JOURNAL OF CHEMICAL EDUCATION
Cite This: J. Chem. Educ. XXXX, XXX, XXX−XXX
Laboratory Experiment
pubs.acs.org/jchemeduc

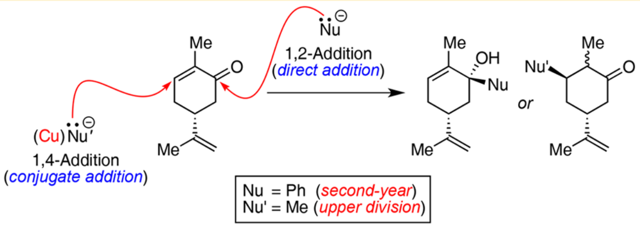
Exploiting Carvone To Demonstrate Both Stereocontrol and Regiocontrol: 1,2- vs 1,4-Addition of Grignard Reagents and Organocuprates

Thai Phat Truong, Sophia J. Bailey, Alexandra E. Golliher, Erika Y. Monroy, Uttar K. Shrestha, and William A. Maio*

Department of Chemistry and Biochemistry, New Mexico State University, Las Cruces, New Mexico 88003, United States

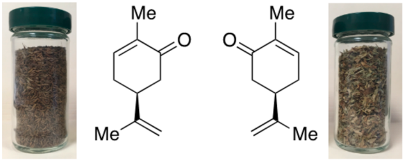
Supporting Information

ABSTRACT: The ability of certain organometallic reagents to react via 1,2- or 1,4-addition to an *α*,*β*-unsaturated ketone is a fundamental example of regioselectivity at the second-year undergraduate organic level. The following two experiments were designed to demonstrate this preference by exploiting carvone as an inexpensive chiral, nonracemic substrate. The first, intended for a typical undergraduate audience, makes use of phenylmagnesium bromide; the second calls for the manufacture of lithium dimethylcuprate from a stock solution of methyl lithium and copper(I) iodide and is envisioned to be carried out by upper-division students. Importantly, due to the chiral nature of carvone, these addition reactions are highly stereoselective and will provide an opportunity for students to revisit stereochemistry. Also discussed are several thoughts on assessment of student learning as well as an easy to adopt protocol that details reaction setup, aqueous workup, purification, waste management, and the analysis of products using ^{1}H NMR spectroscopy.



KEYWORDS: *Second-Year Undergraduate, Upper-Division Undergraduate, Organic Chemistry, Hands-On Learning/Manipulatives, Aldehydes/Ketones, Grignard Reagents, Organometallics, Stereochemistry*

Modern organic chemistry remains dominated by the development of new reactions that demand a high degree of selectivity and efficiency. In terms of efficiency, major strides have been made toward the development of novel, catalytic reactions that replace the nonatom,[1] nonstep,[2] or nonpot economical[3] methods of the past. Perhaps even more important is the fact that many of these newly developed processes are highly regio and stereoselective,[4] yielding products that result from either substrate-[5] or ligand-controlled[6] transition states. While a prodigious number of educational experiments have been designed to demonstrate modern organic practices to a second-year undergraduate audience,[7] there remains a gap in the instruction of regioselective chemical processes to that same audience[8] as well as to upper-division organic chemistry students. In order to address this deficiency, several experiments were designed that are exceedingly amenable to implementation at the undergraduate level. In this manuscript, the exploitation of carvone (**1**, Figure 1) as a competent substrate is described to demonstrate both stereo and regioselectivity, utilizing reagents that are chemoselective in their addition to an *α*,*β*-unsaturated carbonyl.



(*S*)-(+)-**1**
caraway

(*R*)-(−)-**1**
spearmint

Figure 1. Carvone enantiomers.

It is well documented that when 2-cyclohexenone is treated with a Grignard reagent, 1,2-addition occurs.[9] If instead an organocuprate is used, 1,4-addition is predominant.[10] It should also be noted that a preference for conjugate addition can be achieved using a Grignard reagent if it is first mixed with a substoichiometric amount of a copper(I) chloride.[11] However, the relative high cost of 2-cyclohexenone, combined with impurities that develop over time, conspire to make this reagent a poor choice for adoption at the undergraduate level. Pleasingly, either (+)- or (−)-carvone (**1**) can be used as a cost-effective substitute. Perhaps more importantly, in addition to being efficient at demonstrating direct vs conjugate addition, the single chirality center in **1** will also allow for an observation and discussion of stereochemistry, because the addition of a nucleophile either at the *β*-carbon or the carbonyl will lead to products with a high degree of optical purity.[12]

Received: November 17, 2017
Revised: February 5, 2018

DOI: 10.1021/acs.jchemed.7b00892

The following experiments, one at the second-year level and the other aimed at an upper-division audience, will experimentally expose students to the concept of chemo and regioselectivity, while simultaneously allowing for an observation and discussion of stereoselectivity via substrate control. The experiments have been optimized to be highly robust, without the need for specialized glassware; reaction products are routinely obtained in high yield and in acceptable purity. Analysis of either the diastereomeric ratio (*dr*) or the ratio of unreacted starting material to product by ^1H NMR spectroscopy will also serve to highlight a critical theme in modern organic chemistry regarding yield analysis. Importantly, student learning was assessed by requiring a written laboratory report where the regioselectivity was discussed.

