DE GRUYTER

Chemical Papers
DOI: 10.1515/chempap-2015-0232

ORIGINAL PAPER

Hydrogel supported chiral imidazolidinone for organocatalytic enantioselective reduction of olefins in water

Alessandro Sacchetti*, Filippo Rossi*, Arianna Rossetti, Roberto Pesa, Emanuele Mauri

Department of Chemistry, Materials and Chemical Engineering "Giulio Natta", Politecnico di Milano, via Mancinelli 7, 20131 Milan, Italy

Received 15 July 2015; Revised 15 September 2015; Accepted 22 September 2015

Chiral products play an important role particularly in the field of medicinal chemistry, where it is known that enantiomers often have very different biological properties and effects. One of the most powerful tool to obtain a product as a single enantiomer is asymmetric catalysis. Recently, organocatalysis, i.e. the use of small organic molecules to catalyze enantioselective transformations, has emerged as a prominent field in asymmetric synthesis. In this work, the use of hydrogels as a support for a chiral imidazolidinone organocatalyst (MacMillan catalyst) and its application in the reduction of activated olefins mediated by the Hantzsch ester is reported for the first time. Results showed a good activity of hydrogels in respect to both yield and enantioselection.

Keywords: hydrogels, organocatalysis, supported catalysts, MacMillan catalyst

Introduction

Organocatalysis has been widely recognized as a new emerging and promising field in asymmetric organic synthesis (Dalko & Moisan, 2001, 2004; Dondoni & Massi, 2008; Seayad & List, 2005). The process relies on the use of small chiral organic molecules able to efficiently catalyze many different asymmetric organic transformations, usually with high yields and enantiomeric excesses. The mechanisms of action of these catalysts have been in many cases elucidated and two main modes of activation have been described considering the presence of covalent or non-covalent interactions between the catalyst and the reactant. Catalysts can be easily produced by conventional organic synthesis on a multi-gram scale and different lead molecule derivatives can be prepared allowing thus efficient tuning of their activity. The possibility to use organic molecules as catalysts offers a number of advantages. For instance, such catalysts are very stable, easy to use and no particular reaction conditions are required. As the main advantage, in organocatalysis the use of transition metal complexes, which are typically more difficult to prepare and to handle, is avoided. On the other hand, in comparison to the organometallic catalysts, organocatalysts suffer from lower turn over frequency (TOF) and turn over number (TON) since, in many cases, the catalyst concentration of up to 20–30 % mole has to be employed. This also requires the use of a purification step, in order to separate and recover the catalysts from the products. To avoid this problem, many studies on the use of supported organocatalysts and their application in the flow chemistry have been reported (Atodiresei et al., 2015; Itsuno & Hassan, 2014; Munirathinam et al., 2015). Other key aspects of this process are the requirement for an organic solvent to make the catalysts soluble and the employment of water organocatalytic transformation, which is still under-explored (Blackmond et al., 2007; Davoodnia et al., 2011; Hayashi, 2006). As a consequence of these considerations, we decided to explore the possibility of using hydrogels as recoverable supports for organocatalysis in water. Hydrogels are cross-linked hydrophilic polymeric net-

*Corresponding author, e-mail: alessandro.sacchetti@polimi.it, filippo.rossi@polimi.it

works swollen in aqueous media, typically soft and elastic due to their thermodynamic compatibility with water (Annabi et al., 2014; Slaughter et al., 2009). Cross-links and interconnections that bring polymer chains together can be formed by physical entanglements leading to physical hydrogels or by covalent bonds leading to chemical hydrogels.

In this work, preliminary investigations on the use of organic hydrogels as a support for an imidazolidinone MacMillan catalyst (Lelais & MacMillan, 2006; MacMillan, 2008) to be employed in the reduction of olefins (Ouellet et al., 2005, 2007) in water are presented. The biocatalyzed version of this reaction has been already thoroughly investigated by our research group (Brenna, et al., 2012a, 2012b, 2012c, 2013a, 2013b, 2015). Here, the possibility of using a hydrogel previously described by our group (Sacchetti et al., 2014; Santoro et al., 2011) and obtained by means of a synthesis from statistical block polycondensation between agarose, poly(acrylic acid) (PAA), and polyethylene glycol (PEG) was explored. Among the PEG-supported versions of both organic and metal-based catalysts (Danelli et al., 2003; Puglisi et al., 2004), our catalyst was first linked with PEG 2000 via a click azide-alkyne reaction and the obtained product was used to prepare the gel. As an alternative, an MeOPEG 5000-supported catalyst was prepared in the same manner and then incorporated in the polymeric network during its synthesis.

Experimental

Materials and methods

All chemicals were purchased from Sigma–Aldrich (Deisenhofen, Germany) and they were used as received. Solvents (methanol (MeOH), ethyl acetate (EtOAc), acetonitrile (ACN), dimethylformamide (DMF), diethyl ether (Et_2O), tetrahydrofuran (THF), dichloromethane (DCM), chloroform, acetone) were of laboratory grade. Synthesized compounds were characterized by ^{1}H and ^{13}C NMR spectra recorded on a Bruker AC (400 MHz) spectrometer using deuterated chloroform ($CDCl_3$) or dimethyl sulfoxide (DMSO-d_6) as solvents and chemical shifts were reported as δ with respect to TMS as the internal standard. FTIR spectra of the hydrogel samples, after being dipped in excess of solvent for 24 h, freeze-dried and laminated with KBr, were recorded on a Thermo Nexus 6700 spectrometer coupled to a Thermo Nicolet Continuum microscope equipped with a 15× Reflachromat Cassegrain objective at the resolution of 4 cm^{-1}. Environmental scanning electron microscopy (E/SEM) analysis was performed on gold sputtered samples at 10 kV with Evo 50 EP Instrumentation (Zeiss, Jena, Germany). To preserve the actual morphology of the hydrogel under complete swelling, freeze-drying was applied to remove all the liquid phase by sublimation. Because of the low operating values of temperature and pressure, the polymer chains were expected to retain the same conformation they had in wet conditions (Rossi et al., 2012). A comparative evaluation of the superficial and internal morphology of the investigated samples was carried out.

