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

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A new series of dendritic structures was grafted on epoxy activated mesoporous polymethacrylate beads (Sepabeads EB-EP-400). Grafting with the dendritic structures was followed by loading of metal termini to the chelating groups to form metallodendrimer-grafted catalysts. The catalysts were characterized by UV, FTIR, SEM and elemental analysis. Further, a selected catalyst was used to afford β-amino alcohols in a regioselective manner through nucleophilic opening of an oxirane ring with various aromatic amines under solvent-free, mild reaction conditions. The reactions with the developed catalyst at ambient temperature afforded the corresponding β-amino alcohols in high yields (85–99.5%) with excellent regioselectivity. It was found that the developed metallodendrimer-based catalyst is efficient and recyclable without compromising on activity, selectivity and productivity (4 kg L^{-1} h^{-1}).

1. Introduction

Currently, green chemistry has become a major driving force for the development of environmentally friendly processes and catalyst materials for the organic synthesis of various pharmaceuticals, fine chemicals and intermediates. The possibility of performing multi-component reactions under solvent-free conditions, and to enhance the reaction efficiency with 3e's, *i.e.* an ecological, environmental and economical point of view, using a solid recyclable catalyst has received special attention. This approach of green chemistry is currently investigated for the 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 alcohols involves the oxirane ring opening of an epoxide with an excess of amine at high temperatures.[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] and 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] and Fe-MCM-41,[26] have been reported in the literature to perform ring opening reactions. The use of microwave irradiation[27] and $Y(NO_3)_3 \cdot 6H_2O$[28] as a catalyst under solvent-free conditions have also been reported. The amino alcohol synthesis using a variety of air sensitive catalysts[29] and even without a catalyst[30] with aliphatic amines at room temperature has also been reported. Many of these existing methods employ corrosive and expensive catalysts and hazardous organic solvents at high pressures and temperatures, and still offer moderate yields and poor selectivities with long reaction times. Few catalysts are even moisture and air sensitive and non-recyclable. Sometimes, the reaction yields an undesired product through the rearrangement of epoxides to allyl alcohols in a basic medium and through polymerization in an acidic medium, leading to reduced yields and purity of the desired products. Hence, there is a growing need for simple, economic and efficient catalysts which are more active and selective towards aromatic amines, and have reasonable recyclability. To surmount the limitations, we report an easy to handle, solid and recyclable metallodendritic green catalyst based on rigid mesoporous polymeric beads for the green and efficient synthesis of β-amino alcohols at room temperature under solvent-free conditions and without the use of any acid or base.

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

In the present work, rigid, mesoporous polymethacrylate Sepabeads EB-EP-400 were grafted with metallodendritic side groups. The metallodendritic side groups loaded with a series of transition metals encouraged us to explore the beads as an efficient, reusable and convenient promoter catalyst for the opening of the oxirane ring of epoxides with aromatic amines for the synthesis of β-amino alcohols. Based on the design of the metallodendrimer-grafted polymethacrylate beads as an economical as well as environmentally 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 further purification. Sepabeads EB-EP-400 (G0-Sepabeads), rigid, mesoporous polymethrylate beads with epoxy functionality, were obtained from Resindion SRL, Italy, (Mitsubishi chemical Co., Japan). 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 sheets precoated with silica gel 60-F254 to a thickness of 0.25 mm, and the chromatograms obtained were evaluated under long range ultraviolet light (254–264 nm). 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 an Agilent Technologies 6450 Triple Quad mass spectrometer, and for determining the purity on an Agilent Technologies 1200 series high performance liquid chromatography (HPLC). FTIR spectra were recorded on a Shimadzu IR prestige-21 spectrophotometer. The surface morphology was analyzed by scanning electron microscopy (SEM) using a JSM-6380, and elemental analysis was performed on a NCHS&O elemental analyzer (Thermo Scientific, USA).

