## Leveraging academic safety culture as a value-added tool for maximizing the undergraduate research experience

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## Speaker's Chemistry Expertise

- Organometallic synthesis
  - Air sensitive manipulations
  - Lanthanide complexes
  - Actinide complexes
- X-ray crystallography
  - Single crystal
  - Small molecule



## Selected Hazards in Speaker's Laboratory

- Flammable solvents
  - Tetrahydrofuran, diethylether, ethyl acetate, hexanes, etc
  - Routine 500 mL to 1 L scales
  - Solvent purification
    - Currently by SPS (drying columns)
    - Past distillation from active metals
- Active metals & pyrophorics
  - Li, Na, K metals
  - LiH, LiAlH<sub>4</sub>, NaH, KH
  - Alkyl lithium and alkyl potassium salts (solution and solid)



# Selected Hazards in Speaker's Laboratory

- Oxidizers
  - conc.  $H_2SO_4$ , conc.  $HNO_3$ , 30%  $H_2O_2$
- Corrosives
  - conc. HCl, NaOH (s), KOH (s)
- Cryogens
  - Liquid nitrogen, Dry ice
- Compressed gasses
  - N<sub>2</sub>, Ar, He
  - H<sub>2</sub>, HCI



# Selected Hazards in Speaker's Laboratory

- Open flame
  - flame drying glassware; glass blowing
- Carcinogens
  - Nitrosyls, hydrazine, benzene, numerous others
- Ionizing radiation (X-rays)
  - Well interlocked
  - Minimal risk



## **Speaker's Background**

- Indiana Univ. of PA: 1987-1991, B.S. Chem.
  - "Wear your safety glasses & be careful"
- Rutgers Marine Science Lab: summer 1989, intern
  - "You're the chemistry major"
- Virginia Tech: summer 1990, intern
  - "Follow the graduate student's instructions."
- Purdue Univ.: 1991-1996, Ph.D. Chem.
  - "1 cr hour Safety Seminar, first semester"
- Univ. of Alberta: 1997-1999, postdoc
  - "You have a Ph.D.; you know what to do."



## **Speaker's Background**

- Los Alamos: 1999
  - Two weeks of safety training
  - "preventable accidents aren't accidents"
- Illinois State University: 1999-present
  - "You're a chemistry faculty member"
  - "you have the Ph.D., so you are the expert"
  - "you are responsible for your students "
- ACS Committee on Ethics 2006-2014
  - "Safety is one of a Chemist's ethical responsibilities"
- Today at ISU: 2015-present
  - "SOP's for all chemicals in research laboratories"



- Maturation as a faculty member
  - more cognizant of risk
  - More concerned about consequences
- Personal experience



One week later





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- Maturation as a faculty member
  - more cognizant of risk
  - More concerned about consequences
- Personal experience



two weeks later

Shifting institutional standards



Saturday, February 7, 2004

### ISU professor burned in lab accident

NORMAL -- A small flash fire in an Illinois State University chemistry lab burned a professor's hands Friday night and temporarily shut down a piece of safety equipment.

A chemistry professor was about to do an experiment with flammable materials at the Science Laboratory





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### ACS Committee on Ethics

#### Mission

The Committee on Ethics promotes and supports high standards of ethical conduct and integrity in the community of chemistry and related disciplines for the benefit of science and society.

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#### **Resources for ACS members**

- ACS Ethics Resources available at 'Ethics CORE'
- Professional Ethics and Chemical Safety
- Case Studies for Chemistry Ethics Education

#### **Ethical Guidelines**

- Ethical & Professional Guidelines
- Non-ACS Resources



### Responsible Conduct of Research and Other Ethics/Professionalism Matters

A General Chemistry cooperative learning exercise Illinois State University, Department of Chemistry Normal, IL 61790, USA



Prof. G. Ferrence www.ferrites.org



Department of Chemistr



LABORATORY SAFETY for CHEMISTRY STUDENTS





ROBERT H. HILL, JR. DAVID C. FINSTER



**WILEY** 



### About the coauthor

- Junior at ISU
  - Presidential scholar
  - Excellent student with passion and focus
- Safety Major (B.S.)
  - Chemistry as second major (B.S., ACS certified)
- Joined Ferrence group in fall 2014
  - Focus is oxadiazananone syntheses
  - With thoughtful SOP development



## **Process vs. Outcomes Driven Tension**

- Outcomes drive academic chemistry research
  - Particularly with respect to synthesis
  - The outcomes (published science) is measurable
- Process is more critical to safety
  - The process diminishes the negative outcomes
  - Only the negative outcomes are clearly measurable



