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Enantioselective epoxidation of non-functionalised alkenes using a urea–hydrogen peroxide oxidant and a dimeric homochiral Mn(III)-Schiff base complex catalyst

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Abstract—The catalytic enantioselective epoxidation of chromenes, indene and styrene using a urea–hydrogen peroxide adduct as an oxidising agent and the novel dimeric homochiral Mn(III)-Schiff base catalyst **1** has been investigated in the presence of carboxylate salts and nitrogen and oxygen coordinating co-catalysts. Conversions of more than 99% were obtained with all alkenes except styrene. Absolute chiral induction, as determined by ^{1}H NMR using the chiral shift reagent (+)-Eu(hfc)$_3$, was obtained in the case of nitro- and cyanochromene. The catalyst could be re-used for up to five cycles with some loss of activity due to degradation of the catalyst under epoxidation condition with retention of e.e.'s. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

The enantioselective epoxidation of prochiral non-functionalised alkenes constitutes an important tool in organic synthesis.[1–3] Chiral Mn(III)-SALEN type complexes using PhIO,[4] NaOCl,[5] *m*-CPBA,[6] molecular oxygen/aldehyde,[7] dimethyldioxirane,[8] periodate[9] and potassium monopersulphate[10] as oxidising agents have been extensively studied for the enantioselective epoxidation of mono-, tri- and tetra-substituted alkenes. However, all of these oxidants are either expensive or result in undesirable by-products. Hydrogen peroxide was considered as an oxygen source as it is reasonably stable, readily available, inexpensive and generates only water as a by-product.[11] However, the use of hydrogen peroxide in transition metal catalysed epoxidation reactions has limitations because, as a result of homolytic cleavage of the weak O–O bond, peroxy radicals are produced that oxidatively degrade the catalyst. Nevertheless, it is possible to mimic the function of the enzyme cytochrome P450, which also uses H_2O_2 as an oxidant and generate an active high valent metal–oxo intermediate, leading to selective alkene epoxidation.[12] The reactive metal–oxo species is known to be further stabilised by using nitrogenous bases including imidazole, pyridine and tertiary amine *N*-oxides, which can therefore be seen as co-catalysts.[11] Sodium and ammonium salts have also been reported previously as effective co-catalysts in the metallo-porphyrin catalysed epoxidation of alkenes by hydrogen peroxide.[12]

Katsuki et al.[13] and Pietikäinan[14] reported the use of aqueous hydrogen peroxide in the Mn(III)-SALEN catalysed enantioselective epoxidation of alkenes in the presence of substituted imidazoles. We felt that urea–hydrogen peroxide (UHP), an anhydrous source of H_2O_2, a stable and inexpensive solid, would be an attractive oxygen source and we therefore decided to examine its use in this study.

Increasing the molecular weight of the catalyst would lower its solubility, aiding product isolation and catalyst recovery, whilst increasing the number of active reaction sites on the catalyst would also result in higher reactivity catalyst and aid turnover. With these points in mind, we designed and synthesised the homochiral dimeric Mn(III) complex, 5,5-methylene di-[(*R*,*R*)-{*N*-(3-*tert*-butyl salicylidine)-*N*′-(3′,5′-di-*tert*-butyl salicylidene)}-1,2-cyclohexanediaminato(2-) manganese(III) chloride] **1** which carries two active catalytic metal centres.

Herein, we report the highly enantioselective epoxidation of non-functionalised alkenes using **1** as a catalyst and UHP as the oxidising agent in the presence of an ammonium salt or a nitrogen and oxygen coordinating

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co-catalyst. In practice, **1** was found to be less soluble than its monomeric counterpart, and precipitated from hexane; separation of **1** from the product after the reaction then allowed the catalyst to be recycled for a number of reactions.

