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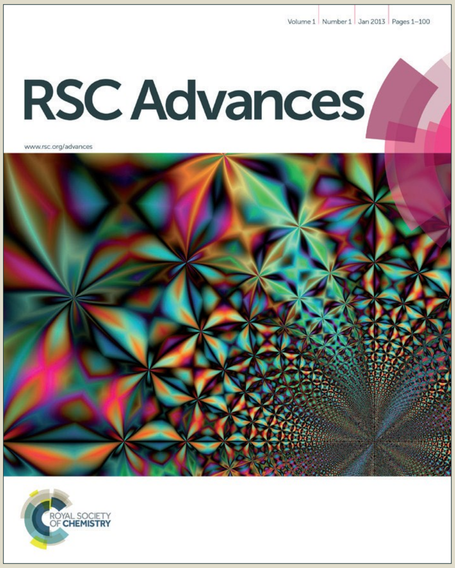

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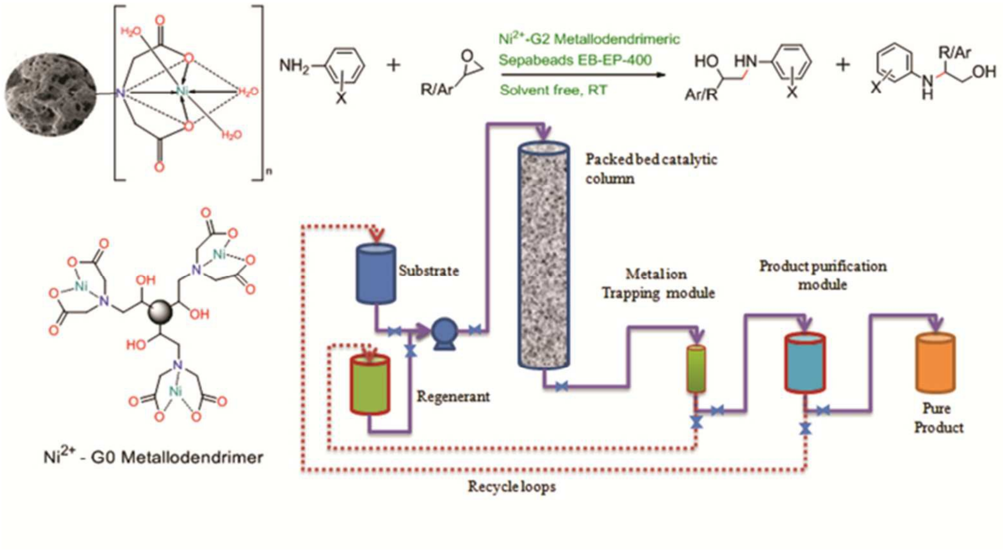

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Highlight

Metallodendrimer grafted mesoporous polymethyacrylate beads for regioselective, solvent free, efficient and scalable catalytic synthesis of β-amino alcohols at ambient temperature.

Catalytic metallodendrimer grafted on mesoporous polymethacrylate beads for regioselective synthesis of β-amino alcohols under solvent-free conditions

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Abstract

A new series of dendrimeric structures were grafted on epoxy activated mesoporous polymethacrylate beads (Sepabeads EB-EP-400) grated with dendritic structures followed by loading of metal termini in the chelating groups to form metallodendrimer grafted catalysts. The catalysts were characterized by UV, FTIR, SEM and Elemental analyzer. Further, selected catalyst was used to afford β-amino alcohols in a regioselective manner through nucleophilic opening of oxirane ring with various aromatic amines under solvent free mild reaction conditions. The reactions with developed catalyst at ambient temperature gave high yields (85%-99.5%) with excellent regioselectivity affording corresponding β-amino alcohols. It was found that developed metallodendrimer based catalyst is efficient and recyclable without compromising on activity, selectivity and productivity (4 kg/lit/h).

Keywords: Metallodendrimer, Sepabeads, β-amino alcohols, catalyst, regioselective, oxirane, epoxides, amines.

1. Introduction

Currently, green chemistry has become a major driving force for development of environment friendly processes and catalyst materials for organic synthesis of various pharmaceuticals, fine chemicals and intermediates. The possibility of performing multi-component reactions under solvent free conditions, and to enhance reaction efficiency with 3e's, i.e. ecological, environmental and economical point of view with use of solid recyclable catalyst has received special attention. This approach of green chemistry is being investigated for simplified synthesis of β-amino alcohols in various laboratories.

Amino alcohols are of importance as versatile intermediates in the synthesis of a wide range of biologically active, natural and synthetic products including pharmaceuticals, synthetic amino acids, pesticides, polymers and chiral auxillaries[1-5]. The most common method used for the synthesis of amino alcohol involves oxirane ring opening of epoxide with an excess of amine at high temperature[6]. However under these conditions, sensitive epoxides and amines undergo undesirable side reactions showing poor regioselectivity and reduced applicability to temperature sensitive reactants like poorly nucleophilic amines or sterically crowded amines/epoxides. In order to overcome such problems in the ring opening of epoxides with sluggish amine nucleophiles, several catalysts, such as metal halides[7-8], metal alkoxide[9], transition metal salts[10-11], ionic liquids[12], Amberlyst-15[13] and various promoters such as $BiCl_3$,[14] $CoCl_2$,[15] $ZrCl_4$,[16] $ZnCl_2$[17], $TaCl_5$[18], $Sm(OTf)_3$[19], $Ti(OiPr)_4$[9,20], $Sc(OTf)_3$[21], $Al(OTf)_3$[22], $B(C_6F_5)_3$[23], aluminosiilicate[24], NaY zeolite[25], Fe-MCM-41[26], have been reported in the literature to perform ring opening reactions. The use of microwave irradiation[27] and $Y(NO_3)_3.6H_2O$[28] as a catalyst in solvent free conditions have also been reported. Amino alcohol synthesis has also been reported using a variety of air sensitive catalysts[29] and even without catalyst[30] with aliphatic amines at room temperature. Many of these existing methods employ corrosive and expensive catalysts and hazardous organic solvents at high pressure andtemperatures and still offer moderate yields poor selectivity with long reaction times. Few catalysts are even moisture and air sensitive and non-recyclabilitySometimes reaction yields undesired product through rearrangement of epoxides to allyl alcohols under basic medium and polymerization under acidic medium leading to reduced yields and purity of desired products.. Hence, there is growing need for simple, economic and efficient catalysts which are more active and selective towards aromatic amines, and having reasonable recyclability. To surmount the limitations, we report an easy to handle, solid recyclable metallodendrimeric green catalyst based on rigid mesoporous polymeric beads for green and efficient synthesis of β-amino alcohols at room temperature under solvent-free conditions and without use of any acid or base.

