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Asymmetric Weitz–Scheffer epoxidation of conformationally flexible and fixed enones with sterically demanding hydroperoxides mediated by optically active phase-transfer catalysts

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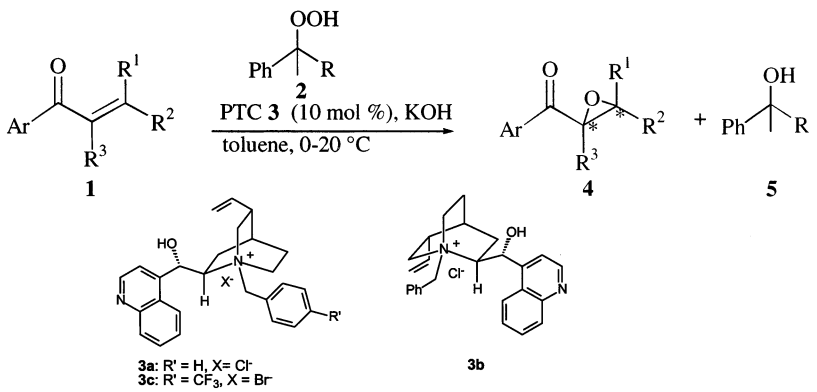
Abstract—The asymmetric Weitz–Scheffer epoxidation of α,β-enones **1a–d** with hydroperoxides **2** and mediated by cinchonine- and cinchonidine-derived phase-transfer catalysts (PTCs) **3** affords the optically active epoxides **4** with moderate to very good e.e.s and in near quantitative yields. For the conformationally flexible enone **1b**, the enantioselectivity decreases with more sterically demanding tertiary hydroperoxides, while an opposite trend is observed for the rigid *s-cis*-enone **1**. With the bulky cumyl hydroperoxide **2c** and the PTC **3c**, the enone **1** was converted to the epoxide **4c** with the highest enantioselectivity (95% e.e.) so far observed for PTC-catalyzed epoxidations using hydroperoxides as oxygen sources. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

The asymmetric Weitz–Scheffer epoxidation of electron-deficient olefins has gained considerable attention in recent years.[1] Initially, Wynberg applied optically active PTCs in the asymmetric Weitz–Scheffer epoxidation of α,β-enones. Using quinine-derived PTCs and achiral hydroperoxides such as *tert*-butyl hydroperoxide, epoxy ketones were obtained in up to 50% e.e.[2] Recently, Arai and Shiori have employed cinchona-derived PTCs and hydrogen peroxide, which afforded optically active epoxides of chalcones in 65–92% e.e. However, for alkyl-substituted enones, significantly lower enantioselectivities (42–57% e.e.) were observed.[1f] Nevertheless, the oxidation of a cyclic dienone with stoichiometric amounts of PTC and *tert*-butyl



Scheme 1.

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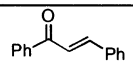
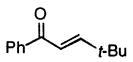
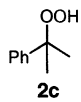
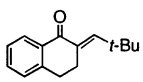
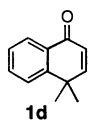
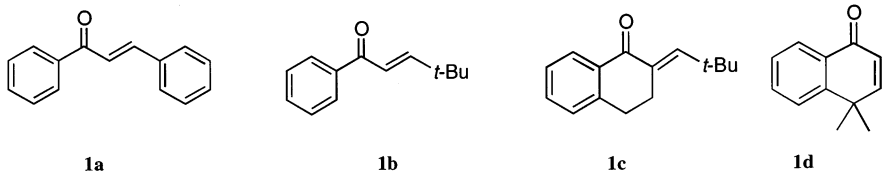
hydroperoxide gave the corresponding epoxide with good e.e.[1e] High enantioselectivity (up to 90% e.e.) was achieved for the epoxidation of enones with rigid cinchona PTCs using NaOCl as the oxygen donor.[1b] Corey has also reported[1c] that the epoxidation of enones with KOCl and PTCs gave the corresponding epoxides with high enantioselectivity.

