

Preparation of Aminals under Continuous Flow Conditions

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Cite This: *J. Chem. Educ.* 2023, 100, 4728–4733

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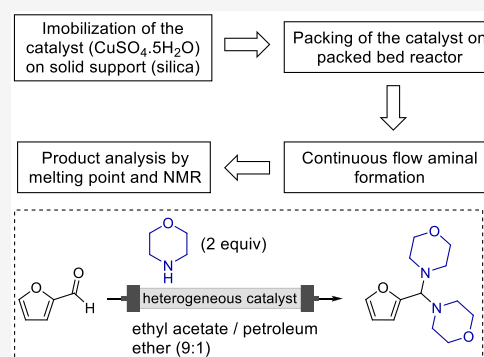
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ABSTRACT: A laboratory experiment was developed for the continuous flow preparation of an aminal derived from the condensation of furfural with morpholine. The experiment introduces the students to concepts of green chemistry, heterogeneous catalysis, and continuous flow. A cheap and easy setup allows the heterogeneous catalyst reactor to be built in class. The use of furfural reinforces the importance of green chemistry by using one of the key synthons obtained from biomass.



KEYWORDS: Second-Year Undergraduate, Organic Chemistry, Hands-On Learning, Aldehydes, Green Chemistry

INTRODUCTION

Aminals are a class of compounds easily accessible from the condensation of aldehydes with secondary amines, which are two fundamental functional groups in the Organic Chemistry curriculum.^{1–15} Despite aminals being known for decades, organic chemists have focused solely on their use as protection of aryl aldehydes prior to lithiation.^{16–18} Recent innovative reports on the use of aminals have emerged,^{19,20} and we described a method to prepare those compounds under mild conditions by using copper catalysts, thus paving the way for new methodologies employing aminals as key synthons.²¹

On the other hand, the development of continuous flow methodologies^{22,23} allows for a more sustainable production of valuable substrates that are advantageous to some processes in comparison to batch mode due to (i) enhanced heat and mass transfer ability; (ii) controlled accuracy; (iii) decreased reaction time; (iv) improved safety of the reaction using extremely dangerous reactive products/intermediates at extreme conditions such as high temperature and pressure and photochemical and electrochemical transformations; (v) high reproducibility; (vi) easy process implementation via a scale-out approach, among others.²⁴ Considering the emerging importance of flow chemical processes in academia and pharmaceutical and fine chemical industries, it is essential to include this topic at the early stages of chemical education and is also advantageous for more sustainable chemistry (Green Chemistry).^{25–36} In fact, continuous flow reactions have been described in the context of undergraduate student's laboratory experiments, namely, in methylation of 2-naphthol by dimethyl carbonate,³⁷ representative synthetic transformations (amidation, esterification, ester hydrolysis, condensation, Grignard

reaction, and bromination),³⁸ synthesis of 5-hydroxymethylfurfural (HMF),³⁹ aryl-aldehyde oxidation,⁴⁰ photocatalytic thiol-ene reaction,⁴¹ biodiesel production,⁴² photopinacol coupling of benzophenone,⁴³ photooxygenation of citronellol,⁴⁴ reaction of diphenyldiazomethane with benzoic acids,⁴⁵ and acetylation of ethylene glycol.⁴⁶

As such, we envisioned the immobilization of copper catalysts on solid supports, which in turn would be packed in a glass column working as a packed bed reactor, allowing for the continuous flow preparation of aminals.

Heterogeneous catalysis is a concept in which the catalyst that promotes the desired reactions is in a different phase than the reactants, often being the catalyst in the solid phase and the reaction mixture in the liquid phase. The catalyst can be a solid by itself or more often than not is composed of an active species immobilized in an "inert" matrix. Despite the typically lower turnover frequency (TOF) compared to homogeneous catalysis, heterogeneous catalysis offers several advantages. Namely, the lower the toxicity of the heterogeneous catalysts, the easier are the purification by separation of the catalyst and reaction media, their robustness, reusability, and recyclability, and the overall increased sustainability.

Due to the importance of heterogeneous catalysis^{47–49} and continuous flow methodologies, a laboratory experiment that

Received: April 10, 2023

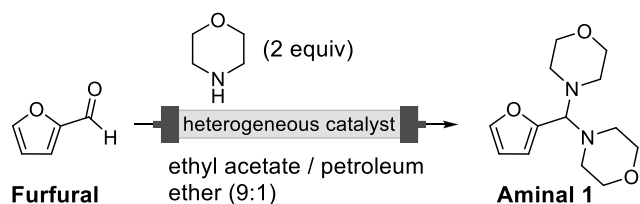
Revised: September 7, 2023

Published: November 17, 2023



integrates both the immobilization of a catalyst on a solid support and the subsequent flow reaction⁵⁰ would be valuable, bridging concepts such as scaleout and sustainability.⁵¹ Herein, we report an experiment performed by second year undergraduate students, where the students immobilized copper sulfate on silica, packed the catalyst on a glass column, and performed the continuous flow preparation of amins from furfural and morpholine (Scheme 1).

