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# Henry reaction catalyzed by recoverable enantioselective catalysts based on copper(II) complexes of α-methoxypoly (ethylene glycol)-*b*-poly(L-glutamic acid) and imidazolidine-4-one ligands

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ABSTRACT

Herein we describe the preparation and characterization of a recoverable catalyst for a Henry reaction based on a Cu(II) complex of block copolymer α-methoxypoly(ethylene glycol)-*b*-poly(L-glutamic acid) with (2*R*,5*S*)- or (2*S*,5*R*)-5-isopropyl-5-methyl-2-(pyridine-2-yl)imidazolidine-4-one. The reactions of substituted aldehydes with nitromethane catalyzed by these catalysts proceed with high chemical yield (70–98%) and with high enantioselectivity (61–92% ee). The reaction mixture is in the form of a colloid system and is formed by self-organized aggregates of the catalysts with average hydrodynamic particle size of 189 ± 3 nm (DLS). After sevenfold recycling, the catalyst exhibited no decrease in the enantioselectivity and only a slight decrease (ca. 18%) in the yield for the Henry reaction of nitromethane with 2-methoxybenzaldehyde.



## 1. Introduction

The asymmetric variant of the Henry reaction catalyzed by Cu(II) complexes represents one of the basic reactions in which a new stereogenic center is created by the formation of a carbon–carbon bond.[1] This reaction is often a key step in preparation of chiral, enantiomerically pure substituted 2-nitroalcohols used in syntheses of medical drugs.[2] In our previous papers,[1n,r,2e] we have described the preparation and characterization of eantiomerically pure substituted imidazolidine-4-ones and their complexes with Cu(II) ions, which were utilized as enantioselective catalysts of the Henry reaction with different aldehydes with nitromethane. In the case of the reaction of 2,2-dimethylpropanal with nitromethane catalyzed by a complex of (2*R*,5*S*)-5-isopropyl-5-methyl-2-(pyridine-2-yl)imidazolidine-4-one with $Cu(OAc)_2$, the product showed[1n] up to 96% ee. However, the applications of homogeneous catalysts are limited due to the impossibility of their recycling. The last decade has seen an increase in the attractiveness and interest concerning the possibility of recycling immobilized homogeneous catalysts. Their use not only lowers the expense of the technological processes, but also reduces the impacts of chemical production on the environment. The heterogenization, that is, the preparation of immobilized catalysts, consists of anchoring homogeneous catalysts to a suitable carrier, such as a polymer or an inorganic material. In the case of organic polymers, the applied polymers can be insoluble, partly soluble, or completely soluble in the reaction medium.[3] The traditionally applied insoluble polymeric carriers include spherical particles of styrene–divinylbenzene copolymer (PS–DVB, Merrifield).[4] The advantage of these systems lies in the easy isolation of the catalyst from the reaction mixture by means of filtration. However, a frequent problem appears in the long reaction times and, hence, low degree of conversion, which is caused by the slow diffusion of reactants through the polymeric matrix to the active center of the catalyst.[4] This problem can be avoided by carrying out the reactions with catalysts anchored to polymers that are soluble in the reaction medium, for example, to functionalized poly(ethylene glycols).[5] Another solution employs micellar or vesicular systems known as self-organized nanoreactors.[6] The preparation of these systems makes use of classic low-molecular surfactants,[7] or amphiphilic block copolymers.[8] Their micro- or nano-dimensions enable us to carry out the reaction under pseudo-homogeneous conditions, which reduces the reaction times. The crucial advantage of such hybrid systems lies in the possibility of their isolation after the reaction (by precipitation or dialysis) and repeated use.[6]

The literature[1f,i,p] describes several examples of immobilized catalysts used for asymmetric Henry reactions. For instance,[1i] the

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reactions of benzaldehydes with nitromethane catalyzed by a series of Cu(II) complexes derived from substituted (1*R*,2*R*)-cyclohexane-1,2-diamines immobilized on the surface of silica achieved up to 61% ee. However, in this case the immobilization led to a decrease in the enantioselectivity, as compared with the original homogeneous catalyst (72% ee).[1i] Another catalytic system based on the Cu(II) complex of substituted (1*R*,2*R*)-cyclohexane-1,2-diaminobithiophene immobilized on poly(ethylene glycol) achieved up to 93% ee, and the efficient recoverability was up to five cycles.[1f] The asymmetric Henry reaction was also performed as a model reaction using a unique self-organized catalytic system based on aggregates prepared by coordination polymerization of Cu(II) with a ditopic bisoxazoline ligand.[1p] The coordination polymer obtained was successfully recycled for up to 11 catalytic cycles while retaining high yields (>90%) and enantioselectivity (>90% ee).

