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Linear Copolymers of Proline Methacrylate and Styrene as Catalysts for Aldol Reactions in Water: Effect of the Copolymer Aggregation on the Enantioselectivity

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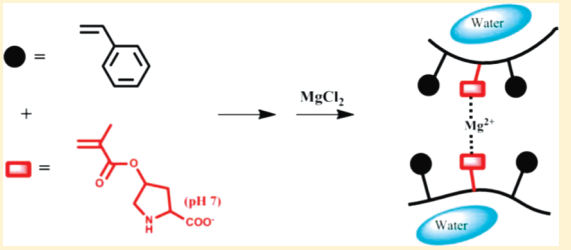
Supporting Information

ABSTRACT: The synthesis and catalytic activity of linear copolymers of proline methacrylate and styrene with different molar ratios are reported. The compounds are soluble catalysts for aldol reactions between aldehydes and ketones in water—without the need of any extra organic solvent. They were designed on the basis that the presence of hydrophobic groups around the proline moiety is beneficial for reactions to proceed in water. The copolymers were tested as catalyst in a model reaction between cylohexanone and *p*-nitrobenzaldehyde. Compared to the inactive proline−methacrylate homopolymers, the presence of styrene was essential for the reaction to proceed. The catalytic efficiency was dependent on the molar ratio proline methacrylate/styrene and the comonomer distribution along the polymer chain. The catalyst with the highest styrene content, which has the largest amount of alternating styrene−proline sequences, gave the highest conversion, showing the effect of the microstructure of the copolymer on the catalytic properties. A significant improvement of stereoselectivity was achieved when the reactions were performed in the presence of divalent salts, with magnesium dichloride giving the best results. In order to understand the effect of the salt on the stereoselectivity of the reaction, dynamic light scattering and ^{1}H HR MAS NMR studies of the copolymers were performed. The results suggested a relationship between the stereoselectivity and the formation of large aggregates leading to the formation of a heterogeneous media during the reaction. The polymers were recovered and reused by precipitation in water at their isoelectric point.



INTRODUCTION

The role of supported proline in organocatalytic aldol reactions is well-known. The use of solid supports facilitates the recovery and recycling of the catalyst.[1] Many examples showing the attachment of proline derivatives such as hydroxyproline to polymer supports are available in the recent literature.[2−4] In these examples, the proline moiety is linked to a "preformed" polymer as PS-based resins[5−7] or linear PEG.[8−10] Recently, Hansen et al.[2,11] and Fernández-Mayoralas et al.[12] described independently the first examples of the preparation of supported prolines using a "bottom-up" approach, where acrylic proline monomers were prepared and polymerized. The work by Hansen and co-workers is noticeable as they prepare successfully heterogeneous acrylic resins using this bottom-up methodology. These polymer beads exhibited excellent catalytic properties in water and lead to aldol products in high yields and stereoselectivity.[2,13,14]

This bottom up methodology gives high flexibility to the synthesis since (1) loading can be easily controlled, (2) multifunctional systems are conceptually possible (just by choosing the right comonomers), and (3) the polymerization offers many possibilities; i.e., PS-like solid resins or linear PEG-like soluble systems could be prepared using the same parent monomer, as Hansen et al.[11] and Fernández-Mayoralas et al.[12] have shown. Both groups used the same hydroxyproline methacrylate to prepare the mentioned heterogeneous acrylic resins and water-soluble polymers, respectively.

With regard to the reaction medium in the previous examples, one of the aims pursued by the modification and supporting of proline was to achieve an efficient catalyst in water. Organocatalytic aldol reactions in water have received much attention over the past years because of its green chemistry perspectives. Despite its solubility in water, the efficiency of proline-catalyzed aldol reactions in this medium is very poor.[15,16] Water may alter the highly organized transition states that are thought to be responsible for the catalytic activity of proline-mediated reactions.[17−19] Considerable effort has been directed to the development of proline analogues with hydrophobic residues that can catalyze reactions in water.[20] In this regard, the

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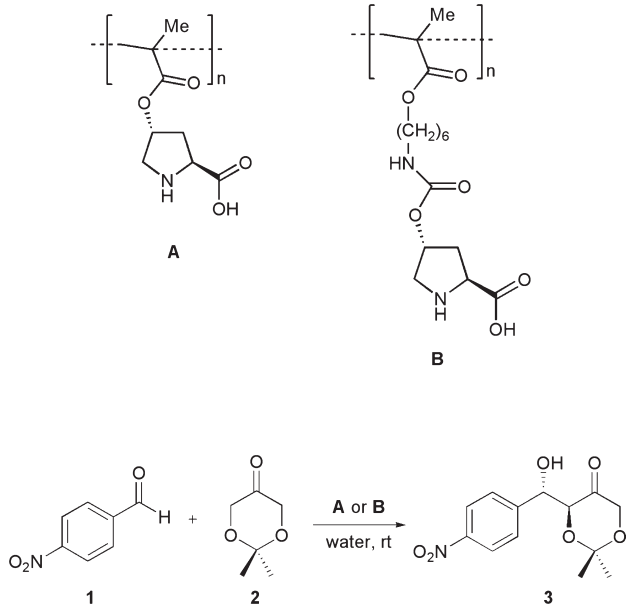
Scheme 1. Homopolymers A and B and Model of Aldol Reaction between *p*-Nitrobenzaldehyde 1 and Dioxanone 2



performance of some solid polystyrene-supported L-proline,[21,22] as well as the mentioned work by Hansen et al. using phenyl methacrylate,[13] provides strong evidence that a hydrophobic aromatic ring located in the proximities of the proline moiety in a heterogeneous catalyst activates the reaction in water. In contrast, our previous work[12] with soluble linear homopolymers of proline methacrylates (see Scheme 1) showed a very low catalytic activity in water. Thus, to study the role of the aromatic moiety, it will be of high interest to introduce the ring in the structure of such linear macromolecular chains carrying proline. To incorporate these hydrophobic groups, we could take advantage of the flexibility of the "bottom-up" approach, since tailor-made macromolecules can be prepared from selected monomers. Very recently, Longbottom and O'Reilly[23] prepared and polymerized a new monomer where the aromatic ring was located as spacer between the active proline and the polymerizable double bond. These polystyrene-based polymers were organocatalytically active in organic solvents, but not in water, where the linear chains were not soluble. Here, a different strategy is presented. New linear copolymers of proline methacrylate and styrene are prepared and evaluated as soluble catalysts for aldol reactions in water. Compared to the O'Reilly et al. work, the design presented here allows easy modulation of the proline/aromatic ring ratio, and therefore, some control on the water solubility could be achieved. Therefore, the aim of this study is to determine if some of these new copolymers bearing proline and styrene are catalytically active in water. Moreover, a study of the reaction in different pHs and adding different salts at different salt concentrations has been carried out. It is well-known that the pH and the type and amount of salts in aqueous media strongly influence the ionization and the inter- and intramolecular charge interaction of copolymers such as the described here bearing ionizable weak carboxylic and secondary amine. All these aspects may be very relevant in the catalytic performance in water.

