Journal of Catalysis 309 (2014) 260–267

Contents lists available at ScienceDirect

Journal of Catalysis

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

Synthesis and characterization of novel polystyrene-supported TBD catalysts and their use in the Michael addition for the synthesis of Warfarin and its analogues

Matteo Alonzi [a], Maria Paola Bracciale [b], Alessandra Broggi [b], Daniela Lanari [c], Assunta Marrocchi [a], Maria Laura Santarelli [b], Luigi Vaccaro [a,*]

[a] *Laboratory of Green Synthetic Organic Chemistry, Dipartimento di Chimica, Università degli Studi di Perugia, via Elce di Sotto 8, 06123 Perugia, Italy*
[b] *Dipartimento di Ingegneria Chimica Materiali Ambiente, Università di Roma Sapienza, via Eudossiana 18, 00185 Roma, Italy*
[c] *Dipartimento di Chimica e Tecnologia del Farmaco, Università di Perugia, via del Liceo, 06123 Perugia, Italy*

ARTICLE INFO

Article history:
Received 5 September 2013
Revised 5 October 2013
Accepted 9 October 2013
Available online 11 November 2013

Keywords:
Polymer supports
Heterogeneous catalyst
1,5,7-Triazabicyclo[4.4.0]dec-5-ene (TBD)
Michael addition
Recyclable

ABSTRACT

In the search for efficient and polymeric supports for organic bases to be used in environmentally friendly media and conditions, novel polystyrene-bound 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) has been prepared and characterized. Their catalytic properties have been tested in the Michael additions of 4-hydroxycoumarin to α,β-unsaturated ketones as a representative useful process for the syntheses of 4-hydroxy-3-(3-oxo-1-phenylbutyl)-2H-chromen-2-one (Warfarin™), 4-hydroxy-3-(1-(4-nitrophenyl)-3-oxobutyl)-2H-chromen-2-one (Acenocumarol™), 4-hydroxy-3-(1-(4-chlorophenyl)-3-oxobutyl)-2H-chromen-2-one (Coumachlor™), and 4-hydroxy-3-(1-(4-methoxyphenyl)-3-oxobutyl)-2H-chromen-2-one. Products were obtained in high to quantitative conversion yields. The novel catalytic systems showed promising catalytic properties, and they could be all easily recovered by filtration and have been reused for three representative consecutive runs without any significant lowering of their activity.

1. Introduction

Polymer-supported catalysts have greatly attracted the interest of the chemical community in recent decades [1]. Immobilization of catalyst over an inert solid support demonstrated to be an efficient strategy to simplify the isolation of products and catalyst recycling, leading to economic and environmental advantages [1]. Among the wide range of supports, chloromethylated polystyrene cross-linked with divinylbenzene (PS/DVB) is one of the most used [1] (Scheme 1). However, when employed as gel-type resin, PS/DVB suffers from a limited accessibility of the reactants to catalytic sites when the reaction medium selected is a poor swelling solvent, and a consequent sensitive reduction in efficiency of the supported catalyst is generally observed [2]. On the other hand, macroporous PS/DVB resins do not generally suffer from such limitations, because of their permanent porous structure that is almost independent from the solvent nature and persists in the dry state [3].

According to our research, which is devoted to the development of an environmentally sustainable chemistry [4,5], the support is truly important for the definition of efficient synthetic procedures especially when safer reaction media are used (e.g. water [4], solvent-free conditions (SolFC) [5] or greener alternative to organic solvents [6]).

Among organic bases, highly basic guanidines, and in particular the bicyclic member 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) (**2**) (Scheme 2) are widely useful in chemical synthesis [7].

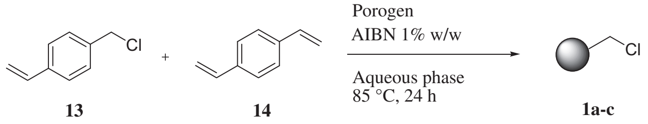
The equivalent PS-TBD is a polymer-supported organocatalyst consisting of a covalently linked guanidinic TBD moiety to polystyrene which has been successfully used in a wide range of reactions [8–12] as epoxide ring opening [9], aldol-type condensation [9], Knoevenagel condensation [9], Michael additions to α,β-unsaturated ketones [9], cyanosilylation of aldehydes, ketones and imines [10], ring opening of aziridines [11] and addition of dialkylphosphites to unsaturated systems [12]. Generally, commercially available PS/DVB has been used as polymeric supports, while as an example, it has been proved that to reach highest efficiency and compatibility with sustainable reaction conditions, support played a dramatic role [5c–d,9,13]. Excellent results have been obtained using Janda polymers [1d,14], but limitations can be encountered if used under solvent-free conditions (SolFC) due to the very low loading of the commercially available materials [13].

In this work, three different chloromethylated macroporous polystyrene–divinylbenzene supports (**1a**–**c**) were successfully prepared by suspension polymerization and used to immobilize TBD (**2**). The supports as well as the resulting catalysts (**3a**–**c**) were

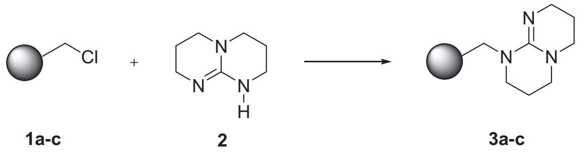
---

* Corresponding author.
E-mail address: luigi.vaccaro@unipg.it (L. Vaccaro).

0021-9517/$ - see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.jcat.2013.10.009



Scheme 1. Synthesis of chloromethylated resins **1a–c**.



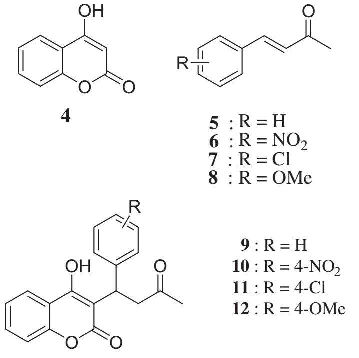
Scheme 2. Synthesis of catalysts **3a–c**.

characterized in terms of composition, structure, thermal stability, and morphology. The commercially available macroporous PS-TBD (**c-PS-TBD**) was also characterized for comparison purposes. The efficiencies of the newly synthesized as well as commercial polymeric-TBD catalysts were evaluated in the Michael reactions between 4-hydroxycumarine (**4**) and α,β-unsaturated ketones (**5–8**) to access Warfarin (**9**) and its analogues (**10–12**) (Scheme 3). Attention has been directed to a Michael addition process which is of very general interest and use in the chemical synthesis of target molecules and considering our goal to investigate the use of polymeric–organic bases in environmentally friendly reaction media, we directly pointed our attention toward the preparation of Warfarins. This process is based on the reactions of 4-hydroxycumarines that are generally poorly reactive and insoluble making the use of heterogeneous catalysts very challenging. Note that Warfarin is one of the most used anticoagulant worldwide [15]. Sold as racemate (Coumadin™), this coumarin-based anticoagulant is one of the most employed for the prevention of thrombosis and thromboembolism. The nitro derivative of Warfarin (**10**) is also a powerful anticoagulant and it is known as Acenocoumarol (Sintrom™). Despite the fact that several methods for the preparation of Warfarin using organocatalysis have been reported in recent years [15,16], the development of catalysts and sustainable efficient catalytic procedures for the synthesis of Warfarin and its analogues is still therefore of great importance. This molecule is thus of great pharmacological and economical relevance, and we found worthy to plan our academic study on this case study.

