

## Introducing Aliphatic Substitution with a Discovery Experiment Using Competing Electrophiles

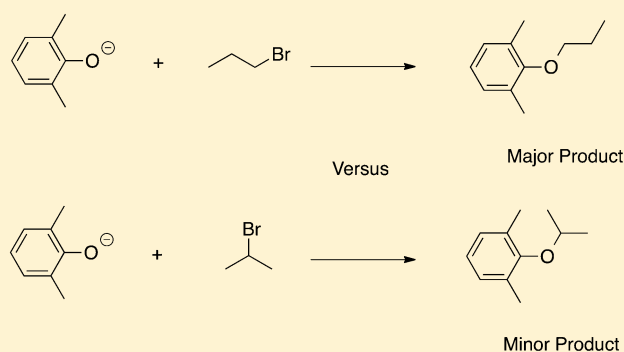
Timothy P. Curran,\* Amelia J. Mostovoy, Margaret E. Curran, and Clara Berger

Department of Chemistry, Trinity College, 300 Summit Street, Hartford, Connecticut 06106, United States

**S** Supporting Information

**ABSTRACT:** A facile, discovery-based experiment is described that introduces aliphatic substitution in an introductory undergraduate organic chemistry curriculum. Unlike other discovery-based experiments that examine substitution using two competing nucleophiles with a single electrophile, this experiment compares two isomeric, competing electrophiles (primary and secondary halides) with a single nucleophile (phenoxide ion). The question posed to students at the start of the experiment is what mechanism explains formation of the observed ether product from reaction of the phenoxide with an alkyl halide. If the reaction proceeds via an  $S_N1$  mechanism, then the major product will come from reaction of the secondary halide. If the reaction proceeds via an  $S_N2$  mechanism, the major product will come from reaction of the primary halide. In this experiment, students are able to discover that the primary halide reacts faster than the secondary halide by a roughly 4:1 margin. This discovery allows students to conclude that the reaction proceeds via an  $S_N2$  mechanism.

**KEYWORDS:** Second-Year Undergraduate, Organic Chemistry, Nucleophilic Substitution, Inquiry-Based/Discovery Learning, Mechanisms of Reactions, Laboratory Instruction



Substitution at  $sp^3$ -hybridized carbon is one of the important reactions covered in the introductory undergraduate organic chemistry course, and a number of substitution experiments have been described and used.<sup>1–15</sup> Some of these experiments are traditional verification experiments in which students perform a substitution reaction in order to confirm what had been covered in the lecture part of the course.<sup>1–8</sup> In contrast, there are several experiments that explore substitution using a guided-inquiry (discovery) approach.<sup>9–15</sup> In these experiments, students can discover one or more aspects of substitution, and the student data can be used to initiate discussion of substitution in the classroom. The discovery experiments that have been described and utilized employ different approaches. In one experiment, a studio approach has been used to discover aspects of substitution.<sup>15</sup> In another experiment, rates of reaction were used to discover aspects of substitution.<sup>14</sup> The most common approach for a discovery-based experiment has been to use two nucleophiles, chloride and bromide ions, competing for a single electrophile, which can be either a primary, secondary, or tertiary halide.<sup>10–12</sup> Alternatively, one experiment describes how to use the competition of a single nucleophile for two structurally similar electrophiles, an alkyl chloride and an alkyl bromide.<sup>9</sup>

At Trinity, introductory organic chemistry is taught using a guided-inquiry approach where students first encounter a new topic in the laboratory, and where student data are used to drive classroom discussion of a topic. A competing nucleophile

experiment<sup>10</sup> has been used for over a decade, but it has been found to be unsatisfactory because it has proven to be difficult to use in a postlab discussion where the student data (GC–MS) do not closely match the predicted outcomes made by students in a prelab lecture. For example, students predict that the product mixture should contain a roughly equal proportion of chloro- and bromoproducts if the reaction goes by an  $S_N1$  mechanism; for an  $S_N2$  mechanism, the bromoproduct should predominate over the chloroproduct. When running this reaction with a tertiary alcohol, which proceeds via an  $S_N1$  mechanism, the chloroproduct predominates over the bromoproduct. This is an outcome that students do not predict, and it is inconsistent with either mechanism. This experimental outcome likely occurs because the alkyl halide products can also undergo substitution; since the chloroproduct is less reactive toward substitution than the bromoproduct, its concentration will increase relative to the bromoproduct. Getting beginning students to understand this complicated dynamic makes it harder for them to learn the basic concepts regarding the two substitution mechanisms.

