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RESEARCH ARTICLE

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Formamide based monomer for highly functionalized polymers

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Abstract

Multicomponent reactions (MCRs) are widely used in organic chemistry to simplify the synthesis of highly functionalized molecules in a single-pot reaction. However, their utility for polymer post-functionalization is severely limited due to the complexity of handling highly reactive and unpleasant isocyanide compounds. In this work, we present a stable methacrylate monomer 2-formamido ethyl methacrylate (FEMA) containing a benign formamide group that can be converted to isocyanide in situ and that can undergo MCRs in a one-pot protocol. Block and random copolymers of FEMA with methyl methacrylate were tested for efficiency in MCRs. As a function of composition and architecture, MCR conversions of >90% was achieved in the polymers. This benign bench stable monomer allows incorporation of complex functionality in a one-pot synthesis to the polymer sidechain using MCRs without direct handling of the isocyanide monomers and polymers.

KEYWORDS

multicomponent reactions, peptide conjugation, polymer post-functionalization

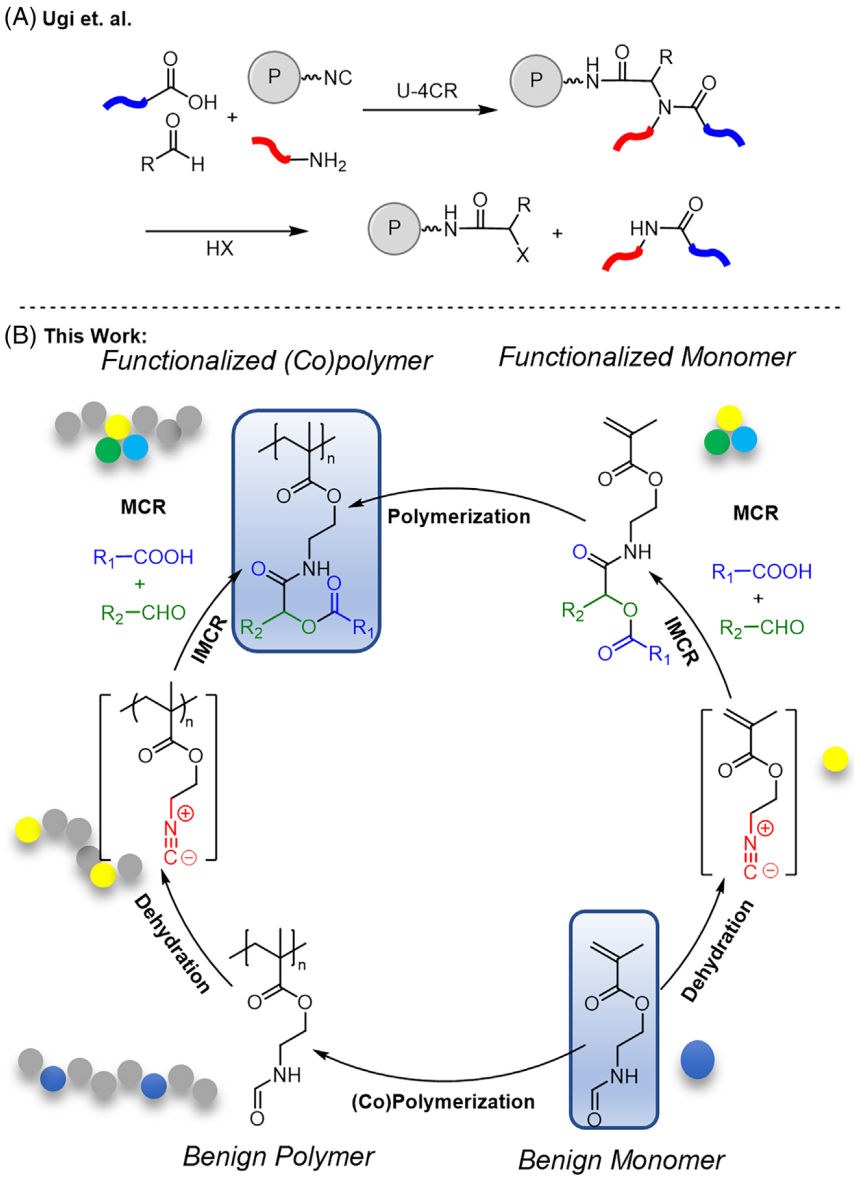
1 | INTRODUCTION

Recent developments in controlled polymerization methods have given unprecedented access to polymers with complex architectures such as bottle brushes, dendritic, stars, and blocks, with a wide range of rheological, electrical, mechanical and thermal properties.[1] Yet strategies for polymer post-functionalization to further fine tune their chemical and physical properties are still needed to address emerging complex problems in biology, energy, and materials science.[2,3] There are a large set of reactions that allow the post-functionalization of polymer sidechains. Some important examples include the use of click reactions like thiol-ene/thiol-yne reactions,[4] copper-catalyzed azide cycloaddition,[5] and Diels-Alder reactions.[6] Other reactive polymer platforms based on activated ester,[7] azlactone[8] and glycidyl[9] groups also allow facile functionalization with amine, thiol, and alcohol based nucleophiles. These methods have been the workhorse for polymer post-functionalization for many decades with applications ranging from biomedical to soft lithography.[10] Yet there are many highly reactive functional groups in organic chemistry with great potential for polymer functionalization that are largely unexplored. One of these functional groups is the isocyanide group.

Isocyanide group has a formally divalent nature and is susceptible to both nucleophilic and electrophilic reactions. It is mostly used in a family of well-known reactions in small molecule chemistry namely multicomponent reactions (MCRs).[11] MCRs incorporate multiple starting materials into a single product in a concerted manner, hence, significantly improving the atom economy of the transformation while greatly reducing the

required purification. The most commonly used family of MCRs relies on the isocyanide functionality, namely isocyanide based multicomponent reaction (IMCR).[12] They are also the first MCRs to find applications in polymer chemistry. In 2011, Meier et al.[13] first introduced IMCR in polymer functionalization as a way to synthesize structurally diverse monomers for acyclic diene metathesis polymerization, as well as polycondensation reactions based on IMCR. This method was applied for post-functionalization of polymers by directly using an isocyanide compound.[14] IMCR based polycondensation has also been explored by Rudick[15] and Li.[16] Similarly, post-functionalization of amine containing polymers with IMCR utilizing small molecule isocyanide has also been demonstrated by Tao.[17] However, IMCRs that utilize isocyanide-bearing polymers for post-functionalization remains a largely unexplored field due to the difficulty in introducing isocyanide groups onto polymers and their limited storage stability.[18]

