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Strategies of Successful Synthesis Solutions: Mapping, Mechanisms, and More

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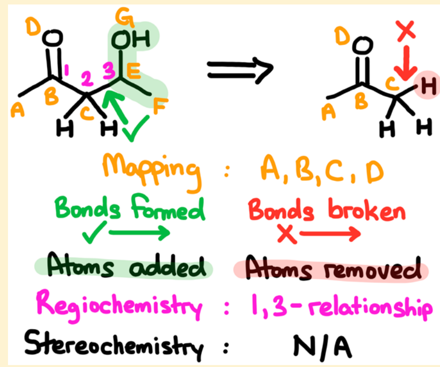
Ⓢ *Supporting Information*

ABSTRACT: Organic synthesis problems require the solver to integrate knowledge and skills from many parts of their courses. Without a well-defined, systematic method for approaching them, even the strongest students can experience difficulties. Our research goal was to identify the most successful problem-solving strategies and develop associated teaching models and learning activities. Specifically we asked: (1) What problem-solving strategies do undergraduate students use when solving synthesis-type problems? Are these strategies used correctly/as intended? (2) What strategies have the highest association with successful answers? (3) What relationships exist between these strategies? We analyzed more than 700 responses to synthesis problems from the final exams of undergraduate organic chemistry courses at a large, research-intensive institution. We analyzed the data using an open-coding system and a theoretical framework based on meaningful learning and representational systems in problem-solving. Our analysis found that successful answers demonstrated six key strategies: (1) identified newly formed bonds in the target molecule, (2) identified atoms added to the starting molecule to form the target, (3) identified key regiochemical relationships, (4) mapped the atoms of the starting material onto the target, (5) used a partial or complete retrosynthetic analysis, and (6) drew reaction mechanisms. The vast majority of successful answers demonstrated the use of multiple strategies in concert. This higher degree of success is logical in the context of meaningful learning and of representational systems in problem-solving. These strategies were often absent from unsuccessful answers, possibly because students did not know these strategies, did not believe them to be useful, or did not write them down. For teaching, our results suggest that students should be taught, encouraged, and given opportunities to use multiple key strategies; sample problems are included herein.



KEYWORDS: *Second-Year Undergraduate, Chemical Education Research, Organic Chemistry, Problem Solving/Decision Making, Synthesis*

FEATURE: Chemical Education Research

■ INTRODUCTION

One of the highest-level learning outcomes of organic chemistry courses is to develop the skills required to solve synthesis-type problems. Although familiar reactions are chosen when designing or choosing synthetic problems, students must recall, use, and integrate knowledge and skills from their previous courses. There can be a large gap in how organic synthesis is taught; students are taught basic reactions, are shown a successful synthetic sequence, and are then expected to propose a full synthesis on their own.[1] A few textbooks describe strategies to solve synthesis problems, but it is unknown whether these strategies help students' skill development.[2−4] Learning activities can provide opportunities for students to practice synthesis skills and can reflect the problem types from synthetic organic chemistry research.[5] For example, interconnected factors fostered graduate students' development into practicing organic chemists, including: "real" course content, authentic activities with concrete instruments for knowledge construction, and scaffolding with feedback.[1,6,7] Students who lack a well-defined strategy tend to be unsuccessful in solving these complex problems.[1]

Our research goal was to identify the problem-solving strategies that were associated with higher success rates on synthesis problems in early undergraduate organic chemistry courses. Problem-solving refers to people's efforts to achieve a goal for which they do not have an automatic solution.[8] We analyzed students' approaches to *problems*, not *exercises*. "The difference between an exercise and a problem is the result of differences in the level of familiarity with similar tasks the individual brings to a given task."[9] For experts, undergraduate-level synthesis questions are trivial exercises that can be accomplished quickly and with little thought; a suitable answer simply "comes" to them. For students, the same questions are problems; they are often daunting and require much effort. We ultimately planned to develop associated learning opportunities

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for students, including instructional models and learning activities.[10]

Further, we analyzed *novices' successful* versus *unsuccessful* answers to these problems rather than comparing experts to novices. Comparing among novices was more appropriate for our purposes, as previous research has found that "successful problem solvers often share more procedural characteristics that distinguish them from unsuccessful subjects than do experts when compared to novices."[11] To compare experts' and novices' problem-solving processes, Randles and Overton designed questions that would serve as problems to both experts and novices while being achievable by both groups.[12] This approach would be very difficult specifically for synthesis problems, because the level of target complexity required to provide a problem to an expert would be next to impossible for a novice.

Some problem-solving models describe a methodical stepwise approach,[13−15] such as Woods' six-step strategy that suggested the solver: (1) Engage (decide that you are capable of and willing to solve the problem); (2) Define the problem; (3) Explore and research; (4) Plan a solution; (5) Solve the problem; and (6) Evaluate the solution.[16] In a means-ends analysis, the solver compares the current situation with the goals and identifies the differences between them, then sets subgoals to reduce the differences. The solver performs operations to achieve the subgoal, repeating the process until the goal is achieved.[17] Wheatley's model stresses that problem-solving is nonlinear in nature, and generally involves considerable trial-and-error, taking useful gains from each trial then moving on.[13] Bodner emphasized the anarchistic nature of Wheatley's model and demonstrated the difference between how experts actually solve problems and what they tell students to do.[18] We believe that Wheatley's model is an essential component of synthesis. Scientists face trial-and-error situations regularly. For example, a chemist might rationally design a synthesis only to have it fail in the laboratory, resulting in years of redesign and experimental work; taxol[19] and quinine[20] are classic examples. We hypothesize that chemistry knowledge and relevant strategies combined with this model could lead to student success.

Regardless of the problem-solving model used, a key phase in the process is the very beginning,[1] in which the relevant information is disembedded from the question and the problem is restructured.[21,22] Bowen and Bodner demonstrated that "One of the most important strategic decisions in solving problems is the representational system to use for a given thought about a task at hand. This choice greatly affects the success of any phase of problem solving."[13] Successful chemistry problem-solvers draw preliminary structures to explore solutions.[9] Although all these frameworks can provide general problem-solving strategies, they to not give domain-specific ones (except the last).

Some frameworks have been identified specifically for approaching synthesis problems. A problem-solver could construct a representational system, which is "a collection of structures and processes that allows a problem solver to construct a solution and communicate it to others."[23] For example, Bowen described verbal, pictorial, and methodological representational systems;[23] Kraft, Strickland, and Bhattacharyya described case-based, rules-based, and models-based reasoning used by students;[24] and representation mapping has been used to capture abstraction in problem-solving in various chemistry courses, including on organic chemistry.[25]

These synthesis frameworks could be essential for analyzing a process and solution at an abstract and higher level; however, concrete strategies may scaffold students' problem-solving in the early stages. Concrete strategies can be more easily applied by novices starting with worked examples,[10] then moving to opportunities for deliberate practice with feedback.[6] This approach may be effective in scaffolding student learning.