2. Results and discussion

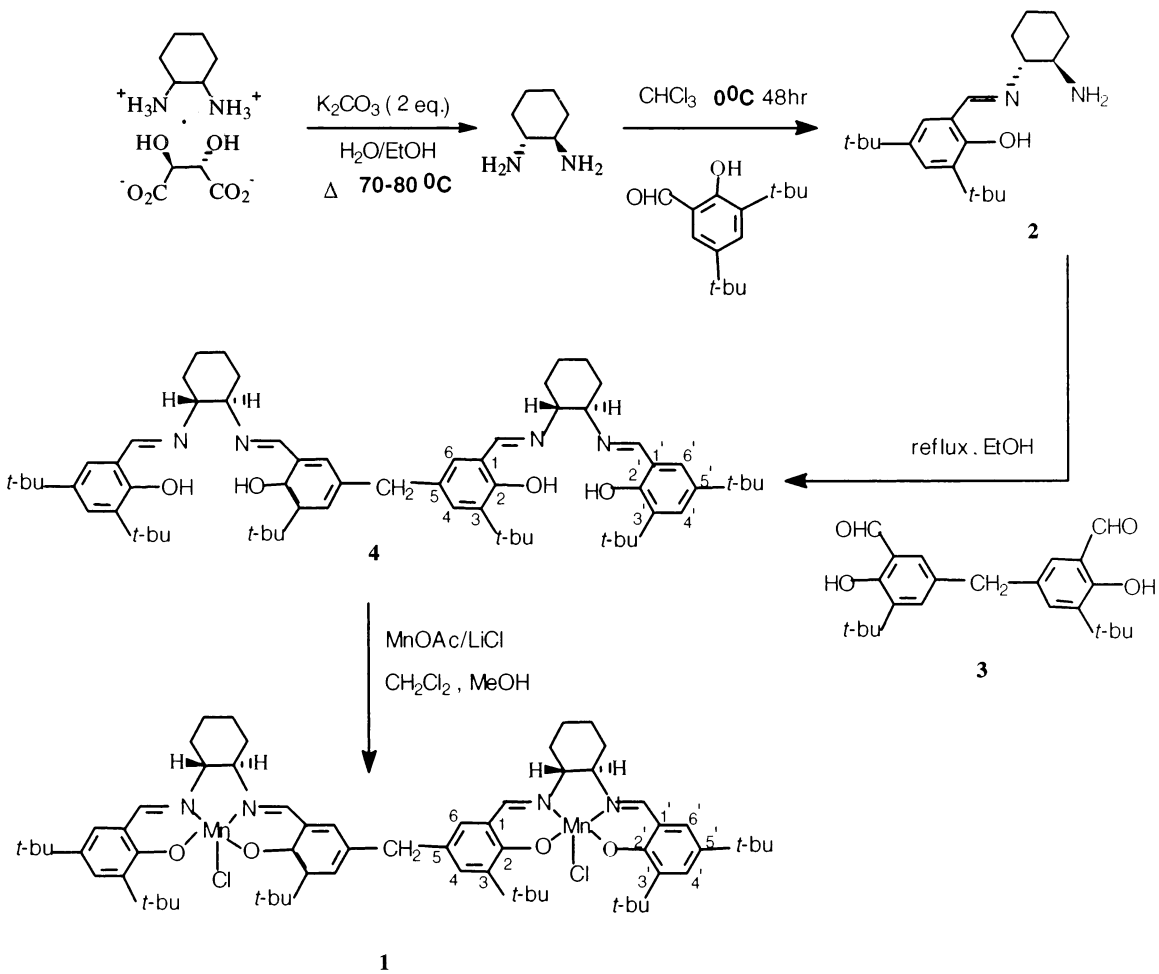
As shown in Scheme 1, the pentacoordinate dimeric complex **1** was formed by condensing first the monotartrate salt of (1*R*,2*R*)-(−)-cyclohexanediamine with 3,5-di-*tert*-butyl salicylaldehyde in a 1:1 molar ratio in $CHCl_3$ at low temperature. The free amine function of **2** was then condensed further with the 5,5-methylene-bis-salicylaldehyde **3**, followed by metallation with Mn(III). Complex **1** was characterised by microanalysis, conductance, optical rotation, UV–vis and IR spectroscopy.

2.1. Enantioselective epoxidation of non-functionalised alkenes

Complex **1** was then used as a catalyst in the epoxidation of 2,2-dimethyl chromene, 6-cyano-2,2-dimethyl chromene, 6-nitro-2,2-dimethyl chromene, 6-methoxy-2,2-dimethyl chromene, spiro[cyclohexane-1,2′-[2*H*][1]-chromene, styrene and indene using a UHP adduct as an oxidant in the presence of ammonium acetate co-catalyst at 2°C in a 1:1 mixture of CH_2Cl_2–CH_3OH. Data regarding the observed enantioselectivities is given in Table 1.

