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Laboratory Experiment

Iron-Based Tandem Catalysis: From Petroleum toward Pharmaceutical Laboratories for Organic Undergraduate Students—Product Identification by TLC and ^{1}H NMR

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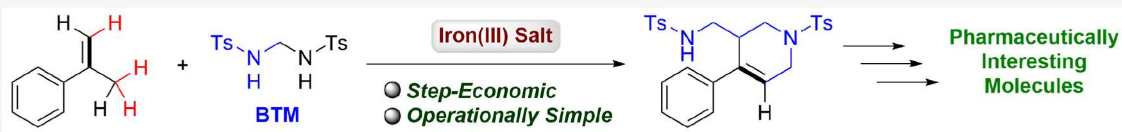

ABSTRACT: Catalysis and catalytic cycles are widely used in both research and industry. The addition of a catalysis experiment into the undergraduate laboratory curriculum is important and necessary training to expand student learning. Here, an experiment demonstrating iron-based tandem catalysis was developed and implemented in an organic chemistry course for second-year and upper-division undergraduate students at Mississippi State University. The experiment uses TLC and ^{1}H NMR to track the reaction and identify the core pharmaceutical structure produced during the experiment. Reactions contained inside the catalytic cycles include iminium generation, imino-ene condensation, and aza-Prins reaction. The catalytic cycle approach allows for a decrease in time for reaction, chemicals, and waste produced. This experiment was successfully tested over two semesters (110 students) at a major university. Learning objectives were met to support student understanding of catalytic cycles and reaction mechanisms. This laboratory experiment provided hands-on experience using TLC and ^{1}H NMR to identify a core structure of pharmaceutical compounds produced from petroleum.

KEYWORDS: *Second-Year Undergraduate, Upper-Division Undergraduate, Organic Chemistry, Laboratory Instruction, Hands-On Learning, NMR Spectroscopy, Catalysis, Thin Layer Chromatography*

INTRODUCTION

The global production of various materials and products, such as pharmaceutical drugs, relies heavily on catalytic reactions. The American Chemical Society Committee on Professional Training encourages undergraduate programs to include chemistry topics such as catalysis.[1] Catalytic reactions emphasize (1) reducing reagent amounts and lowering the energy required for the reaction, (2) minimizing or eliminating waste from reactions, and (3) increasing efficiency in time, energy, or materials required to create products.[2]

Several catalytic reaction laboratory experiments have been published[3−7] for organic chemistry that are air-stable; however, some experiments require the use of a glovebox[8−11] or are designed for upper-level courses.[11−14] Of the organic chemistry air-stable experiments, the time for reactions to complete take longer than half of an hour[3−6] or require multiple sessions for students to complete the experiment.[7] A number of STEM (Science, Technology, Engineering, and Mathematics) careers involve catalytic cycles, for example, chemical engineering[15] and drug development.[16] In industry, catalytic reactions such as the Haber Bosch process is used for ammonia production, which is then used to create fertilizer.[17,18] This catalytic process has dramatically increased the amount of food produced for the ever-growing world population.[19] Catalysis is also used in the pharmaceutical industry for the economical production of drugs.[20,21] In the petrochemical field, fluid catalytic cracking has allowed the production of higher value products important to both industry and research such as gasoline and olefins. However, as fossil fuel resources are depleted, there is more focus toward alternative resources and green chemistry.[22] Atom economy is an aspect of green chemistry where the reaction efficiency of converting reactants to desired products is calculated.[23] This experiment has an atom economy of 60.19%, indicating good reaction efficiency. Green chemistry also promotes minimal waste when designing experiments.[23] This is emphasized with this experiment, and these catalytic reactions as the student product can be recycled to create the standard product used in TLC. Given the importance of catalytic

