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DOI:
10.1021/acs.jchemed.6b00355

JOURNAL OF CHEMICAL EDUCATION

Laboratory Experiment

pubs.acs.org/jchemeduc

Rapid Determination of Enantiomeric Excess via NMR Spectroscopy: A Research-Informed Experiment

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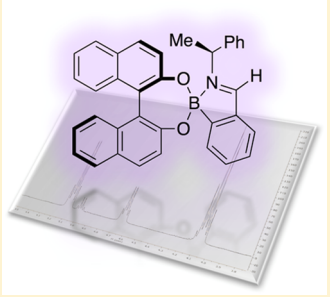
Supporting Information

ABSTRACT: An undergraduate chemistry experiment that draws from primary research is described. The experiment exploits chiral supramolecular assemblies for the determination of enantiomeric excess by ^{1}H NMR spectroscopy. This report describes the delivery of the experiment to a cohort of students, and as a result of feedback from those involved, an optimized protocol is presented. Particular care has been taken to facilitate ready adoption in other institutions by providing comprehensive teaching support materials as well as technical guidance for supporting the experiment.



KEYWORDS: *Second-Year Undergraduate, Organic Chemistry, Analytical Chemistry, Laboratory Instruction, Hands-On Learning/Manipulatives, Computer-Based Learning, Stereochemistry, Chirality/Optical Activity, Enantiomers, NMR Spectroscopy*

INTRODUCTION

Determining the enantiomeric excess (ee) of an asymmetric transformation is an everyday task for synthetic chemists, and being able to accurately measure the enantioenrichment of a product is crucial to a wide range of chemistry,[1] especially in areas such as asymmetric catalysis.[2]

Being able to quickly and accurately measure the ee of a reaction mixture has been a focus for development in industrial and academic settings due to increased demand of quick ee determination in high-throughput screening (HTS) methodologies.[3] Established means of analysis (chiral HPLC) are not ideal for these applications, where hundreds, if not thousands, of asymmetric transformations need to be quantified daily, requiring long method development and lengthy run times. Proton nuclear magnetic resonance (NMR) spectroscopy is a methodology that has been targeted for HTS because a proton NMR spectrum can be obtained in under 5 min and thus can reduce analysis times compared with established chiral chromatography methods.[4] Undergraduate students should be aware of techniques that can form diastereomeric mixtures from enantiomeric mixtures (e.g., Mosher's acid derivitization) and should develop an appreciation that these can be applied to ee determination using NMR spectroscopy.[5]

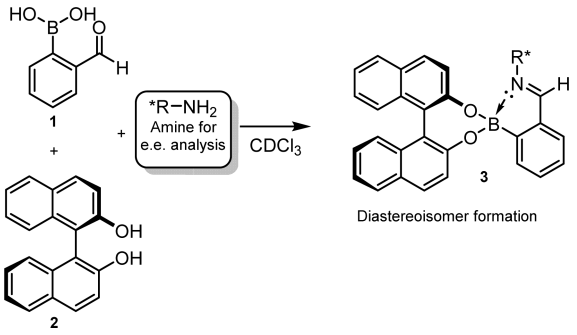
However, undergraduate students do not often have opportunities to gain practical experience in measuring ee. There have been several articles and experiments published within this journal which look at chirality and its quantitation, however none use ^{1}H NMR spectroscopy as a methodology in which to quantify ee.[6] We wished to tackle this through research-informed teaching, applying cutting edge ee determination methodology to reinforce multidisciplinary aspects of undergraduate learning, such as supramolecular, organic, and analytical chemistry. Developing an undergraduate practical procedure based upon chiral HPLC could be both time-consuming and expensive, especially in institutions that do not already possess chiral HPLC capacity. Therefore, we have developed an undergraduate protocol for determination of ee based on ^{1}H NMR spectroscopy and supramolecular assemblies, using commercially available materials, and demonstrating the impact of real life research in the undergraduate laboratory.[7] The utilization of NMR spectroscopy can be viewed as a "green" alternative to HPLC due to the reduction in solvent used per sample (0.6 mL for NMR spectroscopy vs ca. 60 mL for HPLC), and the acquisition time is reduced from up to 60 min for HPLC to 5 min for a ^{1}H NMR experiment. Any institution which possesses a 200 MHz or greater NMR spectrometer will be able to integrate this experiment into its undergraduate course.

