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Laboratory Experiment

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Diastereoselective Allylation of *N-tert*-Butanesulfinyl Imines: An Asymmetric Synthesis Experiment for the Undergraduate Organic Laboratory

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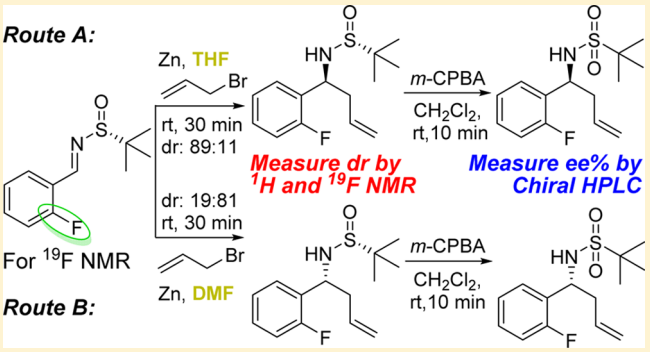
Supporting Information

ABSTRACT: An asymmetric synthetic experiment that encompasses both diastereoselectivity and enantioselectivity is described. In this experiment, Zn-mediated allylation of an (*R*)-*N-tert*-butanesulfinyl imine is first performed to obtain either diastereomer using two different solvent systems, followed by oxidation of the homoallylic *N-tert*-butanesulfinyl amines, which gives either enantiomer of the corresponding products. Purification by flash column chromatography is required at the final step and the desired products are isolated in good overall yields. The diastereomeric ratio (dr) of the allylation products is determined by ^{1}H and ^{19}F NMR spectroscopy, while the enantiomeric excess (ee) of the final products is measured by chiral HPLC. Overall, this experiment can be carried out with readily accessible reagents under mild conditions. Moreover, it enables students to learn the differences between enantiomers and diastereomers, the determination of ee and dr regarding optical compounds using HPLC and NMR spectroscopy, and how a reversal of stereochemical outcome is realized simply by tuning the reaction solvent.



KEYWORDS: *Upper-Division Undergraduate, Laboratory Instruction, Organic Chemistry, Amines/Ammonium Compounds, Asymmetric Synthesis, Diastereomers, Enantiomers, HPLC, Lewis Acids/Bases, Mechanisms of Reactions*

Asymmetric synthesis is a topic of critical importance in organic chemistry with a wide range of applications in pharmaceutical industry.[1] The desire for the elaboration of efficient synthetic strategies has led to a concern for stereochemistry, an important concept frequently encountered in the undergraduate organic chemistry courses. Although traditional textbooks do help students better learn about various kinds of stereochemistry and stereoselectivity, these concepts are sometimes abstract and can be very elusive for beginners to understand. Students were often confronted with reactions wherein there were both enantiomers and diastereomers, but might have difficulty drawing a distinction between them. An illustrative experiment is clearly needed to help students clarify these terms, but developing such an experiment often has several challenges. One of them lies in the condensation of enantioselectivity and diastereoselectivity into a single experiment in limited lab time. While asymmetric catalysis often exhibits high enantioselectivity,[2,3] it sometimes precludes the assessment of diastereoselectivity due to a lack of pre-existing chiral centers in the substrates. Chiral auxiliaries, by contrast, address this issue. Besides a high level of diastereoselectivity, transformations with chiral auxiliaries are usually well-studied,[4] delivering more information about the mechanistic aspects of organic reactions.

Among a number of chiral auxiliaries,[5−10] Evans auxiliaries have been incorporated into undergraduate organic chemistry laboratories by two schools for demonstrative purposes.[11,12] Notably, these experiments covered many important topics in organic chemistry, with an emphasis on the utility of chiral auxiliary in introducing diastereoselectivity. Nevertheless, some other aspects of asymmetric synthesis, such as reaction mechanisms and the concepts of different stereochemistry, are still much less explored in the chemical education literature. It is clear that an illustrative laboratory experiment involving such fundamental elements as enantiomer, diastereomer, enantiomeric excess (ee), diastereomeric ratio (dr), as well as their characterization methods, is still in great demand.