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

Metallodendrimer-grafted mesoporous catalysts were prepared using polymethacrylate-based epoxy activated mesoporous G0-Sepabeads. As per the protocol of Hermanson *et al.* (1992),[40] the G0-Sepabeads were initially washed with water, and then Tris (*i.e.* 2-amino-2-hydroxymethyl-propane-1,3-diol) was coupled to the matrix under alkaline conditions.[40] The Tris-G0-Sepabeads were then epoxy activated using epichlorohydrin (G1-Sepabeads). To these epoxy activated G1-Sepabeads, Tris was again covalently coupled to increase its branching followed by a second epoxy activation using epichlorohydrin to obtain the G2-Sepabeads. Finally, iminodiacetic acid (IDA) was immobilized on the terminal epoxy groups of the G0, G1 and G2 series of activated Sepabeads followed by the loading of the termini with metal ions to form the M^{2+}-metallodendrimer-grafted G0, G1 and G2 series of the mesoporous Sepabead catalysts (ESI†).

2.2. Catalyst characterization

Determination of the metal ion loading on the prepared series of mesoporous Sepabeads grafted with metallodendritic side groups as catalysts, 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 the terminal metal ions. To each series of washed dendrimer-grafted Sepabeads, 10 bead volumes of a 0.5 M solution of either nickel(II) sulphate heptahydrate, copper(II) sulphate pentahydrate, cobalt(II) chloride hexahydrate or ferrous(II) sulphate was added for loading the Ni^{2+}, Cu^{2+}, Co^{2+} or Fe^{2+} ions. Binding was allowed for 12 h under mild shaking conditions at 25 °C. The concentrations of the different ions in the solution before and after the loading of metal ions were determined by the spectrophotometric method of Belew and Porath[41] at their respective λ_{max} (ESI†). The amount of metal ions loaded on each series of dendrimer-grafted Sepabeads was determined by a material balance. The metallodendritic Sepabead catalyst thus prepared, was again washed with 5 bead volumes of deionised water before conditioning it for its actual use. The G0-Sepabeads, Tris immobilized intermediates and epoxy activated intermediates from the G1 and G2 series were also evaluated as controls for metal binding determination.

The surface morphologies of the G0-Sepabeads, dendrimers with IDA-grafted Sepabeads and after loading the termini with metals were analyzed by SEM, and the percentage of CHNS and oxygen was estimated using an elemental analyzer.

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

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

2.4. Product characterization

The synthesized β-amino alcohols were 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% heptafluorobutyric acid in water) with a ratio of 30 : 70 (v/v) at a flow rate of 1 mL min^{-1} was used. 3 μL of each sample (crude, purified product *etc.*) was injected and analyzed for 30 min using a DAD detector (260 nm) and column oven at a temperature of 30 °C.

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

2.5. Reusability and regeneration of the M^{2+}-metallodendrimer-grafted Sepabead catalyst

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

3. Results and discussion

Most recently, solid supported dendrimers with terminal metal complex ligands have gained considerable interest as catalysts 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, an efficient and versatile method for the regioselective synthesis of amino alcohols using M^{2+}-metallodendrimer-grafted Sepabeads as the catalyst is derived. Polymethacrylate-based rigid, mesoporous beads were used to graft a dendrimer with the ability to complex metal ions at the termini (Fig. 1d, representation of the metal termini).

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

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

The ability to synthesize β-amino alcohols in the presence of each metallodendrimer catalyst was studied using aniline as a reference for the amine group and with epichlorohydrin under solvent-free conditions. Among the four different metal ions (Ni^{2+}, Cu^{2+}, Co^{2+} and Fe^{2+}) tested, the Ni^{2+}-G2-metallodendrimer gave maximum catalytic activity with 97% yield in 0.5 h (Table 2, entry 1). The Cu^{2+} catalyst gave 89% yield in 1.5 h, whereas the Co^{2+} and Fe^{2+} catalysts gave 87% and 80% yield in 2 h,