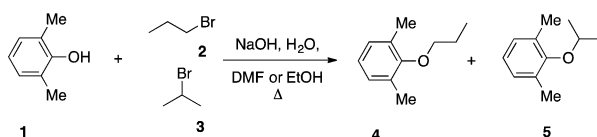
Difficulties in teaching substitution using a guided-inquiry approach and a competing nucleophile experiment led to the development and adoption of the experiment described herein.

Received: May 28, 2015

Revised: January 7, 2016

The premise of this experiment (Scheme 1) is to introduce substitution using a guided-inquiry approach by having a single

### Scheme 1. Reaction Equation for the Competing Electrophile Experiment



nucleophile (a phenoxide ion, derived from the parent phenol 1) compete for two isomeric, but structurally dissimilar, electrophiles (primary and secondary halides, 2 and 3) to produce two different aryl ethers, 4 and 5. The reaction of phenoxides with alkyl halides has been used to demonstrate substitution in traditional laboratory experiments.<sup>6</sup> The advantage of using this reaction is that phenols are commercially available, inexpensive and easily converted to the phenoxide by treatment with hydroxide ion. Similarly, isomeric alkyl halides, such as 2 and 3, are also commercially available and inexpensive. Another advantage is that the unreacted starting compounds are easily removed by either extraction (phenol) or evaporation (alkyl halides). The pedagogical goal for the development of the experiment was to enable students to make a valid conclusion about the mechanism of an aliphatic substitution reaction.

### PRELAB HYPOTHESIS

Prior to this experiment, students have not studied either aliphatic substitution or elimination, and therefore, this experiment is the first encounter students have with aliphatic substitution. The discovery that substitution and elimination often occur in the same reaction happens after completion of this experiment. In a prelab, students are told that a phenol and an alkyl halide will react in the presence of hydroxide ion to yield an aryl ether. For example, reaction of phenol (6) with ethyl bromide (7) in the presence of hydroxide ion yields ethoxybenzene (8) (Scheme 2).

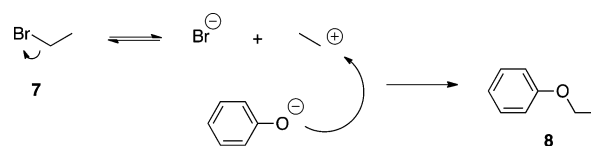
### Scheme 2. Substitution Reaction Used in Prelab Discussion



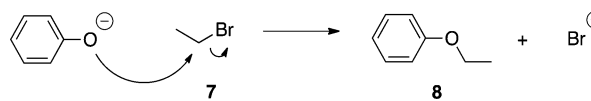
Given this outcome, students propose mechanisms for how this reaction takes place. Since this experiment follows the study of acid–base reactions, students quickly propose that the phenol is deprotonated by the hydroxide ion to produce the phenoxide ion. They propose two possible ways in which the oxygen becomes bonded to the ethyl group. Some students suggest that bromide ion departs from the ethyl group to generate a carbocation, which then couples with the phenoxide to yield the ether (Scheme 3, an S<sub>N</sub>1 mechanism). Other students propose that the phenoxide displaces the bromide ion in a single step (Scheme 4, an S<sub>N</sub>2 mechanism). Because this is a discovery experiment, in the prelab discussion the terms S<sub>N</sub>1 and S<sub>N</sub>2 are not used; they are presented later during a postlab discussion.

With two possible mechanisms, students consider how the mechanism of this reaction could be discerned in a competition

### Scheme 3. Proposed Two-Step Displacement (S<sub>N</sub>1) Mechanism



### Scheme 4. Proposed One-Step Displacement (S<sub>N</sub>2) Mechanism



experiment where 2,6-dimethylphenol (1) is treated with equimolar amounts of 2 and 3 to yield a mixture of the two isomeric ethers, 4 and 5. Students first propose the outcome if the S<sub>N</sub>1 mechanism is operative. With some guidance, students recognize that the slow step in this mechanism is the first step, formation of the carbocation. They then recognize that the two alkyl bromides will yield two different carbocations, and because they had previously studied carbocation stability, they recognize that 3 is more likely to form a carbocation than 2. Knowledge about carbocation stability makes it possible for students to generate a hypothesis that 5 would be the major product in the reaction if an S<sub>N</sub>1 mechanism is operative.

