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Kinetic Resolution of Homoaldols via Catalytic Asymmetric Transacetalization

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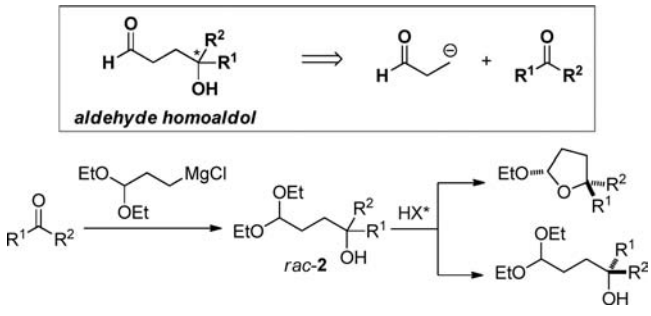
Abstract: The highly enantioselective kinetic resolution of homoaldols via a transacetalization reaction has been achieved. A novel phosphoric acid, STRIP, based on a spirocyclic 1,1′-spirobiindane backbone was designed and identified as a superior catalyst for this transformation. Remarkably, both secondary and tertiary homoaldols gave equally excellent results.

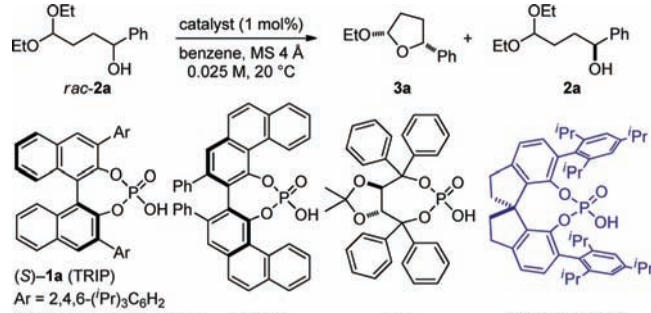
γ-Hydroxycarbonyl compounds, or homoaldols, represent a versatile motif for organic synthesis that can be easily transformed into a vast array of important chiral compounds such as γ-lactones, tetrahydrofurans, pyrrolidines, and others. Consequently, various homoenolate equivalents have been developed, but their use in enantioselective homoaldol reactions invariably relies on stoichiometric chiral ligands or auxiliaries.[1] Recently N-heterocyclic carbenes opened up a new route for the organocatalytic generation of homoenolates.[2] However, their application in asymmetric homoaldol reactions is still rather underdeveloped.[3] Strategically different approaches include catalytic enantioselective reduction of γ-ketoesters[4] and dynamic kinetic resolution of racemic γ-hydroxyamides using combined enzymatic and transition-metal catalysis.[5] Tertiary homoaldols, however, are not accessible by these methods. We recently introduced a chiral Brønsted acid-catalyzed asymmetric transacetalization reaction that generates chiral cyclic acetals from the corresponding acyclic hydroxyacetals.[6] We now report a highly enantioselective kinetic resolution of homoaldol acetals (*rac*-**2**) via a transacetalization reaction (Scheme 1) that is catalyzed by STRIP (**1e**), which is a representative of an entirely new class of phosphoric acid catalysts.[7]

Scheme 1. Kinetic Resolution of Aldehyde Homoaldols



Since the pioneering reports of Akiyama and Terada, BINOL-derived phosphoric acids have become one of the cornerstones of organocatalysis.[8] However, the design of new chiral phosphoric acids has mainly been limited to variations of the 3,3′-substituents of the catalysts, with the notable exception of VAPOL hydrogen phosphate.[9] As a part of our interest in developing novel and structurally different Brønsted acids, we became interested in 1,1′-spirobiindane as a platform for new phosphoric acid catalysts.[10] Although the 1,1′-spirobiindane backbone is well-established in metal catalysis,[11] the corresponding phosphoric acids are largely unknown.[12] We expected these phosphoric acids to provide a geometrically different and more rigid chiral pocket than their BINOL-derived counterparts, offering new and potentially complementary tools for asymmetric Brønsted acid catalysis.

Table 1. Optimization of Reaction Conditions



entry	cat.	conv.	er **3a**	dr	er **2a**
1	**1a**	41%	25:75	14:1	36:64
2	**1b**	47%	39:61	17:1	42:58
3	**1c**	41%	62.5:37.5	7:1	57:43
4	**1d**	26%	45:55	7:1	49:51
5	**1e**	51%	95:5	21:1	92:8
6[a]	**1e**	55%	96.5:3.5	12:1	99:1

[a] CH_2Cl_2 was used as the solvent.

