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Oxidation of Hydroxylamines to Nitrones Catalyzed by (Salen)Mn(III) Complexes. Enantioselective Synthesis of a Protected *cis*-Dihydroxypyrroline *N*-Oxide with Jacobsen Catalyst

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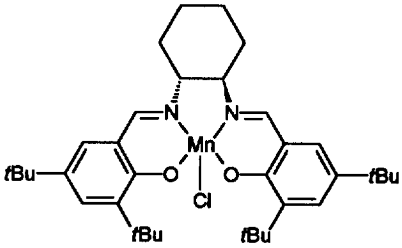
Abstract: Oxidation of *N,N*-disubstituted hydroxylamines to nitrones catalyzed by the Jacobsen catalyst occurs cleanly in the presence of hydrogen peroxide, sodium hypochlorite or iodosylbenzene as the stoichiometric oxidant. *Meso* 3,4-*cis*-isopropylidenedioxy-1-hydroxypyrrolidine gave the corresponding protected 3,4-*cis*-dihydroxypyrroline *N*-oxide in an enantioenriched fashion for the first time (up to 36% e.e.).

Keywords: Oxidation; Nitrones; Catalysis; Enantioselection

Recently, it has been demonstrated by Kochi and co-workers that cationic complexes of Mn(III) chelated by a salen ligand (*N,N'*-bis(salicylidene)ethylenediamine) are able to catalyze efficiently the epoxidation of alkenes by several oxidants, which transform the catalyst precursor into the active metal-oxo species.[1] A few years later, the enantioselective version of the reaction has been realized and developed, mainly by Jacobsen's[2] and Katsuki's[3] groups.[4] For this purpose, several metal salen complexes have been used, with C_2-symmetric ligands being among the most satisfying. The most popular complexes of this type are the so-called Jacobsen catalysts, i.e. the Mn(III) complex 1 and its enantiomer, which have become commercially available. Although the epoxidation of unfunctionalized olefins has been the most studied reaction involving these complexes, other organic compounds (cinnamates,[5] chromenes,[6] dienes,[7] enynes,[7a] sulfides,[8] alkylbenzenes,[9] tetrahydrofurans and pyrans[10]) have been subjected to oxidation catalyzed by (salen)Mn(III) derivatives. However, no report regarding the oxidation of nitrogen containing compounds has appeared, to the best of our knowledge. Being deeply involved in the chemistry of nitrones,[11] we are interested in developing new catalytic oxidation methodologies of amines[12] or hydroxylamines,[13] employing readily available reagents, which can avoid the use of toxic materials or expensive and not commercially available oxidants.[14] Moreover, we were interested in obtaininig a *cis*-dihydroxypyrroline *N*-oxide protected as a cyclic ketal, available up to now only in racemic form,[15,16] in an enantioselective manner for application to the synthesis of alkaloids and their analogues.[11a,17]



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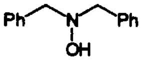
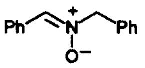
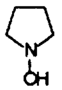
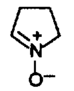
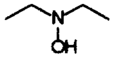
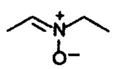
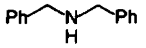
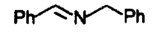
In this communication we report the use of the Jacobsen catalyst for the conversion of hydroxylamines to the corresponding nitrones by using H_2O_2, or UHP, NaClO, and PhIO as the stoichiometric oxidant. The enantioselectivity of the process is then studied in the oxidation of a *meso* hydroxypyrrolidine.

The results of oxidation of three representative hydroxylamines **2**, **4**, and **6** to the corresponding nitrones are reported in Table 1. UHP in MeOH (or 35% H_2O_2 in CH_2Cl_2) was used as the stoichiometric oxidant (1.5 equiv.) in the presence of catalytic amounts (5%) of the (*R*,*R*)-Jacobsen catalyst **1** at room temperature.[18] Reactions were always complete after 1 to 3 hours and the yields of purified nitrones were good and comparable with those obtained by known methods.[14] Therefore, (salen)Mn(III) complexes are very efficient in catalyzing the conversion of hydroxylamines into nitrones. The typical behavior of this catalyst as a metal-oxo derivative acting as a dehydrogenating agent has been proved also by the quantitative oxidation of dibenzylamine (**8**) to the imine **9** (Table 1, entry 4).

