Section 5.1 **Title:** General Reaction Procedure **Revision Date:** 11/01/19
Prepared By: Caleb F. Harris and Michael Roy **P.I.:** Prof. John F. Berry

Prior Approval: This procedure is NOT considered hazardous enough that prior approval is needed from the Principal Investigator.

Involves Use of Particularly Hazardous Substance (PHS)? No
___ Carcinogen ___ Reproductive Toxin ___ High Acute Toxicity
Does this procedure require medical surveillance? No
Does this require use of a fit-tested respirator? No

Brief Description of Procedure:
General protocol for performing reactions

Location: *List the locations (buildings/rooms) where this procedure may be performed. For use of a PHS indicate a more precise location within the room, if appropriate, as a designated area.*
Daniels Chemistry - All Berry group labs

Chemicals Involved:

Chemical	Physical or Health Hazard (e.g. carcinogen, corrosive)
Dependent on chemistry	Consult relevant SDSs for more details

Other Hazards: *Include hazards, other than chemical, that may be present during operation of the procedure.*
Sharps (needles)

Exposure Controls: *(Check all that apply)*
PPE: _X_ Safety Glasses ___ Face Shield ___Chemical Splash Goggles
___Chemical Apron _X_ Gloves (Nitrile) _X_ Lab Coat
___Respirator (type) ___Other:

Engineering Controls:
_X_ Fume Hood ___Biosafety Cabinet _X_ Glove box
___ Vented gas cabinet ___Other:

Administrative Controls: *List any specific work practices needed to perform this procedure (e.g., cannot be performed alone, must notify other staff members before beginning, etc.).*

N/A

Task Hazard Control Table: *For procedures involving numerous steps, it may be convenient to indicate specific requirements for individual tasks in the table below:*

N/A

Waste Disposal: *Describe any chemical waste generated and the disposal method used.*

Dispose of the reagents involved as appropriate. Consult SDSs for more details.

Accidental Spills: *Describe the procedure for handling small chemical spills that may occur during this procedure. Note that for large spills it may be appropriate to call 911.*

Small spills may be cleaned with an absorbing material. The material should be placed in a fume hood to dry after the spill has been cleaned.

Decontamination Procedures (required for PHS use): *Describe the procedure for decontamination of personnel and equipment.*

N/A

Training: *Describe any training needed prior to performing this procedure. Include training performed in-lab and any required demonstrations of competency.*

No formal training or documentation is required. All lab members are encouraged to talk through new procedures with other group members. Any potential hazards should be assessed and brought to the attention of Prof. Berry before the reaction is performed.

Principle Investigator Approval: I have reviewed this procedure and approved it for use. Note: Modifications to the procedure may require update to this form.

Name: John F. Berry Signature: _____ Date: _____

General Reaction Procedure

Largely taken directly from "Not Voodoo"
(http://www2.chem.rochester.edu/~nvd/pages/reaction.php?page=roadmap)

General

You have identified (or have been given) an experiment to carry out. You have never run this reaction before, and you want to be sure that your experiment is successful. The following is a general guideline to aid in running your experiment. If on any step you are ever in doubt, ask for help from another member or Professor Berry.

Step 1. ***Research Literature Precedent***. Do a database search to see if the reaction has been done before on a system like yours. A couple of excellent resources are Reaxys or Scifinder. Look at some of the papers describing your desired transformation and take note of:

- How many examples have been reported.
- How many different authors report similar chemistry.
- How general the chemistry seems.
- How easy the procedure is to carry out.
- Whether the reagents are available and inexpensive.
- Whether the reagents or side products are potentially hazardous.
- How detailed the experimental description is.
- The authors of the paper and the journal it came from.
- If possible, find a review article describing the reaction and read about the scope and limitations of the chemistry.
- Always find and read the original paper that popularized the transformation.
- Choose a procedure to follow, taking all factors into consideration.
- Copy or print the entire journal article, not just the pages you need.

Step 2. ***Planning and Strategy***. Decide on a scale for your reaction and perform the calculations. The following factors will influence your decision:

- Have you run the reaction before? On what scale?
- How precious is the reactant?
- Will you need the reactant for any other experiments?
- How expensive are the reagents?
- What are you doing with the product (*i.e.* is it stable for long-term storage)?

Rules of thumb:

- When an organic reaction is new to you, one millimole is often a good starting point, if reactant is not limiting. If reactant is precious or the reaction involves a metalation step, it should be performed on a smaller scale, 10 - 100 mg is usually a good choice to determine if a desirable outcome is possible from the chosen procedure.
- If you have run the reaction before, you may choose to run a larger scale reaction. It is best to scale up by no more than 3-4 times the previous experiment in case the reaction begins to lose efficiency.
- If you need a lot of the product compound, have experience with similar procedures, or feel sure of success (based on the literature, for example), you might start with larger quantities of reactant.

