Preparation of New Microgel Polymers and Their Application as Supports in Organic Synthesis

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A series of soluble microgel polymers have been synthesized using solution-phase polymerization reactions. In a systematic manner, several variables such as monomer concentration, cross-linker content, reaction solvent and reaction time were examined, and this provided an optimal polymer with both solubility and precipitation characteristics suitable for synthetic applications. Thus, a chemically functionalized microgel polymer was synthesized, and the utility of this polymer in the synthesis of a small array of oxazole compounds has been demonstrated. The advantage of the microgel polymers produced was that they exhibited solution viscosities lower than those of conventional linear polymers even at higher concentrations, and this was found to be beneficial for their precipitation properties. Compounds prepared using the described microgel polymer supports were obtained in similar yields and purity when compared with insoluble resins, and more importantly, the soluble polymer bound intermediates could be analyzed at each step using standard NMR techniques.

Introduction

Solid-phase organic synthesis is now a well-established methodology for the preparation of low molecular weight compound collections. Over the past few years many solid-phase syntheses of libraries for pharmaceutical and agricultural applications have been reported.[1] Additionally, this technology has been utilized in the optimization of catalysts[2] and for applications in materials science.[3] However, there are still numerous problems associated with the use of cross-linked insoluble polymeric supports. These are mainly due to the very specific microenvironment provided by the polymeric matrix, which can lead to unpredictable changes in reaction rates and even pathways.[4] Furthermore, the polymer matrix often hampers the analytical assessment of the attached compound. Consequently, the transfer and optimization of solution-phase protocols to the solid-phase format is still problematic and often time-consuming.

Many of these problems can be avoided by replacing the resinous support with a soluble polymer. This enables reactions to be performed in homogeneous solutions rather than in gel phases in which insoluble polymer-supported reactions are performed. This approach also enables unencumbered analysis of intermediates using standard techniques such as NMR. A large portion of research from our laboratory has taken advantage of this approach that we have termed Liquid-Phase Organic Synthesis (LPOS).[5] The most utilized LPOS supports include non-cross-linked polystyrene (NCPS)[6] and poly(ethylene glycol) (PEG).[7,8] The utility of these soluble polymers in organic synthesis has been demonstrated by the preparation of small libraries, soluble polymer-supported reagents, catalysts, and enzyme-catalyzed reactions.[9]

With the ever-expanding needs of polymer-supported technology, new supports are constantly being conceived and developed. Interestingly, microgels have thus far not been considered as supports for the synthesis of small molecules. To our knowledge, only one example of a "synthetic" application using microgel polymers has been reported. Here, Wulff and co-workers prepared microgel-supported oxazaborolidine catalysts that were used for the asymmetric reduction of ketones.[10] Herein, we report the development of novel microgel polymers and demonstrate their successful application as supports for the synthesis of small molecules.

Results and Discussion

Microgels have been defined as "intramolecularly cross-linked polymers that form stable solutions in an ap-

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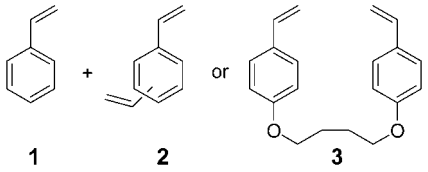

Figure 1. Monomers used for the preparation of microgel polymers.

propriate solvent".[10] These materials can be prepared either by polymerization in the presence of surfactants[11] or more conveniently in homogeneous solution. In the latter approach, the polymerization is performed at low monomer concentrations and the polymer is allowed to grow over a much longer time period when compared to bulk polymerization reactions. However, if the reaction is allowed to proceed for too long, gelation, the transition from a soluble to an insoluble state, occurs and the polymers obtained can no longer be classified as microgels.[10,12] A potential advantage of microgels over other polymers is that even though they are chemically crosslinked, they remain soluble in solvents that are often used in synthetic chemistry. Microgel solutions exhibit lower viscosity even at high concentrations when compared with linear non-crosslinked polymers, and this benefits both handling and precipitation properties. Additionally, the type and extent of cross-linker used and the time and temperature at which the polymerization reaction is performed have a pronounced effect on the microscopic as well as macroscopic physical properties of the microgel polymer produced. Thus, the reactivity of functional groups attached to a microgel can change significantly because of both size exclusion and microenvironmental effects brought about from the different conditions used for their preparation.

Contrary to linear polymers with a comparable chemistry, it is difficult to predict the properties of cross-linked polymers. This is mainly because of the combination of fixed geometry or topological arrangement of the elementary chains leading to a variety of possible conformations with different mechanical and dynamic properties. Because of the difficulty in predicting the optimal constitution of a polymer for synthetic applications, a series of parallel copolymerization reactions were utilized in order to assess the effect of monomer concentration, reaction solvent, reaction time, and cross-linker type and concentration on the microgels' properties.

