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Polymer immobilization of bis(oxazoline) ligands using dendrimers as cross-linkers

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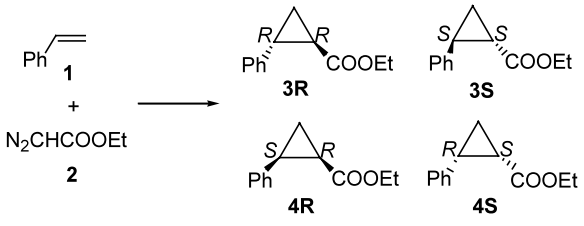
Abstract—Homopolymers of bis(oxazoline) ligands can be used to prepare efficient catalysts for cyclopropanation reactions. However, the low accessibility to most bis(oxazoline) moieties leads to a low copper loading. As a consequence, the transmission of chiral information from the complexed polymer is not very efficient and only a few chiral cyclopropane molecules are obtained from each molecule of chiral ligand. The use of suitable dendrimers as cross-linkers in the polymerization process allows better copper functionalization. As a consequence the productivity of chiral cyclopropanes per molecule of chiral ligand greatly increases, which improves the ligand economy and the chirality transfer. © 2003 Elsevier Science Ltd. All rights reserved.

1. Introduction

Interest in the immobilization of chiral catalysts has increased over the last few years,[1] a situation that is related to the potential advantages of heterogeneous catalysts. In this context, several strategies for the immobilization of bis(oxazoline) metal complexes have been developed.[2] Bis(oxazoline) and azabis(oxazoline)-copper complexes have been immobilized by electrostatic interaction with anionic supports.[3] The same ligands have been grafted to soluble organic polymers and recovered by precipitation after the reaction.[4] Bis(oxazolines) have been covalently bonded to inorganic supports.[5,6] Finally, bis(oxazolines), and the related pyridine-bis(oxazolines), have been immobilized onto organic polymers by grafting and polymerization.[6–9] One of the common features that can be drawn from these studies is that the support has an enormous influence on both the catalytic activity and the stereoselectivity of the reaction. In particular, in the case of organic polymers this influence is clearly related to the morphology of the polymer. In this regard the accessibility of the immobilized chiral ligand is an important factor and we have introduced the concept of ligand economy, defined as the number of molecules of product obtained from each molecule of chiral ligand immobilized.[9] This concept can be considered as a TON referred to the chiral ligand, and it will have the same value as the TON only when all the molecules of immobilized chiral ligand are transformed into catalytic centers. In an effort to clarify this point we compare the behavior of the same bis(oxazolines) in homogeneous phase and immobilized onto different polymers and show that the use of dendrimers as cross-linkers is an extremely useful way to improve ligand economy. The cyclopropanation reaction between equimolecular amounts of styrene and ethyl diazoacetate[10] (Scheme 1) is used as the test case to measure the efficiency of the solid-supported catalysts.



Scheme 1. Cyclopropanation reaction between styrene **1** and ethyl diazoacetate **2**.

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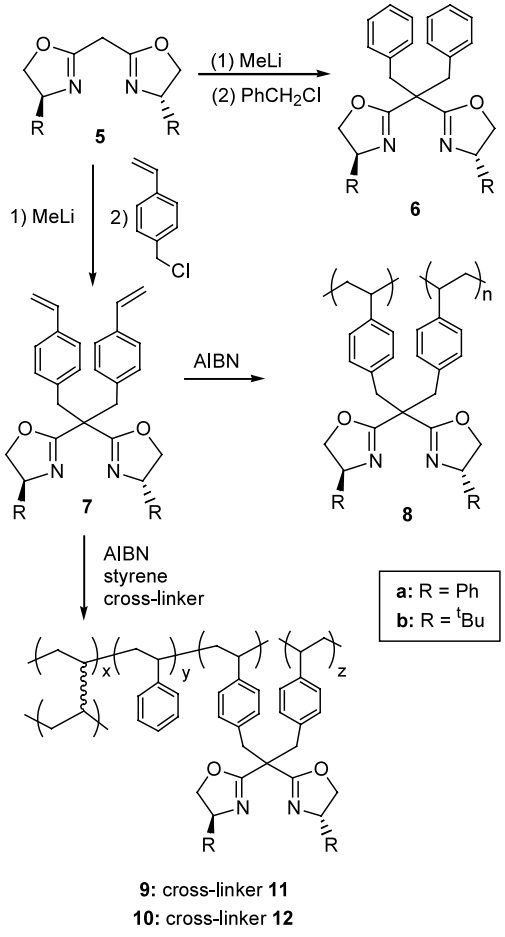
2. Results and discussion