Calculate your reactant and reagent quantities:

- Locate or order the chemicals needed and find out if additional purification will be necessary.
- Predict how long the reaction will take to set up, run, and work up.
- Plan a time to begin the experiment such that you can stay with it and monitor it until it has either gone to completion and you have worked it up OR it has been stirring at a constant temperature for one hour and is less than ~20% complete.

Step 3. ***The Setup.*** Plan for the glassware you'll need and purify any starting materials, if necessary.

- Locate a clean, dry flask, a stirbar, a septum and any other apparatus necessary for the procedure. Calculate the total volume of solution and use a flask with at least twice that capacity.
- If the reaction is moisture or air sensitive, oven- or flame-dry the flask and prepare to run the experiment under an inert atmosphere.
- Purify your reagents and solvents, if necessary.
- Locate syringes and needles of appropriate size, if necessary.
- Weigh your reactants, into your reaction flask, onto weighing paper, or into a separate flask (a conical flask is useful for reagents that will be added as a solution).
- Consult your procedure to see what is necessary.
- Do not weigh sensitive reagents until just before use.

Step 4. ***Analysis During Reaction (Organic).*** If the reaction is homogenous and stirs easily, you can follow the progress of the reaction by periodic analysis using simple TLC or GC and can stay with the reaction until it is complete. You're looking for all the starting material (limiting reagent) to be consumed, and a new product(s) is/are formed cleanly.

- Save a small sample of each reactant in a vial for TLC comparison. An NMR sample works nicely as does a milligram or so in dichloromethane.
- Follow the literature procedure exactly.
- Take a TLC of the reaction mixture shortly after addition of all reagents is complete. Co-spot with your reactant sample(s).
- Record all observations and times in your notebook.
- TLC or GC the reaction at regular intervals. The appropriate interval to employ will depend on the reaction rate- (e.g. every 10 minutes, 60 minutes, or every 6 hours, etc.). Always co-spot with reactant(s).
- When one of the reactants has been consumed, quench the reaction immediately to avoid potential decomposition.

Step 5. ***Quench and Workup.***

- Quench at the temperature and rate recommended. Know what potential side reactions can occur during the quench.
- If gas is evolved during the quench, or it is otherwise exothermic, watch the reaction carefully to be sure it is under control.
- Follow the instructions in your literature procedure.

For an aqueous workup of most organic compounds, this will involve:

- Diluting the reaction mixture with a solvent for workup.

- Add water. Some of the byproducts generated during the reaction will be neutralized or removed by dissolving in the aqueous layer. Ideally, the two layers will be clearly visible and the layers will be based on the density of the organic solvent(s) used. If the result is one cloudy layer, you have an emulsion which can typically be remedied by filtration of the mixture through a 2 mm pad of Celite and/or the addition of saturated NaCl(aq.).
- Drying the organic layer with a drying agent such as magnesium sulfate or sodium sulfate.
- Filtering off the drying agent.
- 'Roto-vap' to remove volatiles.
- The residue left is the crude product, ready for diagnosis. Certain types of compounds are more difficult to isolate than others--if your product might be volatile, soluble in water, charged at low or high pH (e.g. an amine or a carboxylic acid), unstable, or possesses stench, use appropriate precautions.

Step 6. ***Analysis After Workup.***

- TLC the crude product to make sure it matches the reaction mixture.
- If you do not expect reagent peaks to overwhelm product peaks, take an NMR of your crude reaction mixture after workup.
- In most cases, it is important to know about all the products generated from a reaction, not just the major product.
- You can get the ratio of starting material to product (percent conversion).
- You can get the ratio of product to byproduct. This is helpful during optimization.
- You can get ratios of isomers- this is always important data.
- Sometimes chemists think they have isolated the major component of the reaction mixture- a crude NMR can reveal that the minor component was isolated, and the major component is still at large.
- If you observe two products and can identify them by NMR or GC-MS, record the ratio of the products.
- Decide whether the product(s) are worth isolating.

Step 7. ***Purification***.

- Consult the literature. If conditions for successful purification of the compound have been reported, (Crystallization, Distillation, or Chromatography), follow the protocol.
- If literature is unhelpful, you must choose a purification method for your compound by following the Rules of Thumb:
    - When you expect less than a gram of product, column chromatography is the safest purification method.
    - When the molecular weight of your compound is over 350 amu, distillation is not typically a good choice.
    - If your product is a solid and you have multigram quantities, consider crystallization.
    - If you are working on multigram scale and the compound is an oil with molecular weight <350, consider distillation.
    - For all other situations, use column chromatography.

- Save a small sample of the crude product mixture in a vial.

- Carry out the purification. Keep everything until you've identified your product.
- Collect major product components in tared flasks and assign names to each component.
- Compare the components (usually by TLC) with the crude sample in the vial and with the crude NMR to ensure that you have isolated the compounds of interest.
- Calculate the yield of each component, if the identity of the compounds is known.

Step 8. ***Record your data.*** This should be ongoing from Step 1. Always record your procedural steps, reagents and amounts used as well as all experimental results.