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Literature-Based Problems for Introductory Organic Chemistry Quizzes and Exams

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ABSTRACT

Literature-based problems expose students to current, real world applications of chemistry. These types of problems are often confined to graduate and advanced undergraduate courses. We describe incorporation of literature-based problems in Organic I and II courses on quizzes and exams. We give students at least one week to study and discuss portions of a paper, then ask students to answer quiz and exam questions based on the paper. Students show high levels of engagement with and interest in the primary chemical literature when faced with these types of assessments.

KEYWORDS

Second-Year Undergraduate, Organic Chemistry, Collaborative/Cooperative Learning, Testing/Assessment, Problem Solving/Decision Making, Applications of Chemistry

Engaging students with contemporary research problems is a common goal in many chemistry classes. To achieve this, course instructors often require students to read papers from the primary literature to learn about recent discoveries and the latest chemical thinking. While this is commonplace in graduate[1] and some upper-level undergraduate courses,[2] journal articles are less commonly used in introductory classes.[3] Nevertheless, incorporating the primary chemical literature into the introductory organic chemistry sequence holds great promise for promoting learning.[4] At Smith College, goals for the two-semester introductory organic chemistry sequence include: understand real problems in organic chemistry research, recognize familiar reactions/reagents/mechanisms in unfamiliar contexts, and extrapolate from current knowledge to new cases. Six years ago, we hypothesized that literature-based assignments provided an avenue for achieving these goals.

Initially, students were asked to summarize a current literature article in a 1-2 page paper;[5] however, these exercises were not integral to the class and failed to effectively enhance student motivation. Over the past four years, we have pioneered "Real Chemistry" assignments that involve informal student groups focusing on portions of current papers that we then use to develop exam questions. These assignments foster sustained student interactions focused on the chemical literature resulting in enhanced engagement and motivation.

CLASS OVERVIEW

At Smith College, Organic I and II are the second and third semesters of our four-semester introductory chemistry sequence. Approximately 80% of students complete a traditional one-semester general chemistry course before organic chemistry, while the remaining 20% complete an advanced general chemistry course designed to cover General Chemistry I and II in one semester. There are two sections for both Organic I and II with no attempt to segregate students based on prior experience or intended major in either course. A majority of students in Organic I are first-year students while approximately one quarter are sophomores. In Organic II, an overwhelming majority are sophomores. In both courses there are smaller numbers of juniors and seniors. Organic I sections average between 60-90 students, while Organic II sections average between 30-60 students. Many students intend to satisfy prehealth course requirements, and approximately 50% of students in Organic II will graduate as chemistry or biochemistry majors. Classes meet three times per week for 70 to 80 minutes during a 14-week semester. Class time is split between traditional lecture and problem solving formats.

LOGISTICS

In both Organic I and II courses, the logistics for these assignments include distributing the paper and an explanatory cover sheet at least one week before the quiz or exam. The cover sheet highlights specific reaction schemes that students should focus on and lists content they should ignore. Students are encouraged to work collaboratively to understand the mechanistic details of the reactions under consideration, especially regio- and stereoselectivity. Students are able to consult any other literature sources or websites they would like; they are not allowed to discuss the questions with anyone outside of the class. Real Chemistry assignments in Organic I require students to then apply their insight to questions on a take home quiz with literature-based questions. In Organic II, expectations rise and the literature papers serve as the basis for approximately 1/3 of two-hour timed midterm and final exams. In Organic II, in order to promote student collaboration, students are not allowed to speak with course instructors about the Real Chemistry papers or questions. Not surprisingly, students initially complain about this prohibition; however, they often come to realize the importance of learning from each other to prepare well for these assessments. Student groups are created informally and vary by instructor. Groups are encouraged to meet outside of class and sometimes are given class time for discussion. One instructor uses weekly group office hours to promote regular group interaction. Introduction of the Real Chemistry assignments necessitated a reduction in the number of problem set questions during these weeks, but it did not require eliminating any important topics or concepts in either Organic I or II.

