Tetrahedron: *Asymmetry* xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

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

Polystyrene supported benzoylthiourea–pyrrolidine organocatalyst for the enantioselective Michael addition

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ARTICLE INFO

Article history:
Received 31 May 2016
Accepted 22 June 2016
Available online xxxx

ABSTRACT

Herein the preparation of a swellable pearl-like copolymer of styrene with anchored (*S*)-1-benzoyl-3-(pyrrolidine-2-ylmethyl)thiourea (20–600 μm) and its application as a recyclable organocatalyst for the Michael addition of ketones to functionalized β-nitrostyrenes is described. The rate of the reaction taking place in the matrix of the swellable polymeric catalyst was comparable with the reaction rate in homogeneous medium. The corresponding functionalized 4-nitroketones were formed quantitatively with the enantiomeric excesses up to 98% ee. After a fivefold recycling of the catalyst, no decrease in the yield was detected, but the enantioselectivity was slightly lowered (95 → 88% ee).

1. Introduction

Asymmetric organocatalysis represents one of the most intensively developing branches of organic synthesis.[1] The present interest in this type of catalysis is predominantly derived from the fact that it enables the replacement of the enantioselective catalysts based on complexes of heavy metals, which often are very toxic.[2] Other problems associated with catalyzed reactions include the necessity of separation of the product from the catalyst, and the repeated use of homogeneous catalysts that often tends to be impossible or highly demanding economically and technologically. Thus, the used catalysts become components of potentially dangerous waste materials, which have to be further processed or disposed of.[2] From the point of view of sustainable technologies, it is advantageous to immobilize homogeneous catalysts by anchoring then onto carriers,[3] e.g., polymers.[4] A considerable advantage of polymer-supported organocatalysts lies not only in the possibility of their easy separation and recycling, but also in their possible application to continuous-flow enantioselective procedures.[5]

A method, that is very often employed for the immobilization of a catalyst, is post-modification, where the organocatalyst is anchored onto a commercially available reactive polymer.[4] Another method for immobilization is copolymerization, where the organocatalyst represents one of the monomers, which is incorporated into the polymer network during polymerization.[4b,c] A recently published paper[4c] describes the procedure, in which a functionalized thiourea simultaneously carrying an L-valine and styrene fragment, was copolymerized with styrene and the obtained polymer was successfully tested as a highly efficient recyclable organocatalyst for enantioselective aza-Henry and Michael additions.[4c] The organocatalysis itself utilizes various types of intermolecular interactions of the organocatalyst with the reactants.[1] For organocatalysis using molecules such as thiourea-pyrrolidine **1**, a bifunctional type of catalysis takes place. This process is based on the 'enamine' activation of the donor in combination with advantageous spatial orientation and activation of the acceptor due to the hydrogen bond of the thiourea fragment[1,6] (Fig. 1). Previous publications[6] describe the successful application of benzoylthiourea-pyrrolidine catalysts for enantioselective Michael addition reactions, which provided a number of important 1,4-difunctional molecules, that could be used, e.g., as advanced intermediates in syntheses of biologically active compounds.[6] Herein the preparation of a heterogeneous recyclable variant of this catalyst, and testing its catalytic activity in asymmetric Michael addition reactions, as well as investigating the possibility of its recycling is described.

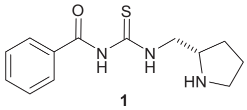

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Figure 1. Structure of organocatalyst thiourea-pyrrolidine **1**.[6]

2. Results and discussion

In addition to the choice of the organocatalyst itself, a key decision also lies in the selection of a suitable polymeric carrier.[3,4] The polymeric carriers that proved successful were the network

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http://dx.doi.org/10.1016/j.tetasy.2016.06.015
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copolymers of styrene, which are distinguished by a high degree of swelling (Merrifield resin™, JandaJel resin™). However, the copolymers of styrene containing carboxylic functional groups are not commonly commercially available. Therefore, we prepared our own swelling pearl-like copolymer of styrene **2**. The synthesis of copolymer **2** made use of a suspension copolymerization of styrene with 2-chloroethyl 4-vinylbenzoate with application of tetra(ethyleneglycol)-bis(4-vinylbenzyl)ether as the crosslinker (2%)[7] (Scheme 1). The quantitative content of the carboxylic groups in the copolymer was simply determined on the basis of the determination of the chlorine content coming from incorporated 2-chloroethyl 4-vinylbenzoate. The subsequent reaction step was hydrolysis of the ester group, which gave copolymer **3**. The carboxylic group was transformed into carboxylic acid chloride group, which upon reaction with potassium thiocyanate gave acylisothiocyanate. The subsequent reaction of (*S*)-2-(aminomethyl)-1-(*t*-butoxycarbonyl)pyrrolidine with acylisothiocyanate gave copolymer **4** with a covalently anchored functionalized thiourea. The protecting *t*-butyloxycarbonyl group was removed by reaction with trifluoroacetic acid, which gave the heterogeneous organocatalyst—pearl-like copolymer **5** (Scheme 1).

