Hindawi Publishing Corporation
Research Letters in Organic Chemistry
Volume 2009, Article ID 109717, 5 pages
doi:10.1155/2009/109717

Research Letter

Solvent-Free Microwave Synthesis of Aryloxypropanolamines by Ring Opening of Aryloxy Epoxides

Rukhsana I. Kureshy,[1] Irshad Ahmad,[2] Kavita Pathak,[1] N. H. Khan,[1] Sayed H. R. Abdi,[1] H. C. Bajaj,[1] and Eringathodi Suresh[3]

[1] *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*
[2] *Leibniz-Institute for Surface Modification e.V. (IOM), Permoserstraße 15, 04318 Leipzig, Germany*
[3] *Analytical Science Division, Central Salt and Marine Chemicals Research Institute (CSMCRI), G. B. Marg, Bhavnagar 364 002, Gujarat, India*

Correspondence should be addressed to Rukhsana I. Kureshy, rukhsana93@yahoo.co.in

Received 18 December 2008; Accepted 26 January 2009

Recommended by Kazuaki Ishihara

The ring opening reaction of aryloxyepoxides with isopropylamine under solvent-free microwave irradiation produced therapeutically useful β-blockers-aryloxypropanolamines in excellent yield (up to 98%) in 10 minutes which is considerably less than the time taken in classical heating (~16 hours).

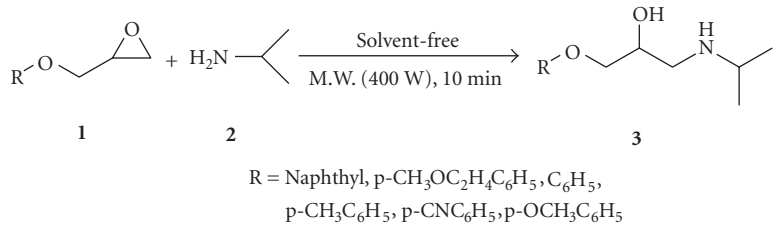
1. Introduction

Aryloxypropanolamines are important class of β-adrenergic blocking agents (β-blockers) and extensively used in medicinal chemistry for the treatment of hypertension, angina pectoris, glaucoma, anxiety, and obesity [1, 2]. The oxirane ring [3] due to its inherent polarity and strain is susceptible to the attack of nucleophiles to give propan-2-ol **3** (Scheme 1), which is known for their β-adrenoceptor antagonist activity. One of the most straightforward synthetic approaches for the preparation of β–blockers involves the heating of epoxides with an excess of amines at elevated temperature [4–7]. In recent years, various metal salts as catalysts have been reported for epoxide ring opening reaction with amine and amine derivatives giving good-to-poor regioselectivity [8–12].

Microwave-assisted organic synthesis is currently gaining ground in synthetic chemistry largely due to the dramatic reduction in reaction time (from days or hours to minutes or even seconds) and advancement in the need-based design of microwave reactors [13, 14]. As a part of our ongoing research in ring opening of epoxides with amines [15–19], herein we report solvent-free microwave-assisted synthesis of aryloxypropanolamines by ring opening of aryloxyepoxides with isopropylamine. Excellent yields (up to 98%) of aryloxypropanolamines were achieved in shorter time (10 minutes) with substantially reduced quantity of amine as compared to method used under classical thermal conditions [20]. Quanitiative yields of 2-aminoalcohols have been reported earlier in the ring opening of epoxides with aliphatic and aromatic amines using montmorillonite K-10, metal salts and metal salts supported on montmorillonite K-10 as catalyst [21–23].

2. Results and Discussion

The ring opening of 3-(1-naphthoxy)-1,2-epoxy propane **1a** with isopropylamine **2** in solvent-free condition was used as a representative reaction to see the effect of strength of microwave wattage and duration of its exposure on % yield of aryloxypropanolamine. Data from Table 1 shows that with an increase in microwave output power as well as reaction time, there is an increase in the formation of the product (Table 1, entries 2–9). Best result (yield, 98%) was achieved in 10 minutes at 400 W of microwave



Scheme 1: Solvent-free microwave-assisted ring opening of aryloxyepoxides with isopropylamine.