Metallodendrimers are gaining significant interest in the field of organometallic catalysis and wide variety of them have been prepared and applied for certain applications. Two specific advantages of catalysts based on dendrimeric ligands grafted on rigid, porous polymeric solid beads are (i) enhanced kinetic performance and better conversions when compared to monomeric complexes owing to its large surface area with large ligand sites and ii) stable macromolecular structures making them suitable for isolation using simple filtration thus providing catalyst recovery and recycling[31]. Reactions which are catalyzed using metallodendrimers include polymerization[31], Suzuki-Miyaura[32], oxidation (33-34), Sonogashira reaction[35], hydroformylation and C-C coupling metathesis(36-38), epoxide ring opening[39] etc.

In the present work, rigid, mesoporous polymethacrylate Sepabeads EB-EP-400 beads were grafted with metallodendritic side groups. The metallodendritic side groups loaded with series of transition metals encouraged us to explore it as an efficient, reusable and convenient promoter catalyst for the opening of oxirane ring of epoxides with aromatic amines for the synthesis of β-amino alcohols Based on designer metallodendrimer grafted polymethrylate beads as an economical as well as environment friendly catalyst, the green process for the aminolysis of epoxides under solvent free conditions is reported.

2. Experimental

All chemicals and reagents used in the study were of analytical grade and used without any further purification. Sepabeads EB-EP-400 (G0-Sepabeads), rigid, mesoporous polymethrylate beads with epoxy functionality was obtained from Resindion SRL (Mitsubishi chemical Co., Japan), Italy. Amines, epoxides and heptafluorobutyric acid (used as an ion pairing agent) were obtained from Sigma-Aldrich, India. Thin layer chromatography (TLC) was performed on Merck aluminium sheet precoated with silica gel 60-F254 to a thickness of 0.25 mm and the chromatograms obtained were evaluated under long range ultraviolet light (254-264nm). Merck Silica gel (100-200 mesh) was used for column chromatography. HPLC grade Acetonitrile and water were obtained from Merck, India and were used for recording mass spectra on Agilent Technologies, 6450 Triple Quad Mass spectrometer, and for determining purity on Agilent Technologies 1200 series High performance liquid chromatography (HPLC. FTIRspectra were recorded on Shimadzu IR prestige-21 spectrophotometer. The surface morphology was analyzed by JSM-6380 scanning electron microscope (SEM) and elemental analysis was performed on NCHS&O elemental analyzer (Thermo scientific, USA).

2.1. Preparation of metallodendrimer grafted rigid, mesoporous polymethacrylate beads as catalyst

Metallodendrimer grafted mesoporous catalyst were prepared using polymethacrylate based epoxy activated mesoporous G0-Sepabeads. As per the protocol of Hermanson et al (1992)[39], initially G0-Sepabeads was washed with water, and then Tris (i.e. 2-Amino-2-hydroxymethyl-propane-1,3-diol) was coupled to the matrix under alkaline condition[39]. The Tris-G0-Sepabeads was then epoxy activated using epichlorohydrin (G1-Sepabeads). To this epoxy activated G1-Sepabeads, Tris was again covalently coupled to increase its branching followed by second epoxy activation using epichlorohydrin to obtain G2-Sepabeads. Finally, iminodiacetic acid (IDA) was immobilized to the terminal epoxy groups of G0, G1 and G2 series of activated Sepabeads followed by loading of termini metal ion to form M^{+2}-metallodendrimer grafted G0 G1 and G2 series of mesoporous Sepabeads catalysts (Supplementary Information, SI).

2.2. Catalyst characterization

Determination of metal ion loading on prepared series of mesoporous sepabeads grafted with metallodendritic side groups as catalyst was carried out. 50 mL of each metal free catalyst was washed with 5 bead volumes (i.e. 250 ml) of deionised water before loading the resin with termini metal ions. To each series of washed dendrimer grafted Sepabeads, 10 bead volumes of 0.5 M solution of nickel (II) heptahydrated sulphate, copper (II) pentahydrated sulphate, cobalt (II) chloride hexahydrated and ferrous (II) sulphate was contacted for loading Ni^{+2}, Cu^{+2}, Co^{+2} and Fe^{+2} ions, separately. Binding was allowed for 12 h under mild shaking conditions at 25° C. Concentrations of different ions in the solution before and after loading of metal ions were determined by spectrophotometric method of Belew and Porath[41] at their respective λ_{max} (SI). Amount of metal ion loaded on each series of dendrimer grafted Sepabeads was determined by material balance. Metallodendrimeric Sepabeads catalyst thus prepared, was again washed with 5 bead volumes of deionised water before conditioning it for actual use. G0-Sepabeads, tris immobilized intermediates and epoxy activated intermediates from G1 and G2 series were also evaluated as controls for the metal binding determinations.

