Organocatalytic Cyclopropanation of (*E*)-Dec-2-enal: Synthesis, Spectral Analysis and Mechanistic Understanding.

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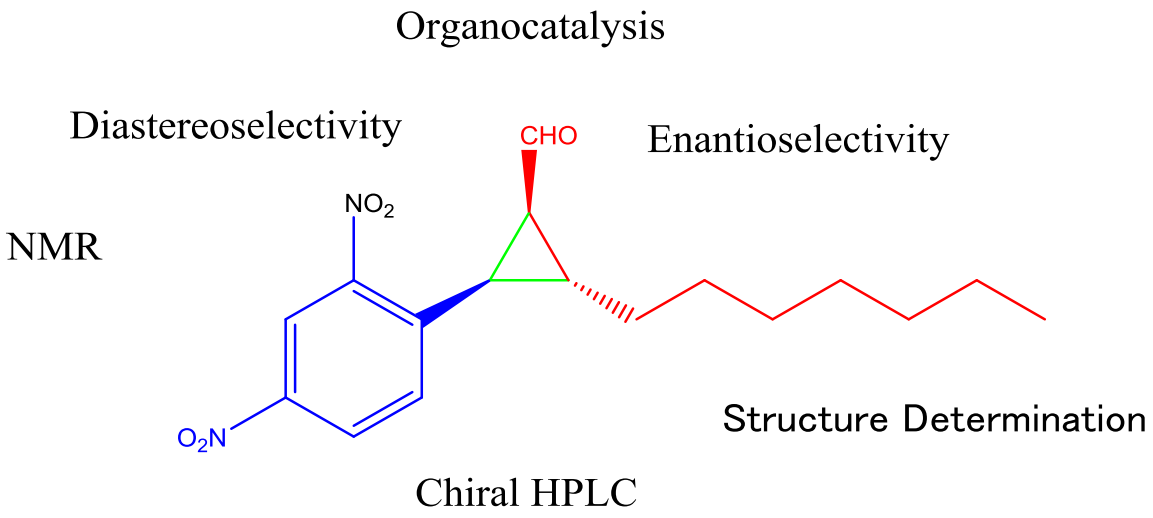
In memoriam Klaus Burger

ABSTRACT

An undergraduate experiment combining synthesis, NMR analysis and mechanistic understanding is reported. The students perform an organocatalyzed cyclopropanation reaction of (*E*)-dec-2-enal and are then required to determine the diastereoselectivity and assign the relative configuration of each product using NMR spectroscopy.

ABSTRACT GRAPHIC



KEYWORDS

Upper Division Undergraduate, Organic Chemistry, Hands-On Learning/Manipulatives, Inquiry-Based/Discovery Learning, Asymmetric Synthesis, NMR Spectroscopy, Diastereomers.

BACKGROUND

In recent years, catalysis has had a huge impact on the nature of organic synthesis. With the increasing emphasis on green chemistry and sustainable processes, the development of new, highly enantioselective methodologies for the synthesis of new, 3D scaffolds has become of paramount importance for organic chemists. A clear example is the 2001 Nobel Prize awarded to K. B. Sharpless, R. Noyori and W. S. Knowles for their contributions to this field. A further step towards the development of greener methodologies was made in 2000 with the "renaissance" of organocatalysis by the pioneering works of B. List[1] and D.W.C. MacMillan.[2] List et *al.*[1] developed the first intermolecular enantioselective aldol reaction catalyzed by proline through enamine activation, while MacMillan and coworkers[2] developed the first organocatalyzed enantioselective Diels-Alder reaction through iminium activation. The benefits of organocatalysis over well-established transition-metal procedures are clear: avoiding transition metal contamination and the use of harsh conditions results in easy-to-handle processes that do not require an inert atmosphere or dry solvents. Despite the growing importance of asymmetric catalysis and sustainable chemistry in industry and academia, and the presence of lecture courses in sustainable chemistry, there are very few laboratory components that incorporate these principles.

Asymmetric organocatalysis has attracted much attention in recent years due to its easy-to-handle green chemistry approach. However, few resources have been

developed to apply the new field of organocatalysis in the undergraduate organic chemistry experimental curriculum. Some examples are: enantioselective aldol reaction catalyzed by prolinamides,[3] use of (*S*)-proline for an aldol reaction and Robinson annulation,[4] the use of achiral NHC carbenes in alcohol acetylation,[5] thiourea- and secondary amine-catalyzed Michael additions[6] and, very recently, the Diels Alder addition catalyzed by the MacMillan catalyst.[7] Herein, a synthesis project[8] for organocatalytic cyclopropanation is described. The nature of these experiment gives the instructor the flexibility to provide opportunities for students to learn topics such as enantioselectivity, diastereoselectivity, optical rotation and organocatalysis, and allows the students to verify an enantioselective mechanism described in the lectures. Compared with other cyclopropanation reactions reported,[9] the easy procedure and the easy prediction of stereochemistry based on a student's previous knowledge, make this experiment highly interesting. The cyclopropanation reaction is monitored by TLC and NMR spectroscopy. The final enantioselective excess of the reaction is determined by chiral HPLC analysis and the diastereoselectivity is determined by NMR spectroscopy.