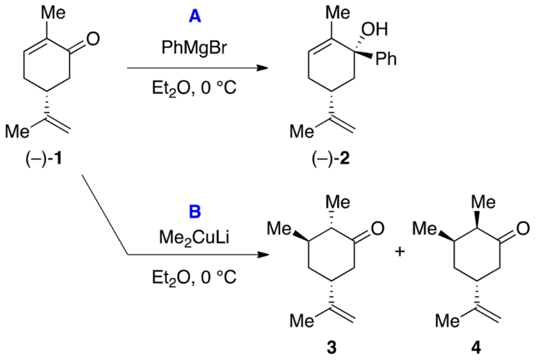
■ EXPERIMENT

The following experiments have been successfully carried out at both the second-year undergraduate and upper-division levels. Students typically work in teams of two or three. Instructor notes as well as full experimental details can be found in the Supporting Information.

Second-Year Undergraduate Level

In this experiment, a typical protocol is followed to generate the requisite Grignard reagent on 11.5 mmol scale from bromobenzene (1.5 equiv) and magnesium turnings (1.8 equiv) using anhydrous diethyl ether (8.5 mL) at room temperature (Scheme 1A). After a period of time, a solution of carvone [(−)-**1**, 1.20 mL, 7.64 mmol] in diethyl ether (3.0 mL) is added to the mixture dropwise at 0 °C. The desired product (**2**) is isolated by aqueous extraction and characterized by ^1H NMR spectroscopy. When following the step-by-step protocol outlined in the Supporting Information section, the entire experiment and associated clean up can be accomplished in under 3 h.

Scheme 1. 1,2- and 1,4-Addition Using Organometallic Reagents



Upper-Division Undergraduate Level

At the upper-division level, it is assumed that the students are capable of being instructed on the proper handling of pyrophoric chemicals and working with small amounts of material. First, lithium dimethylcuprate is generated on 1.66 mmol scale using a solution of methyl lithium in diethyl ether (4.0 equiv) and copper(I) iodide (2.0 equiv) at −10 °C (Scheme 1B). After a period of time, a solution of carvone [(−)-**1**, 0.125 mL, 0.83 mmol] in diethyl ether (2.0 mL) is added to the mixture dropwise at −10 °C. The product of the reaction is isolated as a mixture of diastereomers (**3** and **4**) by aqueous extraction and characterized by ^1H NMR spectroscopy.[13] When following the step-by-step protocol outlined in the Supporting Information section, the entire experiment and associated cleanup can be accomplished in under 2 h.

■ HAZARDS

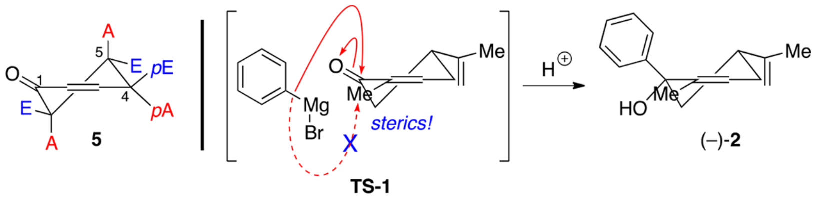
The reactions should only be performed in laboratories with properly ventilated fume hoods and by students wearing appropriate PPE. Students are also required to avoid contact, inhalation, and ingestion of the chemicals in this experiment, which may be toxic or otherwise harmful if swallowed or inhaled. Safety Data Sheets (SDS) should be consulted for all known chemicals used in this experiment. Diethyl ether is extremely flammable and known to form peroxides over time. Bromobenzene can cause liver and nervous system damage and is readily absorbed through the skin. Magnesium metal can be rendered flammable; caution must be taken to avoid direct contact with flame. If a fire should occur, use sand and not water to quench the flames. Methyl lithium is pyrophoric: caution must be taken to limit its contact with air and water; use only with disposable plastic syringes and needles and handle under a balloon of inert gas. For safety reasons, use a 5.0 mL syringe and caution students not to pull the plunger beyond the half way mark. Also of concern, a small quantity of benzene (a known human carcinogen) may result as a byproduct of this experiment, and chloroform-*d*, used for product analysis, is known to cause skin irritation and may be a cancer causing agent: use nitrile gloves at all times to avoid accidental skin contact. Due to the unknown toxicity of the products, students should avoid accidental inhalation/skin contact and properly dispose of these materials after analysis.

■ EDUCATIONAL ASPECTS

The main pedagogic goal of these experiments is to discuss selectivity in modern organic chemistry. Specifically, students at the second-year undergraduate level will gain a deeper understanding of (1) regioselectivity by treating an α,β-unsaturated ketone with a chemoselective Grignard reagent and (2) stereoselectivity by determining the diastereomeric ratio (*dr*) of the products. At the upper-division undergraduate level, the additional pedagogic goal is to (3) demonstrate the regiochemical preference of 1,4-addition when using a lithium diorganocuprate as the nucleophile instead of a Grignard reagent. Students at both levels will also (4) learn how to use ^1H NMR spectroscopy in conjunction with isolated yield to determine the actual yield of their product. As a final note, students can be introduced to the topic of efficiency[2] and atom economy[1] as it pertains to organocuprate and Grignard reagents.