The surface morphology of G0-Sepabeads, dendrimer with IDA grafted sepabeads and after loading metal termini was analyzed by SEM and percentage of CHNS and Oxygen was estimated using elemental analyzer

2.3. Typical procedure for synthesis of β-amino alcohols from epoxides

Synthesis of β-amino alcohols from epoxides was carried out in (water, methanol, chloroform, dichloromethane, toluene, tetrahydrofuran etc.) and solvent free conditions. To a mixture of epoxide (1 mmol) and aromatic amine (1mmol), M^{+2}-metallodendrimer grafted Sepabeads catalyst (4%) was added and the mixture was stirred at ambient temperature. The progress of reaction was monitored on TLC plate using ethyl acetate-hexane (1:9) as mobile phase till complete consumption of epoxide was achieved. The complete disappearance of epoxide was observed within 0.5-3h. The reaction mixture was separated by simple filtration. The recovered catalyst was washed with 2 bead volumes of ethyl acetate and reused. Crude reaction mixture was concentrated under reduced pressure to obtain the crude product. Purity of the crude products and percent conversion of starting material was determined by HPLC analysis. The crude product was purified by using preparative column chromatography on silica gel using ethyl acetate-hexane (1:9) as mobile phase. All pure β-amino alcohols were then characterized using ATR-FTIR (IR- prestige, Shimadzu, Japan) and mass spectra (ESI^+). .

2.4 Product characterization

The synthesized β-amino alcohols was analyzed on an Eclipse Plus C18 reverse phase analytical column (250 × 4.6 mm), particle size 5 µm (Agilent Technologies). An isocratic mobile phase of acetonitrile and HFBA (pH 3.5, 2% heptafluorobutric acid in water) in a ratio of 30:70 (v/v) at a flow rate of 1 mL/min. 3 µL of each sample (crude, purified product etc.) was injected and analyzed for 30 min using DAD detector (260 nm) and column oven at temperature of 30 ^{0}C.

Mass spectra of each purified product was recorded on 6410 Triple Quad Mass spectrometry (Agilent Technologies, USA), system by direct injection of 10 ppm concentration of sample at a flow rate of 1 mL/min for 1.6 min. The mobile phase used was composed of acetonitrile and HFBA (pH 3.5, 2% heptafluorobutyric acid in water) in a ratio of 80: 20 (v/v). Mass Spectrometer was operated in ESI positive mode with a scan range of 50-300*m/z*. Scan type – MS2Scan, scan – 500, fragmentor at 135V. Sources conditions were: capillary at 4500V; pressure limit 0-400 bar; gas temperature at 350^{0}C; gas flow – 8 L/min; Nebulizer at 45 psi. ATR (attenuated total reflection) corrected spectra were also recorded using IR prestige-21 (Shimadzu, Japan). ATR-FTIR was used to detect the functional groups of the amino alcohols over the wave number from 4000 to 400 cm^{-1}.

2.5 Reusability and regeneration of M^{+2}-metallodendrimer grafted Sepabeads catalyst

Reusability of the catalyst was examined by conducting the reaction for up to ten consecutive cycles using M^{+2}-G2 series metallodendrimer grafted Sepabeads catalyst for regioselective synthesis of β-amino alcohols. Series of experiments were carried out using aforementioned reaction conditions to investigate the consistency and efficiency of the catalytic activity and percent conversion. After completion of each cycle, the catalyst was recovered by simple filtration, washed with ethyl acetate, methanol, and distilled water to remove the traces of the product, reactant and impurities. The recovered catalyst was dried at 50-60º C for 2h and was reused for next cycle. After 5 cycles, catalyst was regenerated using 0.5M solution of metal salt as described above and reused in the process.

3. Results and discussion

Most recently, solid supported dendrimers with termini metal complex ligands has gained considerable interest as a catalyst in numerous organic reactions because these catalysts are more active as well as stable in aqueous, aqueous-organic and organic media, and are recyclable. In the present work, efficient and versatile method for regioselective synthesis of amino alcohols using M^{+2}-metallodendrimer grafted Sepabeads as catalyst is deduced. Polymethacrylate based rigid, mesoporous beads was used to graft a dendrimer having ability to complex metal ions termini (**Fig. 1d,** representation of metal termini).

3.1. Catalyst and Product (β-amino alcohol) characterization

Mesoporous Sepabeads EB-EP-400 beads obtained from Resindion SRL (Mitsubishi Chemical Corporation, Japan), Italy was having oxirane content of 42 µmol/ml, particle size of 50-150 µm, and average pore size of 40-50nm. Wavelength scan (200 to 800nm) for each metal ion solution was carried out and their absorbance maxima (λ_{max}) was determined. λ_{max} for solutions of Ni^{+2}, Cu^{+2}, Co^{+2} and Fe^{+2} ions were found to be 390, 760, 510, and 293nm, respectively. Metal binding dendrimer was grafted on the surface of the Sepabeads to obtain G0, G1 and G2 series of activated media followed by metal loading to result into respective series of metallodendrimer grafted Sepabeads with Ni^{+2}, Cu^{+2}, Co^{+2} and Fe^{+2} metal termini separately Representation of Ni^{+2} loaded G0, G1 and G2 series of metallodendritic structures on surface of polymethacrylate beads is shown in **Fig. 2**. A difference in metal loading capacities was observed with each series of catalysts (**Table 1**). The isolated yields of catalyst are 98.2%, 98.7 and 99.6% (w/w) respectively.

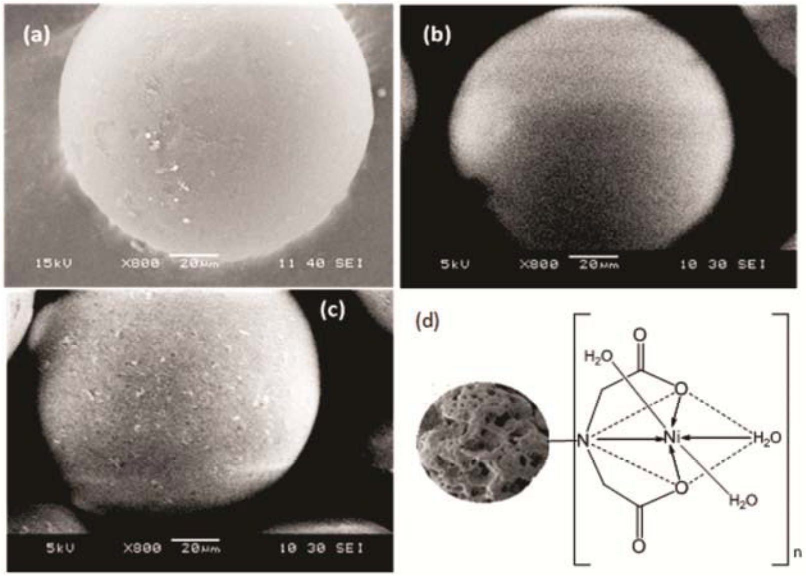


Fig. 1: SEM images of (a) native sepabeads EB-EP-400 (b) Sepabeads EB-EP-400 after grafting dendritic side groups with terminal IDA, (c) Sepabeads EB-EP-400 with grafting of dendritic side groups with metal termini loaded on IDA. (d) Representation of metal termini in designed M^{+2}-metallodendrimer grafted Sepabeads catalyst (Ni^{+2}- G2-metallodendrimer Sepabeads EB-EP-400 catalyst)

