Enantioselective Desymmetrization of *meso*-Epoxides with Anilines Catalyzed by Polymeric and Monomeric Ti(IV) Salen Complexes

RUKHSANA I. KURESHY,* MANISH KUMAR, SANTOSH AGRAWAL, NOOR-UL H. KHAN, BALCHAND DANGI, SAYED H. R. ABDI, AND HARI C. BAJAJ

Discipline of Inorganic Materials and Catalysis, Central Salt and Marine Chemicals Research Institute (CSMCRI), Council of Scientific and Industrial Research (CSIR), G. B. Marg, Bhavnagar, Gujarat, India

ABSTRACT The active catalysts for the enantioselective ring opening (ARO) of *meso*-stilbene oxide, *cis*-butene oxide, cyclohexene oxide, cyclopentene oxide, and cyclooctene oxide with various substituted anilines were generated in situ by the reaction of $Ti(O^iPr)_4$ with poly-[(*R,R*)-*N,N*′-bis-{3-(1,1-dimethylethyl)-5-methylene salicylidene} cyclohexane-1,2-diamine]-**1** and (1*R*,2*R*)-*N,N*′-bis[3,5-di(*tert*-butyl)salicylidene] cyclohexane-1,2-diamine-**2**. These catalysts in the presence of nonracemic imine as an additive provided β-amino alcohol in excellent yield (99%) and chiral purity (enantiomeric excess (*ee*) up to 99%) for the ARO of *meso*-stilbene oxide with aniline. The same protocol was less effective for the ARO of cyclic epoxides; however, when triphenylphosphine was used as an additive, there was a significant improvement in catalyst performance for the ARO of cyclohexene oxide (yield, 85–90%; *ee*, 63–67%). Both in situ generated polymeric and monomeric catalysts performed in a similar manner except that the polymeric catalyst Ti(IV)-**1** was more active and recycled several times with retention of enantioselectivity when compared with the monomeric catalyst Ti(IV)-**2**, which was nonrecyclable. *Chirality 23:76–83, 2011.*

KEY WORDS: enantioselective ring opening; *meso*-epoxides; chiral monomeric and polymeric Ti(IV); salen; *syn* and *anti*-β-aminoalcohol

INTRODUCTION

Enantiomerically pure β-amino alcohols are the key structural units found in many biologically active compounds, fine chemicals, and chiral auxiliaries. In recent years, chiral amino alcohols have found a distinct role as chiral ligands for various metal-catalyzed asymmetric organic transformations.[1–8] To synthesize chiral β-amino alcohols, several strategies, namely, aminohydroxylation of olefins,[9,10] addition of α-hydroxy ketones to imines,[11–13] aminolytic kinetic resolution of racemic terminal/*trans* aromatic epoxides,[14–18] and asymmetric ring opening (ARO) of *meso*-epoxides,[19–34] have been reported in the literature. Among these, metal-catalyzed ARO of *meso*-epoxides with amines is one of the most elegant, atom efficient, and straightforward strategies for the synthesis of chiral β-amino alcohols. Various chiral metal complexes of titanium,[19–21] vanadium,[22] niobium,[23,24] copper,[25] lanthanides,[4,6,8,26,27] chromium,[14,15] scandium,[7,28,29] indium,[30,31] and bismuth[32,33] have been used to catalyze this reaction effectively. Recently, Zhou et al.[34] also reported the use of chiral Ti(IV) salen complex for ARO of *meso* epoxides with dithiophosphorous acid as nucleophile, but catalyst recycling was not attempted. As recycling of chiral catalysts is an important criterion from commercial point of view, therefore, it is highly desirable to develop recyclable catalysts for ARO of *meso*-epoxides with amines. In continuation of our ongoing interest in ARO reactions,[15,19,20,35–37] we present here the application of in situ generated Ti(IV) salen complexes **1** and **2** (derived from polymeric and monomeric chiral salen ligands **1** and **2**) as efficient catalysts for the enantioselective ARO of *meso*-stilbene oxide, *cis*-butene oxide, cyclohexene oxide, cyclopentene oxide, and cyclooctene oxide with anilines as nucleophile at RT in the presence of nonracemic imine and triphenyl phosphine as additives. Both catalysts worked well to give β-amino alcohols in high yield (~99%) and enantiomeric excess (*ee*) (~99%) by the ARO of *meso*-stilbene oxide with aniline in the presence of nonracemic imine as an additive; however, only polymeric Ti(IV)-**1** catalyst was recyclable several times without loosing its efficiency.

Additional Supporting Information may be found in the online version of this article.

Contract grant sponsor: DST
Contract grant sponsor: CSIR Network Project on Catalysis

*Correspondence to: Rukhsana I. Kureshy, Discipline of Inorganic Materials and Catalysis, Central Salt and Marine Chemicals Research Institute (CSMCRI), Council of Scientific and Industrial Research (CSIR), G. B. Marg, Bhavnagar 364 002, Gujarat, India. E-mail: rukhsana93@yahoo.co.in

Received for publication 26 November 2009; Accepted 17 March 2010
DOI: 10.1002/chir.20868
Published online 17 May 2010 in Wiley Online Library (wileyonlinelibrary.com).

EXPERIMENTAL

Materials and Methods

$Ti(O^iPr)_4$, 1*R*,2*R*-(−)-1,2-diaminocyclohexane, (*S*)/(*R*)-1-phenylethylamine, 2-methoxybenzaldehyde, 3-methoxybenzaldehyde, aniline (**4**), 2-methoxyaniline (**5**), 4-methoxy aniline (**6**), 4-methylaniline (**7**), 4-chloroaniline (**8**), 4-nitroaniline (**9**), *meso*-stilbene oxide (**3**), *cis*-butene oxide (**10**), cyclohexene oxide (**11**), cyclopentene oxide (**12**), and cyclooctene oxide (**13**) were purchased from Aldrich Chemicals and were used as received. Racemic (**d**, **e**) and nonracemic imines (**f**, **g**) were synthesized by the condensation of appropriate arylaldehydes with α-methylbenzylamine/(*S*)-1-phenylethylamine/(*R*)-1-phenylethylamine by the reported method.[20] The synthesis and characterization of ligands poly-[(*R,R*)-*N,N*′-bis-{3-(1,1-dimethylethyl)-5-methylene salicylidene} cyclohexane-1,2-diamine]-**1** and (1*R*,2*R*)-*N,N*′-bis-[3,5-di(*tert*-butyl)salicylidene] cyclohexane-1,2-diamine-**2** and their precursors were carried out as described earlier.[15,35,36] The solvents were dried by standard procedures, distilled, and stored under nitrogen. NMR spectra were obtained with a Bruker F113V spectrometer (500 and 125 MHz for ^1H and ^{13}C, respectively) and were referenced internally with TMS. FTIR spectra were recorded on Perkin Elmer Spectrum GX spectrophotometer in KBr window. High-resolution mass spectra were obtained with a LC-MS (Q-TOFF) LC (Waters), MS (Micromass) instruments. For the product purification, flash chromatography was performed using silica gel 100–200 mesh (S.D. Fine-Chem, Mumbai, India). Enantiomeric excesses of the products were determined by HPLC (Shimadzu SCL-10AVP) using Daicel Chiralpak AD, OD, and OJ chiral columns with 2-propanol/hexane as an eluent. Optical rotations were measured with a Digipol 781 Automatic Polarimeter Rudolph Instruments.