Synthesis of (5S)-3-butyl-5-[(4-hydroxyphenyl) methyl]-2,2-dimethylimidazolidin-4-one (I)

Thionyl chloride (10 mL, 139 mmol) was added drop-wise to a stirred solution of L-tyrosine (10.0 g, 55.25 mmol) in dry MeOH (100 mL) at 0 ℃ and the reaction mixture was stirred at ambient temperature for 24 h. Volatiles were removed under diminished pressure to afford L-tyrosine methyl ester hydrochloride (IUPAC name: methyl (2*S*)-2-amino-3-(4-hydroxyphenyl)propanoate hydrochloride) as a white solid (11.73 g, 91.6 % yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.49 (brs, 1H), 8.66 (brs, 3H), 7.0 (d, $J = 8.4$ Hz, 2H), 6.76–6.68 (m, 2H), 4.19–4.06 (m, 1H), 3.65 (s, 3H), 3.11 (dd, $J = 14.1$ Hz, $J = 5.7$ Hz, 1H), 3.02–2.95 (dd, $J = 14.1$ Hz, $J = 7.1$, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 35.08, 52.51, 53.47, 115.43, 124.34, 130.36, 156.70, 169.44.

L-Tyrosine methyl ester hydrochloride (11.73 g, 50.6 mmol) (see above) was added to 1-butylamine (35 mL, 354.5 mmol) and the resulting mixture was stirred at ambient temperature for 48 h. The excess of 1-butylamine was removed under diminished pressure to afford the corresponding *N*-butyltyrosyl amide (IUPAC name: (2*S*)-2-amino-*N*-butyl-3-(4-hydroxyphenyl)propanamide) as a white solid (10 g, 85 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.93 (t, $J = 5.8$ Hz, 1H), 6.26 (d, $J = 8.3$ Hz, 2H), 5.99 (d, $J = 8.3$ Hz, 2H), 2.70 (dd, $J = 8.3$ Hz, $J = 4.8$ Hz, 1H), 2.40 (q, $J = 6.7$ Hz, 2H), 2.20 (dd, $J = 13.6$ Hz, $J = 4.8$ Hz, 1H), 2.00 (t, $J = 7.4$ Hz, 2H), 1.85 (dd, $J = 13.6$ Hz, $J = 8.3$ Hz, 1H), 0.81 (quint, $J = 7.4$ Hz, 2H), 0.17 (t, $J = 7.2$ Hz, 3H).

N-Butyltyrosyl amide (10 g, 36.7 mmol) (see above) dissolved in a mixture of dry MeOH (80 mL) and dry acetone (15 mL), was stirred at 90 ℃ for 24 h, cooled to ambient temperature and then concentrated under diminished pressure to afford crude product *I*. This was purified on a column of silica gel using hexane/EtOAc ($\varphi_r = 3 : 7$) as the eluent to isolate *I* as a white solid (7.3 g, 72 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.09–7.01 (m 2H), 6.79–6.69 (m, 2H), 3.74 (t, $J = 5.2$ Hz, 1H), 3.31 (ddd, $J = 13.9$ Hz, $J = 9.5$ Hz, $J = 6.1$ Hz, 1H), 3.10–2.96 (m, 2H), 1.34–1.22 (m, 2H), 1.28 (s, 3H), 1.18 (s, 3H), 0.91 (t, $J = 7.3$ Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.96, 20.56, 26.52, 28.11, 31.58, 35.88, 40.63, 59.14, 76.55, 115.87, 127.81, 130.95, 155.63, 174.32. These data are in accordance with those already published (Shi et al., 2011).

Synthesis of (5S)-5-{[(4-(2-azidoethoxy) phenyl]methyl}-3-butyl-2,2-dimethylimidazolidin-4-one (II)

A mixture of *I* (1 g, 3.6 mmol), 1,3-dibromopropane (732 mg, 3.6 mmol), NaH (173 mg, 7.2 mmol), and tetrabutylammonium bromide (0.1 g) in ACN (40 mL) was vigorously stirred under reflux for 10 h. After cooling and solvent evaporation, the resulting foam was dissolved in chloroform (50 mL) and washed with water (3 × 200 mL). The organic layer was dried with anhydrous sodium sulfate and concentrated under diminished pressure. The crude product was purified by silica gel column chromatography using hexane/EtOAc ($\varphi_r = 6:4$) as the eluent affording the desired 3-bromopropyl derivative (820 mg, 57 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.36 (dd, $J = 8.5$ Hz, 4.0 Hz, 2H), 6.87 (dd, $J = 8.5$ Hz, 4.6 Hz, 2H), 4.31 (s, 1H), 4.05 (t, $J = 5.8$ Hz, 1H), 3.43 (d, $J = 15.3$ Hz, 1H), 3.10–2.93 (m, 1H), 2.34–2.18 (m, 1H), 2.16 (d, $J = 0.5$ Hz, 1H), 1.68 (s, 3H), 1.50 (s, 8H), 0.97–0.84 (m, 3H).

Sodium azide (270 mg, 4.1 mmol) was added to a solution of a 3-bromopropyl derivative (800 mg, 2.02 mmol) (see above) in DMF (15 mL) and the mixture was stirred and heated at 100 ℃ for 10 h. After cooling, water (20 mL) and Et_2O (20 mL) were added and the organic phase was separated, washed with brine solution (3 × 20 mL), dried with sodium sulfate and concentrated under diminished pressure to obtain pure *II* (550 mg, 76 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.36 (dd, $J = 8.5$ Hz, 4.0 Hz, 2H), 6.87 (dd, $J = 8.5$ Hz, 4.6 Hz, 2H), 4.31 (s, 1H), 4.05 (t, $J = 5.8$ Hz, 1H), 3.12 (d, $J = 15.3$ Hz, 1H), 3.10–2.93 (m, 1H), 2.34–2.18 (m, 1H), 2.16 (d, $J = 0.5$ Hz, 1H), 1.68 (s, 3H), 1.50 (s, 8H), 0.97–0.84 (m, 3H).