EXPERIMENTAL SECTION

General Remarks. 2,2′-Azobis(isobutyronitrile) (AIBN, Merck) was recrystallized twice from ethanol. Other chemicals were purchased puriss p.A. from commercial suppliers or purified by standard techniques. Dioxanone **2** was obtained as previously described.[24,25] The synthesis of monomers **4** and **6** was carried out as previously described by our group.[12] Thin-layer chromatography (TLC) was performed on aluminum sheets 60 F_{254} Merck silica gel, and compounds were visualized by irradiation with UV light and/or by treatment with a solution of Ce_2MoO_4 followed by heating. Flash chromatography was performed using thick walled columns, employing silica gel (Merck 60: 0.040−0.063 nm). NMR (^{1}H, ^{13}C NMR) spectra were recorded on a 300 MHz (Varian Unity 300 or Bruker 300) spectrometer, using $CDCl_3$ or D_2O as solvents at room temperature. Chemical shift values are reported in parts per million (δ) relative to tetramethylsilane (TMS) in ^{1}H and $CDCl_3$ (δ =77.0) in ^{13}C NMR. Coupling constant (J values) are reported in hertz (Hz), and spin multiplicities are indicated by the following symbol: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet). Diastereomeric and enantiomeric excess were calculated by NMR and HPLC Dionex P680 with DAD detector (lecture at 254 nm). Mass spectra were recorded on a HP series 1100 MSD spectrometer. Elemental analyses were carried out on a Heraus CHN-O Rapid analyzer, and compositions are expressed in percentage. Gel permeation chromatography (GPC) analyses were carried out using a Perkin-Elmer apparatus with an isocratic pump serial 200 connected to a differential refractometric detector (serial 200a). Two Resipore columns (Varian) were conditioned at 70 °C and used to elute the samples (1 mg/mL concentration) at 1 mL/min. HPLC grade *N,N*′-dimethylformamide (DMF) supplemented with 0.1% v/v LiBr was used as eluent. Calibration of SEC was carried out with monodisperse standard polystyrene samples in the range of 2.9×10^3−480×10^3 obtained from Polymer Laboratories.

The turbidity change of the aqueous solutions of the polymers (2 mg/mL) as a function of pH was monitored measuring the absorbance at 700 nm in a UV−vis Lambda 35 spectrophotometer (Perkin-Elmer Instruments). The initial polymer solution was freshly prepared in an aqueous solution of 0.15 M NaCl and 0.1 M NaOH. A standard aqueous solution 0.1 M HCl was delivered stepwise. pH was monitored with a Beckman 40 pH-Meter (Beckman Instruments, Fullerton, CA).

Dynamic light experiments were carried out on a Malvern Nano ZS. The concentration of the samples was 7.5 mM catalyst, and the pH was adjusted to neutral values. The polymer concentration was 7.5 mg/mL of $\mathbf{C_{2:1}}$ in distilled water. Additionally, samples containing a phosphate buffer (100 mM), LiCl (1 M), and $MgCl_2$ (1 M) were measured.

Theoretical Determination of Dyads. Assuming that the copolymerization is governed by the terminal model,[26] the molar fractions of dyads were obtained by introducing reactivity ratios from the literature[27] in the software Copol.[28] The terminal model considers that the reactivity of the growing chain depends on the nature of the terminal unit, and in the case of binary copolymerizations, two parameters are needed, reactivity ratios, to describe the reaction. These reactivity ratios are given by

$$r_1 = k_{11}/k_{12} \quad \textit{and} \quad r_2 = k_{22}/k_{21} \tag{1}$$

where k_{ij} $(i, j = 1, 2)$ is the rate constant for the addition of a monomer M_j to a propagating chain end $\sim M_i$. A reactivity ratio value r_1 higher or lower than 1 indicates that a growing chain end $\sim M_1$ is more reactive toward a monomer 1 or 2, respectively. In the case of the copolymerization of methacrylates and styrenes, typically the reactivity ratios are both below 1 (the data used here from the reaction of methyl methacrylate and styrene in DMF are $r_{MMA} = 0.58$ and $r_{STY} = 0.55$),[27] which means that each radical is more reactive toward the heterounit; that is, there is an intrinsic tendency to the alternance. In the case of the

couple methacrylate−benzyl methacrylate described in the Supporting Information, we have also used values from the literature,[29] $r_{MMA} = 0.78$ and $r_{BMA} = 1.38$. In this case, there is not such a tendency to comonomer alternance.

The terminal model allows to describe instantaneously the molar fractions of any sequence using the conditional probabilities: The conditional probabilities p_{ii} and p_{ij} for the i or j monomer addition to a growing chain end $\sim M_i$ ($i, j = 1, 2$), is given by the propagation rates ratio:

$$p_{ii} = \frac{R}{R_{ii} + R_{ij}} = \frac{k_{ii}[M_i]}{k_{ii}[M_i] + k_{ij}[M_i]} = \frac{r_i}{r_i + \frac{[M_j]}{[M_i]}} \quad \text{and} \quad p_{ij} = 1 - p_{ii} \tag{2}$$

where $[M_1]$ and $[M_2]$ are the monomer feed concentrations. Thus, the instantaneous molar fraction of any sequence is equal to the probability of existence of the first unit (f, the copolymer molar fraction) multiplied by the corresponding conditional probabilities. For instance, the i-based dyad molar fractions will be

$$F_{ii} = f_i p_{ii} \qquad F_{ij+ji} = 2 f_i p_{ij} \tag{3}$$

The sequence molar fraction is related to the sequence population and, therefore, to the microstructure of the copolymer (sequence distribution). The software Copol approximates the cumulative molar fraction at 100% conversion (data used in this work) by performing a simple numerical integration of the instantaneous data obtained as explained before.

General Polymerization Procedure. Protected polymers **5** and **7** were prepared by free radical polymerization in *N*,*N*-dimethylformamide (DMF) at 60 °C for 24 h using AIBN as initiator. Reactions were carried out in the absence of oxygen by gently bubbling nitrogen for 20−30 min before sealing the system. The total concentration of comonomers was 1 mol/L (using 1 equiv of styrene and 1, 2, or 4 equiv of proline methacrylate), and the initiator concentration was 0.015 mol/L. After 24 h, the reaction mixture was poured into water, and the resulting precipitate was dried under vacuum overnight.

Polymer ***5*** *(n/m = 2:1).* Polymer **5** (n/m = 2:1) was obtained from **4** (459 mg, 1.3 mmol) and styrene (0.074 mL, 0.65 mmol) as a white solid (495 mg, 94% yield) following the general procedure. ^{1}H NMR (300 MHz, $CDCl_3$, 298 K): δ 7.4−6.6 (m, 5H, Ar), 5.2−4.8 (m, 2 × 1H, H-4pro), 4.4−3.8 (m, 2 × 1H, H-2pro), 3.8−3.0 (m, 2 × 2H, CH_2−5pro), 2.8−0.2 (m, 53H, CH_2−3pro, CH_2CMe, CH−Ar, CH_2CHAr, CH_3 (^{t}Bu), CH_3 (methacryl). GPC data: M_n = 41 000 g/mol. PI (polydispersity index) = 3.7.

Polymer ***5*** *(n/m = 1:1).* Polymer **5** (n/m = 1:1) was obtained from **4** (401 mg, 1.13 mmol) and styrene (0.13 mL, 1.13 mmol) as a white solid (447 mg, 86% yield) following the general procedure. The polymer sample contained traces (8%) of residual monomer that were removed in the next step. ^{1}H NMR (300 MHz, $CDCl_3$, 298 K): δ 7.2−6.7 (m, 5H, Ar), 5.1−4.7 (m, 1 × 1H, H-4pro), 4.4−3.8 (m, 1 × 1H, H-2pro), 3.8−2.9 (m, 1 × 2H, CH_2-5pro), 2.5−2.3 (m, 1 × 1H, CH_2-3$_A$pro), 2.3−2.1 (m, 1× 1H, CH_2-3$_B$pro), 2.0−0.3 (m, 26H, CH_2CMe, CH−Ar, CH_2CHAr, CH_3 (^{t}Bu), CH_3 (methacryl). GPC data: M_n = 40 000 g/mol. PI = 3.6.