We have used a variety of sources to construct our literature-based problems (see Table 1). In Organic I, we are partial to older papers using traditional reaction conditions with analyses available from a secondary source. Nicolaou's *Classics in Total Synthesis*[6] is especially helpful as students work to understand the primary articles. In

Organic II, interesting and accessible papers have been drawn from *Organic Letters*, the *Journal of Organic Chemistry*, the *Journal of the American Chemical Society*, *Angewandte Chemie*, and *Chemical Society Reviews*. Some of the topics covered in our courses, like organometallic cross-coupling reactions and electrocyclic reactions, often appear in Advanced Organic Chemistry classes. Real Chemistry assignments should work equally well in these courses. For a complete collection of literature-based problems used at Smith College, please see the Supporting Information.

Table 1. Papers used for literature-based questions

Assessment	*Papers*
Orgo I Quiz	Sharpless and Masamune's Hexoses Synthesis[7]
	Corey's Prostaglandin Synthesis[8]
Orgo II Exam #1	Hiroya's Lycopladine Synthesis[9]
Orgo II Exam #2	Srikrishna's Valeriananoid Synthesis[10]
	Murphy's Vindoline Synthesis[11]
	Zhai's Sculponeatin Synthesis[12]
Orgo II Exam #3	Bertozzi's Bioorthogonal Click Reactions[13]
Orgo II Final Exam	Reisman's Acutumine Core Synthesis[14]
	Sarpong's Lycoposerramine R Synthesis[15]
	Parker's Kingianin A Synthesis[16]
	Tietze's Spinosyn A Synthesis[17]
	Garg's Tubingensin Synthesis[18]

ORGANIC II EXAMPLES

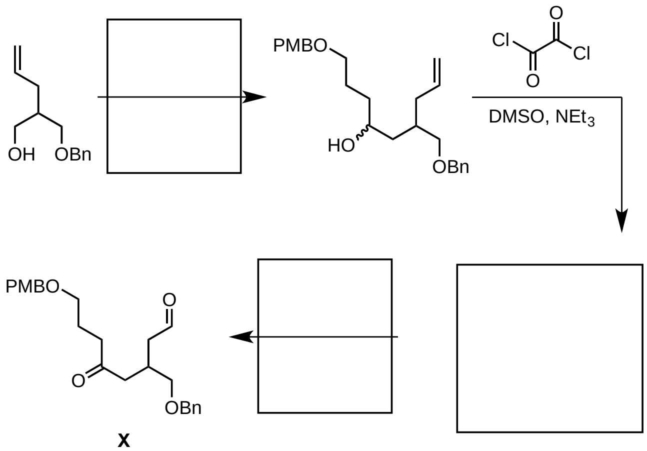
We began to experiment with Real Chemistry assignments in Organic II in 2012. Papers were chosen to showcase course content, such as specific reactions or reagents, in order to demonstrate the utility of organic reactions and mechanisms in contemporary research examples. One week before the exam, the Real Chemistry paper and an explanatory cover sheet were distributed, and we also provided a brief overview in class. The class discussion focused on the context of the research investigations and the "big picture" of the paper without students worrying about being tested on them.

By providing a week for students to discuss each paper, we were able to ask more complex exam questions that would be too challenging without additional time for thought and analysis. In our experience, dedicated student groups do an excellent job focusing on key points in the papers and are prepared to answer challenging exam questions. Furthermore, students become more comfortable working with complicated molecules (or as students describe them, “scary” molecules). Molecular complexity will grow as students progress to more advanced courses in organic and biochemistry, and Organic II is an opportune time to promote the transition from understanding simple to complex organic molecules.

Literature-based problems also provide excellent opportunities to review older material in the context of current chemistry and recent topics. For example, Box 1 illustrates a problem from Murphy’s vindoline synthesis.[11] It begins with a question focusing on a Grignard reaction, carbonyl oxidation, and alkene oxidation, all reactions from earlier in the course. Part b is an intramolecular aldol reaction, a recently discussed topic. Students who previously analyzed this step in the paper quickly recognize that only one enolate leads to a stable cyclohexanone product. Problems like this reinforce the cumulative nature of organic chemistry while also highlighting important new reactions.

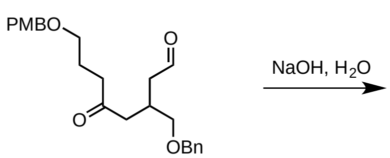
Box 1. Example Organic II exam question

a) Fill in the boxes below with the appropriate reagents or products. You may use any reagents that work to accomplish a given transformation – they **DO NOT** need to be the same reagents reported in the "Real Chemistry" paper.



