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Chiral Mn-Salen Catalyzed Enantiotopic Selective C-H Oxidation of Meso-Pyrrolidine Derivatives

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Abstract: Asymmetric desymmetrization of *meso*-pyrrolidine derivatives was first effected by enantioselective oxidation of the C-H bond α to the nitrogen atom using Mn-salen complex 1b as a catalyst. © 1998 Elsevier Science Ltd. All rights reserved.

Enantiotopic selective catalytic oxidation of C-H bond is a current topic in organic synthesis, and moderate to good enantioselectivities have been observed in the asymmetric oxidation of benzylic¹ and allylic² C-H bonds. On the other hand, desymmetrization of symmetrical compounds such as *meso*-compounds by enantiotopic selective catalytic oxidation of C-H bond is an important strategy for creating new chiral centers. Recently, we have found that (salen)manganese(III) complex **1a** (hereafter abbreviated as Mn-salen complex) is an excellent catalyst for the desymmetrization of prochiral symmetrical cyclic ethers to afford synthetically useful optically active lactones.³ This protocol constitutes an appealing strategy to construct optically active molecules from readily available *meso*-compounds. Another advantage of the protocol is that multi-asymmetric centers can be simply constructed by single manipulation. This strategy should be applicable to other classes of *meso*-compounds and provide a useful tool for the synthesis of chiral heterocyclic compounds.



0040-4039/98/\$ - see front matter © 1998 Elsevier Science Ltd. All rights reserved. *PII:* S0040-4039(98)01810-3 To explore this possibility, we examined the oxidation of *meso*-pyrrolidine derivatives using Mn-salen complexes as catalyst (Eq. 1). Optimization of the catalyst and reaction conditions has led to the development of a useful protocol for the synthesis of optically active chiral lactams which serve as useful building blocks for many biologically important molecules.

Various meso-pyrrolidine derivatives were readily available.⁴ First, we examined the oxidation of Nbenzoyl-8-azabicyclo[4.3.0]nonane 2a as the test material using Mn-salen complex 1a in various solvents in the presence of a terminal oxidant, iodosylbenzene or pentafluoroiodosylbenzene. As expected, oxidation occurred preferentially at the carbon α to the nitrogen atom, affording optically active 2-hydroxypyrrolidine derivative 3a which was further oxidized by Jones reagent to provide chiral lactam 4a.⁵ Enantiomeric excess of 4a was determined by HPLC analysis (Table 1). Through these examinations, acetonitrile was found to be the solvent of choice (entry 7). The reaction with pentafuluoroiodosylbenzene showed the same enantioselectivity as that with iodosylbenzene, but the yield of 4 was better in the former reaction (entry 7). We next examined the reaction using a series of Mn-salen complexes 1a-e and found that complex 1b was the most suitable catalyst for the oxidation of pyrrolidine derivative 2a. Moderate enantioselectivity of 64% ee was obtained in the reaction at -25 °C (entry 9). It is also noteworthy that, in accord with desymmetrization of *meso*-furans, the (R,R)-complex 1b was proven to be better a catalyst for the present oxidation than the diastereometric (R,S)-complex 1e, which was an excellent catalyst for benzylic oxidation.^{1b}



3a

4a

2a Table 1. Desymmetrization of N-benzoyl-8-azabicyclo[4.3.0]nonane

Entry	Catalyst 1	Solvent	Temp. (°C)	Time (h)	Yield(%) ^{a,b}	ced
1	a	Chlorobenzene	rt	2	58	19
2	"		0	4	34	27
3	"		-20	12	41	33
4	н	Ethyl acetate	-20	12	27	4
5	**	Dichloromethane	-20	12	27	10
6	"	Acetone	-20	12	42¢	42
7		Acetonitrile	-20	14	43, 47 ^c	46
8	b	**	-20	12	43¢	61
9	"	н	-25	14	55°	64
10	с	н	-25	14	56 ^c	61
11	d		-25	14	41	29
12	e	н	0	4	37	5
13	н	н	-20	12	29	12

a) Carried out using 1 equivalent of iodosylbenzene as the terminal oxidant.

b) Isolated yield.

c) Pentafluoroiodosylbenzene was used as oxidant.

d) Determined by HPLC analysis using optically active column (DAICEL CHIRALCEL OD-H, hexane/isopropanol 9:1).

