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Manganese Catalyzed Asymmetric Oxidation of Alkanes to Optically Active Ketones Bearing Asymmetric Center at the α – Position

Naruyoshi Komiya, Satoru Noji, and Shun-Ichi Murahashi*

Department of Chemistry, Graduate School of Engineering Science, Osaka University, 1-3, Machikaneyama , Toyonaka, Osaka 560-8531, Japan

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Abstract

Chiral (salen)manganese(III) complex catalyzed oxidation of symmetrical alkanes with iodosylbenzene gives the corresponding optically active ketones (up to 70% ee). The optically active 2-hydroxy-1-indanone (**7**) thus obtained is a versatile precursor of *cis*-1-amino-2-indanol (**8**) which is a key intermediate of chiral auxiliary and anti HIV protease inhibitor (**9**).

Keywords: Manganese and compounds; Oxidation; Asymmetric reaction; Alkanes.

Catalytic asymmetric oxidation of alkanes is one of the important topics in view of synthetic and industrial aspects. Cytochrome P-450 enzyme catalyzed oxidation of alkanes, and its model reactions using metalloporphyrin complexes have been extensively studied [1]. Asymmetric oxidation of alkanes still remains a challenging topic. In 1989, Groves *et al.* first reported enantioselective benzylic hydroxylation to give the corresponding alcohols (up to 72 %ee) using a chiral iron-porphyrin complex [2]. (Salen)manganese(III) complexes (Mn(salen)) have been used for the oxidation of alkanes to alcohols [3]. Recently, Katsuki *et al.* reported that asymmetric hydroxylation of alkylbenzenes [4] and cyclic ethers [5] using chiral Mn(salen) complexes afforded the corresponding alcohols up to 64% ee (29% yield) and 82% ee (59% yield), respectively.

We have disclosed that both ruthenium-catalyzed oxidation of alkanes with peroxides [6] and aerobic oxidation of alkanes with ruthenium, iron [7], copper [8], and manganese porphyrin [9] catalysts in the presence of aldehydes proceed highly efficiently to give the corresponding ketones with high turnover numbers. Mn(salen) and PhIO system was also used for benzylic oxidation to give the corresponding ketones [10]. On the line of our works, we have found that enantiotopic-place selective oxidation of symmetrical alkanes gave optically active ketones using chiral Mn(salen) catalysts [11](eq 1). This is, to the best of our knowledge, the first report on the asymmetric oxidation of alkanes to give optically active ketones bearing asymmetric center at the α–position.

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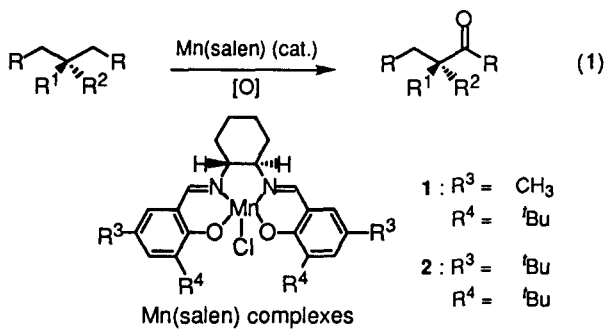
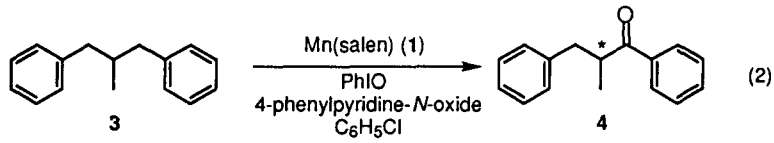


We selected 2-methyl-1,3-diphenylpropane (**3**) as a model compound. Desymmetrisation of compound **3** bearing two symmetrical benzylic positions should give optically active 2-methyl-1,3-diphenyl-1-propanone (**4**) (eq 2). Treatment of **3** with 4 equiv. of PhIO in the presence of 5 mol % of Mn(salen) and 0.5 equiv. of 4-phenylpyridine-*N*-oxide [12] in C_6H_5Cl at room temperature under argon gave **4**. Enantiomeric excess of **4** was determined to be 22% by HPLC analysis using a chiral column (CHIRALCEL OB–H, hexane / 2-propanol = 10 / 1). The effect of oxidants was examined with respect to the reaction of **3**. Peracetic acid



and NaClO can be used (12% ee and 18% ee, respectively). PhIO gave the best result (24 % yield, 22% ee). Other oxidants gave unsatisfactory results. When nonpolar solvents such as C_6H_5Cl and CH_2Cl_2 were used, asymmetry was induced; however, ethyl acetate retarded the reaction.

In view of organic synthesis, asymmetric oxidation of substrates bearing functional groups is particularly important. Indeed, this type of asymmetric oxidation can be applied to the oxidation of substrates bearing oxygen functional groups such as siloxy group (eq 3). Thus the oxidation of 2-*tert*-butyldimethylsiloxyindan (**5**) with PhIO in the presence of Mn(salen) catalyst ((*R*,*R*)-**1**) gave (*R*)-(–)-2-*tert*-butyldimethylsiloxy-1-indanone (**6**). The absolute configuration of **6** was determined after conversion to 2-hydroxy-1-indanone (**7**) [13].