■ THEORETICAL FRAMEWORK

Theory of Meaningful Learning

Our research is based on Ausubel and Novak's theory of meaningful learning.[26] For meaningful learning to occur, the learner must possess prerequisite knowledge with which to anchor the new knowledge. This new knowledge must be perceived by the learner as relevant to other knowledge, and must contain significant concepts and propositions. Furthermore, the learner must consciously choose to relate the new knowledge to previous knowledge in some nontrivial way. The quality of the frameworks that are used to relate knowledge is one of the primary limiting factors in problem-solving.[26] In addition, Domin and Bodner found that successful problem solving depended on the accuracy, abstractness, and completeness of the representational systems that the problem-solver constructed.[27]

The successful problem-solver integrates their knowledge surrounding the task at hand. They accomplish this by forming a representational system that activates an appropriate schema.[26] A schema is a structure that organizes large amounts of information into a meaningful system, which can include generalized knowledge about situations, well-ordered sequences, and procedures.[17] The solver must be capable of (i) integrative reconciliation—linking concepts in nonarbitrary ways— and (ii) progressive differentiation—seeing concepts in new relationships.[28] With these skills, the meaningful learning can be achieved. Because synthesis and retrosynthesis skills are so new to students and have peculiarities specific to organic chemistry,[7] novice students likely do not have an existing schema to activate and may struggle to develop an appropriately meaningful one.

We sought to determine the problem-solving strategies that have the strongest association with a novice's success and how those strategies can be used in concert in a meaningful way. We planned to look for evidence of the knowledge students brought and used in the task, what type of knowledge they identified (e.g., whether it was relevant to the problem or not) and how students linked knowledge and strategies together (i.e., activated an appropriate schema).

In pursuit of our goal, we addressed the following research questions:

1. What problem-solving strategies do undergraduate students use when solving synthesis-type problems? Are these strategies used correctly/as intended?
2. What strategies have the highest association with successful answers? What relationships exist between these strategies?

■ METHODOLOGY

Setting and Course

This research was conducted in Organic Chemistry II courses taught at a large, research-intensive Canadian university. Organic Chemistry II is the students' second semester of

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organic chemistry. Organic Chemistry I is offered in the winter semester of students' first year of their studies and Organic Chemistry II is offered in the summer and fall. Students can take these courses in English or French.

Organic Chemistry II is a 12-week course consisting of two weekly classes (1.5 h each, mandatory, lecture, or flipped format)[29] and a tutorial session (1.5 h, optional, also called a recitation or discussion group). Assessment for the course is generally comprised of two midterms, a final exam, online homework assignments, and class participation using a classroom response system.[30] The course is composed of ∼75% Faculty of Science students, ∼17% Faculty of Health Sciences students, and ∼8% students from other faculties. A new curriculum has been used in the courses since 2012;[31] The topics taught in Organic Chemistry I and II include:

- Structure, properties, stereochemistry, and conformational analysis of organic compounds
- IR and ^{1}H NMR spectroscopy
- Electron-pushing formalism/symbolism
- Acid−base chemistry
- π bond electrophiles (e.g., 1,2-carbonyl addition reactions, acetals and imine formation, addition−elimination reactions, etc.)
- π bond nucleophiles
- Aromaticity and electrophilic aromatic substitution
- S_N1, S_N2, E1, E2
- α-carbons as nucleophiles (e.g., aldol condensation, alkylation)

We analyzed exams from six course sections, A−F; the results from Courses A and B are described in depth herein (Table 1).

Table 1. Summary of Data Sources

Course Code	Instructor	Semester	Enrollment	Response Rate
A	W	Fall 2011	385	385[a]
B	X	Fall 2012	801	109

[a]IRB approval for secondary use of data; all exams were analyzed.

The professor in Course A taught students to use strategies including brainstorming, identifying atoms added/removed, bonds broken/formed, regiochemistry and stereochemistry, and retrosynthetic analysis. In that course, they were not explicitly taught to use a reaction mechanism to solve synthesis questions. To practice, students had numerous, scaffolded, in-class and out-of-class synthesis activities,[6] all with feedback and answers provided; one full class was dedicated to synthesis and a few other classes included synthesis questions. The professor in Course B explained the synthetic routes to target compounds during a few classes over the semester and provided many problem-set questions (e.g., propose a synthesis of x from y), with answers.

Participants and Data Collection

The authors' Institutional Review Board (IRB) reviewed and approved all phases of this research for human subject research; participants provided informed consent as required by the IRB. To protect participants' identities herein, pseudonyms have been used and the authors digitally recopied exemplars of students' answers.

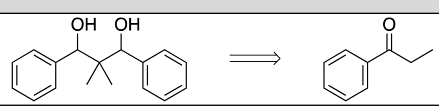
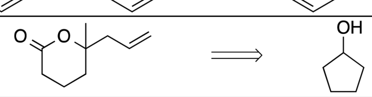
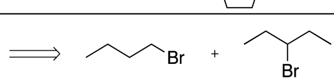
Data sources included answers to final exam questions from 2011−2014 (Table 1). Low response rates in Course B are likely because students were asked for consent two years after completing the course and without any incentive to respond. We are unable to comment on participants' profiles because the IRB approval for Course B only permitted us to examine students' synthesis answers themselves, not the students' grades in the course.

We analyzed different questions on four other courses' exams (Courses D−F) and confirmed that theoretical saturation had been reached.[32] These data sources are summarized in the Supporting Information (SI). That is, our existing coding system could be used on different question types and new codes did not emerge.

Exam Questions

On synthesis questions, students were given the target molecule, at least one starting material, and, sometimes, additional instructions (Table 2). For example, in some questions, students had to provide a brainstorming and analysis plus their proposed synthetic pathway. A brainstorming should consist of all sorts of ideas—right, wrong, and crazy—marked for containing a minimum number of ideas, not correctness. On Question A, students received one mark per idea, for a maximum of two marks. An analysis would consist of well-defined elements and problem-solving strategies, such as identifying the atoms added or removed during the synthesis, bonds broken and formed, regiochemical and stereochemical considerations. Students in Course A were asked to identify stereochemical relationships in a question when appropriate. We coded for these relationships but they were not relevant for the problems in this study. On Question A, the analysis section was marked for correctness. In the other questions, no marks were awarded for brainstorming or analysis.