Styrene **1** was used as the bulk monomer, and the cross-linkers investigated were divinylbenzene **2** and 1,4-bis[4-(vinyl)phenoxy]butane **3**, (Figure 1). The main emphasis of this first part of our study was to produce a polymer that could be reliably and quantitatively recovered by precipitation. As is noted (vide infra), careful attention was paid to the particle size range of the precipitated polymers. All microgels underwent precipitation by the slow addition of a solution of the polymer to vigorously stirred cold methanol and were isolated by filtration using a medium pore glass frit. Each of the isolated polymers was resuspended in methanol and briefly sonicated, and their particle sizes were measured using a microscope. The most desirable particle size was found to lie within a 15−50 μm range; these "powders" could be isolated by filtration in only a few minutes and were easy to handle. Polymers within a size range of 5−25 μm (fine powders) were more troublesome to isolate because their smaller sizes made filtration very time-consuming. Some polymers formed very fine suspensions (<5 μm) after precipitation; these polymers could not be isolated using standard filtration apparatus as the glass frit would clog immediately. Finally, in other cases more coarse particles (50 to >100 μm) were formed. Although these polymers could be isolated very quickly using filtration, it proved difficult to dry them from residual solvent even at elevated temperatures and reduced pressure.

Table 1. Effect of Monomer Concentration on Polymer Properties

entry	[monomer] (wt %)	cross-linker	yield (%)	approx size range (μm)
1	2.5	**2**	30	5−25
2	5.0	**2**	45	5−25
3	10.0	**2**	40	15−50
4	20.0	**2**	20[a]	15−50
5	2.5	**3**	52	5−25
6	5.0	**3**	65	15−50
7	10.0	**3**	67	50 to >100
8	20.0	**3**	0[b]	

[a] Small amount of insoluble polymer was removed prior to precipitation and filtration. [b] Complete gelation observed.

Table 2. Effect of Solvent on Polymer Properties

entry	solvent	cross-linker	yield (%)	approx size range (μm)
1	THF	**2**	45	5−25
2	THF	**3**	65	15−50
3	DME	**2**	42	15−50
4	DME	**3**	59	15−50
5	chlorobenzene	**2**	27	5−25
6	chlorobenzene	**3**	33	5−25

For the first round of polymerizations, the effect of monomer concentration was investigated (Table 1). A standard set of conditions[10] (5 mol % cross-linker, 3 wt % AIBN, THF, 60 °C, 96 h) was employed, and the monomer concentration was varied between 2.5, 5.0, 10.0, and 20.0 wt %. At the lowest monomer concentration (Table 1, entries 1 and 5) the polymers were isolated with poor recoveries and they exhibited too-small particle sizes. In contrast, at the highest monomer concentration (entries 4 and 8) either partial or complete gelation of the polymer was observed, giving rise to low recovery of polymer. It was also noted that the long flexible cross-linker **3** gave polymers with superior precipitation properties.

The next variable investigated was the solvent used in the preparation of the microgels (Table 2). On the basis of the monomer concentration findings, a second set of conditions was utilized (5 mol % cross-linker **2** or **3**, 3 wt % AIBN, 60 °C, 96 h, and 5 wt % monomer concentration) to establish the effect of solvent on the polymers' properties. The solvents investigated were THF, DME, and chlorobenzene. DME gave the slightly superior results, closely followed by THF; however, chlorobenzene was deemed an unsuitable solvent since it produced polymers with small particles sizes and lower yields after precipi-

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Table 3. Effect of Reaction Time on Polymer Properties

entry	time (h)	cross-linker	yield (%)	approx size range (μm)
1	24	**2**	25	<5
2	48	**2**	38	<5
3	72	**2**	42	5−25
4	96	**2**	45	5−25
5	120	**2**	44	5−25
6	24	**3**	49	5−25
7	48	**3**	58	15−50
8	72	**3**	63	15−50
9	96	**3**	65	15−50
10	120	**3**	59	50 to >100

Table 4. Effect of Cross-Linker on Polymer Properties

entry	cross-linker (mol %)	yield (%)	approx size range (μm)	microstucture (mol %, pendant vinyl groups)
1	**2** (2.5)	42	5−25	<0.5
2	**2** (5.0)	45	5−25	1.0
3	**2** (10.0)	50	15−50	2.0
4	**2** (15.0)	40	5−25[a]	6.0
5	**3** (2.5)	33	5−25	<0.5
6	**3** (5.0)	57	15−50	<2.0
7	**3** (10.0)	56	50 to >100	2.0
8	**3** (15.0)	53	50 to >100	5.0

[a] Small amount of insoluble polymer removed prior to precipitation and filtration.

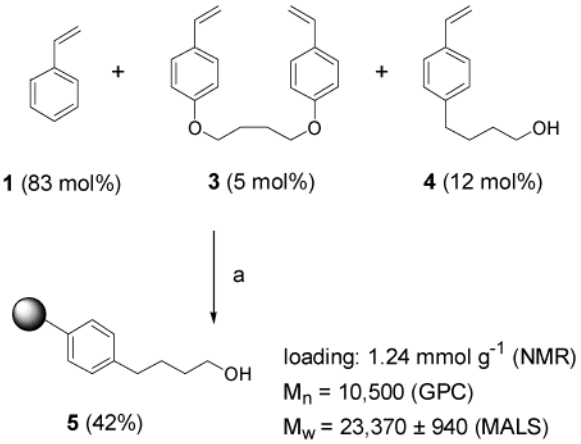
tation. Because THF is more readily available than DME and it was only slightly inferior in this study, it was elected as the solvent of choice for further optimization experiments. Again, cross-linker **3** provided better quality polymers than divinylbenzene **2**.