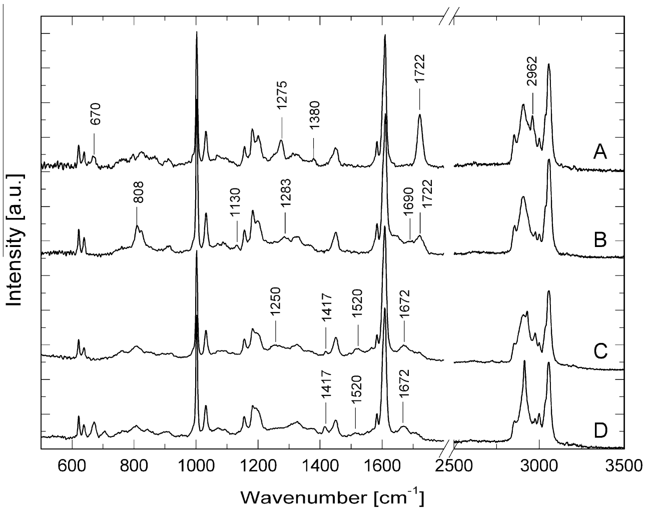
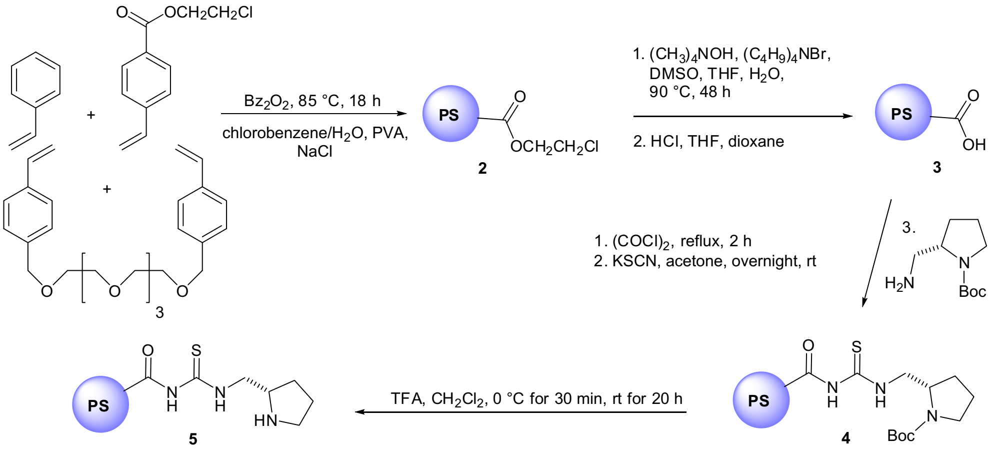


Figure 2. Raman spectra of copolymers: **2** (A), **3** (B), **4** (C) and **5** (D).

The synthesized copolymers **2**–**5** were characterized by Raman spectroscopy (Fig. 2). The Raman spectrum of copolymer **2** (A) exhibits the following bands: 2962 cm^{-1} (—CH_2Cl symmetric vibrations), 1722 cm^{-1} (C═O ester), 1380 cm^{-1} (—CH_2 wagging vibrations of CH_2CH_2Cl), 1275 cm^{-1} (—C—O—C— stretching vibration or —CH_2Cl wagging vibrations) and 670 cm^{-1} (—C—Cl stretching vibration).[8a] The spectrum of copolymer **3** (B) contains the following signals: 1722 cm^{-1} (C═O free carboxyl groups),[8b,c] 1690 cm^{-1} (C═O hydrogen-bonded carboxyl groups),[8b,c] 1283 cm^{-1} (C—O stretching vibration), 1130 cm^{-1} (O—H in-plane bending vibration),[8d] 808 cm^{-1} and 825 cm^{-1} (ring deformation along with the O—C—OH in-plane scissoring).[8d] Furthermore, the spectrum of copolymer **4** (C) shows the following signals: 1672 cm^{-1} (C═O amide I),[8a,e] 1520 cm^{-1} (NH amide II),[8a,e] 1417 cm^{-1} (C—S asymmetric vibration,[8f] 1250 cm^{-1} (—$C(CH_3)_3$ skeletal vibration or/and —C—O—C— stretching vibration).[8a,e] The spectrum of copolymer **5** (D): 1672 cm^{-1} (C═O amide I), 1520 cm^{-1} (NH amide II), 1417 cm^{-1} (C—S asymmetric vibration) (Fig. 2). The hydrolysis of the ester (**2** → **3**) can be proved by the disappearance of the bands at 670 cm^{-1}, and 2962 cm^{-1} and a decrease in intensity of the band at ~1275 cm^{-1} belonging to vibrations of C—Cl, —CH_2Cl and —CH_2CH_2Cl, when the intensity of band at 1722 cm^{-1} is decreased; at the same time, a weak band appears at 1690 cm^{-1} (—COOH). In copolymer **3**, new bands appear at 1130 cm^{-1} and 810 cm^{-1} and 825 cm^{-1}, which belong to the vibrations of the structural units of the carboxylic acid functional groups O—H and O—C—OH. After the reaction of **3** → **4**, all the above mentioned bands disappear, and the formation of bands at 1672 cm^{-1}, 1520 cm^{-1} and 1417 cm^{-1} can be detected, which confirms the incorporation of thiourea structural unit. The band at 1417 cm^{-1} belongs to C—S vibrations of a single bond rather than of a double bond. With high probability, the broad band at 1250 cm^{-1} corresponds to the vibrations of both —$C(CH_3)_3$ and —COC— in the protecting Boc group attached to pyrrolidine. The removal of protecting group (reaction **4** → **5**) was connected with the disappearance of the band at 1250 cm^{-1}.

