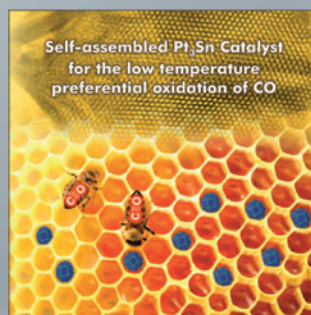
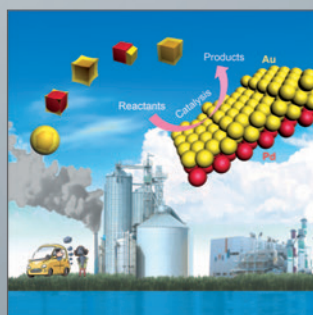
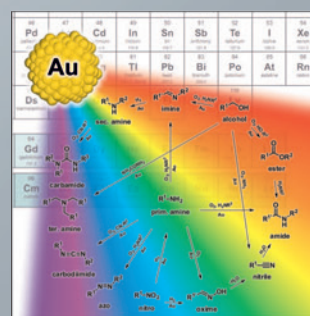
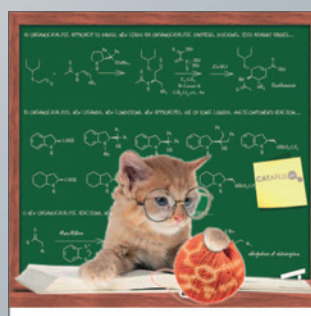
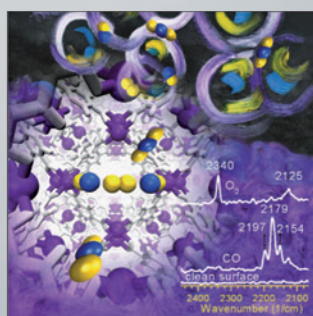
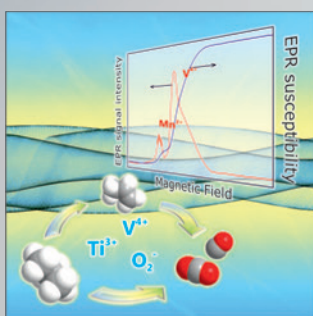
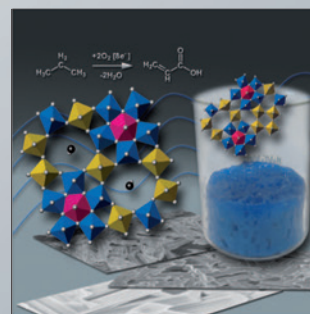
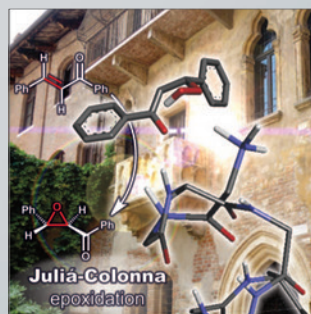
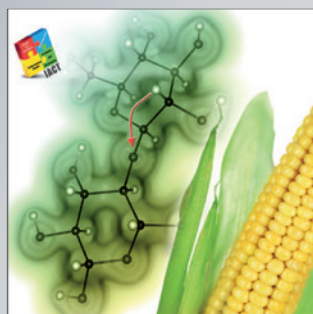
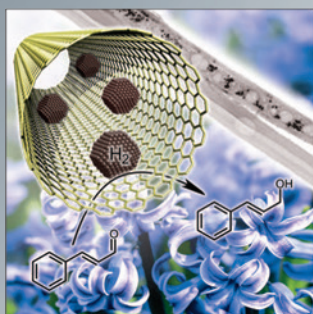


# Heterogeneous & Homogeneous & Bio- CHEM **CAT** CHEM

## CATALYSIS



# Reprint

© Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

A Journal of



WILEY-VCH

[www.chemcatchem.org](http://www.chemcatchem.org)

# Design of Heterogeneous Organocatalyst for the Asymmetric Michael Addition of Aldehydes to Maleimides

György Szöllősi<sup>\*[a]</sup> and Viktória Kozma<sup>[b]</sup>

Dedicated to Prof. Mihály Bartók on his 85<sup>th</sup> birthday.

Asymmetric Michael additions of isobutyraldehyde to maleimides catalyzed by optically pure diamines and their sulfonamides were investigated to develop heterogeneous chiral catalysts for these reactions. Encouraging results, i.e. complete transformations and optically pure products, were obtained using *para*-toluenesulfonamide or methanesulfonamide derivatives. Chiral solid materials were prepared by covalent bonding of the diamines on sulfonyl chloride functionalized supports. Immobilization of the amines was confirmed by FT-IR spectroscopy. The heterogeneous catalyst prepared by bonding

optically pure 1,2-diphenylethane-1,2-diamine to polystyrene support was highly enantioselective, giving results approaching those obtained using soluble sulfonamide derivatives. The anchored catalyst was recyclable few times keeping its activity followed by gradual small decrease in conversion, however, still providing high, up to 97%, enantiomeric excesses. These materials are among the first efficient recyclable catalysts used in the enantioselective Michael addition of aldehydes to maleimides.

## Introduction

Asymmetric catalytic procedures are the most versatile methods to produce optically pure chiral chemicals.<sup>[1]</sup> During the last few decades optically pure organocatalysts became frequently applied in the synthesis of chiral organic building blocks.<sup>[2]</sup> Initially natural compounds and their simple, easily prepared derivatives were employed. Broadening the applicability of these catalysts required finely tuned derivatives. Accordingly, similar with the chiral metal complexes,<sup>[3,4]</sup> heterogenization of organocatalysts became of paramount importance to obtain products using economic, sustainable and environmentally benign processes.<sup>[3,5]</sup>

Chiral organocatalysts are applied in various C–C bond forming enantioselective reactions. Among these, conjugate additions and more specifically, Michael additions, have outstanding practical importance, due to the possible application of a large variety, structurally diverse Michael donors and acceptors.<sup>[6]</sup> Asymmetric additions of carbon nucleophiles on maleimides result in the formation of chiral succinimide derivatives,<sup>[7]</sup> which may be transformed in valuable biologically active products.<sup>[8]</sup> Aliphatic aldehydes are among the frequently investigated carbon nucleophiles. Various chiral amine deriva-

tives were used as catalysts in these reactions,<sup>[9]</sup> such as primary diamine derivatives having 1,2-diphenylethylene or 1,2-cyclohexyl backbone bearing a hydrogen-bond donor group.<sup>[7,10]</sup> These reactions occur through enamine type mechanisms, during which the enamine formed by condensation of the aldehyde and catalyst reacts with the maleimide interacting with the catalyst through hydrogen-bonds. Among the most efficient hydrogen-bond donors is the sulfonamide group. Tuning the catalyst structure by modification of the steric and electronic properties of the substituents on the sulfonamide group was used to improve the performance of the catalysts. However, increasing the complexity of these organocatalysts diminished their major advantages, such as their low price and availability.