### Goals

- Use the process of safety to leverage increases in quality of undergraduate preparation
- Use the process of safety to leverage increases in amount and/or quality of scientific outcomes



### Laboratory-Specific Standard Operating Procedures (SOPs)

Name of SOP

Synthesis of 2-cyclohexylamino-1-phenyl-1-propanol

Jucedure (SOP) Jucedure (SOP) June atter reading a related literature proceeding and or instructions that demarter reading a related interation general and operations. Starten after reading a with PI regarding operations. Starten after reading discussion with PI regarding a proceeding them together e.g. ultre and verbal discussion with PI regarding general and Je.g., ultracentrii and verbal discussion with PI regarding generations and current lab specific safety with a specific procedures and current lab specific IA's requires a written set aving hazardous materials or and/or forming small groups to write specific productions and maintenance manual may serve

If you have any questions regarding the development of SOPs, please contact Environmental Health and Safety at 8-8325.



#### Section I - Process

Provide a summary of the process or experiment involving hazardous chemicals. Include any unique equipment used. If the term process does not apply, proceed to section 2.

2-Isopropylamino-1-phenyl-1-propanol will be synthesized through the alkylation of norephedrine using acetone and sodium borohydride using a literature procedure [1]. The procedure involves use of routine organic chemistry procedures and solvents. SOPs for organic extraction and use of a rotary evaporator, and organic recrystalization should be consulted before carrying out this process.

[1] Hitchcock, S. R.; Casper, D. M.; Vaughn, J. F.; Finefield, J. M.; Ferrence, G. M.; Esken, J. M. <i>J. Org. Chem.</i><br/><br/>(i><br/>, <i>69



### Section 2 - Hazardous Chemicals Involved

List of the hazardous chemicals (or class of chemicals) involved, including any potentially hazardous products or by-products. Include the approximate amounts of chemicals that will be used. Safety Data Sheets for highly reactive or unstable chemicals should be available for review. SDS's for all

chemicals should be readily accessible. Most chemical SDS's are available through the manufacturer or the Stockroom.

(1R, 2S)-norephedrine and/or enantiomer (1S, 2R)-norephedrine acetone, reagent grade ethanol, 100% sodium borohydride sodium bicarbonate solution, saturated, aqueous dichloromethane brine solution, saturated aqueous sodium chloride



#### Section 3 - Potential Hazards

Describe the potential dangers for each hazardous chemical or each element of the hazardous process or procedure. Include physical, health, and environmental hazards. To find hazard information, look up the SDS or look online for other sources such as Cameo Chemicals, Wiser, Merck Index or the NIOSH pocket guide. All of these references provide hazard information in a user friendly format. Sigma-Aldrich also has technical bulletins that provide detailed information about various processes, equipment and classes of chemicals.

(1R, 2S)-norephedrine and/or enantiomer (1S, 2R)-norephedrine: See Sigma-Aldrich MSDS for product numbers 282553 and 317500. acetone, reagent grade: See Sigma-Aldrich MSDS for product number 320110. ethanol, 100%: See Sigma-Aldrich MSDS for product number 459844. sodiumborohydride: See Sigma-Aldrich MSDS For product number 71321 sodium bicarbonate solution, saturated, aqueous: See SDS for LabChem product number LC229471. dichloromethane: See Sigma-Aldrich MSDS for product number PHR1557. brine solution, saturated aqueous sodium chloride: See Teknova Inc. MSDS for product number S0255.



#### Section 4 - Designated Areas

Consider establishing a designated are for this operation within the laboratory. A fume hood/ portion of the laboratory, or the entire laboratory can be the designated area.

The reaction will be conducted in a fume hood.

#### Section 5 - Special Handling Procedures and Storage Requirements

Describe special handling procedures and storage requirements including, (but not limited to): specific laboratory techniques, ventilation requirements, temperature controls, chemical incompatibilities, special containment devices and access restrictions. If applicable, describe safety methods to transport the chemicals.

Norephedrine has a recommended storage temperature of 2-8 C and is light sensitive. Norephedrine is also the stereoisomer for and can be engineered into ???phenylpropanolamine???. This is a narcotic banned in the United States. The quantity of this chemical used must be accounted for.

All other chemicals can be stored with like chemicals and at room temperature.

The scale factor for this SOP is a factor of 2. In other words, this SOP only applies if the reagents in the experiment are no more than doubled.



Prof. G. Ferrence www.ferrites.org

#### Section 11 - Procedure (Optional)

List the basic steps or process of procedure for complex or multi-step experiments. If possible describe indicators that show the process is proceeding as intended.