The main novelty of the present laboratory experiment relies on the determination of the absolute and relative configuration of the formed cyclopropane *via* organocatalysis combining the previously seen different techniques for the first time, thus allowing students to confirm the previous seen mechanism, and improving their skills along the process.

This experiment has been done by advanced undergraduate students (practicals) as part of BSc Chemistry and MChem studies, typically eight UG year/part 3, four UG year/part 4 as well as voluntary summer project students.

The instructor can tailor the practical to suit the students' experiences, highlighting different parts of the experiment that are relevant to the students' course content (*e.g.* NMR spectroscopy for third-year students and stereoselective induction for fourth-year students). This laboratory experiment is envisioned to be done by last year undergraduate students/1st year graduate students in the UK system and first- and second-year graduate students in USA.

PEDAGOGICAL GOALS AND LEARNING OUTCOMES

This experiment is designed to mimic an advanced organic chemistry laboratory taken by chemistry majors (years 3 and 4). Like other advanced practicals, it is designed to mimic a research environment where the student can experience the excitement of a research setting while conducting the experiment under the supervision of an instructor. The laboratory experience not only exposes the students to state-of-the-art organocatalysis, which is not covered in a typical organic chemistry laboratory, but also to the characterization of the compounds synthesized using in-depth analytical techniques such as NMR spectroscopy,[10] HPLC, and optical rotation. During the lab demonstration (in the waiting time during the reaction) the instructor will re-explain the basis of iminium chemistry and the mechanism of the reaction. The students already know the concepts of imine, iminium, Michael addition and cascade reaction from their lectures but, in order to help them, some notes to remember those concepts have been prepared.

The Pedagogical Goals are:

Students will:

1) become familiar with asymmetric synthesis and organocatalysis, NMR experiments and analytical procedures like determination of enantioselectivity by

HPLC. These parts are assessed by formative discussions during the laboratory classes and by the assessment of the report that a student compiles after laboratory sessions.

2) reinforce their previous knowledge of basic NMR spectroscopy, laboratory techniques (column chromatography) and reaction mechanisms (Michael addition, ring closing reactions). The theoretical parts are assessed *e.g.* by a prelab quiz and formative discussions during the laboratory classes, in which the practical skills are also evaluated.

3) be introduced to experimental asymmetric organocatalysis and organocascade reactions.

The Learning Outcomes are:

Students will be able to:

- work with equipment commonly used in an asymmetric synthesis laboratory.
- utilize chiral HPLC, a characterization technique not usually employed in an undergraduate laboratory.
- correctly determine the relative and absolute configuration of organic compounds, based on the mechanism of the reaction and on the interpretation of NMR spectra and HPLC data.
- appropriately plan an experiment in order to utilize the resources and their own time efficiently.

- determine the diastereoselectivity of a given reaction, based on the NMR spectra of the crude mixture.
- purify organic compounds and separate isomers by column chromatography.
- produce a full Control of Substances Hazardous to Health (COSHH) assessment.
- understand basic Michael reactions based on iminium chemistry.
- demonstrate an understanding of chiral HPLC in the determination of enantioselectivity.

Assessment is conducted in a formative manner for the prelab preparation at the start of the experiment: at this stage verbal feedback was given on the students' suggestions to ensure that they – at this point at the latest – are familiar with the relevant practical skills and understood the underlying principles.

The feedback to students on their reports was typically provided verbally and directly to them on an individual basis in any of their lab classes.

The success of the students in achieving these learning outcomes was assessed in a formative manner using a prelab preparation, a written report and from informal conversations between the staff and the students along the experiment. In our experience almost all the students achieve the learning outcomes and reinforce their previous knowledge in NMR spectroscopy and organocatalysis.

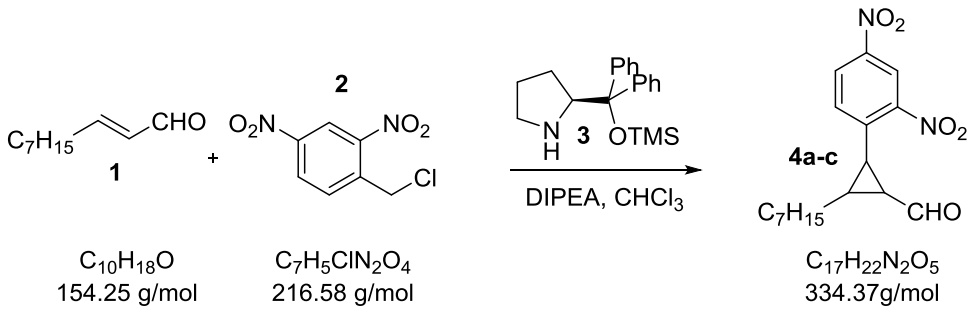
EXPERIMENTAL OVERVIEW

There are two phases for the project. In the first phase the students carry out the cyclopropanation of (*E*)-dec-2-enal (**1**) with 2,4-dinitrobenzyl chloride (**2**)

catalyzed by the commercially available organocatalyst α,α-diphenylprolinol trimethylsilyl ester (**3**). Students are equally divided in two groups, each one using one of the two enantiomers of the organocatalyst (Scheme 1, (*S*)-**3** is shown). In the second phase, the students analyze the spectroscopic data of the cyclopropyl group in order to determine the relative configuration of the product. Students work individually for the synthesis and in pairs for the separation of the isomers. The experiment requires four, 4-h laboratory periods to complete.

