

CLC-INNOVATORS COHORT 1



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TABLE OF CONTENTS

[Licensing](#)

[1: Basic Skills](#)

- [1.1: Excel Proficiency Skills Assessment](#)

[2: General Chemistry Laboratories](#)

- [2.1: Water Quality](#)
- [2.2: Lighting Up – Smokers, Solutions, and Spectroscopy](#)

[3: Organic Chemistry](#)

- [3.1: A3 Coupling Reaction](#)

[Index](#)

[Glossary](#)

[Detailed Licensing](#)

[Detailed Licensing](#)

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A detailed breakdown of this resource's licensing can be found in [Back Matter/Detailed Licensing](#).

CHAPTER OVERVIEW

2: General Chemistry Laboratories

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CHAPTER OVERVIEW

3: Organic Chemistry

[3.1: A3 Coupling Reaction](#)

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3.1: A3 Coupling Reaction

Purpose:

This lab is a research-type experience where you will explore and optimize a metal-catalyzed three-component coupling reaction.

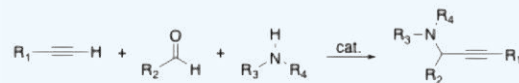


Figure 1: Schematic representation of the A3 Coupling Reaction.

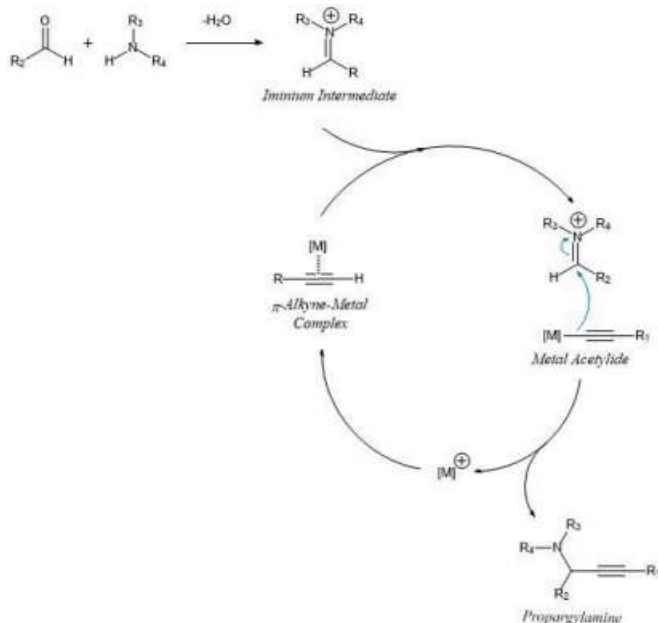
Learning Objectives

- Be able to track reactions by thin layer chromatography
- Understand how to optimize an organic reaction
- Learn what A3 coupling is and how it can be used to synthesize organic molecules

Introduction

The A3 coupling reaction is a highly efficient, atom-economical reaction widely used by organic chemists. It involves the coupling of three components: an aldehyde, an alkyne, and an amine in the presence of a metal catalyst, under very mild reaction conditions to give propargyl amines. Propargyl amines are versatile intermediates in the synthesis of biologically active compounds, natural products, and pharmaceuticals, making the A3 coupling reaction extremely useful in medicinal chemistry and drug discovery.

The development of the A3 coupling reaction stems from the need for more atom-economical and environmentally friendly methods for C–N and C–C bond formation. Traditional methods for the synthesis of propargyl amines often require multi-step processes, harsh reaction conditions, and the use of toxic reagents. In contrast, the A3 coupling reaction is a one-pot procedure, which aligns with the principles of green chemistry by reducing the number of steps, improving yields, and minimizing waste. The reaction is generally catalyzed by transition metals, where copper(I) salts are most commonly employed due to their affordability, high catalytic efficiency, and stability. Traditional transition metals can be sensitive to air and water, necessitating sophisticated lab techniques but this is not the case for this experiment, the reaction can even be done in water. Additionally, different aldehydes, amines and alkynes can be used, providing flexibility in synthesizing diverse propargyl amine derivatives.