Received: April 29, 2016
Revised: August 26, 2016

DOI: 10.1021/acs.jchemed.6b00355
J. Chem. Educ. XXXX, XXX, XXX−XXX

This experiment takes advantage of a boronic acid based assembly, which was reported by Bull, James, and co-workers (Scheme 1).[8] The Bull–James assembly utilizes the ability of a

Scheme 1. Bull–James Assembly Used for the Determination of EE of Primary Amines



boronic acid to bind a diol, as well as an *ortho*-formyl group which can condense with a primary amine to form an imine operating cooperatively to form a three-component assembly. Using a stereodefined diol (e.g., (*R*)-1,1′-bi-2-naphthol (BINOL) (**2**)) with 2-formylphenylboronic acid (2-FPBA) (**1**) (Scheme 1), the ee of a primary amine can be inferred through measurement of the ratio of diastereoisomers formed as observed through NMR spectroscopy. Using this type of assembly introduces undergraduate students to the concepts of enantiomeric excess, chiral shift reagents, and chiral derivatizing agents while building on their knowledge of stereoisomerism (particularly the difference between enantiomers and diastereomers and their respective spectroscopic properties).

Upon addition of a chiral primary amine to 2-FPBA (**1**), an imine is formed, reinforcing undergraduate understanding of carbonyl chemistry, which is a mainstay of organic undergraduate lectures. Subsequent binding of the chiral diol (in this case commercially available (*R*)-BINOL (**2**)) to the boronic acid forms a boronate ester, causing the formation of a three-component assembly, potentially as a mixture of diastereoisomers proportional to the enantiomeric ratio of the original chiral primary amine (Scheme 2).[9] The integration of the peaks in the ^{1}H NMR spectrum corresponding to the two diastereoisomers formed thus infers the ee of the chiral primary amine initially used. This assembly has been shown to be applicable to the determination of ee of a wide variety of different primary amines. For this experiment commercially available α-methylbenzylamine (**4**) was chosen, however we anticipate that this experiment could be modified easily to accommodate a range of primary amines.

The learning outcomes and pedagogic goals of this experiment are to offer practical experience with ee determination; this experiment also introduces undergraduate students to NMR sample preparation and processing software. Students will become comfortable with manual integration of ^{1}H NMR spectra, which is taught in spectroscopy courses. Giving students experience in the processing of NMR spectra is a good introduction into how NMR data are analyzed in research laboratories.

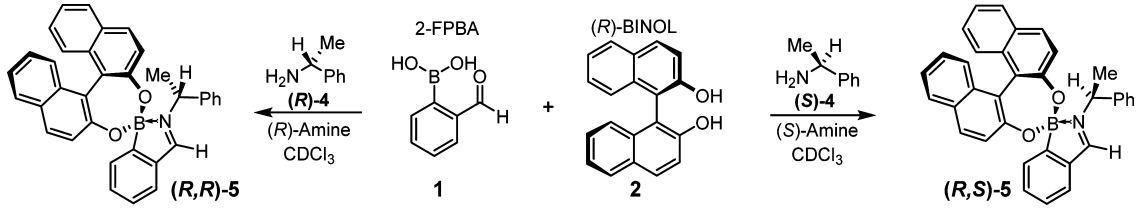
This experiment has been trialed at the University of Birmingham (U.K.) with a cohort of 113 second-year undergraduate chemists during their second semester. The experiment was carried out under the following conditions: students carried out the laboratory section within a fume hood lab at the University of Birmingham (U.K.) while the data analysis was carried out using a computer cluster at the same institution. The following software was used: Microsoft Excel or Sigmaplot (graphing software), MNova or TopSpin (NMR processing, TopSpin is available for free for academic use), Microsoft Word (word processing), and Canvas (online learning platform).[10] This protocol includes developments and improvements that were made as a result of observations and feedback from the students.