Students also consider the outcome of the reaction if an S<sub>N</sub>2 mechanism is operative. Since this is a one-step mechanism, the stability of an intermediate ion is not of concern. Students propose that steric factors would be important here, meaning that reaction of the phenoxide with secondary bromide 3 is likely to go slower than the reaction with primary bromide 2. Accordingly, students hypothesize that if the S<sub>N</sub>2 mechanism is operative, 4 would be the major product.

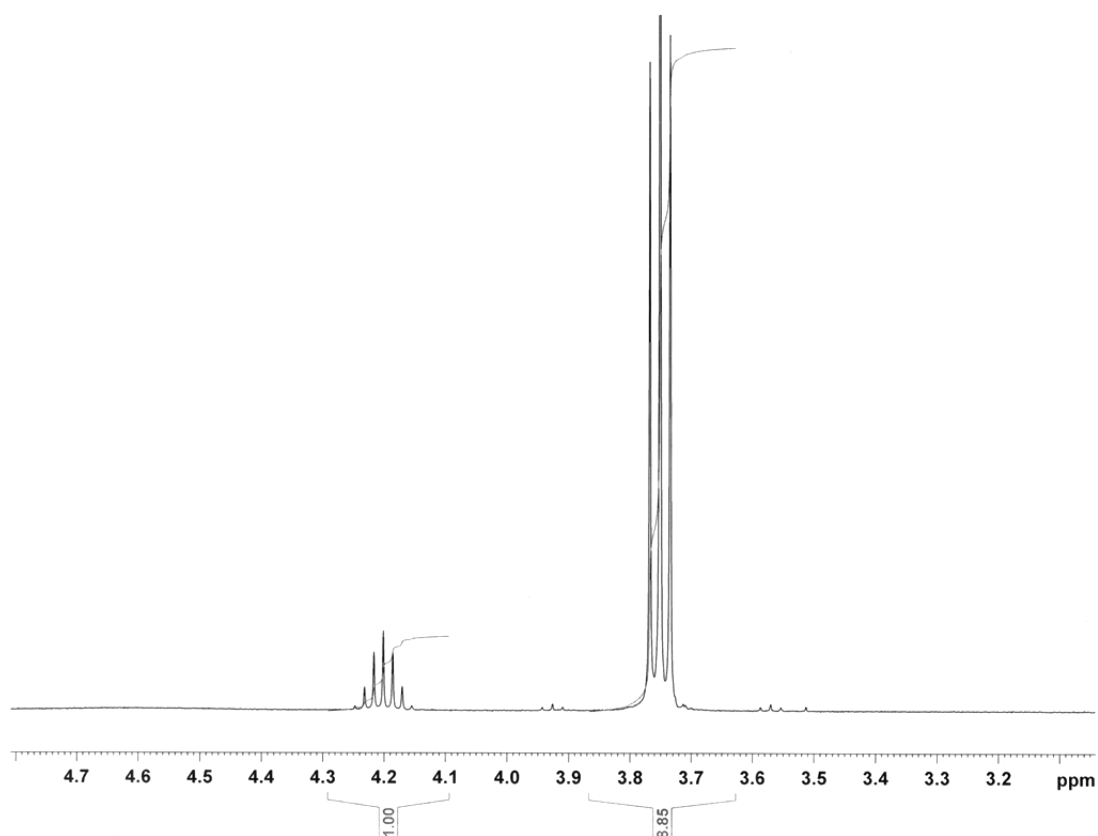
Students review their two hypotheses and see that the two predicted outcomes are different, with an S<sub>N</sub>1 mechanism predicting 5 as the major product and an S<sub>N</sub>2 mechanism predicting 4 as the major product. These predictions demonstrate to students that the results of their laboratory work will allow them to conclude which mechanism best explains this reaction.<sup>16</sup>

### EXPERIMENT

Students work individually and require 3 h to complete the experiment. Students dissolve 1 (5.0 mmol) in equal volumes (1 mL) of ethanol and 20% NaOH, bring the solution to reflux, and add a 1:1 mixture of 2 and 3 (11 mmol each) to the flask.<sup>1</sup> After the solution is heated for 40 min, the ether products are isolated by extraction and rotary evaporation. The crude product, an oil, is analyzed by <sup>1</sup>H NMR spectroscopy and/or GC–MS. More detailed information about the experiment can be found in the Supporting Information.