2. Materials and methods

2.1. General remarks

All the commercially available chemicals were purchased at Sigma–Aldrich and used without any further purification, unless otherwise noted. Commercial polystyrene-bound TBD (**c-PS-TBD**) was purchased at Polymer Laboratories, Varian Inc. (1.81 mmol TBD/g, 100/200 mesh; Elemental Analysis: N: 7.14%; C: 76.71%; H: 7.54%). 4-Vinylbenzylchloride (**13**) and divinylbenzene (**14**) (80% grade) were extracted three times with a 5% w/w NaOH solution to remove the polymerization inhibitor (tert-butyl catechol). AIBN was recrystallized from methanol. (3E)-4-(4-nitrophenyl)-but-3-en-2-one (**6**) and (3E)-4-(4-methoxyphenyl)-but-3-en-2-one (**8**) were prepared according to previously reported procedures [17]. Suspension polymerizations were run using a three-neck cylinder-shaped glass vessel (Fig. 1), equipped with a mechanical stirrer, condenser, and nitrogen inlet. A silicon oil bath was used as heating source. ^{1}H NMR and ^{13}C NMR spectra were recorded using a Bruker DRX-ADVANCE 400 MHz spectrometer. Deuterated solvents were used with the residual peak as internal standard. Elemental microanalyses were performed using a Fison's EA1106 CHN analyzer using atropine, 2,5-bis-2-(5-tert-butylbenzoxazolyl)-thiophene (BBOT) and phenanthrene as reference standard, with an accuracy of ca. 2 μmol/g. Commercial polystyrene-bound TBD (**c-PS-TBD**) was purchased at Polymer Laboratories, Varian Inc. and the porogen used for its preparation is not known (1.81 mmol TBD/g, 100/200 mesh; Elemental Analysis: N: 7.14%; C: 76.71%; H: 7.54%). Modulated differential scanning calorimetry analyses (MDSC) were performed with a TA instruments 2920 calorimeter with modulated cell cooled by nitrogen flow. Samples were analyzed in opened capsules with heating rate of 10 °C/min, ±0.5 °C modulation and 60 s period. Scanning electron microscopy (SEM) analyses were performed using an Auriga Zeiss HR FESEM instrument. SEM imaging of the surfaces of resin samples was performed with accelerating voltages between 5 keV and 30 keV, achieving magnifications ranging from 100× to 200k×. FTIR spectra were recorded on a VERTEX 70 Bruker Optics instrument, spectral range 4000–400 cm^{-1}, resolution 4 cm^{-1}, equipped with single reflection diamond ATR cell. Brunauer–Emmett–Teller (BET) analyses were performed by using an Autosorb iQ-MP/MP-XR instrument (Quantachrome).



Scheme 3. Warfarins and their precursors.

Fig. 1. Suspension polymerization reactor used in this study.

*2.2. Preparation of PS-Cl **1a–c***

*2.2.1. PS-Cl **1a***

A reaction vessel immersed in an oil bath, equipped with condenser, mechanical stirrer and nitrogen inlet/outlet was charged with water (80 mL), polyvinylalcohol (MW 85,000–124,000, 99% hydrolyzed) (0.08 g), and NaCl (2.65 g) and stirred for 24 h at room temperature. A mixture of 4-vinylbenzylchloride (**13**), (1.6 mL), divinylbenzene (**14**) (0.4 mL), 2-ethylhexanoic acid (EEA, 2 mL) and AIBN (0.02 g, 1% w/w monomers) was then added into the reactor. The system was kept under stirring and purged with nitrogen for 30 min. Then, the reaction was warmed up to 85 °C under mechanical stirring. After 24 h, the reaction was allowed to reach room temperature and the polymer beads were filtered. The product was washed in a Soxhlet extractor for 24 h with water, THF and hexanes and vacuum dried overnight (yield 70%, 1.41 g).

*2.2.2. PS-Cl **1b***

The reaction vessel was charged with water (80 mL), polyvinylalcohol (MW 13,000–23,000, 89% hydrolyzed) (0.08 g), NaCl (2.65 g) and stirred for 24 h at room temperature. A mixture of 4-vinylbenzylchloride (**13**) (1.6 mL), divinylbenzene (**14**) (0.4 mL), 1-chlorodecane (CD, 2 mL) and AIBN (0.02 g, 1% w/w monomers) was added. The system was kept under stirring and purged with nitrogen for 30 min. Then, the reaction was warmed up to 85 °C under mechanical stirring. After 24 h, the reaction was allowed to reach room temperature and the polymer beads were filtered. The product was washed in a Soxhlet extractor for 24 h with water, THF and hexanes and vacuum dried overnight (yield 72%, 1.45 g).

*2.2.3. PS-Cl **6c***

Prepared by following the procedure described above for **1a**. Porogen: Cyclohexanol (COX, 2 mL) (yield 65%, 1.31 g).

*2.3. Preparation of catalysts **3a–c***

*2.3.1. Preparation of PS-TBD **3a***

In a round-bottom flask equipped with a magnetic stirrer **1a** (0.4 g, 2.16 mmol), 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) (**2**) (4.45 g, 15 eq) and 3 mL of 1,4-dioxane were added. The reaction was kept under stirring at 100 °C for 7 d. The polymer beads were isolated by filtration and washed with THF (35 mL), chloroform (35 mL) and dichloromethane (35 mL). The collected polymer beads were then vacuum dried overnight at room temperature. The degree of functionalization was determined to be 2.61 mmol TBD/g by elemental analysis: C 68.67, H 14.29, N 10.95 (yield 85%, 0.34 g).

*2.3.2. Preparation of PS-TBD **3b***

In a round-bottom flask equipped with a magnetic stirrer **1b** (0.4 g, 2.16 mmol), 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) (**2**) (4.45 g, 10 eq) and 1.5 mL of 1,4-dioxane were added. The reaction was kept under stirring at 100 °C for 7 d. The polymer beads were isolated by filtration and washed with THF (35 mL), chloroform (35 mL) and dichloromethane (35 mL). The collected polymer beads were then vacuum dried overnight at room temperature. The degree of functionalization was determined to be 2.51 mmol TBD/g by elemental analysis: C 66.18, H 8.21, N 10.55 (yield 80%, 0.32 g).