Scheme 1. Preparation of Furfural Aminoal with Morpholine under Continuous Flow Conditions



PEDAGOGIC GOALS

One main focus of this experiment is the more sustainable preparation of aminoal synthons. The importance of heterogeneous catalysis leads the way to discuss greener methodologies, recycling of the catalyst, reactivity of aldehyde and amine functionalities, and so forth. This is followed by the advantages of continuous flow, on one hand allowing the students to inquire about the challenges of scaling up certain reactions and the ease of scaling out by means of continuous flow methodologies and, on the other hand, by learning about the increased safety and selectivity that these methodologies provide.

Meanwhile, students learn practical information on continuous flow methodologies (e.g., how to determine the reaction volume; how to adjust the flow to the residence time of the reaction).

Furfural was selected as the aldehyde to allow the instructors to discuss another topic of green chemistry, namely, the use of biorenewable building blocks.⁵² Furfural is a mass produced bulk chemical obtained from lignocellulosic material, with a market size reaching 370 K t/y.⁵³ One can then inquire the

advantages and challenges to implement biomass derivatives as alternatives for oil based bulk chemicals.⁵⁴

The undergraduate organic chemistry students will also learn about the reactivity of the carbonyl and amine functional groups, particularly aldehydes, which is a topic of basic organic chemistry courses. The students investigate the importance of using a secondary amine in this experiment and the potential outcome of using primary amines, with the formation of imines being another important topic.

EXPERIMENTAL OVERVIEW

The experiment was carried out by 60 students during the Organic Chemistry II course of the Integrated Master Course of Pharmaceutical Sciences at the Faculty of Pharmacy, University of Lisbon. The students were divided into 30 teams, and the work was aligned with the topic “reactivity of the carbonyl group”. The experiment was performed over 3 h, starting with the preparation of the catalyst and the flow packed bed reactor, followed by the reaction and characterization of the products. In a round-bottomed flask, the students combined copper sulfate pentahydrate and silica in methanol. The mixture was stirred at room temperature for 10 min, followed by evaporation of the solvent at reduced pressure. The solid was dried in an oven at 150 °C for 30 min before preparing the packed bed reactor (see Figure 1 for the schematic of the reactor). The students determined the reactor volume (eq 1) using the solvent used for the reaction (ethyl acetate/petroleum ether (9:1)) and then calculated the flow rate required to achieve a residence time of 2 min (eq 2).

$$V(\text{reactor}) = \frac{(\text{mass}(\text{reactor filled}) - \text{mass}(\text{reactor}))}{\text{density of the solvent}} \quad (1)$$

$$\text{Flow rate} = \frac{V(\text{reactor})}{\text{residence time}} \quad (2)$$

In a beaker, the students prepared the initial reaction mixture consisting of furfural and morpholine in ethyl acetate/petroleum ether (9:1). The mixture is added to the reactor and collected in a beaker. The first two $V(\text{reactor})$ portions are wasted, and then, the reaction is collected for 10 min. The solvent is evaporated