Typical Experimental Procedure for Ring Opening of Epoxides

To a 5-ml round-bottom flask fitted with rubber septum and equipped with a magnetic stirring bar, chiral polymeric **1**/monomeric **2** salen ligand (0.02 mmol) was dissolved in dry toluene (0.8 ml). $Ti(O^iPr)_4$ (0.02 mmol) was added to the above stirring solution at room temperature (27°C). After an interval of 1 h, an appropriate additive (**a–g**) (0.02 mmol) was added to the resulting solution, and the reaction mixture was further stirred for 20 min at RT. An appropriate epoxide, namely, *meso*-stilbene oxide/cyclohexene oxide/cyclooctene oxide/*cis*-butene oxide/cyclopentene oxide (0.1 mmol), was then added to the above stirring mixture. Subsequently after 20 min, an appropriate aniline, namely, aniline (**4**), 2-methoxyaniline (**5**), 4-methoxy aniline (**6**), 4-methyl aniline (**7**), 4-chloroaniline (**8**), and 4-nitroaniline (**9**) (0.1mmol), was added, and the reaction mixture was further allowed to stir for the specified time. The progress of the reaction was checked on TLC using hexane/ethyl acetate (8/2) as mobile phase. After completion of the reaction, solvent was removed under vacuum, and the product was purified by column chromatography using silica gel 100–200 mesh as stationary phase and hexane/ethyl acetate (8:2) as mobile phase. All products were characterized by appropriate spectroscopic techniques, microanalysis, LCMS, and optical rotation, which were found to be in consonance with the reported values.[7,8,19,20]

Recycling of the Catalyst

The recyclability of the polymeric Ti(IV)-1 catalyst was assessed for ARO of *meso*-stilbene oxide (**3**) as a representative substrate with aniline (**4**) as a nucleophile. After the catalytic run, the solvent was completely removed under reduced pressure, and the residue was extracted with hexane to isolate the product. The remaining solid was further washed with hexane (10 ml), dried under reduced pressure at 50°C for 1−2 h, and was used as recovered catalyst **1**.

Characterization Data of Some Selected Compounds

(1*S*,2*S*)-1,2-Diphenyl-2-(phenylamino)-ethanol[19,20]. The title compound was isolated by column chromatography (*n*-hexane/AcOEt: 90/10) as a white solid. Melting point: 100–102°C.[19] *ee* > 99% on HPLC (Chiralpak OD column) mobile phase, 85/15 *n*-hexane/*i*-PrOH; flow rate 1 ml/min, λ = 247 nm, t_R (1*S*,2*S*) = 15.91 min, t_R (1*R*,2*R*) = 20.60 min. LC-MS, *m/z* 290 $[M + H]^+$, 272 (base peak) $[M - OH]^+$, 312 $[M + Na]^+$. ^1H NMR (500 MHz, $CDCl_3$): δ = 2.38 (bs, OH), 4.40 (bs, NH), 4.51 (d, *J* = 5.8 Hz, 1 H), 4.85 (d, *J* = 5.8 Hz, 1 H), 6.50–6.53 (m, 2 H), 6.59–6.67 (m, 1 H), 7.01–7.09 (m, 2 H), 7.21–7.25 (m, 10 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): 64.8, 78.1, 114.2, 117.9, 126.6, 127.3, 127.5, 128.2, 128.5, 129.0, 140.0, 140.6, 147.0 ppm. IR (KBr): 3546, 3407, 3027, 2880, 2849, 1600, 1502, 1451, 1429, 1320, 1033, 752, 695 cm^{-1}.

(1*S*,2*S*)-1,2-Diphenyl-2-(2-methoxy-phenylamino)-ethanol[19,20]. The title compound was isolated by column chromatography (*n*-hexane/AcOEt 90/10) as a white solid. Melting point: 93–95°C.[19] *ee* 99% on HPLC (Chiralpak OJ column) mobile phase, 80/20 *n*-hexane/*i*-PrOH, flow rate 0.5 ml/min, λ = 254 nm, t_R (1*S*,2*S*) = 35.5 min, t_R (1*R*,2*R*) = 40.0 min. $[\alpha]_D^{27}$ = −48 (*c* = 0.54, CH_2Cl_2). LC-MS, *m/z* 661 $[2M + Na]^+$, 320 $[M + H]^+$, 302 (base peak) $[M - OH]^+$, 342 $[M + Na]^+$. ^1H NMR (500 MHz, $CDCl_3$): δ = 2.73 (bs, OH), 3.79 (s, 3 H), 4.43 (d, *J* = 6.2 Hz, 1 H), 4.79 (d, *J* = 6.4 Hz, 1 H), 5.19 (bs, NH), 6.32 (dd, *J* = 1.6 Hz, 7.2 Hz, 1 H), 6.51–6.70 (m, 3 H), 7.12–7.20 (m, 10 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): 55.6, 64.9, 78.3, 109.6, 111.7, 117.1, 121.0, 126.7, 127.3, 127.7, 128.0, 128.3, 131.1, 140.2, 140.7, 140.6, 147.3 ppm. IR (in KBr): 3407, 3062, 3030, 2936, 2835, 1810, 1698, 1601, 1515, 1248, 1027, 846, 740, 700 cm^{-1}.

