Stereoselective Preparation of α-Hydroxycarboxamide by Manganese Complex Catalyzed Hydration of α,β-Unsaturated Carboxamide with Molecular Oxygen and Phenylsilane

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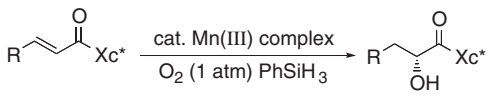
Aerobic oxidation with the combined use of phenylsilane and a manganese complex catalyst was successfully applied to the α,β-unsaturated carboxamide containing a C_2-symmetrical chiral auxiliary to afford the corresponding α-hydroxycarboxamide in good-to-high yield with high stereoselectivity.

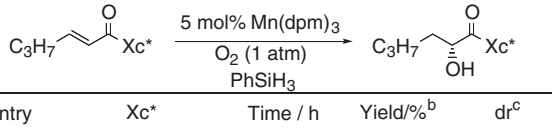
As molecular oxygen is abundant and a ubiquitous oxidant on the earth, much effort has been made to develop efficient aerobic oxidation systems involving various metal complex catalysts. From the view points of green chemistry as well as economic considerations, catalytic aerobic oxidations have been desired as some of the most environmentally benign systems and various kinds of metal complex catalysts have been extensively subjected to various types of aerobic oxidation such as epoxidation,[1] phenol synthesis,[2] the Baeyer–Villiger reaction,[3] alcohol oxidation,[4] dihydroxylations,[5] etc. In biomimetic oxidation systems, the iron porphyrin complexes, e.g., P450 cytochrome, were employed as the catalyst for aerobic oxidation combined with appropriate reductants; e.g., NADPH or NADH.[6] It was reported that a variety of reductants such as 2-propanol,[7] triethylsilane,[8] phenylsilane,[9] or aldehyde[10] has been used with molecular oxygen for the oxidation of carbon–carbon double bonds to obtain epoxides and hydrated products in good-to-high yields. In the presence of a catalytic amount of a manganese(II) complex with phenylsilane, the α,β-unsaturated carbonyl compounds were regioselectively hydrated to afford the corresponding α-hydroxy carbonyl compounds with molecular oxygen,[9b] though the stereoselective aerobic hydration with reducing equivalents still remains to be developed including the enantioselective and diastereoselective versions. Since optically active α-hydroxycarboxylates can be found in various natural products and also employed for their total synthesis, preparative methods have been reported.[11] The stereoselective oxidation of the corresponding enolates has also been examined,[12] however, few reports were found about the direct synthesis of α-hydroxycarboxylates with molecular oxygen. It was reported that the stereoselective α-hydroxylation of α-iodocarboxylates using a chiral auxiliary, such as oxazolidinone or Oppolzer's camphorsultam derivative with molecular oxygen, occurred although a low stereoselectivity was observed because of the high reactivity of the enolate radical with molecular oxygen.[13] As a part of our continuing effort to develop the stereoselective preparation of α-hydroxycarboxylates, we now report an aerobic oxidation system that was successfully applied to the α,β-unsaturated carboxamides containing the C_2-symmetrical chiral auxiliary to afford the corresponding α-hydroxycarboxylates with high stereoselectivity (Scheme 1).

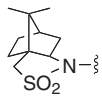
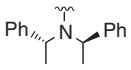
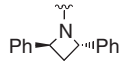
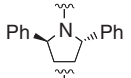
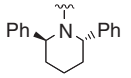
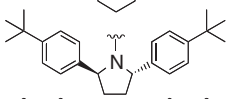
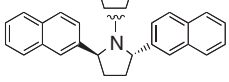


Scheme 1. Stereoselective preparation of α-hydroxycarboxylates.

