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A Biomimetic Catalyst for the Asymmetric Epoxidation of Unfunctionalized Olefins with Hydrogen Peroxide

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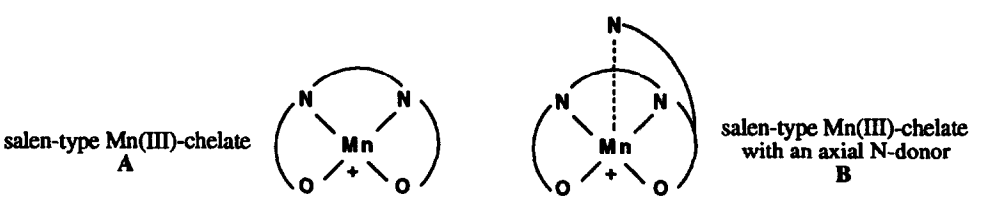
Abstract: A chiral pentadentate dihydrosalen ligand, carrying an imidazole group as the fifth donor, was synthesized in enantiomerically highly enriched form. The corresponding manganese(III) complex catalyzed the epoxidation of olefins with dilute hydrogen peroxide. With 1,2-dihydronaphthalene as substrate and 10 mol-% of catalyst, enantiomeric excess up to 64 % was achieved. The latter value is the highest so far reported for a metal-catalyzed asymmetric epoxidation employing hydrogen peroxide as the terminal oxidant.

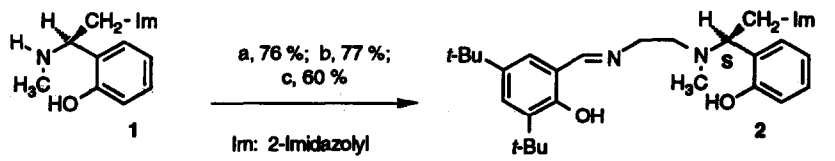
The enantioselective epoxidation of unfunctionalized olefins described by *Jacobsen et al.*[1-3] has greatly expanded the synthetic scope of metal-catalyzed asymmetric oxidations. In this approach, oxygen transfer to the substrate olefin is effected by C_2-symmetric manganese(III)-salen type complexes, using iodosoarenes or hypochlorite as terminal oxidants. As a part of our studies on biomimetic catalysts for selective oxyfunctionalizations[4], we addressed the question whether *hydrogen peroxide* could be employed as the terminal oxidant[5]. Its advantages are obvious: It is a cheap and mild reagent, with only water being formed as waste product[6]. The main challenge associated with this oxidant, however, is favoring the heterolytic O-O bond cleavage - with concomitant formation of the reactive metal-oxene species - over destructive radical pathways[7]. In many peroxidases, i.e. hydrogen peroxide utilizing enzymes, the catalytically active iron center is coordinated by the four pyrrole nitrogen atoms of its heme ligand *plus* an axial imidazole donor[8-10]. This proximal donor is believed to facilitate O-O heterolysis. Not surprisingly, imidazole or derivatives thereof have proven beneficial as co-ligands for manganese-catalyzed epoxidations[11], especially with hydrogen peroxide as the source of oxygen[12,13]. For the efficient utilization of this oxidant in the enantioselective epoxidation of unfunctionalized olefins, it appeared desirable to combine the features of a peroxydase-like coordination sphere and a (chiral) manganese(III)-salen complex (**A**). In such an arrangement, a fifth, axial donor - preferably an imidazole group - should be covalently attached[14] to a salen-type complex (**B**). Herein we describe initial results of this approach.



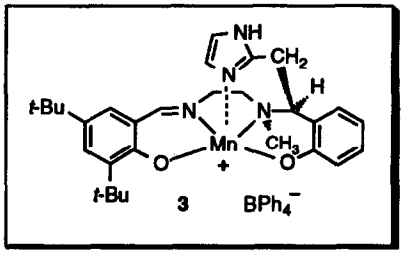
The (S)-configurated pentadentate ligand **2** was prepared from the enantiomerically pure amine **1** by the three-step sequence shown in Scheme 1[15]. Treatment of the ligand **2** with manganese(II) chloride in the presence of air and sodium tetraphenylborate gave the complex **3** in 63 % yield as an amorphous brown powder[16].

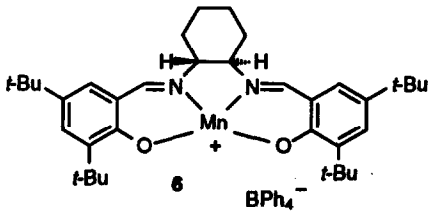
As expected, the complex **3** proved catalytically active in the epoxidation of olefins with hydrogen peroxide. For 1,2-dihydronaphthaline **4** as substrate, the yields and ee-values of its (1R,2S)-epoxide[17] **5** obtained under

Scheme 1: Preparation of the pentadentate ligand **2**[15].



a: 2-(N-Phthalimido)acetaldehyde, $NaBH_3CN$; b: $N_2H_4 \cdot H_2O$; c: 3,5-Di-*t*-butylsalicylaldehyde.

