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Synthesis and characterization of (*S*)-amino alcohol modified M41S as effective material for the enantioseparation of racemic compounds

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Abstract

A new chiral stationary phase (CSP) was synthesized based on (*S*)-1-anilino-3-propyl-2-propanol covalently bonded to the mesoporous semi-crystalline material M41S. Direct semipreparative enantioseparation of mandelic acid could be achieved using medium pressure chromatography. Partly separated could also be the enantiomers of 2,2′-dihydroxy-1,1′-binaphthalene, cyanochromene oxide, diethyl tartrate and 2-phenyl propionic acid. The characterization of CSP was accomplished by microanalysis, cross polarized magic angle spinning (CP-MAS) ^{13}C NMR, powder X-ray diffraction (XRD), FTIR, thermo-gravimetric analysis (TGA), N_2 adsorption–desorption isotherm, scanning electron microscopy (SEM) and solid reflectance UV–vis spectroscopy. Furthermore the stability of CSP was satisfactory as it could withstand three washing and reuse experiments of enantioseparation of mandelic acid without loss in its performance.

Keywords: Enantioseparation; Racemic mandelic acid; 2,2′-dihydroxy-1,1′-binaphthalene; Cyanochromene oxide; Diethyl tartrate; 2-Phenyl propionic acid; Amino alcohol; M41S

1. Introduction

Separation of chiral molecules is required in many areas of research. As enzymes and other biological receptor molecules possess chiral centers, enantiomers of a racemic compound may interact with them in a different manner. Consequently, two enantiomers of a racemic compound have different pharmacological activities in many instances. In order to discern these differing effects, the biological activity of each enantiomer [1,2] needs to be studied separately. This has contributed significantly to the requirement of enantiomerically pure compounds particularly in pharmaceutical industry [3,4] and thereby the need to have chiral chromatography [5].

Attempts have been made in the past for the development of chiral stationary phases using β-cyclodextrin [6,7] notably DAICEL phases [8,9], crown ether [10,11], antibiotics [12] on silicas for HPLC [10–14], MPLC [15], GC [16,17], capillary electrophoresis [18–22] and chiral ligand exchange chromatography (CLEC) [23–27].

Mesoporous semi-crystalline materials (M41S) possess ordered pore structure, a large pore volume and high surface area besides thermal stability and mild acidity. These attributes make these materials a promising candidate for use in chromatography [28]. In the present study, the (*S*)-amino alcohol-silica **1** was synthesized using mesoporous silica M41S. This was achieved by the interaction of (*S*)-epichlorohydrin **2** with 3-aminopropyl triethoxysilane **3**, which was then immobilized on M41S followed by epoxide ring opening with aniline (Fig. 1). Thus, synthesized (*S*)-amino alcohol-silica **1** was used as a chiral selector for the chromatographic separation of mandelic acid, 2,2′-dihydroxy-1,1′-binaphthalene, cyanochromene oxide, diethyl tartrate and 2-phenyl propionic acid. Excellent chiral separation (ee, 99%) was obtained in case of mandelic acid. (*S*)-amino alcohol-silica **1** worked very well up to three repeat experiments without loss in separation performance. To the best of our knowledge, this is the first report concerning the use of (*S*)-amino alcohol-silica **1** as column packing material to separate different racemates.

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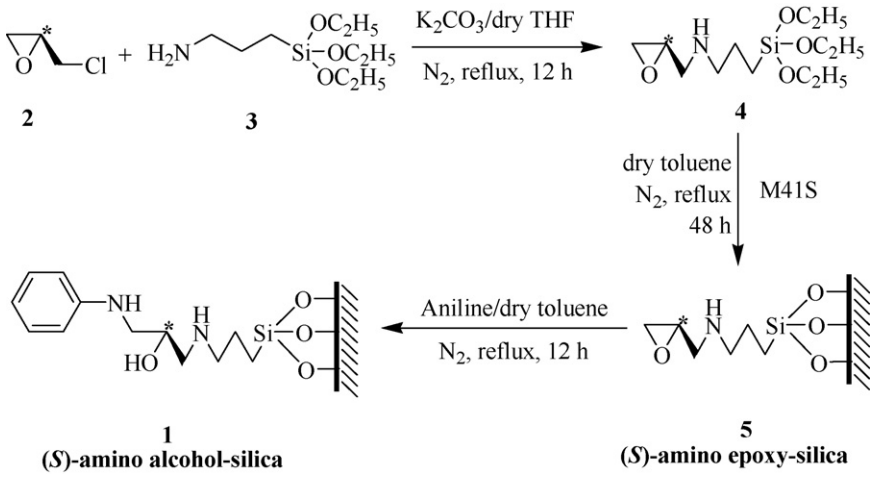

Fig. 1. Synthesis of the immobilized (*S*)-amino alcohol-silica **1**.

