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Synthesis of optically active α-hydroxy ketones by enantioselective oxidation of silyl enol ethers with a fructose-derived dioxirane

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Abstract

Optically active α-hydroxy ketones **3** have been prepared in moderate to high enantioselectivities by the asymmetric oxidation of the silyl enol ethers **2** with *in situ* generated dioxirane from the fructose-derived ketone **1**. Best results (ee values up to 82%) for this novel non-transition metal mediated asymmetric α-hydroxylation may be obtained, when an excess of the fructose-derived ketone **1** is employed at pH ca. 8 and short reaction times. Valuable mechanistic information on the *spiro* versus *planar* transition states for the oxygen-transfer process has been aquired through the absolute configuration of the resulting α-hydroxy ketone **3** products.

The optically active α-hydroxy-keto functional unit is widespread in natural products and has been frequently used for convenient building blocks in organic synthesis during recent years.[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 functionality.[3,4] Alternatively, prochiral enolates have been directly oxidized by optically active oxidants, e.g. chiral oxaziridines.[2,5] Highly enantioselective catalytic oxidations of enol ethers by the osmium-catalyzed asymmetric dihydroxylation[6] and by the (salen)Mn(III)-catalyzed asymmetric oxidation[7,8] have been described.

Recently Shi[9] developed an attractive metal-free, asymmetric epoxidation of *trans* olefins, in which the optically active oxidant was the *in situ* generated dioxirane from the fructose-derived ketone **1**, that operates even under catalytic conditions. In principle, this enantioselective oxidation should be applicable to prochiral silyl enol ethers **2**. Indeed, we report herein that this method constitutes a convenient asymmetric preparation of optically active α-hydroxy ketones **3** (Scheme 1).

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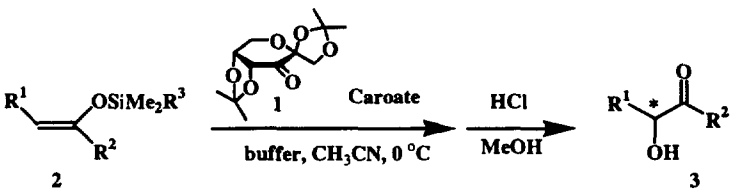

2, 3	R^1	R^2	R^3
a	Ph	Ph	Me
b	Me	Ph	Me
b'	Me	Ph	*t*Bu
c	Et	Ph	Me
d	Ph	Me	Me
e	Ph	*t*Bu	Me

Scheme 1. Asymmetric oxidation of the silyl enol ethers **2** by *in situ* generated dioxirane from the fructose-derived ketone **1**

Table 1
Enantioselective oxidation of the silyl enol ethers **2a–e**[a] by *in situ* generated dioxirane from the fructose-derived ketone **1**

entry	substrate	equiv.[b] of **1**	pH of buffer	t (h)	conv.[c,d] (%)	*ee* (%) [c] **3**	config. [e] **3**
1	**2a**	3.0	8	1.5	36	61	*R* (-)
2	**2a**	3.0	8	18	53	53	*R* (-)
3	**2a**	3.0	10.5	1.5	38	22	*R* (-)
4	**2a**	0.3	10.5	1.5	20	0	-
5	**2b**	3.0	8	1.5	46	54	*R* (+)
6	**2b'**	3.0	8	3.0	92	82	*R* (+)
7	**2b'**	3.0	10.5	1.5	<10	42	*R* (+)
8	**2c**	3.0	8	1.5	33	67	*R* (+)
9	**2d**	3.0	8	1.5	35	18	*R* (-)
10	**2e**	3.0	8	3.0	30	52	*S* (+)
11	**2e**	0.3	10.5	1.5	90	43	*S* (+)