*2.3.3. Preparation of PS-TBD **3c***

In a round-bottom flask equipped with a magnetic stirrer **1c** (0. 4 g, 2.16 mmol), 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) (**2**) (6.1 g, 15 eq) and 5 mL of 1,4-dioxane were added. The reaction was kept under stirring at 100 °C for 7 d. The polymer beads were isolated by filtration and washed with THF (35 mL), chloroform (35 mL) and dichloromethane (35 mL). The collected polymer beads were then vacuum dried overnight at room temperature. The degree of functionalization was determined to be 2.54 mmol TBD/g by elemental analysis: C 68.45, H 7.46, N 10.67 (yield 87%, 0.35 g).

*2.4. Procedure for Michael reaction between 4-hydroxycoumarine (**4**) and α,β-unsaturated ketones **5–8***

*2.4.1. Preparation of 4-hydroxy-3-(3-oxo-1-phenylbutyl)-2H-chromen-2-one (Warfarin, **9**)*

In a screw-capped vial equipped with a magnetic stirrer, 4-hydroxycoumarine (**4**) (0.146 g, 0.9 mmol), (3E)-4-phenyl-but-3-en-2-one (**5**) (0.131 g, 0.9 mmol), catalyst **3c**(0.05 eq) and cyclopentyl methyl ether (0.5 mL) were consecutively added and the mixture was stirred at 100 °C. After 96 h, the catalyst was recovered by filtration, washed with 2-Me-THF (5 mL) and vacuum dried overnight. The organic solvent was evaporated under reduced pressure to give crude 4-hydroxy-3-(3-oxo-1-phenylbutyl)-2H-chromen-2-one (**9**) as a white solid. (0.266 g, 96% yield). ^{1}H NMR ($CDCl_3$, 400 MHz): 1.68, s, 3H; 1.72, s, 3H; 2.07, t , 2H, J = 6 Hz; 2.46, s, 3H; 2.47–2.57, m, 2H; 3.19, s, 1H; 3.31, d, 2H; J = 21 Hz; 3.86, dd, 2H; J_1 = 20 Hz, J_2 = 8 Hz; 4.14–4.19, m , 1H; 4.27–4.31, m, 1H; 4.70, d, 1H, J = 10 Hz; 7.21–7.37, m, 7 H; 7.49–4.59, m , 1H. ^{13}C NMR ($CDCl_3$, 100.6 MHz): 27.7; 28.2; 34.1; 40.0; 42.5; 99.0; 100.4; 101.1; 104.2; 116.5; 116.6; 122.7; 123.0; 123.6; 123.9; 126.5; 126.9; 127.2; 128.6; 129.2; 131.5; 132.0; 141.4; 143.1; 153.0; 158.9; 159.8; 161.2; 162.1.

*2.4.2. Preparation of 4-hydroxy-3-(1-(4-nitrophenyl)-3-oxobutyl)-2H-chromen-2-one (Acenocoumarol, **10**)*

In a screw-capped vial equipped with a magnetic stirrer, 4-hydroxycoumarine (**4**) (0.146 g, 0.9 mmol), (3E)-4-(4-nitrophenyl)-but-3-en-2-one (**6**) (0.172 g, 0.9 mmol), catalyst **3a** (0.05 eq) and cyclopentyl methyl ether (0.5 mL) were consecutively added and the mixture was stirred at 100 °C. After 72 h, the catalyst were recovered by filtration and washed with 2-Me-THF (5 mL), and the solvent was evaporated under reduced pressure to give crude 4-hydroxy-3-(1-(4-nitrophenyl)-3-oxobutyl)-2H-chromen-2-one (**10**) as a brown solid; (0.300 g, 96% yield). ^{1}H NMR ($CDCl_3$, 400 MHz): 1.73, s, 3H; 1.79, s, 3H; 1.93, m, 2H; 2.34, s, 3H; 2.39–2.52, m, 2H; 2.96, s, 1H; 3.24, s, 1H; 3.34, dd, J_1 = 20.3 Hz; J_2 = 2.9 Hz, 2H; 3.90, dd, J_1 = 20.5; J_2 = 2.9 Hz, 2H; 3.90, dd, J_1 = 20.5 Hz, J_2 = 11 Hz, 2H; 4.27, m, 1H; 4.73, dd, J_1 = 12.6 Hz; J_2 = 1.3 Hz, 1H; 7.25–7.44, m, 4H; 7.54, td, J_1 = 7.7; J_2 = 1.3 Hz; 7.59, td, J_1 = 7.7 Hz, J_2 = 1.3 Hz, 1H; 7.82, dd, J_1 = 8.4 Hz, J_2 = 1.3 Hz, 1H; 7.87, dd, J_1 = 8.4 Hz, J_2 = 1.3 Hz, 1H; 8.12–8.18, m, 2H. ^{13}H NMR ($CDCl_3$, 100 MHz): 26.5; 27.2; 35.2; 35.3; 41.9; 99.7; 100.9; 101.0; 102.5; 115.4; 115.6; 116.4; 116.5; 122.8; 122.9; 123.1; 123.6; 124.3; 128.8; 129.0: 132.3.

*2.4.3. Preparation of 4-hydroxy-3-(1-(4-chlorophenyl)-3-oxobutyl)-2H-chromen-2-one (Coumachlor, **11**)*

In a screw-capped vial equipped with a magnetic stirrer, 4-hydroxycoumarine (**4**) (0.146 g, 0.9 mmol), (3E)-4-(4-chlorophenyl)-but-3-en-2-one (**7**) (0.162 g, 0.9 mmol), catalyst **3b** (0.05 eq) and cyclopentyl methyl ether (0.5 mL) were consecutively added and the mixture was stirred at 100 °C. After 96 h, the catalyst were recovered by filtration and washed with 2-Me-THF (5 mL), and the solvent was evaporated under reduced pressure to give crude 4-hydroxy-3-(1-(4-chlorophenyl)-3-oxobutyl)-2H-chromen-2-one (**11**) as a white solid (0.295 g, 96% yield); ^{1}H NMR ($CDCl_3$, 400 MHz): 1.68, s, 3H; 1.72, s, 3H; 1.93, m, 2H; 2.36, s, 3H; 2.38–2.46, m, 2H; 3.23, s, 1H; 3.29, s, 1H; 3.57, s, 1H; 3.86, dd, 2H, J_1 = 19.8 Hz, J_2 = 2.4 Hz; 4.14–4.19, m, 1H; 4.64, dd, 1J, J_1 = 11 Hz, J_2 = 2.5 Hz; 7.13–7.34, m, 4H; 7.52, td, 1H,

J_1 = 6.6 Hz, J_2 = 1.6 Hz; 7.57, td, 1H, J_1 = 6.9 Hz, J_2 = 1.8 Hz; 7.81. dd, 1H, J_1 = 6.6 Hz, J_2 = 1.6 Hz; 7.88, dd, 1H, J_1 = 7.6 Hz, J_2 = 1.6 Hz; 7.95, dd, 1H, J_1 = 7.5 Hz, J_2 = 1.4 Hz; 9.59, s, 1H. ^{13}C NMR ($CDCl_3$, 100 MHz): 27.7; 28.2; 30.1; 34.1; 34.3; 34.8; 39.9; 42.3; 45.2; 99.0; 100.3; 101.2; 103.8; 115.5; 115.8: 116.2; 116.5; 116.7; 122.7; 123.0; 123.7; 124.0; 128.2; 128.4; 128.6; 128.8; 128.9; 129.4; 131.7; 131.9; 140.6; 141.8; 152.9; 152.9; 159.0; 159.7; 162.3; 162.1.