Experiment Overview

For this experiment, your section will work together to *optimize* this A3 coupling reaction. This means that you want to find the best general conditions that will maximize the reaction in the way that you care about (most often yield, but time can also be a measurement). To do this each group will work with others to explore the possible conditions and reagents for the A3 coupling reaction. Given the limited time available and the infinite possibilities for testing, each group will be working with 2 other groups such that each lab section is divided into 3 teams. For the first day of the experiment, each group will run the baseline reaction and collect the final results. Afterwards, each team will come together and determine which reagents/conditions to explore, the goal being that each group within a team can test for one parameter (e.g. amine, aldehyde, catalyst, or solvent) from the list provided below.

For the second day, each team will share their results with the class. Afterwards, each group will come together to determine the optimal conditions for the reaction and then run the reaction with the new conditions. Groups will share/compare results with their teams and determine if the conditions are indeed optimal. *In the field of organic chemistry, an ideal reaction condition results in >90% isolated yield. The goal in this experiment is for you, the student, to develop a condition you believe to be ideal based on the data collected by you and your peers.*

Key Concepts

Concept 1: Catalysis

A catalyst is an active species within a reaction that facilitates the transformation of the starting material to the product without itself being consumed by the reaction.

Concept 2: Lewis Acids

Lewis acids, including many metal ions, are compounds capable of accepting electrons/electron density from some donor group. The donor group could be lone pair electrons or pi-electrons.

Reaction Mechanism

The A3 coupling reaction proceeds via A3 coupling direct dehydrative condensation and typically involves the following key steps:

1. **Activation of the Alkyne:** The reaction begins with the coordination of the terminal alkyne to the metal catalyst forming a π -complex. In this step, the metal catalyst acts as a Lewis acid, accepting pi-electrons from the alkyne. This enhances the acidity of the alkyne proton, allowing for subsequent deprotonation.
2. **C-H activation:** The coordinated alkyne undergoes deprotonation, generating a metal acetylide species.
3. **Imine Formation:** The aldehyde reacts with the amine in-situ forming an imine or iminium ion intermediate. This intermediate is highly reactive and facilitates the next step.
4. **Nucleophilic Attack:** The metal acetylide attacks the imine carbon, forming a new C-C bond, leading to the formation of the propargylamine product. The metal catalyst is regenerated at this stage, enabling the catalytic cycle to continue.

Safety precautions and waste disposal:

All chemicals used in this experiment can be toxic if inhaled or ingested. Avoid inhaling or ingesting them, wear gloves when handling, and avoid direct contact with skin and eyes. Work in a well ventilated fume hood.

Dispose all waste in the appropriate waste containers as per your TAs instructions

Day 1 Part 1 Experimental

To begin, every student will perform the same reaction. This first reaction will get you experience with the experimental setup and reaction purification, and will give you a baseline number for your percent yield. During this reaction, your TA will come by and assign your partnership to a specific group that will investigate how changes to one of the variables (catalyst, amine, or solvent) affects your reaction.

A generic reaction setup/purification is listed below. The variables that can be changed are typed in bold. Your first reaction will follow the steps below, your second reaction will change **one** of the variables in bold in step 1 or step 2.

Reagent	Molar Mass (g/mol)	mmol	Mass (g)	Volume (mL)	Density (g/mL)	Molar Equiv.
---------	-----------------------	------	----------	----------------	-------------------	-----------------

Phenylacetylene	102.13	0.5			0.93	1
Formaldehyde		0.5				1
Piperidine	85.15	0.5			0.86	1
Copper (I) Iodide	190.45	0.05				0.10
Diethyl Ether				5		