We initiated our studies on the kinetic resolution of homoaldols by using secondary homoaldol *rac*-**2a** and BINOL-derived phosphoric acid catalyst **1a** (TRIP),[13] which was identified as the catalyst of choice in our previous transacetalization studies.[6] However, under identical conditions, only a moderate enantioselectivity (er = 25:75) of acetal **3a** was obtained at 41% conversion (Table 1, entry 1). Other known phosphoric acid catalysts (**1b**−**d**) gave only inferior results.

Remarkably, the novel spirocyclic TRIP-analogue STRIP [6,6′-bis(2,4,6-triisopropylphenyl)-1,1′-spirobiindan-7,7′-diyl hydrogen phosphate, **1e**] provided excellent results. The STRIP-catalyzed kinetic resolution of homoaldol *rac*-**2a** afforded cyclic acetal **3a** with an er of 95:5 and enantioenriched **2a** with an er of 92:8 at 51% conversion (Table 1, entry 5). Further optimization identified dichloromethane as the optimal solvent, resulting in higher reactivity and increased enantioselectivity. At 55% conversion, both **3a** and **2a** were obtained in excellent enantiomeric ratios of 96.5:3.5 and 99:1, respectively (entry 6). Cyclic acetal **3a** was obtained as the cis diastereomer with a dr of 12:1. The minor trans diastereomer 5-*epi*-**3a** was obtained as a single enantiomer having the opposite configuration at the alcohol-derived stereocenter.

After establishing the optimal conditions, we set out to explore the substrate scope. Importantly, racemic homoaldols *rac*-**2** are

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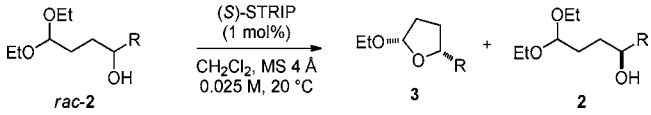
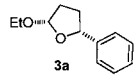
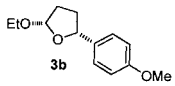
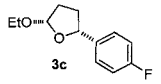
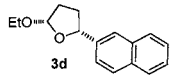
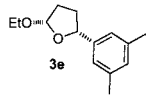
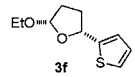
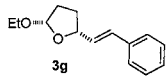
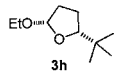
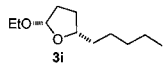
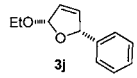
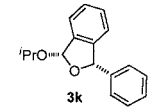
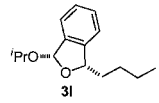
Table 2. Kinetic Resolution of Secondary Homoaldols[a]



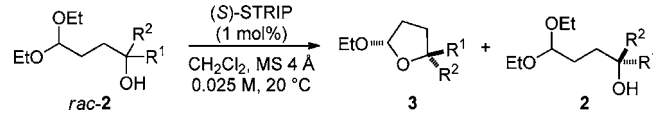
entry	conv. (time)	3	er 3	dr 3[b]	er 2
1	55% (18 h)	 **3a**	97:3	13:1	98.5:1.5
2	55% (16 h)	 **3b**	97:3	12:1	98:2
3	54% (14 h)	 **3c**	96.5:3.5	13:1	97.5:2.5
4	54% (16 h)	 **3d**	96.5:3.5	14:1	96.5:3.5
5	52% (16 h)	 **3e**	97:3	20:1	96:4
6	53% (14 h)	 **3f**	97.5:2.5	19:1	98.5:1.5
7a	56% (14 h)	 **3g**	98:2	8:1	98:2
7b[c]	56% (70 h)		97:3	9:1	96.5:3.5
8	55% (4 h)	 **3h**	93.5:6.5	19:1	98:2
9	68% (10 h)	 **3i**	96.5:3.5	2.9:1	97:3
10	54% (1 h)	 **3j**	89:11	>50:1	95:5
11	55% (12 h)	 **3k**	89.5:10.5	44:1	96.5:3.5
12	64% (6 h)	 **3l**	85:15	8:1	97.5:2.5

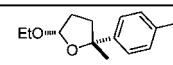
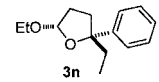
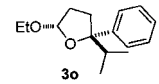
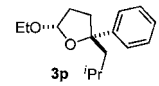
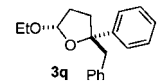
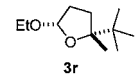
[a] Reactions were performed on a 0.1 mmol scale with molecular sieves (50 mg). [b] The diastereomers were separable by column chromatography, except for **3j**−**l**. Only one enantiomer of the minor trans diastereomer could be detected, except for 5-*epi*-**3h** (er 97:3), 5-*epi*-**3i** (er 99.5:0.5), 5-*epi*-**3k** (er 71:29), and 5-*epi*-**3l** (er 83.5:16.5). [c] Using 0.1 mol % of STRIP at a concentration of 0.1 M.

readily available from commercial materials in high yields in a single step via the addition of an acetal-protected Grignard reagent to aldehydes and ketones (Scheme 1).

