Dimethyl carbonate as a non-innocent benign solvent for the multistep continuous flow synthesis of amino alcohols.

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Supporting Information

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1. General Information

Candida Antarctica Lipase type B (CAL-B, Novozyme 435, 7300 PLU/g) was a gift from Novozyme. All other reagents were purchased from Sigma-Aldrich and used without further purification. ^{1}H and ^{13}C NMR experiments were carried out using a Varian INOVA 500 (^{1}H, 500 MHz and ^{13}C, 125 MHz) spectrometer. The chemical shifts are given in delta (δ) values and the coupling constants (J) in Hertzs (Hz). FTIR spectra were acquired with a MIRacle single-reflection ATR diamond/ZnSe accessory in a JASCO FT/IR-6200 instrument. The mass spectrometry experiments were performed in a hybrid QTOF (quadrupole-TOF-hexapole) with an orthogonal Z-spray interface-electrospray (Micromass, Manchester, UK). Gas chromatography analyses were carried out in a GC VARIAN 3900 using a CYCLODEXB column (30 m x 0.25 mm I.D. x 25 μm). High performance liquid chromatography (HPLC) analyses were carried out in a Merck HITACHI LaChrom chromatograph with a UV detector at 254 nm using a Daicel CHIRALPAK AD column (25 cm × 4.6 mm I.D.).

2. Supplementary Figures

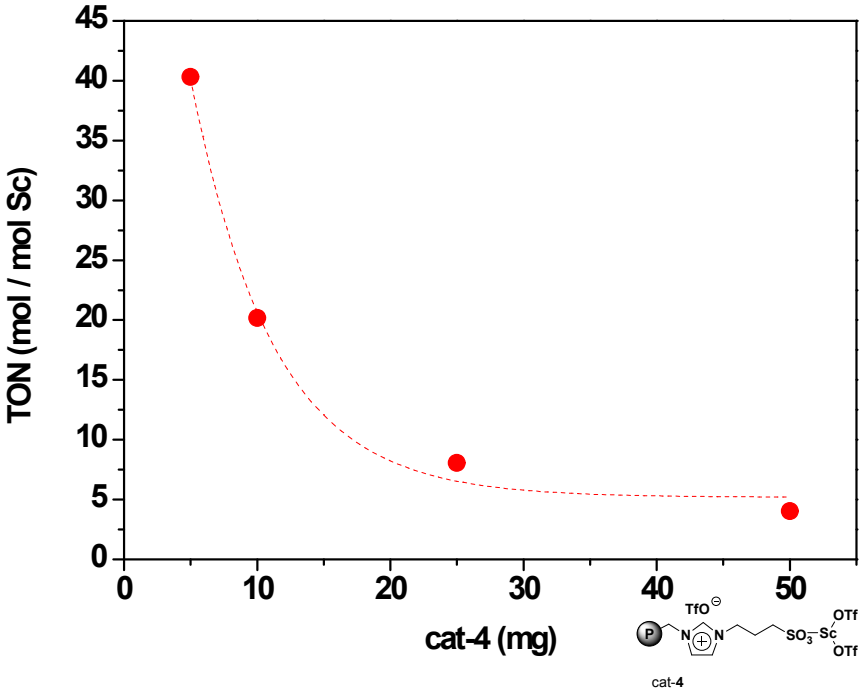


Fig. SI.1. TON *vs.* catalyst loading for the ring opening of cyclohexane oxide with aniline using cat-**4**. Conditions: 0.25 mmoles of ciclohexene oxide (1 eq.), 0.25 mmoles of aniline (1 eq.), 2.5 mL of dimethyl carbonate, 1 h, 150 rpm and room temperature. Yields calculated by NMR from the reaction mixture.

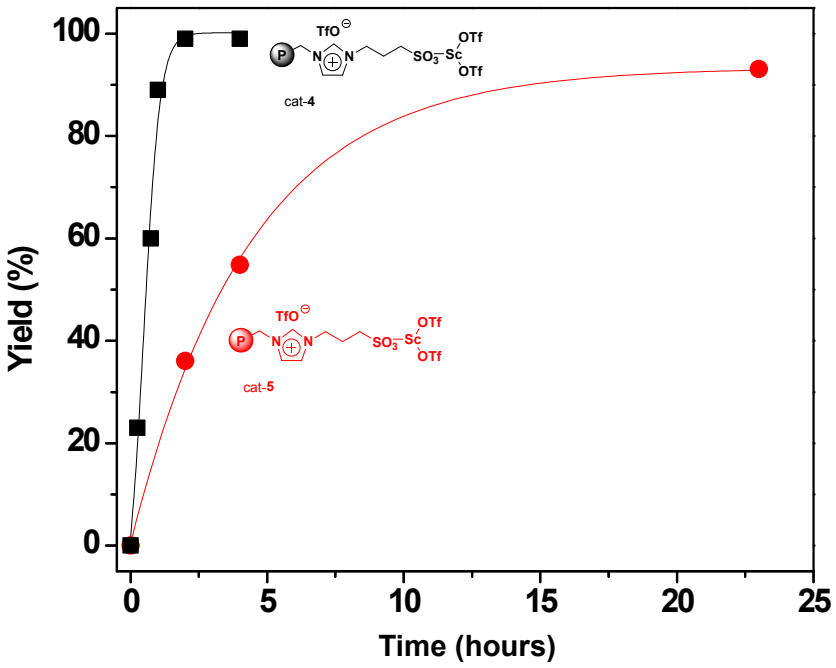


Fig. SI.2. Yield *vs.* time for the ring opening of cyclohexene oxide (**2a**) with aniline (**3a**) using a loading of 2.5 % molar for cat-**4** (■) and 25% molar for cat-**5** (●). Conditions: 0.25 mmoles of ciclohexene oxide (1 eq.), 0.25 mmoles of aniline (1 eq.), 2.5 mL of dimethyl carbonate, 1h, 150 rpm and room temperature. Yield calculated by NMR from the reaction mixture

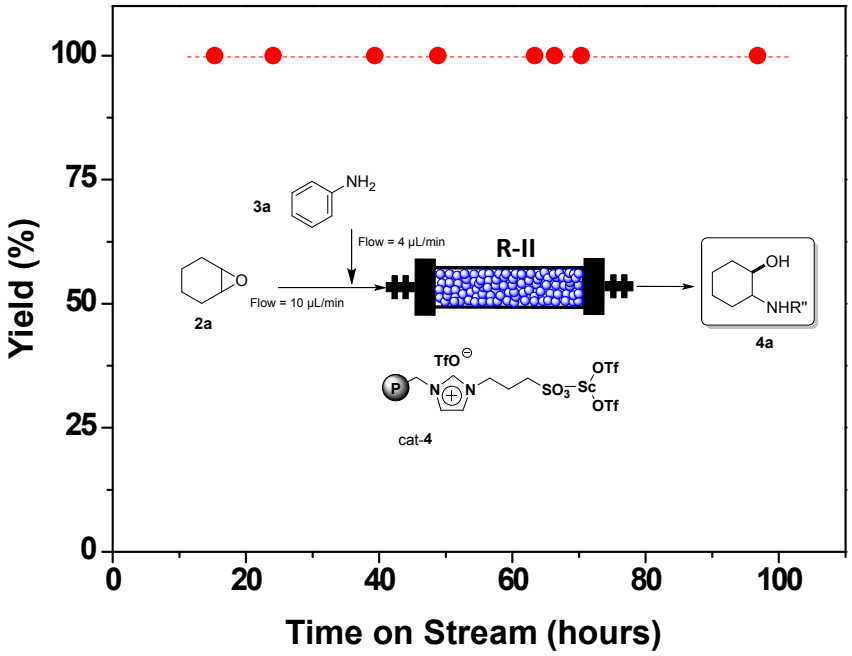


Fig. SI.3. Long-term stability experiments for the use of cat-**4** for the ring opening of cyclohexene oxide (**2a**) with aniline (**3a**) under flow conditions. Conditions: 0.1 M solutions of **2a** and 0.25 M of **3a** in DMC, 1:1 epoxide:aniline molar ratio (10 µL /min for the epoxide and 4 µL/min for aniline, 1 g cat-**4**, 45 ºC.

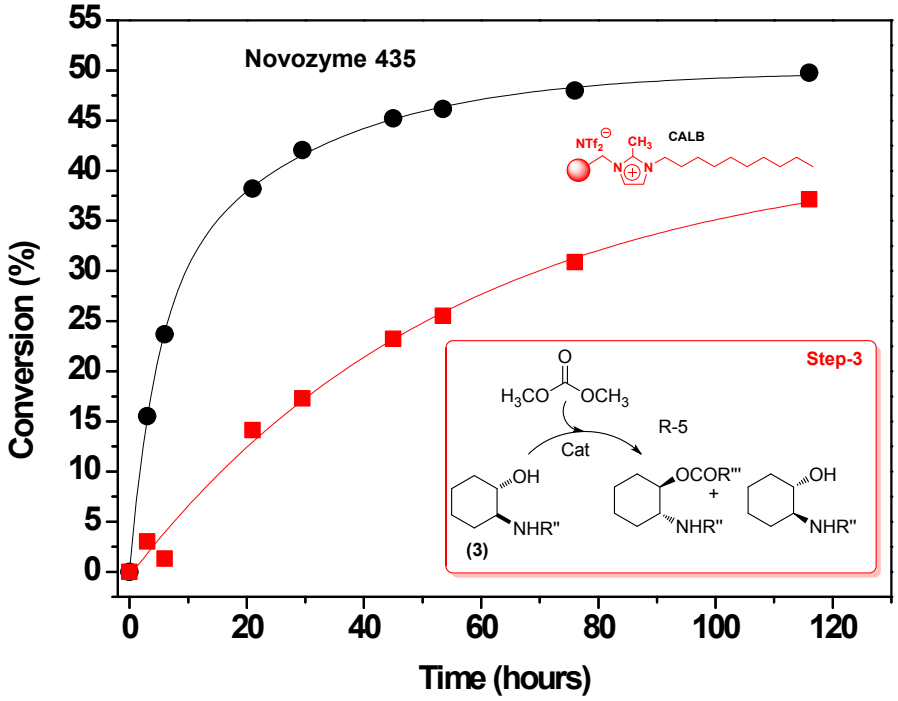


Fig. SI.4. Kinetic resolution of *trans*-2-phenylamine cyclohexanol (*rac*-**4a**) in DMC (0.1 M) as the solvent and acylating agent, under batch conditions, at 50 ºC, 250 rpm. ●: 50 mg of Novozyme 435. ■: 50 mg of cat-**2**.

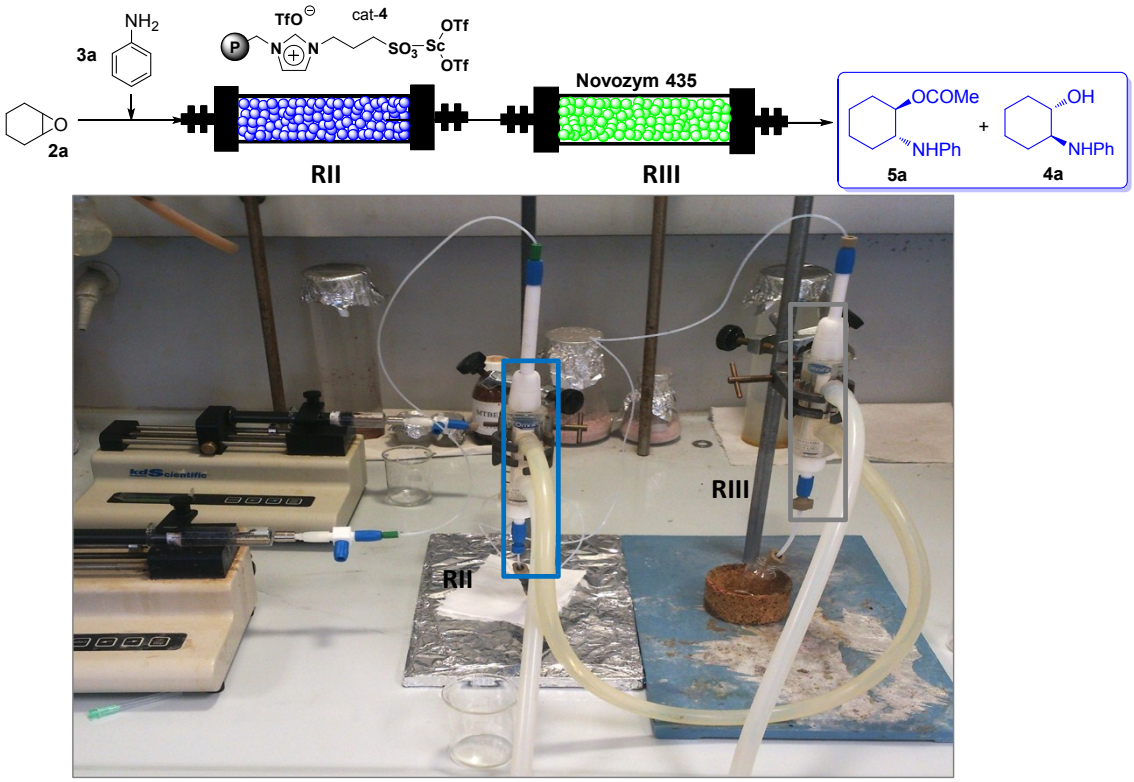


Fig. SI.5. Experimental set-up for the coupling of steps 2 and 3: ring opening of the cyclohexene oxide (**2a**) and kinetic resolution of the *trans*-2-phenylamine cyclohexanol (*rac*-**4a**).