(1*S*,2*S*)-1,2-Diphenyl-2-(4-methoxy-phenylamino)-ethanol[19,20]. The title compound was isolated by column chromatography (*n*-hexane/AcOEt 90/10) as a yellow solid. Melting point: 98–102°C.[19] *ee* 95% on HPLC (Chiralpak OD column) mobile phase, 85/15 *n*-hexane/*i*-PrOH; flow rate 1 ml/min, λ = 247 nm, t_R (1*S*,2*S*) = 18.68 min, t_R (1*R*,2*R*) = 22.52 min. LC-MS, *m/z* 661 $[2M + Na]^+$, 320 (base peak) $[M + H]^+$, 342 $[M + Na]^+$. ^1H NMR (500 MHz, $CDCl_3$): δ = 3.64 (s, 3 H), 4.38 (d, *J* = 6.4 Hz, 1 H), 4.85 (d, *J* = 6.4 Hz, 1 H), 6.47–6.51 (m, 2 H),

6.62–6.66 (m, 2 H), 7.01–7.09 (m, 2 H), 7.15–7.22 (m, 10 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): 55.7, 66.2, 78.1, 114.7, 115.8, 126.7, 127.3, 127.8, 127.9, 128.5, 128.7, 140.3, 140.7, 141.4, 152.6 ppm. IR (in KBr): 3483, 3393, 3026, 2964, 2833, 1807, 1510, 1453, 1254, 1024, 819, 753, 700 cm^{-1}.

(1*S*,2*S*)-1,2-Diphenyl-2-(4-methyl-phenylamino)-ethanol[19,20]. The title compound was isolated by column chromatography (*n*-hexane/AcOEt 90/10) as a white solid. Melting point: 85°C.[19] *ee* > 99% on HPLC (Chiralpak AD column,) mobile phase, 85/15 *n*-hexane/*i*-PrOH; flow rate 1 ml/min, λ = 247 nm, t_R (1*R*,2*R*) = 20.60 min, t_R (1*S*,2*S*) = 17.99 min. LC-MS, *m/z* 304 $[M + H]^+$, 286 (base peak) $[M - OH]^+$. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.15 (s, 3 H), 4.45 (d, *J* = 6.2 Hz, 1 H), 4.81 (d, *J* = 6.2 Hz, 1 H), 6.42–6.46 (m, 2 H), 6.84–6.88 (m, 2 H), 7.19–7.23 (m, 10 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): 20.3, 65.2, 78.0, 114.4, 126.5, 127.2, 127.6, 128.1, 128.3, 129.5, 139.3, 139.5.4, 146.5 ppm. IR (in KBr): 3399, 3061, 3029, 2859, 2831, 1813, 1616, 1518, 1490, 1259, 1044, 815, 768, 700 cm^{-1}.

(2*S*,3*S*)-2-*N*-Phenylamino-3-butanol[20,24]. The title compound was isolated by column chromatography (*n*-hexane/AcOEt 90/10) as an oil. *ee* 19% on HPLC (Chiralpak OD column) mobile phase, 97.5/2.5 *n*-hexane/*i*-PrOH; flow rate 1 ml/min, λ = 247 nm, t_R (2*S*,3*S*) = 35.63 min, t_R (2*R*,3*R*) = 38.57 min. LC-MS, *m/z* 166 $[M + H]^+$, ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.14 (d, *J* = 6.8 Hz, 1H), 1.25 (d, *J* = 6.8 Hz, 3H), 2.61 (brs, 1H), 3.31 (m, 1H), 3.62 (m, 2H), 6.66–6.74 (m, 3H), 7.15–7.18 (m, 2H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 17.3, 19.5, 56.1, 71.4, 114.3, 118.2, 129.3, 147.7 ppm. IR (KBr) 3398, 3053, 2974, 2926, 1922, 1602, 1505, 1439, 1376, 1318, 1254, 1005, 902, 751, 692 cm^{-1}.

(1*S*,2*S*)-2-(Phenylamino)-cyclohexane-1-ol[19,20]. The title compound was isolated by column chromatography (*n*-hexane/AcOEt 90/10) as a white solid. Melting point: 58–60°C.[19] *ee* 67% on HPLC (Chiralpak OJ column) mobile phase, 95/5 *n*-hexane/*i*-PrOH; flow rate 0.4 ml/min, λ = 247 nm, t_R (1*S*,2*S*) = 13.73 min, t_R (1*R*,2*R*) = 15.38 min. LC-MS, *m/z* 192 $[M + H]^+$, 214 $[M + Na]^+$. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.03–1.41 (m, 4 H), 1.71–1.77 (m, 2 H), 2.09–2.15 (m, 2 H), 2.89 (m, 2 H), 3.13 (ddd, *J* = 3.9 Hz, *J* = 10.0 Hz, *J* = 10.1 Hz, 1 H), 3.33 (ddd, *J* = 4.2 Hz, *J* = 10.4 Hz, *J* = 10.5 Hz, 1 H), 6.7–7.2 (m, 2 H), 7.21–7.25 (m, 5 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 24.2, 24.9, 31.5, 33.1, 60.1, 74.4, 114.3, 118.3, 129.3, 147.8. IR (in KBr): 3354, 2931, 2858, 1602, 1501, 1448, 1320, 1067, 748 cm^{-1}.

(1*S*,2*S*)-2-(2-Methoxyphenylamino)-cyclohexane-1-ol[19,20]. The title compound was isolated by column chromatography (*n*-hexane/AcOEt 90/10) as a white solid. Melting point: 68–70°C.[19] *ee* 29% on HPLC (Chiralpak OJ column) mobile phase, 80/20 *n*-hexane/*i*-PrOH; flow rate 0.5 ml/min, λ = 247 nm, t_R (1*S*,2*S*) = 20.54 min, t_R (1*R*,2*R*) = 22.05 min. $[\alpha]_D^{27}$ = +49.6 (*c* = 3.0, CH_2Cl_2, 63% *ee*).^{1}H NMR (500 MHz, $CDCl_3$): ^{1}H NMR ($CDCl_3$): δ = 0.97–1.15 (m, 1 H), 1.24–1.50 (m, 3 H), 1.68–1.78 (m, 2 H), 2.04–2.16 (m, 2 H), 2.85 (bs, 1 H), 3.07–3.19 (m, 1 H), 3.34–3.46 (m, 1 H), 3.83 (s, 3 H), 6.63–6.89 (m, 4 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 24.2, 25.0, 31.5, 33.0, 55.4, 55.6, 74.5, 109.7, 111.4, 117.2, 121.2, 137.5, 147.5 ppm. IR (in KBr): 3616, 3429, 3067, 2964, 1602, 1511, 1456, 1430, 1341, 1247, 1180, 1121, 1050, 1030, 977, 945 cm^{-1}.