EXPERIMENT

In the first session, students perform the reaction in small glass vials at 0 °C for 3 h with 20 mol% of **3** and *N*,*N*-diisopropylamine (DIPEA, 1 equiv) in chloroform. The reaction is monitored by TLC and the sample of the crude mixture was submitted for NMR spectroscopy to calculate the diastereoselectivity. Time-permitting, a chromatography column is packed with silica gel. In the second session, the product is isolated by column chromatography and the diastereomers are separated. The compounds are stored in a freezer. In the third session, samples are prepared and submitted for NMR spectroscopy and chiral HPLC analysis. In the fourth session, students analyze the results from HPLC chromatograms and NMR spectra. A discussion of the results is followed by a written report that is submitted within a few days. A detailed description of the experiment can be found in the Supporting Information.



Scheme 1. Cyclopropanation reaction

In the following days a written report (see Supporting Information) is submitted and instructor feedback provided during a following laboratory class. Students are also encouraged to familiarize themselves with relevant background literature about the catalyst and corresponding synthetic developments.[11]

HAZARDS

All experiments should be performed in well ventilated fume hoods with appropriate personal protective equipment. Students are required to wear safety goggles and use gloves. In addition, students must complete their own experiment risk assessment as part of the pre-laboratory exercise.

The starting materials for the cyclopropanation are irritants; (*E*)-dec-2-enal is allergenic, whereas the benzyl chloride is a lachrymator. Solvents are flammable; the chlorinated solvents are also suspected carcinogens and *n*-hexane is neurotoxic. Amines are also classified as toxic, while acids and bases are corrosive (see Supporting Information for more details). The hazards of the final products are not known; therefore, they have to be treated as toxic. However, with proper training and supervision all synthetic steps can and have been carried out by the students after appropriate risk assessments.

RESULTS AND DISCUSSION

This experiment provides experience for undergraduate chemistry students by familiarizing them with organocatalysis and how these reactions work. For example, the students have the opportunity to explore and understand some reactions such as Michael addition and α-carbon reactivity. The students will also have the opportunity to explore the importance of analytical techniques such as NMR spectroscopy, HPLC and polarimetry, by monitoring their reactions and revisiting concepts such as enantioselectivity, diastereoselectivity, diastereotopicity, stereochemistry and optical rotation, reinforcing their importance in organic synthesis. Interconnecting previous knowledge with new mechanisms and combining what they have learnt in lectures with the experimental laboratory work, encourages their deep learning.

The cyclopropanation reaction (Scheme 1) was completed in 3 h in all the cases, after which a workup was performed and then the products stored in the freezer at -20°C. Before the workup, a sample of the crude was taken to be analyzed by NMR spectroscopy ($CDCl_3$ effectively manage cost for a large number of students) for the d.r. of the reaction and the conversion (full conversion was detected in all the experiments).

In the next laboratory session, the students use column chromatography to purify the cyclopropane compounds (*n*-hexane:ethyl acetate 7:1, more advanced students could use a gradient with tailored advice of an instructor). The cyclopropanes were afforded with good yields ranged between 55 and 89% and good diastereoselectivities from (4:2:1) to (8:2:1) (see section: Determination of the relative configuration of each diastereomer). Few students were able to isolate all

three diastereomers. In all the cases, the major diastereomer **4a** was obtained in pure form at least in some fractions. 70% of students got a mixture of minor diastereomers; in this case the students could identify the peaks of the cyclopropane ring by the different integration of both compounds (2:1 d.r.).

Students recorded the ^{1}H NMR spectra of the crude mixture and after column chromatography in $CDCl_3$. However, if the instructor wants to achieve separation without signal overlap with the cyclopropane hydrogens, the NMR spectra were acquired in CD_3CN. The determination of the reaction's diastereoselectivity can be ascertained by integration of the cyclopropane peaks from the crude mixture. Occasionally, there may be problems with the integration *e.g.* if the shimming is not correct or the sample is too dilute; careful supervision of each student's NMR spectrum is suggested. Between 3.5 and 2.7 ppm the peaks corresponding to the H_c of the cyclopropane ring do not overlap and are clearly visible in the ^{1}H NMR of the crude reaction.

