A One-Pot, Asymmetric Robinson Annulation in the Organic Chemistry Majors Laboratory

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The Robinson annulation is an integral part of the second-year organic curriculum. Here we would like to report a one-pot enantioselective Robinson annulation that was performed in our undergraduate honors–majors lab.

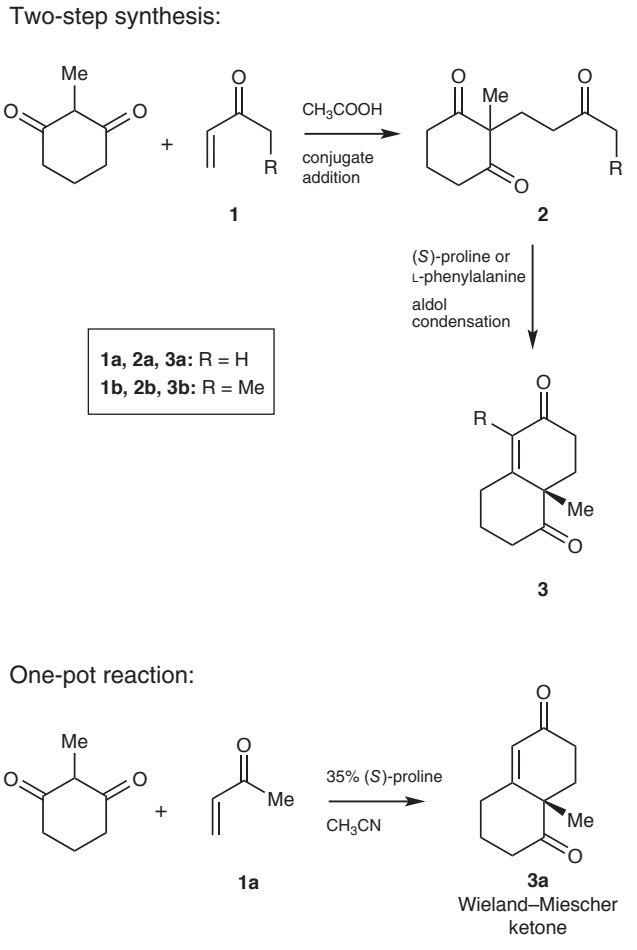
Theory

Stereoselective organic transformations have been of fundamental interest to synthetic chemists since the 1970s but have yet to be incorporated extensively into the second-year organic chemistry curriculum. Additionally, there are few second-year organic experiments that employ asymmetric catalysis, primarily owing to the fact that many of the catalysts for enantioselective reactions are metal complexes that are air-sensitive and expensive, requiring the use of solvent stills and glove boxes, thus making these experiments unfeasible in an undergraduate laboratory setting *(1)*. Two recent developments have promoted our interest in designing experiments that incorporate enantioselective transformations. First, the awarding of the 2001 Nobel Prize in chemistry to Sharpless (asymmetric epoxidations), Noyori, and Knowles (asymmetric hydrogenations) crystallized the realization that we need to update our pedagogy in the undergraduate lab curriculum. Second, the recent renewed interest in organocatalysis in the chemical literature provided inspiration and new avenues to explore: organocatalysts are simple organic molecules that are usually inexpensive, air-tolerant, and environmentally benign, making organocatalysis technically simple for an undergraduate student *(2)*. Most organocatalysts are nontoxic and recyclable and many reactions use water as the solvent, thus falling into the category of green chemistry.

Work in our laboratory has focused on developing methodology for enantioselective organocatalytic reactions in both a research and pedagogical context. The (*S*)-proline-catalyzed, organocatalytic Robinson annulation is an ideal experiment for the second-year organic curriculum. The reaction, often referred to as the Hajos–Parrish–Eder–Wiechert reaction, was developed in the early 1970s and involves a two-step sequence: a non-selective conjugate addition reaction followed by an enantioselective intramolecular aldol condensation reaction (Scheme I, top equation) *(3)*.

