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Gold-Catalyzed Rearrangement of Propargyl Alcohols Using Coupling Constants To Determine Isomeric Ratios

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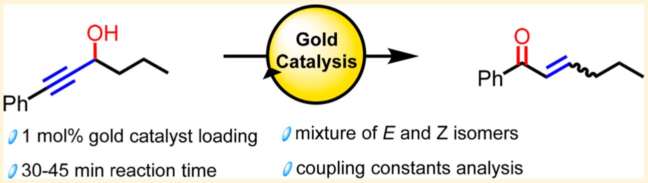
Supporting Information

ABSTRACT: Gold is an increasingly prominent transition metal in organic synthesis. The air-stable, water-insensitive cationic gold(I) catalysts enable varieties of synthetic transformations with a simple reaction setup. However, this increased importance has not coincided with an increase in the application of gold in second-year organic chemistry courses. An experiment is described that includes a gold-catalyzed rearrangement of propargyl alcohols targeted at second-year organic chemistry students. The reaction produces a mixture of *E* and *Z* isomers of an enone product that students analyze by ^{1}H NMR spectroscopy to determine the major product.



KEYWORDS: *Second-Year Undergraduate, Upper-Division Undergraduate, Laboratory Instruction, Organic Chemistry, Inquiry-Based/Discovery Learning, Catalysis, Hands-On Learning/Manipulatives, NMR Spectroscopy*

The past two decades have seen a significant rise in the development of gold catalysis in modern organic synthetic chemistry.[1] Gold(I) or gold(III) complexes have proven to be effective catalysts in many situations due to their soft Lewis acidity that enables the activation of π-bonds toward nucleophilic attack. This is, in part, due to relativistic effects present that cause a contraction of the gold orbitals, allowing gold to form shorter bonds than would be predicted otherwise.[2] Among other types of reactivity, gold and other coinage metals are able to replace toxic mercury in many laboratory settings.[3] While gold has seen many uses in undergraduate organic laboratories, including in the synthesis and functionalization of gold nanoparticles and other inorganic chemistry uses,[4−15] the utility of gold catalysis for organic synthesis has only rarely been included in the second-year undergraduate curriculum. Few undergraduate organic chemistry textbooks mention gold catalysis, and only a small number of experiments featuring gold chemistry have been reported for second-year organic chemistry laboratory. The reported uses include demonstrating the use of a gold(III) salt to replace Hg^{2+} in the hydration of alkynes.[16] In order to highlight the modern use of gold chemistry in organic chemistry, an undergraduate experiment has been designed that is suitable for second-year undergraduate students. This experiment features a gold(I)-catalyzed rearrangement of a propargyl alcohol (Scheme 1) and determination of isomeric ratios through analysis of the ^{1}H NMR spectrum.

■ EXPERIMENT OVERVIEW

The experiment is an adaptation of the Meyer−Schuster rearrangement.[17] Modifications, such as performing the reaction at 60 °C, are made to allow the rearrangement to be carried out within the required time. Most reactions have gone to completion within 30 min of stirring. Thus, the experiment reported herein can be completed in a 3−4 h laboratory setting.

The undergraduate students are generally unfamiliar with gold chemistry, and so, to introduce them to the topic of gold catalysis as it is used in organic synthesis, two videos were prepared (Supporting Information, p S46). These two videos discuss (1) the utility of gold catalysts in modern organic chemistry and the advantages of gold over traditional metals such as mercury, and (2) the mechanism of the gold-catalyzed Meyer−Schuster rearrangement. The videos are prepared using transparent white boards, which allow an instructor to face students during the instruction. This method of lecture preparation has been shown to increase student engagement and learning.[18]

Students work in pairs to perform this experiment. The experimental setup is straightforward. The reagents and the gold catalyst are added to a conical vial that is heated to 60 °C. Students monitor the reaction progress through thin layer chromatography (TLC, Figure 1) and are instructed to stop the reaction upon disappearance of the starting material from their reaction (generally after about 30 min). The product is purified through the use of a pipet column packed with silica gel. No extraction is necessary for this reaction. Students isolate an isomeric mixture of two enone products, check the purity of the product by TLC (Figure 1), obtain an IR spectrum of the mixture, and analyze the results by ^{1}H NMR spectroscopy.[19] Students are not told beforehand which enone geometric isomer is the major product. The analysis includes

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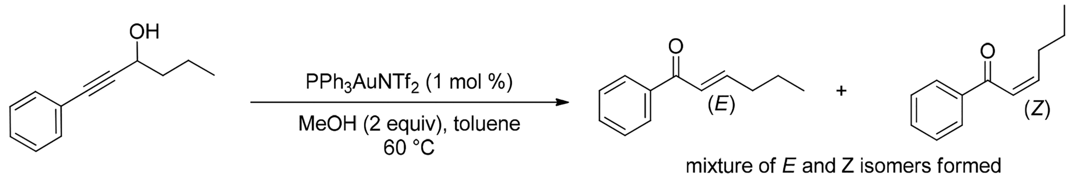
Scheme 1. Synthesis of (*E*)- and (*Z*)-1-Phenyl-2-hexen-1-one