X

b) Draw the product arising from treatment of compound **X** with NaOH along with a complete arrow-pushing mechanism for your proposed transformation.



X

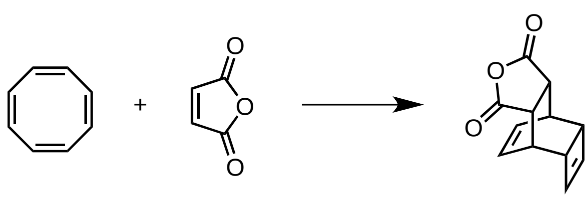
One of the best examples of deep understanding fostered by a Real Chemistry assignment is the problem shown in Box 2. This is from Bertozzi's review of bioorthogonal click chemistry[13] and features two pericyclic reactions. Upon first seeing this scheme, students think this is a straightforward transformation involving a Diels-Alder reaction followed by an electrocyclic ring closure. However, closer inspection of the molecular orbitals involved reveals that the Diels-Alder reaction is a thermal reaction and the 4π electrocyclic process must be photochemical to yield the desired product. The correct analysis is that this mechanism involves a thermal 6π

electrocyclic ring closure followed by a Diels-Alder reaction. Student groups that thought deeply about this reaction performed very well on the exam; students who only thought superficially about the transformation did not analyze the problem correctly.

Besides providing a challenging pericyclic reaction cascade for an exam, Bertozzi's paper served a second important purpose in broadening students' exposure to research problems in chemical biology. In the vindoline example above and most other Real Chemistry assignments, we chose papers that report total syntheses of bioactive natural products to highlight the vital role of organic synthesis in addressing problems in human health and disease. Bertozzi's efforts in bioorthogonal chemistry and *in vivo* reactions offer an entirely different sort of application which students recognized and appreciated.

Box 2. Example Organic II exam question

a) Draw an arrow-pushing mechanism for the reaction.



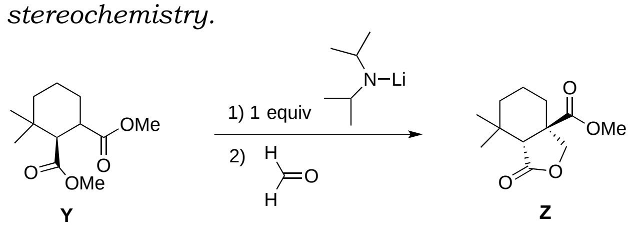
b) The reaction above is a two-step process. Given the stereochemical outcome of the first step, is this a thermal or photochemical process? Justify your answer with molecular orbital (MO) diagrams.

The Real Chemistry example in Box 3 highlights another type of question we have found useful. In addition to asking about material directly from the paper, we ask students to think about the behavior of related molecules. This enables us to address our previously stated goal of having students extrapolate from current knowledge to new cases. Sections a and b are straight from the paper while section c requires application of knowledge from the paper[12] (the mechanism of epimerization) to a case where a chair flip is impossible due to the presence of a *t*-butyl group.

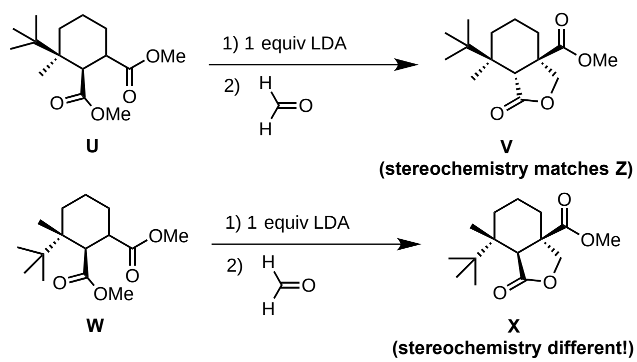
Box 3. Example Organic II exam question

a) Consider the base used in the depicted reaction, which serves to initially deprotonate **Y**. Is this deprotonation reversible or irreversible?

b) **Draw** a complete arrow-pushing mechanism for the transformation of **Y** to **Z** upon sequential addition of LDA and formaldehyde (as shown). *Be mindful of stereochemistry.*



c) Although not discussed in the paper, slight variations in the substrate structure (**U** vs **W**) can alter the course of the reaction. In **U** to **V**, your part b mechanism occurs in the same way and provides the expected product. In **W** to **X**, one or more of the steps in your part b mechanism **NO LONGER OCCURS**. *Your goal is to explain why this is.*



To explain this outcome:

A) **Circle** the step (or steps) in your part b mechanism that does NOT occur in the transformation of **W** to **X**.