With these results in hand, the reaction time used to produce the microgel polymers was investigated (Table 3) using a third set of conditions (5 mol % **2** or **3**, 5 wt % monomer concentration, 3 wt % AIBN, THF, 60 °C). In each case the polymer was isolated by precipitation from methanol after 24, 48, 72, 96, and 120 h. After 24 and 48 h, polymers prepared using cross-linker **2** exhibited small particle sizes that complicated isolation. However, polymers prepared using cross-linker **3** showed optimal physical characteristics after 48 h, and lengthening this reaction time to 96 h gave higher yield of polymer. Lengthening the reaction further to 120 h failed to improve the yield of polymer significantly, and this polymer also had a larger particle size.

Finally, the amount of cross-linker used in the preparation of the microgels was investigated (Table 4). Both cross-linkers **2** and **3** were incorporated in the monomer feed at 2.5, 5.0, 10, and 15 mol % under the following conditions (3 wt % AIBN, 5 wt % concentration in THF, 60 °C, 96 h). After completion of the reactions, each polymer was isolated and assessed for particle size. In addition, the microstructure of each polymer was investigated using ^{1}H NMR. It should be noted that during polymerization a cross-linker can be incorporated into a growing polymer chain; however, the second vinyl group may fail to react or "cross-link". In each case, NMR analysis of the polymer enabled the extent of these unreacted "pendant" vinyl groups to be determined quantitatively. As expected, cross-linkers **2** and **3** gave different results; the best polymer obtained using **2** was by using 10 mol % cross-linker, whereas optimal polymers containing **3** were prepared using 5 mol % cross-linker.

From the optimization studies (vide supra), a "lead" polymer that possessed solubility and precipitation properties deemed suitable for synthetic applications was selected. This polymer was prepared using 5 mol % cross-linker **3** and styrene **1** in a 5 wt % solution of THF using AIBN as the initiator at 60 °C for 96 h. This polymer was obtained in approximately 50% yield after precipitation twice from cold methanol.

Scheme 1. Preparation of Chemically Functionalized Microgel Polymer[a]



[a] (a) 3 wt % AIBN, 5 wt % in THF, 60 °C 96 h.

To provide a chemically functionalized microgel **5** that would enable substrate loading, the optimal conditions were modified to include 4-(4-hydroxybutyl) styrene **4** in the monomer feed of the polymer (Scheme 1). Microgel **5** was very soluble (>10 wt %) in toluene, chlorobenzene, dichloromethane, chloroform, 1,2-dichloroethane, THF, and DME. Additionally, microgel **5** was reasonably soluble (up to 5 wt %) in ethyl acetate, dimethylformamide, dimethylacetamide, *N*-methyl-pyrrolidinone, and warm (50 °C) dimethyl sulfoxide. Simple alcohols such as methanol, ethanol, and 2-propanol were the most successful solvents for precipitation; the polymer formed intractable gums in solvents such as hexanes, diethyl ether, and acetonitrile. The results of molecular weight determination of **5** by gel permeation chromatography (GPC) and multiangle light scattering (MALS) show the expected discrepancy because the GPC was calibrated with linear polystyrene standards.

The microstructure of the polymer was monitored most effectively by standard proton NMR spectroscopy. The quality of the spectra obtained allows for direct assessment of the extent of each monomer incorporated within the polymer and also the degree of pendant vinyl groups (from "non-cross-linked" **3**) content by simple integration of the respective signals. Thus, these NMR studies also enabled a hydroxyl loading of **5** of 1.24 mmol g^{-1} to be determined. Of further note was that the line widths observed are significantly narrower than those seen in the MAS proton NMR spectra of **3**-cross-linked insoluble resins ("*J*anda*J*els").[13] For the 4-hydroxybutyl-linker signals the following half-height line widths were observed: 1-CH2 (δ 2.55 ppm, 53.7 Hz), 4-CH2 (δ 3.63 ppm, 27.8 Hz) (Figure 2).

With what we considered to be a well-characterized microgel for organic synthesis in hand, we set out to validate its use in a multistep synthesis. Our laboratory has recently developed a solid-phase synthesis of ox-

(13) For a discussion of the morphology of polymer supports, see: Sherrington, D. C. *Chem. Commun.* **1998**, *21*, 2275.

