Macroporous Catalysts

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Asymmetric Inter- and Intramolecular Cyclopropanation Reactions Catalyzed by a Reusable Macroporous-Polymer-Supported Chiral Ruthenium(II)/Phenyloxazoline Complex**

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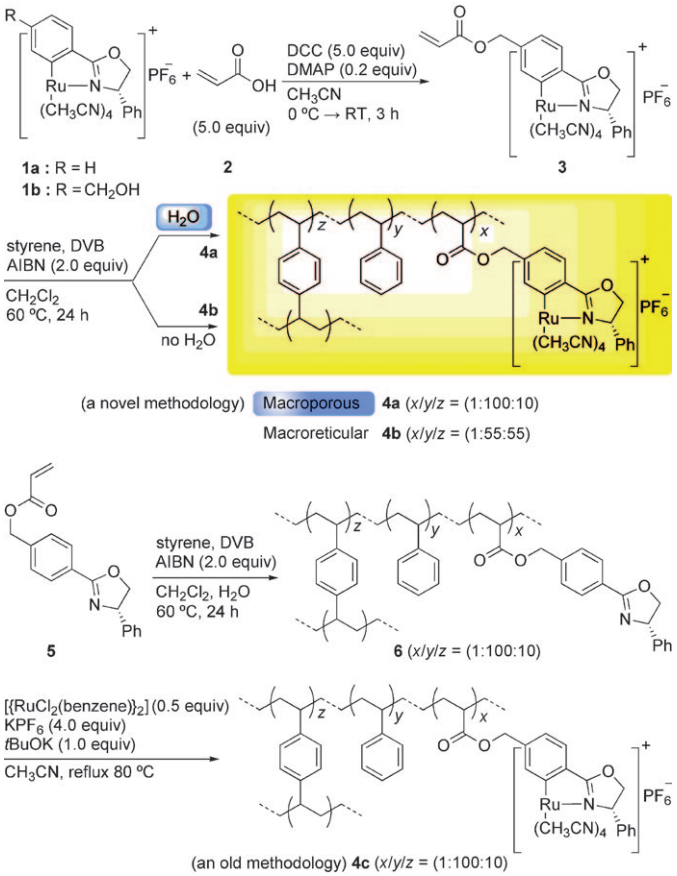
The use of polymer-supported chiral catalysts (PSCCs) in asymmetric synthesis has been extensively investigated over the past three decades, as PSCCs have several advantages over homogeneous catalysts.[1,2] PSCCs are easy to handle and can be readily separated from the reaction mixture and recycled. Further, when using PSCCs, there is little or no contamination of the reaction product by the metal traces. It is well known that PSCCs can be used as powerful catalysts in various asymmetric reactions.[1] Among these reactions, cyclopropanation has been studied in detail by several research groups[2,3] because cyclopropyl moieties are promising structural units that can be easily converted into useful compounds that have medical, pharmaceutical, and insecticidal properties.[4] In addition, cyclopropanes fused to five-or six-membered lactone rings are widely found in natural products.[5] Despite the tremendous efforts devoted to intermolecular cyclopropanations using polymer-supported chiral bis(oxazoline)s[6] or chiral pyridine–bis(oxazoline)s,[7] relatively low to moderate yields have so far been achieved. After an extensive literature survey, we concluded that all of the previously reported PSCCs depended on the polymerization of a monomeric chiral ligand or the grafting of a chiral ligand onto a polymeric support and subsequent complexation with a metal.[1–3] Unfortunately, in the PSCCs synthesized by these methods, there was a lack of certainty in the engagement between all the ligand's sites in the polymer network and the metal centers, as shown by the low yields of the products. Furthermore, we found that most of the cross-linking polymers synthesized previously using the above-mentioned strategies were macroreticular, and that the active sites were mainly present on the surface, because of which the yields obtained in the presence of these catalysts were low. The sterically hindered structure of box, pybox, and their derivatives was possibly one of the factors responsible for the low yields of the products obtained in the cyclopropanation reactions. Such factors are perhaps indicated by the leachability of the metal and the decline in reusability. Hence, the reactivity and enantioselectivity of the previously reported PSCCs were unsatisfactory.