To ascertain the effect of amino-protecting groups on cnantioselectivity, we next examined the oxidation of a series of N-protected 8-azabicyclo[4.3.0]nonanes 2 with complex 1b and pentafluoroiodosylbenzene in acetonitrile (Table 2). Both 4-nitro- and 4-methoxybenzoylated 2 showed less selectivity, suggesting that the electronic effect did not play a major role in cnantioselection (entries 2 and 5). Then, we examined the oxidation of 2 protected with propionyl, naphthoyl, 4-chlorobenzoyl, 4-methylbenzoyl, phenylacetyl, (1naphthyl)acetyl and hydrocinnamoyl groups and found that good enantioselectivity of 76% ee was realized (at -27 °C) when N-phenylacetylpyrrolidine was the substrate (entry 8). Consistently, the oxidation took place chemoselectively on the carbon α to the nitrogen atom in the pyrrolidine ring as the major product along with *ca.* 10% of unidentified oxidized compounds (entries 7-10).



Table 2. Effect of N-Protecting groups								
Entry	R	Temp.(°C)	Time (h)	$Yield(\%)^{a,b}$	ecc			
1	Propionyl	-25	14	65	36d			
2	4-Nitrobenzoyl	"	14	42	43d			
3	4-Chlorobenzoyl	"	14	38	39d			
4	4-Methylbenzoyl	"	12	41	39d			
5	4-Methoxybenzoyl		12	37	28^d			
6	Naphthoyl	"	14	43	58 ^e			
7	Phenylacetyl	0	4	40	44 <i>e</i> ,f			
8	**	-27	14	65	76 ^{e,f,g}			
9	(1-Naphthyl)acetyl	-25	12	45	70eJ			
10	Hydrocinnamoyl	-25	12	42	42 ^e ,f			

a) Carried out in acetonitrile using 1 equivalent of pentafluoroiodosylbenzene as the terminal oxidant.

b) Isolated yield of 4.

c) The % ee of 4.

d) Determined by HPLC analysis using DAICEL CHIRALPAK AD column (hexane/isopropanol= 9:1).

e) Determined by HPLC analysis using DAICEL CHIRALCEL (D-H column (hexane/isopropanol= 9:1).

t) Accompanied with ~10 % of unidentified by-products.

g) Specific rotation of $4 : [\alpha]_D^{25} + 11.3^\circ (c \, 0.2, \text{CHCl}_3)$.



We also studied the oxidation of N-phenylacetyl protected 3,4-dimethyl pyrrolidine 5 and 7azabicyclo[3.3.0]octane 6 under the optimized reaction conditions. As above, the oxidation occurred chemoselectively to give the corresponding optically active hydroxypyrrolidine derivatives 5a and 6a which, on further oxidation with Jones reagent, provided chiral lactams $5b^6$ and 6b with good enantioselectivities (Scheme 1).

To determine the absolute configuration of 4, the phenylacetyl group was deprotected by treatment with aqueous LiOH to afford chiral lactam 7 in quantitative yield and its optical rotation was compared with the literature (Scheme 2).^{7,8}



Scheme 2

In conclusion, we have developed an efficient and useful synthetic methodology for the synthesis of optically active chiral lactams from *meso*-pyrrolidine derivatives by enantioselective C-H oxidation. Further study on this protocol is currently underway in our laboratory.

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- 2-Hydroxypyrrolidines (3a, 5a and 6a) could not be separated from the corresponding starting materials (2a, 5 and 6) and they were isolated as lactams (4a, 5b and 6b) after Jones oxidation. Unreacted starting material was recovered intact, except for the examples described in Table 2 (entries 7-10).
- 6. Pentafluoroiodosylbenzene (44.3mg, 0.14 mmol) was added in one portion to a precooled solution of *N*-phenylacetylated 3,4-dimethyl pyrrolidine 5 (31 mg, 0.14 mmol) and 1b (2.2mg, 2 mol%) in acetonitrile (2 ml) under nitrogen at -25 °C. After stirring 17 h, the reaction mixture was quenched by adding dimethyl sulfide and concentrated *in vacuo*. The residue was passed through a short column of silica gel (ethyl acetate/hexane= 2:3) to afford hydroxypyrrolidine derivative 5a which was further oxidized to lactam 5b by Jones reagent. After purification by silica gel column chromatography using ethyl acetate/hexane (1:4), the optical purity was determined to be 84% ee by HPLC using optically active column (DAICEL CHIRALPAK AD, hexane/isopropanol= 100:1).
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- Although the configurations of compounds 5b and 6b are unknown, they showed the same positive specific rotation as compound 4. Therefore, configurations of 5b and 6b were tentatively assigned as described in Scheme 1.