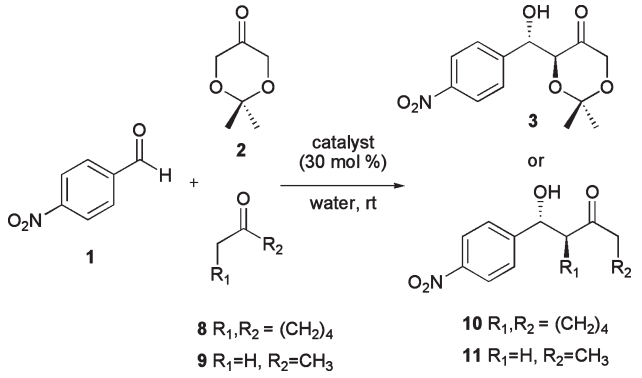
Polymer ***5*** *(n/m = 4:1).* Polymer **5** (n/m = 4:1) was obtained from **4** (554 mg, 1.6 mmol) and styrene (0.045 mL, 0.4 mmol) as a white solid (468 mg, 79% yield) following the general procedure. The polymer sample contained traces (11%) of residual monomer that were removed in the next step. ^{1}H NMR (300 MHz, $CDCl_3$, 298 K): δ 7.2−6.8 (m, 5H, Ar), 5.2−4.8 (m, 4 × 1H, H-4pro), 4.4−4.0 (m, 4 × 1H, H-2pro), 3.8−3.2 (m, 4 × 2H, CH_2-5pro), 2.5−2.3 (m, 4 × 1H, CH_2-3$_A$pro), 2.3−2.1 (m, 4 × 1H, CH_2-3$_B$pro), 2.0−0.3 (m, 95H, CH_2CMe, CH−Ar, CH_2CHAr, CH_3 (^{t}Bu), CH_3 (methacryl). GPC data: M_n = 35 000 g/mol. PI = 3.1.

Polymer ***7*** *(n/m = 2:1).* Similarly, polymer **7** (n/m = 2:1) was obtained from **6** as a white solid (86% yield). ^{1}H NMR (300 MHz, $CDCl_3$, 298 K): δ 7.4−6.7 (m, 5H, Ar), 5.3−5.1 (m, 2 × 1H, H-4 pro), 4.2−4.1 (m, 2 × 1H, H-2pro), 3.9−3.3 (m, 2 × 4H, CH_2-5pro, CH_2OCO), 3.2−3.0 (m, 2 × 2H, CH_2NH), 2.5−2.0 (m, 5H, CH_2-3pro, CH−Ar), 1.8−0.6 (m, 64H, $OCOCH_2CH_2CH_2CH_2CH_2NH$, CH_2CHAr, CH_3 (^{t}Bu), CH_2CMe, CH_3 (methacryl). GPC data: M_n = 33 000 g/mol. PI = 2.4.

General Deprotection Procedure. Dried polymers **5** and **7** were dissolved in 1:2 dichloromethane/trifluoroacetic acid (2 mL per 100 mg of polymer), and the mixture was stirred for 24 h. Ether was added to the mixture, and the precipitate was filtered and dried under vacuum overnight. The solid was suspended in distilled water (7 mL per 100 mg of polymer), and 1 M NaOH was added dropwise until their complete solubilization (pH 8). The solution was dialyzed in distilled water for 1 week. Polymers were recovered by freezing and lyophilization.

Polymer ***$C_{2:1}$*** *(n/m = 2:1).* Polymer $\mathbf{C_{2:1}}$ was obtained as a brown solid. ^{1}H NMR (300 MHz, D_2O, 298 K): δ 7.5−6.8 (m, 5H, Ar), 5.2−5.0 (m, 2 × 1H, H-4pro), 4.0−3.7 (m, 2 × 1H, H-2pro), 3.7−2.8 (m, 5H, CH_2-5pro, CH−Ar), 2.8−2.5 (m, 2 × 1H, CH_2-3$_A$pro), 2.5−2.2 (m, 2 × 1H, CH_2-3$_B$pro), 2.0−0.8 (m, 12H, CH_2CMe, CH_2CHAr, CH_3 (methacryl). IR (KBr): ν = 3435 (br, N−H, COOH), 2978, 2943 (C−H), 1728 (C═O), 1635 (C═O), 1453, 1387, 1134, 763 (C−H δ oop), 704 cm^{-1} (C═C δ).

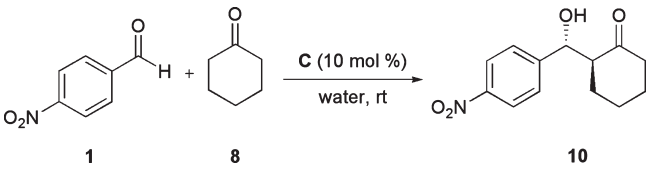
Table 1. Aldol Reaction between Aldehyde 1 and Ketones 2, 8, and 9 Catalyzed by Copolymers $C_{2:1}$ and $D_{2:1}$[a]



entry	catalyst	ketone	time (h)	conv (%)[b]	anti:syn[b]	*ee* (%)[c]
1	$\mathbf{C_{2:1}}$	**2**	24	97	1.4:1	46
2	$\mathbf{D_{2:1}}$	**2**	24	85	1:3	0
3	$\mathbf{C_{2:1}}$	**8**	2	93	2:1	8
4[d]	$\mathbf{C_{2:1}}$	**8**	24	72	1.4:1	22
5[e]	$\mathbf{C_{2:1}}$	**8**	24	40	1.5:1	20
6	$\mathbf{D_{2:1}}$	**8**	2	97	2:1	4
7	$\mathbf{C_{2:1}}$	**9**	24	99		2
8	$\mathbf{D_{2:1}}$	**9**	24	97		2

[a] Reaction conditions: aldehyde (**1**, 0.033 mmol), ketone (**2**, 0.066 mmol; **8**, 0.165 mmol; **9**, 0.825 mmol), catalyst (0.01 mmol), phosphate buffer (0.1 mL, 100 mM, pH 7). [b] Determined by ^{1}H NMR and HPLC analyses. [c] Determined by chiral HPLC; *ee* values are referred to the major isomer. [d] **1** (0.033 mmol), **8** (0.066 mmol), catalyst (0.01 mmol), phosphate buffer (1.3 mL). [e] Same conditions as entry 4 except that sodium 2-naphthalenesulfonate (0.066 mmol) was added.

Table 2. Aldol Reaction between 1 and 8 Catalyzed by Copolymers in a Molar Ratio 4:1, 2:1, and 1:1 Proline Methacrylate/Styrene[a]



catalyst	*t* (h)	conv (%)[b]	anti:syn[b]	*ee anti* (%)[c]	*ee syn* (%)[c]
$C_{4:1}$	20	90	1:1	34	20
$C_{2:1}$	6	88	1:1	26	34
$C_{1:1}$	6	96	1:1	28	38

[a] Reaction conditions: **1** (0.033 mmol), **8** (0.165 mmol), catalyst (0.0033 mmol), phosphate buffer (0.1 mL, 100 mM, pH 7). [b] Determined by ^{1}H NMR and HPLC analyses. [c] Determined by chiral HPLC.