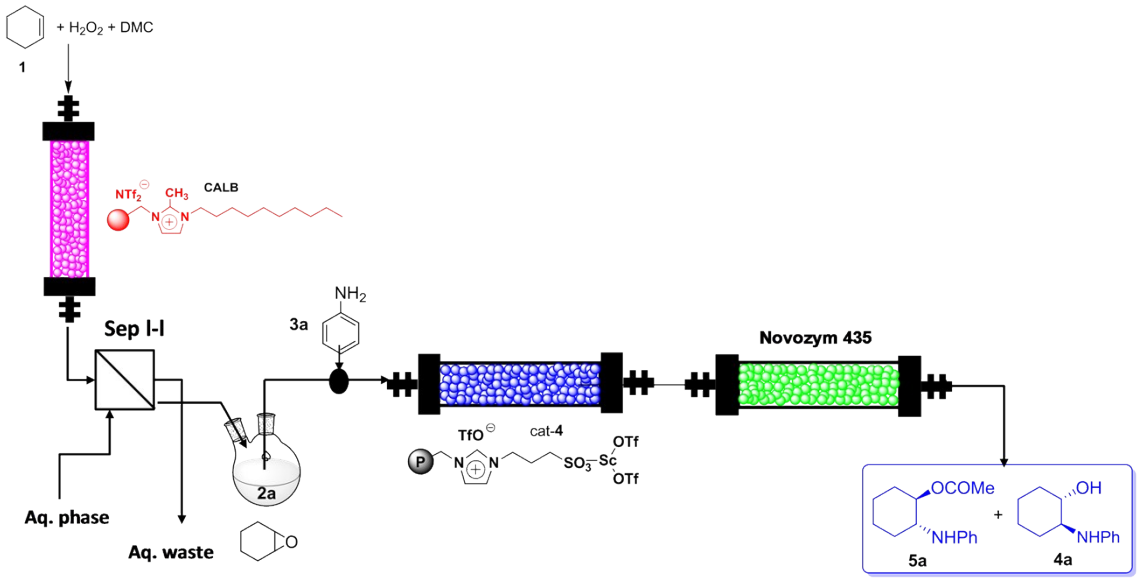
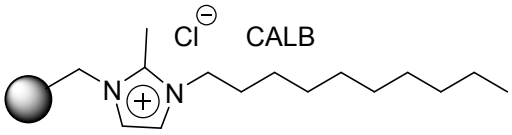


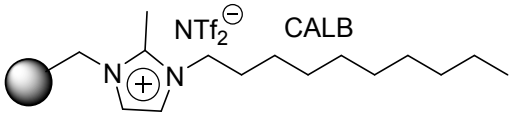
Fig. SI.6. Schematic experimental set-up for the coupling of step 1 and solvent separation to afford the solution to be fed to the combined steps 2 and 3: ring opening of the cyclohexene oxide (**2a**) and kinetic resolution of the *trans*-2-phenylamine cyclohexanol (*rac*-**4a**). The liquid-liquid separation was carried out using a Zaiput Flow Technologies equipment model SEP-10 (PTFE hydrophobic, 0.5 µm pore size). The flow at the entrance of the filter was 10µL/min. The organic flow was collected on a round bottomed flask and the collected flow (after a period of accumulation) was used then directly for the next reaction steps.

3. Synthesis and Characterization of Catalysts

Synthesis and characterization of cat-1 and cat-2



cat-1

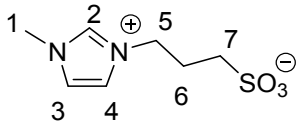


cat-2

The synthesis and characterization of cat-**1** and cat-**2** has been reported in ref. 19 (*Immobilised Lipase on Structured Supports Containing Covalently Attached Ionic Liquids for the Continuous Synthesis of Biodiesel in scCO$_2$*, P. Lozano, E. Garcia-Verdugo, J. M. Bernal, D. F. Izquierdo, M. I. Burguete, G. Sanchez-Gomez and S. V. Luis, *ChemSusChem*, 2012, **5**, 790-798. DOI: 10.1002/cssc.201100692).

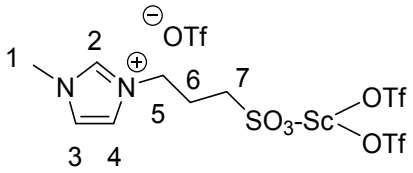
Synthesis and characterization of cat-3

Step 1. Synthesis of 3-(1-methyl-1H-imidazol-3-ium-3-yl)propane-1-sulfonate



1-Methylimidazole (1.94 mL, 24 mmol) was suspended in 5 mL of dichloromethane and 1,3-propane-sultone (3.3 g, 27 mmol) dissolved in 4 mL of dichloromethane was added dropwise while stirring at room temperature. After 18 hours, the white solid formed was filtered under vacuum and washed with CH_2Cl_2 (3 x 20 mL). The product obtained was dried overnight in a vacuum oven at 50 ºC to give a white solid (4.8 g, 98 %). Melting point: 210-214 ºC. ^{1}H-NMR (CD_3OD, 500 MHz): δ 2.18-2.47 (m, 2H, H_7). 2.83 (t, J = 7.1 Hz, 2H, H_6), 3.95 (s, 3H, H_1), 4.44 (t, J = 7.1 Hz, 2H, H_5), 7.59 (s, 1H, H_4), 7.70 (s, 1H, H_3), 8.97 (s, 1H, H_2) ppm. ^{13}C-NMR (CD_3OD, 125 MHz): δ 27.2 (C_6), 36.5 (C_1), 48.5 (C_5), 49.2 (C_7), 123.7 (C_3), 125.0 (C_4), 138.3 (C_2) ppm. FT-IR-ATR (cm^{-1}): 3133, 3100, 3072, 3038, 2950, 2931, 2870, 1690, 1573, 1555, 1465, 1441, 1334, 1266, 1236, 1202, 1170, 1148, 1118, 1078, 1031, 876. MS (ESI+, m/z): 162.1 [(M+H)$^+$, 70 %], 227.0 [(M+Na)$^+$, 100 %], 243.0 [(M+K)$^+$, 50 %]. Elemental analysis for $C_7H_{12}N_2O_3S\cdot(H_2O)_{0.5}$; calculated: C, 39.4; H, 6.1; N, 13.1; Found: C, 39.6; H, 6.5; N, 13.2.

Step 2. Synthesis of trifluorosulfonate of ((3-(1-methyl-1H-imidazol-3-ium-3-yl)propylsulfonate) bis(trifluoromethylsulfonate) scandium (cat-3)

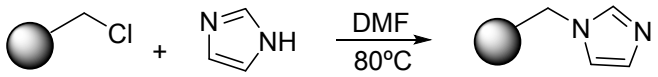


3-(1-Methyl-1H-imidazol-3-ium-3-yl)propane-1-sulfonate (101.1 mg, 0.49 mmol) was suspended in 4 mL of methanol, and $Sc(OTf)_3$ (245.3 mg, 0.49 mmol) was added under stirring at room temperature. After 22 hours, the solvent was removed under reduced

pressure and the product obtained was dried in vacuum to give a hygroscopic oily compound (cat-**3**) (342.2 mg, 99 %). ^{1}H-NMR (CD_3OD, 500 MHz): δ 2.3 (q, J = 6.7 Hz, 2H, H_6), 3.09 (t, J = 6.7 Hz, 2H, H_7), 3.92 (s, 3H, H_1), 4.41 (t, J = 6.5 Hz, 2H, H_5), 7.55 (s, 1H, H_4), 7.62 (s, 1H, H_3), 8.85 (s, 1H, H_2) ppm. ^{13}C-NMR (CD_3OD, 125 MHz): δ 26.2 (C_6), 36.5 (C_1), 48.6 (C_7), 48.9 (C_5), 119.4 (C-F_3), 123.5 (C_3), 125.0 (C_4), 138.0 (C_2) ppm. FT-IR-ATR (cm^{-1}): 3158, 1648, 1579, 1464, 1222, 1168, 1024, 745, 632. MS (ESI+, m/z): 548.33 [$(M+H)^+$, 10 %], 579.0 [$(M+MeOH)^+$, 20 %]. Elemental analysis for $C_{10}H_{12}F_9N_2O_{12}S_4Sc{\cdot}10H_2O$ calculated: C, 13.7; H, 3.7; N, 3.2; Found: C, 13.7; H, 3.5; N, 3.1.

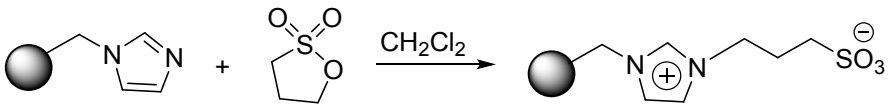
Synthesis and characterization of cat-4

Step 1.



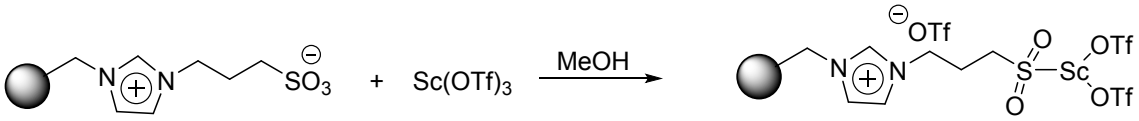
Imidazole (1.27 g, 18.56 mmol) was suspended in 30 mL of DMF, and a Merrifield resin (macroporous, 1.2 meq Cl/g) (5 g, 6 mmol Cl) was added. The mixture was stirred at 80 ºC for 24 hours. Then the polymer was vacuum filtered and washed with THF (3 x 20 mL), CH_2Cl_2 (3 x 20 mL) and MeOH (3 x 20 mL). The polymer obtained was dried overnight under vacuum at 50 ºC to give 5.27 g of the product (**P-IM**). FT-IR-ATR (cm^{-1}): 3024, 2921, 2849, 1602, 1492, 1450, 1148, 1114, 1072, 1026, 757, 699. Elemental analysis found: N, 2.03. Loading of polymer **P-IM**: 0.72 meq/g.

Step 2.



P-IM (3.1 g, 2.23 mmol) was suspended in 25 mL of dichloromethane, and 1,3-propane-sultone (1.3 g, 10.84 mmol) dissolved in 5 mL of dichloromethane was added dropwise under stirring at room temperature. After 24 hours, the polymer was vacuum filtered and washed with THF (3 x 20 mL), CH_2Cl_2 (3 x 20 mL) and MeOH (3 x 20 mL). The polymer obtained was dried overnight under vacuum at 50 ºC to give 3.02 g of the product (**P-IM-SO_3**). FTIR-ATR (cm^{-1}): 3024, 2922, 2851, 1602, 1493, 1453, 1193, 1037, 758, 698. Elemental analysis found: N, 1.46. Loading of polymer **P-IM-SO_3**: 0.52 meq/g.

Step 3.

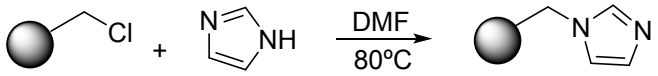


$Sc(OTf)_3$ (447.6 mg, 0.90 mmol) was suspended in 10 mL of MeOH and **P-IM-SO_3** (496.1 mg, 0.26 mmol) was added under stirring at room temperature. After 18 hours, the polymer was vacuum filtered and washed with THF (3 x 20 mL), CH_2Cl_2 (3 x 20 mL) and MeOH (3 x 20 mL). The polymer obtained was dried overnight under vacuum at 50

ºC to give 452 mg of product (cat-**4**). FT-IR-ATR (cm^{-1}): 3024, 2922, 2851, 1602, 1491, 1450, 1255, 1223, 1155, 1030, 755, 696, 636. ICP-MS: 1.24 meq Sc/g.

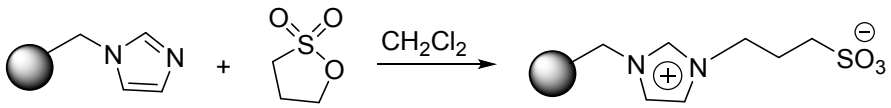
Synthesis and characterization of cat-5

Step 1.



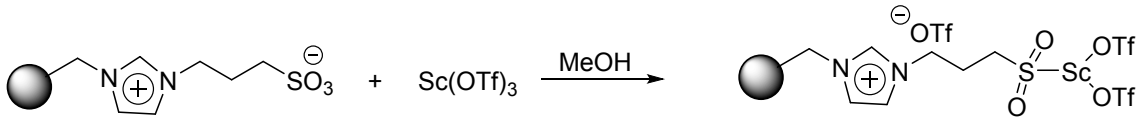
Imidazole (11.85 g, 173 mmol) was suspended in 100 mL of DMF, and a Merrifield resin (macroporous, 5.5 meq Cl/g) (10.29 g, 56.59 mmol Cl) was added. The mixture was stirred at 80 ºC for 24 hours. Then the polymer was vacuum filtered and washed with THF (3 x 20 mL), CH_2Cl_2 (3 x 20 mL) and MeOH (3 x 20 mL). The polymer obtained was dried overnight under vacuum at 50 ºC to give 12.44 g of product (**P-IM**). FT-IR-ATR (cm^{-1}): 2925, 2854, 1670, 1558, 1455, 1423, 1228, 1145, 1074, 1027, 819, 744. Elemental analysis found: N, 10.09. Loading of compound **P-IM**: 3.6 meq/g.