To help facilitate these experiments, a handout was given to the students a week before they were to perform their investigations in the laboratory. This document, included in the Supporting Information section, gives a brief background to the experiments, a full procedure, hazards, and a description of the equipment needed to safely carry out the work. It should be noted that while both experiments are documented in the handout, only the Grignard experiment was utilized at the second-year undergraduate level, with both performed at the upper-division level. Pleasingly, while not all of the students were successful in obtaining their desired product (less than 10% of students recovered only starting material, as evidenced by ^1H NMR spectroscopy), they were all able to fully complete

Scheme 2. Conformation of Cyclohexenone and TS Model for Nucleophilic Attack



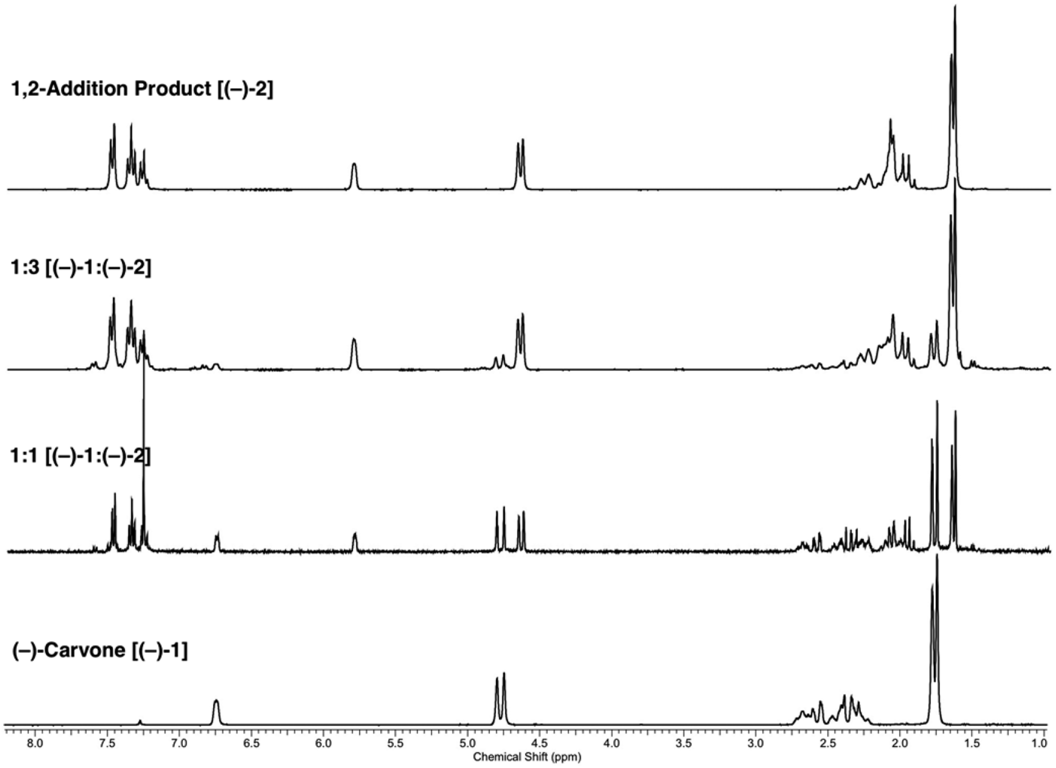


Figure 2. 300 MHz ^{1}H NMR spectra of crude material showing product to starting material ratios.

the steps of the experiments following the procedure, as written, and answer all of the pre and postlaboratory questions.

■ RESULTS AND DISCUSSION

1,2-Addition Experiment

Surprisingly, as a complement to complete regiocontrol, after only a simple workup, followed by drying ($MgSO_4$), filtration, and concentration, the addition of phenylmagnesium bromide to (−)-**1** occurs with a high degree of stereoselectivity (>95%, or higher) and with almost no undesired byproduct formation. In fact, out of the prodigious number of replicate experiments by students (ca. 100 individual experiments over two semesters), the only other compound that was detectable via ^{1}H NMR spectroscopy was unreacted starting material (as high as 50% of the bulk crude material). In those cases, students cite in their laboratory report that moisture was the culprit.

In terms of rationalizing the mode of carbonyl addition, students at the second-year undergraduate level should be familiar with the concept of 1,2-addition for Grignard reagents; however, what may be surprising is the high degree of stereoselectivity displayed in this experiment. In the prelaboratory exercise, students draw two possible stereoisomers for the expected 1,2-addition adduct, classify them as either enantiomers or diastereomers, and assign each new stereocenter as *R* or *S*. This latter exercise proved to be a good review/refresher of the concepts of stereochemistry, with the majority of students knowing the correct answers to these questions.