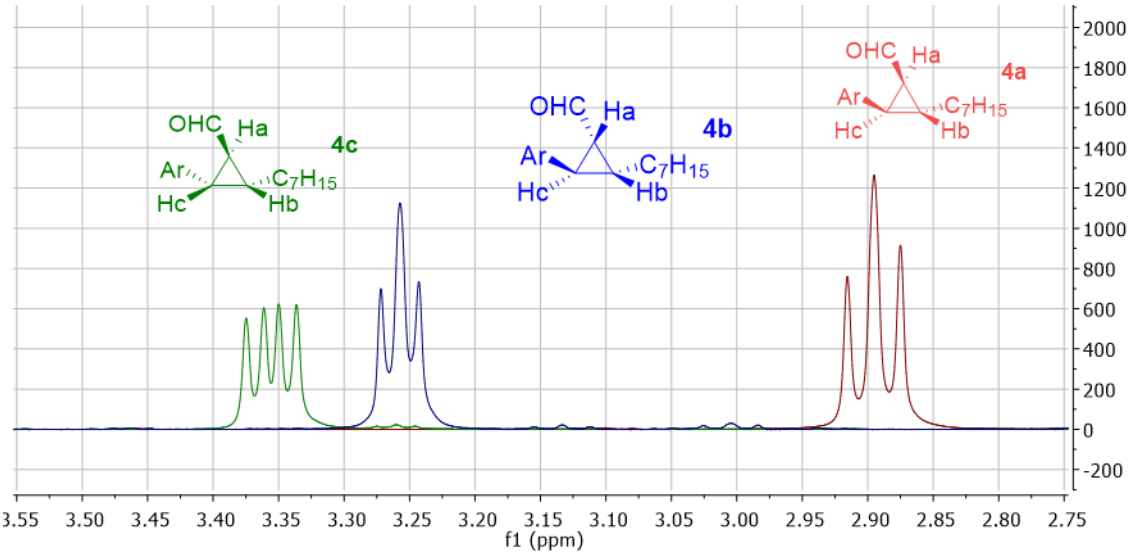


Figure 1. Superposed H_c signals for the three diastereomers (^{1}H NMR $CDCl_3$ 400 MHz Magnified spectra)

The use of the organocatalytic cyclopropanation offers several advantages: the reaction did not require low temperatures or inert conditions, and the cascade reaction occurred within a short period of time (3 h), catering to the need of an undergraduate organic laboratory. Moreover, to the best of our knowledge, the Jørgensen-Hayashi catalyst and the organocatalytic iminium activation have not been used so far in enantioselective reactions for laboratory training purposes.

Determination of the relative configuration of each diastereomer:

The students received a Karplus and/or Bothner-By diagram to ascertain the relative configuration. The relative configuration of the diastereomers was ascertained by ^{1}H NMR (CD_3CN) analysis of the isolated compounds **4a**, **4b** and **4c** (Supporting Information, Figures S1-S4). In cyclopropanes dihedral angles are rigidly fixed by the geometry of the ring system. By using the Karplus or Bothner-By equation (Figure 2), it is possible to determine the magnitude of the coupling constant based in the dihedral angle of both hydrogen atoms that are coupled. As shown in Figure 3, the values of the coupling constants can be determined for all of the possible diastereomers of the reaction.

