

Grignard Reaction – Beyond Labz Virtual ChemLab Activity

Purpose: In this virtual experiment, you will be exploring the effect of the solvent (protic vs. aprotic) on a Grignard reaction. You will be reacting benzaldehyde with ethyl magnesium bromide with the goal of forming 1-phenyl-1-propanol. You will attempt the reaction 3 times, once with water as the solvent, once with ethanol as the solvent, and finally with diethyl ether as the solvent. For the solvent that best supports the formation of the desired alcohol product you will complete the reaction. You will monitor the reaction using thin-layer chromatography (TLC) and compare key signals in the IR spectra of the reactants and products.

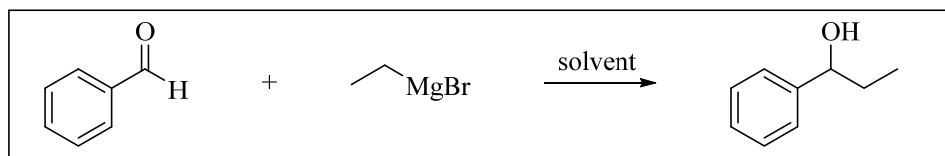


Figure 1. Reaction of ethyl magnesium bromide (EtMgBr) with benzaldehyde (PhCHO)

Introduction: The carbonyl carbon (C=O) is electrophilic and can undergo nucleophilic addition reactions with a variety of nucleophiles.

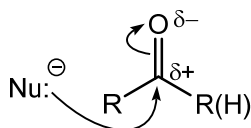
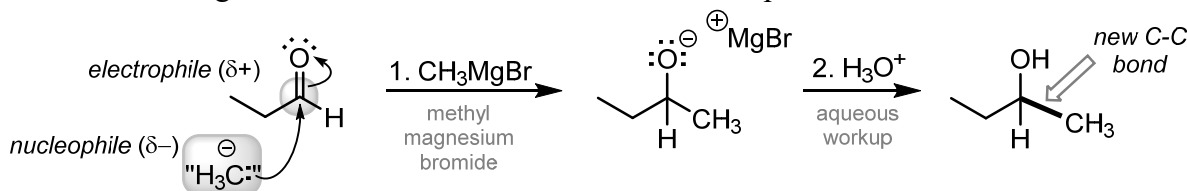
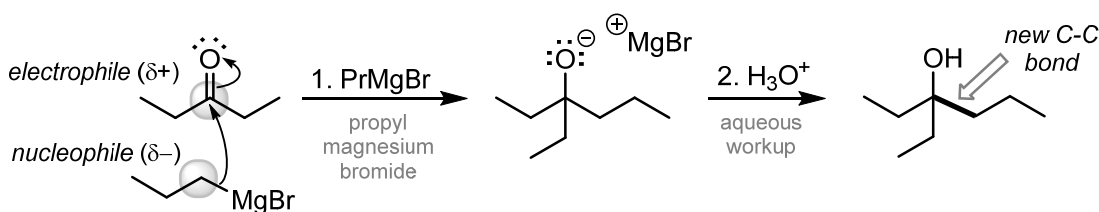


Figure 2. Nucleophilic addition to a carbonyl.

If the nucleophile that adds to the carbonyl is a carbon atom, then a new carbon-carbon bond is formed! In order to be nucleophilic, a carbon must have anionic character. This can be achieved by being bonded to a less electronegative atom, such as a metal. Such compounds, called *organometallic* compounds, contain a nucleophilic carbon atom. Examples of organometallic compounds that you are likely to encounter in your Organic Chemistry course include Grignard reagents (RMgBr), organolithium compounds (RLi) and organocuprates (R₂CuLi). The extremely polar R–M bond is sometimes represented as ionic to simplify mechanisms. Both mechanisms shown below are generally accepted methods to represent the nucleophilic addition of a Grignard reagent to a carbonyl. Protonation of the resulting alkoxide intermediate affords an alcohol product.