In the lecture directly preceding this experiment, teaching assistants asked students to recall the different cyclohexane chair conformers and to discuss the difference between axial and equatorial substituents. Unlike cyclohexane, the half-chair conformer of 2-cyclohexenone (**5**, Scheme 2) is the most stable conformation, with substituents at C(4) occupying pseudoaxial (*p*A) and pseudoequatorial (*p*E) positions to accommodate the different bond lengths and angles when compared to cyclohexane.[14] Also of note, because of ring distortion, in the absence of 1,3-diaxial interactions, the preference for a large substituent to be equatorial at either C(5) or C(6) in 2-cyclohexene is less. For example, compare the $-\Delta G°$ value for an axial methyl group in 4-methyl-cyclohexene (1 kcal/mol)[15] with methylcyclohexane (1.8 kcal/mol).[16] Teaching assistants first described these differences before drawing in a methyl group at C(2) and an equatorial *iso*-propylidene at C(5) on their half-chair conformer of 2-cyclohexenone. Due to the overall shape and the sterics associated with nucleophilic addition to the concave/*re*-face, addition of phenylmagnesium bromide occurs only from the convex/*si*-face of the carbonyl, leading to the predominant formation of compound (−)-**2** (Scheme 2).

DOI: 10.1021/acs.jchemed.7b00892
J. Chem. Educ. XXXX, XXX, XXX−XXX

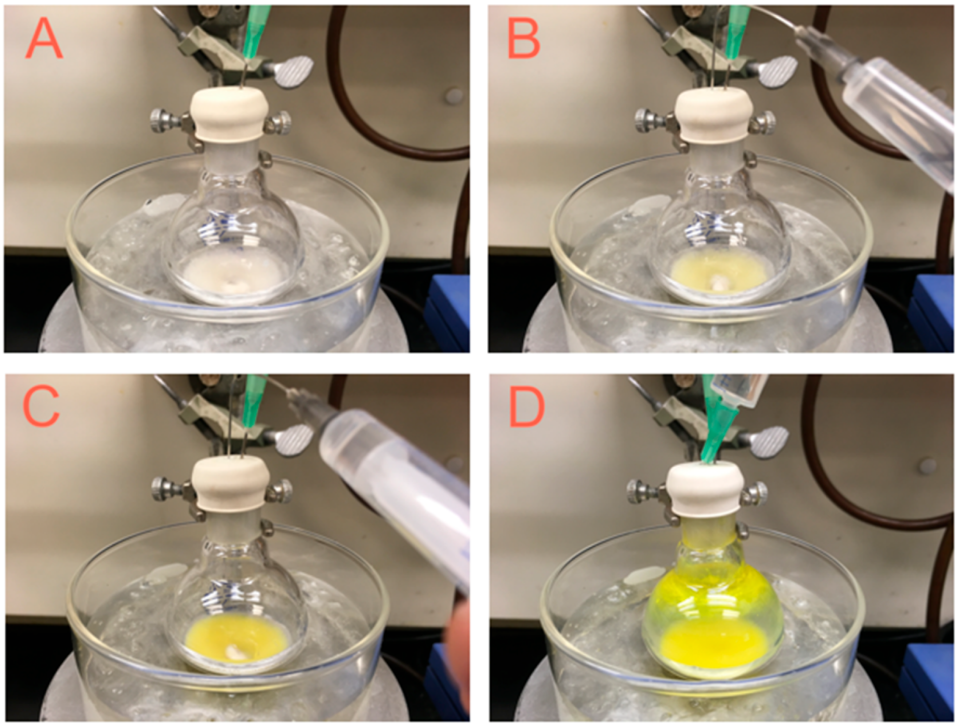


Figure 3. 1,4-addition experiment color changes.

Not surprisingly, the ^{1}H NMR spectra of the crude reaction material for several student experiments showed that the nucleophilic addition did not go to completion—two representative examples are reproduced in Figure 2, the first with a 3:1 ratio of product to starting material, the second with a 1:1 ratio.[17] Unfortunately, crude (−)-**2** is obtained as a yellow oil and cannot be further purified by crystallization. As a result, this became a good opportunity to demonstrate how one might calculate a reaction yield of a crude product using ^{1}H NMR spectrum integration. In order to do this, one would only need molecular weights for the starting material and product (150.22 and 228.33 g/mol, respectively), the weight of the crude material in grams (g_{isolated}), and the integration ratio (NMR spectrum ratio), which relates to the number of moles. To perform this calculation, the previously reported procedure by Olofsson and coworkers was utilized,[18] which outlines the following equations (note: **SM** = carvone, **P** = compound **5**, $\text{mol}_{\text{SM}}{}^{\circ}$ = mol unreacted SM)

$$\text{mol}_{\text{SM}} = \text{mol}_{\text{P}}(\text{expected}) \tag{1}$$

$$g_{\text{isolated}} = g_{\text{SM}} + g_{\text{P}} = \text{mol}_{\text{SM}}{}^{\circ}\bullet(150.22\text{g/mol}) + \text{mol}_{\text{P}}\bullet(228.33\text{g/mol}) \tag{2}$$

$$\text{mol}_{\text{SM}}{}^{\circ} = \text{mol}_{\text{P}}\bullet\text{NMR ratio}\ (\mathbf{SM}/\mathbf{P}) \tag{3}$$

$$g_{\text{isolated}} = [\text{mol}_{\text{P}}\bullet\text{NMR ratio}(\mathbf{SM}/\mathbf{P})]\bullet(150.22\text{g/mol}) + \text{mol}_{\text{P}}\bullet(228.33\text{g/mol}) \tag{4}$$

$$\text{mol}_{\text{P}} = g_{\text{isolated}}/[(228.33\text{g/mol}) + (150.22\text{g/mol})\bullet\text{NMR ratio}(\mathbf{SM}/\mathbf{P})] \tag{5}$$

