Pergamon

Tetrahedron Letters 39 (1998) 8295–8298

TETRAHEDRON LETTERS

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

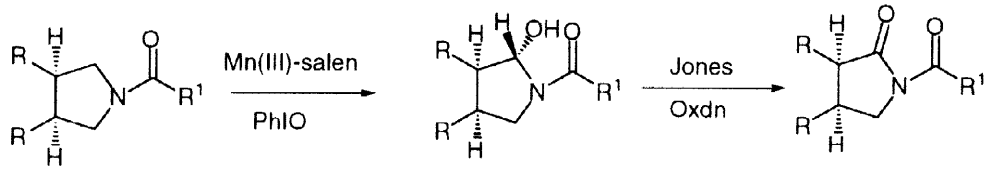
T. Punniyamurthy,† Akio Miyafuji, and Tsutomu Katsuki*

Department of Molecular Chemistry, Graduate School of Science, Kyushu University 33
Higashi-ku, Fukuoka 812-8581, Japan

Received 31 July 1998; revised 24 August 1998; accepted 28 August 1998

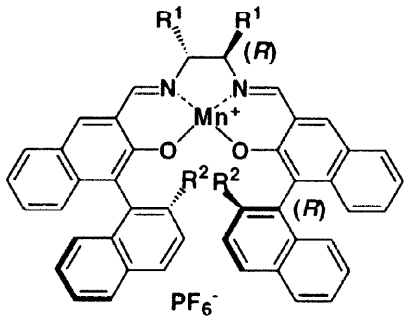
Abstract: Asymmetric desymmetrization of *meso*-pyrrolidine derivatives was first effected by enantioselective oxidation of the C-H bond α to the nitrogen atom using Mn-salen complex **1b** as a catalyst.

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 benzylic[1] and allylic[2] 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.

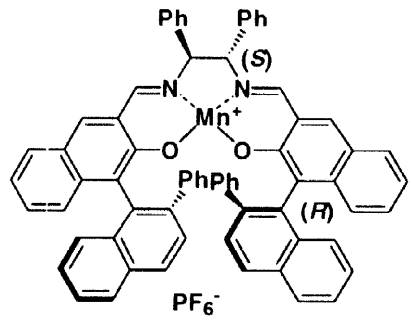


(Eq. 1)

R=Alkyl, R_1=alkyl, aryl



1



1e

a: R^1= -$(CH_2)_4$-, R^2= Ph

b: R^1= R^2=Ph

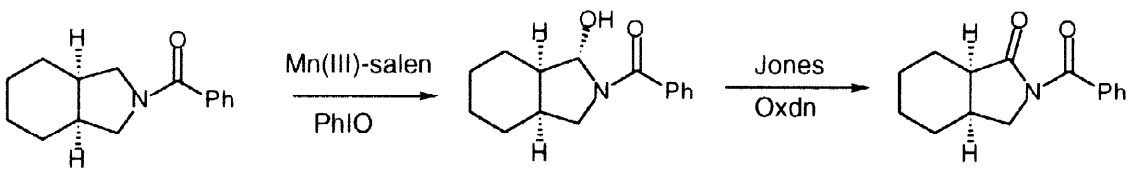
c: R^1= 3,5-$(Me)_2C_6H_3$-, R^2= Ph

d: R^1= Ph, R^2= 4-(TBDPS)C_6H_4-

0040-4039/98/$ - see front matter
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 *N*-benzoyl-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 diastereomeric (*R*,*S*)-complex **1e**, which was an excellent catalyst for benzylic oxidation.[1b]



2a **3a** **4a**

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

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

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

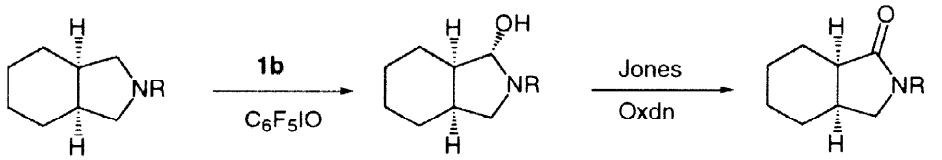
b) Isolated yield.

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 enantioselectivity, 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 enantioselection (entries 2 and 5). Then, we examined the oxidation of **2** protected with propionyl, naphthoyl, 4-chlorobenzoyl, 4-methylbenzoyl, phenylacetyl, (1-naphthyl)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).