Exploration of the substrate scope revealed that various secondary homoaldols undergo a highly efficient kinetic resolution in the presence of only 1 mol % of STRIP (Table 2). In most cases, both cyclic acetal **3** and acetal homoaldol **2** were obtained with excellent enantioselectivity. The nature of the aromatic substituent does not seem to have a significant effect on the reaction, as various aromatic substrates *rac*-**2a**−**e** and heteroaromatic substrate *rac*-**2f** underwent superb kinetic resolutions (Table 2, entries 1−6). Homoaldols with a vinyl or bulky aliphatic substituent behaved equally well (entries 7a and 8).

Table 3. Kinetic Resolution of Tertiary Homoaldols[a]



entry	conv.(time)	3	er 3	dr 3[b]	er 2
1	55% (10 h)	 **3m**	98.5:1.5	9:1	96:4
2	55% (12 h)	 **3n**	98.5:1.5	9:1	98.5:1.5
3	55% (28 h)	 **3o**	97.5:2.5	7:1	92:8
4	57% (24 h)	 **3p**	99:1	5:1	95:5
5	54% (40 h)	 **3q**	99:1	11:1	97.5:2.5
6	51% (3 h)	 **3r**	99:1	18:1	96.5:3.5

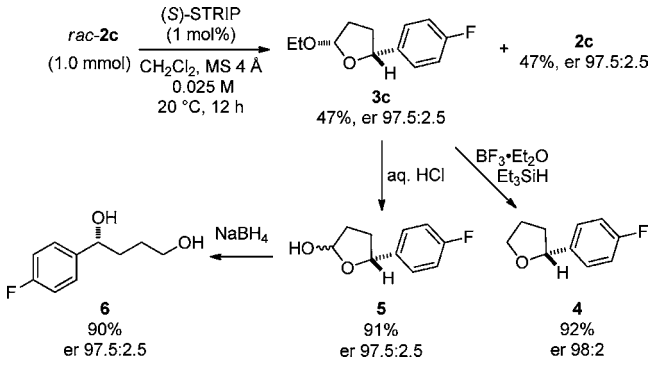
[a] Reactions were performed on a 0.1 mmol scale with molecular sieves (50 mg). [b] The diastereomers were separable by column chromatography, except for **3p**−**q**. Only one enantiomer of the minor trans diastereomer could be detected, except for 5-*epi*-**3m** (er 99.5:0.5), 5-*epi*-**3p** (er 99.5:0.5), and 5-*epi*-**3r** (er 96.5:3.5).

The reaction of linear-aliphatic-substituted homoaldol *rac*-**2i** illustrates a remarkable aspect of our reaction. As an additional acetal stereocenter is created in the transacetalization, the high catalyst control of its formation results in a partial parallel kinetic resolution.[14] Thus, even in cases where the enantiodifferentiation of the starting material is not very pronounced, the less reactive enantiomer is converted into the minor trans diastereomer. This effect enabled us to obtain the major diastereomer of cyclic acetal **3i** with an er of 96.5:3.5 and a perfect theoretical yield (50%) at 68% conversion (entry 9). For comparison, a simple kinetic resolution would require a selectivity factor of 94 to achieve this result. The STRIP-catalyzed kinetic resolution of homoaldols is also extendable to other substrate classes: for example, homoaldols with a cis double bond (*rac*-**2j)** or aromatic tether (*rac*-**2k** and *rac*-**2l**) are also viable substrates (entries 10−12).