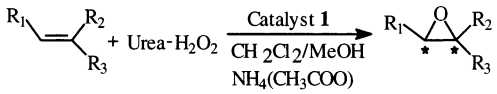
Conversions of $\geq 99\%$ were obtained with all alkenes except styrene, and the reaction was faster in the case of 2,2-dimethyl chromene, 6-methoxy-2,2-dimethyl-chromene and spiro[cyclohexane-1,2′-[2*H*][1]chromene (entries 3–5) compared with the electron deficient nitro- and cyanochromenes. Of the compounds examined, the best chiral induction, with excellent e.e.'s of 100%, was seen in the epoxidation of the electron deficient nitrochromene and cyanochromene (entries 6 and 7). However, the e.e. was a poor 23% in the epoxidation of styrene (entry 1).

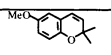
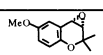
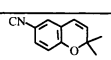
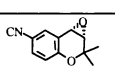
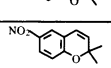
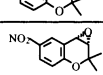
To compare these results with that of Jacobsen's reagent,[5] the epoxidation reaction was conducted with cyanochromene using 2 mol% of Jacobsen's catalyst under similar reaction conditions, which gave an excellent 95% conversion with an e.e. of 98% after 15 h.



Scheme 1.

Table 1. Conversion and e.e. in the UHP/**1** epoxidation of non-functionalised alkenes in the presence of ammonium acetate



entry	Substrate	Product	Conversion[a] (%)	Time (h.)	E.e.[b] (%)	Absolute Configuration[d]
1			68	6.0	23	*R*[c]
2			>99	5.0	64	1*R*,2*S*
3			>99	1.3	67	3*R*,4*R*
4			>99	2.5	84	3*R*,4*R*
5			100	2.0	91	3*R*,4*R*
6			100	5.0	100	3*R*,4*R*
7			100	6.0	100	3*R*,4*R*

Reactions were carried out in CH_2Cl_2:MeOH (1.6 mL) with catalyst (0.025 mmol) substrate (2.5 mmol), co-catalyst (0.2mmol), oxidant(3.0 mmol) at 2 ^{0}C. [a] Determined on GC. [b] By ^{1}H NMR using chiral shift reagent (+)-Eu(hfc)$_3$.[c] By chiral capillary column GTA type. [d] Configuration was determined by the ^{1}H NMR relative chemical shift of the two diastereomers using chiral shift reagent by comparison with an authentic CN-chromene oxide. For other oxides configuration was determined by analogy with the chemical shifts of CN-chromene.

However, using **1** in an identical reaction, epoxidation was complete in 5 h with 100% conversion and 100% e.e. (Table 1, entry 6). This enhanced activity of the dimeric catalyst **1** indicates that the two metal centres are not working in isolation but have some co-operative interaction.

Catalytic runs were also conducted with 2,2-dimethylchromene by changing the co-catalyst used. Pyridine *N*-oxide, 4-phenyl pyridine *N*-oxide, 4-(3-phenyl propyl pyridine *N*-oxide), 4-methyl morpholine *N*-oxide and 1-methyl imidazole were examined as co-catalysts. The results are listed in Table 2.

The reaction time increased to ~8 h with all other nitrogen and oxygen coordinating co-catalysts compared to 2.5 h when ammonium acetate was used. The change in co-catalyst had no significant effect on the conversion. There was marginal improvement in e.e. values in the presence of an oxygen coordinating co-catalyst whilst both conversion and the e.e. decreased in the presence of a nitrogen coordinating co-catalyst. The loading of the catalyst could not be reduced below 0.5 mol%.

To investigate recycling of the catalyst, after completion of the reaction, the organic phase of the reaction mixture was washed with water and brine, and then concentrated. The catalyst was precipitated by adding hexane and used in an identical reaction. This recycling procedure was repeated a further four times and the results obtained are shown in Table 3.

The activity of **1** decreased steadily upon successive use possibly due to minor degradation (weight loss) under the reaction conditions. Whilst the yield of the reaction

Table 2. UHP/**1** catalysed enantioselective epoxidation of 2,2-dimethyl chromene in the presence of different co-catalysts

Entry	Co-catalyst	Conversion (%)[a]	Time (h)	e.e. (%)[b]	Configuration
1	NMO	>99	8	86	3*R*,4*R*
2	4-PhPyNO	>99	7	86	3*R*,4*R*
3	4-PPPyNO	>99	6.5	86	3*R*,4*R*
4	PyNO	>99	7	86	3*R*,4*R*
5	NMeIm	95	7	81	3*R*,4*R*

Reactions were carried out in CH_2Cl_2–MeOH (1.6 mL) with catalyst (0.025 mmol), substrate (2.5 mmol), co-catalyst (0.2 mmol), and oxidant (3.0 mmol) at 2°C.