Various chiral auxiliaries were examined for the oxidative hydration of *trans*-2-hexenoates (Table 1).[14] The reaction was carried out at the atmospheric pressure of oxygen in the presence of the 5 mol% tris(dipivaloylmethanato)manganese(III) complex[15] and phenylsilane in 2-propanol at 0 °C. The optically active oxazolidinones, such as (*R*)-4-phenyl- and (*R*)-4,5,5-triphenyl-2-oxazolidinones, were used in the hydration to obtain the corresponding α-hydroxycarboxylates but the diastereoselection was not observed (Entries 1 and 2). The camphorsultam developed by Oppolzer[16] was employed as a chiral auxiliary and the diastereoselectivity was improved to 70:30 (Entry 3). The C_2-symmetrical chiral auxiliaries were then screened. *trans*-2-hexenamide derived from (*R*,*R*′)-bis(1-phenylethyl)amine was smoothly transformed into the corresponding α-hydroxycarbox-

Table 1. Various chiral auxiliaries for the stereoselective oxidation of *trans*-2-hexenoates with molecular oxygen[a]



Entry	Xc*	Time / h	Yield/%[b]	dr[c]
1	 R = H	3	quant.	56:44
2	 R = Ph	2	99	51:49
3		1	quant.	70:30
4		11	91	62:38
5		2	quant.	73:27
6		2	79	84:16
7		2	82	74:26
8		7	quant.	85:15
9		7	77	90:10

[a]Reaction conditions : 5 mol% of tris(dipivaloylmethanato)manganese(III) complex ($Mn(dpm)_3$), 0.5 mmol of α,β-unsaturated carboxylate and 1.0 mmol of phenylsilane in 2-propanol at 0 °C under O_2 atmosphere. [b]Isolated yield. [c]Determined by ^1H NMR analysis.

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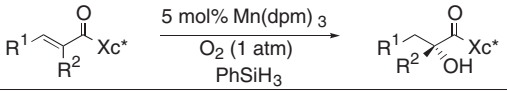
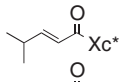
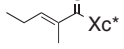
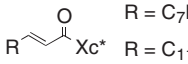
amide with moderate stereoselectivity (Entry 4). The C_2-symmetrical diphenyl-azetidine, -pyrrolidine, and -piperidine were subjected to aerobic hydration, and it was found that the pyrrolidine-type auxiliary improved the diastereoselectivity to 86:14 (Entries 5–7). In a previous communication, the efficient preparation of the optically pure C_2-symmetrical cyclic amines with bulky aryl groups was reported.[17] Thus, the obtained (2*S*,5*S*)-2,5-bis(4-*tert*-butylphenyl)pyrrolidine or (2*S*,5*S*)-2,5-bis(2-naphthyl)pyrrolidine were employed as C_2-auxiliaries. The corresponding α-hydroxycarboxamide was obtained in 85:15 selectivity (Entry 8). During the reaction of *trans*-2-hexenoate with 2,5-bis(2-naphthyl)pyrrolidine, molecular oxygen was stereoselectively introduced to afford the α-hydroxylated product (diastereomer ratio 90:10, Entry 9).

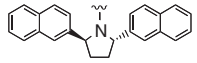
Various alkenoates containing (2*S*,5*S*)-2,5-bis(2-naphthyl)-pyrrolidine as a chiral auxiliary were successfully applied to the stereoselective oxidative hydration reaction (Table 2). The 4-methyl-2-pentenoate was hydrated to the corresponding 2-hydroxycarboxyate in 78:22 selectivity (Entry 1). The 2-methyl-2-pentenoate was smoothly converted to the 2-hydroxylated compound without any contamination of the 3-hydroxylated product (Entry 2). During the hydration reaction of the straight-chain alkenoates, the 2-hydroxylated products were obtained with high diastereoselectivities. The long straight-chain alkenoate, such as 2-undecenoate and 2-pentadecenoate, were converted to the corresponding hydrates in 96:4 and 97:3 diastereoselectivities, respectively. The absolute configuration of the obtained product was determined by ^{1}H NMR analysis along with the authentic sample of α-hydroxycarboxamide derived from commercially available (*S*)-leucic acid. These experiments revealed that (*R*)-α-hydroxycarboxamide was obtained in the reaction of alkenoate containing (2*S*,5*S*)-2,5-diarylpyrrolidine as the chiral auxiliary. It is assumed that the hydrogen atom of phenylsilane was activated by the manganese(III) complex catalyst and added to the β-position of the α,β-unsaturated carbonyl compounds to generate the α-radical intermediate[9b,18] stabilized by the carbonyl group. The α-radical intermediate would capture molecular oxygen and then reduction with phenylsilane afforded the α-hydroxylated carboxylates. It was reported that the amide carbonyl is located opposite to the α-radical in the α-(*N*,*N*-dimethylamidocarbonyl)ethyl radical.[19] Based on these considerations, molecular oxygen would approach the α-radical intermediate as depicted in Scheme 2 to afford (*R*)-hydroxycarboxylate corresponding to the (*S*,*S*)-pyrrolidine auxiliary whereas another face of α-radical would be effectively shielded by the bulky 2-naphthyl group.