Methylenebis[(*S*)-4-phenyl-2-oxazoline] **5a** and methylenebis[(*S*)-4-*tert*-butyl-2-oxazoline] **5b** were dibenzylated at the central methylene bridge to yield the soluble ligands **6**. The alkylation with *p*-vinylbenzyl chloride led to the chiral monomers **7**. These monomers were used to prepare the different polymers following the general protocol for the preparation of monolithic resins (Scheme 2).[7–9,11]

Dendrimers **11** and **12** were used as cross-linkers. These dendrimers were obtained by reacting 1,3,5-trischlorocarbonylbenzene with two different dendrons following a standard procedure (Scheme 3).[12] The dendrons have a hydroxymethyl group as the focal point and were prepared by reaction of 3,5-dihydroxybenzyl alcohol with the appropriate vinyl end-capped bromides following Fréchet's procedure.

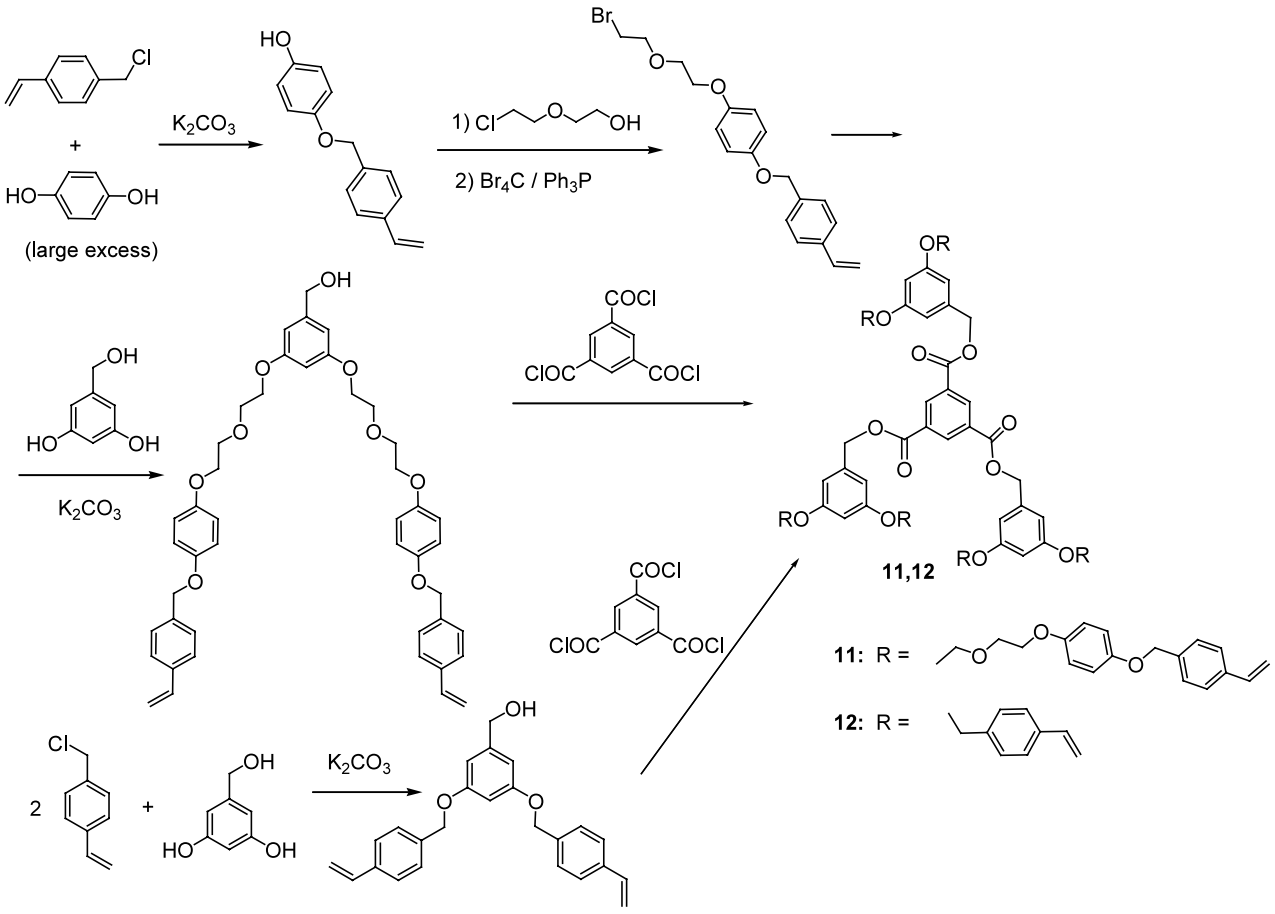
The polymers were characterized by IR spectroscopy and the spectra show bands corresponding to the chiral ligand. Nitrogen analysis was used to determine the amount of bis(oxazoline) incorporated into the polymeric network. Catalysts were obtained by treatment with $Cu(OTf)_2$ followed by filtration, washing and drying. Copper contents were determined by plasma emission spectroscopy. Table 1 shows the monomer compositions of the polymers **8**–**10** together with the bis(oxazoline) contents of these polymers and the copper contents of the catalysts obtained from them. The results of these analyses clearly indicate that the degree of copper functionalization depends on both the polymer morphology and the nature of the chiral ligand.