[a] *Z*/*E* >95:5; [b] the non-catalytic reactions were carried out at 0 °C (bath temperature) with 1.0 equiv. of substrate **2**, 3.0 equiv. ketone **1**, 5.0 equiv. Caroate™ and 15.5 equiv. $NaHCO_3$ in an 1.5:1 CH_3CN/aqu. EDTA (4×10^{-4} M) buffer medium (pH 8), the catalytic reactions were carried out with 0.3 equiv. ketone **1**, 1.38 equiv. Caroate™ and 5.8 equiv. K_2CO_3 in an 1.5:1 CH_3CN/aqu. $Na_2B_4O_7 \cdot 10\ H_2O$ (0.5 M) buffer medium (pH 10.5); [c] 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; [d] yield of isolated product was 60-98% of the converted **2**; [e] configurations were assigned according to literature (Refs. 7b,10,11).

The results of the asymmetric α-hydroxylation of trimethylsilyl- (**2a–e**) and *tert*-butyldimethylsilyl-substituted (**2b'**) enol ethers[6,10,7b] are summarized in Table 1. These oxidations were carried out in an acetonitrile/buffer medium with 3 equiv. of the fructose-derived ketone **1** for the non-catalytic (pH 8)[9a] and 0.3 equiv. for the catalytic method (pH 10.5).[9b] After 1.5 to 18 h of stirring at 0°C, the mixture was diluted with water, extracted with ethyl ether and treated with HCl/MeOH to desilylate the primary α-silyloxy carbonyl product to the corresponding literature-known[7b,10,11] optically active α-hydroxy ketone **3**.

In the case of the diphenyl-substituted silyl enol ether **2a**, for the non-catalytic method (3 equiv. of

ketone **1** at pH 8) a longer reaction time leads to a slightly higher conversion but a lower enantioselectivity (entries 1 and 2). With 3 equiv. of ketone **1** at pH 10.5, a similar conversion as at pH 8 was observed, but the ee value dropped drastically to 22% (entries 1 and 3). Application of the catalytic method (0.3 equiv. of catalyst **1** at pH of 10.5) gives only 20% of a racemic mixture of the α-hydroxy ketone **3a** (entry 4). Control experiments without the fructose-derived ketone **1** showed that only 2% conversion was achieved at pH 8 and 10.5 to afford the racemic product **3a**. This confirms that the enantioselectivity is not lowered by the direct Caroate® oxidation of the enol ether **2a**.

The silyl enol ethers **2b,b′** of propiophenone have the bulky group in the geminal position. For the TMS-substituted derivative **2b**, the enantiomeric excess of the non-catalytic oxidation was 54% (entry 5), but the change to the TBDMS-substituted derivative **2b′** increased the ee value by up to 82% at a conversion of up to 92% (entry 6). This high conversion in only 3 h reaction time encouraged us to test the catalytic method for this substrate. Not only low conversion (<10%), but also a lower enantioselectivity (ee 42%) was obtained (entry 7).

For the substrate **2c**, which bears an ethyl group in the β position to the siloxy group, the non-catalytic method resulted in an *ee* value of 67% for the (*R*)-configured α-hydroxy ketone **3c** (entry 8). The silyl enol ether **2d** (entry 9), with a methyl group in the α position to the siloxy group instead of a phenyl group, possesses through the two bulky *Z* groups more *cis*-like character than the substrates **2a–c**. Presumably, this feature decreases the enantioselectivity to 18% (*R*), as would be expected for *cis* olefins.[12]

When the steric bulk of the α-substituent is increased by means of a *tert*-butyl group, the enol ether **2e** has again more *trans* character and as expected the ee value was significantly augmented: 52% for the non-catalytic (entry 10) and 43% for the catalytic (entry 11) methods. More significantly, while all the other substrates **2a–d** led to (*R*)-configured products, the (*S*) configuration was obtained for the α-hydroxy ketone **3e**. This change in the sense of the dioxirane-mediated, asymmetric α-hydroxylation required further mechanistic scrutiny of this oxygen-transfer process.