Table 2. Synthesis Questions Analyzed in This Study and Their Requirements

Course code and question number	Synthetic problem	Requirements (in addition to a proposed synthesis)
A		• Brainstorming • Analysis
B1		
B2	3-ethyl-3-heptene ⟹ 	• Brainstorming • Analysis • Use Wittig reaction

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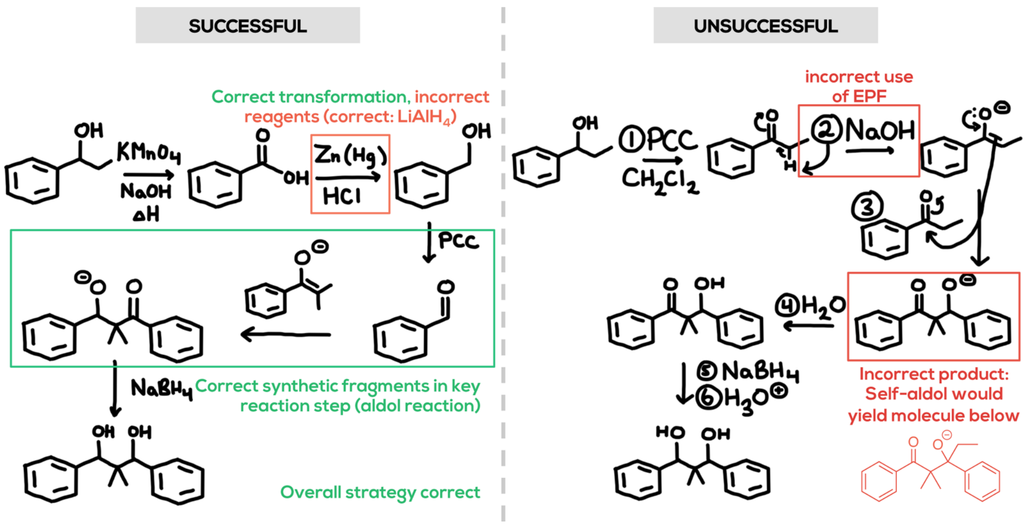

Figure 1. Examples of answer classification. Question A. EPF = electron-pushing formalism.

Methodological Framework: Constructivist Grounded Theory (GT)

We originally began our study by conducting a content analysis based on previous research[23] but found that this procedure did not answer our research questions. We then restarted the analysis using a constructivist grounded theory (GT) framework.[26] Grounded theory studies are inductive in nature; conclusions emerge from the data rather than from the preconceived ideas of the researcher. The constructivist derivative of GT emphasizes the subjective relationship between the researcher and the data.[27] Acknowledging this relationship is important in the context of our theoretical framework, because both of these frameworks emphasize that all human knowledge is constructed based on experience.[26] This approach is in contrast to classic methods of grounded theory, which describe the researcher's role as that of a "neutral observer" and have been criticized for being "overly positivistic"[33] (i.e., unrealistically objective). In both approaches, grounded theory provides a systematic method to analyze the data, adding rigor to the process.[32]

The constructivist GT approach to data analysis stresses two interrelated roles of the researcher: bridling and theoretical sensitivity. Bridling is a metaphor to horseback riding used to describe the "reigning in" or management of preconceptions relevant to the research questions.[34] Theoretical sensitivity is the ability to use one's experience to see how data is relevant to the research questions.[33] While our analysis was informed by the literature and by our own experiences, these concepts provided us with a framework to be thorough in our interpretation of data while still being objective in the conclusions we drew from our analysis.

First, we coded students' written answers to synthesis questions on exams for strategies and errors. To do so, we used the hierarchical coding system of the constant comparative method of analysis, which is typical of studies using a grounded theory approach.[35] The first author openly coded all the exams and the second author coded a subset for four different categories (atoms added, mechanism use, bonds formed, and regiochemistry). In total, 90% of codes matched between raters ($N = 60$). Krippendorff's α values for the respective categories above ($N = 15$ for each category)[36] were 0.779, 0.869, 0.896, and 0.798, which are all close to or above the suggested threshold for inter-rater reliability of 0.80.[37] For the codes that did not match between raters, one researcher's codes were retained for consistency.

We then analyzed the codes to identify core categories (i.e., the focused coding stage).[33] The core categories were those most strongly associated with a plausible synthesis pathway and involved problem-solving strategies that (1) informed successful solutions rather than confounding them (i.e., leading the problem-solver astray) and (2) were frequently associated with successful answers and usually absent from unsuccessful answers. Finally, we identified relationships between strategies that seemed beneficial (i.e., the axial coding stage). The theory of meaningful learning informed this final stage and guided our conclusions.

For the comparisons we made between the use of strategies by successful and unsuccessful students, we performed chi-square tests of independence[38] to determine the probability that the groups were significantly different and calculated Cramér's V (φ_c) to determine effect size.[39] We performed t-tests when comparing the mean number of strategies used between different course groups.[38] We calculated Cohen's d values to determine effect sizes for the t-tests.[40]

Distinguishing Successful versus Unsuccessful Solutions

We distinguished between *successful* and *unsuccessful* problem solving in our analysis instead of using the *expert/novice*

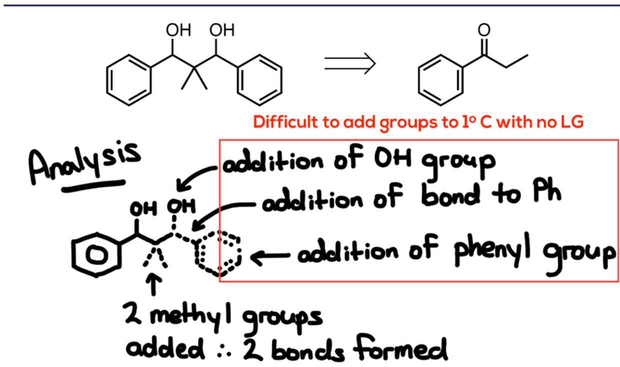

Figure 2. This analysis of bonds formed and atoms added was coded incorrect, because it is highly implausible that it would inform a viable synthesis pathway. LG = leaving group. Question A.