The reaction sequence **2** → **5** was also monitored by means of microanalysis. The chlorine content found in copolymer **2** was ~1 mmol g^{-1}, which corresponds to the content of carboxylic acid groups in copolymer **3**, because hydrolysis of the ester had proceeded quantitatively (<0.3% Cl). The content of nitrogen and sulfur in both copolymers **4** and **5** was ~3 mmol g^{-1} and ~1 mmol g^{-1}, respectively, which corresponds to the ratio of these atoms in a bonded thiourea—pyrrolidine molecule (1 mmol g^{-1}). Furthermore, the polymeric organocatalyst **5** was characterized by means of ^{13}C CP/MAS NMR (cross-polarization magic angle spinning) spectroscopy[9] (Fig. 3). The values of the signals in the spectrum (Fig. 3) can be assigned as follows: 181.2 ppm (C═S, thiourea); 169.2 ppm (C═O); 147.1 ppm (quaternary carbon of benzene ring);



Scheme 1. Preparation of copolymer **2** by suspension polymerization with subsequent transformation giving copolymers **3**–**5**.

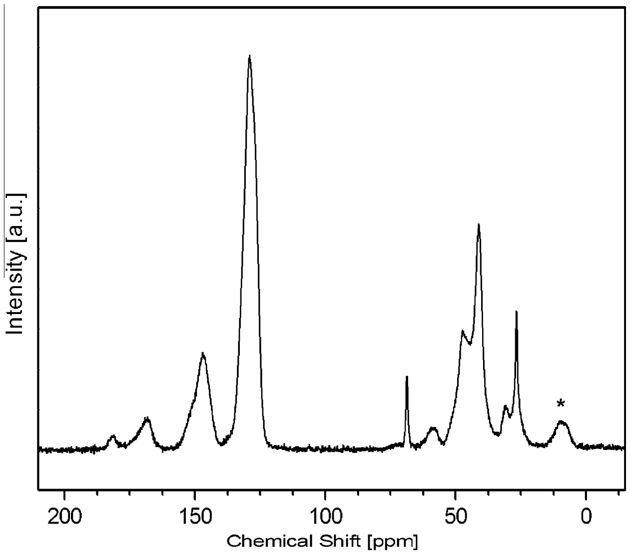


Figure 3. ^{13}C CP/MAS NMR spectra of polymeric organocatalyst (copolymer **5**), spinning speed was 20 kHz, spinning side bands are indicated by asterisk (*).

129.1 ppm (carbon atoms CH and those of benzene ring); 68.8 ppm (a relatively sharp signal typical of the arrangement —O—CH$_2$— in crosslinker); 59–30 ppm (broad signals of carbon atoms CH and CH$_2$ of polymeric chain); 26.8 ppm and 23.6 ppm (carbon atoms of pyrrolidine fragment).[9] The size of prepared spheres was determined by means of optical and electron microscopy, and it was in the range of 20–600 μm (Fig. 4).