*2.4.4. 4-Hydroxy-3-(1-(4-methoxyphenyl)-3-oxobutyl)-2H-chromen-2-one (**12**)*

In a screw-capped vial equipped with a magnetic stirrer, 4-hydroxycoumarine (**4**) (0.146 g, 0.9 mmol), (3E)-4-(4-methoxyphenyl)-but-3-en-2-one (**8**) (0.158 g, 0.9 mmol), catalyst **3b** (0.05 eq) and cyclopentyl methyl ether (0.5 mL) were consecutively added and the mixture was stirred at 100 °C. After 168 h, the catalyst were recovered by filtration and washed with 2-Me-THF (5 mL), and the solvent was evaporated under reduced pressure to give 4-Hydroxy-3-(1-(4-methoxyphenyl)-3-oxobutyl)-2H-chromen-2-one (**12**) as a white solid (0.289 g, 95% yield). ^{1}H NMR ($CDCl_3$, 400 MHz): 1.67, s, 3H; 1.71, s, 3H, 1.99, m, 2H; 2.29, s, 3H; 2.38, dd, 2H, J_1 = 11.4 Hz, J_2 = 6.8 Hz; 2.46, dd, 2H, J_1 = 14 Hz, J_2 = 7.2 Hz; 2.53, dd, 2H, J_1 = 14.0 Hz, J_2 = 2.8 Hz; 3.26, s, 1H; 3.76, s, 3H; 3.77, s, 3H; 3.81–3.90, m, 2H; 4.12, dd, 1 H, J_1 = 11.6 Hz, J_2 = 6.8 Hz; 4.25, dd, 1H; J_1 = 6.8 Hz, J_2 = 2.8 Hz; 4.64, d (b) 1H; 6.80–6.87, m, 2H; 7.13–7.36, m, 4H; 7.49, t, 1H, J = 7.8 Hz; 7.57, td, 5H, J_1 = 7.8 Hz, J_2 = 1.6 Hz; 7.80, dd, 2H, J_1 = 8.0 Hz, J_2 = 1.6 Hz; 7.89, dd, 2H; J_1 = 8.0 Hz, J_2 = 1.6 Hz; 7.93, d, 1H, J = 8.0 Hz. ^{13}C NMR ($CDCl_3$, 100 MHz): 27.7; 28.1; 30.0; 32.2; 34.2; 34.5, 39.8; 42.6; 45.5; 55.2; 55.2; 99.1; 100.5; 101.3; 104.3; 113.5; 114.0; 114.7; 115.5; 115.9; 116.4; 116.6; 122.7; 123.1; 123.5; 123.9; 128.0; 131.4; 131.9; 133.0; 135.1; 152.8; 152.9; 158.1; 158.6; 159.6; 160.7; 161.3.

3. Results and discussion

3.1. PS-TBD catalysts preparation and characterization

The synthesis of PS-TBD catalysts **3a–c** was performed in two steps, i.e. (*1*) suspension co-polymerization of vinylbenzylchloride (**13**) and divinylbenzene (**14**) using 2-ethylhexanoic acid (EEA), 1-chlorodecane (CD) and cyclohexanol (COX) as porogens in 1/1 volume ratio to generate the spherical-beaded chloromethylated polystyrene supports **1a–c** (Scheme 1). Subsequently in step (*2*) nucleophilic substitution of the chlorine atoms by TBD (**2**) in 1,4-dioxane at 100 °C (Scheme 2) furnished the desired catalytic systems. Note that the required porogens in step (*1*) were selected bearing in mind their effectiveness in generating macroporous structures and, consequently, low surface area for styrene–divinylbenzene copolymerization [2,3]. Moreover, the choice of three chemically different porogens (acidic, polar protic, polar aprotic) was made to identify a correlation between characteristics/activity of the catalysts and the nature of the porogen. Typical bead sizes were in the range of 25–100 mesh for chloromethylated resins **1a–c** as well as PS-TBD catalysts **3a–c**. The use of cyclohexanol generated the smallest particles (average size ~100 mesh). The yield of high-quality beads was generally good (65–70%) (see Table 1). Representative scanning electron micrographs of chloromethylated polystyrene supports prepared are reported in Fig. 2. Resin **1a** (Fig. 2a) reveals a clear macropores population even at the bead surface.

Resin **1b** (Fig. 2b) showed a rough contaminated surface with fragments associated with it. The contamination is however superficial, as the high-magnification SEM image of this resin shows access to a discrete macroporous structure (Fig. 2e). Resin **1c** however, shows a fine surface texture, which is rather uniform (Fig. 2c). SEM images of polymer fracture sections clearly show in all cases the formation of a typical macroporous structure (Fig. 2d–f).

BET analyses were performed to determine average pore size and surface area (Table 1). The results indicated that all three of the chosen porogens allowed macroporous structures [3] and consequently low surface area to be obtained (Table 1) [3]. Compared to commercial sample of PS-TBD (Table 1, entry 7), supports **1a–c** showed higher average pore size, thus suggesting an easier accessibility to catalytic sites. Cyclohexanol revealed to be the best porogen in terms of average pore size (see below). As previously reported [18], 1-chlorodecane successfully allowed to obtain a macroporous network. Despite the very different functionalities in 2-ethylhexanoic acid and 1-chlorodecane, they both lead to very similar structures, in terms of average pore size (Table 1, entries 1–2). Not surprisingly, the morphology and pore structure remained substantially unchanged when chloromethylated supports **1a–c** were functionalized with TBD to give **3a–c**, respectively (Figs. 2 and 3 and Table 1). Finally, **1a–c** and **3a–c** were subjected to modulated differential scanning calorimetry (MDSC) analysis, showing high thermal stability in the range of 30–250 °C (see figures in Supporting information).

The results obtained indicate the compatibility of the supported catalysts with a wide range of reaction temperatures. MDSC analysis of commercial TBD is also reported for comparison purposes (see figures in Supporting information). This latter reveals the same thermal stability of **3a–c**.

The principal evidence for anchoring TBD onto polymers **1a–c** was appearance and loss of IR peaks that correspond to replace TBD over chlorine of chloromethylated polystyrene, as exemplified in Fig. 4 for support **1a** and catalyst **3a**. Indeed, by comparing the PS-TBD **3a** IR-spectra with that of the PS-Cl **1a** is clearly visible the gradual disappearing of the 1260 cm^{-1} band corresponding to the CH_2Cl wagging vibration and the 670 cm^{-1} band corresponding to the C-Cl stretching vibration going from PS-Cl **1a** to the more functionalized PS-TBD **3a**. Moreover, it can be noted the appearance of a strong peak at 1600 cm^{-1} relative to the C=N stretching (the weak band observed at the same frequency for PS-Cl spectrum is due to benzene skeleton) and a 1370 cm^{-1} band corresponding to C—N stretching.