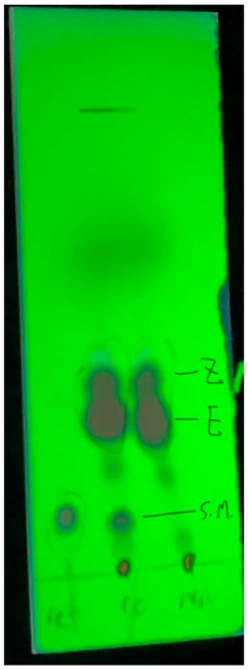


Figure 1. Student obtained TLC plate monitoring the reaction. Labels for starting material (S.M.) and *Z* and *E* products were added afterward for publication.

determining coupling constants to assign the peaks to the correct product structure and using integration to determine the relative ratios of the two products. The alkenic signal region of the ^1H NMR spectroscopy of the product mixture is shown in Figure 2. In this spectrum, the α- and β-hydrogens of the major product are seen at 7.05 and 6.87 ppm. Both of these peaks are doublets of triplets, with the peak on the α-hydrogen showing long-range coupling. The corresponding peaks of the minor product have similar multiplicities and are observed at 6.80 and 6.31 ppm.

■ HAZARDS

All chemistry in this experiment should be performed in the fume hood. 1-Phenyl-1-hexyn-3-ol is a known lachrymator. Toluene and hexane are very hazardous in the case of skin contact and are suspected of damaging fertility or an unborn child. *n*-Hexane (a component of hexanes) is a neurotoxin. Methanol is toxic if swallowed, in contact with skin or inhaled. Ethyl acetate could cause serious eye irritation. Silica gel is an inhalation hazard and may cause lung damage through prolonged or repeated exposure. Deuterated chloroform ($CDCl_3$) is toxic and a suspected cancer agent.

■ EDUCATION ASPECTS

This experiment includes educational aspects that were found to be beneficial to our students. Some of these aspects are reinforcements of principles or techniques learned in previous laboratories, and some (in our curriculum) are unique to this experiment. These include the following:

- An understanding of the role of gold in alkyne activation
- The ability to monitor a reaction by TLC
- Analysis of both IR and NMR spectroscopy
- The use of coupling constants to determine *E*/*Z* stereochemistry

■ RESULTS AND DISCUSSION

The reported experiment has been performed during four different quarters by ~950 students and has been shown to be a dependable lab, as almost every group isolated the desired product mixture. Although the yield varied from 0 to 100%, only 2% of students reported 0% yield and 70% of students reported a yield of 50% or greater. 64% of students were able to complete the lab in 3 h or less, while the remaining students completed the lab in 3.5−4 h.

While the catalyst, PPh_3AuNTf_2, is commercially available from Strem (CAS: 866395-16-6, $300/g), it can be synthesized[20] in one step from the commercially available catalyst precursor PPh_3AuCl at a more economical cost of $100 per gram (Supporting Information, pp S43−S45). Additionally, the catalyst is sufficiently active such that only a small quantity (5.8 mg or 0.005 mmol) is needed. A 0.025 M solution of the catalyst in toluene is prepared for students, which allows them to measure the amount needed and minimizes additional cost due to loss or waste of catalyst. As the reaction progresses, students can clearly see the formation of the two isomers on the TLC plate and are instructed to stop the experiment when all the starting material has been consumed (as measured by TLC).

In analyzing their results, the students noted in their IR spectra (Supporting Information, p S49) the absence of an alcohol O−H stretch at ~3400 cm^{-1} and alkyne stretch at ~2100 cm^{-1}, as well as the appearance of a carbonyl C=O stretch at 1680 cm^{-1}. The appearance of this peak at a lower wavenumber than that of a typical ketone (~1720 cm^{-1}) indicates that the ketone is part of a system in which resonance is present. Taken together, these values support the conclusion that a rearrangement has occurred.

Furthermore, it was found that additional background preparation was necessary for students to perform an analysis of the NMR spectrum. The lab handout (Supporting Information, pp S7−S8) now includes an introduction on finding coupling constants when a signal is split with only one coupling constant, and the worksheet that students complete demonstrates how to find coupling constants when a signal is split by multiple coupling constants. They apply these skills to assign *E*/*Z* stereochemistry of the major and minor products. As time does not allow for an NMR spectrum to be obtained for each student product, sample ^1H and ^{13}C NMR spectra are provided to them (Supporting Information, pp S25−S30).