Procedure was specifically used for for (1R,2S)-2isopropylamino-1-phenyl-1-propanol, but is identical for other enantiomer or racemate

aside from choice of stereochemistry of norephedrine used.

In a 1 L, round bottom flask was placed the (1R,2S)-norephedrine (50.0 g, 330 mmol) and reagent grade acetone (350 mL, 4766 mmol) and the mixture was stirred for 24 hours at room temperature. The reaction solvent (acetone) was removed by rotary evaporation and reconstituted with 100% ethanol (350 mL). To the resulting mixture was added sodium borohydride (25.0 g, 661 mmol) and the reaction mixture was stirred for 2 additional hours. The reaction was then quenched with a saturated solution of sodium bicarbonate and then extracted with dichloromethane (3 x 100 mL). The organic solution was washed with an aqueous saturated solution of brine (100 mL), dried with sodium sulfate, and the solvents were removed by rotary evaporation. The isolated product was recrystallized with diethyl ether to yield [2-isopropylamino-1-phenyl-1-propanol] in 99% yield (63.1 g), as white crystals. Mp = 99-101°C (for pure enantiomer); [α]D25 -15.9° (c 0.69, CHCl3). 1H NMR: δ 0.70 (d, J=6.8 Hz, 1H), 4.70 (d, J=4.4 Hz, 1 H), 7.23-7.35 (m, 5H). 13C NMR: δ 15.2, 23.45, 23.52, 45.6, 55.1, 73.4, 126.1, 127.9, 141.5. See: [1] Hitchcock, S. R.; Casper, D. M.; Vaughn, J. F.; Finefield, J. M.; Ferrence, G. M.; Esken, J. M. <i>J. Org. Chem.</i>

Name of SOP Author:

Gregory M. Ferrence & Nora Fredstrom



### **Revisions and testing**

- Minor adjustments to sections 1 -10
- Substantial modifications to section 11, Procedure
- Changes to solvents and increasing solvent volumes improved outcomes (yield) compared to original (literature) procedure



### **Version 5 – submitted to EH&S**

#### Section 11 - Procedure (Optional)

List the basic steps or process of procedure for complex or multi-step experiments. If possible describe indicators that show the process is proceeding as intended.

In a [500 mL] round bottom flask , (1R,2S)-norephedrine [10.0 g, 55 mmol] was placed with cyclohexanone, [14.0 mL, 132 mmol] and 100% ethanol [70 mL]. The mixture was stirred between 40 and 50 degrees C for at least 48 hours and cooled to room temperature. Sodium borohydride [4.0 g] was added to the reaction mixture. Keep flask around room temperature during reaction using an ice bath. Mixture stirred for an additional two hours. The reaction was then diluted with sodium hydroxide (1 molar, 100 mL) and the ethanol was removed by rotary evaporation under vacuum. The resultant mixture was transfered into a [1 L] round bottom flask and then diluted with ethyl acetate (200 mL). In our experience, at least 3 x 200 mL ethyl acetate resulted in a better yield. The solution was filtered gravimetrically into a seperatory funnel to remove the insoluble precipitate. This can also be done using a Celite filter. The organic layer was then optionally washed with brine (50 mL) in the separatory funnel. We managed better yields omitting the brine wash. The aqueous layer was drawn off and the organic layer decanted into a new round bottom flask. The organic layer was dried using magnesium sulfate or sodium sulfate. In our experience, sodium sulfate was easier to use. The solvent removed by rotary evaporation. The purified product was isolated via recrystallization, affording [19.73 g/5, 3.946 g] of a white solid in 85% yield. Mp: 89-91 C (hexanes/EtOAc). [ $\alpha$ ]\_d^25 = +11.2 (c 1.66 CH~2~Ccl~2~). IR (nujol mll): 3278, 1102, 738, 701 cm^-1. ^1HNMR (CDCl~3~):  $\delta$ , 12.7, 24.9, 24.9, 25.5, 31.8, 32.5, 54.2, 55.8, 72.4, 126.0, 127.0, 128.0, 140.9. HRMS (ESI) calcd for C~15~H~23~NO (M+H)^+: 234.1858. Found: 234.1838. [2]

Name of SOP Author: Gregory M. Ferrence & Nora Fredstrom



### **Version 5 – EH&S comments**

#### Section 11 - Procedure (Optional)

List the basic steps or process of procedure for complex or multi-step experiments. If possible describe indicators that show the process is proceeding as intended.