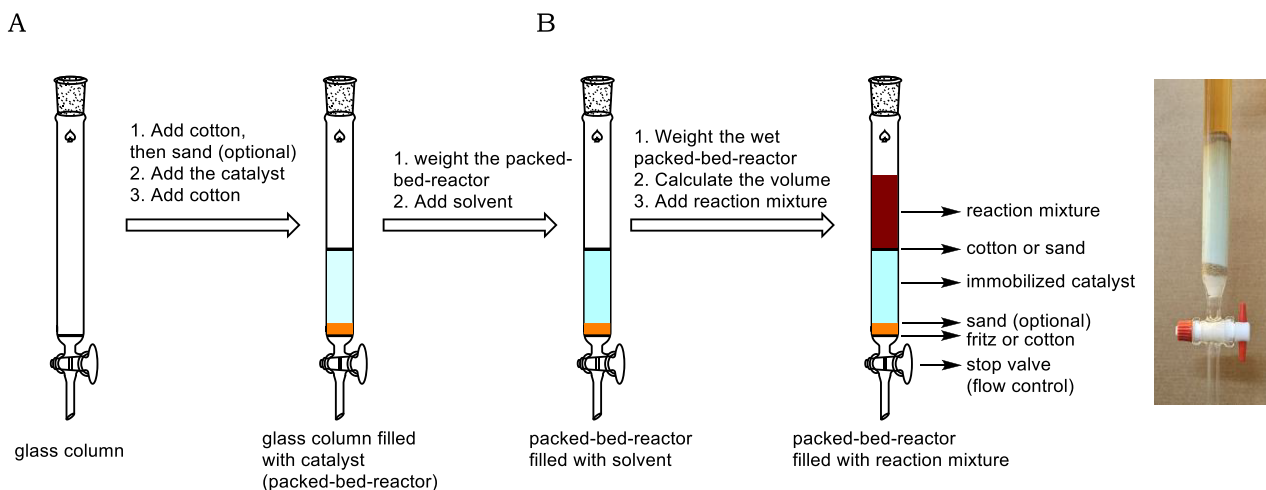


Figure 1. Schematic for the preparation of the packed bed reactor (A). Real life example (B).

yielding the pure product, which is confirmed by melting point and ^1H NMR.

HAZARDS

The use of protective clothing, gloves, and goggles is mandatory, such as common good laboratory practices (GLPs). Handling waste and chemicals is done according to the safety data sheets (SDS). There are no halogenated waste concerns; however, the heterogeneous catalysts should be disposed of properly with a protective mask to protect students from inhaling silica. Furfural is toxic if swallowed or if inhaled, is harmful in the case of skin contact (irritant) or eye contact (irritant), and may cause respiratory irritation. $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ is harmful if swallowed and can cause serious eye damage. Morpholine is a flammable liquid, is toxic if inhaled or in the case of skin contact, is harmful if swallowed, and can cause serious skin burns and eye damage. May cause damage to organs through prolonged or repeated exposure. Ethyl acetate is a highly flammable liquid and vapor, may cause drowsiness or dizziness, and causes serious eye irritation. Petroleum ether is a highly flammable liquid and vapor, may be fatal if swallowed, enters airways, causes skin irritation, and may cause drowsiness or dizziness. It is suspected of damaging fertility and may cause damage to organs through prolonged or repeated exposure. Silica should be handled with care due to the risk of chronic silicosis with prolonged inhalation.

RESULTS AND DISCUSSION

The experiment begins with the preparation of a silica-supported copper heterogeneous catalyst. To this end, copper sulfate is immobilized in silica by stirring in methanol. To evaluate the importance of the silica particle size, the teams were assigned 3 different samples. Seventeen teams used 40–63 μm particle size silica, eleven used 63–200 μm , and the remaining two teams used 35–70 μm .

After evaporation of the solvent under reduced pressure and drying in an oven (150 $^\circ\text{C}$ for 30 min), a blue solid is obtained (Figure 2A). At this stage, we found it was important to thoroughly dry the solid, since traces of methanol will lead to copper leaching during the reaction. A second resuspension of the catalyst in ethyl acetate and evaporation under reduced pressure is suggested before oven drying.

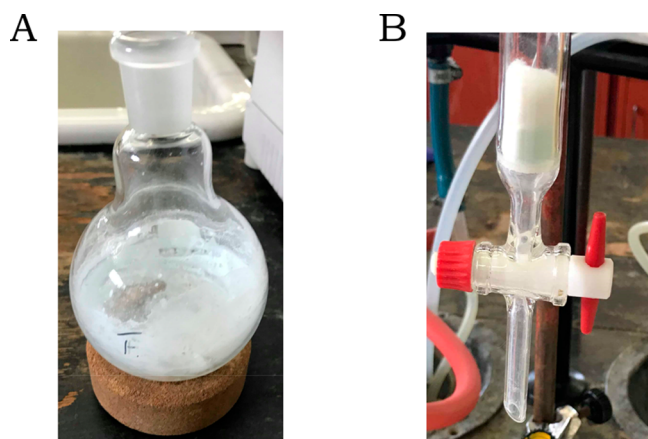


Figure 2. Catalyst appearance after drying (A). Glass column loaded with the catalyst (B).

Following the preparation of the catalyst, the teams packed a common gravimetry glass column for chromatography with the catalyst and weighed the system (Figure 2B).

The packed bed reactor was filled with solvent (ethyl acetate/petroleum ether (9:1)), and the mass of the system was determined to calculate the reactor volume.

After the preparation of the bed reactor, the teams prepared a reaction mixture of furfural and morpholine in a mixture of ethyl acetate/petroleum ether (9:1).