2. Experimental

2.1. Instrumentation

The high-performance liquid chromatography (HPLC, CLASS-VP 10A, 20 μl injection loop, PDA detector, Shimadzu), automatic polarimeter (Digipol-781, Rudolph Instrument, USA) and gas chromatography (GC 14B, Shimadzu) was used for product identification and enantiomeric excess determination. Microanalysis of the products was carried out by a CHN analyzer (Perkin-Elmer Series II, 2400). ^{1}H & ^{13}C NMR spectra were recorded on 200 and 50 MHz spectrometer (Bruker F113V), FTIR spectra were completed in KBr/nujol mull (Perkin-Elmer spectrum GX spectrophotometer), powder X-ray diffraction patterns of the sample were recorded on a Phillips X'pert MPD diffractometer in 2θ range (1.5–10) at scan speed of 0.4 °/s. BET surface area was determined from N_2-sorption data measured at 77K using volumetric adsorption set up (Micromeritics ASAP-2010, USA). The pore diameter of the silica samples was determined from the desorption branch of nitrogen adsorption isotherm employing the Barret-Joyner-Halenda (BJH) model. Thermal measurements and microstructure evaluation of these samples were carried out on Mettler Toledo (TGA/SDTA 851^{e}) instrument and scanning electron microscope (SEM) (LEO 1430VP).

2.2. Reagents, standards and samples

Racemic epichlorohydrin, sodium silicate solution, aniline, 2,4-di-*t*-butyl phenol, racemic 2,2′-dihydroxy-1,1′-binaphthalene (Aldrich, USA), 3-aminopropyl triethoxysilane, racemic mandelic acid, 1*R*,2*R*-(−)-1,2-diaminocyclohexane, racemic diethyl tartrate (Fluka, USA), cetyltrimethylammonium bromide, cobalt acetate (s.d. fine chem. Ltd., India) para formaldehyde, racemic 2,6-dimethyl pyridine (National Chemicals, India), stannous chloride (Merck, Germany), racemic 2-phenyl propionic acid (Across organics, Belgium) were used as received. Anhydrous K_2CO_3 (Rankem, India) was used after heating at 80 °C for 3 h. Cyanochromene oxide was synthesized by the reported method [29]. All the solvents used in the present study were purified by known method [30]. The (*S*)-epichlorohydrin was obtained by the enantioseparation of racemic epichlorohydrin using Jacobsen Co (III)-salen complex as a catalyst under hydrolytic kinetic resolution (HKR) conditions. The purity of the resolved (*S*)-epichlorohydrin was checked on chiral GC column (CHIRALDEX trifluoroacetyl derivatives GTA-type) and by optical rotation. Jacobsen's catalyst was prepared by the known method [31–33]. Synthesis of a highly ordered hexagonal siliceous M41S was carried out by modified hydrothermal crystallization method as described previously [34–37].

2.3. Synthesis of immobilized (S)-amino alcohol-silica *1*

Immobilized chiral ligand **1** and its precursors were synthesized as per the scheme given in Fig. 1.

2.3.1. Synthesis of chiral (2′S)-N-(2′,3′-epoxypropyl)-3-(aminopropyl)-triethoxysilane *4*

A highly dry and inert condition was maintained throughout the reaction using freshly dried reagents and apparatus. Typically, to a stirred suspension of anhydrous potassium carbonate (0.705 g, 5.1 mmol) in THF (5 ml) was added *S*-(+)-epichlorohydrin **2** (0.2 ml, 2.557 mmol) and 3-aminopropyl triethoxysilane **3** (0.598 ml, 2.557 mmol) at room temperature. The reaction mass was then refluxed (65–66 °C) for 12 h, filtered under inert atmosphere. Solvent from the filtrate was removed by the dry nitrogen draft; yield (0.674 g, 95%). As the compound **4** was highly moisture sensitive, an aliquot from the above semisolid was taken for spectroscopic characterization, while rest of the material was directly used for the preparation of **5** without further purification. LCMS: 278 $[M+H]^+$, 302 $[M+Na]^+$. 262, 216, ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.63 (t, $J=7.90$, 2H), 1.22 (t, $J=6.97$, 3H), 1.48–1.63 (m, 2H), 1.85 (bs, NH), 2.67 (t, $J=7.28$, 2H), 2.77 (d, $J=3.96$, 1H), 2.82–2.88 (m, 1H), 3.55 (d, $J=5.53$, 1H), 3.69 (q, $J=6.93$, 13.95, 2H), 3.82 (q, $J=6.99$, 13.93, 2H,); ^{13}C NMR spectroscopy (50 MHz, $CDCl_3$): δ (8.48, 18.86, 27.64, 45.47, 47.99,

52.61, 52.99, 58.97); FTIR (KBr): 3410, 2926, 1653, 1445, 1075, 776, 696 cm^{-1}; CHN analysis data C/H ratio calculated: 5.29, found: 5.21, C/N ratio calculated: 10.29, found: 12.42, Optical rotation $[\alpha]_D^{27} = +43.7^\circ$ (C = 0.35, tetrahydrofuran).