### HAZARDS

Students should wear gloves when carrying out this experiment. Ethanol is a flammable liquid. Both 1-bromopropane and 2-bromopropane are toxic (particularly to the blood, liver and central nervous system), highly flammable liquids that cause irritation to the skin, eyes and respiratory system. They may also cause infertility and may be harmful to an unborn child. 2,6-Dimethylphenol may cause irritation to the skin and eyes.



**Figure 1.** A representative student  $^1\text{H}$  NMR spectrum (400 MHz) of the product mixture. The septet at 4.20 ppm is from the methine group adjacent to the oxygen in **5**. The triplet at 3.75 ppm is from the methylene group adjacent to the oxygen in **4**. In this particular example, the ratio of **4**:**5** is 4.4:1.

Sodium hydroxide is corrosive and is toxic if swallowed or in contact with skin. Deuteriochloroform ( $\text{CDCl}_3$ ) is a skin and eye irritant, suspected of causing cancer, toxic if inhaled or ingested, and may damage fertility or the health of an unborn child. There are no reported material data safety sheets for the ether products; it should be assumed that they are flammable, toxic if ingested or inhaled, and may irritate skin and eyes.

## RESULTS AND DISCUSSION

This experiment has been run for two years with approximately 120 students. In this period, 99% of students completed their laboratory work in 3 h or less. Students who required a longer time had to restart the experiment due to an error, such as forgetting to add one of the reactants to the reaction mixture. The success of Trinity students in using this competing electrophile experiment indicates that it will work well for students and instructors in other schools that teach organic chemistry.

Best results were obtained when students performed the extraction with appropriate volumes of base and thoroughly evaporated the organic layer following extraction. If students did not use the appropriate volumes of aqueous base in the extraction process, then their crude products will contain some unreacted **1**; the presence of **1** did not interfere with the determination of the **4**:**5** ratio by either GC or NMR spectroscopy. If evaporation was not done completely, students found peaks in their NMR spectra from unreacted 1-bromopropane (**2**) and 2-bromopropane (**3**). Although the peaks from **2** and **3** do not overlap with the product peaks of

interest in the  $^1\text{H}$  NMR spectrum, their presence confused some of the students.

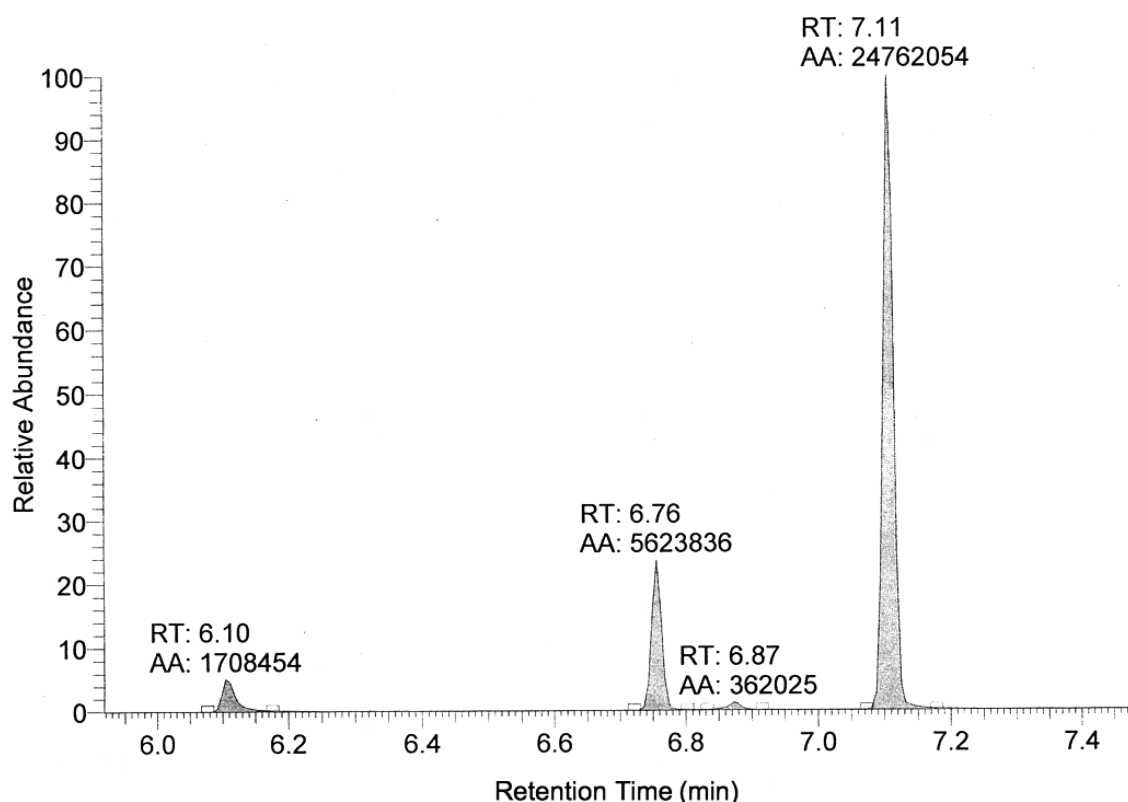
In the NMR spectrum (Figure 1 and Supporting Information), the methylene group adjacent to the oxygen in **4** appears as a triplet at 3.76 ppm, while the methine group adjacent to the oxygen in **5** appears as a septet at 4.22 ppm.