Since the reports of Noyori and co-workers on the use of chiral 1,2-diamine sulfonamides as ligands,<sup>[11]</sup> various diamine derivatives were applied as chiral ligands and organocatalyst.<sup>[7,10,12]</sup> During the present work our aim was to examine the effect of the structure of 1,2-diamine sulfonamides, in order to use these results in the development of efficient heterogeneous chiral organocatalyst for the asymmetric Michael addition of aldehydes to maleimides. To our knowledge, heterogeneous catalysts have not been applied in these enantioselective additions so far.

## Results and Discussion

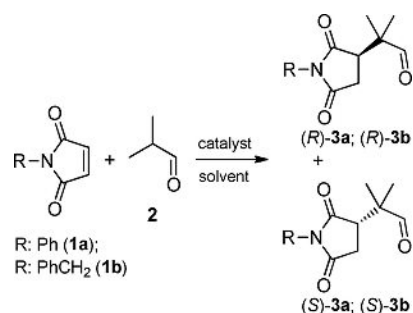
### Effect of the Catalyst Structure

Additions to *N*-phenylmaleimide (**1a**) and *N*-benzylmaleimide (**1b**) of isobutyraldehyde (**2**) were selected as test reactions (Scheme 1) for studying the influence of the chiral catalyst structure. We focused our investigations on using commercially

[a] Dr. G. Szöllősi  
MTA-SZTE Stereochemistry Research Group  
Dóm tér 8  
Szeged 6720 (Hungary)  
E-mail: szollosi@chem.u-szeged.hu

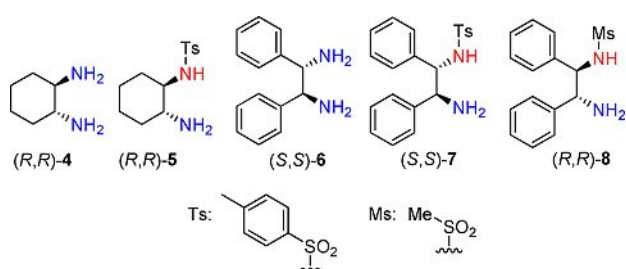
[b] V. Kozma  
Department of Organic Chemistry  
University of Szeged  
Dóm tér 8  
Szeged 6720 (Hungary)

Supporting information for this article is available on the WWW under <https://doi.org/10.1002/cctc.201800919>



**Scheme 1.** Addition of isobutyraldehyde (**2**) to *N*-phenylmaleimide (**1a**) or *N*-benzylmaleimide (**1b**).

available 1,2-cyclohexane and 1,2-diphenylethane derivatives (see Figure 1). Simple *para*-toluenesulfonamide derivatives

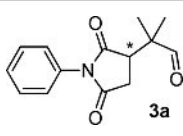
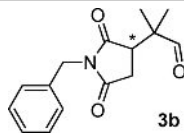


**Figure 1.** Structures of the chiral 1,2-diamine derivatives used as catalysts.

were not yet applied as catalysts in these reactions. Selected results are summarized in Table 1. During an initial screening with using **1a** and (*S,S*)-**7** catalyst in toluene, ClCH<sub>2</sub>CH<sub>2</sub>Cl or CHCl<sub>3</sub> solvents the best results were obtained in the latter, both at room temperature (rt, 24 °C) and 70 °C (not included). Thus, further investigations were carried out in CHCl<sub>3</sub>.

In accordance with previous reports both diamines, (*R,R*)-**4** and (*S,S*)-**6**, were less efficient than the corresponding sulfonamides ((*R,R*)-**5** and (*S,S*)-**7**) and provided lower conversions and *ee* values in reactions of both **1a** and **1b**, respectively. Close to complete conversions could be reached with the cyclohexane-1,2-diamine derived *para*-toluenesulfonamide derivative (*R,R*)-**5** in 5 hours at rt using 2 equivalents (eq.) isobutyraldehyde (Table 1, entry 3). However, the product resulted only in 95% *ee*. In contrast, using the 1,2-diphenylethane-1,2-diamine derivative (*S,S*)-**7** longer reaction time (24 h), higher temperature (70 °C) and higher reactant concentrations (less solvent) were necessary for close to complete transformation of the maleimide derivatives (entry 5). Satisfyingly, this catalyst afforded the **3a** product as single enantiomer (*ee* over 99%), whereas **3b** also resulted in high *ee* (up to 99%). At rt the transformation of the maleimides was not complete even in less solvent following 3 days (entries 6, 7). Slight differences in the results obtained in reactions of **1a** and **1b** were observed, especially when the amount of **2** and catalyst were reduced to half (entries 8, 9). Products resulted in one day reactions using doubled amounts of reactants could be isolated in high yields (entry 5). Interestingly, the methanesulfonamide (*R,R*)-**8** was similarly or even more efficient as the *para*-toluenesulfonamide derivatives (entry 10). Based on these results we considered possible that bonding optically pure 1,2-diphenylethane-1,2-diamine through either aromatic or aliphatic sulfonamide groups to insoluble supports may provide efficient enantioselective heterogeneous catalysts for the above reactions. This type of chiral solid materials were prepared and used previously as chiral ligands for preparing heterogenized metal complexes.<sup>[3e,13]</sup>

**Table 1.** Enantioselective addition of **2** to **1a** or **1b** catalyzed by chiral 1,2-diamines and their sulfonamides.<sup>[a]</sup>

