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Low Temperature Asymmetric Epoxidation of Unfunctionalized Olefins Catalyzed by (Salen)Mn(III) Complexes

Michael Palucki, Gregory J. McCormick, and Eric N. Jacobsen*

Department of Chemistry, Harvard University, Cambridge, Massachusetts 02138

Summary: The enantioselective epoxidation of olefins catalyzed by (salen)Mn(III) complexes can be effected under anhydrous conditions with a variety of primary oxidant systems. The combination of *m*-CPBA and NMO is particularly reactive, allowing for epoxidation reactions to be carried out at -78 °C. Under these low temperature conditions, a variety of unfunctionalized olefins undergo epoxidation with a significant increase in enantioselectivity relative to reaction using aqueous bleach.

The asymmetric epoxidation of unfunctionalized olefins catalyzed by (salen)Mn(III) complexes is emerging as a useful synthetic transformation.¹ Practical features of this reaction include the synthetic accessibility of the catalysts,² the use of sodium hypochlorite (household bleach) as an inexpensive and effective stoichiometric oxidant,³ and the high enantioselectivities (ee's) attained with a wide range of substrates.⁴ Recently, we disclosed that the combination of *m*-chloroperbenzoic acid (*m*-CPBA) and *N*methylmorpholine-*N*-oxide (NMO) is an effective anhydrous oxidant system for the enantioselective epoxidation of styrene at low temperature (-78 °C).⁵ We report here a broad investigation of anhydrous oxidants capable of oxygen atom transfer mediated by (salen)Mn(III) complexes, and the observation that the low temperature reaction protocol leads to improved ee's with a range of unfunctionalized olefins.

Reaction of *cis*-β-methylstyrene provides a useful model for evaluating both enantioselectivity and cis/trans partitioning in epoxidations, and this substrate was used to screen various oxidants (Table 1). Given their tendency to enhance enantioselectivity and/or rates of epoxidation, additives such as 4-phenylpyridine-*N*-oxide (4-PPNO) and NMO were also screened in connection with the different oxidants.^{6,7} In general, it was found that 4-PPNO was the most effective additive for reactions involving aqueous oxidants (e.g. NaOCl), whereas NMO was most effective for anhydrous reactions. The data in Table 1 reflect the optimal choice and loading of additive for each terminal oxidant described.



| Entry | Catalyst | Oxidant | Time | Temp (°C) | Additive (Eq.) ^b | Yield (%) ^c | Ee(%) ^d | Cis/Trans |
|-------|----------|---------|--------|-----------|-----------------------------|------------------------|--------------------|-----------|
| 1 | 1 | NaOCI | 2 h | 0 | 4-PPNO (0.2eq) | 91 | 81 | 20 |
| 2 | 1 | Oxone® | 40 h | 0 | NMO (1.0 eq) | 82 | 86 | 27 |
| 3 | 1 | MMPP | 1 h | 0 | NMO (1.0 eq) | 94 | 85 | 32 |
| 4 | 1 | m-CPBA | 5 min | 0 | NMO (5.0 eq) | 99 | 83 | 14 |
| 5 | 1 | TBHP | 40 h | 0 | NMO (5.0 eq) | 24 | 81 | 2 |
| 6 | 2 | m-CPBA | 15 min | 0 | NMO (5.0 eq) | 80 | 88 | 6 |
| 7 | 3 | m-CPBA | 5 min | 0 | NMO (5.0 eq) | 87 | 91 | 18 |
| 8 | 4 | m-CPBA | 5 min | 0 | NMO (5.0 eq) | 54 | 85 | 9 |
| 9 | 2 | m-CPBA | 30 min | -78 | NMO (5.0 eq) | 54 | 89 | 7 |
| 10 | 3 | m-CPBA | 1 h | -78 | NMO (5.0 eq) | 83 | 96 | 26 |
| 11e | 4 | m-CPBA | 1 h | -78 | NMO (5.0 eq) | 82 | 98 | 23 |

______ Me + Oxidant <u>catalyst (2-4 mol%)</u> additive, CH₂Cl₂

Table 1. Epoxidation of $cis-\beta$ -methylstyrene with various oxidants.^a

^{*a*} With the exception of entry 1, all reactions were carried out under anhydrous conditions. ^{*b*} Relative to olefin. ^{*c*} Yields were determined by capillary GC, by integration of product peaks against an internal quantitative standard (dodecane), correcting for response factors and for the extent of olefin conversion. ^{*d*} Ee's were determined by capillary GC using a commercial chiral column (J&W Scientific Cyclodex-B column 30 m X 0.25 mm id., 0.25 μ m film). ^{*e*} The reaction was carried out with 8 mol % catalyst.

While epoxidation of *cis*- β -methylstyrene with Oxone[®] proceeded slowly at 0 °C under anhydrous conditions (entry 2), reaction using the same oxidant in a biphasic system comprised of CH₂Cl₂ and a buffered aqueous solution (pH = 8) proceeded to complete conversion within 10 min (86% ee, cis/trans = 16). This difference in rate can be attributed to the low solubility of Oxone[®] in organic solvents. A similar effect was also observed using magnesium monoperoxophthalate (MMPP) (entry 3). In the presence of an aqueous phase, complete conversion of olefin occurred within 5 minutes in the presence of 1, whereas under anhydrous conditions a reaction time of 1 hour was required. The use of MMPP at lower temperatures resulted in extremely low reactivity, and only a small increase in enantioselectivity. The rate of reaction using anhydrous TBHP (entry 5) was extremely slow and afforded epoxide in low yield along with a mixture of byproducts. In contrast, epoxidations using a combination of *m*-CPBA/NMO were rapid and clean both at 0 °C (entries 4, 6-8), and at -78 °C (entries 9-11). Further, both the enantioselectivity and cis/trans epoxide ratios were found to increase significantly at low temperature.

