A Very Mild, Catalytic and Versatile Procedure for α-Oxidation of Ketone Silyl Enol Ethers Using (salen)Manganese(III) Complexes; A New, Chiral Complex Giving Asymmetric Induction. A Possible Model for Selective Biochemical Oxidative Reactions Through Enol Formation

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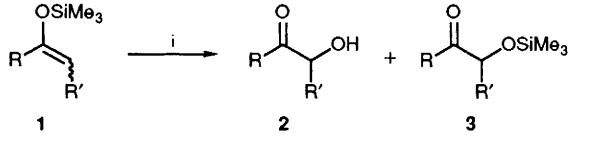
Facile, catalytic, selective (racemic and asymmetric) oxidation of ketone silyl enol ethers to give α-oxygenated products proceeds well under very mild, aprotic conditions using a racemic (salen)manganese(III) complex [H_2salen = bis(salicylidene)ethylenediamine] or a new, chiral C_2-symmetric pyrrolidine-based manganese(III) complex as catalyst, with iodosobenzene as the terminal oxidant at ambient temperature.

Metal complexes play a pivotal role in selective oxidations to give useful natural and non-natural products,[1] and synthetic catalysts based on biological models are of great interest.[2] As part of our efforts to design effective catalytic reagents, we report here the selective, catalytic (racemic and asymmetric) oxidation of ketone silyl enol ethers to give α-hydroxy ketones.

The α-hydroxy carbonyl structural unit is found in many natural products and also represents an interesting class of intermediates in organic synthesis.[1] Previous synthetic protocols were not catalytic and/or required acidic or basic conditions incompatible with many substrates,[3] with the exception of OsO_4 as catalyst with silyl enol ethers.[4] Asymmetric oxidation of the parent carbonyl compounds through enol derivatives has been successful, but most procedures require stoichiometric quantities of chiral auxiliaries.[5] Very recently, Ni^{II}-catalysed oxidation of silyl enol ethers[6] and (salen)manganese(III) complex-catalysed asymmetric epoxidation of unfunctionalized alkenes[7] have been reported.

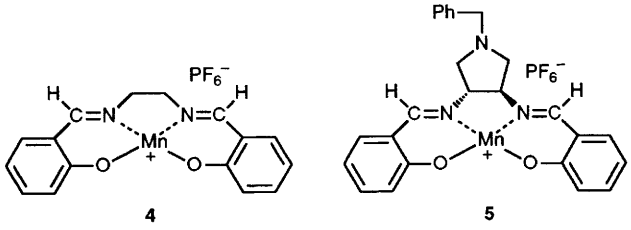
Considering a catalytic route for carbonyl α-hydroxylation to be an important target, we have developed intrinsically simple, mild, aprotic and catalytic (racemic and asymmetric) oxidation procedures to prepare this important chiral unit. We have now shown that a simple (salen)manganese(III) complex **4** catalyses the oxidation of silyl enol ethers at ambient temperature in good to excellent yields (Scheme 1). Moreover, we have developed a simple synthesis of a novel, chiral pyrrolidine-based (salen)manganese(III) complex **5**, which gives moderate asymmetric induction in this reaction.

Catalyst **4** was prepared in three steps and in 72% overall yield from commercially available ethylenediamine and salicylaldehyde.[8] The new chiral catalyst **5** was synthesized in eight steps from readily available natural (+)-tartaric acid in overall yield of 27% (Scheme 2). The known dimesylate **6**,[9] prepared in three steps from natural (+)-tartaric acid, was smoothly converted to the corresponding diazide, which was subsequently reduced to diamine **7**. Chiral diamine **7** was converted to its diimine; subsequent treatment with $Mn(OAc)_2{\cdot}4H_2O$ in the presence of KOH afforded the manganese complex, which was then transformed into the active manganese(III) complex **5** by reaction with ferrocenium hexafluorophosphate, Scheme 2.



1 2 3

Scheme 1 *Reagents and conditions*: i, **4** or **5**, Ph–IO, MeCN, *ca.* 25 °C



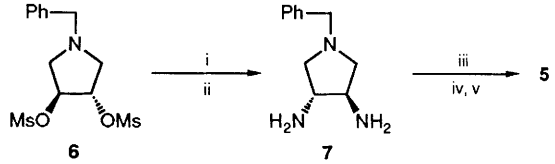
4 **5**

The convenient synthesis of new C_2-symmetric chiral diamine **7** proceeds with an overall yield of 38% by simple transformations from natural (+)-tartaric acid. So far, other known chiral diamines have been prepared by procedures involving optical resolution.[10] This new chiral ligand may lead to a family of rationally designed asymmetric catalysts derived from natural tartaric acid.