Table 1: Ring opening of 3-(1-naphthoxy)-1,2-epoxy propane **1a** with isopropylamine **2** under different conditions (3-(1-naphthoxy)-1,2-epoxypropane (1.0 g, 5 mmol) and isopropylamine (0.59 g, 7.5 mmol) were heated at 50°C in a Teflon reactor for the given time under specified MW power).

Entry	Conditions	Yield[(a)] (%)
1[(b)]	Without MW	90
2	2 min/100 W	45
3	2 min/300 W	56
4	2 min/400 W	64
5	5 min/100 W	69
6	5 min/400 W	75
7	10 min/100 W	67
8	10 min/300 W	85
9	10 min/400 W	98

[(a)] Isolated yield after chromatographic separation.
[(b)] Reaction carried out for 16 hours.

output (Table 1, entry 9) at 50°C temperature hence these conditions were used for our rest of experiments with different aryloxyepoxides **1a–f** to give excellent yield (up to 98%) in 10 minutes (Figure 1). Main advantage of the present microwave-assisted epoxide ring opening protocol lies in substantial decrease in the quantity of isopropylamine (1.5 equivalent) as compared to the classical approach where the amine was used in large excess (10–15 equivalents at rt to reflux temperature)with longer duration of reaction time 4-5 hours.

The regioselectivity of the product aryloxypropanolamines was confirmed by NMR analysis of the crude product. Single crystals X-ray analysis of representative products **3c, 3d**, and **3f** (Figure 1, entries 3, 4, 6) further confirmed that the desired regioisomers (Figure 2) were obtained under our microwave-assisted solvent-free epoxide ring opening reaction procedure.

3. Experimental

^{1}H and ^{13}C NMR spectra were recorded on Bruker F113V. FTIR spectra were recorded on Perkin Elmer Spectrum GX spectrophotometer in KBr window. Microanalysis was done on a Perkin Elmer model 2400 CHNS analyzer. High-resolution mass spectra were obtained with an LC-MS (Q-TOF) LC (Waters), MS (Micromass) instruments. For the product purification, flash chromatography was performed using silica gel 60–200 mesh. ETHOS 1600 Advanced Microwave Lab station was used to conduct experiment under microwave irradiation. CCDC-612074 to-612077 contains the supplementary crystallographic data in CIF format for all the three compounds **3c**, **3d**, and **3f**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/datarequest/cif/.

The aryloxyepoxides were synthesized by the modified reported procedure [3d] given as supplementary materials.

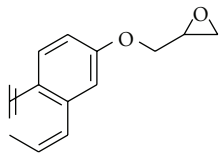
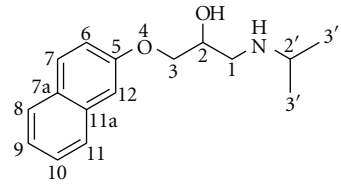
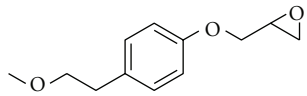
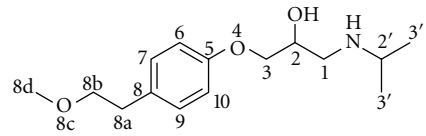
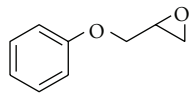
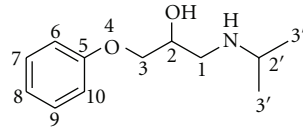
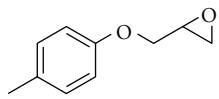
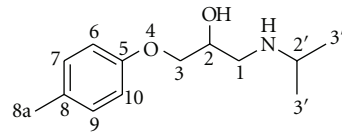
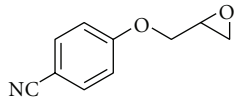
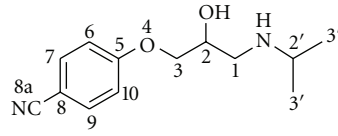
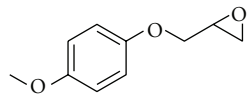
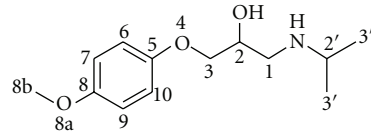
3.1. Procedure for the Preparation of Aryloxypropanolamines by Ring Opening of Aryloxy Epoxides under Solvent-Free MW Irradiation. Aryloxyepoxides **1a–f** (5 mmol) and isopropylamine **2** (7.5 mmol) were taken in a closed Teflon reactor. The reactor was placed in a microwave oven at a selected power (400 W) for 10 minutes. After cooling the reactor to room temperature, excess amine was removed by distillation under reduced pressure. The purification of the reaction products was carried out by flash chromatography on silica gel using CH_2Cl_2:MeOH (95:5), dried over anhydrous Na_2SO_4. All products **3a–f** were characterized by ^{1}H and ^{13}C NMR spectroscopy and data is given as follows.

