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Asymmetric Epoxidation of Unfunctionalized Alkenes with Periodates Catalyzed by Chiral (Salen)Mn(III) Complexes

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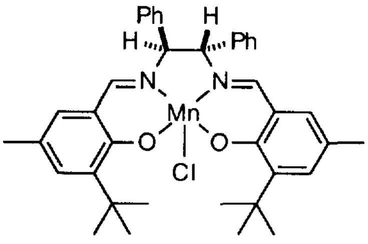
Abstract: Sodium and tetra-*n*-butylammonium periodates were used as oxidants in the asymmetric epoxidation of unfunctionalized alkenes with chiral (salen)Mn(III) complexes **1-2** together with imidazole as donor ligand. Reaction system used consisted of the alkene, oxidant, donor ligand, and salen in ratios of 1: 2.5: 0.75: 0.06. Both *cis*- and *trans*-alkenes were epoxidized with reasonable yield and enantioselectivity (up to 85 % ee for 2,2-dimethylchromene).

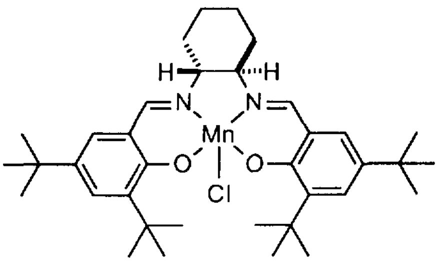
The epoxidation of alkenes is an important reaction in organic chemistry because two new bonds, and in asymmetric cases two new chiral centers, are created in one step. Recently chiral (salen)Mn(III) complexes, first introduced by Jacobsen *et al.*,[1a] have emerged as promising catalysts for the enantioselective epoxidation of unfunctionalized alkenes.[1-2] Their usefulness has been demonstrated in the synthesis of biologically and pharmaceutically important compounds like taxol (taxol side chain) and the calcium channel activator cromakalim.[2c-d] The synthesis of these epoxides were conducted using buffered aqueous sodium hypochlorite (NaOCl) as the oxygen atom donor. Other oxidants that have been employed in epoxidations catalyzed by the "Jacobsen"-type complexes are iodosylarenes,[1,3] O_2 together with pivalaldehyde,[4] and recently[5] also H_2O_2.

New catalytic systems for transition metal-catalyzed epoxidations that would offer mild reaction conditions and high degree of selectivity are still under intensive investigation. Recently, it was shown that periodates ($NaIO_4$ and n-Bu_4NIO_4) are effective oxygen atom donors in the epoxidation of olefins catalyzed by metalloporphyrins.[6a-b] Various unfunctionalized alkenes were epoxidized with high yields catalyzed by a Mn(III)-porphyrin together with imidazole as donor ligand. Because Mn(III)-porphyrins and -salen complexes have common catalytic activities and similar reaction pathways it was expected that periodates would be suitable oxidants for salen-catalyzed reactions.

Here is reported that periodates can be employed for the enantioselective epoxidation of alkenes catalyzed by the "Jacobsen"-type salen complexes **1** and **2**.[2a,c] Three unfunctionalized alkenes (1,2-dihydronaphthalene, *trans*-β-methylstyrene, and 2,2-dimethylchromene) were epoxidized with periodates catalyzed by **1** and **2** in the presence of imidazole as donor ligand.[7] Reactions were performed either in CH_2Cl_2 (n-Bu_4NIO_4) or in CH_2Cl_2-H_2O two-phase medium ($NaIO_4$) containing the alkene, oxidant, imidazole, and salen in ratios of 1: 2.5: 0.75: 0.06. n-Bu_4NBr (0.06 equiv.) was added as phase transfer catalyst in oxidations with $NaIO_4$.[8]