Herein, we report a novel strategy for synthesizing a macroporous polymer-supported chiral ruthenium(II)/phenyloxazoline (Ru^{II}/pheox) complex (**4a**; Scheme 1). **4a**



Scheme 1. A novel strategy for the synthesis of polymer-supported chiral catalysts. DCC = dicyclohexylcarbodiimide, DMAP = 4-(dimethylamino)pyridine.

afforded high reactivity, enantioselectivity, and reusability, even after storage of the used catalyst, without any loss of its catalytic activity or selectivity in inter- or intramolecular cyclopropanation reactions. First, the novel chiral ruthenium(II)/pheox complex **1a** was successfully prepared in a very good yield (80%).[8] Interestingly, **1a** was an efficient and

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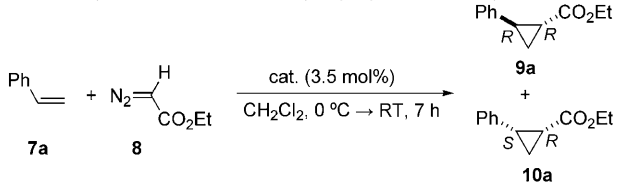
highly enantioselective catalyst for the intermolecular cyclopropanation of styrene with ethyl diazoacetate (EDA, 98% *ee*; Table 1, entry 5). Encouraged by this result, **1a** was easily fuctionalized to afford **1b** in excellent yield (92%). The

Table 1: Comparison of different polymerization strategies and homogeneous catalysts in intermolecular cyclopropanation of styrene.



Entry	Catalyst	Yield [%][d]	*ee* [%][e]		**9a**/**10a**[f]
			9a	**10a**	
1	**4a**[a]	74	94	72	88:12
2	**4a**[b]	70	98	89	90:10
3	**4b**	31	84	38	82:18
4	**4c**	27	74	36	83:17
5	**1a**[c]	66	98	91	90:10

[a] A 0.107 mmol g^{-1} loading of **4a** was used. [b] A 0.210 mmol g^{-1} loading of **4a** was used. [c] Homogeneous catalyst (for preparation details, see the Supporting Information). [d] Yield of isolated product is based on the amount of EDA consumed. [e] Determined by GLC using Chiral β-Dex 120 and the major isomer is indicated in parenthesis. [f] Determined by ^{1}H NMR spectroscopy.

monomeric chiral ruthenium(II)/pheox complex **3** was smoothly prepared from **1b** in 80% yield as a new monomeric complex that readily underwent crosslinking polymerization with styrene and 1,4-divinyl benzene (DVB) in the presence of 2,2′-azobisizobutyronitrile (AIBN) as an initiator. The reaction was carried out in the presence of water to afford the macroporous polymer-supported chiral ruthenium(II)/pheox **4a** in quantitative yield (Scheme 1, Figure 1). To the best of our knowledge, this is the first report of the polymerization of a ruthenium(II)/pheox complex.[1–3]

The exact amount of the chiral ruthenium(II)/pheox complex loaded onto the polymeric network was determined by elemental analysis of the nitrogen content. The FTIR spectrum of the polymeric catalyst **4a** showed absorption bands at 2261 cm^{-1}, 1731 cm^{-1}, and 1617 cm^{-1}, which corresponded to the C≡N group of the acetonitrile ligands, the ester carbonyl group, and the C=N of the oxazoline ring, respectively. Figure 2 shows a comparison of the FTIR specra of **3**, **4a**, and **5**. As expected, the IR spectrum of **3** was similar to that of **4a**, and the peaks in the spectrum of **3** were highly intense and showed slight shifts. However, the C≡N band of the acetonitrile group disappeared from the monomeric ligand **5**.

Initially, we evaluated the catalytic activity of our novel catalyst **4a** in the intermolecular cyclopropanation of styrene with EDA. We optimized the reaction conditions and found that dichloromethane was the ideal swelling solvent, in which a high *ee* value for the *trans* product could be obtained. Furthermore, the product could be isolated in a remarkably high yield (99%) when 6.0 mol% of the active catalyst (ruthenium(II)/pheox complex) was used.[9] In order to

