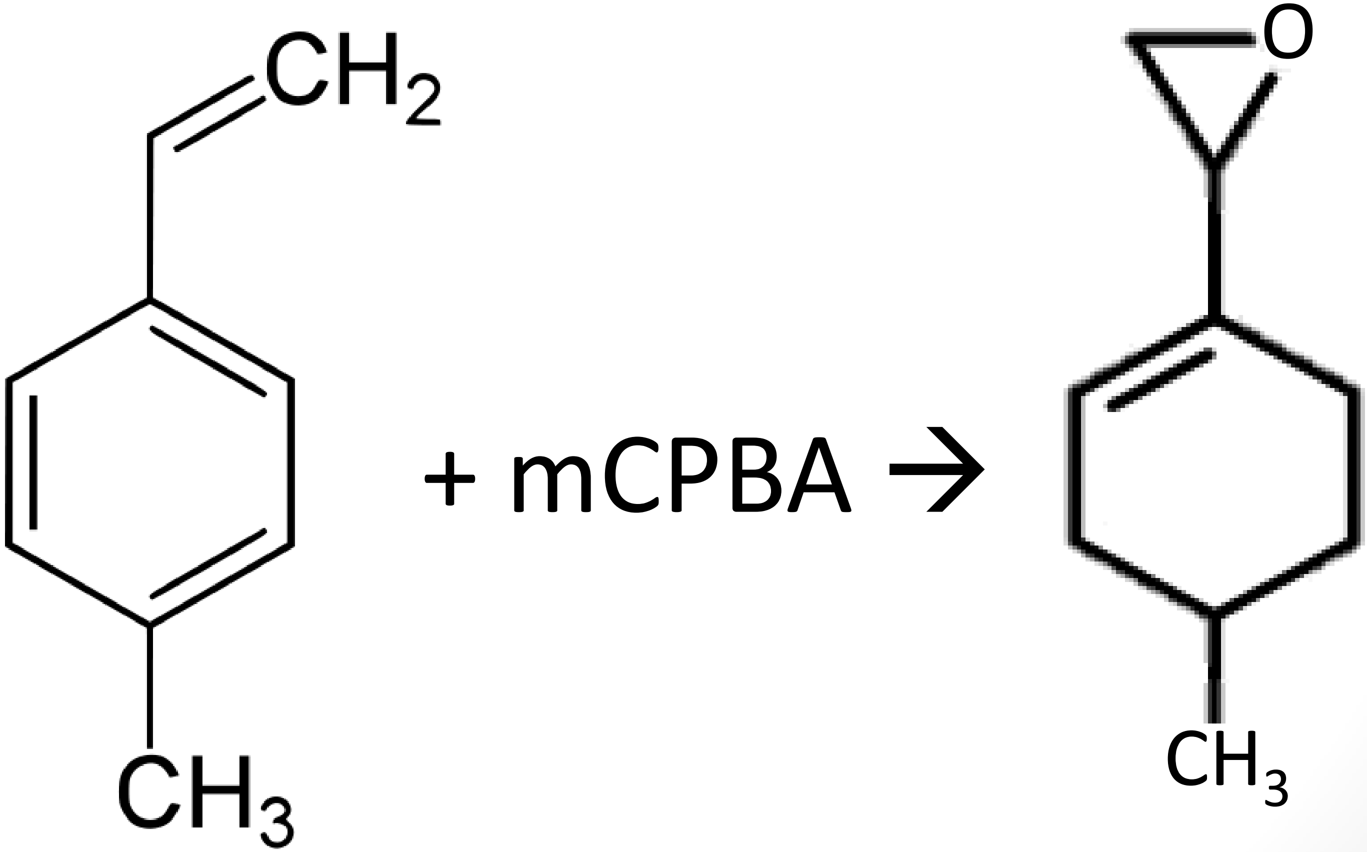
- Combine oxirane with silver pellet and dry ice in metal vial
- Tighten and react in High Speed Ball Mill for 24 hours

Oxirane Synthesis with Substituted Alkenes and Subsequent Reactions

4-methylstyrene

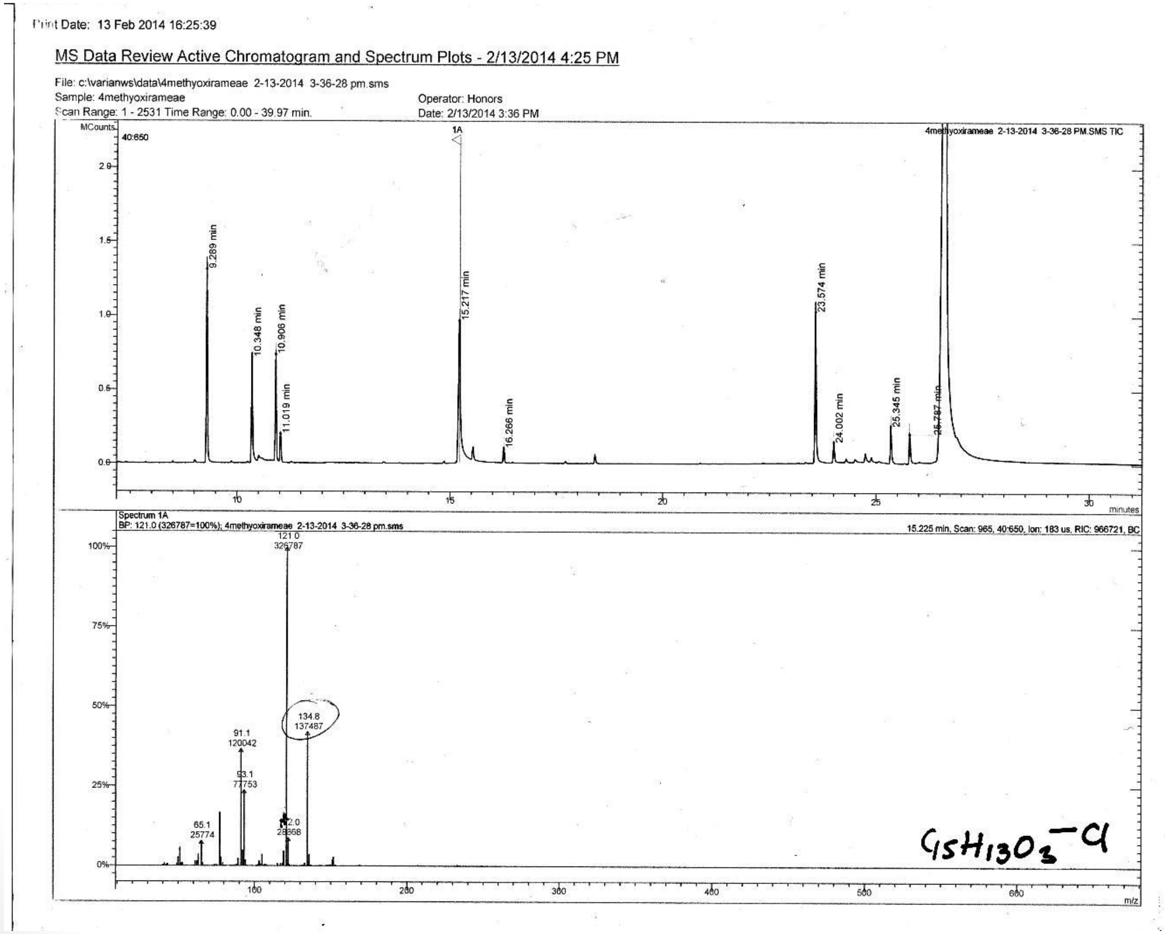
Ayushi and Emily

Oxirane Formation from 4-methylstyrene



2-(4-methylphenyl)oxirane

134 g/mol



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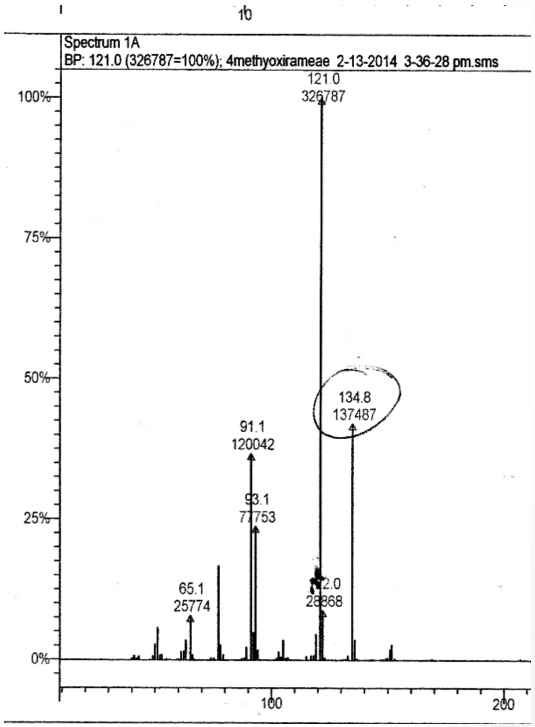
Operator: Honors
Date: 2/13/2014 3:36 PM

Spectrum 1A
BP: 121.0 (326787=100%); 4methyoxirameae 2-13-2014 3-36-28 pm.sms
15.225 min, Scan: 965, 40:650, Ion: 183 us, RIC: 966721, BC

$C_{15}H_{13}O_3$ −Cl



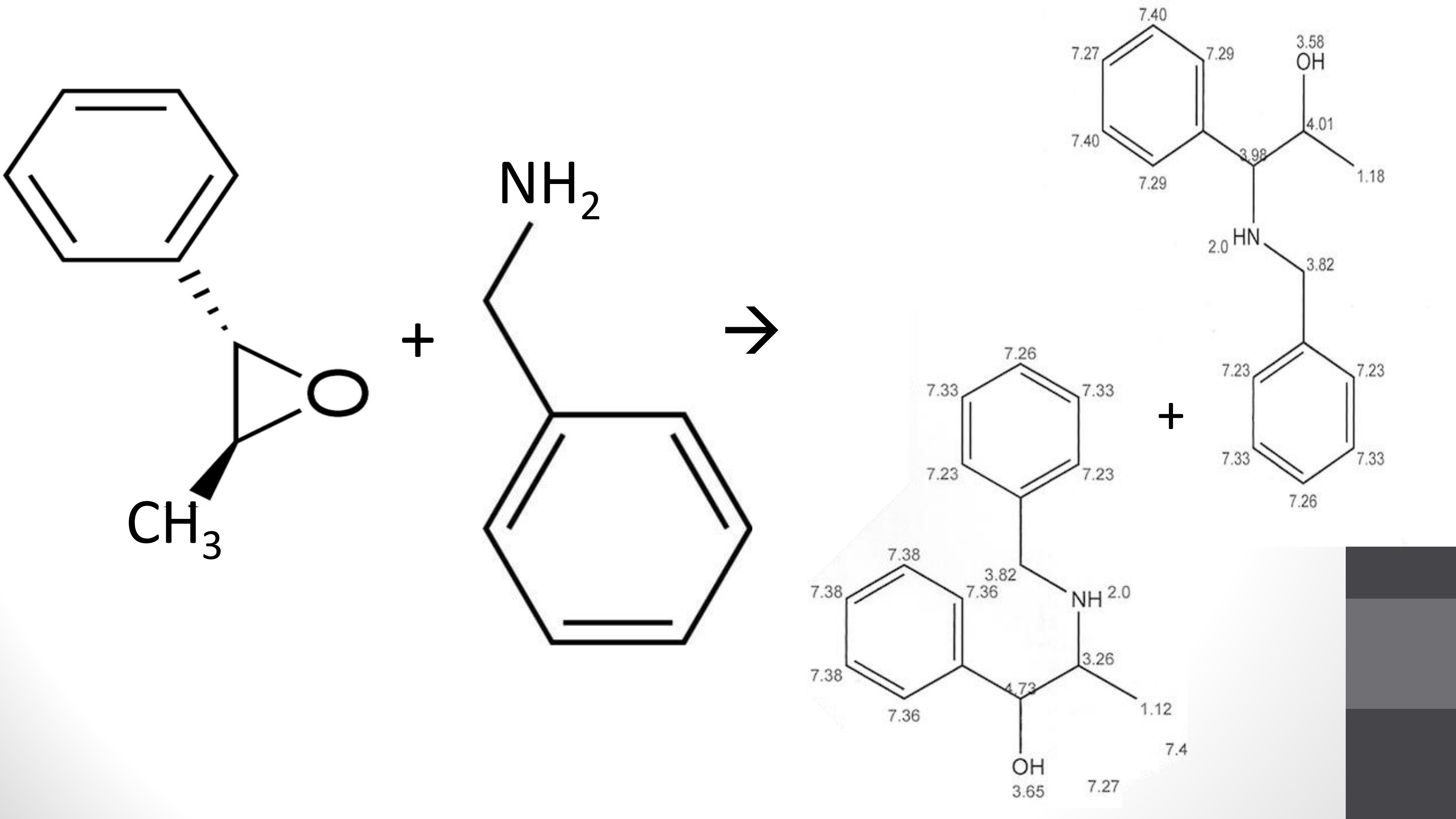
Results

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

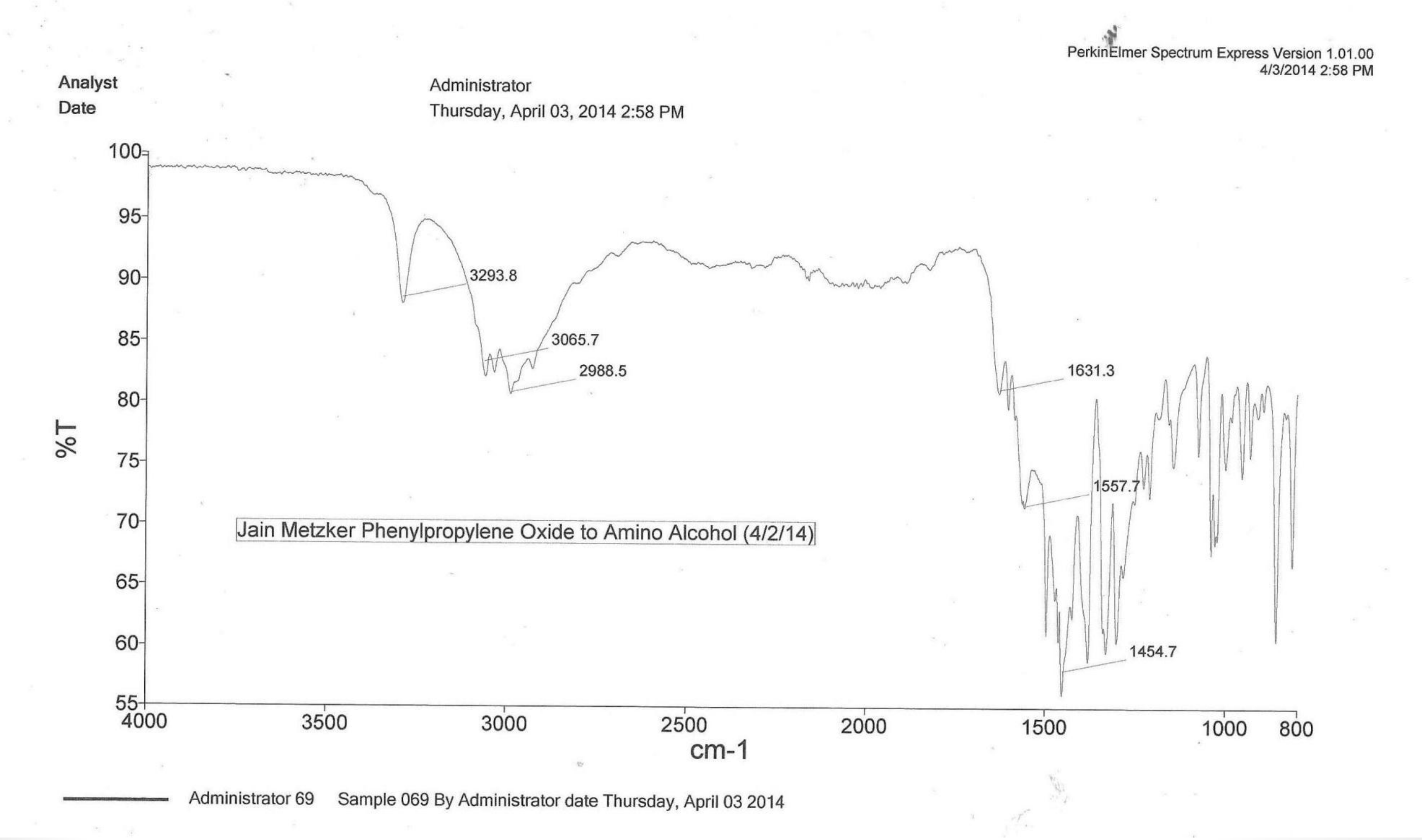
Modifications to Original Procedure:

- 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



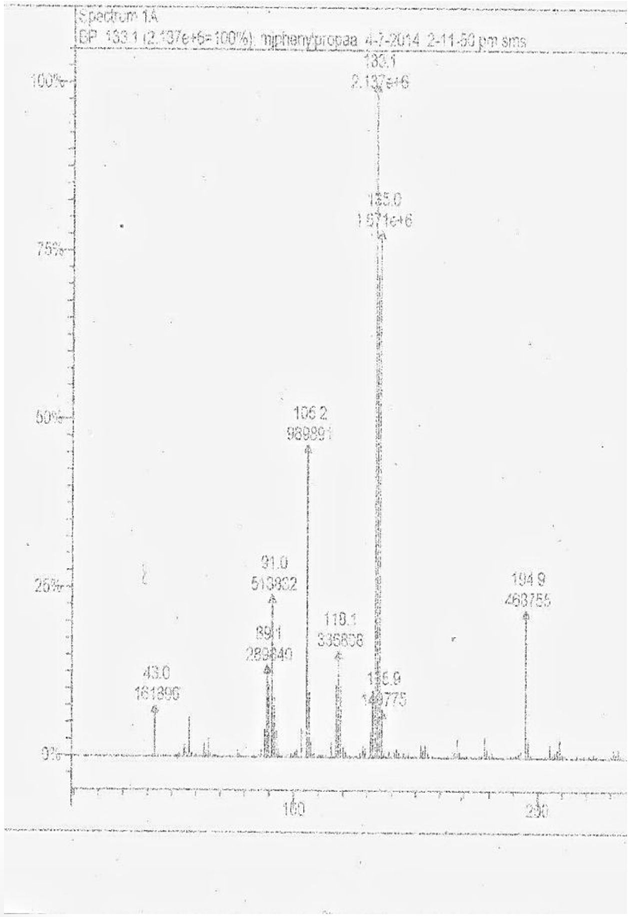
PerkinElmer Spectrum Express Version 1.01.00
4/3/2014 2:58 PM

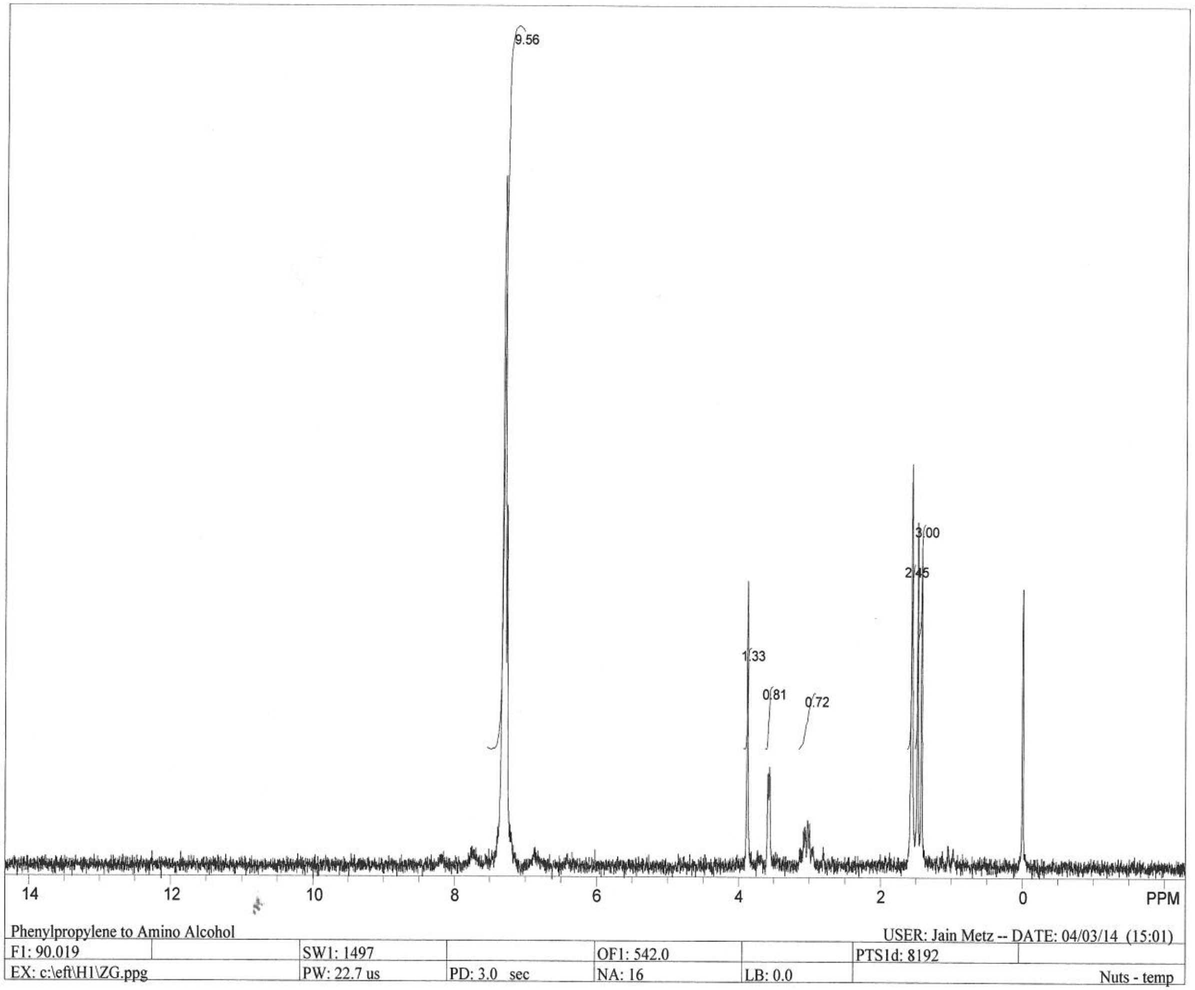
Analyst Administrator
Date Thursday, April 03, 2014 2:58 PM

Jain Metzker Phenylpropylene Oxide to Amino Alcohol (4/2/14)

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

240 g/mol
C16H18ON





Phenylpropylene to Amino Alcohol							USER: Jain Metz -- DATE: 04/03/14 (15:01)
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EX: c:\eft\H1\ZG.ppg		PW: 22.7 us	PD: 3.0 sec	NA: 16	LB: 0.0		Nuts - temp

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

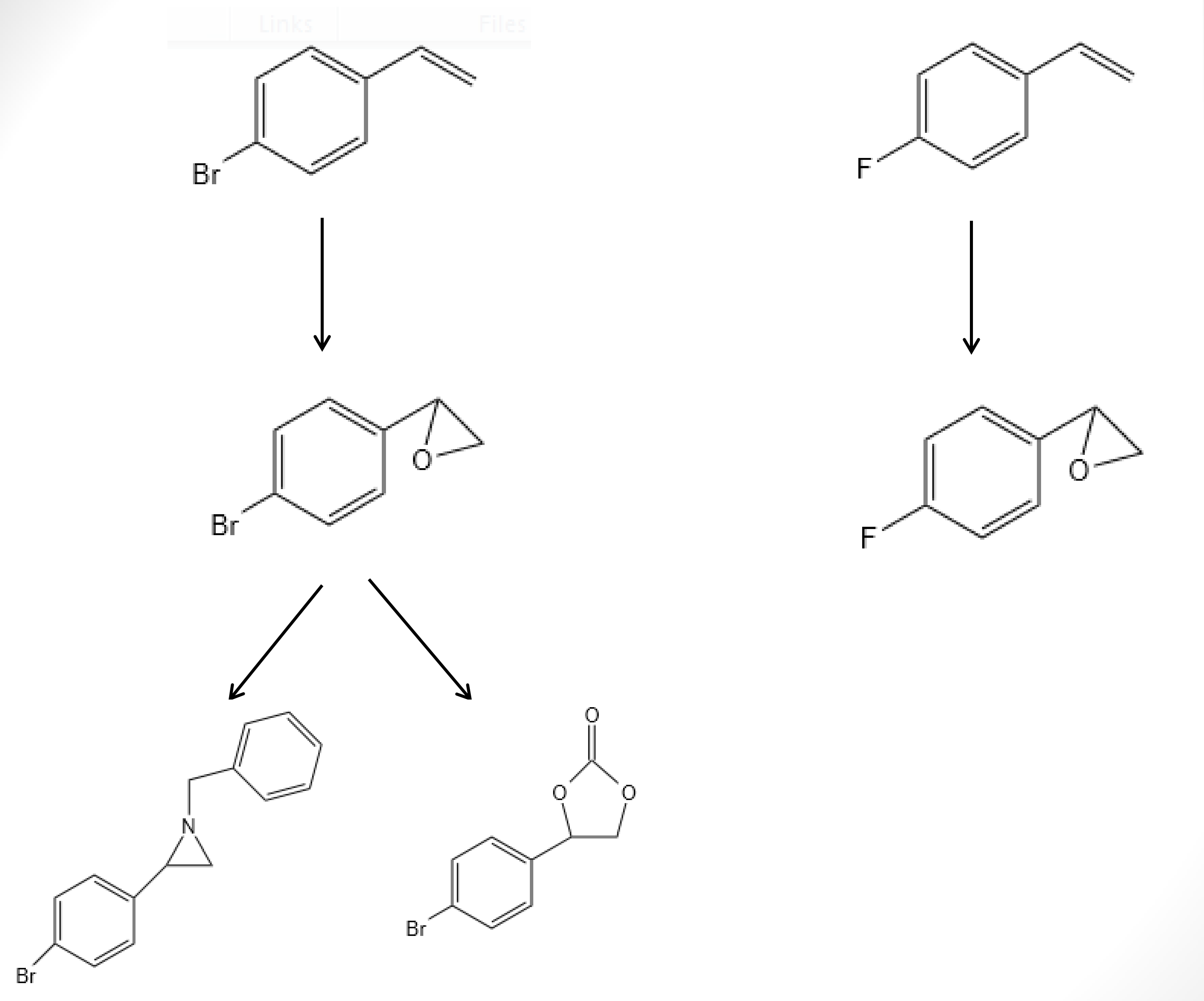
Other Attempted Reactions

- Amino alcohol → Aziridine
  - Insignificant product obtained
- Oxirane → Cyclic Carbonate
- Combined oxirane with dry CO2 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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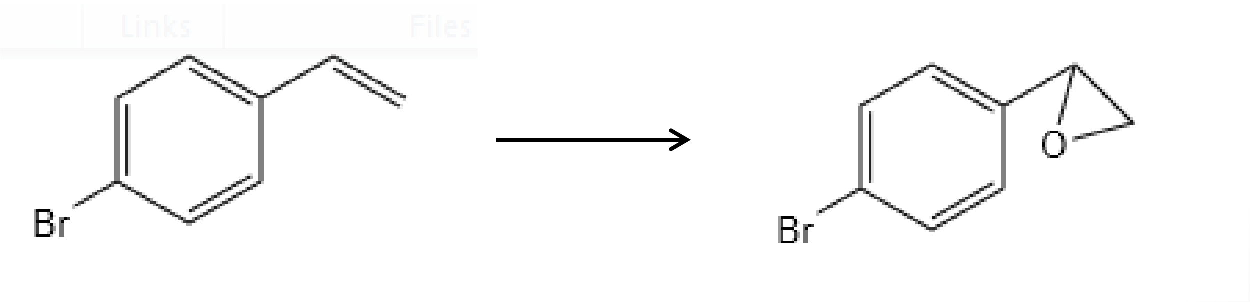
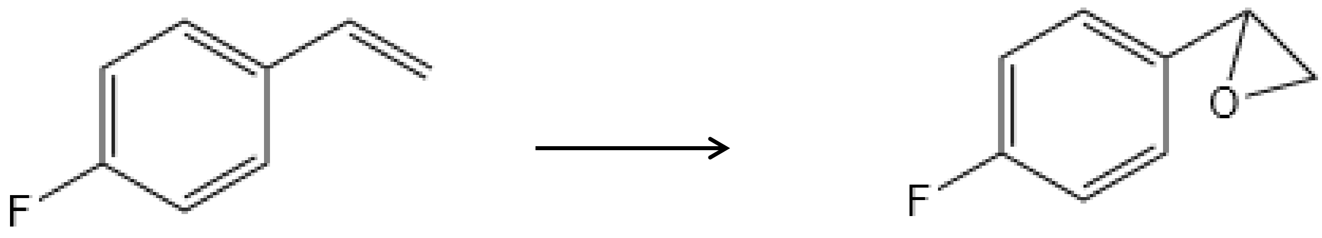
4-bromostyrene to 4-bromostyrene oxide

- 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 vigourously, 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



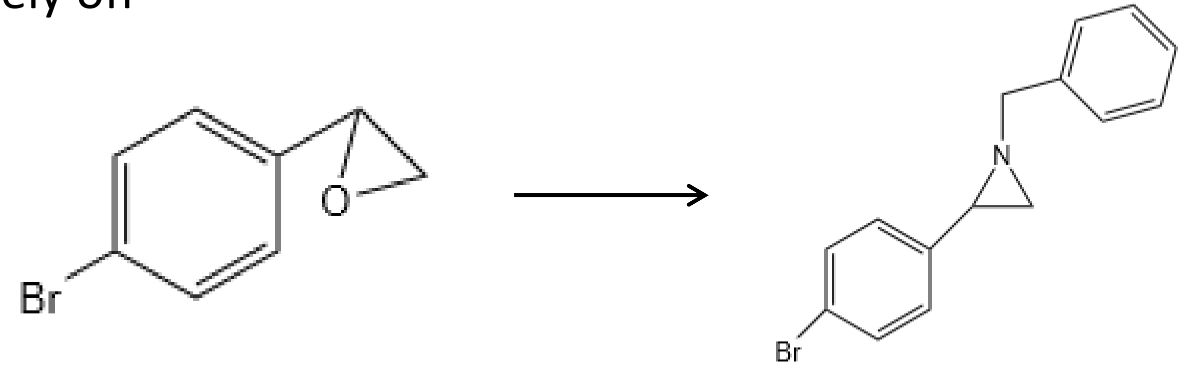
4-fluorostyrene to 4-fluorostyrene oxide

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



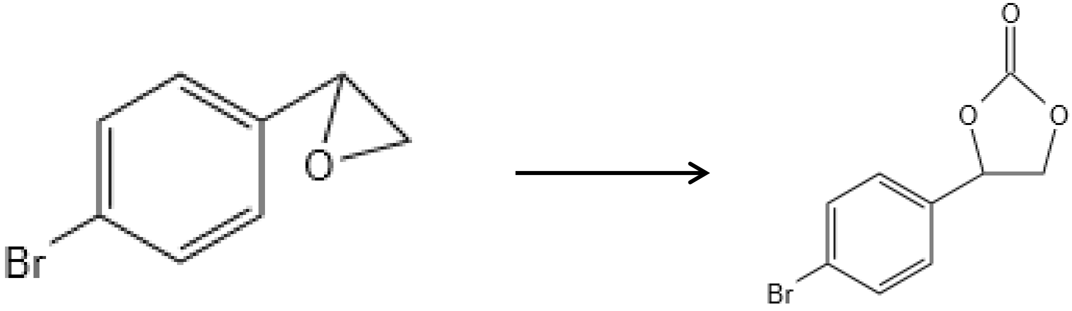
4-bromostyrene oxide to aziridine

- First attempt – stared with 0.2 g of 4-bromostryrene oxide and followed “Organometallics” Paper for Aziridine synthesis
  - Unsuccessful – molecular weight of desired aziridine compound was extremely off
- Second attempt- stated with 1.0 g of new 4-bromostryrene 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_2 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_2 in ball mill for approximately 24 hours
  - IR did not show carbonyl group