A. Setup:

1. To a clean, dry 2-dram vial, add a stir bar, add 5 mL **solvent**, add 0.5 mmol of **amine**, 0.5 mmol of alkyne, and 0.5 mmol of aldehyde.
2. Finally add 10 mol% of **the catalyst** (0.10 equivalents with respect to the other reagents).
3. Place the vial on a magnetic stir plate and allow the reaction to stir at room temperature for 1 hour or until complete by TLC, whichever comes first. Monitor the reaction progress every 20 minutes by TLC. Note that the reaction may become opaque and/or bright yellow. For TLC, use a 10% mixture of ethyl acetate:hexane. *Always record TLC plates and R_f values in your notebook.*
4. While the reaction is progressing, stuff a pipette with a small amount of cotton and add celite (0.5 inch). Flush diethyl ether (1.0 mL) through the celite plug to ensure adequate packing. Stuff a second pipette with cotton *but do not add celite*, this will be used to filter out Na₂SO₄.

B. Workup:

1. After the reaction is complete as observed by TLC (or after one hour has passed), add the reaction mixture to the pipette containing celite and push the liquid through. Repeat until the entire reaction mixture has been filtered. Add 1 mL of Et₂O to the pipette and push the liquid through, repeat once more.
2. Transfer the filtered solution to a separatory funnel and extract the with 5mL 1M HCl (aq), repeat two more times, collecting the aqueous layer in an Erlenmeyer flask.
3. Drain the organic layer into a separate, labelled Erlenmeyer flask and set aside (*do not discard*).
4. Transfer the combined aqueous layer to the separatory funnel, add 15mL of Et₂O and wash with 20 mL 1M NaOH. (Drain *only* the aqueous layer) Repeat wash with another 20 mL 1M NaOH.
5. Remove the aqueous layer and wash the organic layer with 10 mL of brine. Collect the organic layer into an Erlenmeyer flask and dry over Na₂SO₄. This organic layer contains your propargylamine product.
6. Filter out the Na₂SO₄ with a pipette (stuffed with cotton) into a *tared* flask and boil off the solvent. Obtain a percent yield and an IR spectrum. Assign peaks observed on the IR spectrum.
7. Share your percent yield with the other students in your group.
8. What is the average yield for your group?

Day 1 Part 2 - Reaction Condition Testing: Varying Parameters

Now that everyone has had an opportunity to run the reaction, each group will run the reaction again *but with one variable changed* (see list below). With your group, determine which partnerships will test the different possibilities for your assigned variable. Please discuss how changing this variable will affect your reaction and then perform the reaction again. Again, please record the percent yield and annotate the IR spectrum of your material.

Is your percent yield similar to the previous reaction (similar being less than 5% difference between the percent yields)? Was the effect positive or negative (increase or decrease in yield)? If the effect was positive, then how did this variation help the reaction? If negative, then how did this variation hinder the reaction? *Feel free to use the mechanism as a reference and lewis dot structures to show your thought process.*

Variable	Catalyst	Solvent	Amine
Possible Values	Copper (I) Iodide	Hexanes	Piperidine
	Copper (I) Bromide	Diethyl Ether	Diethylamine
	Copper (I) Chloride	Water	Diisopropylamine

	Sodium Chloride	Dichloromethane	Aniline
	Hydrochloric Acid	Toluene	Benzylamine

In the table below, fill out your variable, the changes made, and the new percent yields for your group.

Group:		
Variable	Percent Yield	Reaction Time

Day 2 - Part 1: Sharing Results

With your group, share the results of your testing with the entire class (about 10 minutes for each team)

Please discuss the following:

- Reasoning for the parameter variation (How would this variable benefit/hinder the reaction?)
- Results (Did your yield go up or down?)
- Rationale for change in yield (How do you think this variable affects the reaction?)
- Feel free to use the blackboard*

Day 2 - Part 2: Determining Optimal Reaction Conditions

Now that each team has had an opportunity to share their results; within your team, decide on what the best conditions are for this reaction (optimal conditions) and run the reaction with your partner.

