Tetrahedron: *Asymmetry* 25 (2014) 775–780

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

Polystyrene copolymer supported by substituted (1*R*,2*R*)-1,2-diphenylethane-1,2-diamine-copper(II) complexes: a recyclable catalyst for asymmetric Henry reactions

Ladislav Androvič [a], Pavel Drabina [a,*], Illia Panov [a], Božena Frumarová [b], Andréa Kalendová [c], Miloš Sedlák [a]

[a] *Institute of Organic Chemistry and Technology, Faculty of Chemical Technology, University of Pardubice, Studentská 573, 532 10 Pardubice, Czech Republic*
[b] *Institute of Macromolecular Chemistry, ASCR, Heyrovsky sq. 2, 16206 Prague, Czech Republic*
[c] *Institute of Chemistry and Technology of Macromolecular Materials, Faculty of Chemical Technology, University of Pardubice, Studentská 573, 532 10 Pardubice, Czech Republic*

ARTICLE INFO

Article history:
Received 24 March 2014
Accepted 3 April 2014

Dedicated to Professor Vladimír Macháček on the occasion of his 70th birthday

ABSTRACT

Herein described the preparation of swelling pearl-like copolymer styrene—4-vinylbenzyl chloride cross-linked by means of tetra(ethylene glycol)-bis(4-vinylbenzyl)ether (200–800 μm). The pearl-like polymer was used to anchor (1*R*,2*R*)-1-amino-2-(2,3-dihydro-1*H*-isoindole-2-yl)-1,2-diphenylethane by a covalent bond; the product was subsequently transformed into the corresponding complex with Cu(II) acetate. The synthesized catalyst was used for the catalysis of the Henry reaction of functionalized aldehydes with nitromethane in ethanol. The reactions proceeded in a polymeric matrix of the swelling catalyst at a rate comparable with the rates of reactions in a homogeneous medium. The corresponding functionalized 2-nitroethanols were formed in quantitative yields (20 °C, 24 h) with enantiomeric excess values of up to 96%. The catalyst was recycled five times without losing its effectiveness with regard to the yield and enantioselectivity; only a partial mechanical degradation of the polymeric matrix occurred due to stirring.

1. Introduction

The reaction of aliphatic nitro compounds with aldehydes or ketones (the Henry reaction), in which a covalent bond is formed between the carbonyl carbon atom and the α-carbon atom of the nitro compound is one of the essential reactions of organic chemistry.[1] The asymmetric variant of this synthesis requires the application of a suitable chiral, enantiomerically pure ligand, frequently in combination with metal ions; Cu(II) complexes are the most successful.[1,2] The products of this reaction are enantiomerically pure 2-nitroethanols, which represent significant building blocks designed for the synthesis of many pharmaceutical products.[3] Several recently published papers[1g,i,3c] have described the preparation and characterization of enantiomerically pure functionalized 2-(pyridine-2-yl)imidazolidine-4-ones, whose complexes with Cu(II) acetate represent very efficient catalysts for the Henry reaction (up to 96% ee). Analogous very efficient catalysts of the Henry reaction also include Cu(II) complexes based on derivatives of (1*R*,2*R*)-1,2-diphenylethane-1,2-diamine[1c] or on functionalized (1*R*,2*R*)-cyclohexane-1,2-diamine.[1e]

All of the aforementioned homogeneous catalysts cannot be easily separated from the reaction mixtures, and thus means they cannot be reused. Therefore, the immobilization of homogeneous catalysts represents a method to prepare heterogeneous catalysts that are easily recyclable.[4] These catalysts are often based on spherical particles of suitably functionalized styrene–divinylbenzene copolymer (PS-DVB, Merrifield).[5] A big advantage of immobilized catalysts is their easy separation from reaction media, both in batch-wise and flow-reactor arrangements.[6] However, the application of these catalysts can be limited by long reaction times and thus also low conversions, which is due to the slow diffusion processes during the transport of the reactants in the polymeric matrix of the catalysts.[5c] The increase in efficiency of polymeric carriers is based on the incorporation of a suitable cross-linker, different from that present in the original polymer used by Merrifield. From the standpoint of the diffusion rate of polar reagents, it has proved to be advantageous to cross-link polystyrene by means of polytetrahydrofuran (PTHF) units[7] or poly(ethylene glycol) (PEG).[8] When incorporating ethylene glycol units, the resulting polymeric carrier combines the advantages of soluble polymer (PEG) and insoluble polymer (PS-DVB). Another option of modification consists of the modification of the surface of PS-DVB by means of functionalized PEG (PEG-grafting, TentaGel™, ArgoGel™).[8b]

---

[*] Corresponding author. Tel.: +420 466 037 010; fax: +420 466 037 068.
E-mail address: pavel.drabina@upce.cz (P. Drabina).

