

A Green Protocol for Asymmetric Epoxidation of Olefins Catalyzed by Carbon Dioxide Soluble Chiral Salen-Mn(III) Complexes in Supercritical CO₂

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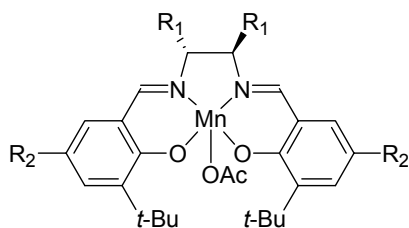
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Present in industry, one of the major challenges for chemists is to develop processes that fulfill the environmental, economical and social goals of green chemistry.¹ The application of supercritical fluids as a solvent in various areas of chemical processes, such as HPLC analysis and a crystallization process, has received much attention over the last decade because of the potential advantage that this technology offers over traditional organic solvents.^{2,3} Especially, supercritical CO₂ (scCO₂) has been widely tested because CO₂ is abundant, cheap, non-toxic and neither combustible nor explosive. Further, it has been successfully demonstrated that organic reaction⁴ can be performed in scCO₂.

We have been interested in using scCO₂ as a reaction solvent because it may provide a different reactivity compared with common organic solvents. In particular, we wanted to perform the asymmetric epoxidation of olefins catalyzed by chiral Salen-Mn(III) complex in scCO₂ to test the potential of scCO₂ as a solvent. Since the Salen-Mn(III) catalyzed epoxidation⁵⁻⁶ has been recognized as one of the most useful reactions to synthesize chiral epoxides,⁷⁻⁹ which are versatile synthetic intermediates for the syntheses of biologically and pharmaceutically important molecules, with high levels of enantioselectivity, it will be interesting to see the effect of scCO₂ to the enantioselectivity of the reaction.

To study the asymmetric epoxidation in scCO₂, a chiral Mn-complex which may be soluble in scCO₂ has to be prepared. It is well known that a perfluorinated alkyl group increases the solubility of organic compounds in scCO₂.¹⁰ Thus, we decided to prepare perfluorinated Salen-Mn(III) complexes and found that Salen-Mn(III) complexes such as **1** and **2** were already reported by Pozzi's group.¹¹ The **1** and **2** contain the sterically hindered *t*-butyl group at C3 and C3' positions that is required to obtain the high degree of enantioselectivity in chiral



R₁ = -(CH₂)₆-, R₂ = -(CF₂)₇CF₃ : (*R,R*)-**1**
R₁ = Ph, R₂ = -(CF₂)₇CF₃ : (*R,R*)-**2**
R₁ = -(CH₂)₆-, R₂ = -*t*-Bu : (*R,R*)-**3**

Salen-Mn(III) complex catalyzed epoxidations of alkenes,¹² and the perfluorinated alkyl group at C5 and C5' position.

The solubility of Salen-Mn(III) complexes **1**, **2** and metal free ligand (**4**) of complex **1** prepared according to the literature procedure¹¹ in supercritical CO₂ was studied and the results were presented in the Figure 1. As shown in the figure, Salen ligand **4** showed a good solubility in CO₂ at below 100 bar and 40 °C. At 60 °C, a higher CO₂ pressure was required to dissolve the ligand. The solubility of Salen-Mn(III) complexes was found to be low compared with Salen ligand **4**. However, both complexes **1** and **2** were soluble in CO₂ at 250 bar and 40 °C. Based on these solubility data, the epoxidation of olefins was performed at 250 bar and 35 °C. Since the enantioselectivity obtained in a catalytic asymmetric reaction is increased, in general, at a low reaction temperature, 35 °C instead of 40 °C was used as the reaction temperature.

Initially, we studied the epoxidation of styrene (1 eq) with PhIO (2 eq) in the presence of 5 mol% of **1** in a 10 mL view cell, at 35 °C and 250 bar pressure in supercritical CO₂ (Table 1). Styrene oxide was obtained in 66% yield with 21% ee. (entry 1).

When the iodosylbenzene was increased up to 4 equivalents

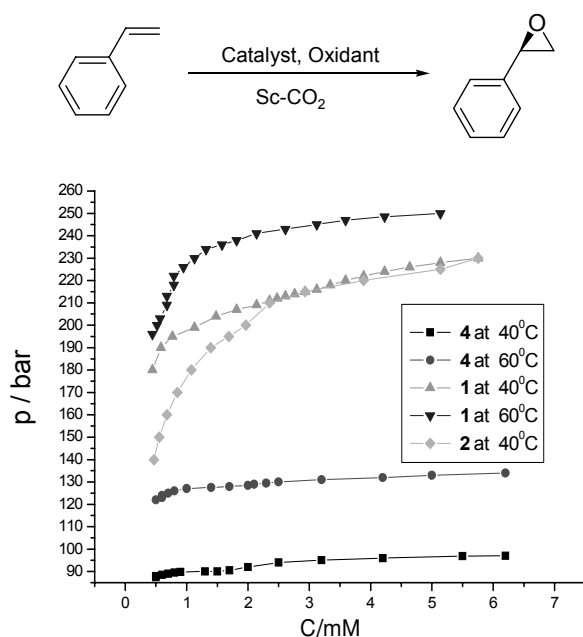


Figure 1. Solubility of salen ligand **4**, salen metal complexes **1** and **2** in CO₂.

