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Kinetic Resolution of Racemic Amino Alcohols through Intermolecular Acetalization Catalyzed by a Chiral Brønsted Acid

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Supporting Information

ABSTRACT: The kinetic resolution of racemic secondary alcohols is a fundamental method for obtaining enantiomerically enriched alcohols. Compared to esterification, which is a well-established method for this purpose, kinetic resolution through enantioselective intermolecular acetalization has not been reported to date despite the fact that the formation of acetals is widely adopted to protect hydroxy groups. By taking advantage of the thermodynamics of acetalization by the addition of alcohols to enol ethers, a highly efficient kinetic resolution of racemic amino alcohols was achieved for the first time and in a practical manner using a chiral phosphoric acid catalyst.

The conversion of racemic compounds into enantiomerically enriched products via kinetic resolution is one of the most fundamental and powerful methods in asymmetric synthesis.[1] Selective esterification is the most common approach to the kinetic resolution of racemic secondary alcohols, and a number of asymmetric methods have been developed to realize enantiomeric enrichments through the use of enzymes and chiral metal catalysts as well as organocatalysts.[2] In contrast, the acetalization of alcohols is one of the most fundamental methods for protecting a hydroxy group. This *O*-protective method is widely utilized in organic synthesis because acetals can be efficiently formed and removed under catalytic acidic conditions.[3] In this context, the selective acetalization of one enantiomer of a racemic mixture of secondary alcohols potentially provides not only an efficient approach to kinetic resolution but also an alternative to conventional esterification procedures. However, the kinetic resolution of racemic secondary alcohols through intermolecular acetalization has not been realized to date. We took up this challenge by utilizing a chiral phosphoric acid catalyst,[4] which has emerged as an efficient chiral Brønsted acid catalyst[5] for a wide variety of enantioselective transformations.[6] Herein we report the first, highly efficient kinetic resolution of racemic 1,2-amino alcohols through intermolecular acetalization using chiral phosphoric acid **1** as the enantioselective catalyst (Figure 1). The developed kinetic resolution provides efficient access to a range of enantiomerically enriched 1,2-amino alcohols **2**, which are common chiral motifs of biologically active and relevant molecules.

In general, acetalization is regarded as an equilibrium process under acidic conditions. Ideally, for kinetic resolution, a largely

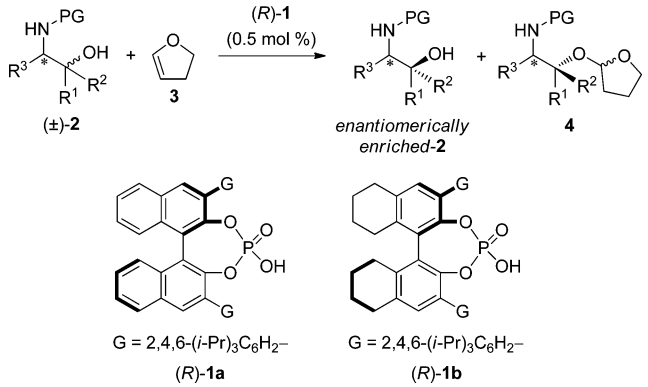

Figure 1. Kinetic resolution of racemic amino alcohols through acetalization catalyzed by chiral phosphoric acid **1**.

irreversible system under high kinetic control is the key to establishing the high enantioselection of one stereoisomer over another. Although a few enantioselective acetalization protocols using chiral Brønsted acid catalysts have been developed,[7] all of them rely on the virtues of intramolecular reactions,[8] in which the formation of thermodynamically stable cyclic acetals suppresses reversible processes. The design of a formal irreversible intermolecular process is entirely another matter. Indeed, intermolecular trans-acetalization is one of the common procedures for the protection of alcohols by an acetal. However, the reaction can readily ensue under equilibrium conditions, which is clearly detrimental to achieving kinetic resolution. We therefore shifted our attention to the use of an alternative method for acetalization. We selected the addition reaction of an alcohol with an enol ether, in which the formed acetal would be thermodynamically more stable than the starting materials.[9] By taking advantage of the thermodynamic properties of the intermolecular addition reaction, we envisaged that kinetic resolution through acetalization would be feasible.[10]