The polymeric organocatalyst **5** was tested in the enantioselective Michael addition reaction of cyclohexanone and β-nitrostyrene (Table 1). First, the reaction was studied in cyclohexanone as the solvent, and the effect of the temperature and of the presence of an additive,[6a] i.e., 4-toluic acid, upon the reaction stereoselectivity was evaluated. Without an additional solvent, the reaction took place in quantitative yields both at room temperature and at 10 °C in 2 days (entries 1, 2). However, lowering the temperature led to a significant increase in enantioselectivity: from 91% ee to 98% ee (Table 1, entries 1 vs 2). In contrast to the results of previous work,[6a] the addition of 4-toluic acid had no effect on the reaction yield and stereoselectivity (Table 1, entries 2 vs 3). Moreover, the reaction was tested in different solvents (CH$_2$Cl$_2$, THF, toluene). Table 1 shows that carrying out of the reaction in a solvent did not affect the overall yield of reaction, but in the case of CH$_2$Cl$_2$ and THF, a

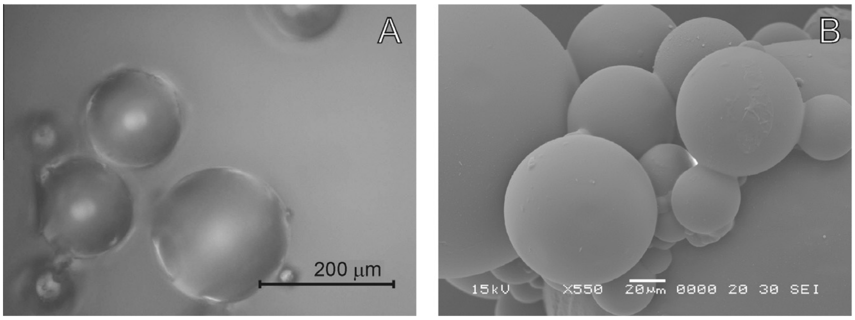
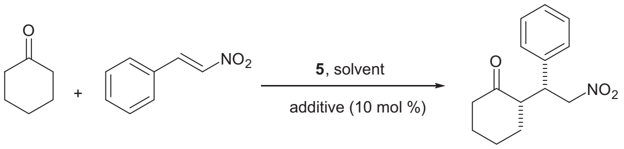


Figure 4. Microscopic (A) and SEM (B) pictures of the prepared pearl-like copolymer organocatalyst **5**.

Table 1
Effects of solvents, temperature and additive on reaction of cyclohexanone with β-nitrostyrene



Entry	Solvent	Catalyst [mol %]	Time [d]	Temp. [°C]	Additive[a]	Yield [%]	*dr* (*anti*/*syn*)[b]	*ee* (*syn*)[c] [%]
1	Neat	20	2	rt	–	>99	5:95	91
2	Neat	20	2	10	–	>99	5:95	98
3	Neat	20	2	10	4-TA	>99	4:96	98
4	CH$_2$Cl$_2$	20	2	rt	–	>99	5:95	75
5	THF	20	2	rt	–	>99	5:95	63
6	Toluene	20	2	rt	–	>99	8:92	88
7	THF	20	2	rt	AA	>99	6:94	75
8	Toluene	20	4	10	–	88	5:95	98
9	Toluene	10	4	rt	–	>99	4:96	92
10	Toluene	10	4	10	–	>99	5:95	97
11	Toluene	20	2	rt	AA	92	16:84	62
12	Toluene	10	14	10	BA	78	5:95	93
13	Toluene	10	14	10	4-TA	98	5:95	94
14	Toluene	10	14	10	2-NBA	77	6:94	96
15	Toluene	10	14	10	2,4-DCBA	98	5:95	98

[a] AA: acetic acid; BA: benzoic acid; 4-TA: 4-toluic acid; 2-NBA: 2-nitrobenzoic acid; 2,4-DCBA: 2,4-dichlorobenzoic acid.
[b] Diastereomeric ratio was determined by NMR spectroscopy.
[c] Enantiomeric excess was determined by chiral HPLC.

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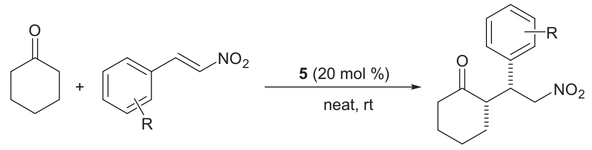
considerable decrease in the enantioselectivity was observed (Table 1, entries 4, 5). The enantioselectivity of the catalyst found in toluene was comparable (88% ee) with the enantioselectivity observed in cyclohexanone. In the case of THF, a mild improvement in enantioselectivity (from 63% ee to 75% ee) was achieved by the addition of acetic acid (Table 1, entries 5 vs 7). Hence, it can be stated that the adopted solvent has a fundamental effect upon the enantioselectivity of immobilized catalyst **5**. On the other hand, the homogeneous variant of catalyst **1**[6a] gave (from cyclohexanone and β-nitrostyrene) the reaction product with high enantiomeric excess (90–95% ee) irrespective of the solvent used or of the type of acidic additive present. In further experiments, the reaction was optimized for toluene, and the effects of the amount of catalyst adopted, reaction temperature, and additives upon the reaction were studied. The results show that lowering the amount of catalyst **5** from 20 mol % to 10 mol % had no effect on the enantiomeric excess in the product (Table 1, entry 6 vs 9). However, in order to reach quantitative course of reaction, it was necessary to prolong the reaction time to 4 days. Lowering the temperature led to higher enantioselectivity (Table 1, entry 6 vs 8). Consequently, we also studied the effect of carboxylic acids, which in the case of the original catalyst **1** was unambiguously positive, especially with regard to reaction yield.[6a] In the case of acetic acid, which increased the enantioselectivity of catalyst **5** in THF (Table 1, entry 7), it was surprising that in toluene the enantioselectivity decreased from 88% ee to 62% ee and, at the same time, the overall yield decreased from >99% to 92%, while the *anti*/*syn* ratio increased from 5:95 to 16:84 (Table 1, entry 11). The addition of functionalized benzoic acids had practically no effect on the enantiomeric excess, but the reaction was significantly decelerated. In order to achieve high yields, it was necessary to prolong the reaction time up to weeks (Table 1, entry 10 vs entries 12–15). The acid additive had a negative effect upon the enantioselectivity and catalytic activity of heterogeneous catalyst **5**, in contrast to the homogeneous variant of catalyst **1**,[6a] where the effect of the additive was positive.