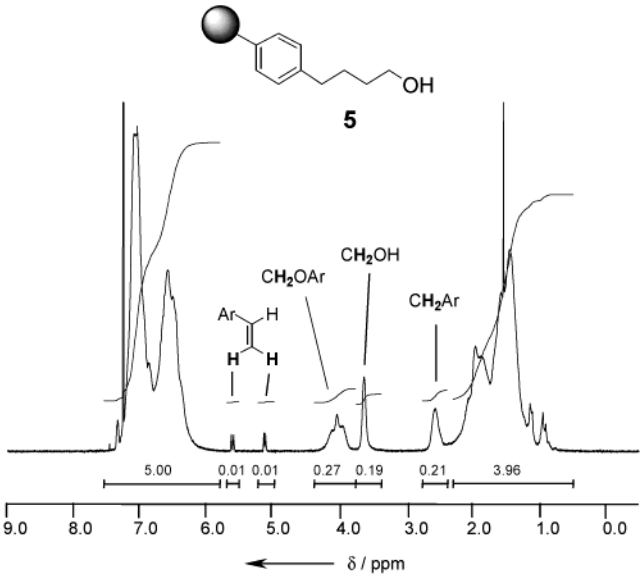


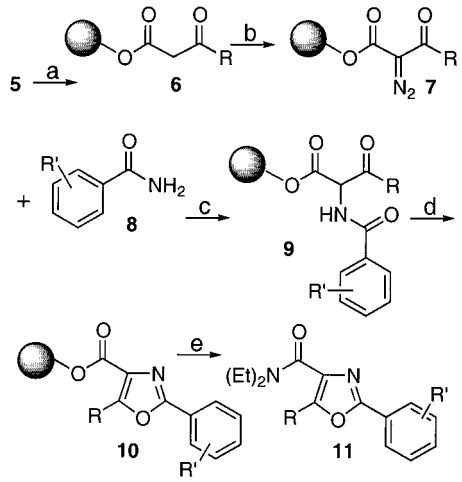
Figure 2. ^{1}H NMR (500 MHz) of microgel **5** (5 mg in $CDCl_3$).

azoles[14] using the rhodium carbenoid N−H insertion strategy developed by Moody.[15] We therefore chose to test the application of hydroxy-microgel **5** using this chemistry, as this presented an ideal opportunity to compare the performance of a soluble microgel with an insoluble *J*anda*J*el resin.

The oxazole synthesis was initiated through the preparation of microgel-bound β-keto esters (**6a** R = Me, **6b** R = Ph) by reaction of hydroxybutyl microgel **5** with either diketene[16] or benzoyl Meldrum's acid adduct (Scheme 2).[17] Progress of ester formation was monitored by IR (appearance of carbonyl peaks at 1740 and 1710 cm^{-1} for R = Me and 1737 and 1687 cm^{-1} for R = Ph, respectively) and by ^{1}H NMR (downfield shift of linker 4-CH_2 from δ 3.63 to 4.16). Next, diazotransfer under standard conditions[18] using 4-dodecylbenzenesulfonyl azide[19] afforded the corresponding α-diazo-β-ketoesters **7**. The IR spectra of **7** provided the characteristic absorption for the diazo group at 2140 cm^{-1}, and a shift to lower wavenumbers of the carbonyl absorptions was observed. NMR analysis revealed a further downshift of the signal for the linker 4-CH_2 group of about 0.1 ppm. Loading of microgels **7a** (R = Me, 1.03 mmol N_2 g^{-1}) and **7b** (R = Ph, 0.65 mmol N_2 g^{-1}) was determined using elemental analysis for nitrogen.

The N−H insertion reaction was carried out with five different benzamides **8** (R′ = H, 3-MeO, 4-F3C, 4-Br, 2-Me). Decomposition of α-diazo-β-ketoesters **7** by rhodium(II) acetate dimer (2 mol %) in the presence of 5 equiv of the respective benzamide **8** in toluene at 60 °C gave in all cases the desired α-(aminobenzoyl)-β-ketoesters **9** in very good yields (polymer recovery). All products showed the expected IR absorptions for the N−H stretch and three carbonyl bands for the ester, ketone, and amide groups, respectively. The characteristic IR absorption for the diazo functionality disappeared, indicating complete reaction of starting material. Furthermore, NMR analysis of the microgels confirmed the exclusive presence of the desired insertion products **9** (Figure 3). No NMR or IR evidence for cyclopropanation (a potential side reaction between the rhodium carbenoid intermediate and unreacted vinyl groups from the polymer) was observed. The study of these intermediates using standard NMR again validates the use of microgel supports in methodology development.

Scheme 2. Microgel-Supported Synthesis of Oxazoles[a]



[a] (a) R = Me: 3 equiv of diketene, cat. DMAP, CH_2Cl_2, −78 °C → rt 18 h; R = Ph, 2.5 equiv of benzoyl-Meldrums' acid adduct, THF, reflux 18 h. (b) 5 equiv of 4-dodecylbenzene-sulfonyl azide, 5.5 equiv of NEt_3, toluene, rt 48 h. (c) 5 equiv of benzamide **8**, 2 mol % $Rh_2(OAc)_4$, toluene, 60 °C 18 h. (d) 2 equiv of Ph_3PBr_2, 4 equiv of NEt_3, CH_2Cl_2, 0 °C 30 min, then rt 3 h; or 10 equiv of Burgess reagent, $Cl(CH_2)_2Cl$, 60 °C 18 h. (e) 2 equiv of $AlCl_3$, 8 equiv of Et_2NH, CH_2Cl_2, 0 °C → rt 18 h.