EXPERIMENTAL OVERVIEW

Laboratory Practical

We suggest that students work in groups of five. The procedure detailed here begins with preparation of a series of known ee mixtures of α-methylbenzylamine (**4**) and a "host" solution of 2-FPBA (**1**) and BINOL (**2**). We recommend that each group make a stock solution of host to which each amine solution is then added. In order to construct a calibration curve, students are given a table of seven ee values (ranging from −75% ee to +75% ee)[11] and corresponding volumes of (*R*)- and (*S*)-α-methylbenzylamine (**4**) in order to make solutions of the tabulated ee values (see the Laboratory Manual). Each person in the group of five will prepare one of the seven suggested solutions, so that the calibration curve will contain five points. We ask the students to think critically about which ee mixtures are the most sensible choices to contribute to their calibration curve. Students use automated pipettes to transfer α-methylbenzylamine (**4**) into 10 mL volumetric flasks and then dilute using chloroform-*d*. The host solution is obtained by weighing out the solid 2-FPBA (**1**) and (*R*)-BINOL (**2**) followed by dissolution in chloroform-*d* in a 10 mL volumetric flask. The solutions of amine are prepared at 60 mM, while the host solution is 50 mM in both 2-FPBA (**1**) and (*R*)-BINOL (**2**). To all of these solutions are added 4 Å molecular sieves, and the solutions are allowed to dry for 10 min. The students are also provided with a selection of seven 60 mM amine solutions of unknown ee prepared before the laboratory period by the instructor or a laboratory technician. Each student in the group of five chooses one of these samples to combine with the host solution and determine its ee. To make the samples ready for NMR spectroscopic analysis, 0.3 mL of the known or unknown amine solution is combined with 0.3 mL of the host

Scheme 2. Boronic Acid Based Three-Component Assembly for the EE Determination of α-Methylbenzylamine



DOI: 10.1021/acs.jchemed.6b00355
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solution in an NMR tube. As designated, each student is responsible for making two NMR samples (one with an amine solution of known ee, and one with unknown ee). The samples are then analyzed by ^{1}H NMR spectroscopy (collection parameters are described in the Laboratory Manual). It was found that the practical part of the experiment described above could be carried out comfortably within 2 or 3 h.

Data Analysis

The second part of this experimental procedure takes place at a computer terminal, ideally in a teaching ready computer room. The NMR data recorded from the samples prepared during the laboratory session are returned to the students in electronic format and then processed using NMR processing software. The students are also provided with printed NMR spectra of each of the three components as pure compounds in chloroform-*d*. They are instructed to identify and compare several key resonances: the aldehyde peak (O═C*H*) in 2-FPBA (**1**) and the imine peaks (N═C*H*) of the diastereoisomers (*R*,*R*)-**5** and (*R*,*S*)-**5** of the assembly, the benzylic protons in the free amine **4** and in the assembly (*R*,*R*)-**5** and (*R*,*S*)-**5**, and the alcohol peak (O*H*) in (*R*)-BINOL (**2**). Students then use the NMR processing software to analyze the relative integrations of peaks in the imine and benzylic regions of their group's spectra to determine the ratio of diastereoisomers (*R*,*R*)-**5** and (*R*,*S*)-**5** and infer the ee of the starting α-methylbenzylamine **4** mixture in their unknown. The students will need to construct two calibration curves (one using the imine protons and one using the benzylic protons) using the spectra of the known ee samples they made as a team. Plotting the observed ee vs the true ee should garner a straight line, and an equation of best fit can be calculated. This equation can then be used to determine the ee of the five unknown amine samples the students have made. The students should plot their own calibration curve using the data from the five students in the team. In the event of some error in sample preparation, instructors may have to substitute data so students can carry out the analysis. Calibration curves for both possible sets of protons (imine and benzylic) should be plotted. Students may find one calibration curve gives a better straight-line correlation and therefore may choose to select one of the two curves to determine their ee values. Students should comment on the accuracy and reproducibility of the data obtained or discarded and then make an informed decision on which data set they believe to be a more accurate measure of the true ee. The proforma to be filled out by the students asks them to justify the decisions they have made throughout the data analysis and also discuss the chemistry involved in this process.

HAZARDS

All hazards are outlined in the laboratory manual,[12] however it is best if the students are reminded of all the below safety issues before beginning the experiment. Safety glasses, nitrile gloves, and a laboratory coat should be worn at all times in the laboratory, and care should be taken when handling the chemicals. Both (*R*)- and (*S*)-α-methylbenzylamine (**4**) can cause severe skin burns and eye damage, and the (*S*)-enantiomer is also toxic in contact with skin. 2-FPBA (**1**) is a skin, eye, and respiratory irritant. (*R*)-BINOL (**2**) is toxic if swallowed, however any risk of ingestion carrying out this procedure is minimal. During the experiment students will be handling significant volumes of deuterated chloroform, which is harmful if swallowed and also suspected of causing cancer. For this reason, students should work in a fume hood when handling chloroform. Acetone is also used to wash glassware; students therefore should be aware that it is flammable and can cause eye irritation in addition to feelings of drowsiness or dizziness. Diastereoisomers (*R*,*R*)-**5** and (*R*,*S*)-**5** also need to be considered for their hazards: as material safety data sheets (MSDS) are not available for these products, students should assume that they are toxic, irritating, and corrosive and thus handle accordingly. However, these products are made in a sealed NMR tube, and thus exposure risk should be minimal.