To date, there are only sporadic reports on isocyanide-bearing polymers or monomers. The earliest report utilized the isocyanide group on insoluble polymer beads as a solid support for peptide synthesis.[19] Peptides were synthesized by coupling N-protected and C-protected peptides on the insoluble substrate using Ugi 4-compomponent (U-4CR) reaction and released from the surface by hydrolysis (Scheme 1A). However, lack of further exploration of the reactivity of isocyanide polymers was largely attributed to the unpleasant and reactive/volatile nature of isocyanide group. Its reactivity towards free radicals[20] and carbanions[21] also make most common polymerization techniques inapplicable on isocyanide bearing monomers. Recent report on polymeric Tosmic reagent[22] utilized ring opening metathesis



SCHEME 1 Polymer-based multicomponent reactions: (A) previous report[19] on use of an isocyanide containing polymer for MCR, and (B) this work on a benign formamide based methacrylate monomer for in situ generation of isocyanide for MCR

polymerization technique to overcome this issue. However, the inherent dependency of the metathesis-based polymerization protocol on a specific family of monomers and expensive noble metal catalysts makes it less broadly applicable. Therefore, an isocyanide monomer that can be incorporated into traditional olefin-based polymerization techniques without directly handling the isocyanide is highly desirable.

To overcome this issue, we turned to the immediate precursor of isocyanide. There are many precursors for the synthesis of isocyanides such as cyanides, dichlorocarbene, and isocyanates,[23] but most of them suffer from limited efficiency of conversion to isocyanides and harsh transformation conditions. The formamide precursor[24] stands out as it affords complete conversion to isocyanide under mild reaction conditions. Our goal in this study was to develop a formamide monomer that is compatible with conventional polymerization methods and can be widely applied for MCRs in both monomeric and polymeric forms. In this work, we first introduce a new methacrylate-based formamide monomer which serves as a precursor for in situ generation of isocyanide for the one-pot IMCR (Scheme 1B). The in situ generated isocyanide is bound to the non-volatile polymer backbone, making this chemistry practical. We demonstrate two different approaches (a) IMCR on the formamide monomer followed by its polymerization, and (b) IMCR based post-functionalization of the formamide bearing polymer. We further demonstrate that copolymerization of this formamide monomer with other comonomers gives soluble polymers for efficient IMCR reactions and characterize the physical properties of the polymers. Finally, we demonstrated the potential application of this system in peptide conjugated polymer synthesis via IMCR.

2 | RESULTS AND DISCUSSION

2.1 | Monomer synthesis, functionalization, and polymerization

We designed and synthesized a new methacrylate monomer (2-formamido ethyl methacrylate, FEMA) following a modified two-step process (Figure 1A) reported for acrylates by Ugi et al.[25] The monomer structure was confirmed by ^{1}H and ^{13}C NMR and electrospray ionization mass spectroscopy (ESI MS) (Figure 1B, experimental section). Following the successful synthesis and purification of this monomer, we first studied the feasibility of the one-pot IMCR on the monomer. We chose Passerini 3-component reaction (P-3CR) with acetic acid and isobutyl aldehyde as the model reactants. After testing

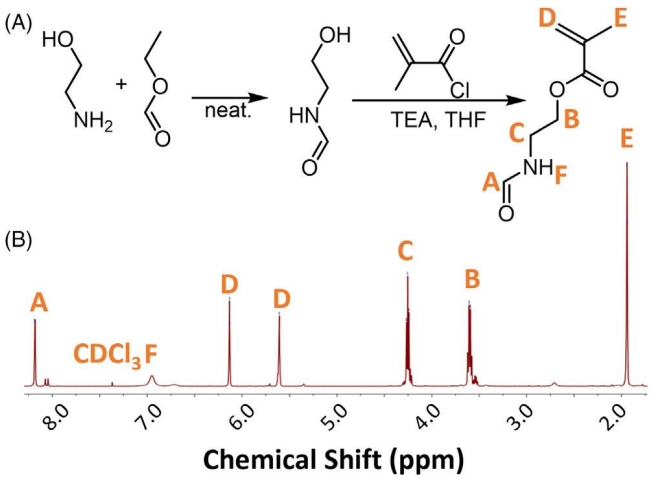


FIGURE 1 Synthesis and characterization of FEMA monomer (A) synthetic scheme for the FEMA monomer and (B) ^{1}H NMR taken in $CDCl_3$

different solvents and reaction temperatures, we found that increasing the temperature from room temperature to 40°C improved the yield from 45% to 86% (Table S1) in dichloromethane (DCM) solvent. To test the polymerizability of the functionalized monomer, reversible addition−fragmentation chain-transfer polymerization (RAFT) was employed (Figure 2A). Gel permeation chromatography (GPC) showed a unimodal trace (M_n = 4898 g/mol, $Đ$ = 1.30). Because of the low molecular weight of this polymer, the chain-end groups were visible

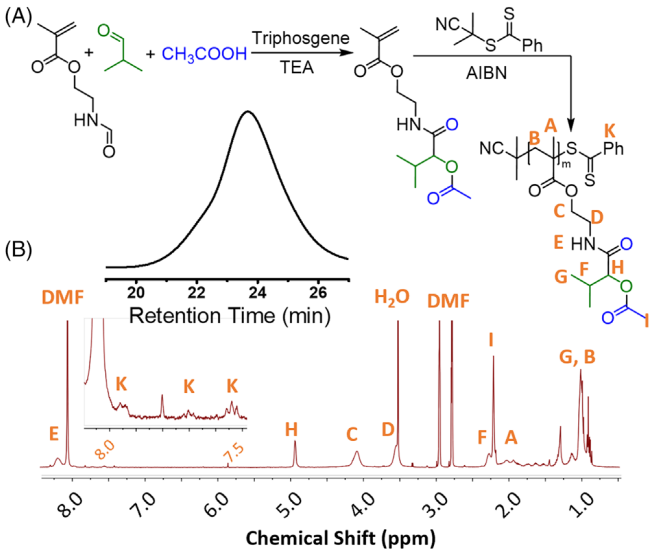


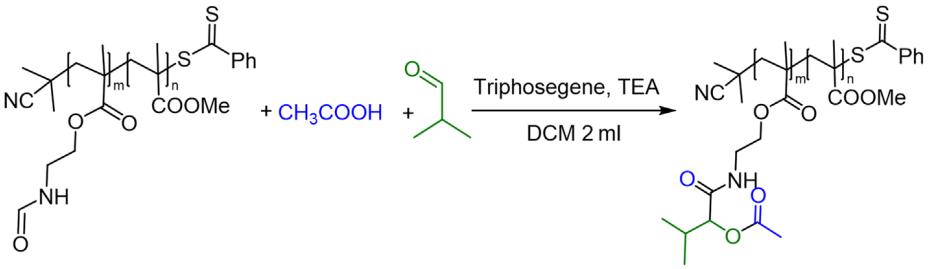
FIGURE 2 (A) Synthetic scheme for P-3CR of FEMA monomer and controlled polymerization to achieve functionalized polymer. (B) ^{1}H NMR and GPC (inset) of the functionalized polymer. Note that peak D overlaps with water peak associated with the NMR solvent. Magnified region shows phenyl end group. ^{1}H NMR taken in DMF-d[7]