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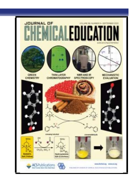
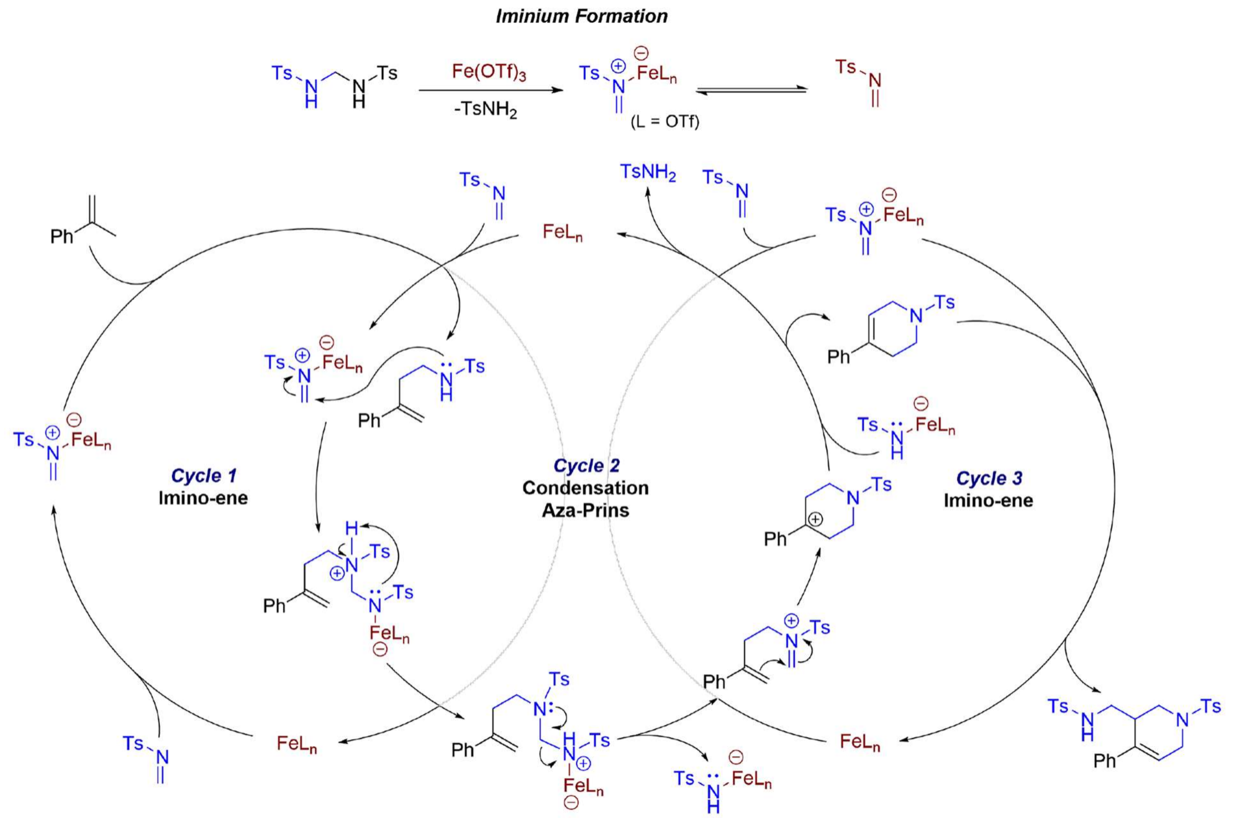


Scheme 1. Overview of Catalytic Cycles



reactions and their use in other areas, undergraduates should be exposed to catalytic cycles and their applications.

To our knowledge, there is no tandem catalysis experiment for undergraduate students designed for producing core pharmaceutical molecule structures. Tandem catalysis is defined as consecutive catalytic transformations of reactants via two or more different catalytic reactions. Catalytic reactions can involve homogeneous or heterogeneous catalysts. Herein, we describe an air-stable tandem catalysis laboratory activity designed for organic II chemistry from the Cui research group.[24] Inside the homogeneous catalytic reactions of this laboratory activity are known mechanisms: iminium generation, imino-ene reaction, and aza-Prins reaction, which overlap with previously covered reactions. The experiment produces core structures in pharmaceutical molecules that combine α-methylstyrene with bis(tosylamido)methane using the Lewis acid iron triflate as the homogeneous catalyst. The final product is 4-methyl-*N*-((4-phenyl-1-tosyl-1,2,3,6-tetrahydropyridin-3-yl)methyl)-benzenesulfonamide, which is a 1,2,3,6-tetrahydropyridine.

PEDAGOGICAL GOALS

This tandem catalysis laboratory experiment is designed to support student understanding of catalytic cycles and their mechanisms and the impact of functional groups and to help students acquire the skills practiced in a research laboratory.