Table.1 Metal loading capacities of M^{+2}*- G2 metallodendrimer based Sepabeads catalysis

Sr. No.	Metal ion	Loading capacity (µM/ml)		
		(G0)	(G1)	(G2)
1	Ni^{+2}	55.28	148.00	358.36
2	Cu^{+2}	351.16	1120.15	3986.29
3	Co^{+2}	59.55	159.87	457.00
4	Fe^{+2}	441.69	1387.21	4828.00

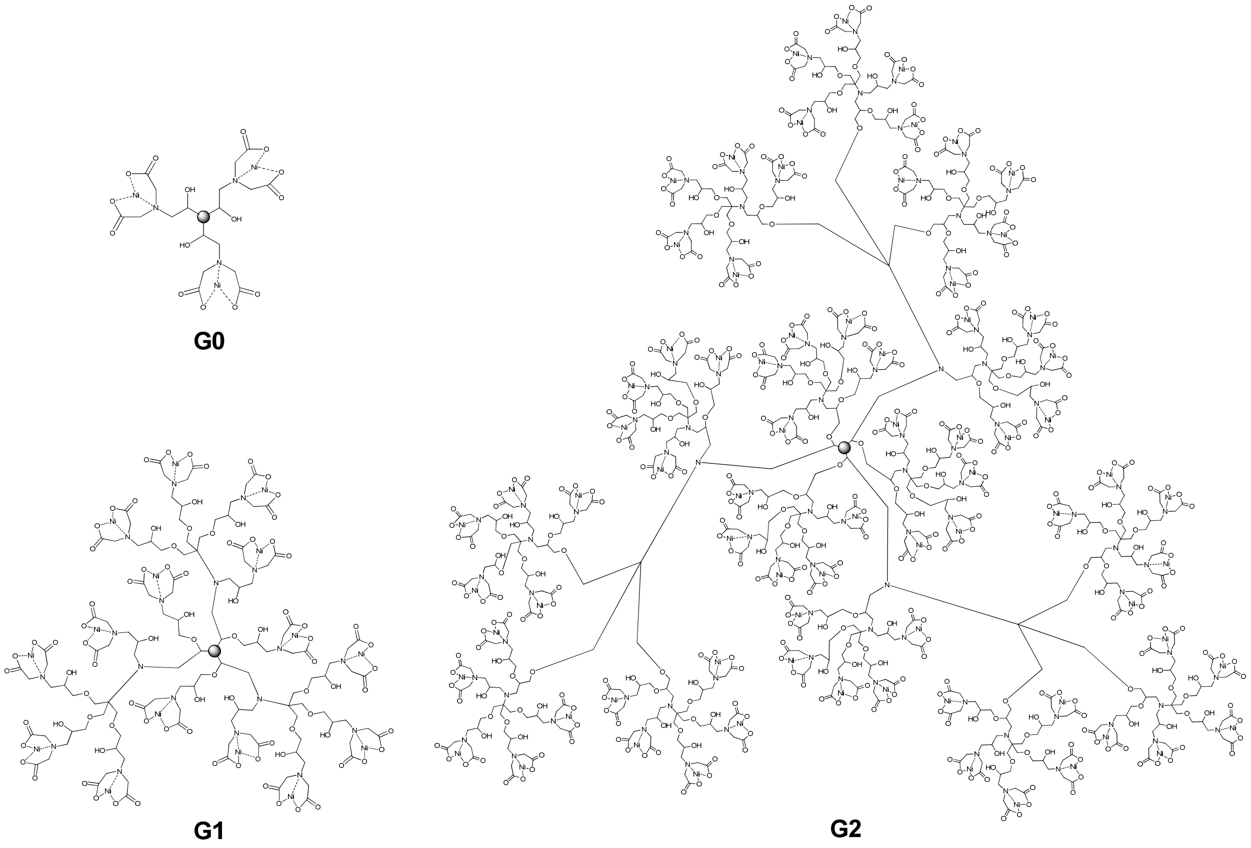


Fig. 2: Representation of Ni^{+2} loaded G0, G1, and G2 series of metallodendritic structures on surface of polymethacrylate based Sepabeads EB-EP-400.

The ability to synthesize β-amino alcohol in the presence of each metallodendrimer catalyst was studied using aniline as a reference from amine group with epichlorohydrin under solvent free condition. Among the four different metal ions (Ni^{+2}, Cu^{+2}, Co^{+2} and Fe^{+2}) tested, Ni^{+2}-G2-metallodendrimer gave maximum catalytic activity with 97% yield in 0.5h (**Table 2** entry 1). Cu^{+2} catalysts gave 89% yield in 1.5h whereas Co^{+2} and Fe^{+2} catalysts gave 87% and 80% yield in 2h, respectively (**Table 2** entry 2-4). Based on these results, Ni^{+2}-G2-metallodendrimer grafted Sepabeads catalyst was chosen for all further studies.