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Name of SOP Author: Gregory M. Ferrence & Nora Fredstrom



### **Version 5 – EH&S comments**

Section 2 - Hazardous Chemicals Involved

List of the hazardous chemicals (or class of chemicals) involved, including any potentially hazardous

products or by-products. Include the approximate amounts of chemicals that will be used. Safety Data Sheets for highly reactive or unstable chemicals should be available for review. SDS's for all chemicals should be readily accessible. Most chemical SDS's are available through the manufacturer or the Stockroom.

	micals like
(1R, 2S)-norephedrine and/or enantiomer (1S, 2R)-norephedrine cyclohexanone ethanol, 100% sodium borohydride sodium hydroxide, 1 M ethyl acetate brine solution, saturated aqueous sodium chloride magnesium sulfate sodium sulfate	therme sulfate



### **Version 5 – EH&S comments**

#### Section 3 - Potential Hazards

Describe the potential dangers for each hazardous chemical or each element of the hazardous process or procedure. Include physical, health, and environmental hazards. To find hazard information, look up the SDS or look online for other sources such as Cameo Chemicals, Wiser, Merck Index or the NIOSH pocket guide. All of these references provide hazard information in a user friendly format. Sigma-Aldrich also has technical bulletins that provide detailed information about various processes, equipment and classes of chemicals.

(1R, 2S)-norephedrine and/or enantiomer (1S, 2R)-norephedrine: See Sigma-Aldrich MSDS for product number 398241. ethanol, 100%: See Sigma-Aldrich MSDS for product number 398241. sodium borohydride: : See Sigma-Aldrich MSDS for product number 71321 sodium hydroxide, 1 M: See Sigma-Aldrich MSDS for product number 71321 sodium hydroxide, 1 M: See Sigma-Aldrich MSDS for product number 2000 ther Sources like MSDS, be included in this would be a good idea} ethyl acetate: See Sigma-Aldrich MSDS for product purplete ting to other sources the stand-alone brine solution, saturated aqueous sodium chloride: S Directing to other sources the stand-alone sodium sulfate: See Sigma-Aldrich MSDS for product purplete ting to the stand-alone sodium sulfate: See Sigma-Aldrich MSDS for product number 2000, which need to be stand-alone sodium sulfate: See Sigma-Aldrich MSDS for product number 2000, which need to be stand-alone sodium sulfate: See Sigma-Aldrich MSDS for product number 2000, which need to be stand-alone sodium sulfate: See Sigma-Aldrich MSDS for product number 2000, which need to be stand-alone sodium sulfate: See Sigma-Aldrich MSDS for product number 2000, which need to be stand-alone sodium sulfate: See Sigma-Aldrich MSDS for product number 2000, which need to be stand-alone sodium sulfate: See Sigma-Aldrich MSDS for product number 2000, which need to be stand-alone sodium sulfate: See Sigma-Aldrich MSDS for product number 2000, which need to be stand-alone sodium sulfate: See Sigma-Aldrich MSDS for product number 2000, which need to be stand-alone stand-alo



### Laboratory-Specific

### Standard Operating Procedures (SOPs)

Name of SOP	Formation of the hydrazine and resultant oxadiazinanone
PI Name	Dr. Greg Ferrence and Nora Fredstrom
Section I - Process	(Hover cursor here for directions)

This SOP describes the hazards involved in forming hydrazines and resultant oxidiazinanone derivatives of norephedrine by reacting N-nitrosamine with lithium aluminium hydride, anhydrous THF, 3 M sodium hydroxide, ethyl acetate, Rochelle's solution, brine, magnesium sulfate, ethyl acetate, hexanes, diethyl carbonate, lithium hydride, 1 M HCl and sodium bicarbonate.

### Section 2 - Hazardous Chemicals Involved

(Hover cursor here for dire



#### Section 3 - Potential Hazards

(Hover cursor here for directions)

Lithium aluminum hydride is a powerful reducing agent. It is known to react violently with water. It reacts violently on contact with oxidizing agents. It ignites by friction. It reacts vigorously with hydroxy compounds such as water, alcohols, carboxylic acids. Ignition may have been caused by head from reactions with impurity water or decompositions of peroxides in ether. Contact with eyes and skin causes severe burns similar to those caused by caustic soda.

Tetrahydrofuran (THF) belongs to the ether reactive group. Like ether, it is highly flammable. THF vapors can cause nausea, dizziness, headache, and anesthesia. It is capable of forming peroxides. Oxidizes readily in air to form unstable peroxides that may explode spontaneously. Peroxides react with lithium aluminum hydride. A violent explosion occurred during the preparation of sodium aluminum hydride from sodium aluminum hydride from sodium and aluminum in a medium of THF. Note that in this reaction, THF is used as a solvent for lithium aluminum hydride, but it is THF (anhydride), so extreme violent reaction is not anticipated.