Once in hand, eq 5 can be used to solve for the number of moles of product (mol_{P} experimental) in the mixture and then eq 3 to solve for the number of moles of unreacted starting material. After these calculations are complete, the mass (eq 6) and overall percent yield of the desired product (eq 7) can be calculated as follows

$$\text{mass of product} = \text{mol}_{\text{P}}\bullet 150.22\text{g/mol} \tag{6}$$

$$\%\ \text{yield of}\ \mathbf{5} = [\text{mol}_{\text{P}}/\text{mol}_{\text{P}}(\text{expected})]\bullet 100 \tag{7}$$

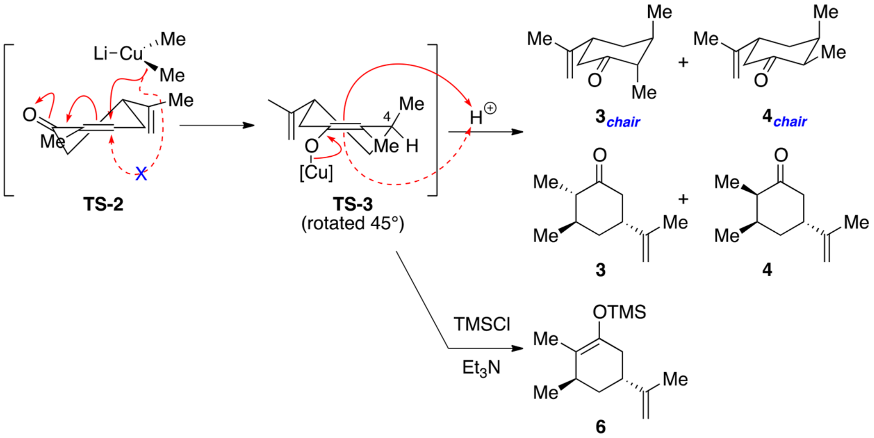
In most cases, some with help of a teaching assistant, students were able to use the above eqs (eq 1−7, provided in the laboratory handout) to calculate percent yield in the event that their reaction did not go to completion. This reinforces the concept that not all reactions go according to plan and oftentimes need purification to remove unreacted starting material and any undesired byproducts. As a final note, the reaction described above is related to the typical carbonyl addition reaction to which students are exposed in their second-year organic chemistry course.

1,4-Addition Experiment

Due to the potential hazard associated with this experiment, before handling methyl lithium (1.6 M in Et_2O), upper-division students were first given a short lecture regarding the proper handling and disposal of pyrophoric reagents. In addition, teaching assistants demonstrated how to, under a balloon of nitrogen gas, draw up the required amount of MeLi and transfer it safely to a septum-covered reaction vessel, also under nitrogen, using disposable 3″ needles [19G (gauge)] and plastic syringes. The authors recommend either a teaching assistant, or instructor, be on hand for each student's MeLi transfer operation. In order to obtain routinely high yields for this process, only freshly purified copper(I) iodide should be used in this experiment.[19]

The formation of lithium dimethylcuprate is incredibly fast at −10 °C; one must pay close attention to the rate of MeLi addition in order to observe the striking color change associated with this process (Figure 3). When a single drop of MeLi is added to a suspension of CuI in diethyl ether (A, Figure 3), a brilliant yellow color corresponding to MeCu will develop (B) that will intensify until one full equivalent of MeLi has been added (C). The color will then disappear as the

Scheme 3. TS Model for Axial 1,4-Attack and α-Enolate Protonation/Trapping



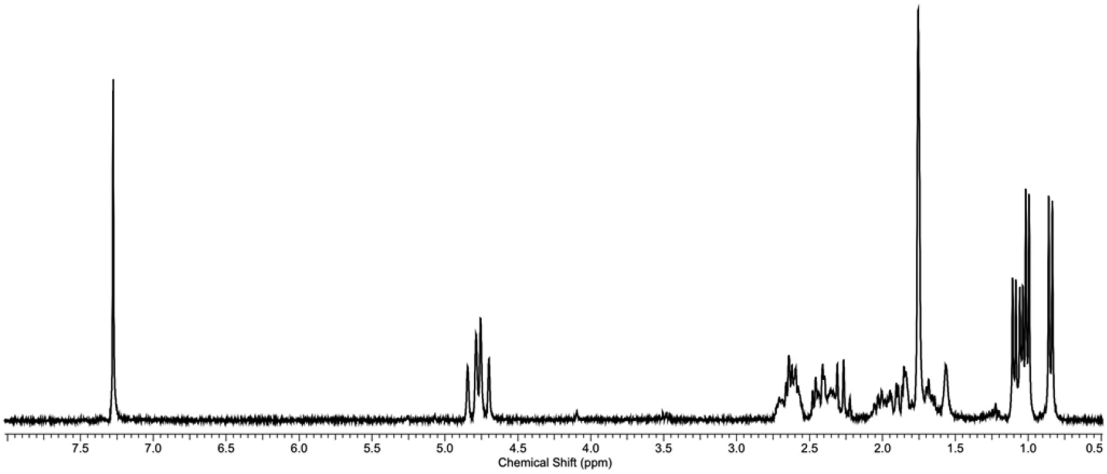


Figure 4. ^{1}H NMR spectrum of epimers **3** and **4** (crude material).