3.1.1. 1-[(1-Methylethyl) Amino]-3-(1-Naphthoxy)-2-Propanol (Propranolol) (3a)

White Solid. Yield 1.27 g (98%); mp: 95–97°C; IR (KBr): ν = 765 (CH wagging, NH bending), 1029 (CN streching), 1582 (aromatic CC stretching), 2835 (CH stretch), 3271 (OH stretch) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.22–8.27 (m, 1H, 8-CH), 7.75–7.80 (m, 1H, 11-CH), 7.29–7.48 (m, 4H, 7, 9, 10-, and 12-CH), 6.77 (d, 1H, J = 7.4 Hz, 6-CH), 4.07–4.18 (m, 3H, OH, and 3-CH_2), 2.75–3.0 (m, 5H, NH, 1-CH_2, 2-CH, 2′-CH), 1.07 (d, 6H, J = 6.2 Hz, 3′-CH_3); ^{13}C NMR (50 MHz, $CDCl_3$): δ 23.7 (2 × 3′-CH_3), 49.7 (2′-CH), 50.4 (1-CH_2), 69.3 (2-CH), 71.6 (3-CH_2), 105.8 (6-CH), 121.3 (12-CH), 122.6 (9-CH), 126.0 (11-CH), 126.4 (10-CH), 126.6 (8-CH), 127.1 (7a-c), 128.3(11a-c), 135.3 (7-CH), (155.2 5-C); LC-MS m/z 260 [M + H]; analytical calculation for $C_{16}H_{21}NO_2$: C, 74.10; H, 8.16; N, 5.40 found C, 74.0; H, 8.10; N, 5.30.

3.1.2. 1-[4-(2-Methoxyethyl) Phenoxy]-3-[(1-Methylethyl) Amino]-2-Propanol (Metoprolol) (3b)

White Solid. Yield 1.249 g (97%); mp: 96–98°C; IR (KBr): ν = 828(CH wagging, NH bending), 1113(CN streching),

Entry	Epoxides	Products	Time (minute)	Yield[a] (%)
1	 **1a**	 **3a**	10	98
2	 **1b**	 **3b**	10	98
3	 **1c**	 **3c**	10	95
4	 **1d**	 **3d**	10	97
5	 **1e**	 **3e**	10	96
6	 **1f**	 **3f**	10	97

[a] Isolated yield after chromatographic separation.

Figure 1: Ring opening of aryloxyepoxides **1a–f** with isopropylamine **2** under MW irradiation.