Synthesis of (5S)-3-butyl-2,2-dimethyl-5-{[(4-(prop-2-yn-1-yloxy)phenyl]methyl)imidazolidin-4-one (III)

A mixture of potassium carbonate (1.5 g, 10.8 mmol), propargyl bromide (80 % solution in toluene, 0.52 g, 4.34 mmol) and *I* (1 g, 3.62 mmol) in DMF (20 mL) was stirred at ambient temperature for 48 h. Subsequently, saturated ammonium chloride solution (30 mL) was added and the reaction mixture was stirred for 2 h. EtOAc (30 mL) was then added and the stirring continued for 30 min. The organic phase was separated and the aqueous phase was extracted with EtOAc (2 × 20 mL). The combined organic layers were stirred with a brine solution for 1 h, separated and dried with anhydrous sodium sulfate. The crude product was purified by silica gel column chromatography using hexane/EtOAc ($\varphi_r = 3:7$) to afford *III* (2.5 g, 73 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.19–7.14 (m 2H), 6.91 (d, $J = 8.6$ Hz, 2H), 4.66 (d, $J = 2.4$ Hz, 2H), 3.72 (t, $J = 5.3$ Hz, 1H), 3.30 (ddd, $J = 13.8$ Hz, 9.4 Hz, 6.1 Hz, 1H), 3.04 (dd, $J = 5.3$ Hz, 2.3 Hz, 2H), 2.90 (ddd, $J = 13.8$ Hz, 9.4 Hz, 5.8 Hz, 1H), 2.50 (t, $J = 2.4$ Hz, 1H), 1.58–1.37 (m, 2H), 1.34–1.22 (m, 2H), 1.26 (s, 3H), 1.16 (s, 3H), 0.92 (t, $J = 7.3$ Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.03, 20.61, 26.76, 28.33, 31.68, 36.22, 40.54, 56.11, 59.11, 75.66, 76.30, 78.81, 115.24, 130.13, 130.95, 156.75, 174.08. These data are in accordance with those already published (Shi et al., 2011).

Synthesis of functionalized PEG 2000 (IV)

A mixture of PEG 2000 (5 g, 2.5 mmol) dissolved in anhydrous DCM (35 mL) and triethylamine (1.01 g, 10 mmol) was added to a solution of methanesulfonyl chloride (1 g, 8.75 mmol) in THF (50 mL) and the solution was stirred at 25 ℃ for 48 h under anhydrous conditions. DCM and THF were subsequently evaporated under diminished pressure; the residue was redissolved in water (100 mL) and extracted with DCM (5 × 200 mL). The combined organic phase was dried with sodium sulfate and the solvent was removed under diminished pressure. The polymer was recovered by precipitation from Et_2O, collected and dried under diminished pressure, yielding a white solid. A part of this product (1.25 g, 0.23 mmol) was dissolved in DMF (20 mL), then sodium azide (521 mg, 8.01 mmol) was added and the mixture was stirred at ambient temperature for two days followed by an addition of DCM (200 mL) and washing a mixture with brine (2 × 200 mL) and water (2 × 200 mL). The organic phase was dried with sodium sulfate, concentrated under diminished pressure followed by an addition of Et_2O to precipitate *IV*, which was collected by suction filtration and dried under diminished pressure (1 g, 71 % yield) (Hiki & Kataoka, 2007). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.46 (t, 2H), 3.63 (s, 180H).

Synthesis of functionalized monomethoxy-PEG 5000 (V)

Sodium hydride (48 mg, 2 mmol) was added to MeOPEG 5000 (5 g, 1 mmol) dissolved in anhydrous THF (35 mL) followed by the drop-wise addition of propargyl bromide (80 % solution in toluene, 0.48 g, 4 mmol) under stirring for 24 h. THF was then evaporated under diminished pressure, the residue was redissolved in water (100 mL) and extracted with DCM (5 × 200 mL). The combined organic phase was dried with sodium sulfate, filtered and the solvent was removed under diminished pressure. The polymer was recovered by precipitation from Et_2O, collected and dried under diminished pressure to yield *V* as a white solid (4.97 g, 96 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.20 (d, $J = 2.4$ Hz, 2H), 3.64 (s, 450 H), 3.37 (s, 3H), 2.42 (t, $J = 2.4$ Hz, 1H).

Synthesis of PEG 2000-catalyst polymer (VI)

Copper iodide (3 mg, 0.0158 mmol) and sodium ascorbate (3 mg, 0.0152 mmol) were added to a mixture of *IV* (2.7 g, 1.35 mmol) dissolved in water (20 mL) and *III* (424 mg, 1.35 mmol) dissolved in acetone (20 mL). Tetramethylethylenediamine (5 drops) was then added and the mixture was stirred at 50 °C for 36 h, cooled to 25 °C and extracted with DCM (3 × 20 mL). The combined organic phase was dried with anhydrous sodium sulfate and the solvent was evaporated under reduced pressure to afford solid *VI* (2.5 g, 81.5 % yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.80 (s, 1H), 7.13 (d, $J = 8.1$ Hz, 2H), 6.90 (d, $J = 8.1$ Hz, 2H), 4.52 (t, $J = 5.1$ Hz, 2H), 3.86 (t, $J = 5.1$ Hz, 2H), 3.62 (s, 183H), 3.44 (dd, $J = 5.9$ Hz, $J = 4.0$ Hz, 1H), 3.36 (t, $J = 5.1$ Hz, 1H), 3.00 (d, $J = 5.1$ Hz, 2H), 2.93 (s, 4H), 2.86 (s, 4H), 1.32–1.22 (m, 9H), 0.90 (t, $J = 7.4$ Hz, 3H).

Synthesis of MeOPEG 5000-catalyst polymer (VII)

Copper iodide (5 mg, 0.0263 mmol), sodium ascorbate (5 mg, 0.0253 mmol) and tetramethylethylenediamine (5 drops) were added to a mixture of *V* (2.1 g, 0.42 mmol) dissolved in water (15 mL) and *II* (350 mg, 1 mmol) dissolved in THF (15 mL) and the mixture was stirred at 50 °C for 36 h, cooled to 25 °C and extracted with DCM (3 × 15 mL). The combined organic phase was dried with anhydrous sodium sulfate, filtered and concentrated under reduced pressure followed by an addition of Et_2O to precipitate *VII*, which was collected by suction filtration and dried (brown solid) under diminished pressure (2.5 g, 82.5 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.57 (s, 1H), 7.13 (s, 4H), 6.86–6.81 (m, 4H), 4.55 (t, $J = 6.9$ Hz, 2H), 3.99 (dt, $J = 24.1$ Hz, $J = 5.9$ Hz, 4H), 3.81 (t, $J = 5.1$ Hz, 3H), 3.64 (s, 429H), 3.37 (s, 3H), 2.94–2.83 (m, 1H), 2.37 (d, $J = 6.4$ Hz, 1H), 2.02 (d, $J = 6.4$ Hz, 1H), 1.15 (d, $J = 5.8$ Hz, 6H).