After completing this experiment, students should be able to

- Practice drawing reaction mechanisms contained within the catalytic cycles
- Prepare a miniature column and understand how it is used to trap the iron catalyst
- Identify the peaks associated with the reaction product in the ^{1}H NMR spectrum
- Analyze a TLC plate to monitor products and byproducts
- Identify the impact of electron-withdrawing groups in creating electrophilic carbons
- Identify the advantages of catalytic cycles

These pedagogical goals were evaluated from written answer post-lab assignment questions and student survey questionnaire responses.

OVERVIEW OF LABORATORY EXPERIMENT

This laboratory experiment was incorporated into an organic II chemistry laboratory course intended for undergraduate students in their second year. This experiment was performed with two groups of upper-level undergraduate students in the summer 2021 semester CH 4521 Organic 2 laboratory course (18 students in total) as well as (92 total students) upper-level undergraduate students in the fall 2021 Organic 2 laboratory course at our institution. Students worked in groups of 3, and all students were able to carry out the experiment in the 3 h laboratory period. Students completed a pre-lab quiz and created a pre-laboratory report in which they demonstrated an understanding of the safety involved. After the experiment, students completed post-laboratory questions to further their understanding of the experiment.

The experiment includes three known mechanisms inside the catalytic cycles. In the first catalytic cycle, two known mechanisms occur: iminium generation and the imino-ene reaction, as shown in Scheme 1 at the top and inside the cycle labeled Cycle 1.

The iminium generation occurs when the bis(tosylamido)-methane is broken apart and one-half is coordinated with the catalyst $Fe(OTf)_3$. This allows for the imino-ene reaction to occur with the iminium ion and the α-methylstyrene. The bond

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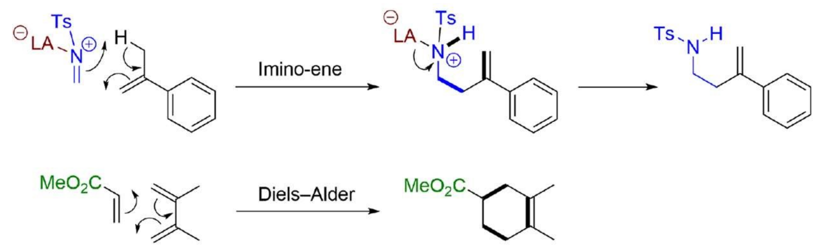
Scheme 2. Comparison of Imino-Ene versus Diels–Alder



forming and breaking patterns of the imino-ene reaction could be compared to those of a Diels-Alder reaction, although different products are formed, as shown in Scheme 2.

The imino-ene creates not only C–C single and double bonds but also an N–H bond in the first catalytic cycle. The second catalytic cycle contains a condensation and aza-Prins reaction shown in the cycle labeled Cycle 2 in Scheme 1. In the condensation reaction, the formed amide unit is converted to a highly reactive iminium, which undergoes an intramolecular aza-Prins reaction with the alkene unit, producing a six-membered heterocyclic alkene intermediate. Finally, the third catalytic cycle performs an iterative imino-ene reaction with this intermediate and the iron-coordinated iminium to afford the final product, as shown in the cycle labeled Cycle 3 in Scheme 1.

■ EXPERIMENTAL DETAILS

Experiment

The reactant, bis(tosylamido)methane, was prepared before lab from commercially available starting materials using an established procedure[24] and stored in a desiccator until the laboratory meeting. When students began the experiment, groups weighed and transferred bis(tosylamido)methane and catalyst into a round-bottom flask and added dichloroethane and α-methylstyrene. The reaction was stirred at 90 °C for 0.5 h. While waiting for the reaction to reflux, students prepared a TLC plate and miniature silica column using a glass pipet. After 0.5 h of refluxing, the reaction mixture was transferred to a 100 mL round-bottom flask and rotovapped. After dichloromethane was added, the reaction mixture was filtered through the silica column using a hand air pump into a new 100 mL round-bottom flask.