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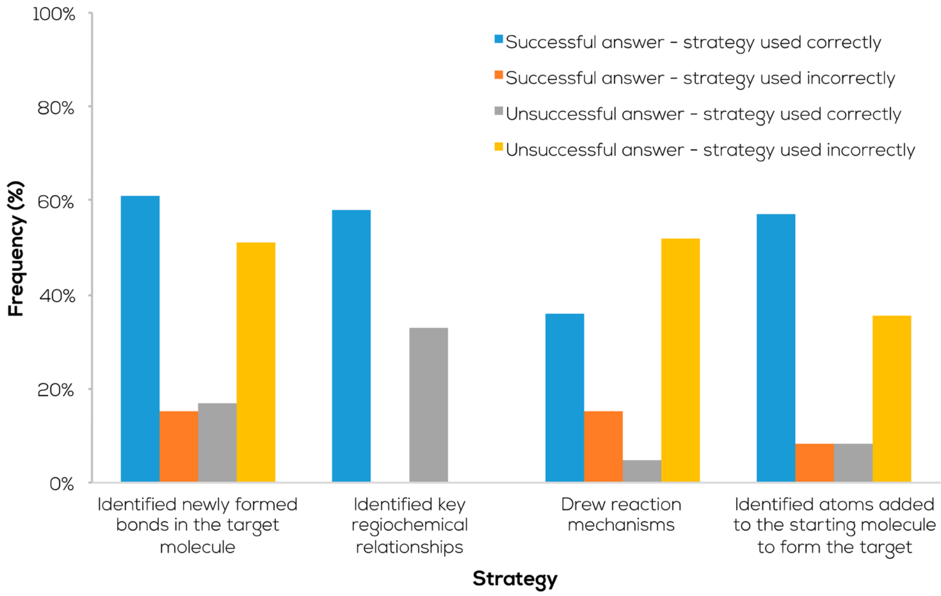

Figure 3. Students' use of key problem-solving strategies when solving Question A (N = 324; 133 successful, 191 unsuccessful).

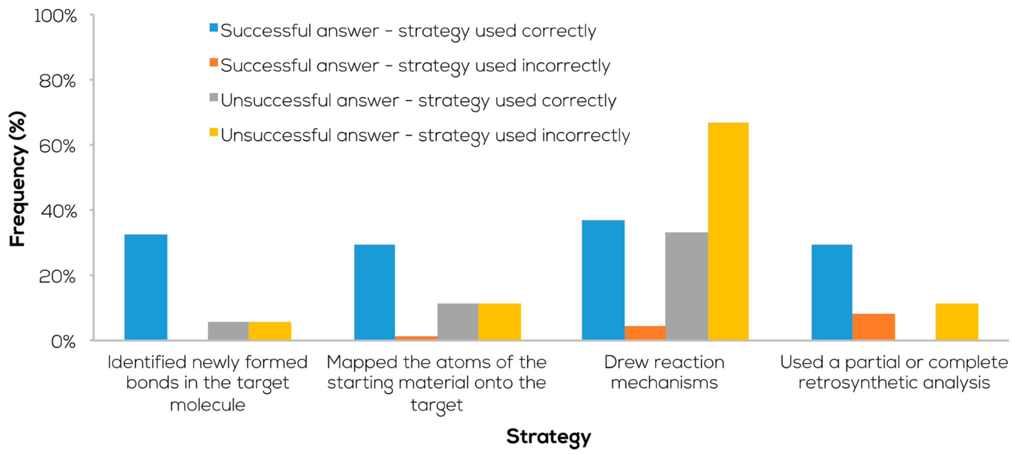

Figure 4. Key problem-solving strategies found in answers to Question B2 (N = 89; 71 successful, 18 unsuccessful).

distinction,[9,25] because the participants in our study were all novices. We also focused more on the problems' solutions than on the individual solving the problem.

After coding the exams for specific strategies and errors, we categorized answers to synthesis problems as successful or unsuccessful. Successful answers contained a correct (or at least plausible) synthetic proposal and could have minor errors; unsuccessful answers had major synthetic errors, such as missing or incorrectly proposing a key reaction step.

The left-hand side of Figure 1 shows an example of a successful answer. In the second step of the synthetic pathway, the student proposed the wrong reagent to produce the next intermediate. However, this error is relatively minor. In contrast, the answer shown on the right-hand side of Figure 1 contains synthetic fragments with the incorrect number of carbons. This second answer was classified as unsuccessful because the student proposed unsuitable synthetic fragments in a key reaction step.

Correct versus Incorrect Use of Problem-Solving Strategies

We also distinguished between the correct and incorrect use of problem-solving strategies (e.g., mapping atoms). A correctly used strategy generated information or insight that led toward the correct answer, while an incorrectly used strategy made finding the correct answer difficult or impossible.[9] For example, the analysis in Figure 2 incorrectly used problem-solving strategies (identifying bonds and atoms added/removed). The student redrew the starting material and used dotted lines to show the atoms and bonds that would be added to that molecule to make the target structure. Although the additions make the correct product, the transformations shown could not be readily be accomplished in a laboratory.

We applied the same coding system to the analysis of each synthesis problem, with slight variation to define the appropriate use of the codes in each question; for example, unique regiochemical analysis was required to solve each problem. The full coding system can be found in the Supporting Information (SI).

Limitations and Other Considerations

Because we only had students' exam artifacts for analysis, we could only analyze clearly defined brainstorming and analysis that students *wrote down*. It is likely that there were meaningful unwritten components to students' answers, as previous research has found that students appear to do more brainstorming "in their heads" rather than writing it on paper.[41]

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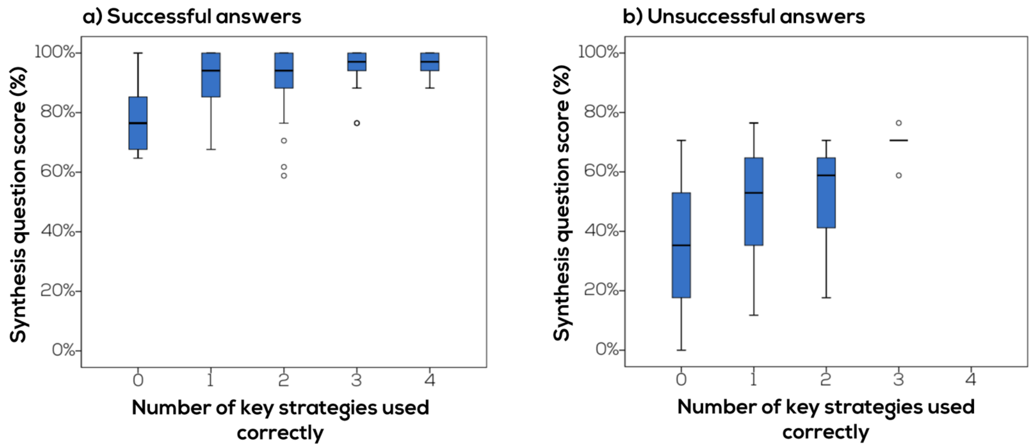

Figure 5. Association between students' scores (%) on Question A with the number of key strategies observed in their brainstorming and analysis for (a) successful and (b) unsuccessful answers.

We removed incomplete responses from the data set because there is no way of knowing why a few students did not provide a complete answer. They may have been limited by other factors, such as time constraints, or did not know how to approach the question. We believe this provides an increase in the quality of the analyzed data that outweighs the small loss in sample size.

