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A Reactivity/Affinity Switch for Parallel Kinetic Resolution: α-Amino Acid Quasienantiomers and the Resolution of Cyclopropene Carboxylic Acids

Lian-an Liao, Fan Zhang, Olga Dmitrenko, Robert D. Bach, and Joseph M. Fox*

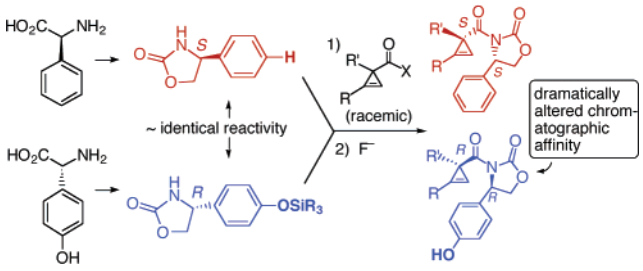
Brown Laboratories, Department of Chemistry and Biochemistry, University of Delaware, Newark, Delaware 19716

Received January 13, 2004; E-mail: jmfox@udel.edu

We report here a new type of parallel kinetic resolution[1] (PKR) in which quasienantiomers[2] with very similar reactivities give products whose chromatographic properties diverge upon the addition of fluoride ion (Scheme 1). This idea of a reactivity/affinity switch represents a complementary approach for acyltransfer systems where the asymmetry is induced by the nucleophile rather than the leaving group.[1] This concept should be applicable to a broad range of problems in kinetic resolution because the reactants are derived from readily available amino acids—ubiquitous as sources of chirality in asymmetric synthesis but novel as reagents for PKR. The specific application pursued in this contribution is the PKR of cyclopropene carboxylic acids with all carbon quaternary centers. With high-level DFT calculations, we also make the novel observation that the acyl transfer of an N-lithiated amide to an anhydride proceeds by a concerted S_N2 transition state in the absence of the anticipated tetrahedral intermediate.

The inherent limitation of kinetic resolution is that both reactant and product cannot be obtained in good yield and high ee unless the efficiency of the reaction is exceptional [selectivity factor[3] (s) ≥100]. Quasienantiomers—tetrahedral molecules that differ in absolute stereochemistry and in the composition of one substitutent—can be powerful tools for overcoming this limitation through the parallel kinetic resolution of a racemate.[1] For idealized quasienantiomers, the intrinsic diastereoselectivity can be observed regardless of conversion; the dependence of ee and conversion[3] is ameliorated because both enantiomeric reactants are depleted simultaneously to give separable quasienantiomeric products.