Step 2.



P-IM (10.08 g, 36.29 mmol) was suspended in 125 mL of dichloromethane, and 1,3-propane-sultone (20.31 g, 166 mmol) dissolved in 100 mL of dichloromethane was added dropwise under stirring at room temperature. After 24 hours, the polymer was vacuum filtered and washed with THF (3 x 20 mL), CH_2Cl_2 (3 x 20 mL) and MeOH (3 x 20 mL). The polymer obtained was dried overnight under vacuum at 50 ºC to give 14.35 g of product (**P-IM-SO_3**). FT-IR-ATR (cm^{-1}): 3104, 2922, 2856, 1557, 1540, 1508, 1455, 1420, 1188, 1034, 825, 728. Elemental analysis found: N, 6.70. Loading of compound **P-IM-SO_3**: 2.39 meq/g.

Step 3.



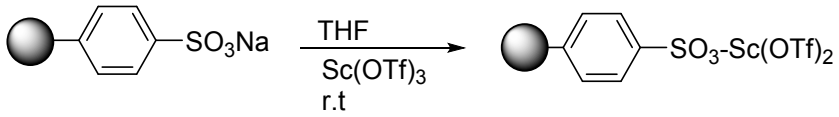
$Sc(OTf)_3$ (4.04 g, 8.12 mmol) was suspended in 10 mL of MeOH, and **P-IM-SO_3** (1.44 g, 3.44 mmol) was added under stirring at room temperature. After 18 hours, the polymer was vacuum filtered and washed with THF (3 x 20 mL), CH_2Cl_2 (3 x 20 mL) and MeOH (3 x 20 mL). The polymer obtained was dried overnight under vacuum at 50 ºC to give 1.72 g of product (cat-**5**). FT-IR-ATR (cm^{-1}): 3145, 2922, 1653, 1557, 1508, 1455, 1422, 1334, 1255, 1221, 1148, 1025, 827, 755. ICP-MS: 5.68 meq Sc/g.

Synthesis and characterization of cat-6

Step 1.

Amberlite IR-120 (washed with MeOH and vacuum dried) (4.6 meq/g) (1.71 g, 7.87 mmol) was suspended in 38 mL of THF, and 6 mL of deionized water, and 15 mL of 1 M NaOH were added. The resulting biphasic mixture was stirred at room temperature. After 21 hours, the polymer was vacuum filtered and washed with H_2O/THF (3 x 20 mL), THF (3 x 20 mL) and CH_2Cl_2 (3 x 20 mL). The polymer obtained was dried overnight under vacuum at 50 ºC to give 1.80 g of product (**IR120-SO_3Na**). FT-IR-ATR (cm^{-1}): 2926, 2370, 1649, 1540, 1174, 1127, 1037, 1006, 829, 775, 673. Elemental analysis found: S, 8.11. Loading of compound **IR120-SO_3Na**: 2.5 meq/g.

Step 2.



$Sc(OTf)_3$ (1.84 g, 3.56 mmol) was suspended in 80 mL of THF, and **IR120-SO_3Na** (814.4 mg, 2.04 mmol) was added under stirring at room temperature. After 174 hours, the polymer was vacuum filtered and washed with deionized water (3 x 20 mL), H_2O/THF (3 x 20 mL), THF (3 x 20 mL) and CH_2Cl_2 (3 x 20 mL). The polymer obtained was dried overnight in a vacuum oven at 50 ºC to give 803.3 mg of product (cat-**6**). FT-IR-ATR (cm^{-1}): 2915, 1634, 1600, 1495, 1450, 1409, 1174, 1127, 1037, 1009, 829, 773, 673. ICP-MS: 1.73 meq Sc/g.

4. Preparation of cyclohexene oxide

Preparation of cyclohexene oxide under *batch* conditions (2a)

The corresponding catalyst (50 mg) was suspended in 2.5 mL of DMC, and cyclohexene (**1**) (25 µL, 0.25 mmol, 0.1 M) and H_2O_2 (50%) (36 µL, 0.63 mmol) were added. The reaction mixture was stirred at 150 rpm with orbital stirring at 30 ºC. After 18 hours, the reaction mixture was analyzed by GC to calculate the yield of cyclohexene oxide.

Preparation of cyclohexene oxide under *continuous flow* conditions (2a)

A solution of cyclohexene (**1**) (100 µL, 0.98 mmol, 0.1 M) and H_2O_2 (50%) (150 µL, 2.45 mmol) in 9.8 mL of DMC was pumped at 10 µL/min through an fixed-bed reactor packed with 2 g of Novozyme 435 or 0.5 g of CALB-SILLP-dec-NTf_2 (cat-**2**) at 45 ºC. Aliquots were taken at different times. The samples were analyzed by GC to calculate the yield of cyclohexene oxide.

Determination of the cyclohexene oxide obtained

The cyclohexene oxide obtained was analysed by GC: CYCLODEXB column (30 m x 0.25 mm I.D. x 0.25 µm); T injector, 230 ºC; T oven: initial 60 ºC; step 1, 60-130 ºC (10 ºC/min); step 2, 130 ºC for 30 min.; T detector, 300 ºC. Retention times: cyclohexene 2.75 min, cyclohexene oxide 5.64 min and dodecane 8.99 min (internal standard). To calculate the yield of cyclohexene oxide the following was used: Relative area (cyclohexene oxide area/dodecane area) = 0.7881 x (mg cyclohexene oxide/mg dodecane), $R^2 = 0.9973$.

Caution note: The presence of remaining peroxy ester in the flow stream represents a potential safety issue, in particular for the work at larger scales. At the scale of the experiments carried out in this work and under the conditions used, we did not detect any safety issue. However, in order to circumvent any potential trouble, we also checked that any excess of peroxy ester could be destroyed with the use of solid manganese dioxide or sodium sulfite without altering the results reported here.

5. Preparation of 1,2-amino alcohols from epoxides

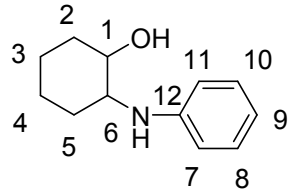
Preparation of *trans*-2-(phenylamino)cyclohexan-1-ol under *batch* conditions (*rac*-4a)

The corresponding catalyst (2.5 to 25 % molar ratio) was suspended in 2.5 mL of DMC. Then cyclohexene oxide (**2a**) (26 µL, 0.25 mmol) and aniline (23 µL, 0.25 mmol) were added to the suspension. The reaction mixture was stirred at 150 rpm by orbital stirring at room temperature. After 23 hours, the reaction mixture was filtered and the solvent removed under reduced pressure and finally dried in vacuum to calculate the yield by NMR.

Preparation of *trans*-2-(phenylamino)cyclohexan-1-ol under *continuous* flow conditions (*rac*-4a)

A solution of cyclohexene oxide (**2a**) 0.1 M in DMC pumped at 10 µL/min was mixed in a T-piece with a flow of aniline (**3a**, 0.25 M in DMC, 4 µL/min). The resulting flow stream (14 µL/min) was passed through a fixed-bed reactor packed with 1 g of cat-**4** at 45 ºC. Aliquots were taken at different time intervals at the out-let of the reactor and analyzed by NMR. The calculated for the different samples yield was > 99 %.

Characterization of *trans*-2-(phenylamino)cyclohexan-1-ol (*rac*-4a)



Light brown solid. Melting point: 63-66 ºC. ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 0.90-1.13 (m, 1H, H_4), 1.13-1.54 (m, 3H, H_3+H_4+H_5), 1.55-1.88 (m, 2H, H_2+H_3), 2.12 (dt, J = 13.7, 2.1 Hz, 2H, H_2+H_5), 3.11-3.17 (m, 1H, H_6), 3.32-3.38 (m, 1H, H_1), 6.72 (d, J = 8.2 Hz, 2H,

H_7+H_{11}), 6.76 (t, J = 6.8 Hz, 1H, H_9), 7.20 (t, J = 7.5 Hz, 2H, H_8+H_{10}) ppm. ^{13}C-NMR ($CDCl_3$, 125 MHz): δ 24.3 (C_3), 25.04 (C_4), 31.7 (C_5), 33.3 (C_2), 60.2 (C_6), 74.5 (C_1), 114.4 (C_7), 118.3 (C_9), 129.4 (C_8), 147.9 (C_{12}) ppm. FT-IR-ATR (cm^{-1}): 3391, 3052, 3024, 2937, 2922, 2856, 1598, 1512, 1495, 1448, 1371, 1320, 1306, 1292, 1253, 1150, 1099, 1048, 932, 863. MS (ESI+, m/z): 192.2 [$(M+H)^+$, 100 %], 214.2 [$(M+Na)^+$, 20 %], 230.2 [$(M+K)^+$, 10 %]. HPLC: Column AD, hex/IPA (99:1), 254 nm, 30 ºC, 0.750 mL/min, $t_{R,R}$ = 45.83 min, $t_{S,S}$ = 54.81 min.

General procedure for the preparation of other α,β-amino alcohols under batch conditions

The catalyst (cat-**4**, 100 mg) was suspended in 2.5 mL of DMC and the corresponding epoxide (**2a-c**, 0.25 mmol) and the amine (**3a-d**, 0.25 mmol), were added. The reaction mixture was stirred at 150 rpm by orbital stirring at 70 ºC. After 21 hours, the mixture was filtered and the solvent removed under reduced pressure. The residue was dried under vacuum to calculate the yield by NMR.

Hot filtration tests to assess or the absence of leached soluble catalytic Sc species were carried out following general protocols for this purpose (*Heterogeneous catalysts for liquid-phase oxidations: Philosophers' stones or Trojan horses?*, R. A. Sheldon, M. Wallau, I. W. C. E. Arends and U. Schuchardt, *Acc. Chem. Res.* 1998, **31**, 485-493; *Pd catalysts immobilized onto gel-supported ionic liquid-like phases (g-SILLPs): A remarkable effect of the nature of the support*, M. I. Burguete, E. García-Verdugo, I. Garcia-Villar, F. Gelat, P. Licence, S. V. Luis and V. Sans, *J. Catal.*, 2010, **269**, 150–160). At intermediate conversions, the supported catalyst was filtered off and the progress of the reaction in the filtered solution was monitored for an additional period of time. No additional progress was observed after the filtration.

Characterization of the different 1,2-amino alcohols

The full characterization of the different α,β-amino alcohols has been reported previously in the works mentioned below. The corresponding data were used for the determination of the formation of the amino alcohols in the different experiments carried out.

An efficient protocol for regioselective ring opening of epoxides using sulfated tungstate: application in synthesis of active pharmaceutical ingredients atenolol, propranolol and ranolazine, S. P. Pathare and K. G. Akamanchi, *Tetrahedron Lett.*, 2013, **54**, 6455-6459, DOI: 10.1016/j.tetlet.2013.09.065

Scandium triflate as an efficient and useful catalyst for the synthesis of β-amino alcohols by regioselective ring opening of epoxides with amines under solvent-free conditions, A. T. Placzek, J. L. Donelson, R. Trivedi, R. A. Gibbs and S. K. De, *Tetrahedron Lett.*, 2005, **46**, 9029-9034, DOI: 10.1016/j.tetlet.2005.10.106

Selective biocatalytic aminolysis of (±)-epichlorohydrin: Synthesis and ICAM-1 inhibitory activity of (S)-(+)-3-arylamino-1-chloropropan-2-ols, P. Gupta, S. Bhatia, A. Dhawan, S. Balwani, S. Sharma, R. Brahma, R. Singh, B. Ghosh, V. S. Parmar and A. K. Prasad, *Bioorg. Med. Chem.*, 2011, **19**, 2263-2268, DOI: 10.1016/j.bmc.2011.02.029.

Boranes in Synthesis. 6. A New Synthesis of .beta.-Amino Alcohols from Epoxides. Use of Lithium Amides and Aminoborane Catalysts To Synthesize .beta.-Amino Alcohols from Terminal and Internal Epoxides in High Yield, C. E. Harris, G. B. Fisher, D. Beardsley, L. Lee, C. T. Goralski, L. W. Nicholson and B. Singaram, *J. Org. Chem.*, 1994, **59**, 7746-7751, DOI: 10.1021/jo00104a034.

Zinc Tetrafluoroborate Hydrate as a Mild Catalyst for Epoxide Ring Opening with Amines: Scope and Limitations of Metal Tetrafluoroborates and Applications in the Synthesis of Antihypertensive Drugs (RS)/(R)/(S)-Metoprolols, B. Pujala, S. Rana, and A. K. Chakraborti, *J. Org. Chem.*, 2011, **76**, 8768-8780, DOI: 10.1021/jo201473f.

Hydrophobic amplification of noncovalent organocatalysis, C. M. Kleiner and P. R. Schreiner, *Chem. Commun.*, 2006, 4315-4317, DOI: 10.1039/B605850G.

