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# α-Hydroxy ketones in high enantiomeric purity from asymmetric oxidation of enol phosphates with (salen) manganese(III) complex

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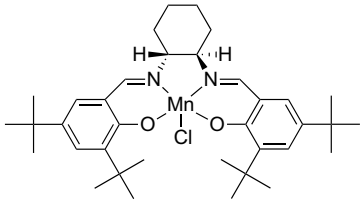
**Abstract**—Optically active α-hydroxy ketones **4** have been prepared in high enantioselectivity by the catalytic, enantioselective oxidation of easily available and stable (*E*)-enol phosphates **2** by (salen) Mn(III) complex.


Chiral α-hydroxy ketones are important structural units in many biologically active natural products.[1] Recently they have been used as convenient building blocks in organic synthesis.[1a,2] Consequently, numerous studies have aimed at their stereoselective synthesis.[3] This class of compounds has been prepared by both nonoxidative[4] and oxidative[3b,5] methods. Metal complexes play a pivotal role in selective oxidation to give useful natural and non-natural products. Stereoselectively controlled epoxidation is particularly valuable because the epoxy functionality can be transformed by stereoselective ring opening into highly functionalized products.

Sharpless et al.[3b] have described enantioselective oxidation of enol ethers by osmium-catalyzed asymmetric dihydroxylation providing optically active α-hydroxy ketones. A recent major advance in catalytic enantioselective epoxidation has been oxidation of prochiral unsaturated compounds with readily accessible (salen) Mn(III) complexes. These complexes have been demonstrated to be highly enantioselective catalysts for epoxidation of conjugated *cis*- di, tri- and tetra-substituted olefins[6] as well as *cis* enol ethers[5a,7] and enol esters.[5a,7a] These epoxy derivatives are easily converted into optically active α-hydroxy ketones and α-hydroxy acetals, respectively.

As a part of our interest in the application of very readily available enol phosphates in the synthesis of new functionalized policyclic compounds,[8] we have elaborated a methodology based on epoxy phosphates intermediates[8,9] as an alternative, general synthesis of α-hydroxy ketones.[10]

In this paper we report that enol phosphates of (*E*) configuration are good prochiral substrates for metal-catalyzed oxidation by Jacobsen's chiral (salen) Mn(III) complex **1**[11] (Fig. 1) to afford optically active α-hydroxy ketones.




**1**

(*R*, *R*)-(-)-*N*,*N*'-Bis(3,5-di-tert-butylsalicylidene)-1,2-cyclohexanediamino-manganese (III) chloride

**Figure 1.** Jacobsen's complex.

(*E*)-enol phosphates are very easy to prepare from commercial materials. They are stable for long periods at rt. If an aromatic or cyclic group is placed in the α-position to the phosphate group as a third substituent, the products are the more persistent α-hydroxy ketones **4**.

A variety of (*E*)-enol phosphates **2**[12] have been converted to epoxides, using NaOCl in a phosphate buffer (pH ~11) as an oxygen source, 4-phenylpyridine

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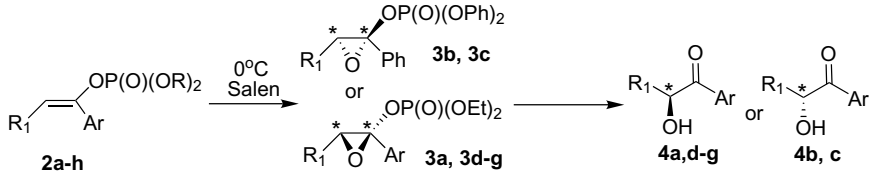
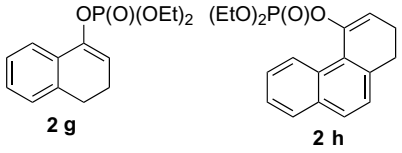



| 2, 3, 4 | $R_1$ | Ar | R |
|---|---|---|---|
| a | Me | Ph | Et |
| b | Me | Ph | Ph |
| c | Et | Ph | Ph |
| d | Pr | Ph | Et |
| e | Ph | Ph | Et |
| f | Me | 4-MeO-Ph | Et |




**Scheme 1.**

*N*-oxide (PPNO) as additive and 7 mol% of (salen) Mn(III) complex **1** as catalyst at 0 °C.[13] Opening of the intermediate epoxy ring has been carried out with 25% $CF_3COOH$ at 5 °C (Scheme 1).[14]

The results of conversion of enol phosphates into α-hydroxy ketones with catalyst **1** are summarized in Table 1.

