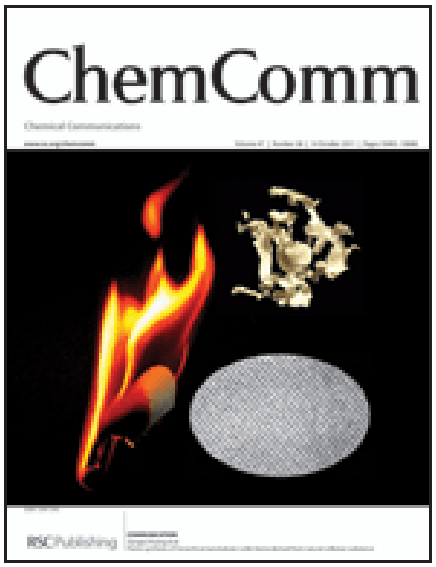

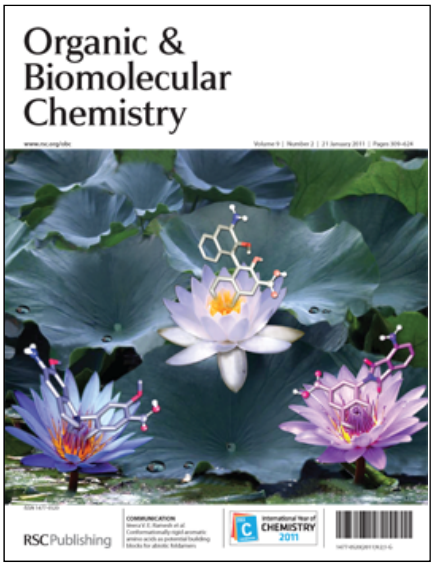

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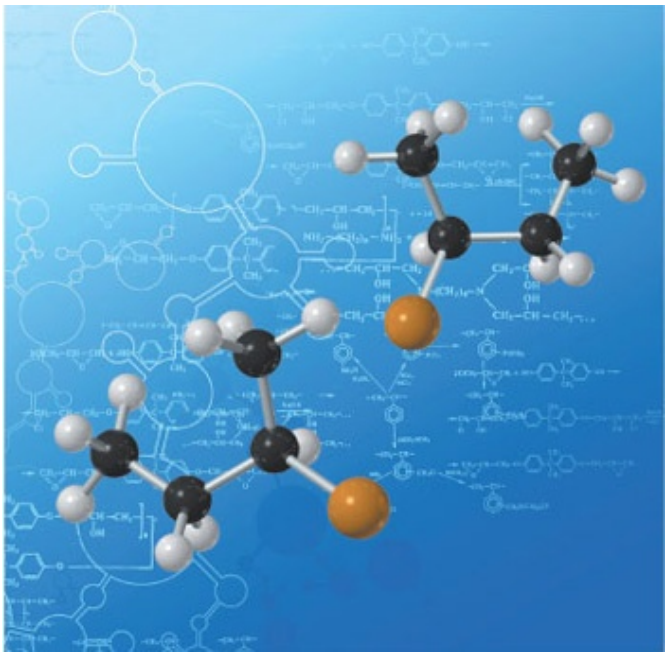

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COMMUNICATION

Enantiomerically enriched *trans*-diols from alkenes in one pot: a multicatalyst approach†‡

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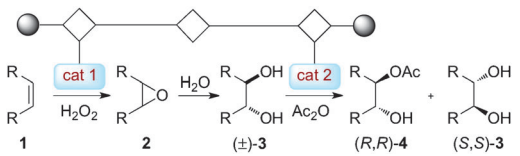
Multicatalysts consisting of non-natural oligopeptides with distinctly different catalytic moieties create molecular complexity in a multistep one-pot sequence starting from simple alkenes yielding highly enantiomerically enriched *trans*-diols.

Organocatalysis has become a powerful tool for the synthesis of enantiomerically pure compounds,[1] and multiple reaction one-pot approaches are particularly attractive by way of their resource and energy efficiency.[2–4] Examples include one catalyst performing several reaction steps or several individual catalysts that catalyze a single reaction step of a longer sequence.[5] Multicatalyst approaches, where different catalytic moieties are connected to one common catalyst backbone, are, however, rare.[6,7] These approaches may share the operational advantages of one-pot reaction sequences and additionally improve the material balance, operational efficiency, and individual reaction steps by providing higher local concentrations at the common catalyst backbone for the individual steps.