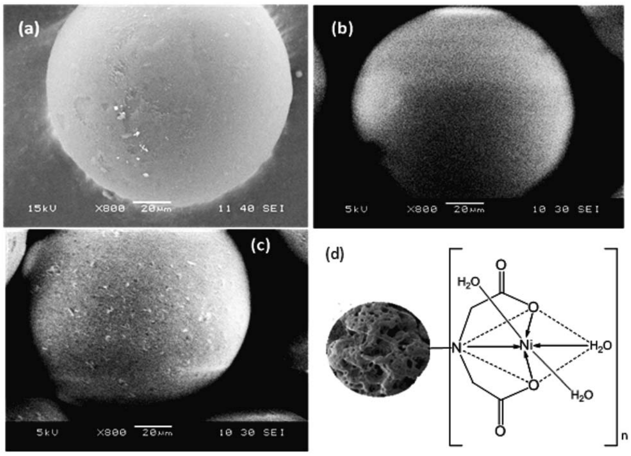


Fig. 1 SEM images of the (a) native Sepabeads EB-EP-400, (b) Sepabeads EB-EP-400 after grafting the dendritic side groups with terminal IDA, (c) Sepabeads EB-EP-400 after grafting the dendritic side groups with the metal termini loaded on IDA. (d) Representation of metal termini in a designed M^{2+}-metallodendrimer-grafted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