http://dx.doi.org/10.1016/j.tetasy.2014.04.004
0957-4166/

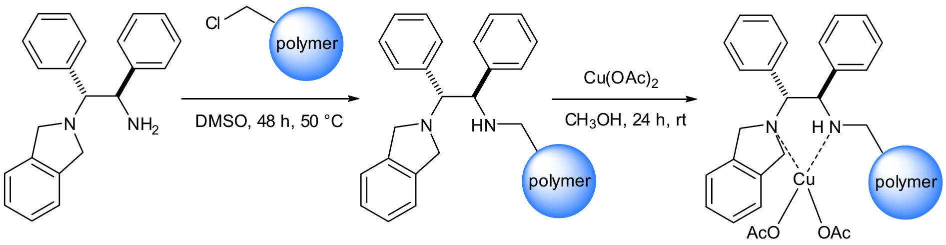
However, the results summarized in a review article[5c] show that the PEG-cross-linked swelling pearl-like polymers are better with regard to the rate of catalysis, than the pearl-like polymers modified only superficially (PEG-grafting). The chosen network polymeric carrier should, first of all, possess a sufficient swelling capacity, and at the same time, it should posses a sufficient mechanical resistance.[9] For this reason, the content of the network agent in the polymer plays a key role: it usually varies between ca. 1% and 2% w/w.[8,9] Herein our aim was to prepare and characterize a recyclable catalyst based on a modified pearl-like polystyrene, which would be applicable to asymmetric Henry reactions. The main requirement to be met by the catalyst was to achieve high conversion in real time while maintaining high enantioselectivity, comparable with that of the original homogeneous catalysts. The easy preparation of the catalysts from commercially available compounds was also important.

2. Results and discussion

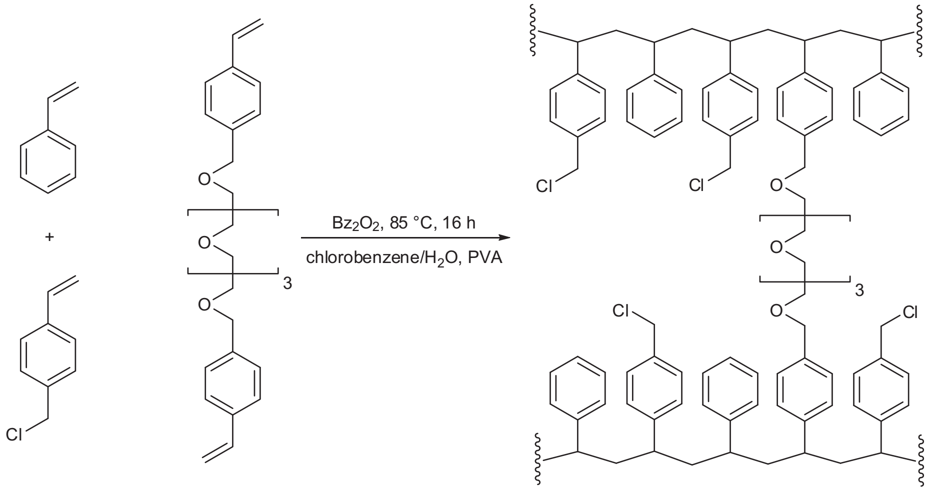
The homogeneous catalyst designed for immobilization needs to attain excellent results in homogeneous media.[4] The reference catalyst chosen in our case was the complex of a Cu(II) acetate with (1*R*,2*R*)-1-amino-2-(2,3-dihydro-1*H*-isoindole-2-yl)-1,2-diphenylethane, which was modified with (*S*)-2,2-dibromomethyl-1,1-binaphthalene (catalyst A).[1c,6] From the literature[1c] it can be seen that this catalyst catalyzes the Henry reaction of 2-nitrobenzaldehyde with nitromethane to give the corresponding 2-nitroethanol with 98% ee, with the yield being quantitative after 24 h at room temperature. The next key step of the preparation of the immobilized catalyst was the choice of suitable polymer.[4–9] First we tested the commercially available chloromethylated polymers Merrifield™ and JandaJel™. These polymers were subjected to the reaction with (1*R*,2*R*)-1-amino-2-(2,3-dihydro-1*H*-isoindole-2-yl)-1,2-diphenylethane and subsequently with Cu(II) acetate (Scheme 1).

The catalysts prepared were further tested in the Henry reaction of 2-nitrobenzaldehyde with nitromethane. However, in both cases with the commercial polymers, the reaction was slow, that is, only ca. 5% conversion was achieved after one-week of reaction at room temperature. Therefore, we prepared another polymeric carrier based on a swelling pearl-like copolymer of styrene (ST) and 4-vinylbenzyl chloride (VBC) transformed into a network by means of tetra(ethylene glycol)-bis(4-vinylbenzyl) ether (TEGBVBE).[8a] The difference between the polymer prepared in this way and the commercial polymers consists in the type and amount of the cross-linker used in the polymerization. The cross-linker used in our case is more polar than polytetrahydrofuran, which was used in the case of polymer of JandaJel™ type.[7] The preparation of the copolymer was carried out by the well-known methodology of suspension polymerization[7–10] (Scheme 2).

The experimental implementation of the suspension polymerization is affected by many physical and chemical factors and represents a relatively complex system.[9,10] One of the key factors for the successful implementation of suspension polymerization is the choice of the stabilization phase. In our case, 88% poly(vinyl alcohol) was successfully used for the preparation of the stabilization phase. The remaining poly(vinyl acetate) (~12%) is adsorbed on the surface of the pearls that are formed and minimizes their gluing together, that is, the formation of conglomerates.[9,10] The content of the cross-linker (TEGBVBE) in the amount of monomers (2% w/w) was chosen on the basis of data following from the earlier studies performed with model copolymers based on polystyrene



Scheme 1. Immobilization of (1*R*,2*R*)-1-amino-2-(2,3-dihydro-1*H*-isoindole-2-yl)-1,2-diphenylethane onto a polymeric carrier with subsequent complexation with Cu(II) acetate.



