Manganese-Catalyzed Oxidative Transformation of Silyl Ethers to Ketones: Enantioselective Synthesis of Optically Active β- and γ-Siloxyketones

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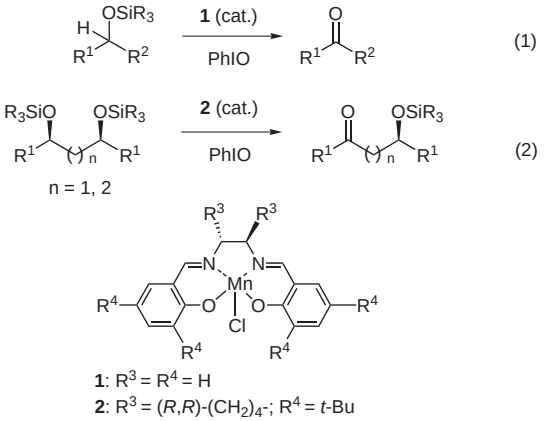
Abstract: (Salen)manganese(III)-catalyzed oxidation of silyl ethers with iodosylbenzene gave the corresponding carbonyl compounds. The enantioselective oxidation of symmetrical 1,3- and 1,4-disilyl ethers gave the corresponding optically active β- and γ-siloxyketones, respectively (up to 93% ee).

Key words: asymmetric oxidation, silyl ethers, manganese catalyst, iodosylbenzene, siloxyketones

The direct catalytic oxidative transformation of silyl ethers to carbonyl compounds is highly useful, because the conversion of silyl ethers to the corresponding carbonyl compounds is often used for organic synthesis and is usually carried out by two steps, that is, deprotection of silyl group and oxidation.[1] Although numerous stoichiometric methods have been reported,[2] the catalytic method reported is the chromiun-catalyzed oxidation of silyl ethers with *t*-BuOOH.[3] This method can be used only for less hindered substrates.[3] To develop a method for direct oxidation of silyl ethers, it is necessary to oxidize an α-C-H bond of silyl ether. We reported that non-activated C-H bonds of alkanes can be oxidized with catalytic systems[4] such as $RuCl_2(PPh_3)_3$/*t*-BuOOH,[5] Ru-C/CH_3CO_3H,[5a,6] $RuCl_3 \cdot nH_2O$/RCHO/O_2,[7] Fe/RCHO/O_2,[7] $Cu(OH)_2$/CH_3CHO/O_2,[8] $CuCl_2$–crown ether/CH_3CHO/O_2,[9] Ru-, Mn-, and Co-porphyrin/CH_3CHO/O_2[10] and Fe-phthalocyanine/CH_3CHO/O_2.[11] We have also reported the oxidative transformation of cyclic acetals of aldehydes to the corresponding carboxylic acid esters.[12]

We wish to report here a new catalytic method for oxidation of silyl ethers to the corresponding ketones using a (salen)Mn(III) complex catalyst [Scheme 1, (**1**)]. We also wish to report that the catalytic oxidation of silyl ethers can be applied to the enantioselective desymmetrization of disilyl ethers. Using chiral (salen)Mn(III) catalysts, enantioselective oxidation of symmetrical 1,3- and 1,4-disilyl ethers occurs efficiently to give the corresponding optically active β- and γ-siloxyketones, respectively [Scheme 1, (**2**)]. This is, to the best of our knowledge, the first report on the direct, catalytic enantioselective transformation of disilyl ethers to optically active β- or γ-siloxyketones, which are important intermediates for the synthesis of biologically active compounds.[13] Oxidative desymmetrization reactions of symmetrical substrates are highly useful, and hence enantioselective, catalytic oxidations of symmetrical alkanes,[14] *meso*-tetrahydrofuran,[15] *meso*-pyrrolidine,[16] and *meso*-diols[17] have been reported.



Scheme 1

We found that (salen)Mn(III) is an efficient catalyst for the oxidation of silyl ethers. Treatment of benzylic silyl ethers with iodosylbenzene in the presence of achiral (salen)Mn(III) complex **1** in MeCN at 25 °C under argon gave the corresponding ketones efficiently. The representative results of the oxidation of silyl ethers using **1** are shown in Table 1. The trimethylsilyl (TMS) ether of 1-phenyl ethanol is readily oxidized to acetophenone (entry 1). Importantly, the oxidation of the hindered *tert*-butyldimethylsilyl (TBDMS) ether also proceeds with high conversion (entry 2), while the chromium-catalyzed oxidation is not effective for the oxidation of the TBDMS ether.[3] The oxidations of the substituted benzylic silyl ethers (*p*-methyl, *p*-methoxy, *p*-chloro) gave the corresponding ketones in high yields (entries 3–5). Diphenylmethyl silyl ether can be converted to benzophenone efficiently (entry 6). The minor products of the reaction mixture could not be identified because of a small amount.

