Asymmetric Catalysis

DOI: 10.1002/anie.201400170

Organocatalytic Asymmetric Hydrolysis of Epoxides**

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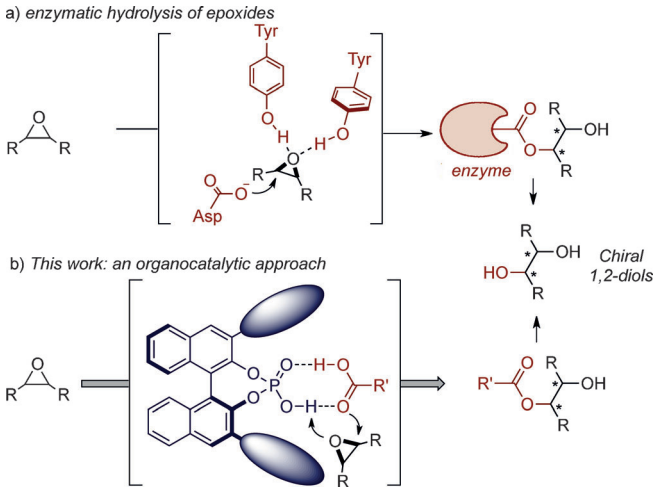
Abstract: *The hydrolytic ring opening of epoxides is an important biosynthetic transformation and is also applied industrially. We report the first organocatalytic variant of this reaction, exploiting our recently discovered activation of carboxylic acids with chiral phosphoric acids via heterodimerization. The methodology mimics the enzymatic mechanism, which involves an enzyme-bound carboxylate nucleophile. A newly designed phosphoric acid catalyst displays high stereocontrol in the desymmetrization of meso-epoxides. The methodology shows wide generality with cyclic, acylic, aromatic, and aliphatic substrates. We also apply our method in the first highly enantioselective anti-dihydroxylation of simple olefins.*

The asymmetric hydrolytic ring opening of epoxides is an important transformation in synthetic chemistry since the produced chiral vicinal diols are valuable building blocks and represent a common motif in natural products and pharmaceuticals.[1] However, the activation of the epoxide moiety and the concomitant enhancement of the typically moderate reactivity of oxygen nucleophiles render this reaction still challenging. In fact, only three systems have previously been described: Jacobsen's cobalt–salen catalyst, a heterobimetallic gallium-based complex by Shibasaki and co-workers, and a scandium–bipiridine complex by Schneider et al.[2–4] All of these methodologies exploit metal-based catalysts and the activation of epoxides in enantioselective organocatalysis has long been elusive.[5] The hydrolysis of epoxides is also very important in the xenobiotic metabolism of living organisms for the detoxification of exogenous substances.[6] This biotransformation is catalyzed by epoxide hydrolases that do not require metal cofactors.[7] Encouraged by this observation and motivated by our previous findings on the activation of carboxylic acids in Brønsted acid catalysis,[8] we focused our attention on the development of a novel organocatalytic approach. Here we show that a newly designed chiral phosphoric acid catalyzes a highly enantioselective carboxylytic ring opening of *meso*-epoxides. The reaction can also be used in a one-pot *anti*-dihydroxylation of *Z*-olefins, complementing established methodologies for the asymmetric *syn*-dihydroxylations of olefins such as that developed by Sharpless et al.[9]

Epoxide hydrolases exploit a bifunctional mode of action, involving hydrogen-bonding to the epoxide oxygen and the concurrent nucleophilic attack of an aspartate carboxylate to deliver an enzyme-bound ester intermediate. Its subsequent hydrolysis then leads to the final enantioenriched 1,2-diol (Scheme 1 a).[10] We recently described the first well-defined activation of carboxylic acids in asymmetric organocatalysis. We showed that the heterodimerization of a carboxylic acid with a chiral phosphoric acid catalyst enhances and directs the carboxylate nucleophilicity in an asymmetric opening of aziridines.[8] We speculated that our approach should also be suitable for the carboxylytic opening of epoxides (Scheme 1 b), resembling the biological epoxide hydrolysis.[11]



Scheme 1. Design of an organocatalytic, asymmetric hydrolysis of epoxides.