A Grignard reaction converts an aldehyde to a secondary alcohol.



A Grignard reaction converts a ketone to a tertiary alcohol.

Figure 3. Grignard reagents react with aldehydes and ketones.

In addition to being powerful nucleophiles, Grignard reagents are also very strong bases, and thus can react with even very weak acids. Consequently, it is important to consider the solvent that is used in a Grignard synthesis. We will explore the use of protic and aprotic solvents, and determine which is better suited for Grignard reactions.

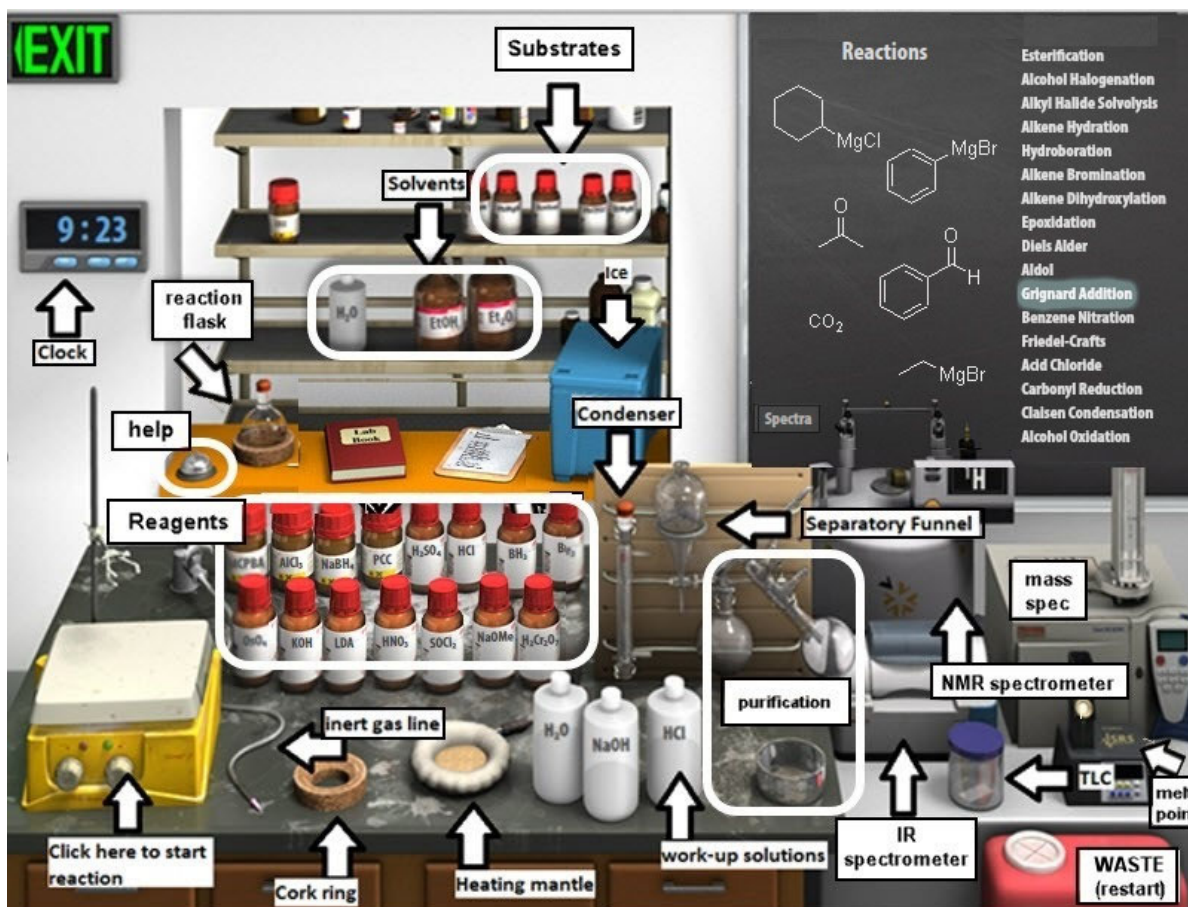


Figure 4. Beyond Labz SYNTHESIS virtual lab.