1512(aromatic CC stretching), 2869(CH stretch), 3301(OH stretching) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.07 (d, 2H, J = 8.2 Hz, 7- and 9-CH), 6.79 (d, 2H, J = 8.2 Hz, 6- and 10-CH), 4.14 (m, 2H, 3-CH_2), 3.90 (m, 3H, OH, NH, and 2′-CH), 3.53 (t, 2H, J = 7.0 Hz, 8a-CH_2), 3.32 (s, 3H, 8d-CH_3), 2.79 (t, 2H, J = 7.0 Hz, 8b-CH_2), 2.76 (m, 3H, 2-CH, 1-CH_2), 1.05 (d, 6H, J = 6.2 Hz, 2 × 3′-CH_3);^{13}C NMR (50 MHz, $CDCl_3$): δ 23.2 (2 × 3′-CH_3), 35.6 (8a-CH_2), 49.2 (2′-CH), 50.1(1-CH_2), 58.9 (8d-CH_3), 68.7 (2-CH), 71.3 (3-CH_2), 74.2 (8b-CH_2), 114.8 (6 and 10-CH), 130.1 (7- and

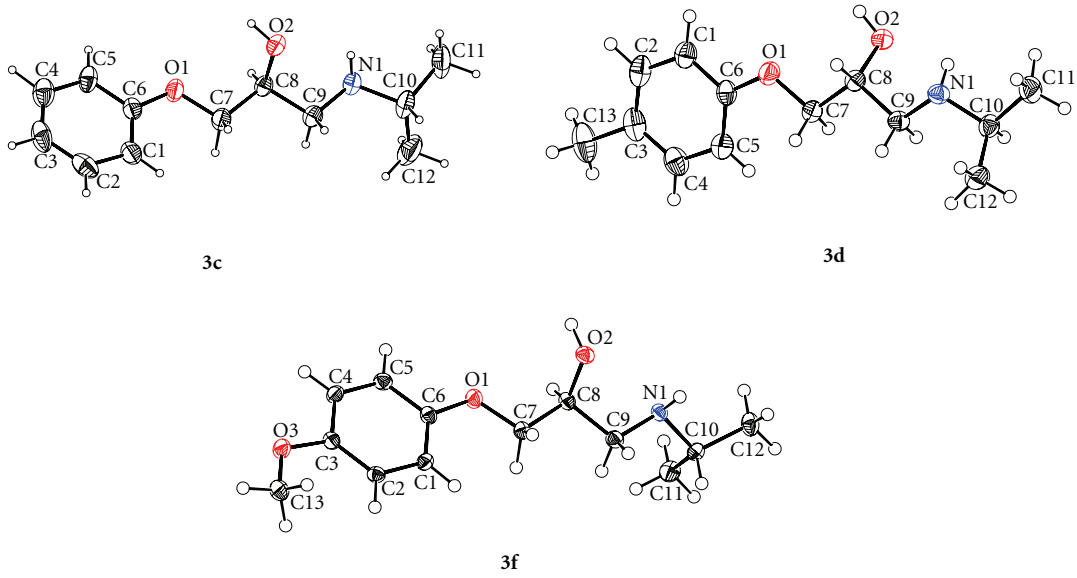


Figure 2: ORTEP diagram (50% probability factor for the thermal ellipsoids) of compounds with atom numbering scheme.

9-CH), 131.7 (8-C), 157.6 (5-C); LC-MS *m/z* 269; analytical calculation for $C_{15}H_{25}NO_3$: C, 67.38; H, 9.42.; N, 5.24 found C, 67.12; H, 9.23; N, 5.12.

3.1.3. 1-[(1-Methylethyl) Amino]-3-(1-Phenoxy)-2-Propanol (3c)