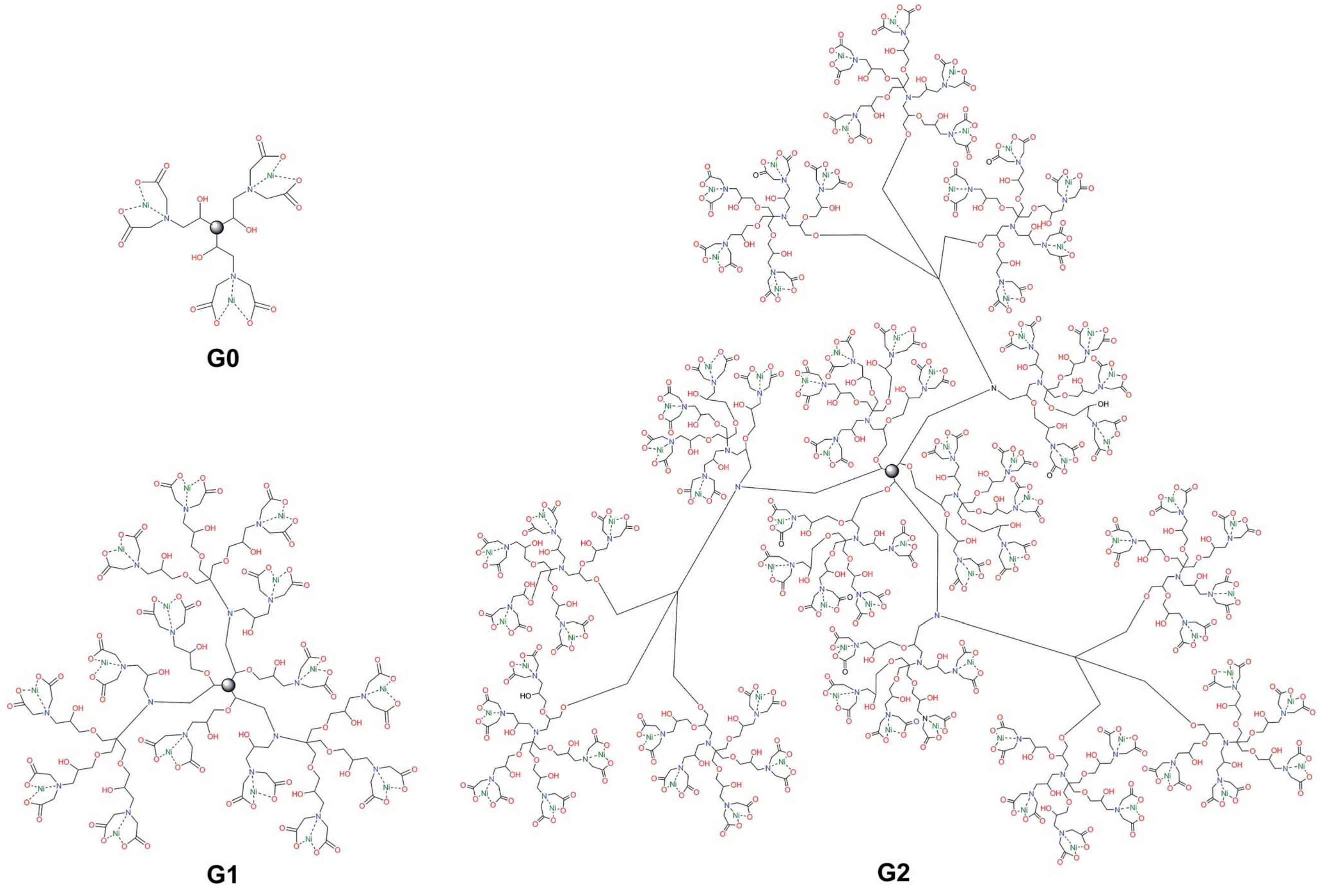


Fig. 2 Representation of Ni^{2+} loaded G0, G1, and G2 series of metallodendritic structures on surface of polymethacrylate-based Sepabeads EB-EP-400.

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

Sr. no.	Metal ion $M^{2+}*$	Loading capacity (μM mL^{-1}) (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

respectively (Table 2, entries 2–4). Based on these results, the Ni^{2+}-G2-metallodendrimer-grafted Sepabead catalyst was chosen for all further studies.

As the resulting dendritic catalyst is highly crosslinked and insoluble in any solvent, characterization was limited to SEM, elemental analysis and ATR-FTIR. The surface morphology of the G0-Sepabeads with and without grafting of metallodendrimer was analyzed by SEM (Fig. 1). Without grafting of metallodendrimer, the mesoporous Sepabeads EB-EP-400 showed a smooth surface, whereas a rough surface was observed after grafting of metallodendrimer onto it. The data of CHNS and oxygen elemental analysis showed only carbon and hydrogen in the case of the G0-Sepabeads, whereas the metallodendrimer-grafted Sepabeads showed the presence of nitrogen (0.8%) and oxygen (13.2%) due to the use of Tris and IDA during grafting of the dendrimer on the 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 (ESI†) showed a characteristic peak for the carbonyl (C=O) group in the glycidyl methacrylate ester at 1728 cm^{-1}. The vibrational band at 961 cm^{-1}, associated with the asymmetric epoxy ring bending, disappeared after metal loading onto terminal IDA. Upon incorporation of the Ni^{2+} moieties to the ligands in the G0, G1, and G2 series of the Sepabeads with IDA groups, the spectra of the compounds exhibited a distinct shift of ν_{sym}(C=O) to lower frequencies 1712, 1705, and 1693 cm^{-1}, respectively. The position of the NH absorption in the spectra of 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 3200–3600 cm^{-1}. Complexation of Ni^{2+} with the IDA ligands was confirmed by the IR spectra of the G0, G1, and G2 dendrimers, in which the OH frequency got shifted to lower frequencies of 3387, 3371, and 3363 cm^{-1}, respectively. Thus, the change in surface morphology, elemental data and ATR-FTIR gave clear indication of the metallodendrimer being grafted onto the Sepabeads EB-EP-400 surface.

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

Entry	Amine	M^{2+}*-G2 Sepabeads EB-EP-400[a]	Solvent	Time (h)	Yield[b] (%)
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 solvent					
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	12.0	39

[a] M^{2+}-divalent transition metals: Ni, Cu, Fe, and Co. [b] The yield refers to isolated product after column purification.