Table 2. Effect of M^{+2}*- G2 metallodendrimer based Sepabeads catalysis under solvent and solvent free conditions for different amines with epichlorohydrin at optimized reaction condition (mol ratio 1:1)

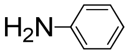
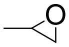
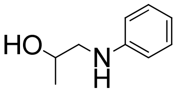
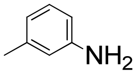
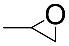
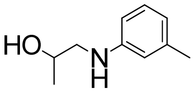
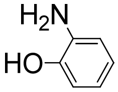
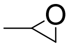
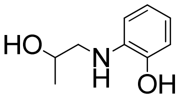
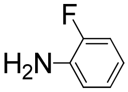
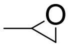
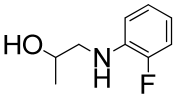
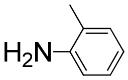
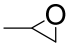
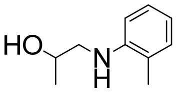
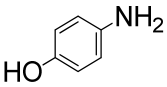
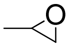
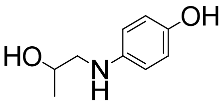
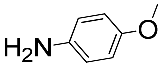
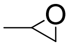
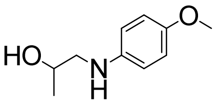
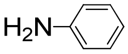
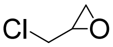
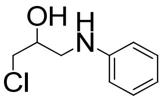
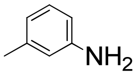
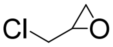
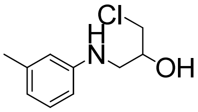
Entry	Amines	M^{+2}*-G2 Sepabeads EB-EP-400	Solvents	Time (h)	Yields $^{\#}$ (%)
		Effect of catalyst			
1	Aniline	Ni^{+2}-G2 Sepabeads EB-EP-400	Solvent free	0.5	97
2	Aniline	Cu^{+2}-G2 Sepabeads EB-EP-400	Solvent free	1.5	89
3	Aniline	Co^{+2}-G2 Sepabeads EB-EP-400	Solvent free	2.0	87
4	Aniline	Fe^{+2}-G2 Sepabeads EB-EP-400	Solvent free	2.0	80
5	Aniline	No catalyst	Solvent free	12.0	44
		Effect of solvents			
6	Aniline	Ni^{+2}-G2 Sepabeads EB-EP-400	Water	3.0	38
7	Aniline	Ni^{+2}-G2 Sepabeads EB-EP-400	Methanol	5.0	35
8	Aniline	Ni^{+2}-G2 Sepabeads EB-EP-400	Chloroform	6.5	23
9	Aniline	Ni^{+2}-G2 Sepabeads EB-EP-400	Dichloromethane	6.0	30
10	Aniline	Ni^{+2}-G2 Sepabeads EB-EP-400	Toluene	6.0	32
11	Aniline	Ni^{+2}-G2 Sepabeads EB-EP-400	Tetrahydrofuran	5.0	30
12	*p*-Aminophenol	Ni^{+2}-G2 Sepabeads EB-EP-400	Water	3.0	40
13	*p*-Aminophenol	Ni^{+2}-G2 Sepabeads EB-EP-400	Methanol	5.0	33
14	*p*-Aminophenol	Ni^{+2}-G2 Sepabeads EB-EP-400	Chloroform	6.5	23
15	*p*-Aminophenol	Ni^{+2}-G2 Sepabeads EB-EP-400	Dichloromethane	6.0	28
16	*p*-Aminophenol	Ni^{+2}-G2 Sepabeads EB-EP-400	Toluene	6.0	35
17	*p*-Aminophenol	Ni^{+2}-G2 Sepabeads EB-EP-400	Tetrahydrofuran	5.0	35
18	*m*-Toluidine	Ni^{+2}-G2 Sepabeads EB-EP-400	water	3.0	45
19	*m*-Toluidine	Ni^{+2}-G2 Sepabeads EB-EP-400	Methanol	5.0	40
20	*m*-Toluidine	Ni^{+2}-G2 Sepabeads EB-EP-400	Chloroform	6.5	29
21	*m*-Toluidine	Ni^{+2}-G2 Sepabeads EB-EP-400	Dichloromethane	6.0	35
22	*m*-Toluidine	Ni^{+2}-G2 Sepabeads EB-EP-400	Toluene	6.0	33
23	*m*-Toluidine	Ni^{+2}-G2 Sepabeads EB-EP-400	Tetrahydrofuran	5.0	37
24	Aniline	No catalyst	Water	12	39

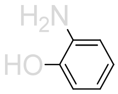
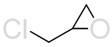
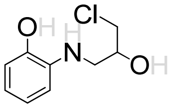
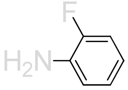
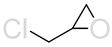
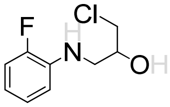
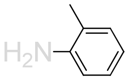
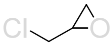
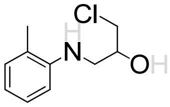
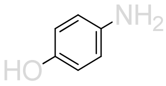
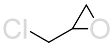
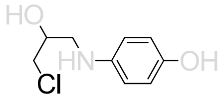
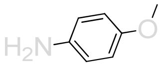
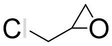
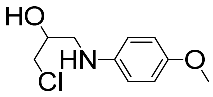
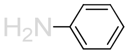
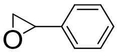
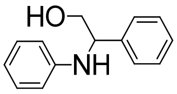
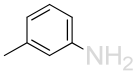
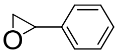
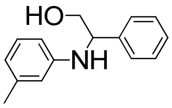
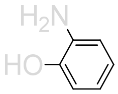
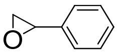
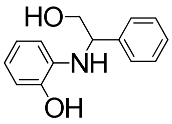
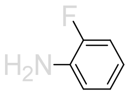
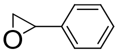
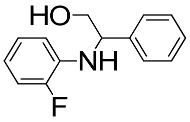
M^{+2}- Divalent transition metals Ni, Cu, Fe, Co, $^{\#}$ Yield refers to isolated product after column purification