When carrying out any laboratory work it is vital that local health and safety procedures are observed. Therefore, before carrying out this experiment in another undergraduate laboratory the process should be assessed to ensure that it adheres to local health and safety requirements.

RESULTS AND DISCUSSION

This experiment has been successfully run with a cohort of 113 students at the University of Birmingham (U.K.). A few minor alterations to the earlier versions of this experiment were made during testing. It was found that students often spilled a small amount of their NMR solutions down the outsides of the NMR tubes while making up their NMR samples, making the tubes unpleasant to handle for the NMR staff running the samples. However, more importantly, soiled tubes are a problem for NMR spectroscopy as dirt will accumulate in the probe and on the spinners over months of intensive use, therefore decreasing the quality of the data obtained. Therefore, instructors should ensure that students wipe the outside of their NMR tubes with a tissue soaked with a small amount of acetone to remove any residue. Direct measurement using graduated pipettes into NMR tubes should be discouraged due to the propensity for NMR tube breakage. Therefore, it is recommended that students make up their solutions in glass vials using a graduated glass pipet, before then transferring an aliquot of this solution into the NMR tube using a Pasteur pipette in the usual fashion.

The most critical aspect for obtaining good quality data is the removal of adventitious water from the NMR samples. It was found that the addition of activated 4 Å molecular sieves to all of the solutions used in this experiment was key to obtaining good quality NMR spectra. This enabled accurate determination of diastereomeric ratios, which gave inferred ee values that were accurate to within ±10% of the true ee values in the hands of undergraduate students. Any residual water can hydrolyze the formed imine and can potentially compete with the (*R*)-BINOL (**2**) to bind with the boron atom.

Use of the correct ratio of amine solution to host solution is important to obtain accurate diastereomeric ratios by NMR spectroscopic analysis. More specifically, it is important that the amine is in excess and that kinetic resolution based on the preferential formation of one diastereoisomer is not observed.[8e] If the host solution is in excess, residual BINOL (**2**) can produce a very broad peak (corresponding to the phenolic protons) in the same region of the ^{1}H NMR spectrum as the benzylic protons of the diastereoisomers created upon assembly formation. Therefore, the presence of excess BINOL (**2**) leads to a benzylic region which cannot be used to accurately determine the true ee value of the starting amine due to overlap between free BINOL (O*H*) and benzylic resonances. Some students observed this phenomenon, possibly due to inaccurate preparation of host and/or amine solutions. In cases where this occurs (this was a rare occurrence; around 1 group in 5 may

DOI: 10.1021/acs.jchemed.6b00355
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have an anomalous point), after the student has plotted the calibration curve and observed that there are anomalous points (which obviously do not fit a linear regression), if there is time to repeat the experiment this is of course the best method to remedy inconsistent data. However, where there are lab space and time restraints in order to complete the experiment in a timely manner and for students to get accurate ee determinations, instructors may guide groups to ignore points in the calibration, or offer replacement data as they deem appropriate (students are never encouraged to ignore data). Such observations are also incorporated into the assessment, as students are asked to critically evaluate the quality of their data and make judgements as to whether it is ever appropriate to omit data points. This critical analysis is pivotal within a research environment, so developing these skills during undergraduate learning is important to their future success in a research setting.

During the data analysis session, it was noted that a thorough introduction into the use of NMR processing software was required. The majority of students had no experience with NMR data processing and struggled to use the programs effectively without precise instructions. The Student Laboratory Manual includes a short introduction to MNova 10 and TopSpin, and video files demonstrating the basic functions of MNova and TopSpin are provided; however, any program which can open and integrate NMR data can be used.

REFLECTIONS

This experiment has been carried out by a cohort of 113 second-year undergraduate students (groups of 20 students took part in the experiment over a series of 6 weeks) at the University of Birmingham (U.K.). This exercise was part of a general undergraduate laboratory program carried out during the second semester, however this procedure could potentially be used as part of an organic, physical organic, or analytical chemistry course. During the testing of this experiment we learned several ways in which our initial protocol could be improved, and these improvements have been implemented into the described experimental procedures.