A ratio of **4** to **5** is obtained by comparing the integration of the methylene group in **4** with twice the integration of the methine group in **5**; the uncertainty in the integration is  $\pm 5\%$ . In the GC chromatogram (Figure 2 and Supporting Information), **4** elutes from the column prior to **5**; both are identified from their molecular ions. The ratio of **4**:**5** is obtained by taking the ratio of the peak area integrations. Ratios of **4**:**5** have varied between 3.0:1 and 4.8:1, and averaged out to 4:1.

The 4:1 ratio of **4**:**5** was ideal for the aims of this experiment since it can be obtained using GC and/or  $^1\text{H}$  NMR spectroscopy. Because the NMR integration process relied on students performing the spectrum phasing and integration, there can be a relatively high uncertainty associated with this data; in contrast, integration of the GC peaks was automated and had a relatively low uncertainty. Between the two methods of analysis, the most precise data were obtained using GC.

## POSTLAB DISCUSSION

The data from this experiment were presented and discussed in class after all students had completed the experiment and had time to analyze their data. A PowerPoint presentation (see Supporting Information) was used to facilitate the discussion. Students immediately concluded that the primary halide (**2**)



**Figure 2.** A representative student gas chromatogram of the product mixture. The peak at  $R_t$  6.76 min is **5**, while the peak at  $R_t$  7.11 min is **4**. Unreacted 2,6-dimethylphenol elutes at 6.10 min. The peak areas (AA) are given with each peak in the chromatogram. The ratio of **4**:**5** in this particular experiment was 4.4:1.

reacted faster than the secondary halide (**3**). Further, they recalled that this outcome supported an  $S_N2$  and not an  $S_N1$  mechanism for this reaction. The ability of students to make these conclusions in the postlab discussion indicated that the pedagogical goal of the experiment (to have students make a valid conclusions about the mechanism of an aliphatic substitution reaction) had been achieved. That students are able to generate data that were used to make conclusions about a mechanism is a very attractive feature of this experiment. The data from this experiment allowed a discussion of the  $S_N2$  reaction to expand to other nucleophiles, e.g., cyanide, azide, enolate and alkynyl anions. The results from this experiment were discussed, again, when elimination reactions were studied. Students explained that if elimination products had been formed, propene gas would have been produced, which would have been lost during the product isolation procedure, and therefore, no elimination products were observed.

## SUMMARY

This experiment was developed in order to have students explore aliphatic substitution using a guided-inquiry approach in the introductory organic chemistry course.

It is a robust experiment that works well for students of varying abilities. The experiment was easily completed in a typical 3 h laboratory period; generated consistent, high quality data; and worked well in a guided-inquiry format. GC and/or NMR spectroscopy can be employed for data analysis. When the NMR integrations were done well, the GC and NMR data gave nearly identical results, showing that both analytical techniques are reliable and produce precise results. Using NMR

spectroscopy to measure the product ratios serves to reinforce student understanding of this analytical technique.

The pedagogic goal for the experiment was to enable students to draw a valid conclusion about the mechanism of an aliphatic substitution reaction. On the basis of the ability of students to draw the correct conclusion during the postlab discussions, this goal was achieved over the last two years. Each student who ran this experiment obtained data that were consistent with a 4:1 ratio of the products **4**:**5**. Their success with this guided-inquiry experiment allowed for deeper and more extensive discussions of substitution reactions in the lecture part of the organic chemistry course than had been possible using a competing nucleophile experiment.