Table 1
Polymers **1a–c** and TBD-bound analogues **3a–c**. Syntheses and solid-state porosity data.

Entry	Polymers	Porogen	Surface area (m^2/g)	Average pore volume (cm^3/g)	Average pore radius (Å)	Yield[a] (%)
1	**1a**	2-Ethylhexanoic acid	6.8	0.03	160	72
2	**1b**	1-Chlorodecane	23	0.17	140	70
3	**1c**	Cyclohexanol	21	0.20	398	65
4	**3a**	2-Ethylhexanoic acid	6.6	0.03	155	85
5	**3b**	1-Chlorodecane	25	0.18	142	80
6	**3c**	Cyclohexanol	20	0.22	385	87
7	**c-PS-TBD**	–[b]	316.6	0.63	79.8	–

[a] Yield of beads obtained.

[b] Porogen used for the commercial **c-PS-TBD** is not known.

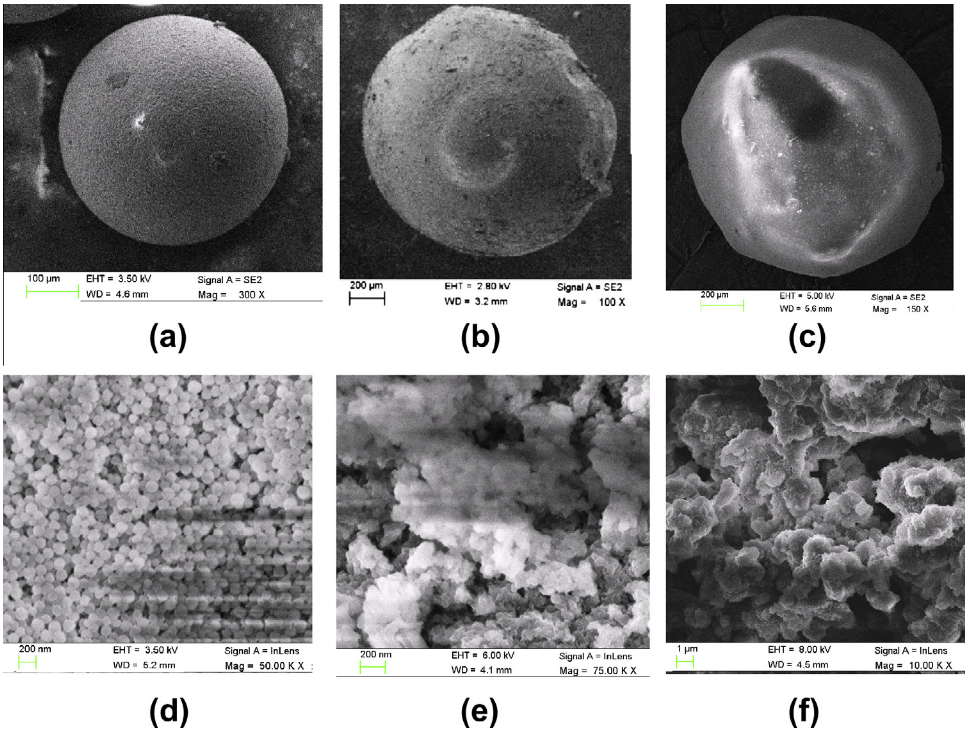


Fig. 2. Scanning electron microscopy images of chloromethylated resin beads prepared by using (a) EEA porogen; (b) CD porogen; (c) COX porogen, and (d–f) the corresponding macroporous resin fractures.

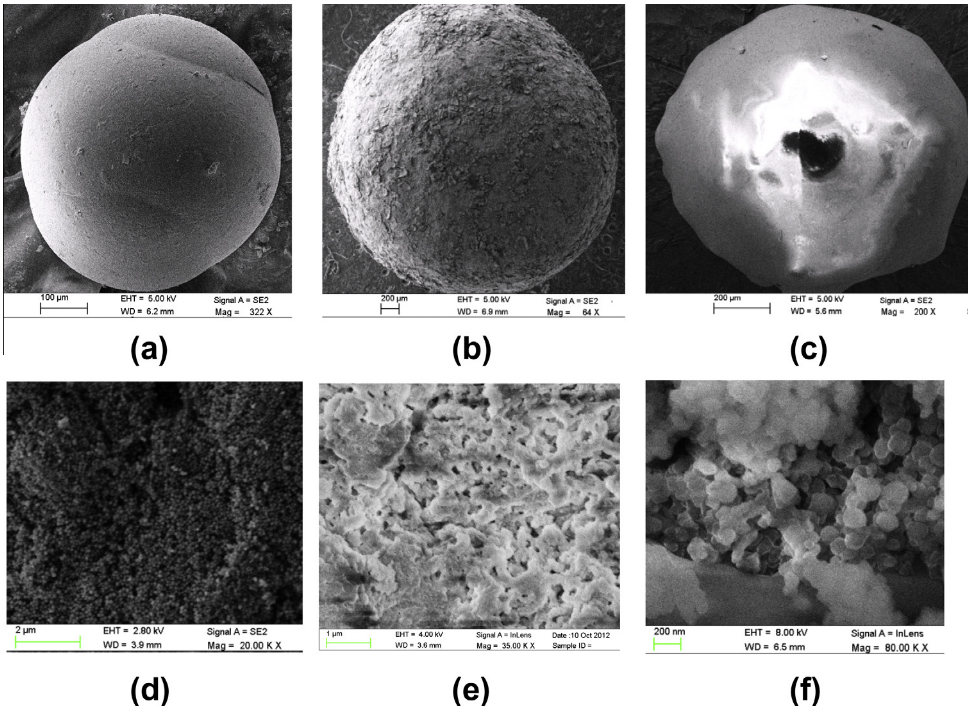


Fig. 3. Scanning electron microscopy images (a–c) of TBD-functionalized resin beads prepared by using (a) EEA porogen; (b) CD porogen; (c) COX porogen, and (d–f) the corresponding macroporous resin fractures.

The IR spectrum of commercial macroporous PS-TBD (**c-PS-TBD**) is also reported for comparison purposes (Fig. 5), showing a very high similarity with that for catalyst **3a**.

The nitrogen content of resins **3a–c** was also determined quantitatively by elemental analysis that obtained 10.95%, 10.55% and 10.67% respectively.

