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Synthesis of optically active C_2-symmetric ketones for the asymmetric epoxidation of prochiral olefins by dioxiranes generated *in situ* with Caroate™ as a peroxide source †

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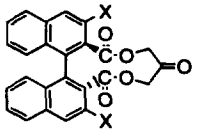
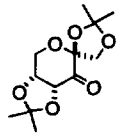
Abstract: The new optically active C_2-symmetric ketones **3a** (from mannitol) and **3b** (from TADDOL) were prepared and the *in-situ*-generated dioxiranes (with Caroate™ as peroxide source) were shown to serve as effective oxidants for the asymmetric epoxidation (ee values up to 81%) of prochiral *trans* and trisubstituted olefins. © 1997 Elsevier Science Ltd. All rights reserved.

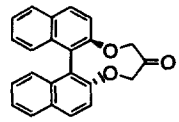
The importance of dioxiranes, especially the dimethyl derivative DMD, either *in situ*-generated or in isolated form as acetone solution, in selective oxidations is clearly evident from the numerous applications of this unusual oxidant in modern synthesis during the last decade.[1] The use of chiral dioxiranes, generated *in situ* from appropriate optically active ketones, for asymmetric epoxidations, is documented since the very beginning of dioxirane chemistry;[2] however, only recently have high enantioselectivities been achieved,[3,4] which in efficacy rival the metal-catalyzed epoxidations of unfuntionalized olefins.[5] To guarantee high stereocontrol, the approach of the olefinic substrate onto the two diastereotropic oxygen atoms in the nonracemic dioxirane must be sterically efficiently differentiated. For this purpose, Yang[3] employed C_2-symmetric binaphthalene-derived ketones, while Shi[4] utilized a quasi 'C_2-symmetric' fructose derivative. The latter was shown to perform adequately even under catalytic conditions, but its persistence is limited due to oxidative destruction.[4]



Yang (Ref. 3)



Shi (Ref. 4)



Song (Ref. 6)

While our work was in progress, most recently Song reported a C_2-symmetric binaphthol-derived ketone for asymmetric epoxidation.[6] Also our experiences with it were unsatisfactory compared to those claimed for Yang's ketone,[3] in that for the ketone of (*R*)-(+)-1,1′-bi-2-naphthol with 2.0 equiv. (based on ketone) of *trans*-stilbene and pH 8.0[3a] the corresponding epoxide[7] was obtained with an ee value of only 27%. Also at pH 10.5,[4b] at which the epoxidation proceeded faster, the ee value was only 30%. The epoxidation of triphenyl-ethylene at pH 10.5 led to the (*R*)-(−)-epoxide with an ee value of 24%. Although the chiral moiety is closer to the oxygen-transfer site in the Song's ketone compared to that of Yang, it is discouraging that the enantioselectivity is significantly less for the former. These facts prompt us to disclose herein our preliminary results with the C_2-symmetric ketones prepared from the chiral auxiliaries **1a** and **b**.

The synthesis is shown in Scheme 1. The optically active diols **1a** and **b** were prepared in good yields according to literature from starting materials of the chiral pools, mannitol for **1a**[8] and (*R*,*R*)-(+)-tartaric acid for **1b** (TADDOL).[9] The most effective cyclization of the C_2-symmetric diols **1a** and

