Catalytic Reduction of Cinnamyl Alcohol and NMR Assessments of the Product(s)

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Abstract. The described laboratory experiment has been designed to introduce undergraduate students to multiple organic chemistry laboratory techniques by conducting catalytic hydrogenation of the *E*-isomer of cinnamyl alcohol, but *without* the use of compressed hydrogen gas. The combination of tetrahydroxydiboron ($B_2(OH)_4$, a solid), a tertiary amine (4-methylmorpholine, 4-MM), and 5% Pd/C allows the harvested hydrogen gas produced *in situ* to reduce the olefin. This protocol allows a demonstration of this powerful addition reaction that is taught early in sophomore organic chemistry, while eliminating the hazards associated with the storage and use of compressed hydrogen gas. The key laboratory techniques incorporated, besides the reaction setup, are development and visualization of thin-layer chromatograms, column chromatography over silica-gel, and solvent extraction. For product analysis, the ^{1}H, $^{13}C\{^{1}H\}$, and HMQC NMR spectra of cinnamyl and the hydrogenated hydrocinnamyl alcohols are obtained. Herein, we show two spectra of products obtained, one containing only product and the other containing an overreduction product. This provides an opportunity to discuss calculation of product ratios and to reinforce NMR spectroscopy concepts. The entire protocol would constitute activities associated with conducting a reaction, isolating, and evaluating the product. In our labs two undergraduate students, one with two semesters of undergraduate organic chemistry and the other with no prior organic chemistry laboratory experience performed the laboratory protocol and the collection and analysis of NMR data. At the end of the experiment, they were evaluated by a post-laboratory report.

Introduction

Among the library of reactions that chemically modify alkenes, catalytic hydrogenation is one of the addition reactions that is introduced quite early in the sophomore undergraduate organic chemistry course. Because this is one of the simplest transformations in organic chemistry that is widely utilized in both laboratory and industrial processes (cracking of hydrocarbons, denitrification, deoxygenation, etc.), the hands-on experience is anticipated to reinforce this reaction in the minds of students [1–3]. Catalytic hydrogenation is often represented as shown in Scheme 1, with a description that hydrogen atoms from $H_2(g)$ are adsorbed onto the surface of the metal. The *syn* addition of hydrogen atoms is explained by a cartoon depiction of the type shown in Scheme 1.

Generally, catalytic hydrogenation conditions for reducing alkenes and alkynes to the corresponding alkanes consist of a transition metal catalyst (Pd, Rh, Ir, among others) and an external source of $H_2(g)$ that is almost always obtained from a compressed gas cylinder [4]. The metal catalyst could be either heterogeneous or homogeneous. A heterogeneous catalyst does not dissolve in the reaction medium such as tiny portions or shavings of the transition metal (Ni, Pd, or Pt) [5], whereas a homogenous catalyst is soluble in the reaction medium and include examples such as Wilkinson's catalyst as well as palladium acetate [5, 6]. Furthermore, altering the catalyst, such as the poisoned Lindlar catalyst, or use of bimetallic systems leads to partial and/or selective hydrogenation [7, 8].

Given the importance and wide use of catalytic hydrogenations and the minimal number of reagents required, we believed that it would constitute a laboratory module for undergraduate students. With that said, in a previous publication O'Connor *et al.* noted 23 reports of alkene hydrogenation and have reported a solventless method in this journal [9, 10]. Whereas these reports

involve the reduction of a certain substrate, they differ in the protocols. For example, (a) the utilization of elaborate hydrogenation setups or special equipment (for example, portable data collection devices or homemade autoclaves) to conduct the reaction [9, 11, 12], (b) taking advantage of unique conditions such as catalytic transfer hydrogenation or electrochemical systems to generate H_2(g) *in situ* [13–17], (c) the preparation and employment of a different catalyst other than palladium on carbon [11], (d) exploiting substrates that yield a color change once they are hydrogenated [18], and (e) the various post-laboratory data analysis exercises such as structure determination by NMR or IR spectroscopy techniques or by utilizing gas law equations to understand correlations between the decrease in H_2(g) and the amount of alkene consumed in the reaction [9,18]. With these as the background, we present a simple catalytic reduction protocol that utilizes *in situ* production of H_2(g) and concomitant reduction.