Furfural was selected as a model aldehyde for this reaction in order to introduce the concept of biomass-derived synthons and sustainability to the students. By doing so, we comply with several of the “12 principles of green chemistry”, such as the use of biomass raw materials and heterogeneous catalysts. Additionally, furfural is a very cheap reagent (0.06 €/g from Sigma-Aldrich).

The reaction was added to the column, and the flow was adjusted to around 1 drop per second, which roughly corresponds to a 2 min residence time. The students started to collect the reaction mixture after the initial volume in a beaker and stopped after 10 min. The solvent was evaporated, yielding the pure product, which was confirmed by melting point and ^1H NMR spectroscopy. Additional experiments may be performed, such as ICP-MS to evaluate the copper leaching. Under similar conditions, a slight copper leaching was observed, which may promote discussion on what impact this may have on the long-term reuse of the system.^{55,56}

The student teams were able to achieve moderate to good yields (Table 1). An overall average yield of 73% was obtained,

Table 1. Yield Range of the Amino Preparation in Accordance with the Solid Support Used

Furfural		Aminoal 1
Silica Particle Size (μm)	Teams	Average Yield (%)
40–63	17	83 \pm 10.3
63–200	12	61 \pm 15.3
35–70	2	67 \pm 13.4

with the best yields being obtained using the silica with 40–63 μm particle size. A detailed list of the yields and melting points obtained from the different teams can be accessed in Table S1.

Upon analysis of the ^1H NMR spectra, the students are asked to identify the aminoal C–H, significantly shielded in comparison with the starting aldehyde C–H (Figure 3). Additional 2D experiments were performed for a further discussion of the spectroscopic data. Importantly, ^{13}C NMR exhibits overlapping signals. HSQC experiments are particularly useful to reveal this information.

It is worth mentioning that in some cases, depending on the CDCl_3 used for the preparation of the sample, hydrolysis of the aminoal on the NMR tube is observed leading to trace amounts of furfural, allowing us to introduce the topic of reverse hydrolysis of the aminoals and the involved reaction mechanism. In such

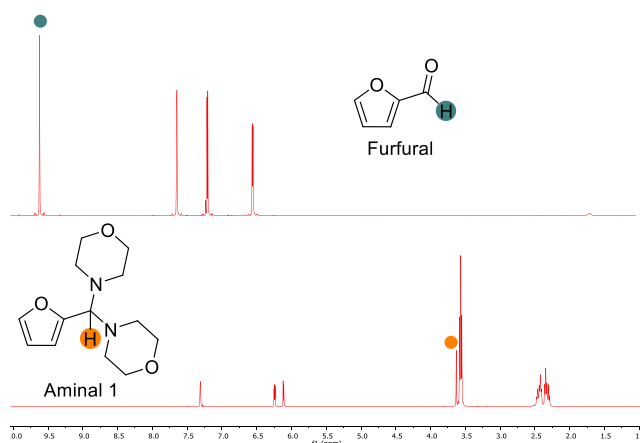


Figure 3. ^1H NMR of furfural (Top) and aminoal 1 (Bottom).

cases, the addition of triethylamine to CDCl_3 inhibits the hydrolysis.

ASSESSMENT

Assessment of the learning outcomes was performed during the laboratory experiment and from a final quiz. The students were already proficient in common laboratory practices such as weighing, preparing solutions, evaporating solvents under reduced pressure, and calculating reaction yields. In fact, all students were able to calculate the yield, most of them above 70%. Additionally, upon evaporation, 3 student teams obtained a brown oil instead of orange crystals. In these cases, the students did not control the flow rate of the reaction properly and the residence time was higher (around 10 min), which led to the formation of side products, namely, *trans*-4,5-diamino-cyclopentenones.

The students were asked to solve a quiz concerning the topics of green chemistry, flow chemistry, and the aminoal functional group. 90% of the students were able to correctly determine a flow rate given the specific reaction parameters and know that it is a key parameter to optimize flow conditions. The students were able to suggest the reduction of flow rate in order to increase the residence time if an incomplete reaction is encountered. 100% of the students were able to identify the aminoal product upon condensation of benzaldehyde and morpholine, despite most not proposing an iminium intermediary (60% performed the direct addition of a second amine to an hemiaminal intermediary). This hints toward the need of better highlighting the mechanism of the reaction during the introduction to the experiment. 62% of the students were able to identify the imine product from the condensation of a primary amine and an aldehyde, with the remaining students suggesting the corresponding aminoal. Most students (75%) identified the hydrolysis product of the aminoal in the presence of an aqueous acidic solution. Finally, 90% of the students identified 3 principles of green chemistry, most notably the use of renewable feedstocks and the use of catalysis, among others. This assessment revealed that the students learned key concepts of green chemistry, continuous flow conditions, and aldehyde chemistry, although more effort by the instructors concerning the reaction mechanisms of aminoal formation is suggested.