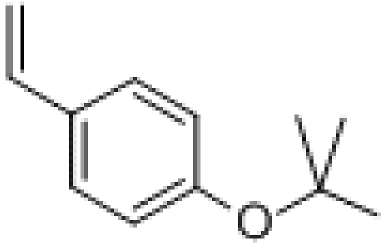


Oxirane Synthesis with Substituted Alkenes and Subsequent Reactions

4-*tert*-butoxystyrene

Elliana and Kelsey

Assessment of Starting Material



Compound	4-*tert*-Butoxystyrene
Molecular Weight	176.25 g/mol
Melting Point	−38 °C
Boiling Point	72-73 °C0.1 mm Hg
Density	0.936 g/mL at 25 °C

Hypothesis:

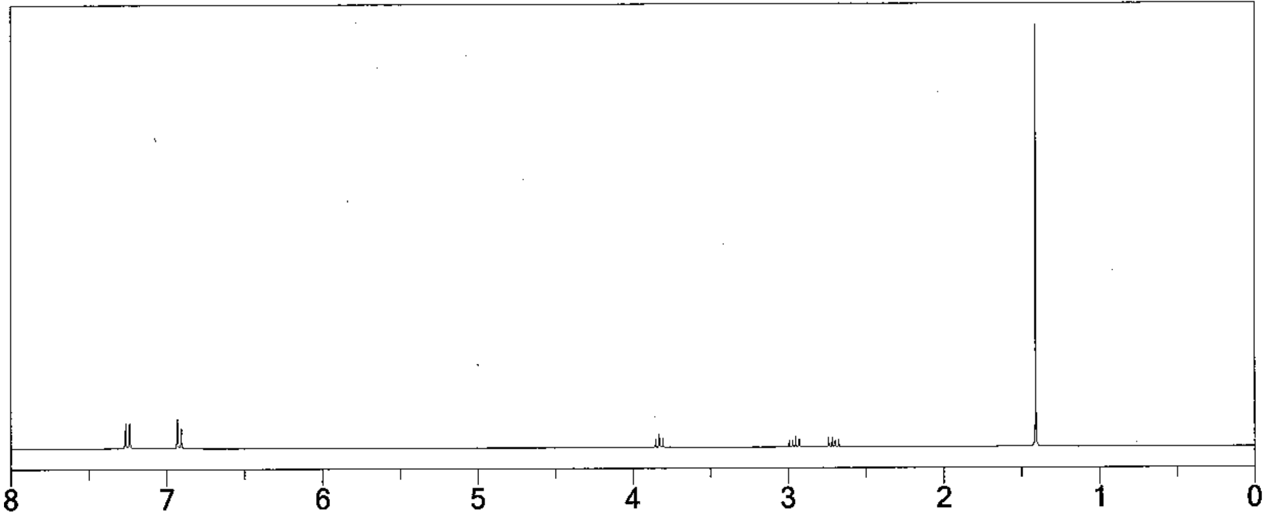
- Due to the electron donating effect of the *tert*-butoxy substituent, it will be possible to synthesize 4-*tert*-butoxystyrene oxide from 4-tert-butoxystyrene.
- As such, it will be possible to synthesize aziridine and oxazolidinone from the resulting oxirane product.

Synthesis of Oxirane

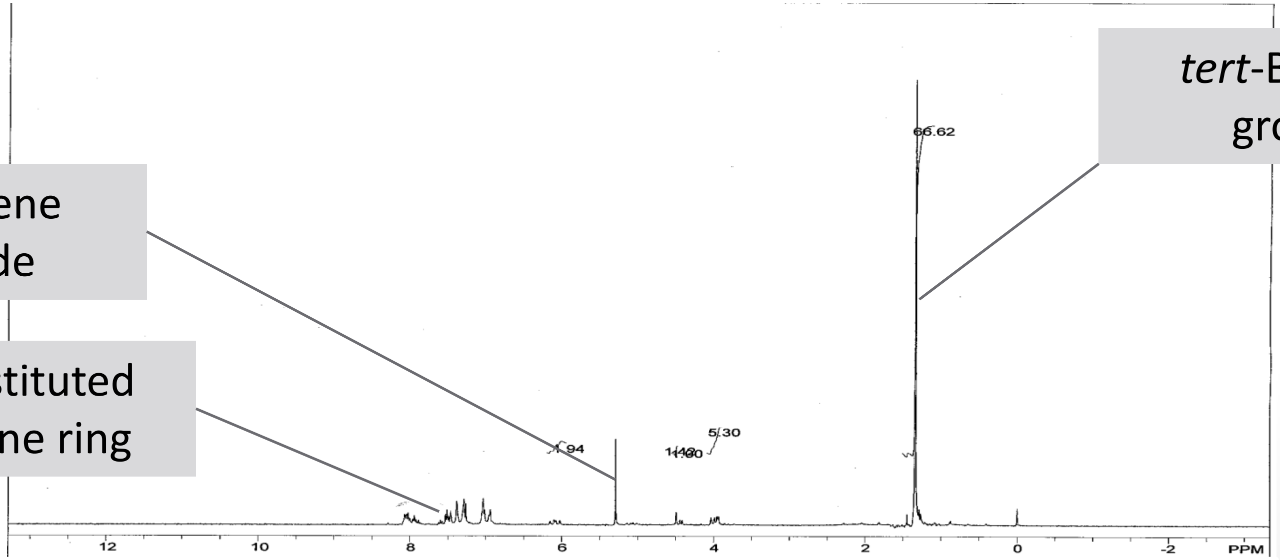
- **First Attempt:** Starting Material Present
  - GCMS was inconclusive, contained no M peak
  - NMR confirmation of 4-*tert*-Butoxystyrene

- **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)



tert-Butoxy group

Methylene chloride

P-substituted benzene ring

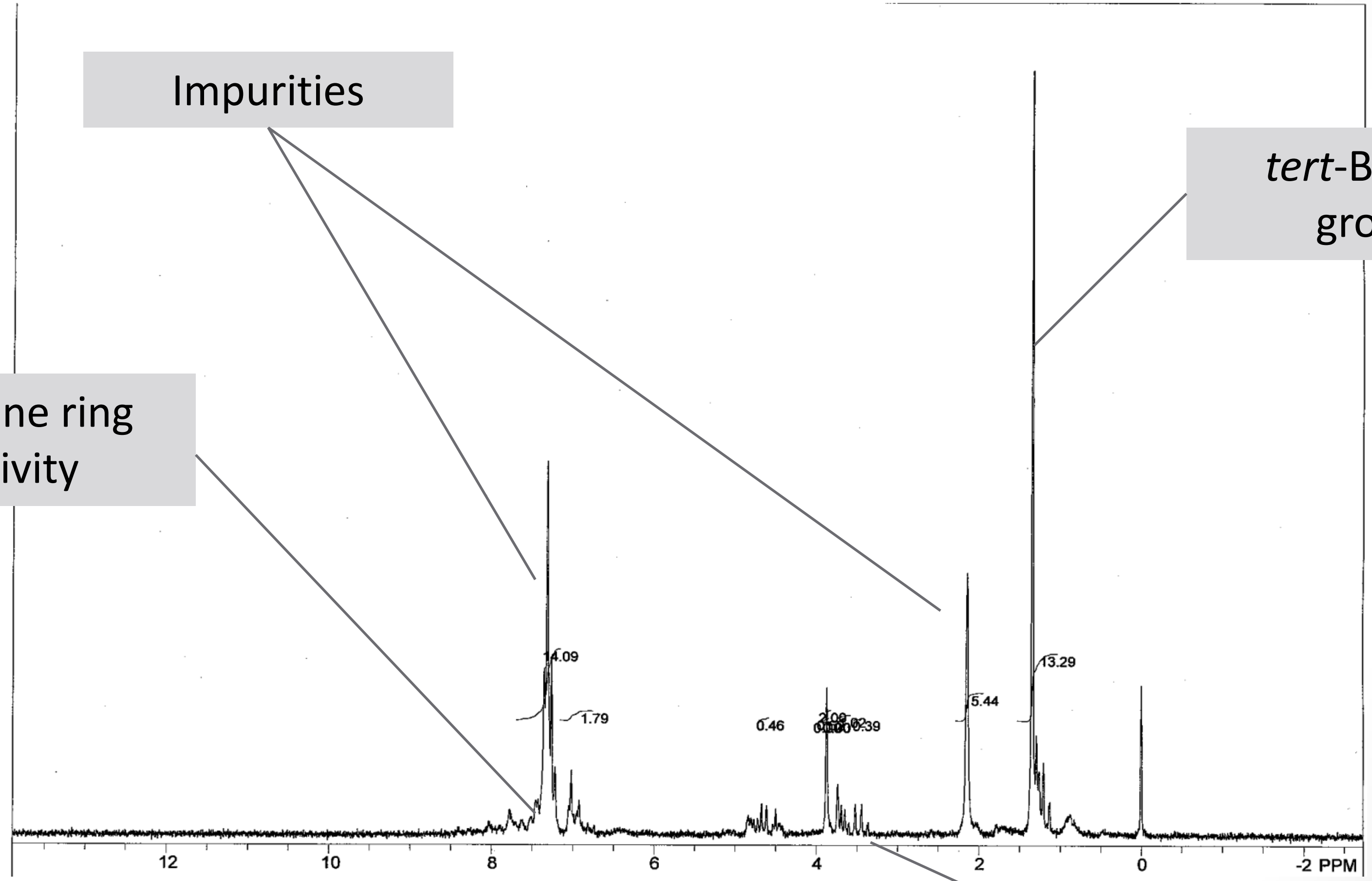
Real NMR (above)

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



Impurities

tert-Butoxy group

Benzene ring activity

Aziridine Hydrogens

NMR Aziridine

Synthesis of Oxazolidinone

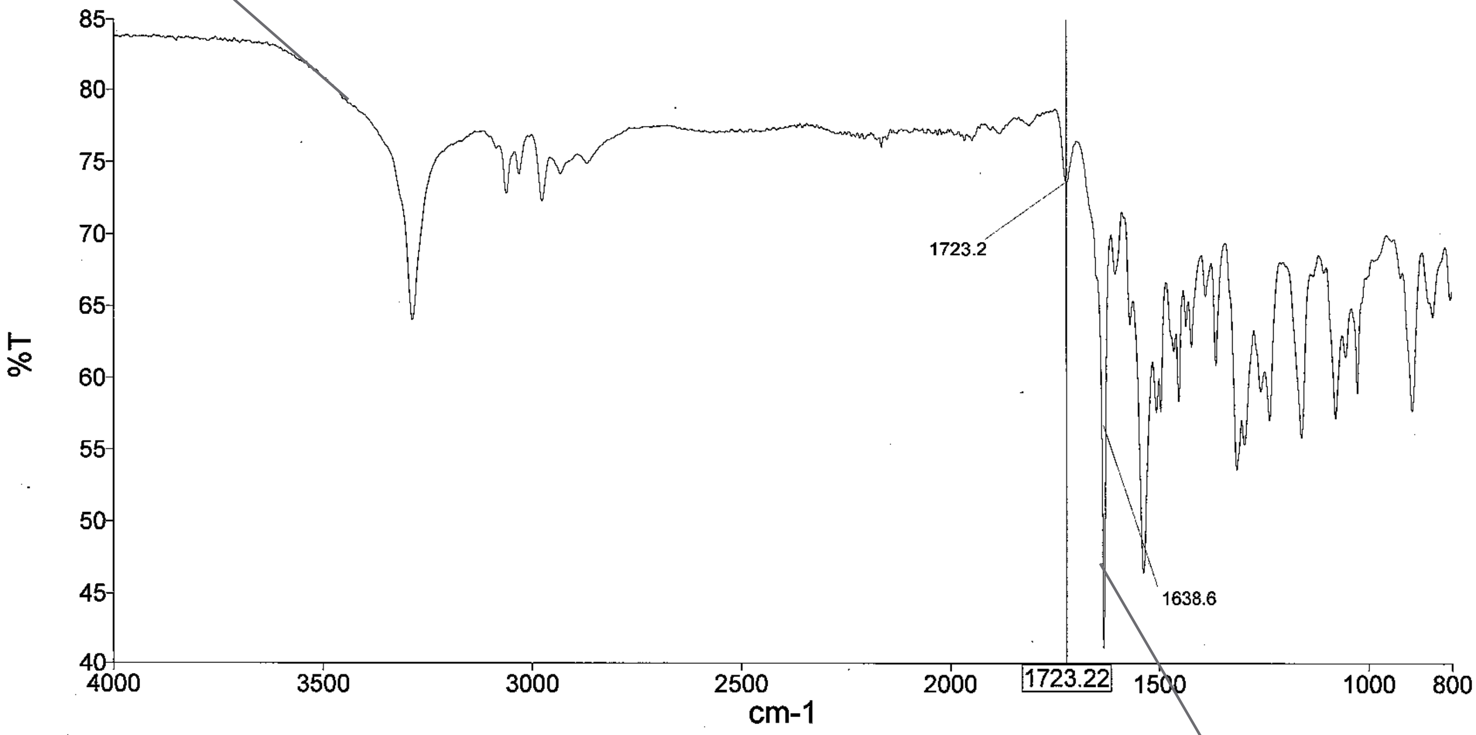
- Inconclusive evidence of product
  - Carbonyl peak observed
  - GCMS inconclusive; no M peak observed