We decided to adapt recently published work from our laboratories that broadly explored catalytic hydrogenation on a variety of substrates by *in situ* produced H_2(g) [19]. Building on the work of Stokes et al. [20], for the reductions we had used a combination of tetrahydroxydiboron ($B_2(OH)_4$, a solid), 4-methylmorpholine (4-MM, a liquid), and Pd/C, in 1,2-dichloroethane (DCE). We selected the *E*-isomer of cinnamyl alcohol (henceforth called cinnamyl alcohol) because it undergoes fairly rapid reduction, and all reagents are budget friendly [21]. Furthermore, the reduction of cinnamyl alcohol can potentially produce *n*-propylbenzene as a byproduct [22]. Thus, a part of the exercise can involve the assessment of the integration values from the ^{1}H NMR spectra to determine the percentage of this byproduct. From a general interest standpoint, cinnamyl alcohol and the hydrogenated hydrocinnamyl alcohol (3-phenyl-1-propanol) have been shown to be biologically and/or chemically significant. For example, administration of cinnamyl alcohol to sepsis-induced mice decreased inflammatory reactions within many organs, while increasing the

survival rate by 20% [23]. Also, due to the natural features (aroma and molecular structure) of cinnamyl alcohol, it has been used in the synthesis of common flavors and aromas that may be found in multiple consumer products [24, 25]. The hydrocinnamyl alcohol moiety is found in Dapoxetine, a potent selective serotonin reuptake inhibitor that is used to treat forms of anxiety and depression [26]. We thought these aspects will invite discussions and/or increase student interest in the exercise. The overall pedagogic aims of this experiment are:

- To expose students to a novel set of conditions to safely generate H_2(g) for catalytic reduction of an alkene.
- Build undergraduate confidence in multiple laboratory practices such as reaction setup, thin-layer chromatography to assess reaction progress, column chromatography to isolate product, and solvent extraction to remove water-soluble impurities.
- Illustrate one- and two-dimensional NMR spectroscopy techniques for structure determination, for providing a comparison of the spectra of starting material and product(s), and assessment of ratio of product and byproduct in the case the latter is formed.

Experimental Overview

The catalytic hydrogenation reaction is presented in Scheme 2. The reagents utilized for the presented experiment were obtained from commercial vendors and did not require any further purification (DCE was distilled but use of high-purity DCE will eliminate this). A step-by-step procedure for students to follow is provided in the Supporting Information (SI). The sequence of events is: (a) reaction setup, (b) thin-layer chromatographic assessment of the reaction, (c) isolation and purification of desired reduced material, and (d) the characterization of the starting material and recovered product by NMR spectroscopic methods.

The formation of H_2(g) is a bit more complex to understand. In their work, Stokes et al. used water for obtaining the hydrogen atoms and propose the formation of "Pd–H" species [20]. In our work, we also propose the formation of "Pd–H" species. Experiments involving a deuteriated tertiary amine (where "Pd–D" species would be formed) indicate that the D atoms and by extension the H atoms are likely obtained from the α-positions to the amine nitrogen atom. A simplified catalytic cycle that shows utility of a "Pd–H" species for the reduction and regeneration of the active catalyst is shown within the box in Scheme 2.

Briefly, cinnamyl alcohol (1.50 mmol, 1.0 eq.) was weighed into a clean vial (vial-1) and transferred to a clean 18 mL PYREX™ screw cap culture tube using DCE. The procedure described (please see the Supporting Information) teaches students how to completely transfer material with a calculated amount of solvent. Then, $B_2(OH)_4$ (3.30 mmol, 2.2 eq.), and 5% Pd/C (0.1 eq.), a clean stir bar were added, followed by the addition of the remaining DCE is added so as to wash down materials from the walls of the culture tube. The screw neck of the culture tube was then wrapped with Teflon tape for creating a good seal when capped, and then 4-MM (7.50 mmol, 5.0 eq.) was added to the reaction mixture. The reaction vessel was capped and sealed with Parafilm, placed in a pre-equilibrated sand bath (50 ºC), and stirred for 80 mins. At the end of the reaction time, the culture tube was removed and allowed to cool to room temperature, before opening. The reaction contents were then transferred to a dry silica gel column for a rapid filtration, using a mixture of EtOAc and hexanes as eluent. Based upon TLC analysis of the collected fractions, those containing UV-active (254 nm) material were pooled in a separatory funnel. The organic layer was extracted with water and then brine, collected in an Erlenmeyer flask, and dried over anhydrous Na_2SO_4. The dried organic layer was filtered into a pre-weighed round-bottom flask and the filtrate was evaporated under reduced pressure. The contents of the round bottom