At the outset of our studies on the kinetic resolution through intermolecular acetalization, *N*-protected 2-amino-1-phenylethanol **2** was chosen as the model substrate. Thorough screening for the reaction parameters was conducted by changing the reaction solvent, the *N*-protective group, the reaction temperature, the amount of enol ether **3**,[11] and the chiral phosphoric acid catalyst **1**.[12] The initial screening was performed

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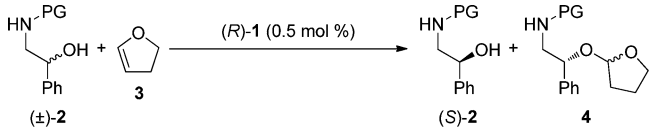
Table 1. Optimization of Reaction Conditions[a]



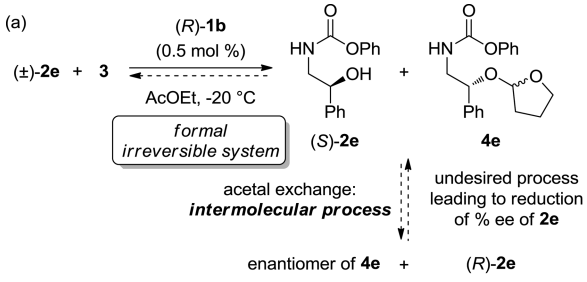
entry	2 (PG)	conditions	4	NMR ratio of 2/4 (%)	(S)-2 ee (%)[b]	s[c]
1	**2a**: Cbz	CH_2Cl_2, 30 °C, 20 min	**4a**	57/43	38	4.3
2	**2a**	toluene, 30 °C, 50 min	**4a**	72/28	9	1.7
3	**2a**	AcOEt, 30 °C, 4.5 h	**4a**	69/31	27	5.2
4	**2b**: Ts	AcOEt, 30 °C, 1.5 h	**4b**	70/30	4	1.3
5	**2c**: Bz	AcOEt, 30 °C, 1.5 h	**4c**	74/26	2	1.1
6	**2d**: Boc	AcOEt, 30 °C, 1.5 h	**4d**	66/34	33	6.3
7	**2e**: PhO_2C-	AcOEt, 30 °C, 1.5 h	**4e**	62/38	43	8.6
8[d]	**2e**	AcOEt, 0 °C, 2 h	**4e**	59/41	56	16
9[e]	**2e**	AcOEt, −20 °C, 13 h	**4e**	51/49	75	18
10[e,f]	**2e**	AcOEt, −20 °C, 23 h	**4e**	45/55	91	21

[a]Unless otherwise noted, all reactions were carried out using 0.001 mmol of (*R*)-**1a** (0.5 mol %), 0.2 mmol of **2**, and 0.12 mmol of **3** (0.6 equiv) in solvent (1.0 mL, 0.2 M). [b]The enantiomeric excess of (*S*)-**2** was determined by chiral stationary phase HPLC analysis. Absolute stereochemistry was determined after derivatization to the stereochemically known compound.[13] See Supporting Information for details. [c]Selectivity factor (*s*) was calculated in accordance with the reported method.[1] [d]Using 0.6 mmol of **3** (3.0 equiv). [e]Using 2.0 mmol of **3** (10 equiv). [f]Using 0.001 mmol of (*R*)-**1b** (0.5 mol %).

using racemic *N*-Cbz-protected amino alcohol **2a**, 0.5 mol % of chiral phosphoric acid **1a**, and 0.6 equiv of dihydrofuran **3** as the enol ether at 30 °C. As shown in Table 1, kinetic resolution through acetalization was realized, albeit weakly (entry 1). It is noteworthy that the efficiency of the kinetic resolution is markedly dependent on the solvent used (entries 1−3) as well as the protective group introduced at the nitrogen atom (entries 3−7). Among the solvents tested, ethyl acetate exhibited the best selectivity factor (*s*).[1] The carbamate-type protective group exhibited a higher *s* value than the tosyl and benzoyl groups (entries 3, 6, and 7 vs 4 and 5). The highest *s* value was achieved using the phenoxycarbonyl group (entry 7). Further optimization of the reaction conditions by changing the reaction temperature, the chiral phosphoric acid catalyst, and the equivalent of enol ether markedly improved the *s* value (entries 8−10). Henceforth, the reaction of *N*-phenoxycarbonyl amino alcohol **2e** with excess enol ether **3** (10 equiv) under the influence of 0.5 mol % of H_8-BINOL-derived phosphoric acid (*R*)-**1b** in 0.2 M ethyl acetate solution at −20 °C resulted in a high *s* value (*s* = 21) (entry 10). After 23 h, remaining alcohol **2e** exhibited a high enantiomeric excess at 55% conversion, reaching 91% ee with an (*S*)-configuration.[13,14]