[a] Determined by GC.

[b] Determined by ^{1}H NMR using the chiral shift reagent (+)-Eu(hfc)$_3$.

Table 3. UHP/**1** catalysed enantioselective epoxidation of 2,2-dimethyl chromene in the presence of ammonium acetate co-catalyst: catalyst recycling investigations

Run	1	2	3	4	5
Conversion (%)	100	85	70	59	53
e.e. (%)	84	84	84	84	84
Time (h)	2.5	3	5	6.5	10

reduced with repeated use of **1**, the e.e. values remained consistent through the recycling process.

3. Conclusion

The dimeric Mn(III)-Schiff base complex **1** successfully catalysed the enantioselective epoxidation of the non-functionalised alkenes examined in this study. The best chiral induction, with excellent e.e. of 100%, was obtained in the epoxidation of nitro- and cyanochromene. The reaction rate was found to be slower in the presence of nitrogen and oxygen coordinating co-catalysts compared to reactions in which ammonium acetate was used.

The catalyst could be recovered after the reaction and re-used without purification. The activity of the recycled catalyst gradually decreased upon successive use, possibly due to minor degradation during the reaction. Whilst the reaction times increased and the yields reduced, the enantioselectivity of the reactions was unaffected on recycling the catalyst five times.

4. Experimental

4.1. Methods

All the solvents used were purified by a known procedure. Indene and styrene were both passed through a pad of neutral alumina before use. (1*R*,2*R*)-(−)-Cyclohexane diamine was resolved from the technical grade *cis–trans* mixture by the reported procedure.[15] 2,2-Dimethyl chromene, 6-cyano-2,2-dimethyl chromene, 6-nitro-2,2-dimethyl chromene, 6-methoxy-2,2-dimethyl chromene, and spiro[cyclohexane-1,2′-[2*H*][1]chromene were synthesised by known methods.[16] 3,5-Di-*tert*-butyl salicylaldehyde was synthesised by a reported procedure.[17] The purity of the solvents, substrates and products was determined by GLC using a Shimadzu GC 14B machine with a 2 m long, 3 mm ID, 4 mm OD stainless steel column packed with SE30, 5% mesh size 60–80 and an FID detector. For styrene and indene, the column temperature was programmed between 70 and 150°C while for chromenes it was 150°C isothermal. Nitrogen was used as the carrier gas with a flow of 30 mL min^{-1} and an injection temperature of 200°C. Internal standard methods were used to determine yields by comparison of peak height and area. The enantiomeric purity of the product was determined using a Chiraldex GTA chiral capillary column or ^{1}H NMR using the chiral shift reagent (+)-Eu(hfc)$_3$.

4.2. Synthesis of 5,5-methylene-di-3-*tert*-butyl salicylaldehyde 3

3-*tert*-Butyl salicylaldehyde (0.12 mol) was treated with a solution of paraformaldehyde (0.06 mol) in glacial acetic acid (16 mL) and sulphuric acid (2 mL) under nitrogen. The resulting solution was allowed to heat to 90°C with stirring for 24 h. The reaction mixture was poured into cold water and allowed to stand overnight. The deposited dark brown solid was extracted with petroleum ether (3×15 mL). The organic phase was dried over sodium sulphate. The dark brown compound was purified by silica gel column chromatography using hexane–ethyl acetate as eluent to yield **3** as a solid (30.9 g, 70%), mp 99–100°C; ^{1}H NMR ($CDCl_3$, 200 MHz): δ ppm 11.72 (s, 2H, OH), 9.82 (s, 2H, HCO), 7.37 (d, 2H, aromatic $J_m = 2.14$), 7.14 (d, 2H, aromatic, $J_m = 2.14$), 3.93 (s, 2H, methylene), 1.40 (s, 9H, methyl). Anal. calcd for $C_{23}H_{28}O_4$: C, 74.97; H, 7.66. Found: C, 74.80; H, 7.58%.