At the outset of these investigations, we focused our attention on the ring opening of cyclohexene oxide **1a** with benzoic acid, catalyzed by binol-derived phosphoric acids **3** (Scheme 2). Indeed, the reaction catalyzed by (*S*)-TRIP (**3a**) afforded the desired product **2a** in quantitative yield and promising enantioselectivity (e.r. = 78.5:21.5, Scheme 2). An initial screening of phosphoric acid catalysts revealed the importance of bulky aromatic groups in the 3,3′ positions of the binol backbone (see the Supporting Information, Table S1). Since catalysts bearing *ortho,ortho*-disubstituted aryl moieties were particularly effective in the transformation,[12] we realized that the development of new even more sterically demanding phosphoric acid catalysts would be crucial for our studies and potentially could also contribute to the advancement of the field of asymmetric Brønsted acid

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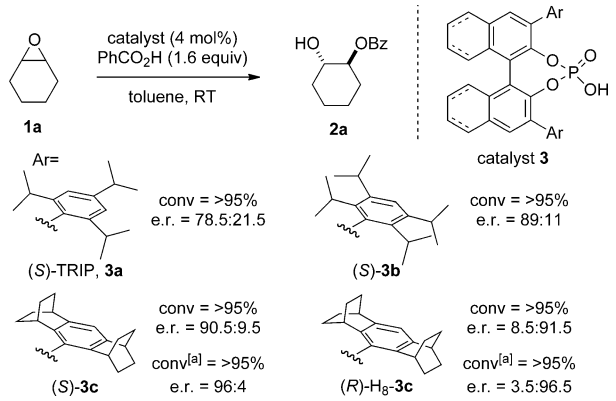
[**] Generous support by the Max-Planck-Society and the European Research Council (Advanced Grant "High Performance Lewis Acid Organocatalysis, HIPOCAT") is gratefully acknowledged. We thank the members of our mass spectrometry department for their excellent service.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201400170.



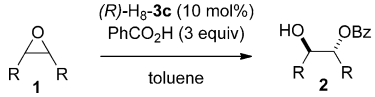
Scheme 2. Reactions were carried out on 0.05 mmol scale in toluene (0.4 mL). Conversions were determined by ^{1}H NMR spectroscopy. Enantiomeric ratios were determined by HPLC on a chiral stationary phase. a) Reactions performed at −40 °C with 10 mol % of catalyst and 3 equiv of benzoic acid.

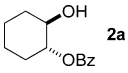
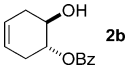
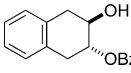
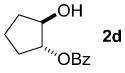
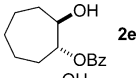
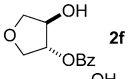
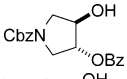
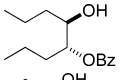
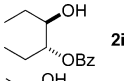
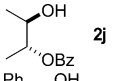
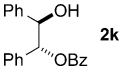
catalysis in general.[13] We designed a new class of binol-based phosphoric acids bearing alkyl groups both in *ortho* and *meta* positions of the 3,3′-aryl substituents (Scheme 2). We expected these catalysts to provide a twofold beneficial effect. On the one hand, confinement of the catalytic pocket would decrease the phosphate nucleophilicity. On the other hand, the steric demand may enhance the stereochemical communication within reacting ion pair intermediates.[14]

Confirming our expectations, phosphoric acid **3b** gave better results (e.r. = 89:11, Scheme 2) than TRIP. Next we synthesized the conformationally more constrained catalyst variants **3c** and H_8-**3c**, bearing a polycyclic ring system, which proved to be even more selective. In particular phosphoric acid H_8-**3c**, bearing a hydrogenated-binol scaffold, was identified as the optimal catalyst, and at −40 °C the desired product was delivered in excellent yield and enantiomeric ratio (yield = 85 %, e.r. = 96.5:3.5).[15]