In our reaction design for kinetic resolution through intermolecular acetalization, the addition of amino alcohol **2e** to enol ether **3** proved beneficial. The inherent problem, however, still lies in minimizing the intermolecular acetal exchange between alcohol **2e** and formed acetal **4e** under acidic conditions (Figure 2a). In particular, the acetal exchange between (*S*)-**2e** and **4e** derived from (*R*)-**2e** leads to reduction of the enantiomeric excess of resultant **2e**. Thus, there is concern that this undesired process would become a serious problem as the concentrations of resolved (*S*)-**2e** and formed acetal **4e** increase.

Bearing the concentration issues of **2e**/**4e** in mind, we investigated the influence of the concentration on the enantiomeric excess of resultant **2e** in the overall kinetic resolution process (Figure 2b). As a result, enantioselective acetalization at a high concentration (0.5 M) led to a significant decrease in the *s* value (*s* = 14) (Figure 2b-(2) vs 2b-(1)), while a similar *s* value to that observed at 0.2 M was obtained when the



(b)

(±)-2e + 3 (10 equiv) —(R)-1b (0.5 mol %), AcOEt, -20 °C→ (S)-2e + 4e

	concentration	time	2e/4e	% ee of (S)-2e	s
(1)	0.2 *M*	23 h	45 / 55	91% ee	21
(2)	0.5 *M*	9 h	49 / 51	76% ee	14
(3)	0.05 *M*	48 h	67 / 33	43% ee	22

Figure 2. (a) Mechanistic considerations for the kinetic resolution of *N*-phenoxycarbonyl 2-amino-1-phenylethanol **2e** by the formation of acetal with dihydrofuran **3** using chiral phosphoric acid catalyst (*R*)-**1b**. (b) Concentration effect on the kinetic resolution of **2e**.

reaction was conducted at a low concentration (0.05 M) (Figure 2b-(3): *s* = 22 vs 2b-(1): *s* = 21). These results suggest that the undesired acetal exchange could be suppressed at 0.2 M concentration.[15]

Modification of the optimal conditions by adding molecular sieve (MS) 4A led to the establishment of a reliable and efficient kinetic resolution of racemic amino alcohols **2** through acetalization without any detrimental effect on the individual *s* values.[16] Table 2 summarizes the experiments carried out to probe the substrate scope. The present resolution method is applicable to a range of 1,2-amino alcohols having an aromatic group at the stereogenic center, albeit with a slight reduction of the *s* value (*s* = 13−16). We further extended the methodology to aliphatic-substituted 1,2-amino alcohols. In particular, secondary alkyl groups at the stereogenic center resulted in fairly good resolution; for example, isopropyl and cyclohexyl substituents gave *s* values of 11 and 19, respectively. The introduction of a *tert*-butyl group led to a significant increase in the *s* value (close to

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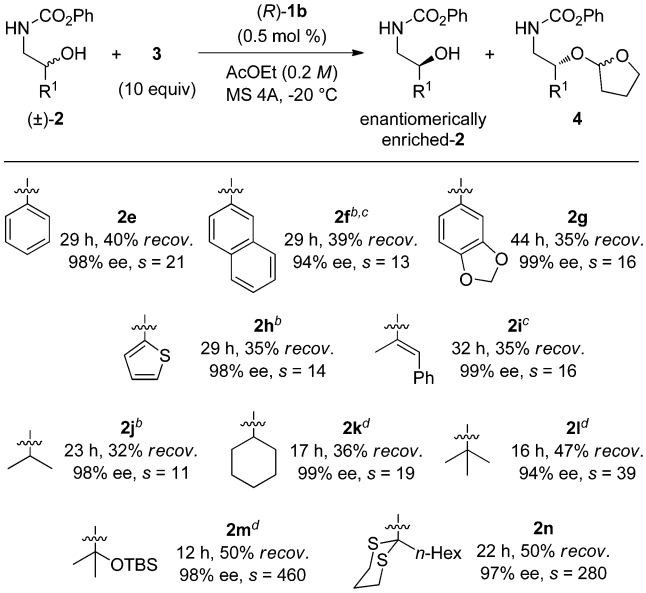
Table 2. Scope of Substrates[a]