Virtual Lab Instructions (video instructions also available). Help is available by clicking on the bell on the stockroom counter. **As you work through the procedure, record your observations**, either in your lab notebook or by using the electronic notebook provided by Beyond Labz (on the shelf at the back of the lab, next to the reaction flask).

Part 1. Grignard reaction using water as the solvent.

1. Start the Beyond Labz program and go to the Virtual ChemLab – Organic Synthesis.
2. From the Stockroom list, click on “**Grignard Addition**,” and you will see the available substrates (drawn on the board and in bottles on the shelf). You will notice that there are 3 different carbonyl-containing compounds and 3 different Grignard reagents available from the “stockroom,” so be sure to select the correct reagents to make the target alcohol!
3. *Clicking and dragging (or in some cases by double-clicking) adds materials into the round-bottom flask, via syringe through the rubber septum that is fitted on the flask opening. **Although in real life the solvent is often added first, in this simulation the solvent must be added LAST!***
4. **Add aldehyde substrate.** Click on the benzaldehyde bottle and it will be added to the flask. The simulation doesn't allow us to weigh the reagents. Assume that 1.50 mL of benzaldehyde was added – you will need this number for calculations! Be sure to include the volume in your Lab Book observations.

5. **Add Grignard reagent.** Click on the ethyl magnesium bromide bottle and it will be added to the flask. Grignard reagents are typically added in excess. Assume that a slight excess of Grignard reagent was added.
6. **Add solvent.** Scroll to the top of the list to see the available Solvents. Click on the H₂O bottle and it will be added to the flask. Assume that a volume of ~10 mL was added.
7. Confirm that the reagents and the solvent have been properly added to the flask by hovering your mouse over the flask. The contents of the flask will display on the chalk board.
8. **Secure reaction flask to ring stand.** Double click on the flask to move it to the clamp above the stirring hot plate.
9. Check the **Live Data** tab to verify that your flask contains the correct aldehyde, Grignard reagent, and solvent.
10. The top of the flask is sealed with a rubber septum, so double-click on the nitrogen line to add it the top of the flask.
11. This Grignard reaction is fast, so we won't need to heat it.
12. **Collect initial TLC.** Before starting the reaction, check the initial (total reaction time = 0 minutes) TLC by clicking on the TLC chamber and dragging the plate to the flask. The TLC plate will always have two lanes – one that shows the starting materials (left), and one that shows what was in the flask at the time you measured the TLC (right). Since this is before the reaction has started, the two lanes should look identical because they both contain just the benzaldehyde starting material. Close the TLC plate and copy it to Lab Book by clicking Save.
13. **Start the reaction** by clicking the right knob on the stir plate.
14. Advance the clock, 1 minute at a time, until the Grignard reagent has been consumed (*i.e.*, it is no longer displayed on the Live Data tab). Record the contents of the flask, as given in the Flask Contents, in your Lab book.
15. **Collect final TLC.** Check the TLC plate at the end of the reaction. Close the TLC plate and copy it to Lab Book by clicking Save.
16. Reset the synthesis lab by clicking on the waste container to “Clear Lab” and discard all materials.

Part 2. Grignard reaction using ethanol as the solvent.

1. Follow the exact procedure as in Part 1, but modify Step 6 to use ethanol as the solvent instead of water: **Add solvent.** Click on the EtOH bottle to add it to the flask. Assume a volume of ~10 mL was added.

Part 3. Grignard reaction using diethyl ether as the solvent.