In 2000, Barbas reported that (*S*)-proline could successfully catalyze a one-pot Robinson annulation between methyl vinyl ketone **1a** and 2-methyl-1,3-cyclohexanedione to form the (*S*)-Wieland–Miescher ketone **3a** in 76% ee *(4)*. However, the reaction took 89 hours to reach completion and required the use of DMSO as the solvent. Barbas also reported that other amino acids were not successful in catalyzing the one-pot Robinson annulation.

In 1995, Markgraf, Fei, and Ruckman reported the synthesis of the 5-methyl analog of Wieland–Miescher ketone **3b** in a second-year organic lab setting *(5)*. This experiment was not a one-pot Robinson annulation but rather two different tandem experiments (an acetic acid-catalyzed Michael reaction to form substrate **2b** followed by an (*S*)-phenylalanine-catalyzed aldol cyclization) to eventually produce ketone **3b** in 80% ee (Scheme I, top equation). However, their reaction did not work well with substrate **1a**, and the Wieland–Miescher ketone product **3a** was essentially racemic (10% ee). Markgraf's lab experiment was published prior to the discovery of the one-pot organocatalytic Robinson annulation, and at a time when the mechanism and stereochemistry-determining step of the reaction were not well-established. Moreover, column chromatography was problematic for the second step of their experiment: product **2a** had the same R_f as compound **3a** (Scheme I), thereby requiring GC–MS and IR to determine product ratios.



Scheme I. Asymmetric syntheses of the Wieland–Miescher ketone.

We were able to improve on Barbas's one-pot Robinson annulation in our research laboratory with a change of solvent: by using acetonitrile instead of DMSO, we obtained the desired Wieland–Miescher ketone **3a** in 67% ee (84:16 enantiomer ratio), with excellent product conversion. Additionally none of the intermediate compound **2** was observed thereby making column chromatography trivial. We were thus able to adapt Barbas's experiment and are excited to report the first enantioselective one-pot Robinson annulation of the Wieland–Miescher ketone in a second-year organic laboratory *(6, 7)*.

Timetable

This experiment is performed during two consecutive lab periods. In the first lab period the instructor gives an in-depth lab lecture and the students set up the reaction and dry-pack the pipet column in preparation for the next lab period. In the second lab period the students work up the reaction, isolate the pure product through column chromatography, and prepare samples for NMR analysis and GC or HPLC. The samples are run with autosamplers and sent to the students electronically. The students analyze the data and write a formal lab report after completion of the lab.

Experimental Procedure

All reagents were used without prior purification. The reaction was performed in a 25 mL 14/20 round-bottom flask that was sealed with a septum to prevent evaporation of solvent over the course of the week. The flask was placed in a water bath at 35 °C during the reaction setup and then transferred to a digitally-controlled oil bath–stir plate where it was heated at 35 °C for a week. (A digitally-controlled hot water bath can be substituted for the oil bath). The reaction mixture is originally a white suspension but turns into a brown solution over the course of the experiment. During the second day, the solution is quenched with saturated ammonium chloride, extracted under standard work-up conditions, and concentrated in vacuo. Purification is performed on a silica gel pipet column to produce the Wieland–Miescher ketone in about 75% yield. Column fractions were identified by TLC in comparison with a commercially available sample of the Wieland–Miescher ketone. Characterization of the product was achieved through ^{1}H NMR (see the online material).

Analysis of enantioselectivity was achieved by chromatographic comparison of the product with a commercially available sample of Wieland–Miescher ketone (Figure 1). The separation of enantiomers was achieved on either chiral GC or chiral HPLC (detailed conditions are given in the online material).

