Organocatalysis

DOI: 10.1002/anie.200800641

Enantioselective Kinetic Resolution of *trans*-Cycloalkane-1,2-diols**

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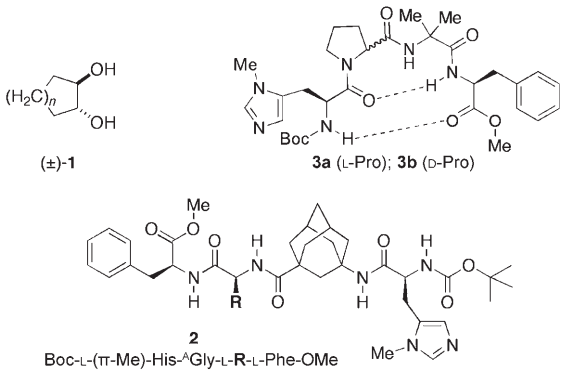
The kinetic resolution[1] of chiral *trans*-cycloalkane-1,2-diols (**1**) presents a formidable challenge[2] and a rare case where chemical methods are superior to enzymatic approaches. Taking the kinetic resolution of *trans*-cyclohexane-1,2-diol (**1a**, $n=2$) through monoacylation as the delineating test reaction, it was shown that various *Pseudomonas* lipases display both low activities (reaction times typically within the range of days) and low selectivities.[3] Purely chemical transformations utilizing benzoyl transfer in Cu^{II}-catalyzed reactions with C_2-symmetric bisoxazoline ligands give good *ee* values for the monobenzoylated product (around 80%) and good conversions (37–46%; selectivity factor $s=14$–22) within hours;[4,5] Diol **1a** is resolved with up to 66% *ee*.[4] Hence, the availability of a practical chemical method for the catalytic enantioselective kinetic resolution of diols **1** is desirable.



Herein we present an approach that utilizes the novel lipophilic chiral tetrapeptide platform **2** (Boc = *tert*-butoxycarbonyl, AGly = γ-aminoadamantanecarboxylic acid; AGly in our shorthand notation emphasizes the relationship to the α-amino acid glycine[12]), which is equipped with a nucleophilic *N*-π-methylhistidine moiety for enantioselective acyl transfer.[6] Miller et al. have been highly successful[7,8] in the resolution of monoprotected diols and amino alcohols,[9] as well as of polyols through acyl transfer.[8] The tetrapeptide catalysts such as **3** utilized in some of these reactions are, at least in our hands, much less effective for the resolution of (±)-**1a** (see Figure 1 and the Supporting Information). Toniolo et al. improved the efficacy of **3** also through the introduction of lipophilic α-methylvaline.[10]

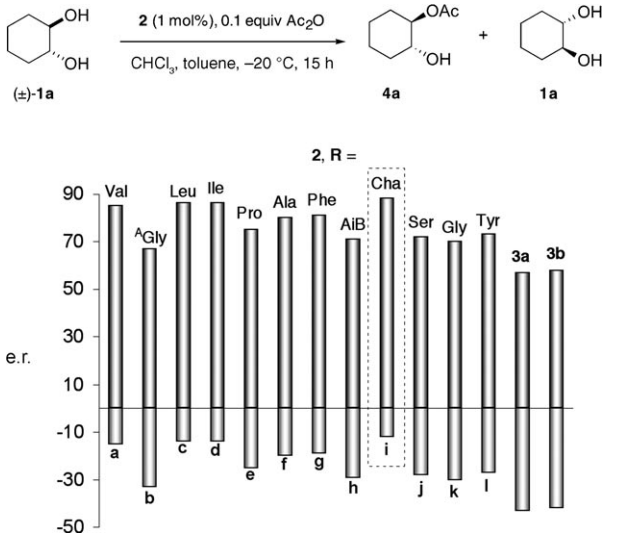


Figure 1. Catalyst screening (**2**) for the enantioselective acylation test reaction. Reactions were run at low conversions (<10%) to determine maximum activity. Enantiomeric ratios (e.r.) are given for **4a**. The most efficient catalyst, **2i**, is outlined with a dotted line.