† Dedicated to Professor R. Curci (Bari), a good friend and appreciated colleague, on the occasion of his 60th birthday.
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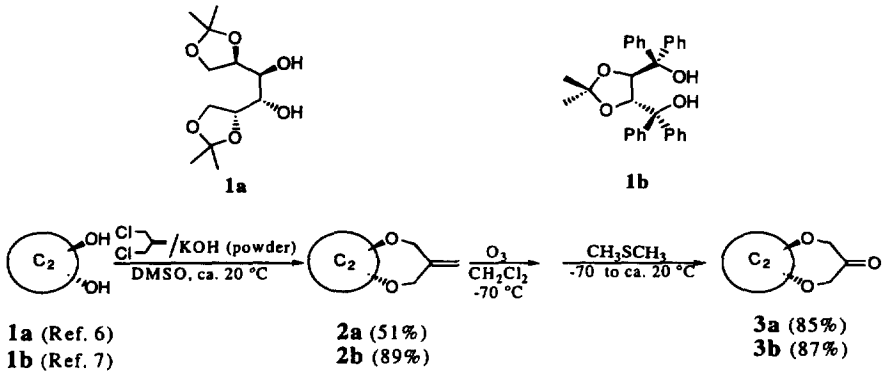
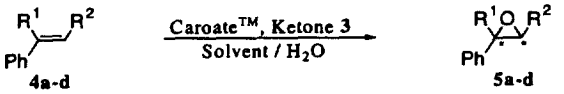
b entailed treatment with 3-chloro-2-chloromethyl-1-propene with powdered KOH in DMSO to the olefins **2a** and **b** and subsequent ozonolysis, followed by reaction with dimethyl sulfide, to afford the optically active ketones **3a** and **b** in high yields. The results of the asymmetric epoxidation of the prochiral olefins **4** by the *in-situ*-prepared optically active dioxiranes of the chiral ketones **3a** and **b** are collected in Table 1.



Scheme 1. Synthesis of C_2-symmetric optically active ketones **3a** and **b**.

The mannitol-derived ketone **3a** performed oxidations quite fast at pH 8 in a 1.5:1 CH_3CN:H_2O mixture,[3a] yet only a moderate ee value of *ca.* 39% was obtained with *trans*-stilbene **4a** as the substrate (entry 2). Shorter reaction time or lower reaction temperature did not enhance the enantioselectivity (entries 1 and 3). More seriously, ketone **3a** does not persist under the reaction conditions, such that catalytic oxidation is not feasible and further work with ketone **3a** was abandoned.

Table 1. Asymmetric epoxidation of prochiral olefins with ketones **3a** and **b**[a]



Entry	Ketone (equiv.)	Substrate	Solvent[b]	pH[c]	Time (h)	Conv.[d] (%)	ee[e] (%)	Config.[f]
1	**3a** (2.0)		CH_3CN	8.0	0.4	39	38.9	(R,R)-(+)
2	**3a** (2.0)	Ph, Ph	CH_3CN	8.0	24	72	38.3	(R,R)-(+)
3	**3a** (2.0)[g]	**4a**	CH_3CN	8.0	1.5	37	39.0	(R,R)-(+)
4	**3b** (1.0)[h]		CH_3CN	8.0	72	39	1.0	(R,R)-(+)
5	**3b** (1.0)[h]		dioxane	8.0	168	54	32.6	(R,R)-(+)
6	**3b** (1.0)[h]		dioxane	10.5	5	67	64.8	(R,R)-(+)
7	**3b** (1.0)[h]	Ph, Ph	dioxane	8.0	84	55	66.0	(R)-(-)
8	**3b** (1.0)[h]		dioxane	10.5	5	70	80.5	(R)-(-)
9	**3b** (0.1)	**4b**	dioxane	10.5	5	12	78.7	(R)-(-)
10	**3b** (1.0)[h]	Ph, OH	dioxane	8.0	240	40	14.2	(R,R)-(+)
11	**3b** (1.0)[h]	**4c**	dioxane	10.5	5	51	79.7	(R,R)-(+)
12	**3b** (1.0)[h]	Ph, $OSiMe_2{}^tBu$	dioxane	10.5	5	78	77.0[i]	(R,R)-(+)[j]
13	**3b** (0.5)[h]	**4d**	dioxane	10.5	5	80	78.8[i]	(R,R)-(+)[j]

a: Carried out with 1 equiv. substrate at room temperature (*ca.* 20 °C). b: CH_3CN/H_2O = 1.5 mL/1.0 mL or 1,4-dioxane/H_2O = 4.0 mL/1.0 mL for 0.1 mmol substrate. c: At pH 8.0, 5 equiv. Caroate™, 15.5 equiv. $NaHCO_3$ in 4×10^{-4} M aqu. EDTA solution (Ref. 3a); at pH 10.5, 1.38 equiv. Caroate™, 5.8 equiv. K_2CO_3 in 0.05 M $Na_2B_4O_7$ buffer and 4×10^{-4} M aqu. Na_2EDTA solution (Ref. 4b). d: Determined by ^1H-NMR analysis, error limits ≤5% of the stated values, yields ≥95% based on conversion in all cases. e: Determined by chiral HPLC analysis (Chiralcel OD or OD-H, UV detection at 220 nm, 9:1 hexane/isopropanol, flow rate 0.6 mL/min), error limits <5% of the stated values. f: Configuration of the major isomer determined by comparing the specific rotation with literature values (Ref. 4a). g: At 0 °C. h: Ketone **3b** was recovered in over 84% in all cases without loss of optical activity. i: Determined for the desilylated epoxy alcohol **5c** (Ref. 4a). j: Configuration was assigned for the epoxy alcohol **5c** (Ref. 4a).