Scheme 1. Reactivity/Affinity Switch for PKR

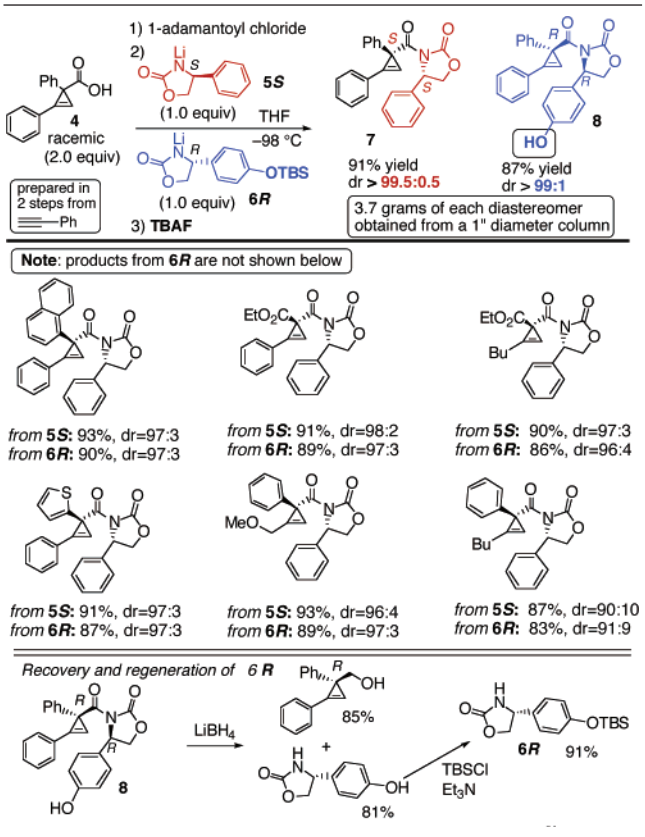


There are two fundamental requirements for a useful pair of quasienantiomeric resolving agents: (1) both should react with nearly identical rates and selectivities (i.e. chemo-, regio-, and diastereoselectively) and (2) the quasienantiomeric products should be easily separable on large scale. Designing an appropriate pair of quasienantiomers is nontrivial because many functional groups (e.g. hydroxyl, amino) that dramatically alter the solubilities and chromatographic affinities of molecules also tend to alter their reactivities. This dichotomy is further complicated by the practical consideration that the quasienantiomers must be readily available. Thus, while some elegant systems for quasienantiomer PKR have been reported[1a,4]—including a three-phase catalytic system[4a]—it is still an infrequently used tool for synthesis.

Although α-amino acids provide the basis for a remarkable spectrum of asymmetric transformations, they have not been applied in PKR. We recognized the potential utility of a number of inexpensive amino acid quasienantiomers such as L-phenylalanine/D-tyrosine, L-valine/D-threonine, and L-phenylglycine/D-*p*-hydroxyphenylglycine. For these pairs of amino acids, we reasoned that the hydroxyl group of the latter quasienantiomer would significantly alter the chromatographic affinity relative to the former. Moreover, we felt that we could equate their reactivity by masking the hydroxyl of the latter quasienantiomer as a silyl ether. This concept of using a reactivity/affinity switch in PKR is outlined in Scheme 1 with the specific example of oxazolidinone quasienantiomers in the PKR of cyclopropene carboxylic acids. This approach is complementary to that of Vedejs in which the asymmetry is derived from the nucleofuge, and the products are distinguished through differential reactivity of the transferred acyl groups.[1] The strategy outlined here should be generally useful when the asymmetry is induced by the nucleophile—a situation where it is difficult to distinguish the products through selective reactivity of their carbonyl groups.

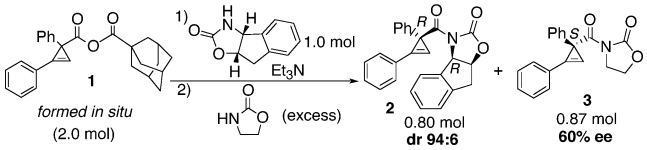
The development of new methods for preparing enantiomerically