Using the combination of *m*-CPBA/NMO, a number of olefins were subjected to the low temperature protocol and the results are listed in Table 2. Although certain substrates were found to be either unreactive under these conditions or did not improve appreciably relative to epoxidations with aqueous bleach (e.g. entries 10-11), ee's were improved substantially for many other olefins. Epoxidation of terminal olefins (entries 1-5) exhibited the largest increase in enantioselectivity. For these substrates, the increase in

| | R ¹ | _R ² ∕ + <i>m</i> -CPB | catalyst (2-8 mol%) | H ⁻ H ⁻ | |
|-------|-------------------|--------------------------------------|---|-------------------------------|----------------------------|
| | Ň | R ³ | NMO, CH ₂ Cl ₂ , -78 °C | O R ³ | |
| Entry | Substrate | Catalyst | Isolated yield (%) ^c | ee (%) ^a | ee (%), NaOCl ^b |
| 1 | \bigcirc | 4 | 89 | 86 | 69 |
| 2 | F | 4 | 83 | 85 | 62 |
| 3 | F ₃ C | 4 | 85 | 82 | 56 |
| 4 | H ₃ C | 5 | 83 | 80 | 64 |
| 5 | HO ₂ C | 4 | 45 ^c | 72 | no epoxidation |
| 6 | PhMe | 4 | 71 | 98 | 89 |
| 7 | | 4 | 89 | 96 | 88 |
| 8 | \bigcirc | 4 | 83 | 97 | 92 |
| 9 | Ph Ph | 2 | 82 | 97 | 92 |
| 10 | PhCO2Et | 2 | no reaction | | 93 |
| 11 | | 6 | 91 | 97 | 97 |

Table 2. Epoxidation of various olefins at -78 °C.8

^{*a*} Enantioselectivities for entries 1, 2, 4, 6 8, and 11 were determined by capillary GC using a commercial chiral column (J&W Scientific Cyclodex-B column 30 m x 0.25 mm id., 0.25 μ m film) and entry 3 using a commercial chiral column (Chiraldex Gamma-cyclodextrin Trifluoroacetyl column 20 m x 0.25 mm id., 0.25 μ m film). Enantioselectivity for entry 5 was determined as the methyl ester via reaction with diazomethane. Enantioselectivities for entries 7 and 9 were determined by chiral HPLC using commercial columns, Chiralcel OB and Whelk-O respectively. ^{*b*} Ee's observed using the same catalyst under optimized bleach conditions (see reference 3). ^{*c*} Isolated yield after conversion to the corresponding methyl ester.

enantioselectivity is attributable to both an increase in enantiofacial selectivity in the initial C-O bondforming step, as well as to suppression of the trans pathway in the second step.⁹ As shown previously, the latter constitutes an enantiomeric leakage pathway for terminal olefins.⁵ Enantioselectivities in the epoxidation of several more highly substituted olefins (entries 6-9) also improved under the low temperature conditions. The epoxidation of vinylbenzoic acid (entry 5) represents the first example of the successful asymmetric epoxidation of a free carboxylic acid-bearing substrate with (salen)Mn catalysts. Reaction of this substrate using bleach as the terminal oxidant did not afford epoxide, presumably because

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of the generation and solubility of the corresponding carboxylate in the basic aqueous bleach phase. However, reaction under the anhydrous low temperature conditions provided the corresponding epoxide in 72% ee and moderate yield.

In conclusion, a variety of oxidants are effective oxygen atom donors for olefin epoxidation in the presence of chiral (salen)Mn(III) complexes. The combination of m-CPBA and NMO was found to be particularly effective for low temperature reactions. Epoxidation of a wide array of unfunctionalized olefins proceeded with an increase in enantioselectivity under the anhydrous low temperature conditions relative to biphasic reactions employing bleach. Other olefins which are either water-soluble or which decompose in the presence of aqueous bleach are also now viable substrates for the epoxidation reaction.

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- 7. These *N*-oxide derivatives were found to be unreactive under the conditions of epoxidation in the absence of an additional stoichiometric oxidant.
- 8. General experimental procedure: A round bottom flask equipped with a magnetic stir bar was charged with olefin (0.59 mmol), CH₂Cl₂ (5 mL), catalyst (0.029 mmol) and NMO (2.93 mmol). The solution was cooled to -78 °C before the addition of precooled, solid *m*-CPBA (1.17 mmol) in two roughly equal portions. The reaction was monitored by GC. Upon consumption of the olefin, the reaction was quenched by the addition of a solution of dimethyl sulfide (2.72 mmol) in CH₂Cl₂ (1 mL) precooled to -78 °C. A solution of 2N NaOH (6 mL) was then added, and the organic layer was separated, washed with distilled water, and dried over Na₂SO₄. The drying agent was removed by filtration and filtrate concentrated. The crude product was purified by flash chromatography on silica gel.
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