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Asymmetric Oxidation of β-Keto Esters Using Chiral Cyclic Diols

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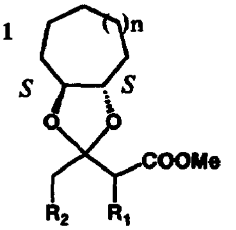
Key Words: (S,S)-cyclohexane-1,2-diol; (S,S)-cycloheptane-1,2-diol; asymmetric oxidation, asymmetric epoxydation; chiral auxiliary, chiral enol ether

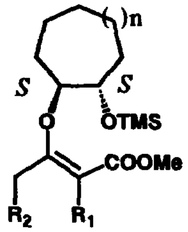
Abstract: *Oxidation of chiral β'-trimethylsilyloxy enol ethers **2a-d** and β'-hydroxy enol ethers **3a-e**, prepared from the corresponding β-keto esters, with MCPBA afforded α-hydroxy esters (**4a-d** and **5a-e**) in a highly diastereoselective manner. The absolute configurations of the newly generated stereogenic center in **4** and **5** were found to be contrary.*

In the course of our study on asymmetric reaction using C_2-symmetric cycloalkane-1,2-diols as a chiral auxiliary,[1] we wish to report a diastereoselective oxidation[2] of chiral enol ethers **2a-d** and **3a-e** to afford α-hydroxy esters **4a-d** and **5a-e**, respectively. Two types of substrates **2** and **3** were prepared from the corresponding acetals **1a-e** by the following procedure. Treatment of chiral acetals **1a-e** with LDA (2-4 eq.) in the presence of TMSCl (3-5 eq.) in THF at -40°C afforded β'-trimethylsilyloxy enol ethers **2a-e** in quantitative yields. Subsequent desilylation was achieved by treatment with $ZnBr_2$ in $CHCl_3$ (**a-c**) or HF/pyridine (**d,e**) to afford β'-hydroxy enol ethers **3a-e** in 90-95% yields.

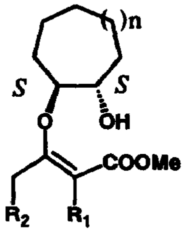
Fig. 1



1a: $R_1,R_2 = -(CH_2)_2-$, n=1
1b: $R_1,R_2 = -(CH_2)_3-$, n=1
1c: $R_1,R_2 = -(CH_2)_3-$, n=0
1d: $R_1 = Me$, $R_2 = H$, n=1
1e: $R_1 = Me$, $R_2 = H$, n=0



2a-e

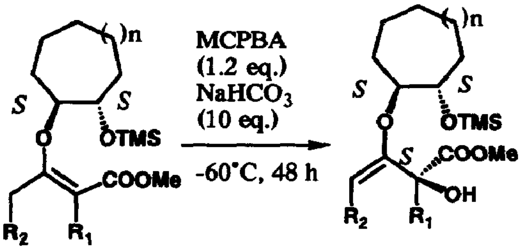


3a-e

Oxidation of **2a-d** with MCPBA (1.2 eq.) in CH_2Cl_2 at -60°C proceeded in a highly diastereoselective manner to afford α-hydroxy esters **4a-d** with *S*-configuration[3] in 50-70% yields (82-99% d.e.)(Table 1). Oxidation of **2a** in other solvents such as toluene (at -40°C), hexane (at 0°C) and THF (at r.t.) resulted in reduced diastereoselectivity (50-53% d.e.). Addition of a large excess amount of $NaHCO_3$ was to avoid cleavage of enol ether. That is to say, in the case of reaction of **2a** without $NaHCO_3$, the yield of **4a** was reduced (40% yield), but no decrease of its d.e. value was observed (89% d.e.). The above results suggest that $NaHCO_3$ did not affect the diastereoselectivity of oxidation. The d.e. of **4a-d** was determined by 270 MHz ^1H-NMR spectra after conversion into the corresponding acetal (5-type) (90-95% yields) by treatment with TMSOTf (0.1 eq.) at -50°C. In striking contrast to the above results, oxidation of **3a-e** with MCPBA diastereoselectively afforded α-hydroxy acetals **5a-e** with *R*-configuration[3] in 85-96 % yields (73-99% d.e.)(Table 2). In these reactions, it is noteworthy that acyclic substrates **3d,e** afforded **5d,e** in a completely diastereoselective manner. In Table 2, the effect of a

basic additive on diastereoselectivity was unambiguously observed. That is to say, reaction of 3a without the additive afforded 5a of 67% d.e. (85% yield). But the d.e. of 5a was increased by addition (10 eq.) of LiOH (56% yield, 85% d.e.), K_2CO_3 (85% yield, 84% d.e.) and Li_2CO_3 (85% yield, 89% d.e.).

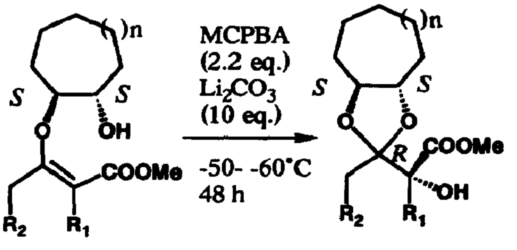
Table 1



2a-d **4a-d**

Entries	Substrates	Yields (%)		% d.e.
1	**2a**	**4a**	70	90
2	**2b**	**4b**	63	>99
3	**2c**	**4c**	60	>99
4	**2d**	**4d**	50	82

Table 2



3a-e **5a-e**

Entries	Substrates	Yields (%)		% d.e.
1	**3a**	**5a**	85	89
2	**3b**	**5b**	93	73
3	**3c**	**5c**	94	83
4	**3d**	**5d**	96	>99
5	**3e**	**5e**	90	>99

These results were explained by assuming intermediates **A** and **B** in Fig. 2 for the initial epoxidation. In the intermediate **A**, the silicon atom would coordinate to the carbonyl oxygen and MCPBA might attack from the convex face.[4] In the case of intermediate **B**, benzoylperoxy anion would approach olefin from the concave face.

Fig. 2

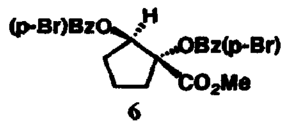


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Fig.3

References and notes

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2. a) Tang, S.; Kennedy, R. M. *Tetrahedron Lett.*, **1992**, 33, 7823; b) Sugimura, T.; Nishiyama, N.; Tai, A.; Hakushi, T. *Tetrahedron: Asymmetry*, **1993**, 4, 43. c) For oxidation of TMS enol ether: Andriamialisoa; R. Z.; Langlois, N.; Langlois, Y. *Tetrahedron Lett.*, **1985**, 26, 3563.
3. Absolute configuration of **5a** was determined by CD spectra after conversion into bis(*p*-bromobenzoate) **6** (Fig. 3) *via* a three-step sequence [i) H^+; ii) $NaBH_4$, -60°C; iii) *p*-bromobenzoyl chloride]. The CD spectrum of **6** (89 % e.e.) showed a negative first Cotton effect ($\Delta\varepsilon_{250}$ -20.1), which suggests the absolute configuration of **5a** to be *R*. Absolute configuration of **4c** was determined in a similar manner. Those of **2d** and **3d,e** were assumed based on mechanistic consideration.
4. This assumption was based on the following result. Oxidation of the substrate (**2a**-type), which has a *tert*-butyldiphenylsilyl group instead of a trimethylsilyl group, afforded α-hydroxy ester (**4a**-type) of 40% d.e. The decrease of diastereoselectivity might be attributable to bulky substituents on the silicon atom, which hinder coordination between the silicon atom and the carbonyl function.

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