Acylation, Diastereoselective Alkylation, and Cleavage of an Oxazolidinone Chiral Auxiliary

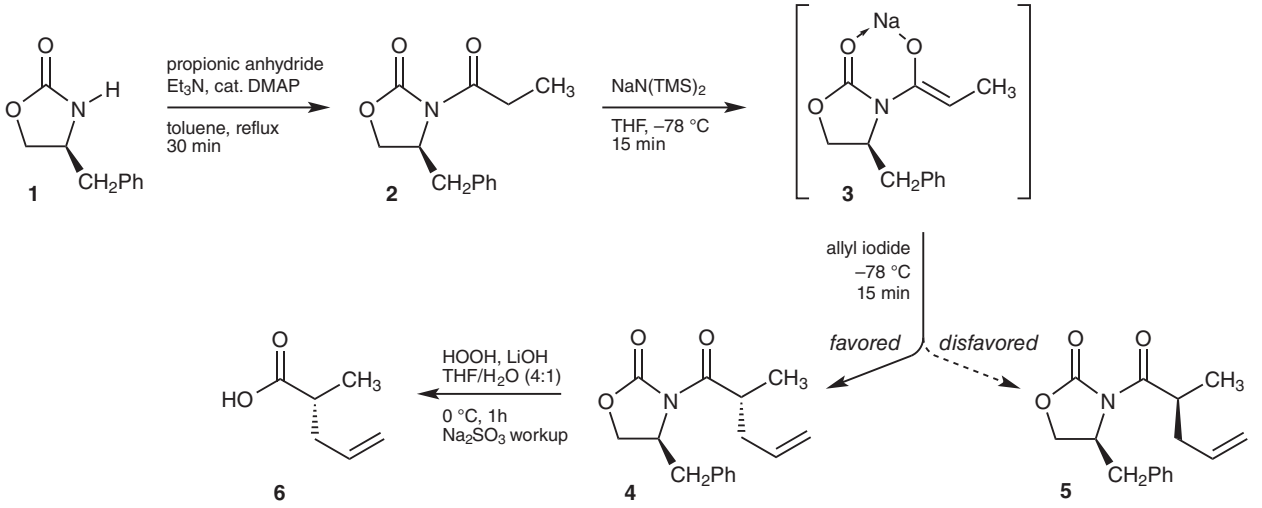
A Multistep Asymmetric Synthesis Experiment for Advanced Undergraduates

Thomas E. Smith,* David P. Richardson, George A. Truran, Katherine Belecki, and Megumi Onishi
Department of Chemistry, Williams College, Williamstown, MA 01267; *tsmith@williams.edu

Asymmetric synthesis, the science and art of assembling complex molecules *as single enantiomers* from relatively simple starting materials, is a critical topic in modern organic chemistry *(1, 2)*. In the pharmaceutical industry, for example, single enantiomer drugs have become increasingly important; currently almost all newly introduced chiral drugs are marketed as single enantiomers *(3)*. This move away from the use of racemates has occurred because, often, only one of the enantiomers has desired biological activity. Inclusion of the other enantiomer leads to significantly greater costs with respect to testing and production and leads to the therapeutic disadvantage of effectively doubling the metabolic burden incurred by the patient to clear the ineffective (or worse) half of the pharmaceutical agent *(4)*.

There are four general approaches to the selective synthesis of one enantiomeric form of a target molecule. They involve (i) resolution, (ii) use of "chiral pool" starting materials, (iii) temporary installation of chiral auxiliaries, and (iv) asymmetric catalysis. Chiral pool sourcing is the most efficient solution, but a suitable chiral pool precursor is often not available. Although catalytic asymmetric induction is the most elegant method by virtue of its ability to *amplify* asymmetry, its routine application is frequently limited by issues of substrate generality and predictability *(5)*. Moreover, evaluation of enantioselectivity usually requires chiral chromatographic methods, and if selectivity is not high, the challenge of removing the minor enantiomer product may not be trivial. Chiral auxiliary-based methods, while perhaps not as attractive philosophically, are frequently chosen based upon their practical advantages. These reactions are applicable to a wide array of substrates and proceed with a predictable sense of asymmetric induction. Since the products of these reactions are diastereomers (rather than enantiomers) their ratios can be measured by standard NMR and achiral chromatographic methods. Importantly, even if the selectivity for the asymmetric induction step is not high, the diastereomeric intermediates typically can be separated before the chiral auxiliary is cleaved, thus leading to product in enantiomerically pure form.