(1*S*,2*S*)-2-(4-Methoxyphenylamino)-cyclohexane-1-ol[19,20]. The title compound was isolated by column chromatography (*n*-hexane/AcOEt 85/15) as a white solid. Melting point: 62–64°C.[19] *ee* 36% on HPLC (Chiralpak OD column) mobile phase, 80/20 *n*-hexane/*i*-PrOH; flow rate 0.5 ml/min, λ = 247 nm, t_R (1*S*,2*S*) = 22.30 min, t_R (1*R*,2*R*): 27.48 min. $[\alpha]_D^{27}$ = +40.1 (*c* = 3.2, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.85–1.10 (m, 1 H), 1.12–1.40 (m, 3 H), 1.60–1.80 (m, 2 H), 2.0–2.18 (m, 2 H), 2.92–3.04 (m, 1 H), 2.60 (bs, 1 H), 3.24–3.55 (m, 1 H), 3.73 (s, 3 H), 6.66 (d, *J* = 8.8 Hz, 2 H), 6.76 (d, *J* = 8.8 Hz, 2 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 24.2, 25.0, 31.4, 33.0, 55.6, 61.6, 74.3, 114.7, 116.3, 141.5, 152.8 ppm. IR (in KBr): 3677, 3529, 3366, 3021, 3013, 2938, 2861, 2836, 1612, 1512, 1465, 1450, 1401, 1296, 1239, 1221, 1180, 1136, 1067, 1038 cm^{-1}.

(1*S*,2*S*)-2-(4-Methylphenylamino)-cyclohexane-1-ol[19,20]. The title compound was isolated by column chromatography (*n*-hexane/AcOEt 90/10) as a brownish liquid. *ee* 38% on HPLC (Chiralpak OD column) mobile phase, 90/10 *n*-hexane/*i*-PrOH; flow rate 0.8 ml/min, λ = 247 nm, t_R (1*S*,2*S*):17.99 min, t_R (1*R*,2*R*): 20.60 min. ^{1}H NMR (500 MHz, $CDCl_3$); δ = 1.01–1.05 (m, 2H), 1.23–1.40 (m, 5 H), 1.70–1.75 (m, 2 H), 2.24 (s, 3 H), 3.062–3.10 (m, 1 H), 6.64 (d, 2 H, *J* = 8 Hz), 7.00 (d, 2 H, *J* = 8 Hz) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.40, 24.31, 25.11, 31.60, 33.10, 60.73, 74.55, 114.81, 129.88 ppm. IR (in KBr): 3665, 3390, 3105, 3019, 2928, 2860, 2734, 1866, 1617, 1519, 1451, 1451, 1405, 1300, 1252, 1182, 1128, 1066, 936 cm^{-1}.

(1*S*,2*S*)-2-(Phenylamino)-cyclooctane-1-ol[4,20]. The title compound was isolated by column chromatography (*n*-hexane/AcOEt 90/10) as a white solid. Melting point 55–56°C.[20] *ee* 46% on HPLC (Chiralpak OD column) mobile phase, 95/5 *n*-hexane/*i*-PrOH; flow rate 0.8 ml/min, λ = 247 nm, t_R (1*S*,2*S*) = 27.12 min, t_R (1*R*,2*R*) = 29.34 min. LC-MS, *m/z* 218 $[M + H]^+$; ^{1}H NMR (500 MHz, $CDCl_3$): 1.05–1.45 (m, 4H), 1.50–2.15 (m, 8H), 3.40–3.50 (m, 1H), 3.60–3.70 (m, 1H), 4.50 (br, 1H), 6.70–7.20 (m, 6H) ppm. IR (KBr): 3315, 3107, 3054, 3027, 2941, 1923, 1690, 1604, 1498, 1465, 1306, 1256 cm^{-1}.

RESULTS AND DISCUSSION

The active catalysts for the asymmetric epoxide ring-opening reaction with anilines as nucleophile were generated in situ by the reaction of poly-[(*R,R*)-*N,N*′-bis-{3-(1,1-dimethylethyl)-5-methylene salicylidene} cyclohexane-1,2-diamine]-**1**/(1*R*,2*R*)-*N,N*′-bis[3,5-di(*tert*-butyl)salicyliden] cyclohexane-1,2-diamine-**2** with $Ti(O^iPr)_4$ (Fig. 1). To begin with we have carried out ring opening of *meso*-stilbene oxide (**3**) taken as model substrate with aniline (**4**)

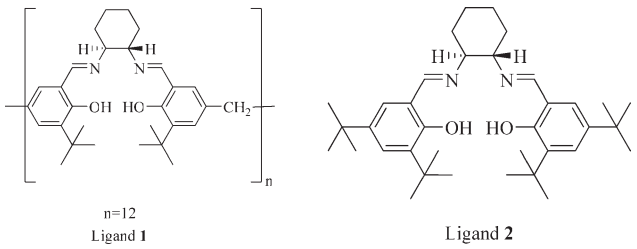
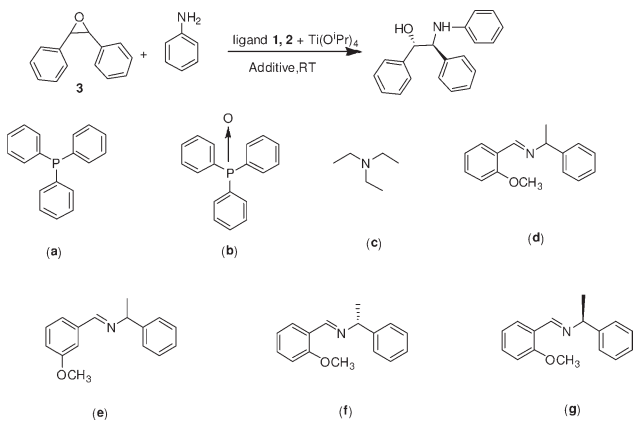


Fig. 1. Structure of chiral polymeric and monomeric salen ligands **1** and **2**.