3.2. Catalytic activity

The efficiency of the supported catalysts **3a–c** has been firstly tested in the model Michael addition between 4-hydroxycoumarine (**4**) and (3E)-4-phenyl-but-3-en-2-one (**5**) to generate Warfa-

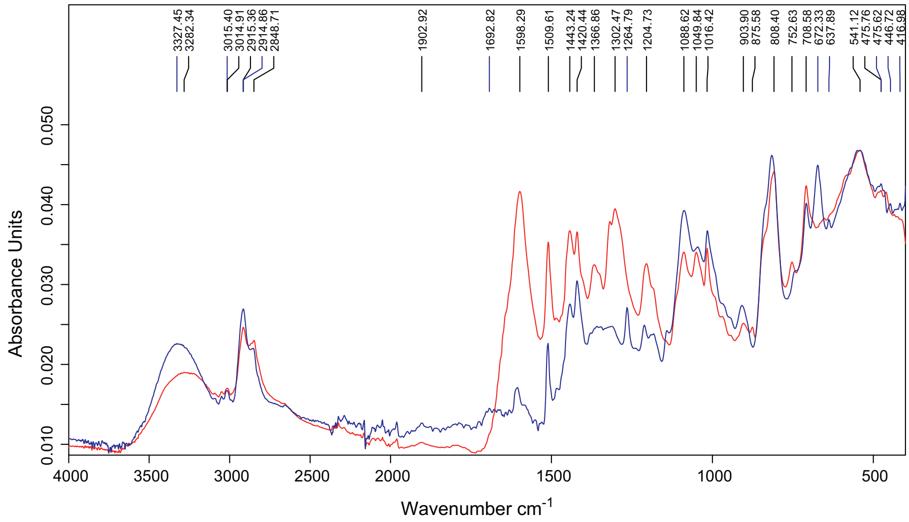


Fig. 4. IR spectra of **1a** (blue line) and **3a** (red line). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

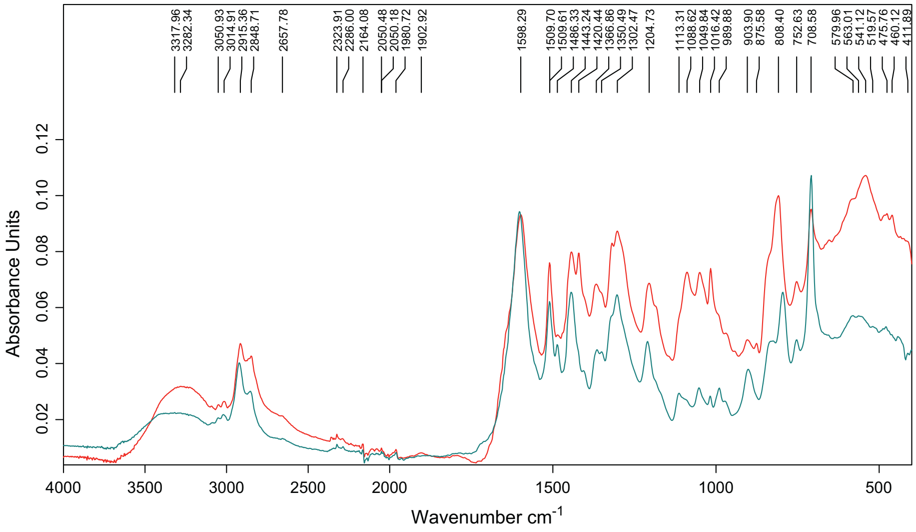
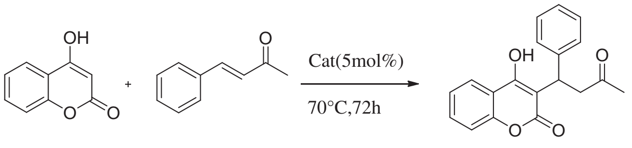


Fig. 5. IR spectra of **3a** (red line) and commercial macroporous PS-TBD (**c-PS-TBD**) (green line). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

rin (**9**). The most significant data are reported in Tables 2 and in Charts 1 and 2.

Initially, it was selected the reaction medium (dioxane) focusing our selection on the most environmentally friendly options [6] used in 0.55 mL/mmol.

Table 2
Solvent choice for the Michael addition of 4-hydroxycoumarine (**4**) to α,β-unsaturated ketone **5** catalyzed by polymer-supported TBD **3a–c** at 70 °C for 72 h.



4 5 9

Entry	Catalyst	Solvent	Conversion (%)[a]
1	**3a**	CPME	82
2	**3b**	CPME	77
3	**3c**	CPME	82
4	**3a**	2-Me-THF	76
5	**3b**	2-Me-THF	63
6	**3c**	2-Me-THF	77

[a] Determined by ^{1}H NMR analysis.

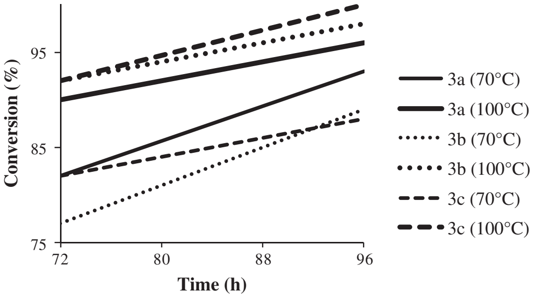


Chart 1. Effect of time and temperature on the reaction of **4** with **5** in CPME catalyzed by 5 mol% of **3a–c**.

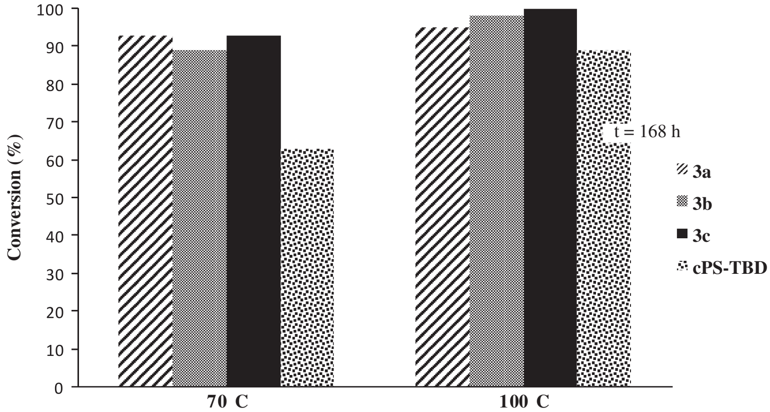


Chart 2. Effect of the temperature on the efficiency of catalysts **3a–c** and **c-PS-TBD** in the reaction of **4** with **5**.

Good conversions (63–82%, Table 2, entries 1–5) were obtained when catalysts **3a–c** were used at 70 °C for 72 h in cyclopentyl methyl ether (CPME) or 2-methyltetrahydrofuran (2-Me-THF), which have been selected because they are included in the list of green solvents [6]. CPME allowed slightly better results and while in 2-Me-THF complete consumption of the reactants was never observed, after changing reaction conditions CPME allowed complete conversion to desired Warfarin **9** (see data below in Charts 1 and 2). Poorer results were obtained using other media such as teramyl methyl ether and alcohols which are desirable reaction media but in this process led to unsatisfactory results due to the concomitant formation of the corresponding acetal of **5**, which prevents the progress of the Michael addition.