Severe solubility problems were the reason why the TADDOL-derived ketone **3b** did not work well at pH 8 in 1.5:1 CH_3CN:H_2O (entry 4). Best conversions and enantioselectivities were obtained in a 4:1 mixture of 1,4-dioxane:H_2O. Thus, for stilbene **4a** the conversion was 54% in 84 h with an ee value of 33% for the epoxide **5a** (entry 5) and similar results were obtained for substrate **4b** under these conditions (entry 7). Still less satisfactory was cinnamic alcohol **4c** as substrate under these conditions, since the conversion was only 40% in 240 h with an ee value of 14% for its epoxide **5c** (entry 10).

In view of the excessively long reaction times, the background epoxidation by Caroate™ cannot be avoided. This necessarily masks the real ability for asymmetric epoxidation by the dioxirane derived from ketone **3b** and explains, at least in part, the low ee values obtained with it. Indeed, at the higher pH of 10.5, the reaction rates and enantioselectivities were dramatically improved. The reaction time was shortened to 5 h and good to high ee values were obtained for all the substrates **4** studied (entries 6, 8, 11, 12).[10] The best ee value (81%) was observed (entry 8) for triphenylethylene **4b**, while the greatest improvement (from 14 to 80%) was achieved (entry 11) with cinnamic alcohol **4c**.

Since ketone **3b** survives the reaction conditions and can be recovered without loss of optical activity, epoxidations with catalytic amounts of **3b** were conducted. Preliminary results for substrate **4b** show that even with 0.1 equiv. of ketone **3b** the ee value of the epoxide **5b** was the same within error limits; of course, the conversion was much lower (entries 8 and 9). For the silyl ether **4d** with 0.5 equiv. of ketone **3b**, the conversion and ee value were about the same as when a stoichiometric amount was used (entries 12 and 13).

In summary, the new C_2-symmetric optically active ketone **3b** derived from TADDOL serves as an attractive precursor for the corresponding *in-situ*-generated dioxirane to conduct the asymmetric epoxidation of unfunctionalized prochiral olefins. Already quite high (*ca.* 80%) ee values have been obtained for this oxidatively persistent ketone under catalytic conditions. We contend that it should be worthwhile to modify the TADDOL structure appropriately to prepare more soluble (higher reactivity under catalytic conditions) and more sterically hindered (higher enantioselectivity) derivatives for still more effective asymmetric oxidations.

Acknowledgements

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10. *General procedure for asymmetric epoxidation*: to a solution of ketone **3b** (52.1 mg, 0.1 mmol), the olefinic substrate **4** (0.1 mmol) and Bu_4NHSO_4 (1.5 mg, 4.0 μmol) in 1,4-dioxane (4.0 mL) was added 0.05 M $Na_2B_4O_7$ in 4×10^{-4} M Na_2EDTA (1.0 mL) with stirring at room temperature (*ca.* 20°C). Solutions of Caroate™ (85 mg, 0.138 mmol) and K_2CO_3 (80 mg, 5.8 mmol) in 0.65 mL of 4×10^{-4} M Na_2EDTA each were added simultaneously by means of separate syringes over a period of 1.5 h. The reaction mixture was further stirred for 3.5 h, diluted with water (20 mL) and extracted with ether (3×20 mL). The combined extracts were washed with water (10 mL), dried over $MgSO_4$, concentrated (20°C/10 mbar) and purified by chromatography on silica gel (deactivated with 1% Et_3N solution in hexane) with hexane:ethyl acetate (1:0 to 10:1) as the eluent, to afford the epoxide **5** and the recovered ketone **3b** (Table 1).

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