Synthesis of hydrogels VIII and IX

PEG, both functionalized and pure, was added to Carbomer 974P dissolved in a PBS-based solution and the mixture was stirred at ambient temperature for 45 min and left to settle for 30 min. (Note: The use of two PEG types was justified by the need of a polymer acting as the organocatalyst in the reaction mixture, the role of PEG functionalized with catalyst, and a polymer able to react chemically in hydrogel scaffold formation via cross-linking with other chains to achieve adequate hydrophilicity and permeability, the role of pure PEG). A 1 M NaOH solution was then added to adjust pH to 7 and subsequently, agarose powder (1 mass %) was added. Due to its insolubility at ambient temperature, the reaction mixture was microwave-irradiated (500 W irradiated power for 20 s) and heated up to 70–80 °C to induce condensation reactions through interconnections of hydroxyl groups (reactions between carbonyl groups of Carbomer 974P and OH terminals of agarose and used PEG resulted in ester bonds formation and, consequently, in the three-dimensional matrix of the hydrogel). After electromagnetic stimulation, the solution was cooled to 55 °C, diluted with distilled water ($\varphi_r = 1 : 1$), placed in steel cylinders (150 μL each, with the cylinder diameter of 0.2 cm) and left at ambient temperature until reaching complete gelation and thermal equilibrium. Composition of the hydrogels is reported in Table 1.

Table 1. Hydrogel composition

Hydrogel components	*VIII*	*IX*
PBS/mL	9	9
Carbomer 974P/mg	50	50
PEG 2000/mg	580	580
VI/mg	100	0
VII/mg	0	100
Agarose/mg	50	50

General procedure for catalytic reaction

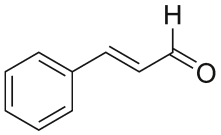
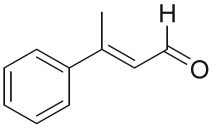
Obtained hydrogels *VIII* and *IX* were tested in catalytic reduction of aldehydes as follows: Hantzsch ester (65 mg, 0.25 mmol) was added to cinnamaldehyde (13 mg, 0.1 mmol) or β-methyl cinnamaldehyde (15 mg, 0.1 mmol) suspended in distilled water (2 mL) in a polypropylene syringe (size 10 mL) equipped with a porous polypropylene disc at the bottom (porosity 70 μm). Subsequently, the desired number of hydrogel *VIII* or *IX* tablets was added (Table 2) and the resulting suspension was shaken at ambient temperature for the indicated time (Table 2). Finally, the used tablets of gel were recovered by suction filtration of the reaction mixture through the bottom of the syringe and washed with distilled water.

Results and discussion

Starting from L-tyrosine, catalyst *I* was easily obtained by a three-step procedure (via the corresponding L-tyrosine methyl ester in the first step and *N*-butyltyrosyl amide in the second step) in a 61 % overall yield (after purification) by a procedure similar to that already published (Shi et al., 2011). Product *III* was then obtained from a reaction of *I* with propargyl bromide (an analogy with Shi et al., 2011), whereas azide *II* was prepared by a reaction of *I* with 1,3-dibromopropane followed by a treatment with sodium azide in DMF as shown in Fig. 1.

Mono azido-PEG 2000 derivative (*IV*) was synthesized via the activation of the hydroxyl group with

Table 2. Results of catalyzed reduction reactions[a]

Aldehyde	Hydrogel	Catalyst loading[b]/%	Time/h	Yield[c]/%	ee^d/%
	*VIII*	0.1	24	6	–
		0.3	24	19	–
		0.3	96	21	–
		1	24	49	–
	IX	0.1	24	8	–
		0.3	24	24	–
		0.3	96	41	–
		1	24	61	–
	*VIII*	0.1	24	6	83
		1	24	51	79
	IX	0.1	24	7	83
		1	24	64	81

a) Reactions were carried out in water with 0.1 mol of the substrate and 0.25 mol of the Hantzsch ester; *b*) mole % with respect to substrate; *c*) percentage of enantiomeric excess calculated from the GC/MS analysis of the crude product; *d*) percentage determined by chiral GC analysis.

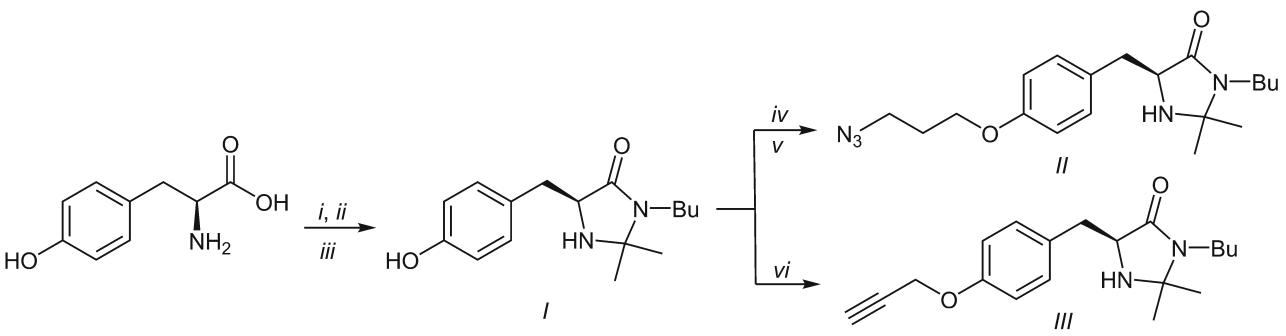


Fig. 1. Synthesis of the azido (*II*) and propargyl (*III*) catalysts. Reaction conditions: *i*) thionyl chloride, MeOH; *ii*) 1-butylamine; *iii*) MeOH, acetone, 61 % overall yield; *iv*) NaH, 1,3-dibromopropane; *v*) NaN_3, DMF, 43 % overall yield; *vi*) propargyl bromide, K_2CO_3, DMF, 73 % overall yield; Bu = 1-butyl.