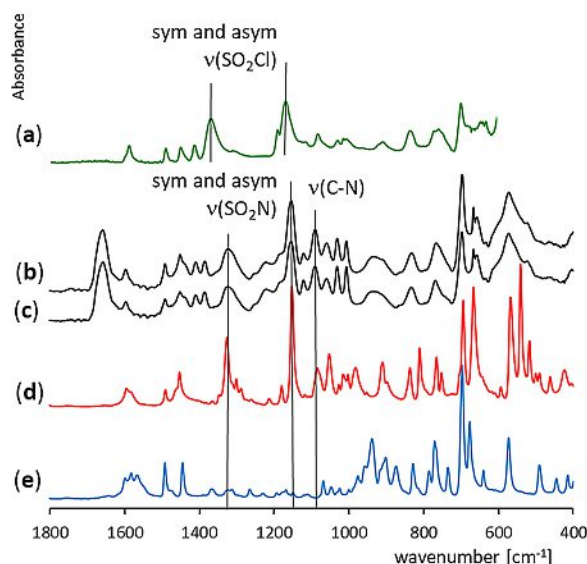
Entry	Catalyst	Vol (CHCl <sub>3</sub> ); T [mL; °C]	t [h]	 <b>3a</b>		 <b>3b</b>	
				Conv <b>1a</b> <sup>[b]</sup> [%]	<i>ee</i> <sup>[c]</sup> [%]	Conv <b>1b</b> <sup>[b]</sup> [%]	<i>ee</i> <sup>[c]</sup> [%]
1 <sup>[d]</sup>	( <i>R,R</i> )- <b>4</b>	2; 24	3	22	5 ( <i>R</i> )	18	8 ( <i>R</i> )
2 <sup>[d]</sup>	( <i>R,R</i> )- <b>5</b>	2; 24	3	92	95 ( <i>R</i> )	73	89 ( <i>R</i> )
3	( <i>R,R</i> )- <b>5</b>	2; 24	5	> 99	95 ( <i>R</i> )	93	90 ( <i>R</i> )
4	( <i>S,S</i> )- <b>6</b>	1; 70	24	93	75 ( <i>S</i> )	88	72 ( <i>S</i> )
5	( <i>S,S</i> )- <b>7</b>	1; 70	24	98; 88 <sup>[f]</sup>	> 99 ( <i>S</i> )	95; 86 <sup>[f]</sup>	98 ( <i>S</i> )
6	( <i>S,S</i> )- <b>7</b>	1; 24	72	55	99 ( <i>S</i> )	43	98 ( <i>S</i> )
7	( <i>S,S</i> )- <b>7</b>	0.5; 24	72	71	> 99 ( <i>S</i> )	62	99 ( <i>S</i> )
8 <sup>[d]</sup>	( <i>S,S</i> )- <b>7</b>	1; 70	24	99	> 99 ( <i>S</i> )	92	97 ( <i>S</i> )
9 <sup>[d,e]</sup>	( <i>S,S</i> )- <b>7</b>	1; 70	24	88	97 ( <i>S</i> )	80	97 ( <i>S</i> )
10	( <i>R,R</i> )- <b>8</b>	1; 70	24	99	> 99 ( <i>R</i> )	98	99 ( <i>R</i> )

[a] Reaction conditions: 0.03 mmol catalyst, 0.3 mmol **1a** or **1b** and 1.2 mmol **2** in CHCl<sub>3</sub> solvent; [b] conversions of **1a** or **1b** determined by gas-chromatography (GC); [c] enantiomeric excess (*ee*) determined by GC, in brackets the absolute configuration (*abs. conf.*) of the product according to previous reports<sup>[10]</sup>; [d] using 0.6 mmol **2**; [e] 0.015 mmol catalyst; [f] isolated yields of purified (by flash-chromatography) products obtained in reactions using 0.6 mmol **1a** or **1b**.

## Preparation and Application of Heterogeneous Chiral Catalysts

Immobilization of chiral organocatalysts on insoluble supports is a convenient method to prepare enantioselective heterogeneous chiral catalysts.<sup>[3,5,14]</sup> Various solid catalysts were developed for application in asymmetric Michael additions.<sup>[13]</sup> However, to our knowledge heterogeneous chiral catalysts were not yet applied in the enantioselective addition of aldehydes to maleimide derivatives. According to results obtained in homogeneously catalyzed reactions using optically pure 1,2-diamine-derived sulfonamides, anchoring 1,2-diamines by sulfonamide linkers on solid materials may result in efficient chiral catalysts, due to formation of the sulfonamide hydrogen-bond donor group on the surface during immobilization. Several sulfonyl chloride functionalized inorganic and organic materials are available commercially, which may be used as supports. Applying such materials we have prepared chiral solids both from optically pure cyclohexane-1,2-diamines and 1,2-diphenylethane-1,2-diamines, respectively (Scheme 2). Supports used in these experiments had different functional group loadings, different particle sizes, moreover the resins were cross-linked to different extent, as indicated by suppliers (see Experimental Section). Therefore, the obtained materials contained various amounts of anchored chiral amine, as calculated based on their N contents, as follows: **9-*R,R*-6** 0.75 mmol/g; **10-*R,R*-6** 1.15 mmol/g, **10-*S,S*-6** 1.15 mmol/g, **11-*S,S*-6** 1.25 mmol/g and **10-*R,R*-4** 1.10 mmol/g, respectively.

Immobilization of the chiral diamines by covalent bonding on supports was examined by infrared spectroscopy (FT-IR). The FT-IR spectra of **10-*S,S*-6** and **10-*R,R*-6** are shown in Figure 2 (b, c). These spectra were compared with that of the sulfonyl chloride functionalized support **10** (Figure 2, a) and those of (*S,S*)-**7** and (*S,S*)-**6** (Figure 2, d, e). The two chiral solids gave identical spectra. In accordance with previously published observations,<sup>[15]</sup> the symmetric O=S=O valence vibration band (at 1367 cm<sup>-1</sup> in the spectrum of **10**) appeared at 1323 cm<sup>-1</sup> in the spectra of the chiral solids, whereas the asymmetric O=S=O band shifted from 1168 cm<sup>-1</sup> (in the spectrum of **10**) to 1142 cm<sup>-1</sup>. Additionally, the band corresponding to the stretching vibration of the C–N bond may be identified at 1094 cm<sup>-1</sup>. Several other absorption bands found in the spectrum of (*S,S*)-**7**

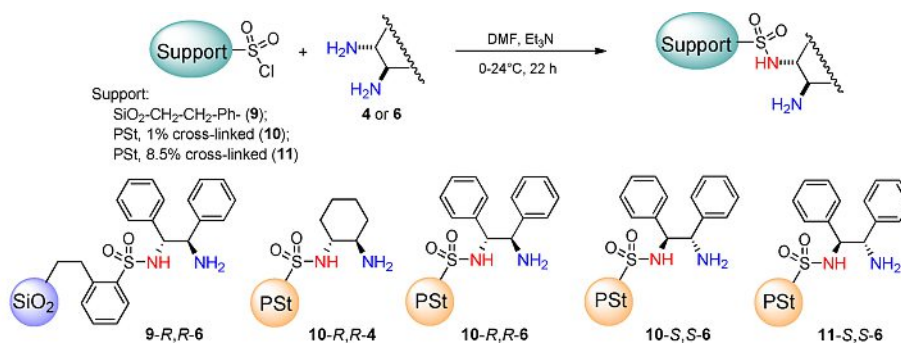


**Figure 2.** FT-IR spectra of **10** (a), **10-*S,S*-6** (b), **10-*R,R*-6** (c), (*S,S*)-**7** (d) and (*S,S*)-**6** (e).

also appeared in the spectra of the chiral resins overlapped with the characteristic vibration bands of the polymer support. The broad intense band at 1662 cm<sup>-1</sup> may be attributed to swelling of the polymer in *N,N*-dimethylformamide (DMF), the solvent used during the preparation of these materials. The above observations are indicative of polymer-bonded sulfonamide group formation.<sup>[15]</sup> Accordingly, we concluded that the chiral diamines were immobilized on the resin by sulfonamide linker groups.

