Organocatalytic asymmetric epoxidation reactions in water–alcohol solutions

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The diastereo- and enantioselective organocatalytic epoxidation of α,β-unsaturated aldehydes in aqueous solutions is presented. By the screening of the reaction conditions for the epoxidation of cinnamic aldehyde applying hydrogen peroxide as the oxidant and 2-[bis-(3,5-bis-trifluoromethyl-phenyl)-trimethylsilanyloxy-methyl]-pyrrolidine as the catalyst, a highly stereoselective reaction has been developed. The scope of the diastereo- and enantioselective organocatalytic epoxidation in aqueous solutions is documented by the asymmetric epoxidation of α,β-unsaturated aldehydes with enantioselectivities up to 96% ee.

Introduction

Organic reactions in aqueous media have attracted a great deal of attention in recent years.[1] Water is cheap, safe and environmentally friendly compared with organic solvents. For the synthetic chemists, reactions performed in aqueous conditions have several advantages over the anhydrous equivalents; for instance, problems associated with drying of solvents and substrates are avoided. Catalytic asymmetric reactions in aqueous solutions are attractive, but rare.[1b,2]

Catalytic asymmetric epoxidation reactions play an important role in organic chemistry since the optically active epoxy products are among the most valuable building blocks.[3] Although a variety of efficient synthetic methods have been proposed for epoxidations reactions catalyzed by chiral Lewis acids[4] or organocatalysts,[5] all these reactions usually are performed in an organic solvent, especially chlorinated hydrocarbons. It is therefore a challenge for chemists to perform catalytic asymmetric epoxidation reactions in a safe, harmless and more benign solvent, *e.g.* in water solutions.

Previously our group reported the asymmetric organocatalytic epoxidation of α,β-unsaturated aldehydes with H_2O_2 using a chiral secondary amine as the catalyst.[6] Thus, a major step towards more environmentally friendly conditions for this important reaction would be to perform it in aqueous solution, and hopefully maintain the high stereoselectivity.

This paper shows that the organocatalytic epoxidation of α,β-unsaturated aldehydes with H_2O_2 as the oxidant can successfully take place in water–alcohol solution and the optically active epoxides are formed with high enantiomeric excess.

Results and discussion

The reaction of cinnamic aldehyde (**1a**) with different oxidation reagents catalyzed by 2-[bis-(3,5-bis-trifluoromethyl-phenyl)-trimethylsilanyloxy-methyl]-pyrrolidine (**3**) (10 mol%) was investigated for the screening process in various solvents and solvent compositions [eqn (1)]. Table 1 shows some results from this process.

$$(1)$$
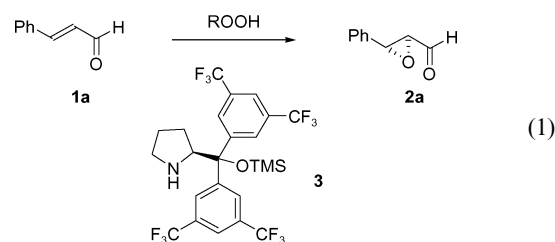
When the catalytic asymmetric epoxidation reaction of cinnamic aldehyde **1a** with 3 equivalent H_2O_2 (35% w/w in H_2O) was carried out in an organic solvent, *e.g.* CH_2Cl_2, full conversion to the epoxy product **2a** was achieved in 4 h and **2a** was formed with 96% ee and a dr of 97 : 3 (Table 1, entry 1). Thus, the 2-[bis-(3,5-bis-trifluoromethyl-phenyl)-trimethylsilanyloxy-methyl]-pyrrolidine catalyst (**3**) is compatible with water derived from the H_2O_2 solution. This findings prompted us to investigate the catalytic asymmetric epoxidation reaction in aqueous media. The catalytic activity of **3** in H_2O as the solvent was not