After characterization, the catalyst was employed in 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 β-amino alcohols were analyzed by mass spectrometry 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).

3.2. 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 the ring opening of epoxides with amines giving the corresponding β-amino alcohols (Scheme 1). The catalytic activity of the Ni^{2+} metallodendrimer catalyst for the regioselective ring opening of epoxides with amines under optimized reaction conditions, is shown in Table 3. The ring opening of epichlorohydrin with aniline was used as a model system and it was found that Sepabeads grafted with the G2 generation of the metallodendrimer are more active and gave higher yields than those with the G0 and G1 generations. The effect of the G0, G1 and G2 generations could be attributed to the concentration of metal ions, where the catalytic activity of the G2 series was found to be 6 to 7 times higher than that of the G0 series and 2.5 to 3 times better than that of the G1 series catalysts for the respective metal ions. This demonstrates the effect of metal ion content on the ring opening of epoxides with amines. We also prepared the G3 series of the Ni^{2+}-metallodendrimer-grafted Sepabead catalyst using a similar protocol mentioned earlier, and used it in the reaction. With the G3 series of the metallodendrimer catalysts loaded with different metal termini, we obtained a reduced reaction rate, conversion and yield with all metals (data not shown), which could be attributed to the drawback of dendritic catalysis commonly observed with the increase in dendrimer generation, known as the negative dendritic effect.[35] Therefore, the G2 series of the catalyst was selected for further studies. The high catalytic activity of developed G2 catalyst can also be attributed to the mesoporous nature of the beads with a high surface area (550 $m^2\ g^{-1}$), leading to superior mass transfer and pore diffusion.[42,43] It is relevant to highlight that the same reaction when conducted without catalyst did not proceed to any appreciable extent even after 12 h where only 44% yield was obtained (Table 2, entry 5).