Students collected a small sample with a capillary tube, dotted their TLC plate, repeated for the standard product (hexane/ethyl acetate 2:1, R_f (retention factor) = 0.45), and allowed the TLC to develop. The round-bottom flask was rotovapped to isolate the product. Students used the TLC to determine if the desired product was created by comparing their product against the standard product. Students completed post-laboratory questions that included analysis of results, drawing the catalytic cycle mechanisms, identification of reaction categories, as well as identifying peaks in a provided product ^{1}H NMR spectrum. The Supporting Information contains a detailed description of the experiment.

^{1}H NMR Spectrometry

The ^{1}H NMR spectrum was obtained on a Bruker AVANCE III 500 MHz spectrometer.

Safety Hazards

Students must wear proper personal protective equipment (PPE) at all times during the laboratory experiment. Students should wear gloves when handling reagents, solvents, and solutions and transferring with pipettes to avoid skin contact and caution when using hypodermic needles to transfer. Handle and disposal of all hazardous materials should be in accordance with the recommendations of their Material Safety Data Sheet (MSDS). Dichloromethane, dichloroethane, α-methylstyrene, silica, hexane, ethyl acetate, and iron(III) trifluoromethanesulfonate are hazardous if inhaled, ingested, or contact is made with the eye or skin. Toxicity of bis(tosylamido)methane is not known; avoid contact with eyes, skin, inhalation, or ingestion. Toxicity of 4-methyl-*N*-((4-phenyl-1-tosyl-1,2,3,6-tetrahydropyridin-3-yl)methyl)benzenesulfonamide is not known; avoid contact with eyes, skin, inhalation, or ingestion.

■ RESULTS AND DISCUSSION

The tandem catalysis reaction of α-methylstyrene with bis(tosylamido)methane using the Lewis acid iron triflate was chosen in the design of this experiment to demonstrate the creation of a pharmaceutically active core molecule from petroleum derivatives. The experimental setup is a simple reflux apparatus in a fume hood, as shown in the laboratory manual, as the reaction is air-stable and does not require the use of a glovebox or Schlenk line. The use of a glass pipet column and TLC exposes students to techniques used in research laboratories. All students who carried out the experiment had been introduced to organic II chemistry. Students were required to read a detailed laboratory introduction, which consisted of the theoretical background and experimental protocol. On the basis of graded post-laboratory questions collected from the fall 2021 semester, the following results were noted as accomplishments of the six pedagogical goals:

(a) On a post-laboratory assignment question, students were asked to draw the mechanism arrows for the mechanisms contained within the catalytic cycles, as shown in Table 1.

Table 1. Percentage Correct and Partially Correct with Catalytic Drawing Mechanisms

question	% correct (number of students)	% partially correct (number of students)
(3a) imino-ene reaction	76.09 (70)	19.57 (18)
(3b) condensation reaction	66.30 (61)	32.61 (30)
(3c) aza-Prins reaction	84.78 (78)	7.61 (7)
(3d) imino-ene reaction (final catalytic cycle)	83.70 (77)	10.87 (10)

(b) Students were asked how they know the iron is trapped in the column on a post-laboratory assignment question: 89.13% (82) answered correctly, and 2.17% (2) were able to partially answer how they know the iron is trapped in the column. An image of students purifying their solution with their glass pipet column is shown in Figure 1.

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Figure 1. Students purifying solution with a glass pipet column.

(c) Students were asked to assign as many peaks as possible for their molecule on the ^{1}H NMR spectrum on a post-laboratory assignment question: 77.17% (71) were able to assign at least 3 out of 17; 8.70% (8) were able to assign peaks partially, and 14.13% (13) did not assign any peaks.

(d) Students were asked to use TLC to determine if they correctly made the product on a post-laboratory assignment question. Students were also asked to describe what any extra components might represent: 85.87% (79) were able to fully interpret their TLC and identify the extra components as byproducts or contaminates, and 6.52% (6) were able to partially answer. An example TLC is shown in Figure 2.

(e) Students were asked to identify why the circled carbon in the catalytic mechanism is such a good electrophile on a post-laboratory assignment question: 70.65% (65) correctly identified that the electron-withdrawing group was impacting the carbon.

(f) Students were asked to explain why the experiment is called a tandem catalytic cycle and what are some advantages of tandem catalytic cycles on a post-laboratory question: 88.04% (81) correctly identified the advantages of catalytic cycles.