Table 1 Screening results for the asymmetric epoxidation of cinnamic aldehyde **1a** by different oxidation reagents and in various solvents catalyzed by 2-[bis-(3,5-bis-trifluoromethyl-phenyl)-trimethylsilanyloxy-methyl]-pyrrolidine (**3**) (10 mol%)[a]
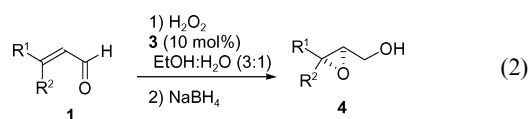
Entry	Oxidant	Solvent	Conv. (%)	Dr[b]	Ee[c] (%)
1	H_2O_2	CH_2Cl_2	99 (4 h)	97 : 3	96/—
2	H_2O_2	H_2O	28 (18 h)	58 : 42	90/10
3	Cum-O_2H[d]	H_2O	96 (18 h)	78 : 28	16/91
4	UHP[e]	H_2O	41 (18 h)	43 : 57	90/0
5	t-BuO$_2$H	H_2O	93 (18 h)	2 : 98	76/19
6	H_2O_2	H_2O + KHSO$_4$	11 (20 h)	69 : 31	93/18
7	H_2O_2	H_2O + NaH$_2$PO$_4$	58 (20 h)	17 : 83	28/6
8	H_2O_2	H_2O + NaHCO$_3$	40 (20 h)	93 : 7	76/16
9	H_2O_2	EtOH	96 (14 h)	85 : 15	92/—
10	H_2O_2	EtOH–H_2O (9 : 1)	99 (9 h)	87 : 13	91/—
11	H_2O_2	EtOH–H_2O (3 : 1)	94 (9 h)	85 : 15	93/—
12	H_2O_2	EtOH–H_2O (1 : 1)	97 (9 h)	87 : 13	92/—
13	H_2O_2	THF–H_2O (1 : 1)	53 (9 h)	84 : 16	92/—

[a] Reaction performed at 0.5 mmol scale of cinnamic aldehyde **1a** and 3 equivalent of the oxidant in 1 mL of solvent at room temperature. [b] Dr determined by chiral GC. [c] Ee determined by chiral GC. [d] Cumene hydroperoxide. [e] UHP = Urea hydrogen peroxide.

promising and product **2a** was obtained with low conversion and diastereoselectivity, however, a high enantiomeric excess of major diastereoisomer (90% ee) was found (entry 2). Cumene hydroperoxide is a suitable oxidation agent in H_2O giving high conversion, but unfortunately, low enantioselectivity was obtained for the major diastereoisomer (entry 3). For urea hydrogen peroxide (UHP) as the oxidation reagent moderate yield and a non-diastereoselective epoxidation took place, however, the enantiomeric excess of one of the diastereoisomers was 90% ee (entry 4). The epoxidation with t-BuO$_2$H gave the opposite diastereoisomer, compared to the use of H_2O_2 as the oxidation reagent; however, the enantioselectivity of the major diastereoisomer was only 19% ee (entry 5). To study the pH-effect on the outcome of the asymmetric epoxidation reaction, various salts were added to the water solution; however, low conversions were observed (entries 6–8). We were pleased to find, that the catalytic asymmetric epoxidation proceeded very well in EtOH, another environmental friendly solvent, with high conversion and good selectivity (85 : 15 dr and 92% ee for the major diastereoisomer, entry 9). Furthermore, the epoxidation reaction also performed smoothly in H_2O–EtOH mixtures and increasing the amount of H_2O to 1 : 1 H_2O : EtOH, did not affect the diastereo- and enantioselectivity of the asymmetric epoxidation reaction compared to the reaction in EtOH (entries 10–12). Changing the solvent H_2O–EtOH to H_2O–THF gave low conversion, however, the epoxidation reaction was highly stereoselective (entry 13).

A series of different α,β-unsaturated aldehydes **1a–h** all reacted with H_2O_2 in EtOH : H_2O (3 : 1) solution with full conversion affording the corresponding epoxy aldehydes with high enantioselectivities using 2-[bis-(3,5-bis-trifluoromethyl-phenyl)-trimethylsilanyloxy-methyl]-pyrrolidine (**3**) (10 mol%) as the catalyst. However, in order to have compounds easy to analyze, the epoxy aldehydes were reduced *in situ* to the epoxy alcohols **4a–h**. The results for the organocatalytic asymmetric epoxidation of the different aldehydes are presented in Table 2.