flask were briefly dried under high vacuum and the flask was then weighted to obtain the weight of the product obtained.

An NMR sample was then prepared in a clean vial (vial-2). After dissolving the material the solution was transferred to a clean NMR tube. The NMR tube was capped and sealed with Parafilm before using the NMR spectrometer for data acquisition. A step-by-step student procedure is provided in the Supporting Information.

Results and Discussion

This experiment module was carried out by two undergraduate chemistry students with supervision from senior members of the laboratory, as would be the case with students in an instructional laboratory with Teaching Assistants overseeing progress. Both students had completed two semesters of undergraduate organic chemistry courses but did not possess practical experience in an organic chemistry laboratory. Before the two students undertook this project, they participated in discussions on the background knowledge of laboratory techniques and safety protocols. This can be compared with pre-laboratory instructional lectures.

We initially set about determining an appropriate amount of 5% Pd/C. Through these experiments we observed that 160 mg of 5% Pd/C (5 mol% of Pd) gave fairly rapid reduction. By ^{1}H NMR, complete consumption of cinnamyl alcohol was noted based upon the complete disappearance of the vinylic proton resonances at δ = 6.62 and 6.38 ppm (in $CDCl_3$ at 500 MHz). In principle, as a separate experiment (not described here) ^{1}H NMR can be used as a tool to gain insight to the progress of the reaction and/or for calculating the amount of any residual starting material present at the end of the reaction (a standard ^{1}H NMR spectrum of cinnamyl alcohol can be provided to students for comparison).

With the optimal amount of 5% Pd/C, the reactions were complete within 80 min. After cooling the reaction mixture to room temperature, a sample of the reaction mixture was utilized for analysis by thin-layer chromatography (TLC). Upon using silica gel-coated TLC plates and 20% EtOAc in hexanes as eluting solvent, both the starting material and desired product had similar R_f values under UV radiation, or upon staining with $KMnO_4$ or I_2. This is likely because reduction causes only a minor change in polarity (olefin to a single bond). Nevertheless, product isolation was done, by performing a filter column with the crude reaction mixture on silica gel. After several trials, we found that performing the elution with 10% EtOAc in hexanes followed by 40% EtOAc in hexanes provided majority of the desired material. Analysis of the isolated material by ^{1}H NMR ($CDCl_3$) showed resonances for the desired hydrocinnamyl alcohol and additional aliphatic resonances. The isolated material also had a faint odor of 4-MM, leading to our belief that the additional proton resonances were related to 4-MM-based byproducts.

We tested this by spotting a sample of 4-MM and the isolated material on a TLC plate and eluting with 20% EtOAc in hexanes. Because 4-MM is not UV active the TLC plate was stained with Iodine. 4-MM appeared as a brown-orange spot that smears on the TLC plate and has a similar R_f value to the isolated material. These combined observations led to an aqueous extraction, because 4-MM and related products should be water soluble. The ^{1}H NMR spectrum of the material after the aqueous extraction was clean with resonances corresponding to the reduced hydrocinnamyl alcohol.