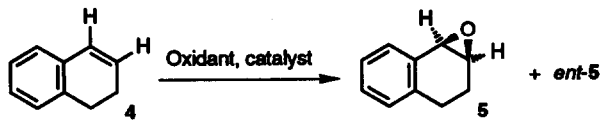




various conditions are summarized in Table 1. Typically, 40 µmol of the olefin, 4 µmol (10 mol-%) of the catalyst **3** (81 % ee, except for entry 5b) and ca. 40 µmol 1,2-dibromobenzene (as internal standard) were dissolved in 1.5 mL of the solvent. The oxidant (400 µmol of "active O", i.e. 10 eq. relative to the olefin) was added at once and the mixture was stirred magnetically at the temperatures stated in the legend of Table 1.When acetonitrile was used as solvent, the epoxide **5** was obtained in yields up to 60 % and 34 % ee (Table 1, entry 1). Under identical conditions, the Mn(III)-salen catalyst **6**[3] afforded a somewhat higher ee (48 %), but a lower chemical yield (43 %). As is evident from Table 1, both yield and enantioselectivity of the epoxidation catalyzed by **3** could be enhanced by switching to methylene chloride as solvent: At ca. 20 °C, with 30 % hydrogen peroxide, 68 % of the epoxide **5** were obtained, with an ee of 45 % (Table 1, entry 2). As shown in Table 1, entries 4, 5a,b, *even 1 % hydrogen peroxide* could be used as oxidant! With enantiomerically pure catalyst **3** (prepared from the *Schiff's* base **2** of > 98 % ee), the epoxide **5** was obtained in 72 % yield and 64 % ee (entry 5b). Lowering the reaction temperature to 0 °C had little effect on the ee of the product (Table 1, entries 2,3;4,5a). Replacing our catalyst **3** by the Mn(III)-salen **6**[3] - under constant experimental conditions - resulted in less than 8 % production of epoxide **5**, addition of excess 2-methylimidazole did not result in any improvement. Satisfying results were also obtained employing adducts of hydrogen peroxide, such as its clathrate with urea or "sodium percarbonate" (Table 1, entries 6,7): 66 - 70 % epoxide were formed, with an enantiomeric excess as high as 53 %. Under the experimental conditions of entries 6 and 7, the salen-type catalyst **6**[3] only gave low yields of epoxide (urea clathrate: < 13 %, percarbonate: < 3 %). Epoxidation with oxidants other than hydrogen peroxide could also be catalyzed by **3**. For example, when 2 eq. of iodosobenzene and 10 mol-% of catalyst (relative to the olefin) were used in methylene chloride, the epoxide **5** was obtained in 68 % yield and 52 % ee (Table 1, entry 8). As an example for a terminal olefin, styrene was transformed to the (R)-epoxide[20] with 30 % hydrogen peroxide in 66 % yield and 27 % ee (conditions similar to Table 1, entry 1).

As already mentioned, the (1R,2S)-epoxide **5** was predominantly formed from 1,2-dihydronaphthaline **4** in all cases. Inspection of space filling models revealed that the approach of the (3*re*)-face of the prochiral olefin **4** to the oxygen atom of an intermediate Mn=O species is indeed disfavored by nonbonding interactions with the distorted chiral ligand[19].

Table 1: Epoxidation of 1,2-dihydronaphthaline **4** catalyzed by the manganese chelate **3**[a].



Entry	Solvent	Oxidant	Reaction Time [h]	Olefin 4 Consumed [%]	Epoxide 5 Formed[b,c] [%]	ee[d] [%]
1	CH_3CN	30 % H_2O_2	12[e]	87	60 (69)	34
2	CH_2Cl_2	30 % H_2O_2	1	88	68 (77)	45
3	CH_2Cl_2[f]	30 % H_2O_2	1	93	73 (78)	45
4	CH_2Cl_2	1 % H_2O_2	1	92	77 (84)	48
5a	CH_2Cl_2[f]	1 % H_2O_2	1	91	65 (71)	50
5b	CH_2Cl_2[f]	1 % H_2O_2	1	93	72 (77)	64[g]
6	CH_2Cl_2	$(H_2N)_2CO$ •H_2O_2	1	94	70 (74)	48
7	CH_2Cl_2	Na_2CO_3 •1.5 H_2O_2	29	87	66[h] (76)	53
8	CH_2Cl_2	Ph-IO[i]	1	83	68 (82)	52

a) Reactions were carried out at ca. 20 °C as described in the text. No formation of epoxide/consumption of olefin occurred in the absence of the catalyst. As stated in ref. 15, the catalyst **3** was prepared from the *Schiff's* base **2** of 81 % ee.

b) Yields determined by capillary GC, employing 1,2-dibromobenzene as internal standard.

c) Values in parentheses are corrected for incomplete conversion of olefin.

d) Determined by capillary GC on a heptakis(2,6-di-O-methyl-3-O-pentyl)-β-cyclodextrin column and confirmed by ^{1}H-NMR shift experiments employing (+)-Eu(hfc)$_3$. The absolute configuration of the predominantly formed enantiomer was (1R,2S) in all cases[17].

e) The oxidant was added as a solution in acetonitrile by means of a syringe pump over a period of 12 h.

f) Epoxidation carried out at 0 °C.

g) Catalyst **3** prepared from the *Schiff's* base **2** of > 98 % ee.

h) Yields of isolated, chromatographically purified material could be raised to 77 % by driving the reaction to full conversion of the olefin.

i) Two equivalents (rel. to olefin) of iodosobenzene were added at once.

Earlier reports on asymmetric metal-catalyzed epoxidations of unfunctionalized olefins with hydrogen peroxide involved platinum complexes with chiral phosphine ligands[22] or the iron(III)-complex of bleomycin[23]. Compar-

ed to the catalyst **3**, lower yields and/or lower enantioselectivities were generally obtained. We are presently investigating the substrate spectrum of **3** and variations of the ligand for further optimizing this promising new type of catalyst.

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