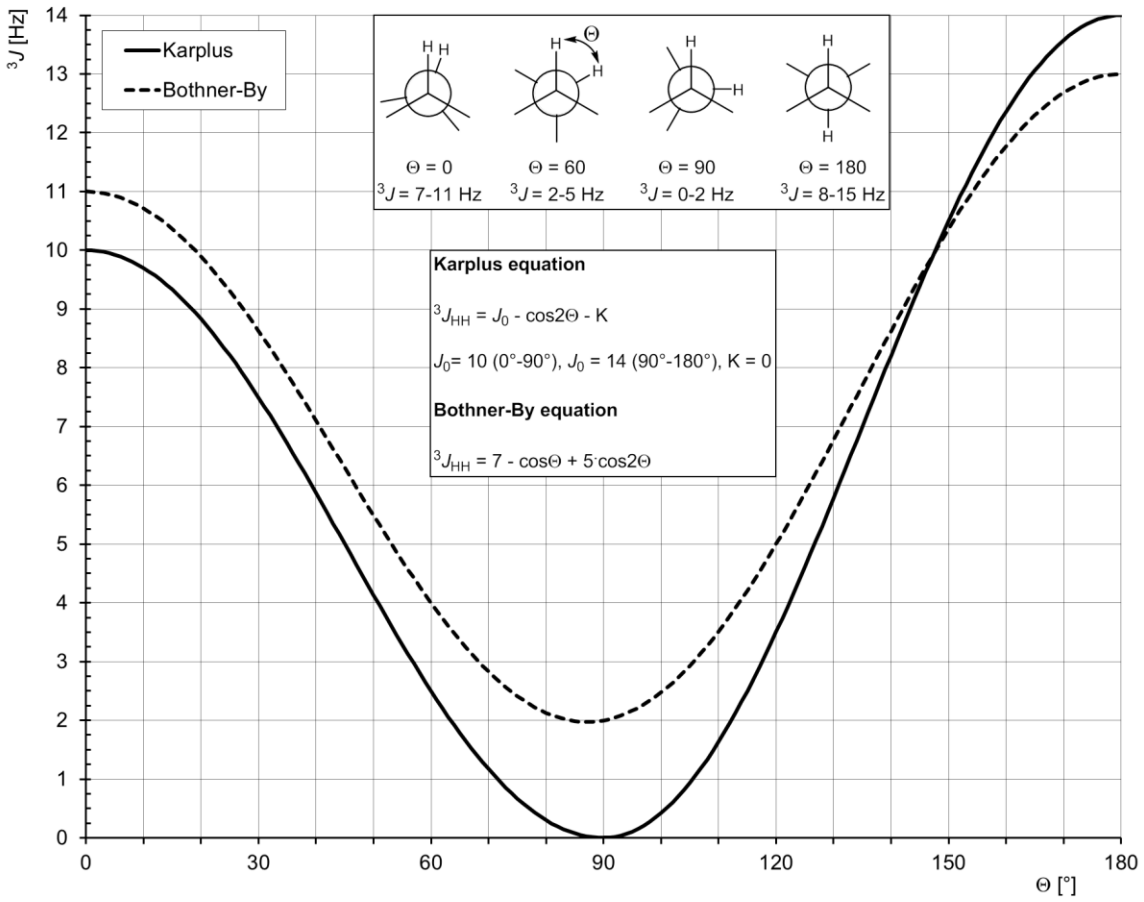


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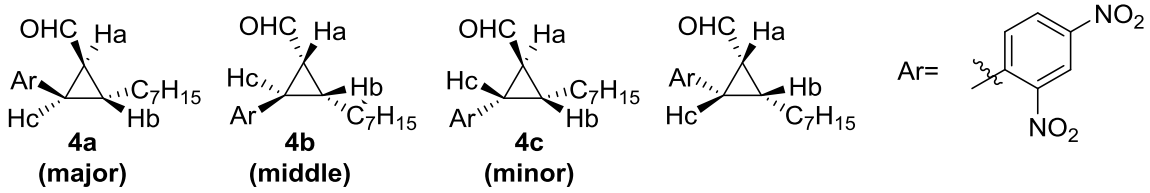
Figure 2. Karplus and Bothner-By diagrams.



Ha-Hb 120°	Ha-Hb 0°	Ha-Hb 120°	Ha-Hb 0°
Hc-Ha 0°	Hc-Ha 120°	Hc-Ha 120°	Hc-Ha 0°
Hc-Hb 120°	Hc-Hb 120°	Hc-Hb 0°	Hc-Hb 0°

Figure 3. Dihedral angles for each possible diastereomer of the cyclopropanation.

The ^{1}H NMR spectra (recorded in CD_3CN to obtain a better resolution) of each diastereomer were analyzed on this basis. Peaks corresponding to cyclopropane protons appear in the 3.5-2.0 ppm region. In all of the compounds, the most deshielded hydrogen will be H_c, and the most shielded will be H_b, H_a being in the middle. In the spectra of the major diastereomer (**4a**, Figure 4), the coupling constants are: $J_{Ha\text{-}Hb}$ = 4.9 Hz, $J_{Ha\text{-}Hc}$ = 9.0 Hz, $J_{Hb\text{-}Hc}$ = 7.5 Hz, that are in accordance with a *cis* relationship between H_a and H_c (0° large coupling constant) and a *trans* relationship between H_b and H_c, and H_a and H_b (120° smaller coupling constant). The configuration is confirmed by X-ray analysis of a single crystal.[8] In the second diastereomer (**4b**, Figure 5) the coupling constants are: $J_{Ha\text{-}Hb}$ = 9.6 Hz, $J_{Ha\text{-}Hc}$ = 5.3 Hz, $J_{Hb\text{-}Hc}$ = 6.7 Hz. This indicates a *cis* relationship between H_a and H_b (0° large coupling constant) and a *trans* relationship between H_c and H_a or H_b (120° smaller coupling constant). In the minor diastereomer (**4c**, Figure 6) the coupling constants are: $J_{Ha\text{-}Hb}$ = 5.4 Hz, $J_{Ha\text{-}Hc}$ = 5.4 Hz, $J_{Hb\text{-}Hc}$ = 9.9 Hz. This indicates a *cis* relationship between H_c and H_b (0° large coupling constant) and a *trans* relationship between H_a and H_c or H_b (120° smaller coupling constant).

Importantly, some of the questions of the students were related to the different ^{1}H NMR spectra obtained in the crude and in the final compound. This was easily explained by the use of different deuterated solvents. We understand that this could cause confusion, but it also offers an opportunity to discuss these effects. CD_3CN could be used in the crude NMR, although increasing the cost of the laboratory experiment.