We next examined the enantioselective oxidation of symmetrical disilyl ethers using a chiral (salen)Mn catalyst. Asymmetric oxidative desymmetrization of *cis*-1,3-disiloxyindane (**3**) bearing two silyl ethers using a chiral

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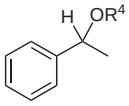
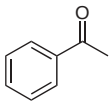
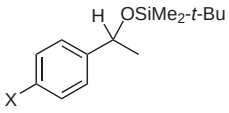
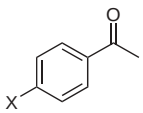
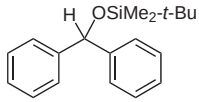
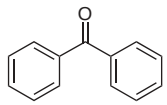
Table 1 Catalytic Oxidation of Silyl Ethers Using (salen)Mn(III) (**1**)[a]

Entry	Substrate	Product	Conv. (%)[b]	Yield (%)[c]
				
1	$R^4 = SiMe_3$		84	81
2	$R^4 = SiMe_2t\text{-}Bu$		80	81
				
3	X = OMe		91	71
4	X = Me		87	61
5	X = Cl		78	85
6			83	91

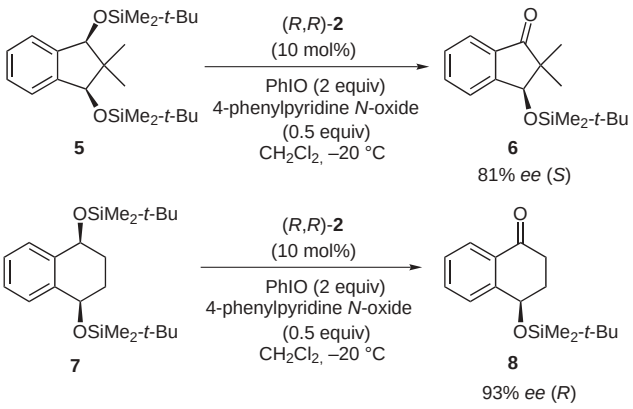
[a] A mixture of substrate (0.10 mmol), (salen)Mn(III) **1** (0.015 mmol), PhIO (0.40 mmol), and MeCN (1.0 mL) was stirred at r.t. for 6 h.
[b] Determined by GLC analysis based on the starting substrate using an internal standard.
[c] Determined by GLC analysis based on the converted substrate.

(salen)Mn complex catalyst gives the corresponding optically active 3-siloxy-1-indanone (**4**). The representative results of the enantioselective oxidation of **3** are shown in Table 2.

The oxidation of *cis*-1,3-di(*tert*-butyldimethylsiloxy)indane (**3a**) with iodosylbenzene in the presence of (*R*,*R*)-**2**[18] catalyst gave siloxyketone **4a** with 57% ee (*R*, entry 1). The absolute configuration of **4a** was assigned in comparison with the reported optical rotation value after converting to 3-hydroxy-1-indanone.[13] The addition of 4-phenylpyridine *N*-oxide as an axial ligand of the catalyst improved both the conversion and the enantioselectivity (entry 2).[19] When the reactions were carried out at lower temperatures such as 0 °C and –20 °C, the enantioselectivities of **4a** were improved to 78% ee and 89% ee, respectively (entries 3–5). The effect of the silyl group is remarkable. The asymmetric oxidation of less hindered trimethylsilyl (TMS) derivative **3b** gave the product **4b** with lower enantioselectivity (49% ee, entry 6). On the other hand, the oxidations of the substrates bearing sterically bulky triisopropylsilyl (TIPS) and *tert*-butyldiphenylsilyl (TBDPS) groups are not effective. The oxidation of non-protected *cis*-1,3-indandiol (**3c**) was examined using (*R*,*R*)-**2** catalyst at 0 °C (entry 7). The enantioselectivity of 3-hydroxyindane-1-one (**4c**) was 51% ee, which is lower than (78% ee) that of **4a** (entry 4).

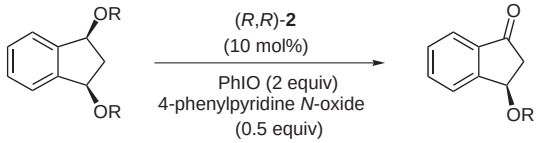
The siloxy groups and their size have considerable influence for the improvement of the enantioselectivity, and *tert*-butyldimethylsiloxy group is the most suitable for the present asymmetric oxidation reaction. The oxidative desymmetrization of other substrates also proceeds with high enantioselectivity (Scheme 2).

