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Enantioselective epoxidation of chromenes using chiral Mn(III) salen catalysts with built-in phase-transfer capability

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Abstract—New chiral Mn(III) salen epoxidation catalysts **1** and **2** (a catalyst loading in the range of 2.0–0.4 mol%) have been investigated for enantioselective epoxidation of chromene derivatives to chromene epoxides using pyridine *N*-oxide as a proximal ligand with excellent conversions and chiral induction.

The design of a new chiral metal catalyst for enantioselective epoxidation of alkenes constitutes an important strategy for the synthesis of chiral pharmaceuticals and fine chemicals.[1] Among several catalytic methods, chiral Mn(III) salen complexes have been reported to give high enantioselectivity in the epoxidation of non-functionalised *cis* or cyclic alkenes using NaOCl as oxidant under biphasic reaction conditions.[2] Furthermore, it has been observed that the use of *N*-oxides,[3] specifically 4-phenyl pyridine *N*-oxide[4] (PPNO) and 4-phenylpropyl pyridine *N*-oxide,[5] (PPPNO) as proximal ligand not only stabilises the catalytically active intermediate species Mn(V)-oxo, but also act as phase-transfer reagents. Although, PPNO and PPPNO have imparted the best results, these are expensive and get degraded under the reaction conditions. In the present study, we report the new chiral Mn(III) salen complexes **1** and **2** with built-in phase-transfer capability due to the methylene aminoalkyl groups at the 5,5′-positions of the substituted salicylaldehyde moiety so that simple *N*-oxides can be used effectively. With these new catalysts, chromene and substituted chromenes were used as model substrates as their epoxides are useful in the synthesis of selective potassium channel activator drugs.[6] The complexes were prepared as shown in Scheme 1. Thus, in a stepwise manner, 3-*t*-butyl salicylaldehyde was chloromethylated[7] (**a**), and reacted with dioctylamine (**b**), to give 2-hydroxy-3-*t*-butyl-5-(*N*,*N*-dioctylmethylene)benzaldehyde hydrochloride **5**. Compound **5** on condensation with 1*S*,2*S*-(+)-cyclohexanediamine and 1*R*,2*R*-(+)-diphenyldiamine in a 2:1 molar ratio gave ligands **6** and **7**, respectively. Finally, ligands **6** and **7** were complexed with manganese to give chloro - (*S*,*S*) - [[2,2′] - (1,2 - cyclohexanediyl)bis(nitrilomethylidyne)]bis[4 - (methylene - *N*,*N*′ - dioctylamino) - 6-(1,1 - dimethylethyl)phenolato] - [*N*,*N*′,*O*,*O*′]manganese-(III) **1** and chloro-(*R*,*R*)-[[2,2′]-(1,2-diphenyl-1,2-ethanediyl)bis(nitrilomethylidyne)]bis[4 - (methylene - *N*,*N* - dioctylamino)-6-(1,1-dimethylethyl)phenolato]-[*N*,*N*′,*O*,*O*′]-manganese(III) **2**, respectively.

Asymmetric epoxidation reactions were performed with 2 mol% of the complexes **1** and **2** with 2,2-dimethylchromene, 6-cyano-2,2-dimethylchromene, 6-methoxy-2,2-dimethylchromene and spiro[cyclohexane-1,2′-[2*H*]-[1]chromene] as substrates[10] in dichloromethane using buffered NaOCl (pH 11.3) as the oxidant at 0°C in the presence of pyridine *N*-oxide as a proximal ligand. As shown in Table 1, high conversions (>99%) were obtained with all chromenes (entries 1–8) in 3.5–9.5 h, using the complexes **1** and **2**. Both catalysts gave 98–99% chiral induction with 6-cyano-2,2-dimethylchromene (entries 3 and 4). Catalyst **2** gave a lower ee (65%) for 6-methoxy-2,2-dimethylchromene (entry 6) and moderate ee's for spiro[cyclohexane-1,2′-[2*H*][1]chromene] (entry 8) and 2,2-dimethylchromene (entry 2) while the ee's were better in the case of catalyst **1** (81–87%) (entries 1, 5 and 7). Overall, catalyst **1** seems to be better than the catalyst **2**.

Keywords: Mn(III) salen; chiral; epoxidation; chromene; phase transfer.

