JOURNAL OF CHEMICAL EDUCATION

Laboratory Experiment

pubs.acs.org/jchemeduc

Investigating a Chemoselective Grignard Reaction in an Undergraduate Discovery Lab To Predict Reactivity and Final Products

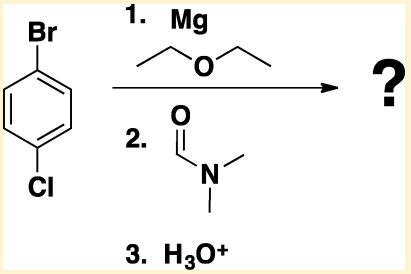
Michael J. Maher,*[,†] Colin O. Hayes,[†] Francesca A. Vaccaro,[‡] Cailyn B. Flynn,[‡] R. Paxton Thedford,[†] and Clifton J. Stephenson*[,‡]

[†]Department of Chemistry, The University of Texas at Austin, 105 East 24th Street, A5300, Austin, Texas 78712, United States

[‡]Department of Chemistry, Loyola University New Orleans, 6363 Saint Charles Avenue, New Orleans, Louisiana 70118, United States

Supporting Information

ABSTRACT: A discovery-based Grignard experiment that emphasizes several important concepts in organic chemistry is reported. The Grignard reagent from 1-bromo-4-chlorobenzene was prepared and reacted with dimethylformamide (DMF) to synthesize 4-chlorobenzaldehyde. Students were tasked with predicting halogen reactivity in the formation of the Grignard reagent, predicting the final product, and drawing a reasonable mechanism for the reaction with DMF. The Grignard reaction with tertiary amides is typically not discussed in the organic chemistry curriculum, so the students have an opportunity to apply concepts covered in lecture to a new situation. Lastly, the students experimentally verified the identity of the product using thin layer chromatography, melting point analysis, gas chromatography, IR and NMR spectroscopy, and mass spectrometry.



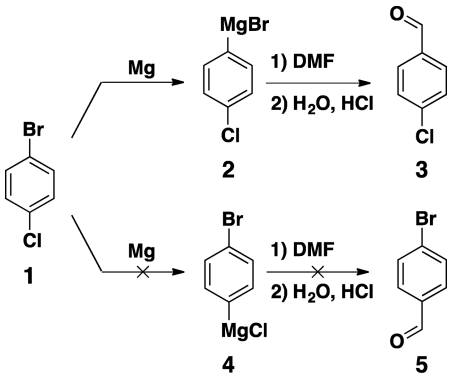
KEYWORDS: *Organic Chemistry, Grignard Reagents, Aldehydes/Ketones, Laboratory Instruction, Inquiry-Based/Discovery Learning, Second-Year Undergraduate, Upper-Division Undergraduate*

INTRODUCTION

The Grignard reaction is a fundamental tool in organic chemistry because it forms new carbon−carbon bonds and introduces new functional groups. As a result, the Grignard reaction is taught in all organic chemistry classes. In teaching laboratories, students often prepare the Grignard reagent of bromobenzene and react it with carbon dioxide or benzophenone to yield benzoic acid or triphenylmethanol, respectively.[1] Over the years, the emphasis on discovery-based pedagogy[2] has resulted in the design of many new Grignard experiments.[3−5] However, until very recently, no attention has been given to experiments where students prepare a Grignard reagent selectively from the more reactive halogen in a dihalogenated species.[6] Furthermore, most Grignard exercises result in the formation of highly predictable products such as tertiary alcohols. To the best of the authors' knowledge, there are no published lab exercises that use less conventional electrophiles where the product is not obvious to the students.