- 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

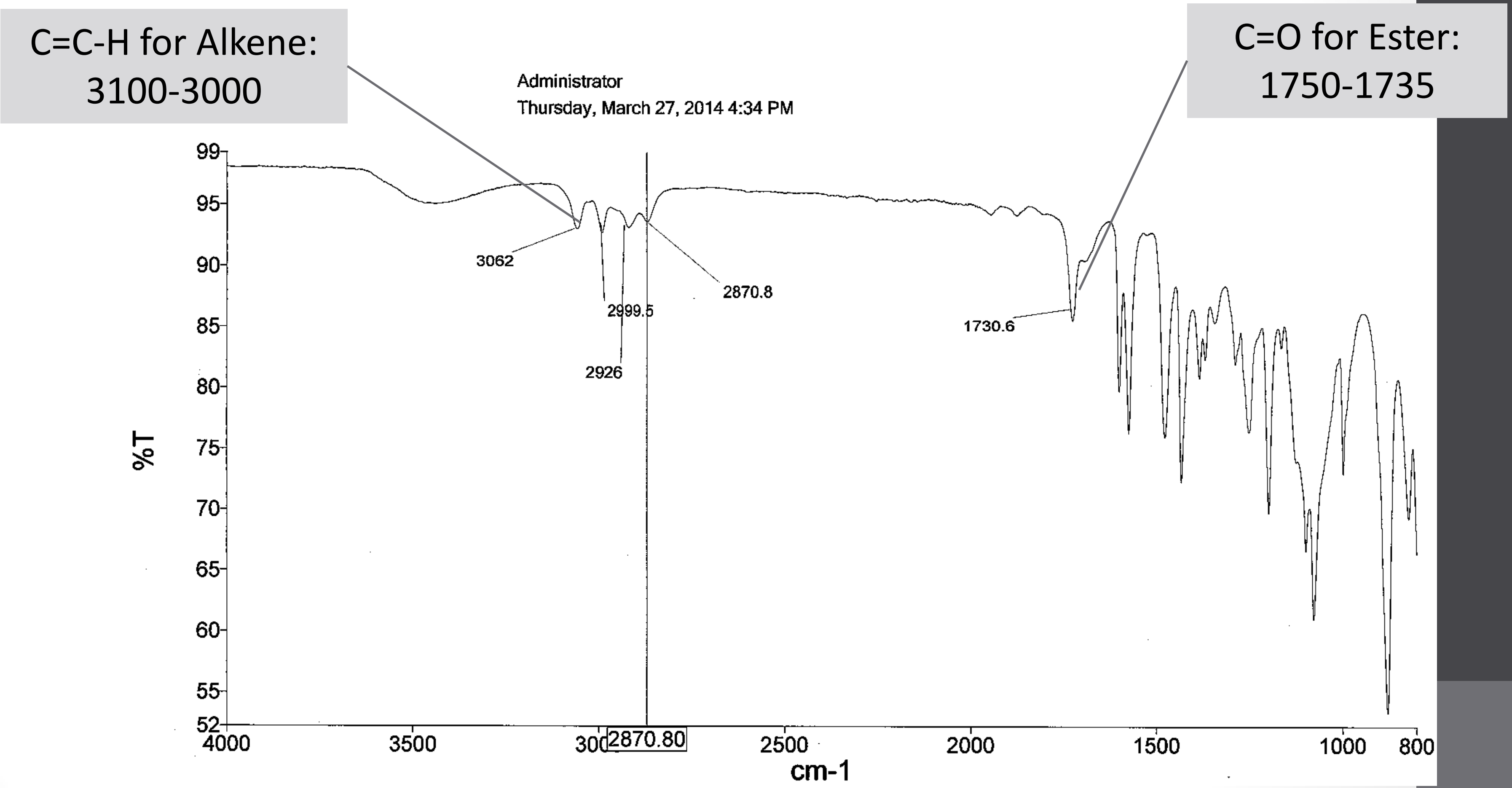
Synthesis of Cyclic Carbonate

- 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

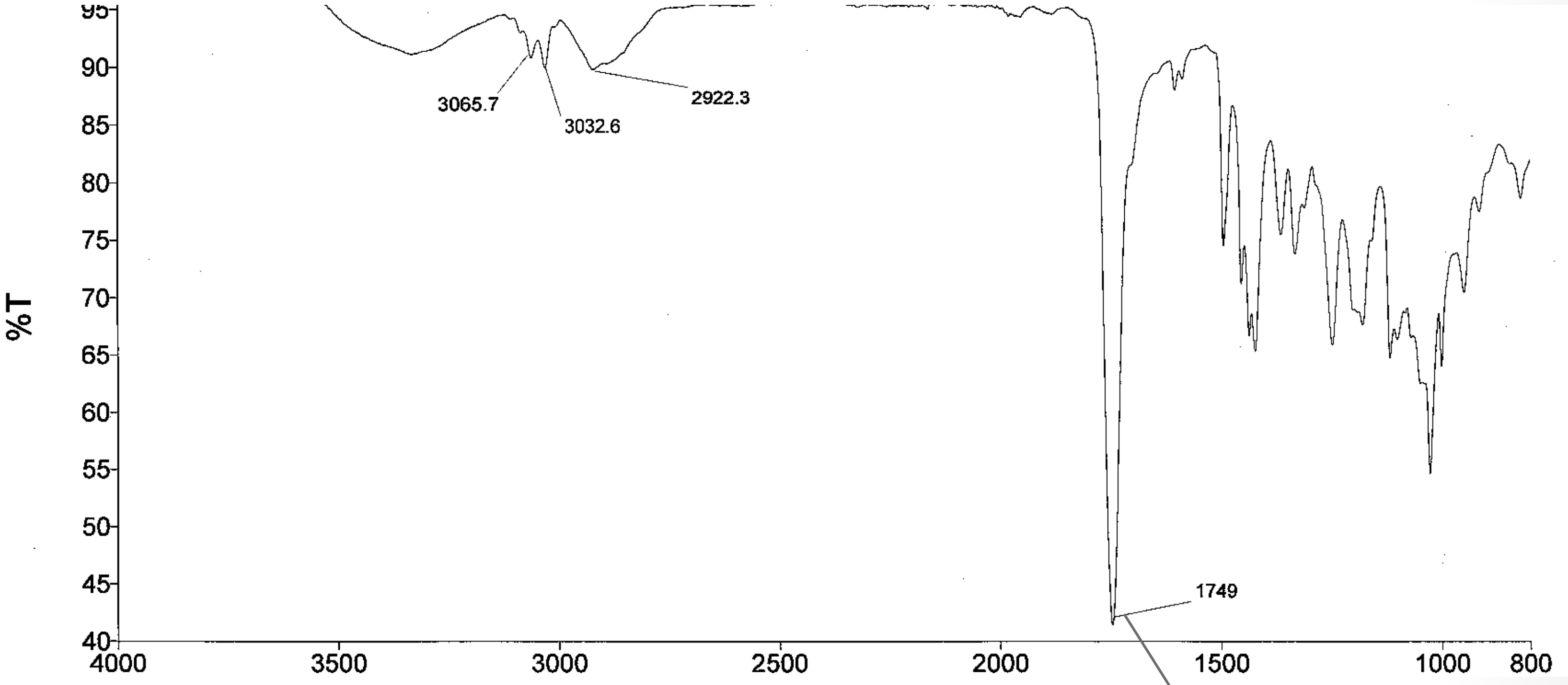
C=O for Ester: 1750-1735

Administrator
Thursday, March 27, 2014 4:34 PM

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

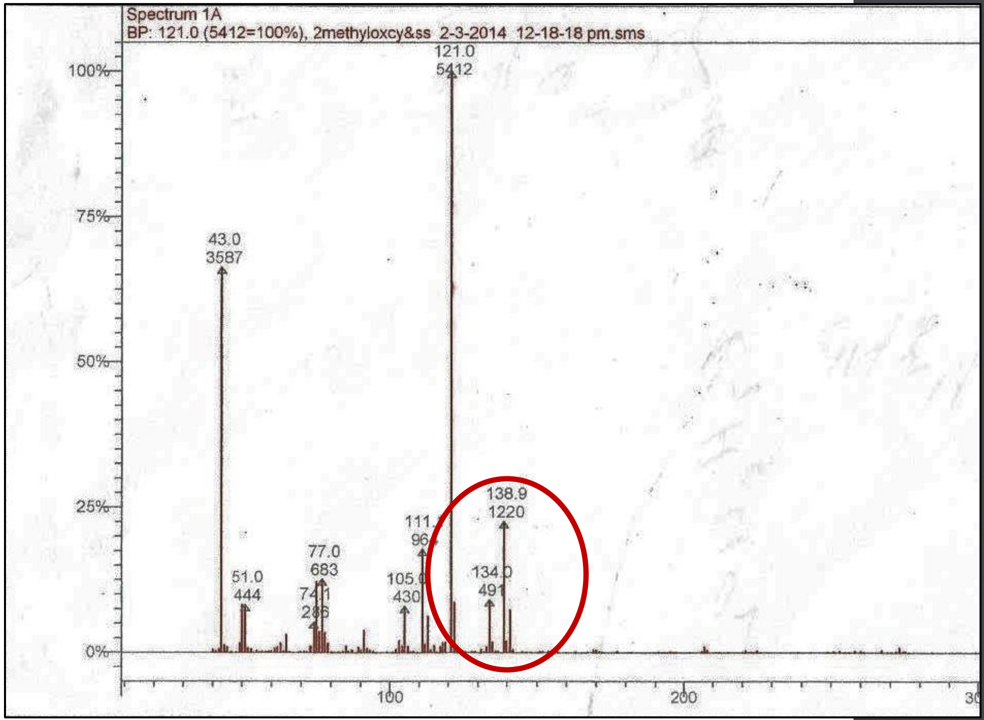
First Attempt - Oxirane

Method

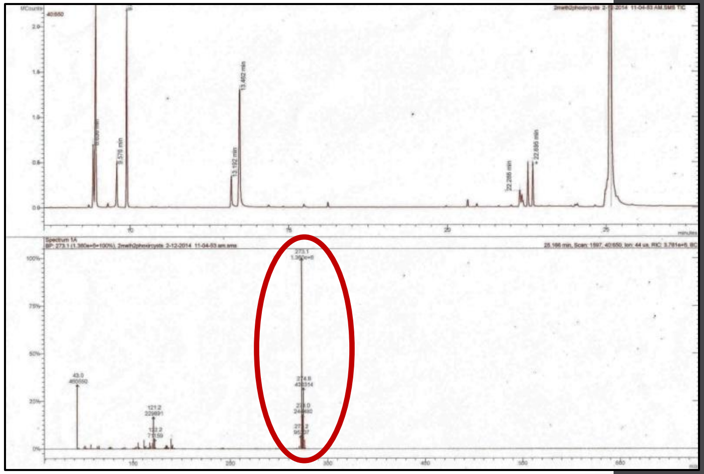
- Traditional procedure

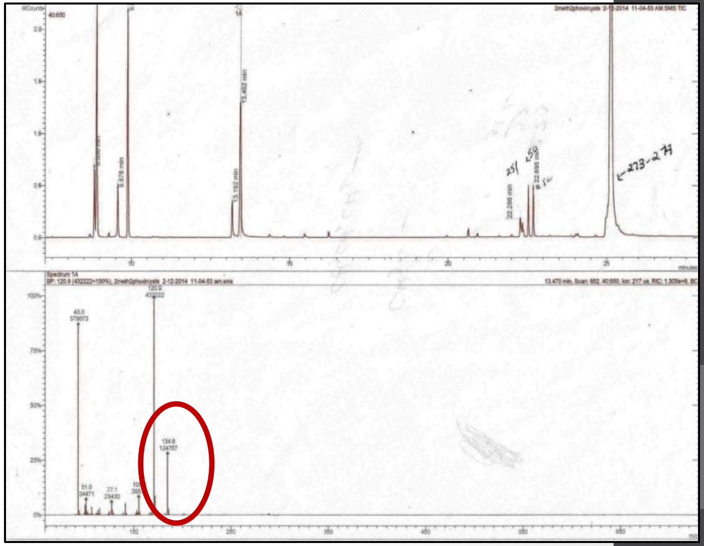
Results

- 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 cm^{-1} (mCPBA present)

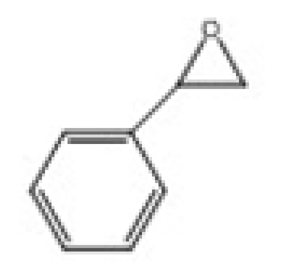
Fourth Attempt - Oxirane

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)



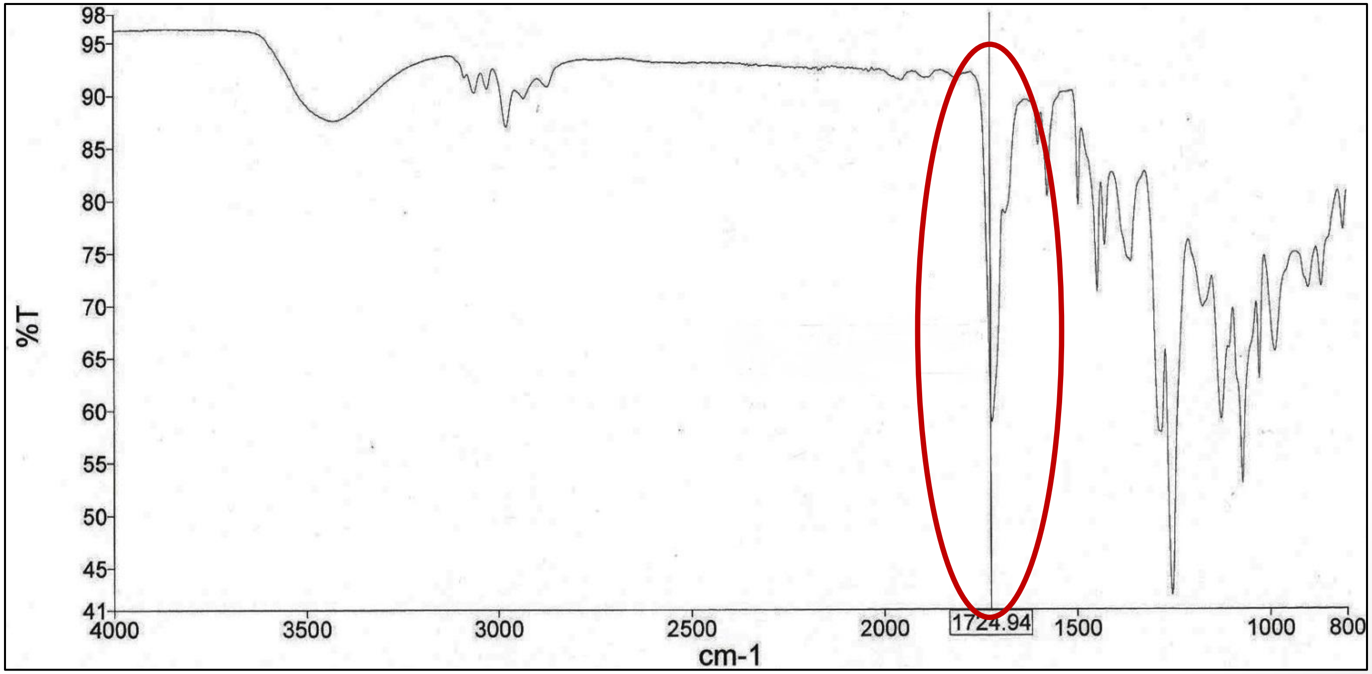
Next Steps

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



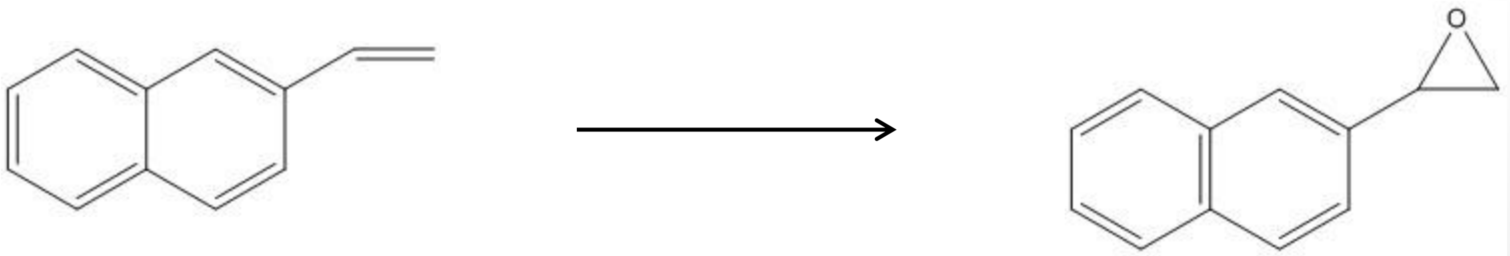
Oxirane Synthesis with Substituted Alkenes and Subsequent Reactions

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

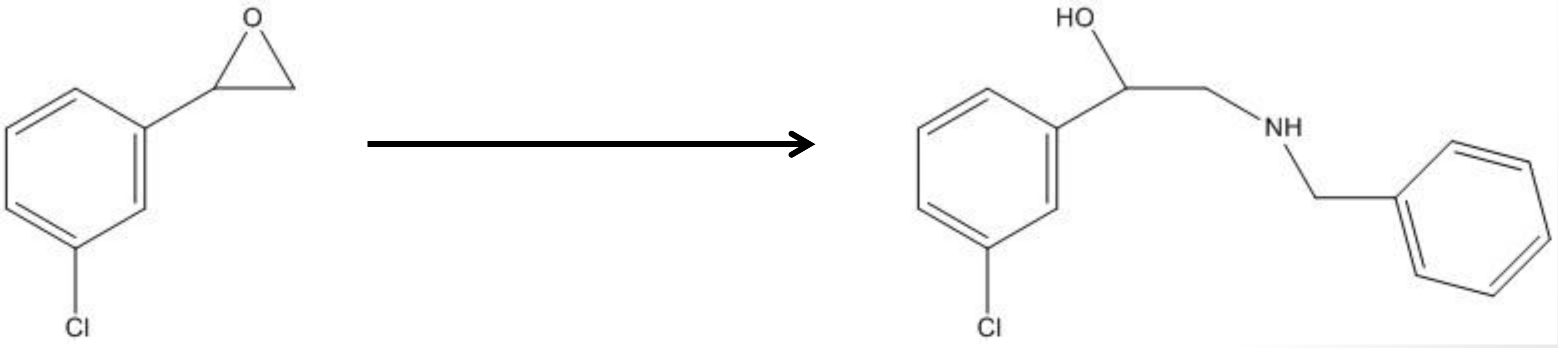


Results

- <u>First attempt</u>: no oxirane acquired, temperature fluctuated during heating process of 1 hour
- <u>Second attempt</u>: 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

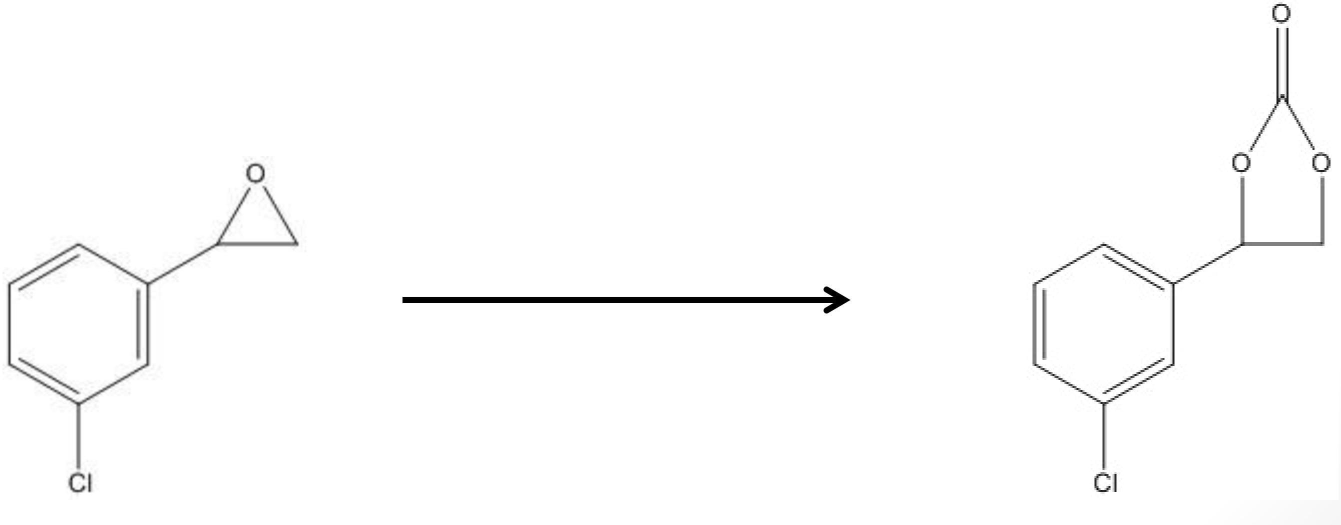
- First Attempt: we had a viscous yellow solution which required a large amount of hexane, product potentially left on filter paper
  - Rinsed out of paper with dichloromethane and repeated procedure
  - This resulted in an orange colored solution
  - GCMS identified product as not being an Amino Alcohol

Results (cont.)