Scheme 2. Suspension polymerization of styrene (ST), 4-vinylbenzyl chloride (VBC), and tetra(ethylene glycol)-bis(4-vinylbenzyl) ether (TEGBVBE).

with different contents of cross-linkers derived from the series of bis(4-vinylbenzyl) ethers.[8] The content of the cross-linker used in our case proved to be advantageous in particular from the standpoint of the high swelling ability of the polymer and the concomitant easy diffusion of reagents. The swelling ability of the polymer was determined by a simple method,[11] and in the case of 96% ethanol, it represents 11 mL/1 g polymer. However, with a cross-linker content lower than 2% w/w the polymer lost its mechanical strength and began to disintegrate as early as the subsequent extraction of the residual monomers, which is always performed after the polymerization is finished. The content of chlorine in the copolymer ST–VBC–TEG was determined by microanalysis (Cl, 5.84%; 1.65 mmol/g). The size of the prepared spheres was determined by means of optical microscopy and varied in the range of 200–800 μm (Fig. 1).

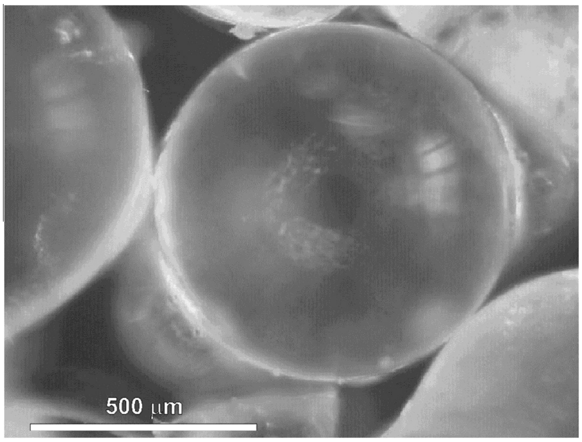


Figure 1. Microscopic picture of the prepared pearl-like copolymer ST–VBC–TEG.

In the next step, the enantiomerically pure ligand ((1*R*,2*R*)-1-amino-2-(2,3-dihydro-1*H*-isoindole-2-yl)-1,2-diphenylethane) was anchored to the prepared polymer by means of a covalent bond. The reaction was carried out by heating the solution of the ligand in dimethyl sulfoxide (50 °C) with the suspended polymer ST–VBC–TEG (Scheme 1). The nitrogen content was determined by microanalysis to be 2.26%, which corresponded to 0.83 mmol ligand per 1 g polymer. The last step of the preparation of catalyst B consisted of the coordination of Cu(II) acetate onto the modified polymeric carrier. After extraction and drying of catalyst B, its Cu content was determined by means of AAS. The determined copper content (5.21%) indicated that one Cu(II) ion was attached to two nitrogen atoms. The prepared starting copolymer, that is, ST–VBC–TEG, the copolymer with the anchored ligand and the polymeric catalyst B were further characterized by means of Raman spectrometry (Fig. 2), which proved to be successful in the characterization of the PS copolymers and is often used in combinatorial synthesis.[8b] This spectroscopic method has the advantages of being rapid, consuming small amount of samples, and being non-destructive.[12] The Raman bands near 677 cm^{-1} (C–Cl vibrations) and 1266 cm^{-1} (CH_2–Cl wagging vibrations)[12] can be seen in the spectrum of the prepared copolymer ST–VBC–TEG. The anchoring of the ligand to the copolymer caused the total disappearance of these bands and the appearance of new bands near 1562 cm^{-1} (N–H deformation vibrations in secondary amines), and an increase in the intensity of the bands near 1073 cm^{-1} and between 750 and 800 cm^{-1} (C–N stretching vibrations in tertiary amines).[13] The following formation of the complex with Cu(II) acetate was accompanied by the formation of a new band near 1704 cm^{-1} (vibration of acetate ion, which is bonded to Cu(II) ion as a unidentate ligand[14]).

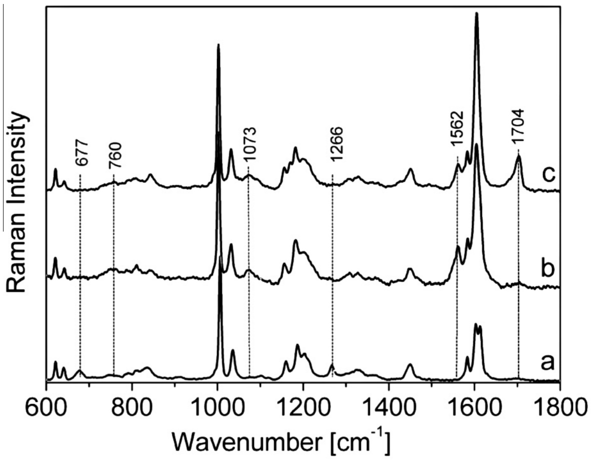
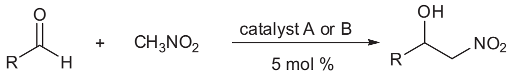


Figure 2. Raman spectra of the polymer ST–VBC–TEG (a); polymer ST–VBC–TEG with anchored (1*R*,2*R*)-1-amino-2-(2,3-dihydro-1*H*-isoindole-2-yl)-1,2-diphenylethane (b) and catalyst B (c).

We next tested the polymeric catalyst B in the Henry reaction of functionalized aldehydes with nitromethane: the corresponding 2-nitroethanols are formed in non-racemic form.[1c] The results obtained were compared with those published on the homogeneous catalyst A[1c] (Table 1).