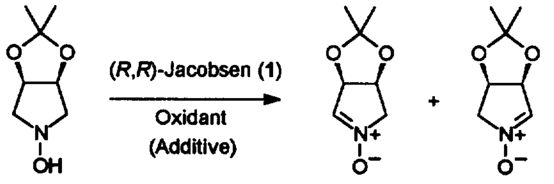
Table 1. Catalytic Oxidation of *N*,*N*-Disubstituted Hydroxylamines and Dibenzylamine with Jacobsen Catalyst and UHP in MeOH.[a]

Entry	Amine	Product	Yield (%)	Entry	Amine	Product	Yield (%)
1[b]	 **2**	 **3**	81	3[c]	 **6**	 **7**	70
2	 **4**	 **5**	60	4	 **8**	 **9**	100

[a] See ref. 18 for reaction conditions. [b] A reaction carried out in CH_2Cl_2 at rt for 6 h using 1.5 equiv. of 35% H_2O_2 as the oxidant gave a 84% yield of nitrone **3**. [c] Use of 3% of the Jacobsen catalyst gave the same results.

The results of the enantioselective oxidation of *meso cis*-dihydroxy substituted cyclic hydroxylamine **10** to the corresponding nitrone **11**,[19] implying an unprecedented enantiotopic discrimination, are reported in Table 2.[20] UHP, NaClO, PhIO have been employed as stoichiometric oxidants. The absolute configuration of the major nitrone (2*R*,3*S*, as shown in Table 2) has been assigned from a study of partial kinetic resolution on racemic **11** carried out in our laboratories.[21] Blank experiments have demonstrated that **10** is quite prone to oxidation at room temperature,[22] being converted also in absence of catalyst, albeit in longer times (entries 1,6 and 10). The maximum enantiomeric excess obtained by the catalyzed reaction at room temperature was 10% with any of the oxidants. However, competition of oxidation without involvement of the catalytic species can be highly detrimental to the obtained e.e.s, especially when NaClO is used; the same effect has been recently emphasized in the epoxidation of sterically hindered olefins.[23] Lowering the reaction temperature[24] may reduce this competition. The best results for each oxidant are highlighted in Table 2. 4-PPNO (4-phenylpyridine *N*-oxide), reported to increase the rate and selectivity of the catalyzed oxidation,[25] has been used as an additive in several runs (entries 5, 9, 12, 13). At 0 °C a good improvement in enantioselectivity was achieved with UHP (30% e.e., entry 3), in contrast to the other oxidants. Further lowering of the reaction temperature was, however, ineffective also with UHP, presumably due to reduced rate of the oxidation. The results with the use of 4-PPNO are somewhat contrasting. Its use brought a general increase in reaction rates and yields (entries 5, 9). However, the enantioselectivity of the reaction was improved slightly in the case of NaClO (entry 9) and much more with PhIO (entry 13), but decreased with UHP (entry 5) in spite of the lower reaction temperature. Finally, the use of the oxidizing mixture *m*CPBA/NMO, recently proposed by Jacobsen for alkene epoxidation,[24] allowed the reaction to run at an uniformly low temperature (entry 15), without interference from the uncatalyzed oxidation (entry 14), and gave the best observed enantioselectivity (36% e.e.).[26]

Table 2. Oxidation of *Meso* 3,4-*cis*-Isopropylidenedioxy-1-hydroxypyrrolidine Catalyzed by Jacobsen Catalyst.[a]



***meso*-10** **(2*R*,3*S*)-11 major** **(2*S*,3*R*)-11 minor**

Entry	Oxidant	Additive (equiv.)	Catalyst (%)	Solvent	T (°C)	Time (h)	Yield (%)	E.e. (%)
1	UHP	—	—	CH_3OH	rt	6	30[b]	—
2	UHP	—	5	CH_3OH	rt	3	42	10
3	**UHP**	**—**	**5**	**CH_3OH**	**0**	**28**	**45**	**30**
4	UHP	—	5	CH_3OH	-70→rt	16	25	30
5	UHP	4-PPNO (1.5)	5	CH_3OH	-70→-18	21	57	12
6	NaClO	—	—	CH_2Cl_2	rt	6	40	—
7	NaClO	—	3	CH_2Cl_2	0	0.5	39	10
8	NaClO	—	3	THF	-70	1.5	40	0
9	**NaClO**	**4-PPNO (0.2)**	**3**	**CH_2Cl_2**	**0**	**1**	**58**	**14**
10	PhIO	—	—	CH_2Cl_2	rt	20	39	—
11	PhIO	—	5	CH_3OH	0	2.5	40	0
12	PhIO	4-PPNO (1)	5	CH_3OH	-40	24	37	0
13	**PhIO**	**4-PPNO (1)**	**5**	**CH_2Cl_2**	**0**	**2.5**	**40**	**30**
14	*m*CPBA/NMO	—	—	CH_2Cl_2	-70	1	—	—
15	***m*CPBA/NMO**	**—**	**5**	**CH_2Cl_2**	**-70**	**1**	**25**	**36**