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

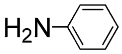
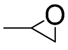
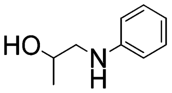
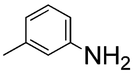
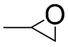
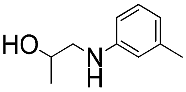
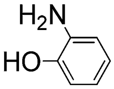
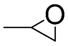
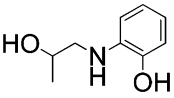
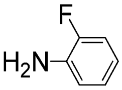
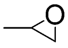
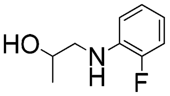
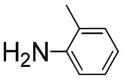
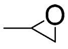
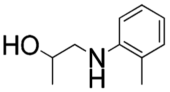
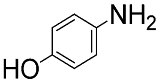
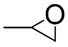
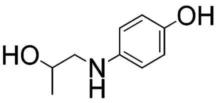
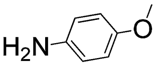
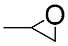
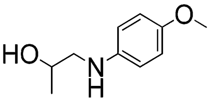
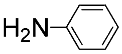
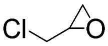
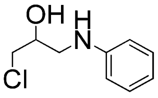
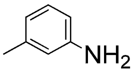
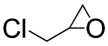
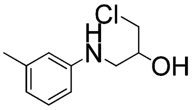
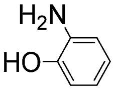
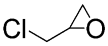
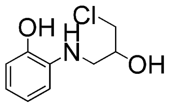
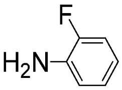
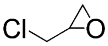
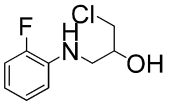
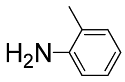
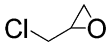
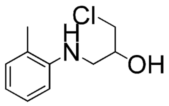
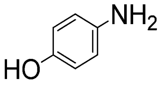
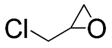
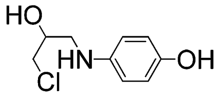
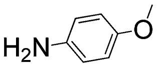
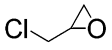
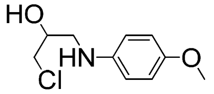
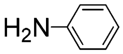
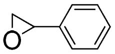
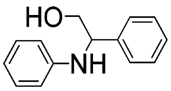
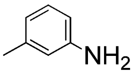
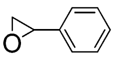
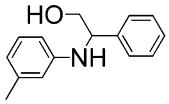
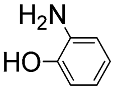
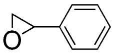
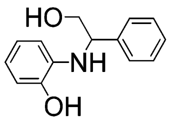
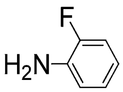
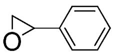
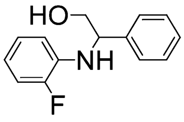
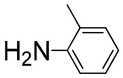
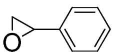
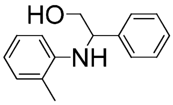
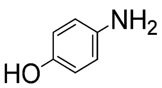
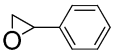
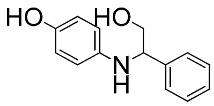
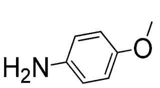
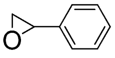
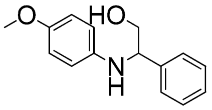
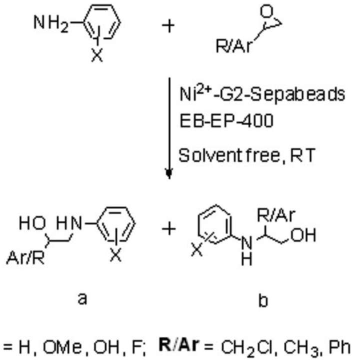
Entry	Amine	Epoxide	β-Amino alcohol	Time (h), RT	Yield[b] (%)	*E* factor
1			 **1a**	0.5	98.0	0.1363
2			 **2a**	1.5	95.0	0.0526
3			 **3a**	2.0	93.0	0.0752
4			 **4a**	2.0	96.0	0.0416
5			 **5a**	2.0	94.0	0.0638
6			 **6a**	1.0	98.0	0.0204
7			 **7a**	2.0	96.0	0.0416
8			 **8a**	0.5	97.0	0.0309
9			 **9a**	1.0	99.5	0.0050
10			 **10a**	1.0	92.0	0.0869
11			 **11a**	1.5	89.0	0.1235

Table 3 (*Contd.*)

Entry	Amine	Epoxide	β-Amino alcohol	Time (h), RT	Yield[b] (%)	*E* factor
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

[a] Epoxides (1 mmol) were treated with anilines (1 mmol) and the catalyst: Ni^{2+}-G2 metallodendrimer Sepabeads EB-EP-400 (4%) (temperature: RT, under solvent-free conditions, reaction time: 0.5 to 3 h). [b] Yields refer to isolated products after column chromatography.



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

3.2.1 Effect of solvent. The solvent effect on the catalytic activity of the Ni^{2+}-metallodendrimer catalyst was also studied, and the results of the aminolysis of epoxides are summarized in Table 2. It was observed that the catalytic rate was higher with divalent transition metals (*e.g.* Ni^{2+}) ligated onto the metallodendrimer-grafted Sepabeads EB-EP-400 catalyst under solvent-free conditions (Table 2, entries 1–4) than in the presence of aqueous and organic solvents (Table 2, entries 6–23). From Table 2 (entries 6–23), it can be seen that the polarity of the solvent has a significant effect on the catalytic activity of the Ni^{2+}-metallodendrimer catalyst. Among the different solvents studied, polar solvents, *i.e.* water (Table 2, entries 6, 12 and 18), gave a better catalytic activity and yield than the comparatively non-polar or intermediate polar solvents tested. The catalytic activity was substantially reduced with non-polar or intermediate polarity solvents for the 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 the presence of water without a catalyst, the reaction after 12 h gave only 39% yield (Table 2, entry 24). Hence, this effect could be due to the hydrophobic solvent getting adsorbed on the solid metallodendrimer catalyst, making a lower number of sites accessible for the reaction. On the other hand, with water and under solvent-free conditions, a large number or all sites remain accessible for the reactant molecules to yield a high conversion in less time. In particular, when the reaction was carried out using the 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 under solvent-free conditions with the designed regioselective Ni^{2+}-metallodendrimer catalyst (Table 3, entry 9).