With an overall experimental protocol, both students repeated the reaction separately on multiple occasions to understand the reproducibility of this experiment. During these repeated reactions, there were slight differences in the outcomes between the two students. Whereas Student-1 obtained only hydrocinnamyl alcohol, additional minor resonances were discernible in

the ^{1}H NMR spectrum of the product obtained by Student-2. This byproduct is *n*-propylbenzene, which can form by a hydrogenolysis of cinnamyl alcohol followed by a subsequent reduction of the olefin (see Scheme 2). The average yield of hydrocinnamyl alcohol obtained by Student-1 in three consistent runs was 57%, without significant formation of the byproduct in the isolated material. On the other hand, based on NMR analysis, Student-2 obtained a mixture with an average of 85% of the desired material and 15% of *n*-propylbenzene (in the example in Figure 1, the amount is *ca.* 19%). By employing the ratio found in each NMR sample together with the weight of the isolated material, it was determined that Student-2 obtained hydrocinnamyl alcohol in an average yield of 63%. This particular aspect provides a pedagogical perspective into calculation of percentages of byproducts in reactions as well as the use of this data to calculate the amount of desired product in the mixture. Figure 1 shows the ^{1}H NMR spectra of cinnamyl alcohol and representative products obtained by Students 1 and 2. In the case of product obtained by Student 2, the resonances in red correspond to *n*-propylbenzene (a full expansion of the aliphatic region can be found in the NMR spectrum in the Supporting Information).

With the completion of the experiment, both students prepared a post-laboratory report that included the following components: Abstract, Introduction, Methods, Results and Discussion, and a Reference(s). These reports as well as observations of a senior member supervising the two students during their hands-on experience were used as a method of evaluating both students.

Suggestions for 2- or 1-laboratory period experimentation

In considering the duration of a 3- or 4-hour laboratory period, we have four proposed suggestions below that may alleviate a possible time constraint. The first takes into consideration the NMR experiments as part of the exercise. For this, the module can be divided into two phases. The first phase (laboratory period 1) is to prepare and conduct the reaction, followed by filtering

the reaction mixture through the silica gel column. Eluted UV-active material can then be transferred to a round-bottom flask (rbf), evaporated and then stored in the refrigerator for the following laboratory session. In the second phase (laboratory period 2), the contents in the rbf can be diluted with EtOAc for aqueous workup followed by drying the organic phase, and evaporation under reduced pressure. The resulting material can then be subjected to NMR analysis, where the students can prepare their NMR samples and spend the remainder of the time obtaining and analyzing the recorded spectral data. A second recommendation is preparing a bulk solution of cinnamyl alcohol in DCE, where the concentration of this prepared solution is 200 mg/mL. This will allow students to quickly obtain the desired amount of starting material, without the issue of individually weighing the material into a vial and breathing in the cinnamon-scented fumes for a longer period. The third suggestion pertains to the time period that the reaction is stirring/heating in the sand or oil bath. During this window, students can prepare the TLC plate needed at the end of the reaction time. Additionally, students can prepare the silica gel filter column and a rack of test tubes to collect the fractions during the operation of the column. This is also a great time for students to clean up their workstation and record any notes or observations during the module. Not only will this allow students to effectively practice time management skills in the laboratory, but also gives them ample time to develop their skills to correctly prepare a silica gel column and a TLC plate.

On the other hand, if the experiment is to span a single laboratory period and/or there is not the easy availability of an NMR instrument, then as a fourth suggestion the bromine addition test can be incorporated in place of the NMR experiments. For this we prepared solutions of cinnamyl alcohol and hydrocinnamyl alcohol in EtOAc (20 mg of each and 3 mL EtOAc in two test tubes)

and treated them with 5 drops of a 5% solution of pyridinium bromide perbromide (PBP) in ethanol (EtOH). The results of these experiments are shown in Figure 2.

To prove that the color change was not due to the presence of solvents (EtOAc and EtOH), control experiments were performed where cinnamyl alcohol and hydrocinnamyl alcohol were exposed to the two solvents (students do not need to perform these two experiments but they could be demonstrated by the instructor with previously prepared solutions). The test tubes in Figure 2 are: (1) 5 drops of 5% PBP in EtOH added to EtOAc, (2) cinnamyl alcohol + EtOAc, (3) cinnamyl alcohol + EtOH, (4) cinnamyl alcohol in EtOAc + 5 drops of 5% PBP in EtOH, (5) hydrocinnamyl alcohol + EtOAc, (6) hydrocinnamyl alcohol + EtOH, and (7) hydrocinnamyl alcohol in EtOAc + 5 drops of 5% PBP in EtOH. The loss of color in test tube #4 relative to #1 is very clear. However, some loss of color was also observed in test tube #5. This is likely because PBP is known to oxidize alcohols [27] by the simplified mechanisms shown in Scheme 3 based on the oxidation of alcohols by aqueous bromine [28]. Nevertheless, the visual intensity of the color in test tube #7 is still greater than that in #4.