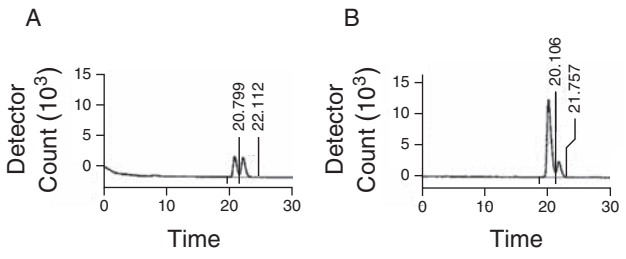


Figure 1. Separation of Wieland–Miescher ketone on chiral HPLC: (A) separation of a racemic mixture and (B) separation of product obtained from an (*S*)-proline-catalyzed reaction.

Special Equipment, Chemicals, and Instruments

1. Digitally-controlled hot water or oil bath (for example, IKA RCT Basic hotplate–stirrer)
2. Capillary gas chromatograph equipped with a Supelco β-dex column and FID detector or HPLC equipped with a Chiralcel OD-H column

Hazards

All experiments should be performed in fume hoods with suitable eye protection, gloves, and lab coats. Dichloromethane and deuterated chloroform are suspected cancer agents—eye and skin contact and ingestion of any of the chemicals should be avoided. (*S*)-Proline may be harmful if absorbed through the skin, inhaled, or swallowed. Acetonitrile is toxic by inhalation, ingestion, or skin absorption; it is an irritant and a possible teratogen. 2-Methyl-1,3-cyclohexanedione may be harmful if absorbed through the skin, inhaled, or swallowed. 3-Buten-2-one (methyl vinyl ketone) is flammable and toxic. It should be available to students in a small bottle and used in the hood.

Discussion

This experiment is, to our knowledge, the first one-pot Robinson annulation in an undergraduate laboratory setting. (Markgraf's synthesis of the 5-methyl analog of the Wieland–Miescher ketone, **3b**, was a very nice lab experiment; however, their synthesis did not invoke a single-step Robinson annulation, but rather a Michael addition followed by an aldol condensation in two discrete steps. They also obtained low asymmetric induction for Wieland–Miescher ketone **3a.**) Although our reaction does take the same quantity of time (two lab periods) as the previously reported two-step procedure, it is a one-pot reaction and thus involves less student effort to set up, work up, and purify the final product. Thus there is sufficient time during the lab period for an in-depth discussion on the theory (the mechanism, catalyst cycle, and model for asymmetric induction) along with hands-on work on the HPLC or GC. Additionally, we do not observe any of the intermediate **2a**, encounter any problems in purifying the final product by column chromatography, or need to resort to GC–MS or IR for structural elucidation. The high product conversion that we observe might be attributed to either the choice of (*S*)-proline as the catalyst or the use of acetonitrile as the solvent—our reaction was less successful with other organic solvents *(8)*. A drawback to our reaction is that it is substrate-specific for compound **1a** and substrate versatility has not yet been tested. Therefore if one wanted to synthesize other substrates, the 2-step protocol might be more appropriate.

In recent years List et al. have made significant progress in determining the mechanism and models for asymmetric induction for the annulation (Scheme II) *(9)*. The proposed reaction mechanism and catalyst cycle of a proline-catalyzed Robinson annulation are more elaborate than what is typically presented to second-year organic students; proline is said to react with methyl vinyl ketone to form an imminium ion **B**, lowering the