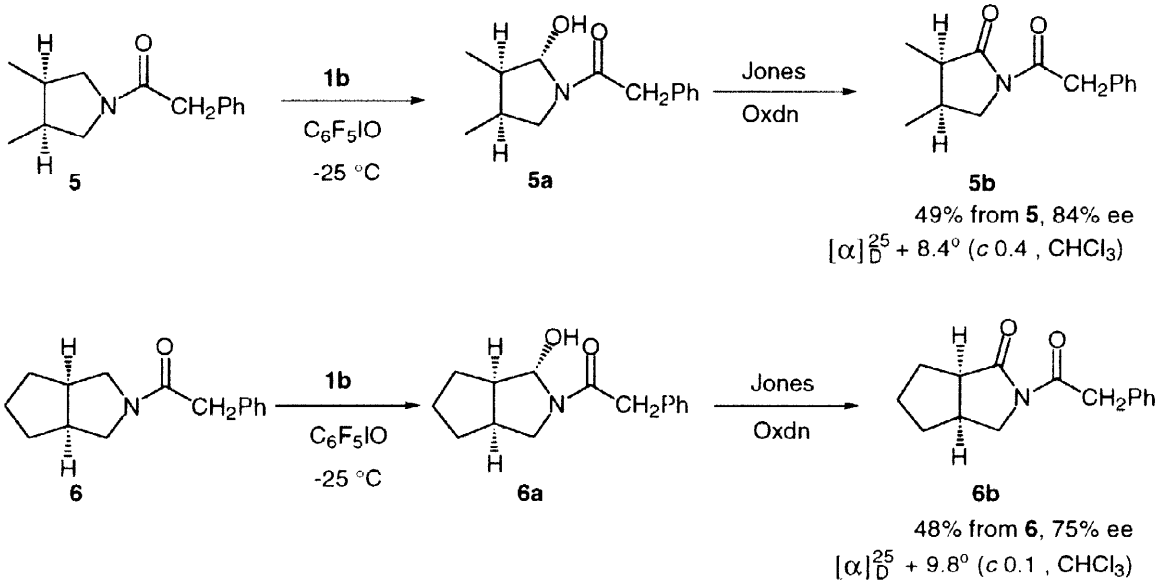


2 **3** **4**

Table 2. Effect of *N*-Protecting groups

Entry	R	Temp.(°C)	Time (h)	Yield(%)[a,b]	ee[c]
1	Propionyl	-25	14	65	36[d]
2	4-Nitrobenzoyl	"	14	42	43[d]
3	4-Chlorobenzoyl	"	14	38	39[d]
4	4-Methylbenzoyl	"	12	41	39[d]
5	4-Methoxybenzoyl	"	12	37	28[d]
6	Naphthoyl	"	14	43	58[e]
7	Phenylacetyl	0	4	40	44[e,f]
8	"	-27	14	65	76[e,f,g]
9	(1-Naphthyl)acetyl	-25	12	45	70[e,f]
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 OD-H column (hexane/isopropanol= 9:1).
f) Accompanied with ~10 % of unidentified by-products.
g) Specific rotation of **4** : $[\alpha]_D^{25}$ +11.3°(*c* 0.2, $CHCl_3$).

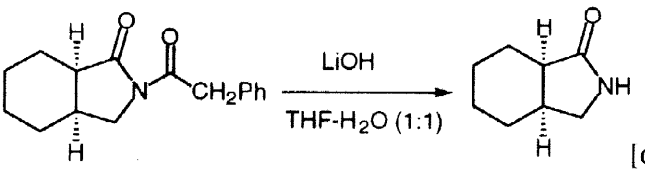


Scheme 1

We also studied the oxidation of *N*-phenylacetyl protected 3,4-dimethyl pyrrolidine **5** and 7-azabicyclo[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]



4 **7**

$[\alpha]_D^{25}$ -22.4° (*c* 0.25, $CHCl_3$)

$[\alpha]_D^{25}$ -24° (*c* 0.5, $CHCl_3$) (88% ee)[7]

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.

Acknowledgment: Financial support from a Grant-in-Aid for Scientific Research (No. 08245104) from the Ministry of Education, Science, Sports and Culture, Japan, and Asahi Glass Foundation is gratefully acknowledged.

References and Notes

† Postdoctoral Research Fellow of the Japan Society for the Promotion of Science.

1. a) Groves, J.T.; Viski, P. *J. Org. Chem.* **1990**, *55*, 3628-3634. b) Hamachi, K.; Irie, R.; Katsuki, T. *Tetrahedron Lett.* **1996**, *37*, 4979-4982. c) Hamada, T.; Irie, R.; Mihara, J.; Hamachi, K.; Katsuki, T. *Tetrahedron*, **1998**, *54*, 10017-10028.
2. a) Gohale, A.S.; Minidis, A.B.E.; Pfaltz, A. *Tetrahedron Lett.* **1995**, *36*, 1831-1834. b) Andrus, M.B.; Argade, A.B.; Chen, X.; Pamment, M.G. *Tetrahedron Lett.* **1995**, *36*, 2945-2948. c) Levina, A.; Muzart, J. *Tetrahedron : Asymmetry* **1995**, *6*, 147-156. d) Kawasaki, K.; Tsumura, S.; Katsuki, T. *Synlett*, **1995**, 1245-1246. e) Rispens, M.T.; Zondervan.; Feringa, B.L. *Tetrahedron: Asymmetry* **1995**, *6*, 661-664. f) Zondervan, C.; Feringa, B.L. *Tetrahedron : Asymmetry* **1996**, *7*, 1895-98. g) DattaGupta, A.; Singh, V.K. *Tetrahedron Lett.* **1996**, *37*, 2633-2636. h) Sodergen, M.J.; Andersson, P.G. *Tetrahedron Lett.* **1996**, *37*, 7577. i) Kawasaki, K.; Katsuki, T. *Tetrahedron* **1997**, *53*, 6337-6350.
3. a) Miyafuji, A.; Katsuki, T. *Synlett*, **1997**, 836-838. b) Miyafuji, A.; Katsuki, T. *Tetrahedron* , **1998**, *54*, 10339-10348.
4. Bettoni, G.; Cellucci, C.; Beradi, F. J. *Hetereocyclic Chem.* **1980**, *17*, 603.
5. 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).
7. Matsuki, K.; Inoue, H.; Ishida, A.; Takeda, M.; Nakagawa, M.; Hino, T. *Chem. Pharm. Bull.* **1994**, *42(1)*, 9-18.
8. 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.