2.3.2. Synthesis of (S)-amino epoxy-silica **5**

To a solution of **4** (0.709 g, 2.557 mmol) in toluene (15 ml) was added calcined and freshly activated (at 250 °C) M41S (2 g) under an inert atmosphere and the resulting suspension was refluxed for 48 h with stirring. After cooling, the powder was collected by filtration, washed successively with dry toluene and then dried under vacuum. The dried material was subjected to Soxhlet-extraction with toluene for 10 h followed by drying the sample under vacuum [37]. FTIR (KBr) 458, 577, 801, 1078, 1634, 2359, 2936, 3413 cm^{-1}, Solid reflectance UV–vis: 230, 245, 290 nm.

2.3.3. Synthesis of (S)-amino alcohol-silica **1**

Under dry and inert atmosphere, aniline (455 μl, 5 mmol) was added to a suspension of **5** (2.5 g) in dry toluene (15 ml). The suspension was refluxed with stirring for 12 h. The reaction mixture was cooled to room temperature and the solid was filtered, washed repeatedly with dry toluene and subjected to the Soxhlet-extraction with toluene and 2-propanol (70:30) for 10 h. Finally the sample was dried under vacuum at 40 °C. Solid-state ^{13}C CP–MAS NMR (50 MHz), δ ppm 137 (aromatic carbons originated from aniline), 77–68 and 37–21 (alkyl carbons from epichlorohydrin modified aminopropyl chain), FTIR (KBr) 461, 554, 702, 801, 961, 1082, 1445, 1499, 1600, 1630, 2361, 2937, 3429, 3776 cm^{-1}, CHN analysis (Found) C: 12.76, H: 2.14, N: 1.90% (C/N = 6.71, C/H = 5.96), diffuse reflectance UV–vis: 230, 245, 290 nm.

2.4. Column chromatography

Slurry of (*S*)-amino alcohol-silica **1** in *n*-hexane and 2-propanol (9:1) was packed in a 260 mm × 16 mm glass column using medium pressure (0.5 kp/cm^2) of nitrogen at room temperature. The analyte solution in 2-propanol/*n*-hexane (1:1) was loaded on thus packed column that was equilibrated for 1 h. Each fraction of the size 4 ml was collected at the pressure mentioned above, which were subjected to HPLC analysis using an appropriate chiral column.

3. Results and discussion

The preparation of immobilized chiral (*S*)-amino alcohol-silica **1** is depicted in Fig. 1. The species **2** was synthesized by hydrolytic kinetic resolution (HKR) of racemic epichlorohydrin using Jacobsen Co (III)-salen complex as a catalyst and was characterized for its chemical and chiral purity by GC using GTA column, ^1H NMR using chiral shift reagent $Eu(hfc)_3$ and optical rotation [31–33]. The interaction of **2** in THF with 3-aminopropyl triethoxysilane gave **4**, which was fully characterized by ^1H, ^{13}C NMR, FTIR and optical rotation before it was anchored on calcined M41S to form (*S*)-amino epoxy-silica **5**.

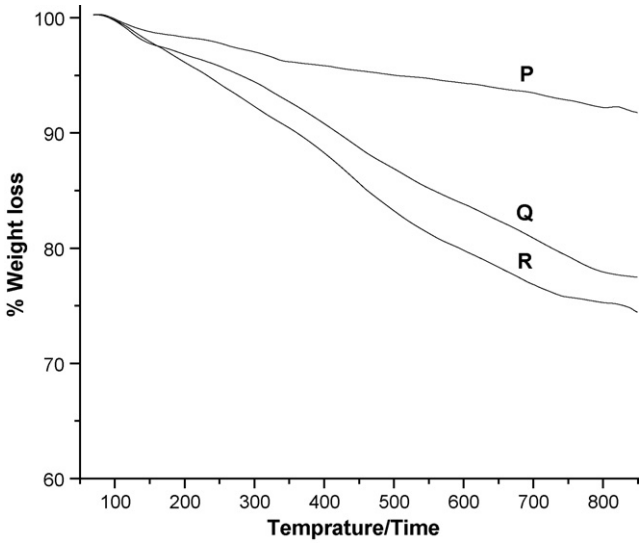

Fig. 2. TGA curve of calcined M41S (P), (*S*)-amino epoxy-silica **5** (Q) and (*S*)-amino alcohol-silica **1** (R).