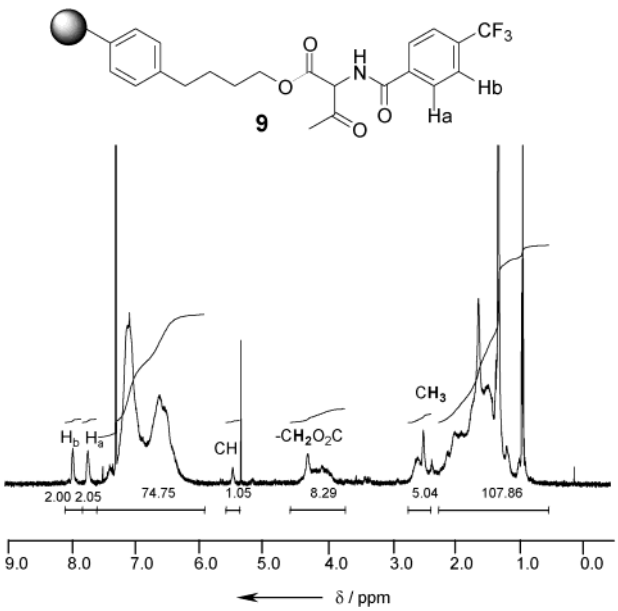


Figure 3. ^{1}H NMR (500 MHz) of microgel-bound α-acylamino-β-ketoester **9** (5 mg in $CDCl_3$).

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Table 5. *N,N*-Diethyl Oxazole-4-carboxamides 11 Released from Microgels Using Diethylamine/Aluminum Chloride

11	R	R′	purity[a] (%)	yield[b] (%)
a	Me	H	90	36
b	Me	3-MeO	90	26
c	Me	4-F_3C	69	23
d	Me	4-Br	88	19
d	Me	2-Me	87	20
f	Ph	H	80	29
g	Ph	3-MeO	96	31
h	Ph	4-F_3C	91	21
i	Ph	4-Br	93	27
k	Ph	2-Me	96	33

[a] Purity of crude product determined by RP-HPLC (254 nm). [b] After purification by preparative TLC.

Cyclodehydration of microgel-bound **9** to the corresponding oxazoles **10** was performed using a modified Wipf procedure.[20] However, in analogy to our solid-phase oxazole synthesis, slightly better yields and product purities were observed when recently introduced Burgess' reagent mediated cyclodehydration conditions were employed.[21] Finally, the oxazoles **10** were cleaved from the microgel as their corresponding amides **11** using an amidation/cleavage reaction with diethylamine, performed in the presence of aluminum chloride.[22] Upon completion, the reaction was quenched with in situ precipitation of the polymer by pouring the mixture into methanol. The methanol solution containing product was separated from the polymer by filtration, passed through a mixed bed ion-exchange resin, and concentrated to give essentially pure oxazoles **11** as estimated by HPLC (Table 5). The only trace impurity observed in these compounds was a low molecular weight fraction of the microgel matrix. Analytically pure samples of all oxazole-4-carboxamides **11** were obtained in good yield based upon OH loading of 4-hydroxybutyl microgel **5**, after preparative TLC (Table 5). It should be noted that both the purity of crude product and the yield of purified product are similar to those obtained when using insoluble resin beads[15] (16 examples, 22−53%).

Conclusion

In summary, we have investigated in a systematic fashion the effect of monomer concentration, solvent type, reaction time, cross-linker type, and concentrations used in the production of a new microgel that has promising utility for organic synthesis. We note that this is the first time that a multistep synthesis has been successfully performed using a microgel as a soluble polymeric support. The advantage of using these polymers over traditional linear polymers is that they form solutions that exhibit lower viscosity and enable facile reaction workup. In addition, the outcome of each individual reaction step can be easily monitored by simple proton NMR, an option not available when using insoluble polymers. Thus, microgels provide another valuable tool for the optimization of synthetic sequences on a polystyrene-based matrix and the preparation of small to medium sized compound collections by LPOS. The exploration of further microgel applications such as the introduction of other linker groups, the preparation of microgel-supported reagents and catalysts, and the construction of further compound collections will be reported in due course.

Experimental Section:

General procedures have been previously reported.[24] High performance liquid chromatography (HPLC) was performed using a Hitachi system: L-5000 LC controller, 655A variable wavelength UV monitor, 655A-12 liquid chromatograph, and D-2000 chromato-integrator. Conditions: Vydac 201SP column (5 μm RP C_{18}) 4.6 mm × 250 mm, acetonitrile + 0.1% TFA/water + 0.1% TFA isocratic 45:55 (for compounds **11a**−**e**) or 60:40 (for compounds **11f**−**k**), flow 1 mL min^{-1}, detection UV (λ = 254 nm), injection loop 2 μL.