It was our goal to design a discovery-based experiment where students apply concepts learned in lecture to both the formation of the Grignard reagent and its subsequent reaction with an unknown electrophile. First, students prepared the Grignard reagent from 1-bromo-4-chlorobenzene (**1**, Scheme 1). In the presence of two different aryl halogens, the more reactive halogen will react with magnesium selectively.[7−9] In this case, since the C_{aryl}−Br bond is weaker and more labile than the C_{aryl}−Cl bond, the organomagnesium bromide (**2**) forms selectively over the organomagnesium chloride (**4**). Second, the students reacted the Grignard reagent with dimethylformamide (DMF) to synthesize 4-chlorobenzalde-

Scheme 1. Preparation of the Grignard Reagent and Subsequent Reaction with Dimethylformamide[a]



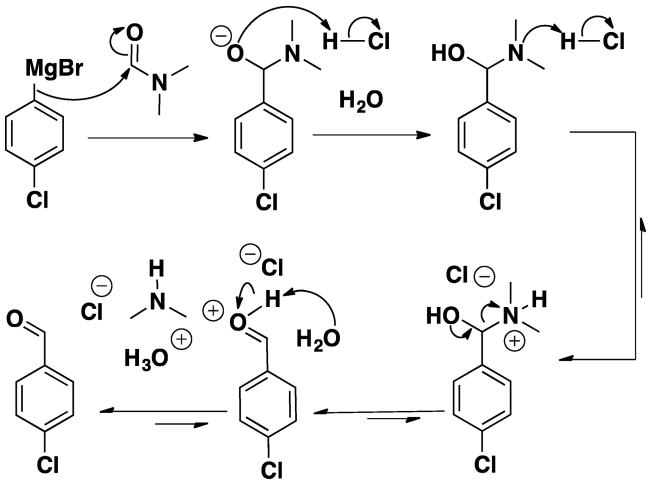
[a]The organomagnesium bromide (**2**) forms selectively over the organomagnesium chloride (**4**). The reaction with DMF produces an aldehyde after hydrolysis.

Received: June 9, 2015
Revised: June 10, 2016

DOI: 10.1021/acs.jchemed.5b00453
J. Chem. Educ. XXXX, XXX, XXX−XXX

hyde (**3**) and not 4-bromobenzaldehyde (**5**). This powerful reaction is known as the Bouveault aldehyde synthesis,[10] but it is not usually covered in undergraduate lecture. The product of the reaction is not obvious; however, the students can predict the correct product and propose a mechanism leading to the aldehyde. The students should recognize that the nucleophilic Grignard reagent attacks the electrophilic carbonyl in DMF. Upon formation of the Grignard reagent and addition to DMF, the initial product is a hemiaminal salt, which cannot undergo further reaction. Upon acidic workup, the hemiaminal (analogous to a hemiacetal) decomposes to the aldehyde (Scheme 2). The key is recognizing that the hemiaminal is unstable and is the same intermediate observed in imine hydrolysis. In lab, the students can verify the identity of the product using IR spectroscopy, melting point, mass spectrometry (MS), gas chromatography (GC), and NMR spectroscopy.

Scheme 2. Mechanism of the Reaction between a Grignard Reagent and Dimethylformamide and Subsequent Hydrolysis



This experiment has been performed by 10 undergraduates at the University of Texas at Austin as part of a research class and by 24 undergraduates over the past two years in the major's section of the Organic II Lab course at Loyola University New Orleans, which meets twice a week for 3-h periods. The experiment was performed over the course of four 3-h periods, but can be easily tailored to be completed in two or three 3-h lab slots. At Loyola, the students were presented an outline of the experiment but were not told what the correct product should be. The students were given a prelaboratory assignment (Supporting Information) that guided them toward a better understanding of the mechanism, which helped them predict the correct product before entering the lab. The students performed the experiment in pairs, and individual understanding was assessed based on a postlaboratory quiz (Supporting Information).

PEDAGOGICAL SIGNIFICANCE

This lab focused on three main goals. The first goal was to help students generate hypotheses about chemical reactivity in a method that emphasizes generative learning. The students should be capable of discerning the difference in reactivity of the C_{aryl}–Cl and the C_{aryl}–Br bond in the formation of the Grignard reagent. However, because the students have never been exposed to the reaction of a Grignard reagent with tertiary amides, the students needed to develop their own answers. The second goal was to teach new laboratory techniques such as column chromatography. The third goal was to have the students demonstrate mastery of a new concept by characterizing their product and reflecting on how their predications aligned with experimental results.