Scheme 2. Preparation of homopolymers **8** and copolymers with different cross-linkers.

The next question concerns how these parameters can influence the catalytic behavior of these systems. Although better yields can be obtained by using an excess of styrene,[7] the use of equimolecular amounts of both reagents allows an easier comparison of the TON based on both copper and the chiral ligand. These values, together with the different selectivities, are gathered in Table 2 for both homogeneous and polymeric catalysts. With the homopolymers **8a** and **8b** the TON based on copper is improved with regard to the analogous homogeneous ligands **6a** and **6b**, without a decrease in the enantioselectivity. However, the low copper functionalization makes the TON based on bis(oxazoline) similar with both homogeneous and heterogeneous catalysts. As this parameter is really important for efficient transmission of the chiral information, we tried to improve it by using dendrimers as cross-linkers, leading to a significant modification in polymer morphology. The use of dendrimer **11** leads to different results as a function of the chiral ligand. The polymer with the phenyl bis(oxazoline) **9a** shows a spectacular improvement in the TON wrt both copper and chiral ligand, reaching a cyclopropanes/box ratio of 101, with the same enantioselectivity. However, with the *tert*-butyl substituted polymer **9b** low TON and enantioselectivity are obtained. The nature of the dendrimeric cross-linker has an important effect, as shown by the results with polymers containing the dendrimer **12**. The cyclopropanes/box ratio increases to 141 with **10a** and 132 with **10b**, with no decrease in enantioselectivity compared to the analogous homogeneous catalysts **6a** and **6b**. Although recovered catalysts are less active and longer reaction times are needed, re-use allows a further improvement of both TON, up to 242 cyclopropanes/box with **10a**. Given that leaching of copper is not detected, deactivation may be due to deposition of by-products that reduces accessibility to the catalytic centers. New dendrimers are being designed with the aim of solving this problem.

It can be concluded that the use of suitable dendrimers as cross-linkers allows a better use of the chiral ligand and hence a better transmission of chiral information, with up to 140 new chiral molecules produced per ligand molecule. The structure of both the dendrimer and the chiral monomer is important to optimize the results. In fact, it is known that the selection of the cross-linker is a key point for the enantioselective reactions promoted by chiral copolymers. These parameters are related with the copper functionalization of the chiral ligand and the accessibility of the catalytic centers.



Scheme 3. Preparation of dendron precursors for dendrimeric cross-linkers.

Table 1. Immobilized catalysts prepared from polymers **8–10** and $Cu(OTf)_2$[a]

Polymer	Composition of the monomers mixture			Functionalization		
	Box **7**	Styrene	Cross-linker	Box (mmol g^{-1})	Cu (mmol g^{-1})	Box/Cu
8a[b]	100	–	–	1.74	0.140	12.4
8b[b]	100	–	–	2.01	0.070	28.8
9a[c]	9	77	14	0.15	0.015	10.0
9b[c]	11	74	15	0.19	0.004	47.5
10a[c]	5	85	10	0.21	0.080	2.6
10b[c]	9	73	18	0.28	0.043	6.5

[a] Polymerization conditions: 80°C, monomer mixture/porogen = 40/60, 1% AIBN.
[b] Porogen: mixture toluene/1-dodecanol (1/5 w/w).
[c] Porogen: mixture toluene/1-dodecanol/DMF (1/4/1).