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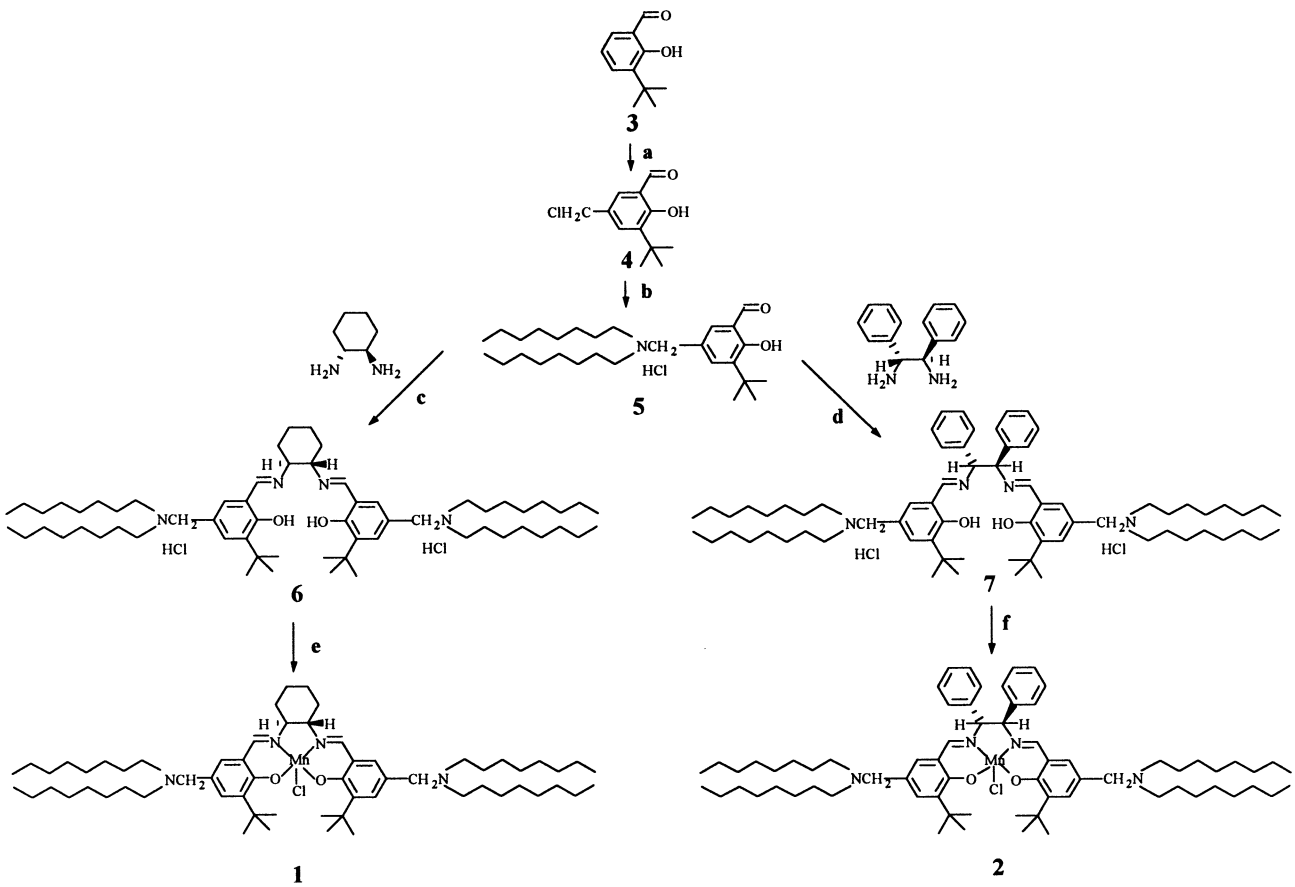
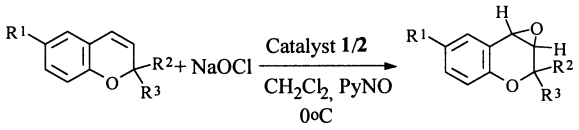