using variable loadings of the above in situ generated complexes as catalyst in toluene at RT (Table 1, entries 1–6). The results showed that 20 mol % of both the catalysts is optimum (entries 3, 4) in terms of yield and *ee* of the product β-aminoalcohol **4′** at RT. Further, in view of well-known impact of temperature on enantioselectivity and product yield in an asymmetric organic transformation; we carried out present ring-opening reaction at 10 and 0°C as well and found out that there was only a marginal increase in the enantioselectivity (entries 7–10) by lowering the reaction temperature from RT. The advantage of this little increase in the enantioselectivity was however outweighed by the increase in the reaction time and low product yields. Hence, our next effort to increase the reactivity and enantioselectivity of ARO reaction was on application of various achiral (**a–c**) and racemic (**d,e**)/nonracemic additives (**f,g**) with the above optimized process. The efficacy of these additives has been previously reported by us on the enantioselective epoxide ring-opening reaction to form chiral β-amino alcohols.[19,20] Among the various additives (Fig. 2) used, the use of single enantiomer of additive (**f**) with 20 mol % catalyst loading at RT for the ARO of *meso*-stilbene oxide (**3**) produced chiral β-amino alcohol (**4′**) in high yield (99%) and *ee* (>99%) within 9–12 h (entries 21,22). Noticeably, the use of (**g**), which is opposite enantiomer of (**f**), caused decrease in yield and *ee* of the

TABLE 1. Optimization of reaction condition for *meso*-stilbene oxide (3) with aniline (4) using in situ generated chiral Ti(IV) polymeric and monomeric complexes 1 and 2



Entry	Catalyst (mol %)	Additive	Temperature (°C)	Solvent	Time (h)	β-Aminoalcohol **4′** Yield (%)[a]	β-Aminoalcohol **4′** *ee* (%)[b]
1(2)[c]	10	–	RT	Toluene	18 (25)	65 (60)	22 (20)
3(4)	20	–	RT	Toluene	12 (18)	75 (72)	43 (42)
5(6)	40	–	RT	Toluene	10 (15)	76 (74)	44 (42)
7(8)	20	–	10°C	Toluene	13 (20)	67 (60)	46 (44)
9(10)	20	–	0°C	Toluene	24 (36)	63 (51)	52 (49)
11(12)	20	**a**	RT	Toluene	10 (14)	85 (79)	55 (50)
13(14)	20	**b**	RT	Toluene	10 (14)	83 (80)	48 (35)
15(16)	20	**c**	RT	Toluene	10 (16)	55 (40)	46 (40)
17(18)	20	**d**	RT	Toluene	10 (14)	75 (70)	54 (50)
19(20)	20	**e**	RT	Toluene	10 (16)	61 (50)	69 (67)
21(22)	20	**f**	RT	Toluene	9 (12)	99 (99)	>99 (99)
23(24)[d]	20	**g**	RT	Toluene	9 (12)	95 (90)	75 (72)
25(26)	20	**f**	RT	DCM	9 (14)	88 (85)	87 (84)
27(28)	20	**f**	RT	THF	9 (16)	75 (70)	62 (54)

[a]Isolated yield.
[b]The *ee* was determined using chiral OD column.
[c]Data in parenthesis given for complex **2**.
[d]Reaction conducted in the presence of (*R*)-*N*-(2-methoxybenzylidene)-1-phenylethanamine as additive.

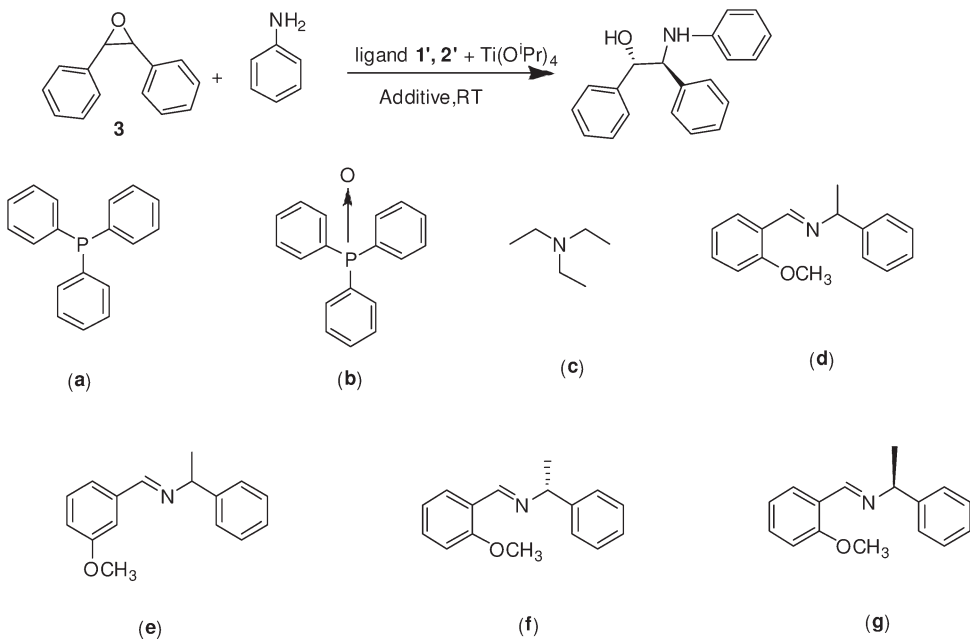
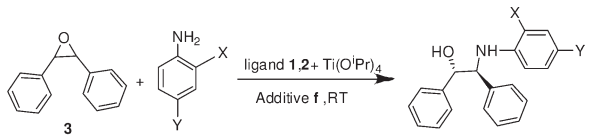


Fig. 2. Structure of additives.

desired product (Table 1, entries 23, 24). These results suggest the existence of synergy between the catalyst and the additive during the transfer of chirality during the epoxide ring-opening reaction in the catalytic cycle. Such an observation had also been reported previously for chiral BINOL and Schiff base systems.[38,20] Furthermore, we also checked the solvent dependence of this catalytic ARO protocol and found that dichloromethane and THF (entries 25–28) are not as good as toluene (entries 21, 22).