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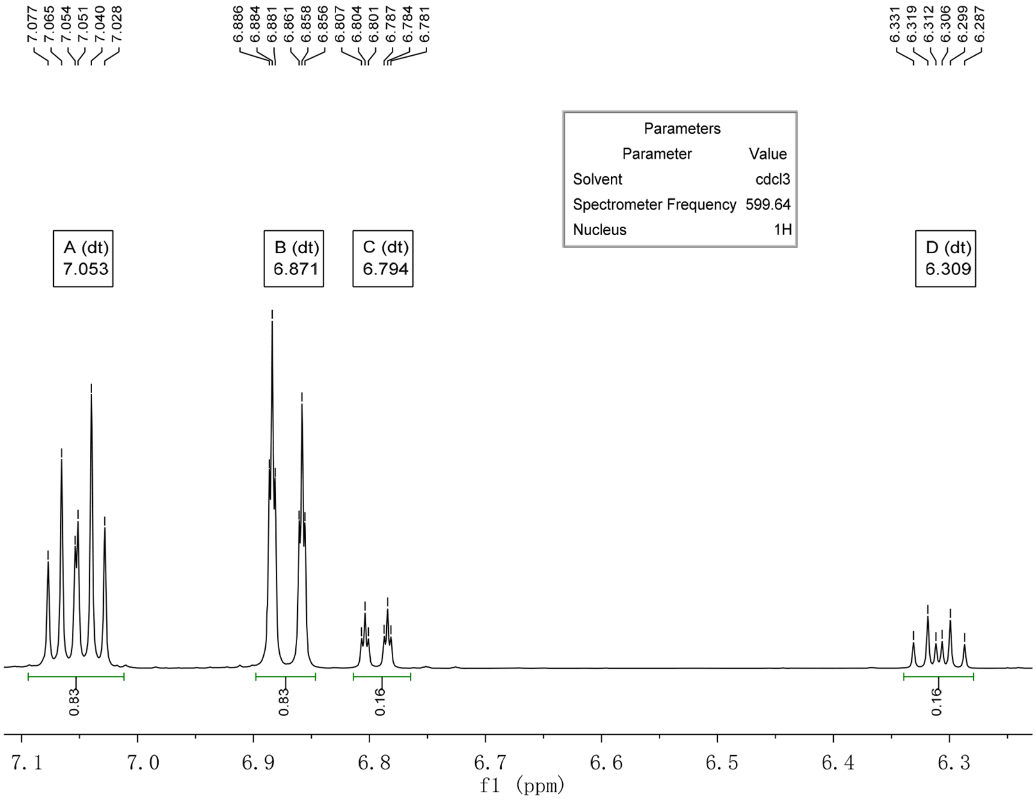

Figure 2. ^{1}H NMR spectroscopy of the product mixture, showing the peaks arising from the enone portion of the molecules.

Samples of student products were collected and were found to contain *E*/*Z* isomeric ratios ranging from 61/39 to 96/4 (Supporting Information, pp S50−S55). These spectra also revealed that at room temperature the *Z* isomer will isomerize to the *E* isomer and that the *E* isomer is stable at room temperature. None of the sample showed the presence of the starting propargyl alcohol in the ^{1}H NMR spectrum.

At the conclusion of this lab, the students completed worksheets in which they were asked to explain the role of gold in this experiment, as well as the advantages of using gold (rather than mercury) in a lab setting, to trace their TLC plates and explain what they learned from them, to explain what peaks in their IR spectra suggested a rearrangement did occur, and to provide a conclusion (based on the provided ^{1}H NMR spectrum) regarding which was the major product (*E* or *Z*) and explaining how the NMR analysis supported this conclusion. Students scored an average of ∼90% on this worksheet. Additionally, as part of the educational assessment for this experiment, the final exam featured questions that tested the students' understanding of coupling constants and splitting diagrams. Of the 175 students tested, 126 students were able to correctly predict that the b-hydrogen on an aliphatic enone would appear as a doublet of triplets. Also, 61% and 64% of students were able to correctly find the coupling constants of a quintet and doublet of triplets, respectively.

■ CONCLUSION

The experiment introduced the students to many concepts that, although important, are generally not covered in-depth (if at all) in second-year organic chemistry lecture courses. These include the use of gold in organic chemistry and its use to replace toxic metals such as mercury, a practical application of coupling constants to find *E*/*Z* isomeric ratios, and a synthetic approach to enones that is complementary to the aldol condensation. The experiment has been performed by over 950 students, can be performed in a 3 or 4 h lab section, and produces the product in good yields.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available on the ACS Publications website at DOI: 10.1021/acs.jchemed.9b00007.

Materials and methods, equipment and supplies, student handout, prelab assignment, postlab assignment, characterization data, and instructor notes (PDF, DOCX)

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Notes

The authors declare no competing financial interest.

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