(*S,S*)-1



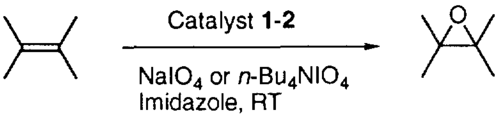
(*R,R*)-2

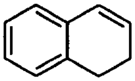
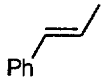
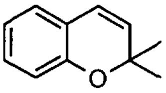
Results of the epoxidation of *1,2-dihydronaphthalene* are summarized in Table 1, entries 1-6. Initially, the reactions were allowed to prodeed overnight (24 h), but it was soon found out that the reactions reached over 90 % completion (as analyzed by ^1H NMR) after only 3-6 hours. In fact longer reaction times lowered slightly both the yield and enantiomeric excess (ee) of the epoxide (e.g. entry 2 *vs* 3). Generally, it was observed that the yield of the epoxide was independent of the periodate oxidant used. On the other hand, epoxidations with n-Bu_4NIO_4 proceeded with higher asymmetric induction than with $NaIO_4$, the difference in ee being 7-8 percentage units (entry 1 *vs* 2, entry 5 *vs* 6). Oxidations catalyzed by salen complex **1** afforded 5-15 % higher yields of the epoxide than by catalyst **2** (e.g. entry 3 *vs* 6), but the optical yields were similar regardless of the catalyst used. Lowering the reaction temperature from 22 °C (room temperature) to 4 °C increased ee slightly (entry 4).

As expected, epoxidation of trans-*β-methylstyrene* proceeded with substancially lower enantioselectivity than in the case of 1,2-dihydronaphthalene (Table 1, entries 7-11).[9] In similar conditions, *trans*-β-methylstyrene oxide was obtained in 47 % ee (e.g. entry 8) compared to 64 % ee for the epoxide from *cis*-alkene (entry 3). Generally, yield and enantiomeric excess of the *trans*-epoxide were not dependent on the periodate oxidant used. Also, both catalysts produced the *trans*-epoxide with equal enantioselectivity. On the other hand, epoxidations of *trans*-β-methylstyrene catalyzed by **2** afforded 10 % higher yields of the epoxide than by catalyst **1**. This was in contrast with the results obtained in the epoxidation of 1,2-dihydronaphthalene. Lowering the reaction temperature increased both the yield (from 63 to 69 %) and ee (from 47 to 54 %) of the product (entry 10 *vs* 11).

Finally, the reaction system using n-Bu_4NIO_4 as terminal oxidant was applied to the epoxidation of *2,2-dimethylchromene*[10] (Table 1, entries 12-15), a member of a synthetically important class of alkenes. 2,2-Dimethylchromene has earlier been epoxidized with particularly high enantioselectivities with catalyst **2**.[2b,d] Here catalysts **1** and **2** produced dimethylchromene oxide with equal enantioselectivity (82-85 % ee) both at room temperature and at 4 °C. These ee-values are considerably lower than those obtained by Jacobsen *et al.* with NaOCl and catalyst **2** (>90 % ee).[2b,d] The origin of this difference in asymmetric induction is unclear.

Table 1. Epoxidation of Unfuctionalized Alkenes with Periodates and Catalysts **1-2**[a]



entry	alkene	catalyst	oxidant $(M^+IO_4^-)$	reaction time (h)	yield (%)[b]	ee (%)[c]	epoxide confign[d]
1		**1**	Na	24	45	56	1*S*,2*R*-(–)
2	"	**1**	*n*-Bu$_4$N	24	48	61	1*S*,2*R*-(–)
3	"	**1**	*n*-Bu$_4$N	3	**55**	64	1*S*,2*R*-(–)
4	"	**1**	*n*-Bu$_4$N	24[e]	52	**69**	1*S*,2*R*-(–)
5	"	**2**	Na	6	40	58	1*R*,2*S*-(+)
6	"	**2**	*n*-Bu$_4$N	3	40	63	1*R*,2*S*-(+)
7		**1**	Na	6	51	46	1*S*,2*S*-(–)
8	"	**1**	*n*-Bu$_4$N	3	53	47	1*S*,2*S*-(–)
9	"	**2**	Na	6	60	46	1*R*,2*R*-(+)
10	"	**2**	*n*-Bu$_4$N	3	63	47	1*R*,2*R*-(+)
11	"	**2**	*n*-Bu$_4$N	24[e]	**69**	**54**	1*R*,2*R*-(+)
12		**1**	*n*-Bu$_4$N	3	**82**	83	(3*S*,4*S*)[f]
13	"	**1**	*n*-Bu$_4$N	18[e]	78	**85**	(3*S*,4*S*)[f]
14	"	**2**	*n*-Bu$_4$N	3	79	82	(3*R*,4*R*)[f]
15	"	**2**	*n*-Bu$_4$N	18[e]	64	84	(3*R*,4*R*)[f]