Dynamic Kinetic Resolution Allows a Highly Enantioselective Synthesis of cis-a-Aminocycloalkanols by Ruthenium-Catalyzed Asymmetric Hydrogenation, S. Liu, J.-H. Xie, L.-X. Wang and Q.-L. Zhou, *Angew. Chem. Int. Ed.*, 2007, **46**, 7506-7508, DOI: 10.1002/anie.200702491

6. Kinetic resolution

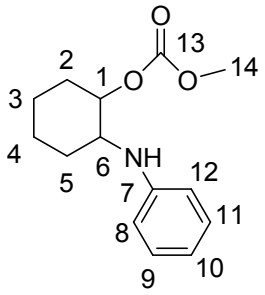
Kinetic resolution of *trans*-2-phenylamine-cyclohexanol under *batch* conditions (4a)

A suspension of racemic *trans*-2-phenylamine-cyclohexanol (**4a**) (222.7 mg, 1.16 mmol) and the enzyme Novozyme 435 (570.6 mg) in DMC (11.6 mL) were stirred under a nitrogen atmosphere at 250 rpm by orbital stirring at 50 ºC. Aliquots were regularly analysed by HPLC until around 50 % conversion was reached. The reaction was stopped and the enzyme filtered off using CH_2Cl_2 (3 x 5 mL). The solvent was evaporated under reduced pressure and the reaction was purified by flash chromatography (silica gel, 5 % MeOH/CH_2Cl_2), giving the corresponding optically enriched carbamate and alcohol.

Kinetic resolution of *trans*-2-phenylamine-cyclohexanol under *continuous flow* (4a)

A solution of racemic *trans*-2-phenylamine-cyclohexanol (**4a**) (187 mg, 0.98 mmol, 0.1 M) in 9.8 mL of DMC was pumped at 15 µL/min through a fixed bed reactor packed with 2 g of Novozyme 435 at 45 ºC. The samples were regularly analysed by HPLC until around 47 % conversion was reached, providing the corresponding optically enriched carbamate and alcohol.

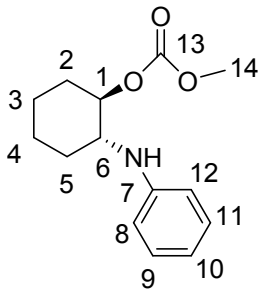
Synthesis and characterization of methyl (2-(phenylamino)cyclohexyl) carbonate (*rac*-7)



Cs_2CO_3 (38.5 mg, 0.12 mmol, 5 % molar) was suspended in 3 mL of DMC, and 2-(phenylamino)cyclohexan-1-ol (*rac*-**4a**) (84.3 mg, 0.44 mmol) was added. The reaction mixture was stirred at 60 ºC. After 143 hours, the reaction mixture was filtered and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (silica gel, CH_2Cl_2/5 % MeOH) to obtain the product as a yellow solid (98 mg, 89 %). Melting point: 58-60 ºC. ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 1.19-1.32 (m, 1H, H_3), 1.32-1.46 (m, 2H, H_4+H_5), 1.51-1.65 (m, 1H, H_3), 1.68-1.76 (m, 1H, H_2), 1.76-1.87 (m, 1H, H_4), 2.04-2.12 (m, 1H, H_5), 2.16-2.25 (m, 1H, H_2), 3.43 (td, 1H, H_6), 3.69 (s, 3H, H_{14}), 4.64 (td, 1H, H_1), 6.64 (d, J = 7.5 Hz, 2H, H_8+H_{12}), 6.69 (t, J = 7.3 Hz, 1H, H_{10}), 7.16 (t, J = 7.3, 1.7, 0.5 Hz, 2H, H_9+H_{11}) ppm. ^{13}C-NMR ($CDCl_3$, 125 MHz): δ 23.7 (C_3), 23.9 (C_4), 30.6 (C_5), 31.6 (C_2), 54.7 (C_6), 56.2 (C_{14}), 79.5 (C_1), 113.3 (C_8+C_{12}), 117.4 (C_{10}), 129.2 (C_9+C_{11}), 147.3 (C_7), 156.0 (C_{13}) ppm. FT-IR-ATR (cm^{-1}): 3400, 3053, 3022, 2937, 2860, 1736, 1602, 1508, 1497, 1439, 1318, 1255, 1179, 1155, 1114, 998, 941, 927, 867, 788, 747, 691. MS (ESI+, m/z): 250.2 [(M+H)$^+$, 100 %], 272.1 [(M+Na)$^+$,

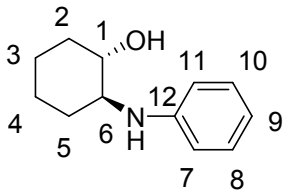
25 %], 288.1 [(M+K)$^+$, 8 %]. HPLC: Column AD, hex/IPA (99:1), 254 nm, 30 ºC, 0.750 mL/min, $t_{S,S}$ = 16.02 min, $t_{R,R}$ = 16.95 min.

Characterization of methyl ((1*R*,2*R*)-2-(phenylamino)cyclohexyl) carbonate (*R*,*R*-7)



Colourless viscous liquid. MS (ESI+, m/z): 250.2 [(M+H)$^+$, 100 %], 272.2 [(M+Na)$^+$, 20 %], 288.1 [(M+K)$^+$, 5 %]. $[\alpha]_D^{25}$ = -27.1 (c = 0.01, CH_3OH) for ee > 99 %. HPLC: Column AD, hex/IPA (99:1), 254 nm, 30 ºC, 0.750 mL/min, $t_{R,R}$ = 16.95 min.

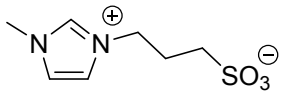
Characterization of (1*S*,2*S*)-2-(phenylamino)cyclohexan-1-ol (*S*,*S*-4a)

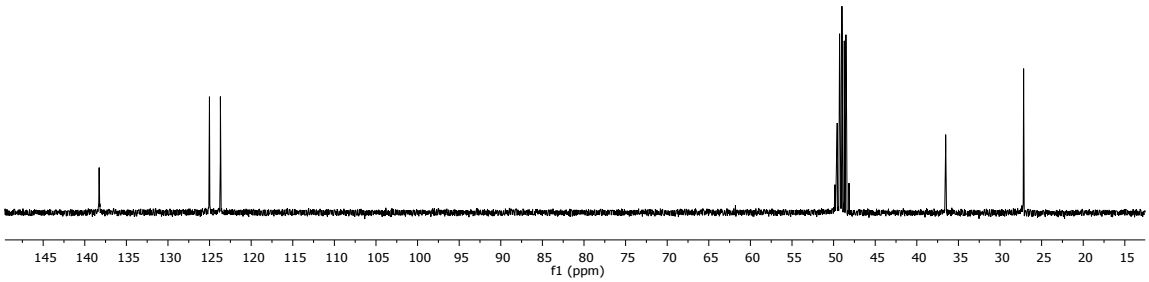


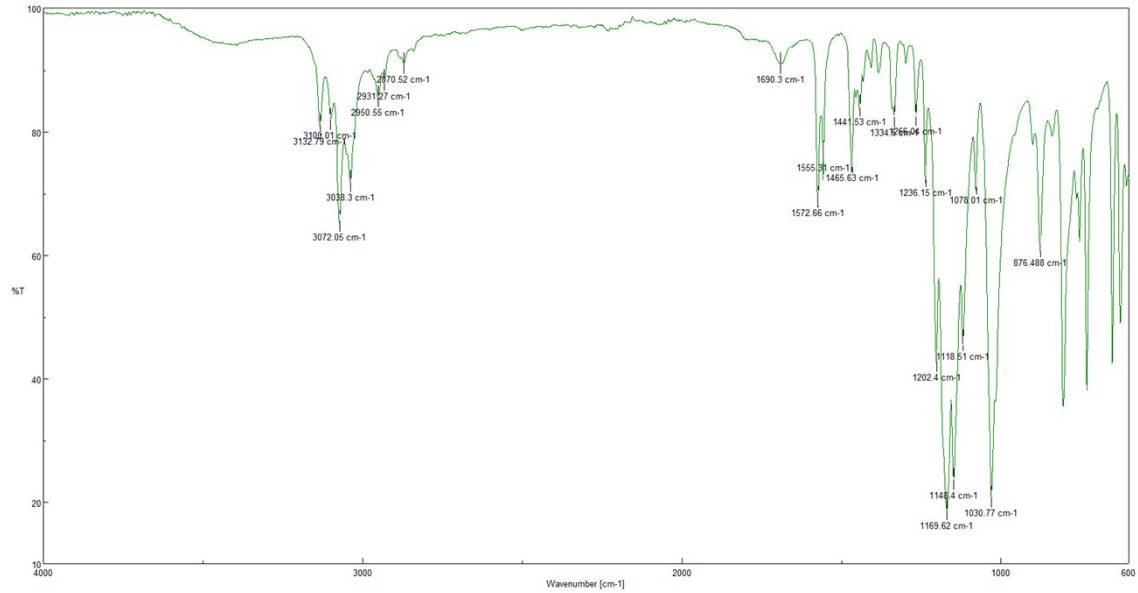
Light brown solid. Melting point: 80-83 ºC. MS (ESI+, m/z): 192.2 [(M+H)$^+$, 100 %], 214.2 [(M+Na)$^+$, 20 %], 230.2 [(M+K)$^+$, 5 %]. $[\alpha]_D^{25}$ = 43.18 (c = 0.01, CH_3OH) for ee > 93 %. HPLC: Column AD, hex/IPA (99:1), 254 nm, 30 ºC, 0.750 mL/min, $t_{S,S}$ = 54.81 min.

7. Spectral Data: NMR, IR and HPLC

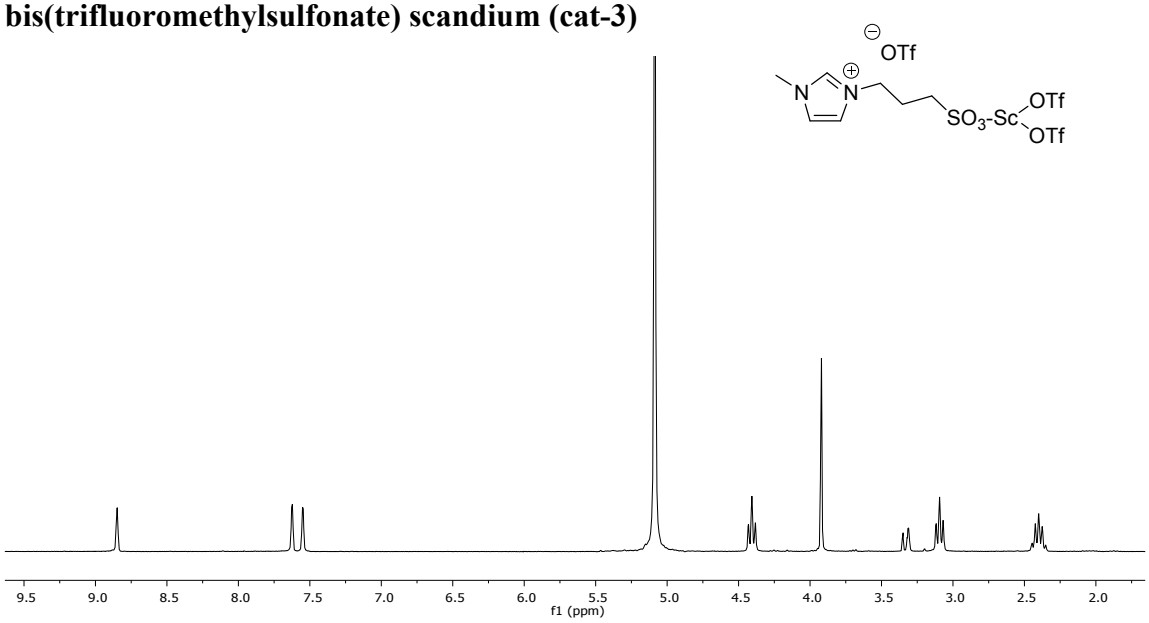
3-(1-methyl-1H-imidazol-3-ium-3-yl)propane-1-sulfonate