The set of chosen (*E*)-configured enol phosphates **2a**, **d**, **e**, **f** with Me, Pr, Ar substituents in the β-position to the phosphate group and enol phosphates **2g**, **h** with cyclic substituents afforded the corresponding α-hydroxy ketones **4a**, **4d**–**h** with high enantiomeric excess in the range 81–96% of the (*S*)-enantiomer (entries 1, 4–7). Catalytic oxidation of enol phosphates **2b** and **2c**, which have bulkier phenoxy substituents at phosphorus instead of ethoxy substituents, was performed to compare the influence on stereochemistry of the bulkier phosphate group. For substrate **2b** the ee value decreased to 68% (entry 2) compared to 96% for substrate **2a** (entry 1). The observed sense of absolute asymmetric induction, which was opposite [(*R*) configuration] to that of the other enol phosphates investigated (Fig. 2), provided an important insight into the factors controlling stereoinduction in the epoxidation of enol phosphates.

The stereochemistry of the products obtained in the manganese-assisted oxyfunctionalization of various olefins, including enol ethers, has been rationalized on the basis of the widely accepted mechanism for oxo-transfer, which involves direct substrate attack at the oxo ligand with concerted or stepwise C–O bond formation.[3e] Generally, a skewed side-on approach of trisubstituted olefins has been proposed to account for observed enantioselectivites.[3e,6d] Adam et al. considered a metallaoxetane mechanism as more adequate for the oxofunctionalization of silyl enol ethers and ketene acetals to the corresponding α-hydroxy ketones and α-hydroxy acetals.[5a] Choice between radical and metallaoxetane models for our stereochemical results is not possible at present. Further investigation of the influence of substituents at phosphorus and their mechanistic implication continues.

**Table 1.** Enantioselective synthesis of α-hydroxy ketones **4a**–**h** by catalyst (*R*,*R*)-(−) (salen) Mn(III) **1** with NaOCl

| Entry | Substrate | Product | Yield[a] (%) | Ee[b] (%) | Configuration[c] **4** |
|---|---|---|---|---|---|
| 1 | **2a** | **4a** | 52 | 96 | (*S*)-(−)[d] |
| 2 | **2b** | **4a** | 47 | 68 | (*R*)-(+)[e] |
| 3 | **2c** | **4c** | 48 | 81 | (*R*)-(+)[f] |
| 4 | **2d** | **4d** | 58 | 83 | (*S*)-(−)[g] |
| 5 | **2e** | **4e** | 56 | 89 | (*S*)-(+)[h] |
| 6 | **2f** | **4f** | 60 | 87 | (*S*)-(−)[i] |
| 7 | **2g**[k] | **4g** | 37 | 83 | (*S*)-(−)[j] |
| 8 | **2h** | **4h** | 22[l] | 81 | (+)[m] |

[a] Yield of isolated compounds **4** (see Refs. 14 and 15), based on enol phosphates **2**.

[b] Determined by HPLC analysis (Chiracel OD, for details see Ref. 16) using racemic compounds as references (see Ref. 17).

[c] Configurations were assessed by comparison of the sign of the optical rotation with literature data (footnotes d–j), for **4d** by analogy to the sign of the rotation for similar ketols of known configuration.[3b,5a,18a,d]

[d] (*S*)-**4a**: $[\alpha]_D^{20} = -80.9$ (*c* 2.0, $CHCl_3$), ee = 95%;[18a] $[\alpha]_D^{20} = -58.3$ (*c* 2.0, $CHCl_3$), ee = 62%;[18c] this work: $[\alpha]_D^{20} = -82.7$ (*c* 3.6, $CHCl_3$).

