

Resolution of Diols via Catalytic Asymmetric Acetalization

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S Supporting Information

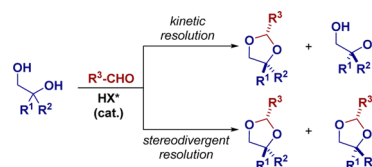
ABSTRACT: A highly enantioselective kinetic resolution of diols via asymmetric acetalization has been achieved using a chiral confined imidodiphosphoric acid catalyst. The reaction is highly efficient for the resolution of tertiary alcohols, giving selectivity factors of up to >300. Remarkably, even in cases where the selectivity factors are only moderate, highly enantioenriched diols are obtained via a stereodivergent resolution to diastereomeric acetals.

Enantiomerically pure diols are common in natural products and are valuable synthetic building blocks.¹ Their synthesis has attracted much attention and still constitutes an important challenge. Next to the Sharpless dihydroxylation of olefins,² other methods have been developed, such as epoxide opening,³ asymmetric hydrogenation of α -hydroxyketones,⁴ α -oxyamination/reduction of carbonyls,⁵ diboration/oxidation of alkenes,⁶ and others.⁷ However, synthetic approaches capable of delivering diols with tertiary alcohol stereocenters with high enantioselectivity are much less common.^{2c,7d,e} Since racemic diols are readily accessible, kinetic resolution can be an attractive alternative strategy for the preparation of enantioenriched diols.⁸ Methods for kinetic resolution of diols via asymmetric acylation and silylation are known,⁹ but they have been rarely applied to tertiary diols.⁹ⁱ

Next to ester and silyl groups, acetals are particularly useful protecting groups for alcohols, with complementary stability and deprotection conditions. Nevertheless, processes for the kinetic resolution of alcohols via acetal formation are still in their infancy, with asymmetric acetalization reactions being developed only very recently.¹⁰ High selectivity was previously achieved only in the kinetic resolution of alcohols via intramolecular transacetalization.^{10b} Now we report that direct acetalization of aldehydes with racemic diols provides an efficient method for the kinetic resolution of diols possessing valuable tertiary alcohol stereocenters. Furthermore, as the acetalization reaction creates an additional stereocenter, a complementary stereodivergent resolution of diols into two separable diastereoisomers is possible when the kinetic enantiomer differentiation is unsatisfactory (Scheme 1).^{8b} The method also enables access to enantioenriched 1,3-dioxolanes possessing two stereocenters, itself a valuable motif.¹¹

We initiated our studies using terminal diol *rac*-2a as a model substrate and confined imidodiphosphoric acid catalyst 1a, which has previously been identified as an excellent catalyst for asymmetric acetalizations.^{10d} Using 1 mol% of the catalyst and isovaleraldehyde in toluene at 20 °C, kinetic resolution proceeded with a very high selectivity factor of 118, giving diol 2a in 46% isolated yield with an enantiomeric ratio (er) of 97.5:2.5 and

Scheme 1. Resolution of Diols via Asymmetric Acetalization



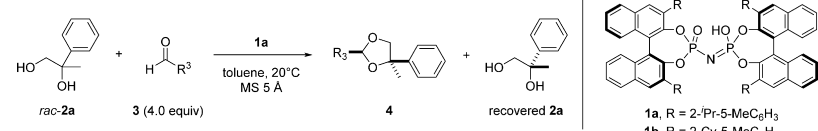
cyclic acetal 4a in 50% isolated yield with an er of 98.5:1.5 and a diastereomeric ratio (dr) of 58:1 (Table 1, entry 1). Exploration of different aldehydes revealed that efficient kinetic resolution of diol *rac*-2a can be achieved in the presence of only 1–2 mol% of 1a to give a variety of 1,3-dioxolanes 4 with excellent enantioselectivities and diastereoselectivities (Table 1). Replacing isovaleraldehyde with less bulky *n*-pentanal or acetaldehyde resulted in still high selectivity factors of 64 and 39, respectively (entries 2 and 3). Increased steric bulk at the α -position of isobutyraldehyde resulted in a higher selectivity factor of 79, although a higher catalyst loading was required (entry 4). When even more sterically demanding pivalaldehyde was used, the reaction did not proceed at all (entry 5). Considering that the use of isovaleraldehyde, which is bulkier than linear aldehydes and at the same time less bulky than α -trisubstituted aldehydes, resulted in the highest selectivity factor, we wondered if increasing the bulkiness at the β -position could be beneficial. Indeed, 3,3-dimethylbutyraldehyde gave an excellent selectivity factor of 122 (entry 6). However, because of its significantly lower reactivity, we used isovaleraldehyde for examining the diol scope of the acetalization.