CONCLUSIONS

The preparation of aminoal from furfural and morpholine under continuous flow conditions is an experiment that was performed

successfully by the undergraduate students of the Integrated Master Pharmaceutical Sciences course. The experiment allowed the introduction of specific concepts such as green chemistry, heterogeneous catalysis, and continuous flow reactions and also consolidated the reactivity of aldehyde and amine functionalities. The purity of the crystalline products can be easily determined with a melting point apparatus, and no specific glassware is required for this experiment, other than common organic classroom glassware available in a teaching laboratory of Organic Chemistry. Overall, the feedback from the students was positive, and for most of them, the experiment was the first contact with the aforementioned concepts.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available at <https://pubs.acs.org/doi/10.1021/acs.jchemed.3c00306>.

Notes for instructors; experimental procedures; student handout; quiz; characterization (PDF)

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

The authors acknowledge Fundação para a Ciência e Tecnologia (FCT) for financial support (PTDC/QUI-QOR/32008/2017, UIDB/04138/2020, UIDP/04138/2020) and second year students from the Integrated Master Pharmaceutical Sciences course of the Faculty of Pharmacy of University of Lisbon for reproducing the experiment. The project leading to this application has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No. 951996. The NMR spectrometers are part of the National NMR Network (PTNMR) and are partially supported by Infrastructure Project No. 022161 (cofinanced by FEDER through COMPETE 2020, POCI and PORL and FCT through PIDDAC).

REFERENCES

- (1) Koroluk, K. J.; Jackson, D. A.; Dicks, A. P. The Petasis Reaction: Microscale Synthesis of a Tertiary Amine Antifungal Analog. *J. Chem. Educ.* **2012**, 89 (6), 796–798.
- (2) Rodrigues, C. A. B.; Martinho, J. M. G.; Afonso, C. A. M. Synthesis of a Biologically Active Oxazol-5-(4H)-One via an Erlenmeyer–Plöchl Reaction. *J. Chem. Educ.* **2015**, 92 (9), 1543–1546.
- (3) Thompson, M. P.; Agger, J.; Wong, L. S. Paternò–Büchi Reaction as a Demonstration of Chemical Kinetics and Synthetic Photochemistry Using a Light Emitting Diode Apparatus. *J. Chem. Educ.* **2015**, 92 (10), 1716–1720.