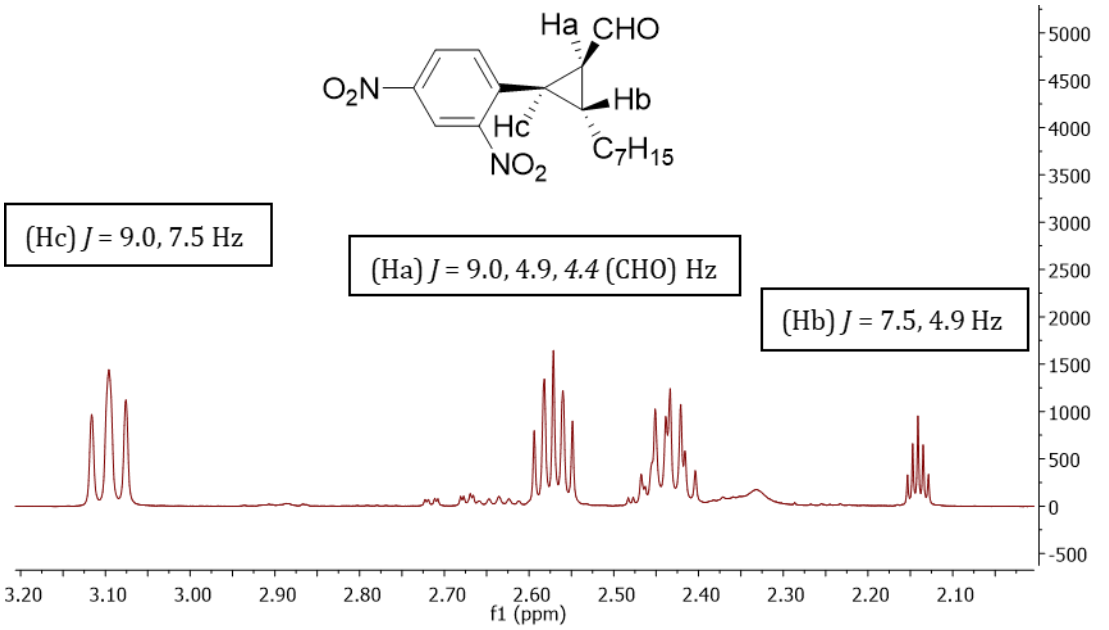


Figure 4. ^{1}H NMR (CD_3CN, 400 MHz) of cyclopropane ring: major diastereomer **4a** (value H_b-C_7H_{15} omitted, italics indicate couplings with CHO).

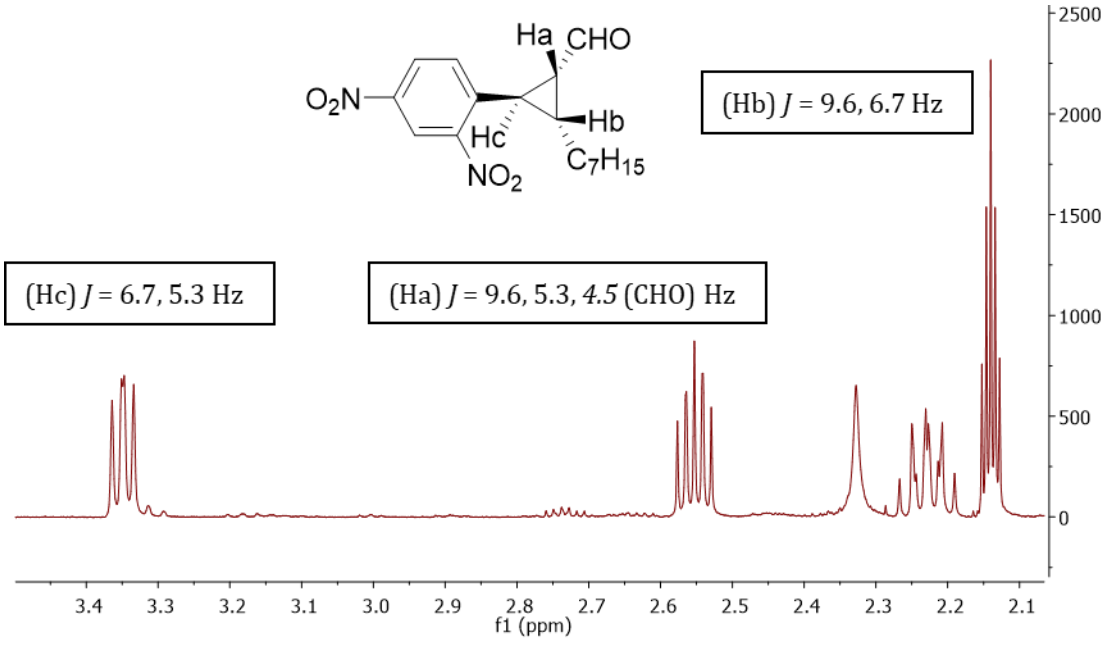


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Figure 5. ^{1}H NMR (CD_3CN 400 MHz) of diastereomer **4b** of cyclopropane ring, value H_b-C_7H_{15} omitted, italics indicate couplings with CHO. That indicates a *cis* relationship between H_a and H_b (0° large coupling constant) and a *trans* relationship between H_c and H_a or H_b (120° smaller coupling constant).