Our strategy for developing a practical method for the resolution of (±)-**1** was the preparation and utilization of more lipophilic and somewhat structurally less flexible oligopeptides; we hoped that diminished catalyst self-association (dimerization or folding) would lead to low catalyst loadings and would allow the use of nonpolar organic solvents. It has been shown recently that organic solvents of low polarity play a key role in the effective regeneration of the catalyst such that they even allow the omission of auxiliary base in 4-dimethylaminopyridine(DMAP)-catalyzed acylation reactions.[11] Not having to use an additional base simplifies the workup and product purification.[9]

Our approach does not follow established design principles for oligopeptide catalysts which emphasize the formation of catalytically important secondary structures (indicated by the internal hydrogen bonds in **3**).[6,8] Our concept culminated in tetrapeptide catalysts of type **2** incorporating a rigid nonnatural γ-aminoadamantanecarboxylic acid as well as several hydrophobic natural as well as nonnatural amino acids.

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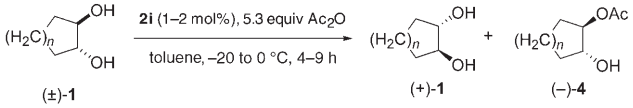
[**] This work was supported by the Deutsche Forschungsgemeinschaft (SPP1179). We thank Prof. Scott J. Miller (Yale University) for providing us his protocol for the synthesis of *N*-π-methylhistidine and Dr. E. Röcker for competent analytical support.

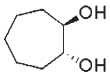
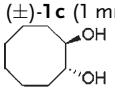
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.200800641.

Oligopeptides **2** with a variation only in R can be prepared in a straightforward manner by automated solid-phase peptide-coupling methods (see the Supporting Information for details), and we prepared and screened a large variety of structures; the coupling of the novel Fmoc-protected bulky adamantyl γ-amino acid proved unproblematic despite its bulkiness.[12]

Miller's peptide catalyst **3** (with variation in using L- and D-proline) was prepared for comparison by published protocols.[9] Catalyst **3b** (D-pro) was shown to be highly effective for the kinetic resolution of *trans*-1,2-acetamidocyclohexanol, which provides additional amide hydrogen-bond interactions with the catalyst.[6] The β-hairpin structure of **3b**, which was inferred by NMR experiments, was held responsible for its high selectivity ($s = 28$). In contrast, the kinetic resolution of monoacylated (±)-**4a** proved rather difficult ($s = 1.4$).[13] Our experiments with **3a** and **3b** confirm these findings and also show that the kinetic resolution of (±)-**1a** is practically ineffective (Figure 1).

Table 1: Enantioselective kinetic resolution of *trans*-cycloalkane-1,2-diols with oligopeptide catalyst **2i** in toluene.



Substrate	Cat. [mol%]	T [°C]	t [h]	Conv. [%][a]	*ee* [%] (+)-**1**	*ee* [%] (−)-**4**	s[a]
 (±)-**1a**	2	−20	4	57	>99	75	>50
(±)-**1a** (0.4 mmol)[b]	1	0	5	39[d]	>99	78	>50
(±)-**1a** (1 mmol)[c]	1	0	4	37[e]	>99	78	>50
 (±)-**1b**	2	−20	9	63	85	49	8[f]
 (±)-**1c**	2	−20	5	57	>99	77	>50
(±)-**1c** (0.4 mmol)[b]	1	0	5	39[d]	97	80	37
(±)-**1c** (1 mmol)[c]	1	0	5	41[e]	>99	79	>50
 (±)-**1d**	2	−20	6	55	>99	83	>50
(±)-**1d** (0.4 mmol)[b]	1	0	5	40[d]	>99	82	>50
(±)-**1d** (1 mmol)[c]	1	0	5	44[e]	>99	85	>50

[a] Conversions and *s* factors determined following the procedure of Kagan and Fiaud;[14] *s* factors above 50 are not reliable; since *s* factors do not vary with catalyst concentration (1–10 mol%), the approximate formula is valid up to 50.[1,15] [b] Preparative experiment on a 0.43 mmol scale. [c] Preparative experiment on a 1.0 mmol scale. [d] Yield of isolated product for **1** in preparative experiments on a 0.43 mmol scale. [e] Yield of isolated product for **1** in preparative experiments on a 1.0 mmol scale. [f] Dichloromethane added for solubility.