- (4) Goldstein, S. W.; Cross, A. V. Solvent-Free Reductive Amination: An Organic Chemistry Experiment. *J. Chem. Educ.* **2015**, *92* (7), 1214–1216.
- (5) Nelson, D. J.; Kumar, R.; Ramasamy, S. Comparing Carbonyl Chemistry in Comprehensive Introductory Organic Chemistry Textbooks. *J. Chem. Educ.* **2015**, *92* (7), 1171–1177.
- (6) Silverberg, L. J.; Coyle, D. J.; Cannon, K. C.; Mathers, R. T.; Richards, J. A.; Tierney, J. Azeotropic Preparation of a C-Phenyl N-Aryl Imine: An Introductory Undergraduate Organic Chemistry Laboratory Experiment. *J. Chem. Educ.* **2016**, *93* (5), 941–944.
- (7) Kelly, M. J. B.; Fallot, L. B.; Gustafson, J. L.; Bergdahl, B. M. Water Mediated Wittig Reactions of Aldehydes in the Teaching Laboratory: Using Sodium Bicarbonate for the in Situ Formation of Stabilized Ylides. *J. Chem. Educ.* **2016**, *93* (9), 1631–1636.
- (8) Estevão, M. S.; Martins, R. J. V.; Afonso, C. A. M. Synthesis of *Trans*-4,5-Bis-Dibenzylaminocyclopent-2-Enone from Furfural Catalyzed by $\text{ErCl}_3 \cdot 6\text{H}_2\text{O}$. *J. Chem. Educ.* **2017**, *94* (10), 1587–1589.
- (9) Obhi, N. K.; Mallov, I.; Borduas-Dedekind, N.; Rousseaux, S. A. L.; Dicks, A. P. Comparing Industrial Amination Reactions in a Combined Class and Laboratory Green Chemistry Assignment. *J. Chem. Educ.* **2019**, *96* (1), 93–99.
- (10) Sterner, E. S. Three Ways to Polyamides: The Impact of Polymerization Mechanism on Polymer Properties. *J. Chem. Educ.* **2019**, *96* (9), 2003–2008.
- (11) Mullins, J. J.; Prusinowski, A. F. Microwave-Promoted Synthesis of a Carbocyclic Curcuminoid: An Organic Chemistry Laboratory Experiment. *J. Chem. Educ.* **2019**, *96* (3), 606–609.
- (12) Yates, N. D. J.; Brabham, R. L.; Spears, R. J.; Keenan, T.; Helliwell, P. A.; Pugh, D. S.; Parkin, A.; Hurst, G. A.; Fascione, M. A. Chemical Bioconjugation of Proteins in an Undergraduate Lab: One-Pot Oxidation and Derivatization of the N-Terminus. *J. Chem. Educ.* **2019**, *96* (6), 1245–1249.
- (13) Battersby, G. L.; Beeley, C.; Baguley, D. A.; Barker, H. D.; Broad, H. D.; Carey, N. C.; Chambers, E. S.; Chodaczek, D.; Blackburn, R. A. R.; Williams, D. P. Go Fischer: An Introductory Organic Chemistry Card Game. *J. Chem. Educ.* **2020**, *97* (8), 2226–2230.
- (14) Şen, Ş. ChemistDice: A Game for Organic Functional Groups. *J. Chem. Educ.* **2021**, *98* (2), 535–539.
- (15) Lambert, K. M.; Kelly, C. B.; Milligan, J. A.; Tilley, L. J.; Reynolds, R. P.; McGuire, K. P.; Anzalone, L.; Del Sesto, K. E.; Walsh, S. A Practical Oxidation Experiment for Undergraduate Students: Bobbitt's Salt as a "Green" Alternative. *J. Chem. Educ.* **2022**, *99* (9), 3249–3258.
- (16) Couture, A.; Deniau, E.; Grandclaudeon, P.; Hoarau, C. Total Syntheses of Taliscanine, Velutinam, and Enterocarpam II. *J. Org. Chem.* **1998**, *63* (9), 3128–3132.
- (17) Harris, T. D.; Roth, G. P. Ortho Lithiation via a Carbonyl Synthon. *J. Org. Chem.* **1979**, *44* (12), 2004–2007.
- (18) Carpenter, A. J.; Chadwick, D. J. Chemoselective Protection of Heteroaromatic Aldehydes as Imidazolidine Derivatives. *Tetrahedron* **1985**, *41* (18), 3803–3812.
- (19) Liu, C.; Chen, M.-X.; Li, M. Synthesis, Crystal Structures, Catalytic Application and Antibacterial Activities of Cu(II) and Zn(II) Complexes Bearing Salicylaldehyde-Imine Ligands. *Inorg. Chim. Acta* **2020**, *508*, No. 119639.
- (20) Kaiser, D.; Tona, V.; Gonçalves, C. R.; Shaaban, S.; Oppedisano, A.; Maulide, N. A General Acid-Mediated Hydroaminomethylation of Unactivated Alkenes and Alkynes. *Angew. Chem., Int. Ed.* **2019**, *58* (41), 14639–14643.
- (21) Pereira, J. G.; António, J. P. M.; Mendonça, R.; Gomes, R. F. A.; Afonso, C. A. M. Rediscovering Amino Chemistry: Copper($\text{scp}>\text{ii}$/<math>\text{Scp}>\text{>}) Catalysed Formation under Mild Conditions. *Green Chem.* **2020**, *22* (21), 7484–7490.
- (22) Rogers, L.; Jensen, K. F. Continuous Manufacturing – the Green Chemistry Promise? *Green Chem.* **2019**, *21* (13), 3481–3498.
- (23) Plutschack, M. B.; Pieber, B.; Gilmore, K.; Seeberger, P. H. The Hitchhiker's Guide to Flow Chemistry. *Chem. Rev.* **2017**, *117* (18), 11796–11893.