Herein our aim was to prepare and characterize recoverable polymer–metal ion hybrid catalysts for the Henry reaction, based on complexes of the Cu(II) salt of block copolymer α-methoxypoly(ethylene glycol)-*b*-poly(L-glutamic acid) (PEG-*b*-PGA) with (2*R*,5*S*)- and (2*S*,5*R*)-5-isopropyl-5-methyl-2-(pyridine-2-yl)imidazolidine-4-ones.[1n] It can be expected that the double hydrophilic polymer functionalized in this way will create, in the reaction medium, aggregated (micellar or vesicular) systems, that is, self-organized micro- or nano-reactors. Another aim of our work was to verify and evaluate the advantages of the newly suggested system in comparison with the original catalyst.[1n]

## 2. Results and discussion

PEG-*b*-PGA was prepared by the well-known NCA method:[9] the ring-opening polymerization of γ-benzyl-L-glutamic acid *N*-carboxyanhydride, initiated by α-amino-ω-methoxypoly(ethylene glycol) ($M_w$ = 5000). The results of the $^1$H NMR spectroscopy showed that the poly(ethylene glycol) chain was statistically linked with 16 units of γ-benzyl-L-glutamic acid. The second reaction step was deprotection of the γ-carboxyl groups with hydrogen catalyzed by 10% Pd/C (20 bar, 25 °C, 10 h). The deprotection reaction course was monitored by means of $^1$H NMR, using the disappearance of the benzyl group signals at $\delta$ 5.00 ppm (–O–C*H*$_2$–C$_6$H$_5$, 2*H*) and at 7.33 ppm (–O–CH$_2$–C$_6$*H*$_5$, 5*H*). The synthesized polymer PEG-*b*-PGA ($M$ = 6935 g mol$^{-1}$) was purified by means of dialysis (MWCO 1000), and after lyophilization, it was characterized by means of $^1$H NMR, GPC, FT-IR, and microanalysis. The copper(II) salt of α-methoxypoly(ethylene glycol)-*b*-poly(L-glutamic)acid (PEG-*b*-PG-Cu) was prepared by the reaction of an aqueous solution of PEG-*b*-PGA with suspended copper(II) carbonate. The excess solid copper(II) carbonate was removed by centrifuging, and the product was isolated by lyophilization. The synthesized salt PEG-*b*-PG-Cu was characterized by means of FT-IR (Fig. 1) and microanalysis, with the copper content being determined by means of AAS. The content of the copper(II) ions corresponds to one Cu(II) ion bound to two carboxylic functional groups. According to earlier studies,[9e,10] the peptide block of the salt PEG-*b*-PG-Cu in an aqueous solution can assume either an α-helix or random coil formation, depending on the temperature and pH.

Subsequently, PEG-*b*-PG-Cu was dissolved in ethanol, and the obtained solution was mixed with an ethanolic solution of (2*S*,5*R*)-5-isopropyl-5-methyl-2-(pyridine-2-yl)imidazolidine-4-one (L-1) or (2*R*,5*S*)-5-isopropyl-5-methyl-2-(pyridine-2-yl)imidazolidine-4-one (L-2). The amount of the added ligand L-1 or L-2 was equivalent to the content of copper(II) (Scheme 1).