Table 1. Epoxidation of styrene at various amounts of oxidant and chiral salen-Mn(III) catalysts in scCO₂.

Entry	Catalyst (mol%)	Oxidant (eq)	Time (hr)	Yield ^a (%)	% ee ^b
1	(<i>R,R</i>)- 1 (5)	PhIO (2)	5	66	21(<i>R</i>) ^c
2	(<i>R,R</i>)- 1 (5)	PhIO (4)	5	100	21(<i>R</i>)
3	(<i>R,R</i>)- 2 (5)	PhIO (2)	5	27	27(<i>R</i>)
4	(<i>R,R</i>)- 2 (5)	PhIO (4)	5	31	27(<i>R</i>)
5	(<i>R,R</i>)- 2 (10)	PhIO (4)	5	57	27(<i>R</i>)
6	No catalyst	PhIO (4)	5	0	-
7	(<i>S,S</i>)- 3 (5)	PhIO (4)	5	29	3(<i>S</i>)

^aGC yields. ^bDetermined by GC with Supelco chiral β-dex 325 column. ^cAbsolute configuration of major isomer was assigned according to the literature procedure.

to styrene, the yield was improved significantly (entry 2), however, without any effect on the enantioselectivity. The enantioselectivity was slightly improved when a sterically hindered catalyst **2** was used as the catalyst (entry 3-5). However, the enantioselectivity was remained even though the catalyst amount was increased to 10 mol% (entry 5). The same result was observed even in the presence of 4-phenylpyridine *N*-oxide as an additive. Low yield and enantioselectivity was obtained with Jacobsen's catalyst **3** (entry 7) which may be due to the insolubility of this catalyst in supercritical CO₂. The epoxide was not produced without the catalyst under the same reaction condition (entry 6). The reaction was not proceeded when H₂O₂ was used as oxidant, even in the presence of additives such as NMO and *N*-methylimidazole.

Encouraged by the styrene results, we examined the reaction with several olefins under the optimized conditions¹³ (Table 2). In the epoxidation of *cis*-β-methylstyrene, *cis*-β-methylstyrene oxide of 47% ee was obtained (entry 1). However, a large amount of *trans*-epoxide was also produced (*cis/trans*-epoxide = 3.2) in the reaction. The result was not improved even with catalyst **2** (entry 2). The epoxidations of 1,2-dihydronaphthalene and indene also produced their epoxides with 38-46% ee. The enantioselectivities are slightly improved when a sterically hindered catalyst **2** was used as the catalyst compared with catalyst **1**.

Overall, the moderate enantioselectivity values were obtained in scCO₂, and these values are slightly lower than the result with organic solvent.^{12,14} However, our attempts made us to proceed to a clean and green method. Another important feature of this procedure is the stability of a variety of epoxides under these reaction conditions. Epoxides did not react with CO₂ and were isolated after completion of the reaction. This procedure not only preserves the simplicity of this reaction but also produces chiral epoxides in good yields with moderate % ee values.

In summary, we demonstrated that the perfluorinated chiral Salen-Mn(III) complexes were soluble in scCO₂ and served as efficient catalysts in the asymmetric epoxidation of olefins with PhIO in scCO₂. This result revealed the great potential of supercritical CO₂ as a green solvent and was, to our knowledge, the first report regarding the catalytic enantioselective epoxidation of olefins in scCO₂.

Table 2. Chiral salen-Mn(III) complexes catalyzed PhIO (4 eq.) epoxidations of olefins in supercritical carbon dioxide.

Entry	Substrate	Catalyst (mol%)	Yield ^a (%)	% ee ^b (config) ^c
1	<i>Cis</i> -β-methylstyrene	1 (5)	100(3.2) ^d	47(<i>R,S</i>)
2	<i>Cis</i> -β-methylstyrene	2 (10)	60(3.2) ^d	47(<i>R,S</i>)
3	1,2-Dihydronaphthalene	1 (5)	100	38(1 <i>R</i> ,2 <i>S</i>)
4	1,2-Dihydronaphthalene	2 (10)	71	45(1 <i>R</i> ,2 <i>S</i>)
5	Indene	1 (5)	100	43(<i>R,S</i>)
6	Indene	2 (10)	68	46(<i>R,S</i>)
7	2,2-Dimethyl-2H-chromene	1 (5)	No ^e	--

^aGC yields. ^bDetermined by GC with Supelco chiral β-dex 325 column. ^cAbsolute configuration was assigned according to the literature procedure. ^d*cis/trans*-epoxide ratio. ^eEpoxide was decomposed.

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- The general procedure used for the epoxidation reactions is as follows: To a 10 mL high pressure view cell, olefin (0.5 mmol), internal reference (mesitylene), PhIO (4 eq) and 5 - 10 mol % of catalyst were added. Then, CO₂ was injected to the view cell. The mixture was stirred at 35 °C and 250 bar pressure for 5 hr (entries 1-10). After completion of reaction, the high pressure was released. The product was extracted with methylene chloride, washed by aqueous sodium bisulfite and the organic phase was dried over MgSO₄ and concentrated in vacuo giving a residue which was subjected to analysis using GC.
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