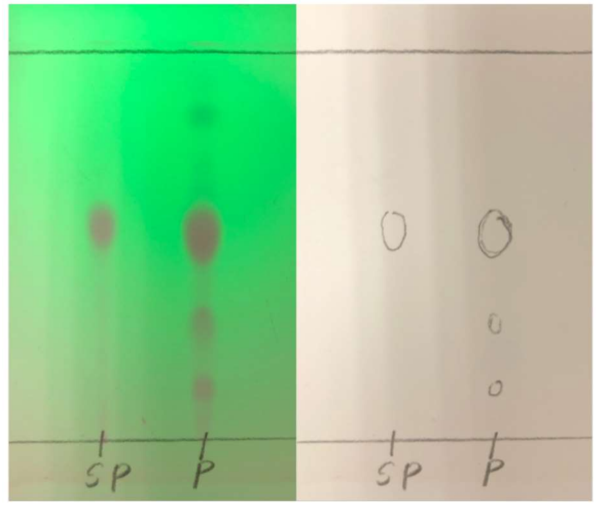

Figure 2. Prepared and developed TLC plate.

In addition, an anonymous student response survey consisting of 13 Likert scale questions and three open-ended questions was conducted to evaluate student satisfaction toward the developed laboratory experiment from summer 2021 (15 of 18 completed surveys). Evaluating student satisfaction toward the new experiment, Figures 3 and Figures 4 summarize the student responses to the Likert scale student questionnaire.

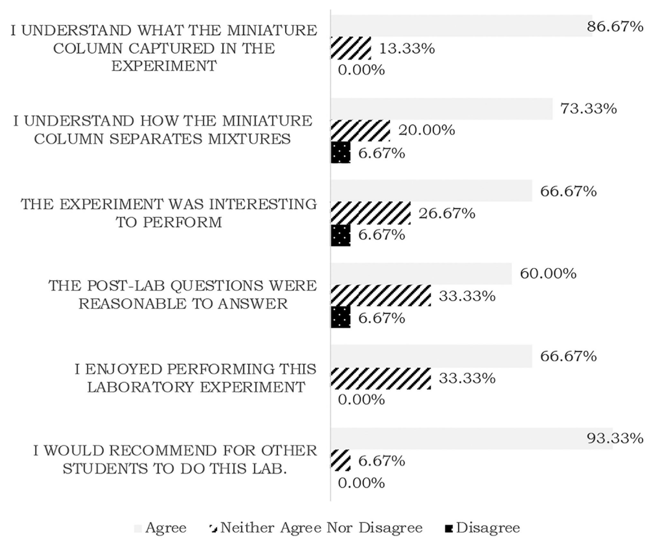

Figure 3. Student responses to the Likert scale student questionnaire (questions 1−7).

A larger number of students responded positively toward the new lab and their understanding, with very few or no students unsatisfied with the implementation or understanding of the tandem catalysis lab. When reviewing student responses on open-ended questions, the question "What did you like about this experiment?" students noted being able to easily follow along and understand the procedure, how quick the lab was, and being able to obtain the product and feel successful. Responding to the question "What did you not like about this experiment?", a few students complained about the wait time of the reaction

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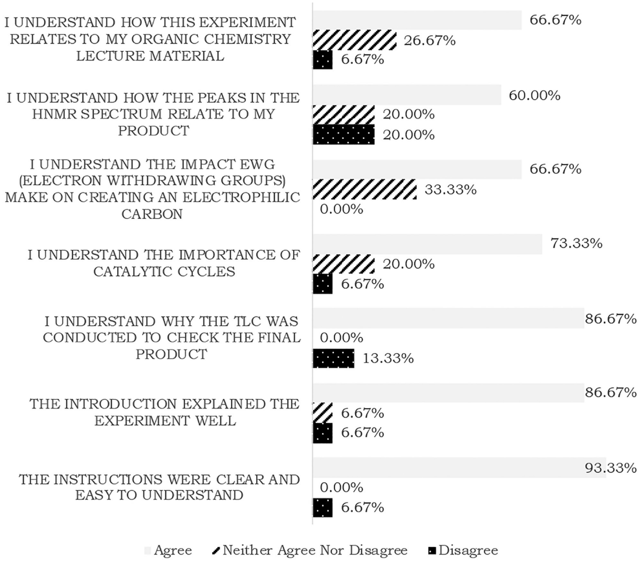

Figure 4. Student responses to the Likert scale student questionnaire (questions 8−13).

refluxing (30 min). Finally, responding to the question "If you were to repeat this experiment, what would you change about the instructions?", most students believed that the procedure did not need changes.