After the lyophilization, the synthesized catalysts PEG-*b*-PG-CuL-1 and PEG-*b*-PG-CuL-2 were characterized by means of IR, powder X-ray diffraction, microanalysis, and AAS. The FT-IR spectra (Fig. 1) of PEG-*b*-PGA, PEG-*b*-PG-Cu, PEG-*b*-PG-CuL-1, and PEG-*b*-PGA-CuL-2 are very similar and contain two bands: amide I at 1652 cm$^{-1}$ (C=O vibration), and amide II at 1548 cm$^{-1}$ (N–H and C–N vibration) for PEG-*b*-PGA. In the spectrum of PEG-*b*-PG-Cu, the band of amide II was shifted to lower values (1541 cm$^{-1}$) and in the case of PEG-*b*-PG-CuL-1(2) to the value of 1544 cm$^{-1}$. The bands of the poly(ethylene glycol) chain in the range of 1466–842 cm$^{-1}$ were virtually identical in the case of both the block polymer itself and its copper(II) salt and complex. In contrast to the spectra of PEG-*b*-PGA and PEG-*b*-PG-Cu, the FT-IR spectrum of PEG-*b*-PG-Cu-L-1 contains an additional band at 1608 cm$^{-1}$ which corresponds to the C=C stretching vibration of a 2-substituted pyridine. Other differences in the FT-IR spectra of PEG-*b*-PGA, PEG-*b*-PG-Cu a PEG-*b*-PG-CuL-1(2) can only be seen in the fingerprint range (Fig. 1).

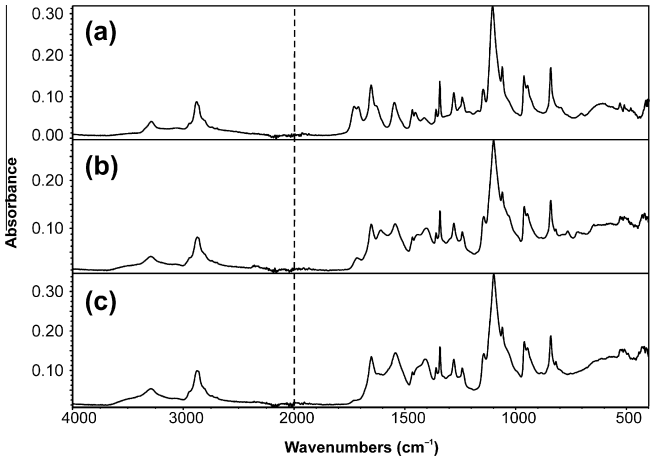


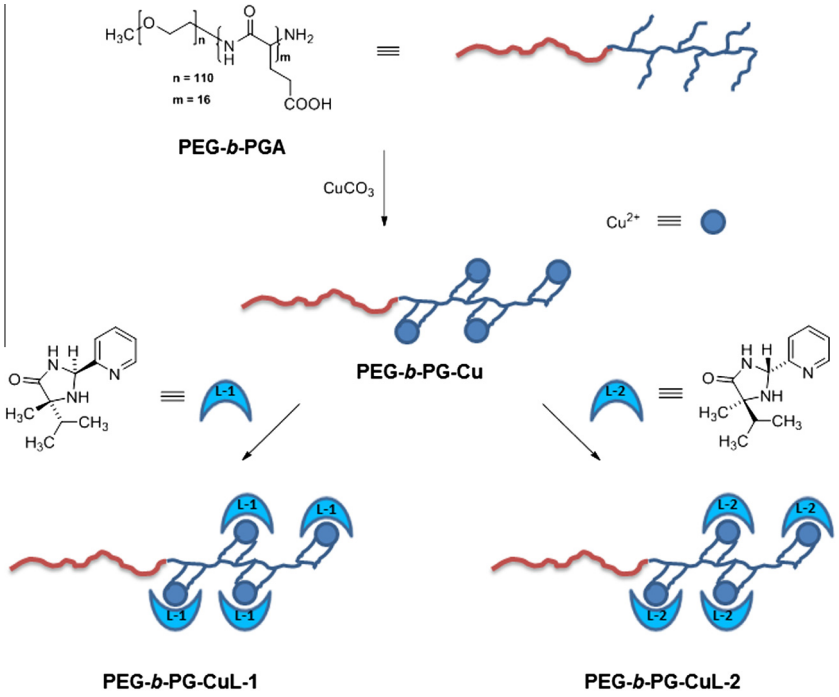

**Figure 1.** FT-IR spectrum of PEG-*b*-PGA (a); PEG-*b*-PG-CuL-1 (b) and PEG-*b*-PG-Cu (c).

Figure 2 presents the powder X-ray diffractograms of PEG-*b*-PG-Cu and PEG-*b*-PG-CuL-1(2), which are virtually identical with the diffractogram of the starting polymer PEG-*b*-PGA. From the diffractograms it can be seen that the copper(II) ions do not form independent diffracting clusters but are dispersed in the polymer PEG-*b*-PGA. The presence of a ligand in PEG-PG-CuL-1 or in PEG-*b*-PG-CuL-2 does not cause any significant change in crystal structure of the starting polymer PEG-*b*-PGA either.