The oxidation of *cis*-1,3-di(*tert*-butyldimethylsiloxy)-2,2-dimethylindane (**5**) at –20 °C gave the siloxyketone **6** with 81% ee (*S*, conversion 5%).[20] Furthermore, the oxidation of *cis*-1,4-di(*tert*-butyldimethylsiloxy)tetraline (**7**) gave **8** with 93% ee (*R*, 15%).[21] The chiral 3-siloxyindanone **6** and 4-siloxytetralone **8** obtained can be readily converted to the corresponding chiral 3-hydroxyindanone and 4-hydroxytetralone, respectively. The chiral 3-hydroxyindanone unit is found in the natural product such as indatraline,[22] while the chiral 4-hydroxytetralone unit is present in biologically active compounds such as cataponol,[23] isoshinanolone,[24] and palmarumycin CP_4.[25]



Scheme 2

Table 2 Enantioselective Oxidation of 1,3-Disiloxyindanes Using (*R*,*R*)-**2** Catalyst[a]



R = $SiMe_2$-*t*-Bu (**3a**)
= $SiMe_3$ (**3b**)
= H (**3c**)

4a–c

Entry	Substrate	Additive[b]	Temp (°C)	Conv. (%)[c]	Ee (%)[d]
1	**3a**	None	25	13	57 (*R*)
2	**3a**	4-PPN	25	24	66 (*R*)
3	**3a**	4-PPN	0	5	78 (*R*)
4[e]	**3a**	4-PPN	0	17	78 (*R*)
5[e]	**3a**	4-PPN	–20	8	89 (*R*)
6	**3b**	4-PPN	0	30	49[f] (*R*)
7	**3c**	4-PPN	0	19	51[g] (*R*)

[a] To a mixture of 1,3-disiloxyindane **3** (0.050 mmol), 4-phenylpyridine *N*-oxide (0.025 mmol), and (*R*,*R*)-**2** (0.0025 mmol) in CH_2Cl_2 (1.0 mL) was added PhIO (0.10 mmol). The mixture was stirred for 12 h.
[b] 4-PPN = 4-phenylpyridine *N*-oxide.
[c] Determined by GLC analysis based on the starting substrate using an internal standard.
[d] Determined by HPLC analysis using a chiral column (CHIRALPAK AD, hexane/2-propanol = 500:1).
[e] Reaction was carried out for 72 h.
[f] Determined by HPLC analysis using a chiral column (CHIRALPAK AS, hexane/2-propanol = 20:1).
[g] Determined by HPLC analysis using a chiral column (CHIRALPAK OB-H, hexane/2-propanol = 10:1).

To determine the rate-determining step of the reaction, the deuterium isotope effect was examined. The reaction rates were determined for the **1**-catalyzed oxidations of 1-phenylethyl *tert*-butyldimethylsilyl ether ($k_H = 1.2 \times 10^{-6}$ $M^{-1}s^{-1}$) and 1-deuterio-1-phenylethyl *tert*-butyldimethylsilyl ether ($k_D = 1.7 \times 10^{-7} M^{-1}s^{-1}$) with PhIO in dichloromethane at 10 °C under pseudo first order reaction conditions.[26] Kinetic isotope effect ($k_H/k_D = 7.1$) indicates that the C–H bond cleavage occurs in the transition state. The present oxidation might proceed via the following mechanism. The (salen)Mn(III) complex reacts with iodosylbenzene to give (salen)Mn(V)=O species, which undergoes the rate-determining hydrogen atom abstraction from a substrate[14,27] to generate α-siloxybenzyl radical intermediate and (salen)Mn(IV)-OH. Hydroxy ligand transfer from (salen)Mn(IV)-OH to the radical intermediate would give the corresponding α-siloxyalcohol and (salen)Mn(III) to complete the catalytic cycle.[14] The α-siloxyalcohol is rapidly converted to the corresponding ketones by elimination of the corresponding silanol under the reaction conditions. This was confirmed by the detection of *tert*-butyldimethylsilanol, which is identified by comparison with the authentic sample. The siloxy group plays an important role to improve the enantioselectivity by enhancing the steric effect between the siloxy group of the substrates and (salen)Mn catalysts.

In conclusion we developed a new method for direct oxidation of silyl ethers to the corresponding ketones using (salen)Mn(III) catalysts. The catalytic system can be applied to the enantioselective oxidative transformation of 1,3- and 1,4-disilyl ethers to the corresponding optically active β- and γ-siloxy ketones, respectively, with high enantioselectivity (up to 93% ee).

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