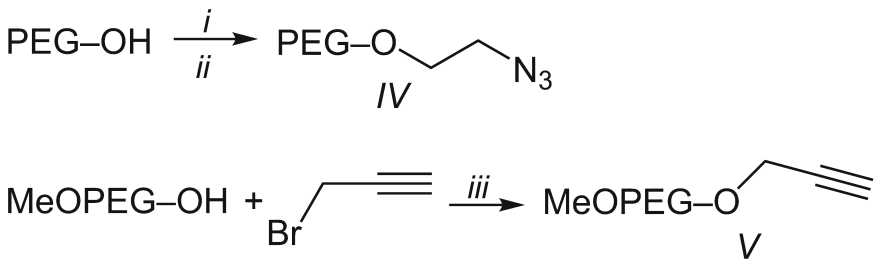


Fig. 2. Synthesis of functionalized PEG polymers *IV* and *V*. Reaction conditions: *i*) methanesulfonyl chloride, THF, triethylamine, DCM; *ii*) NaN_3, DMF; *iii*) NaH, THF, toluene.

methanesulfonyl chloride (MsCl) and a subsequent substitution reaction with sodium azide, whereas the reaction of propargyl bromide with MeOPEG 5000 directly afforded polymer *V*, as illustrated in Fig. 2.

The PEG polymers were coupled with the respective catalyst by a Cu(I) catalyzed azide–alkyne Huisgen reaction ("click" reaction) (Kolb et al., 2001; Moses & Moorhouse, 2007) as shown in Fig. 3. Each reaction proceeded smoothly in a water/acetone mixture and afforded the desired product in an almost quantitative yield. The structure of polymers was confirmed by ^{1}H NMR data.

Once the PEG-supported catalysts were obtained, hydrogels *VIII* and *IX* were prepared by microwave irradiation of a PBS solution of Carbomer 974P, PEG 2000, agarose and a PEG-supported catalyst. The hydrogels were obtained in form of cylinders (150 μL each, with the cylinder diameter of 0.2 cm) and were

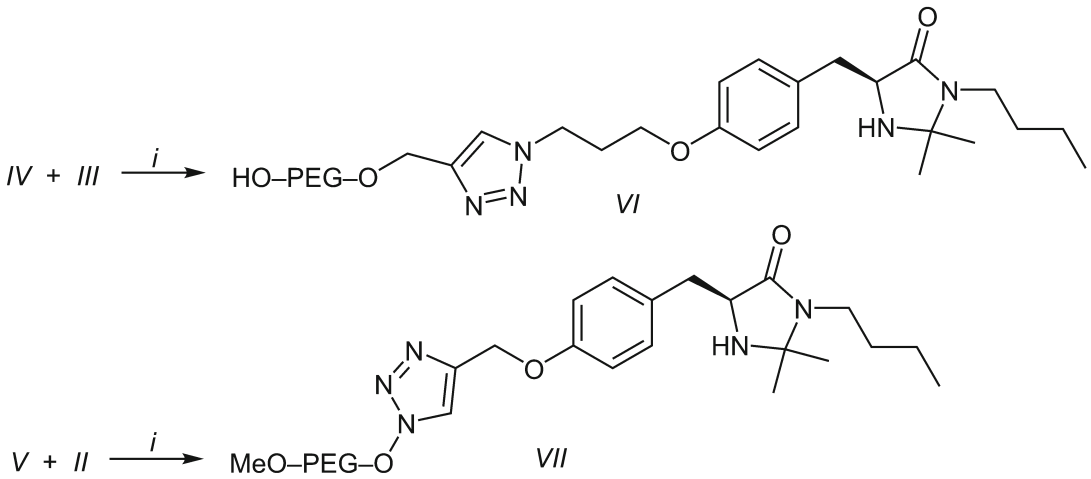


Fig. 3. Synthesis of the polymer supported catalysts. Reaction conditions: *i*) CuI, acetone/water, 50 °C.