The scanning electron micrographs of the support **10** and **10-*S,S*-6** showed that the spherical shape of the particles was not altered during the preparation of the chiral catalyst (Figure 3). However, the particle diameter increased from 70–120 μm to 130–170 μm due to swelling of the polymer in DMF; the presence of this solvent was detected by FT-IR spectroscopy (see above). This means a 2–6-fold increase in the volume of the particles.

Results obtained using the chiral solid catalysts in the addition of **2** to **1a** are summarized in Table 2. All heterogeneous chiral materials provided better *ees* than the correspond-



**Scheme 2.** Chiral solid catalysts prepared by immobilization of optically pure diamines through sulfonamide linkers (abbreviation of the catalysts: **support-*abs.conf*-diamine**).

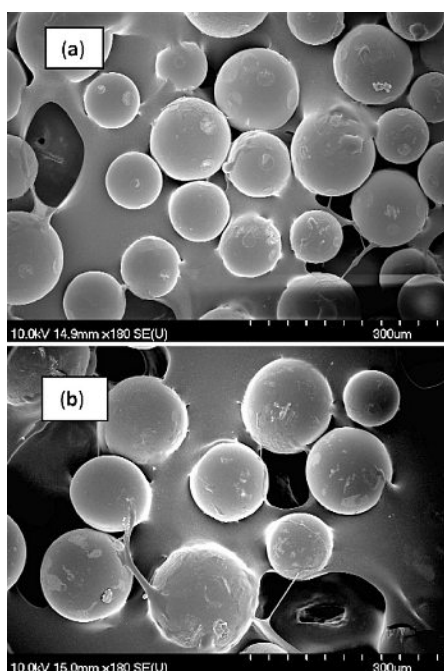


Figure 3. SEM micrographs of **10** (a) and **10-S,S-6** (b).

Entry	Catalyst	T [°C]	t [h]	Conv <sup>[b]</sup> [%]	ee <sup>[c]</sup> [%]
1	<b>9-R,R-6</b>	70	24	54	86 (R)
2	<b>9-R,R-6</b>	24	168	86	90 (R)
3 <sup>[d]</sup>	<b>9-R,R-6</b>	24	168	46	82 (R)
4	<b>10-R,R-4</b>	24	24	> 99	62 (R)
5	<b>10-R,R-6</b>	70	24	95 <sup>[e]</sup>	96 (R)
6	<b>10-S,S-6</b>	70	24	94	96 (S)
7	<b>10-S,S-6</b>	24	72	44	95 (S)
8	<b>11-S,S-6<sup>[f]</sup></b>	70	24	35	87 (S)
9	(S,S)- <b>6</b> + TsOH <sup>[g]</sup>	70	24	80	64 (S)
10	(S,S)- <b>6</b> + TsOH <sup>[h]</sup>	70	24	25	92 (S)

[a] Reactions performed using 100 mg chiral catalyst, 0.3 mmol **1a** and 1.2 mmol **2** in 1 mL CHCl<sub>3</sub>; [b] conversions of **1a** determined by GC; [c] enantiomeric excess (ee) determined by GC, in brackets the *abs. conf.* of the excess enantiomer; [d] result with reused catalyst; [e] the product was isolated in 80% yield; [f] 60 mg catalyst; [g] reaction using 0.03 mmol (S,S)-**6** and 0.015 mmol TsOH; [h] reaction using 0.03 mmol (S,S)-**6** and 0.03 mmol TsOH.

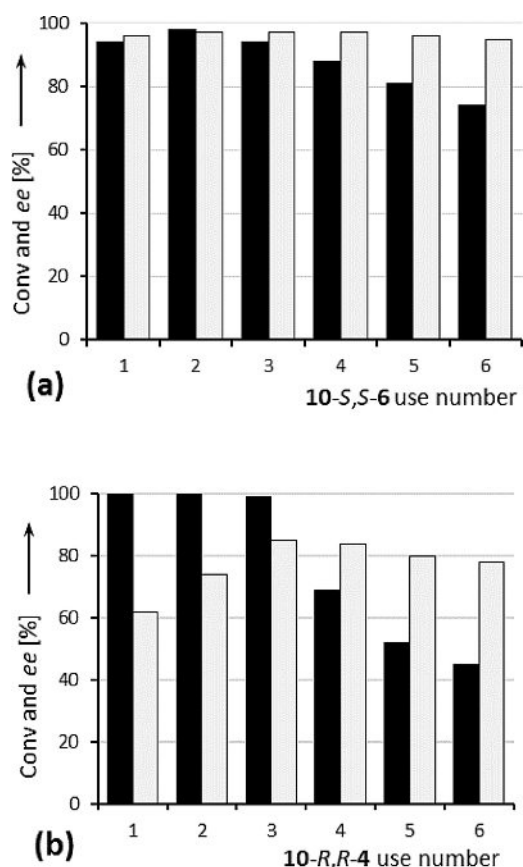
ing soluble diamines, i.e. (S,S)-**6** or (R,R)-**4** (compare Table 1, entries 1 and 4 with Table 2). Using the functionalized silica gel **9** or the polystyrene (PSt) resin **11** (higher degree of cross-linking as compared with **10**, see Experimental Section) as supports for bonding **6**, resulted in less active and less enantioselective catalysts (entries 1, 2 and 8), as compared with materials obtained from **10**. We assume that the silica surface had detrimental effect on the catalytic performance (**9-R,R-6**), due to involvement of the oxide surface both in bonding the diamine and in the asymmetric reaction. Moreover, upon recycling of the used catalyst the conversion decreased significantly (entry 3). The poor results obtained with catalyst **11-S,S-6** may be ascribed to less accessible catalytic species under the reaction conditions (different solvents are used

during immobilization and Michael additions, i.e. DMF and CHCl<sub>3</sub>, respectively) as compared with the catalysts prepared from **10**.

Slightly lower *ees* were attained with catalysts prepared using **10** as support as compared with the soluble sulfonamide (S,S)-**7** (entries 5–7). However, these values were much higher as compared with those resulted by the use of diamine (S,S)-**6**. These results showed that immobilization of diamines by sulfonamide linkers to solid materials may result in efficient chiral catalyst when a proper support is used. Lower *ee* was obtained using the immobilized cyclohexane-1,2-diamine **10-R,R-4** (entry 4), when compared with (R,R)-**5**, however, this solid catalyst also performed better than the corresponding soluble diamine (R,R)-**4**.