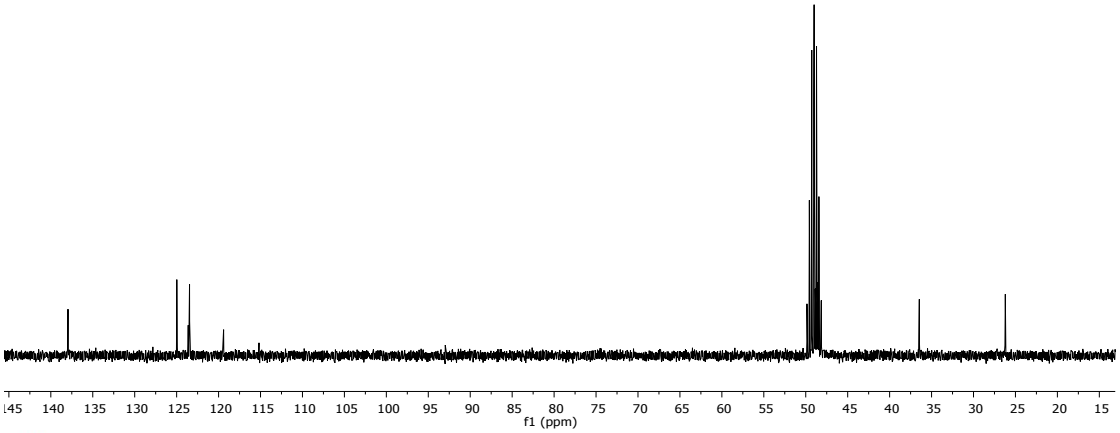


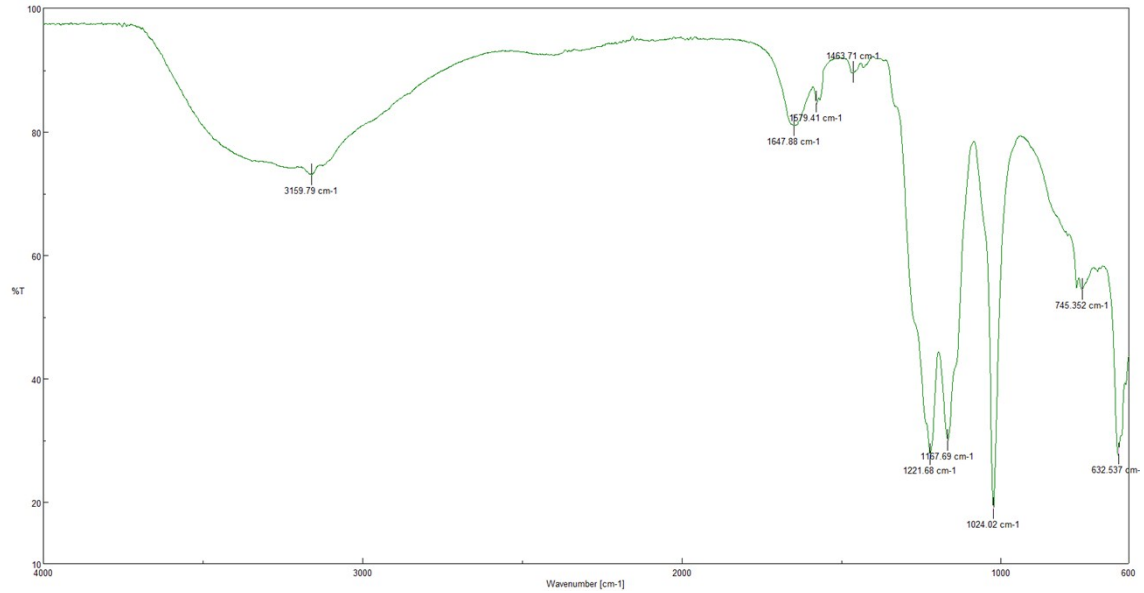




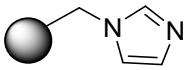
Trifluorosulfonate of ((3-(1-methyl-1H-imidazol-3-ium-3-yl)propylsulfonate) bis(trifluoromethylsulfonate) scandium (cat-3)

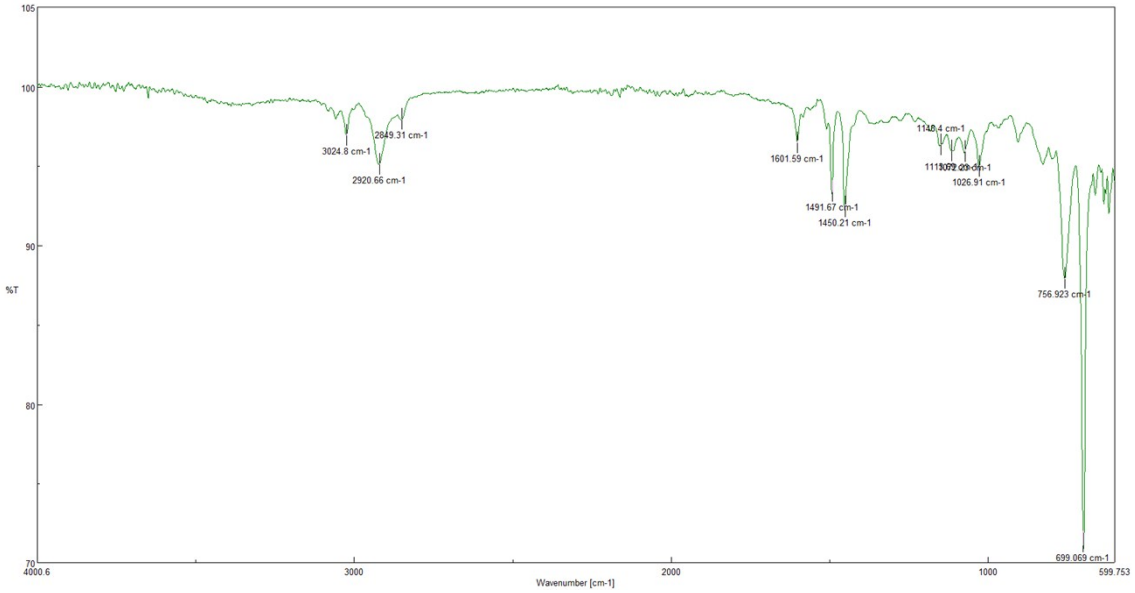




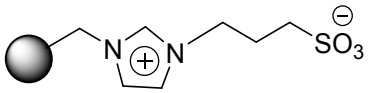


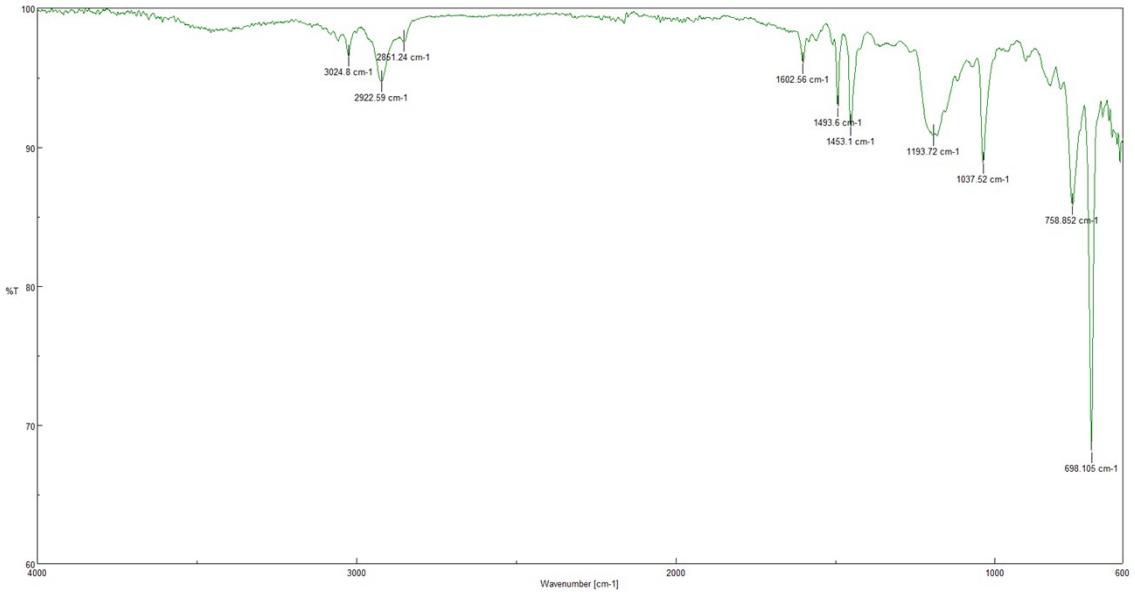
P-IM (Low loading)



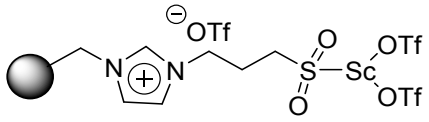


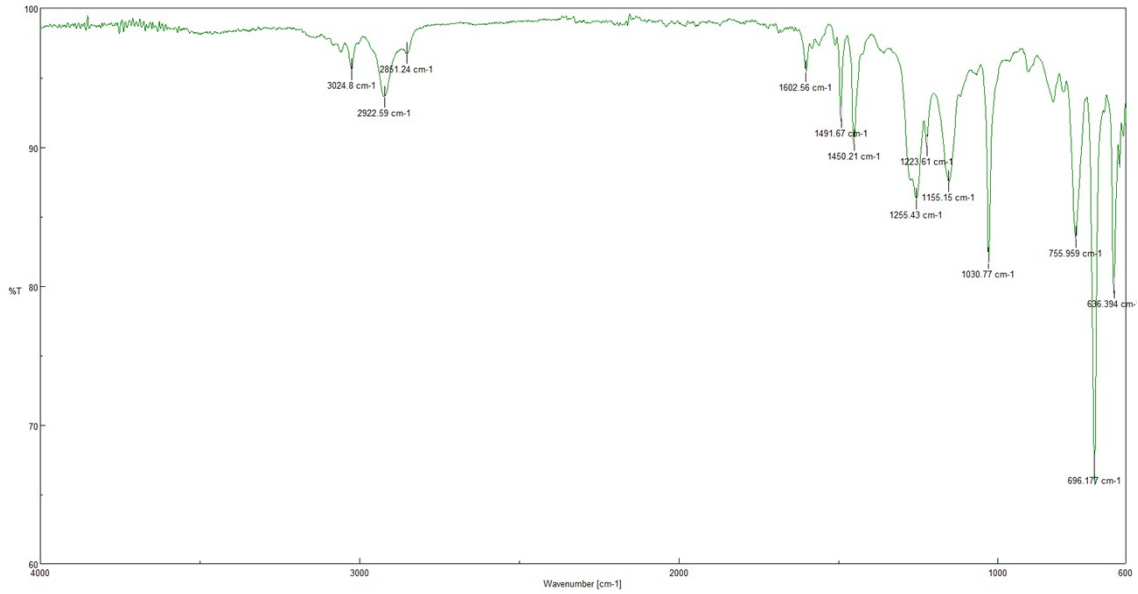
P-IM-SO_3 (Low loading)





Cat-4 (Low loading)





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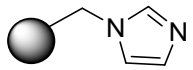