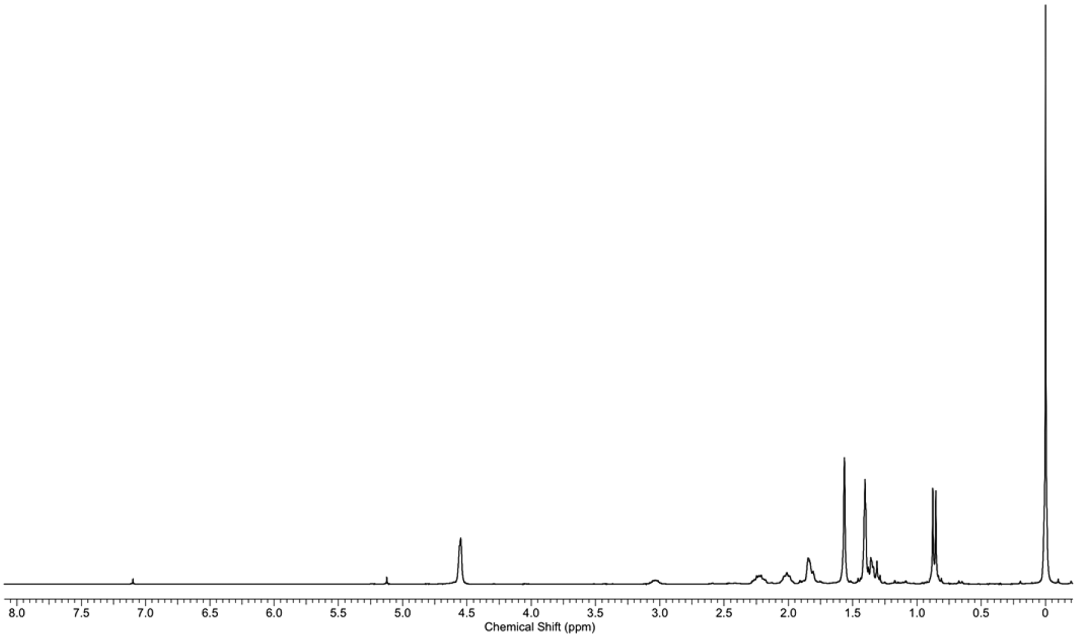


Figure 5. ^{1}H NMR spectrum of silylenol ether **6** (crude material).

second equivalent of MeLi is added (not shown), en route to the formation of the lithium dimethylcuprate. Upon the

DOI: 10.1021/acs.jchemed.7b00892
J. Chem. Educ. XXXX, XXX, XXX−XXX

dropwise addition of carvone at −10 °C, the solution should again turn yellow (D), signifying methyl transfer and the regeneration of MeCu.

As predicted, the 1,4-addition of a methyl group to carvone occurs with a high degree of stereoinduction—axial attack on the face opposite the substituent at C(5) leading to a copper-bound enolate (**TS-3**, Scheme 3; note: **TS-3** is rotated 45° from **TS-2**) where the recently added methyl substituent occupies a pseudoaxial position in the reorganized half-chair intermediate in order to reduce bond/angle strain. Surprisingly, upon addition of a saturated aqueous solution of ammonium chloride, protonation occurs on both faces of the enolate, leading to diastereomers **3** and **4** (Scheme 3) in roughly equal amount (the ratio of diastereomers is 0.7:1), as evidenced by ^{1}H NMR spectrum integration of the crude material after a simple aqueous workup (Figure 4). This observation can be due, in part, to the size of a proton in conjunction with diminished steric hindrance about the top (1-*si*, 2-*re*) face of the enolate due to the C(3) methyl group being pseudoaxial and not axial (Scheme 3).[13] Unfortunately, these C(2)-epimers could not be separated either by crystallization or chromatography, and the integration of multiplets at δ = 4.83−4.68 ppm and δ = 1.09−0.82 ppm[17] allows one to calculate the diastereomeric ratio (*dr*) as 0.7:1.

In the laboratory period directly following this 1,4-addition experiment, upper-division students considered ways in which only one diastereomer could be obtained from this reaction. Two suggestions were offered and discussed: the first involved a dynamic equilibrium event, in which the less stable diastereomer could be converted into the more stable C(2) epimer. Unfortunately, when the mixture of diastereomers was treated with potassium carbonate in methanol, full conversion to a single product was never achieved, even after allowing the reaction to stir at 50 °C for 48 h. The second suggestion involved trapping the enolate intermediate as a silylenol ether,[20] eliminating the stereocenter at C(2). Pleasingly, after (−)-carvone is allowed to react with lithium dimethylcuprate for 20 min, the in situ-generated copper enolate was treated with triethylamine and chlorotrimethylsilane; when allowed to stir for an additional 30 min, silylenolether **6** was obtained as the major product as evidenced by ^{1}H NMR spectroscopy directly on the crude material (Figure 5). This simple modification to the experiment was instrumental in reinforcing the concept of axial attack and further supports the observation of substrate-directed stereoselectivity for this regioselective, 1,4-addition reaction.