The configuration of the obtained functionalized 2-nitroethanols was established as (*S*) when using catalyst A.[1c] The enantiomeric excess was determined chromatographically using the method described earlier.[1g] The results given in Table 1 indicate that the yields obtained with polymeric heterogeneous catalyst B are comparable with those obtained with the reference catalyst A in homogeneous media. The prepared pearl-like copolymer ST–VBC–TEG is advantageous for the Henry reactions studied with regard to the overall reaction rate. In this case, the prepared polymeric matrix represents a system, which minimally affects the overall reaction rate by diffusion processes. The reagents easily reach the catalytic center, and the reaction product is easily transported from the polymeric matrix to the solution. The observed slight lowering of the enantioselectivity of catalyst B compared with that of catalyst A can be explained by the substituent at the 2-amino group. The functionalization with (*S*)-2,2-dibromomethyl-1,1-binaphthalene leads to different steric requirements of the chelating ligand, as in the case of the differently N,N-dialkylated cyclohexane-1,2-diamines.[15] Another factor is that the reference catalyst A possesses a higher number of stereogenic centers than the prepared catalyst B. The immobilization of a homogeneous catalyst often leads to a decrease in its enantioselectivity due to undesirable interactions of the substrate with the relatively rigid polymeric matrix.[4] The application of polymeric catalyst B was connected to a decrease in enantioselectivity by ca. 5% ee in the case of benzaldehyde, by ca. 8–9% ee in the case of 2-methoxybenzaldehyde (entries 1 and 2), and by ca. 15% ee in the case of 2- and 4-nitrobenzaldehyde (entries 6 and 7). However, in the cases of aliphatic aldehydes, that is, *n*-pentanal, cyclohexanecarbaldehyde, and pivaloyl aldehyde (entries 8–10), the results were virtually identical with those obtained in the case of the homogeneous catalyst A. The higher enantioselectivity observed in the reactions of aliphatic aldehydes can probably be explained by their lower interaction with the polymeric matrix itself. In the case of aromatic aldehydes, it is possible that a π–π interaction between the substrate and aromatic polymer takes place.[4] It is highly probable that these interactions cause a decrease in the activation energy of the reaction path leading to the opposite enantiomer, which means a decrease in the enantioselectivity. The worst

Table 1
Henry reaction of nitromethane with various aldehydes catalyzed by recoverable polymeric catalysts



Entry	R	Catalyst A[a]			Catalyst B[c]		
		Time (h)	Yield[d] (%)	ee[e] (%)	Time (h)	Yield[d] (%)	ee[e] (%)
1	Ph	120	94[b]	91	24	>99	86
2	2-$MeOC_6H_4$	72	>99	95	24	96	90
3	4-CNC_6H_4		–	–	24	>99	82
4	4-ClC_6H_4		–	–	24	>99	84
5	4-PhC_6H_4		–	–	24	98	76
6	2-$NO_2C_6H_4$	24	>99	98	24	>99	82
7	4-$NO_2C_6H_4$	24	>99	93	24	>99	79
8	n-C_4H_9	48	95	93	24	>99	90
9	t-C_4H_9	48	92	93	24	98	93
10	c-C_6H_{11}	48	96	97	24	97	96

[a] Results published in previous work.[1c] Reaction conditions: solvent – *n*-PrOH (0.6 mL); rt; aldehyde (0.3 mmol); nitroethane (0.16 mL).
[b] 0 °C, 120 h.
[c] Reaction conditions: solvent – EtOH (1.5 mL); rt; aldehyde (1 mmol); nitroethane (0.54 mL).
[d] The values are isolated yields after chromatographic purification.
[e] The enantiomeric excess determined by HPLC using Chiralcel OD-H or Chiralpak AD-H.

enantioselectivity (76% ee) was obtained with 4-phenylbenzaldehyde (entry 5), that is, a substrate which has two benzene rings and which presumably will exhibit the strongest π–π interactions.

We also tested the possibility of recycling the catalyst B for the reaction of pivaloyl aldehyde with nitromethane. From Figure 3 is obvious that after 5 reaction cycles, neither a change in the yield (∼98%) nor a change in enantioselectivity (∼93% ee) occurs. However, after the fourth reaction cycle, a visible mechanical degradation of polymeric matrix of catalyst was observed.

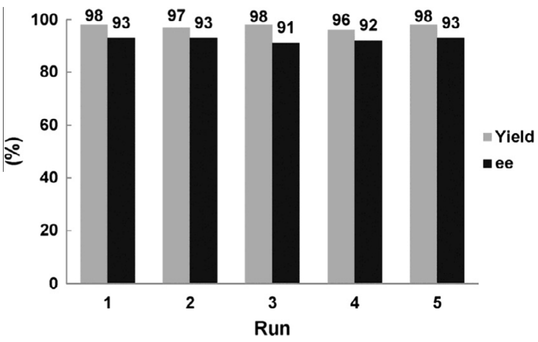


Figure 3. Proof of recoverability of catalyst B (up to 5 times) in the catalytic enantioselective Henry reaction of $MeNO_2$ with t-C_4H_9CHO.

The observed degradation of catalyst B was caused by the mechanical effect of the stirrer during the reaction. However, the mechanical effect of the stirrer could be eliminated by the use of a flow-reactor. However, such an arrangement of the reaction will always require the preparation of a strictly monodispersion polymeric carrier.[6]

Furthermore, we verified the efficiency of catalysts containing other available anchored optically active amines complexed with Cu(II) acetate: (1*R*,2*R*)-1,2-diphenylethane-1,2-diamine (catalyst C; Fig. 4), (1*R*,2*R*)-cyclohexane-1,2-diamine (catalyst D; Fig. 4).