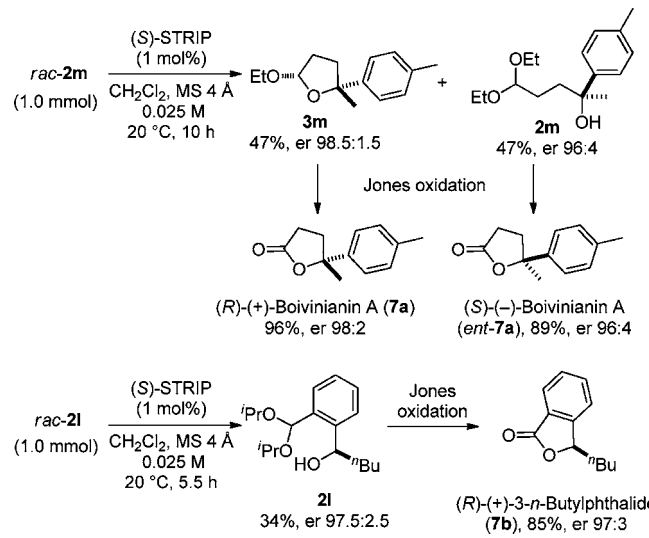
The exceptional results that STRIP delivered with secondary homoaldols encouraged us to also explore the kinetic resolution of *tertiary* homoaldols. Although chemical kinetic resolutions of secondary alcohols have been well-studied,[15] these methods are generally not easily extendable to resolutions of tertiary alcohols, and biocatalytic processes are also limited.[16,17] The few nonenzymatic methods include chiral reagents[18] and catalytic methods with peptide-based catalysts[19] and metal catalysts.[20]

Remarkably, tertiary alcohols perform exceedingly well in our asymmetric transacetalization, and STRIP-catalyzed resolution of tertiary homoaldols *rac*-**2m**−**r** proceeded as efficiently as with secondary homoaldols (Table 3). Both cyclic acetals **3m**−**r** and acyclic acetal homoaldols **2m**−**r**, which possess valuable quaternary stereocenters, were obtained with excellent enantioselectivity. The kinetic resolution of substrates with sterically similar substituents is remarkable. Highly efficient enantiodifferentiation between aryl and bulky aliphatic groups (Table 3, entries 3−4) and even between

Scheme 2. Utility of Cyclic Acetals **3**



Scheme 3. Application in Natural Product Synthesis



aryl and benzyl groups (entry 5) was observed. Excellent results were also obtained with substrate *rac*-**2r** bearing only aliphatic substituents (entry 6). For comparison, a simple kinetic resolution would have to operate at a selectivity factor of >300 to deliver the product in 48% yield with 99:1 er.

Gratifyingly, the transacetalization reaction can be performed even with a catalyst loading of only *0.1 mol %* and a more concentrated reaction mixture. For example, the kinetic resolution of *rac*-**2g** proved to be equally effective under these conditions, which resulted in almost identical enantiomeric ratios (Table 2, entry 7b).

Relative configurations of cyclic acetals **3a**, **3k**, **3l**, and **3m** were determined by nuclear Overhauser effect spectroscopy (NOESY) experiments. The absolute configuration of tetrahydrofuran **3a** was determined by comparison of the optical rotation of the γ-butyrolactone derivative obtained after Jones oxidation with the literature value (see the Supporting Information). The configurations of other secondary homoaldol products were assigned by analogy.

The acetal group in cyclic acetals can easily be modified, giving access to a wide variety of products.[21] To briefly demonstrate the utility of our products, we performed the kinetic resolution of *rac*-**2c** on a preparative scale (1.0 mmol) to obtain enantiomerically enriched **2c** and **3c** in high yields and enantiomeric ratios (Scheme 2). Direct reduction of **3c** led to tetrahydrofuran **4**, whereas hydrolysis of **3c** liberated aldehyde homoaldol **5**, which was readily reduced to diol **6**.

To verify the absolute configurations of the tertiary homoaldols and further demonstrate the utility of our products, we submitted **3m** and **2m** to Jones oxidation conditions. Both enantiomers of the natural product boivinianin A (**7a**) were obtained in excellent yields and enantiomeric ratios (Scheme 3).[22] Likewise, straightforward oxidation of benzene-fused acetal **2l** provided access to phthalides, another important and diverse class of natural products.[23] 3-*n*-Butylphthalide (**7b**) is found in a variety of plants, such as celery, and possesses a wide range of pharmacological activities.[24]

In summary, we have developed an efficient kinetic resolution of alcohols tethered to an acetal moiety via a catalytic asymmetric transacetalization reaction. Key to this highly enantioselective transformation is the newly designed spirocyclic phosphoric acid STRIP. It is noteworthy that our kinetic resolution represents a very atom-economical method that, unlike common alternative resolution methods, does not require any stoichiometric reagents and forms ethanol as the only byproduct. The acetal group in cyclic acetals **3** can easily be modified (e.g., oxidized, reduced, or substituted), giving access to enantioenriched tetrahydrofurans and γ-butyrolactones. Our method is applicable to the resolution of a wide range of secondary and tertiary homoaldols. Further studies regarding the development of related transformations and applications of our new catalyst class are ongoing.

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Supporting Information Available: Experimental procedures and compound characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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