Next, to see the efficacy of this protocol, we further explored the use of various nucleophiles, namely 2-methoxyaniline (**5**), 4-methoxyaniline (**6**), 4-methylaniline (**7**), 4-chloroaniline (**8**), and 4-nitroaniline (**9**), in the ring opening of *meso*-stilbene oxide (**3**) with in situ generated polymeric/monomeric complexes **1** and **2** in combination with nonracemic imine (**f**) as an additive at RT. The results summarized in Table 2 have shown that the substituents present on aniline have profound affect on its nucleophilicity. The electron-donating substituents like OMe and Me increase the nucleophilicity of the aniline making the epoxide ring-opening reaction more facile (entries 3–8), thus resulting in high yield (85–92%) of β-amino alcohols and high chiral induction (*ee*; up to 99%) (entry 3), whereas substituents like NO_2 and Cl drastically reduced the availability of lone pair of electrons on the nitrogen of the aniline, thereby making these nucleophiles ineffective to open the epoxide ring (entries 9–12). Overall, both the in situ generated complexes **1** and **2** gave comparable yields and enantioselectivities of β-aminoalcohols; however, reaction took longer time with monomeric complex **2** as catalyst against polymeric complex **1**. The enhanced reactivity in the case of polymeric complex **1** may be attributed to the increase reactive sites, which may be

TABLE 2. Asymmetric ring opening of *meso*-stilbene oxide (3) with various amines (4–9) using in situ generated chiral polymeric and monomeric Ti(IV) salen complexes 1 and 2 in the presence of nonracemic imine (f) as additive[a]

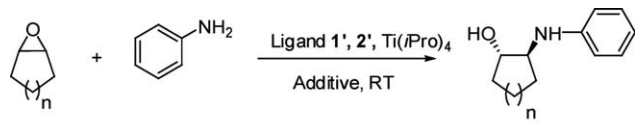


4 X=Y=H
5 X=OMe,Y=H
6 X=H,Y=OMe
7 X=H,Y=Me
8 X=H,Y=Cl
9 X=H,Y=NO_2

			β-Aminoalcohol **4′-9′**	
Entry	Amine	Time (h)	Yield (%)[b]	*ee* (%)[c]
1(2)[d]	**4**	9(12)	99 (99)	>99 (99)
3(4)	**5**	10 (14)	92 (91)	99 (95)
5(6)	**6**	10 (16)	90 (89)	95 (95)
7(8)	**7**	10 (16)	92 (85)	77 (63)
9(10)	**8**	24 (24)	–	–
11(12)	**9**	24 (24)	–	–

[a]All reactions were carried out at room temperature using 0.1 mmol epoxide, amine 0.1 mmol, complexes **1** and **2** 0.02 mmol in the presence of 0.02 mmol additive.
[b]Isolated yield.
[c]The *ee* was determined using chiral OD, OJ, AD column.
[d]Data in parenthesis given for complex **2**.

TABLE 3. Asymmetric ring opening of epoxides (10–13) with aniline (4) in the presence of different additives using in situ generated chiral polymeric and monomeric Ti(IV) salen complexes 1 and 2[a]



				β-Aminoalcohol **10′-13′**	
Entry	Oxide	Additive	Time (h)	Yield (%)[b]	*ee* (%)[c]
1(2)[d]	**10**	**f**	10	80 (76)	19 (15)
3(4)		**a**	12	85 (80)[d]	Racemic
5(6)		**b**	12	75 (70)	Racemic
7(8)		**c**	10	67 (65)	Racemic
9(10)	**11**	**f**	24	57 (50)	28 (22)
11(12)		**a**	12	90 (85)	67 (63)
13(14)		**b**	15	75 (70)	30 (25)
15(16)		**c**	12	77 (70)	Racemic
17(18)	**12**	**f**	12	81 (75)	Racemic
19(20)		**a**	10	80 (75)	37 (32)
21(22)		**b**	15	70 (65)	Racemic
23(24)		**c**	15	75 (70)	Racemic
25(26)	**13**	**f**	15	33 (30)	Racemic
27(28)		**a**	12	46 (40)	46 (38)
29(30)		**b**	15	54 (50)	33 (30)
31(32)		**c**	15	47 (40)	Racemic

[a]All reactions were carried out at room temperature using 0.1 mmol epoxide, amine 0.1 mmol, complexes **1** and **2** 0.02 mmol in the presence of 0.02 mmol additive.
[b]Isolated yield.
[c]The *ee* was determined using chiral AD, OD, OJ column.
[d]Data in parenthesis given for complex **2**.

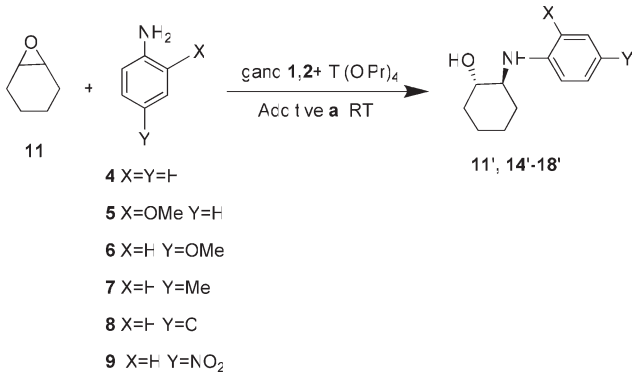
working in cooperation.[39] Recyclability of polymeric catalyst **1** was another advantage over monomeric catalyst **2,** which was nonrecyclable.

The scope of this protocol for the ring-opening reaction was further extended to *cis*-butene oxide (**10**), cyclohexene oxide (**11**), cyclopentene oxide (**12**), and cyclooctene oxide (**13**) with aniline (**4**) as nucleophile and nonracemic (**f**) as an additive for the synthesis of respective β-amino alcohols (Table 3 entries 1, 2, 9, 10, 17, 18, 25, and 26). In most of the cases, although the product yield was good to excellent, the reaction took racemic pathway. These results led us to explore the use of nonchiral additives with these epoxides without changing other reaction parameters. The triethylamine (**c**) as an additive failed to show any enantioselectivity (entries 7, 8, 15, 16, 23, 24, 31, and 32), whereas triphenylphosphine (**a**) performed better. The best results with this additive (**a**) using catalysts **1** and **2** were obtained in the case of ring opening of cyclohexene oxide (**11**) with aniline (**4**) (yield, 90 and 85%; *ee*, 67 and 63% entries 11, 12).

Further, on conducting the ARO of cyclohexene oxide (**11**) with electron-rich substituted anilines (**4–7**) using in situ generated complexes **1** and **2** as catalysts and triphenylphosphine (**a**) as an additive, only moderate product yield with low *ee* for respective aminoalcohols was achieved (Table 4, entries 3–8). On the other hand, electron-deficient anilines (**8,9**) failed to react with cyclohexene oxide (**11**) under this condition (Table 4). In all the catalytic runs, (*S*) enantiomer of the product chiral β-amino alcohols (**11′, 14′–18′**) formed in excess with the (*R*)-form of in situ generated Ti (IV) salen complexes **1** and **2**.