We also studied the effect of substituents in the aromatic section of starting β-nitrostyrene on the reaction parameters (Table 2). The reactions were carried out at room temperature, and the starting cyclohexanone was used in excess, i.e., it served simultaneously as the reactant and solvent. The results given in Table 2 show that in comparison with unfunctionalized β-nitrostyrene, the derivatives with substituents 4-NO_2 and 4-$N(CH_3)_2$ react more slowly. In order to attain quantitative conversion, it was necessary to prolong the reaction time of 4-NO_2 derivative to 4 days (Table 2, entry 8). In the case of the 4-$N(CH_3)_2$ derivative, which achieved 92% conversion, the reaction time had to be prolonged to 14 days (Table 2, entry 3). This significant deceleration of the reaction can be explained by a mutual push–pull action of both substituents in the starting substrate. This effect causes electron delocalization and so also negatively effects the reaction centre at the α-carbon atom of β-nitrostyrene. None of the substituents in the aromatic moiety of β-nitrostyrene (as compared with unfunctionalized β-nitrostyrene) affects the reaction enantioselectivity (91–93% ee). The best values of the *anti*/*syn* ratio in product were achieved in the case of 4-OCH_3 derivative (Table 2, entry 5; 2:98).

Lastly, we studied the Michael addition reaction of different ketones with β-nitrostyrene. Table 3 summarizes the results of the addition reactions of acetone, butanone and cyclohexanone; Table 3 shows that the selectivity of reaction increases with the rigidity of the ketone molecule. The best result was achieved in the addition reaction of cyclohexanone (Table 3, entry 2). The addition reaction of butanone proceeded regioselectively with the formation of 3-methyl-5-nitro-4-phenylpentane-2-one.[10c] In all of the cases mentioned, the reaction yields were high and no double addition was observed.

We tested the possibility of recycling of polymeric organocatalyst **5** for the Michael addition reaction of cyclohexanone and β-nitrostyrene carried out without solvent in excess of cyclohexanone. The amount of catalyst was 20 mol % and the reaction time was 2 days at room temperature. Figure 5 shows, that the reaction

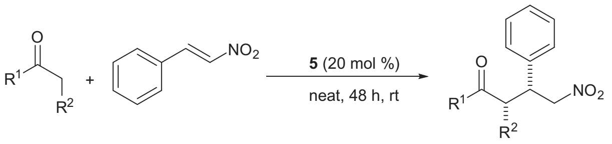
Table 2
Effect of substituents in β-nitrostyrene on reaction with cyclohexanone



Entry	R	Time [d]	Yield [%]	*dr* (*anti*/*syn*)[a]	*ee* (*syn*)[b] [%]
1	H	2	>99	5:95	91
2	4-Cl	2	>99	4:96	93
3	4-$N(CH_3)_2$	14	92	4:96	92
4	4-Br	2	>99	5:95	93
5	4-OCH_3	2	>99	2:98	91
6	4-CN	2	>99	4.96	93
7	4-CH_3	2	>99	5:95	91
8	4-NO_2	4	>99	5:95	93

[a] Diastereomeric ratio was determined by means of NMR spectroscopy.
[b] Enantiomeric excess was determined by means of chiral HPLC.[10]

Table 3
Reaction of β-nitrostyrene with different ketones



Entry	R^1	R^2	Yield [%]	*dr* (*anti*/*syn*)[a]	*ee* (*syn*)[b] [%]
1	CH_3	H	>99	–	29
2	CH_3	CH_3	>99	6:94	70
3	$(CH_2)_4$		>99	5:95	91