Here we show a multicatalyst approach for the preparation of enantiomerically enriched *trans*-1,2-diols (**3**) starting from simple symmetrical alkenes (**1**). We envisioned that epoxidation of **1** by an *in situ* generated peracid (cat 1) should give the corresponding epoxides **2**. Opening of **2** with water would lead to the diols (±)-**3** that can be kinetically resolved *via* catalytic enantioselective acylation using a nucleophilic *N*-π-methyl histidine moiety as the active center (cat 2) (Scheme 1).[8–10] As multicatalysts we focused on short oligopeptides **A–F** (Schemes 2 and 3) that allow ready and automated variation of all components.[11]



Scheme 1 One-pot sequence from alkenes **1** to enantioenriched diols **3** and monoprotected diols **4** with a multicatalyst.

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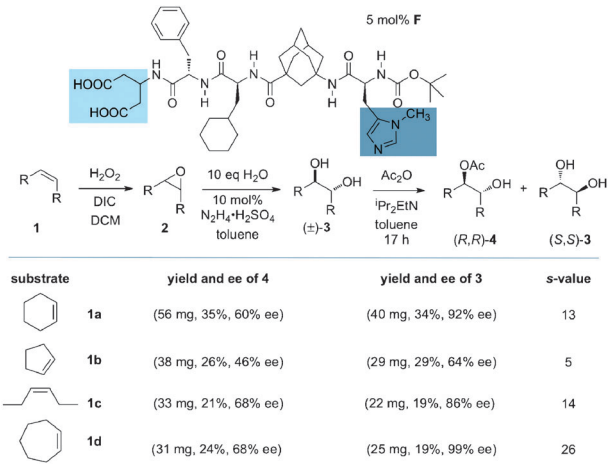


substrate		yield and ee of 4	yield and ee of 3	*s*-value
	1a	(56 mg, 35%, 60% ee)	(40 mg, 34%, 92% ee)	13
	1b	(38 mg, 26%, 46% ee)	(29 mg, 29%, 64% ee)	5
	1c	(33 mg, 21%, 68% ee)	(22 mg, 19%, 86% ee)	14
	1d	(31 mg, 24%, 68% ee)	(25 mg, 19%, 99% ee)	26

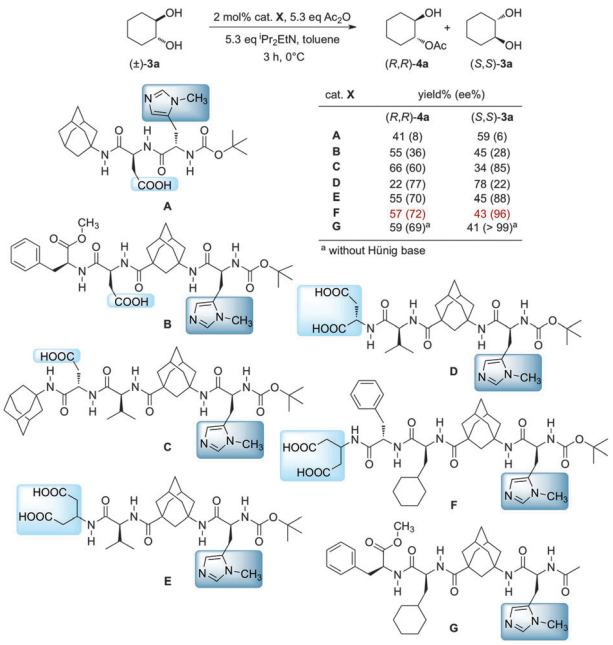
Scheme 2 Peptide **F** multicatalyst leading to enantioenriched *trans*-diols **3** and monoacylated diols **4** from simple alkene **1**.