Conclusions

This module presents a step-by-step method for the hydrogenation of inexpensive cinnamyl alcohol, using a method that generates H_2(g) *in situ*. The procedure, while reinforcing the concept of catalytic hydrogenation, is anticipated to eliminate some limiting factors such as need for compressed hydrogen gas cylinders and associated hazards, as well as need for more complex reaction setups. This protocol involves minimal equipment using common glassware that is generally found in an undergraduate organic chemistry laboratory. Students have the opportunity to progress from reaction setup to product isolation and purification, and lastly to structure determination as well as assessment of byproduct formation (if it occurs), all in one module. At

the end of the module, students were evaluated on a post-laboratory report and on their proficiency on instrumental laboratory techniques. We also provide suggestions on possible time management strategies.

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Supporting Information

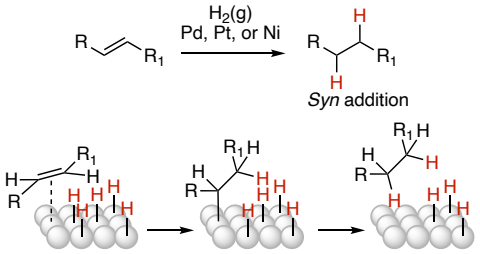
A separate document accompanies this article with information such as hazards (chemical, experimental, and waste), a complete step-by-step student procedure, and an additional modification to the student procedure (two-phase laboratory experiment as well as a single laboratory period procedure). Additionally, pre-, and post-lab questionnaires, ^{1}H and $^{13}C\{^{1}H\}$ NMR characterization data of the starting material and reduced product, and copies of ^{1}H, ^{13}C, and HMQC NMR spectra are provided.

References

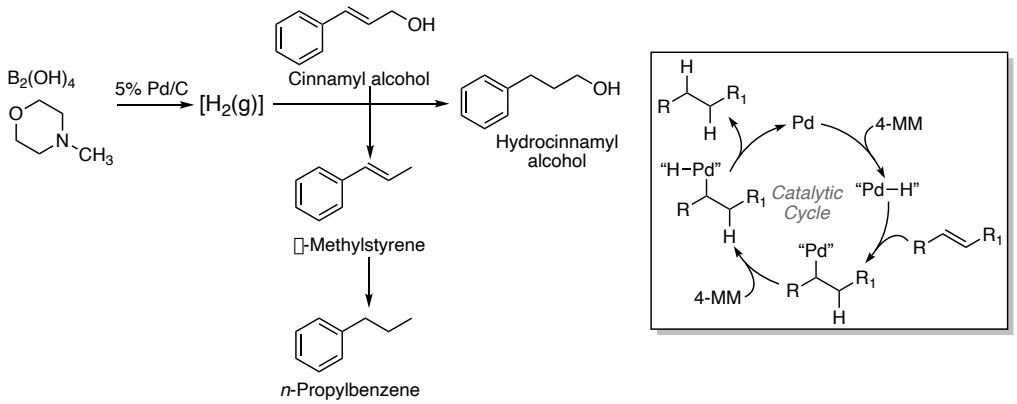
1. Smith, A. M.; Whyman, R. *Chem*. *Rev*. **2014**, *114*, 5477–5510. DOI: 10.1021/cr400609m
2. Andrade, M. A.; Martins, L. M. D. R. S. *Processes*. **2020**, *8*, 1172. DOI: 10.3390/pr8091172
3. Anand, S.; Pinheiro, D.; Sunaja Devi, K. R. *Asian J. Org. Chem*. **2021**, *10*, 3068–3100. DOI: 10.1002/ajoc.202100495