EXPERIMENTAL OVERVIEW

A detailed experimental procedure, list of chemicals, and instrumentation can be found in the Supporting Information (See Instructor Notes).

Lab Period 1

Students synthesized **3**. The Grignard reagent from 1 equiv of magnesium and 1 equiv of **1** was prepared in refluxing diethyl ether. After 1 h of refluxing, the Grignard reagent (**2**) was cooled to 0 °C in an ice bath and DMF was slowly added. After stirring for 20 min, the solution was acidified with 1 N HCl. The product was extracted with diethyl ether, and the crude product was obtained by evaporation of the solvent using a gentle stream of nitrogen.

Lab Periods 2 and 3

Students were given a lecture about thin layer chromatography (TLC) and flash chromatography. Then, the students performed TLC and compared the R_f value of the crude product and starting material using several different TLC conditions. Selective stains for aldehydes (2,4-dinitrophenylhydrazine, DNP) were introduced and used to stain the TLC plates. Then flash chromatography using silica gel as the stationary phase and 7% diethyl ether in hexanes as the mobile phase was performed in groups of two. Students collected approximately 10–20 15 mL fractions. TLC was used to determine which fractions contained the product. Rotary evaporation was used to remove the solvent to yield purified product.

Lab Period 4

Students collected characterization data, including IR and NMR spectroscopy, melting point, GC, and MS.

SAFETY HAZARDS

Splash-proof goggles, gloves, and lab coats should be worn during the lab. All reactions should be performed in a properly functioning fume hood. All organic solvents used within this lab are flammable and irritants. Hexanes contain *n*-hexane, which is a known neurotoxin and should be handled with special care. Diethyl ether is prone to form explosive peroxides, and only fresh and anhydrous diethyl ether should be used. The reaction with DMF is highly exothermic. DMF should be added dropwise to the cooled solution of Grignard reagent. Flash chromatography uses pressurized columns (~2–4 psi), and a vent should be used to relieve excess pressure. Students should assume that the product is an irritant and toxic. Additional safety data may be found in the SDS for each compound.

RESULTS AND DISCUSSION

Students were assigned a prelaboratory exercise for which about half predicted that the C–Br bond of **1** would react preferentially, with most basing their prediction on the better leaving group ability of bromide over chloride in nucleophilic substitution reactions. However, the better leaving group argument may not be the best explanation for the Grignard reaction because the Grignard reagent formation is suggested to

DOI: 10.1021/acs.jchemed.5b00453
J. Chem. Educ. XXXX, XXX, XXX–XXX

occur via single electron transfer or halogen abstraction.[11] In most undergraduate organic classes, the mechanism for the formation of Grignard reagents is not discussed, and this laboratory exercise presented a prime opportunity to discuss these concepts with the students. After completion of the lab, the reactivity was explained to the students in terms of bond dissociation energies. In this experiment, the C_{aryl}–Br bond is weaker than the C_{aryl}–Cl bond by approximately 13 kcal/mol, which makes it more labile in the reaction.[12] At 308 K, this difference in bond dissociation energies corresponds to a selectivity of 10^9:1, which could explain why **2** forms much faster than **4**.

As part of the prelaboratory exercises, the students were required to draw the mechanism for an acid catalyzed hydrolysis of an acetal. Then, the students were asked to draw the mechanism for the reaction between a Grignard reagent and DMF and the subsequent hydrolysis. About one-third of the students were able to correctly predict the product and draw an acceptable mechanism. A majority of students stopped at the hemiaminal and did not recognize that hemiaminals hydrolyze analogously to hemiacetals. At this point, showing the students the correct product before revealing the whole mechanism gave them another opportunity to work through the mechanism. The full mechanism was discussed later, after students turned in drafts of their formal lab reports.