Further experiments were therefore performed using CPME as reaction medium.

The influence of the reaction temperature on the efficiency of the supported TBD catalysts can be also seen in Chart 2. For comparison the reaction using commercially available macroporous polystyrene-supported TBD (**c-PS-TBD**) is also showed. Importantly, it was found that the **c-PS-TBD** allowed lower conversions both at 70 and 100 °C. The most efficient results were accomplished at 100 °C after 96 h, where catalyst **3c** led to complete conversion to **9**. It can be noted that the effect of temperature increase was smaller for **3a** than for **3b–c**.

Table 3
Michael addition of 4-hydroxycoumarin (**4**) to α,β-unsaturated ketones **5–8** catalyzed by PS-TBD **3a–c**.

Entry	Catalyst	Ketone	Product	Time (h)	Conversion (%)[a]
1	**3c**	**5**	**9**	96	100[b]
2	**3a**	**6**	**10**	72	100[b]
3	**3b**	**6**	**10**	72	100[b]
4	**3c**	**6**	**10**	72	100[b]
5	**c-PS-TBD**	**6**	**10**	72	88
6	**3a**	**7**	**11**	72	93
7	**3b**	**7**	**11**	72	97[c]
8	**3c**	**7**	**11**	72	90
9	**c-PS-TBD**	**7**	**11**	72	85
10	**3a**	**8**	**12**	96	82[d]
11	**3b**	**8**	**12**	96	83[d]
12	**3c**	**8**	**12**	96	76
13	**c-PS-TBD**	**8**	**12**	96	80

[a] Determined by ^{1}H NMR analysis.
[b] Yield of the corresponding isolated pure product was 95–96%.
[c] After 96 h conversion of **7** to **11** was complete and the pure product **11** was isolated in 96% yield after filtration (see experimental).
[d] After 168 h conversion of **8** to **12** was complete and the pure product **12** was isolated in 95% yield after filtration (see experimental).

To broaden the scope of the catalysts, ketones **6–8** were also used in the Michael addition with **4** (Table 3). The results showed that good to excellent conversion yields could be reached in all cases (76–100% after 96 h). Product **12** could be prepared in high yields avoiding column chromatography purification after longer reaction time (168 h). For all the three Michael acceptors the catalysts activity order was **3b** ≈ **3a** > **3c**. As expected, Michael addition of **4** to 4-(4-nitrophenyl)-but-3-en-2-one (**6**) was faster and reached quantitative conversion yields with all the synthesized catalysts, and in a shorter time compared to the corresponding **5** (Table 3, entries 2–4 *vs* 1), while the commercial analogue gave only 88% conversion yield (Table 3, entry 5) without reaching complete conversion even after weeks, confirming the higher catalytic activity of **3a–c**.

These results confirmed that supports prepared with 2-ethylhexanoic acid and 1-chlorodecane as porogens allowed to obtain the most accessible structure, in spite of the relative average pore size detected by BET analysis (Table 1). In fact, since the highest average pore radius was detected in **3c** (398 Å), catalytic sites should be more accessible by substrates respect to **3a–b** (160 and 140 Å) (Table 1). Such apparently contradictory effect could be explained taking into account that the average pore size might not reflect the pore size distribution. In fact, since pore sizes are not homogeneous, it may be hypothesized that the observed activity of the catalyst is determined by a smaller percent of bigger pores, which are mediated with micropores in the BET analyses. Moreover, it is important to bear in mind that the BET experiment does not probe effectively pores size > 200 nm [19].

Finally, the recovery and reuse of the catalytic systems has been investigated and the results reported for the reaction of 4-hydroxycoumarine (**4**) with α,β-unsaturated ketone **5** carried out in the best conditions. After the reaction was completed, the catalyst used was recovered by filtration. The recovered catalyst was then washed, dried, and subsequently reused. As reported in Table 4, all the prepared catalysts **3a–c** demonstrated to substantially retain their catalytic activity even after three consecutive runs.

Table 4
Recycling of catalysts **3a–c** in the Michael addition of 4-hydroxycoumarine (**4**) to (4*E*)-4-phenyl-but-3-en-2-one (**5**).

Catalyst	Conversion (%)		
	Run 1	Run 2	Run 3
3a	95	95	96
3b	99	96	86
3c	98	97	94

4. Conclusion

In conclusion, three macroporous chloromethylated polystyrene (PS) supports were successfully prepared and used to immobilize TBD. The supports as well as the resulting catalysts were characterized in terms of composition, structure, thermal stability, and morphology. Importantly, they were found to show excellent thermal stability, and no appreciable modification of the support morphology after TBD-functionalization. For comparison, commercial PS-TBD was also characterized. The efficiency of the newly synthesized as well as commercial PS-TBD catalysts was evaluated in the Michael reactions between 4-hydroxycumarine and α,β-unsaturated ketones to access Warfarin and its analogues. All the newly synthesized supported catalysts revealed to be superior in terms of catalytic activity with respect to their commercial analogue, allowing in most cases the preparation of these important pharmacologically active molecules in a quantitative conversion yield. All the reactions were run without any additive, using equimolar amounts of reagents and minimized amounts of green solvents, thus opening the route to the definition of environmentally friendly approach to the above target systems. A correlation between catalysts' characteristics/activity and the nature of the porogen used (acidic, polar protic, polar aprotic) was identified. Particularly, although the all three new PS-TBD catalysts **3a–c**, showed excellent catalytic activity, 2-ethylhexanoic acid and 1-chlorodecane revealed to be the best porogen choices for their preparation, leading to the most active catalysts. The supported catalysts were easily recovered by simple filtration and display no loss of activity when recycled. Further investigations on the application of these catalysts are under way in our laboratory.

Acknowledgments

We gratefully acknowledge the Ministero dell'Istruzione, dell'Università e della Ricerca (MIUR) within the project "Firb-Futuro in Ricerca" the Università di Perugia for financial support. This work was also supported by the Israel-Italy Joint Innovation Program for Scientific and Technological Cooperation in R&D 2012-2014. M.P.B., A.B., and M.L.S. thank Dr. Francesco Mura, Sapienza Nanoscience & Nanotechnology Laboratories (CNIS-SSN-Lab), for his helpful assistance in SEM analyses.

Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jcat.2013.10.009.

References

[1] (a) P. Agrigento, M.J. Beier, J.T.N. Knijnenburg, A. Baikerb, M. Gruttadauria, J. Mater. Chem. 22 (2012) 20728–20735;
(b) V. Sans, F. Gelat, M.I. Burguete, E. Garcia-Verdugo, S.V. Luis, Catal. Today 196 (2012) 137–147;
(c) V. Sans, F. Gelat, N. Karbass, M.I. Burguete, E. Garcia-Verdugo, S.V. Luis, Adv. Synth. Catal. 352 (2010) 3013–3021;
(d) J. Lu, P.H. Toy, Chem. Rev. 109 (2009) 815–838.