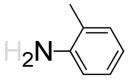
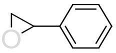
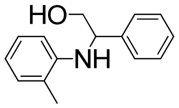
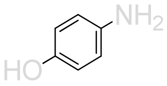
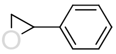
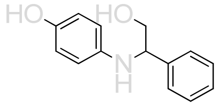
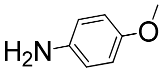
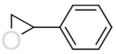
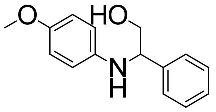
As the resulting dendrimeric catalyst is highly crosslinked and insoluble in any solvent, characterization was limited to SEM, elemental analyzer and ATR-FTIR. The surface morphology of G0-Sepabeads with and without grafting of metallodendrimer was analyzed on SEM (**Fig. 1**). Without grafting of metallodendrimer, mesoporous Sepabeads EB-EP-400 showed smooth surface whereas rough surface was observed after grafting of metallodendrimer on it. The data of CHNS and Oxygen elemental analysis showed only carbon and hydrogen in case of G0-Sepabeads whereas metallodendrimer grafted Sepabeads showed presence of nitrogen (0.8%) and oxygen (13.2%) due to use of tris and IDA during grafting of dendrimer on its surface. ATR-FTIR spectra recorded on IR prestige-21 (Shimadzu, Japan) in the transmission mode at a resolution of 4 cm^{-1} with 40 scans (**SI**) showed characteristic peak for the carbonyl (C=O) group in glycidyl methacrylate ester at 1728cm^{-1}. The vibrational band at 961cm^{-1} associated with asymmetric epoxy ring bending disappeared after metal loading with terminal IDA. Upon incorporation of the Ni^{+2} moieties to the ligand in G0, G1, and G2 series of Sepabeads having IDA groups, the spectra of compounds exhibited a distinct shift of υ_{sym}(C=O) to a lower frequency 1712,1705, 1693cm^{-1}, respectively. The position of the NH absorption in the polymeric complexes remained particularly unaltered as it occurred in the OH frequency region. The occurrence of lattice water in the complex and the IDA ligand showed strong and broad OH frequency absorptions at 3200-3600cm^{-1}. Complexation of Ni^{+2} with IDA ligand was confirmed from IR spectras G0, G1, and G2 dendrimers in which OH frequency got shifted to lower frequency i.e 3387, 3371, 3363cm^{-1} resepectively. Thus, the change in surface morphology, elemental data and ATR-FTIR gave clear indication of metallodendrimer being grafted onto Sepabeads EB-EP-400 surface.

After catalyst characterization, it was employed for the synthesis of β-amino alcohols under solvent and solvent free conditions (**Table 2**). The progress of the reaction was determined by HPLC analysis and the functional groups of the amino alcohols were identified by ATR-FTIR. The identification of β-amino alcohols were analyzed by mass spectrometery as shown in **Table 3**, entry 1a: (ESI-MS) *m/z*: 152.2 (M+1); entry 2a: (ESI-MS(+) *m/z*: 166.2, entry 7a: (ESI-MS(+) *m/z*: 182.2 (M+1), 240.3, entry 8a: (ESI-MS) *m/z*: 186.6 (M+1), 188.2 (M+2, Cl isotope); entry 9a: (ESI-MS) *m/z*: 200.2 (M+1), 202.2 (M+2, Cl isotope), 182.2 (M-18, loss of H_2O molecule); entry 10a: (ESI-MS) *m/z*: 202.2 (M+1), 204.2 (M+2, Cl isotope); entry 12a: (ESI-MS) *m/z*: 200.3 (M+1), 202.3 (M+2, Cl isotope); entry 14a: (ESI-MS) *m/z*: 216.2 (M+1), 218.6 (M+2, Cl isotope); entry 16b: (ESI-MS) *m/z*: 228.3 (M+1), 134.2; entry 21b: (ESI-MS) *m/z*: 244.3 (M+1).

Table 3. Ring opening of epoxides by Ni^{+2}- G2 metallodendrimer based Sepabeads EB-EP-400 catalyst under solvent free conditions.

Entry	Amines	Epoxides	β-amino alcohols	Time(h), RT	Yields[#] (%)	E factor
1			 **1a**	0.5	98.0	0.1363
2			 **2a**	1.5	95.0	0.0526
3			 **3a**	2.0	93.0	0.0752
4			 **4a**	2.0	96.0	0.0416
5			 **5a**	2.0	94.0	0.0638
6			 **6a**	1.0	98.0	0.0204
7			 **7a**	2.0	96.0	0.0416
8			 **8a**	0.5	97.0	0.0309
9			 **9a**	1.0	99.5	0.0050

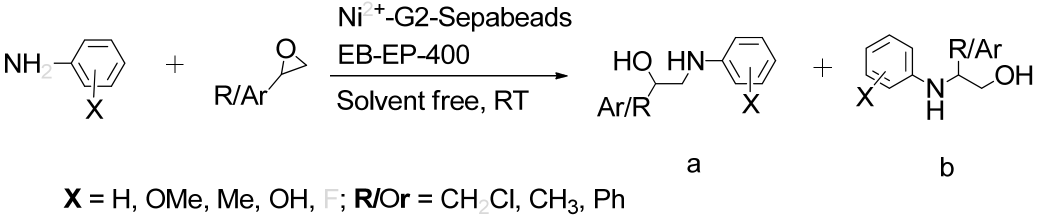
10			 **10a**	1.0	92.0	0.0869
11			 **11a**	1.5	89.0	0.1235
12			 **12a**	1.0	95.0	0.0526
13			 **13a**	1.0	99.0	0.0101
14			 **14a**	1.0	94.0	0.0638
15			 **15b**	2.0	85.0	0.1764
16			 **16b**	1.5	90.0	0.1111
17			 **17b**	1.5	89.0	0.1235
18			 **18b**	1.5	81.0	0.2345

19			 **19b**	1.5	85.0	0.1764
20			 **20b**	1.0	91.0	0.0989
21			 **21b**	1.0	83.0	0.2048

Epoxides (1 mmol) were treated with anilines (1 mmol), catalyst: Ni^{+2}- G2 metallodendrimer Sepabeads EB-EP-400 (4%), Temperature: RT, under solvent free conditions, reaction time 0.5 to 3 h.
[#]Yields refers to isolated product after column.

3.3. Catalytic performance

To estimate the scope and applicability of the catalyst, epoxides were reacted with different aromatic amines. The designed Ni^{+2} metallodendrimer catalyst was used for ring opening of epoxides with amines giving corresponding β-amino alcohols (**Scheme 1**).