The representative results of the asymmetric oxidation of **5** using various Mn(salen) catalysts are shown in Table 1. Ketone **6** was isolated as a main product (10-15% yield) along with small amounts of the corresponding alcohols, and the conversion of the reaction was 10-15%. The bulky ^{t}Bu groups of Mn(salen) complexes (**1**-**2**) retard the catalytic activity, although they are essential for the asymmetric induction. This shows limitation of Mn(salen) catalyzed oxidation of unactivated hydrocarbons [4][10], because dimerization of catalysts and oxidation of ligands occur under the reaction conditions. By using (*R*,*R*)-**2** complex bearing ^{t}Bu groups at the C5 and C5' positions, the enantioselectivity was improved to 41% ee (entries 1 and 2).

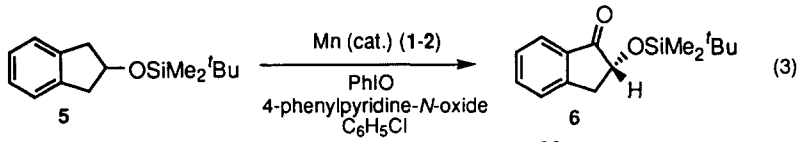


Table 1. Asymmetric Oxidation of 5 using Various Mn(salen) Catalysts.[a]

entry	catalyst	temp (°C)	yield (%)[b]	ee (%)[c]	Config.
1	(*R*, *R*) – **1**	rt	15	33	(*R*)
2	(*R*, *R*) – **2**	rt	11	41	(*R*)
3	(*R*, *R*) – **2**	40	13	70	(*R*)
4	(*S*, *S*) – **2**	40	10	67	(*S*)

[a]The reaction was carried out as described in the text. [b]Isolated yield. [c]Determined by HPLC analysis using a chiral column (CHIRALPAK AS, hexane / 2-propanol = 1000/2).

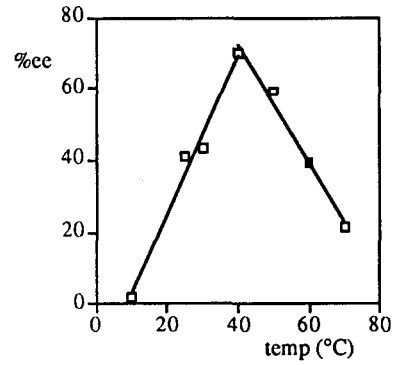
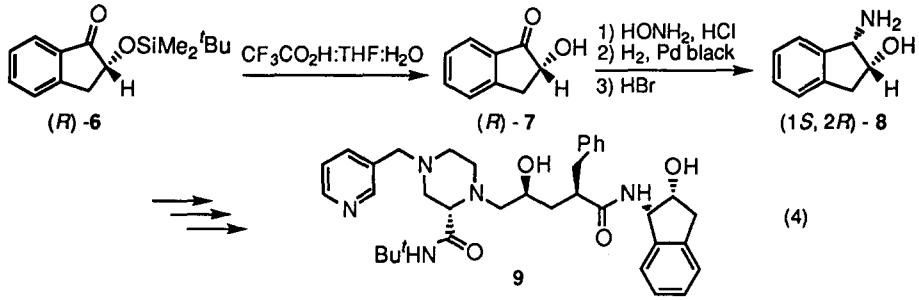


Figure 1. Temperature effect of asymmetric oxidation of 5 using (*R*, *R*)-Mn(salen) (2)

Remarkable temperature effect was observed as shown in Figure 1. Generally, enantioselectivity is improved by lowering reaction temperature; however, the present oxidation gave a maximum enantioselectivity (70% ee), when the reaction was carried out at 40 °C. The opposite enantiomer (*S*)-**6** was obtained by using Mn(salen) catalyst ((*S*,*S*)-**2**) (entry 4). There is a non-linear relationship between reaction temperature and enantioselectivity. This may be due to two main factors which are steric repulsion and chelation effect between the Mn=O species and the 2-siloxy group. The balance of these two factors which depend on the reaction temperature resulted in such an interesting non-linear relationship.

The typical experimental procedure is as follows. To a solution of **5** (52 mg, 0.21 mmol), Mn(salen) **2** (6.4 mg, 0.01 mmol), and 4-phenylpyridine-*N*-oxide (18 mg, 0.11 mmol) in C_6H_5Cl (1.5 mL) was added PhIO (176 mg, 0.84 mmol) with stirring at 40°C under argon. After stirring for an additional 4.0 h, the mixture was quenched by a 5% aqueous Na_2SO_3 solution and extracted with ethyl acetate. The combined organic layer was washed with H_2O and dried over Na_2SO_4, and the filtrate was evaporated. The residue was subjected to preparative TLC on silica gel (hexane – EtOAc = 3 : 1) to give **6** in 13% yield. Enantiomeric excess of **6** was determined to be 70% by HPLC analysis using a chiral column (CHIRALPAK AS, hexane / 2-propanol = 1000 / 2).

The optically active ketone **6** can be easily converted into optically active *cis*-(*1S*,*2R*)-1-amino-2-indanol (**8**) stereoselectively by protonation, oximation, and palladium catalyzed hydrogenation [14] (eq 4). This is the attractive method for the short step synthesis of *cis*-1-amino-2-indanol, which is a key intermediate for the synthesis of chiral auxiliaries [15] and various biologically active compounds such as anti HIV protease inhibitor components (L-735,524) (**9**) [16].



In conclusion, we have found the first direct oxidation of alkanes to optically active ketones using Mn(salen) complex catalysts. Work is in progress to provide definitive mechanistic information, and highly enantioselective catalytic oxidation will be explored.

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