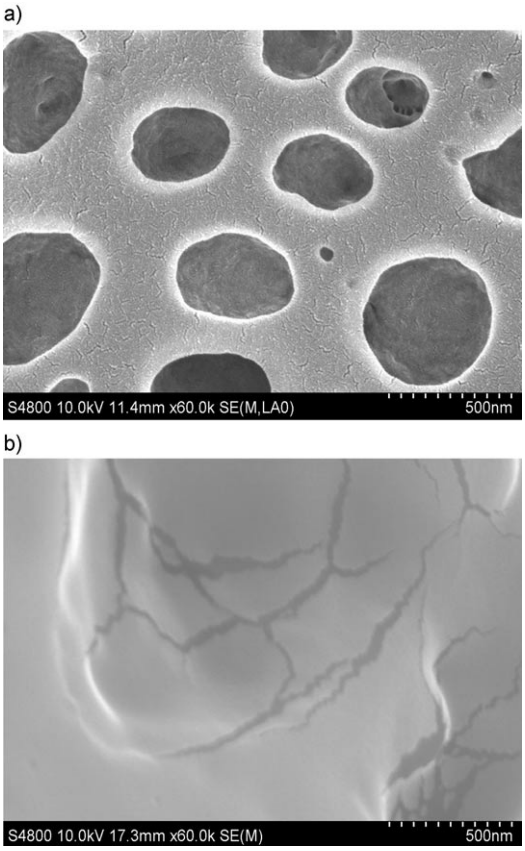


Figure 1. SEM images of a) macroporous **4a** and b) macroreticular **4b** polymer-supported chiral Ru^{II}/pheox complex.

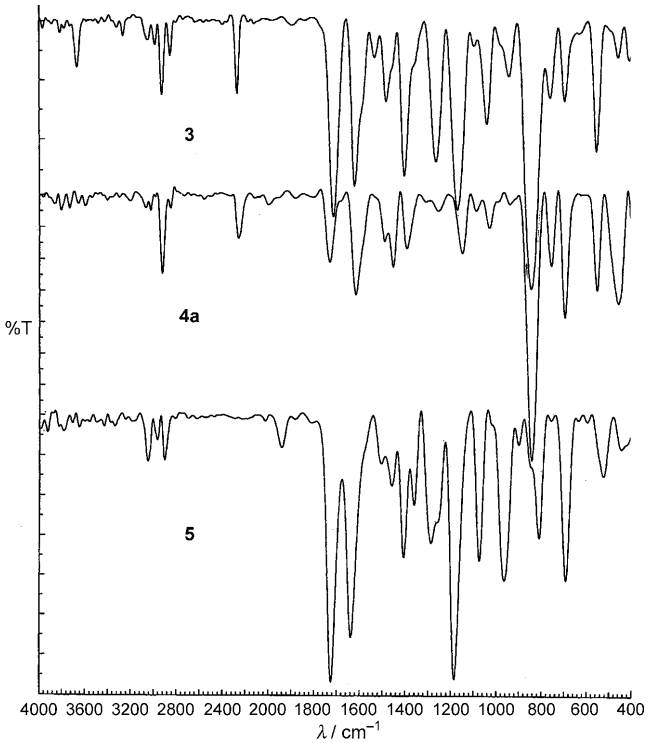


Figure 2. Comparison between the FTIR spectra of **3**, **4a**, and **5**.

confirm the potential activity and selectivity of catalyst **4a**, we compared its catalytic efficiency with the classical polymer-supported preparation techniques and the homogeneous catalyst, as represented by **4c** (polymerization of the ligand followed by complexation with the metal), **4b** (macroreticular type), and **1a** (homogeneous catalyst), as shown in Table 1. Interestingly, the reactivities and enantioselectivities of **4a** in the intermolecular cyclopropanation of styrene with EDA were found to be higher than those of **4c** and **4b** (Table 1, entries 1–4). In addition, the yield of the cyclopropanation product obtained with **4a** was considerably higher than that of the product obtained in the presence of a homogeneous catalyst (Table 1, entry 5). We attributed the high catalytic efficiency of **4a** to its macroporous structure, as revaled by SEM (Figure 1).[10] Because of this macroporosity, the internal surface area of **4a** was greater than that of the rigid macroreticular-type catalysts which were used in most of the previous studies.[6b,11] In contrast to bis(oxazoline) and its derivatives,[1–3] which are sterically hindered, our pheox complex has a simple structure with much-less steric hinderance, because of which the reagents can easily reach the active sites, as shown in the mechanism Figure 3.