The catalytic oxidative reactions were carried out in degassed, dry acetonitrile under argon atmosphere with 0.2–1 mol% of catalyst **4** or **5**, using iodosobenzene as the source of oxygen. We have examined different ratios of catalyst **4** and iodosobenzene in the oxidation of 1-(trimethylsilyl)oxycyclohexene. Yields are essentially equal in all experiments. With catalyst ratios of ≤1 mol%, the reaction time increases significantly. An excess of iodosobenzene does not affect reaction time, however. The presence of activated, powdered molecular sieves during the reaction did not improve the yields of products. With iodosobenzene alone, in the absence of catalyst, 1-(trimethylsilyl)oxycyclooctene decomposed to starting ketone over *ca.* 10 h, and no trace of the catalyst-produced α-oxygenated products was detected.

We have abridged our results from a wide range of substrates in Table 1. The efficiency and generality of catalyst **4** or **5** in providing good to excellent yields of (racemic or chiral) α-silyloxy and α-hydroxy ketonic products from various silyl enol ethers[11] are notable. All compounds have been characterized extensively by ^1H NMR, ^{13}C NMR, IR, and mass spectral data. Desilylation to provide entirely the α-hydroxy ketone product has been shown to proceed simply upon KF/MeOH workup.[6] Asymmetric induction varies from 14 to 62% enantiomeric excess (e.e.). The rigid conformation and C_2-symmetry of our catalyst markedly reduce the number of possible conformations of the chiral catalyst and the coordinated substrate.

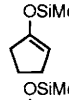
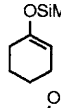
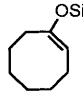
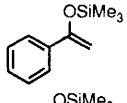
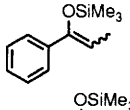
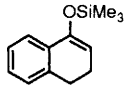
This is the first catalytic procedure for asymmetric hydroxylation of silyl enol ethers. Since the catalyst is readily synthesized, it should be possible to enhance the e.e. of



6 **7**

Scheme 2 *Reagents and conditions*: i, LiN_3, DMF (77%); ii, $LiAlH_4$, THF (77%); iii, salicylaldehyde (85%); iv, $Mn(OAc)_2{\cdot}4H_2O$ (89%); v, $(C_5H_5)_2Fe^+PF_6^-$, (93%)

Table 1 Catalytic oxidation of ketone silyl enol ethers with catalysts **4** or **5** and iodosobenzene[a]

Entry[b]	Substrate	Catalyst **4** Yield (%) (min)[c]	Catalyst **4** Ratio **2**:**3**	Catalyst **5** Yield (%) (min)[c]	Catalyst **5** Ratio **2**:**3**	e.e.[d] (Rotation)[e]
1		85 (180)	1.4:1	70 (240)	2.6:1	30[f] (−)
2[4]		87 (180)	1.4:1	78 (60)	1.4:1	51[f] (−)
3[3]		86 (180)	0.9:1	68 (60)	0.8:1	15[f] (−)
4		90 (45)	2.4:1	73 (60)	1.9:1	14[h] (−)
5[4]		94 (10)	0.8:1	—	—	—
6[4]		91 (45)	0.4:1	94 (15)	0.2:1	29[i] (−)-*S*[g]
7[3]		85 (30)	0.8:1	72 (20)	0.8:1	62[f] (+)

[a] All reactions were carried out under argon with silyl enol ether (1 mmol), catalyst **4** or **5** (0.01 mmol), and iodosobenzene (1.5 mmol), at *ca.* 25 °C in acetonitrile (3.5 ml). [b] References are given for literature examples, in which other reagents were used. [c] Total product yield, **2** + **3** (reaction time, min). [d] The e.e. of the alcohol product was determined by preparation and analysis of the Mosher ester derivative. [e] $[\alpha]_D$ values, which could be calculated from experimental rotations and e.e. values, are not given here, because the rotations were obtained for α-hydroxy compounds, which were isolated by flash column chromatography but were not analytically pure substances. Absolute configurations are not yet determined since literature analogies are not available for Mosher esters of cyclic carbonyl derivatives. The exception is one compound which has been rigorously assigned in the literature (see note *g* below). [f] Analysed by separation on chiral HPLC column (Chiralcel OJ column, mobile phase 90:10 hexanes–propan-2-ol) and also by 500 MHz ^{1}H NMR. [g] F. A. Davis, M. S. Haque, T. G. Ulatowski and J. C. Towson, *J. Org. Chem.*, 1986, **51**, 2402. [h] Analysed by 188.2 MHz ^{19}F NMR. [i] Analysed by 500 MHz ^{1}H NMR; Mosher esters not resolved on (Chiralcel OJ column) chiral HPLC column.

products by systematic variation of ligands such as the chiral diamine and salicylaldehyde. Application of this type of ligand in other asymmetric processes is plausible.

It is well established that an oxomanganese(v) complex is initially formed.[12] Choice among single electron transfer (SET), metallaoxetane, or electrophilic attack mechanisms is not possible at present. Our attempts to isolate possible intermediates have so far failed.

These results may be relevant to biochemical oxidative reactions in nature, *i.e.*, introduction of hydroxy groups selectively α to carbonyl functionalities by cytochrome P_{450} through transitory enol formation.

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