Inspired by the pioneering work of Davis[13−15] and Ellman,[16−19] who advanced the synthesis and applications of sulfinamide, several reaction conditions have been developed for the Zn-mediated allylation of *N-tert*-butanesulfinyl imines.[20−24] In light of the above pedagogic goals, there are multiple benefits of adapting this synthetic methodology into an undergraduate experiment. First, either diastereomer can be produced from a single sulfinimine enantiomer by appropriate selection of reaction solvents, a phenomenon that would encourage students in sorting out how stereoselectivity is reversed by solvent change. Second, some reaction conditions only afford the amine products with moderate dr, but in these

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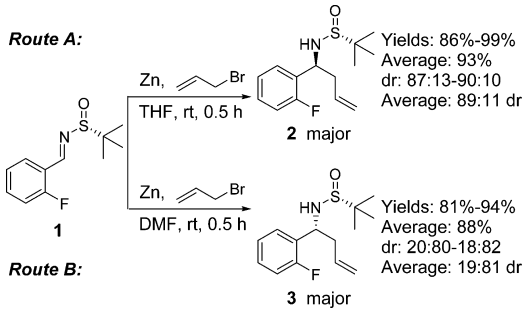
cases, both diastereomers will appear in the ^{1}H NMR spectra, and their relative abundance clearly exemplifies the concept of diastereoselectivity. Third, the amine derivatives can be readily oxidized by *meta*-chloroperbenzoic acid (*m*-CPBA),[25] and, with concomitant loss of a chiral center in the substrates, the resulting enantiomers also serve as an indicator of enantioselectivity in a chiral HPLC test. A study of a number of solvents and additives for the Zn-mediated allylation of *N*-*tert*-butanesulfinyl imines showed that when tetrahydrofuran (THF) was replaced with *N*,*N*-dimethylformamide (DMF), a significant reversal of stereochemical outcome was observed. Noticeably, both reactions gave rise to the desired products in mild diastereoselectivity and were completely devoid of additives.[20] Since this experiment involves relatively simple procedures and obviates the need for complex chemical reagents, it is a suitable experiment to familiarize students with some basic concepts of asymmetric synthesis. Herein, an 8 h (two 4 h laboratory periods) laboratory experiment is described that has been conducted successfully four times with 84 students in an advanced undergraduate organic chemistry laboratory course.

EXPERIEMENTAL OVERVIEW

A pre-lab assignment includes an overall review of concepts associated with enantioselective and diastereoselective reactions, chiral auxiliary, Barbier reactions, NMR spectroscopy and HPLC technologies, and a general understanding of previous research in this field (see Supporting Information). During the first lab period, students work in pairs to complete two individual reactions (Scheme 1). (*R*)-*N*-*tert*-Butanesulfinyl

Scheme 1. Diastereoselective Synthesis of Homoallylic *N*-*tert*-Butanesulfinyl Amines

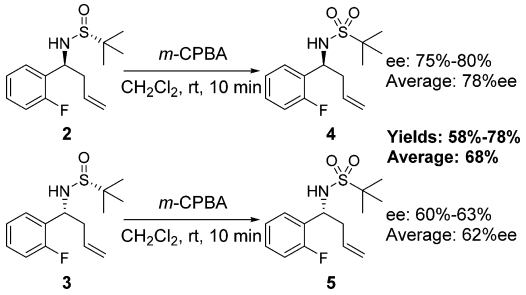


imine **1** is diastereoselectively allylated under two reaction conditions that vary only by solvent choice. THF is used by one-half of the students while DMF is used by the other half. The intermediate products **2** and **3** are subsequently treated with *m*-CPBA in dichloromethane (DCM) to afford both enantio-enriched forms of the final products **4** and **5** (Scheme 2).[25] During the second lab period, **4** and **5** are purified by column chromatography and characterized by both ^{1}H NMR spectroscopy and chiral HPLC. From these measurements, students obtain dr and ee values of their products, which, along with their own analysis, are integrated into lab reports.

EXPERIMENT

In the first 4 h period, students prepare homoallylic amine **2** or **3** with (*R*)-*N*-*tert*-butanesulfinyl aldimine **1**, active zinc powder and allyl bromide in dry THF or DMF under argon in test tubes. After 0.5 h at room temperature, thin-layer chromatography is used to determine the completeness of the reactions. After workup, the intermediate products **2** and **3** (10 mg each) are characterized by ^{1}H and ^{19}F NMR spectroscopy. The remaining products are oxidized by *m*-CPBA in DCM at room temperature. The corresponding crude products are kept at room temperature. In the second lab period, the final products (**4** and **5**) are purified by flash column chromatography and characterized by ^{1}H NMR spectroscopy and chiral HPLC. See Supporting Information for detailed procedures.

Scheme 2. Oxidation of the Homoallylic *N*-*tert*-Butanesulfinyl Amines



HAZARDS

All experiments should be performed in fume hoods. Students are required to wear safety goggles and use gloves. Potential risks include the use of allyl bromide, which is a known toxic and flammable reagent. Direct contact with DMF, DCM or chloroform-*d* should be absolutely avoided since they are known or potential carcinogenic agents. THF, isopropyl alcohol and ethyl acetate are irritants and are highly flammable. *n*-Hexane is neurotoxic when inhaled and exposure to its vapor should be strictly minimized. *m*-CPBA should be handled with extreme care since it is an oxidizing reagent that is highly explosive and corrosive. Silica gel is highly toxic when inhaled and may lead to lung diseases and lung cancer, so students should wear masks when loading columns. (*R*)-*N*-*tert*-Butanesulfinyl imine and products in this experiment are harmful if swallowed or put in contact with skin. Students need to complete their own risk assessment in the pre-lab assignments to ensure that they are fully aware of the potential hazards in this experiment.