1. Start the Beyond Labz program and go to the Virtual ChemLab – Organic Synthesis.
2. From the Stockroom list, click on “**Grignard Addition**,” and you will see the available substrates (drawn on the board and in bottles on the shelf). You will notice that there are 3 different carbonyl-containing compounds and 3 different Grignard reagents available from the “stockroom,” so be sure to select the correct reagents to make the target alcohol!
3. *Clicking and dragging (or in some cases by double-clicking) adds materials into the round-bottom flask, via syringe through the rubber septum that is fitted on the flask opening. **Although in real life the solvent is often added first, in this simulation the solvent must be added LAST!***
4. **Add aldehyde substrate.** Click on the benzaldehyde bottle and it will be added to the flask. The simulation doesn't allow us to weigh the reagents. Assume that 1.50 mL of benzaldehyde was added – you will need this number for calculations! Be sure to include the volume in your Lab Book observations.

5. **Add Grignard reagent.** Click on the ethyl magnesium bromide bottle and drag to add it to the flask. Grignard reagents are typically added in excess. Assume that a slight excess of Grignard reagent was added.
6. **Add solvent.** Click on the Et₂O bottle to add it to the flask. Assume that a volume of ~10 mL was added.
7. Confirm that the reagents and the solvent have been properly added to the flask by hovering your mouse over the flask. The contents of the flask will display on the chalkboard.
8. **Secure reaction flask to ring stand.** Double click on the flask to move it to the clamp above the stirring hot plate.
9. Check the **Live Data** tab to verify that your flask contains the correct aldehyde, Grignard reagent, and solvent.
10. The top of the flask is sealed with a rubber septum, so double-click on the nitrogen line to add it the top of the flask.
11. This Grignard reaction is fast, so we won't need to heat it.
17. **Collect initial TLC.** Before starting the reaction, check the initial (total reaction time = 0 minutes) TLC by clicking on the TLC chamber and dragging the plate to the flask. The TLC plate will always have two lanes – one that shows the starting materials (left), and one that shows what was in the flask at the time you measured the TLC (right). Since this is before the reaction has started, the two lanes should look identical because they both contain just the benzaldehyde starting material. Close the TLC plate and copy it to Lab Book by clicking Save.
12. **Start the reaction** by clicking the right knob on the stir plate.
13. Advance the clock, 10 minutes at a time, until the Grignard reagent has been consumed (*i.e.*, it is no longer displayed on the chalkboard). Record the contents of the flask, as given on the chalkboard, in your notebook.
14. **Collect final TLC.** Check the TLC plate at the end of the reaction, and sketch the plate or save it to your lab notebook by clicking save. Close the TLC plate by clicking OK.
15. **Reaction workup.** Stop the reaction by double-clicking on the separatory funnel to move it to the flask. The Live Data will display what is in the flask, which should be the solvent and the product as an alkoxide salt (refer to Figure 3).
16. To protonate the alkoxide and form the alcohol product, double-click on the aqueous hydrochloric acid solution (plastic bottle labeled "HCl") to add it to the separatory funnel.
17. You will now see two layers of liquid in the funnel, the less dense ether layer ("organic layer") will float on top of the aqueous layer. If you hover your mouse over the layers, it will display if the layer is organic or aqueous and the Live Data tab will display the chemicals contained within each layer.
18. Remove the lower aqueous layer and discard it into the waste container by clicking and dragging it from the separatory funnel to the cork ring (this will move it into a round bottom flask), and then you can drag it into the red waste container. Use the information in the Live Data tab to make sure the correct layer is in the Flask Contents before throwing it away!
19. Click and drag the ether layer to the cork ring support. This step assumes that you evaporated the solvent using a rotatory evaporator, leaving you with just the product in the flask.
20. Record the IR spectrum of the product by clicking on the IR spectrometer and dragging the salt plate icon to the round bottom flask. This will display the IR spectrum on the screen. Click Save to save it to your lab notebook. Click X to close the spectrum window.
21. Your virtual experiment is now complete!