Scheme 1. *Reagents and conditions*: (a) HCHO, conc. HCl, rt, 48 h, 97%; (b) *N*,*N*-dioctylamine, benzene, reflux, 6 h, 97%; (c) (1*S*,2*S*)-(+)-1,2-diaminocyclohexane, abs. EtOH, reflux, 7 h, 95%;[8a] (d) (1*R*,2*R*)-(+)-diphenyldiamine, abs. EtOH, reflux, 8 h, 86%;[8b] (e) (1) $Mn(CH_3COO)_2{\cdot}4H_2O$, EtOH, N_2, reflux, 7 h, (2) LiCl, rt, 4 h, 92%;[9a] (f) (1) $Mn(CH_3COO)_2{\cdot}4H_2O$, EtOH, N_2, reflux, 8 h, (2) LiCl, rt, 4 h, 91%.[9b]

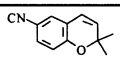
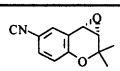
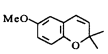
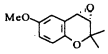
In all the catalytic runs where the catalyst **1** (*S*,*S* configuration) was used the dominant enantiomer of the product epoxides was *S*,*S*, whilst with catalyst **2** (*R*,*R* configuration), it was *R*,*R*. Jacobsen complex[11] with 2 mol% catalyst loading gave 96% conversion with 97% ee's in 6-cyano-2,2-dimethylchromene in 9 h (with 10 mol% of 4-phenyl pyridine *N*-oxide). However, under similar reaction conditions, even with simple pyridine *N*-oxide, the complexes **1** and **2** take only 6–6.5 h with >99% conversion and 98 and 99% ee's, respectively. It has been found that by replacing the pyridine *N*-oxide with 10 mol% of 1,4-dioxane as a proximal ligand under similar reaction conditions, the reactivity and selectivity were comparable (epoxidation of 6-cyano-2,2-dimethylchromene with conversion >99%, ee's >97%, time 8 h). This shows that even water-soluble *O*-coordinating proximal ligands are able to impart the requisite activity and selectivity in the catalyst. This feature may be attributed to the built-in phase-transfer capability in the catalytic system created by way of introducing the *N*,*N*-dioctylaminomethylene at the 5,5′-position of the substituted salicylaldehyde moiety of the catalyst. As a result the transportation of HOCl to the organic phase as required with Jacobsen's catalyst,[5] may not be necessary with the present system. Moreover, 0.4 mol% of catalyst **1** is sufficient to achieve similar conversion and selectivity for cyanochromene within 10 h. Further reduction in catalyst loading (0.2 mol%) caused a reduction in the reaction rate with a decrease in the ee value (92% in the case of the cyanochromene) in 20 h. Below 0.2 mol% of catalyst loading, the reaction rate and selectivity deteriorated rapidly.

In conclusion, we have developed new, efficient Mn(III) salen complexes with a built-in phase-transfer capability as epoxidation catalysts for chromene derivatives. Excellent conversions were obtained with all chromenes, but 98, 99% chiral induction was obtained only with cyanochromene by ^{1}H NMR and HPLC. Furthermore, a catalyst loading of 0.4 mol% under similar epoxidation conditions, works well with some loss of activity, however, the ee's remain unaltered.

Table 1. Data for the enantioselective epoxidations of chromene derivatives catalysed by complexes **1** and **2** with pyridine *N*-oxide



R1 = H, CN, OCH_3; R2,R3 = CH_3; R2-R3 = cyclohexane

entry	Catalyst	Substrate	Product	Conversion[a] (%)	Time (h)	ee[b,c] (%)
1(2)	**1 (2)**			>99(>99)	9(9.5)	81(75)
3(4)	**1 (2)**			>99(>99)	6(6.5)	>99(>98)
5(6)	**1 (2)**			>99(>99)	3.5(5)	87(65)
7(8)	**1 (2)**			>99(>99)	6(7)	87(78)

Reactions conditions: catalyst (2 mol% in 1 ml CH_2Cl_2), substrate (1.29 mmol), pyridine *N*-oxide (0.13 mmol), NaOCl (2.75 mmol).

[a] Determined by GC.

[b] By ^1H NMR using the shift reagent (+)-Eu(hfc)$_3$/HPLC-Chiralcel OJ.

[c] The configuration of the major enantiomer was determined by comparing the chemical shifts/retention time (using HPLC) with that of an authentic sample of (3*S*,4*S*)-CN-chromene oxide. For other oxides, the absolute configuration was assigned by analogy to (3*R*,4*R*)-CN-chromene oxide. In all the cases where catalyst **1** was used, the configuration of the product epoxides was 3*S*,4*S* whilst with catalyst **2**, it was 3*R*,4*R*.