3.2.2 Effect of catalyst loading and substrate. The effect of catalyst loading (1 to 6.5 mol%) on the performance in the reaction was also studied, where the increase in initial catalyst concentration up to 4 mol% showed an increase in yield of the corresponding amino alcohols (ESI†). The increase in the amount of catalyst from 4 to 6.5 mol% did not show an incremental effect on the yield of the desired amino alcohols (ESI†). Further, applicability of the Ni^{2+}-metallodendrimer catalyst for the ring opening reactions of different epoxides with amines having a different structure and charge, was evaluated (Table 3, entries 1–21). Comparatively higher conversions were 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, we did not observe any side products in the reaction (by mass spectrometry analysis). The reaction of aniline with styrene oxide gave the maximum yield (91%) for a single isomer showing superior regioselectivity of the present catalyst (Table 3, entry 20). The aliphatic epoxides predominantly gave the type 'a' isomer whereas the aromatic (styrene) oxide predominantly gave the type 'b' isomer. This could be attributed to the charge/electronic effects favoring the attack at a less substituted carbon atom of aliphatic epoxides (Table 3, entries 1–14) and the possible localization of the positive charge of the oxygen on a highly substituted benzylic carbon in styrene oxide (Table 3, entries 15–21). The metallodendrimer catalyst has also shown strong tolerance to electron donating/withdrawing groups on aniline leading to the predominant formation of a single type of isomer (Table 3, entries 1–21), demonstrating its regioselective capability. This study further reveals that the type of epoxide is a major determining factor for the type of isomer formed in the aminolysis reaction. In the present work, both aliphatic and aromatic epoxides gave high yields with superior regio- and chemoselectivity.

3.2.3 Catalyst recycling and catalysis in a packed column. Catalyst recycling studies were conducted, and the performance in each cycle was determined. It was found that 92% conversion was obtained even after the 10th cycle. Thus, the catalyst was found to be reusable and studies indicated that metal ions did not leach from the catalyst during the course of its use, making the process techno-economically viable and environmentally friendly.

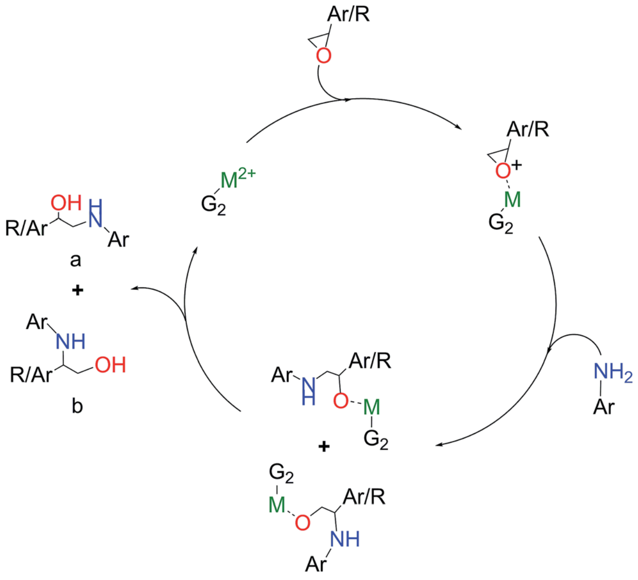


Fig. 3 Proposed mechanism of the ring opening of epoxides with the dendritic catalyst.