3 M sodium hydroxide is a strongly basic solution of sodium hydroxide. It reacts rapidly and exothermically with organic and inorganic acids, organic and inorganic acid anhydrides, organic and inorganic acid chlorides. Attacks aluminum ap c with evolution of flammable hydrogen gas. It is incompatible with cellulose and mineral/clay-based absorbents sever

Agnesium sulfate is an anhydro commenter Magnesium sulfater Magnesium sulfater Magnesium sulfater Magnesulf as routes. Mildly en peroxide, nitiric acid.

potassium tartrate is hazardous in case of

Magnesium sulfate is an anhydrom sait used to absorb water from solutions. It is hazardous in case of ingestion and an irritant

in case of skin and eye contact and inhalation.

Hexanes are highly flammable. Aspiration causes sever lung irritation, coughing, pulmonary edema, excitement followed by depression. Hexane may be sensitive to light. It may also be sensitive to prolonged exposure to heat. This compound can react vigorously with oxidizing materials. This would include compounds such as liquid chlorine, concentrated O2, sodium hypochlorite and calcium hypochlorite. It is also incompatible with dinitrogen tetraoxide. It will attack some forms of plastics, rubber and coatings. (NTP, 1992).

Diethyl carbonate is highly flammable and easily ignitied by heat, sparks, or flames. Vapors may form explosive mixtures with air. Vapors may travel and flash back and most vapors are heavier than air. High vapor concentration can cause headache, irritation of eyes and respiratory tract, dizziness, nausea, weakness, and loss of consciousness. It reacts with acid to liberate heat and carbon dioxide. Strong oxidizing acids may cause a vigorous reaction that may ignite the reaction products. Heat is also generated by the interaction with caustic solutions. Flammable hydrogen is generated by mixing with alkali metals and hydrides.

Lithium hydride is a strong reducing agent. The solid may decompose violently in contact with most oxidizing materials. It reacts exothermically with water to form caustic lithium hydroxide and hydrogen gas. May ignite spontaneously in moist

surve extense in the extense extense in the extense lab and what we assess as notable risk in our setting and what we assess as notable fisk in our setting, against inclusion of all information from extant SDS,

taken through to the next step in th



etc. Oxadiazinanone formed is toxic and secondally carcinogenic. Avoid skin contact.

#### Section 8 - Spill and Accident Procedures

(Hover cursor here for directions)

In case of skin contact, immediately flush skin with plenty of water for at least 15 minutes. Cover the irritated skin with an emollient. Remove contaminated clothing and shoes. For other reagents, cold water may be used. Wash clothing before reuse. Throughly clean shoes before reuse. Get medical attention.

In case of eye contact, check for and remove any contact lenses. Immediately flush eyes with plenty of water for at least 15 minutes. Cold water may be used. Get medical attention immediately.

If swallowed, do not induce vomiting unless directed to do so by medical personnel. Never give anything by mouth to an unconscious person. Loosen tight clothing such as a collar, tie, belt or waistband. Get medical attention immediately.

If inhaled, evacuate the victim to a safe area as soon as possible. Loosen tight clothing such as a collar, tie, belt or waistband. If breathing is difficult, administer oxygen. If the victim is not breathing, perform mouth-to-mouth resuscitation. WARNING: It may be hazardous to the person providing aid to give mouth-to-mouth resuscitation when the inhaled material is toxic, infections or corrosive. Seek immediate medical attention.

some information is near boiler plate from University Chemical Hygiene Plan, but needed to be included to If the spill occurs inside a fume hood, shut sash and put fume in emergency. If necessary, use sort And the second se up the liquid. Dispose in spill kit bucket. Use water to wipe down area. For large spills call

#### Section 9 - Waste Disposal

(Hover cursor here for directions)

#### PRIOR TO COMBINING WASTE, CHECK WASTE BOTTLE CONTENT LIST FOR INCOMPATIBLES AS LISTED IN SECTION 4.

All liquid should be collected in the organic waste bottle located in the waste fume hood. Record components and quantities of the waste on the content sheet.

All solid waste should be collected in the solid waste bucked located in the waste fume hood. Record components and quantities of the waste on the content sheet.



### Conclusions

- Good experience for current student
- Unclear if transferrable to the average student, particularly chemistry majors who don't take coursework in safety
- The safety (potential hazards) seems to be more disconnected from the chemistry (procedure) than anticipated



### Acknowledgements

- ISU Departments of Safety and Chemistry
- ACS Division of Professional Relations (PROF)
- ACS IPG program
- Pacifichem 2015
- Audience (you)