3. Experimental

3.1. General

^1H and ^{13}C NMR spectra ($CDCl_3$, δ ppm, J Hz) were obtained using a Varian FT-300 or Gemini FT-200 instrument with TMS as standard. MS spectra were obtained by the Universidad Autónoma de Madrid (Servicio Interdepartamental de Investigación, S.I.D.I.) mass spectroscopy facility. Spectra matrix: dithranol (MALDI-TOF). Quantitative elemental analyses were performed in duplicate on a Perkin–Elmer 2400 instrument. Copper analyses were carried out by plasma emission spectroscopy on a Perkin–Elmer Plasma 40 emission spectrometer. Transmission FTIR spectra of self supported wafers evacuated ($<10^{-4}$ Torr) at 50°C were obtained with a Mattson Genesis series FTIR spectrophotometer. Gas chromatography was carried out on two Hewlett-Packard 5890 chromatographs equipped with FID detectors.

3.2. Preparation of dendrimers

3.2.1. General procedure for 3,5-bis(*p*-vinylphenylmethyl oxy)phenylmethyl 1,3,5-benzenetricarboxylate, 11 and 3,5-bis(*p*-vinylphenylmethyloxy-*p*-phenyloxyethylenoxy

Table 2. Results obtained from the cyclopropanation reaction between styrene **1** and ethyl diazoacetate **2** with homogeneous and polymeric catalysts[a]

Ligand	Run	Time (days)	**3**+**4**/Cu[b]	**3**+**4**/box[b]	*trans*/*cis*[c]	% ee (*trans*)[d]	% ee (*cis*)[d]
6a	1	1	3.2	3.2	70/30	50	40
6b	1	1	23	23	33/67	70	79
8a	1	1	204	17	52/48	57	53
8b	1	1	287	10	37/63	78	72
9a	1	11	1000	101	59/41	58	42
9b	1	7	113	2.4	55/45	6	16
10a	1	3	368	141	57/43	58	56
	2	14	262	101	58/42	52	56
10b	1	4	860	132	50/50	74	68
	2	10[e]	400	61	54/46	60	60

[a] Using equimolecular amounts of styrene and ethyl diazoacetate at room temperature.
[b] Molar ratio calculated using the amount of cyclopropanes determined by GC at total conversion of ethyl diazoacetate.
[c] Determined by GC.
[d] Determined by GC. **3*R*** and **4*S*** are the major enantiomers.
[e] Reaction carried out at 50°C.

ethylenoxy)phenylmethyl 1,3,5-benzenetricarboxylate, 12. A mixture of dendron **13** (3.03 mmol) or **14** (0.65 mmol) and an equimolar amount of 4-dimethylaminopyridine was dissolved in anhydrous THF (10 mL) under Ar in a 100 mL Schlenk tube. After 5 min, 1,3,5-trischlorocarbonylbenzene (1.01 and 0.22 mmol, respectively) was added dropwise. The reaction mixture was stirred for 4 h at room temperature. The amine hydrochloride was filtered off and the solvent was evaporated. The solid residue was purified as indicated below.

Compound 11: was obtained in 90% yield after recrystallization (ethyl acetate/hexane). Mp: 113–115°C. ^{1}H NMR: 8.90 (s, 3H); 7.39 and 7.36 (d, 12H, A_2 of A_2B_2 system, $J=8$ Hz); 7.35 and 7.32 (d, 12H, B_2 of A_2B_2 system, $J=8$ Hz); 6.73–6.63 (m, 12H); 6.56 (t, 3H, $J=2$ Hz); 5.72 (dd, 6H, $J_{gem}=1$ Hz, $J_{trans}=18$ Hz); 5.33 (s, 6H); 5.23 (dd, 6H, $J_{gem}=1$ Hz, $J_{cis}=11$ Hz); 5.00 (s, 12H). ^{13}C NMR: 167.6, 160.1, 137.7, 136.4, 136.1, 134.9, 131.2, 127.7, 126.4, 114.1, 107.3, 102.1, 69.9 and 67.2. MS (MALDI-TOF), m/z: 1295.5 $(M+Na)^+$.