The ring opening of the epoxy species **5** was done with aniline in toluene to get **1**.

The loadings of chiral organic moiety in compound **5** and **1** were found to be 22.5% and 25.6%, respectively, as determined from the weight loss measured by thermo-gravimetric analysis carried out in the temperature range between 50 and 800 °C (Fig. 2).

The X-ray diffraction pattern of M41S expectedly [34–37] showed (Fig. 3) hexagonal lattice with a major peak assigned to reflection corresponding to plane (1 0 0) and two additional peaks with lower intensity corresponding to reflections from (1 1 0) and (2 0 0) planes. It was observed (Fig. 3) that upon surface functionalization of M41S with organic moieties viz.,

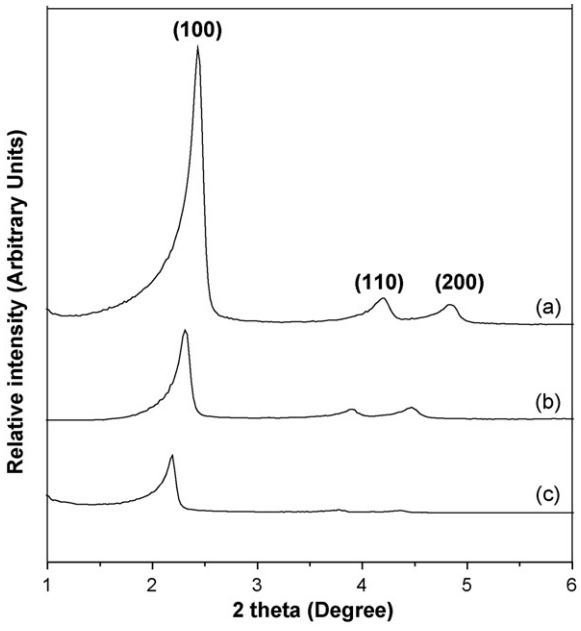

Fig. 3. Powder X-ray diffraction pattern of calcined M41S (a), (*S*)-amino epoxy-silica **5** (b) and (*S*)-amino alcohol-silica **1** (c).

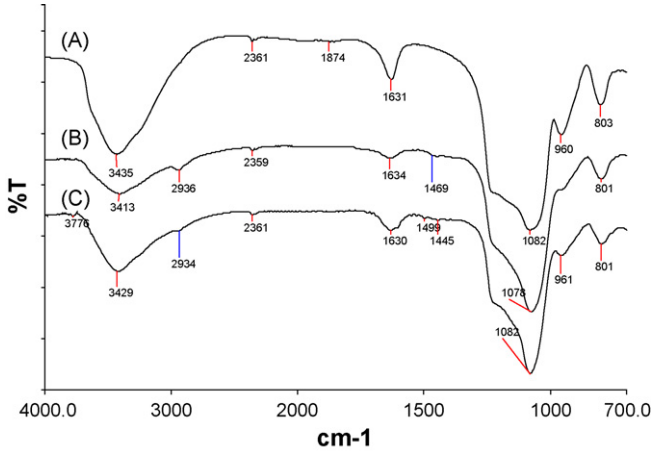

Fig. 4. FTIR spectra of calcined M41S (A), (*S*)-amino epoxy-silica **5** (B) and (*S*)-amino alcohol-silica **1** (C).

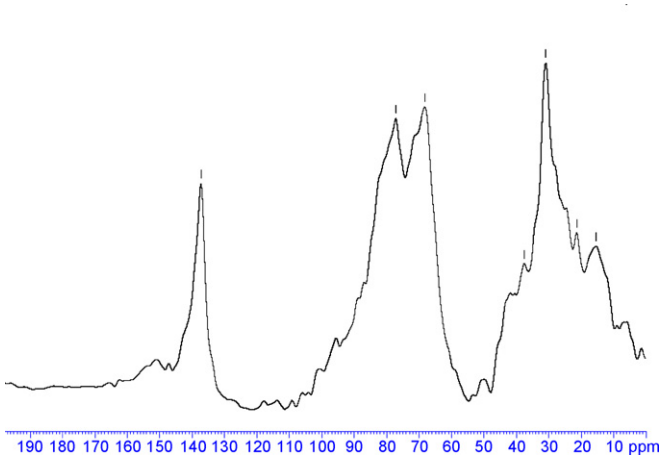

Fig. 5. Solid-state ^{13}C CP–MAS NMR spectra of (*S*)-amino alcohol-silica **1**.