Polymer ***C*$_{1:1}$** *(n/m = 1:1).* Polymer $\mathbf{C}_{1:1}$ was obtained as a brown solid. ^{1}H NMR (300 MHz, D_2O, 298 K): δ 7.7−6.4 (m, 5H, Ar), 5.4−0.3 (m, 14H, H-4pro, H-2pro, CH_2-5pro, *CH*−Ar, CH_2−3pro, CH_2CMe, CH_2CHAr, CH_3 (methacryl). IR (KBr): ν = 3436 (br, N−H, COOH), 3022, 2978, 2942 (C−H), 1728 (C═O), 16351 (C═O), 1494, 1454, 1388, 1179, 1132, 763 (C−H δ oop), 703 cm^{-1} (C═C δ).

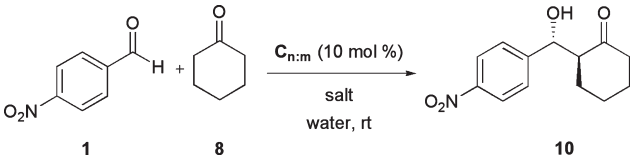
Polymer ***C*$_{4:1}$** *(n/m = 4:1).* Polymer $\mathbf{C}_{4:1}$ was obtained as a white solid. ^{1}H NMR (300 MHz, D_2O, 298 K): δ 7.5−6.8 (m, 5H, Ar), 5.4−5.0 (m, 4 × 1H, H-4pro), 4.3−3.7 (m, 4 × 1H, H-2pro), 3.7−3.1 (m, 4 × 2H, CH_2-5pro), 2.8−0.3 (m, 31H, CH_2-3pro, *CH*−Ar, CH_2CMe, CH_2CHAr, CH_3 (methacryl). IR (KBr): ν = 3436 (br, NH, COOH), 2982 (C−H), 1727 (C═O), 1630 (C═O), 1388, 1146, 705 cm^{-1} (C═C δ).

Polymer ***D*$_{2:1}$** *(n/m = 2:1).* Polymer $\mathbf{D}_{2:1}$ was obtained as a white solid. ^{1}H NMR (300 MHz, D_2O, 298 K): δ 7.8−6.3 (wide singlet, 5H, Ar), 5.3−5.1 (m, 2 × 1H, H-4pro), 4.1−4.0 (m, 2 × 1H, H-2pro), 3.7−3.4 (m, 2 × 2H, CH_2-5pro), 3.3−2.5 (m, 9H, CH_2OCO, CH_2NH, *CH*−Ar), 2.3−0.6 (m, 32H, CH_2-3pro, OCO$CH_2CH_2CH_2CH_2CH_2$NH, OC-$H_2CH_2CH_2CH_2CH_2CH_2$NH, CH_2CHAr, CH_2CMe, CH_3 (methacryl).

General Procedure for Asymmetric Aldol Reaction. To a solution of polymer (10−30 mol %) in phosphate buffer (100 μL, 100 mM, pH 7) (it could require sonication for complete solubilization), aldehyde **1** (5 mg, 0.033 mmol) and the corresponding ketone (**2**, 0.066 mmol; **8**, 0.165 mmol; or **9**, 0.825 mmol) were added. The mixture was stirred at room temperature for the time indicated in Tables 1 and 2. After the specified time elapsed, water was added (1 mL), and the mixture was extracted with dichloromethane (3 × 1 mL). The organic phase was concentrated under reduced pressure. Conversions and stereoselectivities are summarized in Tables 1 and 2.

*(3S,4S)-4-p-Nitrophenyl-1,3,4-trihydroxy-1,3-O-isopropyliden-butan-2-one (**3**).* ^{1}H NMR (300 MHz, $CDCl_3$, 298 K): δ (major isomer) 8.21 (d, *J* = 8.1 Hz, 2H, ArH), 7.60 (d, *J* = 8.1 Hz, 2H, ArH), 5.01 (d, *J* = 7.5 Hz, 1H, *CH*OH), 4.5−4.1 (m, 3H), 3.8−3.7 (m, 1H), 1.39 (s, 3H, Me), 1.21 (s, 3H, Me). ^{13}C NMR (75 MHz, $CDCl_3$, 298 K): δ 210.6 (CHO), 146.5 (Ar), 138.3 (Ar), 127.9 (Ar), 123.2 (Ar), 101.4 (Ac), 75.8 (C-4), 71.7 (C-3), 66.6 (C-1), 23.4 (CH_3), 23.3 (CH_3). MS (EI): *m*/*z* 585.3 (2*M* + 23). Anal. Calcd (%) for $C_{13}H_{15}NO_6$: C, 55.51; H, 5.38; N, 4.98. Found: C, 55.33; H, 5.22; N, 5.18. All spectroscopic data were in agreement with reported values.[30,31] Retention time (HPLC, Daicel Chiralpak OD-H, hexano/*i*-PrOH = 90:10, flow rate 1 mL/min, λ = 254 nm): t_R = 11.17 (anti, major), t_R = 12.79 (anti, minor), t_R = 16.62 (syn). Retention time (HPLC, Daicel Chiralpak AD-H, hexane/*i*-PrOH = 96:4, flow rate 1 mL/min, λ = 254 nm): t_R = 25.88 min (anti, major), t_R = 27.98 min (anti, minor), t_R = 44.49 min (*syn,* minor), t_R = 60.62 min (syn, major).

Table 3. Aldol Reaction between Aldehyde 1 and Ketone 8 Catalyzed by $C_{1:1}$, $C_{2:1}$, and $C_{4:1}$ in the Presence of Salts[a]



entry	salt, concentration	catalyst	time (h)	conv (%)[b]	anti:syn[b]	*ee* (%)[c]
1	LiCl 1 M	$C_{2:1}$	48	83	1.5:1	40
2	$MnCl_2$ 1 M	$C_{2:1}$	96	38	3:1	92
3	$CaCl_2$ 1 M	$C_{2:1}$	96	28	3:1	74
4	$BaCl_2$ 1 M	$C_{2:1}$	96	26	3:1	86
5	$MgCl_2$ 1 M	$C_{2:1}$	96	45	4:1	90
6	$MgCl_2$ 0.5 M	$C_{2:1}$	168	66	7:1	94
7	$MgCl_2$ 0.1 M	$C_{2:1}$	24	72	1:1	34
8	$MgCl_2$ 1 M	$C_{4:1}$	96	18	3:1	66
9	$MgCl_2$ 1 M	$C_{1:1}$	96	60	5:1	92
10	$MgCl_2$ 0.5 M	$C_{1:1}$	55	82	>20:1	96
11[d]	no salt added	$C_{2:1}$	72	76	4:1	92

[a] Reaction conditions: **1** (0.033 mmol), **8** (0.165 mmol), salt (0.1−1 M), catalyst (0.0033 mmol), water (0.1 mL). [b] Determined by ^{1}H NMR and HPLC analyses. [c] Determined by chiral HPLC; *ee* values are referred to the major isomer. [d] Reaction conditions: **1** (0.264 mmol), **8** (1.32 mmol), catalyst (0.0264 mmol), water (0.1 mL) (polymer is precipitated, since it is insoluble under these conditions).