As a final note, the 1,4-addition experiment outlined above is an excellent demonstration of regioselectivity aimed at an upper-division organic chemistry audience. The reaction is relevant not only to modern organic chemistry but also exemplifies the typical conjugate addition reaction that students are exposed to in their second-year organic chemistry course.

Assessment

In order to assess student learning at the second-year level, students were required to turn in a detailed laboratory report for this experiment. Students analyzed their data in the context of a ^{1}H NMR spectrum provided (3:1 ratio of product to starting material) and showed mechanistic details for the experiment, an analysis of the different stereoisomers that could result from a 1,2-addition, and discussed any sources of error associated with a low yield/incomplete reaction. At the upper-division level, students were also assessed on how they were able to place these experiments into the broader context of modern organic chemistry, specifically the atom economy. Students were each given a copy of the seminal Trost manuscript[1] and asked to compare Grignard reagents and organocuprates with attention paid to whether or not the waste associated with each process is acceptable in all cases.[21]

■ CONCLUSION

In this experiment, carvone was used as an inexpensive reagent that allows for a demonstration of regioselectivity at both the second-year and upper-division undergraduate organic chemistry levels. The experiments also exposed students to the concept of chemoselectivity by using two different organometallic reagents and stereoselectivity by exploiting a starting material where nucleophilic addition is governed by substrate control. The experiments have been designed to be highly robust and easy to follow, with product analysis by ^{1}H NMR spectroscopy straightforward.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available on the ACS Publications website at DOI: 10.1021/acs.jchemed.7b00892.

> Instructor information; detailed experimental procedures; pre and postlaboratory assignments (with answers); and a detailed handout that outlines background information and a succinct protocol for students to follow (PDF, DOCX)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: wmaio@nmsu.edu.

ORCID

William A. Maio: 0000-0001-8561-2273

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This research was financially supported by a National Science Foundation CAREER Award (1452489). We are also grateful to William Quintana at New Mexico State University for providing laboratory space and seed funding for these experiments and to the teaching assistants who helped facilitate the second-year experiments: Christopher Cook, Laxmi Devkota, Junhui Hu, Thuy Nguyen, and Yifan Yin. This manuscript is dedicated to James A. Ciaccio (Fordham University), who knows why or should, and to Gary H. Posner (Johns Hopkins University) for sharing his love of organocuprate chemistry.

■ REFERENCES

(1) Trost, B. M. The atom economy – a search for synthetic efficiency. *Science* **1991**, *254*, 1471−1477.

(2) Wender, P. A.; Verma, V. A.; Paxton, P. J.; Pillow, T. H. Function-oriented synthesis, step economy, and drug design. *Acc. Chem. Res.* **2008**, *41*, 40−49.

(3) Hayashi, Y. Pot economy and one-pot synthesis. *Chem. Sci.* **2016**, *7*, 866−880.

(4) For recent reviews, see: (a) Brill, Z. G.; Condakes, M. L.; Ting, C. P.; Maimone, T. J. Navigating the chiral pool in the total synthesis of complex terpene natural products. *Chem. Rev.* **2017**, *117*, 11753−

11795. (b) Newton, C. G.; Wang, S.-G.; Oliveira, C. C.; Cramer, N. Catalytic enantioselective transformations involving C−H bond cleavage by transition-metal complexes. *Chem. Rev.* **2017**, *117*, 8908−8976. (c) Bhat, V.; Welin, E. R.; Guo, X.; Stoltz, B. M. Advances in stereoconvergent catalysis from 2005 to 2015: transition-metal-mediated stereoablative reactions, dynamic kinetic resolutions, and dynamic kinetic asymmetric transformations. *Chem. Rev.* **2017**, *117*, 4528−4561.

(5) For an example of substrate control in a modern total synthesis, see: Adams, G. L.; Carroll, P. J.; Smith, A. B., III Total synthesis of (+)-scholarisine A. *J. Am. Chem. Soc.* **2012**, *134*, 4037−4040.

(6) For the ligand-controlled, stereoselective 1,2-addition of a Grignard reagent to a ketone, see: Osakama, K.; Nakajima, M. Asymmetric direct 1,2-addition of aryl Grignard Reagents to aryl alkyl ketones. *Org. Lett.* **2016**, *18*, 236−239.