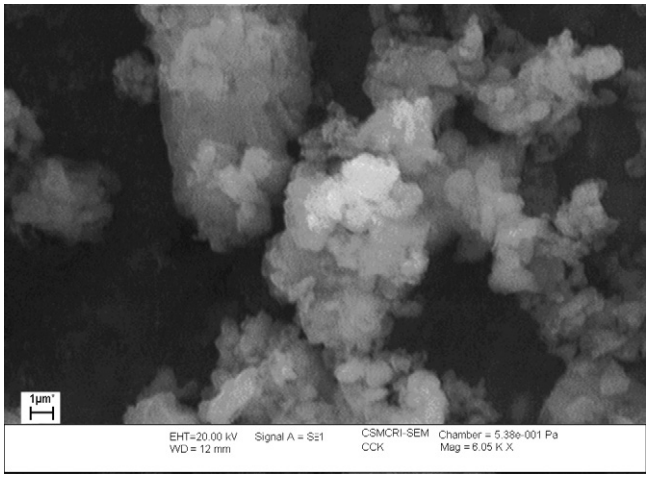

Fig. 6. Scanning electron microscopy (SEM) image of calcined M41S.

epoxy and amino alcohol in **5** and **1**, the intensity of all of peaks decreased marginally with a small shift toward lower 2θ value. This could be due to the presence of ligand inside the pores that cause an increased in the amount of scattering power within the pores, resulting in overall loss of intensity due to phase cancellation between pore walls and the guest ligand [38]. However, the presence of major reflections corresponding to M41S even after surface functionalization shows that the mesoporous M41S structure is retained.

The FTIR spectra (Fig. 4) of M41S showed the characteristic band at 1082 cm^{-1} of Si–O–Si and 3435 cm^{-1} for the Si–OH bond. After immobilization of **4** (Fig. 1) on M41S surface, an additional band appeared at 2936 cm^{-1} due to $\nu(CH_2)$ of propyl arm belonging to silylation agent in **5** (Fig. 4). However, after carrying out ring opening reaction with aniline (**1** in Fig. 1), new band due to ν(C–N) and ν(C=C) of aromatic ring appeared at 1499 cm^{-1} and 1600 cm^{-1}, respectively, along with broad band centered around 3429 cm^{-1} with enhanced intensity due to merging of ν(C–N), ν(O–H) along with Si–O–Si bands confirming the formation of supported (*S*)-amino alcohol **1**.

The presence of organic moiety in **1** was further confirmed by solid state (CP-MAS) ^{13}C NMR that showed peaks both in aromatic and aliphatic regions corresponding to carbons originating from aniline and epichloroydrin modified aminopropyl silane (Fig. 5). Scanning electron microscopy (Fig. 6) confirms the expected particle morphology with their size of around 1 μm.

The total pore volume of the sample was estimated from the amount of N_2 adsorption at relative pressure of about 0.995. N_2 adsorption–desorption isotherm of M41S of IV type is also confirmed the well-ordered mesopores. The primary mesopore volume V_p was calculated from the slope of a linear portion of the *t*-plot in the pressure range above the pressure of nitrogen condensation in primary mesopores. The data on BET surface area, pore diameter, total pore volumes obtained are summarized in Table 1. A large decrease in BET surface area was observed (1064–771 m^2/g) upon functionalization of modified M41S represented as **5** in Fig. 1. Similarly, reduction in the mesoporous diameter from 35 to 32 Å and in pore volume from 0.942 to 0.625 cm^3/g was also observed (Table 1). Moreover, further decrease in BET surface area 771 to 680 m^2/g in pore diameter from 32 to 30 Å and pore volume from 0.625 to 0.512 cm^3/g was observed upon ring opening reaction with aniline (**1**, Fig. 1) indicates that the internal pores of the M41S are occupied by the amino alcohol and structure of the mesopore is maintained after modification (Fig. 7).

Table 1
Physico-chemical data of M41S, (*S*)-amino epoxy-silica **5** and (*S*)-amino alcohol-silica **1**

Compound	BET surface area (m^2/g)	Total pore volume (cm^3/g)	BJH pore diameter (Å)	Wall thickness (Å)
M41S	1064	0.942	35.4	6.31
Compound **5**	771	0.625	32.4	11.51
Compound **1**	680	0.512	30.1	16.46