[a] Diastereomeric ratio was determined by means of NMR spectroscopy.
[b] Enantiomeric excess was determined by means of chiral HPLC.[10]

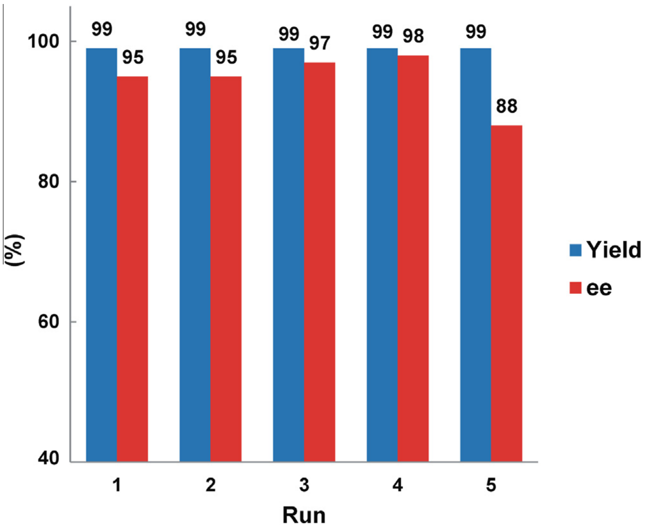


Figure 5. Proof of recoverability of organocatalyst **5** (up to five times) in the asymmetric Michael addition reaction of cyclohexanone and β-nitrostyrene.

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virtually proceeded quantitatively in all five catalytic cycles. However, in the fifth cycle, the enantioselectivity decreased to 88% ee (Fig. 5). After fivefold recycling, a partial mechanical degradation of polymeric matrix of catalyst took place, which complicated its separation from the reaction medium and reuse.

3. Conclusion

The (*S*)-1-benzoyl-3-(pyrrolidine-2-ylmethyl)thiourea covalently bonded into a polymeric matrix of a swellable pearl-like copolymer of styrene (20–600 μm) **5** was prepared by a series of reactions. The heterogeneous organocatalyst **5** prepared in this way was used for the catalysis of the Michael addition reaction of acetone, butanone and cyclohexanone with β-nitrostyrene and its derivatives. The selectivity of this addition reaction increased with an increase in the rigidity of the ketone molecule, with the best result being obtained with cyclohexanone. The most suitable reaction medium found was toluene and/or cyclohexanone itself without an added acid. Under these conditions, the enantioselectivity of immobilized catalyst **5** was comparable with the enantioselectivity of the homogeneous variant, i.e., catalyst **1**.[6a] In the case of the addition reaction of cyclohexanone, the effects of substituents in the aromatic moiety of β-nitrostyrene upon the reaction parameters were studied. The corresponding functionalized 4-nitroketones were formed quantitatively with high ee values (up to 98% ee). The possibility of recycling of heterogeneous organocatalyst **5** was also studied. In the first four catalytic cycles, the enantioselectivity of catalysts was very high (95–98% ee); only in the fifth cycle, did a partial decrease in enantioselectivity take place (95 → 88% ee). The attained chemical yields were virtually quantitative in all five cycles. After fivefold recycling, a partial mechanical degradation of polymer matrix of catalyst was observed, which probably could be prevented by placing the catalyst into a continuous-flow reactor. The prepared polymeric catalyst possesses a high application potential for the practical realization of a Michael addition reaction, and simultaneously it fulfils a number of demands placed by green and sustainable chemistry.

4. Experimental

4.1. General

Unless otherwise stated, the starting chemicals and solvents were obtained from Sigma–Aldrich or Acros Organics and used without further purification. ^{1}H NMR spectra were recorded on a Bruker Avance 400 instrument or Bruker Avance 500 instrument. Chemical shifts δ were referenced to the 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 ($\delta = 77.23$). The ^{13}C CP/MAS NMR experiments were performed at 125.613 MHz frequency for ^{13}C, equipped with a MAS probe head using 4 mm ZrO_2 rotors. A sample of glycine was used for setting the Hartmann–Hahn condition, and glycine was used as a secondary chemical shift reference ($\delta = 176.04$ ppm) from external TMS. 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 styrene-VBC-TEG was determined by means of optical microscope Nikon Eclipse LV100D with 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 top speed of scanning with the output image resolution 2560 × 1920 pix is 7.2 frames per second. At the highest resolution of the output image and using the lens with the highest magnification, the length of one pix corresponds to 0.1 microns. High-resolution mass spectra were measured on the Thermo Fisher Scientific MALDI LTQ Orbitrap instrument. The used matrices were 0.2 M solutions of 2,5-dihydroxybenzoic acid (DHB) in $MeCN/H_2O$ (95:5) or 2-[(2*E*)-3-(4-*tert*-butylphenyl)-2-methylprop-2-enylidene]malononitrile (DCTB) in MeCN. HPLC analyses were performed on Watrex HPLC instrument with UV–Vis DAD (200–800 nm) SYKAM 3240 and with chiral Daicel columns: Chiralcel OD-H, Chiralpak AS-H and Chiralpak AD-H (250 mm × 4.6 mm). The microanalyses were performed on an apparatus of FISONS Instruments, EA 1108 CHNS.