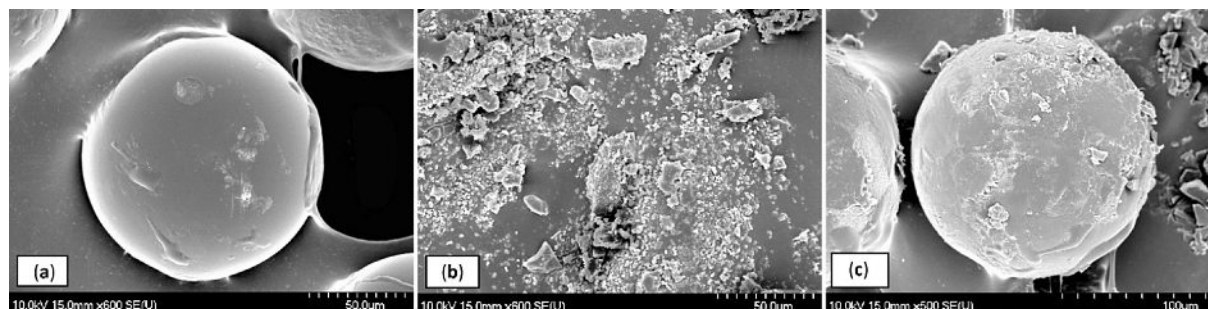
We considered possible that the lower *ee* values obtained with solid catalyst may be due to the presence of the corresponding chiral diamine bonded by ionic interactions on sulfonic acid surface groups. These groups could be generated during the immobilization process by hydrolysis of the surface sulfonyl chloride in the presence of trace amounts of water. Accordingly, control experiments were carried out to check the effect of a sulfonic acids using (S,S)-**6** catalyst and *para*-toluenesulfonic acid (TsOH) additive (entries 9, 10). Half eq. acid (as compared with the chiral diamine) resulted in decrease in the conversion and *ee* (compare Table 1, entry 4 with Table 2, entry 9). In presence of 1 eq. TsOH the conversion decreased drastically and the *ee* approached but didn't reached those obtained with the catalyst **10-S,S-6** or the soluble sulfonamide (S,S)-**7**. These results confirmed that the presence of surface sulfonic acid groups might decrease slightly both the conversion and the *ee*. However, the high stereoselectivities obtained using the solid catalysts may be attributed to the active surface sites resulted by bonding 1,2-diamines through sulfonamide linkers.

The recyclability of the enantioselective catalysts obtained using the polymeric support **10** was also examined. Selected results obtained by reusing these catalysts are shown in Figure 4. The activity of **10-S,S-6** decreased gradually starting from the fourth use while the *ee* value was unaltered even in the sixth run (Figure 4, a). The conversion decrease may be attributed to either deactivation of the surface chiral centers or the decrease of the number of the active sites due to deterioration of the solid material during reactions. However, the high *ee* values showed that the remaining sites were unaffectedly stereoselective. The catalyst having surface-bonded cyclohexane-1,2-diamine (**10-R,R-4**) also started to lose its activity following three uses (Figure 4, b). Interestingly, during the first three reactions the *ee* increased from 62% to 85%, followed by small decrease in succeeding runs. This initial *ee* increase may be explained by the previously suggested immobilization of the diamine by ionic bonding. These species will catalyze the reaction with lower stereoselectivity. However, may leach easily into solution during reactions. Accordingly, the remaining covalently bonded chiral sites will provide higher enantioselectivities in the second and third run as compared with the first. Following this the deterioration and deactivation of the chiral surface sites occurs.



**Figure 4.** Conversions (black bars) and ees (grey bars) obtained in recycling experiments of **10-S,S-6** (a) and **10-R,R-4** (b) catalysts in the Michael addition of **2** to **1a**; for reaction conditions see Table 2 entry 6 (a) and entry 4 (b).

Leaching of the material due to mechanical deterioration during stirring was verified using catalyst **10-S,S-6** in experiments carried out at room temperature by shaking the reaction mixture instead of magnetic stirring. The conversion hardly decreased even in the fifth run (from 44% to 41%), whereas the ee remained 95%. Thus, the decrease of the catalyst activity may be ascribed in part to leaching of the material owing to attrition of the particles. Deterioration of the catalyst particles during reactions was checked by SEM measurements (Figure 5). Using magnetic stirring the catalyst shredded in small pieces following five reactions (b). By shaking the mixture besides some smaller catalyst pieces most of the particles kept their



**Figure 5.** SEM micrographs of the as prepared **10-S,S-6** (a), **10-S,S-6** following 5 runs using magnetic stirring (b) or using agitation in a shaker (c).

spherical shape and size (c). However, irreversible transformation of the surface primary chiral amines by reaction with the excess aldehyde is also a possible reason of catalyst deactivation, as suggested in other asymmetric reactions catalyzed by heterogenized organocatalysts.<sup>[16]</sup>

The performances of the above heterogeneous chiral catalysts were also examined in the addition of **2** to **1b**. The amount of **2** was reduced to half (2 eq. instead of 4) in order to diminish the effect of the undesired irreversible transformation of the surface primary amine in reactions with the large excess of aldehyde. We also kept the conversions at slightly lower values to reveal clearly the catalysts performances upon reuse. Selected results are presented in Table 3. Similar tendencies

**Table 3.** Enantioselective addition of **2** to **1b** catalyzed by 1,2-diamines immobilized through sulfonamide linkers.<sup>[a]</sup>

Entry	Catalyst	Run no.	T [°C]	Conv <sup>[b]</sup> [%]	ee <sup>[c]</sup> [%]
1	<b>10-R,R-6</b>	1	70	83 <sup>[d]</sup>	97 (R)
2	<b>10-R,R-6</b>	2	70	86 <sup>[d]</sup>	97 (R)
3	<b>10-R,R-6</b>	3	70	84 <sup>[d]</sup>	97 (R)
4	<b>10-R,R-6</b>	4	70	75	97 (R)
5 <sup>[e]</sup>	<b>10-R,R-6</b>	1	24	25	96 (R)
6	<b>10-S,S-6</b>	1	70	81	97 (S)
7	<b>10-R,R-4</b>	1	24	> 99	61 (R)
8	<b>10-R,R-4</b>	2	24	> 99	78 (R)
9	<b>10-R,R-4</b>	3	24	92	85 (R)
10	<b>10-R,R-4</b>	4	24	70	86 (R)

[a] 100 mg chiral catalyst, 0.3 mmol **1b** and 0.6 mmol **2** in 1 cm<sup>3</sup> CHCl<sub>3</sub>, 24 h; [b] conversions of **1b** determined by GC; [c] enantiomeric excess (ee) determined by GC, *abs. conf.* of the excess enantiomer; [d] products obtained in these runs were unified and isolated in 75% yield. [e] 72 h.

were observed in this reaction, as in the previous (**1a**+**2**). The initial activity of **10-S,S-6**, which afforded around 85% conversions in three consecutive reactions, decreased in the fourth run, while the ee didn't alter by recycling the catalyst. In this reaction ee values as high as 97% could be obtained. Increase in the ee by recycling of **10-S,S-4** was observed in this reaction, too, similarly with the reaction of **1a**, accompanied by a more significant conversion decrease as compared with the **10-S,S-6** catalyst.

