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Increased Polymer Length of Oligopeptide-Substituted Polynorbornenes with LiCl

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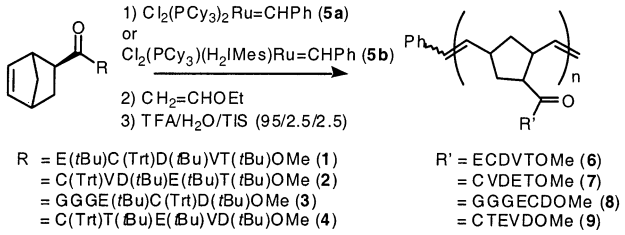
Abstract: The ring-opening metathesis polymerization (ROMP) reaction is extraordinarily useful for the preparation of a large variety of polymers. We report that the length ($n = 25-50$) of high-substituent-density oligopeptide polymers synthesized by ROMP is dramatically improved upon addition of LiCl to reduce polymer and oligopeptide aggregation. This methodology should significantly expand the variety of polymers that may be prepared by ROMP and be of general use with norbornyl oligopeptides of any sequence.

Ring-opening metathesis polymerization (ROMP) has emerged as a truly remarkable and versatile synthetic strategy in polymer and organic chemistry. Its popularity is due in part to the versatile and robust nature of alkylidene molybdenum and ruthenium catalysts designed by Schrock[1] and Grubbs.[2] These catalysts show either exceptional functional group tolerance or stereoselectivity and allow the synthesis of polymers with narrowly defined molecular weights.

These catalysts have been applied in a wide variety of systems ranging from polymer composites[3] to neoglycopolymers.[4] For use in our studies to dissect the roles of sperm ADAM proteins in mammalian fertilization, we required oligopeptide-substituted polynorbornenes of varying lengths. Various strategies have been utilized to prepare high-density polynorbornenes substituted with bioactive, water-soluble molecules with use of Grubbs' catalyst, ruthenium carbene $Cl_2(PCy_3)_2Ru{=}CHPh$. In the first approach, polymerizations are performed with monomers that are themselves water-soluble. For example, homogeneous mixtures of polar solvents have been used to prepare neoglycopolymers. However, emulsion conditions that utilize a phase-transfer reagent are often required for preparing longer ($n = 100$) polymers that have lower solubility in nonaqueous polar solvents.[5] A second strategy employed in the preparation of neoglycopolymers was polymerization of a norbornene active ester under homogeneous nonaqueous conditions followed by conjugation of the biomolecule.[6] However, we found that the utility of this strategy is limited by the efficiency of the conjugation that can be obtained. In our system, this may be due to either steric hindrance or aggregation as suggested by later experiments described below. In a third approach, polymerizations are performed with protected monomers that are organic-soluble under homogeneous, nonaqueous conditions. The polymers are subsequently deprotected to yield water-soluble polymers. This is the approach that has previously been utilized to prepare oligopeptide polynorbornenes with fully protected peptides;[7] however, the more reactive 2,3-dihydroimidazolylidene ruthenium catalysts were required. To date, the longest high-density oligopeptide polymers reported are 10-mers.[7a] We report here that significantly longer polymers with high-density pendent oligopeptides may be obtained by using the third synthetic strategy with either of Grubbs' catalysts, $Cl_2(PCy_3)_2Ru{=}CHPh$ or $Cl_2(PCy_3)(H_2IMes)Ru{=}CHPh$, by including lithium chloride in the polymerization reaction to reduce peptide aggregation. This method appears to be independent of peptide sequence.

SCHEME 1. Reaction Sequence for ROMP



We initially explored all three strategies in our studies to prepare polymers in which the fertilization inhibition peptide ECDVT derived from fertilinβ, or a scrambled control, is incorporated into a polymer. We found that polymerization of side-chain protected peptides with norbornene at the N-terminus, e.g., **1**, in homogeneous solvent conditions (CH_2Cl_2/MeOH, 3:1) with alkylidene **5a** and a catalytic amount of acid,[8] gave the most reproducible results and the cleanest product (Scheme 1 and Table 1, entries 1 and 2). The average DP determined by ^{1}H NMR of 8 corresponded to the $[M]_o/[C]_o$ of 10/1 in the reaction mixture. However, upon increasing the $[M]_o/[C]_o$ to 20/1 or 50/1, we again obtained short polymers with DP of 10 (Table 1, entries 3 and 4). We obtained early termination products accompanied by precipitation, regardless of peptide sequence (Table 1, entry 5). Several factors may influence the size and length of the polymers formed. These factors include activation of the catalyst, aggregation of the growing polymer chain, or steric interactions. We employed the more active and temperature stable, second generation dihydroimidazolylidene catalyst **5b** and found no improvement (Table 1, entry 6). Early chain termination still occurred. Our observations combined with earlier reports of the difficulties of