(7) (a) St. Germain, E. J.; Horowitz, A. S.; Rucco, D.; Rezler, E. M.; Lepore, S. D. Teaching experiment to elucidate a cation−π effect in an alkyne cycloaddition reaction and illustrate hypothesis-driven design of experiments. *J. Chem. Educ.* **2017**, *94*, 240−243. (b) Fennie, M. W.; Roth, J. M. Comparing amide-forming reactions using green chemistry metrics in an undergraduate organic laboratory. *J. Chem. Educ.* **2016**, *93*, 1788−1793. (c) Oliveira, D. G. M.; Rosa, C. H.; Vargas, B. P.; Rosa, D. S.; Silveira, M. V.; de Moura, N. F.; Rosa, G. R. Introducing undergraduates to research using a Suzuki−Miyaura cross-coupling organic chemistry miniproject. *J. Chem. Educ.* **2015**, *92*, 1217−1220.

(8) For some recent examples, see: (a) Johnston, M. R.; Makriyannis, A.; Whitten, K. M.; Drew, O. C.; Best, F. A. Biocatalyzed regioselective synthesis in undergraduate organic laboratories: multistep synthesis of 2-arachidonoylglycerol. *J. Chem. Educ.* **2016**, *93*, 2080−2083. (b) Leslie, J. M.; Tzeel, B. A. Gold(III)-catalyzed hydration of phenylacetylene. *J. Chem. Educ.* **2016**, *93*, 1100−1102. (c) Bichler, K. A.; Van Ornum, S. G.; Franz, M. C.; Imhoff, A. M.; May, C. M. Investigation of the regioselectivity of alkene hydrations for the undergraduate organic laboratory. *J. Chem. Educ.* **2015**, *92*, 1426−1428. (d) Andersh, B.; Bosma, W. B.; Hammar, M. K.; Graves, J. A.; Moon, K. N.; Newborn, C. R. Addition of "HOBr" to *trans*-anethole: investigation of the regioselectivity and the stereoselectivity of an addition reaction. *J. Chem. Educ.* **2013**, *90*, 1504−1508. Also see: (e) Miles, W. H.; Nutaitis, C. F.; Berreth, C. L. Hydrochlorination of (*R*)-Carvone. *J. Chem. Educ.* **1994**, *71*, 1097.

(9) Smith, M. B.; March, J. *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, 5th ed.; Wiley-Interscience: New York, NY, 2001; pp 1205−1209.

(10) (a) Vellekoop, A. S.; Smith, R. A. J. The Mechanism of organocuprate 1,4-addition reactions with α,β-unsaturated ketones: formation of cuprate-enone complexes with lithium dimethylcuprate. *J. Am. Chem. Soc.* **1994**, *116*, 2902−2913. (b) See reference 8, pp 1027−1030.

(11) For an early example, see: Kharasch, M. S.; Tawney, P. O. Factors determining the course and mechanisms of Grignard Reactions. II. The effect of metallic compounds on the reaction between isophorone and methylmagnesium bromide. *J. Am. Chem. Soc.* **1941**, *63*, 2308−2316.

(12) Several laboratory textbooks feature an easy to follow experiment concerning the extraction and purification of (−)-carvone via steam distillation that can be paired with the given protocol: Mohrig, J. R.; Hammond, C. N.; Schatz, P. F.; Morrill, T. C. *Modern Projects and Experiments in Organic Chemistry: Miniscale and Williamson Microscale*, 2nd ed.; W. H. Freeman and Company: New York, NY, 2002; pp 37−46.

(13) A modification of this experiment that leads to a single stereoisomeric product (**6**) is also included in the Supporting Information.

(14) Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry Part A: Structure and Mechanisms*, 4th ed.; Kluwer Academic/Plenum Publishers: New York, NY, 2000; pp 143−144.

(15) Rickborn, B.; Lwo, S.-Y. Conformational effects in cyclic olefins. Kinetics and stereochemistry of epoxidation of some alkyl-substituted cyclohexenes. *J. Org. Chem.* **1965**, *30*, 2212−2216.

(16) Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry Part A: Structure and Mechanisms*, 4th ed.; Kluwer Academic/Plenum Publishers: New York, NY, 2000; p 142.

(17) Expanded spectra with exact integral values can be found in the Supporting Information section.

(18) Olofsson, B.; Peterson, T. B. Calculation of NMR Yields. http://www.organ.su.se/bo/Gruppfiler/NMR%20yield%20calculation.pdf (accessed January 2018).

(19) We have found that the best way to purify copper(I) iodide is by repeated extraction using a Soxhlet apparatus and tetrahydrofuran (6−18 h depending on initial purity) before drying using an Abderhalden pisol overnight (to remove excess solvent and trace amounts of water). Purified CuI should appear off white/light grey and will remain free of major byproducts for up to one year if kept tightly sealed, away from light (in a foil-covered container), in a desiccator.

(20) (a) Meulemans, T. M.; Stork, G. A.; Macaev, F. Z.; Jansen, B. J. M.; de Groot, A. Total synthesis of dihydroclerodin from (*R*)-(−)-carvone. *J. Org. Chem.* **1999**, *64*, 9178−9188. (b) Verstegen-Haaksma, A. A.; Swarts, H. J.; Jansen, B. J. M.; de Groot, A. *S*-(+)-carvone as starting material in synthesis (part 4). Conjugate addition of cyanide and Grignard nucleophiles followed by annulation to functionalized decalones. *Tetrahedron* **1994**, *50*, 10073−10082.

(21) For the sake of brevity, please see the Supporting Information section (pg S14) for more details.