White Solid. Yield 0.993 g (95%); mp: 75–78°C; IR (KBr): ν = 802(CH wagging, NH bending), 1177(CN streching), 1513(aromatic CC stretching), 2875(CH stretch), 3308(OH stretching) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.25 (m, 2H, 7- and 9-CH), 6.91 (m, 3H, 6-, 8-, and 10-CH), 4.11 (m, 3H, 3-CH_2, and 2-CH), 3.94 (m, 1H, 2′-CH), 3.56 (bs, 1H, OH), 2.64 − 2.90 (m, 3H, NH, 1-CH_2), 1.07 (d, 6H, J = 6.4 Hz, 2 × 3′-CH_3); ^{13}C NMR (50 MHz, $CDCl_3$): δ 23.2 (2 × 3′-CH_3), 49.5 (2′-CH), 50.1 (1-CH_2), 68.8 (2-CH), 71.2 (3-CH_2), 115.1 (6- and 10-CH), 121.5 (8-CH), 130.0 (7- and 9-CH), 159.2 (5-C); LC-MS *m/z* 211; analytical calculation for $C_{12}H_{19}NO_2$: C, 68.87; H, 9.15; N, 6.69 found C, 68.58; H, 9.00; N, 6.59.

3.1.4. 1-[(1-Methylethyl) Amino]-3-(4-Methylphenoxy)-2-Propanol (3d)

White Solid. Yield 1.048 g (94%); mp: 75–77°C; IR (KBr): ν = 803(CH wagging, NH bending), 1177(CN streching), 1513(aromatic CC stretching), 2875(CH stretching), 3308 (OH stretching) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.07 (d, 2H, J = 8.4 Hz, 7- and 9-CH), 6.81 (d, 2H, J = 8.4 Hz, 6- and 10-CH), 4.08 (m, 2H, 3-CH_2), 3.92 (m, 2H, OH, and 2-CH), 3.28 (bs, 1H, NH), 2.63 − 2.89 (m, 3H, 1-CH_2, 2- and 2′-CH), 2.27 (s, 3H, 8a-CH_3), 1.10 (d, 6H, J = 6.2 Hz, 2 × 3′-CH_3); ^{13}C NMR (50 MHz, $CDCl_3$): δ 21.0 (8a-CH_3), 23.4 (2 × 3′-CH_3), 49.5 (2′-CH), 50.1(1-CH_2), 69.0(2-CH), 71.4 (3-CH_2), 115.0 (6- and 10-CH), 130.5 (8-C), 130.7 (7- and 9-CH),157.2 (5-C); LC-MS *m/z* 224; analytical calculation for $C_{13}H_{21}NO_2$: C, 69.92; H, 9.48; N, 6.27 found C, 69.86; H, 9.38; N, 6.20.

3.1.5. 1-[(1-Methylethyl) Amino]-3-(4-Cynophenoxy)-2-Propanol (3e)

Colorless Solid. Yield 1.123 g (96%); mp: 108–110°C; IR (KBr): ν = 839(CH wagging, NH bending), 1173(CN streching), 1508(aromatic CC stretching), 2932(CH stretching), 3504(OH stretching) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.58 (d, 2H, J = 8.2, 7- and 9-CH), 7.01 (d, 2H, J = 8.2 Hz, 6- and 10-CH), 4.22 (m, 2H, 3-CH_2), 4.02 (bs, 1H, OH), 3.30 (bs, 1H, NH), 2.66 − 2.89 (m, 4H, 1-CH_2, 2- and 2′-CH), 1.08 (d, 6H, J = 6.2 Hz, 2 × 3′-CH_3); ^{13}C NMR (50 MHz, $CDCl_3$): δ 23.3 (2 × 3′-CH_3), 49.4 (2′-CH), 49.7 (1-CH_2), 68.6 (2-CH), 71.5 (3-CH_2), 104.5 (8-C), 115.8 (6- and 10-CH), 118.0 (8a-CN), 134.4 (7- and 9-CH), 162.5(5-C); LC-MS *m/z* 235; analytical calculation for $C_{13}H_{18}N_2O_2$: C, 66.64; H, 7.74; N, 11.96 found C, 66.51; H, 7.60; N, 11.88.