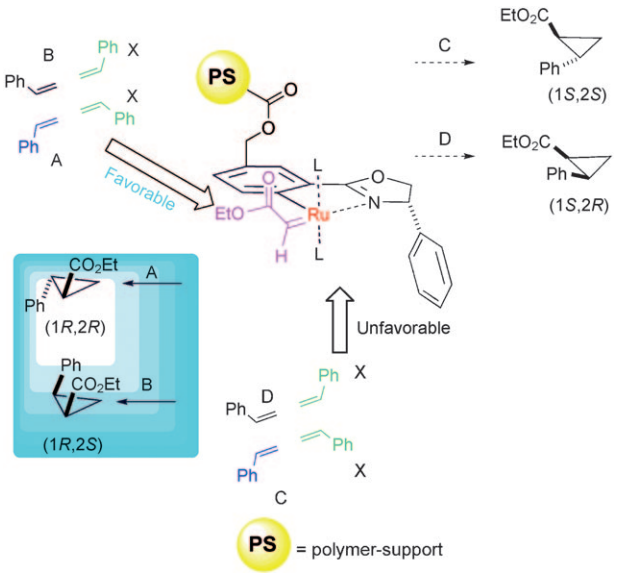
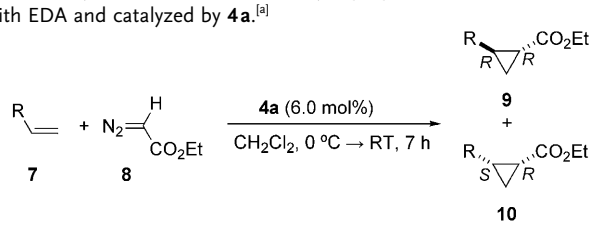
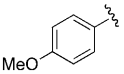
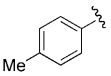
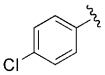
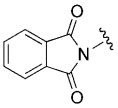
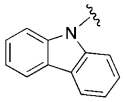
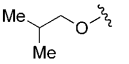
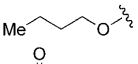


Figure 3. Plausible mechansim for the **4a**-catalyzed intermolecular cyclopropanation of styrene with EDA.

To examine the catalytic activity of **4a** with various substrates, the intermolecular cyclopropanation reactions of a series of terminal olefins with various electronic properties were carried out using EDA as a carbene source (Table 2). With the slow addition of EDA (to avoid the dimerization as side-products), the intermolecular cyclopropanation reactions of styrene and its electron-donating and electron-withdrawing derivatives (Table 2, entries 1–4) were achieved in high yields and with excellent *trans* selectivities and diastereoselectivities. Impressive results were also obtained for the intermolecular cyclopropanation of various *N*-vinyl derivatives (Table 2, entries 5–9). It is noteworthy that **4a** also appeard to be effective for the intermolecular cyclopropanation of sterically and nonsterically hindered vinyl ethers (Table 2, entries 10–12). In addition, vinyl acetate was readily cyclopropanated (Table 2, entry 13) in good yield and with excellent enantio- and diastereoselectivity. Next, the reusability of **4a** was examined by isolating it from the reaction mixture (centrifugation, washing with *n*-hexane, diethyl ether, and acetonitrile, then drying). Interestingly, **4a** could be reused more than ten times, even after three months of storage of the used catalyst, without any loss in its catalytic

Table 2: Asymmetric intermolecular cyclopropanation of various olefins with EDA and catalyzed by **4a**.[a]



Entry	R		Yield [%][b]		ee [%][c] 9		ee [%][c] 10		9/10[d]
1		**7a**	99	**9a**	98	**10a**	71	89:11	
2		**7b**	93	**9b**	98	**10b**	53	94:06	
3		**7c**	91	**9c**	98	**10c**	96	94:06	
4		**7d**	>99	**9d**	98	**10d**	28	94:06	
5		**7e**	96	**9e**	96	**10e**	>99	88:12	
6		**7f**	94	**9f**	94	**10f**	n.d.	99:01	
7		**7g**	90	**9g**	97	**10g**	55	92:08	
8		**7h**	96	**9h**	>99	**10h**	n.d.	99:01	
9		**7i**	96	**9i**	91	**10i**	91	70:30	
10		**7j**	90	**9j**	96	**10j**	86	76:24	
11		**7k**	98	**9k**	96	**10k**	92	90:10	
12		**7l**	99	**9l**	91	**10l**	62	80:20	
13		**7m**	80	**9m**	97	**10m**	95	90:10	

[a] A 0.107 mmol g^{-1} loading of **4a** was used. [b] Yield of isolated product is based on the amount of EDA consumed. [c] Determined by GLC or HPLC analysis and the major isomer is indicated in parenthesis. [d] Determined by ^{1}H NMR spectroscopy. n.d. = not determined.

activity or selectivity in the intermolecular cyclopropanation of the electron-rich *tert*-butyl vinyl ether (unstable towards Lewis acids and affords easily separable *cis* and *trans* isomers) with EDA, as shown in Table 3.