Catalysts C and D were prepared and characterized similarly as in the case of catalyst B. Catalysts C and D were tested under the same conditions as those used with catalyst B in the reaction of 2-methoxybenzaldehyde (24 h, 18 °C). It was found out that under these conditions, quantitative conversions are achieved in both cases, but the corresponding functionalized (1*S*)-2-nitro-1-phenylethan-1-ol is formed with a distinctly lower enantiomeric excess values: 76% ee (catalyst C) and 53% ee (catalyst D).

3. Conclusion

The prepared swelling pearl-like copolymer ST–VBC–TEG containing 2% w/w cross-linker was used to anchor (1*R*,2*R*)-1-amino-2-(2,3-dihydro-1*H*-isoindole-2-yl)-1,2-diphenylethane, which was subsequently transformed into a complex by reaction with Cu(II) acetate. The reactions of functionalized aldehydes with nitromethane, catalyzed by this catalyst, proceed quantitatively and with high enantioselectivity of up to 96% ee. The transport of reagents in a polymeric matrix of catalyst carrier almost does not affect the observed reaction rate. The reaction proceeds at a rate comparable with that observed with the analogous homogeneous catalyst. A slight decrease in enantioselectivity was observed in the reactions of aromatic aldehydes, which can be explained by the π–π interactions between the substrate and the aromatic polymer. Catalyst B can be recycled at least five times without any loss of yield or enantioselectivity. After fivefold recycling, mechanical degradation of the polymeric matrix of the catalyst was observed

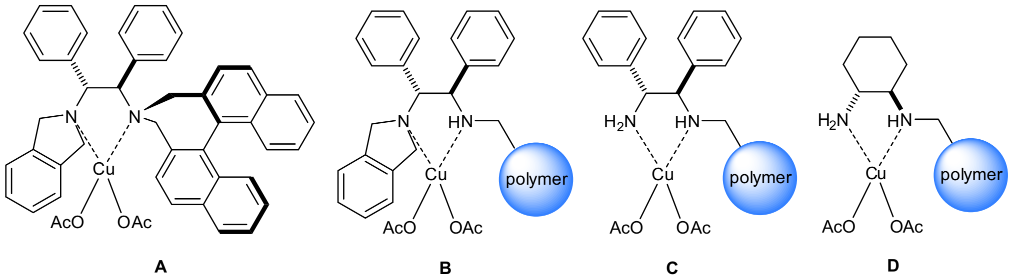


Figure 4. Structure of catalysts A–D.

due to mechanical stirring, which can probably be eliminated by placing the catalyst in a flow-reactor. The prepared polymeric catalyst possesses great potential for Henry reactions.

4. Experimental

4.1. General

Unless otherwise stated, the starting chemicals and solvents were purchased from Sigma–Aldrich or Fluka and used without further purification. The ^{1}H NMR spectra were recorded on a Bruker Avance 400 instrument (400.13 MHz for 1H). Chemical shifts δ were referenced to residual peak of the CDCl$_3$ at 7.26 ppm. The ^{13}C NMR spectra were calibrated with respect to the middle signal in the multiplet of solvent (δ = 77.23 ppm). The Raman spectra were measured at room temperature using FT-IR spectrophotometer IFS 55 provided with Raman FRA-106 accessory (Bruker) for back scattering method. The YAG: Nd^{3+} laser line (1064 nm) was used for excitation. The resolution was 2 cm^{-1} and the laser power was 50 mW. The FT-Raman data are presented in cm^{-1} (w, weak; m, medium; s, strong; sh, shoulder). The morphology and grain size of the pearl-like polymer ST–VBC–TEG were determined by means of an optical microscope Nikon Eclipse LV100D with a detachable head having high resolution power Nikon DS-Fi1 with software NIS Elements AR. The scanning head allows color scanning; the resolution of the CCD chip is 5.07 Mpix. The microanalyses were performed on an apparatus of FISONS Instruments, EA 1108 CHN. The determination of Cu was carried out with an Aavanta P double beam atomic absorption spectrometer (GBC Scientific Equipment Pty. Ltd, Australia) in the flame atomization mode. Microwave digestion of samples was carried out in the Speedwave TM MWS-3+ (Berghof, Germany) microwave system with the maximum total output of the microwave generator 1450 W. Quantification of Cu concentrations was performed by establishing a calibration curve by linear regression. Optical rotations were measured on a Perkin–Elmer 341 instrument; the concentration *c* is given in g/100 mL.