4.2. Synthesis

4.2.1. 2-Chloroethyl 4-vinylbenzoate

A mixture of 4-vinylbenzoic acid (5 g; 34 mmol), oxalyl chloride (15 mL; 175 mmol), DMF (2 drops) and $CHCl_3$ (15 mL) was refluxed for 5 h. The solvent and excess of oxalyl chloride were evaporated off and the residue was mixed with a solution of freshly distilled 2-chloroethanol (10 mL, 150 mmol) and Et_3N (16 mL, 115 mmol) in CH_2Cl_2 (15 mL). The mixture was stirred overnight at room temperature and then evaporated under reduced pressure. The crude product was purified by column chromatography (SiO_2/CH_2Cl_2, R_f 0.56). Yield: 5.5 g (78%); yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.08 (m, 2H, Ar), 7.52 (m, 2H, Ar), 8.80 (dd, 1H, $J = 10.8$ Hz; 17.6 Hz), 5.92 (dd, 1H, $J = 0.8$ Hz, 17.6 Hz), 5.45 (dd, 1H, $J = 0.8$ Hz, 10.8 Hz), 4.62 (t, 2H, $J = 5.5$ Hz), 3.87 (t, 2H, $J = 5.5$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.1, 142.5, 136.1, 130.3, 128.9, 126.4, 116.9, 64.6, 41.6; HR-MALDI-MS: calcd. for $C_{11}H_{11}ClO_2$ *m*/*z* 211.05203 ($[M+H]^+$), found 211.05222.

4.2.2. Preparation of pearl-like copolymer 2 (suspension polymerization)

The preparation of pearl-like copolymer by suspension polymerization was performed in accordance with the literature in a defined apparatus of 500 mL.[7] The vessel was charged with a solution of NaCl (15 g) and poly(vinyl alcohol) (88% hydrolyzed polymer; M = 85–124 kDa) (1.34 g) in water (400 mL), followed by a solution of benzoyl peroxide (410 mg; 1.64 mmol), 2-chloroethyl 4-vinylbenzoate (5.52 g; 26.2 mmol), styrene (8.2 g; 78.8 mmol), and tetra(ethylene glycol)-bis(4-vinylbenzyl)ether[7] (250 mg; 0.66 mmol) in chlorobenzene (6 mL). The stirrer was adjusted at a rate of 500 rpm, and the temperature of the reaction mixture was increased to 85 °C for 30 min. The obtained suspension of the spherical particles of the organic phase was continuously stirred and kept at 85 °C for 18 h. After cooling, the obtained pearl-like copolymer was collected by filtration and washed with water (3 × 100 mL), MeOH (3 × 100 mL), THF (3 × 100 mL) and CH_2Cl_2 (3 × 100 mL). The polymer was then extracted in a Soxhlet extractor for 48 h with THF. The prepared pearl-like polymer (20–600 μm) was dried under reduced pressure at the temperature of 40 °C. The yield was 7.9 g of polymer with elemental composition: C, 75.76; H, 6.82; Cl, 3.74; FT-Raman: 620 (m), 637 (m), 670 (w), 761 (w), 796 (w), 823 (w), 867 (w), 908 (w), 1001 (s), 1032 (m), 1068 (w), 1095 (w), 1155 (m), 1182(m), 1200 (m), 1226 (w), 1250 (sh), 1275 (m), 1323 (w), 1380 (w), 1450 (m), 1584 (m), 1609 (s), 1722 (s), 2853 (sh), 2908 (s), 2962 (s), 3001 (m), 3040 (sh), 3056 (s).