The synthesized complexes PEG-*b*-PG-CuL-1 and PEG-*b*-PG-CuL-2 form colloidal opalescent solutions in ethanol. The opalescence is caused by the formation of ethanol-soluble aggregates, which were confirmed by means of dynamic light scattering (DLS). Figure 3 presents the hydrodynamic size distribution of the aggregates at the concentrations of PEG-*b*-PGACu-L-1: 25 mg mL$^{-1}$ (189 ± 3 nm) and 2.5 mg mL$^{-1}$ (134 ± 1 nm). It was found that the size of the aggregates formed depends upon the concentration of the polymeric complex in ethanol. This finding corresponds to the presence of dynamic self-organized aggregates, which can be arranged in both micellar and vesicular systems.[6a]

In the next part of our study, the prepared complexes PEG-*b*-PG-CuL-1 and PEG-*b*-PG-CuL-2 were tested as recoverable catalysts of the nitroaldol (Henry) reaction of benzaldehyde, substituted benzaldehydes and 2,2-dimethylpropanal with nitromethane to give the corresponding 2-nitroalcohols (Table 1).

The Henry reaction took place in a colloid system containing the corresponding aldehyde, nitromethane, ethanol, and catalyst. At a concentration of 50 mg PEG-*b*-PG-CuL-1 in 2 mL of reaction mixture, the average hydrodynamic size of the particles was 189 ± 3 nm (DLS) (Fig. 3). The salt PEG-*b*-PG-Cu (6 mol %) alone successfully catalyzed the Henry reaction of 2-methoxybenzaldehyde (92%); however, the enantioselectivity was negligible (~2% ee), which is probably due to the relatively large distance between