To evaluate the recycle ability of the in situ generated chiral polymeric and monomeric Ti(IV) salen complexes **1** and **2**, we conducted catalytic runs using *meso*-stilbene oxide (**3**) as a model substrate with aniline (**4**) in presence of nonracemic imine (**f**) as an additive at RT. The in situ generated polymeric complex **1** was precipitated out after the first catalytic run by the addition of excess amount of *n*-hexane to the reaction mixture, and the resulting catalyst was collected by filtration. The recovered catalyst **1** was thoroughly washed with hexane and dried under vacuum at RT. The recovered catalyst was characterized by

TABLE 4. Asymmetric ring opening of cyclohexene oxide (11) with various amines (4-9) using in situ generated chiral polymeric and monomeric Ti(IV) salen complexes 1 and 2 in presence of triphenylphosphine a as additive[a]



			β-Aminoalcohol **11′, 14′-18′**	
Entry	Amine	Time (h)	Yield (%)[b]	*ee* (%)[c]
1(2)[d]	**4**	12	90 (85)	67 (63)
3(4)	**5**	13	70 (64)	29 (25)
5(6)	**6**	15	72 (68)	36 (33)
7(8)	**7**	17	75 (71)	37 (32)
9(10)	**8**	24	–	–
11(12)	**9**	24	–	–

[a]All reactions were carried out at room temperature using 0.1 mmol epoxide, 0.1 mmol amine, complexes **1** and **2** 0.02 mmol in the presence of 0.02 mmol additive.
[b]Isolated yield.
[c]The *ee* was determined using chiral OD, OJ, column.
[d]Data in parenthesis given for complex **2**.

TABLE 5. Data for the asymmetric ring opening of *meso*-stilbene epoxide (3) with aniline (4) in the presence of nonracemic imine (f) as additive using in situ generated chiral polymeric Ti(IV) salen complex 1

Run	Time (h)	Yield (%)[a]	*ee* (%)[b]
1	9	99	>99
2	12	97	98
3	13	95	>99
4	15	93	97
5	16	92	97
6	17	92	97

[a]Isolated yield.
[b]The *ee* was determined using chiralpak HPLC OD column.

various physicochemical methods before its reuse. The IR spectral analysis showed no apparent structural change in the catalyst (Figure given in Supporting Information). The recovered catalyst **1** was used as such in the manner same as fresh catalyst for the ring-opening reaction of *meso*-stilbene epoxide (**3**) with aniline (**4**); however, in each reuse run, fresh addition of nonracemic additive (**f**) was required to achieve consistent results. Similar activity and enantioselectivity was achieved in the recycle experiments (Table 5, runs 2–6) though there was some increase in reaction time. The in situ generated monomeric complex **2** could not be recycled possibly because of high solubility of the complex, which failed to precipitate out on adding excess amount of *n*-hexane in a postcatalytic work up step. To the best of our knowledge, this is the first report where recyclable Ti(IV) polymeric complex **1** was used for *meso*-epoxide ring-opening reaction with amines with added advantage of six times catalyst recyclability.

CONCLUSION

Nonracemic in situ generated polymeric and monomeric Ti(IV) salen complexes were used for ARO of *meso*-epoxides with anilines in the presence of achiral, racemic, and nonracemic additives at RT. Excellent yields (99%) of β-amino alcohol and high optical purity (*ee* up to 99%) were achieved for the ARO of *meso*-stilbene oxide with aniline. However, among the cyclic epoxides used, best results in term of yield and enantioselectivity in this study were achieved for ARO of cyclohexene oxide with aniline using triphenylphosphine as an additive. Although comparable yields and enantioselectivities were achieved with both catalysts, the in situ generated polymeric Ti(IV) salen complex was more reactive than monomeric complex. To the best of our knowledge, this is the first report on ARO of *meso*-epoxides using polymeric Ti(IV) salen complex as catalyst that showed steady performance in reuse experiments (six times).

ACKNOWLEDGMENTS

RIK is thankful to "Analytical Discipline" for providing instrumentation facilities.

LITERATURE CITED

1. Hodgson DM, Gibbs AR, Lee GP. Enantioselective desymmetrisation of achiral epoxides. Tetrahedron 1996;52:14361–14384.
2. Jacobsen EN, Wu MH. In: Jacobsen EN, Pfaltz A, Yamamoto H, editors. Cr(salen) catalysed asymmetric ring opening reactions of epoxides in room temperature ionic liquids. Comprehensive asymmetric catalysis, Vol.3. Berlin: Springer; 1999. p1309.
3. Schneider C. Synthesis of 1,2-difunctionalized fine chemicals through catalytic, enantioselective ring-opening reactions of epoxides. Synthesis 2006;23:3919–3944.
4. Hou XL, Wu J, Dai LX, Xia LJ, Tang MH. Desymmetric ring-opening of *meso*-epoxides with anilines: a simple way to chiral β-amino alcohols. Tetrahedron: Asymmetry 1998;9:1747–1752.
5. Sagawa S, Abe H, Hase Y, Inaba T. Catalytic asymmetric aminolysis of 3,5,8-trioxabicyclo[5.1.0]octane providing an optically pure 2-amino-1,3,4-butanetriol equivalent. J Org Chem 1999;64:4962.
6. Sekine A, Ohshima T, Shibasaki M. An enantioselective formal synthesis of 4-demethoxydaunomycin using the catalytic asymmetric ring opening reaction of *meso*-epoxide with *p*-anisidine. Tetrahedron 2002;58:75–82.
7. Schneider C, Sreekanth AR, Mai E. Scandium-bipyridine-catalyzed enantioselective addition of alcohols and amines to meso-epoxides. Angew Chem Int Ed 2004;43:5691.
8. Carree F, Gil R, Collin J. Enantioselective ring opening of *meso*-epoxides by aromatic amines catalyzed by lanthanide iodo binaphtholates. J Org Lett 2005;7:1023–1026.
9. Li G, Chang HT, Sharpless KB. Catalytic asymmetric aminohydroxylation (AA) of olefins. Angew Chem Int Ed Engl 1996;35:451–454.
10. Brien PO. Sharpless asymmetric aminohydroxylation: scope, limitations, and use in synthesis. Angew Chem Int Ed 1999;38:326–329.
11. List B. The direct catalytic asymmetric three-component mannich reaction. J Am Chem Soc 2000;122:9336–9337.
12. Córdova A, Notz W, Zhong G, Betancort JM, Barbas CF. A highly enantioselective amino acid-catalyzed route to functionalized α-amino acids. J Am Chem Soc 2002;124:1842–1843.
13. Trost BM, Terrell LR. A direct catalytic asymmetric Mannich-type reaction to *syn*-amino alcohols. J Am Chem Soc 2003;125:338–339.
14. Bartoli G, Bosco M, Carlone A, Locatelli M, Massaccesi M, Melchiorre P, Sambri L. Asymmetric aminolysis of aromatic epoxides: a facile catalytic enantioselective synthesis of *anti*-β-amino alcohols. Org Lett 2004;6:2173–2176.
15. Kureshy RI, Singh S, Khan NH, Abdi SHR, Agrawal S, Jasra RV. Enantioselective aminolytic kinetic resolution (AKR) of epoxides catalyzed by recyclable polymeric Cr(III) salen complexes. Tetrahedron: Asymmetry 2006;17:1638–1643.
16. Keith JM, Larrow JF, Jacobsen EN. Practical considerations in kinetic resolution reactions. Adv Synth Catal 2001;343:5–26.
17. Label H, Jacobsen EN. Chromium catalyzed kinetic resolution of 2,2-disubstituted epoxides. Tetrahedron Lett 1999;40:7303–7306.
18. Bandini M, Cozzi PG, Melchiorre P, Umani-Ronchi A. Kinetic resolution of epoxides by a C−C bond-forming reaction: highly enantioselective addition of indoles to *cis*, *trans*, and *meso* aromatic epoxides catalyzed by [Cr(salen)] complexes. Angew Chem Int Ed 2004;43:84–87.
19. Kureshy RI, Singh S, Khan NH, Abdi SHR, Suresh E, Jasra RV. Facile enantioselective ring-opening reaction of meso epoxides with anilines using (S)-(−)-BINOL-Ti complex as a catalyst. Eur J Org Chem 2006;2006:1303–1309.
20. Kureshy RI, Prathap KJ, Agrawal S, Khan NH, Abdi SHR, Jasra RV. Highly enantioselective syntheses of chiral β-amino alcohols in the presence of chiral TiIV Schiff base complexes as catalysts. Eur J Org Chem 2008;18:3118–3128.
21. Sun J, Yuan F, Yang M, Pan Y, Zhu C. Enantioselective ring-opening reaction of meso-epoxides with ArSH catalyzed by heterobimetallic Ti-Ga-Salen system. Tetrahedron Lett 2009;50:548–551.
22. Sun J, Dai Z, Yang M, Pan X, Zhu C. Vanadium-salan catalyzed enantioselective ring opening of *meso*-epoxides with aromatic amines. Synthesis 2008;2008:2100–2104.

