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Synthesis of Optically Active α-Hydroxycarbonyl Compounds by (Salen)Mn(III)-Catalyzed Oxidation of Silyl Enol Ethers and Silyl Ketene Acetals

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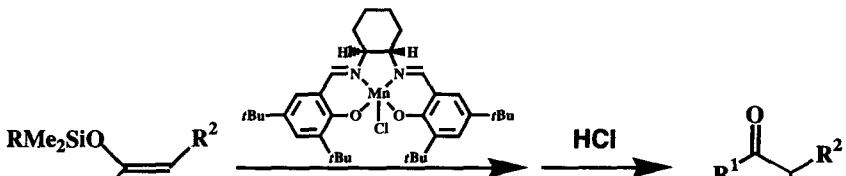
Abstract: Optically active α-hydroxy ketones and esters have been prepared by (salen)Mn(III)-catalyzed asymmetric oxidation of silyl enol ethers and silyl ketene acetals in high enantioselectivity, with *ee* values up to 81% for the α-hydroxy ketons and up to 57% for α-hydroxy esters. The extent of conversion and the enantioselectivity depends strongly on the type of oxygen donor, the pH of the aqueous bleach medium, the additive, and the substitution pattern at the enol functionality. Copyright © 1996 Elsevier Science Ltd

The optically active α-hydroxy ester and α-hydroxy keto structural units are widespread in natural products and have during the last years been frequently used as convenient building blocks in organic synthesis.[1] Consequently, efficient methods for the construction of enantiomerically pure or at least enriched α-hydroxy carbonyl compounds are in demand.[2] Their preparation has mainly employed electrophilic hydroxylation of enolates, in which the optically active organic or organometallic auxiliary is covalently bound to the enol unit.[3,4] Alternatively, prochiral enolates have been directly oxidized by optically active oxidants, e.g. chiral oxaziridines.[2,5] A highly enantioselective catalytic oxidation of enol ethers by the osmium-catalyzed asymmetric dihydroxylation has been described by Sharpless.[6]

We report herein a convenient, catalytic asymmetric α-hydroxylation of prochiral silyl enol ethers and ketene acetals to the corresponding optically active α-hydroxy carbonyl compounds by a chiral (salen)Mn(III)-complex, which was developed by Jacobsen[7] for the asymmetric epoxidation of unfunctionalized *cis*-configurated alkenes (Scheme 1). In this context, previously a chiral pyrrolidine-based



	1a	1b	1c	1d	2a	2b
R	Me	*t*Bu	Me	*t*Bu	-	-
R^1	Ph	Ph	OMe	OMe	Ph	OMe
R^2	Me	Me	Ph	Ph	Me	Ph

Scheme 1: Asymmetric α-Hydroxylation of Silyl Enol Ethers **1a,b** and Silyl Ketene Acetals **1c,d**

(salen)manganese(III) complex was employed as catalyst for the enantioselective oxidation of silyl enol ethers with iodosobenzene (*ee* 14-62%)[8].

The results of the asymmetric α-hydroxylation of trimethylsilyl- and *t*-butyldimethylsilyl-[1-phenyl-1-propenyl)oxy]silane (**1a,b**; only *Z* isomers) [6,9] and the phenylketene methyl trimethylsilyl acetal (**1c**; 70:30 *E/Z*)[10] and the *t*-butyldimethylsilyl analogue (**1d**; only *Z* isomer)[11] are summarized in Table 1. These catalytic

Table 1: Oxidation of Silyl Enol Ethers **1a,b** and Silyl Ketene Acetals **1c,d** by the (salen)Mn(III) Catalyst

entry	substrate	oxidant (equiv.)	(*S,S*) catalyst (mol %)	additive [a] (equiv.)	conv.[b,c] (%)	*ee* (%)[d] **2**	config.[e] **2**
1	**1a**	NaOCl (7.5)[f]	7	---	76	42	*R* (+)
2	**1a**	NaOCl (7.5)[f]	7	PPNO (0.3)	95	42	*R* (+)
3	**1a**	NaOCl (7.5)[g]	7	PPNO (0.3)	99	50	*R* (+)
4	**1a**	PhIO (1.5)	7	PPNO (0.3)	92	39	*R* (+)
5	**1a**	3,5-Dinitro-PBA (2.0)[h]	7	NMO (5.0)	61	18	*R* (+)
6	**1a**	PBA (2.0)[h]	7	NMO (5.0)	64	33	*R* (+)
7	**1a**	mCPBA (2.0)[h]	7	NMO (5.0)	63	48	*R* (+)
8	**1a**	4-Methoxy-PBA (2.0)[h]	7	NMO (5.0)	50	70	*R* (+)
9	**1a**	H_2O_2 (5.0)[i]	5	imidazole (0.7)	23	20	*R* (+)
10	**1b**	NaOCl (7.5)[f]	7	PPNO (0.3)	>95	81	*R* (+)
11	**1b**	NaOCl (7.5)[g]	7	PPNO (0.3)	99	69	*R* (+)
12	**1b**	NaOCl (7.5)[f]	7[j]	PPNO (0.3)	>95	79	*S* (-)
13	**1b**	PhIO (1.5)	7	PPNO (0.3)	54	67	*R* (+)
14	**1c**	NaOCl (7.5)[f]	7	---	10	9	*S* (+)
15	**1c**	NaOCl (7.5)[f]	7	PPNO (0.3)	64	22	*S* (+)
16	**1c**	NaOCl (7.5)[f]	7[j]	PPNO (0.3)	36	18	*R* (-)
17	**1c**	PhIO (1.5)	7	PPNO (0.3)	41	19	*S* (+)
18	**1c**	H_2O_2 (5.0)[i]	5	imidazole (0.7)	8	27	*S* (+)
19	**1d**	NaOCl (7.5)[f]	7	PPNO (0.3)	37	57	*S* (+)
20	**1d**	NaOCl (7.5)[g]	7	PPNO (0.3)	54	48	*S* (+)
21	**1d**	PhIO (1.5)	7	PPNO (0.3)	21	27	*S* (+)