Most recently, we have demonstrated the efficacy of optically active hydroperoxides for the asymmetric Weitz–Scheffer epoxidation of α,β-enones.[3] Although achiral hydroperoxides have been used in the PTC-mediated asymmetric Weitz–Scheffer epoxidation, the potential of chiral hydroperoxides as oxygen sources in this enantioselective oxidation has not been assessed so far. Possibly, synergistic effects of the chirality in the hydroperoxide and PTC may enhance the enantioselectivity of the epoxidation.[4] Therefore, we have investigated the asymmetric epoxidation of the enones **1a–d** by employing the racemic hydroperoxides **2a** and **2b**, and, for comparison, the achiral cumyl **2c** and *tert*-butyl **2d** hydroperoxides as oxygen sources and cinchona-derived PTCs **3a–c** (Scheme 1). The results are summarized in Table 1.

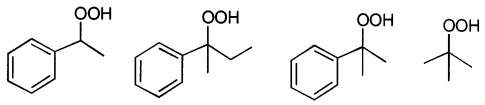
Table 1. Enantioselective Weitz–Scheffer epoxidation of α,β-enones **1a–d** by hydroperoxides **2** and the optically active phase-transfer catalysts **3**[a]

entry	substrate	ROOH	PTC	enantiomeric excess (%)[b] epoxide **4**[c]	R*OH **5**	R*OOH **2**
1	 **1a**	 **2a**	**3a**	49 (α*S*,β*R*)	27 (*R*)	28 (*S*)
2			**3c**	32 (α*S*,β*R*)	15 (*R*)	12 (*S*)
3		**2a**	**3c**	62 (α*S*,β*R*)	8 (*R*)	12 (*S*)
4		 **2b**	**3c**	36 (α*S*,β*R*)	9 (*R*)	11 (*S*)
5			**3a**	47 (α*S*,β*R*)	5 (*R*)	6 (*S*)
6	 **1b**		**3b**	33 (α*R*,β*S*)	6 (*S*)	8 (*R*)
7		 **2c**	**3c**	28 (α*S*,β*R*)	-	-
8		 **2d**	**3c**	27 (α*S*,β*R*)	-	-
9		**2a**	**3c**	84 (α*S*,β*R*)	26 (*R*)	24 (*S*)
10	 **1c**	**2b**	**3c**	92 (α*S*,β*R*)	18 (*R*)	10 (*S*)
11		**2b**	**3a**	82 (α*S*,β*R*)	22 (*R*)	12 (*S*)
12		**2c**	**3c**	95 (α*S*,β*R*)	-	-
13		**2d**	**3c**	89 (α*S*,β*R*)	-	-
14	 **1d**	**2b**	**3a**	18 (-)	4 (*R*)	2 (*S*)
15		**2b**	**3b**	8 (-)	6 (*S*)	5 (*R*)

[a] Epoxidations were carried out at 0–25°C on 0.1–0.5 mmol of the enone **1** with 2.0 equiv. of hydroperoxide **2** and 10 mol% PTC **3** until all the enone was consumed. [b]Determined by HPLC analysis on a Chiralcel OD column with isopropanol–hexane (5:95) as eluent [epoxide **4c** on a Chiralcel OB-H column with isopropanol–hexane (20:80) as eluent], error <3% of the stated values; the signs of the optical rotation were determined polarimetrically on a Chiralyzer (IBZ Messtechnik, Hannover, Germany) directly during the HPLC analysis, detected at 220 nm; the configuration of the major isomer or the sign of the optical rotation are given in parentheses. [c]The configurations of the epoxides **4a–c** were assigned according to literature data (Refs 3 and 5).