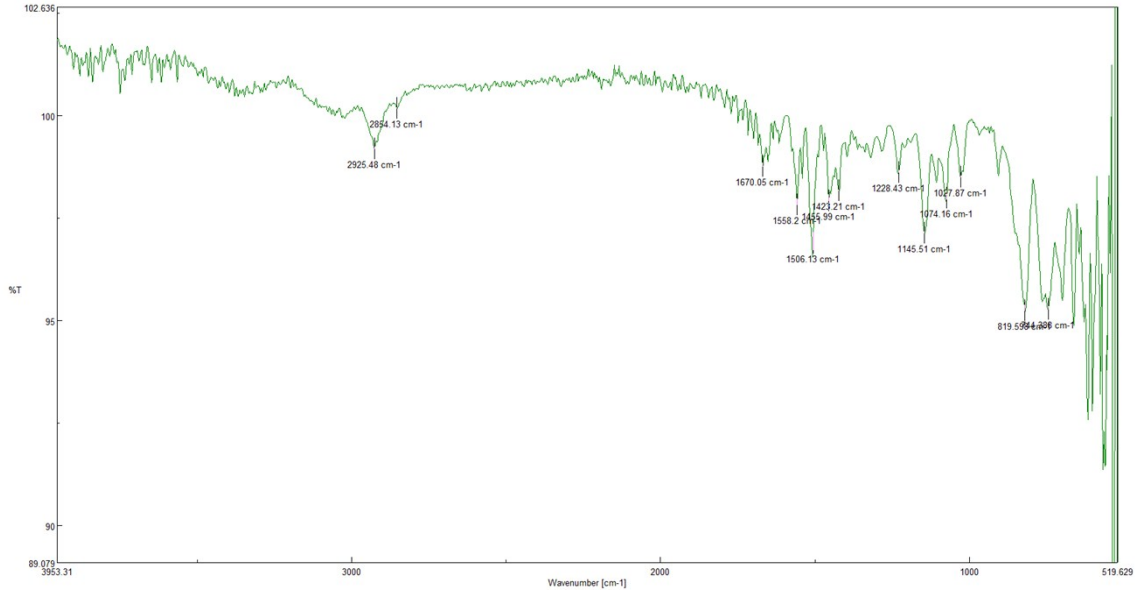

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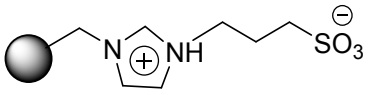
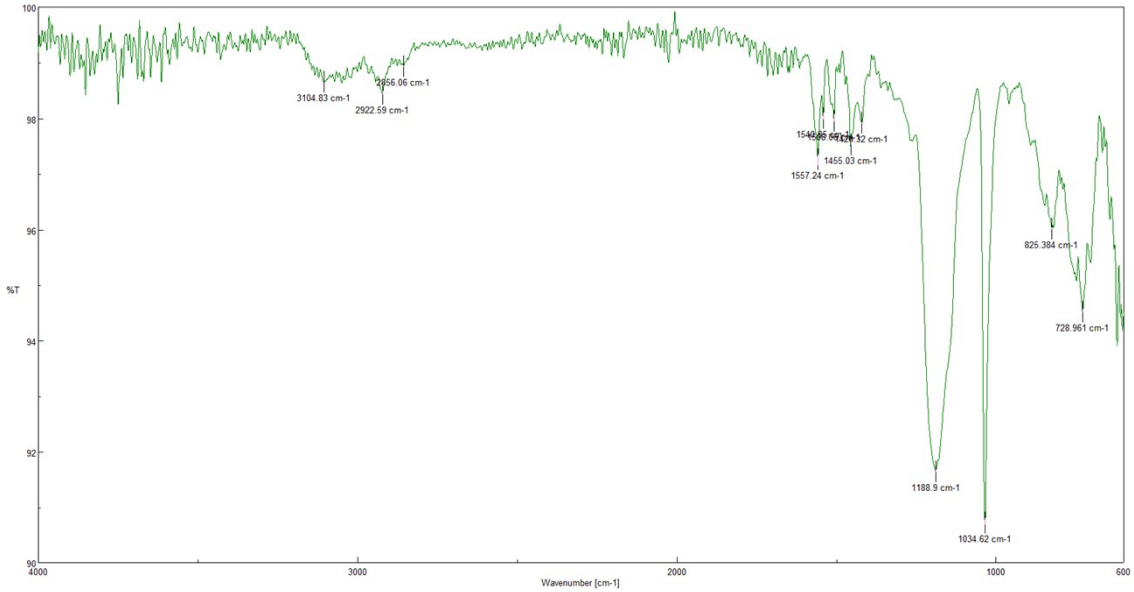
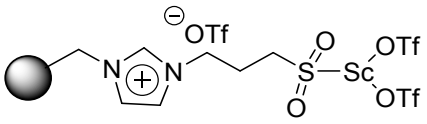
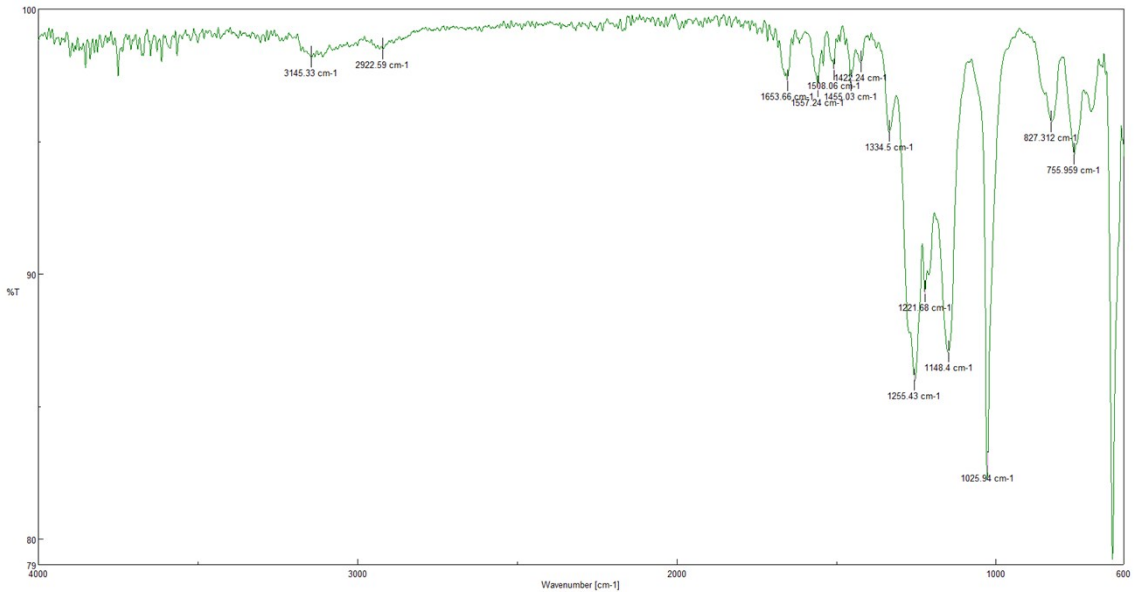


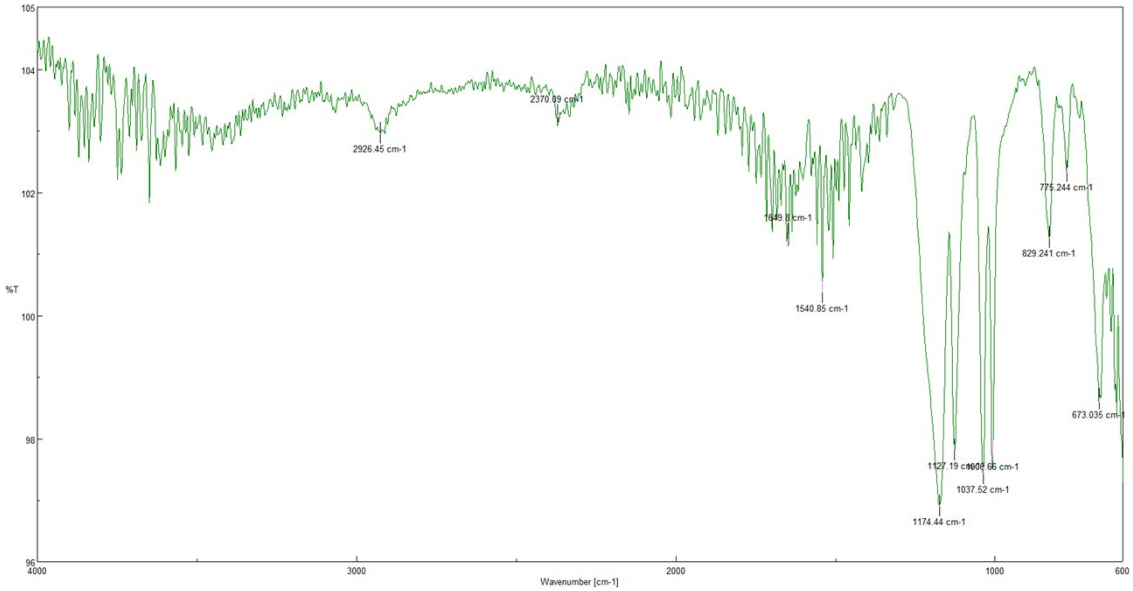


Cat-5 (High loading)