[e] (*R*)-**4a**: $[\alpha]_D^{20} = +81.0$ (*c* 1.5, $CHCl_3$);[19] $[\alpha]_D^{20} = +82.2$ (*c* 2.0, $CHCl_3$), ee = 96%;[18b] this work: $[\alpha]_D^{20} = +65.4$ (*c* 0.75, $CHCl_3$).

[f] (*S*)-**4c**: $[\alpha]_D^{20} = -30.8$ (*c* 2.24, $CHCl_3$), ee = 95% was determined by $Eu(hfc)_3$ NMR shift reagent of acetate derivative;[18a] this work: $[\alpha]_D^{20} = +40.5$ (*c* 0.3, $CHCl_3$).

[g] **4d** this work: $[\alpha]_D^{20} = -14$ (*c* 0.3, $CHCl_3$).

[h] (*S*)-**4e**: $[\alpha]_D^{20} = +114.9$ (*c* 1.5, acetone), ee = 95%;[18a,c] this work: $[\alpha]_D^{20} = +138.4$ (*c* 0.25, $CHCl_3$); (*R*)-**4e**: $[\alpha]_D^{20} = -230.5$ (*c* 1.0, benzene);[19] $[\alpha]_D^{20} = -170.1$ (*c* 1.0, benzene), ee = 70%.[18b]

[i] (*S*)-**4f**: $[\alpha]_D^{20} = -33.4$ (*c* 1.05, MeOH);[19] this work: $[\alpha]_D^{20} = -30.7$ (*c* 0.875, $CHCl_3$); (*R*)-**4f**: $[\alpha]_D^{20} = +33.6$ (*c* 1.0, MeOH), ee = 94%;[18b] $[\alpha]_D^{20} = +32.8$ (*c* 1.36, MeOH), ee = 99%.[3b]

[j] (*R*)-**4g**: $[\alpha]_D^{20} = +21.4$ (*c* 0.59, $CHCl_3$), ee = 49%;[20] this work: $[\alpha]_D^{20} = -27.0$ (*c* 0.1, $CHCl_3$).

[k] Epoxidation of the enol phosphate derivative of β-tetralone proceeded with formation of the corresponding naphthalene derivative.[6c]

[l] Low yield is due in part to the participation of an aromatization pathway leading to the corresponding phenanthrene derivative (see footnote k).

[m] Configuration has not been determined.

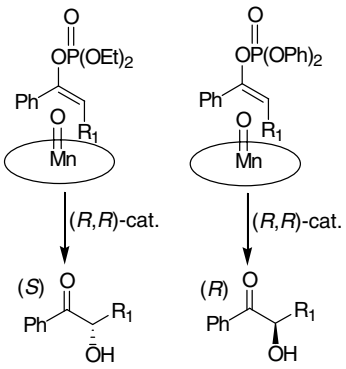



**Figure 2.**

In summary, we have shown that really easily available (*E*)-enol phosphates can be stereoselectively epoxidized and than converted into α-hydroxy ketones with high enantioselectivity up to 96% by (salen) Mn(III) Jacobsen's complex. Our results demonstrate that absolute configuration of α-hydroxy ketones was controlled by the steric bulk and electronic factors of the phosphate group in enol phosphates. The synthetic scope of (salen) Mn(III)-catalyzed asymmetric epoxidation is extended by conversion of (*E*)-enol phosphates into the pool of successful substrates.