Overall, the experiment was successful. Around 75% of the student groups successfully formed the Grignard reagent. The remainder of the groups were instructed to start the experiment over. After the second attempt, all groups were able to form the Grignard reagent and isolate a product. In many cases, the crude product was isolated as a waxy solid, which is normal because the melting point of the product is relatively close to room temperature. The authors have demonstrated that the crude product is typically more than 90% pure and further purification is not necessary for characterization and completion of the laboratory exercise. However, column chromatography was used at Loyola to teach a new purification technique. First, the students were taught how to use TLC to determine separation conditions. In most cases, the students' TLC plates showed one or two spots. After staining with a solution of DNP, the major spot turned red-orange, which suggests the presence of an aldehyde.[13] The students were taught that aldehydes and ketones react with DNP to form a hydrazone, which caused the aldehyde spot to turn color on the TLC plate. Then, the students collected fractions by eluting their product through a silica column using 7% ether in hexanes as the eluent. TLC was used to confirm which fractions contained the desired product, and rotary evaporation of the solvent resulted in a white solid. Crude yields ranged between 50 and 80%. However, the yields dropped to around 15–30% after purification by chromatography. Although the percent yields were low, each group had enough material to fully characterize their product.

The purity and identity of the product can be determined by a variety of chromatographic methods, including GC. Figure 1 shows the GC of the starting material (**1**), potential products (**3**, **5**), and product from the reaction. The retention time of the product matches the retention time of **3**. Additionally, a mixture of the experimental product and **3** showed one peak, further supporting that the product is **3** as predicted. Students then measured the melting point of their product and compared it to the melting points of **1**, **3**, and **5**. Representative data for the melting points are shown in Table 1. As shown, the melting point of the product nearly matches that of **3**.

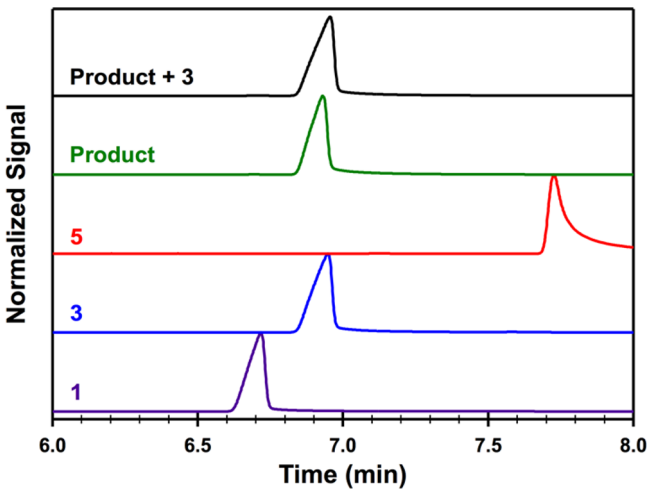


Figure 1. Gas chromatography data of the product and potential products. Suggested separation conditions are listed in the Supporting Information.

Table 1. Melting Point Data

Molecule	Melting Point (Lit. Value),[a] °C
1-Bromo-4-chlorobenzene (**1**)	67–69 (68)
4-Bromobenzaldehyde (**5**)	59–60 (58)
4-Chlorobenzaldehyde (**3**)	46–49 (47)
Product of reaction	Crude: 43–45
	Post column: 47–49

[a]See ref 14.