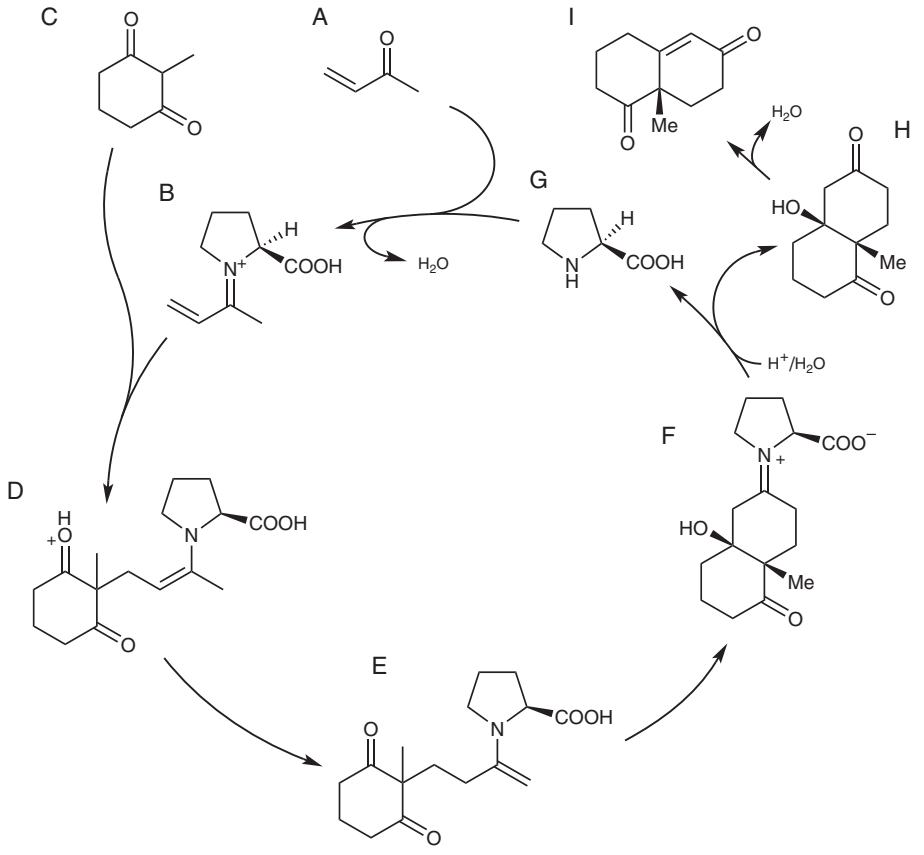
LUMO of the ketone, thereby promoting conjugate addition of the nucleophile (the diketone); followed by tautomerization of the resulting enamine **D**; aldol cyclization; and hydrolysis of the catalyst leading to catalytic turnover and removal of water. An in-depth prelab lecture and handouts were provided to the students to ensure that they had complete comprehension of the material. Models explaining asymmetric induction (which is believed to occur from the step **E** to **F**), calculation of enantiomeric excess, and an explanation of chiral GC or HPLC were also provided to the students. (For a student handout of the catalyst cycle and rationale for asymmetric induction, see the online material).

Despite the fact that the enantioselectivity is not extremely high (67% ee, 84:16 enantiomer ratio), the difference between major and minor enantiomer is clearly significant and the experiment works well as a proof of concept. Students are able to compare products from a racemic reaction with that of an enantioselective reaction and calculate the enantiomeric excess (Figure 1).

The Wieland–Miescher ketone reaction product has been used as a chiral synthon for many natural product syntheses. In order that students understand the synthetic utility of the experiment, examples were provided of compounds that had been synthesized from the (*S*)-Wieland–Miescher ketone (see the online material) *(10)*.

Assessment and Analysis of the Merit of the Experiment

The pedagogical value of the experiment was assessed through a formal lab report, test, final examination, and an anonymous survey (see the online material). Since this experiment required students to have a good conceptual grasp of a variety of topics—enantiomers, enantioselective reactions, catalyst-turnover, formation of enamines, conjugate addition, tautomerization, aldol cyclization, elimination, acid-promoted hydrolysis of proline—we were concerned about the level of student comprehension of the experiment. We were pleased to discover that, although the mechanism of the reaction and the topics of enantioselectivity and asymmetric induction were challenging concepts, enough background information had been provided to the students to enable them to comprehend the material at a level comparable to that of any other experiment conducted during the course of the semester. Additionally, students were not overwhelmed by the material and were especially comfortable with the underlying concepts of the lab upon completion of the experiment—see the online material.



Scheme II. Proposed catalyst cycle for the reaction *(9)*.

Acknowledgments

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