*(2S,1′R)-2-(Hydroxy(4-nitrophenyl)methyl)cyclohexan-1-one (**10**).* ^{1}H NMR (300 MHz, $CDCl_3$, 298 K): δ (major isomer) 8.19 (d, *J* = 8.7 Hz, 2H, ArH), 7.49 (d, *J* = 8.7 Hz, 2H, ArH), 4.88 (d, *J* = 8.4 Hz, 1H, CHOH), 4.02 (wide singlet, 1H), 2.63−2.54 (m, 1H), 2.50−2.33 (m, 1H), 2.31−2.21 (m, 1H), 2.14−2.06 (m, 1H), 1.83−1.79 (m, 1H), 1.73−1.52 (m, 3H), 1.49−1.28 (m, 1H). All spectroscopic data were in agreement with reported values.[6,32] Retention time (HPLC, Daicel Chiralpak AD-H, hexane/*i*-PrOH = 80:20, flow rate 0.5 mL/min, λ = 254 nm): t_R = 23.79 (syn, minor), t_R = 25.40 (syn, major), t_R = 27.30 (*anti,* minor), 34.60 (*anti,* major).

*(4R)-4-Hydroxy-4-(4′-nitrophenyl)butan-2-one (**11**).* ^{1}H NMR (300 MHz, $CDCl_3$, 298 K): δ (major isomer) 8.21 (d, *J* = 8.8 Hz, 2H, ArH), 7.54 (d, *J* = 8.8 Hz, 2H, ArH), 5.27 (dd, *J* = 2.9, 3.3 Hz, 1H, CHOH), 3.59 (d, *J* = 3.3 Hz, 1H), 2.85 (d, *J* = 2.9 Hz, 2H), 2.22 (s, 3H). All spectroscopic data were in agreement with reported values.[32] Retention time (HPLC, Daicel Chiralpak AD-H, hexane/*i*-PrOH = 96:4, flow rate 1 mL/min, λ = 254 nm): t_R = 37.50 (*S*, minor), t_R = 38.50 (*R*, major).

General Procedure for Asymmetric Aldol Reaction in the Presence of Salts. To a solution of known concentration of the corresponding salt in water (0.1 mL), polymer **C** (10 mol %) was added, and the mixture was stirred until solubilization (it could require sonication for complete solubilization). Then, aldehyde **1** (5 mg, 0.033 mmol) and ketone **8** (0.165 mmol) were added over this solution. The mixture was stirred at room temperature for the time indicated in Table 3. After the specified time elapsed, water was added (1 mL), and the mixture was extracted with dichloromethane (3 × 1 mL). The organic phase was concentrated under reduced pressure. Conversions and stereoselectivities are shown in Table 3.

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General Procedure for Recovering and Recycling Experiments of Polymer $C_{2:1}$. To a solution of $MgCl_2$ in water (0.5 M, 4.16 mL), polymer $C_{2:1}$ (30 mol %) was added, and the mixture was stirred until solubilization (it could require sonication for complete solubilization). Aldehyde **1a** (210 mg, 1.39 mmol) and ketone **8** (6.95 mmol) were added over this solution. The mixture was stirred at room temperature for 72 h. After this time, the mixture was extracted with dichloromethane (6 × 20 mL), the organic phase was separated, and the products were isolated. Phosphate buffer (4.16 mL, 200 mM, pH 2.9) was added to the aqueous phase, and the mixture was stirred for 30 min until precipitation. The polymer was separated by centrifugation, rinsed with water (2 × 5 mL) and dichloromethane (4 × 5 mL), dried in vacuum for 2 h, and reused in the next experiment. The results are summarized in Table 4.

Proton High-Resolution MAS NMR. Proton high-resolution MAS NMR measurements were performed on a Bruker Avance 400 wide bore (89 mm i.d.) spectrometer (Bruker Instruments, Karlsruhe, Germany) operating at 9.4 T (proton Larmor frequency at 400.14 MHz). All spectra were acquired at 20 °C (293 K) using a Bruker double tuned broadband solid-state CP/MAS probe head. Typically, for each sample ~80 μL of polymer solution was placed into a 4 mm i.d. zirconia rotor. The spectra were acquired using a pulse sequence with a single radio-frequency pulse of 90°. The spinning rate was 5.0 kHz. The spectral width was 15 kHz, 8K data points, and the number of scans varied between 64 and 256 with a repetition rate of 1.5 s. All FIDs were processed with a 2 Hz line broadening.

Table 4. Recovery and Reuse of the Catalyst $C_{2:1}$ for the Reaction of 1 and 8 in the Presence of $MgCl_2$ (0.5 M) in Water

run	yield of recovered polymer (%)	yield (%)[a]	anti:syn[b]	*ee* (%)[c]
1		68	8:1	98
2	99	72	10:1	96
3	91	70	9:1	>99

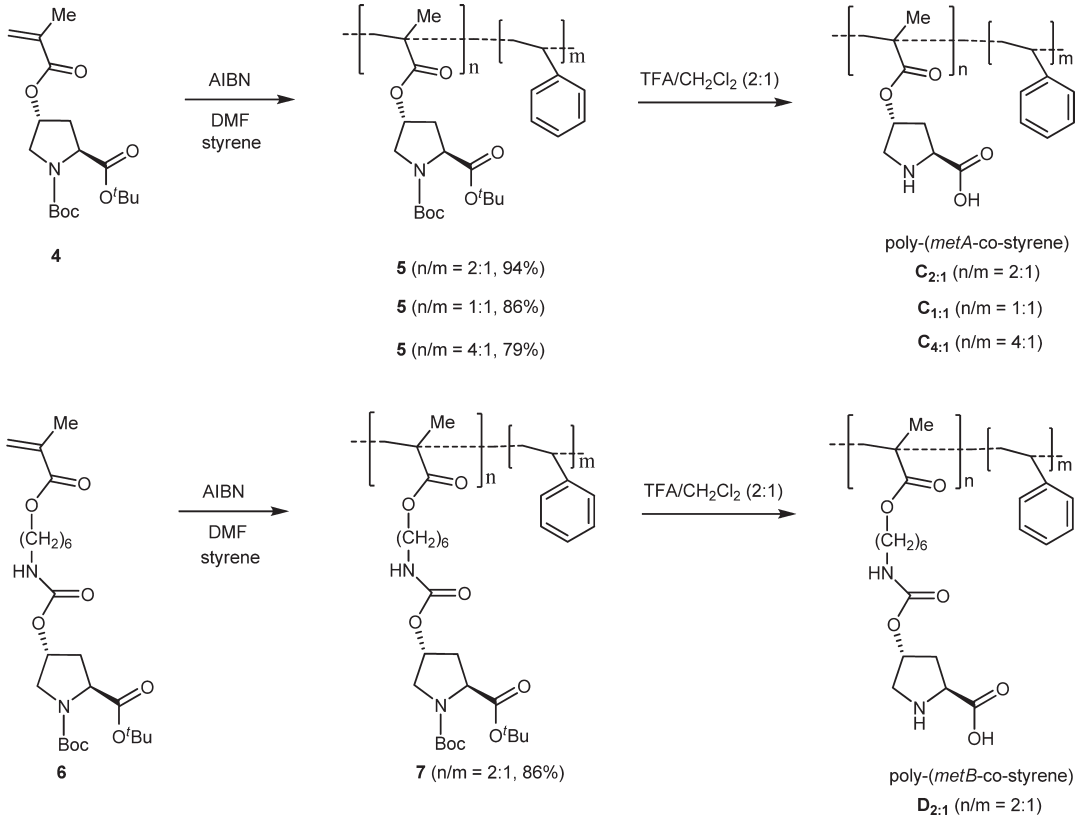
[a] Isolated yield after 72 h. [b] Determined by ^{1}H NMR and HPLC analyses. [c] Determined by chiral HPLC; *ee* values are referred to the major isomer.