Student responses to the questionnaire also supported the accomplishment of 5 of the 6 pedagogical goals. For goal 2, 86.67% (13 of 15) agreed to understanding what the miniature column captured in the experiment; 73.33% (11 of 15) agreed to understanding how the miniature column separates mixtures, with only 6.67% (1 of 15) disagreeing. For goal 3, 60% (9 of 15) agreed to understanding how the peaks in the ^{1}H NMR spectrum relate to the product, while only 20% (3 of 15) disagreed. For goal 4, 86.67% (13 of 15) agreed to understanding why the TLC was conducted to check the final product, while only 13.33% (2 of 15) disagreed. For goal 5, 66.67% (10 of 15) agreed to understanding the impact of electron-withdrawing groups on creating an electrophilic carbon with no disagreement. For goal 6, 73.33% (11 of 15) agreed to understanding the importance of catalytic cycles.

CONCLUSIONS

An iron-based tandem catalysis from petroleum toward a pharmaceutical lab experiment, illustrating product identification by TLC and ^{1}H NMR, was developed and implemented in an upper-level organic chemistry laboratory for undergraduates. This experiment is an important addition to the curriculum as students improve their experimental skills and gain hands-on experience with research laboratory techniques. Furthermore, students can understand how tandem catalysis is used in industries such as the pharmaceutical industry to create a core structure of pharmaceutical compounds from petroleum.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available at https://pubs.acs.org/doi/10.1021/acs.jchemed.2c00451.

Brief descriptions with file formats indicated; customization of the material; materials, equipment, instructor's notes, student laboratory manual, pre-lab quiz, and post-lab questions (PDF)

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) American Chemical Society Committee on Professional Training. *Undergraduate Professional Education in Chemistry ACS Guidelines and Evaluation Procedures for Bachelor's Degree Programs*; https://www.acs.org/content/dam/acsorg/about/governance/committees/training/2015-acs-guidelines-for-bachelors-degree-programs.pdf (accessed April 27, 2021).

(2) *ACS Green Chemistry Catalysis*; https://www.acs.org/content/acs/en/greenchemistry/research-innovation/catalysis.html (accessed April 27, 2021).

(3) Chen, S. Let There Be Light: Hypothesis-Driven Investigation of Ligand Effects in Photoredox Catalysis for the Undergraduate Organic Chemistry Laboratory. *J. Chem. Educ.* **2018**, *95* (5), 872−875.

(4) Hill, N. J.; Hoover, J. M.; Stahl, S. S. Aerobic Alcohol Oxidation Using a Copper(I)/TEMPO Catalyst System: A Green, Catalytic Oxidation Reaction for the Undergraduate Organic Chemistry Laboratory. *J. Chem. Educ.* **2013**, *90* (1), 102−105.

(5) Lang, P. T.; Harned, A. M.; Wissinger, J. E. Oxidation of Borneol to Camphor Using Oxone and Catalytic Sodium Chloride: A Green