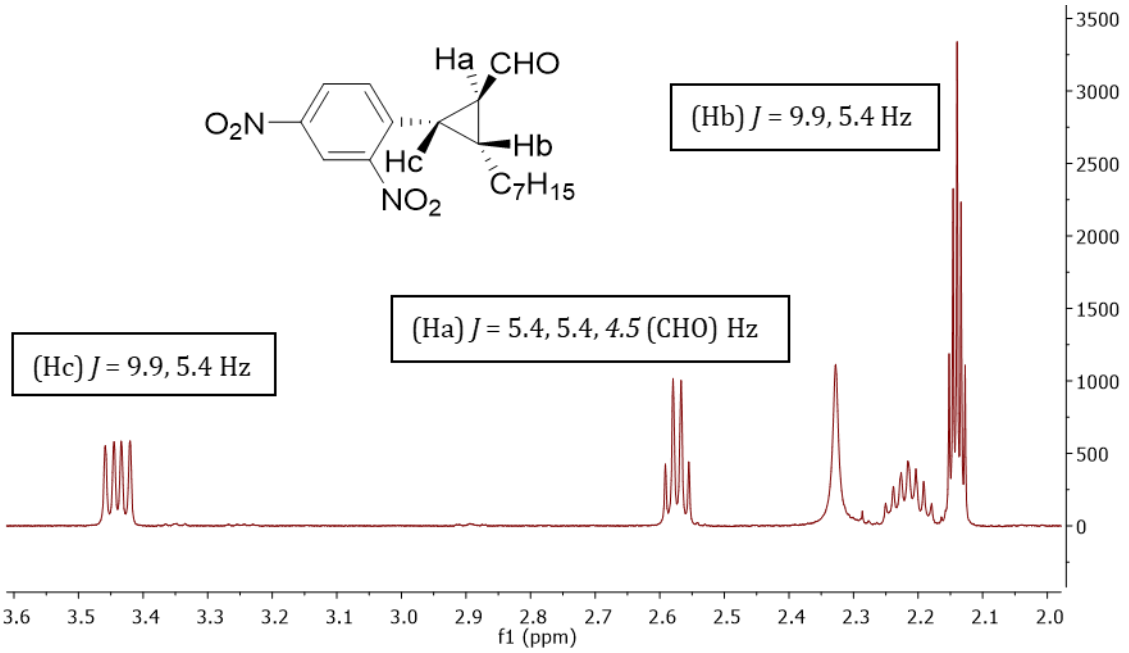

Figure 6. ^{1}H NMR (CD_3CN 400 MHz) of cyclopropane ring of minor diastereomer **4c,** value H_b-C_7H_{15} omitted, italics indicate couplings with CHO. There is a *cis* relationship between H_b and H_c (0° large coupling constant) and a *trans* relationship between H_a and H_b or H_c (120° smaller coupling constant).

Once the students had the ^{1}H NMR spectra of the products, the major isomer was analyzed by HPLC to determine the enantioselectivity of the process. First, a racemic sample was prepared by mixing the major diastereomer obtained by using each enantiomer of the catalyst. In this way the students saw the importance of racemic mixtures and saw the two enantiomeric peaks in the HPLC (Figure S14). Then each student's sample was injected in order to determine the enantioselectivity (95-99% in all the examples). Finally, the optical rotation of the major diastereomer of each student was measured. The absolute configuration of the major diastereomer can be found in the literature[8] and the students can compare the optical rotation of the compounds obtained with the reported value. Students can then validate the accepted mechanism for iminium reactions. Since students are familiar with enamine and iminium concepts (explained during lab

session 1), they should be able to understand the stereochemical outcome based on these principles.

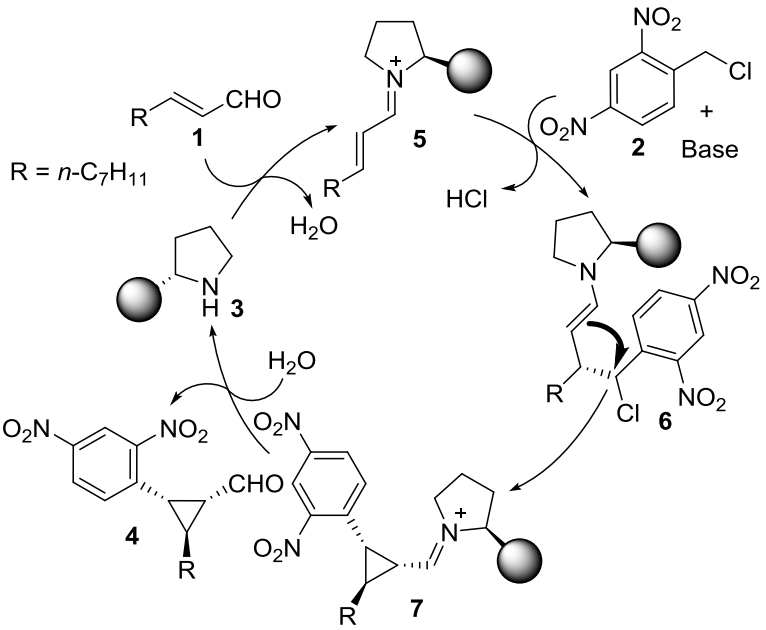

Figure 7. Proposed mechanism

As shown in Figure 7, the α,β-unsaturated iminium ion **5** was initially formed by the reaction of diphenyl prolinol silyl ether catalyst **3** with the α,β-unsaturated aldehyde **1**. At this stage, the bulky group of catalyst **3** shields the *Si*-face of α,β-unsaturated iminium ion **5**. Intermediate **6** was therefore formed by nucleophilic attack of **2** predominantly on the *Re*-face of iminium ion **5** *via* Michael addition, followed by intramolecular ring-closing reaction between the enamine and the secondary alkyl chloride. Iminium ion **7** is hydrolyzed to the desired product **4** and catalyst **3** is regenerated.

The experiment has been done in two consecutive years by 6 students each year. The results obtained are summarized in the following paragraph.

In all the examples the reaction was stirred for 3 h, followed by acquisition of a ^{1}H NMR spectrum of the crude product, followed by column chromatography. Sometimes no full conversion has been achieved after 3 h; however, in all cases, significant amounts of the products were isolated. In almost all the examples the students were able to isolate the major diastereomer in pure form. Few (30%) were able to isolate the three diastereomers, while the rest got the two minor diastereomers as a mixture. The HPLC results (an example is shown in Figure 8) show that in all the examples the enantioselectivities obtained were in the 95-99% range for the major diastereomer.