1a **1b** **1c** **1d**



rac-**2a** *rac*-**2b** **2c** **2d**

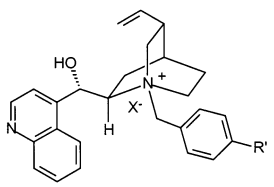
2. Results and discussion

In order to establish the reaction conditions, the initial experiments were performed on the enone **1a** as a model substrate. With 2.0 equiv. of the racemic secondary hydroperoxide **2a** and 10 mol% PTC **3a**, the epoxide **4a** was obtained in >95% yield and a moderate e.e. value of 49%, after total consumption of the enone (entry 1). As expected, the asymmetric epoxidation of **1a** led to the kinetic resolution of hydroperoxide **2a**, but with poor enantioselectivity, affording **2a** in 28% e.e. and **5a** in 27% e.e. With PTC **3c**, the enantioselectivity for the **1a**/**2a** combination was worse and lower e.e. values were observed for all three chiral products **2a**, **4a** and **5a** (entry 2).

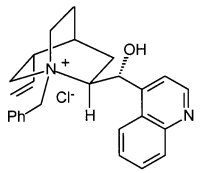
To examine whether steric effects in the substrate would enhance the stereochemical control, the bulkier β-*tert*-butyl-substituted enone substrate **1b** was chosen. Indeed, a substantially higher e.e. value of the epoxide **4b** was observed in the epoxidation of **1b** by the secondary hydroperoxide **2a** using PTC **3c** (entry 3). The larger racemic tertiary hydroperoxide **2b** with PTC **3c** gave the epoxide **4b** with a significantly lower e.e. value of 36% (entry 4) compared to the secondary hydroperoxide **2a** (entry 3). A similar enantioselectivity was observed for the combination **1b**/**2b** with the PTC **3a** (entry 5). As expected,[1b] the cinchonidine-derived PTC **3b** afforded the opposite enantiomers of the epoxide, alcohol and hydroperoxide products compared to the PTCs **3a** and **3c** (entries 4 and 5), but again low e.e. values were observed (entry 6).

For comparison, the sterically demanding achiral cumyl **2c** and *tert*-butyl **2d** hydroperoxides were employed as oxygen sources in the epoxidation of substrate **1b**, catalyzed by PTC **3c**. Indeed, as in the case of the racemic tertiary hydroperoxide **2b** (entry 4), significantly lower enantioselectivity (27–28% e.e.) was observed for the epoxidation with the hydroperoxides **2c** and **2d** (entries 7 and 8) compared to that for the secondary hydroperoxide **2a** (entry 3).

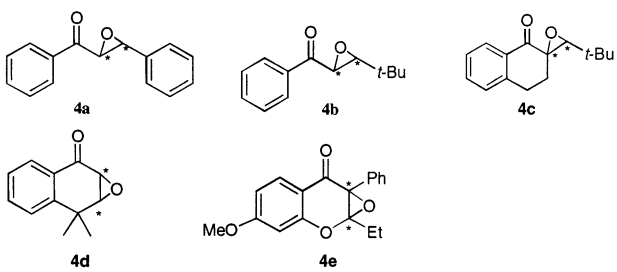
The influence of enone geometry was assessed by performing the epoxidation on the conformationally fixed enones **1c** and **1d**, the former with a rigid *s*-*cis*- and the