For gel permeation chromatography (GPC) a Shimadzu system was used: SCL-10A system controller, SPD-10AV UV−vis detector, LC-8A pump, and CR-501 chromatopac integrator. Conditions: Waters Styragel HR4, HR3, HR2 column bank, 7.8 mm × 300 mm, mobile phase tetrahydrofuran, flow 1 mL min^{-1}, detection UV (λ = 254 nm), injection loop 20 μL. Polystyrene molecular weight standards (M_p = 1290, 629.5, 170.6, 66, 28.5, and 12.5 kD) were obtained from Polymer Laboratories Inc., Amherst, MA.

Light scattering experiments were performed on a Dawn EOS multiangle light scattering (MALS) detector (Wyatt Technology Corp., Santa Barbara, CA) operating in "micro batch" mode. A solution of the polymer sample in freshly distilled THF (ca. 1 mg mL^{-1}) was pumped through the detector cell using a 0.2 μm inline membrane filter and a syringe pump (flowrate 1 mL min^{-1}).

Preparation of 4-Hydroxybutyl Microgel 5. A solution of styrene **1** (7.79 mL, 68 mmol, 83 mol %), cross-linker **3** (1.18 g, 4 mmol, 5 mol %), and 4-(4′-hydroxybutyl)styrene **4** (1.76 g, 10 mmol, 12 mol %) in THF (225 mL) was purged for 15 min by a gentle stream of argon. Then 2,2′-azobisisobutyronirile (300 mg, 3 wt %) was added, and the reaction mixture was stirred for 96 h at 60 °C oil bath temperature under positive argon pressure (after 24 h a second portion of AIBN (300 mg) was added). After cooling to room temperature the reaction mixture was concentrated in vacuo to approximately 50 mL. The slightly viscous pale yellow residue was slowly added to cold vigorously stirred methanol (500 mL). The precipitaed polymer was filtered off and washed with cold methanol (50 mL), redissolved on CH_2CL_2 (50 mL) and precipitated from methanol a second time. Vacuum drying overnight at room temperature afforded microgel **5** as a colorless finely divided powder (4.16 g, 42% polymer recovery). IR: 3446 (OH), 3025, 2921, 2851, 1602, 1509, 1493, 1452, 1240, 1175, 1028, 829, 757, 697. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.55 (2H, ArC**H$_2$**), 3.63 (2H, C**H$_2$**OH), 4.03 (4H, C**H$_2$**OAr, cross-linker), 5.12 (d, 1H, =C**H**H, J = 11.4), 5.61 (d, 1H, =CH**H**, J = 17.3). Microstructure: 16 mol % 4′-hydroxybutyl-linker, 5 mol % cross-linker, 2 mol % pendant vinyl groups, 77 mol % styrene; loading 1.24 mmol g^{-1}). ^{13}C NMR (125 MHz, $CDCl_3$): δ 26.08* (C-2,3), 27.52° (C-2), 32.37° (C-3), 35.18° (C-1), 40.40 and 43.93 (br, backbone), 62.80° (C-4), 67.52* (C-1,4), 114.00 br, 125.64 br, 127.94 br, 145.31 br (° = cross-linker, * = 4′-hydroxybutyl-linker). GPC analysis: M_n = 10,500. MALS analysis: M_w = 23,370 ± 940.

Preparation of Microgel-Bound β-Ketoesters 6. (**6a**, R = Me) A solution of 4′-hydroxybutyl microgel **5** (1.0 g, ca. 1 mmol) and 4-(dimethylamino)-pyridine (6 mg, 50 μmol) in CH_2Cl_2 (20 mL) was cooled to −78 °C, and a solution of diketene

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(21) Wipf, P.; Miller, C. P. *J. Org. Chem.* **1993**, *58*, 3604.

(22) Brain, C. T.; Paul, J. M. *Synlett* **1999**, 1642. Burgess reagent [(methoxycarbonylsulfamoyl) triethylammoniumhydroxide inner salt) was purchased from Fluka. See also: Burgess, E. M.; Penton, H. R., Jr.; Taylor, E. A. *J. Org. Chem.* **1973**, *38*, 26.

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(24) Clapham, B.; Cho, C.-W.; Janda, K. D. *J. Org. Chem.* **2001**, *66*, 868.