- <u>Second Attempt</u>: 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 (CO_2) in ball mill tube
  - Ran ball mill for ~16 hours
  - Identified product using IR



Results

- <u>First Attempt</u>: no product, ran reaction again
- <u>Second Attempt</u>: 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)

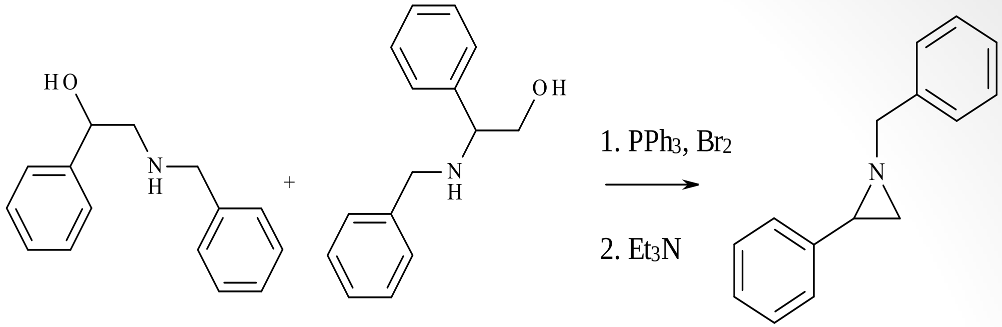
Aziridine Synthesis – standard preparation versus new method

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!

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MS Data Review Active Chromatogram and Spectrum Plots - 2/7/2014 12:52 PM

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Sample: aziridG4CM
Scan Range: 1 - 2547 Time Range: 0.00 - 39.97 min.

Operator: Honors
Date: 2/7/2014 11:53 AM

Traditional Method

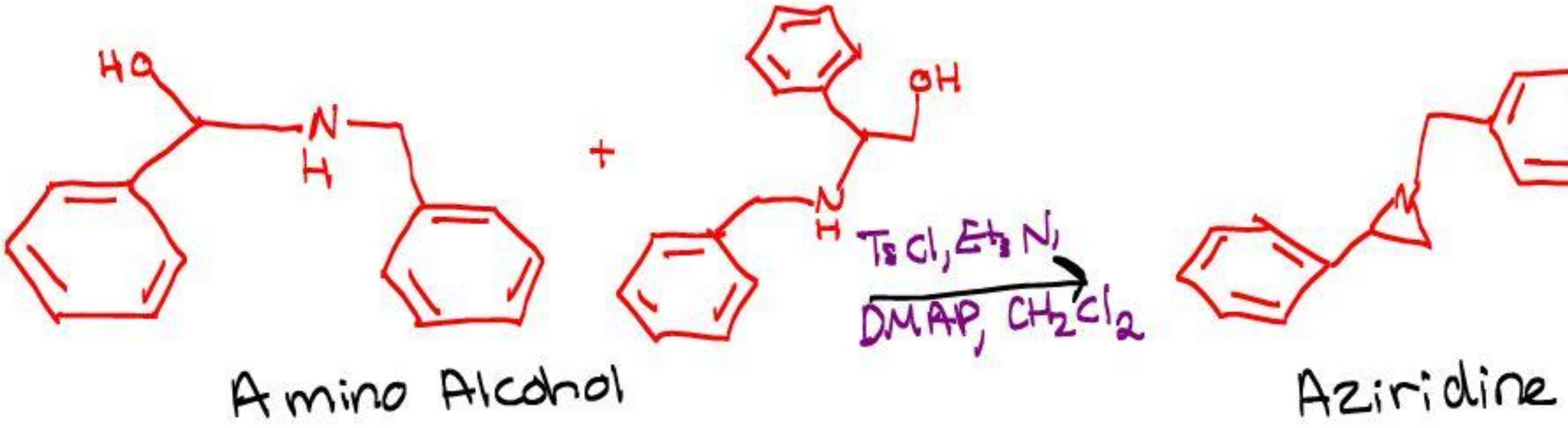
Spectrum 1A
BP: 91.0 (638720=100%), aziridg4cm 2-7-2014 11-53-46 am.sms

20.036 min, Scan: 1274, 40.650, Ion: 104 us, RIC: 2.045e+6, BC

209.1
Aziridine!

New Aziridine Method

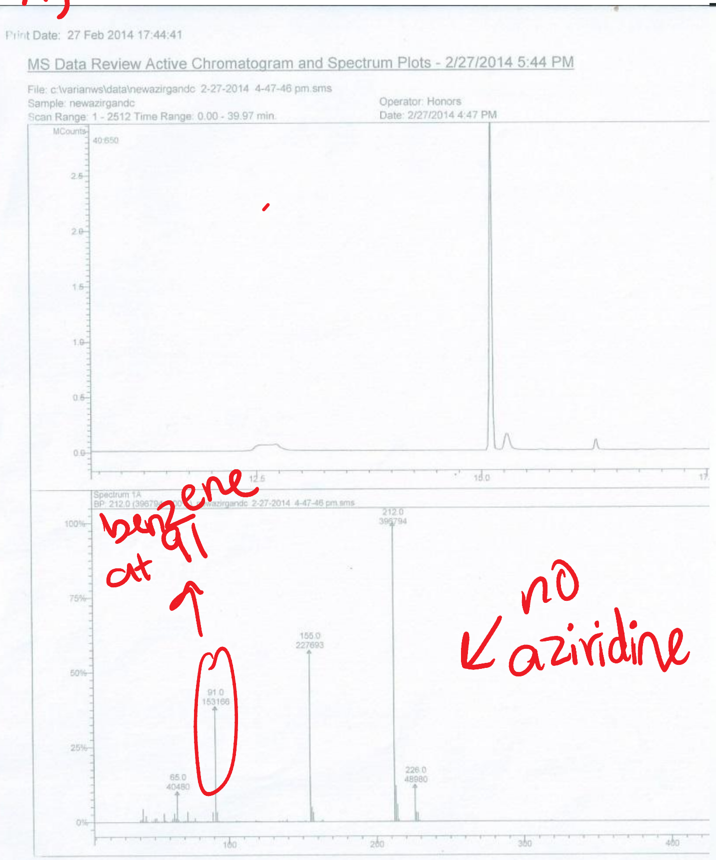
- One pot method from Vicario et al. using Amino Alcohol, DMAP, TsCl, Et_3N, CH_2CL_2 and saturated NH_4Cl



New Aziridine Method cont.

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

A)


Print Date: 27 Feb 2014 17:44:41

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

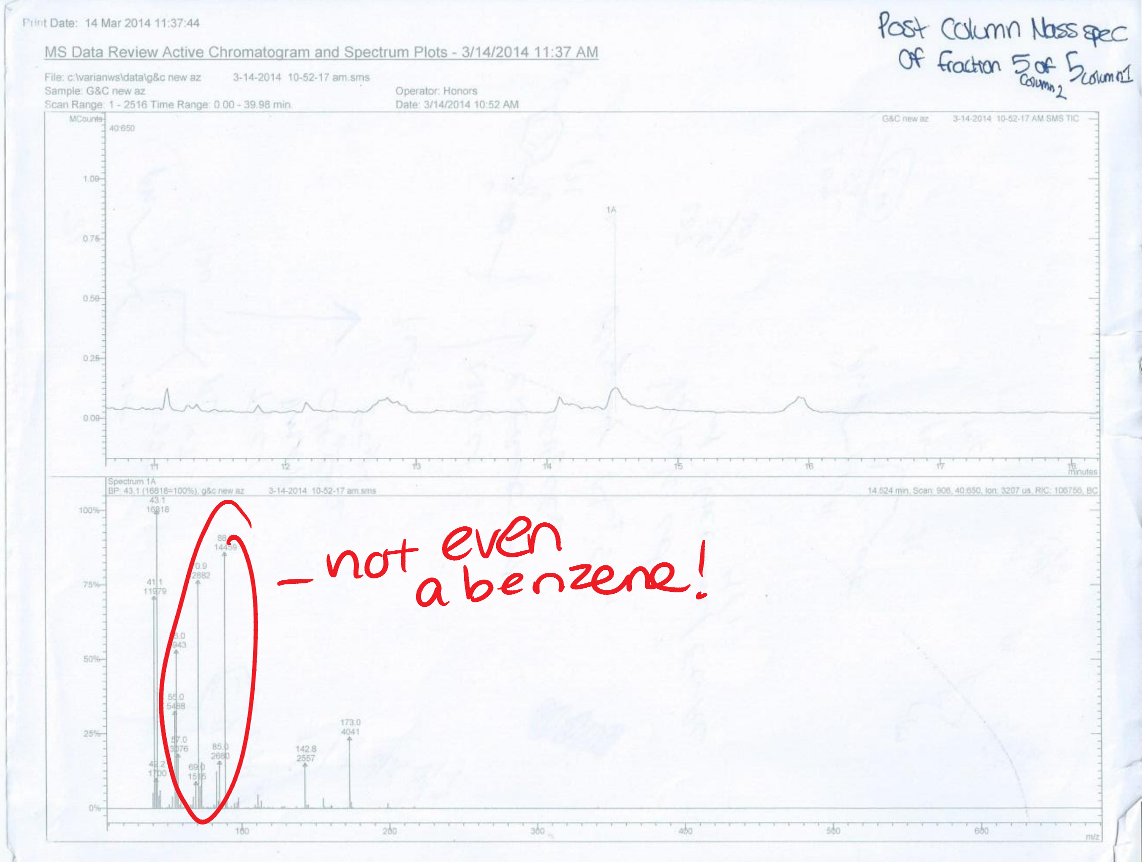
File: c:\varianws\data\newazirgandc 2-27-2014 4-47-46 pm.sms
Sample: newazirgandc
Scan Range: 1 - 2512 Time Range: 0.00 - 39.97 min.
Operator: Honors
Date: 2/27/2014 4:47 PM

Spectrum 1A
BP: 212.0 (396794 [illegible]) newazirgandc 2-27-2014 4-47-46 pm.sms

benzene at 91

no aziridine

B)


Print Date: 14 Mar 2014 11:37:44

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

File: c:\varianws\data\g&c new az 3-14-2014 10-52-17 am.sms
Sample: G&C 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 column 1
column 2

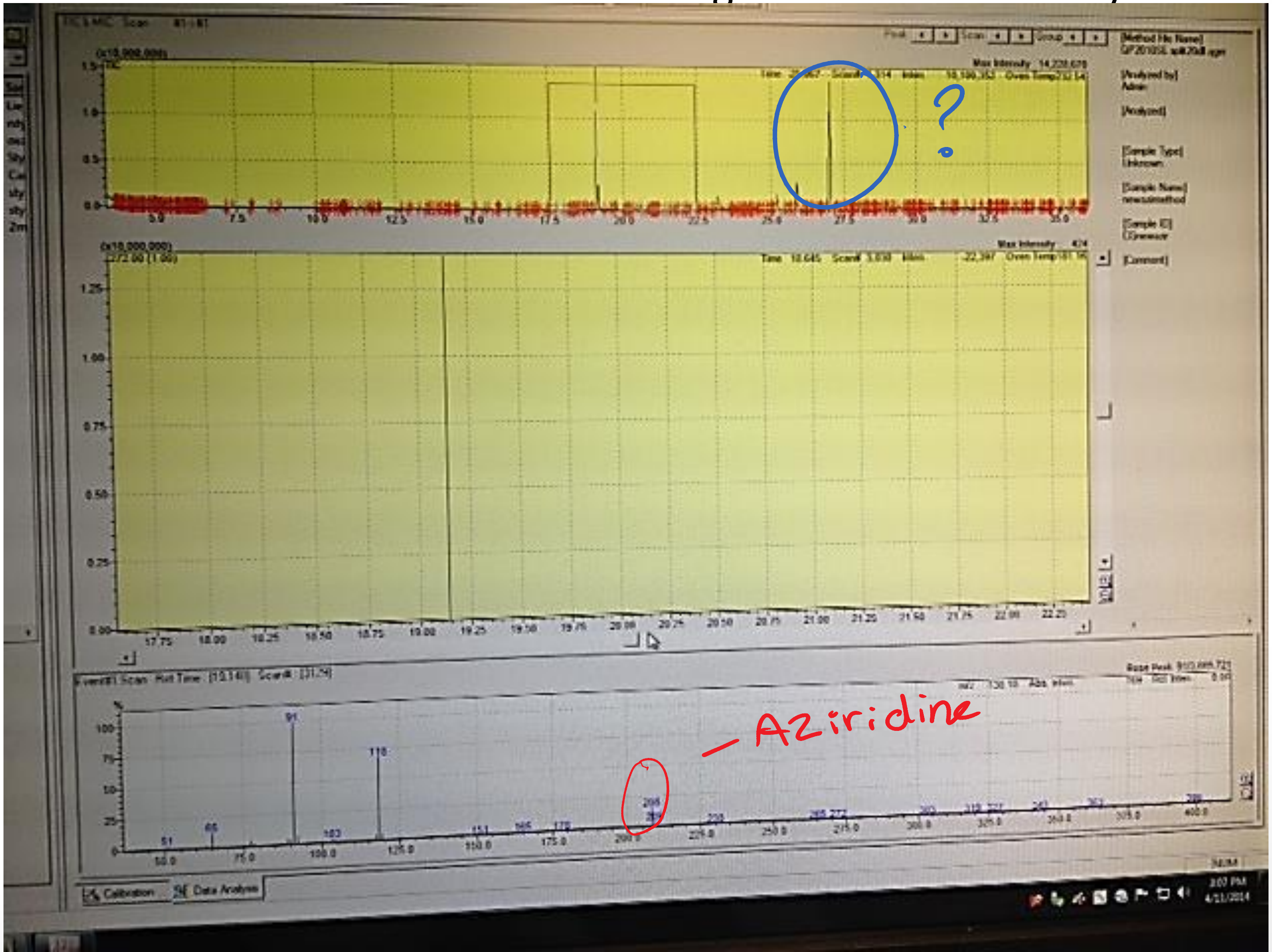
G&C new az 3-14-2014 10-52-17 AM.SMS TIC

Spectrum 1A
BP: 43.1 (16818=100%), g&c new az 3-14-2014 10-52-17 am.sms
14.524 min. Scan: 906, 40.650, Ion: 3207 us, RIC: 106756, BC

- not even a benzene!