Table 3: Reusability of **4a** in intermolecular cyclopropanation of *tert*-butyl vinyl ether with EDA.[a]

Run	1	2	3	4	5	6	7	8	9	10	11[b]
trans ee [%]	96	96	96	96	96	96	96	96	96	95	96
cis ee [%]	86	85	86	86	86	86	85	86	86	84	85
Yield [%]	90	90	90	90	91	91	90	90	90	90	90

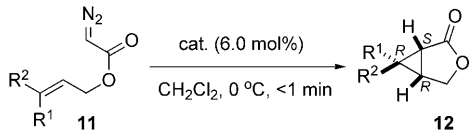
[a] Reaction conditions are the same as in Table 2. [b] **4a** was reused after the ten-time-used catalyst had been stored for three months.

Moreover, **4a** could be reused at least three times in the case of *N*-vinyl-2-pyrrolidone (Table 2, entry 5).[12] As an evidence of the durability of this catalyst, we checked whether or not it has a leaching ability by suspending it in dichloromethane and stirring for one day then decanting the filtrate and washing the catalyst several times. The catalytic activity of this filtrate was tested in the intermolecular cyclopropanation of styrene with EDA and, as we expected, no products were formed except for small amounts of dimers and starting materials.

Intramolecular cyclopropanation is a useful reaction for the synthesis of natural products.[5,13] To the best of our knowledge, there have been no reports of asymmetric intramolecular cyclopropanation reactions catalyzed by PSCCs. Herein, we also report the first application of a polymer-supported chiral ruthenium(II)/pheox catalyst to an asymmetric intramolecular cyclopropanation of a series of *trans*-allylic diazoacetates. Based on the optimized reaction conditions for intermolecular cyclopropanations, we evaluated the catalytic efficiency of **4a** in comparison with homogeneous catalyst **1a** and other types of polymers (**4b**, **4c**) in the intramolecular cyclopropanation of *trans*-cinnamyl diazoacetates (Table 4, entries 1–4). We found that **4a** showed excellent reactivity and enantioselectivity not only compared with other types of polymers but also compared with the homogeneous catalyst analogue. Furthermore, **4a** has the ability to be reused at least five times with no loss in activity or selectivity. To explore the scope and limitations of this intramolecular cyclopropanation reaction by using **1a** or **4a** as the catalyst, the reaction of a diverse range of *trans*-allylic diazoacetates, which were derived from the corresponding allylic alcohols using the Fukuyama method,[14] were also studied (Table 4, entries 5–18). Excellent reactivities and enantioselectivities were obtained with both the homogeneous and heterogeneous catalysts. Interestingly, **1a** promoted the intramolecular cyclopropanations of all of the diazo substrates in less than 1 minute with high yields and *ee* values compared with the recently reported homogeneous catalysts.[15,16] In addition, *trans*-cinnamyl diazoacetates with electron-donating and electron-withdrawing substituents in the *para*-position (Table 4, entries 5–10) could be effectively cyclopropanated. Similar results were also obtained with *trans*-allylic diazoacetates derivatives containing long and short aliphatic chains (Table 4, entries 11–18).