For the results presented in Table 2, it should be noted, that although full conversion was observed in all reactions, partly hydrolysis–acetalization of aldehyde functionality lowered the isolated yield compared to the reactions performed in an organic solvent. α,β-Unsaturated aldehydes having aromatic substituents in the β-position **1a–d** were all converted to the corresponding optically active epoxides in moderate yields and good diastereo- and enantioselectivities (Table 2, entries 1–4). The highest enantioselectivity (96% ee) was obtained for *p*-chlorocinnamic aldehyde (**1c**) (entry 3). 4-Oxo-but-2-enoic acid ethyl ester (**1e**) containing an ethyl ester functionality in the

β-position gave 53% yield, 81 : 19 dr and 88% ee (entry 5). For the alkyl substituted α,β-unsaturated aldehydes **1f, g** a non-diastereoselective epoxidation reaction was found, however, the high enantiomeric excesses of the epoxides were maintained (entries 6, 7). Citral **1h**, having two substituents in the β-position, was also readily epoxidized and the corresponding optically active epoxide was obtained with 86% ee (entry 8).

In summary, we have demonstrated that the organocatalytic asymmetric epoxidation reaction of α,β-unsaturated aldehydes catalyzed by 2-[bis-(3,5-bis-trifluoromethyl-phenyl)-trimethylsilanyloxy-methyl]-pyrrolidine takes place in water–alcohol solutions using hydrogen peroxide as the oxidation reagent. The reactions proceed in moderate to good yields and with up to 96% ee of the optically active epoxides in a safe, harmless and environmentally benign solvent composition.

Experimental

General methods

The ^{1}H NMR and ^{13}C NMR spectra were recorded at 400 MHz and 100 MHz, respectively. The chemical shifts are reported in ppm relative to CHCl$_3$ ($\delta = 7.26$) for ^{1}H and relative to the central CDCl$_3$ resonance ($\delta = 77.0$) for ^{13}C NMR. Flash chromatography (FC) was carried out using Merck silica gel 60 (230–400 mesh). Optical rotation was measured on a Perkin-Elmer 241 polarimeter. All diastereoselectivities were measured by ^{1}H NMR spectroscopy. The enantiomeric excess (ee) of the products were determined by chiral HPLC using Daicel Chiralpak or Daicel Chiralcel columns with hexane–2-propanol as eluent.

Materials

Cinnamic aldehyde **1a** and the α,β-unsaturated aldehydes **1e–1h**, H_2O_2 and other oxidant reagents were purchased commercially and used as received. The α,β-unsaturated aldehydes[7] **1b–1f** and 2-[bis-(3,5-bis-trifluoromethyl-phenyl)-trimethylsilanyloxy-methyl]-pyrrolidine[8] **3** were prepared according to literature procedures.

General reaction conditions

The catalytic asymmetric epoxidation reactions were performed at 0.5 mmol scale of the α,β-unsaturated aldehyde and 3 equiv. of the H_2O_2 in 0.75 mL EtOH and 0.25 mL H_2O (distilled) mixture as the solvent at room temperature. After 16 h the reaction mixture was extracted with Et$_2$O and dried over anhyd. Na$_2$SO$_4$. The solvent was evaporated and the residue was redissolved in 2 mL MeOH and followed by addition of NaBH$_4$ (50 mg). After 20 min, the reaction was quenched by H_2O, extracted with Et$_2$O, dried over anhyd. Na$_2$SO$_4$ and concentrated *in vacuo* to give the isolated product after FC. See reference 6 for spectroscopic data of the optically active products.

(2)

Table 2 Catalytic asymmetric epoxidation of aldehydes **1a–h** with H_2O_2 catalyzed by 2-[bis-(3,5-bis-trifluoromethyl-phenyl)-trimethyl-silanyloxy-methyl]-pyrrolidine (**3**) (10 mol%) at room temperature in EtOH : H_2O (3 : 1)

Entry	R^1	R^2	Yield^a (%)	Dr^b	Ee^c (%)
1	Ph	H: **1a**	**4a**: 43	86 : 14	92
2	*p*-F-Ph	H: **1b**	**4b**: 34	85 : 15	85
3	*p*-Cl-Ph	H: **1c**	**4c**: 40	84 : 16	96
4	*p*-NO$_2$-Ph	H: **1d**	**4d**: 56	83 : 17	90
5	CO$_2$Et	H: **1e**	**4e**: 53	81 : 19	88
6	CH$_2$OBn	H: **1f**	**4f**: 38	43 : 57	85
7	*i*-Pr	H: **1g**	**4g**: 48	50 : 50	91
8	(CH$_2$)$_2$CH=CMe$_2$	Me: **1h**	**4h**: 40	69 : 31	86

^{a} Isolated yield. ^{b} Dr determined by chiral GC and ^{1}H NMR. ^{c} Ee determined by chiral GC and HPLC.

Notes and references

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