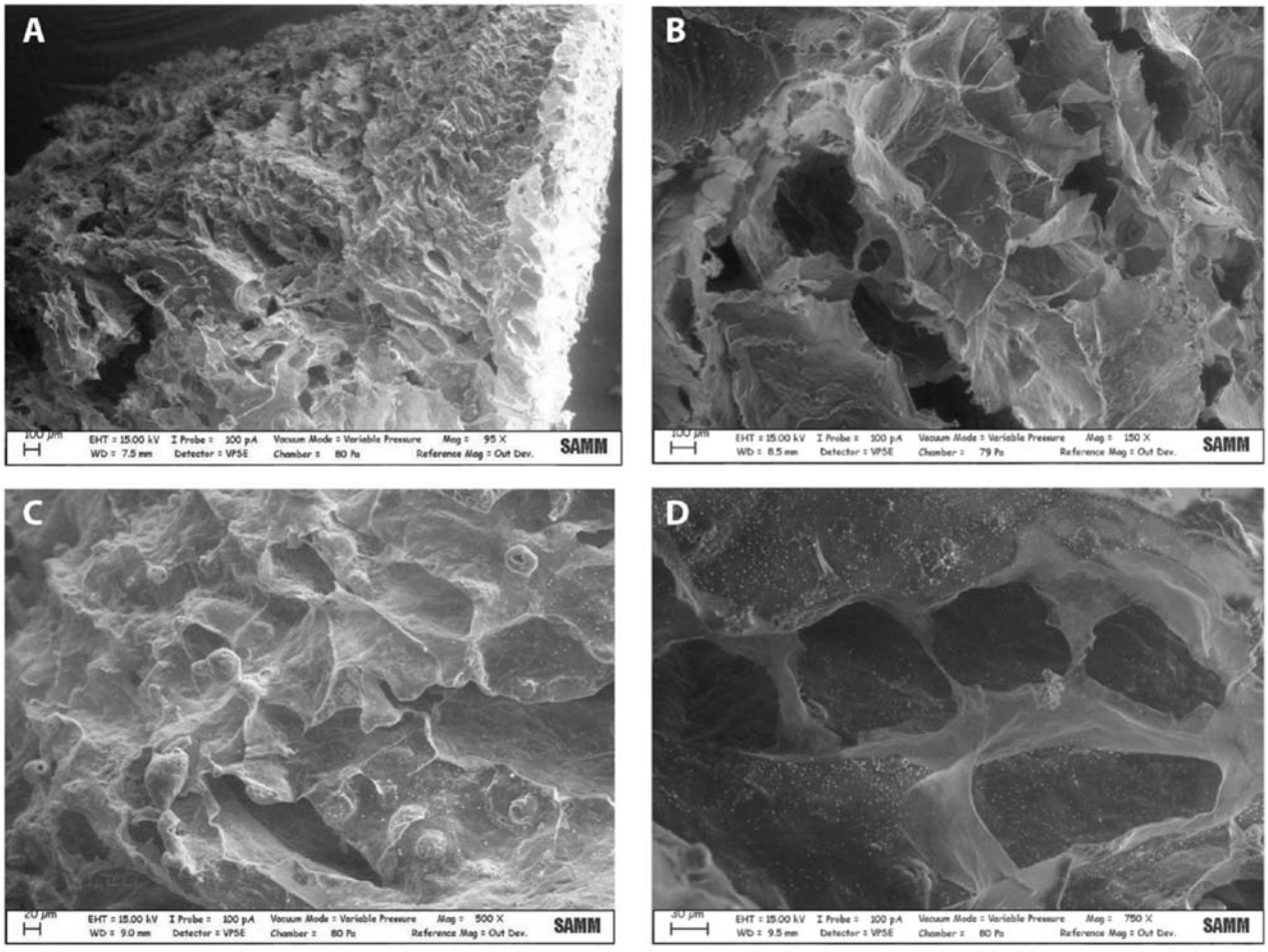


Fig. 4. SEM analysis of hydrogel *VIII*. Magnification: 95× (A); 150× (B); 500× (C); 750× (D); scale bars: 100 μm (A and B); 20 μm (C); 30 μm (D). Analogous images were observed by SEM analysis of a sample of hydrogel *IX*.

characterized by SEM (Fig. 4) and FTIR (Fig. 5). The samples were prepared by a freeze-drying method, followed by coating with a thin layer of gold prior to SEM imaging. Some previously published works on SEM morphology of dried PEG-based hydrogels can be found; however, much care must be taken when preparing dried samples for SEM analysis since the removal of water entrapped within the porous hydrogel scaffolds may disrupt the structural stability and result in collapse of the structure or the formation of

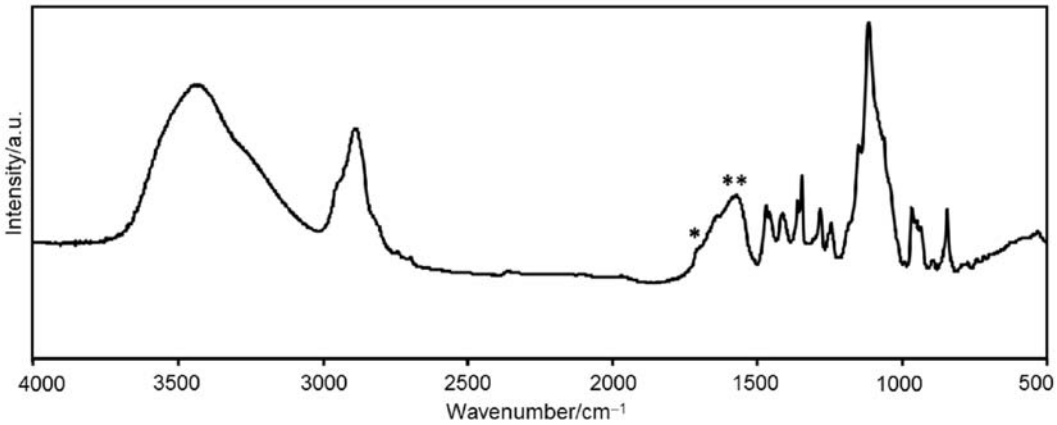


Fig. 5. FTIR spectrum of hydrogel *VIII* showing two distinct peaks of amide I and II bands at 1670 cm^{-1} and 1560 cm^{-1}, respectively, indicating the presence of catalysts within the hydrogel polymeric network.

artifacts upon drying (Ford et al., 2006; Zhu et al., 2009). Our results revealed that dried hydrogels possess a highly entangled structure. More details were observed from the SEM image with higher amplification (Fig. 4d); there are some bigger pores containing small holes and some fibrillar networks on the pore walls.

In addition, most of the pores are interconnected, which demonstrates that hydrogels present a microscopic porous structure with a complex 3D construction in the dried state and, compared with previous studies (Sacchetti et al., 2014), the presence of a catalyst does not affect the polymer network.

FTIR spectrum of hydrogel *VIII* (Fig. 5) showed a broad peak at $\sim$ 3450 cm^{-1} due to the stretching vibration of O—H bonds, whereas peaks at $\sim$ 2940 cm^{-1} are due to the C—H stretch. According to our previous studies, the formation of ester bonds is demonstrated by symmetric ($\sim$ 1600 cm^{-1}) and asymmetric ($\sim$ 1400 cm^{-1}) COO stretches.

The spectrum also shows peaks related to the C—O—C stretching vibration in the range of 900–1000 cm^{-1} that represent the glycosidic bond between the monosaccharide units (typical of the agarose structure) and ester groups. In general, building blocks or subunits of macromolecules form a stable structure made up mostly of C—C bonds, usually referred to as the "carbon skeleton". C—C and C—H bonds are nonpolar and thus tend to be less reactive and sometimes result in an inert under the applied degradation conditions. Building blocks of macromolecules act as discrete subunits because their internal structure consists of C—C bonds. Furthermore, C—O bonds link the subunits representing degradable bonds constituted by oxygen or nitrogen atoms. Here, the obtained FTIR results allow stating that the most important groups in the studied gels are: OH, CH, COO (carboxylates), vinyl groups and C—O—C. The presence of the catalyst is evident from peaks corresponding to amine I (*, 1670 cm^{-1}) and amine II (**, 1560 cm^{-1}) groups (Zhu et al., 2009). The same considerations can be also referred to the FTIR spectrum of hydrogel *IX*.