[a] Reactions carried out with UHP (1.5 equiv.), 3.5% NaClO (1.2 equiv.), PhIO (1.2 equiv.), or 70% *m*CPBA (2 equiv.)/NMO (5.6 equiv.) as oxidant. [b] Conversion was 50%.

The most addressed topic in enantioselective synthesis using (salen)Mn(III) complexes has been enantioface discrimination.[4] Enantioselective oxygenations of enantiotopic groups have also been studied in the oxidation of prochiral sulfides[8] and benzylic C-H bonds.[9a] A single precedent concerns, as in the present case, an enantiotopic group regioselective discrimination.[10,27] However, in that case an oxygenation reaction occurs, while the oxidation reported here is the first case of enantioselectivity induced by a chiral salen-metal catalyst in a dehydrogenation process.

The new oxidation method reported in this work, albeit only moderately enantioselective when applied to the hydroxylamine **10**, made available for the first time nitrone **11** enriched in principle in both enantiomeric forms. Further work is in progress in our laboratories in order to synthesize nitrones **11** enantiomerically pure.[16]

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REFERENCES AND NOTES

1. (a) Srinivasan, K.; Michaud, P.; Kochi, J. K. *J. Am. Chem. Soc.* **1986**, *108*, 2309-2320. (b) Srinivasan, K.; Perrier, S.; Kochi, J. K. *J. Mol. Catal.* **1986**, *36*, 297-317.
2. Zhang, W.; Loebach, J. L.; Wilson, S. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1990**, *112*, 2801-2803.
3. Irie, R.; Noda, K.; Ito, Y.; Katsuki, T. *Tetrahedron Lett.* **1991**, *32*, 1055-1058.
4. For recent reviews, see: (a) Jacobsen, E. N. In "Catalytic Asymmetric Synthesis", Ojima, I.; Ed.; VCH Publishers: New York, 1993, pp. 159-202. (b) Katsuki, T. *Coord. Chem. Rev.* **1995**, *140*, 189-214.
5. Jacobsen, E. N.; Deng, L.; Furukawa, Y.; Martínez, L. E. *Tetrahedron* **1994**, *50*, 4323-4334.
6. (a) Lee, N. H.; Muci, A. R.; Jacobsen, E. N. *Tetrahedron Lett.* **1991**, *32*, 5055-5058. (b) Adam, W.; Jekó, J.; Lévai, A.; Nemes, C.; Patonay, T.; Sebók, P. *Tetrahedron Lett.* **1995**, *36*, 3669-3672.
7. (a) Lee, N. H.; Jacobsen, E. N. *Tetrahedron Lett.* **1991**, *32*, 6533-6536. (b) Zhang, W.; Lee, N. H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1994**, *116*, 425-426. (c) Rasmussen, K. G.; Thomsen, D. S.; Jørgensen, K. A. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2009-2017.
8. (a) Palucki, M.; Hanson, P.; Jacobsen, E. N. *Tetrahedron Lett.* **1992**, *33*, 7111-7114. (b) Noda, K.; Hosoya, N.; Yanai, K.; Irie, R.; Katsuki, T. *Tetrahedron Lett.* **1994**, *35*, 1887-1890. (c) Kokubo, C.; Katsuki, T. *Tetrahedron* **1996**, *52*, 13895-13900.
9. (a) Hamachi, K.; Irie, R.; Katsuki, T. *Tetrahedron Lett.* **1996**, *37*, 4979-4982. (b) Lee, N. H.; Lee, C.-S.; Jung, D.-S. *Tetrahedron Lett.* **1998**, *39*, 1385-1388.
10. Miyafuji, A.; Katsuki, T. *Synlett* **1997**, 836-838.
11. See for example: (a) Goti, A.; Fedi, V.; Nannelli, L.; De Sarlo, F.; Brandi, A. *Synlett* **1997**, 577-579. (b) Anichini, B.; Goti, A.; Brandi, A.; Kozhushkov, S. I.; de Meijere, A. *Synlett* **1997**, 25-26. (c) Cardona, F.; Valenza, S.; Picasso, S.; Goti, A.; Brandi, A. *J. Org. Chem.* **1998**, *63*, 7311-7318. And references cited therein.