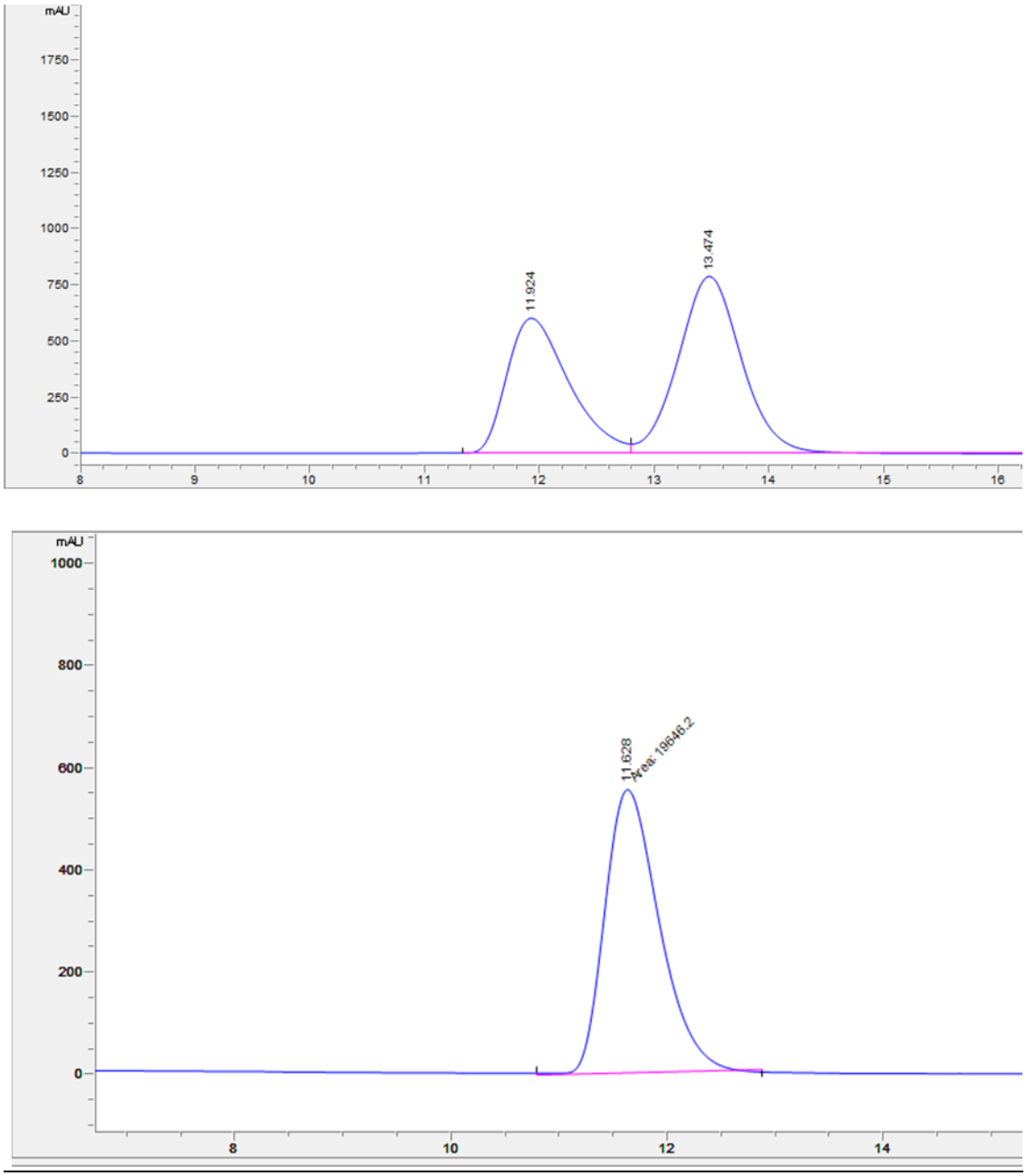

Figure 8. HPLC (OD-H chiral column, *n*-hexane:isopropanol 80:20, λ = 210 nm, 1 mL/min flow) of major diastereomer 4a. Top: racemic (mixture of the two enantiomers). Bottom: chiral product obtained using *S* catalyst. X-axis: retention time.

CONCLUSIONS

In conclusion, the students who tested this reaction have been able to determine the diastereoselectivity of the reaction and to isolate at least the major

diastereomer in its pure form. Students were able to assign the relative configuration of all diastereomers, the absolute configuration of the major diastereomer by comparison between the optical rotation of the product obtained and the data reported in the literature. With these information, the students applied what they have learned in lectures regarding enantioselectivity and diastereoselectivity and how to determine them.

The mechanism explaining the stereochemical control is complex, but a practical experience like this will help and motivate students to explore unknown avenues in organic chemistry literature. The range of concepts and techniques employed allow the instructor to adapt the focus in some parts of the laboratory experience to fit better the expected learning outcomes based on the course/level of the students.

The experience and feedback from this practical supported the students to move forward with similar or more complex organic synthetic challenges that followed later in the course of their studies.

ASSOCIATED CONTENT

Supporting Information

Supporting Information, experimental procedures and spectroscopic data of compounds **4a-c**, sample student report, teaching assistant notes.

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