**Scheme 1.** Preparation of catalysts PEG-*b*-PG-CuL-1 and PEG-*b*-PG-CuL-2.

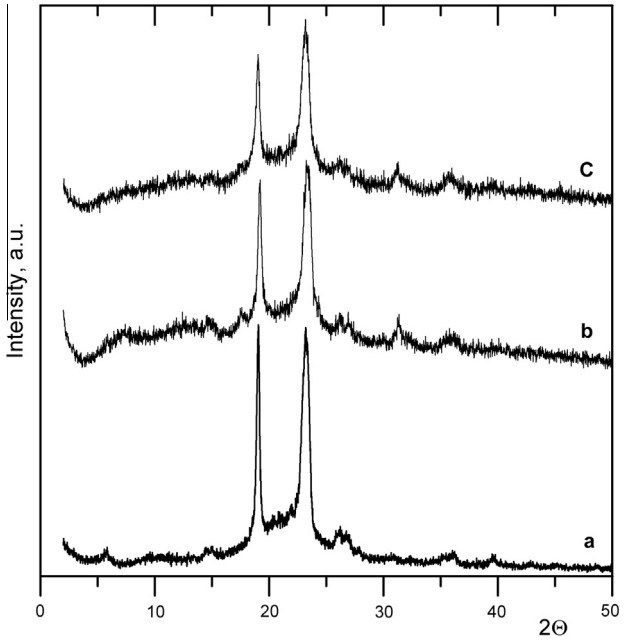



**Figure 2.** XRD patterns of PEG-*b*-PGA (a); PEG-*b*-PG-Cu (b) and PEG-*b*-PG-CuL-1(2) (c).

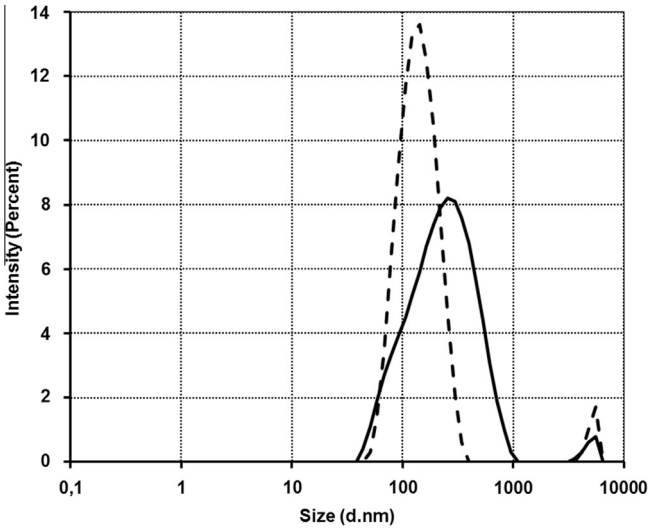


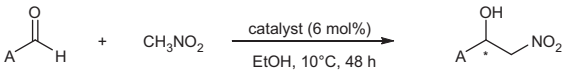

**Figure 3.** Hydrodynamic size distribution of aggregates at PEG-*b*-PG-CuL-1 concentrations: 25 mg $mL^{-1}$ (solid line) and 2.5 mg $mL^{-1}$ (dash line) in ethanol at 25 °C.

the stereogenic center of poly(L-glutamic)acid and the Cu(II) ion. Table 1 presents yields and enantiomeric excesses for the reactions of the individual aldehydes in comparison with the literature,[1n] in which the catalyst used was a combination of ligand L-1 and copper(II) acetate. Table 1 shows that the application of catalyst PEG-*b*-PG-CuL-1 (6 mol %) gave results comparable with the previous ones (entries 2 and 6). In some cases, the enantioselectivity was slightly decreased (entries 1 and 3; Δ% ee: 6; 8). In the case of the reactions of 4-bromobenzaldehyde and 4-phenylbenzaldehyde, the observed decrease in enantioselectivity was more significant (Table entries 4 and 5; Δ% ee: 14; 31). The reaction of 2-methoxybenzaldehyde with nitromethane catalyzed by complex PEG-*b*-PG-CuL-2 achieved a comparable yield (96%) and ee (91%); however, it gave the product with an opposite configuration, that is, (*S*)-1(2-methoxyphenyl)-2-nitroethanol.[1n]

After the estimated reaction time, some ethanol was distilled off, the distillation residue was mixed with diethyl ether, and the precipitated solid catalyst was collected by centrifuging (Fig. 4). The reaction products, that is, the respective functionalized 2-nitroalcohols, were obtained after distillation of combined diethyl ether phases, centrifuging, and column chromatography. The washed catalyst was dried in air at room temperature and then reused.

Figure 5 shows a diagram of the change in yield and change in enantiomeric excess attained in the individual cycles with

**Table 1**
Henry reaction of nitromethane with various aldehydes catalyzed by the L-1/$Cu(OAc)_2$ complex and recoverable catalyst PEG-*b*-PG-CuL-1




| Entry | Aldehyde | L-1/$Cu(OAc)_2$[a] | | PEG-*b*-PG-CuL-1 | |
|---|---|---|---|---|---|
| | A | Yield[b] (%) | ee[c] (%) | Yield[b] (%) | ee[c] (%) |
| 1 | Ph | 97 | 92 | 98 | 84 |
| 2 | 2-$MeOC_6H_4$ | 97 | 92 | 96 | 90 |
| 3 | 4-$ClC_6H_4$ | 97 | 90 | 91 | 84 |
| 4 | 4-$BrC_6H_4$ | 97 | 92 | 89 | 61 |
| 5 | 4-$PhC_6H_4$ | 97 | 92 | 98 | 78 |
| 6 | *t*-Bu | 87 | 96 | 70 | 92 |

[a] The results were published[1n] in our previous work.
[b] The values are yields of isolated substances after chromatographic purification.
[c] The enantiomeric excesses determined by HPLC using Chiralcel OD-H or Chiralpak AD-H.