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7. (a) White crystalline solid, mp 63–65°C; IR and NMR data is in accordance with the reported data in Refs. 7b and 7c; (b) Viscous oil, 96%. See: Minutolo, F.; Pini, D.; Petri, A.; Salvadori, P. *Tetrahedron: Asymmetry* **1996**, *7*, 2293–2302; (c) Yellow crystalline solid, yield 99% mp 62.2–62.9°C. See: Canali, L.; Cowan, E.; Deleuze, H.; Gibson, C. L.; Sherrington, D. C. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2055–2066.
8. (a) Mp 190–191°C; ^1H NMR (200 MHz, $CDCl_3$): δ 14.25, 13.66, 11.94, 9.48 (4 bs, 4H exchangeable), 8.42 (s, 2H), 7.51 (s, 4H), 4.33 (s, 4H), 3.47 (m, 2H), 3.20–2.91 (bs, 16H), 1.89 (bs, 8H), 1.38–1.43 (bs, 40H), 1.39 (s, 18H), 0.87 (t, $J=6$ Hz, 12H); IR (KBr): 3427, 2944, 2862, 2365, 1627, 1446, 1270, 1207, 1165, 899, 785 cm^{-1}. Anal. calcd for $C_{62}H_{110}Cl_2N_4O_2$: C, 73.45; H, 10.86; N, 5.53. Found: C, 73.46, H, 10.88; N, 5.49; (b) Mp 138–139°C; ^1H NMR (200 MHz, $CDCl_3$): δ 14.20, 12.18, 12.01, 11.88, 9.43 (5bs, 4H exchangeable), 8.43 (s, 2H), 8.38 (s, 2H), 7.98 (s, 2H), 7.31–7.22 (m, 10H), 4.17–4.14 (m, 2H), 2.98–2.91 (bs, 20H), 1.82–1.71 (m, 40H), 1.37 (s, 18H), 0.86 (t, $J=6$ Hz, 12H); IR (KBr): 3428, 2944, 2863, 2362, 1625, 1442, 1276, 1206, 1164, 893, 785 cm^{-1}. Anal. calcd for $C_{70}H_{112}Cl_2N_4O_2$: C, 75.61; H, 10.08; N, 5.04. Found: C, 75.57; H, 10.03; N, 5.02.
9. (a) Complex **1**: Anal. calcd for $C_{62}H_{106}ClMnN_4O_2$; C, 72.34; H, 10.31; N, 5.45. Found: C, 72.36; H, 10.27; N, 5.40. IR (KBr): ν_{max} 3402, 2928, 2858, 1616, 1543, 1344, 1312, 1169, 830 cm^{-1}; UV–vis (MeOH): λ_{max} (ε) 234 (6334), 260 (6244), 290 (4264), 404 (1332), 408 (1324); CD λ_{max} $\Delta\varepsilon$ (CH_2Cl_2): 284 (+8.8), 318 (+9.6), 414 (+5.3), 505

(+1.0), 623 (−1.0); $[\alpha]_D^{25}=+240$ (c 0.104, CH_2Cl_2); configuration (S); $\mu_{eff.}$ (BM): 4.85; Λ_M (MeOH): 3 mho cm^{-1} mol^{-1}; MS (FAB): m/z (1028); (b) Complex **2**: Anal. calcd for $C_{70}H_{108}ClMnN_4O_2$: C, 74.57; H, 9.59; N, 4.97. Found: C, 74.52; H, 9.54; N, 4.93. IR (KBr): 3422, 2927, 2856, 1611, 1541, 1458, 1386, 1309, 1167, 851 cm^{-1}; UV–vis (MeOH): λ_{max} (ε) 234 (7574), 266 (7322), 286 (6789), 304 (6967), 418 (3026); CD λ_{max} $\Delta\varepsilon$ (CH_2Cl_2): 440 (−2.5), 500 (+0.5), 625 (+4.2); $[\alpha]_D^{25}=+123$ (c 0.114, CH_2Cl_2); configuration (R); $\mu_{eff.}$ (BM): 4.8; Λ_M (MeOH): 3 mho cm^{-1} mol^{-1}; MS (FAB): m/z (1126) [Mn–Cl)].$^+$.

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