Our previous studies[12] showed that the incorporation of a rigid non-natural γ-amino adamantane carboxylic acid[13] leads to a lipophilic (for use in organic solvents) and structurally defined oligopeptide that effectively separates the catalytic centers.[12]

We present the key results first, followed by an analysis of the development and optimization of the sequence; peptide **F** turned out to be the most efficient multicatalyst.§ The β-aspartate moiety catalyzes the epoxidation of **1** to **2**, followed by opening of **2** with hydrazine bisulfate[14] and water in toluene leading to the corresponding diol (±)-**3**, which was kinetically resolved to the enantiomerically enriched monoacetylated **4** in the last step. Overall yields of up to 34% (the maximum would be 50%) and enantioselectivities up to 99% for the recovered diol (*s*-values[15] up to 26 at the preparative scale) could be obtained with this three step one-pot reaction sequence (Scheme 2).

The catalysts **A–F** were optimized with regard to the terminal *kinetic resolution*. The role of the spacer is crucial and we found that the optimal distance between the catalytic moieties should be three amino acids. The solvent of choice for these types of reactions is known to be toluene, which promotes secondary interactions between the acylium ion and the 1,2-diol responsible for the enantioselectivity (Scheme 3).[8,10]

We focused next on the *epoxidation*, the first step of the desired reaction sequence. The challenge is to avoid oxidation of the catalyst during the epoxidation and interference of the

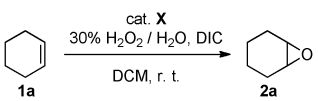


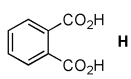
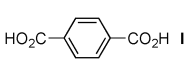
Scheme 3 Kinetic resolution of *trans*-cyclohexane-1,2-diol (±**3a**) by bifunctional catalysts **A–F** containing an α- or β-aspartate moiety (cat 1) and a *N*-π-methyl histidine moiety (cat 2); the performance of the monofunctional catalyst **G** is additionally given for comparison.

epoxidation side products with the subsequent transformations. The epoxidation of alkenes was studied with carboxylic acids as catalysts, hydrogen peroxide as the oxidant and carbodiimide as the dehydrating agent; phthalic acid was found to be a powerful organocatalyst in this reaction.

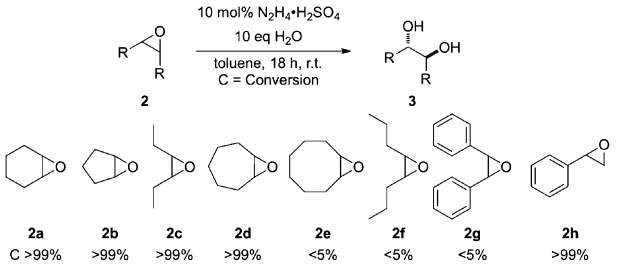
Comparing its reactivity with terephthalic acid, we conclude that the epoxidation proceeds through internal anhydride formation followed by opening with hydrogen peroxide and epoxidation of the alkene through the phthalic monoperacid intermediate (Table 1).[16] The epoxidation proceeds in DCM as well as in toluene. A diacid moiety containing multicatalysts **D**, **E**, and **F** proved to be active; catalysts **E** and **F** with C-terminal β-aspartate led to good conversions (Table 1). In the case of the peptide multicatalysts DCM was the solvent of

Table 1 Comparison of the catalytic activity of phthalic acid, terephthalic acid, and multicatalysts **D–E** in the epoxidation of cyclohexene



Catalyst	mol%	Conversion (%) 4 h	18 h	24 h	48 h
	2	50[a]	54[a]	60[a]	—
	5	—	90[a]	92[a]	—
	10	—	92[a]	93[a]	—
 I	2	<10[a]	—	20[a]	—
D	5	—	—	—	10[b]
E	5	—	—	—	87[b]
F	5	—	—	—	88[b]

[a] 1.2 eq. H_2O_2, 1.2 eq. DIC. [b] Additional 1.2 eq. H_2O_2 and 1.2 eq. DIC were added after 24 h.