There are many aspects to synthesis that we have not addressed in this study, such as analyzing students' answers for practicality, cost, or safety. Most of the synthetic targets are quite small, and we expect students to have trouble identifying side reactions or seeing the molecule as a whole as indicated by previous research.[1,7,42]

RESULTS AND DISCUSSION

Strategies Used in Successful versus Unsuccessful Problem Solving

We first analyzed strategies associated with successful answers compared to unsuccessful answers (Figures 3 and 4), including whether the strategies were used correctly or incorrectly. The Supporting Information contains data for other problem solving strategies that were observed but had little or no association with success. Students' answers revealed six strategies that were more often associated with successful answers than unsuccessful answers:

- Identified newly formed bonds in the target molecule
- Identified atoms added to the starting molecule to form the target
- Identified key regiochemical relationships
- Mapped the atoms of the starting material onto the target
- Used a partial or complete retrosynthetic analysis
- Drew reaction mechanisms

Some answers were not successful although they used a correct strategy. Clearly, using a strategy correctly was not always sufficient to achieve success, although the answer typically had at least portions of the synthesis achieved correctly. For example, many answers (74) that proposed a self-aldol condensation were deemed unsuccessful, although the rest of the synthesis was successful. However, students' scores trended higher when more strategies were used, regardless of whether they were successful or not (Figure 5). The box plots depict univariate, nonparametric numerical data through their quartiles, where the box itself represents the interquartile range (IQR). The line inside the box represents the second quartile (median); the top and bottom of the box represent the first and third quartiles. The caps on the lines extending from the boxes (fences) represent the maxima and minima of the data sets, except in cases where outliers are present. Outliers are defined as values that are either 1.5 times smaller or larger than the IQR,[43] and are plotted as individual points (circles).

The average number of key strategies used per successful student was significantly higher on answers to question A than question B2, $t(156.9) = 5.742$, $p < 0.001$, with a large effect size, $d = 0.83$ (Figure 6). This was likely because the instructor of

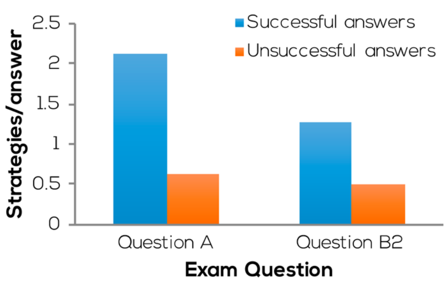

Figure 6. Number of key problem-solving strategies used correctly per answer to Questions A (N = 324; 133 successful, 191 unsuccessful) and B2 (N = 89; 71 successful, 18 unsuccessful).

course A had an increased focus on teaching synthetic problem-solving strategies. In spite of different teaching methodologies, some of the same key strategies were observed in both courses.

The vast majority of successful answers demonstrated at least one of the key strategies (Figure 7)—89% for Question A and 82% for Question B2. 35% of successful answers demonstrated three or four strategies, while only 6% of successful answers did not demonstrate any of the key strategies. Half of the unsuccessful answers did not show evidence of using any of the key strategies.

The difference in how many strategies successful students used correctly was statistically significant for both Question A, χ^2 (4) = 147.8, $p < 0.001$, with a moderate practical significance, $\varphi_c = 0.34$, and for Question B2, χ^2 (4) = 20.73, $p < 0.001$, with a moderate practical significance, $\varphi_c = 0.24$. These values could be incomplete because students might have used one of those strategies—or different ones—mentally. However, we hypothesize that explicitly constructing a pictorial representation using

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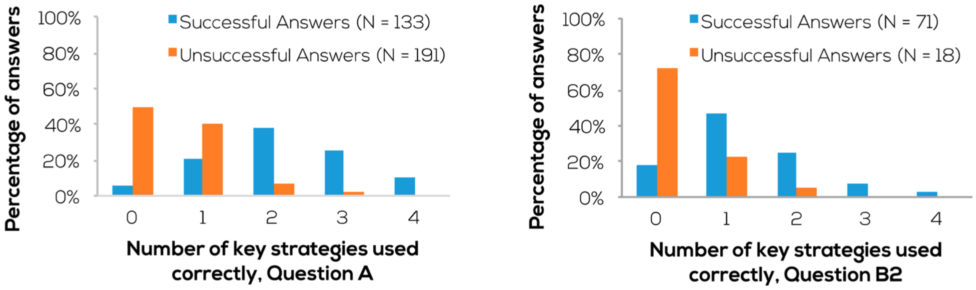

Figure 7. Number of key strategies used correctly in successful and unsuccessful answers to Questions A (N = 324) and B2 (N = 99).

these strategies makes the synthetic design process more meaningful to the problem-solver than using the strategies mentally.

Bond-Forming Analysis

The first strategy—identifying bonds formed in the target molecule—had the largest discrepancy between correct use in successful answers and incorrect/implausible use in unsuccessful answers; the difference was statistically significant for both Question A, χ^2 (1) = 70.27, $p < 0.001$, with a moderate practical significance, φ_c = 0.55, and Question B2, χ^2 (1) = 11.98, $p <$ 0.001, with a moderate to large practical significance, φ_c = 0.69. On Question A, 61% of successful answers employed this strategy correctly, while 51% of unsuccessful answers employed this strategy incorrectly. Similar trends are observed for Question B2.

Incorrectly identifying sites of bond formation can lead to unsuitable synthetic fragments. The site of bond formation was incorrectly identified in 17% of unsuccessful answers to Question A (Figure 8); in those answers, 1-phenylpropan-1-one was identified as the starting material to make the target diketone.

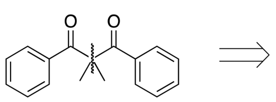

Figure 8. Incorrect identification of bond formation sites: 17% of answers to Question A identified 1-phenylpropan-1-one as the starting material to make the target diketone based on this specific error in bond-forming site analysis.

Regiochemical Analysis

The product in question A (Table 2) arose from an aldol reaction following by functional group modification. Every answer that identified the 1,3-relationship between the oxygen atoms in the product did so correctly, including answers that were ultimately unsuccessful. This was a relatively easy relationship to recognize and map[1,6] because this common reaction was one of the last ones learned in the course, and so it is not a surprise that all students were able to do so correctly. Thus, by itself, the regiochemical analysis strategy does not provide enough information to solve the problem and seems far more useful when other strategies are also used (Figure 9). For example, unsuccessful students may still be able to memorize the association between a 1,3-diol and an aldol reaction (i.e., rote learning), but without fully understanding how to use that information in designing a synthesis (which would require meaningful learning[9] to have occurred).