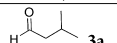
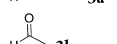
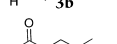

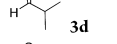
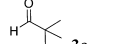
A variety of diols with substituted aromatic rings was tested for the kinetic resolution (Table 2, entries 1–6). By placing chloro-, methoxy-, or methyl-substituents at the *para*-position of the aromatic ring of the diol, we obtained very high selectivity factors from 64 to 99 with 2–3 mol% of the catalyst (Table 2, entries 1–3). Kinetic resolutions employing diols with *meta*- or *ortho*-substituents proceeded with increased enantioselectivity compared to those bearing *para*-substitution (entries 4 and 5); excellent selectivity factors of 110 and 135 were obtained in these cases. 2-Naphthyl-substituted diol *rac*-2l gave a superb kinetic resolution with a selectivity factor of 389 (entry 6). 1,2-Diol 2l was isolated in 45% yield, with an er of 98.5:1.5, while 1,3-dioxolane 4l was obtained with er over 99.5:0.5, and a dr of 93:1, in 44% isolated yield. Encouraged by these results, we next explored the possibility of replacing the methyl group with other substituents. Gratifyingly, the reaction of ethyl-substituted diol

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Table 1. Identification of Suitable Aldehydes for Kinetic Resolution



entry	aldehyde	catalyst loading	time	conv. ^a	yield 2a ^b	er 2a ^c	yield 4 ^b	er 4 ^{d,e}	dr 4 ^d	s ^f
1		1 mol%	22 h	50%	46%	97.5:2.5	50%	98.5:1.5	58:1	118
2		1 mol%	23 h	55%	40%	99:1	48%	94:6	20:1	39
3		1 mol%	12 h	49%	47%	94.5:5.5	47%	97:3	57:1	64
4		2 mol%	36 h	52%	42%	99:1	49%	98:2	26:1	79
5		2 mol%	10 d	-	-	-	<2% ^g	-	-	-
6		2 mol%	96 h	52%	39%	99.5:0.5	47%	98:2	52:1	122

^aTheoretical conversion calculated from ee values of the product and the recovered starting material (see SI). ^bIsolated yield on a 0.5 mmol scale. ^cDetermined by HPLC analysis on a chiral stationary phase. ^dDetermined by GC analysis on a chiral stationary phase. ^eFor most minor diastereomers er >99.5:0.5. ^fCalculated from theoretical conversion and enantiomeric excess of enantioenriched diol (see SI). ^gDetermined by ¹H NMR analysis.

rac-2m proceeded with 2 mol% of **1a** with a selectivity factor of 115 (entry 7). Interestingly, even the isopropyl-substituted diol *rac-2n* exhibited an impressive selectivity factor of 372, with only 1 mol% of the catalyst (entry 8). It is rather remarkable that such a high selectivity factor could be obtained with a diol that possesses two similarly bulky substituents, phenyl and isopropyl.

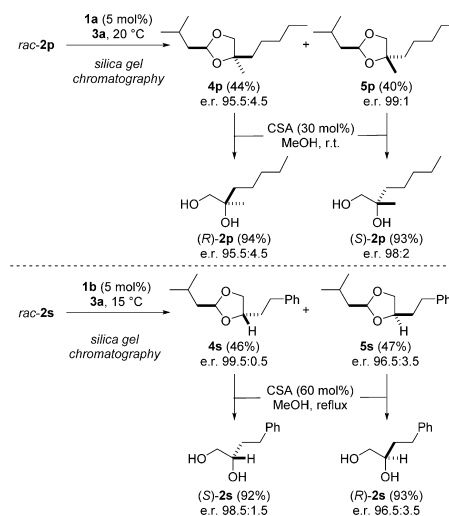
The exceptional results with aryl,alkyl-substituted 1,2-diols encouraged us to also explore the kinetic resolution of dialkyl-substituted diols. Gratifyingly, the reaction of methyl,cyclohexyl-substituted diol *rac-2o* proceeded with a selectivity factor of 23 (entry 9). With methyl,hexyl-substituted diol, the reaction still proceeded with a reasonable selectivity factor of 9 (entry 10). Diol **2p** could be isolated with a good er of 93:7 in 33% yield. Product **4p** was obtained with an excellent er of 98.5:1.5 and a dr of 4:1. This example further demonstrates how excellent stereocontrol of the acetal stereocenter formation is accomplished by the catalyst independently of the diol substrate. Good enantioselectivities of dialkyl-substituted diols could be obtained at higher conversion, even if the selectivity factor is not particularly high.

We next investigated the applicability of our catalytic system to 1,3-diols. Although the reactivity and selectivity declined slightly, additional screening of conditions and use of the bulkier catalyst **1b** resulted in good selectivity factors. With methyl,phenyl-substituted 1,3-diol, a selectivity factor of 29 was achieved, providing 1,3-diol **2q** in 40% yield and excellent enantioselectivity, with an er of 99:1 (entry 11). A 1,3-diol with methyl and naphthyl substituents afforded a still good but slightly lower selectivity factor of 16 (entry 12).