The amino acid backbone presented in the twelve tetrapeptides **2a**–**2l**, with only a variation in R, turned out to be generally effective for the enantioselective acylation of (±)-**1a** ($n = 2$), which we utilized as our test reaction (Figure 1). More lipophilic R groups give better results, with R = methylenecyclohexane (**2i**, Cha as building block) being the most effective. The optimal conditions for our acylation protocol with nonpolar toluene as the only solvent and 1–2 mol% catalyst loading are also applicable to other racemic *trans*-1,2-diols (Table 1). The selectivities for these reactions are generally very good; *trans*-cyclopentane-1,2-diol (**1b**) is the exception, partially because addition of some CH_2Cl_2 is necessary to overcome the poor solubility of **1b** in toluene. As anticipated, the selectivities indeed largely depend on solvent polarity. For comparison, we also examined the acylation of **1a** in acetonitrile, CH_2Cl_2, and trifluoromethylbenzene under otherwise identical conditions. The reaction times were much longer to achieve appreciable conversions and the *s* factors were significantly lower: 2.4 (CH_3CN, 5.1% conversion, 48 h), 9.6 (CH_2Cl_2, 23.5% conversion, 24 h), and 8.9 ($PhCF_3$, 23.2% conversion, 4 h) (for details see the Supporting Information).

The omission of auxiliary base is possible because acetic acid ($pK_a = 4.74$) equilibrates with the methylimidazolium ion ($pK_a = 7.3$)[16] such that an appreciable amount of unprotonated catalyst is always available; the pK_a values are likely to be more similar in organic solvents owing to the higher polarizability of methylimidazole. As a consequence, other anhydrides delivering even weaker acids could show even higher selectivities. Indeed, using isobutyric anhydride under otherwise identical conditions for the resolution of (±)-**1**, we found marginally better selectivity, however, at a much longer reaction time for comparable conversion. This is apparently because of higher steric demand; pivalic anhydride, with even greater steric demand, is practically unreactive.

We also determined the absolute stereochemistry of enantiomerically pure (+)-**1a** obtained with **2i** as 1*S*,2*S* by comparison with literature data (for details see the Supporting Information).[3] The (−) enantiomer can be prepared readily by changing the stereochemistry at the histidine moiety and the R position in tetrapeptide **2**. This is remarkable as this implies that the stereochemistry is determined by the homo configuration of the amino acid defining R and the catalytically active His moiety. We followed up on this finding and searched for indications of secondary-structure formation of **2i** by NMR polarization-transfer experiments, but these did not provide clear indications of specific intramolecular interactions. Hence, there must be a structure-forming element at the stage of the complexed acylium ion. As NMR studies of such ions are hampered by various issues, we resorted to a molecular dynamics search for low-lying conformations of the catalyst/acylium ion adduct utilizing the Merck Molecular Force Field

(MMFF);[17] as we used a nonpolar solvent, this comparison should be qualitatively valid. Irrespective of the starting geometry, the most favorable conformers always placed the cyclohexyl group in **2i** in close proximity to the imidazole/acylium ion adduct (Figure 2).

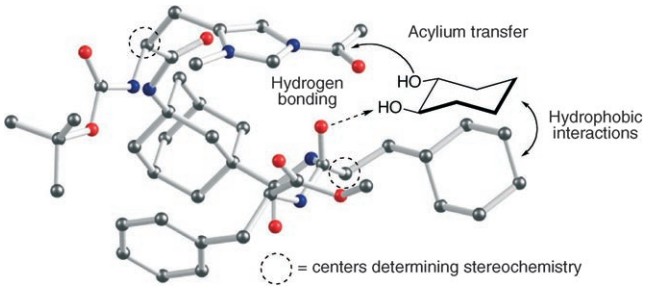


Figure 2. Model for the enantioselective acylation of *trans*-cycloalkane-1,2-diols in the "pocket" of the acylated catalyst. Hydrogen atoms on the catalyst are omitted for clarity. C gray, N blue, O red.