In summary, we have successfully designed and synthesized a novel macroporous polymer-supported chiral ruthenium(II)/phenyloxazoline (Ru^{II}/pheox) complex (**4a**). This catalyst system showed excellent reactivity and enantioselectivity when used along with a variety of substrates in inter-

Table 4: Asymmetric intramolecular cyclopropanation of various *trans*-allylic diazoacetates catalyzed by **4a** or **1a**.[a]



Entry	Substrate **11**	R^1	R^2	cat.	**12**	Yield [%][c]	*ee* [%][d]
1				**4a**[b]		99	97
2				**4b**		57	85
3	**11a**	H	C_6H_5	**4c**	**12a**	80	91
4				**1a**		98	96
5				**4a**		99	84
6	**11b**	H	*p*-$NO_2C_6H_4$	**1a**	**12b**	99	>99
7				**4a**		96	95
8	**11c**	H	*p*-MeC_6H_4	**1a**	**12c**	98	96
9				**4a**		98	83
10	**11d**	H	*p*-$MeOC_6H_4$	**1a**	**12d**	98	83
11				**4a**		98	89
12	**11e**	CH_3	CH_3	**1a**	**12e**	>99	95
13				**4a**		98	94
14	**11f**	CH_3	prenyl	**1a**	**12f**	99	97
15				**4a**		97	93 (92)[e]
16	**11g**	CH_3	geranyl	**1a**	**12g**	99	97 (98)[e]
17				**4a**		94	96
18	**11h**	CH_3	2-propenyl	**1a**	**12h**	97	96

[a] Reaction time with **1a** was less than 1 min and with **4a** it was 1–4 h. [b] **4a** loading (0.75 mmol g^{-1}). **4a** could be reused at least five times without any loss of reactivity and enantioselectivity. [c] Yield of isolated product. [d] Determined by GC or HPLC analysis and the major isomer is indicated in parenthesis. [e] The *cis* isomer.

and intramolecular cyclopropanation reactions. Furthermore, it could be reused even after ten applications and three months of storage without loss of its catalytic activity and selectivity. In addition, no significant leaching of the catalyst was detected. The polymer-supported chiral ruthenium(II)/pheox catalyst is expected to provide many further opportunities in asymmetric catalysis. Further investigation is currently underway to extend this methodology with various homogeneous catalysts.

Experimental Section

General procedure for intermolecular cyclopropanation catalyzed by **4a**: The polymer-supported chiral ruthenium(II)/pheox complex **4a** (170.0 mg, 0.018mmol) was evacuated and backfilled with argon and suspended in CH_2Cl_2 (3.5 mL). An olefin (1.50 mmol) was injected through the side-arm via syringe and a toluene solution of EDA (34.2 mg, 0.30 mmol, ca. 0.2 M) was injected through a microsyringe controlled by mechanical feeder (ca. 0.37 mL h^{-1}) over 4 h at 0 °C. After stirring for an additional 3 h, the mixture was concentrated under reduced pressure and the polymeric catalyst was recoverd from the reaction mixture (centrifugation, washing with *n*-hexane, diethyl ether, and acetonitrile, then drying). The combined filtrate which contains the cyclopropane product was concentrated under reduced pressure and the residue was purified by column chromatography on silica gel with *n*-hexane/EtOAc as an eluent to give the desired product. The *trans*/*cis* ratios were determined from the crude NMR spectra, and the *ee* values were determined by GLC or HPLC analysis.

General procedure for intramolecular cyclopropanation reactions catalyzed by **4a**: A solution of allylic diazoacetate in CH_2Cl_2 (0.1 mmol, ca. 0.1 M) was added to a suspension of polymer-supported ruthenium(II)/pheox complex (**4a**) (80.0 mg, 0.006 mmol) in CH_2Cl_2 (2.0 mL) at 0 °C. After the starting material had completely reacted (1–4 h), *n*-hexane (4.0 mL) was added, followed by centrifugation of the mixture. The product was collected by decantation and the residue was washed three times with CH_2Cl_2/*n*-hexane (1:4 v/v). The polymer was dried under vacuum before the next cycle. The collected product was condensed under vaccum and the residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc = 10:1) to afford the corresponding bicyclic lactone. The enantiomeric excesses of products were determined by HPLC or GC analysis.

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[8] For the preparation of homogeneous catalyst **1a**, see the Supporting Information.

[9] For more details about the solvent effect and catalyst loading, see the Supporting Information.

[10] The SEM images of macroporous (**4a**) and macroreticular catalysts (**4b**; before and after use) are available in the Supporting Information.

[11] a) For discussions of the advantages of the macroporous polymer over the macroreticular type, see: G. Odian, *Principles of Polymerization*, Wiley, New York, **2004**, p. 762; b) F. Z. Dörwald, *Organic Synthesis on Solid Phase*, Wiley-VCH, Weinheim, **2000**, p. 19.

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