With the optimized conditions in hand,[16] we investigated the scope of the transformation and the results are shown in Table 1. Several *meso*-epoxides, cyclic and acyclic, were successfully transformed into the corresponding glycol monoesters with high levels of stereocontrol. Six-membered-ring substrates **1b** and **1c** reacted smoothly giving the expected products in good yields and very good enantioselectivity (entries 2 and 3). Monoprotected *trans*-diols bearing a five- or seven-membered-ring scaffold were obtained with excellent stereocontrol (entries 4 and 5). The transformation was compatible with the presence of heteroatoms in the cyclic scaffold, delivering products **2f**,**g** with very good selectivity albeit higher temperatures were required.[17] The remarkable generality of the system was demonstrated when acyclic substrates **1h**–**k** were investigated. Despite its small size, substrate **1j** reacted smoothly, giving **2j** with a very high enantiomeric ratio (e.r. = 95:5), thus highlighting the inherently high selectivity of our sterically confined catalyst system.[14] In case of epoxide **1i**, both catalyst H_8-**3c** and its fully aromatic version **3c** gave the desired product enantioselectively, with the latter catalyst being slightly superior (see

Table 1: Scope of the ring-opening reaction.[a]



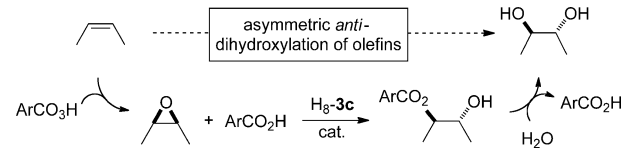
Entry	Product	T [°C]	Yield [%]	e.r.[b]
1	 **2a**	−40	85	96.5:3.5
2	 **2b**	−5	86	93.5:6.5
3	 **2c**	−5	73	94.5:5.5
4	 **2d**	−20	64	95.5:4.5
5	 **2e**	−5	78	95.5:4.5
6	 **2f**	10	84	95:5
7	 **2g**	25	83	94:6
8	 **2h**	−5	55	95:5
9	 **2i**	−5	60	96:4
10[c]		−5	85	3.5:96.5
11	 **2j**	−20	76	95:5
12	 **2k**	25	85	91:9

[a] Reactions were carried out on 0.1 mmol scale in toluene (0.8 mL). [b] Determined by HPLC on a chiral stationary phase. [c] Reaction performed with catalyst **3c**. Cbz = carboxybenzyl.

Supporting Information for the full reaction scope with catalyst **3c**). The challenging (*Z*)-stilbene derived epoxide **1k** was compatible with the reaction conditions and the desired product was isolated with high yield and good enantioselectivity (entry 12).[18]

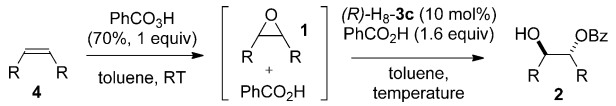
While enantioselective *syn*-dihydroxylations of olefins are well developed, analogous non-enzymatic asymmetric *anti*-dihydroxylations are unknown.[9,19] We reasoned that our approach could potentially be utilized in this context. In fact, the Prilezhaev reaction, that is, the oxidation of alkenes with simple peracids, delivers both an epoxide and a carboxylic acid, which is the exact combination of substrates for the reaction reported here. Accordingly, adding catalyst H_8-**3c** to the Prilezhaev reaction mixture should directly furnish the corresponding and enantioenriched hydroxy ester product. The designed overall *anti*-dihydroxylation of olefins (Scheme 3) would fully resemble the corresponding biosynthetic pathway.[20]

To test this idea, we treated a variety of olefins **4** with perbenzoic acid in toluene and subjected the resulting reaction mixture to our desymmetrization conditions (entries 1–4, Table 2). The expected glycol monoester products were obtained in good yields and with enantioselectiv-



Scheme 3. Towards a non-enzymatic *anti*-dihydroxylation of olefins.