4. Li, L.; Lei, M.; Sakaki, S. *Organometallics*. **2017**, *36*, 3530−3538. DOI: 10.1021/acs.organomet.7b00457
5. Klein, D. Addition Reactions of Alkenes. In *Organic Chemistry*, 3rd ed.; Wiley, 2017; pp 370.
6. Li, M.; Bäckvall, J. *Acc*. *Chem*. *Res*. **2021**, *54*, 2275–2286. DOI: 10.1021/acs.accounts.1c00122
7. Lindlar, H.; Dubuis, R. *Org*. *Synth*. **1966**, *46*, 89–90. DOI: 10.15227/orgsyn.046.0089
8. Louis, C.; Delannoy, L. Selective Hydrogenation of Polyunsaturated Hydrocarbons and Unsaturated Aldehydes Over Bimetallic Catalysts. In *Advances in Catalysis*, Vol. 64; Elsevier, 2019; pp 1–88. DOI: 10.1016/bs.acat.2019.08.002
9. O'Connor, K. J.; Zuspan, K.; Berry, L. *J. Chem. Educ.* **2011**, *88*, 325–327, DOI: 10.1021/ed1007475
10. Fry, D.; O'Connor, K. *Chem. Educator* **2013**, *18*, 144–146. DOI: 10.1333/s00897132487a
11. Landgrebe, J. A. *J. Chem. Educ.* **1995**, *72*, A220– A222, DOI: 10.1021/ed072pA220
12. Touaibia, M.; Selka, A.; Levesque, N. A.; St-Onge, P. A. *J. Chem. Educ.* **2020**, *97*, 2296− 2301. DOI: 10.1021/acs.jchemed.9b01026
13. Plummer, B. *J. Chem. Educ.* **1989**, *66*, 518– 519. DOI: 10.1021/ed066p518
14. Wilen, S. H.; Kremer, C. B. *J. Chem. Educ*. **1962**, *39*, 209– 210. DOI: 10.1021/ed039p209
15. Alwaseem, H.; Donahue, C. J.; Marincean, S. *J. Chem. Educ.* **2014**, *91*, 575− 578. DOI: 10.1021/ed300476u
16. Navarro, D. M. D. A. F.; Navarro, M. *J. Chem. Educ.* **2004**, *81*, 1350– 1352. DOI: 10.1021/ed081p1350
17. De, S.; Gambhir, G.; Krishnamurthy, H. G. *J. Chem. Educ.* **1994**, *71*, 992– 993. DOI: 10.1021/ed071p992

18. Wagner, C. E.; Marshall, P. A.; Cahill, T. M.; Mohamed, Z. *J. Chem. Educ.* **2013**, *90*, 930−933. DOI: 10.1021/ed3002489
19. Korvinson, K. A.; Akula, H. K.; Malinchak, C. T.; Sebastian, D.; Wei, W.; Khandaker, T. A.; Andrzejewska, M. R.; Zajc, B.; Lakshman, M. K. *Adv*. *Synth*. *Catal*. **2020**, *362*, 166– 176. DOI: 10.1002/adsc.201901099
20. Cummings, S. P.; Le, T.-N.; Fernandez, G. E.; Quiambao, L. G.; Stokes, B. J. *J*. *Am*. *Chem*. *Soc*. **2016**, *138*, 6107–6110. DOI: 10.1021/jacs.6b02132
21. For example, a search of common suppliers yielded reasonable costs for $B_2(OH)_4$: \$1.1/g and 4-MM: \$0.092/mL, cinnamyl alcohol: \$0.068/g.
22. Nishimura, S.; Onoda, T.; Nakamura, A. *Bull. Chem. Soc. Jpn.* **1960**, *33*, 1356–1359. DOI: 10.1246/bcsj.33.1356
23. Zou, L.; Li, C.; Chen, X.; Yu, F.; Huang, Q.; Chen, L.; Wu, W.; Liu, Q. *Ann*. *Transl*. *Med*. **2022**, *10*, 1– 10. DOI: 10.21037/atm-21-6130
24. Worzakowska, M. *Molecules*. **2015**, *20*, 10594–10603. DOI: 10.3390/molecules200610594
25. Letizia, C. S.; Cocchiara, J.; Lalko, J.; Lapczynski, A.; Api, A. M. *Food Chem*. *Toxicol*. **2005**, *43*, 837– 866. DOI: 10.1016/j.fct.2004.09.012
26. Kang, S.; Lee, H. *J. Org*. *Chem*. **2010**, *75*, 237– 240. DOI: 10.1021/jo902176s
27. Mathur, D.; Sharma, P. K.; Banerji, K. K. *J. Chem. Soc., Perkin Trans. 2*, **1993**, 205–208. DOI: 10.1039/P29930000205
28. Deno, N. C.; Potter, N. H. *J. Am. Chem. Soc.* **1967**, *89*, 3555–3556. DOI: 10.1021/ja00990a036