Referring to the hydrogel formulations it can be estimated that each tablet of hydrogel *VIII* contained 0.6 mg of catalyst *VI*, whereas 1.1 mg of catalyst *VII* were enclosed in the polymeric matrix of *IX*. Next, hydrogel-supported catalysts were tested in the reduction of cinnamaldehyde and β-methyl cinnamaldehyde, respectively, using the Hantzsch ester. In order to increase the catalyst loading, an increasing number of tablets was used in different experiments. The reactions were performed in water at ambient temperature under gentle mechanical shaking to preserve the integrity of the tablets. Obtained results are reported in Table 2.

All hydrogel tablets were able to convert the olefin to the respective saturated aldehyde. As expected, the higher the catalyst loading was (i.e., adding more tablets to the reaction mixture), the higher the yields were (up to 64 %). Catalyst in hydrogel *IX* proved to be slightly more efficient regarding the conversion, although in the β-methyl cinnamaldehyde reduction, both catalysts showed similar enantiomeric excess (*ee*) of the final product (up to 83 %). At the end of each reduction cycle, used catalysts were easily recovered by filtration of the mixture. However, the reuse of the hydrogel tablets afforded very low yields due to extensive degradation of the polymeric network. For comparison purposes, the reduction of β-methyl cinnamaldehyde with the Hantzsch ester and free catalyst *I* (20 mole %) was performed. It was observed that due to the limited solubility of both the catalyst and the substrate, a THF/water ($\varphi_r = 1:4$) mixture had to be used as a solvent to provide the desired product. Also, in accordance with literature, the addition of trifluoroacetic acid (TFA) to the solution in equimolar ratio with respect to the catalyst was necessary. Under such conditions, the product was obtained in a 94 % yield and 84 % *ee* after 18 h. Lowering the catalyst loading to 5 mole % led to similar results

after 72 h. The most relevant observation was that when using our hydrogel-supported catalysts, no TFA addition was required. This is most probably due to the presence of free carboxylic groups from PAA in the hydrogel, which are able to provide the required acidic environment. It was also observed that satisfactory yields were achieved when using 1 mole % of the loaded catalyst. This remarkable result is in agreement with recent reports on low loading organocatalysis even with water as the solvent (Park et al., 2015; Giacalone et al., 2012).

Conclusions

In this work, the first application of a hydrogel as the support for a chiral imidazolidinone based catalyst for the reduction of activated olefins is described. Results are promising for further applications of this strategy; however, some improvement in the loading of the catalyst and in the hydrogel mechanical stability is still necessary. These issues are currently under investigation in our laboratory.

References

Annabi, N., Tamayol, A., Uquillas, J. A., Akbari, M., Bertassoni, L. E., Cha, C., Camci-Unal, G., Dokmeci, M. R., Peppas, N. A., & Khademhosseini, A. (2014). 25th Anniversary article: Rational design and applications of hydrogels in regenerative medicine. *Advanced Materials*, *26*, 85–124. DOI: 10.1002/adma.201303233.

Atodiresei, I., Vila, C., & Rueping, M. (2015). Asymmetric organocatalysis in continuous flow: Opportunities for impacting industrial catalysis. *ACS Catalysis*, *5*, 1972–1985. DOI: 10.1021/acscatal.5b00002.

Blackmond, D. G., Armstrong, A., Coombe, V., & Wells, A. (2007). Water in organocatalytic processes: Debunking the myths. *Angewandte Chemie International Edition*, *46*, 3798–3800. DOI: 10.1002/anie.200604952.

Brenna, E., Gatti, F. G., Manfredi, A., Monti, D., & Parmeggiani, F. (2012a). Enoate reductase-mediated preparation of methyl (*S*)-2-bromobutanoate, a useful key intermediate for the synthesis of chiral active pharmaceutical ingredients. *Organic Process Research & Development*, *16*, 262–268. DOI: 10.1021/op200086t.

Brenna, E., Gatti, F. G., Monti, D., Parmeggiani, F., & Sacchetti, A. (2012b). Cascade coupling of ene reductases with alcohol dehydrogenases: Enantioselective reduction of prochiral unsaturated aldehydes. *ChemCatChem*, *4*, 653–659. DOI: 10.1002/cctc.201100418.

Brenna, E., Gatti, F. G., Monti, D., Parmeggiani, F., & Sacchetti, A. (2012c). Productivity enhancement of C=C bioreductions by coupling the *in situ* substrate feeding product removal technology with isolated enzymes. *Chemical Communications*, *48*, 79–81. DOI: 10.1039/c1cc16014a.

Brenna, E., Cosi, S. L., Ferrandi, E. E., Gatti, F. G., Monti, D., Parmeggiani, F., & Sacchetti, A. (2013a). Substrate scope and synthetic applications of the enantioselective reduction of α-alkyl-β-arylenones mediated by Old Yellow Enzymes. *Organic & Biomolecular Chemistry*, *11*, 2988–2996. DOI: 10.1039/c3ob40076j.

Brenna, E., Gatti, F. G., Malpezzi, L., Monti, D., Parmeggiani, F., & Sacchetti, A. (2013b). Synthesis of robalzotan, ebalzotan, and rotigotine precursors via the stereoselective multienzymatic cascade reduction of α,β-unsaturated aldehydes. *The Journal of Organic Chemistry*, *78*, 4811–4822. DOI: 10.1021/jo4003097.

Brenna, E., Gatti, F. G., Monti, D., Parmeggiani, F., Sacchetti, A., & Valoti, J. (2015). Substrate-engineering approach to the stereoselective chemo-multienzymatic cascade synthesis of *Nicotiana tabacum* lactone. *Journal of Molecular Catalysis B: Enzymatic*, *114*, 77–85. DOI: 10.1016/j.molcatb.2014.12.011.

Dalko, P. I., & Moisan, L. (2001). Enantioselective organocatalysis. *Angewandte Chemie International Edition*, *40*, 3726–3748. DOI: 10.1002/1521-3773(20011015)40:20<3726::aid-anie3726>3.0.co;2-d.

Dalko, P. I., & Moisan, L. (2004). In the golden age of organocatalysis. *Angewandte Chemie International Edition*, *43*, 5138–5175. DOI: 10.1002/anie.200400650.

Danelli, T., Annunziata, R., Benaglia, M., Cinquini, M., Cozzi, F., & Tocco, G. (2003). Immobilization of catalysts derived from *Cinchona* alkaloids on modified poly(ethylene glycol). *Tetrahedron: Asymmetry*, *14*, 461–467. DOI: 10.1016/s0957-4166(02)00830-3.