[a]Unless otherwise noted, all reactions were carried out using 0.0025 mmol of (*R*)-**1b** (0.5 mol %), 0.50 mmol of **2**, 5.0 mmol of **3** (10 equiv), and 50 mg of MS 4A in AcOEt (2.5 mL, 0.2 M) at −20 °C. The recovered yield of enantiomerically enriched **2** was determined after isolation. [b]Using 1.5 mmol of **3** (3.0 equiv) at 0 °C. [c]0.1 M. [d]Using (*R*)-**1a** as the catalyst.[16]

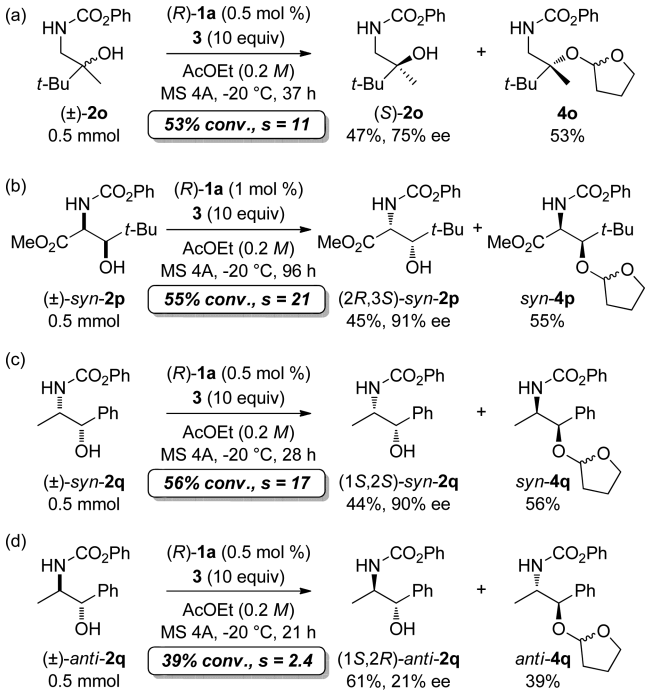
40). Further enhancement of the *s* value was achieved by using even more sterically demanding groups, and exclusive resolution was accomplished. This gave rise to nearly enantiomerically pure alcohols (<99% ee) in almost quantitative yields (<50%). More importantly, the developed resolution method had high tolerance for other functional groups, such as silyl ether and dithioacetal.

The present resolution system was further applied to the reaction of a variety of amino alcohol derivatives with chiral phosphoric acid (*R*)-**1a** (Scheme 1).[17] The developed methodology was found to be applicable to not only secondary alcohols but also tertiary alcohol **2o**, albeit with a slight decrease in *s* value (Scheme 1a). The densely functionalized *syn* amino alcohol **2p** also resolved well to afford an unnatural α-amino acid derivative with high enantiomeric excess (Scheme 1b). Notably, the resolution of each set of racemic diastereomers exhibited a marked difference in *s* values; for example, racemate *syn*-**2q** resolved with a high *s* value of 17, whereas the *s* value of *anti*-**2q** reached only 2.4 (Scheme 1c and 1d).[18]

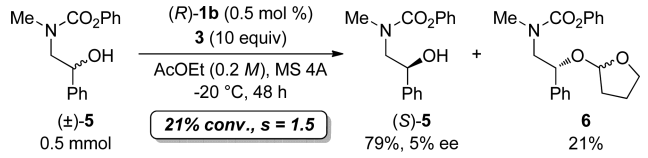
As shown in Scheme 1c and 1d, the resolution efficiency was markedly dependent on the relative stereochemistry of diastereomeric amino alcohol **2q**. The results imply that the vicinal nitrogen functionality significantly influences the overall stereodifferentiation process. We propose the necessity for the substrate to form a relatively stable intramolecular hydrogen bond between N−H and the oxygen atom of the hydroxy group.[19] Indeed, a control experiment using **5** (*N*-Me substrate of **2e**) proceeded with poor selectivity (*s* = 1.5) and a low acetalization rate (Scheme 2). The results indicate that the N−H functionality plays a key role in achieving the efficient kinetic resolution of amino alcohols as well as in accelerating the acetalization process.