4.2. Synthesis

4.2.1. Suspension polymerization (preparation of ST–VBC–TEG polymer)

The preparation of a pearl-like copolymer by suspension polymerization was performed according to the literature[7,8a] in a defined apparatus of 500 mL volume, equipped with a floating stir bar.[8a] The vessel was charged with a solution of sodium chloride (5 g) and poly(vinyl alcohol) (88% hydrolyzed polymer; *M* = 85–124 kDa) (8 g) in water (200 mL), followed by a solution of benzoyl peroxide (200 mg; 0.8 mmol), 4-vinylbenzyl chloride (1.96 g; 12.8 mmol), styrene (4 g; 27.6 mmol), and tetra(ethylene glycol)-bis(4-vinylbenzyl) ether (120 mg; 0.32 mmol) in chlorobenzene (5 mL). The stirrer was adjusted at a rate of 600 rpm, and the temperature of the reaction mixture was increased to 85 °C during 30 min. The obtained suspension of spherical particles of organic phase was continuously stirred and kept at 85 °C for a period of 24 h. After cooling, the obtained pearl-like copolymer was collected by filtration and washed with water (50 mL), methanol (3 × 50 mL), acetonitrile (3 × 50 mL), and tetrahydrofuran (3 × 50 mL). Next, the polymer was extracted in Soxhlet extractor for 24 h with a mixture of acetonitrile and water (3:1) and 48 h with tetrahydrofuran. The prepared pearl-like polymer (200–800 μm) was dried under reduced pressure at 40 °C. The yield was 5 g polymer of elemental composition: C, 83.62; H, 7.40; Cl, 5.84; FT-Raman: 215 (w), 409 (w), 620 (m), 641 (m), 677 (m), 748 (w), 792 (sh), 811 (sh), 836 (w), 908 (w), 1002 (s), 1031 (m), 1156 (m), 1183 (m), 1200 (sh), 1266 (m), 1328 (w), 1370 (sh), 1450 (m), 1584 (m), 1603 (s), 1613 (s), 2853 (w), 2906 (m), 2960 (sh), 2976 (sh), 3005 (w), 3037 (sh), 3054 (s).

4.2.2. (1*R*,2*R*)-1-Amino-2-(2,3-dihydro-1*H*-isoindole-2-yl)-1,2-diphenylethane

The compound was prepared according to the procedure described in the literature.[1c] ^{1}H NMR (CDCl$_3$): δ 2.11 (br s, 2H); 4.00–4.10 (m, 5H); 4.56 (d, ^{3}J = 8.3 Hz, 1H); 7.08–7.25 (m, 14H); ^{13}C NMR (CDCl$_3$): δ 16.6, 55.2, 56.1, 56.1, 63.3, 73.1, 122.2, 126.6, 126.8, 127.2, 127.7, 127.9, 128.0, 129.9, 136.2, 139.7, 142.9; $[\alpha]_{D}^{20}$ = +20.8 (*c* 0.6, CHCl$_3$).

4.2.3. General method for the immobilization of the chiral amines

The suspension of the polymer (500 mg) in a solution of (1*R*,2*R*)-1-amino-2-(2,3-dihydro-1*H*-isoindole-2-yl)-1,2-diphenylethane[1c] (300 mg) or (1*R*,2*R*)-1,2-diphenylethane-1,2-diamine (300 mg) or (1*R*,2*R*)-cyclohexane-1,2-diamine in dimethyl sulfoxide (10 mL) was heated at 50 °C under an argon atmosphere for 48 h. After cooling, the polymer was washed with water (50 mL), 5% aqueous solution of NaHCO$_3$ (50 mL), water (50 ml), methanol (50 mL), and tetrahydrofuran (50 ml). Next, the polymer was extracted with tetrahydrofuran in a Soxhlet extractor for 24 h. The modified copolymer was dried under reduced pressure at 25 °C.

4.2.3.1. Copolymer supported by (1*R*,2*R*)-1-amino-2-(2,3-dihydro-1*H*-isoindole-2-yl)-1,2-diphenylethane. Yield: 590 mg; elemental composition: C, 84.14; H, 7.18; N, 2.32; Cl, 0.03; FT-Raman: 220 (w), 620 (m), 642 (m), 760 (w), 792 (sh), 810 (w), 843 (w), 1002 (s), 1031 (m), 1073 (w), 1156 (m), 1182 (m), 1202 (sh), 1308 (w), 1327 (w), 1370 (sh), 1427 (sh), 1450 (m), 1584 (m), 1605 (s), 2853 (w), 2906 (m), 2976 (w), 3002 (w), 3037 (sh), 3055 (s).

4.2.3.2. Copolymer supported by (1*R*,2*R*)-1,2-diphenylethane-1,2-diamine. Yield: 580 mg; elemental composition: C, 86.71; H, 7.92; N, 2.18; Cl, 0.04; FT-Raman: 221 (w), 620 (m), 642 (w), 651 (w), 759 (sh), 809 (w), 836 (w), 1001 (s), 1030 (m), 1038 (sh), 1156 (m), 1170 (sh), 1182 (m), 1201 (sh), 1324 (w), 1364 (sh), 1415 (w), 1449 (m), 1582 (sh), 1601 (s), 1611 (sh), 1646 (w), 2852 (w), 2908 (m), 2975 (w), 3003 (w), 3037 (sh), 3053 (s), 3059 (sh).

4.2.3.3. Copolymer supported by (1*R*,2*R*)-cyclohexane-1,2-diamine. Yield: 560 mg; elemental composition: C, 84.63; H, 7.54; N, 2.43; Cl, 0.03; FT-Raman: 220 (w), 620 (m), 642 (m), 760 (w), 1002 (s), 1031 (m), 1073 (w), 1156 (m), 1182 (m), 1202 (sh), 1308 (w), 1327 (w), 1370 (sh), 1427 (sh), 1450 (m), 1584 (m), 1605 (s), 2853 (w), 2906 (m), 2976 (w), 3002 (w), 3037 (sh), 3055 (s).

4.2.4. General method of preparation of the catalysts

The copolymer was stirred with the corresponding anchored diamine (500 mg) in a solution of Cu(II) acetate (50 mg) in methanol (20 mL) at room temperature for 48 h. After filtration and washing with methanol (3 × 5 mL), the catalyst was extracted with methanol in a Soxhlet extractor for 24 h and then dried under reduced pressure at 25 °C.