RESULTS AND DISCUSSION

Styrene was chosen as hydrophobic comonomer since it is well-known that during the radical copolymerization of methacrylates and styrene the incorporation of both units exhibits a tendency to the alternance.[33] A basic discussion of this point can be found in the Supporting Information.

For the synthesis of copolymers with styrene (Scheme 2), we first used two proline methacrylates: one with the aliphatic spacer (**6**) and the other without any spacer (**4**). Differences in catalytic activity of the corresponding copolymers derived from **4** and **6** would inform us about the influence of the spacer for catalysis. The synthesis of **4** and **6** was described previously.[12] The copolymerization was carried out in DMF in the presence of AIBN as radical initiator using a 2:1 molar ratio of proline methacrylate (**4** or **6**) to styrene. ^{1}H NMR spectra of the protected polymers **5** and **7** exhibited the typical broad peaks of the polymeric species and were consistent with the proposed structures. Considering the peak integral values for the aromatic protons of styrene and the broad singlet assigned to proton H-4 of proline, the ratio of proline methacrylate/styrene units was determined as 2:1 (see Supporting Information for more details). This value is in agreement with the molar ratio of monomers used for the copolymerization. Acid hydrolysis of protecting groups from the proline ring led to polymers with free amino and carboxylic acid groups in the

Scheme 2. Synthesis of Polymers $C_{4:1}$, $C_{2:1}$, $C_{1:1}$, and $D_{2:1}$



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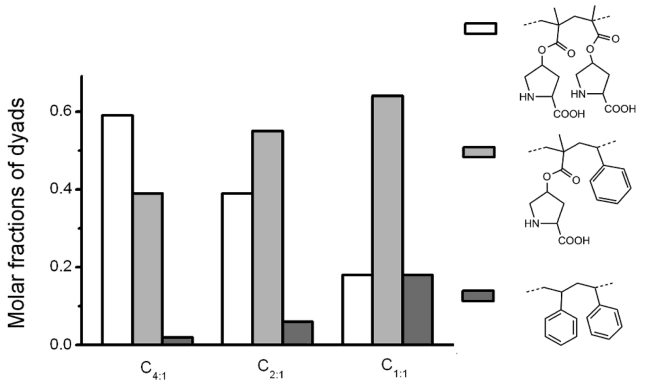

Figure 1. Theoretical molar fraction of dyads along the copolymer chains used in this study, obtained as described in the Experimental Section.

side chain, poly(*metA-co*-styrene) (67:33 mol %) and poly(*metB-co*-styrene) (67:33 mol %), named in a simplified way $\mathbf{C_{2:1}}$ and $\mathbf{D_{2:1}}$, respectively. Molecular weights of the copolymers were characterized by GPC in the protected form, using polystyrene standards as reference. Number-average molecular weights of polymers **5** (n/m = 2:1) and **7** (n/m = 2:1) were 41 000 and 33 000 g/mol, respectively. The polydispersity index for polymers **5** and **7** was 3.7 and 2.4, respectively, which are expected values in conventional radical polymerizations.

Polymers $\mathbf{C_{2:1}}$ and $\mathbf{D_{2:1}}$ were tested as catalysts of the aldol addition in phosphate buffer (0.1 mL, 100 mM, pH 7) of *p*-nitrobenzaldehyde (**1**, 0.033 mmol) with three different ketones: 2,2-dimethyl-1,3-dioxan-5-one (**2**, 0.066 mmol), cyclohexanone (**8**, 0.165 mmol), and acetone (**9**, 0.825 mmol). Results are summarized in Table 1. At 30 mol % catalyst loading excellent conversion was obtained after 2−24 h, being the catalyst more active with the hydrophobic cyclohexanone. Polymer $\mathbf{C_{2:1}}$ was shown to be effective under diluted solutions (entry 4). These results, when compared with the low catalytic activity obtained using proline−methacrylate homopolymers,[12] indicate that the presence of the phenyl rings in the new copolymers promotes the reaction in water. We hypothesize that the aromatic residues of the polymer interact with the ketone substrate, and as a result, this hydrophobic interaction brings the substrate close to the catalytic proline unit. This hypothesis is supported by the results obtained with reactions performed under diluted conditions in the presence of a hydrophobic salt, i.e., sodium naphthalenesulfonate. The salt could compete with the ketone for the interaction with the styrene units inhibiting, in part, the reaction (compare entries 4 and 5 in Table 1).

The results of aldol reactions were similar for both $\mathbf{C_{2:1}}$ and $\mathbf{D_{2:1}}$, indicating that the influence of the spacer is small. Therefore, further studies were carried out with copolymers derived from proline methacrylate without spacer $\mathbf{C_{2:1}}$. Two additional copolymers with molar ratios of 4:1 and 1:1 proline methacrylate−styrene were prepared to test the influence of phenyl ring density on the outcome of the reaction ($\mathbf{C_{4:1}}$ and $\mathbf{C_{1:1}}$, respectively, in Scheme 2). Number-average molecular weights of the protected polymers (polymers **5**: n/m = 4:1 and 1:1) were 40 000 and 35 000 g/mol, respectively, with polydispersities of 3.6 and 3.1. In view of the high activity observed in previous assays, the catalyst loading was reduced to 10 mol %. As it could be expected, the reaction rate between aldehyde **1** and ketone **8** was higher with copolymers containing higher molar ratio of styrene ($\mathbf{C_{1:1}}$ > $\mathbf{C_{2:1}}$ > $\mathbf{C_{4:1}}$, Table 2). With catalyst $\mathbf{C_{1:1}}$ an almost complete conversion of aldehyde (96%) was obtained after 6 h.

These differences in conversion between the three polymers $\mathbf{C_{1:1}}$, $\mathbf{C_{2:1}}$, and $\mathbf{C_{4:1}}$ are not only related to the styrene load but also —at least to some extent—to their microstructure. Figure 1 shows the cumulative molar fractions of *metA*−*metA*, *metA*−styrene* (*metA*−styrene + styrene−*metA*), and styrene−styrene dyads, obtained theoretically as described in the Experimental Section. The *metA*−*metA* dyad is, in some way, a noneffective sequence since the homopolymer (constituted only by sequences *metA*−*metA*) was shown to be inactive in water.[12] The styrene−styrene is also nonactive, being the alternating dyads *metA*−styrene* the active ones. Figure 1 shows that, within the composition range studied here, an increase of styrene in the copolymers decreases the load of proline but increases the molar fraction of active dyads *metA*−styrene*, which is in agreement with the results shown in Table 2. At the same time the content in nonuseful styrene−styrene dyads increases as well. It is worth noting that the tendency toward the formation of alternating sequences mentioned above causes that the dyads *metA*−styrene* are the most abundant in the $\mathbf{C_{2:1}}$ and $\mathbf{C_{1:1}}$ copolymers. This may also influence the water solubility of the polymers, since even the $\mathbf{C_{1:1}}$ copolymer with high styrene content is soluble in this medium.