RESULTS AND DISCUSSION

This experiment has been carried out in an upper-division experimental synthetic organic chemistry laboratory course. Both reactions performed by students typically culminated in good yields and stereoselectivity (Schemes 1 and 2). Yields for **2** ranged between 86% and 99% with an average of 93%; yields for **3** ranged between 81% and 94% with an average of 88%. Students recorded the ^{1}H NMR and ^{19}F NMR spectra for **2** and **3**; the ^{1}H NMR signals for the allylic hydrogen (benzylic hydrogen as well) was used at 4.7 and 4.8 ppm and the ^{19}F signals were used to determine the dr (Figure 1). The dr ranged between 87:13 and 90:10 for **2** with an average of 89:11, and between 20:80 and 18:82 for **3** with an average of 19:81. The oxidation of **2** and **3** gave yields for **4** and **5**, respectively, that ranged between 58% and 78% with an average of 68%. Students recorded the ^{1}H NMR spectra (see Supporting Information) and chiral HPLC traces (Figure 2) for **4** and **5**. The ee from chiral HPLC analysis ranged between 75% and 80% for **4** with

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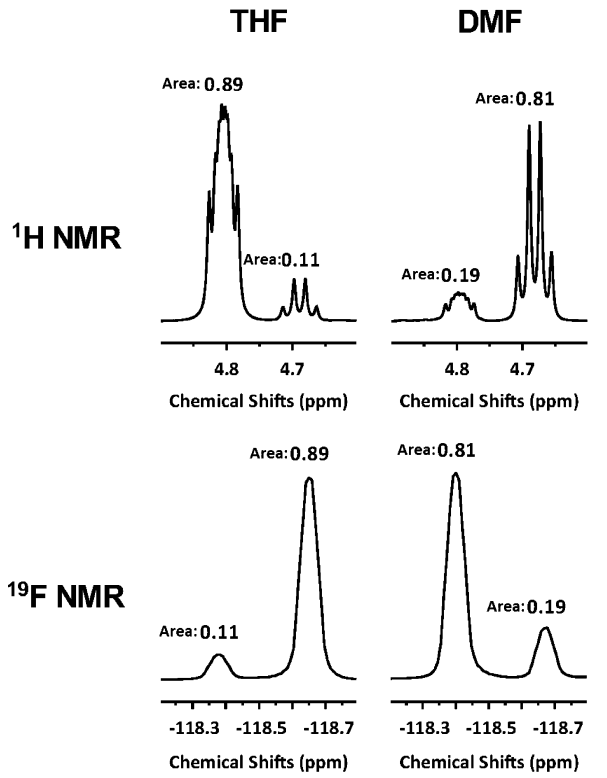

Figure 1. NMR analyses of the homoallylic *N-tert*-butanesulfinyl amines obtained from the THF system (left) and the DMF system (right).

an average of 78%, and between 60% and 63% for **5** with an average of 62%.

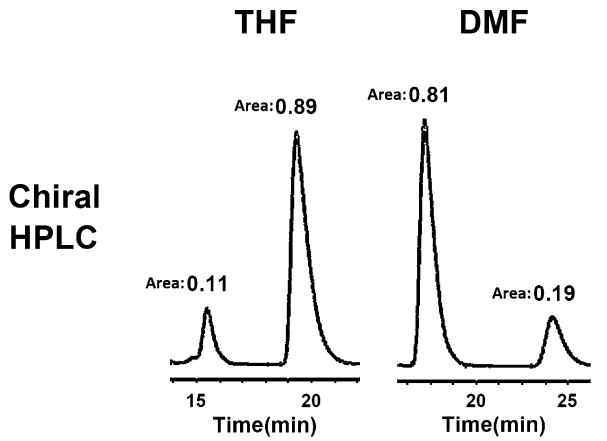

Figure 2. Chiral HPLC analyses of the homoallylic *N-tert*-butanesulfonyl amines obtained from the THF system (left) and the DMF system (right).

Numerous stereoselective reactions are considered true milestones in the history of organic synthesis and have been widely used as crucial steps in producing natural products.[1] This experiment offered students an opportunity to explore the influence of different solvents on the direction of asymmetric synthesis. The laboratory exercise incorporated various concepts in organic chemistry. Pedagogically, this experiment provided students an opportunity to explore the reactions of aldimines and their derivatives, and to learn how to handle multistep experiments. Additionally, it deepened their understanding of some important concepts such as enantioselectivity, diastereoselectivity, enantiomeric excess and diasteromeric ratio. A wide range of analytical techniques were used—thin-layer chromatography, column chromatography, chiral HPLC, ^{1}H NMR and ^{19}F NMR spectroscopy, further reinforcing their importance to organic chemistry research.