4.2.4.1. Catalyst B—copolymer supported by (1*R*,2*R*)-1-amino-2-(2,3-dihydro-1*H*-isoindole-2-yl)-1,2-diphenylethane-Cu(OAc)$_2$. Yield: 580 mg; elemental composition: C, 83.29; H, 7.14; N, 2.22; Cu, 5.21; FT-Raman: 217 (w), 620 (m), 642 (m), 760 (w), 792 (sh), 806 (w), 843 (w), 1002 (s), 1031 (m), 1073 (w), 1156 (m), 1169 (sh), 1182 (m), 1203 (sh), 1306 (w), 1323 (w), 1370 (sh), 1427 (sh), 1450 (m), 1584 (m), 1605 (s), 1704 (m), 2853 (w), 2906 (m), 2976 (w), 3002 (w), 3037 (sh), 3055 (s).

4.2.4.2. Catalyst C—copolymer supported by (1*R*,2*R*)-1,2-diphenylethane-1,2-diamine-Cu(OAc)$_2$. Yield: 560 mg; elemental composition: C, 82.77; H, 7.56; N, 2.06; Cu, 5.32; FT-Raman: 223 (w), 409 (w), 621 (m), 641 (w), 708 (w), 789 (sh), 792 (w), 811 (w), 841 (w), 909 (w), 1002 (s), 1031 (m), 1156 (m), 1182 (m), 1199 (sh), 1305 (sh), 1325 (w), 1369 (sh), 1450 (m), 1526 (w), 1583 (m), 1602 (s), 2851 (w), 2905 (s), 2976 (w), 3001 (w), 3036 (sh), 3053 (s), 3059 (sh).

4.2.4.3. Catalyst D—copolymer supported by (1*R*,2*R*)-cyclohexane-1,2-diamine-Cu(OAc)$_2$. Yield: 550 mg; elemental composition: C, 83.89; H, 7.36; N, 2.09; Cu, 4.86; FT-Raman: 218 (w), 410 (w), 621 (m), 642 (w), 772 (sh), 800 (w), 842 (w), 1002 (s), 1032 (m), 1076 (w), 1117 (w), 1155 (m), 1181 (m), 1198 (sh), 1327 (w), 1372 (w), 1408 (w), 1445 (sh), 1450 (m), 1562 (sh), 1583 (m), 1602 (s), 1642 (sh), 2856 (w), 2910 (m), 2930 (sh), 2976 (w), 3000 (w), 3037 (sh), 3051 (s).

4.2.4.4. Merrifield supported by (1*R*,2*R*)-1-amino-2-(2,3-dihydro-1*H*-isoindole-2-yl)-1,2-diphenylethane-Cu(OAc)$_2$. Yield: 555 mg; elemental composition: C, 82.49; H, 7.59; N, 2.25; Cu, 2.38; FT-Raman: 210 (w), 621 (m), 640 (m), 799 (w), 842 (w), 1001 (s), 1030 (m), 1155 (m), 1182 (m), 1198 (m), 1209 (sh), 1328 (w), 1331 (w), 1416 (w), 1445 (m), 1581 (m), 1603 (s), 1607 (sh), 2853 (w), 2913 (m), 3004 (w), 3037 (sh), 3052 (s).

4.2.4.5. JandaJel supported by (1*R*,2*R*)-1-amino-2-(2,3-dihydro-1*H*-isoindole-2-yl)-1,2-diphenylethane-Cu(OAc)$_2$. Yield: 550 mg; elemental composition: C, 83.96; H, 7.62; N, 1.81; Cu, 1.86; FT-Raman: 220 (w), 409 (w), 620 (m), 642 (w), 799 (w), 701 (w), 759 (w), 795 (w), 809 (w), 841 (w), 905 (w), 1001 (s), 1031 (m), 1070 (w), 1097 (sh), 1155 (m), 1182 (m), 1198 (sh), 1327 (w), 1450 (w), 1583 (m), 1602 (s), 2852 (w), 2903 (m), 2975 (m), 3001 (w), 3037 (sh), 3052 (s), 3163 (w), 3198 (w).

4.3. General procedure for the asymmetric Henry reaction

One of the catalysts (0.05 mmol Cu(II)) was stirred for 1 h in a mixture of ethanol (1.5 mL) and CH_3NO_2 (0.54 mL, 10 mmol). The solution was cooled to the appropriate temperature, and then the aldehyde (1 mmol) was added and the mixture was stirred for 24 h. The solvents were removed under reduced pressure, and diethyl ether was added. The catalyst was isolated by filtration and washed with ethanol (1 × 2 mL) and diethyl ether (2 × 2 mL). The crude product was isolated after evaporation of the combined ethanol and diethyl ether phase and purified by column or flash chromatography (AcOEt/hexane; 1:4 (v/v)). The enantiomeric excess was determined by HPLC. The characterization data for the enantiomers of the nitroalcohols were in accordance with the literature.[1]

Acknowledgment

The authors acknowledge the financial support from the project GAČR 14-00925S.