in the ^{1}H NMR (Figure 2B). The degree of polymerization measured by the end-group analysis of 25 was significantly higher than the GPC value of 15. The resulting monomer conversion was 67%. Lower yield and molecular weight are expected for such bulky monomers.[26]

2.2 | Polymerization of FEMA monomer and post-functionalization

The efficient P-3CR on the monomer confirmed that the formamide bearing monomer indeed can be used as a benign precursor to isocyanide. To broaden the scope of this monomer it is important to demonstrate IMCR not just on the monomer but also via post-functionalization reaction on the formamide polymer. The polymerization of the FEMA monomer was conducted by RAFT. However, the resulting homopolymer PFEMA had large dispersity due to its poor solubility in most organic solvents (Figure S1). To improve the solubility of the polymer, a comonomer methyl methacrylate (MMA) was incorporated into the polymer in both block copolymer (BCP) architecture and random copolymer (RCP) architecture with varying FEMA: MMA molar ratio (Table S2, Figure S2–S7). All polymerizations were conducted with M: CTA: AIBN ratio of 100:1:1. The copolymers indeed exhibited improved solubility, forming translucent colloidal to clear solution based on the specific composition in DCM (Table 1 entry 6-11). The solubility of the copolymer was further improved by the addition of methanol to DCM. This is reasonable as formamide group is known to form H-bonding, which can hamper the dissolution of the polymer.[27]

With soluble copolymers on hand, the P-3CR on the formamide side group in the copolymers was explored (Scheme 2). Different reaction conditions (Table 1 entry 1–6) were tested with an RCP with FEMA: MMA = 1:0.9 (RCP 1:0.9) to optimize the reaction. By applying the optimized protocol from monomer P-3CR discussed above, 42% conversion was achieved (entry 1). To improve the efficiency of the reaction in the copolymers, we systematically increased the amount of dehydrating agent triphosgene, base, acetic acid, and isobutyl



SCHEME 2 Post-functionalization of P-3CR on RCPs or BCPs

TABLE 1 P-3CR on the RCPs and BCPs

Entry	Copolymer[a]	Molar ratio (*x*:*y*:*z*)[b]	Temperature	Solubility[c]	Conversion[a]
1	RCP 1:0.9	1.3:0.4:2.4	45°C	+	42%
2	RCP 1:0.9	2.6:0.8:4.8	45°C	+	34%
3	RCP 1:0.9	2.6:0.8:4.8	r. t.	+	N.R.
4	RCP 1:0.9	1.3:0.4:2.4[d]	45°C	+	62%
5	RCP 1:0.9	1.3:0.8:4.8[d]	45°C	+	41%
6	RCP 1:0.9	2.6:0.4:2.4[e]	45°C	+	68%
7	BCP 1:1.3	1.3:0.4:2.4[e]	45°C	+	90%
8	BCP 1:4.4	1.3:0.4:2.4[e]	45°C	+	83%
9	BCP 1:18	1.3:0.4:2.4[e]	45°C	+	67%
10	RCP 1:2.5	1.3:0.4:2.4[e]	45°C	++	78%
11	RCP 1:6.0	1.3:0.4:2.4[e]	45°C	++	92%

Abbreviations: BCP, block copolymer; RCP, random copolymer.

[a]Determined by ^{1}H NMR.

[b]Equivalents of acetic acid and isobutyl aldehyde are represented by *x*, triphosgene and triethylamine are represented by *y* and *z*, respectively. 0.2 mmol copolymer was used for the functionalization.

[c]+, translucent colloid formed; ++, clear solution formed.

[d]Triphosgene solution was added in two equal batches.

[e]Reaction continued for 72 h.

aldehyde (entry 2). Unfortunately, a significant decrease in conversion, due to partial decomposition of the polymer sidechains was observed as the intensity of the peaks at 4.06 and 3.55 ppm from the two side-chain methylene bridge protons decreased. This indicates potential hydrolysis of the ester bond due to phosgenation side reactions such as anhydride and acyl chloride formation.[28] Attempts to reduce the reaction temperature to minimize side reactions (entry 3) gave no reaction at all. Since phosgene is acting as the active dehydration agent in the reaction, we reasoned that by controlling the rate of phosgene generation, the conversion can be improved, and side reactions can be reduced. Hence, we devised a process where the triphosgene was added in 2 batches in 15-min intervals to maximize the dehydration efficiency (entry 4), which resulted in vastly improved conversion from 42% to 62%. Further increase in the amount of triphosgene gave diminished yield (entry 5). Further increased equivalence of acetic acid and isobutyl aldehyde reactants, as well as increasing the reaction time from 24 to 72 h led to modest increase in conversion to 68% (entry 6). Direct comparison of the ^{1}H NMR peak assignments of this polymer with that obtained from the polymerization of P-3CR functionalized FEMA monomer (Figure S8) shows good agreement.

The BCPs and RCPs with a range of MMA compositions were studied for their reactivity in the P-3CR (entry 6–11). Overall, we observed that increase in MMA content resulted in increased polymer solubility in DCM and hence increased conversion. This led us to conclude that the major limiting factors for efficient IMCR are the solubility of polymer and the rate of generation of phosgene. With the optimized conditions, for both RCPs and BCPs >90% conversion was achieved (Table 1). GPC traces with lower retention times were observed after the P-3CR for entries 6–11, confirming molecular weight increase due to functionalization while maintaining the dispersity of the parent copolymers (Table S2, Figure S2-S7). We also noticed that entries 7–8 show a high molecular weight shoulder in the GPC (Figure S2-S3). We suspected that this is due to hydrogen-bonding induced aggregation of the block copolymers. In fact, dynamic light scattering (DLS) (Figure S9) shows the presence of a large aggregate (620.2 nm) peak in addition to small peak at 11.6 nm. Typically, amide-based block copolymers have been observed to self-assemble into micelle in appropriate solvent, resulting in a shoulder in the GPC.[29] We believe we are observing similar behavior in our BCPs.