3.1.6. 1-[(1-Methylethyl) Amino]-3-(4-Methoxyphenoxy)-2-Propanol (3f)

Colorless Solid. Yield 1.123 g (94%); mp: 80–82°C; IR (in KBr): ν = 830(CH wagging, NH bending), 1115(CN streching), 1525(aromatic CC stretching), 2928(CH stretching), 3301(OH stretching) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.8 (s, 4H, 6, 7, 9-, and 10-CH), 4.08 (m, 2H, OH, 3-CH_2), 3.80–4.0 (m, 1H, 2-CH), 3.73 (s, 3H, 8b-CH_3), 2.95–3.20 (bs, 1H, NH), 2.62–2.87 (m, 4H, 1-CH_2, 2- and 2′-CH), 1.06 (d, 6H, J = 6.2 Hz, 2 × 3′-CH_3); ^{13}C NMR (50 MHz, $CDCl_3$): δ 23.4 (2 × 3′-CH_3), 49.4 (2′-CH), 50.2 (1-CH_2), 56.1 (8b-CH_3), 69.1(2-CH), 72.1(3-CH_2), 115.2 (6- and 10-CH), 116.0 (7- and 9-CH), 153.5 (5-C), 154.5 (8-C); LC-MS

m/z 240 $[M + H]^+$; analytical calculation for $C_{13}H_{21}NO_3$: C, 65.25; H, 8.84; N, 5.85 found C, 65.20; H, 8.69; N, 5.78.

Acknowledgments

R. I. Kureshy is thankful to DST and CSIR Net Work Project on Catalysis.

References

[1] T. Seki, T. Takezaki, R. Ohuchi, H. Ohuyabu, T. Ishimori, and K. Yasuda, "Studies on agents with vasodilator and beta-blocking activities—I," *Chemical & Pharmaceutical Bulletin*, vol. 42, no. 8, pp. 1609–1616, 1994.

[2] T. Fujioka, S. Teramoto, T. Mori, et al., "Novel positive inotropic agents: synthesis and biological activities of 6-(3-amino-2-hydroxypropoxy)-2(1*H*)-quinolinone derivatives," *Journal of Medicinal Chemistry*, vol. 35, no. 20, pp. 3607–3612, 1992.

[3] J. G. Smith, "Synthetically useful reactions of epoxides," *Synthesis*, vol. 1984, no. 8, pp. 629–656, 1984.

[4] Y. Tsuda, K. Yoshimoto, and T. Nishikawa, "Practical syntheses of [R]- and [S]-1-alkylamino-3-aryloxy-2-porpanols from a single carbohydrate precursor," *Chemical & Pharmaceutical Bulletin*, vol. 29, no. 12, pp. 3593–3600, 1981.

[5] H. Sasai, T. Suzuki, N. Itoh, and M. Shibasaki, "Catalytic asymmetric synthesis of propranolol and metoprolol using a La-Li-BINOL complex," *Applied Organometallic Chemistry*, vol. 9, no. 5-6, pp. 421–426, 1995.

[6] R. A. Joshi, M. K. Gurjar, N. K. Tripathy, and M. S. Chorghade, "A new and improved process for celiprolol hydrochloride," *Organic Process Research & Development*, vol. 5, no. 2, pp. 176–178, 2001.

[7] J. K. Mehra, A. Choubey, B. K. Srivastava, R. K. Porwal, and P. Gautam, "Metoprolol manufacturing process," US patent no. 20050107635, 2005.

[8] M. Chini, P. Crotti, and F. Macchia, "Regioalternating selectivity in the metal salt catalyzed aminolysis of styrene oxide," *The Journal of Organic Chemistry*, vol. 56, no. 20, pp. 5939–5942, 1991.

[9] I. Cepanec, M. Litvić, H. Mikuldaš, A. Bartolinčić, and V. Vinković, "Calcium trifluoromethanesulfonate-catalysed aminolysis of epoxides," *Tetrahedron*, vol. 59, no. 14, pp. 2435–2439, 2003.

[10] T. Ollevier and G. Lavie-Compin, "Bismuth triflate-catalyzed mild and efficient epoxide opening by aromatic amines under aqueous conditions," *Tetrahedron Letters*, vol. 45, no. 1, pp. 49–52, 2004.