The students also characterized their products using IR (Figure S1) and NMR spectroscopy (Figure 2). In the IR spectra, the fingerprint region can be used to distinguish **3** and **5**. Typically, carbon–halogen bonds absorb below 1000 cm^{-1}.[15] However, the C_{aryl}–halogen stretch absorbs at 1000–1100 cm^{-1}.[16] In the IR spectra shown in Figure S1, the C_{aryl}–Cl

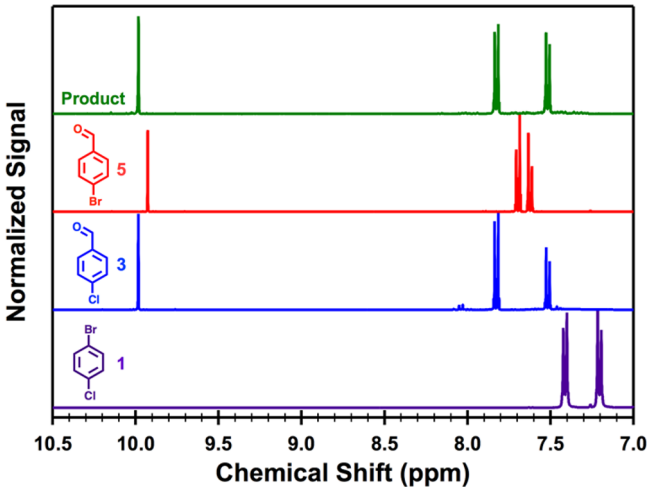


Figure 2. NMR spectra in $CDCl_3$ of the starting material, potential products, and the product of the Grignard reaction. The spectra have been referenced to the solvent residual peak (7.26 ppm), which has been removed for clarity.