Scheme 1: Reaction scheme for ring opening reaction of epoxides with amines using designed catalyst

The catalytic activity of Ni^{+2} metallodendrimer catalyst for regioselective ring opening of epoxides with amines under optimized reaction conditions is shown (**Table 3**). The ring opening of epichlorohydrin with aniline was used as model system and it was found that Sepabeads grafted with G2 generation of metallodendrimer is more active and gave higher yields than G0 and G1 generations. The effect of G0, G1 and G2 generation could be attributed to the concentration of metal ions, where catalytic activity with G2 series was found to be 6 to 7 times higher than G0 series and 2.5 to 3 times better than G1 series of catalysts for respective metal ions. This demonstrates the effect of metal ion content on ring opening of epoxides with amines. We also prepared G3 series of Ni^{+2}-metallodendrimer grafted Sepabeads catalyst using similar set of protocol mentioned earlier and used in the reaction. With G3 series of metallodendrimer catalysts loaded with different metal termini, we obtained reduced rate of reaction, conversion and yield with all metals (data not shown) which could be attributed to the drawback of dendritic catalysis commonly observed with increase in dendrimer generation known as negative dendritic effect [35]. Therefore, G2 series of catalyst was selected for further studies. High catalytic activity of developed G2 catalyst can also be attributed to the mesoporous nature of beads with high surface area (550 m^2/gm) leading to superior mass transfer and pore diffusion[42,43]. It is relevant to highlight that same reaction when conducted without catalyst did not proceed to any appreciable extent even after 12h and only 44% yield was obtained (**Table 2**, entry 5).

3.3.1 Effect of solvent

The solvent effect on catalytic activity of Ni^{+2}-metallodendrimer catalyst was also studied and results of amminolysis of epoxides are summarized in **Table 2**. It was observed that catalytic rate was higher with divalent transition metal (e.g. Ni^{+2}) grafted in the form of metallodendrimer catalyst on Sepabeads EB-EP-400 under solvent free conditions (**Table 2**, entry 1-4) than in presence of aqueous and organic solvents (**Table 2**, entries 6-23). From **Table 2**, entries 6-23, it can be seen that polarity of solvent has significant effect on catalytic activity of Ni^{+2}-metallodendrimer catalyst. Among the different solvents studied, polar solvent i.e. water (**Table 2**, entries 6, 12, 18) gave better catalytic activity and yield than relatively non-polar or intermediate polar solvents tested. Catalytic activity was substantially reduced with non-polar or intermediate polarity solvents for ring opening reaction of epoxides with aniline (**Table 2**, entries 7-11), *p*-Aminophenol (**Table 2**, entries 13-17) and *m*-Toluidine (**Table 2**, entries 19-23 When aniline was used in presence of water without catalyst, reaction after 12h gave only 39% yield (**Table 2**, entry 24). Hence, this effect could be due to hydrophobic solvent getting adsorbed on solid metallodendrimer catalyst making lesser number of sites accessible for the reaction. On the other hand, with water and solvent free condition large number or all sites remains accessible for reactant molecules for high conversion in lesser time. Specifically, when the reaction was carried out using Ni^{+2}-metallodendrimer catalyst, aniline was completely consumed (99% conversion) and 97% yield of the desired product (**Table 3,** entry 8) was obtained after column chromatography. The maximum yield (i.e. 99.5%) was obtained in solvent free condition with designed regioselective Ni^{+2}-metallodendrimer catalyst (**Table 3,** entry 9).

3.3.2 Effect of catalyst loading and substrate

The effect of catalyst loading (1 to 6.5 mole %) on performance of reaction was also studied, where increase in initial catalyst concentration upto 4 mol% showed increase in yield of corresponding amino alcohols (**SI**). Increase in the amount of catalyst from 4 to 6.5 mol % did not show incremental effect on the yield of the desired amino alcohols (**SI**). Further, applicability of Ni^{+2}-metallodendrimer catalyst for ring opening reactions of different epoxides with amines having different structure and charge was evaluated (**Table 3**, entries 1-21). Relatively higher conversion was obtained when epichlorohydrin instead of propylene oxide and styrene oxide was reacted with amines. Although epichlorohydrin has many reactive positions and can lead to some other side products but we did not observe (by mass spectrometry analysis) any side product in the reaction. The reaction of aniline with styrene oxide gave maximum yield (91%) for single isomer showing superior regioselectivity of present catalyst (**Table 3**, entry 20). The aliphatic epoxides predominantly gave type 'a' isomer whereas aromatic (styrene) oxide predominantly gave type 'b' isomer. This could be attributed to the charge/electronic effects favoring the attack at less substituted carbon atom of aliphatic epoxides (**Table 3**, entries 1-14) and possible localization of positive charge of oxygen on highly substituted benzylic carbon in styrene oxide (**Table 3**, entries 15-21). The metallodendrimer catalyst has also shown strong tolerance to the electron donating/withdrawing groups on aniline leading to predominant formation of singly type of isomer (**Table 3**, entries 1-21) demonstrating its regioselective capability. This study further reveals that the type of epoxides is a major determining factor of the type of isomer formed in amminolysis reaction. In the present work both aliphatic and aromatic epoxides gave high yields with superior regioselectivity and chemoselectivity.

3.3.3 Catalyst recycle and catalysis in packed column

The catalyst recycling studies were conducted and performance in each cycle was determined.. It was found that 92% conversion was obtained even after 10th cycle. Thus, the catalyst was found to be reusable and studies indicated that metal ion did not leach from the catalyst during course of use, making the process techno-economically viable and environment friendly.

The proposed mechanism for the ring opening of oxirane ring with different amines in the presence of Ni^{+2}-metallodendrimer based Sepabeads EB-EP-400 catalyst is shown (**Fig. 3)**. To explore the feasibility of using designed catalyst continuously and to prove the industrial viability, we developed a system consisting packed bed of catalyst coupled with metal ion trapping and product purification module as shown (**Fig. 4).** Metal ion trapping module was a column (1/100th of the volume of catalytic column) packed with chelating resin Diaion CR11 (Mitsubishi Chemical Corporation, Japan). This was used to avoid any possibility of passage of metal ion into the product. Purification module consisted of silica gel operating under conditions described earlier. The catalytic column was operated continuously with 1:1 mole ratio of reactants (**Table 3**, entry 1). It was found that, under the column mode catalyst required about 20 min of residence time to achieve >99.5% conversion of reactants into corresponding β-amino alcohol. Recently, few reports on polymer catalyst appeared describing ring opening of epoxides at high temperature with long reaction time and in presence of solvent[44-45] and in non catalyzed reaction conditions[46].