Grignard Reaction - Assignment

Prelab Questions

Name: _____

Before working with compounds in the laboratory, it is important to look up key physical properties and hazards for the chemicals that you are working with. For the benzaldehyde, ethyl magnesium bromide, and 1-phenylpropanol, look up the formula weight (FW), boiling point (b.p.), density, and hazards and complete the table below. A good place to look up information is a company that sells chemicals for laboratory use, try: www.sigmaaldrich.com.

	FW (g/mol)	b.p. (°C)	Density (g/mL)	Hazards
benzaldehyde				
ethyl magnesium bromide				
1-phenyl-1-propanol				

1. The procedure indicates that the starting amount of benzaldehyde is 1.50 mL. How many moles does 1.50 mL of benzaldehyde contain? Show calculation with units for full credit.

2. If 1.50 mL of benzaldehyde reacts with an excess of the Grignard reagent, calculate the theoretical yield (in grams) of the alcohol product. Show calculation with units for full credit.

Experimental Results

Part 1 Results (water solvent)

1. Draw the four components that were present in the flask after the Grignard reagent was consumed.
2. A proton-transfer reaction occurred between the ethyl magnesium bromide and the solvent. Draw the mechanism and products of the acid-base reaction.
3. Explain why water is described as a protic solvent, and discuss whether or not it is a suitable solvent for a Grignard reaction.

TLC Observations.

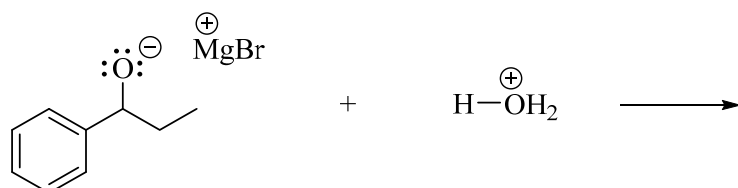
4. Sketch (or screen capture) two TLC plates: at the beginning ($t = 0$), and after the reaction went to completion. Label each spot on each plate (with compound name or structure).
5. In this failed experiment, the reaction mixture being analyzed contains diethyl ether and ethane, yet those compounds would not appear on the TLC plate. Propose an explanation for this observation. (*hint: consider the boiling points of these compounds*)

Part 2 Results (ethanol solvent)

6. Draw the four components that were present in the flask after the Grignard reagent was consumed. Was the alkoxide intermediate leading to the expected product among them?
7. A reaction occurred between the ethyl magnesium bromide and the solvent. Draw the mechanism and products of this reaction.