For a chiral auxiliary to be useful, three fundamental conditions need to be met: First, it must be readily attached—in either enantiomerically pure form—to a substrate. Second, it should mediate a highly diastereoselective transformation. Third, it must be easily removed without racemization of the newly-created stereogenic center(s), and be separable from the cleaved product so that it may be recycled. Although a number of chiral auxiliaries meeting these criteria have been developed *(6)*, the class of chiral oxazolidinones (such as **1**, Scheme I) developed by David Evans have proved to be the gold standard to which all others are compared *(7)*. These chiral auxiliaries have been successful in directing exceedingly diastereoselective alkylations, aldol additions, α-aminations, Michael additions, and Diels–Alder cycloadditions, among others. Importantly, the products of these reactions can be transformed into a number of synthetically useful enantiopure intermediates that have been used to advantage in myriad academic and industrial



Scheme I. Introduction, diastereoselective alkylation, and cleavage of an Evans oxazolidinone chiral auxiliary.

applications. Herein, we present an optimized protocol for the introduction, diastereoselective alkylation, and cleavage of the Evans chiral auxiliary, 4-benzyl-2-oxazolidinone, **1**.

Overview of the Experiment

Oxazolidinone[1] **1** is acylated with propionic anhydride using 4-dimethylaminopyridine (DMAP) as an acyl transfer catalyst. The resulting *N*-propionyl oxazolidinone, **2**, is deprotonated with sodium bis(trimethylsilyl)amide,[2] $NaN(TMS)_2$, at low temperature to give the rigidly chelated (*Z*)-enolate, **3**. Alkylation with allyl iodide occurs preferentially from the less hindered face (i.e., trans to the bulky benzyl substituent) to give diastereomeric products **4** and **5** in a typical ratio of 98:2 as determined by GC analysis. After chromatographic purification, the major allylated product, **4**, is hydrolyzed to give the free auxiliary, **1**, and the chiral carboxylic acid, **6**, in high enantiomeric purity.

Hazards

Standard precautions should be taken when handling all chemicals. Toluene, THF, and ethyl acetate are flammable. Diethyl ether is exceedingly flammable and should be used with extreme care. Ethyl acetate can be substituted for diethyl ether in all extractions. Allyl iodide is a strong alkylating agent and is a highly toxic lachrymator. Aqueous (30%) hydrogen peroxide is a strong, corrosive oxidant that can decompose explosively when heated. $NaN(TMS)_2$ is a strong base and reacts violently with water. Propionic anhydride is a corrosive lachrymator.

Discussion

This experiment has been utilized successfully in the advanced undergraduate synthetic organic chemistry course since 1999. It has been optimized to be performed over four, 4-hour laboratory periods but could be adjusted to suit other schedules.

The first step is a modification of a literature procedure developed by Ager for the acylation of related chiral auxiliaries under mild conditions *(8)*. Typically, acyl groups are attached by deprotonation of the chiral auxiliary with *n*-BuLi at −78 °C, followed by acylation with an acid chloride. When the acyl transfer catalyst DMAP is employed, however, the neutral oxazolidinone is sufficiently nucleophilic and the acylation can be completed at room temperature in THF overnight —making it a much simpler operation. We have demonstrated that the reaction time can be shortened to 30 minutes, if desired, by heating to reflux in toluene. Literature *(8)* yields for this reaction range from 73–78% and student yields are comparable or better.