In the experiments with incomplete conversion, typically two small peaks around 3.9 and 4.3 ppm corresponding to unreacted isocyanide groups were observed. To monitor the generation and conversion of isocyanide group, we conducted extensive studies on the RCP 1:1.25 with higher MMA content. Three parallel reactions that were terminated at different stages, namely after the dehydration stage, 1 day after P-3CR (partial conversion) and 3 days of P-3CR (complete conversion), were set up and the products were analyzed by ^{1}H NMR and FT-IR (Figure 3). The FT-IR taken after dehydration step and 1-day reaction, had a distinct peak at 2156 cm^{-1} from the stretching of isocyanide group. By comparing the FT-IR and ^{1}H NMR of polymer before P-3CR and after P-3CR with partial (1 day) and complete (3 days) reaction, the intensity of the isocyanide peak can be qualitatively matched to the conversion. In the NMR spectra, the proton attached to the N (proton C from amide/aldehyde) was completely removed after dehydration. However, after the P-3CR reaction, not only a broad peak

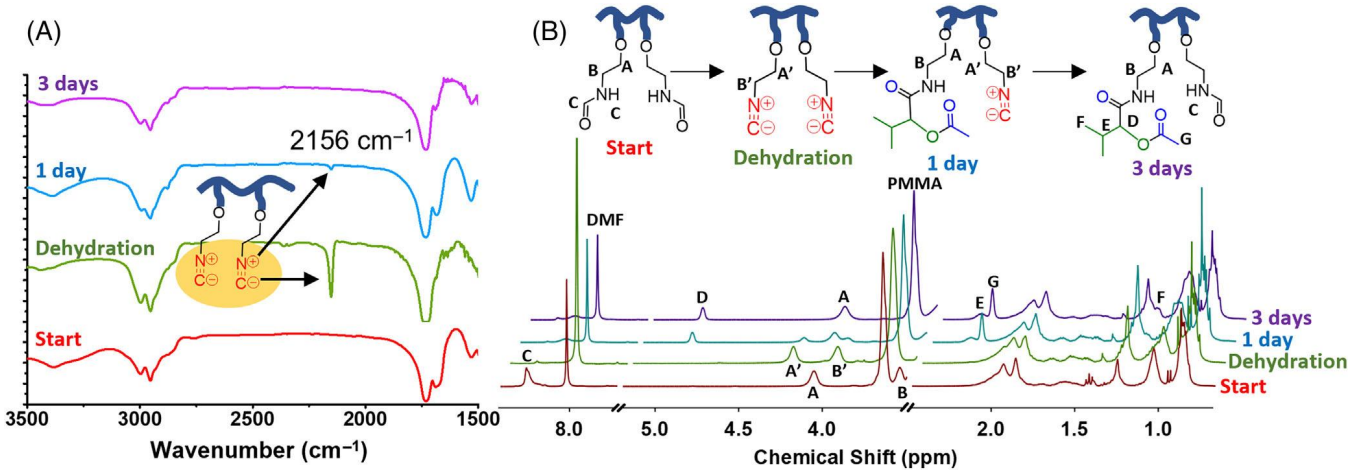


FIGURE 3 Characterization of the in situ generation and consumption of isocyanide group: (A) IR spectrum of polymer at different stages of the P-3CR, to track the isocyanide stretching. (B) ^{1}H NMR at different stages of polymer one-pot P-3CR. Corresponding polymer structures are shown above the NMR spectrums with peak assignments. ^{1}H NMR taken in DMF-d_7

corresponding to amide proton at 8.16 ppm appeared in the product, but also a smaller but sharp aldehyde peak at 8.27 ppm from the reformed formamide group was observed (Figure S10). These results confirm that the isocyanide is quantitatively generated in situ and acts as an intermediate for the P-3CR reaction and that isocyanide groups are consumed completely after 3 days by either the P-3CR reaction or hydrolysis reaction that regenerates the formamide group.

Thermogravimetric analysis (TGA) analysis of the new polymers namely, PFEMA homopolymer, block copolymer (BCP 1:1.3) and its post-functionalized product, was conducted to characterize their stability. TGA traces (Figure 4) showed a two-step decomposition of PFEMA polymer starting at 140°C. The weight loss in the first stage was 48.7% corresponds to the loss of the ethylene formamide sidechain (—CH_2CH_2NHCHO). Hence, the sidechains are significantly less stable than the polymethacrylate backbone. This observation is consistent with previous reports on the thermal degradation of nitrogen-containing polymers, where side chains are decomposed into volatile small molecules.[30] For the BCP, the first stage weight loss was 31.4%, which corresponds to the sum of the ethylene formamide side chain of PFEMA and the methyl side chain from PMMA block. Hence, the introduction of PFEMA block facilitates the decomposition of PMMA side chains. The lowering of the PMMA decomposition temperature in the BCP is reminiscent of the effect of photoinitiators on the PMMA decomposition.[31] For the P-3CR product, significantly larger percentage weight loss observed in the first step is consistent with the bulkier side chain from post-functionalization. For both the BCP and its functionalized product, the onset temperature for decomposition increased by ~19°C compared to PFEMA homopolymer. Since this increase is the same for copolymers both before and after the P-3CR, we believe this effect comes from the incorporation of PMMA block. Differential calorimetric scanning (DSC) analysis (Figure 4B) gave the glass transition temperature (T_g) for PFEMA homopolymer to be 71.5°C with a M_n of 42, 714 g/mol and $Đ \sim 3.06$. A similar transition at 77.1°C was also observed for the BCPs. The T_g for the PMMA block is perceptible at ~110°C though not as distinct as the PFEMA block. For the functionalized BCP sample, a much higher T_g of 84.8°C was observed due to the bulky side chains. The functionalized polymer also shows an endothermic peak at 120.4°C, which was observed in all subsequent heating cycles. Currently the origin of this peak is unclear.