Finally, the synthetic utility of the present kinetic resolution through intermolecular acetalization was demonstrated by a

Scheme 1. Kinetic Resolution of a Range of *N*-Phenoxycarbonyl 1,2-Amino Alcohols Using Chiral Phosphoric Acid Catalyst (*R*)-1a

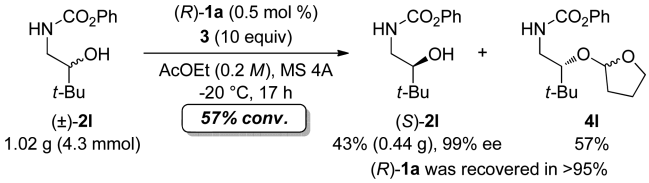


Scheme 2. Control Experiment of *N*-Me Substrate 5



gram-scale experiment using racemic **2l** under the optimal reaction conditions. As highlighted in Scheme 3, the chiral

Scheme 3. Gram-Scale Experiment of Kinetic Resolution of Racemic 2l Catalyzed by Chiral Phosphoric Acid (*R*)-1a



Brønsted acid catalyzed acetalization afforded enantiomerically enriched (*S*)-**2l** in 43% yield with a nearly enantiopure form (99% ee). Formed acetal **4l** was readily separable from resolved alcohol (*S*)-**2l** by silica gel column chromatography, and (*R*)-**1a** was also recovered in more than 95% yield.

In summary, the catalytic kinetic resolution of alcohols through intermolecular acetalization has been accomplished for the first time with moderate to excellent *s* values. This was realized by formulating a system that undergoes an essentially irreversible process, specifically by virtue of the favorable thermodynamics of reacting alcohols with an enol ether under low organocatalytic acid concentrations. The innovative system demonstrated here exemplifies the potential of our organocatalytic resolution strategy. Our method not only provides

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enantiomerically enriched amino alcohols in a highly enantioselective and readily separable manner but also is operationally simple and features a low catalyst loading. In addition, there is no need to rigorously exclude air or to use transition metals. As acetalization is one of the most fundamental methods for the protection of a hydroxy group, its successful application to kinetic resolution has opened doors to a new frontier for the production of enantiomerically enriched compounds from racemic mixtures.

■ ASSOCIATED CONTENT

Supporting Information

Representative experimental procedure, spectroscopic data, determination of the absolute stereochemistry of **2e**, and mechanistic studies on kinetic resolution of racemic amino alcohols. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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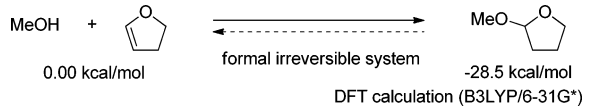
(9) As shown in the following scheme, the formed acetal is thermodynamically much more stable than the alcohol and enol ether.



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(11) Screening of enol ethers was also conducted. See Supporting Information (SI) in details.

(12) Screening of chiral phosphoric acids was also conducted. See SI in details.

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(14) Formed acetal **4e** was obtained as a *ca.* 1:1 diastereomeric mixture.

(15) Other factors that caused the reduction of the *s* value at high concentration also cannot be ruled out at this point.

(16) The acetalization rate was reproduced well in the presence of MS 4A.

(17) (*R*)-**1a** was employed instead of (*R*)-**1b**, because the acetalization rate of (*R*)-**1a** was higher than that of (*R*)-**1b** in those substrates without any detrimental effect on the individual *s* values.

(18) Application of the resolution system to a racemic 1,3-amino alcohol as well as the substrate possessing a tertiary alkyl amine moiety resulted in the low *s* values. See SI in details.

(19) Plausible structures of the intramolecular hydrogen bonding models of **2e** and **5** are illustrated in the SI.

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