12. (a) Goti, A.; Nannelli, L. *Tetrahedron Lett.* **1996**, *37*, 6025-6028. (b) Goti, A.; Romani, M. *Tetrahedron Lett.* **1994**, *35*, 6567-6570.
13. Goti, A.; De Sarlo, F.; Romani, M. *Tetrahedron Lett.* **1994**, *35*, 6571-6574.
14. For an account of oxidations to nitrones, see: Döpp, D.; Döpp, H. In "Houben-Weyl - Methoden der organischen Chemie", vol. E14b, Klamann, D.; Hagemann, H.; Eds.; Georg Thieme Verlag: Stuttgart, 1990.
15. (a) Mc Caig, A. E.; Wightman, R. H. *Tetrahedron Lett.* **1993**, *34*, 3939-3942. (b) Tronchet, J. M. J.; Zosimo-Landolfo, G.; Balkadjian, M.; Ricca, A.; Zsély, M.; Barbalat-Rey, F.; Cabrini, D.; Lichtle, P.; Geoffroy, M. *Tetrahedron Lett.* **1991**, *32*, 4129-4132.
16. For an alternative approach to differently protected *cis*-dihydroxypyrroline *N*-oxides employing starting materials from the chiral pool, see: Cicchi, S.; Nunes, J., Jr.; Goti, A.; Brandi, A. *Eur. J. Org. Chem.* **1998**, 419-421.
17. Brandi, A.; Cicchi, S.; Cordero, F. M.; Frignoli, R.; Goti, A.; Picasso, S.; Vogel, P. *J. Org. Chem.* **1995**, *60*, 6806-6812.
18. Typical procedure: a 10 mL reaction flask was charged sequentially with anhydrous CH_3OH (2 mL), the hydroxylamine (0.5 mmol), and Jacobsen catalyst (**1**, 16 mg, 5%). The mixture was cooled to 0 °C and UHP (70 mg, 0.75 mmol) was added in two portions. The reaction mixture was then reacted with stirring at room temperature until completion (1-3 h, TLC control with Et_2O as eluent). The crude reaction mixture was then concentrated. Dichloromethane was added to induce the precipitation of urea and the mixture was filtered through a pad of Celite. The crude product was finally purified by flash column chromatography.
19. For the synthesis of racemic **11**, see ref. 15a.
20. The e.e.s of nitrone **11** have been evaluated with the chiral shift reagent $Yb(hfc)_3$. Addition of 5% of this reagent to the enantiomeric mixture of nitrones **11** causes the splitting of methyl groups of the acetonide. A careful integration can be taken at the upper field Me signals ($\Delta\delta = 0.1$ ppm).
21. Cardona, F.; Valenza, S.; Goti, A.; Brandi, A. submitted for publication.
22. For an explanation of the easy oxidation of 3-hydroxy substitued hydroxypyrrolidines, see: Goti, A.; Cicchi, S.; Fedi, V.; Nannelli, L.; Brandi, A. *J. Org. Chem.* **1997**, *62*, 3119-3125.
23. Janssen, K. B. M.; Parton, R. F.; Jacobs, P. A. *Tetrahedron: Asymmetry* **1997**, *8*, 3039-3042.
24. (a) Palucki, M.; Pospisil, P. J.; Zhang, W.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1994**, *116*, 9333-9334. (b) Palucki, M.; McCormick, G. J.; Jacobsen, E. N. *Tetrahedron Lett.* **1995**, *36*, 5457-5460.
25. (a) Jacobsen, E. N.; Zhang, W.; Muci, A. R.; Ecker, J. R.; Deng, L. *J. Am. Chem. Soc.* **1991**, *113*, 7063-7064. (b) Brandes, B. D.; Jacobsen, E. N. *Tetrahedron Lett.* **1995**, *36*, 5123-5126.
26. The Referee suggested that the observed low e.e.s might arise from the oxidations of two *meso* diastereoisomers, occurring with opposite enantioselectivity.
27. Note Added in Proof. After submission of this paper, the enantiotopic oxidation of *meso* 1-acylpyrrolidines to the corresponding 2-hydroxy derivatives catalyzed by (salen)Mn(III) complexes has been published: Punniyamurthy, T; Miyafuji, A.; Katsuki, T. *Tetrahedron Lett.* **1998**, *39*, 8295-8298.