Davoodnia, A., Allameh, S., Fazli, S., & Tavakoli-Hoseini, N. (2011). One-pot synthesis of 2-amino-3-cyano-4-arylsubstituted tetrahydrobenzo[*b*]pyrans catalysed by silica gel-supported polyphosphoric acid (PPA–SiO2) as an efficient and reusable catalyst. *Chemical Papers*, *65*, 714–720. DOI: 10.2478/s11696-011-0064-8.

Dondoni, A., & Massi, A. (2008). Asymmetric organocatalysis: From infancy to adolescence. *Angewandte Chemie International Edition*, *47*, 4638–4660. DOI: 10.1002/anie.200704684.

Ford, M. C., Bertram, J. P., Hynes, S. R., Michaud, M., Li, Q., Young, M., Segal, S. S., Madri, J. A., & Lavik, E. B. (2006). A macroporous hydrogel for the coculture of neural progenitor and endothelial cells to form functional vascular networks *in vivo*. *Proceedings of the National Academy of Sciences of the United States of America*, *103*, 2512–2517. DOI: 10.1073/pnas.0506020102.

Giacalone, F., Gruttadauria, M., Agrigento, P., & Noto, R. (2012). Low-loading asymmetric organocatalysis. *Chemical Society Reviews*, *41*, 2406–2447. DOI: 10.1039/c1cs15206h.

Hayashi, Y. (2006). In water or in the presence of water? *Angewandte Chemie International Edition*, *45*, 8103–8104. DOI: 10.1002/anie.200603378.

Hiki, S., & Kataoka, K. (2007). A facile synthesis of azido-terminated heterobifunctional poly(ethylene glycol)s for "click" conjugation. *Bioconjugate Chemistry*, *18*, 2191–2196. DOI: 10.1021/bc700152j.

Itsuno, S., & Hassan, M. M. (2014). Polymer-immobilized chiral catalysts. *RSC Advances*, *4*, 52023–52043. DOI: 10.1039/c4ra09561h.

Kolb, H. C., Finn, M. G., & Sharpless, K. B. (2001). Click chemistry: Diverse chemical function from a few good reactions. *Angewandte Chemie International Edition*, *40*, 2004–2021. DOI: 10.1002/1521-3773(20010601)40:11<2004::aid-anie2004>3.0.co;2-5.

Lelais, G., & MacMillan, D. W. C. (2006). Modern strategies in organic catalysis: The advent and development of iminium activation. *Aldrichimica Acta*, *39*, 79–87.

MacMillan, D. W. C. (2008). The advent and development of organocatalysis. *Nature*, *455*, 304–308. DOI: 10.1038/nature07367.

Moses, J. E., & Moorhouse, A. D. (2007). The growing applications of click chemistry. *Chemical Society Reviews*, *36*, 1249–1262. DOI: 10.1039/b613014n.

Munirathinam, R., Huskens, J., & Verboom, W. (2015). Supported catalysis in continuous-flow microreactors. *Advanced Synthesis & Catalysis*, *357*, 1093–1123. DOI: 10.1002/adsc.201401081.

Ouellet, S. G., Tuttle, J. B., & MacMillan, D. W. C. (2005). Enantioselective organocatalytic hydride reduction. *Journal of the American Chemical Society*, *127*, 32–33. DOI: 10.1021/ja043834g.

Ouellet, S. G., Walji, A. M., & MacMillan, D. W. C. (2007). Enantioselective organocatalytic transfer hydrogenation reactions using Hantzsch esters. *Accounts of Chemical Research*, *40*, 1327–1339. DOI: 10.1021/ar7001864.

Park, S. Y., Lee, J. W., & Song, C. E. (2015). Parts-per-million level loading organocatalysed enantioselective silylation of alcohols. *Nature Communications*, *6*, 7512, DOI: 10.1038/ncomms8512.

Puglisi, A., Benaglia, M., Cinquini, M., Cozzi, F., & Celentano, G. (2004). Enantioselective 1,3-dipolar cycloadditions of unsaturated aldehydes promoted by a poly(ethylene glycol)-supported organic catalyst. *European Journal of Organic Chemistry*, *2004*, 567–573. DOI: 10.1002/ejoc.200300571.

Rossi, F., Perale, G., Storti, G., & Masi, M. (2012). A library of tunable agarose carbomer-based hydrogels for tissue engineering applications: The role of cross-linkers. *Journal of Applied Polymer Science*, *123*, 2211–2221. DOI: 10.1002/app.34731.

Sacchetti, A., Mauri, E., Sani, M., Masi, M., & Rossi, F. (2014). Microwave-assisted synthesis and click chemistry as simple and efficient strategy for RGD functionalized hydrogels. *Tetrahedron Letters*, *55*, 6817–6820. DOI: 10.1016/j.tetlet.2014.10.069.

Santoro, M., Marchetti, P., Rossi, F., Perale, G., Castiglione, F., Mele, A., & Masi, M. (2011). Smart approach to evaluate drug diffusivity in injectable agar–carbomer hydrogels for drug delivery. *The Journal of Physical Chemistry B*, *115*, 2503–2510. DOI: 10.1021/jp1111394.

Seayad, J., & List, B. (2005). Asymmetric organocatalysis. *Organic & Biomolecular Chemistry*, *3*, 719–724. DOI: 10.1039/b415217b.

Shi, J. Y., Wang, C. A., Li, Z. J., Wang, Q., Zhang, Y., & Wang, W. (2011). Heterogeneous organocatalysis at work: Functionalization of hollow periodic mesoporous organosilica spheres with MacMillan catalyst. *Chemistry – A European Journal*, *17*, 6206–6213. DOI: 10.1002/chem.201100072.

Slaughter, B. V., Khurshid, S. S., Fisher, O. Z., Khademhosseini, A., & Peppas, N. A. (2009). Hydrogels in regenerative medicine. *Advanced Materials*, *21*, 3307–3329. DOI: 10.1002/adma.200802106.

Zhu, J., Tang, C., Kottke-Marchant, K., & Marchant, R. E. (2009). Design and synthesis of biomimetic hydrogel scaffolds with controlled organization of cyclic RGD peptides. *Bioconjugate Chemistry*, *20*, 333–339. DOI: 10.1021/bc800441v.