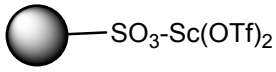


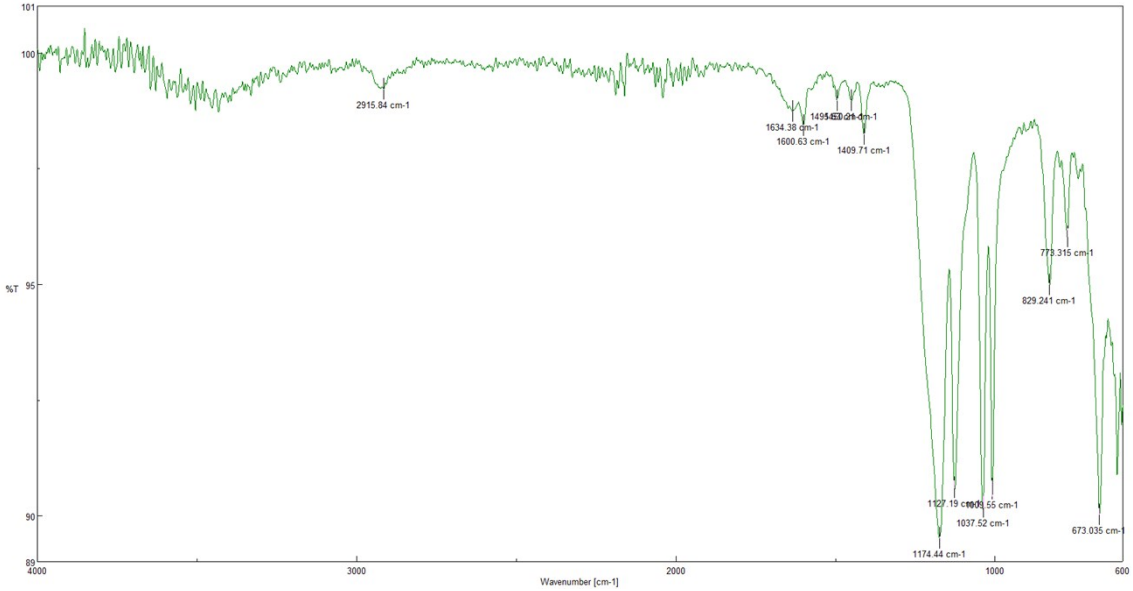


IR120-SO_3Na

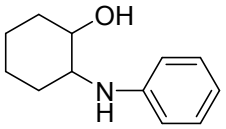


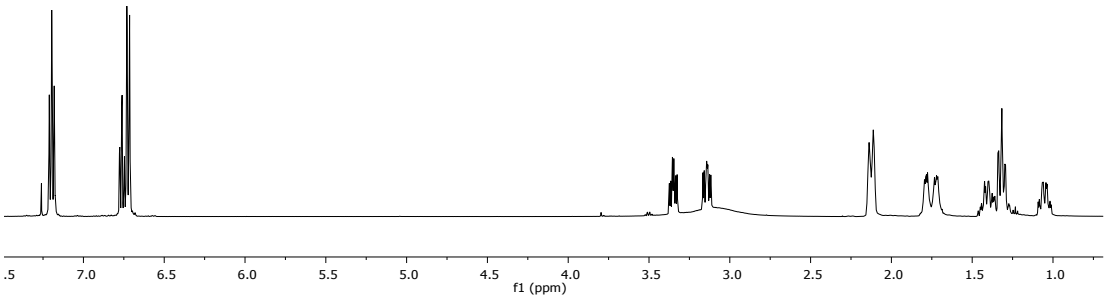
Cat-6

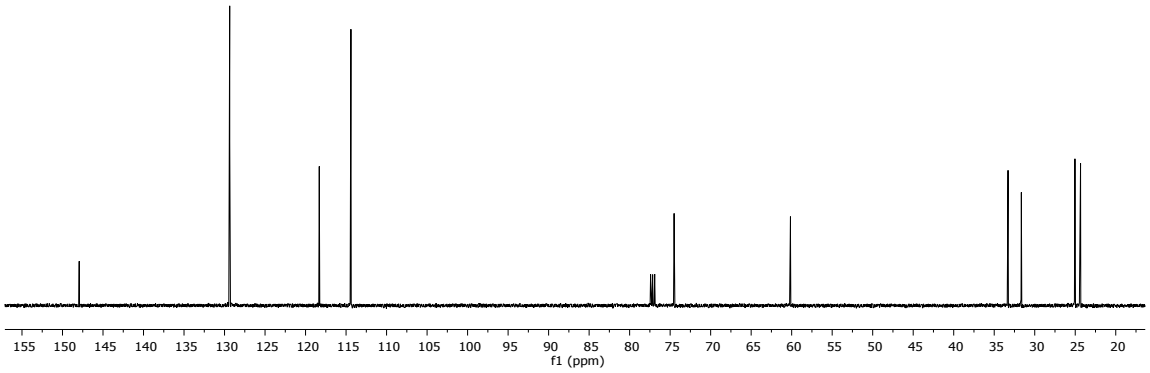


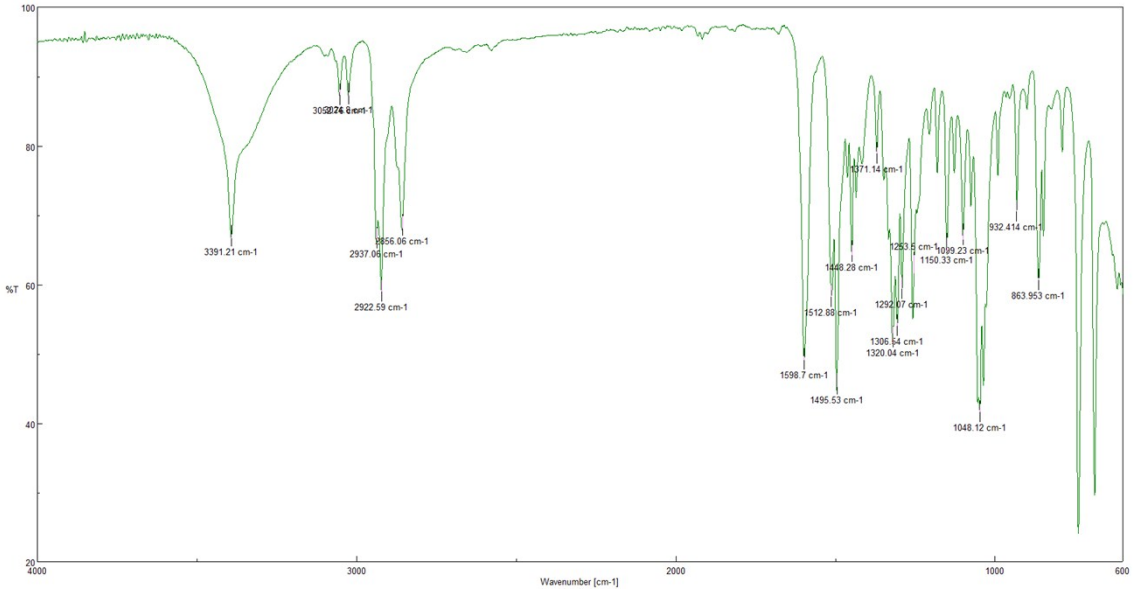


***Trans*-2-(phenylamino)cyclohexan-1-ol (*rac*-4a)**








100
80
60
40
20
%T
4000
3000
2000
1000
600
Wavenumber [cm-1]
3391.21 cm-1
2937.06 cm-1
2856.06 cm-1
2922.59 cm-1
1598.7 cm-1
1512.88 cm-1
1495.53 cm-1
1448.28 cm-1
1371.14 cm-1
1292.07 cm-1
1306.54 cm-1
1320.04 cm-1
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1048.12 cm-1
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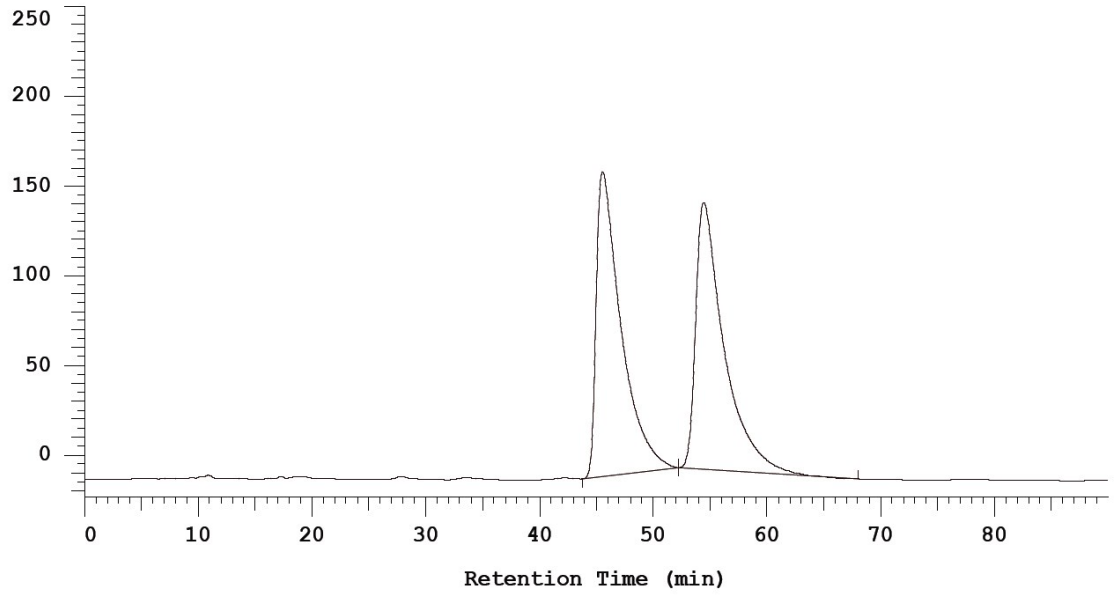
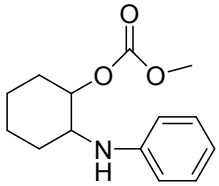
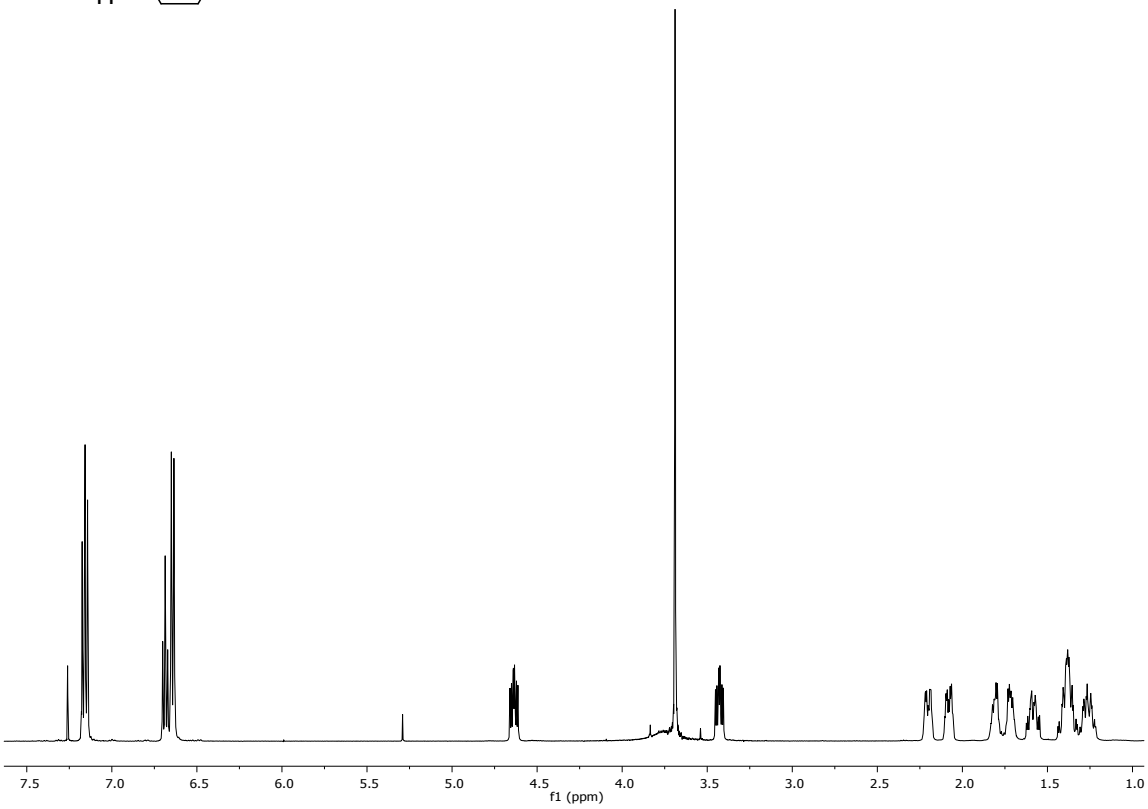
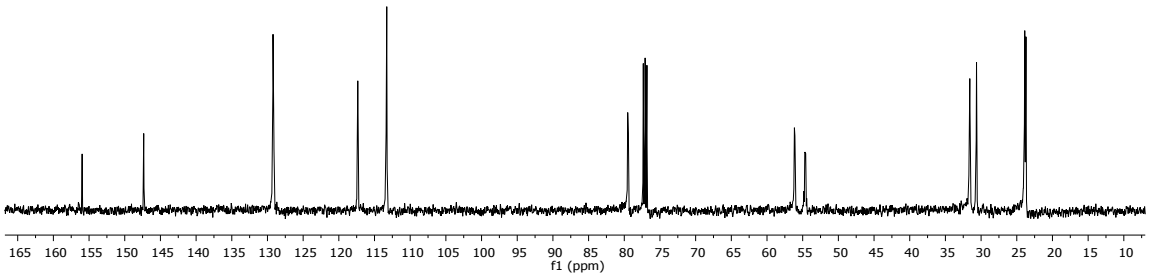
863.953 cm-1


250
200
150
100
50
0
0
10
20
30
40
50
60
70
80
Retention Time (min)

Methyl (2-(phenylamino)cyclohexyl) carbonate (*rac*-7)



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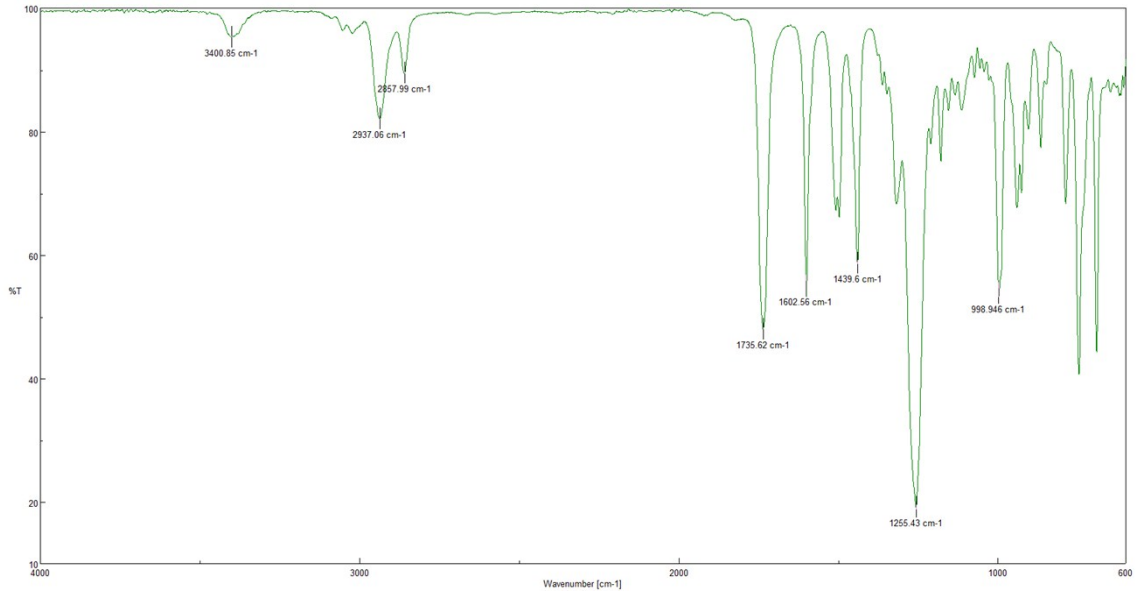
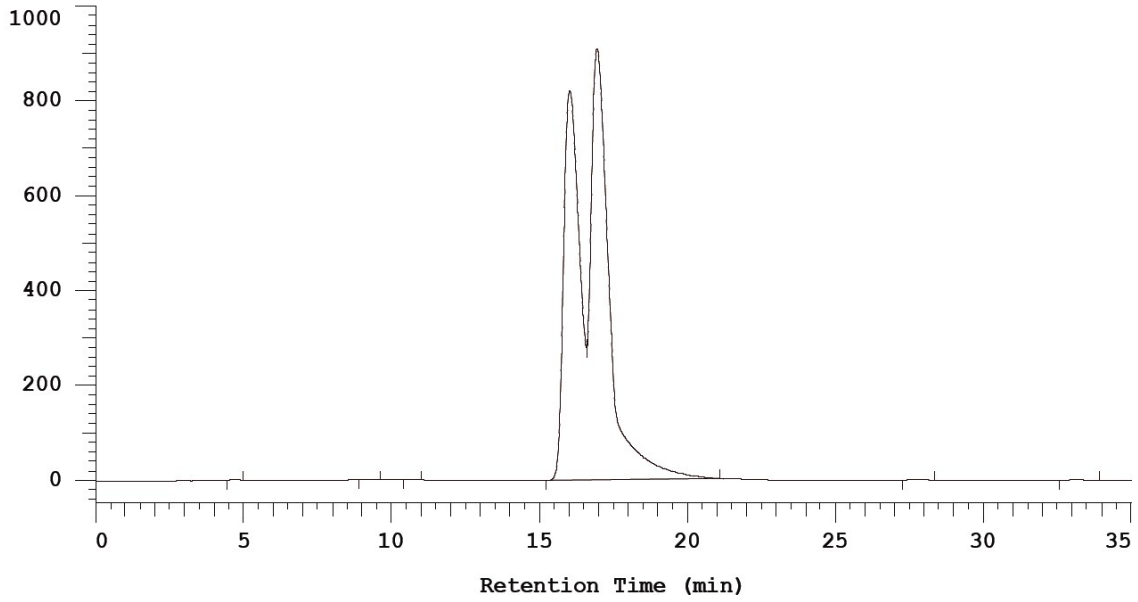
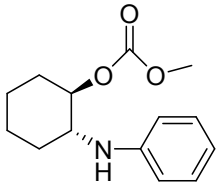
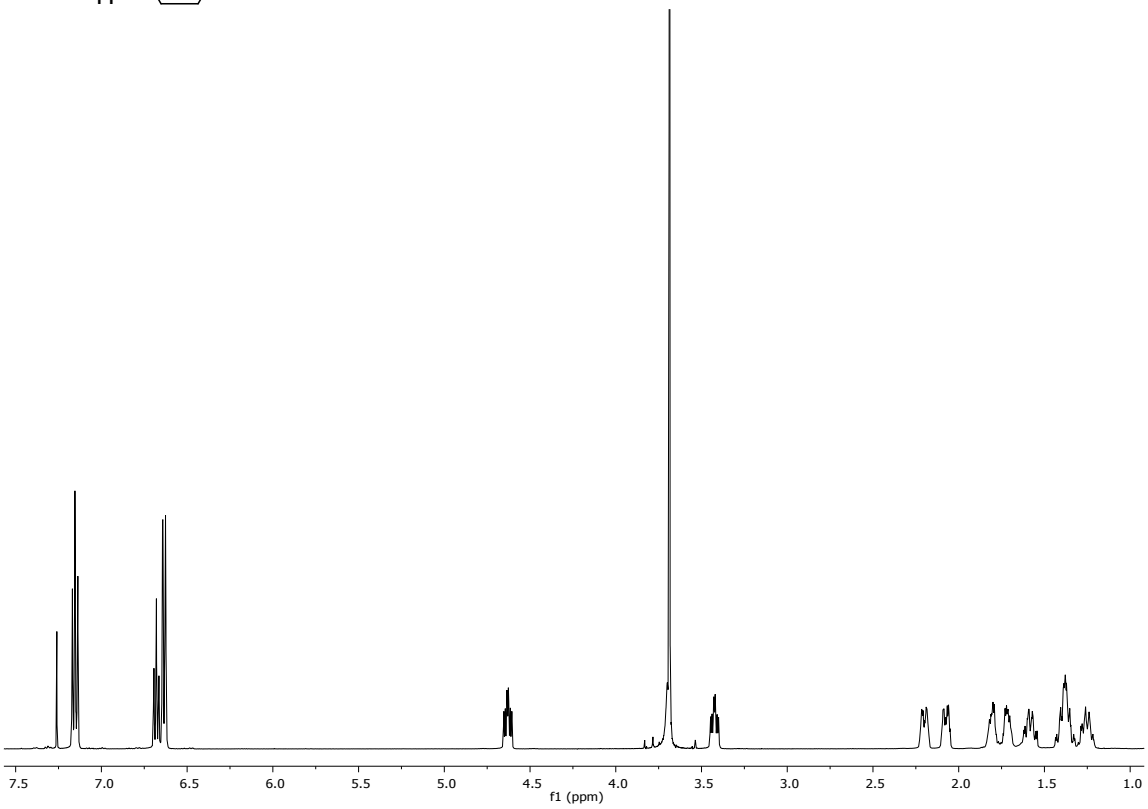
f1 (ppm)