2.3 | Peptide conjugated monomer by Ugi reaction

We illustrate the utility of the FEMA monomer, by exploring the synthesis of a peptide-containing monomer by Ugi 4-component reaction (U-4CR). Peptide functionalized polymers have great potential in the field of biomedicine including bio surfaces, drug delivery, and therapeutics.[32] Peptides conjugated polymers are typically synthesized by grafting to, grafting through or grafting from approaches.[33] Most of these protocols append the peptide end-on to the side chain. However, by utilizing the isocyanide group, U-4CR reaction allows the conjugation of two different peptides or amino acids to a single junction point to create a longer peptide or lead to lateral attachment of peptides to the polymerizable unit. To illustrate this concept, we synthesized a glycine-phenylalanine (GF) dipeptide functionalized monomer

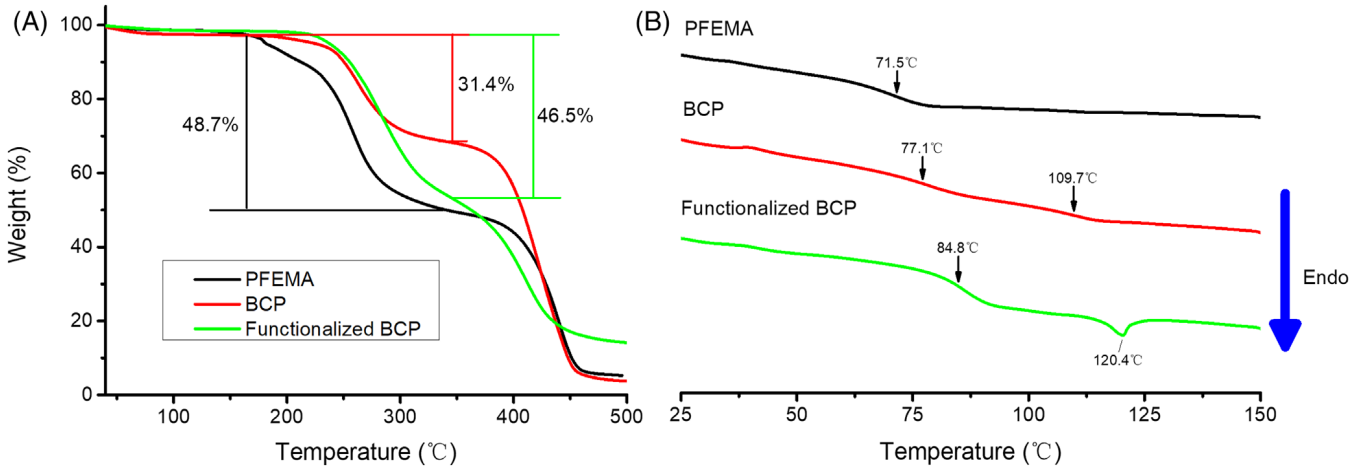


FIGURE 4 (A) TGA traces and (B) DSC curves (second heating cycle) for PFEMA, BCP 1:1 and functionalized BCP. Glass transition's midpoint temperature is marked out

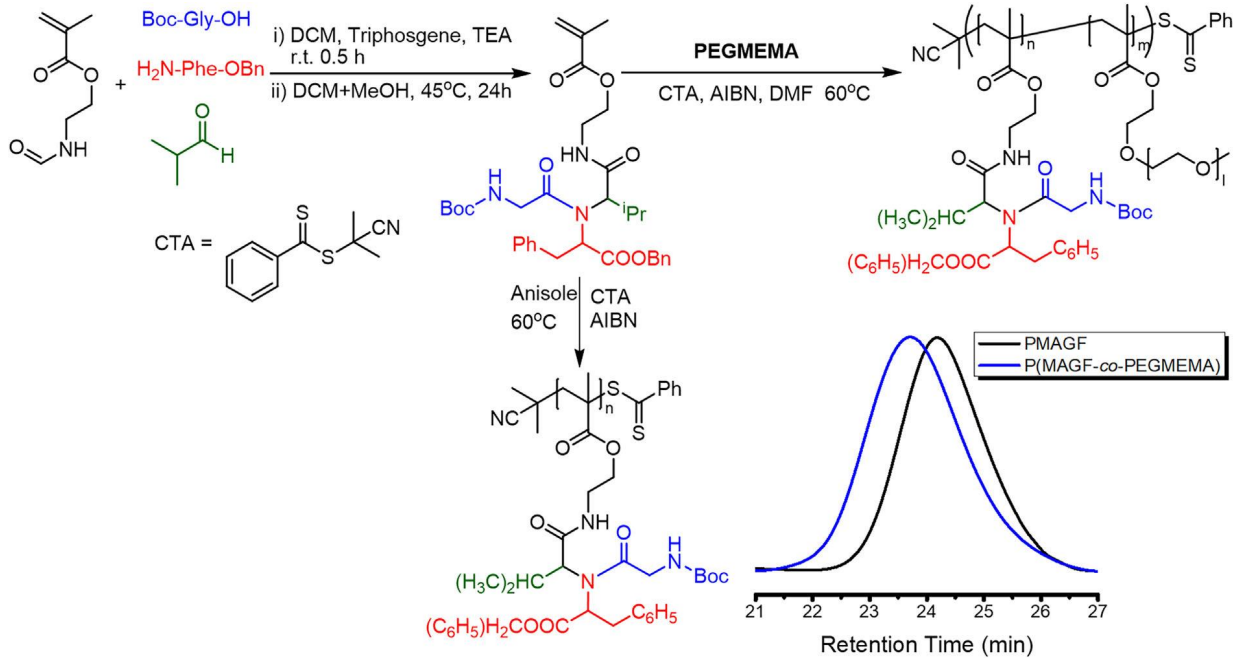


FIGURE 5 Synthesis scheme for the MAGF monomer and homopolymerization and (co)polymerization with PEGMEMA. Inset shows the GPC traces of the homopolymer of MAGF and its random copolymer with PEGMEMA

from FEMA by U-4CR (Figure 5) that we will refer to as MAGF (Methacrylate-GF) from now on. The FEMA monomer was reacted with N-(tert-butoxycarbonyl) glycine, isobutyl aldehyde and L-phenylalanine benzyl ester to synthesize the MAGF monomer. The structure of the monomer was confirmed by ^{1}H and ^{13}C NMR, COSY, HSQC as well as ESI MS (Figure S11–S12, experimental section).