B) For the intermediate in the reaction of **U** that is poised to undergo the step you circled in A, **draw** the **most stable conformer** below. *Important: be sure your drawing accurately represents the conformation of this intermediate.*

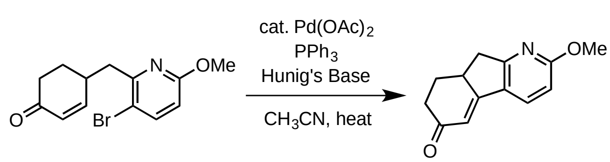
C) Repeat B for the reaction of **W**.

D) Compare your structural drawings – **why is U required to proceed via your part b mechanism while W is not**? Explain in 1-2 sentences.

The final exam is fertile ground for reviewing topics encountered throughout the two-semester organic chemistry sequence. It also provides our only test-based opportunity to assess student learning for our unit on transition metal catalyzed cross-coupling reactions. There are a multitude of synthetic applications for Stille, Suzuki, and Heck reactions and the example problem in Box 4 illustrates a Heck reaction from Sarpong's lycoposerramine R synthesis.[15] Similar to the example in Box 2, this is another problem that requires prolonged analysis to fully understand. Many students mistakenly think this is a standard Heck reaction involving oxidative addition, alkene insertion, bond rotation, syn elimination, and catalyst regeneration. Student groups that looked more deeply into this mechanism realized that bond rotation is impossible, thus preventing the standard intramolecular syn elimination. Puzzled by this result, students who continued thinking about the transformation realized that this reaction necessitates an E2 reaction promoted by Hunig's base to form the alkene while simultaneously regenerating the Pd(0) catalyst.

Box 4. Example Organic II final exam question.

a) Draw a stepwise mechanism to explain this reaction. There is no need to show the formation of Pd(0). This will form under the reaction conditions, and your mechanism can begin with the reaction of Pd(0) and the starting material.



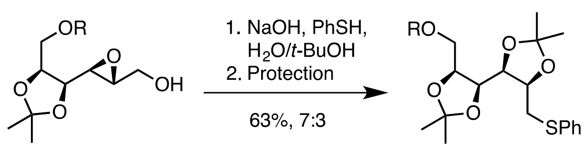
b) The alkene formation step in this mechanism is unusual for a Heck reaction. Clearly explain this step focusing on why it is different than most Heck reactions (including the one you performed in lab). Hint: It is essential to focus on the stereochemistry of the alkene insertion and alkene formation steps to explain this correctly.

ORGANIC I EXAMPLE

After our successful implementation of Real Chemistry in Organic II, we decided to expand its reach into Organic I. Our goal was to continue with rigorous problems from the literature, but to reduce the overall stress level by moving the problems from a timed exam to an untimed take home quiz. We also only do one Real Chemistry assignment near the end of the semester, and class discussion spans several classes to help address common questions and misconceptions. Box 5 illustrates a quiz question from the Sharpless and Masamune hexose synthesis paper.[7] This builds on recent class discussions related to stereochemistry and epoxide reactions, and it tests students' ability to understand the stereochemistry of complex molecules and a complicated mechanism, the regiochemistry of epoxide opening.

Box 5. Example Organic I quiz question.

For this problem, let's focus on the conversion shown below from the Sharpless and Masamune paper.



a) What is the mechanism for the first step of this sequence (the NaOH, PhSH, H_2O/*t*-BuOH reaction)?
b) This transformation proceeds in 63%; 7:3. What do these numbers mean?
c) Draw the enantiomer of the reactant above. Draw the structure of the product of the two-step sequence above starting with this molecule (the enantiomer of the reactant).