The established mechanism of dioxirane epoxidation is a *spiro*-structured transition state, in which steric repulsions of the dioxirane and olefin substituents are minimized.[13] This geometry is also favored by Shi[9a,c] in the epoxidation of *trans* alkenes by the *in situ* generated, fructose-derived dioxirane. Calculations performed by Bach et al. show that a *spiro*-like transition state benefits from the stabilizing interaction of an oxygen lone pair with the π* orbital of the alkene.[14] For the *planar* arrangement of the oxygen transfer, usually more severe steric interactions between the substituents of the *trans* olefin and the chiral dioxirane would afford the minor epoxide enantiomer.[9c]

Application of this *spiro* model to the enol–ether substrates **2** is illustrated in Fig. 1, with the **2a** derivative as a prototype for those derivatives which afford mainly the (*R*)-enantiomer. The approach of the chiral dioxirane is defined by Plane 1, with the dioxirane moiety in this plane; the favored orientation of the **2a** substrate is defined by Plane 2, with the π bond horizontally aligned and all its substituents within that plane. Oxygen-atom transfer, rearrangement of the silyloxy-substituted epoxide, and desilylation leads to the observed (*R*)-configured α-hydroxy ketone **3a** as final product.

How can the opposite product configuration be rationalized for substrate **2e**? For the **2e** substrate, the *spiro* transition state would also predict the (*R*)-configured α-hydroxy ketone **3e**. However, in this case R^2 is the bulky *tert*-butyl group and the steric interaction of this R^2 group with the fructose moiety of the dioxirane is larger than in the substrates **2a–d**. This steric repulsion in the *spiro* transition state of substrate **2e** outweighs the stabilizing interaction of the oxygen lone pair with the π* orbital of the alkene and the (*S*) enantiomer is observed as the major enantiomer.[9c] Inspection of molecular models reveals that in the *planar* transition state, with the π bond vertical and all its substituents also in Plane 2 (Fig. 1, right-hand structure), the non-bonded interactions between the dioxirane and olefin are minimal,

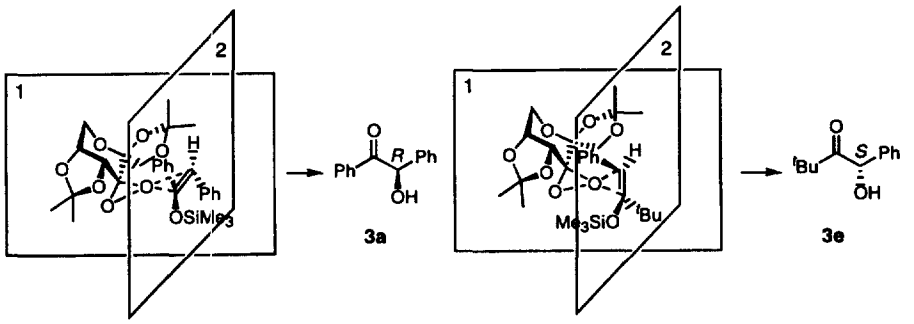

Fig. 1. Orientation of the enol ether **2a** (also for **2b–d**) in the *spiro* and the *planar* transition states for the substrate **1e**

so that the (*S*)-configured α-hydroxy ketone **3e** should result, as observed (Table 1). This constitutes the first case for which the *planar* dioxirane–olefin arrangement is preferred. Thus, a judicious choice of the substitution pattern in the olefinic substrate permitted us to probe the preferred substrate–oxidant arrangement through the resulting configuration of the oxidation product from the oxygen transfer with the chiral dioxirane of the fructose-derived ketone **1**.

In summary, the optically active, *in situ* generated dioxirane from the fructose-derived ketone **1** oxidizes silyl enol ethers **2** enantioselectively to the corresponding α-hydroxy ketones **3** with *ee* values up to 82% for the non-catalytic method. The (*R*) configuration of the resulting α-hydroxy ketones **3a–d** is in accordance with a *spiro* transition state, but the (*S*)-configured α-hydroxy ketone **3e** implicates a preferred *planar* geometry. This unprecedented asymmetric oxidation constitutes a synthetically valuable α-hydroxylation of ketones without the use of transition-metal oxidants.

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