Table 2: Asymmetric *anti*-dihydroxylation of olefins[a]



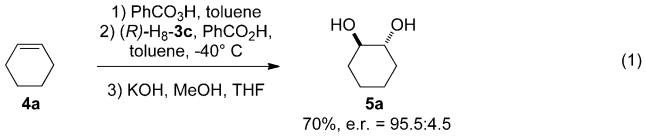
Entry	Alkene	T [°C]	Yield [%]	e.r.[b]
1	**4a**	−40	80	96:4
2	**4f**	10	82	95:5
3	**4h**	−5	42	94.5:5.5
4[c]	**4i**	−5	54	4:96
5[d]	**4a**	−20	71	93.5:6.5

[a] Reactions were carried out on 0.1 mmol scale in toluene (0.8 mL). [b] Determined by HPLC on a chiral stationary phase. [c] Reaction performed with catalyst **3c**. [d] *m*CPBA was used as the oxidant and no additional carboxylic acid was added in the second step.

ities similar to those shown in Table 1. In these reactions, the catalyst was always added in solution together with additional benzoic acid to reach the previously optimized conditions. We also performed the reaction sequence with the commonly used *meta*-chloroperbenzoic acid (*m*CPBA) as oxidant (entry 5, Table 2). After epoxidation, the addition of catalyst H_8-**3c** converted the mixture of the initially produced two components into the desired product in good yield and enantioselectivity. In this case, no additional carboxylic acid was added in the epoxide-opening reaction. It is noteworthy that the overall sequence of Prilezhaev epoxidation followed by carboxylysis exhibits perfect atom economy.

Importantly, the products obtained in the reported cascade can be easily converted into the corresponding diols under mild conditions. In fact, a three-step, one-pot *anti*-dihydroxylation protocol has been devised that includes such a final hydrolysis step terminating the epoxidation and desymmetrization sequence. Accordingly, cyclohexene (**4a**) reacts to (*R*,*R*)-cyclohexane-1,2-diol (**5a**) in good yields and enantioselectivity utilizing the newly developed reaction sequence [Eq. (1)].[2c]

In conclusion, we have reported the first asymmetric hydrolytic ring opening of epoxides under metal-free conditions. The transformation exploits the activation of carboxylic acids by self-assembly with chiral phosphoric acids and a high level of stereocontrol is ensured by a novel confined phosphoric acid catalyst. Our organocatalytic approach is arguably the most general variant for this carboxylytic desymmetrization reaction. In addition, the methodology, coupled with the peracid-mediated epoxidation of olefins and hydrolysis, complements the Sharpless *syn*-dihydroxylation and represents the first effective system to perform asymmetric *anti*-dihydroxylations of unactivated olefins. Further investigations on the activation of carboxylic acids in asymmetric Brønsted acid catalysis and on our novel class of phosphoric acid catalysts are currently ongoing in our laboratories.



(1)

Experimental Section

Catalytic asymmetric synthesis of **5a**: In a dried screw-cap vial a solution of perbenzoic acid (70% w/w, 0.2 mmol, 1 equiv) in toluene (0.8 mL) was added to alkene **4a** (0.2 mmol, 16.4 mg, 1 equiv). The reaction mixture was stirred at room temperature for 24 h and then cooled down to −40 °C. Then a solution of benzoic acid (0.32 mmol, 39.1 mg, 1.6 equiv) and the catalyst H_8-**3c** (0.02 mmol, 16.6 mg, 10 mol%) in toluene (0.8 mL) was added. The reaction mixture was stirred for 4 days and then the temperature was raised to room temperature. Potassium hydroxide (100 mg) in tetrahydrofuran (2 mL) and methanol (0.1 mL) were then added and the resulting mixture was stirred for 12 h. After workup with methyl *tert*-butyl ether and water, the desired compound was isolated by purification by flash column chromatography on silica gel.

Received: January 7, 2014
Revised: March 20, 2014
Published online: June 24, 2014

Keywords: biomimetic chemistry · carboxylysis · dihydroxylation · epoxides · organocatalysis

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[16] For the full optimization screening of the reaction conditions see the Supporting Informations.

[17] The presence of an additional competing hydrogen-bonding acceptor moiety may be the reason for the observed lower reactivity.

[18] We have also tested one tetrasubstituted epoxide, 1,2-dimethylcyclohexene oxide, which was found to be unreactive under our reaction conditions.

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