MAGF monomer was homopolymerized successfully by RAFT (Figure 5and Figure S13), resulting in a polymer with narrow dispersity (Mn = 3742 g/mol, Đ = 1.15). Conventional free radical polymerization gave polymer with large molecular weight (M_n = 20, 643 g/mol) and very broad distribution ($Đ$ = 6.42) (Figure S14). MAGF was evaluated for its ability to copolymerize with typical monomers such as poly(ethylene glycol) methyl ether methacrylate (PEGMEMA) that are used for fabrication of cytophobic surfaces.[34] Specifically, we synthesized a RCP of MAGF and PEGMEMA (Figure 5). The copolymerization proceeded successfully resulting in low dispersity and low molecular weight polymer (M_n = 4505 g/mol, $Đ$ = 1.20). ^{1}H NMR characterization shows an incorporation ratio of MAGF:PEGMEMA of 1:5.7 (Figure 5and Figure S13). Identical U-4CR reaction conducted on RCP 1:2.5 resulted in the expected structure with a functionalization efficiency of 76% calculated from ^{1}H NMR, and a GPC measured M_n of 12,789 g/mol, $Đ$ of 1.12 (Figure S15). This demonstration of appending two amino acids to the single junction point on FEMA via U-4CR to create a dipeptide laterally conjugated to a monomer can potentially be extended to larger peptides to create biosurfaces. Given the hydrophilic nature of the formamide side groups in FEMA, facile copolymerization of FEMA to provide such reactive sites to copolymers is very useful.

3 | CONCLUSIONS

In conclusion, we have demonstrated the proof of concept for a new family of formamide bearing vinyl monomers that can serve as benign precursors for in situ generation of isocyanides and its subsequent reactivity in MCR reactions. Specifically, we have synthesized a methacrylate based formamide monomer, demonstrated its homo, random-, and block-copolymerization, and conversion to functional side groups via P-3CR and U-4CR in the monomer and polymeric forms. The ability to conduct IMCR on the formamide polymers with different types of reactions demonstrates the versatility of this monomer. The benign "bench stable" precursor monomer bearing a formamide group expands the isocyanide based reactive chemistry to impart multifunctionality to polymers without directly handling highly reactive monomers. This system brings IMCR into polymer side-chain chemistry for conventional vinyl-based polymerization and allows the facile construction of complex and diverse side-chain functionalities. This monomer can

potentially serve as a template to introduce a myriad of new chemistries and other potential methodology based on multi-substituted sidechains to polymer chemistry, which are relevant to pharmaceutical, battery research, biomaterials, and for commodity applications.

4 | EXPERIMENTAL SECTION/METHODS

General Method: All chemicals used in this work were purchased from Sigma-Aldrich. MMA was distilled with CaH_2 prior to use. Other chemicals were used as received.

The GPC was performed on a Waters GPC set up using N, N-dimethylformamide (DMF) with 0.05 mol/L LiBr additive as mobile phase. The system was running at a flow rate of 1.0 ml/min and column temperature was 80°C. Sample was dissolved in solution described above and filtered with 0.2 μm syringe filter (13 mm PTFE filter, GE Healthcare). GPC system was calibrated with PSt standard.

Nuclear magnetic resonance (NMR) spectra were taken on Bruker Avance-400,400 MHz spectrometer.

DLS spectra were taken on Brookhaven Lab Zetasizer Nano spectrometer.

Transmission Fourier-transform infrared spectroscopy (FT-IR) was measured on a Nicolet Magna 860 FT-IR system using potassium bromide (KBr) palette method. Spectral pure KBr was purchased from Sigma-Aldrich.

ESI MS was done on a Thermo Q Exactive Plus spectrometer. Ten mmol/L NH_4OAc/Acetonitrile was used as solvent.

Synthesis of 2-Formamido Ethyl Methacrylate (FEMA): 2-formamido ethyl methacrylate was synthesized following a modified two-step procedure from Ugi's work.[22]

First, 40 mmol of ethyl formate (2.9632 g, 3.25 ml) was added to a round bottom flask fitted with a water-cooled condenser. Then, 30 mmol of ethanolamine (1.8324 g, 1.81 ml) was slowly added to the reaction over 10 min. After addition, the reaction was allowed to reflux at 80°C for 24 h. The resulting mixture was rotavaped to remove unreacted substrate and distilled under reduced pressure. Then the crude product achieved was passed through a column of basic alumina with DCM: MeOH = 9:1 as eluent. Crude 2-formamido ethanol as a viscous light-yellow liquid with a quantitative yield (2.6725 g, quantitative) was obtained and used as was.

Then 30 mmol of 2-formamido ethanol (2.673 g), 33 mmol of triethylamine (3.34 g, 4.60 ml) and 15 ml of DCM was added into a round bottom flask fitted with condenser. The flask was cooled to 0°C in ice bath. Then 31.5 mmol of methacryloyl chloride (3.29 g, 3.08 ml) was dissolved in 4 ml of DCM. The solution was slowly added to the reaction mixture in 45 min under constant cooling and vigorous stirring. After addition was completed, the system was allowed to reflux at 70°C overnight. Then the TEA hydrochloric salt precipitate was filtered off with ethyl acetate as solvent. The solution was subjected to rotavap to remove all solvents. Resulting mixture was distilled with picric acid as inhibitor under reduced pressure. The crude product from the distillation was further purified with columns on silica gel with DCM: TEA = 100:3 mixture as eluent until product was pure. 2-formamido ethyl methacrylate was obtained as yellow liquid with a yield of 46%. ^{1}H NMR(400 MHz, $CDCl_3$, δ): 8.19(s, 1H, —CHO), 6.50 (br s, 1H, NH), 6.12(s, 1H, CH_2), 5.60(t, 1H, CH_2), 4.25 (t, 2H, CH_2), 3.61(dt, 2H, CH_2), 1.93(s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 167.40(C═O), 161.52(CHO), 135.84 ($C(CH_3)$═C), 126.25(CH_2═), 63.17(CH_2), 37.32(CH_2), 18.26 (CH_3). HRMS (ESI) *m/z*: $[M + Na]^+$ calc. = 180.0631, measured = 180.0632.