In all reactions discussed above, both diastereo- and enantioselectivity were poor. Changes in pH (6 or 8) and temperature (4 or 50 °C) did not result in significant modifications of the stereoselectivity (results not shown). However, improvements in stereoselectivity were achieved when the reaction between aldehyde **1** and ketone **8** in water was performed in the presence of salts (Table 3). While a modest increase in stereoselectivity was obtained with 1 M LiCl in the presence of copolymer $\mathbf{C_{2:1}}$ (entry 1), the addition of divalent salts at 1 M concentration afforded an appreciable increase of both diastereo- and enatioselectivity at the expense of the conversion (entries 2−5). Among the salts tested ($MgCl_2$, $MnCl_2$, $CaCl_2$, $BaCl_2$), $MgCl_2$ gave the best results. Reducing the concentration of $MgCl_2$ (0.5 M, entry 6) resulted in good diastereoselectivity (anti:syn, 7:1) and excellent enantioselectivity (94% *ee*). However, at low concentration of $MgCl_2$ (0.1 M), the stereoselectivity was practically lost. These results are in agreement with those obtained in a recent work on the prolinamide-catalyzed reaction of acetone and methylglyoxal.[34] A small increase in enantioselectivity after addition of $MgSO_4$ was observed, while the addition of Na_2SO_4 had no effect on the reaction. A chelation control by magnesium ion was proposed. Remarkably, we observed that the salt effect on stereoselectivity and conversion was higher with increasing molar ratio of styrene in the catalyst (compare entries 5, 8, and 9 in Table 3). Using $\mathbf{C_{1:1}}$ as catalyst and $MgCl_2$ at 0.5 M concentration (entry 10), the reaction proceeded with high conversion (82%) and excellent stereoselectivity (anti:syn, > 20:1; *ee*, 96%).

To understand the relationship between the addition of salts and the enantioselectivity observed, dynamic light scattering experiments were performed. Figure 2 shows correlation and size distribution curves for solutions of $\mathbf{C_{2:1}}$ in pure water, in phosphate buffer, and solutions with LiCl (1 M) and $MgCl_2$ (1 M). In pure water, the copolymer exhibits hydrodynamic sizes of $R_h \sim 5$ nm. Similar results were obtained using phosphate buffer solutions. Taking into account the copolymer microstructure (alternation of hydrophilic and hydrophobic monomer units), and due to the electrostatic repulsion between the proline units (negatively charged at this pH) along the chain, the hydrodynamic radius observed correspond to individual chains, also known as

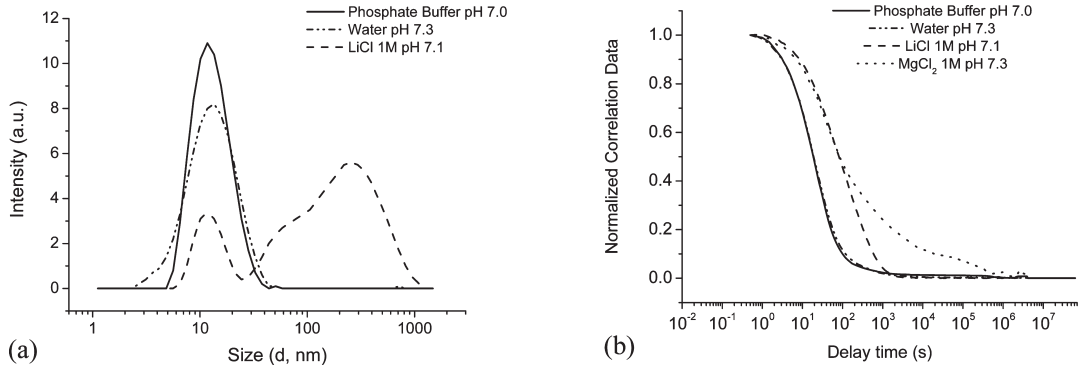

Figure 2. (a) Size distribution of copolymer $C_{2:1}$ in different environments: phosphate buffer (100 mM), in water and with LiCl 1 M. (b) Autocorrelation function obtained for copolymer $C_{2:1}$ with different salts (phosphate buffer 100 mM, LiCl 1 M, and $MgCl_2$ 1 M) and in water.

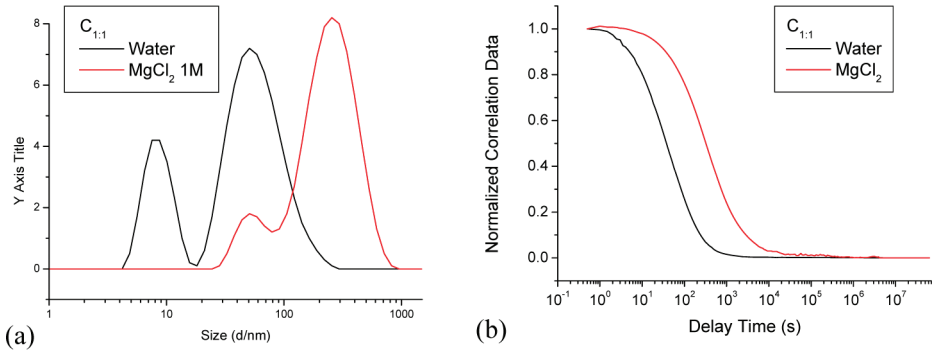

Figure 3. Size distribution (a) and autocorrelation function (b) of copolymer $C_{1:1}$ in water and after adding $MgCl_2$ to a 1 M concentration.

unimolecular micelles.[35] The addition of monovalent or divalent salts significantly modifies the morphology observed. Using LiCl, the correlation curve shifted to higher delay times, and as a consequence, two relaxation modes corresponding to individual chains and the formation of large aggregates with average sizes around 200−300 nm in diameter were observed. The addition of a large excess of a monovalent salt leads to a screening of the charges preventing the polyelectrolyte repulsion between the chains. Nevertheless, the polymer remains in solution. On the contrary, the addition of $MgCl_2$ significantly affects the solubility of the polymer in the aqueous media. For polymer $\mathbf{C_{2:1}}$, the polymer remains in solution but starts to form large aggregates with a wide distribution of sizes, as it could be concluded from the correlation curve. After 24 h, the precipitation was completed and the copolymer formed a heterogeneous system. Similar behavior was observed for polymer $\mathbf{C_{4:1}}$.

The copolymer $\mathbf{C_{1:1}}$ exhibited distinct behavior. In water, $\mathbf{C_{1:1}}$ exhibits two relaxation modes associated with individual ($R_h \sim$ 5 nm) and larger aggregates ($R_h \sim$ 25 nm). Compared to previous copolymers ($\mathbf{C_{2:1}}$ and $\mathbf{C_{4:1}}$), the formation of aggregates is enhanced. The lower density of negative charges (less units of proline within the copolymer) and the increase of hydrophobic interactions due to a higher amount of styrene units in the copolymer are, most likely, responsible of the behavior observed. The addition of $MgCl_2$ to this copolymer formed large aggregates as suggested by the shift observed in the correlation curve to larger relaxation times, as shown in Figure 3b. Two different populations could be observed. One population of aggregates with a R_h similar to those formed in water ($R_h \sim$25 nm) and a second population with average sizes of

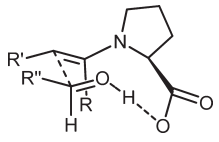

Figure 4. Transition state model for the proline-catalyzed aldol reactions.