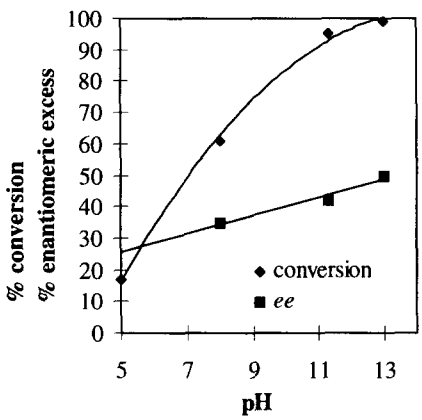
[a] PPNO = 4-phenylpyridine-*N*-oxide, NMO = *N*-methylmorpholine-*N*-oxide, the reactions were carried out in CH_2Cl_2; [b] determined by HPLC analysis (RP-18, 64:34:2 MeOH/H_2O/CH_3CN, flow 1.0 ml/min); [c] yield of isolated product 80-98% relative to the amount of conversion; [d] determined by HPLC analysis (Chiralcel OD, 9:1 *n*-hexane/2-propanol, flow 0.6 ml/min), error limits ca. 5% of the stated values; [e] configurations according to literature (refs. 9,12); [f] as 0.5 M solution in phosphate buffer (pH 11.3); [g] as 0.5 M solution in phosphate buffer (pH 13); [h] -78 °C, 4 h; [i] as 30% aqueous solution; [j] for the (*R,R*) catalyst.

oxidation reactions were carried out in dichloromethane with 5-7 mol% of the (*S,S*) Jacobsen catalyst [for entry 12 and 16 the (*R,R*) catalyst was used]. After 20 h of stirring at 5 °C, the mixture was treated with HCl/MeOH to desilylate the primary oxidation product, namely the α-silyloxy carbonyl derivative, to the corresponding optically active α-hydroxy carbonyl compound.

In the case of bleach as the oxygen source, it can be seen that the additive PPNO (4-phenylpyridine-*N*-oxide) is essential to improve the amount of conversion (entry 1, 2) and also the enantioselectivity (entry 14, 15). The steric demand of the silyl group also plays an important role in the enantioselectivity of the oxidation. The trimethylsilyl-substituted enol ether **1a** with bleach at pH 11.3 leads to an *ee* value of 42% (entry 2), while the corresponding *t*-butyldimethylsilyl derivative **1b** increases the enantioselectivity to 81% (entry 10). A similar increase of the *ee* value is also displayed by the ketene acetals **1c,d** (entries 15, 19); however, the low *ee* value for the oxidation of **1c** derives from the fact that a 70:30 mixture of *E/Z* diastereomers for the starting material was used.

The oxidation of the enol ethers **1a,b** is sensitive to the pH of the buffered bleach solution. For substrate **1a**, the conversion increases from 17% at pH 5 (not shown in Table 1) up to 99% at pH 13 (entry 3) due to the higher hydrolytic stability of the substrate at the higher pH. The *ee* value also increases significantly to 50% (entry 3), a dependence which has not been described before (Figure 1).

Figure 1: Dependence of the Oxidation of Silyl Enol Ether **1a** on pH



In contrast to the two-phase oxidation with aqueous bleach and methylene chloride as cosolvent, a one-phase reaction applies (entries 4, 13, 17, 21) for iodosobenzene as oxygen source; but surprisingly, lower conversions were registered than for the bleach system. Similarly, although 30% aqueous hydrogen peroxide has been successfully employed as oxygen donor for (salen)Mn catalysts[13], in our experiments (entries 9, 18) only 23% and 8% conversions were achieved. Moreover, the enantioselectivity for the H_2O_2 oxidation of **1a** is only half that of the bleach (entries 2, 9).

To exclude medium effects as a reason for the difference in the *ee* values, the oxidation with four differently substituted peracids (PBA) as oxygen donors were conducted at -78 °C and NMO (*N*-methylmorpholine-*N*-oxide) as additive.[14] The results (entries 5-8) show that the electron-rich 4-methoxyperbenzoic acid gives much higher *ee* values than the electron-poor 3,5-dinitroperbenzoic acid, while the *ee* values of the 3-chloro and the unsubstituted peracid fall in between.[15] This unusual trend reflects the electrophilic character of these peracids, i.e. 3,5-diNO_2 > m-Cl > H > p-MeO, and implies direct nonselective

oxidation of substrate **1a** in competition with the asymmetric oxygen transfer by the (salen)Mn(V)oxo complex. Indeed, attempts to oxidize the electron-rich silyl derivatives **1** with dimethyldioxirane as oxygen source[16] for the Jacobsen catalyst led only to the racemic α-hydroxy carbonyl product in a high yield. Furthermore, the oxidation with *t*-butyl hypochlorite as oxygen donor in CH_2Cl_2 proceeded in low conversions with an *ee* value lower than 5%, while with caroate in an aqueous buffer solution (pH 7) *ee* values of only 25% for derivatives **1a,b** and 10% for **1c,d** were obtained.

In summary, the optically active (salen)Mn(III) complex oxidizes silyl enol ethers and silyl ketene acetals catalytically and enantioselectively to the corresponding α-hydroxy ketones (81% *ee*) and esters (up to 57%), when aqueous bleach is used as oxygen donor at pH 11.3 and PPNO as additive. Not only the conversion, but also the enantioselectivity depend strongly on the type of oxygen source, the additive, and the pH of the aqueous medium.

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