(231 μL, 3 mmol) in CH_2Cl_2 (5 mL) was slowly added. After completion of the addition the reaction was warmed to room temperature overnight with stirring. The clear yellow solution was concentrated to 5 mL and added to cold, stirred methanol (200 mL). The precipitated polymer was filtered off, washed with cold methanol (2 × 10 mL), and vacuum-dried to afford a pale yellow fine powder (1.08 g, quant. polymer recovery). IR: 1740 (C═O, ester), 1710 (C═O, ketone). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.25 (3H, COC**H$_3$**), 2.56 (2H, C**H$_2$**Ar), 3.45 (2H, C**H$_2$**COCH$_3$), 4.04 (4H, C**H$_2$**OAr), 4.16 (2H, C**H$_2$**O$_2$C). (**6b**, R = Ph) A solution of 4′-hydroxybutyl microgel **5** (1.5 g, ca. 1.5 mmol) and 5-(hydroxy-phenylmethylene)-2,2-dimethyl-[1,3]-dioxane-4,6-dione (930 mg, 3.75 mmol) in THF (35 mL) was heated to reflux for 18 h. After cooling, the mixture was concentrated under reduced pressure to yield a yellow oil. The crude product was dissolved in chloroform (5 mL) and precipitated as above, affording a pale yellow powder (1.41 g, 85% polymer recovery). IR: 1737 (C═O, ester), 1687 (C═O, ketone). ^{1}H NMR (500 MHz, $CDCl_3$)**:** δ 2.48 (2H C**H$_2$**Ar), 3.98 (2H, C**H$_2$**-COPh), 4.03 (4H, C**H$_2$**OAr), 4.17 (2H, C**H$_2$**O$_2$C), 7.34 (2H, Ph**H**-3,5), 7.53 (1H, Ph**H**-4), 7.93 (2H, Ph**H**-2,6).

General Procedure for the Diazotransfer Reaction, Preparation of Microgel-Bound α-Diazo-*β*-ketoesters 6. A solution of a *β*-ketoester **6** (1 g, ca. 1 mmol), triethylamine (0.76 mL, 5.5 mmol), and 4-dodecylbenzenesulfonyl azide (1.68 mL, 5 mmol) in toluene (12 mL, 10 wt %) was protected from light and stirred for 48 h. The clear dark solution was concentrated to a volume of 5 mL and added to cold stirred methanol (100 mL). The precipitated polymer was filtered off, washed with cold methanol (2 × 5 mL), and dried by suction. The precipitation was repeated a second time in order to remove traces of unreacted sulfonyl azide. Drying under vacuum afforded the products as yellow powders.

7a (R = Me): 913 mg, 92%. IR: 2138 (C═N$_2$), 1718 (C═O, ester), 1658 (C═O, ketone). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.48 (3H, COC**H$_3$**); 2.56 (2H, C**H$_2$**Ar), 4.04 (4H, C**H$_2$**OAr), 4.25 (2H, C**H$_2$**O$_2$C). Elemental analysis: N, 2.88% (loading, 1.03 mmol g^{-1} C═N$_2$).

7b (R = Ph): 1.34 g, 96%. IR: 2140 (C═N$_2$), 1722 (C═O, ester), 1689 (C═O, ketone). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.48 (2H, C**H$_2$**Ar), 4.03 (4H, C**H$_2$**OAr), 4.19 (2H, C**H$_2$**O$_2$C), 7.34 (2H, Ph**H**-3,5), 7.52 (1H, Ph**H**-4), 7.62 (2H, Ph**H**-2,6). Elemental analysis: N, 1.82% (loading, 0.65 mmol g^{-1} C═N$_2$).

General Procedure for the Rhodium-Catalyzed Insertion Reaction. To a solution of α-diazo-*β*-ketoester **7** (150 mg, 0.15 mmol) in toluene (5 mL) was added benzamide **8** (0.75 mmol). The reaction vial was sealed with a rubber septum, purged with argon, and placed in a preheated oil bath (60 °C). Then, a 12 mM solution of rhodium(II) acetate dimer in toluene (0.25 mL, 3 μmol, 2 mol %) was injected in one portion to the vigorously stirred reaction mixture. After an induction period of a few minutes effervescence of nitrogen was observed. After 30 min no further nitrogen was liberated, and stirring was continued overnight. The mixture cooled to room temperature, and unreacted benzamide was filtered off. The filtrate was concentrated to a volume of ca. 1 mL and added to stirred cold methanol (25 mL). The precipitated polymer was filtered off, washed with cold methanol (2 × 5 mL), and dried by suction. Further drying in a high vacuum overnight at room temperature afforded the polymer bound α-(benzoylamino)-*β*-ketoesters **9** as finely divided tan powders (polymer recovery, 79−99%).

Selected Data for 9. 9c (R^1 = Me, R^2 = 4-F$_3$C): 155 mg, 97%. IR: 3419 (N−H), 1747 (C═O, ester), 1726 (C═O, ketone), 1672 (C═O, amide), 1324 (CF_3). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.43 (3H, COC**H$_3$**), 2.55 (2H, C**H$_2$**Ar), 4.02 (4H, C**H$_2$**OAr), 4.25 (2H, C**H$_2$**O$_2$C), 5.43 (1H, CH), 7.70 (2H, Ar**H**-2,6), 7.94 (2H, Ar**H**-3,5). **9h** (R^1 = Ph, R^2 = 4-F$_3$C): 132 mg, 83%. IR: 3402 (N−H), 1739 (C═O, ester), 1689 (C═O, ketone), 1677 (C═O, amide), 1324 (CF_3). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.40 (2H C**H$_2$**Ar), 3.99 (4H, C**H$_2$**OAr), 4.20 (2H, C**H$_2$**O$_2$C), 5.34 (1H, CH), 7.43 (3H, Ph**H**-2,4,6), 7.70 (2H, Ar**H**-2,6), 7.91 (2H, Ph**H**-3,5), 8.16 (2H, ArH-3,5).