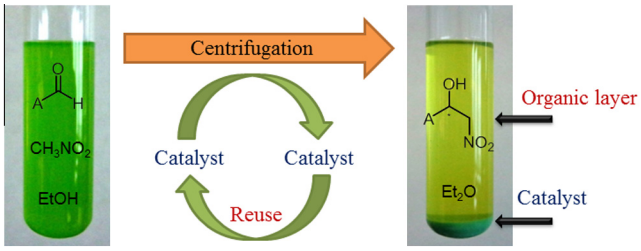



**Figure 4.** Principle of recycling of catalyst PEG-*b*-PG-CuL-1(2).

repeated use of the catalyst PEG-*b*-PG-CuL-1 for the reaction of 2-methoxybenzaldehyde with nitromethane. The data obtained show that the catalyst does not exhibit any significant decrease in enantioselectivity even after seven cycles (90–89% ee). Only a very slight decrease was observed after more than eight cycles (81–85% ee). On the other hand, the decrease in yield is more significant, namely from 95% to 73% during the observed 10 cycles. The yield decrease can be due to the mass loss of the catalyst during recycling. In the first cycle, the amount of catalyst was 55 mg (6 mol %), and each subsequent cycle was connected with a mild mass loss of the catalyst caused by handling (55 → 53 → 52 → 50 → 49 → 47 → 45 → 43 → 41 → 39 mg; ca. 4 mol %).

Considering this fact, we studied the influence of the amount of the catalyst (5; 2, and 0.5 mol%) on the Henry reaction of 2-methoxybenzaldehyde with nitromethane by determining the conversion-time dependences (Fig. 6). The kinetic dependences obtained show that the conversion decreases when decreasing the amount of the catalyst.

A further explanation for the conversion decrease after more cycles can also be the lowering of chemical activity of the catalyst during recycling. Therefore, we measured and compared the kinetic dependences for the fresh catalyst and for the catalyst which had been recycled ten times (Fig. 7). We found that the recycled catalyst attained significantly lower conversion in whole time range than the fresh catalyst. The results obtained can be summarized that the observed decrease in conversion during the 10 cycles (Fig. 5) was caused partly by the mass loss of catalyst and also by the lowering of the chemical activity of the catalyst during the recycling.

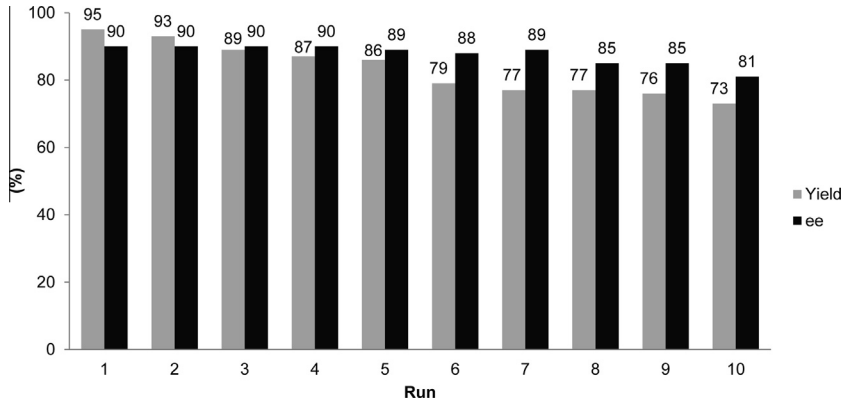



**Figure 5.** Proof of recoverability of PEG-*b*-PG-CuL-1 (up to 10 times) in the catalytic enantioselective Henry reaction of $MeNO_2$ with 2-$MeOC_6H_4CHO$.

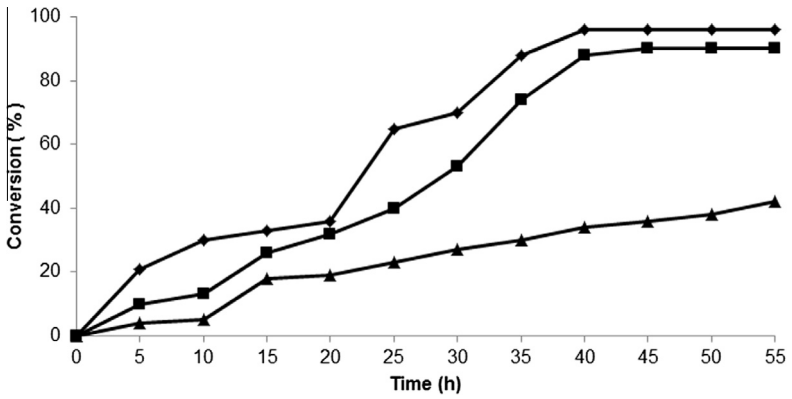



**Figure 6.** The time (h) dependence of conversion (%) of Henry reaction of $MeNO_2$ with 2-$MeOC_6H_4CHO$ catalyzed by different amounts of catalyst (PEG-*b*-PG-CuL-1): 5 mol % (♦) 2 mol % (■) 0.5 mol % (▲) at 10 °C.