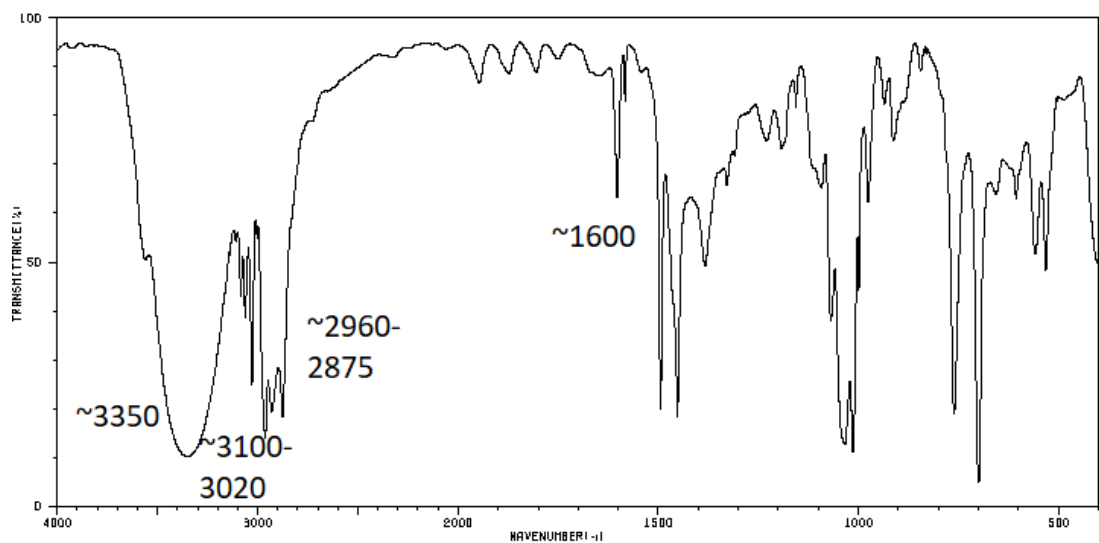
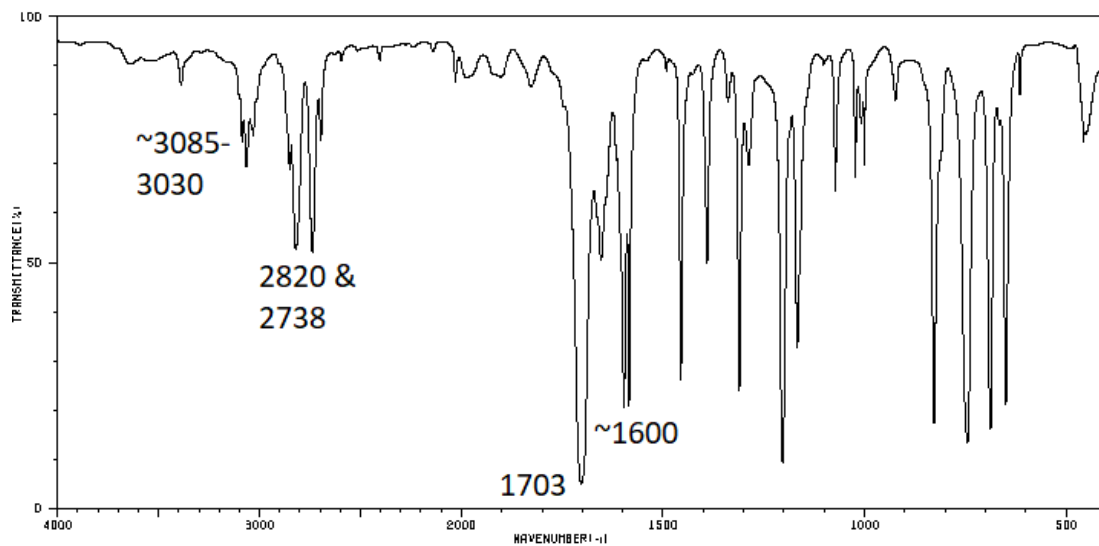
Part 3 Results (diethyl ether solvent)

8. **TLC Observations.** Sketch (or screen capture) two TLC plates: at the beginning ($t = 0$) and after the reaction went to completion. Label each spot on each plate (with compound name or structure). Which compound has the lower R_f , the starting material or the product? Explain why this difference in R_f makes sense.
9. If 1.12 grams of product are formed from 1.50 mL of benzaldehyde in this reaction, calculate the percent yield of the reaction.
10. The initial product of the Grignard reaction in part 3 was an alkoxide intermediate (magnesium bromide 1-phenyl-1-propoxide). An aqueous workup (with aq. HCl) furnishes the neutral product. Draw the curved arrows for this proton transfer reaction, and draw the organic product.