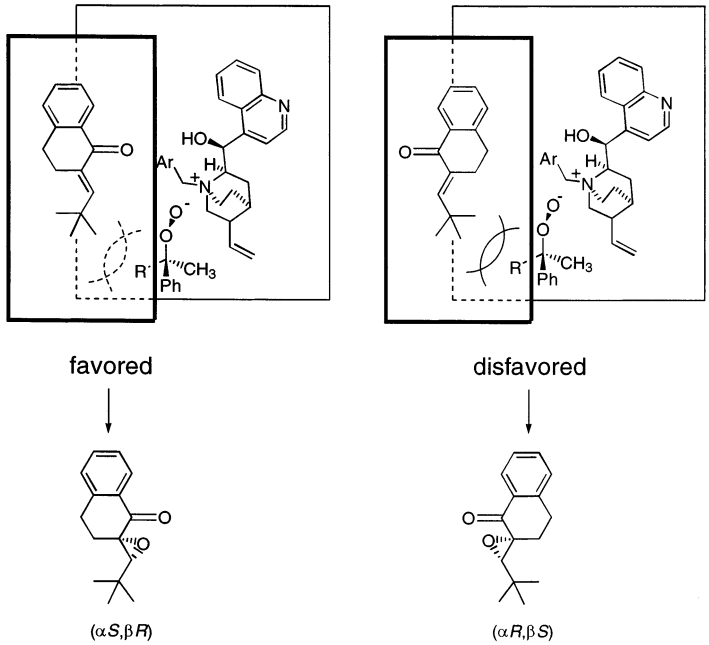
3a: R' = H, X= Cl^-
3c: R' = CF_3, X = Br^-



3b



4a **4b** **4c** **4d** **4e**



Scheme 2.

latter with a rigid *s-trans*-conformation. The *s-cis*-enone **1c** was substantially less reactive than the acyclic derivative **1b** in the Weitz–Scheffer epoxidation with the hydroperoxides **2** and the PTCs **3**; whilst **1b** was completely consumed after 12 hours, **1c** required ca. 96 hours to react. Appreciably higher enantioselectivity was obtained with substrate **1c** (84% e.e., entry 9) than for the conformationally flexible **1b** (entry 3) when racemic secondary hydroperoxide **2a** and PTC **3c** were used in combination.

When the sterically encumbered racemic hydroperoxide **2b** was used with PTC **3c** (entry 10), the epoxide **4c** was formed with a somewhat higher e.e. of 92%. Using the PTC **3a**/peroxide **2b** reagent combination in the oxidation of **1c** (entry 11), epoxide **4c** was obtained with 82% e.e., which is similar to that obtained when the PTC **3c** and peroxide **2a** were used (entry 10).

The best enantioselectivity in the oxidation of **1c**, producing **4c** with an e.e. of 95%, was observed with the bulky achiral cumyl hydroperoxide **2c** and the PTC **3c** (entry 12); indeed, this is the highest e.e. value obtained so far in PTC-mediated epoxidations using hydroperoxide as the oxygen source. With an e.e of 89%, *tert-b*utyl hydroperoxide **2d** (entry 13) was less effective than cumyl hydroperoxide (entry 12), but it is noteworthy that hydrogen peroxide, a commonly used oxygen donor in PTC-catalyzed Weitz–Scheffer epoxidations, in combination with PTC **3c** afforded epoxide **4c** in only 50% e.e. (not shown in Table 1).

Despite the high enantioselectivity (82–92% ee) for the epoxide **4c** in the oxidation of the substrate **1c** (entries 9–11), the kinetic resolution of the racemic hydroperoxides **2a**,**b** is poor (12–24% e.e.). Since the chinchona-derived PTCs **3** do not show any appreciable preference for a particular enantiomer of these racemic hydroperoxides, this method is not suitable for the kinetic resolution of hydroperoxides.

The conformationally rigid *s-trans*-enone **1d** with the hydroperoxide **2b** and the PTCs **3a** and **3b** (entries 14 and 15) gave the epoxide **4d** with very poor e.e. values compared to the *s-cis*-enone **1c** (entries 9 and 10). Evidently, the *s-cis*-geometry is advantageous for good enantiocontrol.