DOI: 10.1021/acs.jchemed.5b00453
J. Chem. Educ. XXXX, XXX, XXX–XXX

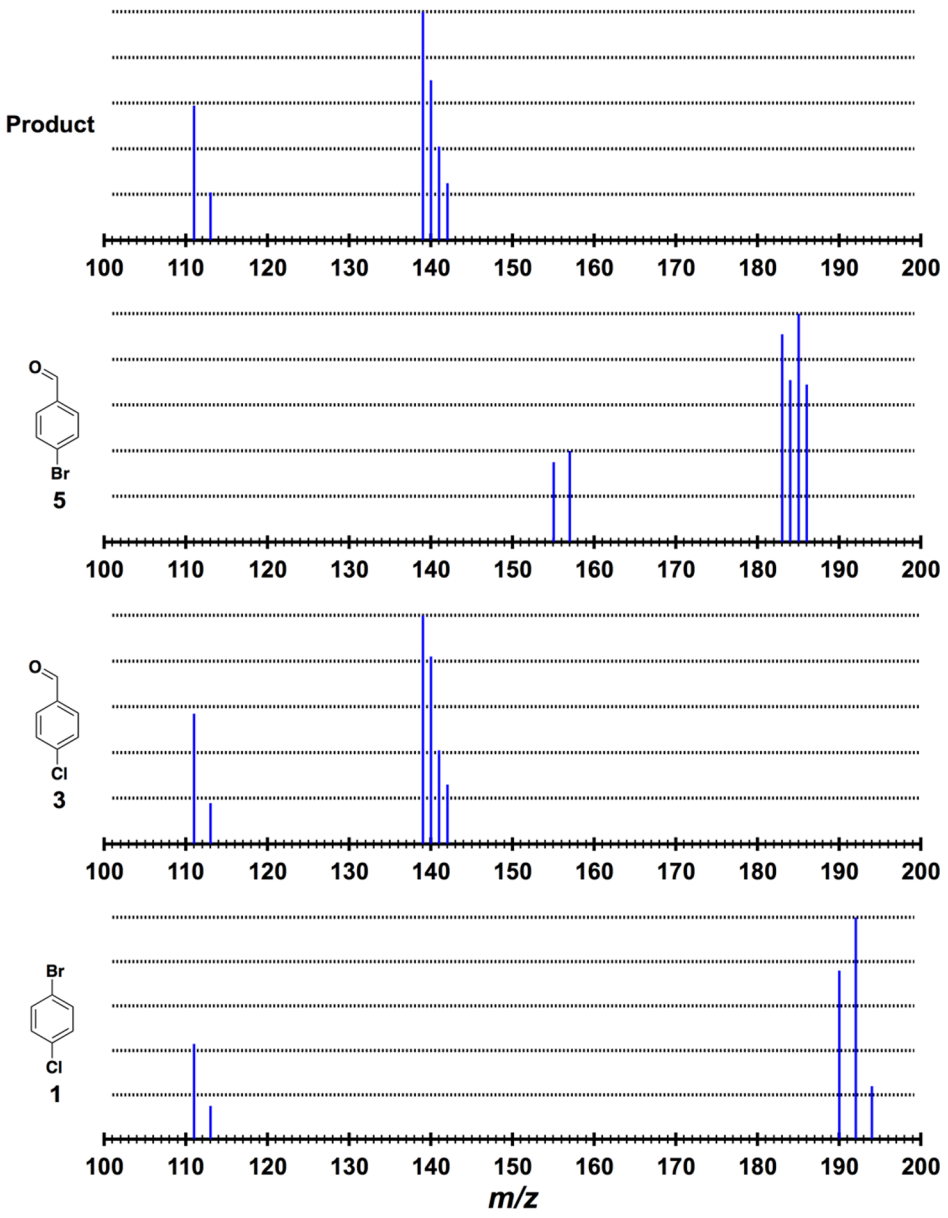


Figure 3. Mass spectrometry data using electron ionization.

bond is present at 1080 cm^{-1}. The C_{aryl}–Br bond in **5**, being weaker, absorbs at a lower frequency (1065 cm^{-1}) and is not observed in the product. Figure 2 shows the ^1H NMR spectra of the starting material, the two potential products, and the product from the experiment. The singlet near 10 ppm is characteristic of an aldehydic proton. The product can be referenced to the known spectra of **3** and **5**. The aldehydic proton in **3** is slightly downfield relative to **5**.

The IR and ^1H NMR spectra, without reference to literature spectra, would not be able to distinguish **3** and **5**. However, the identity of the product can be fully verified by MS using electron ionization. Figure 3 shows the spectra of the **1**, **3**, **5**, and the experimental product. It is clear from the molecular ion peaks alone that the product is **3** and not **5**. The MS data can be used as an additional exercise to complement what the students have learned in lecture. For example, both **3** and **5** have M + 2 peaks because of the halogen isotopes. However, using the relative abundance of each peak, it is clear that the product has 1 Cl and 0 Br atoms. Additionally, the base peak is the M − 1, which is the MS signature of the aldehyde functional group. The key fragments are listed in Table 2. Attempting to assign each fragment is an excellent exercise for the students.

This experiment worked very well at Loyola. The Loyola students were all able to synthesize, isolate, and purify **3**. This experiment was taught as part of an advanced synthesis and characterization lab for second-year chemistry majors. As such, students were expected to use and apply their knowledge from previous experiments while learning advanced synthesis, characterization, and purification techniques. This experiment allows students to draw on knowledge learned in class and apply it to a reaction that was not directly addressed during lecture. Additionally, a major focus of this experiment was training students to use modern instrumentation to characterize their product. The use of flash chromatography, IR and NMR spectroscopy, and MS allows students to observe the power of modern purification and characterization techniques.

DOI: 10.1021/acs.jchemed.5b00453
J. Chem. Educ. XXXX, XXX, XXX−XXX

Table 2. List of Relevant Mass Spectrometry Fragments

Molecule	Peak	m/z
1-Bromo-4-chlorobenzene (**1**)	$[M]^+$	190
	$[M + 2]^+$	192
	$[M + 4]^+$	194
	$[Chlorophenyl]^+$	111
	$[Chlorophenyl + 2]^+$	113
4-Bromobenzaldehyde (**5**)	$[M]^+ - 1$	183
	$[M]^+$	184
	$[M + 2]^+ - 1$	185
	$[M + 2]^+$	186
	$[Bromophenyl]^+$	155
	$[Bromophenyl + 2]^+$	157
4-Chlorobenzaldehyde (**3**)	$[M]^+ - 1$	139
	$[M]^+$	140
	$[M + 2]^+ - 1$	141
	$[M + 2]^+ - 1$	142
	$[Chlorophenyl]^+$	111
	$[Chlorophenyl + 2]^+$	113