## Conclusions

In the present study, we designed heterogeneous chiral materials to catalyze the asymmetric Michael addition of aldehydes to *N*-substituted maleimides. For this purpose, the performances of simple optically pure 1,2-diamines and their commercially available sulfonamides were investigated. According to the results of these experiments we found promising the immobilization of the diamines through sulfonamide linkers starting from sulfonyl chloride functionalized supports. The chiral solid catalysts obtained using a polystyrene support and optically pure 1,2-diphenylethane-1,2-diamines were highly active and enantioselective heterogeneous catalysts, giving results which approached those attained with soluble catalysts. The catalysts were recyclable keeping their activity few runs followed by gradual small decrease in conversions, however still providing high, up to 97%, enantiomeric excesses. These chiral solid materials are the first heterogeneous catalysts, which were used in the enantioselective addition of an aldehyde to maleimides.

## Experimental Section

Supports used for preparing the heterogeneous chiral catalysts: 4-ethyl benzenesulfonyl chloride functionalized silica gel, 200–400 mesh, 1 mmol/g loading (**9**, Aldrich); polymer-bound sulfonyl chloride, 100–200 mesh, 1.5–2.0 mmol/g loading, 1% cross-linked (**10**, Aldrich) and polymer-bound sulfonyl chloride, 70–90 mesh, 2.5–3.0 mmol/g loading, 8.5% cross-linked with divinylbenzene (**11**, Aldrich) were commercial products. The optically pure diamines and sulfonamides, maleimides and isobutyraldehyde were obtained from Aldrich and used without purification. Solvents and reagents used in the preparation of the catalysts, in the asymmetric Michael additions and during chromatographic purifications were of analytical grade.

### Preparation and Characterization of the Heterogeneous Catalysts

All heterogeneous catalysts were prepared according to the following procedure; however, the support or reactants quantities were modified depending on the support functional group loading. In a 50 mL cylindrical glass flask having two inlets and containing a glass filter (Merrifield vessel) 1 g functionalized support (**10**) was suspended in 10 mL DMF. Following 5 min. swelling 4 mmol Et<sub>3</sub>N and 4 mmol (*S,S*)-**6** was added and the suspension was shaken 24 h. The liquid was removed by suction and the remaining solid material was washed once with 10 mL DMF and twice with 10 mL CH<sub>2</sub>Cl<sub>2</sub>, dried at rt and stored in a glass vial until use. By this method 1.11 g **10-S,S-6** catalyst was obtained from **10** and (*S,S*)-**6**. The chiral compound content was calculated based on results of elemental analysis using a Perkin-Elmer 2400 CHNS elemental analyser. Infrared spectra were collected with a Bio-Rad Digilab Divison FTS-65 A/896 FT-IR spectrometer operated in diffuse reflectance mode between 4000 and 400 cm<sup>-1</sup> at 2 cm<sup>-1</sup> resolution by averaging 256 scans. Scanning electron microscopic (SEM) measurements were carried out on a Hitachi S-4700 Tyle II FE-SEM microscope. The samples were mounted on a conductive carbon tape and sputter coated by a thin Au/Pd layer in Ar atmosphere prior to measurements.

## Michael Additions: General Procedure and Product Analysis

Michael additions were carried in 4 mL closed glass vials. In a typical run the given amount of catalyst was introduced into the reactor dissolved or suspended in the given amount of CHCl<sub>3</sub> followed by addition of 0.3 mmol *N*-fenil- or *N*-benzylmaleimide and the required amount of isobutyraldehyde (0.6 or 1.2 mmol). The vial was closed and was either stirred or shaken at room temperature or immersed in a preheated oil bath and stirred magnetically. After the given time the mixture was diluted to 3 mL with CHCl<sub>3</sub>. The soluble catalysts were extracted with 1 mL saturated NH<sub>4</sub>Cl aqueous solution, the aqueous phase was washed twice with 2 mL CHCl<sub>3</sub>, the unified organic phases were dried over MgSO<sub>4</sub> and analyzed. The suspensions obtained using heterogeneous catalysts were diluted to 3 mL with CHCl<sub>3</sub> and the catalyst was centrifuged. The solid was washed twice with 1 mL CHCl<sub>3</sub> and the obtained unified organic solution was treated as described for homogeneous reactions.

Products were identified by mass spectrometric analysis using Agilent Techn. 6890 N GC – 5973 MSD and a 30 m DB1-MS UI capillary column. Conversions and enantiomeric excesses (*ee*) were determined by gas-chromatographic analysis using Agilent 6890 N GC-FID equipped with a 30 m Cyclosil-B chiral capillary column (Agilent, J&W) and *n*-decane as internal standard. Products were isolated by flash chromatography on silica gel 60, 40–63 μm, using hexane isomers/ethyl acetate 2/1 (**3a**) or 4/1 (**3b**) mixtures as eluent. The purity of the fractions was checked by thin-layer chromatography on Kieselgel-G (Merck Si 254 F) layers. NMR spectra of the purified products were recorded on a Bruker Ascend 500 instrument at 500 (<sup>1</sup>H NMR) or 125 MHz (<sup>13</sup>C NMR) using CDCl<sub>3</sub> as solvent (see the Supporting Information).

## Acknowledgements

Financial support of the Hungarian National Science Foundation through OTKA Grant K 109278 is appreciated. The work was supported by the ÚNKP-17-2-II. New National Excellence Program of the Ministry of Human Capacities, Hungary (V. Kozma.). The authors thank to Tamás Gyulavári, Prof. Klára Hernádi, Dr. Gábor Varga and Dr. Gergő Motyán for their help in characterization of the chiral solid catalysts.

## Conflict of Interest

The authors declare no conflict of interest.