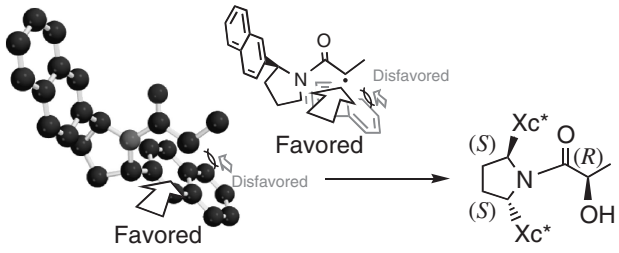
Table 2. Various α,β-unsaturated compounds[a]



Entry	Substrate	Time	Yield /%[b]	dr[c]
1		10 d	62	78:22
2		9 h	84	86:14
3	R = C_3H_7	7 h	77	90:10
4	 R = C_7H_{15}	7 h	87	91:9
5	R = $C_{11}H_{23}$	17 h	81	96:4
6	R = $C_{15}H_{31}$	17 h	81	97:3

[a]Reaction conditions: 5 mol% of tris(dipivaloylmethanato)manganese(III) complex (Mn(dpm)$_3$), 0.5 mmol of α,β-unsaturated carboxylate and 1.0 mmol of phenylsilane in 2-propanol at 0 °C under O_2 atmosphere. [b]Isolated yield. [c]Determined by ^{1}H NMR analysis.

Xc* = 



Scheme 2. Plausible explanation for the stereoselection.

It is noted that the α-hydroxycarboxamide was directly produced in high stereoselectivity and high yield from the α,β-unsaturated carboxamide containing (2*S*,5*S*)-2,5-bis(2-naphthyl)-pyrrolidine as the chiral auxiliary upon treatment with molecular oxygen and phenylsilane in the presence of a catalytic amount of the tris(dipivaloylmethanato)manganese(III) complex.

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14 Typical procedure: To a solution of Mn(dpm)$_3$ (15.1 mg, 0.025 mmol) in 2-propanol (1 mL) was added the α,β-unsaturated carboxamides (Table 1, Entry 6) (159.7 mg, 0.5 mmol) in 2-propanol (1.5 mL) at 0 °C under an oxygen atmosphere, and then $PhSiH_3$ (123 μL, 1.0 mmol) was added to the solution. After stirring for 2 h at 0 °C, the reaction was quenched with saturated aqueous $Na_2S_2O_3$. The organic materials were extracted with ethyl acetate, washed with brine and dried over Na_2SO_4. The crude product was purified by flash chromatography on silica gel to obtain the corresponding α-hydroxycarboxylates (125.7 mg, 79% yield, 84% stereoselectivity). The diastereomer ratio was determined by ^{1}H NMR analysis.
15 Mn(dpm)$_2$ gave the same results as Mn(dpm)$_3$, but because of the stability of the complex, Mn(dpm)$_3$ was used throughout the experiment.
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