4.3. Synthesis of *N*-(2-hydroxy-3,4-di-*tert*-butyl benzaldehyde)-1-amino-2-cyclohexeneimine 2

Synthesis of the chiral Schiff base was carried out with a minor modification to the reported method.[18] The monotartarate salt of (1*R*,2*R*)-(−)-cyclohexane diamine (0.0112 mol) and K_2CO_3 (0.0225 mol) were dissolved in distilled water (15 mL) with stirring. Ethanol (6 mL) was added and the resulting cloudy mixture was heated under reflux at 70–80°C for 2 h. The solvent was completely removed and the liberated diamine was extracted with chloroform (4×5 mL). The free diamine was stirred with a solution of 3,5-di-*tert*-butyl salicylaldehyde (0.0112 mol) in $CHCl_3$ (20 mL) for 48 h at 0°C. Removal of the solvent gave **2** as a yellow solid. ^{1}H NMR ($CDCl_3$, 200 MHz): δ ppm 1.23 (s, 9H), 1.41 (s, 9H), 1.58–2.25 (m, 11H, 2H exchangeable with D_2O), 3.34 (1H), 6.89 (s, 1H), 7.26 (s, 1H), 13.72 (b, 1H, exchangeable with D_2O). Anal. calcd for $C_{21}H_{34}N_2O$: C, 76.31; H, 10.37; N, 8.48. Found: C, 76.26; H, 10.30; N, 8.40%.

4.4. Synthesis of 5,5-methylene di-[(*R*,*R*)-{*N*-(3-*tert*-butyl salicylidine)-*N*′-(3′,5′-di-*tert*-butyl salicylidene)}-1,2-cyclohexanediamine] 4

A solution of **2** (0.002 mol) in dichloromethane and 5,5-methylene-di-3-*tert*-butyl salicylaldehyde **3** (0.002 mol) in ethanol was refluxed for 6–8 h. The resulting solution, on concentration, precipitated out the desired chiral ligand, which was isolated in 85% yield. IR (KBr): 1620 cm^{-1} ν(H–C=N); ^{1}H NMR ($CDCl_3$, 200 MHz): δ ppm 1.23 (s, 18H), 1.40 (s, 36H), 1.54–2.0 (m, 16H), 3.2 (s, 4H), 3.68 (s, 2H), 6.74 (s, 4H), 7.05 (s, 4H), 8.21 (s, 4H), 13.69 (bs, 4H exchangeable with D_2O). Anal. calcd for $C_{65}H_{92}N_4O_4$: C, 78.58; H, 9.34; N, 5.64. Found: C, 78.26; H, 9.30; N, 5.47%.

4.5. Synthesis of 5,5-methylene di-[(*R*,*R*)-{*N*-(3-*tert*-butyl salicylidine)-*N*′-(3′,5′-di-*tert*-butyl salicylidene)}-1,2-cyclohexanediaminato(2-) manganese(III) chloride] 1

Schiff base **4** (0.001 mol in CH_2Cl_2) was stirred under reflux with manganese acetate (0.002 in CH_3OH) under an inert atmosphere for 8–10 h. The reaction mixture was cooled to room temperature. Lithium chloride (0.006 mol) was added and the mixture was stirred for a further 5 h while exposed to air. The mixture was filtered and the solvent was removed from the filtrate. The evaporation residue was extracted with dichloromethane, and the dichloromethane extracts were combined and washed with water, brine and dried over sodium sulphate. On partial removal of the solvent and addition of petroleum ether (40–60°C fraction), **1** precipitated from solution. The mixture was filtered and the filter cake dried to afford **1** (4.45 g, 90%). Anal. calcd for $C_{65}H_{92}Cl_2Mn_2N_4O_6$: C, 67.81; H, 8.06; 4.87. Found: C, 67.60; H, 8.02; N, 4.83%. IR (KBr): 3431 (br), 2947 (s), 2866 (s), 1612 (s), 1538 (s), 1475 (sh), 1435 (s), 1388 (m), 1342 (s), 1309 (s), 1285 (sh), 1238 (sh), 1201 (m), 1170 (m), 1100 (w), 1030 (m), 940 (w), 833 (m), 780 (w), 731 (w), 690 (w), 568 (s), 475 (w) cm^{-1}. UV–vis (CH_2Cl_2): λ_{max} (ε) 250 (50000), 266 (49960), 345 (47540), 420 (41460), 451 (41040), 510 (36060). $[\alpha]_D^{30} = -50.4$ (c 0.12, CH_2Cl_2). Absolute configuration (*R*); Λ_M (MeOH) 4 mho cm^{-1} mol^{-1}.