- (24) Britton, J.; Majumdar, S.; Weiss, G. A. Continuous Flow Biocatalysis. *Chem. Soc. Rev.* **2018**, *47* (15), 5891–5918.
- (25) Reyes, K. M. D.; Bruce, K.; Shetranjiwalla, S. Green Chemistry, Life Cycle Assessment, and Systems Thinking: An Integrated Comparative-Complementary Chemical Decision-Making Approach. *J. Chem. Educ.* **2023**, *100* (1), 209–220.
- (26) Ang, J. W. J. Integrating Green Chemistry into Teaching Laboratories: Aqueous Suzuki–Miyaura Cross-Coupling Reaction Using a Recyclable Fluorous Precatalyst. *J. Chem. Educ.* **2021**, *98* (1), 203–207.
- (27) Gawlik-Kobylińska, M.; Walkowiak, W.; Maciejewski, P. Improvement of a Sustainable World through the Application of Innovative Didactic Tools in Green Chemistry Teaching: A Review. *J. Chem. Educ.* **2020**, *97* (4), 916–924.
- (28) Mooney, M.; Vreugdenhil, A. J.; Shetranjiwalla, S. A Toolkit of Green Chemistry and Life-Cycle Analysis for Comparative Assessment in Undergraduate Organic Chemistry Experiments: Synthesis of (*E*)-Stilbene. *J. Chem. Educ.* **2020**, *97* (5), 1336–1344.
- (29) Wu, N.; Kubo, T.; Sekoni, K. N.; Hall, A. O.; Phadke, S.; Zurcher, D. M.; Wallace, R. L.; Kothari, D. B.; McNeil, A. J. Student-Designed Green Chemistry Experiment for a Large-Enrollment, Introductory Organic Laboratory Course. *J. Chem. Educ.* **2019**, *96* (11), 2420–2425.
- (30) Armstrong, L. B.; Rivas, M. C.; Zhou, Z.; Irie, L. M.; Kerstiens, G. A.; Robak, M. T.; Douskey, M. C.; Baranger, A. M. Developing a Green Chemistry Focused General Chemistry Laboratory Curriculum: What Do Students Understand and Value about Green Chemistry? *J. Chem. Educ.* **2019**, *96* (11), 2410–2419.
- (31) Barcena, H.; Tuachi, A.; Zhang, Y. Teaching Green Chemistry with Epoxidized Soybean Oil. *J. Chem. Educ.* **2017**, *94* (9), 1314–1318.
- (32) Edgar, L. J. G.; Koroluk, K. J.; Golmakani, M.; Dicks, A. P. Green Chemistry Decision-Making in an Upper-Level Undergraduate Organic Laboratory. *J. Chem. Educ.* **2014**, *91* (7), 1040–1043.
- (33) Dintzner, M. R.; Kinzie, C. R.; Pulkarabek, K.; Arena, A. F. The Cyclohexanol Cycle and Synthesis of Nylon 6,6: Green Chemistry in the Undergraduate Organic Laboratory. *J. Chem. Educ.* **2012**, *89* (2), 262–264.
- (34) Song, Y.; Wang, Y.; Geng, Z. Some Exercises Reflecting Green Chemistry Concepts. *J. Chem. Educ.* **2004**, *81* (5), 691.
- (35) Cann, M. C.; Dickneider, T. A. Infusing the Chemistry Curriculum with Green Chemistry Using Real-World Examples, Web Modules, and Atom Economy in Organic Chemistry Courses. *J. Chem. Educ.* **2004**, *81* (7), 977.
- (36) Hjerresen, D. L.; Boese, J. M.; Schutt, D. L. Green Chemistry and Education. *J. Chem. Educ.* **2000**, *77* (12), 1543.
- (37) Tundo, P.; Rosamilia, A. E.; Aricò, F. Methylation of 2-Naphthol Using Dimethyl Carbonate under Continuous-Flow Gas-Phase Conditions. *J. Chem. Educ.* **2010**, *87* (11), 1233–1235.
- (38) König, B.; Kreitmeier, P.; Hilgers, P.; Wirth, T. Flow Chemistry in Undergraduate Organic Chemistry Education. *J. Chem. Educ.* **2013**, *90* (7), 934–936.
- (39) Simeonov, S. P.; Afonso, C. A. M. Batch and Flow Synthesis of 5-Hydroxymethylfurfural (HMF) from Fructose as a Bioplatfrom Intermediate: An Experiment for the Organic or Analytical Laboratory. *J. Chem. Educ.* **2013**, *90* (10), 1373–1375.
- (40) Kairouz, V.; Collins, S. K. Continuous Flow Science in an Undergraduate Teaching Laboratory: Bleach-Mediated Oxidation in a Biphasic System. *J. Chem. Educ.* **2018**, *95* (6), 1069–1072.
- (41) Santandrea, J.; Kairouz, V.; Collins, S. K. Continuous Flow Science in an Undergraduate Teaching Laboratory: Photocatalytic Thiol–Ene Reaction Using Visible Light. *J. Chem. Educ.* **2018**, *95* (6), 1073–1077.
- (42) Leibfarth, F. A.; Russell, M. G.; Langley, D. M.; Seo, H.; Kelly, L. P.; Carney, D. W.; Sello, J. K.; Jamison, T. F. Continuous-Flow Chemistry in Undergraduate Education: Sustainable Conversion of Reclaimed Vegetable Oil into Biodiesel. *J. Chem. Educ.* **2018**, *95* (8), 1371–1375.
- (43) Volpe, K.; Podlesny, E. E. Modernization of a Photochemical Reaction for the Undergraduate Laboratory: Continuous Flow Photopinacol Coupling. *J. Chem. Educ.* **2020**, *97* (2), 586–591.