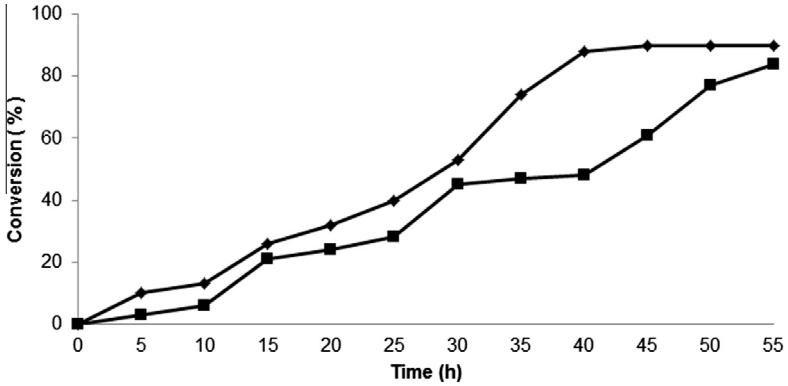



**Figure 7.** The time (h) dependence of conversion (%) of the Henry reaction of $MeNO_2$ with 2-$MeOC_6H_4CHO$ catalyzed by fresh catalyst (♦) and catalyst after 10 cycles (■) (PEG-*b*-PG-CuL-1, 3 mol %, 10 °C).

## 3. Conclusion

The results obtained confirmed that the synthesized complexes PEG-*b*-PG-CuL-1 (L-2) catalyze the Henry reaction of functionalized aldehydes with nitromethane and give high chemical yields (70–98%) and high enantioselectivity (61–92% ee). In contrast to the original homogeneous complex of copper(II) acetate with (2*R*, 5*S*)-5-isopropyl-5-methyl-2-(pyridine-2-yl)imidazolidine-4-one, the polymeric complex PEG-*b*-PG-CuL-1 (L-2) can be easily isolated from the reaction mixture. Moreover, immobilization of the ligand on the block copolymer enables the recovery of the catalyst from the reaction mixture and its reuse. The achieved effectiveness was very high even after several recycling steps (77% yield and 89% ee after 7 cycles). Only a minor decrease in the enantioselectivity (Δ9% ee) and the yield (Δ22%) was observed after ten cycles. The kinetic dependences show that the conversion decrease is caused by a lowered activity of the catalyst and also by the mass loss of the catalyst during recycling.

## 4. Experimental

### 4.1. Materials and methods

The starting substances were purchased from Sigma–Aldrich. Ethanol was dried over 4 Å molecular sieves before use. $^1$H NMR spectra were recorded on a Bruker Avance 400 instrument (400.13 MHz for 1H). Chemical shifts $\delta$ were referenced to a residual peak of the DMSO-$d_6$ at 2.50 ppm. Gel permeation chromatography's HEMA-BIO columns (hydrophilic modification HEMAGel, particle size 10 mm, porosity 40:100:300:1000) was used for the estimation of $M_w$ PEG-*b*-PGA at 25 °C using an RI detector. Redistilled water (pH 7.1) was used as the eluent. The columns were calibrated with a series of standard PEGs (Merck) of various molecular masses. The FT-IR spectra were measured in KBr pellets. The FT-IR spectra of mulls were recorded in the region of 3500–700 $cm^{-1}$ at room temperature with a resolution of 4 $cm^{-1}$ using an IFS-66/S FT-IR spectrometer (Bruker, Germany). A demountable cell with $CaF_2$ windows and a 50 μm Teflon spacer was used. 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. Powder X-ray diffraction data (Cu Kα, $\lambda$ = 1.5418 Å) were collected on a D8 Advance diffractometer (Bruker AXS, Germany) with Bragg–Brentano Θ–Θ goniometer (radius 217.5 mm) equipped with a secondary beam curved graphite monochromator and Na(Tl)I scintillation detector. The generator was operated at 40 kV and 30 mA. The scan was performed at room temperature from 2° to 65° (2Θ) in 0.02° step with a counting time of 10 s per step. The average particle size and size distribution of the aggregates were determined by dynamic light scattering using a Zetasizer Nano ZS (Malvern Instruments, UK). The measurements were performed at the temperature of 25 °C with the scattering angle of 173° using disposable sizing cuvettes in ethanol.