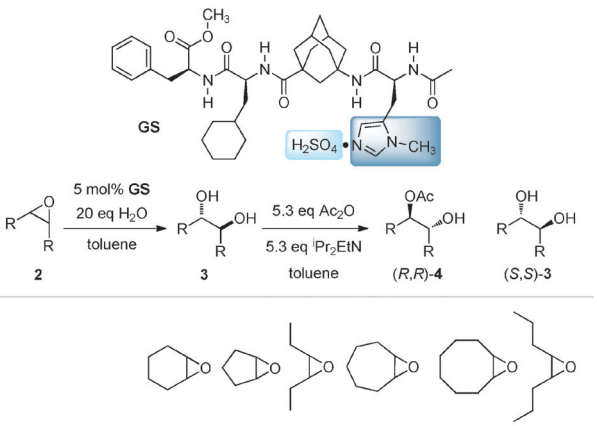


Scheme 4 Opening of epoxides using hydrazine bisulfate as organocatalyst.

choice because it is able to dissolve all components of the reaction.

We screened a large variety of small organocatalysts using cyclohexene oxide (**2a**) as the model compound for the *epoxide opening* step (for details see ESI‡). Hydrazine bisulfate[14] was found to be the catalyst of choice as its solubility in water and insolubility in nonpolar organic solvents lead to Brønsted acid catalyzed biphasic epoxide opening (Scheme 4). In polar solvents such as DCM or acetonitrile the opening proceeds more slowly because of the addition of the bisulfate to the epoxide. In the case of the **2e**, **2f**, and **2g** this protocol failed and 1 eq. of TFA (see ESI‡ for details) was required to form the corresponding TFA esters, which were subsequently hydrolyzed by Hünig base and water to the diols **3**. The same was observed for **2e** and **2g** in the chromium–salen complex catalyzed opening with azide.[17]

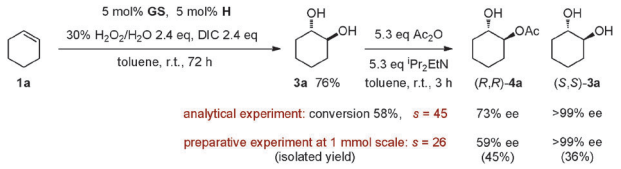
Focusing on the last two steps of the sequence, we observed that the one-pot epoxide opening catalyzed by hydrazine bisulfate and subsequent acetylation led to highly



	2a[a]	2b	2c	2d	2e	2f
time of opening (h)	18 (24)	18	18	42	72[d]	72[d]
conversion (%)	>99 (>99)	>99	>99	83	79	>99
time of resolution (h)	1.5 (2)	48	4	2	2.5	5
conversion (%)	57 (25[b], 54[c])	71	68	58	62	67
s-value	48 (33)	4	19	40	29	19
ee acetyldiol (%)	74 (65)	32	48	70	61	48
ee diol (%)	>99 (>99)	78	>99	>99	>99	>99

[a] values in parentheses indicate a preparative experiment at 1 mmol scale; [b]yield of isolated **3a**; [c]yield of isolated **4a**. [d]1. step: opening of epoxides with TFA; 5 mol% **G**, 1 eq TFA, 72 h. 2. step: hydrolysis of the TFA ester with 5.3 eq H□nig base and 2 eq of water; conversions determined by GC-MS.

Scheme 5 Catalytic opening of epoxides (**2**) to *trans*-alkane-1,2-diols (**3**) and subsequent kinetic resolution catalyzed by the peptide salt **GS**.



Scheme 6 One-pot epoxidation of **1a** catalyzed by phthalic acid, subsequent opening with water catalyzed by the bisulfate moiety on the peptide and *N*-π-methyl histidine catalyzed enantioselective acetylation.

enantioenriched *trans*-diol **3a** (Scheme S1, ESI‡). Remarkably, the acylation was not affected by the 10 eq. of water present in the reaction mixture, neither through the hydrolysis of the acetic anhydride nor through the H-bonding capability of water destroying the crucial catalyst–substrate interactions.

As the epoxide opening is acid catalyzed, we thought of combining this with the acylation step by preparing the bisulfate salt of the nucleophilic peptide **G**, simply by mixing **G** (**G** is the *N*-acylated analogue of our highly effective acylation catalyst and shows nearly the same efficiency;[12] the *N*-Boc group is thereby exchanged with the acetyl group). The resulting salt **GS** indeed catalyzes the epoxide opening step and the neutral catalyst **G** is subsequently regenerated by addition of Hünig base. This protocol proved to be highly efficient for a variety of *meso* epoxides with *s*-values up to 48 at the preparative scale (Scheme 5).