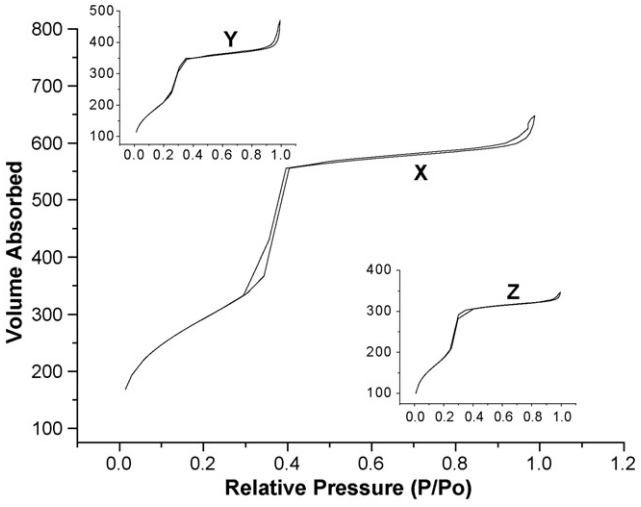

Fig. 7. Nitrogen adsorption–desorption isotherms of M41S (X), (*S*)-amino epoxy-silica **5** (Y) and (*S*)-amino alcohol-silica **1** (Z).

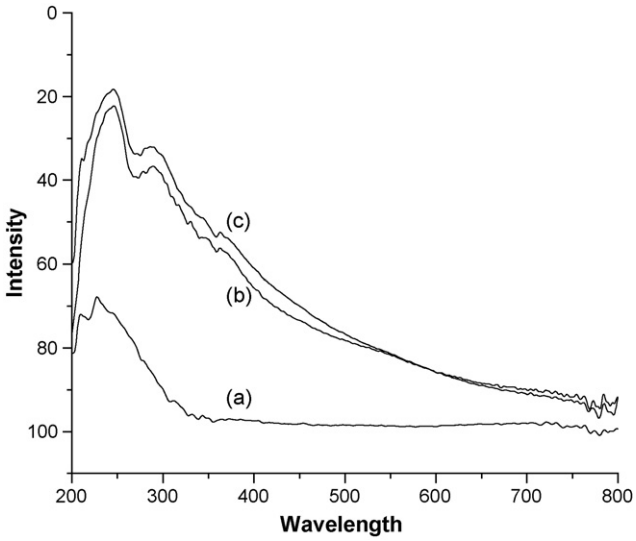

Fig. 8. Solid reflectance UV-vis spectra of calcined M41S (a), (*S*)-amino epoxy-silica **5** (b) and (*S*)-amino alcohol-silica **1** (c).

The solid reflectance UV–vis spectrum of the immobilized (*S*)-amino epoxy-silica **5** shows ligand charge transfer band at 230, 260 and 330 nm. After formation of (*S*)-amino alcohol-silica **1** the spectrum remains similar with an increase in the intensity of all the bands (Fig. 8) showing the presence of amino alcohol covalently bonded to M41S (Fig. 8).

The separation activity of the (*S*)-amino alcohol-silica **1** for enantioseparation of racemic mandelic acid (Fig. 9) was carried out by medium pressure column chromatography by varying the amount of (*S*)-amino alcohol-silica **1** as well as that of analyte as shown in Table 2. mandelic acid (30 mg) in the form of slurry in *n*-hexane/2-propanol (9:1) was loaded on column packed with **1** (2 g). The excellent enantioseparation of (*R*)-(−)-mandelic acid in some of the fraction with ee up to 99.4% was achieved (entry 1). The ee of mandelic acid was determined by HPLC using chiralcel OD column and the HPLC chromatogram of racemic and resolved mandelic acid is shown in Fig. 10, respectively. After the 30 fractions of 4 ml each the chiral stationary phase **1** was washed with 2-propanol to retrieve the (*S*)-mandelic acid (recovery, 9 mg; ee, 47.3%). Table 3 and Fig. 11 show the elution profile and the amount of mandelic acid obtained after separation. For the sake of convenience in weighing we have combined the fractions 1–13, 14–22 and 23–30 which were found to be 4, 5 and 11 mg with ee 4.2, 53.2 and 95.6%, respectively. As a result 11 mg of (*R*)-(−)-mandelic acid with ee >95% was recovered which is >72% of the (*R*)-enantiomer present in 30 mg of the

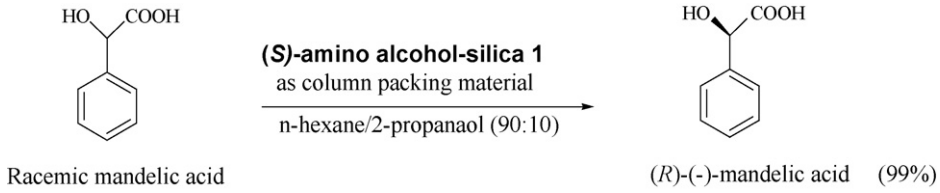

Fig. 9. Chiral separation of racemic mandelic acid.