https://doi.org/10.1021/acs.jchemed.2c00451
J. Chem. Educ. 2022, 99, 3259−3264

Experiment for the Undergraduate Organic Chemistry Laboratory. *J. Chem. Educ.* **2011**, *88* (5), 652−656.
(6) Rezende, M. C.; Aliaga, C.; Barriga, G.; Vidal, M. Visualization of Phase-Transfer Catalysis through Charge-Transfer Complexes. *J. Chem. Educ.* **2018**, *95* (9), 1631−1635.
(7) Torres King, J. H.; Wang, H.; Yezierski, E. J. Asymmetric Aldol Additions: A Guided-Inquiry Laboratory Activity on Catalysis. *J. Chem. Educ.* **2018**, *95* (1), 158−163.
(8) Weiss, C. J.; Porter, L. A. Synthesis and Use of a Nickel Oxidation Catalyst Using Glove Box Methods. *J. Chem. Educ.* **2020**, *97* (6), 1655−1659.
(9) Niewahner, J. H.; Walters, K. A. Synthesis of Bis(1,2-dimethylimidazole)copper(I) Hexafluorophosphate: An Experiment Using a Glove Box. *J. Chem. Educ.* **2007**, *84* (4), 702.
(10) Whited, M. T.; Hofmeister, G. E. Synthesis and Migratory-Insertion Reactivity of CpMo(CO)3(CH3): Small-Scale Organometallic Preparations Utilizing Modern Glovebox Techniques. *J. Chem. Educ.* **2014**, *91* (7), 1050−1053.
(11) Miecznikowski, J. R.; Caradonna, J. P.; Foley, K. M.; Kwiecien, D. J.; Lisi, G. P.; Martinez, A. M. Introduction to Homogenous Catalysis with Ruthenium-Catalyzed Oxidation of Alcohols: An Experiment for Undergraduate Advanced Inorganic Chemistry Students. *J. Chem. Educ.* **2011**, *88* (5), 657−661.
(12) Cerrillo, J. L.; López-Hernández, I.; Palomares, A. E. Catalytic Removal of Bromates from Water: A Hands-On Laboratory Experiment to Solve a Water Pollution Problem through Catalysis. *J. Chem. Educ.* **2021**, *98* (5), 1726−1731.
(13) Ison, A.; Ison, E. A.; Perry, C. M. Oxorhenium Complexes for Catalytic Hydrosilylation and Hydrolytic Hydrogen Production: A Multiweek Advanced Laboratory Experiment for Undergraduate Students. *J. Chem. Educ.* **2017**, *94* (6), 790−794.
(14) Ison, E. A.; Ison, A. Synthesis of Well-Defined Copper N-Heterocyclic Carbene Complexes and Their Use as Catalysts for a "Click Reaction": A Multistep Experiment That Emphasizes the Role of Catalysis in Green Chemistry. *J. Chem. Educ.* **2012**, *89* (12), 1575−1577.
(15) Lechner, M.; Güttel, R.; Streb, C. Challenges in polyoxometalate-mediated aerobic oxidation catalysis: catalyst development meets reactor design. *Dalton Transactions* **2016**, *45* (42), 16716−16726.
(16) Shultz, C. S.; Krska, S. W. Unlocking the Potential of Asymmetric Hydrogenation at Merck. *Acc. Chem. Res.* **2007**, *40* (12), 1320−1326.
(17) Smith, C.; Hill, A. K.; Torrente-Murciano, L. Current and future role of Haber-Bosch ammonia in a carbon-free energy landscape. *Energy Environ. Sci.* **2020**, *13* (2), 331−344.
(18) Leigh, G., Haber-Bosch and Other Industrial Processes. *Catalysts for Nitrogen Fixation*; Springer, 2004; pp 33−54.
(19) Smil, V. *Enriching the Earth: Fritz Haber, Carl Bosch, and the Transformation of World Food Production*; MIT Press, 2001.
(20) Busacca, C. A.; Fandrick, D. R.; Song, J. J.; Senanayake, C. H. The growing impact of catalysis in the pharmaceutical industry. *Advanced Synthesis & Catalysis* **2011**, *353* (11−12), 1825−1864.
(21) Hawkins, J. M.; Watson, T. J. Asymmetric catalysis in the pharmaceutical industry. *Angew. Chem., Int. Ed.* **2004**, *43* (25), 3224−3228.
(22) Primo, A.; Garcia, H. Zeolites as catalysts in oil refining. *Chem. Soc. Rev.* **2014**, *43* (22), 7548−7561.
(23) Anastas, P.; Eghbali, N. Green Chemistry: Principles and Practice. *Chem. Soc. Rev.* **2010**, *39* (1), 301−312.
(24) Qian, X.; Zhou, H.; Chaminda Lakmal, H. H.; Lucore, J.; Wang, X.; Valle, H. U.; Donnadieu, B.; Xu, X.; Cui, X. Fe(III)-Based Tandem Catalysis for Amidomethylative Multiple Substitution Reactions of α-Substituted Styrene Derivatives. *ACS Catal.* **2020**, *10* (18), 10627−10636.

https://doi.org/10.1021/acs.jchemed.2c00451
J. Chem. Educ. 2022, 99, 3259−3264