For completeness sake we decided to perform the entire one-pot sequence starting from cyclohexene with two separate catalysts, phthalic acid (5 mol%) for the epoxidation of **1a** and **GS** (5 mol%) for opening of **2a** to **3**. After the addition of Hünig base peptide **G** was deprotonated and catalyzed the enantioselective acetylation of the diol with an impressive *s*-value of 45 at the preparative scale (Scheme 6).

Consequently, we prepared the bisulfate salt of **F**, which should allow catalysis of all three steps of the sequence without additional catalyst. Unfortunately, this corresponding **FS** salt was completely insoluble in organic solvents.

We have developed a one-pot three step sequence starting from simple symmetrical alkenes leading to highly enantiomerically enriched *trans*-1,2-diols and monoacylated diols using a peptide multicatalyst with orthogonal catalytic moieties. This study shows that in a simplified way it is possible to mimic the work of nature, where reactions occur in the active sites of enzymes and the products are transferred to another active site for a subsequent chemical transformation. The next step is to expand on the number of catalytic steps with more catalytic sites on a single backbone and to establish this as a strategy toward reverse catalyst design in the sense of *retrocatalysis* analogous to retrosynthesis.

Notes and references

§ *Typical procedure for the one-pot epoxidation, epoxide opening and acetylation sequence catalyzed by peptide* **F**: Catalyst **F** (0.05 mmol, 21.9 mg, 5%), cyclohexene (1 mmol, 101 μL, 1 eq.) and DIC (1.2 mmol, 185 μL, 1.2 eq.) were dissolved in 2 mL DCM. To this mixture 30% H_2O_2 (130 μL, 1.2 eq.) was added and the resulting mixture was allowed to stir at rt for 24 h. After this time the addition of DIC (1.2 mmol, 185 μL, 1.2 eq.) and 30% H_2O_2 (130 μL, 1.2 eq.) was repeated and the reaction was stirred under the same conditions for 24 h. Then toluene (6 mL) was added, followed by the addition of H_2O (10 mmol, 180 μL, 10 eq.) and hydrazine sulfate (0.1 mmol, 13 mg, 0.1 eq.) and the reaction was stirred at rt for 18 h. In the next step toluene (180 mL) and $^{i}Pr_2EtN$ (5.3 mmol, 876 μL, 5.3 eq.) were added and the reaction was cooled to 0 °C. Ac_2O (5.3 mmol, 540.6 μL, 5.3 eq.) was added and the kinetic resolution was monitored by chiral GC. After 17 h the reaction was quenched with MeOH (10 mL), the solvents were evaporated under reduced pressure and column chromatography on silica gel in hexane/EtOAc 1 : 1 provided 56 mg (35%) of 1-acetoxy-cyclohexan-2-ol (60% ee) **4a** and 40 mg (34%) of cyclohexane-1,2-diol **3a** (92% ee).

Typical procedure for the sequence catalyzed by salt **GS**: Cat. **GS** (0.05 mmol, 40.0 mg, 5 mol%) and cyclohexene oxide (1.0 mmol, 98.1 mg, 101 μL) were dissolved in toluene (1 mL) and water (20 mmol, 360 μL, 20 eq.) was added. The mixture was stirred at rt for 18 h. In the next step toluene (180 mL) and $^{i}Pr_2EtN$ (5.3 mmol, 901 μL, 5.3 eq.) were added and the reaction was cooled to 0 °C. Ac_2O (5.3 mmol, 501 μL, 5.3 eq.) was then added to start the acylation and the kinetic resolution was monitored by chiral GC. The reaction mixture was then quenched with 10 mL of methanol, filtered through silica gel (30 g), suspended with ethyl acetate, and washed with ethyl acetate to remove the catalyst. After evaporation of the solvent *in vacuo* the products were purified by column chromatography. Eluting with ethyl acetate afforded 85.5 mg (0.54 mmol; 54%; 65% ee) of the acetylated diol (R_f = 0.46) and 28.3 mg (0.24 mmol; 24%; >99% ee) of the diol (R_f = 0.22).

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