The two geometrically near C=O groups are likely to provide the hydrogen-bonding contacts needed for chiral recognition of the diols. Our finding that more hydrophobic R groups provide higher *ee* values could also be rationalized by the additional hydrophobic interactions with the substrate. The model also emphasizes that the ^{A}Gly building block provides the scaffold that holds the catalytic site and the centers governing recognition and stereochemistry in place. This model will provide the basis for further catalyst development.

We have identified a tetrapeptide incorporating natural and unnatural amino acids capable of stereoselective acyl-group transfer onto *trans*-cycloalkane-1,2-diols. The kinetic resolutions presented here provide exceptionally high selectivities that are made possible through the interplay of an unnatural cage γ-amino acid that provides some rigidity and a lipophilic amino acid in the chain allowing for hydrophobic interactions in our proposed transition-state model. The lack of secondary structure in the free catalyst implies that the factors determining the stereochemistry are developed in the charged acylium ion complex with the peptide catalyst and the subsequent stereodifferentiating interactions of this complex with the substrate.

Experimental Section

Tetramer **2i** was synthesized on solid support using commercially available Wang polystyrene resin end-capped and preloaded with Fmoc-protected L-phenylalanine (0.405 g, 0.74 mmol g^{-1}, 0.3 mmol). Fmoc cleavage was performed by shaking the resin twice in 25% piperidine in DMF (v/v). The resin was washed five times each with DMF, dichloromethane, and DMF. Chain elongation with Fmoc-L-Cha-OH was performed by a double coupling procedure (1 h shaking per coupling step) using Fmoc-L-Cha-OH (0.237 g, 0.6 mmol), *O*-(benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HBTU; 0.228 g, 0.6 mmol), 1-hydroxy-1*H*-benzotriazole monohydrate (HOBt·H_2O (0.092 g, 0.6 mmol), and diisopropylethylamine (DIPEA; 0.155 g, 204.1 μL, 1.2 mmol) per coupling step (2:2:2:4 equiv, respectively). After washing and subsequent cleavage of the Fmoc protecting group as described above, the peptide was elongated using Fmoc-^{A}Gly-OH (0.250 g, 0.6 mmol), HBTU, HOBt, and DIPEA in the same stoichiometric ratio as given above. After washing and subsequent cleavage of the Fmoc protecting group as described above, the peptide was elongated using another double coupling strategy (2 h shaking per coupling step) Boc-L-(π-Me)-His-OH (0.121 g, 0.45 mmol), HBTU (0.228 g, 0.6 mmol), HOBt (0.092 g, 0.6 mmol), and DIPEA (0.155 g, 204.1 μL, 1.2 mmol) per coupling step (1.5:2:2:4 equiv, respectively). After washing (five times each with DMF, dichloromethane, and diethyl ether), **2i** was cleaved from the resin by shaking two times for two days with methanol, triethylamine, and THF (9:1:1, v/v). The resin was filtered off and washed several times with THF. The collected solutions were concentrated and the residue was purified by HPLC (eluent: *tert*-butyl methyl ether(TBME)/CH_3OH 85:15, 6 mL min^{-1}; UV detector $\lambda = 254$ nm, $E_{max} = 2.56$; refractometer; column l = 250 mm, $d = 8$ mm, LiChrosorb Diol (7 μm, Merck); retention time (**2i**) = 10.43 min). The peptide was characterized by ESI-MS, HR-ESI-MS, NMR, IR, and EA.