$R_h \sim$ 120−130 nm. Nevertheless, contrary to the systems with higher content of hydrophilic proline units, copolymers $C_{1:1}$ remained soluble. The results from DLS described above confirmed the formation of aggregates upon addition of $MgCl_2$.

Furthemore, results of proton high-resolution MAS NMR mesurements performed on these polymer systems support the formation of aggregates (spectra can be found in the Supporting Information). The addition of divalent salts leads to broadening of the polymer peaks that increases with increasing concentration. The effect is less pronounced in the presence of LiCl. In particular, the peak associated with the protons of the proline unit (at ∼5.2 ppm) is clearly visible in the spectra with no salt and with LiCl 1.0 M but is more difficult to assess its presence in the spectra corresponding to the polymer solutions with $MgCl_2$.

The formation of aggregates is likely related to the enhanced selectivity observed after addition of the salt. The transition state model for the proline-catalyzed aldol reactions is depicted in Figure 4. This transition state involves a chairlike arrangement of enamine and carbonyl atoms, with the substituent of the aldehyde in a pseudoequatorial position, and the nucleophilic attack of the enamine taking place on the *re*-face of the aldehyde.[36,37] Proton transfer from the carboxylic acid group

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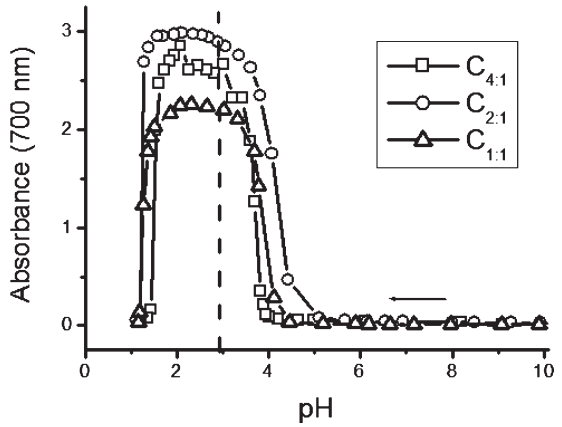

Figure 5. Absorbance at 700 nm vs the pH for the copolymers $\mathbf{C_{4:1}}$ (□), $\mathbf{C_{2:1}}$ (○), and $\mathbf{C_{1:1}}$ (Δ) at ionic strength = 0.15. The pH of the buffer used in the precipitation is indicated as a dashed line.

to the forming alkoxide is essential for charge stabilization and to facilitate C−C bond formation. It has been suggested[17−19] that water molecules can alter the organized transition state and, therefore, reduce the stereoselectivity. In our systems, the formation of the aggregates could produce hydrophobic regions assembled with the hydrophobic reactants, where the reaction catalyzed by proline occurs away from the bulk of the water and, thus, proceeds with stereoselectivity. In this context, it is worth noting the highly stereoselective reactions reported with cross-linked polymer beads obtained by polymerization of a proline derivative with benzyl methacrylate in the presence of an acrylic cross-linker.[13] We could conceptually compare the systems studied here with these beads, considering that the entities formed by the linear copolymers when $MgCl_2$ is added, as reversible aggregates, and the cross-linked beads as examples of extreme irreversible aggregation. Also, this analysis is in agreement with the results obtained with the polymer $\mathbf{C_{2:1}}$ without adding salt but in heterogeneous conditions, namely, with a 8-fold increase of reactants and catalyst, maintaining the volume of water to keep polymer insoluble under these conditions (entry 11 in Table 3). Aldol products were obtained with good stereoselectivity, similar to that obtained in the presence of $MgCl_2$. This result could be rationalized as the reaction take place in hydrophobic patches of a thick paste with exclusion of water. All these data suggest that some kind of aggregation is needed to obtain stereoselectivity.

The catalysts were tested for several cycles of recovery and reuse. This task was undertaken on the basis that amphiphilic polymers bearing zwitterionic units precipitate in water at the isoelectric point (IEP). Hydrophobic polyzwitterions are normally insoluble in aqueous media at the IEP because the Coulombic interactions between opposite charges are maximal at this point. Above and below the IEP, the net charge is negative or positive, respectively, since the stoichiometry is lost allowing linear macromolecular chains to expand, solvate, and eventually dissolve. The solubility changes as a function of pH of polymers $\mathbf{C_{4:1}}$, $\mathbf{C_{2:1}}$, and $\mathbf{C_{1:1}}$ were monitored by turbidity measurements (Figure 5) under low ionic strengths. If the IEP is taken as the average pH between cloud points (the two limiting pH values at which the solution changes from transparent and homogeneous to nontransparent and heterogeneous), the IEPs for all copolymers are very similar and fall in the pH interval 2.5−3. This value of IEP is in agreement with our previous results on the homopolymer[10] and with those of similar polyzwitterions.[38]

Taking the standard reaction catalyzed by polymer $\mathbf{C_{2:1}}$, we evaluated its recovery and reuse using this approach. At the end of the reaction, products and nonreacted substrates were extracted with dichloromethane, phosphate buffer solution (pH = 2.9) was added over the aqueous phase, and the mixture was stirred until precipitation. The polymer was separated by centrifugation and rinsed with water and dichloromethane and reused in the next run. The results are summarized in Table 4. They showed a high recovery of supported catalyst (less than 10% weight loss), while yield and stereoselectivity of the reaction remained practically unchanged.

CONCLUSIONS

In summary, we have applied a new approach to the synthesis of catalytically active linear copolymers based on the monomers, which offers flexibility in the design of the catalyst. In the present work, a series of copolymers that readily work and recycle in water without the need of any extra solvent have been prepared. Two main issues have been faced: (1) The catalytic activity itself; that is, is it actually the reaction taking place in water with a reasonable rate? (2) If the reaction occurs, is it stereoselective? Regarding the first point, we have found that the incorporation of styrene allows the reaction to proceed feasibly in water. In addition, it has been shown that the activity of the catalyst in water could be modulated by the molar ratio of comonomers used for copolymerization. An increase in the content of hydrophobic styrene lead to an increase in the activity of the catalyst. This behavior suggests that reactions are promoted by hydrophobic interactions between the ketone substrate and the phenyl ring of the catalyst, as indicated by the increased activity obtained with more hydrophobic ketones and with catalyst bearing higher styrene molar ratio. Regarding the second aspect, stereoselectivity, it is very significant the effect of the addition of salts, such as $MgCl_2$, since the stereoselectivity is negligible in the absence of salts. Results of dynamic light scattering and ^{1}H MAS NMR measuments have shown that the addition of $MgCl_2$ leads to the formation of aggregates, suggesting the need of hydrophobic regions where the reaction could take place for obtaining stereoselectivity. The role of styrene is therefore related to two key issues: (a) styrene is needed to allow the reaction to proceed, and (b) styrene itself seems to be involved in the aggregation and in the stereoselectivity. Although these copolymers present some limitations and more work remains to be done to improve their catalytic efficiency, the present study shows, in addition to recently reported works,[2,11,13,22] that this novel approach for the synthesis of catalytic polymers offers the potential of engineering the properties of the catalyst to the desired application.

ASSOCIATED CONTENT

Supporting Information. Dyad analysis, detail of the ^{1}H NMR spectra of 5 and 7 and proton high-resolution MAS NMR spectra of polymers in the presence of salts. This material is available free of charge via the Internet at http://pubs.acs.org.

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