Scheme 1. A representative scheme for catalytic hydrogenation and a cartoon depiction of delivery of H_2 leading to *syn* addition



Scheme 2. Catalytic reduction of cinnamyl alcohol and a simplified, proposed catalytic cycle

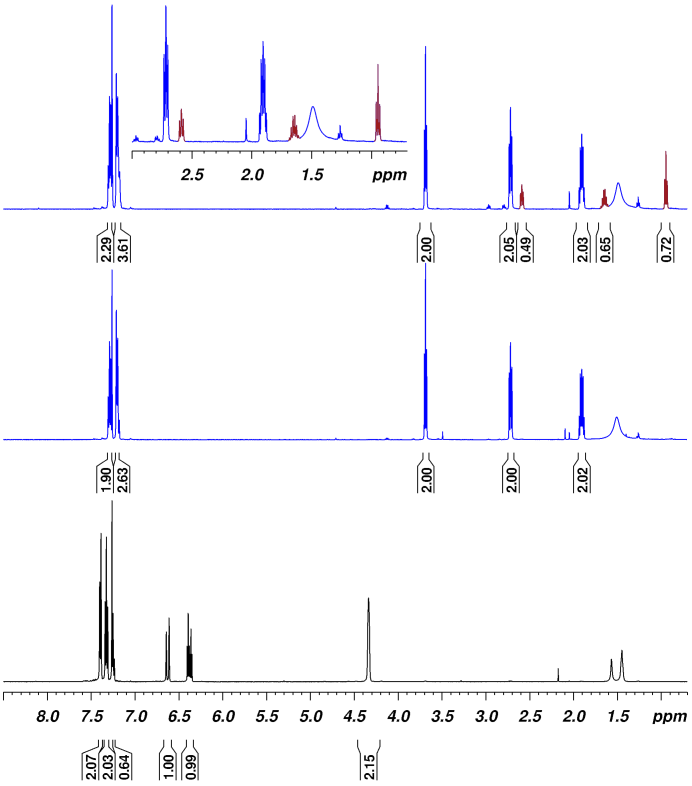


Figure 1. 500 MHz ^{1}H NMR spectra of cinnamyl alcohol (lower spectrum), product obtained by Student 1 (middle spectrum), and product obtained by Student 2 (top spectrum). In the top spectrum, the aliphatic resonances of the small amount of *n*-propylbenzene formed are shown in red color (the inset shows an expansion of this region).

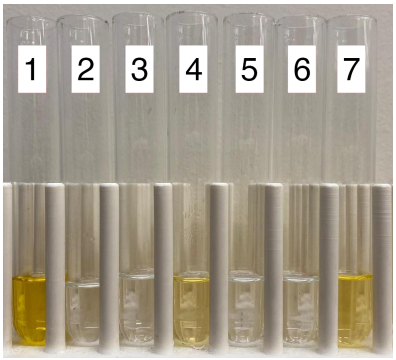
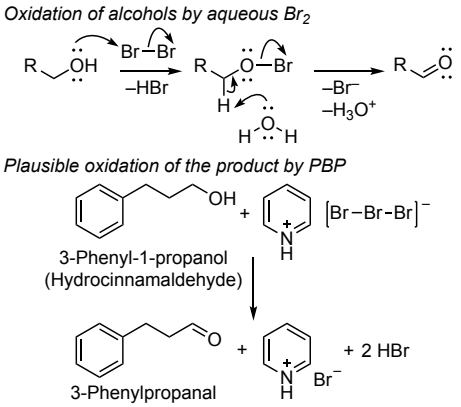


Figure 2. Results from the test for alkenes using pyridinium bromide perbromide (PBP).



Scheme 3. Plausible oxidation of alcohols by aqueous Br_2 and hydrocinnamyl alcohol (3-phenyl-1-propanol) by PBP.