a) See ref. 8 for typical reaction conditions. b) Yield of isolated epoxide. c) Determined by ^{1}H NMR analysis (200 MHz) in the presence of Eu(hfc)$_3$. d) Determined by comparison of the sign of $[\alpha]_D$ to the literature values.[11] e) Reaction was performed at 4 °C. f) See ref. 2d for assignment of the epoxide configuration.

In this paper, it was shown that both *cis*- and *trans*-alkenes could be epoxidized with reasonable yield and enantioselectivity using periodates as terminal oxidants together with chiral salen catalysts in very mild, and neutral conditions. Most suitable oxidation system for 1,2-dihydronaphthalene consisted of n-$\mathrm{Bu_4NIO_4}$ and catalyst **1**. The epoxidation of *trans*-β-methylstyrene was best catalyzed by salen **2**. Finally, 2,2-dimethylchromene was epoxidized with equal enantioselectivity using catalysts **1** and **2**. This promising reaction system could easily be applied for other enantioselective salen-catalyzed reactions e.g. for oxidation of sulfides to sulfoxides.[12]

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6. a) Mohajer, D.; Tangestaninejad, S. *J. Chem. Soc. Chem. Commun.* **1993**, 240. b) Mohajer, D.; Tangestaninejad, S. *Tetrahedron Lett.* **1994**, *35*, 945. Other examples of Fe- and Mn-porphyrin catalyzed epoxidations with periodates: c) Takata, T.; Ando, W. *Tetrahedron Lett.* **1983**, *24*, 3631; d) Suslick, K. S.; Acholla, F. V.; Cook, B. R. *J. Am. Chem. Soc.* **1987**, *109*, 2818.
7. For discussion concerning the role of donor ligand see e.g. references 3, 4b, and 5.
8. Typical reaction procedure: To a solution of 1,2-dihydronaphthalene (0.499 mmol), imidazole (0.375 mmol), and catalyst **1** (0.03 mmol) in solvent ($\mathrm{CH_2Cl_2}$, 2.5 ml) was added 1.25 mmol of oxidant (solid n-$\mathrm{Bu_4NIO_4}$, or aq. 0.2 M $\mathrm{NaIO_4}$). n-$\mathrm{Bu_4NBr}$ (0.031mmol) was added as phase transfer catalyst in reaction with $\mathrm{NaIO_4}$. The mixture was stirred at room temperature (3-24 h), diluted with $\mathrm{CH_2Cl_2}$ and transferred into a separatory funnel containing water. The organic layer was separated, dried over $\mathrm{Na_2SO_4}$, and concentrated. The residue was analysed by 200 MHz ^{1}H NMR and the epoxide was isolated by flash chromatography on silica gel (hexane/EtOAc). The ee of the epoxide was determined by ^{1}H NMR in the presence of the chiral shift reagent tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]europium(III), $\mathrm{Eu(hfc)_3}$.
9. *Trans*-alkenes are known to react slower and with lower enantioselectivity in transition metal complex-catalyzed epoxidations than *cis*-olefins. See examples in refs 1, 3, and 5a.
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