References

1. (a) Evans, D. A.; Seidel, D.; Rueping, M.; Lam, H. W.; Shaw, J. T.; Downey, C. W. *J. Am. Chem. Soc.* **2003**, *125*, 12692–12693; (b) Sedlák, M.; Drabina, P.; Keder, R.; Hanusek, J.; Císařová, I.; Růžička, A. *J. Organomet. Chem.* **2006**, *691*, 2623–2630; (c) Arai, T.; Watanabe, M.; Yanagisawa, A. *Org. Lett.* **2007**, *9*, 3595–3597; (d) Blay, G.; Domingo, L. R.; Hernández-Olmos, V.; Pedro, J. R. *Chem. Eur. J.* **2008**, *14*, 4725–4730; (e) Constable, E. C.; Zhang, G.; Housecroft, C. E.; Neuburger, M.; Schaffner, S.; Woggon, W.-D. *New J. Chem.* **2009**, *33*, 1064–1069; (f) Jones, M. D.; Cooper, C. J.; Mahon, M. F.; Raithby, P. R.; Apperley, D.; Wolowska, J.; Collison, D. *J. Mol. Catal. A* **2010**, *325*, 8–14; (g) Panov, I.; Drabina, P.; Padělková, Z.; Šimůnek, P.; Sedlák, M. *J. Org. Chem.* **2011**, *76*, 4787–4793; (h) Tydlitát, J.; Bureš, F.; Kulhánek, J.; Mlostoń, G.; Růžička, A. *Tetrahedron: Asymmetry* **2012**, *23*, 1010–1018; (i) Drabina, P.; Karel, S.; Panov, I.; Sedlák, M. *Tetrahedron: Asymmetry* **2013**, *24*, 334–339; (j) Ananthi, N.; Velmati, S. *Indian J. Chem., Sect B* **2013**, *52*, 87–108; (k) Boruwa, J.; Gogoi, N.; Saikia, P. P.; Barua, N. C. *Tetrahedron: Asymmetry* **2006**, *17*, 3315–3326; (l) Palomo, C.; Oiarbide, M.; Laso, A. *Eur. J. Org. Chem.* **2007**, 2561–2574.
2. (a) Maggi, R.; Lanari, D.; Oro, C.; Sartori, G.; Vaccaro, L. *Eur. J. Org. Chem.* **2011**, 5551–5554; (b) Angulo, B.; García, J. I.; Herrerías, C. I.; Mayoral, J. A.; Minana, A. C. *J. Org. Chem.* **2012**, *77*, 5525–5532; (c) Bandini, M.; Benaglia, M.; Sinisi, R.; Tommasi, S.; Umani-Ronchi, A. *Org. Lett.* **2007**, *11*, 2151–2153; (d) Bhosale, D. S.; Drabina, P.; Palarčík, J.; Hanusek, J.; Sedlák, M. *Tetrahedron: Asymmetry* **2014**, *25*, 334–339.
3. (a) Guo, Z.-L.; Deng, Y.-Q.; Zhong, S.; Lu, G. *Tetrahedron: Asymmetry* **2011**, *22*, 1395–1399; (b) Arai, T.; Taneda, Y.; Endo, Y. *Chem. Commun.* **2010**, 7936–7938; (c) Panov, I.; Drabina, P.; Hanusek, J.; Sedlák, M. *Synlett* **2013**, 1280–1282.
4. Jimeno, C.; Sayalero, S.; Pericàs, M. A. In *Heterogenized Homogenous Catalysts for Fine Chemicals Production: Covalent Heterogenization of Asymmetric Catalysts on Polymers and Nanoparticles*; Barbaro, P., Liguori, F., Eds.; Springer Science and Business Media: Dordrecht, 2010; pp 123–170.
5. (a) Merrifield, R. B. *J. Am. Chem. Soc.* **1963**, *85*, 2149–2154; (b) McNamara, C. A.; Dixon, M. J.; Bradley, M. *Chem. Rev.* **2002**, *102*, 3275–3300; (c) Kristensen, T. E.; Hansen, T. *Eur. J. Org. Chem.* **2010**, 3179–3204.
6. Arai, T.; Watanabe, M.; Fujiwara, A.; Yokoyama, N.; Yanagisawa, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 5978–5981.
7. Toy, P. H.; Janda, K. D. *Tetrahedron Lett.* **1999**, *40*, 6329–6332.
8. (a) Wilson, M. E.; Paech, K.; Zhou, W.-J.; Kurth, M. J. *J. Org. Chem.* **1998**, *63*, 5094–5099; (b) Grøtli, M.; Gotfredsen, C. H.; Rademann, J.; Buchardt, J.; Clark, A. J.; Duus, J. Ø.; Meldal, M. *J. Comb. Chem.* **2000**, *2*, 108–119.
9. Goodall, A. R.; Greenhill-Hooper, M. J. *Macromol. Chem. Symp.* **1990**, *35–6*, 499–507.
10. Dowding, P. J.; Vincent, B. *Colloids Surf., A* **2000**, *161*, 259–269.
11. Bouillon, I.; Soural, M.; Miller, M. J.; Krchňák, V. *J. Comb. Chem.* **2009**, *11*, 213–215.
12. Altava, B.; Burguete, M. I.; García-Verdugo, E.; Luis, S. V.; Vicent, M. J. *Tetrahedron* **2001**, *57*, 8675–8683.
13. Socrates, G. *Infrared and Raman Characteristic Group Frequencies: Tables and Charts*, 3rd ed.; John Wiley & Sons: Chichester, 2001.
14. Nakamoto, K. *Infrared and Raman Spectra of Inorganic and Coordination Compounds. Part B: Applications in Coordination, Organometallic, and Bioinorganic Chemistry*, 5th ed.; John Wiley & Sons: New York, 1997.
15. Chunhong, Z.; Liu, F.; Gou, S. *Tetrahedron: Asymmetry* **2014**, *25*, 278–283.