## Acknowledgements

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14. General procedure for epoxidation: To a stirred solution of NaOCl (4 mL, 7 equiv) and phosphate buffer (4 mL, pH = 11) the mixture of appropriate enol phosphate (1.1 mmol, 1 equiv), 4-phenylpyridine N-oxide (PPNO) (30 mol%), and (salen) Mn(III) complex **1** (7 mol%) in 4 mL $CH_2Cl_2$ was added at 10 °C temperature. The stirring of the reaction mixture was continued at 0 °C for 18 h (the reaction was monitored by TLC), *n*-hexane (40 mL) was added, organic layer was separated, washed with distilled water and dried ($MgSO_4$). Evaporation of solvent afforded crude epoxide, which was diluted with $Et_2O$ and treated with $CF_3COOH$ in $H_2O$ (10 mL) at 0 °C. Stirring was continued until TLC analysis revealed the complete consumption of epoxide. Then the mixture was washed with $NaHCO_3$, $CHCl_3$ was added, the organic layer was separated, washed with water, and dried. After removal of the solvent, the residue was subjected to silica gel column chromatography with hexane–ethyl acetate (3:1 v/v) as the eluent, to afford pure, optically active α-hydroxy ketones **4**.
15. α-Hydroxy ketones **4a**–**g** gave satisfactory spectroscopic characterization. **4h** (3-Hydroxy-2,3-dihydro-1H-phenanthren-4-one): Yellow oil; $R_f = 0.58$ (petrol-EtOAc, 1:1 v/v); $[\alpha]_D^{20} = +17.5$ (*c* 0.4, $CHCl_3$); $\nu_{max}/cm^{-1}$ (film): 3454 (br w, OH), 2962 (s, C–H), 1663 (s, C=O), 1602 (m, C=C), 1460 (m, C=C); $\delta_H$ (200 MHz, $CDCl_3$): 2.16 (ddd, $J = 4.8$, 12.8, 17.5 Hz, 1H, $CH_2$), 2.61 (dd, $J = 5.8$, 6.1 Hz, 1H, $CH_2$), 3.20 (dd, $J = 4.0$, 17.5 Hz, 1H, $CH_2$), 3.99 (ddd, $J = 4.3$, 13, 17.3 Hz, 1H, $CH_2$), 4.48 (dd, $J = 5.0$, 13.6 Hz, 1H, C*H*–OH), 4.31 (br s, 1H, OH), 7.31 (d, $J = 8.4$ Hz, 1H, Ar*H*), 7.53 (t, $J = 7.4$ Hz, 1H, Ar*H*), 7.66 (dd, $J = 7.4$, 8.1 Hz, 1H, Ar*H*), 7.83 (d, $J = 8.1$ Hz, 1H, Ar*H*), 7.97 (d, $J = 8.4$ Hz, 1H, Ar*H*), 9.35 (d, $J = 8.6$ Hz, 1H, Ar*H*); $\delta_C$ (50.33 MHz, $CDCl_3$): 22.084 ($CH_2$), 32.240 ($CH_2$), 73.781 (CHOH), 124.805 (Ar*C*), 125.842 (Ar*C*), 126.241 (Ar*C*), 126.744 (Ar*C*), 128.365 (Ar*C*), 129.120 (Ar*C*), 132.491 (Ar$C^{IV}$), 135.038 (Ar$C^{IV}$), 146.444 (Ar$C^{IV}$), 148.321 (Ar$C^{IV}$), 201.571 (C=O); *m/z* (CI, isobutene): 213 ($[M^+ + H]$, 100%); HRMS: Calcd for $C_{14}H_{13}O_2$ ($C_{14}H_{12}O_2 + H^+$) 213.09155. Found 213.09102.

16. HPLC conditions: For entries 1, 2, 5, 8: Chiralcel OD, 5% *i*-PrOH in hexane, 0.4 mL/min; For entry 3: Chiralcel OD, 4% *i*-PrOH in hexane, 0.4 mL/min; For entry 4: Chiralcel OD, 3% *i*-PrOH in hexane, 0.3 mL/min; For entry 6: Chiralcel OD, 0.25% *i*-PrOH in hexane, 0.3 mL/min; For entry 7: Chiralcel OD, 0.5% *i*-PrOH in hexane, 0.5 mL/min. All runs were carried out at room temperature.
17. Racemic α-hydroxy ketones **4** were obtained by MCPBA acid oxidation of the corresponding enol phosphates **2a**–**h** followed by the hydrolysis of resulted epoxides **3a**–**h** with 25% of trifluoroacetic acid in ether solution at 5–10 °C.
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