At Loyola, the students were assessed with a postlab quiz (average score ∼75%), which was compared to the results of the prelaboratory assignment (average score ∼60%). In the mechanism problem (Question 1, Supporting Information), about 75% of the students were able to correctly show the addition of the Grignard reaction with DMF. About 50% of the students were able to successfully draw the hydrolysis of the hemiaminal to the aldehyde. Around half of the students were also able to predict the product of a Grignard reaction with a different tertiary amide (*N*,*N*-dimethylbenzamide), which results in ketone. A majority of the students seemed to demonstrate mastery of reaction as demonstrated by their writing in their lab reports.

Beyond what was done at Loyola, this experiment has the potential to be pedagogically versatile. At Loyola, this experiment was covered over a two-week period (four 3-h laboratories). It is the authors' opinion that the time can be reduced to two 3-h lab periods if no purification technique is used. Another benefit of this experiment is that the aldehyde can also be used for a subsequent reaction in a multistep synthesis. For example, the students at Loyola carried out a Wittig reaction (not reported here) with **3** to synthesize (*E*)-1-chloro-4-styrylbenzene. Overall, each instructor can tailor this reaction to focus on the concepts he or she feels need additional emphasis. For example, this experiment combines the topics of bond strengths, Grignard formation, nucleophilic addition, hydrolysis, and important characterization techniques. The authors believe that the students have learned to think more clearly about chemical reactivity and learned how to support/refute their hypotheses.

CONCLUSIONS

A new Grignard experiment was employed that challenges students on many fronts. In this experiment, the students synthesized 4-chlorobenzaldehyde from the reaction of DMF with the Grignard reagent from 1-bromo-4-chlorobenzene. First, the students decided which Grignard reagent forms given an option of two. Second, the Grignard reaction with DMF is one that is not covered in lecture, which allowed the students to apply concepts learned in class to a new situation. Lastly, students characterized their products using common laboratory techniques.

This experiment would be a strong addition to an introductory organic chemistry class or an upper level synthesis lab class depending on how each instructor tailors it. This experiment combines hypothesis-driven discovery with characterization techniques to help support a predicted mechanism/product. This experiment also provides instructors a versatile platform for teaching pedagogy related to mechanistic understanding of reactions, synthetic techniques, and advanced characterization techniques.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available on the ACS Publications website at DOI: 10.1021/acs.jchemed.5b00453.

Student handout, prelaboratory exercise, postlaboratory quiz, list of chemicals, instructor notes, and Figure S1 (PDF, DOCX)

AUTHOR INFORMATION

Corresponding Authors

*E-mail: mmaher13@utexas.edu.

*E-mail: cjs@loyno.edu.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

The authors thank the undergraduates who participated in the testing of this experiment. M.J.M. thanks Katie Hurley for a detailed reading of the manuscript and thoughtful suggestions. M.J.M. thanks the National Science Foundation Graduate Research Fellowship (Grant No. DGE-1110007) for financial support. Any opinion, findings, and conclusions or recommendations expressed in this material are those of the authors and do not necessarily reflect the views of the National Science Foundation or the sponsors.

REFERENCES

(1) Williamson, K. L.; Masters, K. M. *Macroscale and Microscale Organic Experiments*; 6th ed.; Brooks/Cole: Belmont, CA, 2011; pp 490−506.

(2) Martin, L. J. *Development of a Discovery-Based Organic Chemistry Lab Module: Evaluation of Student Attitudes and Ability to Interpret Spectroscopy*. Ph.D. Dissertation, Middle Tennessee State University: 2014. http://jewlscholar.mtsu.edu/handle/mtsu/4329 (accessed May 2016).