Synthesis of 2-(2-Acetoxy-3-Methylbutanamido)Ethyl Methacrylate: 0.2 mmol of 2-formamido ethyl methacrylate (31.4 mg), 0.48 mmol of triethylamine (48.6 mg, 67.5 μl) and 1 ml DCM were added into an Ar-charged Schlenk flask. The mixture was allowed to stir at room temperature for 10 min. 0.08 mmol of triphosgene (23.74 mg) in 1 ml of DCM solution was add to the reaction mixture dropwise, then the mixture was allowed to react for 30 min. After dehydration was completed, 0.26 mmol of acetic acid (15.6 mg, 15.0 μl) and isobutyl aldehyde (18.8 mg, 23.4 μl) were added to the mixture, The reactioin was carried out at refluxing temperature for 24 h. The crude product was purified on silica gel column with DCM: MeOH = 20:1 eluent. After purification, P-3CR monomer product 2-(2-acetoxy-3-methylbutanamido)ethyl methacrylate was obtained as yellow solid with a yield of 86%. ^{1}H NMR(400 MHz, $CDCl_3$, δ): 6.43 (s, 1H, NH), 6.12 (p, J = 1.0 Hz, 1H, CH_2), 5.61 (p, J = 1.6 Hz, 1H, CH_2), 5.07 (d, J = 4.3 Hz, 1H, CH), 4.39–4.20 (m, 2H, CH_2), 3.59 (qd, J = 5.5, 5.0, 0.9 Hz, 2H, CH_2), 2.29 (pd, J = 6.9, 4.3 Hz, 1H, C**H**$(CH_3)_2$), 2.18 (s, 3H, CH_3), 1.95 (t, J = 1.1, 3H, CH_3), 0.94 (dd, J = 8.8, 6.9 Hz, 6H, CH(C**H**$_3)_2$). ^{13}C NMR (101 MHz, $CDCl_3$, δ) 169.79, 169.59, 167.69, 135.84, 126.29, 77.94, 63.04, 38.92, 30.48, 20.80, 18.68, 18.26, 16.83. HRMS (ESI) *m/z*: $[M + H]^+$ calc. = 272.1492, measured = 272.1491.

Polymerization of 2-(2-Acetoxy-3-Methylbutanamido) Ethyl Methacrylate: 1 mmol of 2-(2-acetoxy-3-methylbutanamido) ethyl methacrylate (271.3 mg), 0.01 mmol of chain transfer agent 2-cyano-2-propyl benzodithioate (2.3 mg) and 0.02 mmol of azobisisobutylnitrile (1.7 mg) and 1 ml N, N-dimethylformamide were added to an Ar-charged Schlenk flask. The mixture was purged with Ar for 30 min. Three more frozen-thaw cycles were

carried out, then the reaction was heated up to 60°C under stirring for 18 h. Resultant polymer was precipitated in hexane for 5 times. The resulting polymer was 0.1777 g (67% yield).

Polymerization of FEMA: *Homopolymerization*: 5 mmol of 2-formaimdo ethyl methacrylate (785.4 mg), 0.05 mmol of chain transfer agent 2-cyano-2-propyl benzodithioate (11.1 mg), 0.025 mmol of azobisisobutylnitrile (4.1 mg) and 5 ml N, N-dimethylformamide were added to an Ar-charged Schlenk flask. The mixture was purged with Ar for 30 min. After that, three more frozen-thaw cycles were done, then the reaction was heated up to 70°C under stirring for 18 h. Resultant polymer was filtrated from the solution and the supernatant was added to 50 ml of hexane for precipitation. After that, all solid material collected was washed with hexane, toluene and methanol until product was pure. 0.7782 g (99% yield) of product was obtained. NMR and GPC see Figure S1.

Block Copolymerization: 3 mmol of MMA (300.4 mg, 319.5 μl), 0.06 mmol of chain transfer agent 2-cyano-2-propyl benzodithioate (13.3 mg), 0.03 mmol of azobisisobutylnitrile (5.0 mg) and 5 ml N, N-dimethylformamide were added to an Ar-charged Schlenk flask. The mixture was purged with Ar for 30 min. After that, three frozen-thaw cycles were done, then the reaction was heated up to 60°C under stirring for 18 h. The reaction mixture was dried under air to remove DMF and redissolved in 5 ml of DCM and one drop of methanol. The solution was reprecipitated in hexane for 5 times. Then the precipitate was collected in a vial and dried under vacuum.

The resulting polymer was then added to an Ar-charged Schlenk flask with 3 mmol of 2-formaimdo ethyl methacrylate (471.2 mg), 0.03 mmol of azobisisobutylnitrile (5.0 mg) and 5 ml N, N-dimethylformamide. The reaction mixture was again purged with Ar for 30 min prior to three frozen-thaw cycles. Then the reaction was heated up to 60°C under stirring for 18 h. Then 10 mg AIBN and 0.1 ml tributyltin hydride were added and reaction was allowed to proceed for 18 h more to remove the benzodithioate chain end. The reaction mixture was dried under air to remove DMF and redissolved in 5 ml of DCM and one drop of methanol. The solution was reprecipitated in hexane for 5 times. Then the precipitate was collected in a vial and dried under vacuum. The resulting polymer was white brittle solid. The weight was 0.6395 g, yield was 83%. The incorporation ratio was FEMA: MMA = 1:1.3 Other composition can be achieved by varying the ratio of two monomers while keep the total amount of monomers to 6 mmol.

Random Copolymerization: 3 mmol of 2-formaimdo ethyl methacrylate (471.2 mg), 3 mmol of MMA (300.4 mg, 319.5 μl), 0.06 mmol of chain transfer agent 2-cyano-2-propyl benzodithioate (13.3 mg), 0.06 mmol of azobisisobutylnitrile (5.0 mg) and 5 ml N, N-dimethylformamide were added to an Ar-charged Schlenk flask. The mixture was purged with Ar for 30 min. After that, three frozen-thaw cycles were done, then the reaction was heated up to 60°C under stirring for 18 h. Resultant polymer was precipitated in 50 ml hexane. The precipitate was then dissolved in 5 ml of DCM and one drop of methanol and reprecipitated in hexane for 5 times. Then the precipitate was collected in a vial and dried in vacuum. Then the product, 5 ml of N, N-dimethylformamide, 10 mg AIBN and 0.1 ml tributyltin hydride were added to an Ar-charged flask and heated to 60°C under stirring and reaction was allowed to proceed for 18 h more to remove the benzodithioate chain end. The reaction mixture was dried under air to remove DMF and redissolved in 5 ml of DCM and one drop of methanol. The solution is reprecipitated in hexane for 5 times. Then the precipitate was collected in a vial and dried under vacuum. The resulting polymer was white brittle solid. The weight was 0.6521 g, yield was 85%. The incorporation ratio was FEMA: MMA = 1:0.9. Other composition can be achieved by varying the ratio of two monomers while keep the total amount of monomers to 6 mmol.