4.6. Enantioselective epoxidation of non-functionalised alkenes

Enantioselective epoxidation reactions were typically performed according to the established procedure[1] using complex **1** (1 mol%) with 2,2-dimethylchromene, 6-cyano-2,2-dimethylchromene, 6-nitro-2,2-dimethylchromene, 6-methoxy-2,2-dimethylchromene, spiro[cyclohexane-1,2′-[2*H*][1]chromene, styrene and indene (2.5 mmol) as substrate in 1:1 dichloromethane: methanol (1.6 mL) in the presence of a co-oxidant viz. ammonium acetate, pyridine *N*-oxide, 4-phenyl pyridine *N*-oxide, 4-(3-phenyl propyl pyridine *N*-oxide), 4-methyl morpholine *N*-oxide and 1-methyl imidazole (0.2 mmol) using a urea–H_2O_2 adduct (3.0 mmol) in six equal portions as an oxidant at a reaction temperature of 2°C. The progress of the epoxidation reaction was monitored by GC. After completion of the reaction, the solvent was removed and the residue was extracted with CH_2Cl_2, washed with water and dried over sodium sulphate. The catalyst was separated from the epoxide by precipitation with hexane for further use.

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References

1. Barf, G. A.; Hoek, D. V. D.; Sheldon, R. A. *Tetrahedron* **1996**, *52*, 12971–12978.
2. Schurig, V.; Betschinger, F. *Chem. Rev.* **1992**, *92*, 873–888.
3. Jacobsen, E. N. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: New York, 1993; pp. 159–202.
4. Zhang, W.; Loebach, J. L.; Wilson, S. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1990**, *112*, 2801–2803.
5. (a) Jacobsen, E. N.; Zhang, W.; Guler, M. L. *J. Am. Chem. Soc.* **1991**, *113*, 6703–6704; (b) Jacobsen, E. N.; Zhang, W.; Muci, A. R.; Ecker, J. R.; Deng, L. *J. Am. Chem. Soc.* **1991**, *113*, 7063–7064; (c) Zhang, W.; Jacobsen, E. N. *J. Org. Chem.* **1991**, *56*, 2296–2298.
6. Palucki, M.; McCormick, G. J.; Jacobsen, E. N. *Tetrahedron Lett.* **1995**, *36*, 5457–5460.
7. Mukaiyama, T.; Yamada, T.; Nagata, T.; Imagawa, K. *Chem. Lett.* **1993**, 327–330.
8. Adam, W.; Jeko, J.; Levai, A.; Nemes, C.; Patonay, T.; Sebok, P. *Tetrahedron Lett.* **1995**, *36*, 3666–3672.
9. Pietikainen, P. *Tetrahedron Lett.* **1995**, *36*, 319–322.
10. Pietikainen, P. *Tetrahedron Lett.* **1999**, *40*, 1001–1004.
11. Pietikainen, P. *Tetrahedron* **1998**, *54*, 4319–4326.
12. (a) Renaud, J. P.; Battioni, P.; Bartoli, J. F.; Mansuy, D. *J. Chem. Soc., Chem. Commun.* **1985**, 888–889; (b) Battioni, P.; Renaud, J. P.; Bartoli, J. F.; Mansuy, D. *J. Chem. Soc., Chem. Commun.* **1986**, 341–343.
13. Irie, R.; Hosoya, N.; Katsuki, T. *Synlett* **1994**, 255–256.
14. Pietikäinen, P. *Tetrahedron Lett.* **1994**, *35*, 941–944.
15. Larrow, J. F.; Jacobsen, E. N.; Gao, Y.; Hong, Y.; Nie, X.; Zepp, C. M. *J. Org. Chem.* **1994**, *59*, 1939–1942.
16. Bergmann, R.; Gericke, R. *J. Med. Chem.* **1990**, *33*, 492–504.
17. Deng, L.; Jacobsen, E. N. *J. Org. Chem.* **1992**, *57*, 4320–4323.
18. Janssen, K. B. M.; Laquiere, I.; Dehaen, W.; Parton, R. F.; Vankelecom, I. F. J.; Jacobs, P. A. *Tetrahedron: Asymmetry* **1997**, *8*, 3481–3487.