Table 2
Separation of mandelic acid varying amount of mandelic acid and packing material

Entry	Amount of mandelic acid[a] (mg)	Column packing material **1** (g)	Eluent[b]	% ee max[c]	Repeat experiment[d]
1	30	2.00	Hex/IPA = 9:1	99.4	1st
2	30	1.90	Hex/IPA = 9:1	99.0	2nd
3	30	1.87	Hex/IPA = 9:1	98.8	3rd
4	30	2.00	Hex/IPA = 9:1	99.3	–
5	10	2.00	Hex/IPA = 9:1	98.5	–
6	10	M41S[e]	Hex/IPA = 9:1	–	–

[a] Separation by HLPC, using chiralcel OD column, eluent *n*-hexane/2-propanol = 9:1 at 220 nm, mandelic acid loaded on column after dissolving in 2-propanol/*n*-hexane.
[b] Hex = *n*-hexane, IPA = 2-propanol.
[c] Enantiomeric excess of (*R*)-(−)-mandelic acid determined by the comparison of HPLC profile with authentic samples.
[d] Reuse of chiral stationary phase for chromatographic separation of fresh racemic mandelic acid.
[e] 2 g M41S as column packing material.

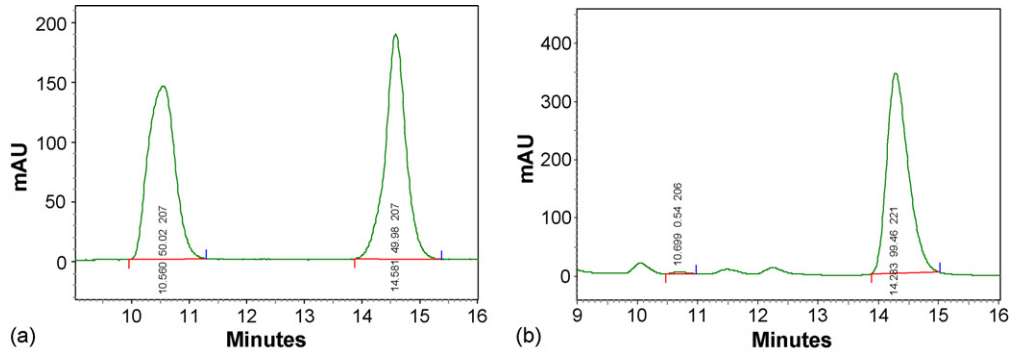

Fig. 10. HPLC chromatogram of racemic mandelic acid (a), HPLC chromatogram of (*R*)-(−) mandelic acid (b) after column chromatography carried out on chiralcel OD column using *n*-hexane/2-propanol (80/20) mobile phase at 0.5 ml/min flow rate.

racemic mandelic acid. In all >96% of the mandelic acid was recovered at the end of chromatographic separation.

After completion of one chromatographic run the column material was subjected to the Soxhlet-extraction with toluene and 2-propanol (70:30), dried under vacuum and reused for another separation experiment with fresh racemic mandelic acid under the condition used for first separation experiment. The data for two repeat use of the recovered column material **1**

Table 3
Data for separation of racemic mandelic acid with elution of *n*-hexane/2-propanol = 9:1 by medium pressure column chromatography[a]

Fractions	Time (min)	Area % of (*S*)-(−)-mandelic acid[b]	Area % of (*R*)-(−)-mandelic acid[b]	Weight of fractions (g)	ee (%)
1	0	49.74	50.26		
2	20	49.74	50.26		
3	40	49.68	50.32		
4	60	49.31	50.69		
5	80	49.25	50.75		
6	100	48.96	51.04		
7	120	48.68	51.32		
8	140	48.29	51.71		
9	160	47.22	52.78		
10	180	46.17	53.83		
11	200	44.79	55.21		
12	220	42.93	57.07		
13	240	42.12	57.88	0.004[c]	4.2
14	260	37.91	62.09		
15	280	36.96	63.04		
16	300	34.77	66.23		
17	320	25.06	74.95		
18	340	21.24	78.76		
19	360	17.55	82.45		
20	380	14.08	85.92		
21	400	11.64	88.36		
22	420	11.44	88.56	0.005[d]	53.2
23	440	5.85	94.15		
24	460	3.23	96.77		
25	480	2.54	97.46		
26	500	2.25	97.75		
27	520	1.73	98.27		
28	540	0.77	99.23		
29	560	0.74	99.26		
30	580	0.36	99.64	0.011[e]	95.6
Total weight of fractions 1–30				0.020	
Recovery after washing column with 2-propanol				0.009[f]	47.3
Total recovery				0.029	

[a] Mandelic acid loading 30 mg, Flow rate 0.2 ml/min and amount of each fraction is 4 ml at 0.5 kp/cm^2 pressure.
[b] Area % is calculated through HPLC Chromatogram.
[c] Weight obtained by combining fractions 1–13.
[d] Weight obtained by combining fractions 14–22.
[e] Weight obtained by combining fractions 23–30.
[f] Weight obtained after washing the column with 2-propanol after retrieving fractions 1–30.