^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 7.35$ [s, 1H, C*H*-imidazole (His)], 7.24–7.15 [m, 3H, H_{Ar} (Phe)], 7.05–7.01 [m, 2H, H_{Ar} (Phe)], 6.79 [s, 1H, C*H*-imidazole (His)], 6.44 [d, $J = 7.8$ Hz, 1H, N*H* (Phe)], 5.91 [d, $J = 7.9$ Hz, 1H, N*H* (Cha)], 5.68 [s, 1H, N*H* (^{A}Gly)], 5.09 [d, $J = 8.3$ Hz, 1H, N*H* (His)], 4.78–4.70 [m, 1H, H_α (Phe)], 4.41–4.30 [m, 1H, H_α (Cha)], 4.13–4.03 [m, 1H, H_α (His)], 3.64 (s, 3H, OCH_3), 3.54 (s, 3H, NCH_3), 3.09–2.98 [m, 2H, H_β (Phe)], 2.98–2.88 [m, 2H, H_β (His)], 2.13 (m, 2H, adamantane), 1.93–1.80 (m, 6H, adamantane + Cha), 1.71–1.51 (m, 12H, adamantane + Cha), 1.40–1.36 (m, 1H, Cha), 1.37 [s, 9H, C(CH_3)$_3$], 1.23–1.00 (m, 4H, Cha), 0.92–0.69 ppm (m, 2H, Cha). ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 176.3$ (C=O), 171.9 (C=O), 171.6 (C=O), 169.7 (C=O), 155.4 (C=O), 138.3, 135.7, 129.2, 128.6, 128.2, 127.2, 127.2, 80.5, 54.4, 53.2, 52.3, 50.7, 42.5, 42.1, 40.3, 40.3, 39.5, 38.2, 38.0, 37.8, 35.1, 34.2, 33.5, 32.7, 31.5, 29.1, 29.1, 28.3, 26.8, 26.3, 26.1, 26.1 ppm; IR (KBr): $\tilde{\nu} = 3427$, 2921, 2853, 2912, 1746, 1661, 1510, 1518, 1450, 1366, 1280, 1249, 1169 cm^{-1}. MS: a) ESI: $m/z = 761.5$ $[M+H]^+$ (calcd $m/z = 761.5$), $m/z = 783.4$ $[M+Na]^+$ (calcd $m/z = 783.4$), $m/z = 1521.3$ $[2M+H]^+$ (calcd $m/z = 1521.9$), $m/z = 1543.3$ $[2M+Na]^+$ (calcd $m/z = 1543.9$); b) HR-ESI: $m/z = 761.45963$ $[M+H]^+$ (calcd $m/z = 761.45963$). Anal. calcd for $C_{32}H_{43}N_5O_6$: C 66.29, H 7.95, N 11.04; found C 64.45, H 7.75, N 10.33.

Example illustrating the general procedure for the preparative kinetic resolution of the cyclic diols: Catalyst **2i** (3.3 mg, 0.0043 mmol, 1 mol%) and diol (±)-**1a** (50 mg, 0.43 mmol) were dissolved in 80 mL of anhydrous toluene to produce a clear solution. The reaction mixture was cooled to 0°C, and acetic anhydride (0.215 mL, 2.28 mmol, 5.3 equiv), which was cooled to 0°C, was added and allowed to stir for 4.5 h at 0°C. The reaction mixture was quenched with 10 mL methanol and filtered using 37 g silica gel suspended with EtOAc to remove the catalyst and acetic acid (the silica gel was washed with EtOAc). After the filtration, the solvents were removed under reduced pressure. The crude product was then applied directly to a silica gel column. Eluting with EtOAc afforded 33.9 mg (0.214 mmol, 50.0%) of monoacetate **4a** ($R_f = 0.47$) and 19.4 mg (0.167 mmol, 38.8%) of diol **1a** ($R_f = 0.20$). The products were then directly characterized by chiral GC analysis and NMR.

Received: February 8, 2008
Revised: April 14, 2008
Published online: July 10, 2008

Keywords: acylation · alcohols · kinetic resolution · organocatalysis · peptides

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