We also examined whether diols with secondary alcohol stereocenters, which are usually preferred substrates for other kinetic resolutions,^{8,9} are suitable substrates for our catalytic system. Disappointingly, almost no selectivity was observed for the resolution of diol *rac-2s* (entry 13). However, an important aspect of our acetalization reaction was revealed in this case. Because of the exceptional enantiocontrol of our catalyst in creating the acetal stereogenic center, the kinetic resolution is applicable even to cases where the actual enantiomer differentiation is poor. As the enantiomers are being converted into two different diastereomers, the reaction can be run to full

conversion of the *rac*-diol, as exemplified with *rac-2p* ($s = 9$) and *rac-2s* ($s = 1.6$) (Scheme 2). Although the enantiomer

Scheme 2. Stereodivergent Access to Enantioenriched Diols



differentiation is not satisfactory in these cases, excellent control of the acetal stereocenter channels the two diol enantiomers into two highly enantioenriched acetal diastereomers. These can be separated by chromatography on silica gel. In the subsequent deprotection step, enantioenriched diols (*R*)-**2p**, (*S*)-**2p** and (*R*)-**2s**, (*S*)-**2s** could be obtained from the corresponding acetals (Scheme 2). It is noteworthy that, from a single asymmetric reaction using one configuration of catalyst, both enantiomers of the diols *rac-2p* and *rac-2s* could be obtained with very high enantiomeric ratios.

Based on our previous results,^{10d} we propose that the cyclization of an oxocarbenium intermediate is the enantio-discriminating step in our reaction (Figure 1). The OH group at the tertiary stereocenter is presumably hydrogen bonded to the chiral imidodiphosphate anion, placing the alcohol stereocenter in its close vicinity, which results in an efficient kinetic resolution

Table 2. Diol Scope

entry	catalyst	time	conv. ^a	2	yield ^b /er ^c	4	yield ^b /er ^{c,d}	dr ^d	s ^e
1	1a , 3 mol%	10 h	49%		47% / 94.5:5.5		45% / 98.5:1.5	52:1	87
2	1a , 2 mol%	17.5 h	50%		49% / 96.5:3.5		48% / 98.5:1.5	53:1	99
3	1a , 2 mol%	13 h	52%		44% / 97.5:2.5		46% / 96:4	52:1	64
4	1a , 1 mol%	19 h	46%		54% / 90.5:9.5		45% / 98.5:1.5	124:1	110
5	1a , 1 mol%	17 h	49%		51% / 96.5:3.5		47% / 98.5:1.5	92:1	135
6	1a , 1 mol%	22 h	50%		45% / 98.5:1.5		44% / >99.5:0.5	93:1	389
7	1a , 2 mol%	20 h	52%		46% / 99.5:0.5		44% / 98:2	36:1	115
8	1a , 1 mol%	11 h	50%		44% / 99:1		49% / 99.5:0.5	191:1	372
9	1a , 2 mol%	15 h	55%		45% / 95.5:4.5		49% / 95.5:4.5	11:1	23
10	1a , 2 mol%	15 h	61%		33% / 93:7		54% / 98.5:1.5	4:1	9
11 ^f	1b , 2 mol%	38 h	58%		40% / 99:1		54% / 91:9	17:1	29
12 ^f	1b , 2 mol%	40 h	56%		38% / 94.5:5.5		55% / 89:11	20:1	16
13	1b , 2 mol%	15 h	81%		10% / 69:31		80% / 99.5:0.5	1.1:1	1.6

^aTheoretical conversion calculated from ee values of the product and the recovered starting material (see SI). ^bIsolated yield on a 0.5 mmol scale. ^cDetermined by HPLC or GC analysis on a chiral stationary phase. ^dFor most minor diastereomers er \geq 98:2. ^eCalculated from theoretical conversion and enantiomeric excess of enantioenriched diol (see SI). ^fThe reaction was performed at 0 °C.

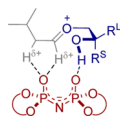


Figure 1. Suggested pre-transition-state assembly explaining the preferred *cis*-diastereomer selectivity.

in the cyclization step. Additional oxocarbenium C–H \cdots anion hydrogen bonding potentially further stabilizes the transition state.¹² The aldehyde alkyl chain and the larger alcohol substituent both take pseudoequatorial positions in the five-membered transition state, resulting in their *cis* relationship in the products.¹³

In summary, the first kinetic resolution of diols via asymmetric acetalization reaction has been disclosed, achieving selectivity

factors up to >300.¹⁴ The reaction provides free enantioenriched diols and acetal-protected diols with excellent enantioselectivities. 1,2-Diols possessing similar aliphatic substituents at the tertiary alcohol stereocenter, which are hard to obtain by other methods, can be resolved via separation of diastereomeric acetal products. Further studies regarding the applications of asymmetric acetalizations and our confined Brønsted acids are ongoing.

■ ASSOCIATED CONTENT

📄 Supporting Information

Experimental procedures and compound characterization. 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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