(3) Ciaccio, J. A.; Bravo, R. P.; Drahus, A. L.; Biggins, J. B.; Concepcion, R. V.; Cabrera, D. Diastereoselective Synthesis of (±)-1,2-Diphenyl-1,2-Propanediol. A Discovery-Based Grignard Reaction Suitable for a Large Organic Lab Course. *J. Chem. Educ.* **2001**, *78* (4), 531−533.

(4) Pointer, R. D.; Berg, M. A. Using a Premade Grignard Reagent to Synthesize Tertiary Alcohols in a Convenient Investigative Organic Laboratory Experiment. *J. Chem. Educ.* **2007**, *84* (3), 483−484.

(5) Teixeira, J. M.; Byers, J. N.; Perez, M. G.; Holman, R. W. The Question-Driven Laboratory Exercise: A New Pedagogy Applied to a Green Modification of Grignard Reagent Formation and Reaction. *J. Chem. Educ.* **2010**, *87* (7), 714−716.

(6) Hein, S. M.; Kopitzke, R. W.; Nalli, T. W.; Esselman, B. J.; Hill, N. J. Use of ^{1}H, ^{13}C, and ^{19}F-NMR Spectroscopy and Computational Modeling to Explore Chemoselectivity in the Formation of a Grignard Reagent. *J. Chem. Educ.* **2015**, *92* (3), 548−552.

(7) Knochel, P.; Dohle, W.; Gommermann, N.; Kneisel, F. F.; Kopp, F.; Korn, T.; Sapountzis, I.; Vu, V. A. Highly Functionalized

DOI: 10.1021/acs.jchemed.5b00453
J. Chem. Educ. XXXX, XXX, XXX−XXX

Organomagnesium Reagents Prepared Through Halogen-Metal Exchange. *Angew. Chem., Int. Ed.* **2003**, *42* (36), 4302−4320.
(8) Bhat, A. P. I.; Bhat, B. R. Single-Step Oxidative Homocoupling of Aryl Grignard Reagents via Co(II), Ni(II) and Cu(II) Complexes Under Air. *Appl. Organomet. Chem.* **2014**, *28* (6), 383−388.
(9) Ke, J.; Tang, Y.; Yi, H.; Li, Y.; Cheng, Y.; Liu, C.; Lei, A. Copper-Catalyzed Radical/Radical C_{sp}^3-H/P-H Cross-Coupling: a-Phosphorylation of Aryl Ketone *O*-Acetyloximes. *Angew. Chem., Int. Ed.* **2015**, *54* (22), 6604−6607.
(10) Smith, L. I.; Bayliss, M. The Bodroux-Tschitschibabin, and the Bouveault Aldehyde Syntheses. *J. Org. Chem.* **1941**, *6* (3), 437−442.
(11) Rogers, H. R.; Hill, C. L.; Fujiwara, Y. Mechanism of Formation of Grignard Reagents. Kinetics of Reaction of Alkyl Halides in Diethyl Ether with Magnesium. *J. Am. Chem. Soc.* **1980**, *102* (1), 217−226.
(12) Blanksby, S. J.; Ellison, G. B. Bond Dissociation Energies of Organic Molecules. *Acc. Chem. Res.* **2003**, *36* (4), 255−263.
(13) Pirrung, M. C. *The Synthetic Organic Chemist's Companion*; John Wiley & Sons, Inc.: Hoboken, NJ, 2007; pp 98−103.
(14) *CRC Handbook of Chemistry and Physics*, 88th ed.; Lide, D. R., Ed.; CRC Press: Boca Raton, FL, 2007.
(15) Silverstein, R. M.; Webster, F. X.; Kiemle, D. J. *Spectrophotometric Identification of Organic Compounds*, 7th ed.; John Wiley & Sons: Hoboken, NJ, 2005.
(16) Pavia, D. L.; Lampman, G. M.; Kriz, G. S.; Vyvyan, J. A. *Introduction to Spectroscopy*, 5th ed.; Cengage Learning: Stamford, CT, 2015; pp 84−85.

DOI: 10.1021/acs.jchemed.5b00453
J. Chem. Educ. XXXX, XXX, XXX−XXX