Table 4
Data for separation of different compounds by medium pressure column chromatography[a]

Entry	Name of compound (racemic)	Amount of analyte[b] (mg)	Column packing material **1** (g)	Eluent[c]	% ee max	Absolute config.[d]
7	BINOL[e]	10	2.0	Hex/IPA = 8:2	19.5	*R*
8	CNCR[f]	10	2.0	Hex/IPA = 9:1	3.8	3*S*,4*S*
9	Diethyl, tartrate[g]	10	2.0	Hex/IPA = 8:2	11.5	2*R*, 3*R*
10	2-Phenyl propionic acid[h]	10	2.0	Hex/IPA = 9.5:0.5	33.5	*S*

[a] All the experiments were conducted under the same condition unless otherwise stated. Temperature (27 °C), amount of sample $m = 0.0100 \pm 0.0001$ g, column diameter $d = 16$ mm, length = 260 mm, enantiomeric excess was determined by HPLC analysis by mentioned columns ($l = 25$ cm, $d = 0.46$ cm).
[b] Analyte loaded on column after dissolving in 2-propanol/*n*-hexane.
[c] Hex = *n*-hexane, IPA = 2-propanol.
[d] The absolute configuration were determined by the comparison of HPLC profile with authentic samples.
[e] Chiralpak AD column, eluent *n*-hexane/2-propanol = 8:2 at 254 nm.
[f] Cyanochromene oxide (CNCR) chiralcel OD column, eluent *n*-hexane/2-propanol = 9:1 at 254 nm.
[g] Chiralpak AD column, eluent *n*-hexane/2-propanol = 9:1 at 220 nm.
[h] Chiralcel OD column, eluent *n*-hexane/2-propanol/formic acid = 98:2:1 at 254 nm.

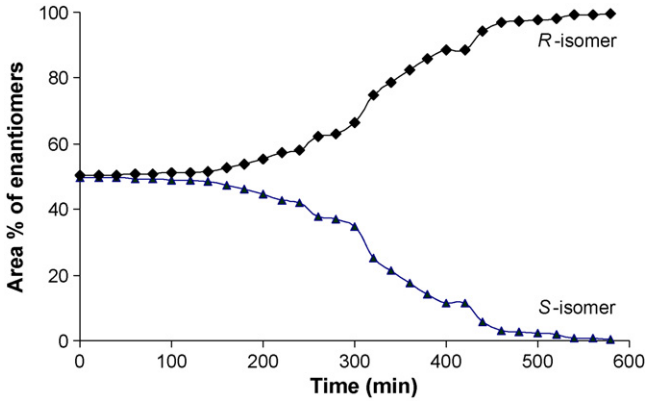

Fig. 11. Elution profile from the medium pressure column chromatography (Table 3).

(Table 2; entries 2 and 3) show that the material is stable and retain the enantioseparation capability under the separation conditions used and drying the column material under vacuum. Furthermore, even 2 g of column packing material and 10 mg of analyte are sufficient to achieve similar results (entry 5). In a control experiment for the chromatographic separation of racemic mandelic acid (10 mg) using calcined M41S (2 g) as packing material was carried out (Table 2, entry 6) but, no chiral separation was affected. It is therefore concluded that the chiral separation occurred due to the modification of M41S with chiral amino alcohol.

(*S*)-amino alcohol-silica **1** (2 g) was further explored for carrying out the resolution of other racemic compounds viz. 2,2′-dihydroxy-1,1′-binaphthalene, cyanochromene oxide, diethyl tartrate and 2-phenyl propionic acid under optimized reaction conditions and data is given in Table 4. Of all compounds used, better chiral separation was achieved with 2-phenyl propionic acid (entry 10).

4. Conclusions

A new chiral (*S*)-amino alcohol covalently bonded on modified M41S was synthesized and used to separate different racemic compounds such as mandelic acid, 2,2′-dihydroxy-1,1′-binaphthalene, cyanochromene oxide, diethyl tartrate, and 2-phenyl propionic acid. Excellent chiral separation (ee, 99%) in case of mandelic acid was achieved. The enantioseparation system worked very well up to three separation cycles without loss in separation performance. We are in the process of making large pore size silica material suitably modified with a chiral auxiliary in anticipation of better separation for bigger racemic molecules.

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