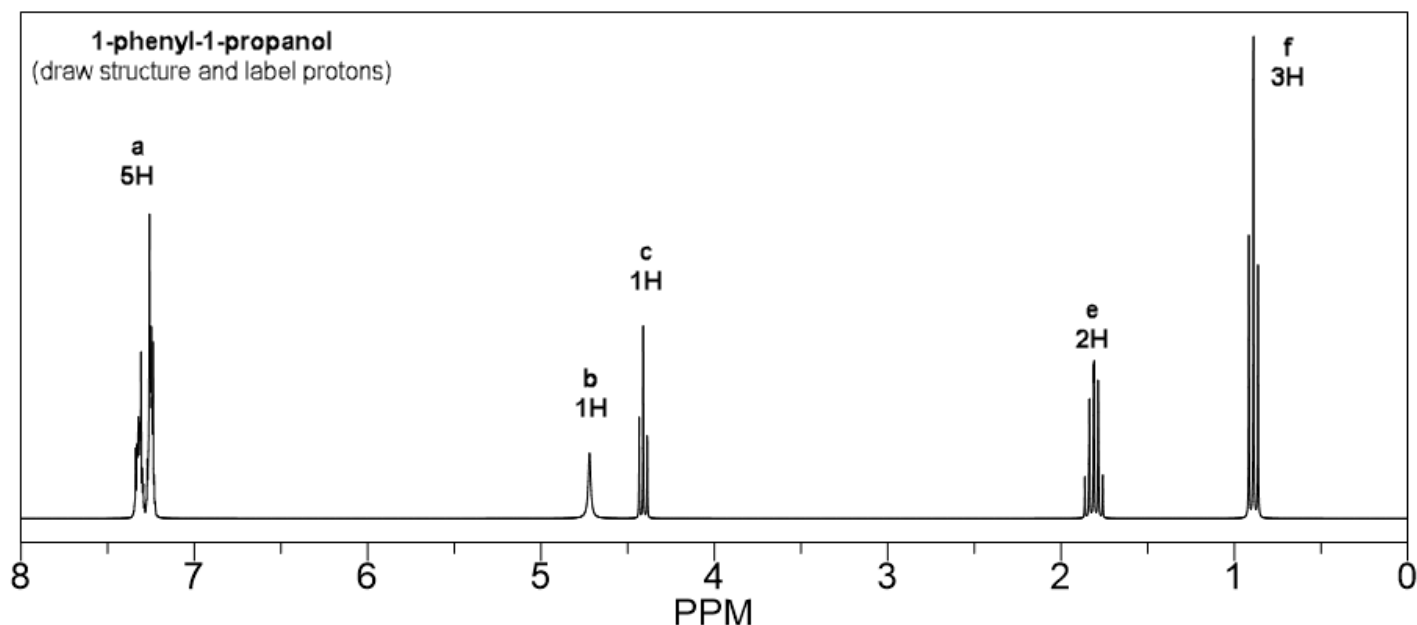


11. Which type of solvent is the best choice for a Grignard reaction, protic or aprotic? Explain briefly, referring to the three trials you ran in Beyond Labz.

12. **IR Analysis.** Identify each of the following IR spectra (draw the corresponding structure of the benzaldehyde substrate or the alcohol product), and label the significant peaks.



13. **NMR Analysis.** In the table below, draw the structure of 1-phenyl-1-propanol, with every H atom drawn out explicitly. The peaks in the NMR spectrum are labeled a-f. Label each proton on your drawing to match the corresponding peak in the NMR.



IRL Extension. The Grignard reaction is an exceptionally interesting reaction to conduct in real life. Here are two video demonstrations to watch. In each case, the chemist begins with bromobenzene (PhBr) and adds it slowly to a flask containing solvent and magnesium metal, to create the Grignard reagent (PhMgBr) via a metal insertion reaction.

- a. The first video has a good view of the magnesium metal turnings (yes, you use actual chunks of metal!) and a nice discussion of methods to help *initiate* the formation of the Grignard reagent. It can be tricky, but once the reaction starts going, you can continue adding the rest of the halide and watch the metal turnings slowly dissolve as the metal reacts.

<https://www.youtube.com/watch?v=Pgv0y8iSBWk>

- b. The second video has a good demonstration of the reaction workup.

<https://www.youtube.com/watch?v=s3sShnm1ArM>

14. Describe two methods you can use to initiate the formation of a Grignard reagent, and how do you know the reaction has begun?

15. In the second video, the glassware was stored in an oven before being used. What is the purpose of using an oven this way, and how does it make it more likely to have a successful Grignard reaction?