STUDENT FEEDBACK

Not surprisingly, Real Chemistry assignments are not popular with all students. Many students are used to standard exams that require memorization and regurgitation rather than the deep thinking required for analysis of interesting problems from the literature. However, over the course of their time in organic chemistry, many students begin to appreciate the importance of the critical analysis and problem solving skills needed to fully understand these literature-based problems. In five different classes, a majority of students rated the Real Chemistry assignments as helpful or very helpful for their learning (Figure 1). Students also provided thoughtful narrative feedback on course evaluations with many stating that these assignments helped them learn course content better, that extended time for discussion and analysis was critical for understanding, and that their interest and engagement in organic chemistry increased. For example, one student wrote, “The paper helped me recognize the importance/function of stereochemistry and alkene reactions which ultimately helped me to better understand them.”

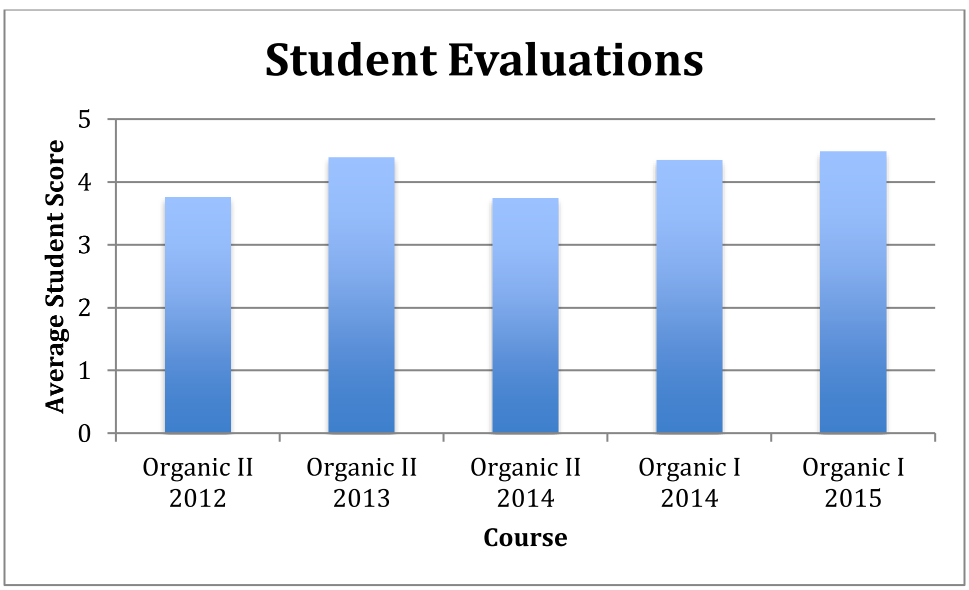


Figure 1. Student evaluation responses to the question of how important Real Chemistry assignments were for their learning (1 not helpful – 5 very helpful).

Gratifyingly, students recognized and appreciated the use of Real Chemistry to incorporate more difficult problems on quizzes and timed exams. Specific narrative feedback included: “It was incredibly helpful to have the paper ahead of time and would have felt impossible otherwise. I felt like we were prepared and enabled to succeed.” Further, students stated that: “The paper and assignment were very challenging but when the material finally started to make sense, it was a wonderful way to explore the class topics,” and “it was very stressful and time consuming but rewarding once I felt like I’d figured it out.”

Additionally, student narrative feedback suggests that Real Chemistry achieved its goal of introducing students to current problems in organic synthesis and that they valued this glimpse at the research frontier. “As a biology major I loved the real life connection between organic synthesis and biological molecules”, “It was very interesting and cool to know that I understood some of what was going on in a scientific paper”, and “It made me realize how interested I am in organic chemistry.”

CONCLUSION

In order for students to transition from novice to expert thinkers, they must grapple with problems that are expert level, problems that require applying content knowledge in unfamiliar contexts and resemble the work that experts in the field pursue. Incorporating Real Chemistry problems on exams enables us to position understanding of research results, an expert-level problem, as an integral part of the course and maximizes focused student effort on these important learning opportunities. We challenge our introductory-level students to engage deeply with complicated reactions and mechanisms, and they demonstrate their ability to tackle these problems on take-home quizzes and in-class exams. Our students report broad satisfaction with these exercises, and we find these assignments among the most satisfying methods to introduce our students to the fascinating world of modern organic chemistry.

ASSOCIATED CONTENT

Supporting Information

All literature-based problems, answers, and explanatory cover sheets are provided. Data for the generation of Figure 1 are provided.

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