Students were required to fill in a proforma for this experiment, and several observations were made from the marking of these assessments. First, the construction of the calibration curves was achieved with variable success. A key training point was the construction of the calibration graphs. Despite difficulties in the construction of the graphs students were successful in applying these graphs to determine the ee of unknown samples. Students found it difficult to deal with hypothetical situations, such as the reasons for potential error being introduced into this experiment, with many students constructing answers relating to human-based errors, or specific examples that they encountered. The essay style questions were designed to challenge the critical thinking of the students and to encourage them to assess and question the validity of the data they obtained; some students found it challenging to answer these questions. Some were reluctant to comment on the quality of their data, perhaps feeling that critical self-assessment would lead to a loss of marks. However, the mark scheme is specifically designed to encourage the critical evaluation of data, regardless of results obtained, and students may need to be reassured of this during the experiment.

The student experience from this experiment appeared mainly positive. Each student was given a feedback questionnaire about what they liked and disliked about the protocol. In the majority they found the laboratory instructions to be clear and easy to follow. They did note that, due to this being the first time that they experienced using NMR processing software, they found it confusing in places. Therefore, in this revised version we have produced written and video instructions for software use.

Overall, this protocol demonstrated a practical introduction into the use of ^{1}H NMR spectroscopy as a technique for determining the ee of a primary amine, via diastereoisomer formation, including an introduction to the use of NMR processing software. In addition to this, the experiment reminds students of the relationships between diastereoisomers and enantiomers and reinforces knowledge of carbonyl condensation chemistry with amines. It also introduces them to the reversible, covalent, supramolecular interactions between boronic acids and diols[13] and aims to encourage students to critically analyze their decisions and results, both in the laboratory and during data analysis.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available on the ACS Publications website at DOI: 10.1021/acs.jchemed.6b00355.

Student laboratory manual (PDF, DOCX)
Technician notes (PDF, DOCX)
Demonstrator notes (PDF, DOCX)
Proforma assessment (PDF, DOCX)
Marking guide, for the proforma (PDF, DOCX)
NMR analysis software videos (ZIP)
Reference NMR data (ZIP)

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Author Contributions

All authors contributed to the preparation of the manuscript. J.S.F. is the first and corresponding author; all other authors are listed alphabetically. J.S.F. designed the undergraduate experiment and conceived this manuscript. E.V.A., S.D.B., and T.D.J. provided academic input toward the experiment and its original research-inspired concepts. B.M.C., D.T.P. and W.D.G.B. wrote the body of text and contributed toward the Supporting Information. B.M.C. and J.A.C.L. investigated the experimental methodology. W.D.G.B. provided laboratory instruction and undergraduate support to the first cohort of students. D.T.P. marked and provided feedback on the assessment of the first cohort of students. C.S.L.D. and C.V.M. designed the NMR analysis and data acquisition procedures. K.A.R. produced the NMR software videos. G.L. contributed toward the production of the Supporting Information. S.L. ran a preliminary version of the experiment and provided feedback.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

The authors would like to thank Katie Topham and Rachel Sturman (University of Birmingham Undergraduate Laboratory Technicians), Ian Shannon (University of Birmingham Director of Undergraduate Laboratories), John Snaith (University of Birmingham Head of Education), and Wenlei Zhai for support

DOI: 10.1021/acs.jchemed.6b00355
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in the running of this experiment. J.S.F. would like to thank the Royal Society for an Industrial Fellowship and the EPSRC for funding (EP/J003220/1). J.S.F., E.V.A., W.D.G.B., and B.M.C. are particularly grateful for a Royal Society International Exchange Grant that facilitated much of this investigation. E.V.A. also thanks the Welch Regents Chair for support (F-0046). J.S.F., D.T.P., and W.D.G.B. would like to thank the University of Birmingham for support. D.T.P. and W.D.G.B. would like to thank the Royal Society of Chemistry and the Society for Chemical Industry for travel grants. The Catalysis and Sensing for our Environment (CASE) group is thanked for providing essential networking opportunities.[14] The second-year undergraduate class of chemistry students (2015−2016) at the University of Birmingham (UK) are thanked for undertaking this experiment with their usual academic enthusiasm and are awesome.

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(11) −Ee and +ee refer to opposite enantiomer in excess. −100% ee is defined as a solution of pure (*S*)-MBA, and + 100% ee is defined as a solution of pure (*R*)-MBA.
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