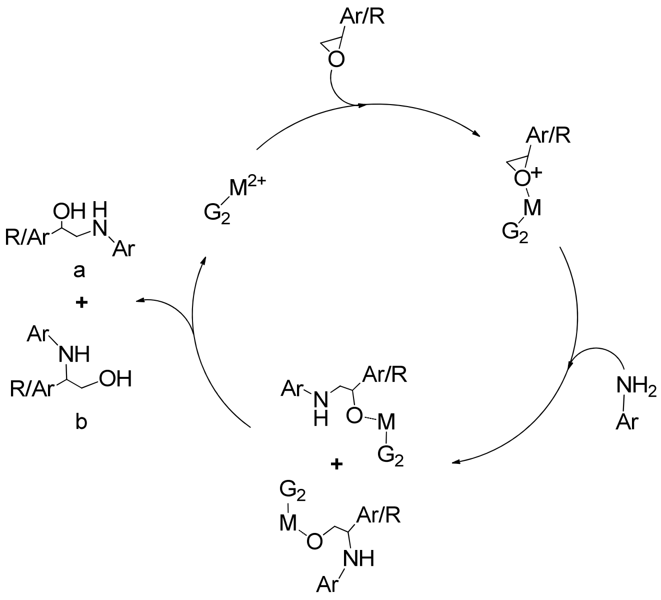


Fig. 3: Proposed mechanism of ring opening of epoxides with dendrimeric catalyst

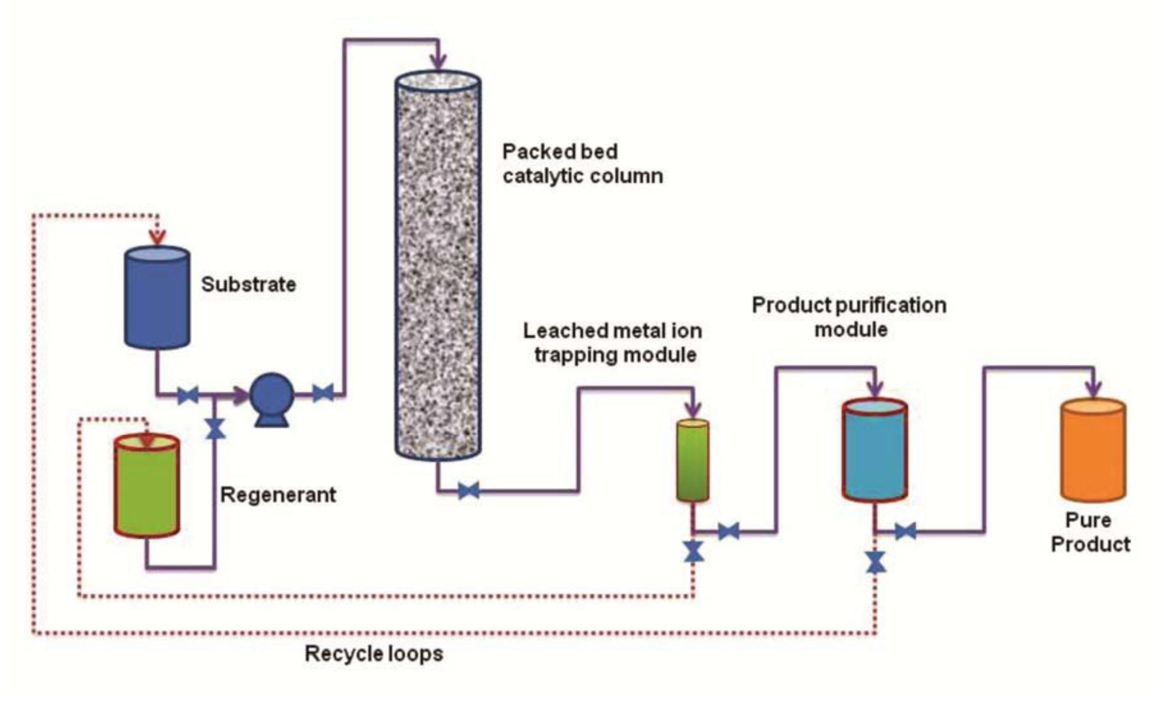


Fig. 4: Packed bed system for continuous catalytic reaction using Ni^{+2}- G2-metallodendrimer Sepabeads EB-EP-400 catalyst

The comparison of designed Ni^{+2}-metallodendrimer based Sepabeads EB-EP-400 catalyst with few catalysts reported in the literature for synthesis of β-amino alcohols showed much superior catalytic activity, higher yields (97% to 99% yield) in much lesser time (0.5 to 1.0 h) as compared to a recent report where nano Fe_3O_4 catalyst[47] is used for the synthesis of β-amino alcohol (SI).

3. Conclusions

The present work has led to the design of mild and efficient method for the ring opening of epoxides without destruction of solid catalyst. Designed Ni^{+2} based metallodendrimer grafted polymethacrylate beads based catalyst showed high activity and regioselectivity for the synthesis of β-amino alcohols. Thus, designed Ni^{+2} based metallodendrimer grafted Sepabeads catalyst offers many advantages of solid catalyst over other catalysts in viewpoint of green chemistry such as solvent free condition, simplification of work up, formation of cleaner product with no side product, improved reaction rates, low catalytic amount, catalyst recycle and easy isolation procedure making it a better alternative to existing catalysts. Further, under the stated conditions, catalytic column was also operated continuously for 72 h which gave high productivity (4 kg/lit/h). During this operation, no significant reduction in conversion and productivity was observed which proves the industrial feasibility of the catalyst in synthesis of β-amino alcohol.

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