Compound 12: was obtained in 63% yield after recrystallization from dichloromethane/ethanol. Mp: 52–55°C. ^{1}H NMR: 8.87 (s, 3H); 7.43 and 7.39 (d, 12H, A_2 of A_2B_2 system, $J=8$ Hz); 7.37 and 7.33 (B_2 of A_2B_2 system, $J=8$ Hz); 6.73 (dd, 6H, $J_{cis}=11$ Hz, $J_{trans}=18$ Hz); 6.59 (d, 6H, $J=2$ Hz); 6.48 (t, 3H, $J=2$ Hz); 5.74 (dd, 6H, $J_{gem}=1$ Hz, $J_{trans}=18$ Hz); 5.28 (s, 6H); 5.25 (dd, 6H, $J_{gem}=1$ Hz, $J_{cis}=11$ Hz); 4.97 (s, 12H); 4.09 (m, 24H); 3.87 (m, 24H). ^{13}C NMR: 164.6, 160.1, 153.1, 137.6, 137.2, 136.8, 136.4, 134.9, 131.2, 127.6, 126.3, 115.8, 115.6, 114.0, 107.1, 101.6, 99.4, 70.4, 70.0, 69.8, 68.1, 67.6 and 67.2. MS (MALDI-TOF), m/z: 2375.7 $(M+Na)^+$.

3.2.2. 3,5-Bis(*p*-vinylphenylmethyloxy)benzyl alcohol, 13. A mixture of 3,5-dihydroxybenzyl alcohol (10 mmol), 4-vinylbenzyl chloride (21 mmol), potassium carbonate (22 mmol) and Aliquat 336 (5%) in 35 mL of acetone was placed in a 100 mL round-bottomed flask fitted with a reflux condenser. The reaction was heated for 12 h at 80°C. Inorganic salts and Aliquat 336 were removed by filtration through Florisil®, the solvent was evaporated and the crude product was crystallized from ethyl acetate/hexane as a white solid. Mp: 63–65°C. Yield 90%. ^{1}H NMR: 7.44 and 7.40 (d, 4H, A_2 of A_2B_2 system, $J=8$ Hz); 7.38 and 7.34 (d, 4H, B_2 of A_2B_2 system, $J=8$ Hz); 6.72 (dd, 2H, $J_{trans}=18$ Hz, $J_{cis}=11$ Hz); 6.61 (d, 2H, $J=2$ Hz); 6.53 (t, 1H, $J=2$ Hz); 5.76 (dd, 2H, $J_{gem}=1$ Hz, $J_{trans}=18$ Hz); 5.26 (dd, 2H, $J_{gem}=1$ Hz, $J_{cis}=11$ Hz); 5.02 (s, 4H); 4.62 (s, 2H). ^{13}C NMR: 160.6, 143.9, 137.9, 136.9, 128.2, 126.9, 114.6, 112.8, 106.3, 101.9, 70.4 and 65.8. MS (EI), m/z: 372 $(M)^+$.

3.2.3. 4-(*p*-Vinylphenylmethyloxy)phenol. A mixture of 1,4-hydroquinone (80 mmol), 4-vinylbenzyl chloride (20 mmol), potassium carbonate (20 mmol) and Aliquat 336 (2 mmol) in acetone (75 mL) was placed in a 250 mL round-bottomed flask fitted with a reflux condenser. The reaction was heated for 24 h at 80°C. The inorganic salts were filtered off and the solvent was evaporated. Chloroform was added to precipitate the excess 1,4-hydroquinone, which was removed together with the Aliquat 336 by filtration over Florisil®. The solvent was evaporated and the crude product was purified by column chromatography (SiO_2; hexane/ethyl acetate, 9:1). The pure product was obtained by recrystallization from ethyl acetate/hexane. Mp: 143–144°C. Yield 62%. ^{1}H NMR: 7.44 and 7.41 (d, 2H, A_2 of A_2B_2 system, $J=8$ Hz); 7.39 and 7.36 (d, 2H, B_2 of A_2B_2 system, $J=8$ Hz) 6.87–6.67 (m, 5H); 5.75 (dd, 1H, $J_{gem}=1$ Hz, $J_{trans}=18$ Hz); 5.25 (dd, 1H, $J_{gem}=1$ Hz, $J_{cis}=11$ Hz); 4.99 (s, 2H). ^{13}C NMR: 153.0, 149.7, 137.3, 136.8, 136.5, 127.7 126.4, 116.1, 116.0, 114.0 and 70.5. MS (EI), m/z: 226 $(M)^+$.