General Procedure for the Preparation of Microgel-Bound Oxazoles 10 by Cyclyzation of α-(Benzoylamino)-*β*-ketoesters 9 with Dibromotriphenylphosphorane. To a solution of microgel **9** (105 mg, ca. 68 μmol) and triethylamine (38 μL, 0.27 mmol) in CH_2Cl_2 (3 mL) was added dibromotriphenylphosphorane (59 mg, 0.14 mmol) in one portion at 0 °C with stirring. The clear yellow solution was stirred for 3 h at room temperature under argon. Then, the reaction mixture was added to stirred cold methanol (30 mL), and the precipitated polymer was filtered off, washed with cold methanol (2 × 5 mL), and air-dried. High vacuum drying at room temperature for 5 h gave the polymer-bound oxazoles **10** as tan colored powders (polymer recovery, 78−95%).

Selected Data. 10f (R^1 = Ph, R^2 = H): 95 mg, 90%. IR: 1730(C═O, ester). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.50 (2H, C**H$_2$**Ar), 4.03 (very broad, 4H, C**H$_2$**OAr), 4.53 (2H, C**H$_2$**O$_2$C); 7.48 (6H, Ar**H**), 8.17 (2H, Ar**H**), 8.24 (2H, Ar**H**).

General Procedure for the Preparation of Microgel-Bound Oxazoles 10 by Cyclyzation of α-(Benzoylamino)-*β*-ketoesters 9 with Burgess Reagent. A solution of microgel **9** (150 mg, ca. 0.15 mmol) and Burgess reagent (174 mg, 0.75 mmol) in 1,2-dichloroethane (3 mL) was heated overnight at 70 °C (oil bath) in a sealed 10 mL reaction vial. After cooling to room temperature the clear brown colored solution was added to cold stirred methanol (25 mL). The precipitated polymer was filtered off, washed with cold methanol (2 × 5 mL), and dried under vacuum (rt, 6 h) to afford a beige colored powder (polymer recovery. 90% to quant.).

Selected Data. 10c (R^1 = Me,R^2 = 4-CF_3): 138 mg, 92%. IR: 1716(C═O, ester), 1321 (CF_3). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.55 (2H, C**H$_2$**Ar), 2.69 (3H, 5-C**H$_3$**), 4.03 (very broad, 4H, C**H$_2$**OAr), 4.38 (2H, C**H$_2$**O$_2$C), 7.70 (2H, Ar**H**-2,6), 8.18 (2H, Ar**H**-3,5).

General Procedure for Cleavage with Diethylamine/Aluminum Chloride. 5-Methyl-2-phenyloxazole-4-carboxylic acid diethylamide (11a). A 0.25 M $AlCl_3$/1 M Et_2NH stock solution was prepared by dropwise addition of freshly distilled diethylamine (1 mL, 10 mmol) to a stirred suspension of anhydrous aluminum chloride (333 mg, 2.5 mmol) in CH_2Cl_2 (9 mL) at 0 °C. After all aluminum chloride had dissolved, the solution was ready for use and stored under argon.

An aliquot of the above solution (0.92 mL, 2 equiv of $AlCl_3$, 8 equiv of Et_2NH) was added by syringe to a solution of polymer-bound oxazole (120 mg, 115 μmol, loading, 0.96 mmol g^{-1}) in CH_2Cl_2 (3 mL). After stirring at room temperature overnight the dark orange reaction mixture was added to vigorously stirred methanol (25 mL). Precipitated polymer and aluminum salts were removed by filtration, and the filtrate was concentrated to 5 mL, passed through a mixed bed ion-exchange resin, and evaporated to dryness to give the crude product. HPLC: t_R = 12.52 min (purity 90%). Purification by preparative TLC (ethyl acetate/hexanes 1:3) afforded **11a** as an off white crystalline solid (10.8 mg, 36%); TLC: R_f = 0.35); IR: 2968, 2931, 1626 (C═O amide-I), 1561, 1478, 1449, 1379, 1337, 1260, 1195, 1095, 1074, 863, 778, 710, 691; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (br t, J = 7.3 Hz, 3H), 1.32 (br t, J = 7.0 Hz, 3H), 2.63 (s, 3H), 3.52 (br q, J = 6.6 Hz, 2H), 3.77 (br q, J = 7.0 Hz, 2H), 7.43−7.48 (m, 3H), 7.99−8.02 (m, 2H). HRMS: calcd for $C_{15}H_{18}N_2O_2$ 259.1441, found 259.1448.

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Supporting Information Available: Procedures for the synthesis of monomer **4** and analytical data for compounds **11a**−**k**. This material is available free of charge via the Internet at http://pubs.acs.org. This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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