- (44) Renner, M.; Griesbeck, A. Think and Print: 3D Printing of Chemical Experiments. *J. Chem. Educ.* **2020**, *97* (10), 3683–3689.
- (45) Zhang, S.; Xu, R.; Zhu, H.; Kern, R. E. B.; Spillman, M. G.; Chen, E. S.; Deng, Y.; Shen, S.; Kwag, S.; Clayton, E. A.; Mendelsohn, M. M.; Ozturk, A. N.; Burnham, A. E.; Erlinger, G. M.; Pederson, J. P.; Gelbaum, C.; Liotta, C. L.; Pollet, P. Reaction of Diphenyldiazomethane with Benzoic Acids in Batch and Continuous Flow. *J. Chem. Educ.* **2021**, *98* (2), 469–477.
- (46) Sun, M.; Liang, C.; Shen, X.; Li, J.; Cheng, R.; Ye, J. Continuous Flow Science in an Undergraduate Teaching Laboratory: Synthesis of Ethylene Glycol Diacetate Using Heterogeneous Catalysts in Continuous Flow. *J. Chem. Educ.* **2021**, *98* (2), 572–576.
- (47) Friend, C. M.; Xu, B. Heterogeneous Catalysis: A Central Science for a Sustainable Future. *Acc. Chem. Res.* **2017**, *50* (3), 517–521.
- (48) Li, Z.; Ji, S.; Liu, Y.; Cao, X.; Tian, S.; Chen, Y.; Niu, Z.; Li, Y. Well-Defined Materials for Heterogeneous Catalysis: From Nanoparticles to Isolated Single-Atom Sites. *Chem. Rev.* **2020**, *120* (2), 623–682.
- (49) Bavykina, A.; Kolobov, N.; Khan, I. S.; Bau, J. A.; Ramirez, A.; Gascon, J. Metal–Organic Frameworks in Heterogeneous Catalysis: Recent Progress, New Trends, and Future Perspectives. *Chem. Rev.* **2020**, *120* (16), 8468–8535.
- (50) Di Filippo, M.; Bracken, C.; Baumann, M. Continuous Flow Photochemistry for the Preparation of Bioactive Molecules. *Molecules* **2020**, *25* (2), 356.
- (51) Werpy, T.; Peterson, G.; Aden, A.; Bozell, J.; Holladay, J.; White, J.; Manheim, A. *Top Value Added Chemicals From Biomass*; U.S. Department of Energy, 2004; <https://www.nrel.gov/docs/fy04osti/35523.pdf>.
- (52) Dragone, G.; Kerssemakers, A. A. J.; Driessen, J. L. S. P.; Yamakawa, C. K.; Brumano, L. P.; Mussatto, S. I. Innovation and Strategic Orientations for the Development of Advanced Biorefineries. *Bioresour. Technol.* **2020**, *302*, No. 122847.
- (53) Dalvand, K.; Rubin, J.; Gunukula, S.; Clayton Wheeler, M.; Hunt, G. Economics of Biofuels: Market Potential of Furfural and Its Derivatives. *Biomass Bioenergy* **2018**, *115*, 56–63.
- (54) Ubando, A. T.; Felix, C. B.; Chen, W.-H. Biorefineries in Circular Bioeconomy: A Comprehensive Review. *Bioresour. Technol.* **2020**, *299*, No. 122585.
- (55) Cavaca, L. A. S.; Coelho, J. A. S.; Lucas, S. D.; Loureiro, R.; Gomes, R. F. A.; Afonso, C. A. M. Upgrading furanic platforms to α -enaminones: tunable continuous flow hydrogenation of bio-based cyclopentenones. *Reaction Chemistry & Engineering* **2023**, *8*, 482–489.
- (56) Gomes, R. F. A.; Cavaca, L. A. S.; Gonçalves, J. M.; Ramos, R.; Peixoto, A. F.; Arias-Serrano, B. I.; Afonso, C. A. M. Silica-Supported Copper for the Preparation of trans-4,5-Diamino-Cyclopent-2-Enones under Continuous Flow Conditions. *ACS Sustainable Chem. Eng.* **2021**, *9* (48), 16038–16043.