3.2.4. 1,4-(Hydroxyethyleneoxyethyleneoxy),(*p*-vinylphenyl oxymethyloxy)benzene. A mixture of 4-(*p*-vinylphenylmethyloxy)phenol (10 mmol), KOH (15 mmol), 2-(2-chloroethoxy)ethanol (12 mmol) and TBAB (9%) was heated in the absence of solvent for 32

h at 80°C. Acetone was added and the inorganic salts were filtered off. The crude product was purified by column chromatography (SiO_2; hexane/ethyl acetate, 3:1). After the undesired products had been removed, ethyl acetate was then used as eluent. The product was obtained as a white solid. Mp: 100–101°C (ethanol). Yield 60%. ^{1}H NMR: 7.44 and 7.40 (d, 2H, A_2 of A_2B_2 system, $J=8$ Hz); 7.39 and 7.35 (d, 2H, B_2 of A_2B_2 system, $J=8$ Hz); 6.91–6.81 (m, 4H); 6.72 (dd, 1H, $J_{cis}=11$ Hz, $J_{trans}=18$ Hz); 5.75 (dd, 1H, $J_{gem}=1$ Hz, $J_{trans}=18$ Hz); 5.25 (dd, 1H, $J_{gem}=1$ Hz, $J_{cis}=11$ Hz); 5.00 (s, 2H); 4.09 (t, 2H, $J=5$ Hz); 3.83 (t, 2H, $J=4$ Hz); 3.74 (t, 2H, $J=4$ Hz); 3.68 (t, 2H, $J=4$ Hz). ^{13}C NMR: 153.2, 153.0, 137.3, 136.8, 136.5, 127.7, 126.4, 115.9, 115.7, 114.0, 72.5, 70.4, 69.8, 68.1 and 61.8. MS (EI), m/z: 314 $(M)^+$.

3.2.5. 1,4-(Bromoethyleneoxyethyleneoxy)(*p*-vinylphenyloxy-methyloxy)benzene. In a flame-dried Schlenk tube was placed carbon tetrabromide (15 mmol), 1,4-(hydroxyethyleneoxyethyleneoxy),(*p*-vinylphenyloxymethyloxy)benzene (4 mmol) and triphenylphosphine (15 mmol); dry THF was added (20 mL) and the mixture was stirred at room temperature under an argon atmosphere for 4 h. Triphenylphosphine oxide formed was filtered off and the solvent was evaporated. The crude product was purified by column chromatography (SiO_2; hexane/ethyl acetate, 8:1). For further purification the product was crystallized from ethanol. Mp: 72–74°C. Yield 87%. ^{1}H NMR: 7.44 and 7.40 (d, 2H, A_2 of A_2B_2 system, $J=8$ Hz); 7.39 and 7.35 (d, 2H, B_2 of A_2B_2 system, $J=8$ Hz); 6.91–6.81 (m, 4H); 6.72 (dd, 1H, $J_{cis}=11$ Hz, $J_{trans}=18$ Hz); 5.75 (dd, 1H, $J_{gem}=1$ Hz, $J_{trans}=18$ Hz); 5.25 (dd, 1H, $J_{gem}=1$ Hz, $J_{cis}=11$ Hz); 5.00 (s, 2H); 4.09 (t, 2H, $J=5$ Hz); 3.91–3.82 (m, 4H); 3.49 (t, 2H, $J=6$ Hz). ^{13}C NMR: 153.2, 153.0, 137.3, 136.8, 136.5, 127.7, 126.4, 115.9, 115.7, 114.0, 71.4, 70.4, 69.8, 68.1 and 30.2. MS (EI), m/z: 376 $(M)^+$, 378 $(M+2)^+$.