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available on the ACS Publications website at DOI: 10.1021/acs.jchemed.5b00394.

PowerPoint presentation used in lecture when discussing the data (ZIP)

Student handouts (PDF, DOCX)

Instructor notes (which include detailed procedures, representative student data, CAS numbers, prelab assessment, and postlab assessments) (PDF, DOCX)

## AUTHOR INFORMATION

### Corresponding Author

\*E-mail: timothy.curran@trincoll.edu.

## Notes

The authors declare no competing financial interest.

## ACKNOWLEDGMENTS

We thank Denise Rau, Cheyenne Brindle and Olivier Nicaise for their constructive criticisms and their insights into the safe operation of this experiment. We also thank the reviewers for their helpful suggestions on how to improve the manuscript.

## REFERENCES

- (1) Howell, B. A.; Kohrman, R. E. Preparation of 2-Bromopentane. *J. Chem. Educ.* **1984**, *61* (10), 932–934.
- (2) Clennan, M. M.; Clennan, E. L. A GC-MS Analysis of an  $S_N2$  Reaction for the Organic Laboratory. *J. Chem. Educ.* **2005**, *82* (11), 1676–1678.
- (3) Shepherd, J. N.; Stenzel, J. R. Synthesis of Unsymmetrical Alkynes via the Alkylation of Sodium Acetylides. *J. Chem. Educ.* **2006**, *83* (3), 425–428.
- (4) Williamson, K.; Masters, K. *Macroscale and Microscale Organic Experiments*, 6th ed.; Cengage Learning: Belmont, CA, 2010; pp 318–325.
- (5) Esteb, J. J.; Magers, J. R.; McNulty, L.; Morgan, P.; Wilson, A. M. A Simple  $S_N2$  Reaction for the Undergraduate Organic Laboratory. *J. Chem. Educ.* **2009**, *86* (7), 850–852.
- (6) Nimitz, J. S. *Experiments in Organic Chemistry*; Prentice Hall: Englewood Cliffs, NJ, 1990; pp 228–230.
- (7) Mobley, T. A. NMR Kinetics of the  $S_N2$  Reaction between BuBr and  $\Gamma^-$ : An Introductory Organic Chemistry Laboratory Exercise. *J. Chem. Educ.* **2015**, *92* (3), 534–537.
- (8) Pace, R. D.; Regmi, Y. The Finkelstein Reaction: Quantitative Reaction Kinetics of an  $S_N2$  Reaction Using Nonaqueous Conductivity. *J. Chem. Educ.* **2006**, *83* (9), 1344–1348.
- (9) Newton, T. A.; Warren, H. W. Nucleophilic Substitution Reactions: Modifications and an Extension. *J. Chem. Educ.* **1980**, *57* (10), 747.
- (10) Jarret, R. M.; McMaster, P. D. Teaching Organic Chemistry with Student-Generated Information. *J. Chem. Educ.* **1994**, *71* (12), 1029–1031.
- (11) Ault, A. *Techniques and Experiments for Organic Chemistry*, 6th ed.; University Science Books: Sausalito, CA, 1998; pp 407–410.
- (12) Pavia, D. L.; Lampman, G. M.; Kriz, G. S.; Engel, R. G. *Introduction to Organic Laboratory Techniques: A Small-Scale Approach*, 2nd ed.; Brooks/Cole: Belmont, CA, 2004; pp 171–181.
- (13) Kjonaas, R. A.; Tucker, R. J. F. A Discovery Based Experiment Involving Rearrangement in the Conversion of Alcohols to Alkyl Halides. *J. Chem. Educ.* **2008**, *85* (1), 100–101.
- (14) Horowitz, G. A Safer, Discovery-Based Nucleophilic Substitution Experiment. *J. Chem. Educ.* **2009**, *86* (3), 363–364.
- (15) Collison, C. G.; Cody, J.; Stanford, C. An  $S_N1$ - $S_N2$  Lesson in an Organic Chemistry Lab Using a Studio-Based Approach. *J. Chem. Educ.* **2012**, *89* (6), 750–754.
- (16) Another possibility is that both the  $S_N1$  and  $S_N2$  mechanisms are operative in this reaction. This possibility has not been proposed by any of the students who have completed this experiment. Given that the reaction takes place under strongly basic conditions, the  $S_N1$  mechanism, which requires formation of a strongly acidic carbocation intermediate, is an unlikely pathway for this reaction.