**Keywords:** Michael addition · asymmetric · heterogeneous · organocatalyst · maleimide

- [1] a) I. Ojima (Ed.) *Catalytic Asymmetric Synthesis*, 2nd ed., John Wiley & Sons, Hoboken, New Jersey, **2000**; b) H. U. Blaser, E. Schmidt (Eds.) *Asymmetric Catalysis on Industrial Scale: Challenges, Approaches and Solutions*, Wiley-VCH, Weinheim, **2004**; c) K. Mikami, M. Lautens (Eds.) *New Frontiers in Asymmetric Catalysis*, John Wiley & Sons, Hoboken, New Jersey, **2007**; d) I. Ojima (Ed.) *Catalytic Asymmetric Synthesis*, 3rd ed., John Wiley & Sons, Hoboken, New Jersey, **2010**.
- [2] a) B. List, K. Maruoka (Eds.) *Science of Synthesis: Asymmetric Organocatalysis*, Thieme, Stuttgart, **2012**; b) M. Waser, *Asymmetric Organocatalysis in Natural Product Synthesis*, Springer, Wien, **2012**; c) P. I. Dalko

- (Ed.) *Comprehensive Enantioselective Organocatalysis: Catalysts, Reactions, and Applications, Vol. 1–3*, Wiley-VCH, Weinheim, 2013.
- [3] a) K. Ding, Y. Uozumi (Eds.) *Handbook of Asymmetric Heterogeneous Catalysis*, Wiley-VCH, Weinheim, 2008; b) M. Gruttadauria, F. Giacalone, (Eds.) *Catalytic Methods in Asymmetric Synthesis: Advanced Materials, Techniques and Applications*, John Wiley & Sons, Hoboken, New Jersey, 2011; c) R. Šebesta (Ed.) *Enantioselective Homogeneous Supported Catalysis*, RSC Green Chemistry No. 15, RSC Publ., Cambridge, 2012; d) A. F. Trindade, P. M. P. Gois, C. A. M. Afonso, *Chem. Rev.* 2009, 109, 418–514; e) Gy. Szöllösi, *Catal. Sci. Technol.* 2018, 8, 389–422.
- [4] J. M. Fraile, J. I. García, C. I. Herreras, J. A. Mayoral, E. Pires, *Chem. Soc. Rev.* 2009, 38, 695–706.
- [5] a) M. Gruttadauria, F. Giacalone, R. Noto, *Chem. Soc. Rev.* 2008, 37, 1666–1688; b) M. Benaglia, *Recoverable and Recyclable Catalysts*, John Wiley & Sons, Chichester, 2009.
- [6] a) A. Berkessel, H. Gröger, *Asymmetric Organocatalysis*, Wiley-VCH, Weinheim, 2005, ch. 4, pp. 45–84; b) Y. Zhang, W. Wang, *Catal. Sci. Technol.* 2012, 2, 42–53; c) R. Rios, X. Companyó in *Comprehensive Enantioselective Organocatalysis, Vol. 3* (Ed.: P. I. Dalko), Wiley-VCH, Weinheim, 2013, ch. 33, pp. 977–1012; d) M. M. Heravi, P. Hajiabbasi, H. Hamidi, *Curr. Org. Chem.* 2014, 18, 489–511; e) D. A. Alonso, A. Baeza, R. Chinchilla, C. Gómez, G. Guillena, I. M. Pastor, D. J. Ramón, *Molecules* 2017, 22, 895.
- [7] P. Chauhan, J. Kaur, S. S. Chimni, *Chem. Asian J.* 2013, 8, 328–346.
- [8] a) A. Fredenhagen, S. Y. Tamura, P. T. M. Kenny, H. Komura, Y. Naya, K. Nakanishi, *J. Am. Chem. Soc.* 1987, 109, 4409–4411; b) M. L. Curtin, R. B. Garland, H. R. Heyman, R. R. Frey, M. R. Michaelides, J. Li, L. J. Pease, K. B. Glaser, P. A. Marcotte, S. K. Davidsen, *Bioorg. Med. Chem. Lett.* 2002, 12, 2919–2923; c) S. C. Bergmeier, K. A. Ismail, K. M. Arason, S. McKay, D. L. Bryant, D. B. McKay, *Bioorg. Med. Chem. Lett.* 2004, 14, 3739–3742; d) J. Pohlmann, T. Lampe, M. Shimada, P. G. Nell, J. Pernerstorfer, N. Svenstrup, N. A. Brunner, G. Schiffer, C. Freiberg, *Bioorg. Med. Chem. Lett.* 2005, 15, 1189–1192; e) J. Uddin, K. Ueda, E. R. O. Siwu, M. Kita, D. Uemura, *Bioorg. Med. Chem.* 2006, 14, 6954–6961; f) M. Kabata, T. Suzuki, K. Takabe, H. Yoda, *Tetrahedron Lett.* 2006, 47, 1607–1611; g) G.-J. Lin, S.-P. Luo, X. Zheng, J.-L. Ye, P.-Q. Huang, *Tetrahedron Lett.* 2008, 49, 4007–4010; h) J.-F. Bai, L.-L. Wang, L. Peng, Y.-L. Guo, L.-N. Jia, F. Tian, G.-Y. He, X.-Y. Xu, L. X. Wang, *J. Org. Chem.* 2012, 77, 2947–2953; i) K. Kamiński, J. Obniska, I. Chlebek, B. Wiklik, S. Rzepka, *Bioorg. Med. Chem.* 2013, 21, 6821–6830; j) M. Sortino, A. Postigo, S. Zacchino, *Molecules* 2013, 18, 5669–5683; k) Z. Han, P. Li, Z. Zhang, C. Chen, Q. Wang, X.-Q. Dong, X. Zhang, *ACS Catal.* 2016, 6, 6214–6218; l) K. Kamiński, *Curr. Top. Med. Chem.* 2017, 17, 858–874.
- [9] a) G.-L. Zhao, Y. Xu, H. Sundén, L. Eriksson, M. Sayad, A. Córdova, *Chem. Commun.* 2007, 734–735; b) T. Miyura, A. Masuda, M. Ina, K. Nakashima, S. Nishida, N. Tada, A. Itoh, *Tetrahedron: Asymmetry* 2011, 22, 1605–1609; c) T. C. Nugent, A. Sadiq, A. Bibi, T. Heine, L. L. Zeonjuk, N. Vankova, B. S. Bassil, *Chem. Eur. J.* 2012, 18, 4088–4098; d) C. G. Kokotos, *Org. Lett.* 2013, 15, 2406–2409; e) W. Yang, K.-Z. Jiang, X. Lu, H.-M. Yang, L. Li, Y. Lu, L.-W. Xu, *Chem. Asian J.* 2013, 8, 1182–1190; f) S. Muramulla, J.-A. Ma, J. C.-G. Zhao, *Adv. Synth. Catal.* 2013, 355, 1260–1264; g) C. E. Grünenfelder, J. K. Kisunzu, H. Wennemers, *Angew. Chem. Int. Ed.* 2016, 55, 8571–8574; *Angew. Chem.* 2016, 128, 8713–8716; *Angew. Chem.* 2016, 128, 8713–8716; *Angew. Chem. Int. Ed.* 2016, 55, 8571–8574; h) T. C. Nugent, A. A. E. D. Hussein, S. Ahmed, F. T. Najafian, I. Hussain, T. Georgiev, M. K. Aljournhawy, *Adv. Synth. Catal.* 2017, 359, 2824–2831.