3.2.6. 3,5-Bis(*p*-vinylphenylmethyloxy-*p*-phenyloxyethylene oxyethylenoxy)benzyl alcohol, 14. A mixture of 1,4-(bromoethyleneoxyethyleneoxy),(*p*-vinylphenyloxymethyloxy)benzene (2.65 mmol), KOH (2.70 mmol), 3,5-dihydroxybenzyl alcohol (1.07 mmol) and tetrabutylammonium bromide TBAB (9%) was heated without solvent for 24 h at 80°C. Ethyl acetate (20 mL) was added, the inorganic salts were filtered off and the solvent was evaporated. The crude product was purified by column chromatography (SiO_2; hexane/ethyl acetate, 1:1). The desired compound was obtained as a white solid after crystallization from ethanol. Mp: 105–107°C. Yield 68%. ^{1}H NMR: 7.44 and 7.40 (d, 4H, A_2 of A_2B_2 system, $J=8$ Hz); 7.39 and 7.35 (d, 4H, B_2 of A_2B_2 system, $J=8$ Hz); 6.91–6.81 (m, 8H); 6.72 (dd, 2H, $J_{cis}=11$ Hz, $J_{trans}=18$ Hz); 6.53 (d, 2H, $J=2$ Hz); 6.43 (t, 1H, $J=2$ Hz); 5.75 (dd, 2H, $J_{gem}=1$ Hz, $J_{trans}=18$ Hz); 5.25 (dd, 2H, $J_{gem}=1$ Hz, $J_{cis}=11$ Hz); 4.99 (s, 4H); 4.60 (s, 2H); 4.15–4.07 (m, 8H); 3.92–3.86 (m, 8H). ^{13}C NMR: 160.1, 153.1, 143.3, 137.3, 136.8, 136.5, 127.7, 126.4, 115.8, 115.7, 114.0, 105.6, 100.9, 99.4, 70.4, 70.0, 69.9, 68.2, 67.6 and 65.3. MS (EI), m/z: 732 $(M)^+$.

3.3. Preparation of polymeric catalysts

The polymerization mixture was prepared with 40% (w/w) monomers (in the molar ratio shown in Table 1) and 60% porogen (toluene/1-dodecanol = 1/5 or toluene/1-dodecanol/DMF = 1/4/1, w/w). This mixture was placed in a glass mould and purged with nitrogen in the presence of azoisobutyronitrile (1% w/w). The mould was closed and heated at 80±2°C for 24 h. The mould was broken and the polymer was washed with THF, dried by suction and crushed in a mortar. The polymer was washed in a Soxhlet apparatus with THF for 24 h and dried under vacuum at 50°C overnight. Typical yields were in the range 75–95%. The Cu complexes were prepared by adding the corresponding amount of polymer (1 equiv. box) to a pre-filtered solution of $Cu(OTf)_2$ in methanol. The suspension was stirred at room temperature for 24 h. The solid was filtered off, thoroughly washed with methanol and dried under vacuum at 50°C overnight.

3.4. Catalytic tests

To a suspension of the corresponding supported catalyst (20 mg), styrene (175 mg, 1.68 mmol) and *n*-decane (25 mg) in methylene chloride (3 mL) under an Ar atmosphere, was slowly added a solution of ethyl diazoacetate (96 mg, 0.84 mmol) in methylene chloride (0.5 mL) using a syringe pump. The reaction was monitored by gas chromatography and, after consumption of the diazoacetate, a second portion of diazoacetate was added in the same way. After completion of the reaction the catalyst was filtered off, washed with methylene chloride and dried. The recovered catalysts were reused following the same method.

Yields and *trans*/*cis* selectivities were determined with a cross-linked methylsilicone column: 25 m×0.2 mm×0.33 μm. Oven temperature program: 70°C (3 min), 15°C/min to 200°C (5 min). Retention times: ethyl diazoacetate 4.28 min, styrene 5.03 min, *n*-decane 6.93 min, diethyl fumarate 8.73 min, diethyl maleate 9.04 min, *cis*-cyclopropanes **4** 11.84 min, *trans*-cyclopropanes **3** 12.35 min. The asymmetric induction (Scheme 1) was determined with a Cyclodex-B column: 30 m×0.25 mm×0.25 μm. Oven temperature program: 125°C isotherm. Retention times: (1*S*,2*R*)-cyclopropane (**4S**) 28.3 min, (1*R*,2*S*)-cyclopropane (**4R**) 29.1 min, (1*R*,2*R*)-cyclopropane (**3R**) 33.9 min, (1*S*,2*S*)-cyclopropane (**3S**) 34.3 min.

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