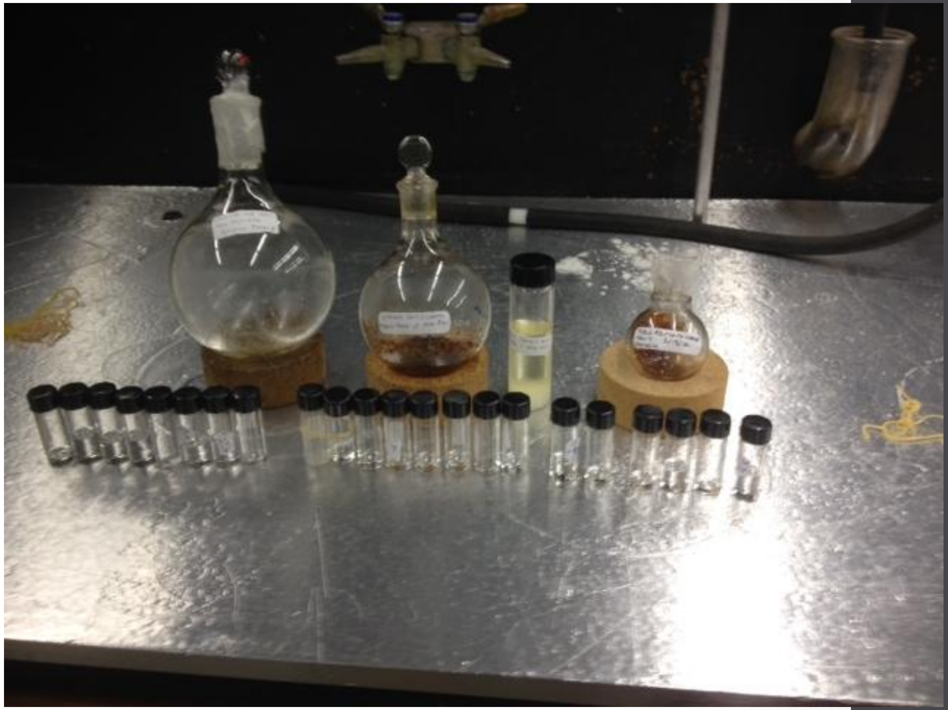
New Aziridine Method Cont.

- 3rd 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!

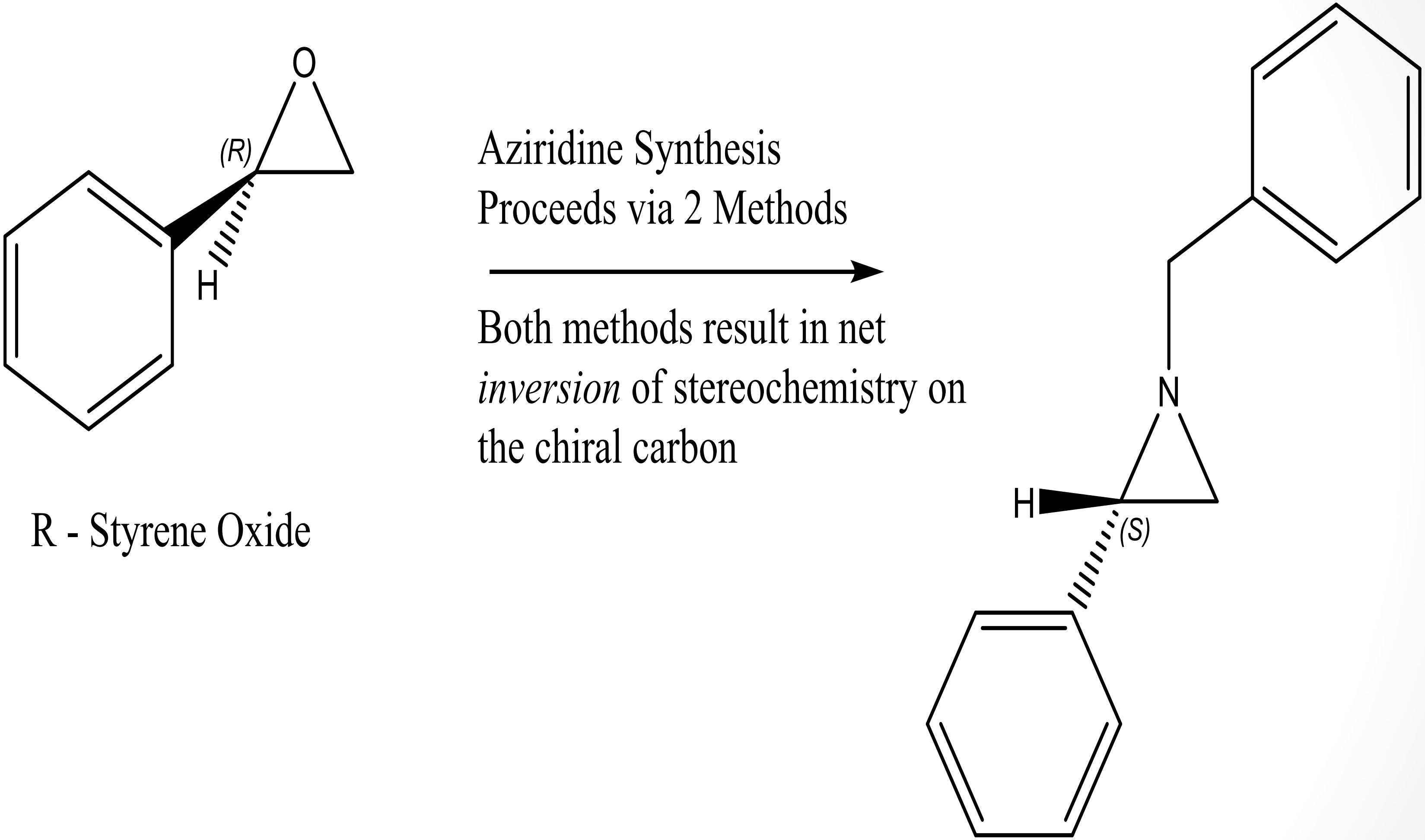


Oxazolidinone Chirality

Alex, Cory and Evan

Stereochemical Mechanism

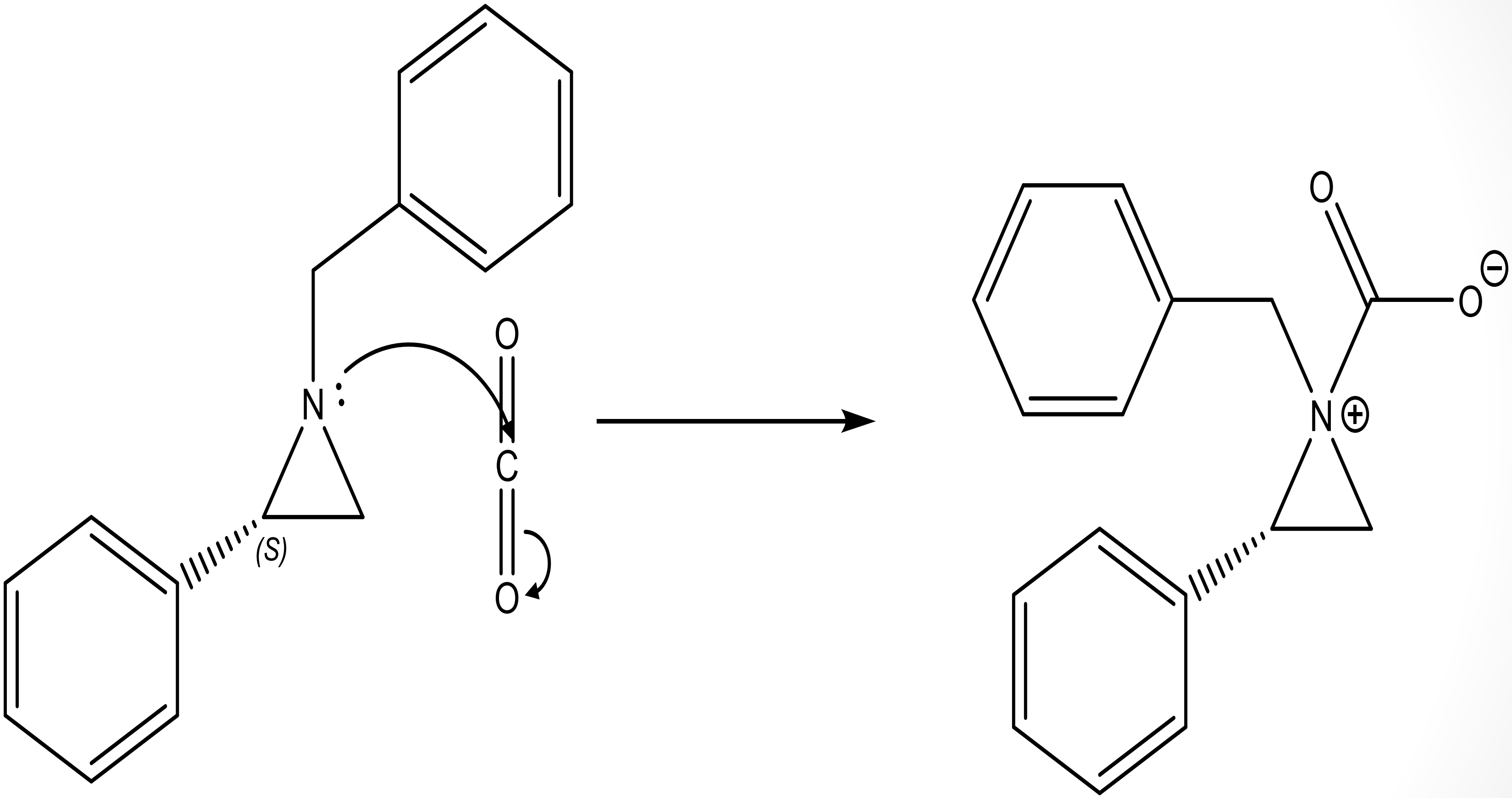
Formation of Oxazolidinone



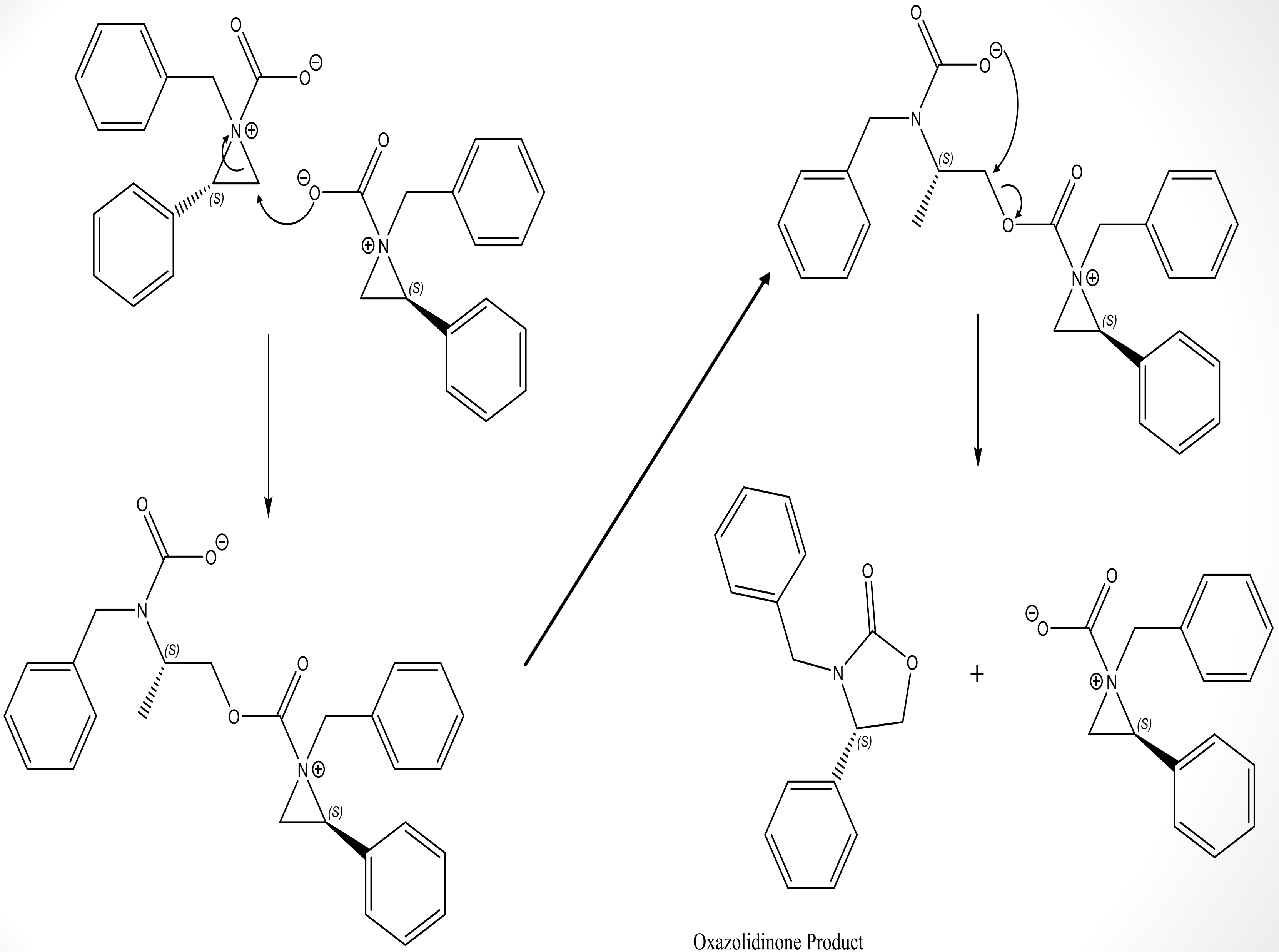
Aziridine Synthesis
Proceeds via 2 Methods