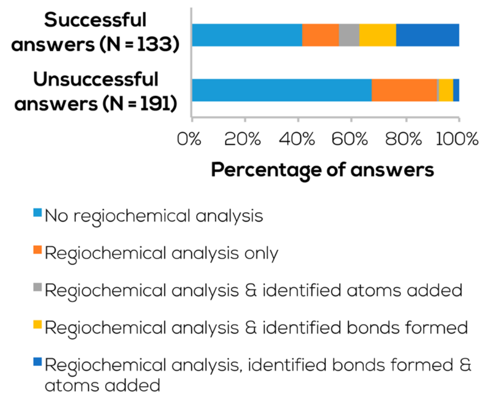

Figure 9. Students' use of a regiochemical analysis with and without other key problem-solving strategies. Strategies were only counted when used correctly. Question A (N = 324).

Few answers (5%) contained a regiochemical analysis when not prompted to do so, such as Questions B1 and B2; these syntheses also did not involve an aldol reaction.

Mapping Analysis

Mapping carbon atoms was a common strategy in answers to Question B2. Students typically mapped the atoms of each starting material within the target by highlighting the corresponding atoms, much like the example in Figure 10. This strategy was used in successful answers significantly more often than in unsuccessful answers, χ^2 (1) = 6.851, p = 0.009, with a moderate practical significance, φ_c = 0.51.

In answers to Question A, carbon atoms were often numbered consistently between the starting material and product, but no explicit link was made (Figure 11). Students were likely mapping atoms and electrons between starting materials and products, which likely directed their synthesis, although we cannot be sure without more information. A stronger correlation existed between the consistent numbering of these atoms and successful answers, χ^2 (2) = 17.039, $p <$ 0.001, but with a small practical significance, φ_c = 0.162. Furthermore, there was not always sufficient evidence (e.g., a written purpose statement by the student in their brainstorming and analysis) to establish any meaningful purpose behind this numbering. However, based on the strong practical significance of mapping atoms that was observed in question B2, numbering atoms could also be an effective strategy for mapping carbons if students made an explicit link between the starting materials and products.

Retrosynthetic Analysis

In successful answers to Question B2, retrosynthetic analyses were commonly shown (30%), although not required. Statistically, the use of this analysis by successful students was

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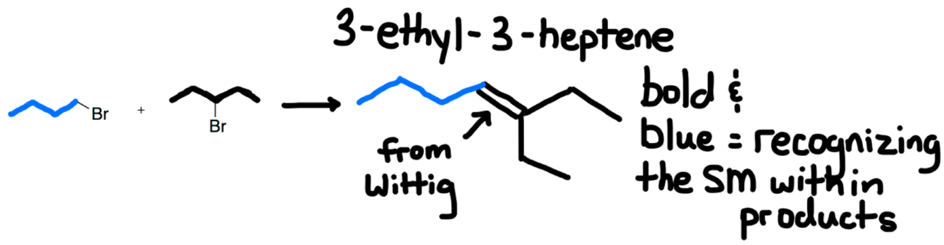

Figure 10. Some students used a color-coding system to map carbons. Question B2.

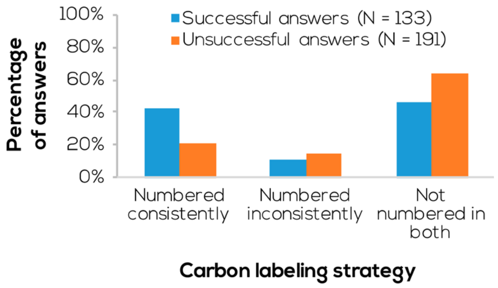

Figure 11. Methods by which carbon atoms were labeled between the starting material and product of Question A (N = 324).

significantly different from its use by unsuccessful students, χ^2 (1) = 5.639, p = 0.018, with a moderate practical significance, φ_c = 0.441. These answers typically did not explicitly show bonds formed/broken or atoms added/removed; students chose to only show the resulting synthetic intermediates from each disconnection. Because these strategies (i.e., bonds broken/formed and atoms added/removed) are implicitly required to perform a retrosynthetic analysis, students who did not use these strategies elsewhere most likely did this analysis mentally rather than writing it out on paper.

One possible source of error in the retrosynthetic disconnections made in the responses to question B2 is that those students are "splitting atoms" rather than breaking bonds, as in the example in Figure 8. Requiring that students explicitly show bonds formed/broken or atoms added/removed could be advantageous to avoid situations in which students make implausible disconnections because of their inability to correctly visualize the bonds and atoms at each step. Many answers to Question A1 did not have a retrosynthetic analysis (and it was not explicitly required), perhaps because they had to explicitly show bonding changes.

Knowledge of Reactions Alone Is Not Enough to Be Successful

The difference in the reaction types named in successful and unsuccessful answers was statistically significant, χ^2 (6) = 54.75, p < 0.001, with a small practical significance, φ_c = 0.168. There were many cases where an incorrect answer demonstrated students' knowledge of reactions but an inability to use that knowledge effectively. For example, the majority of unsuccessful answers to Question A (60%) had an aldol reaction drawn or named (Figure 12) in their brainstorming and analysis.

A self-aldol condensation (Figure 13) began based on the idea that the two starting ketones could fuse to form the product; the student incorrectly analyzed bond-formation as shown in Figure 8. However, the student's answer correctly identified that this error would lead to the wrong product (using a mechanism), and constructed a correct solution via trial and error with new reactants.

This student clearly had a grasp on all the reactions learned in the course that were relevant to this problem. They could not initially use those reactions because of their incorrect initial representation of the problem, but they could do so after further analysis. This trend was relatively common—in which further analysis allowed students to produce successful answers despite an unsuccessful initial attempt. Students who took more than one attempt to solve the problem produced successful answers more often than not (Figure 14), likely because of more frequent use of the aforementioned key strategies than students who did not produce successful answers.

These results show how reflecting upon previous steps of the problem-solving process, as most models suggest, may also increase one's chances of success, especially if the problem-solver has well-defined strategies for performing the initial stages of their analysis.

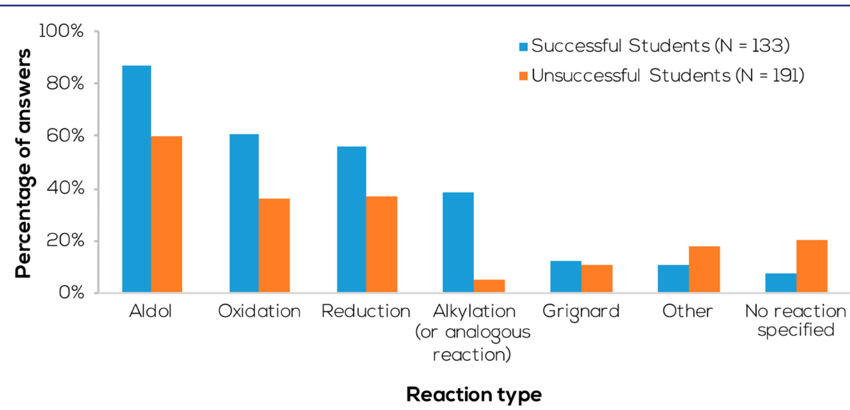

Figure 12. Trends in the reaction types found in the brainstorming and analysis sections of Question A (N = 324).