23. Arai K, Salter MM, Yamashita Y, Kobayashi S. Enantioselective desymmetrization of *meso* epoxides with anilines catalyzed by a niobium complex of a chiral multidentate binol derivative. Angew Chem Int Ed Engl 2007;46:955–957.
24. Arai K, Lucarini S, Salter MM, Ohta K, Yamashita Y, Kobayashi S. The development of scalemic multidentate niobium complexes as catalysts for the highly stereoselective ring opening of *meso*-epoxides and *meso*-aziridines. J Am Chem Soc 2007;129:8103–8111.
25. Tanaka K, Oda S, Shiro M. A novel chiral porous metal-organic framework: asymmetric ring opening reaction of epoxide with amine in the chiral open space. Chem Commun 2008;7:820–822.
26. Fu XL, Wu SH. A regio-and stereoselective synthesis of β-amino alcohols. Synth Commun 1997;27:1677–1683.
27. Carrée F, Gil R, Collin J. Samarium iodides catalyzed *meso*-epoxides ring opening by aromatic amines. Tetrahedron Lett 2004;45:7749–7751.
28. Mai E, Schneider C. Scandium-bipyridine-catalyzed enantioselective aminolysis of meso-epoxides. Chem Eur J 2007;13:2729–2741.
29. Azoulay S, Manabe K, Kobayashi S. Catalytic asymmetric ring opening of *meso*-epoxides with aromatic amines in water. Org Lett 2005;7:4593–4595.
30. Mai E, Schneider C. Indium-bipyridine catalyzed, enantioselective aminolysis of *meso*-epoxides. Synlett 2007;13:2136–2138.
31. Gao B, Wen Y, Yang Z, Huang X, Liu X, Feng X. Asymmetric ring opening of *meso*-epoxides with aromatic amines catalyzed by a new proline-based N,N′-dioxide-indium tris(triflate) complex. Adv Synth Catal 2008;350:385–390.
32. Ogawa C, Azoulay S, Kobayashi S. Bismuth triflate-chiral bipyridine complex catalyzed asymmetric ring opening reactions of meso-epoxide in water. Heterocycles 2005;66:201–206.
33. Paster IM, Yus M. Asymmetric ring opening of epoxides. Curr Org Chem 2005;9:1–29.
34. Zhou ZH, Li ZM, Liu B, Li KY, Wang LX, Zhao GF, Zhou QL, Tang CC. (Salen)Ti(IV)-catalyzed asymmetric ring-opening of *meso* epoxides using dithiophosphorus acid as the nucleophile. Chin Chem Lett 2006;17:143–146.
35. Kureshy RI, Prathap KJ, Agrawal S, Kumar M, Khan NH, Abdi SHR, Jasra RV. Highly efficient recyclable CoIII-salen complexes in the catalyzed asymmetric aminolytic kinetic resolution of aryloxy/terminal epoxides for the simultaneous production of N-protected 1,2-amino alcohols and the corresponding epoxides in high optical purity. Eur J Org Chem 2009;17:2863–2871.
36. Kureshy RI, Prathap KJ, Singh S, Agrawal S, Khan NH, Abdi SHR, Jasra RV. Chiral recyclable dimeric and polymeric Cr(III) salen complexes catalyzed aminolytic kinetic resolution of trans-aromatic epoxides under microwave irradiation. Chirality 2007;19:809–815.
37. Kureshy RI, Singh S, Khan NH, Abdi SHR, Agrawal S, Mayani VJ, Jasra RV. Microwave-assisted asymmetric ring opening of *meso*-epoxides with aromatic amines catalyzed by a Ti-*S*-(−)-BINOL complex. Tetrahedron Lett 2006;47:5277–5279.
38. Nakamura S, Sato N, Sugimoto M, Toru T. A new approach to enantioselective cyanation of imines with Et_2AlCN. Tetrahedron: Asymmetry 2004;15:1513–1516.
39. Khan NH, Agrawal S, Kureshy RI, Abdi SHR, Prathap KJ, Jasra RV. Enantioselective cyanosilylation of ketones catalyzed by recyclable polymeric and dimeric Mn(III) salen complexes at room temperature. Chirality 2009;21:262–270.