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

R - Styrene Oxide

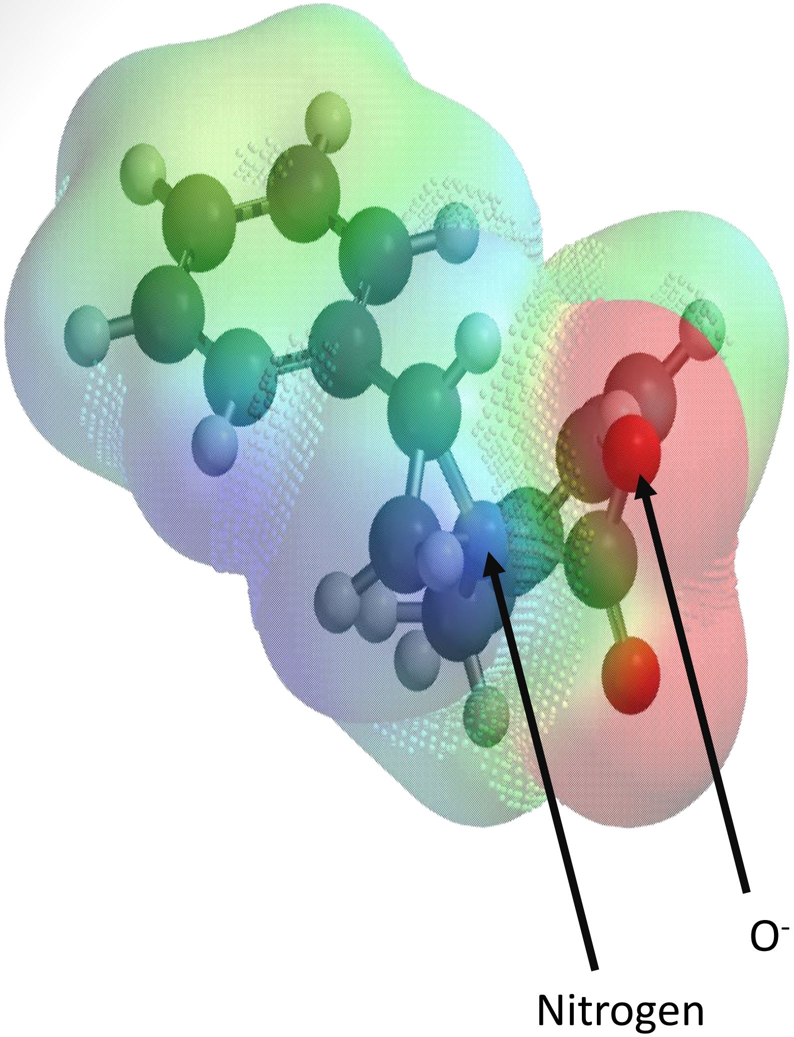

N
(S)
O
C
O
O
O
N
O

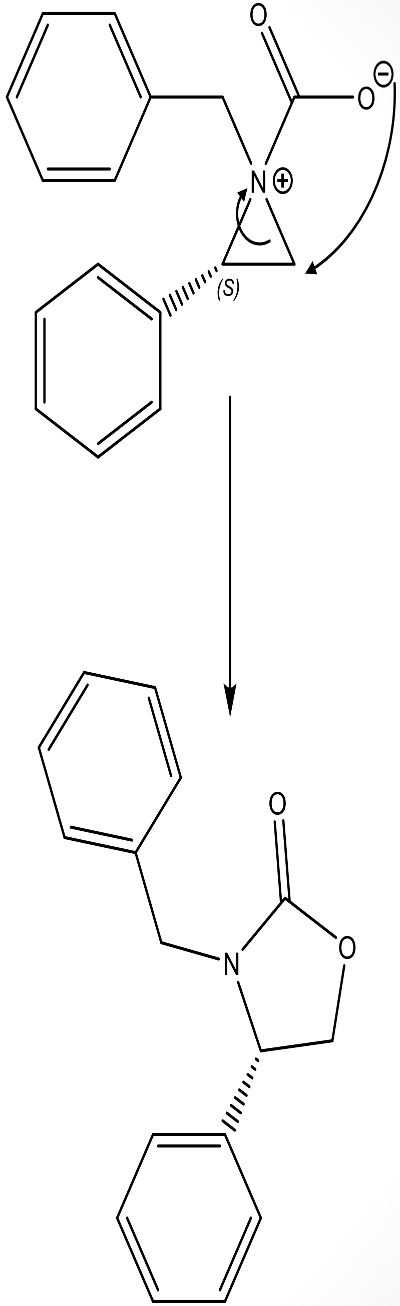
Mechanism One



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

Mechanism Two

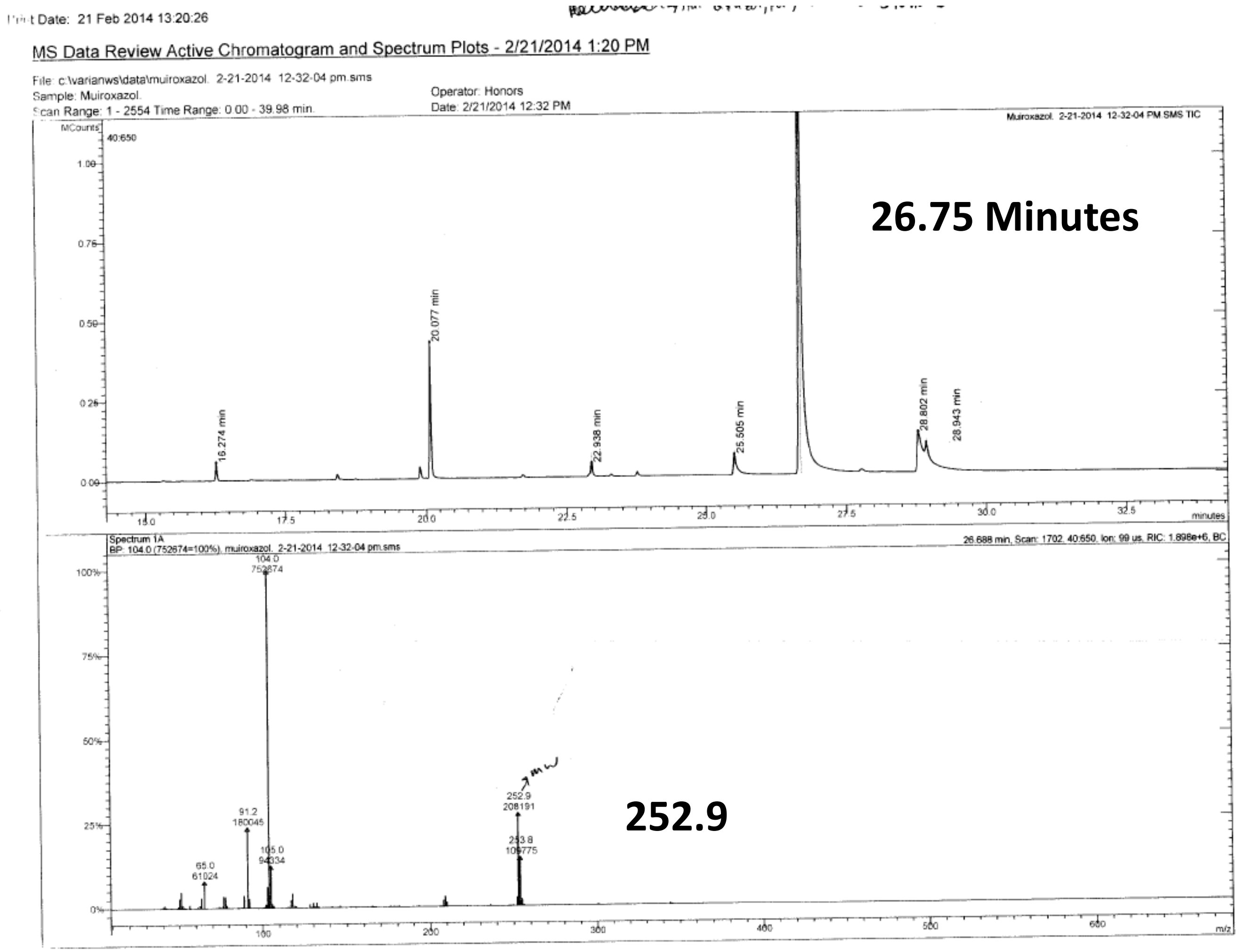

O⁻
Nitrogen


O
O⊖
N⊕
(S)
O
N
O

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:\varianws\data\muiroxazol. 2-21-2014 12-32-04 pm.sms
Sample: Muiroxazol.
Scan Range: 1 - 2554 Time Range: 0.00 - 39.98 min.

Operator: Honors
Date: 2/21/2014 12:32 PM

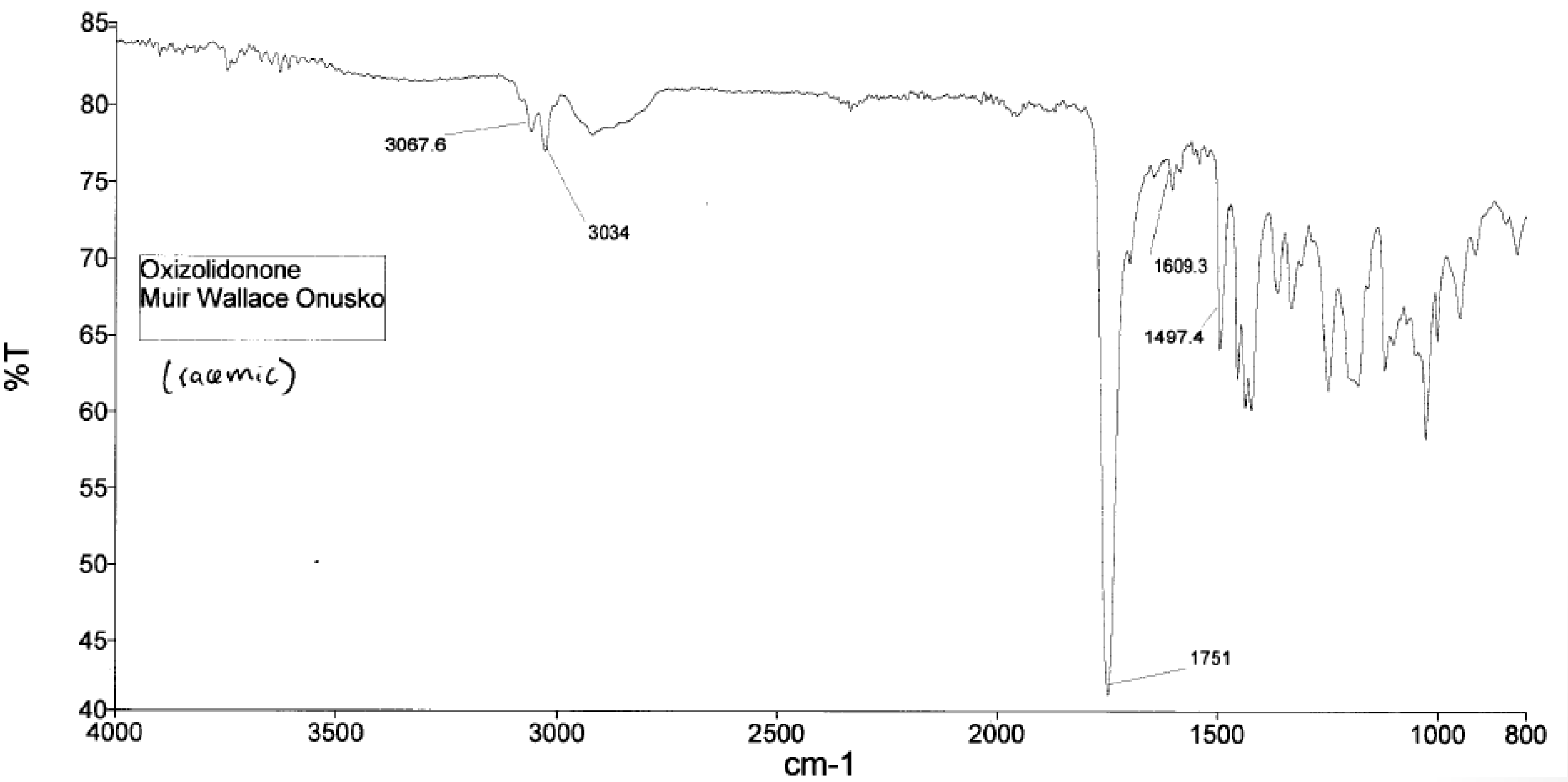
Spectrum 1A
BP: 104.0 (752674=100%), muiroxazol. 2-21-2014 12-32-04 pm.sms

26.688 min, Scan: 1702, 40:650, Ion: 99 us, RIC: 1.898e+6, BC

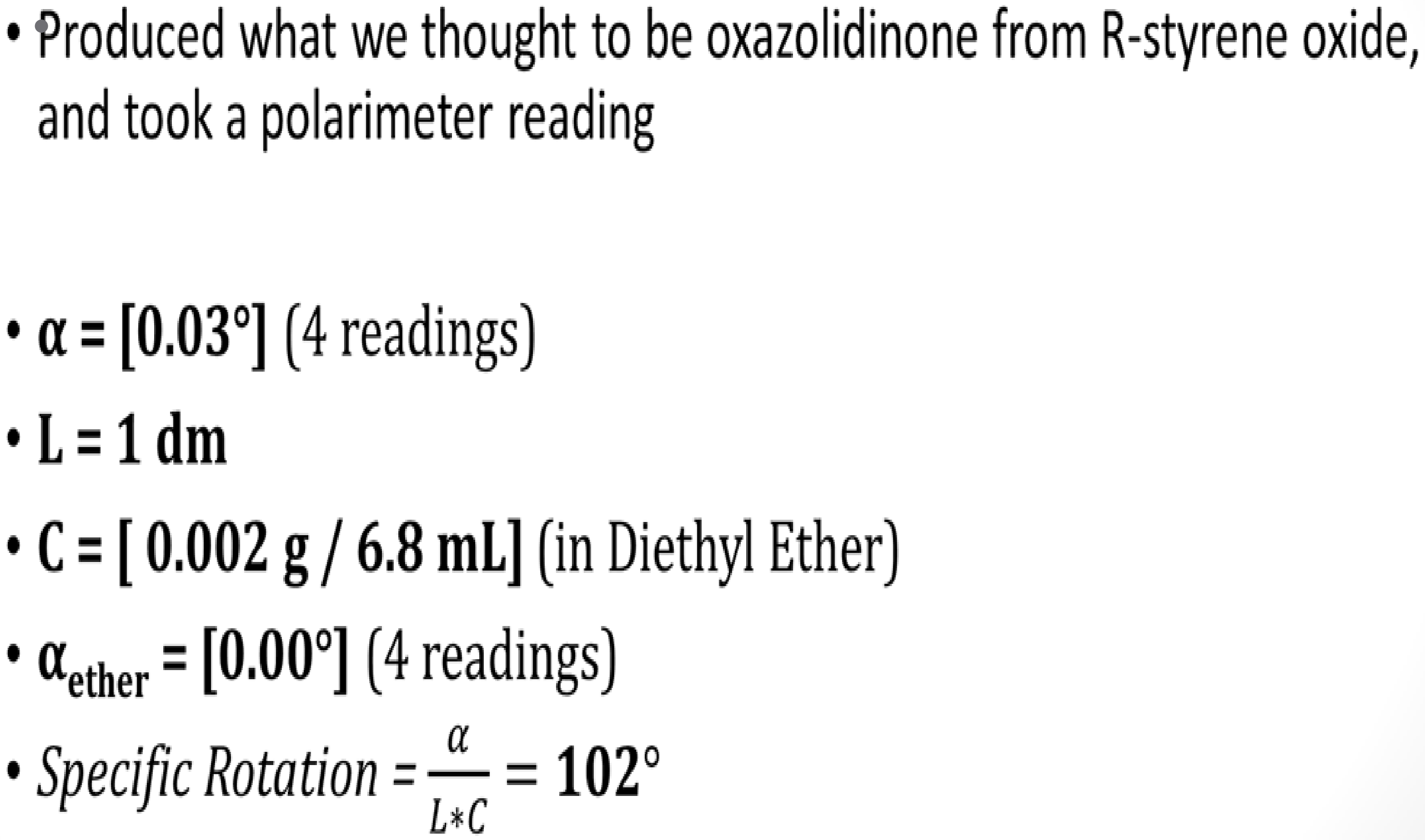
26.75 Minutes

252.9

IR of Racemic Oxazolidinone



Polarimeter Reading



- Produced what we thought to be oxazolidinone from R-styrene oxide, and took a polarimeter reading

- **α = [0.03°]** (4 readings)
- **L = 1 dm**
- **C = [0.002 g / 6.8 mL]** (in Diethyl Ether)
- **α_{ether} = [0.00°]** (4 readings)
- *Specific Rotation* $= \frac{\alpha}{L*C}$ = **102°**

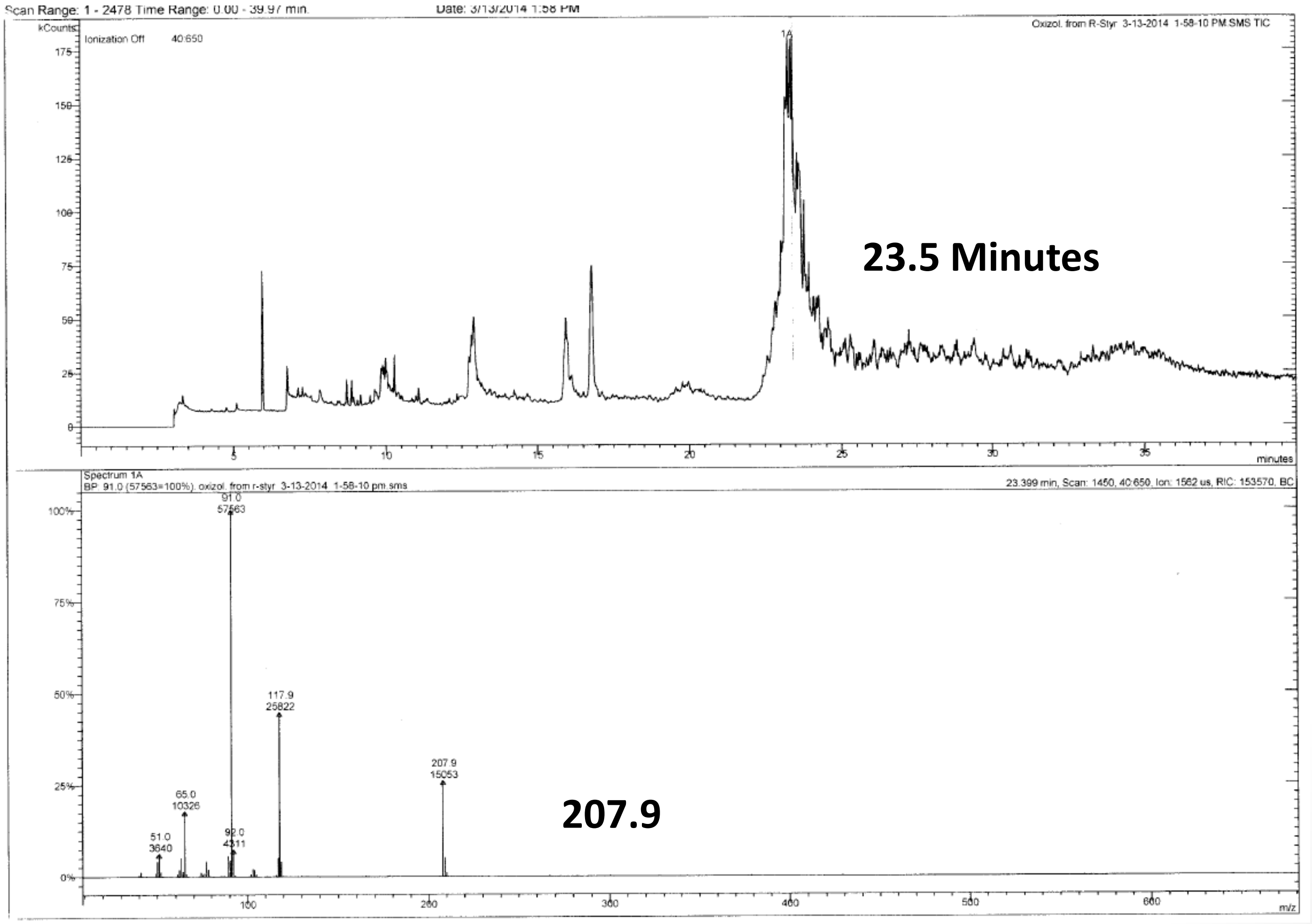
Testing Polarimeter Material

- 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.