Post-Functionalization of FEMA Copolymers: Polymer with an 0.2 mmol of FEMA repeating unit (98.9 mg for RCP 1:0.9), 0.48 mmol of triethylamine (48.57 mg, 67.46 μl) and 1 ml of anhydrous DCM were added to an Ar-charged Schlenk flask and stirred at room temperature for 10 min. Additional 5 min of sonication was done for less soluble polymers. Then 0.04 mmol of triphosgene (24.3 mg) was dissolved in 0.5 ml of DCM and added to the reaction dropwise under constant stirring. After 15 min of reaction, another 0.04 mmol of triphosgene in 0.5 ml DCM was added to the reaction and the reaction was allowed to stir under room temperature for another 15 min. After dehydration was completed, 0.26 mmol of acetic acid (15.6 mg, 15.0 μl) and isobutyl aldehyde (18.75 mg, 23.35 μl) were added to the reaction. The reaction was then heated up to reflux. After 24 h, another 0.26 mmol of acetic acid and isobutyl aldehyde were added and the reaction was allowed to go on for another 48 h.

After the reaction was completed, the solution was washed with 50 ml of 3% w/w $NaHCO_3$ aqueous solution twice and DI water once. Then the solution was precipitated in 50 ml of hexane for 3 times. The resulting polymer was dried under vacuum. The product was white brittle solid that weighed 94.1 mg (70% yield). The functionalization efficiency was calculated by NMR (Figure S5).

Synthesis of Peptide Conjugated Monomer: 1 mmol of 2-formamido ethyl methacrylate (157.1 mg), 2.4 mmol of triethylamine (242.9 mg, 334.5 μl) and 1 ml anhydrous

DCM were added into an Ar-charged Schlenk flask. The mixture was allowed to stir at room temperature for 10 min. 0.4 mmol of triphosgene (78.7 mg) was dissolved in 1 ml of DCM and 0.5 ml of the solution was added to the reaction mixture dropwise, then the mixture was allowed to react for 15 min. Then remaining triphosgene solution was added and the reaction was carried out for another 15 min. After dehydration was completed, 1.3 mmol of N-(tert-butoxycarbonyl) glycine (227.7 mg), isobutyl aldehyde (93.7 mg) and L-phenylalanine benzyl ester (331.9 mg) were added in this order to the mixture with 2 ml of methanol. The reaction was carried out at 45°C for 24 h. After reaction completed, the crude product was purified on silica gel column with hexane: ethyl acetate = 20:1 to 1:1 mobile phase. After purification, 569.8 mg (0.91 mmol, 91% yield) pure MAGF was obtained as yellow solid. ^{1}H NMR (500 MHz, CDCl3, δ) 7.21 (m, 10H, Ar-H), 6.09 (s, 1H, Vinyl-H), 5.56 (s, 1H, Vinyl-H), 5.05 (m, 2H, CH_2), 4.64(m, 1H, CH), 4.22 (m, 3H, CH_2), 3.91 (d, 1H, CH), 3.71–3.19 (m, 5H, CH_2), 1.90 (m, 3H, CH_3), 1.56 (s, 9H, CH_3), 1.45 (m, 6H, CH_3). HRMS (ESI): $[M + H]^+$ calc. = 624.3279, measured = 624.3278. See Figure S9–S10 for COSY and HSQC NMR confirming the structure of the compound.

RAFT Polymerization of Peptide Conjugated Monomer: 0.4 mmol MAGF (249.3 mg), 0.016 mmol AIBN (2.6 mg), 0.016 mmol 2-cyano-2-propyl benzodithioate (3.5 mg) and 2 ml anisole were added to an Ar-charged flask. The reaction was purged with Ar for 30 min, and then heated to 60°C for 18 h. Resultant polymer was precipitated in hexane for 5 times. 180.7 mg product (72.5% yield) was achieved as pink solid.

Free Radical Polymerization of Peptide Conjugated Monomer: 0.4 mmol MAGF (249.3 mg), 0.016 mmol AIBN (2.6 mg) and 2 ml anisole were added to an Ar-charged flask. The reaction was purged with Ar for 30 min, and then heated to 60°C for 18 h. Resultant polymer was precipitated in hexane for 5 times. The 31.7 mg prodcut (12.7% yield) was achieved as yellow solid.

Random copolymerization of Peptide Conjugated Monomer: P(MAGF-*co*-PEGMEMA) polymerization was done by RAFT free radical polymerization. 0.1 mmol of MAGF (62.3 mg), 0.39 mmol of PEGMEMA (115.7 mg) (M_n = 300 g/mol), 0.02 mmol AIBN (3.3 mg), 0.02 mmol 2-cyano-2-propyl benzodithioate (4.4 mg) and 2 ml DMF were added to an Ar-charged flask. The reaction was purged with Ar for 30 min, and then heated to 60°C for 18 h. Resultant polymer was reprecipitated in hexane 5 times. Quantitative yield of 178.0 mg of product was obtained as a pink viscous liquid.

RCP post-functionalization by U-4CR: 85.7 mg of RCP 1:2.5 (0.2 mmol of formamide group), 0.48 mmol of triethylamine (48.57 mg, 67.46 μl) and 1 ml of anhydrous DCM were added to an Ar-charged Schlenk flask and stirred at room temperature for 10 min. Then 0.04 mmol of triphosgene (11.9 mg) was dissolved in 0.5 ml of DCM and added to the reaction dropwise under constant stirring. After 15 min of reaction, another 0.04 mmol of triphosgene in 0.5 ml DCM were added to the reaction and the reaction allowed to proceed at room temperature for another 15 min. After dehydration was complete, 0.26 mmol of isobutyl aldehyde (18.75 mg, 23.35 μl), N-(tert-butoxycarbonyl) glycine (45.6 mg), and L-phenylalanine benzyl ester (66.4 mg) were added to the reaction, and the reaction was refluxed. After 24 h, another 0.26 mmol of isobutyl aldehyde, N-(tert-butoxycarbonyl) glycine, and L-phenylalanine benzyl ester were added and the reaction was allowed to proceed for additional 48 h.

After the reaction was completed, the solution was washed with 50 ml of 3% w/w $NaHCO_3$ aqueous solution twice and DI water once. The solution was then precipitated in 50 ml of hexane 5 times, and the resulting polymer was dried under vacuum. 0.1394 g (66% yield) of white solid was obtained. Functionalization efficiency was quantified by the ^{1}H NMR (Figure S15).

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