### 4.2. Preparation of catalysts

#### 4.2.1. Methoxypoly(ethylene glycol)-*b*-poly(L-glutamic acid)[9] PEG-*b*-PGA

Mp 156–159 °C; $^1$H NMR: $\delta$ 1.98 (m, $CH_2$, 64H); 3.33 (s, $CH_3O$, 3H); 3.43 (m, O–$CH_2CH_2$, 440H), 4.09 (m, CH, 16H); 8.21 (m, NH, 16H), 12.13 (bs, COOH, 16H) FT-IR: $\nu$/$cm^{-1}$ 3290, 2880, 1729, 1710, 1652, 1548, 1466, 1453, 1413, 1359, 1342, 1279, 1241, 1147, 1104, 1099, 1060, 962, 946, 842, 704, 607, 529, 509, 480, 412, 401; $M_w/M_n$ = 1.28. Anal. Calcd for $C_{301}H_{557}N_{17}O_{158}$ ($M$ = 6935 g $mol^{-1}$) C, 52.02; H, 8.03; N, 3.43; Found: C, 51.83; H, 7.89; N, 3.64.

#### 4.2.2. Methoxypoly(ethylene glycol)-*b*-poly(L-glutamic acid) copper salt PEG-*b*-PG-Cu

To a solution of PEG-*b*-PGA (693 mg; 0.1 mmol) in redistilled water (30 mL) was added $CuCO_3$ (248 mg; 2 mmol). After 24 h of intensive mixing, the excess $CuCO_3$ was removed by centrifuge (3000 rpm; 30 min). The salt was isolated by lyophilization (720 mg, 97%). FT-IR (KBr): $\nu$/$cm^{-1}$ 3292, 2876, 1730, 1651, 1542, 1466, 1409, 1359, 1341, 1279, 1241, 1144, 1099, 1060, 961, 946, 841, 818, 518, 509, 443, 426, 410; Anal. Calcd for $C_{301}H_{541}N_{17}O_{158}Cu_8$ ($M$ = 7428 g $mol^{-1}$) C, 52.02; H, 8.03; N, 3.43; Cu 6.85; Found: C, 51.83; H, 7.71; N, 3.70; Cu, 6.92.

#### 4.2.3. PEG-*b*-PG-CuL-1 or PEG-*b*-PG-CuL-2

To a solution of PEG-*b*-PG-Cu (50 mg; 7 μmol) in anhydrous ethanol (5 mL) was added a solution of L-1 or L-2 (12.2 mg; 0.023 mmol) in ethanol (5 mL). After 24 h, ethanol was removed by distillation and the product was dried under vacuum (62 mg; 99%) FT-IR (KBr): $\nu$/$cm^{-1}$ 3293, 2873, 2358, 1716, 1652, 1608, 1544, 1466, 1402, 1359, 1341, 1279, 1241, 1144, 1099, 1060, 961, 947, 841, 765, 718, 571, 527, 519, 509, 461, 429, 409, 404. Anal. Calcd for $C_{397}H_{677}N_{41}O_{166}Cu_8$ ($M$ = 9180 g $mol^{-1}$) C, 51.90; H, 7.37; N, 6.25; Cu, 5.55; Found: C, 52.23; H, 7.62; N, 6.36; Cu, 5.77.

### 4.3. General procedure for the asymmetric Henry reaction

Complex PEG-*b*-PG-CuL-1 or PEG-*b*-PG-CuL-2 (55 mg, 6 μmol) 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 48 h. The solvents were removed under reduced pressure, after which diethyl ether was added. The catalyst was isolated by centrifugation (3000 rpm; 30 min) and the crude catalyst was washed by diethyl ether (3 × 2 mL). The crude product was isolated after evaporation of the combined 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 all of the enantiomers of the nitroalcohols were in accordance with the literature.[1n]

## Acknowledgement

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