After collecting the results, compare them with your team and with the class: Did the yield for this reaction increase compared to when you first ran the reaction? If so, how did the variation(s) benefit the reaction?

If not, how did the variation(s) hinder the reaction?

Feel free to use the reagent table below as a template, remember to fill in the boxes with the correct values (i.e. the density of liquids can differ from compound to compound). The experimental procedure is the same as for Day 1.

Reagent	Molar Mass (g/mol)	mmol	Mass (g)	Volume (mL)	Density (g/mL)	Molar Equiv.
Alkyne		0.5				1
Amine		0.5				1
Aldehyde		0.5				1
Catalyst		0.05				0.10
Solvent				5		

Waste disposal:

Review the SDS.

Pre lab Questions:

- How does the Lewis acidity of the metal species help catalyze the reaction?
- Why is this reaction referred to as the A3 coupling reaction?

3. How will you determine the success of the A3 reaction in lab?
4. The baseline reaction calls for 5 mL of solvent. How would the rate of the reaction change if the solvent volume was reduced to 2.5 mL?
5. In this lab, we will ask you to change the solvent to probe the reaction. Consider water and toluene. Please make a prediction on how these solvents can help/hinder the reaction.

Post lab Questions/in-lab discussion points?:

1. Compare the effect of water and toluene as solvents on the reaction.
 - a. List some of the differences between water and toluene (i.e. polarity, protic/aprotic) More polar solvents should work better given the intermediates are charged
 - b. In which reaction did the solvent proceed faster, water or toluene?
 - c. Water is a byproduct of this reaction. Why then does reaction not just revert back to starting material when performed in water (as would be predicted by Le Chatelier's principle).

Consider the effect of the catalyst on the reaction

2. During the experiment, various catalysts were used but not all were successful. What feature was needed for the catalyst to be effective in this reaction?
3. How did you know when your reaction was complete?
4. How did you modify the experimental procedure to get the best possible yield of the reaction? List all the ways. Here they should pick the best conditions from all the groups and write those
5. You have been hired by Acme Pharmaceutical to scale up this reaction. What safety and environmental considerations will you take into account? Consider the hazards involved and waste disposal
6. Did your TLC indicate the reaction went to completion? If so, why did you not get a 100% yield?

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 - [InfoPage](#) - *Undeclared*
 - [Table of Contents](#) - *Undeclared*
 - [Licensing](#) - *Undeclared*
 - [1: Basic Skills](#) - *Undeclared*
 - [1.1: Excel Proficiency Skills Assessment](#) - *Undeclared*
 - [2: General Chemistry Laboratories](#) - *Undeclared*
 - [2.1: Water Quality](#) - *Undeclared*
 - [2.2: Lighting Up – Smokers, Solutions, and Spectroscopy](#) - *Undeclared*
 - [3: Organic Chemistry](#) - *Undeclared*
 - [3.1: A3 Coupling Reaction](#) - *Undeclared*
 - [Back Matter](#) - *Undeclared*
 - [Index](#) - *Undeclared*
 - [Glossary](#) - *Undeclared*
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 - [InfoPage](#) - *Undeclared*
 - [Table of Contents](#) - *Undeclared*
 - [Licensing](#) - *Undeclared*
 - [1: Basic Skills](#) - *Undeclared*
 - [1.1: Excel Proficiency Skills Assessment](#) - *Undeclared*
 - [2: General Chemistry Laboratories](#) - *Undeclared*
 - [2.1: Water Quality](#) - *Undeclared*
 - [2.2: Lighting Up – Smokers, Solutions, and Spectroscopy](#) - *Undeclared*
 - [3: Organic Chemistry](#) - *Undeclared*
 - [3.1: A3 Coupling Reaction](#) - *Undeclared*
 - [Back Matter](#) - *Undeclared*
 - [Index](#) - *Undeclared*
 - [Glossary](#) - *Undeclared*
 - [Detailed Licensing](#) - *Undeclared*
 - [Detailed Licensing](#) - *Undeclared*