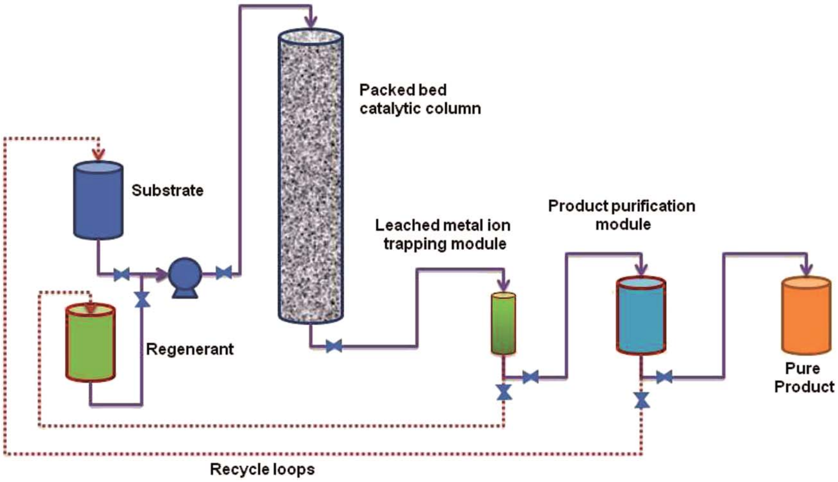


Fig. 4 Packed bed system for the continuous catalytic reaction using the Ni^{2+}-G2-metallodendrimer Sepabeads EB-EP-400 catalyst.

The proposed mechanism for the ring opening of the oxirane ring with different amines in the presence of the Ni^{2+}-metallodendrimer-based Sepabeads EB-EP-400 catalyst is shown in Fig. 3. To explore the feasibility of using the designed catalyst continuously and to prove the industrial viability, we developed a system consisting of a packed bed of catalyst coupled with metal ion trapping and product purification modules as shown in Fig. 4. The metal ion trapping module was a column (1/100th of the volume of the catalytic column) packed with the chelating resin Diaion CR11 (Mitsubishi Chemical Corporation, Japan). This was used to avoid any possibility of passage of metal ions into the product. The purification module consisted of silica gel operating under the conditions described earlier. The catalytic column was operated continuously with a 1 : 1 molar ratio of the reactants (Table 3, entry 1). It was found that, under the column mode, the catalyst required about 20 min of residence time to achieve >99.5% conversion of the reactants into the corresponding β-amino alcohol. Recently, few reports on polymer catalysts appeared to describe the ring opening of epoxides at high temperatures with long reaction times and in the presence of solvent[44,45] as well as under non-catalyzed reaction conditions.[46] Comparison of the designed Ni^{2+}-metallodendrimer-based Sepabeads EB-EP-400 catalyst with the few catalysts reported in the literature for the synthesis of β-amino alcohols showed much superior catalytic activity, and higher yields (97–99% yield) in significantly less time (0.5 to 1.0 h) for our catalyst as compared to a recent report where a nano Fe_3O_4 catalyst[47] is used for the synthesis of β-amino alcohols (ESI†).

4. Conclusions

The present work has led to the design of a mild and efficient method for the ring opening of epoxides without destruction of the solid catalyst. The designed Ni^{2+}-based metallodendrimer-grafted polymethacrylate beads-based catalyst showed high activity and regioselectivity for the synthesis of β-amino alcohols. Thus, the designed Ni^{2+}-based metallodendrimer-grafted Sepabeads catalyst offers many advantages of a solid catalyst over other catalysts from the viewpoint of green chemistry such as solvent-free conditions, simplification of the work-up, formation of cleaner products with no side products, improved reaction rates, low catalytic amounts, catalyst recycling and an easy isolation procedure, making it a better alternative to existing catalysts. Furthermore, under the stated conditions, a catalytic column was also operated continuously for 72 h which showed high productivity (4 kg L^{-1} h^{-1}). During this operation, no significant reduction in conversion and productivity was observed which proves the industrial feasibility of the catalyst for the synthesis of β-amino alcohols.

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