- [10] a) F. Yu, Z. Jin, H. Huang, T. Ye, X. Liang, J. Ye, *Org. Biomol. Chem.* 2010, 8, 4767–4774; b) F. Xue, L. Liu, S. Zhang, W. Duan, W. Wang, *Chem. Eur. J.* 2010, 16, 7979–7982; c) J.-F. Bai, L. Peng, L.-L. Wang, L.-X. Wang, X.-Y. Xu, *Tetrahedron* 2010, 66, 8928–8932; d) T. Miura, S. Nishida, A. Masuda, N. Tada, A. Itoh, *Tetrahedron Lett.* 2011, 52, 4158–4160; e) Z.-W. Ma, Y.-X. Liu, W.-J. Zhang, Y. Tao, Y. Zhu, J.-C. Tao, M.-S. Tang, *Eur. J. Org. Chem.* 2011, 6747–6754; f) Z.-W. Ma, Y.-X. Liu, P.-L. Li, H. Ren, Y. Zhu, J.-C. Tao, *Tetrahedron: Asymmetry* 2011, 22, 1740–1748; g) A. Avila, R. Chinchilla, C. Nájera, *Tetrahedron: Asymmetry* 2012, 23, 1625–1627; h) M. Durmaz, A. Sirit, *Tetrahedron: Asymmetry* 2013, 24, 1443–1448; i) A. Avila, R. Chinchilla, E. Gómez-Bengoa, C. Nájera, *Tetrahedron: Asymmetry* 2013, 24, 1531–1535; j) S. Orlandi, G. Pozzi, M. Ghisetti, M. Benaglia, *New J. Chem.* 2013, 37, 4140–4147; k) A. Avila, R. Chinchilla, E. Gómez-Bengoa, C. Nájera, *Eur. J. Org. Chem.* 2013, 5085–5092; l) Z.-T. Song, T. Zhang, H.-L. Du, Z.-W. Ma, C.-H. Zhang, J.-C. Tao, *Chirality* 2014, 26, 121–127.
- [11] a) A. Fujii, S. Hashiguchi, N. Uematsu, T. Ikariya, R. Noyori, *J. Am. Chem. Soc.* 1996, 118, 2521–2522; b) N. Uematsu, A. Fujii, S. Hashiguchi, T. Ikariya, R. Noyori, *J. Am. Chem. Soc.* 1996, 118, 4916–4917; c) K. Matsumura, S. Hashiguchi, T. Ikariya, R. Noyori, *J. Am. Chem. Soc.* 1997, 119, 8738–8739.
- [12] a) T. Ikariya, A. J. Blacker, *Acc. Chem. Res.* 2007, 40, 1300–1308; b) J. E. D. Martins, M. Wills, *Tetrahedron: Asymmetry* 2008, 19, 1250–1255; c) L. Chen, S. Luo, *Chiral Primary Amine Catalysis, in: Enantioselective Organocatalyzed Reactions I: Enantioselective Oxidation, Reduction, Functionalization and Desymmetrization*, (Ed.: R. Mahrwald) Springer Sci., 2011, pp 147–184; d) W. Wang, J. Wang, S. Zhou, Q. Sun, Z. Ge, X. Wang, R. Li, *Chem. Commun.* 2013, 49, 1333–1335; e) M. Tsakos, C. G. Kokotos, *Tetrahedron* 2013, 69, 10199–10222; f) D. Wang, D. Astruc, *Chem. Rev.* 2015, 115, 6621–6686; g) R. H. Morris, *Acc. Chem. Res.* 2015, 48, 1494–1502; h) S. G. Zlotin, S. V. Kochetkov, *Russ. Chem. Rev.* 2015, 84, 1077–1099; i) H. G. Nedden, A. Zanotti-Gerosa, M. Wills, *Chem. Rec.* 2016, 16, 2623–2643.
- [13] R. Marcos, C. Jimeno, M. A. Pericàs, *Adv. Synth. Catal.* 2011, 353, 1345–1352.
- [14] a) Y. Arakawa, M. Wiesner, H. Wennemers, *Adv. Synth. Catal.* 2011, 353, 1201–1206; b) S. B. Ötvös, I. M. Mándity, F. Fülöp, *ChemSusChem* 2012, 5, 266–269; c) T. Tsubogo, T. Ishiwata, S. Kobayashi, *Angew. Chem. Int. Ed.* 2013, 52, 6590–6604; *Angew. Chem.* 2013, 125, 6722–6737; *Angew. Chem.* 2013, 125, 6722–6737; *Angew. Chem. Int. Ed.* 2013, 52, 6590–6604; d) R. Dalpozzo, *Green Chem.* 2015, 17, 3671–3686; e) R. Zhang, G. Yin, Y. Li, X. Yan, L. Chen, *RSC Adv.* 2015, 5, 3461–3464; f) R. Porta, F. Coccia, R. Annunziata, A. Puglisi, *ChemCatChem* 2015, 7, 1490–1499; g) J. Li, X. B. Li, S. S. Ma, J. Liu, B. H. Li, B. L. Li, *Bull. Korean Chem. Soc.* 2016, 37, 1259–1264; h) Á. Molnár, A. Papp, *Coord. Chem. Rev.* 2017, 349, 1–65; i) I. M. Mándity, S. B. Ötvös, Gy. Szöllösi, F. Fülöp, *Chem. Rec.* 2016, 16, 1018–1033; j) Gy. Szöllösi, L. Kovács, V. Kozma, V. J. Kolcsár, *React. Kinet. Catal.* 2017, 121, 293–306; k) Gy. Szöllösi, D. Gombkötő, A. Zs. Mogyorós, F. Fülöp, *Adv. Synth. Catal.* 2018, 360, 1992–2004.
- [15] a) A. del Prado, N. Briz, R. Navarro, M. Pérez, A. Gallardo, H. Reinecke, *Macromolecules* 2012, 45, 2648–2653; b) A. Mazumder, P. Garg, D. Pardasani, A. Kumar, A. Kumar Purohit, D. Kumar Dubey, *Anal. Methods* 2011, 3, 1574–1581;
- [16] H. Miyamura, G. C. Y. Choo, T. Yasukawa, W.-J. Yoo, S. Kobayashi, *Chem. Commun.* 2013, 49, 9917–9919.

Manuscript received: June 8, 2018

Accepted Article published: July 18, 2018

Version of record online: August 8, 2018