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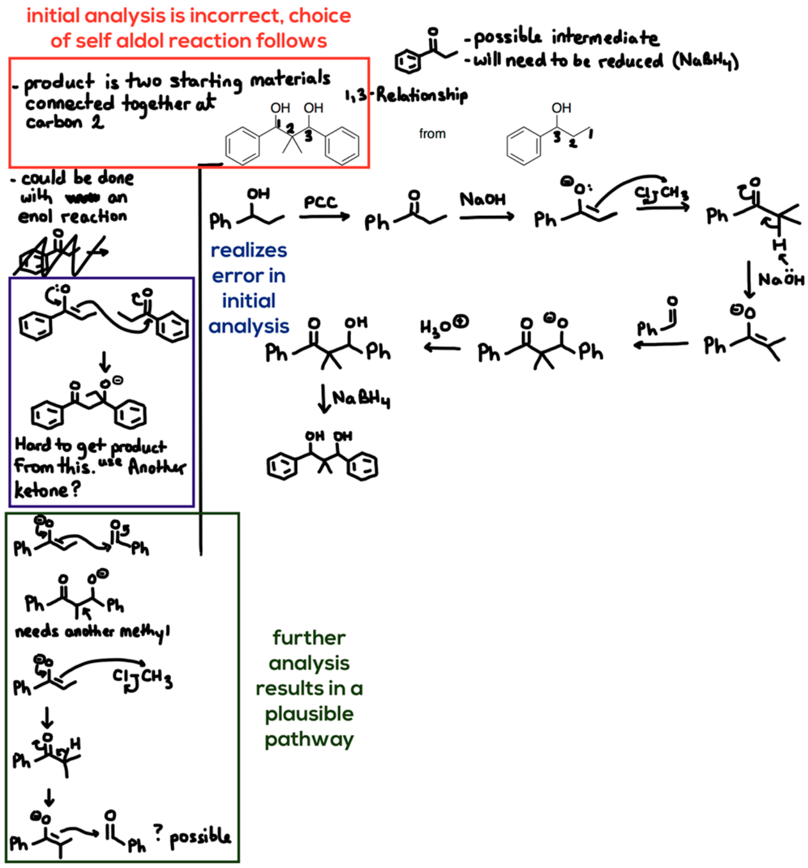

Figure 13. A self-aldol condensation was drawn first, then the student identified that this would not work. He/she then continued working—on paper and using a mechanism—to ultimately correctly solve the problem. Question A.

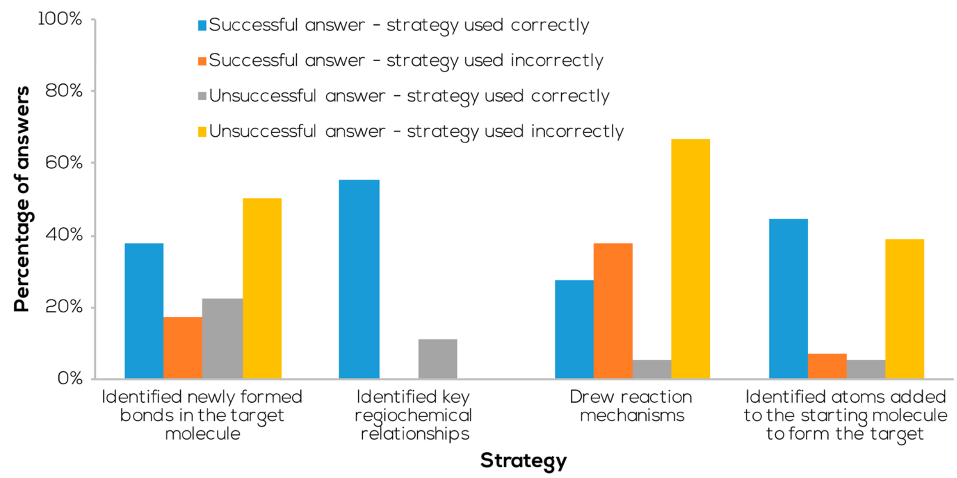

Figure 14. Key problem-solving strategies in answers with more than one attempt on Question A. The distinction between correct/incorrect use of a strategy is based on the final attempt to solve the problem (N = 45; 29 successful, 17 unsuccessful).

Benefit to Prompting Students to Provide Their Analysis

Our results showed that proposed synthetic pathways are more likely to be successful when multiple strategies are used (i.e., written down) in concert. Students were less likely to write down their strategies when they were not explicitly prompted to do so (e.g., Table 3, Question B1). Students more often produced a successful answer when they construct verbal and pictorial representations of the problem rather than attempting to visualize a solution mentally. There seems to be a benefit to prompting students to provide their analysis and teaching students how to do such an analysis.

The large difference in successful answers to Questions B1 and B2 was associated with a large difference in the amount of brainstorming and analysis demonstrated in the answers (Table 3). Question B1 did not contain a prompt to provide analysis; Question B2 did. Students probably did brainstorm when problem-solving but did so mentally rather than writing any of it down. In contrast to answers to question B2, there was no written brainstorming or analysis in a high proportion of

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Table 3. Association between the Use of Well-Defined Strategies and Successful Answers to the Synthesis Questions on Exam B

Question	Analysis Rate[a]	Success Rate
B1 (did not contain a prompt to write down analysis)	57%	42%
B2 (contained prompt to write down analysis)	93%	66%

[a]Refers to students who used at least one well-defined strategy in their analysis.

successful answers to Question B1 (49%). Question B1 could just be an easier problem or perhaps writing ideas down is unnecessary. However, students are not likely capable of visualizing an entire synthesis. In either case, writing down the brainstorming and analysis does not seem detrimental.