Our results show that the enantioselectivity in the PTC-catalyzed epoxidation of the conformationally rigid enone **1c** was consistently high (>84% e.e.), especially when bulky hydroperoxides were employed (entries 9, 10, 12 and 13 in Table 1). Much lower ($\leq$62% e.e.) control was obtained for the conformationally flexible enone **1b** (entries 3, 4, 7 and 8); moreover, the e.e. values for the latter decrease substantially as the size of the hydroperoxide increases. These results may be rationalized in terms of the mechanistic model shown in Scheme 2. The *s-cis*-enone **1c** in the upper plane (LHS structure) approaches the ion pair between the PTC and the hydroperoxide from the more exposed side to avoid repulsion of the β-*tert*-butyl substituent within the ion pair. The resulting transition structure is favored over the opposite approach (RHS structure) not only for steric reasons, but presumably also because of assistance through hydrogen bonding between the enone carbonyl group and the hydroxy functionality of the PTC.[1f] With increasing size of the hydroperoxide, the steric repulsion between the bulky β-*tert*-butyl group and the substituents of the hydroperoxide intensifies and a higher enantioselectivity is expected, as is observed for the enone **1c**.

In contrast to the conformationally fixed *s-cis*-enone **1c**, for the β-*tert*-butyl-substituted acyclic derivative **1b**, both s-*cis*- and *s-trans*-conformations are possible. For

this flexible enone, the approach of its *s-cis*-conformer towards the ion pair will be less favored as the steric bulk of the hydroperoxide increases and, thus, proportionally more of the *s-trans*-conformer reacts. The low enantioselectivity (8–18% e.e., entries 14, 15) observed in reaction of the conformationally rigid *s-trans*-enone **1d** implies that the stereocontrol in the *s-trans*-conformer of the substrate **1b** should also be poor. Consequently, the enantioselectivity in the epoxidation of the conformationally flexible enone **1b** should decrease for the sterically larger hydroperoxides, as was found experimentally (entries 3, 4, 7, 8).

In summary, the PTC-mediated asymmetric Weitz–Scheffer oxidations of enones **1a–d** by the racemic hydroperoxides **2a** and **2b** and sterically demanding achiral derivatives **2c** and **2d** afforded the corresponding optically active epoxides in nearly quantitative yields and, for some PTC–hydroperoxide combinations, with very good enantioselectivity. For the conformationally rigid *s-cis*-enone **1c**, excellent e.e. values of up to 95% were achieved with cumyl hydroperoxide **2c**, which is unprecedented.

3. Experimental

3.1. General aspects

^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC 200 (^{1}H: 200 MHz; ^{13}C: 50 MHz) or a Bruker AC 250 (^{1}H: 250 MHz; ^{13}C: 63 MHz) spectrometer and IR spectra were determined on a Perkin–Elmer 1600 FT-IR spectrophotometer. Optical rotations were measured on a Perkin–Elmer Polarimeter 241 MC. Solvents and commercially available chemicals were purified by standard procedures.

3.2. Representative procedure

To a stirred mixture of the enone **1a** (104 mg, 0.50 mmol) and the hydroperoxide **2a** (138 mg, 1.00 mmol) in toluene (5.0 mL) was added at 0°C the phase-transfer catalyst **3a** (10 mol%). After 5 min stirring, a 1.0 M aqueous solution of KOH (1.0 mL) was added at 0°C and the reaction was monitored by TLC. Stirring was continued at 0–20°C until the enone was completely consumed (nearly 50% of the 2 equiv. of hydroperoxide was consumed). The reaction mixture was diluted with water (5.0 mL) and extracted with ethyl ether (2×5 mL). The aqueous layer was neutralized with 1.0N HCl by adjusting the pH to 6.0–7.0 and extracted with ethyl ether (2×5 mL). The ethereal extracts were combined and washed with brine (5 mL), dried over $MgSO_4$, and the solvent was removed on a rotary evaporator (25°C, 30 torr). The residual crude product mixture was submitted to flash chromatography on silica gel (3:97–10:90 ether–petroleum ether as eluent) to afford the epoxide **4a** (106 mg, 95%), the hydroperoxide **2a** (62 mg, 91%) and the alcohol **5a** (53 mg, 88%). The e.e. values are given in Table 1.

Acknowledgements

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