To the best of our knowledge, *tert*-butanesulfinamides had not been used as chiral auxiliaries in diastereoselective reactions for laboratory instruction purposes. In this experiment, this auxiliary offered a number of advantages. As a common reagent, mild stereocontrol was attained in both reaction conditions. Furthermore, it was accessible to oxidation by *m*-CPBA at room temperature,[25] a reaction that afforded the desired enantiomer without further purification of the previous product. With this readily accessible reagent, the two-step reaction occurred under mild conditions within a short period of time, catering to the need of an undergraduate organic laboratory. Overall, it was a practical asymmetric synthesis experiment that can be readily incorporated into an undergraduate chemistry curriculum.

One of the essential challenges in asymmetric synthesis lies in the preparation of enantiopure products of both enantiomers. In this experiment, a remarkable reversal of stereoselectivity was observed with a switch in the solvent. The possible mechanisms are based on the X-ray crystal structure of *N-tert*-butanesulfinyl aldimine **6**, which shows that the aldimine exists in the *E* configuration and the C═N bond is pseudo-*cis* to the S═O bond (Figure 3).[22] So, when THF is used as a

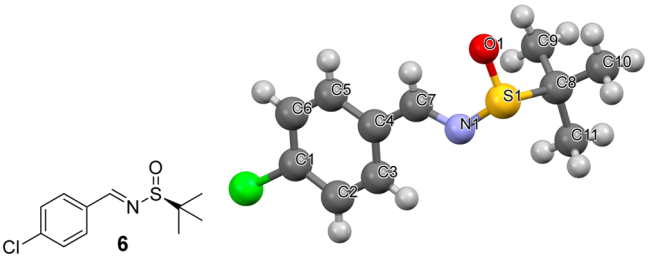

Figure 3. X-ray crystal structure of *N-tert*-butanesulfinyl aldimine **6**.

solvent, the nucleophilic addition is completed via a six-membered, chairlike transition state model (TS-1 in Figure 4).

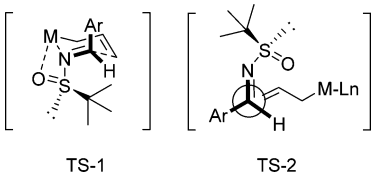

Figure 4. Mechanistic proposals for stereocontrol.

In this cyclic chelation model, the allymetal that coordinates to both nitrogen and sulfinyl oxygen of the imine makes the tertiary butyl group occupy the *Re*-face, directing the allyl attack to the sterically unblocked *Si*-face of the imine to produce the (*S*)-amine.[20] By contrast, the allymetal is shielded from coordinating to the substrate in the presence of DMF, a Lewis base that has a much higher affinity for the metal (TS-2 in Figure 4). In this case, the uncoordinated (*R*)-*N-tert*-butanesulfinyl imine is in its natural conformation, with its tertiary butyl group occupying the *Si*-face. As a result, the allyl addition would occur on the less hindered *Re*-face of imine, thereby facilitating (*R*)-amine formation.[20] While students

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should postulate on the mechanisms in their reports, the basic requirement was that students interpret the results using the fundamental concepts presented in the above mechanisms.

As assessment of the achievement of pedagogic goals was especially important to chemical education, the post-lab questions (see Supporting Information) were meticulously designed to reflect the pedagogic aims of this experiment. A survey of students' lab reports revealed that students exhibited an appreciable understanding of the different stereoisomers and stereoselectivity described in this experiment. Furthermore, by virtue of the transition state models (Figure 4), students also became better acquainted with some important concepts in asymmetric synthesis, such as Newman projections, Zimmerman-Traxler transition state, Lewis acids and bases, as well as steric hindrance. The considerable reversal of stereocontrol caused by solvent change provided students with motivation for this experiment, as they became more energetic and engaged in discussions with instructors after the lab. Therefore, it is suggested that, if desired, questions of similar reaction mechanisms can be incorporated into post-lab quizzes,[26,27] which aim to test students' proficiency in using the above conceptual tools to account for the stereoselectivity of other reactions.

In conclusion, the experiment provided a series of advantages, featuring simple strategies, abundant skills training and mind-expanding mechanisms. The experiment should stimulate student interest in learning more about asymmetric synthesis and its related mechanisms.

■ ASSOCIATED CONTENT

Supporting Information

Instructions for students, notes for instructors and sample spectra (Chiral HPLC, ^{1}H and ^{19}F NMR). This material is available via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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