A question remains: Why did some students not use the key strategies, especially in Course A when most of the strategies were explicitly taught? Perhaps the students did not find the strategies to be meaningful, and as such, chose not to use them. Alternatively, perhaps they did not use the strategies because they were not comfortable with the symbolism required, such as deriving the meaning of the connectivity of atoms in a line structure, as we observed in many cases such as Figure 8, as have others.[18,44]

We were also surprised by the low number of answers with evidence of multiple attempts (i.e., evidence of using a trial-and-error strategy): only 47 on question A, 8 on question B1, and 8 on question B2 (only answers with complete solutions were considered). We are concerned that students believe they have to produce a correct answer the first time and that "trial and error is not legitimate strategy."[18]

Analysis of the Data from Smaller Sample Sizes Added No New Information

While any results obtained from analyzing Exams C−E (SI) would be less reliable because of smaller sample sizes, the data obtained from these sections did not add anything to our findings; any large discrepancies between the use of strategies that had already been identified in that earlier analysis. Furthermore, there was little evidence of any brainstorming and analysis. Analysis of these questions was still beneficial, as it helped to ensure that our analysis had reached theoretical saturation, where further analysis would have nothing to add.

■ APPLICATION TO PRACTICE

All the key strategies can be used in concert to form a quality pictorial representation of any given synthesis problem. An example is presented in Figure 15 where key strategies are combined into a rich retrosynthetic analysis. We feel that these strategies should be used in concert, because certain strategies are likely implicit elements of others; for instance, identifying the atoms added or removed is likely an implicit element of mapping. Reaction mechanisms are also encouraged to "check one's work" in the solution. Students can use many methods to make the strategies meaningful to them, including colors, letters, numbers, or symbols. For instance, we used letters to map atoms in the problem in Figure 15, arrows (i.e., symbols) to identify bonds formed and broken, and numbers to perform

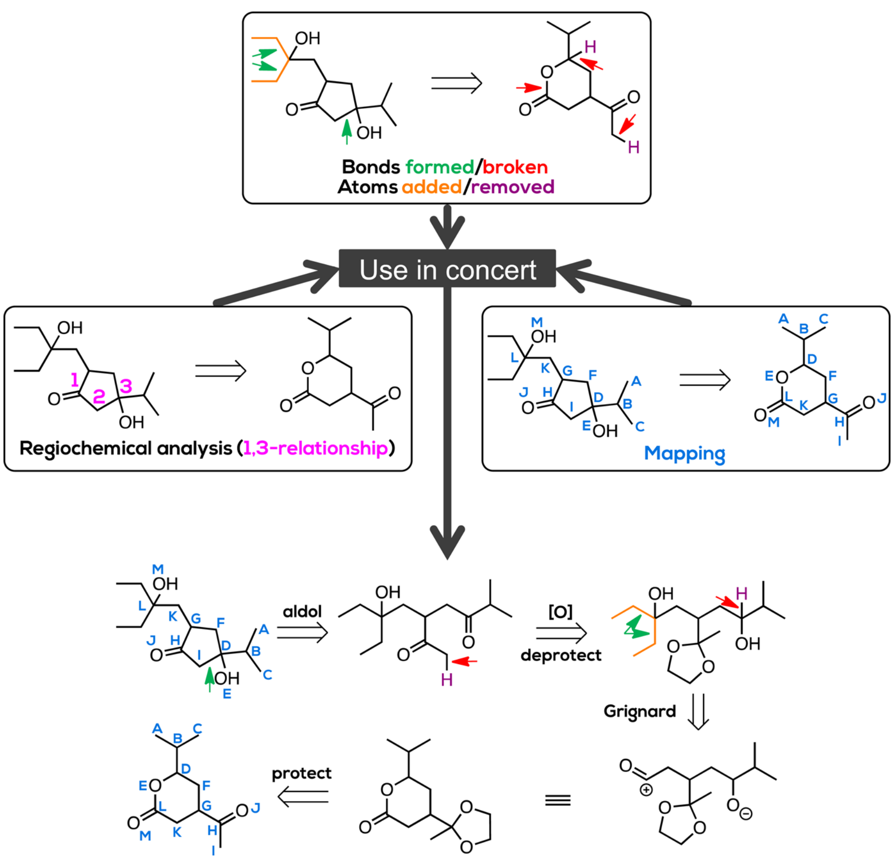

Figure 15. Key strategies can be used in concert to form a representational framework. The information from each individual strategy complements the information derived from the others to construct a retrosynthetic analysis of the problem.

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a regiochemical analysis. Additional or fewer strategies could be used as long as they are meaningful to the problem-solver.

CONCLUSIONS AND IMPLICATIONS FOR INSTRUCTION

In this study, we investigated two research questions:

1. What problem-solving strategies do undergraduate students use when solving synthesis-type problems? Are these strategies used correctly/as intended?
2. What strategies have the highest association with successful answers? What relationships exist between these strategies?

Our results revealed six key problem-solving strategies that were most often associated with successful answers, in which the solver:

- Identified newly formed bonds in the target molecule
- Identified atoms added to the starting molecule to form the target
- Identified key regiochemical relationships
- Mapped the atoms of the starting material onto the target
- Used a partial or complete retrosynthetic analysis
- Drew reaction mechanisms

When used correctly, these strategies can form a coherent representational framework that has a positive correlation with success rates. The most successful answers used multiple key strategies, likely used in concert with one strategy informing the other. Using strategies in concert is likely an example of integrative reconciliation, an essential component of meaningful learning.

Students need opportunities to observe and practice such problem-solving strategies, in line with models of representational systems[23] and the theory of meaningful learning.[26] For organic synthesis, students can do in- or out-of-class activities to learn and practice using the key strategies.[3,4,6] Such practice, with authentic activities,[7] should help students activate schema that contain relevant and meaningful information.[27] Students with a well-defined approach to solving synthesis problems are also more likely to recognize whether errors are present in their brainstorming and analysis than students who are less thorough in their analysis of the problem.

We designed a synthesis problem set that asks students to employ each of these strategies in a stepwise fashion; it is available in the Supporting Information. This problem set is based on the findings of this paper and future research will be required to study how the set impacts students' problem-solving skill development as well as skill instruction. That said, the pronounced correlation between success and the use of these strategies both individually and in concert shows that these strategies are essential components of synthesis problem solving.

FUTURE WORK

The schemas are activated in association with the representational systems students construct and are an important aspect of problem-solving.[9] Studying students' schemas went beyond the scope of this research.

More study is also needed to understand the effect on instruction on strategy use. Because we analyzed one exam question that required evidence of brainstorming and analysis in a course that included strategy instruction (Course A) and different exam questions in courses that did not have the exam requirements or strategy instruction, we do not yet know the impact of instruction. Future research will also examine students' mental processes while solving synthesis problems.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available on the ACS Publications website at DOI: 10.1021/acs.jchemed.5b00900.

A synthesis problem set, the coding system used to analyze exams, and a description of synthesis questions from other exams that were analyzed but not fully described in this manuscript (PDF, DOCX)

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Notes

The authors declare no competing financial interest.

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