[2] C. Sherrington, Chem. Commun. (1998) 2275–2286.

[3] (a) Q. Liu, Y. Li, S. Shen, Z. Shanshan, Mater. Chem. Phys. 125 (2011) 315–318;
(b) X. Huanga, N. Qiua, D. Yuana, B. Huang, Talanta 78 (2009) 101–106;
(c) Q. Liu, L. Wang, A. Xiao, H. Yu, Q. Tan, J. Ding, G. Ren, J. Phys. Chem. 112 (2008) 13171–13174;
(d) Q.-Q. Liu, L. Wang, A.-G. Xiao, H.-J. Yu, Q.-H. Tan, Eur. Polym. J. 44 (2008) 2516–2522;
(e) A.K. Nyhus, S. Hagen, A. Bergej, J. Polym. Sci. 76 (2000) 152–159;
(f) A.K. Nyhus, S. Hagen, A. Bergej, J. Polym. Sci. A 38 (2000) 1366–1378;
(g) O. Okay, Prog. Polym. Sci. 25 (2000) 711–779.

[4] (a) D. Lanari, O. Piermatti, F. Pizzo, L. Vaccaro, Synthesis 44 (2012) 2181–2184;
(b) S. Calogero, D. Lanari, M. Orrù, O. Piermatti, F. Pizzo, L. Vaccaro, J. Catal. 282 (2011) 112–119;
(c) S. Bonollo, D. Lanari, F. Pizzo, L. Vaccaro, Org. Lett. 13 (2011) 2150–2152;
(d) D. Lanari, R. Ballini, A. Palmieri, F. Pizzo, L. Vaccaro, Eur. J. Org. Chem. (2011) 2874–2884;
(e) S. Bonollo, F. Fringuelli, F. Pizzo, L. Vaccaro, Synlett (2008) 1574–1578;
(f) S. Bonollo, F. Fringuelli, F. Pizzo, L. Vaccaro, Synlett (2007) 2683–2686;
(g) F. Fringuelli, R. Girotti, F. Pizzo, L. Vaccaro, Org. Lett. 8 (2006) 2487–2489;
(h) S. Bonollo, F. Fringuelli, F. Pizzo, L. Vaccaro, Green Chem. 8 (2006) 960–964.

[5] (a) G. Strappaveccia, D. Lanari, D. Gelman, F. Pizzo, O. Rosati, M. Curini, L. Vaccaro, Green Chem. 15 (2013) 199–204;
(b) S. Bonollo, D. Lanari, J.M. Longo, L. Vaccaro, Green Chem. 14 (2012) 164–169;
(c) T. Angelini, S. Bonollo, D. Lanari, F. Pizzo, L. Vaccaro, Org. Lett. 14 (2012) 4610–4613;
(d) T. Angelini, D. Lanari, R. Maggi, F. Pizzo, G. Sartori, L. Vaccaro, Adv. Synth. Catal. 354 (2012) 908–916;
(e) A. Zvagulis, S. Bonollo, D. Lanari, F. Pizzo, L. Vaccaro, Adv. Synth. Catal. 352 (2010) 2489–2496;
(f) F. Fringuelli, D. Lanari, F. Pizzo, L. Vaccaro, Green Chem. 12 (2010) 1301–1305;
(g) F. Fringuelli, D. Lanari, F. Pizzo, L. Vaccaro, Eur. J. Org. Chem. (2008) 3928–3932.

[6] .R. Henderson, C. Jimenez-Gonzalez, D. Constable, Green Chem. 13 (2011) 854–862.

[7] (a) D. Leow, C.-H. Tan Chem, Asian J. 4 (2009) 488–507;
(b) T. Ishikawa, T. Kumamoto, Synthesis (2006) 737–752.

[8] (a) R. Ballini, D. Fiorini, R. Maggi, C. Oro, A. Palmieri, G. Sartori, Synlett (2006) 1849–1851;
(b) S. Boisnard, J. Chastanet, J. Zhu, Tetrahedron Lett. 40 (1999) 7469–7472;
(c) Y.V.S. Rao, D.E. De Vos, P.A. Jacobs, Angew. Chem. Int. Ed. 36 (1997) 2661–2663;
(d) K. Iijima, W. Fukuda, M. Tomoi, J. Macromol. Sci. Pure Appl. Chem. (1992) 249–261.

[9] (a) S. Bonollo, D. Lanari, T. Angelini, F. Pizzo, A. Marrocchi, L. Vaccaro, J. Catal. 285 (2012) 216–222;
(b) F. Fringuelli, F. Pizzo, C. Vittoriani, L. Vaccaro, Chem. Commun. (2004) 2756–2757.

[10] S. Matsukawa, S. Fujikawa, Tetrahedron Lett. 53 (2012) 1075–1077.

[11] S. Yasuda, T. Yarada, Org. Biomol. Chem. 10 (2012) 4886–4890.

[12] D. Simoni, R. Rondanin, M. Morini, R. Baruchello, F.P. Invidiata, Tetrahedron Lett. 41 (2000) 1607–1610.

[13] D. Lanari, R. Ballini, S. Bonollo, A. Palmieri, F. Pizzo, L. Vaccaro, Green Chem. 13 (2011) 3181–3186.

[14] (a) As representative examples see: H.-L. Liu, H.-F. Jiang, Tetrahedron 64 (2008) 2120–2125;
(b) H.S. He, C. Zhang, C.K.-W. Ng, P.H. Toy, Tetrahedron 61 (2005) 12053–12057;
(c) C.W.Y. Chung, P.H. Toy, Tetrahedron 61 (2005) 709–715;
(d) L.-J. Zhao, H.S. He, M. Shi, P.H. Toy, J. Comb. Chem. 6 (2004) 680–683;
(e) T.J. Dickerson, N.N. Reed, K.D. Janda, Chem. Rev. 102 (2002) 3325–3344;
(f) P.H. Toy, K.D. Janda, Acc. Chem. Res. 33 (2000) 546–554.

[15] D. Du, J. Dong, Org. Biomol. Chem. 10 (2012) 8125–8131.

[16] (a) M. Rogozińska, A. Adamkiewicz, J. Mlynarski, Green Chem. 13 (2011) 1155–1157;
(b) M. Sodeoka, Y. Tsuchiya, Y. Hamashima, Org. Lett. (2006) 4851–4854;
(c) N. Halland, T. Hansen, K.A. Jorgensen, Angew. Chem. Int. Ed. 42 (2003) 4955–4957.

[17] H.-J. Knölker, B. Ahrens, P. Gonser, M. Heininger, P.G. Jones, Tetrahedron 56 (2000) 2259–2271.

[18] Q. Liu, L. Wang, A. Xiao, H. Yu, Q. Tan, J. Ding, G. Ren, J. Phys. Chem. C 112 (2008) 13171–13174.

[19] F.S. Macintyre, D.C. Sherrington, Macromolecules 37 (2004) 7628–7636.