4.2.3. Preparation of pearl-like copolymer 3 (polystyrene carboxylic acid)

A mixture of polymer **3** (2.5 g), $Me_4N^+OH^- \cdot 5H_2O$ (5 g; 27.5 mmol), $Bu_4N^+Br^-$ (5 mg; 15 μmol), DMSO (100 mL), water (30 mL) and THF (40 mL) was heated at 90 °C for 48 h. After

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cooling, the polymer was collected by filtration and washed with water (2 × 100 mL), THF (2 × 100 mL) and ethanol (2 × 100 mL). The acidification was performed by stirring the crude polymer in a mixture of HCl (36%; 20 mL), water (20 mL), dioxane (40 mL) and THF (20 mL) at room temperature for 2 h. After filtration, the polymer was washed with water (50 mL) and THF (3 × 100 mL) and dried under reduced pressure at 40 °C. Yield: 1.4 g; elemental composition: C, 81.95; H, 6.97; Cl <0.3%; FT-Raman: 620 (m), 637 (m), 808 (m), 825 (m), 912 (w), 1001 (s), 1032 (m), 1091 (w), 1129 (w), 1155 (w), 1182 (m), 1200 (sh), 1288 (m), 1323 (w), 1364 (sh), 1450 (m), 1584 (m), 1609 (s), 1654 (w), 1690 (w), 1722 (m), 2853 (sh), 2908 (s), 2979 (w), 3001 (m), 3040 (sh), 3056 (s).

4.2.4. Preparation of pearl-like copolymer 4 (polystyrene Boc-protected pyrrolidine-thiourea)

The suspension of polymer **3** (1 g), oxalyl chloride (10 mL; 116 mmol), CH_2Cl_2 (20 mL) and DMF (3 drops) was refluxed for 2 h and then, stirred at room temperature overnight. The crude polymer-acylchloride was collected by filtration and washed with dry CH_2Cl_2 (2 × 50 mL). The polymer-acylchloride was stirred in a solution of KSCN (1 g; 10 mmol) in acetone (20 mL) at room temperature overnight. After filtration, the polymer was washed with acetone (3 × 50 mL) and DMSO (3 × 50 mL). Next, the suspension of polymer-isothiocyanate in a solution of (*S*)-2-(aminomethyl)-1-(*tert*-butoxycarbonyl)pyrrolidine (350 mg; 1.75 mmol) was stirred at room temperature for 3 days. After filtration, the polymer was washed with DMSO (3 × 50 mL), CH_2Cl_2 (3 × 50 mL), MeOH (3 × 50 mL), acetone (3 × 50 mL) and THF (3 × 50 mL) and dried under reduced pressure at 40 °C. Yield: 1.2 g; elemental composition: C, 76.39; H, 7.25; N, 4.18; S, 3.37; FT-Raman: 620 (m), 637 (m), 761 (w), 807 (w), 855 (sh), 918 (w), 1001 (s), 1032 (m), 1083 (br), 1155 (m), 1195 (sh), 1250 (br), 1325 (w), 1365 (sh), 1419 (w), 1450 (m), 1520 (w), 1584 (m), 1609 (s), 1671 (m), 1720 (w), 2853 (sh), 2910 (sh), 2929 (s), 2979 (w), 3001 (m), 3040 (sh), 3057 (s).

4.2.5. Preparation of pearl-like copolymer 5 (organocatalyst)

To a stirred suspension of polymer **4** (1 g) cooled at 0 °C in CH_2Cl_2 (10 mL) was added trifluoroacetic acid (6 mL) over 5 min. The mixture was then stirred for 2 h at 0 °C and then for 20 h at room temperature. After filtration, the polymer was washed with CH_2Cl_2 (3 × 50 mL), THF (3 × 50 mL), NH_3(aq) (10%; 3 × 50 mL), water (3 × 50 mL), THF (3 × 50 mL), DMSO (3 × 50 mL) and THF (3 × 50 mL) and dried under reduced pressure at 40 °C. Yield: 1 g; elemental composition: C, 72.76; H, 6.99; N, 4.19; S, 3.53; FT-Raman: 620 (m), 637 (m), 670 (m), 705 (w), 762 (w), 807 (w), 849 (sh), 905 (w), 1001 (s), 1032 (m), 1069 (w), 1094 (w), 1155 (m), 1200 (sh), 1250 (br), 1325 (w), 1379 (sh), 1417 (w), 1450 (m), 1520 (w), 1584 (m), 1609 (s), 1671 (m), 1720 (w), 2853 (sh), 2915 (s), 2978 (w), 3001 (m), 3040 (sh), 3057 (s). ^{13}C CP/MAS NMR: δ 181.2, 169.2, 147.1, 129.1, 68.8, 59.4, 47.5, 31.0, 26.8, 23.6.

4.3. General procedure for the asymmetric Michael addition of ketones to β-nitrostyrenes

A suspension of catalyst **5** (0.34 mmol, or 0.167 mmol) and dry ketone (1.67 mmol) in dry solvent (1.5 mL) was stirred for 15 min at room temperature. Next, the additive (0.34 mmol, or 0.167 mmol) was added and the reaction mixture was stirred for 15 min. To the resulting mixture was added β-nitrostyrene (0.34 mmol) at an appropriate temperature. After the reaction was complete (monitored by TLC; SiO_2, AcOEt/petroleum ether 1:2) the product was isolated by evaporation after filtration of the catalyst.

Acknowledgment

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

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