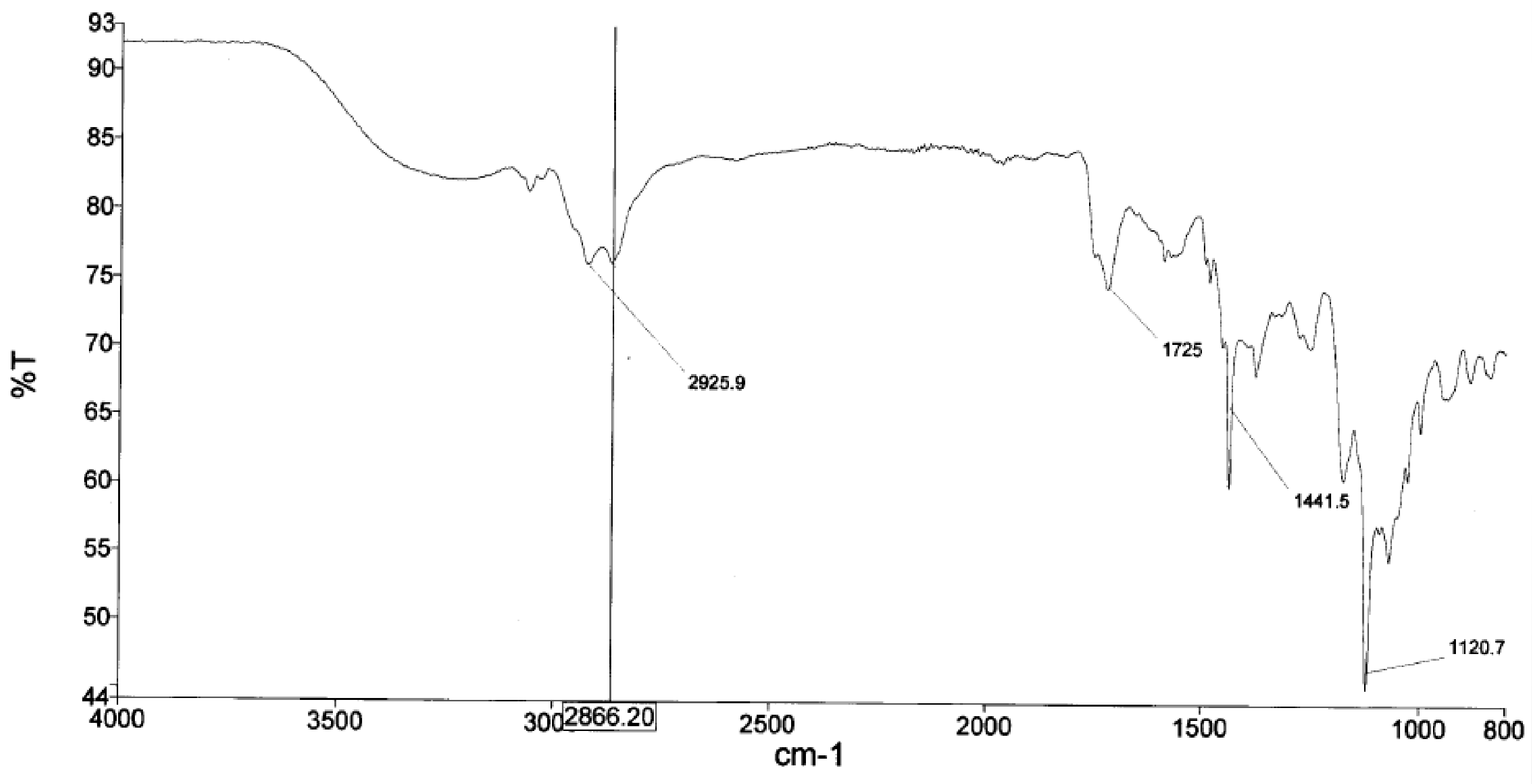
GC-MS



23.5 Minutes

207.9

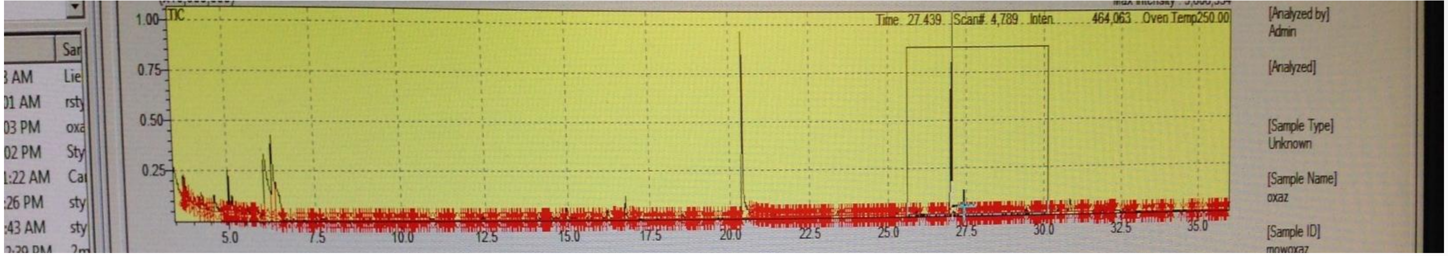
IR Peaks


93
90
85
80
75
70
65
60
55
50
44
%T
4000
3500
3000
2500
2000
1500
1000
800
cm-1
2866.20
2925.9
1725
1441.5
1120.7

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


Time: 27.439 Scan#: 4,789 Inten.: 464,063 Oven Temp250.00

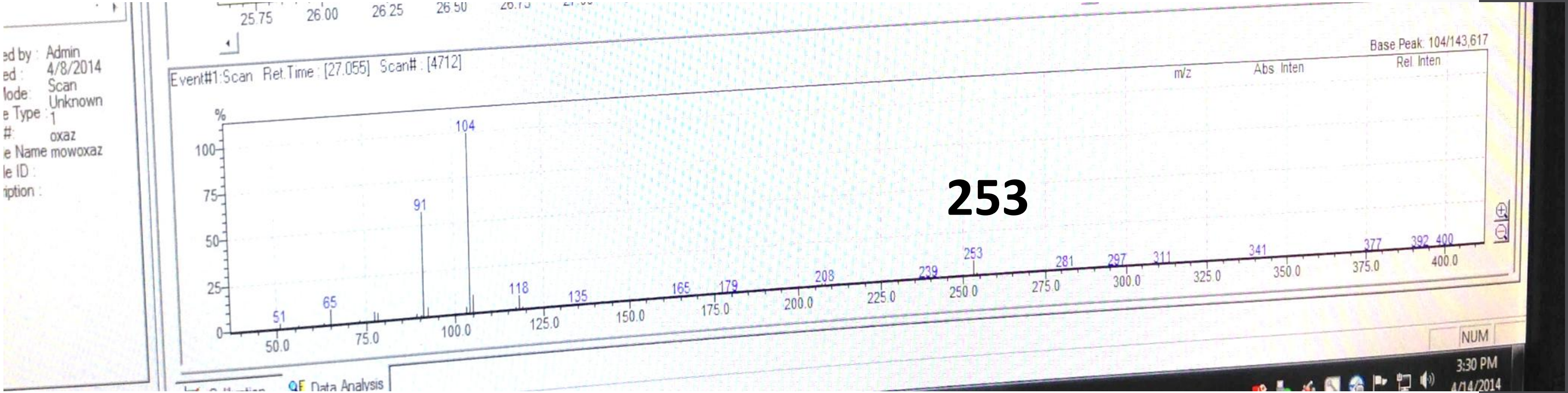
[Analyzed by]
Admin

[Analyzed]

[Sample Type]
Unknown

[Sample Name]
oxaz

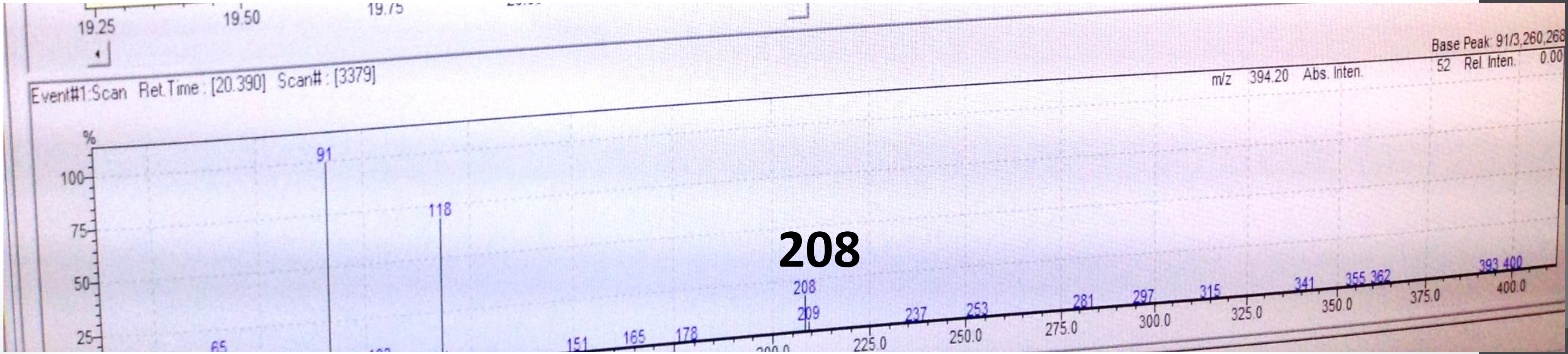
[Sample ID]
mowoxaz


Event#1:Scan Ret.Time : [27.055] Scan# : [4712]

Base Peak: 104/143,617

ed by : Admin
ed : 4/8/2014
lode: Scan
e Type : Unknown
#: 1
e Name oxaz
le ID : mowoxaz
iption :

253

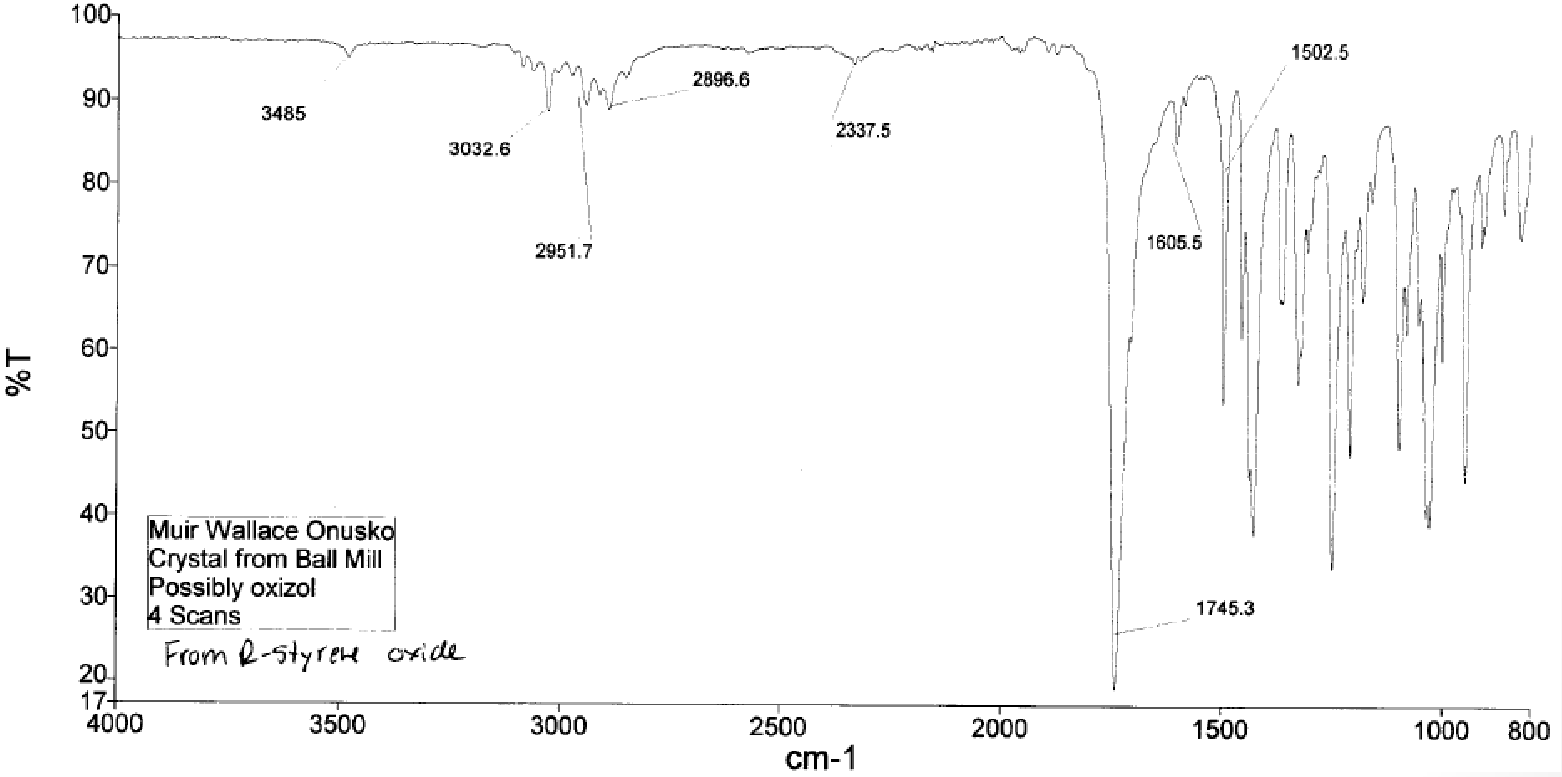

Event#1:Scan Ret.Time : [20.390] Scan# : [3379]

Base Peak: 91/3,260,268

m/z 394.20 Abs. Inten. 52 Rel. Inten. 0.00

208

IR of Sample


%T
cm-1
100
90
80
70
60
50
40
30
20
17
4000
3500
3000
2500
2000
1500
1000
800
3485
3032.6
2951.7
2896.6
2337.5
1605.5
1502.5
1745.3
Muir Wallace Onusko
Crystal from Ball Mill
Possibly oxizol
4 Scans
From R-styrene oxide

Recrystallization

- Crystal is likely oxazolidinone, and the oil is likely aziridine.

- Crystal product was insoluble in isopropyl alcohol, while yellow oil was soluble.

- Recrystalization 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