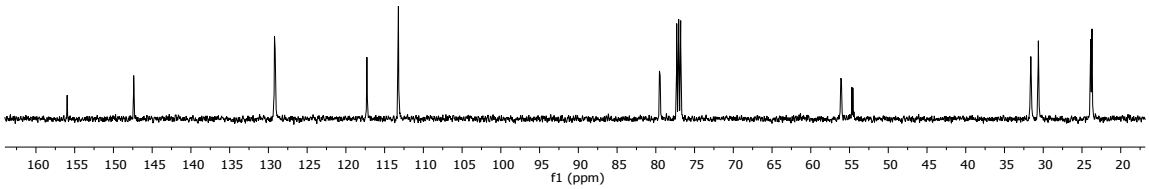

100
80
60
40
20
10
%T
3400.85 cm-1
2937.06 cm-1
2857.99 cm-1
1735.62 cm-1
1602.56 cm-1
1439.6 cm-1
1255.43 cm-1
998.946 cm-1
4000
3000
2000
1000
600
Wavenumber [cm-1]

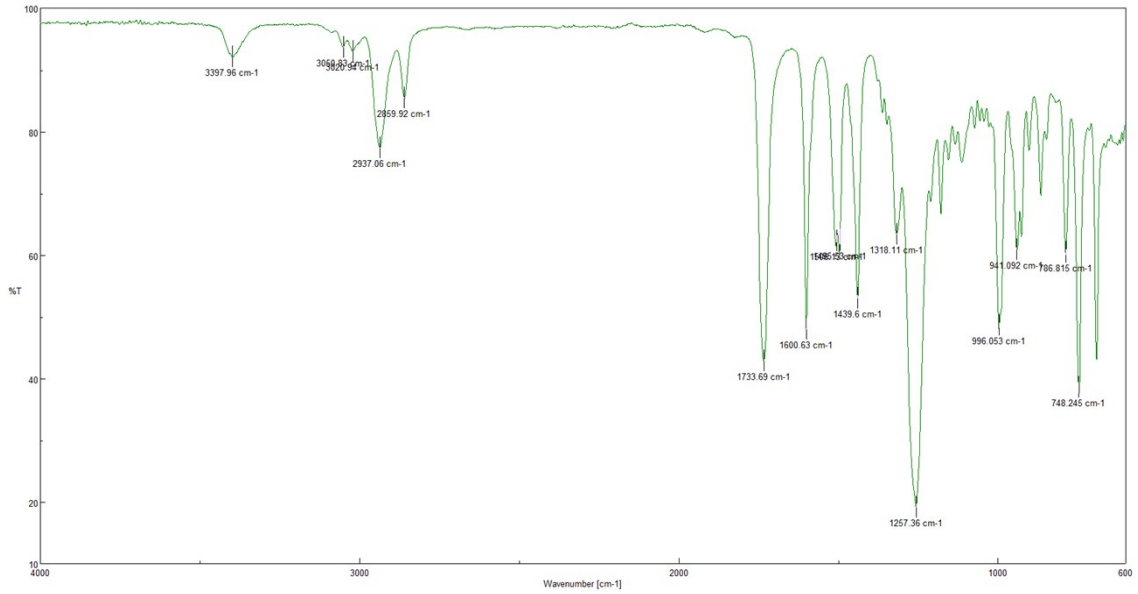

1000
800
600
400
200
0
0
5
10
15
20
25
30
35
Retention Time (min)

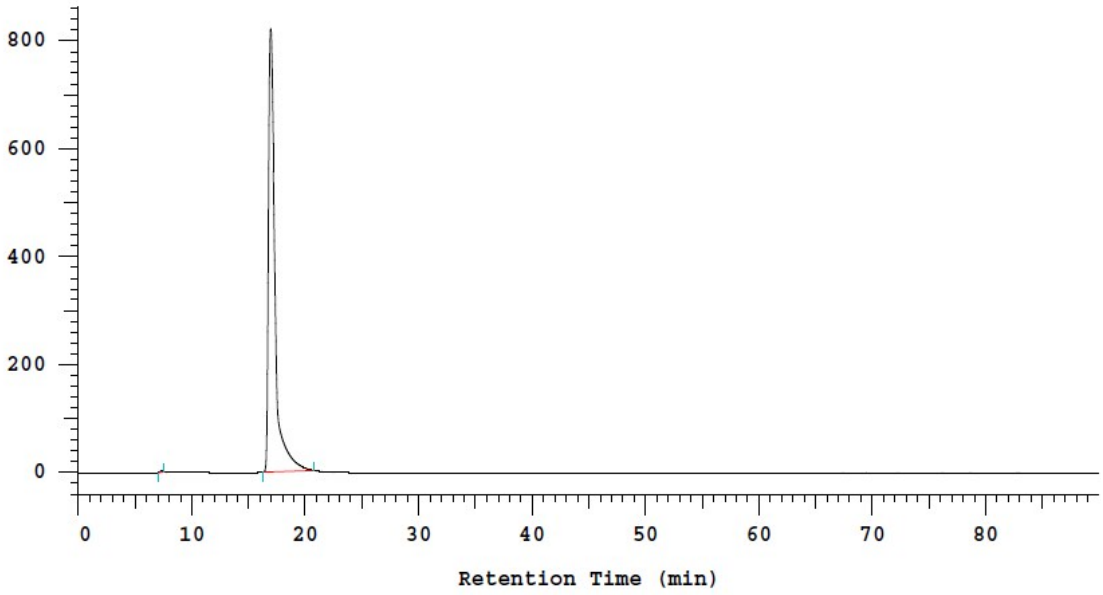
Methyl ((1*R*,2*R*)-2-(phenylamino)cyclohexyl) carbonate (*R*,*R*-7)



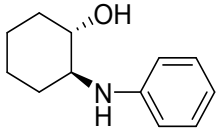


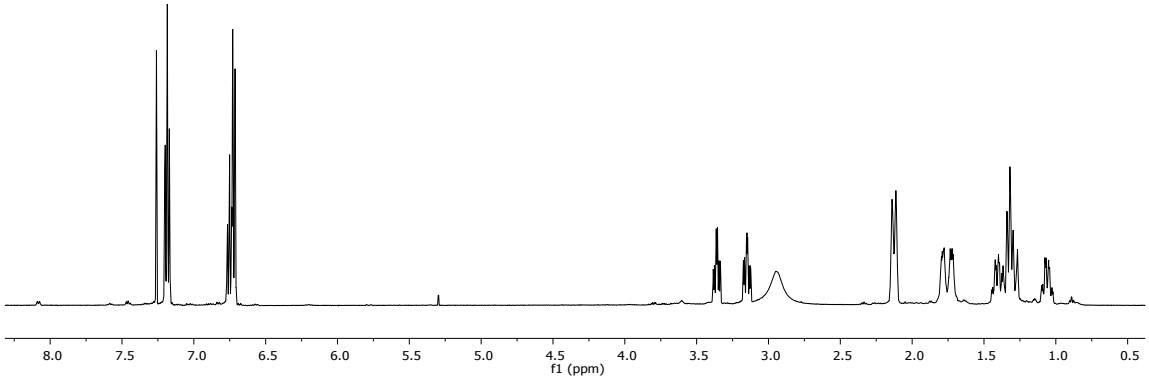

160 155 150 145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20
f1 (ppm)

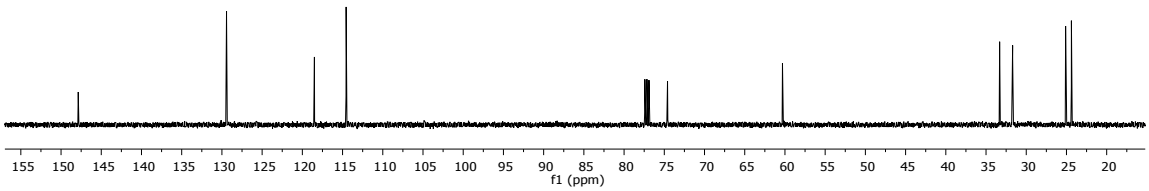

%T
100
80
60
40
20
10
4000
3000
2000
1000
600
Wavenumber [cm-1]
3397.96 cm-1
2937.06 cm-1
2859.92 cm-1
1733.69 cm-1
1600.63 cm-1
1439.6 cm-1
1318.11 cm-1
1257.36 cm-1
996.053 cm-1
941.092 cm-1
786.815 cm-1
748.245 cm-1

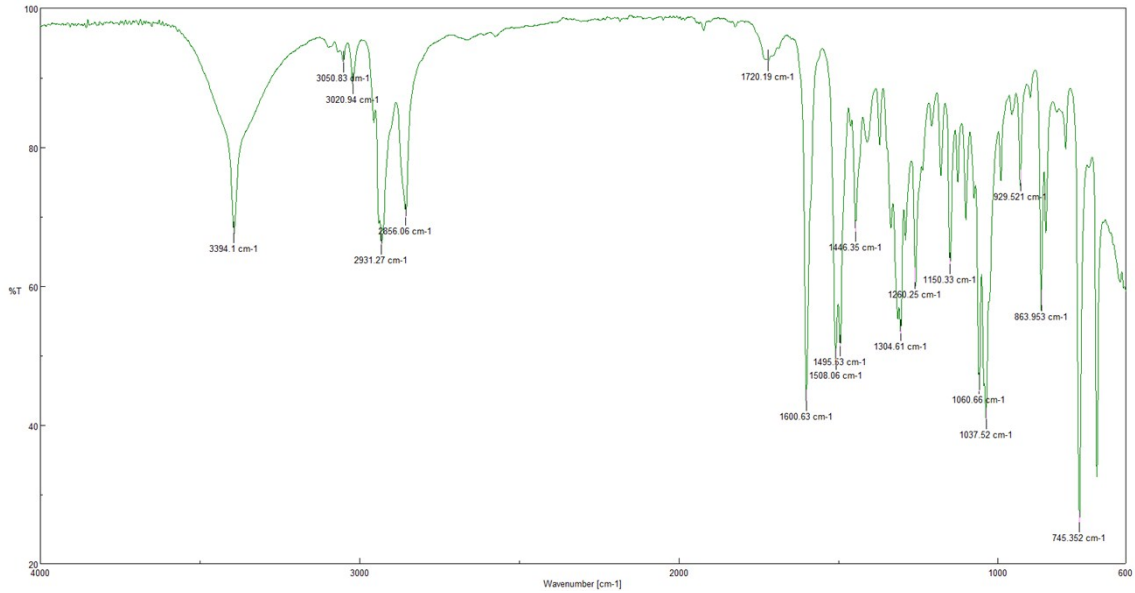

800
600
400
200
0
0
10
20
30
40
50
60
70
80
Retention Time (min)

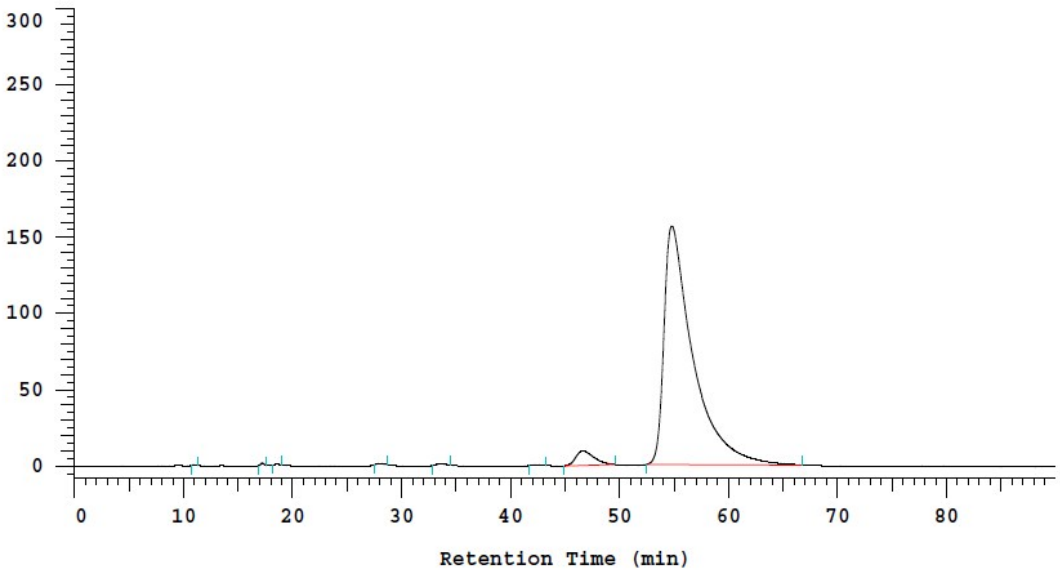
(1*S*,2*S*)-2-(phenylamino)cyclohexan-1-ol (*S*,*S*-4a)






155 150 145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20
f1 (ppm)


100
80
60
40
20
%T
3394.1 cm-1
3050.83 cm-1
3020.94 cm-1
2931.27 cm-1
2856.06 cm-1
1720.19 cm-1
1600.63 cm-1
1508.06 cm-1
1495.33 cm-1
1446.35 cm-1
1304.61 cm-1
1260.25 cm-1
1150.33 cm-1
1060.66 cm-1
1037.52 cm-1
929.521 cm-1
863.953 cm-1
745.352 cm-1
4000
3000
2000
1000
600
Wavenumber [cm-1]


300
250
200
150
100
50
0
0
10
20
30
40
50
60
70
80
Retention Time (min)