The diastereoselective alkylation step is, of course, central to the purpose of this exercise. A variety of electrophiles can be used successfully, but we have highlighted allyl iodide for its combination of reactivity, selectivity, and dispersion of product signals in the ^1H NMR spectrum. Other strong bases, such as lithium diisopropylamide (LDA), can also be used, but the best and most reproducible alkylations in our hands were those done with $NaN(TMS)_2$ *(9)*. Even though low-temperature and syringe techniques are needed here, given sufficient care, the reaction is quite robust in student hands.

Flash chromatography *(10)* of the alkylation product is necessary to isolate the major diastereomer in pure form, but given the high selectivity in the alkylation, this purification step could be omitted without significant detriment to the educational goals of the exercise. Interestingly, alkylation product **4** has been used in several complex total syntheses including those of the cholesterol lowering agents compactin and mevinolin *(11),* the immunosuppressant FK-506 *(12),* and the microtubule-stabilizing antitumor agent epothilone B *(13)*. Literature yields for the allylation reactions range from 61–77% and our yields are in agreement.

Finally, hydrolytic cleavage of the chiral auxiliary is done with alkaline hydrogen peroxide *(14)*. As was demonstrated early on by Evans *(15),* reaction with hydroxide alone leads also to cleavage at the endocyclic carbonyl. In alkaline H_2O_2, however, the hydroperoxide anion is the effective nucleophile that selectively cleaves the exocyclic imide carbonyl. The initial product of this cleavage is actually the peroxyacid, which is reduced in situ with sodium sulfite to yield the desired carboxylic acid, **6**. Student yields here are typically 60–80%. Polarimetry can be used to assess the optical purity of the final product. Better still, chiral GC analysis (Astec Chiraldex B-DM column) can be used to resolve the two product enantiomers. The diastereomeric purity measured for the starting material is faithfully expressed in the enantiomeric purity of the cleaved product; no racemization is observed.

Only two other laboratory exercises involving chiral auxiliaries have been published in this *Journal (16)*. Both experiments, however, are quite different from ours. The first case involves the Diels–Alder reaction of L-menthyl acrylate with cyclopentadiene. The second example uses the Helmchen imidazolidinone auxiliary and demonstrates an aldol reaction. While the importance of the asymmetric aldol reaction to modern synthesis is indisputable (these reactions are also mediated by Evans oxazolidinones) the rationale for the observed diastereoselectivity is much less straightforward. Transition states that must invoke the Zimmerman–Traxler model as well as a dipole minimization component, are convoluted when the purpose is to give the student a first introduction to asymmetric induction in acyclic systems. In contrast, the diastereoselective transformation examined herein (**3** → **4**) is easily rationalized and provides an ideal conceptual framework for the subsequent investigation of more intricate stereochemical models.

Conclusion

We have developed a multistep experiment in synthetic organic chemistry for advanced undergraduates. The power of chiral auxiliaries in asymmetric synthesis is demonstrated using the highly utilized and well-understood Evans oxazolidinone system. Beyond the central alkylation reaction, this experiment provides a springboard for the discussion of several other important concepts in synthetic organic chemistry. The acylation step, for example, provides an opportunity to consider the mechanistic details of DMAP catalysis. The selective

transformation of acyl oxazolidinone **2** into (*Z*)-enolate **3** can be used to consider allylic strain conformational control elements. The ^{1}H NMR spectra of all reaction intermediates are beautifully resolved and allow for a detailed discussion of the difference between homotopic, diastereotopic, and enantiotopic atoms. In recent years, we have split the lab group into two teams—one using the (*R*)-chiral auxiliary, the other the (*S*)—and then we have compared the optical purity of their final products using polarimetry. Related to these last two examples, and perhaps of greatest import from a pedagogical standpoint, is that this experiment clearly serves to reinforce the critical conceptual distinction between *absolute* and *relative* stereochemical control.

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Notes

1. The chiral auxiliary, 4-benzyl-2-oxazolidinone, is commercially available in both enantiomeric forms from multiple vendors. It also can be prepared according to ref *14*.
2. Sodium bis(trimethylsilyl)amide, $NaN(TMS)_2$, also known as sodium hexamethyldisilazane (NaHMDS), is available from Aldrich as a 1.0 M solution in THF.

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