[11] J. S. Yadav, A. R. Reddy, A. V. Narsaiah, and B. V. S. Reddy, "An efficient protocol for regioselective ring opening of epoxides using samarium triflate: synthesis of propranolol, atenolol and RO363," *Journal of Molecular Catalysis A*, vol. 261, no. 2, pp. 207–212, 2007.

[12] K. Tabatabaeian, M. Mamaghani, N. O. Mahmoodi, and A. Khorshidi, "Solvent-free, ruthenium-catalyzed, regioselective ring-opening of epoxides, an efficient route to various 3-alkylated indoles," *Tetrahedron Letters*, vol. 49, no. 9, pp. 1450–1454, 2008.

[13] C. O. Kappe and D. Dallinger, "The impact of microwave synthesis on drug discovery," *Nature Reviews Drug Discovery*, vol. 5, no. 1, pp. 51–63, 2006.

[14] C. O. Kappe, "Controlled microwave heating in modern organic synthesis," *Angewandte Chemie International Edition*, vol. 43, no. 46, pp. 6250–6284, 2004.

[15] R. I. Kureshy, S. Singh, N. H. Khan, S. H. R. Abdi, E. Suresh, and R. V. Jasra, "Facile enantioselective ring-opening reaction of *meso* epoxides with anilines using (*S*)-(-)-BINOL-Ti complex as a catalyst," *European Journal of Organic Chemistry*, vol. 2006, no. 5, pp. 1303–1309, 2006.

[16] R. I. Kureshy, S. Singh, N. H. Khan, et al., "Microwave-assisted asymmetric ring opening of *meso*-epoxides with aromatic amines catalyzed by a Ti-*S*-(-)-BINOL complex," *Tetrahedron Letters*, vol. 47, no. 30, pp. 5277–5279, 2006.

[17] R. I. Kureshy, S. Singh, N. H. Khan, S. H. R. Abdi, S. Agrawal, and R. V. Jasra, "Enantioselective aminolytic kinetic resolution (AKR) of epoxides catalyzed by recyclable polymeric Cr(III) salen complexes," *Tetrahedron: Asymmetry*, vol. 17, no. 11, pp. 1638–1643, 2006.

[18] R. I. Kureshy, K. J. Prathap, S. Singh, et al., "Chiral recyclable dimeric and polymeric Cr(III) salen complexes catalyzed aminolytic kinetic resolution of *trans*-aromatic epoxides under microwave irradiation," *Chirality*, vol. 19, no. 10, pp. 809–815, 2007.

[19] R. I. Kureshy, K. J. Prathap, S. Agrawal, N. H. Khan, S. H. R. Abdi, and R. V. Jasra, "Highly enantioselective syntheses of chiral β-amino alcohols in the presence of chiral Ti^{IV} Schiff base complexes as catalysts," *European Journal of Organic Chemistry*, vol. 2008, no. 18, pp. 3118–3128, 2008.

[20] D. S. Bose and A. V. Narsaiah, "An efficient asymmetric synthesis of (*S*)-atenolol: using hydrolytic kinetic resolution," *Bioorganic & Medicinal Chemistry*, vol. 13, no. 3, pp. 627–630, 2005.

[21] W. Tan, B.-X. Zhao, L. Sha, et al., "Microwave-assisted ring opening of epoxides in solvent-free conditions," *Synthetic Communications*, vol. 36, no. 10, pp. 1353–1359, 2006.

[22] D. Ghazanfari, M. M. Hashemi, M. M. Mottaghi, and M. M. Foroughi, "An efficient method for the ring opening of epoxides with aromatic amines by Sb(III) chloride under microwave irradiation," *Journal of Chemical Research*, vol. 2008, no. 4, pp. 220–221, 2008.

[23] T. Ollevier and E. Nadeau, "Microwave-enhanced bismuth triflate-catalyzed epoxide opening with aliphatic amines," *Tetrahedron Letters*, vol. 49, no. 9, pp. 1546–1550, 2008.