Table 1. One-Pot Parallel Kinetic Resolution of Cyclopropenes



10.1021/ja049779t CCC: $27.50

Scheme 2. Kinetic Resolution of Cyclopropene Mixed Anhydrides

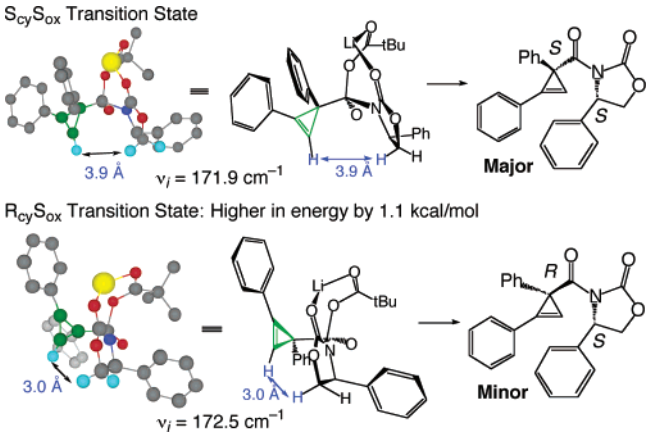


pure cyclopropenes fits within the context of our research program to use the thermodynamic "currency" of high-strain molecules to quickly generate molecular complexity. For example, we and others have shown that cyclopropene carbometalation[5a,b] and hydrometalation[5c,d] reactions can be used to access highly functionalized chiral cyclopropenes that cannot be prepared by cyclopropanation of alkenes. Although racemic cyclopropene carboxylic esters can be prepared easily and in quantity by the reactions of stabilized diazo compounds with alkynes,[6] methods that produce enantiomerically enriched cyclopropenes are rare.[7] The groups of Doyle, Müller, and Shapiro have described catalytic asymmetric cyclopropenation reactions using chiral Rh-catalysts.[7] For intermolecular catalytic asymmetric cyclopropenation reactions, excellent enantioselectivities have been obtained for the reactions of several terminal alkynes using $[MEPY]_4Rh_2$.[7a,c,d] Still, reactions that produced enantiomerically enriched cyclopropenes with quaternary centers were unknown prior to this work of our group and concurrent work carried out by Davies and co-workers.[8]

We recently showed that oxazolidinones are remarkably useful reagents for resolving diverse types of cyclopropene carboxylic acids.[9a] The merits of this method are simplicity and generality, while the limitation is that it is not amenable to multigram scale. The optimized procedure included DMAP to catalyze the acyl-transfer reaction. Serendipitously, we discovered a kinetic resolution that took place when the DMAP was excluded from the reaction—an optimized example is shown in Scheme 2. Although the product (**2**) was formed in a respectable 94:6 dr, the unreacted starting material showed only 60% ee, as determined by conversion to **3**. The result could not be improved by changing the chiral oxazolidinone. To make this a useful process for the resolution of cyclopropenes, we applied the idea outlined in Scheme 1. Commercially available oxazolinone **5*S*** is inexpensive when purchased in quantity, and quasienantiomer **6*R*** can be synthesized on a 15-g scale by a straightforward method. For a variety of cyclopropene carboxylic acids that have all-carbon quaternary centers, the diastereoselectivity is excellent (Table 1). Importantly, the parallel kinetic resolutions can be carried out on significant scale by a simple one-pot procedure. Thus, nearly 4 g of the quasienantiomers **7** and **8** were obtained after separation on a 1-in. diameter column of silica. It is also shown in Table 1 that the oxazolidinone **6*R*** can be recovered in high yield upon $LiBH_4$ cleavage (to give useful 3-hydroxymethylcyclopropenes[5a]) and treatment with TBSCl.

We have developed a model for the diastereomeric transition states that are involved in the kinetic resolution of **4** with **5*S*** (Scheme 3). Calculations were performed with the B3LYP functional with the 6-31+G(d,p) basis set. The development of the models in Scheme 3 was multilayered and began with calculations on acetic anhydride and oxazolidinone.[9b] For the present system (with the minor modification from the experimental system that *t*-Bu replaces adamantyl), multiple trajectories of nucleophilic attack were studied. The lowest-energy *transition states* for each diastereomer are displayed in Scheme 3. Concerted S_N2-like addition to carbonyl systems is well documented computationally and experimentally (both solution and gas phase) for acyl transfer reactions of strong nucleophiles with leaving groups that are better than alkoxide.[9b,c] In accord with the experimental observation, the

Scheme 3. Diastereomeric Transition States from B3LYP [6-31+G(d,p)]



transition state that leads to the major product is calculated to be lower in energy by 1.1 kcal. Both transition structures are characterized by single imaginary frequencies around 172i cm^{-1}, the animation of which indicates *both* concerted C−N bond formation and C−O bond cleavage. A notable difference between the two structures is the distances between the alkene hydrogen and that of C5 of the oxazolidinone. Efforts are underway to use this observation in a predictive manner to further enhance selectivity.

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Supporting Information Available: Full experimental and characterization details, ^1H and ^{13}C NMR spectra; archive data, Cartesian coordinates, and total energies for the minima and transition states described in this work. This material is available free of charge via the Internet at http://pubs.acs.org.

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