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TABLE 1. Solvent Conditions Surveyed for ROMP of Norbornyl Oligopeptides[a]

entry	monomer	catalyst	solvent	$[M]_o/[C]_o$[b]	av *n* (DP)[c]	% yield[d]
1	**1**	**5a**	CH_2Cl_2/MeOH (3:1)	10/1	NR[e]	0
2	**1**	**5a**	CH_2Cl_2/MeOH (3:1), 1 N HCl[f]	10/1	8	40
3	**1**	**5a**	CH_2Cl_2/MeOH (3:1), 1 N HCl	25/1	10	9
4	**1**	**5a**	CH_2Cl_2/MeOH (3:1), 1 N HCl	50/1	10	38
5	**2**	**5a**	CH_2Cl_2/MeOH (3:1), 1 N HCl	10/1	NR	0
6	**1**	**5b**	CH_2Cl_2/MeOH (3:1)	50/1	10	35
7	**3**	**5a**	CH_2Cl_2/MeOH (3:1), 1 N HCl	25/1	10	40
8	**2**	**5a**	CH_2Cl_2/MeOH (3:1), 1 N HCl, 6 M LiCl	25/1	24	54
9	**2**	**5a**	TFE	25/1	NR	0
10	**2**	**5a**	TFE, 1 N HCl	25/1	NR	0
11	**2**	**5a**	TFE, 1 N HCl, 6 M LiCl	25/1	8	20
12	**2**	**5a**	CH_2Cl_2/MeOH (3:1), 6 M LiCl	25/1	25	68
13	**2**	**5a**	CH_2Cl_2/MeOH (3:1), 6 M LiCl	50/1	50	52
14	**2**	**5a**	CH_2Cl_2/MeOH (3:1), 1 N HCl, 6 M LiCl	50/1	40	47

[a] General reaction conditions: rt, 3−4 h, $[M]_o$ = 0.2−0.3 M. [b] Initial feed ratio. [c] Calculated from ^{1}H NMR spectrum. [d] Isolated yield after purification and deprotection. [e] NR: no reaction or less than 5% product formed as monitored by TLC. [f] [HCl] = $[C]_o$.

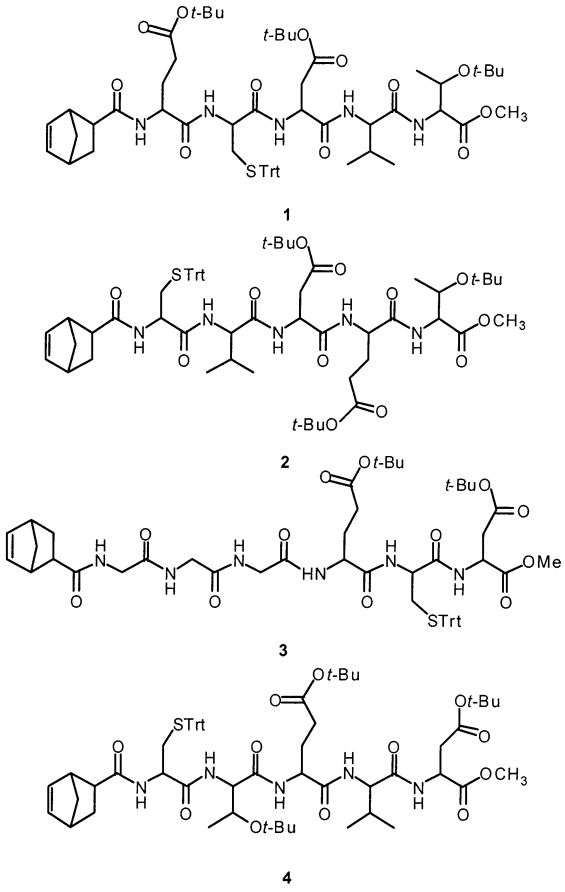

FIGURE 1. Monomers prepared for ROMP.

synthesizing short (DP = 10) polymers with pendent oligopeptide and no reports of longer polymers with 100% pendent oligopeptide suggested to us that either aggregation of the oligopeptide chains during polymerization or steric interactions at the catalyst center could be the cause of the early termination of our polymerizations. To test whether steric interactions at the catalyst reaction center were the cause, we synthesized a new monomer, **3**, that incorporated a triglycine linker between the norbornene and the ECD. However, polymerizations with this monomer also terminated early with a DP of 10 regardless of the $[M]_o/[C]_o$ used (Table 1, entry 7).

We next focused on the possibility that aggregation of the growing polymer chain was the predominant reason for early termination. It is well-known in solid-phase peptide synthesis that secondary structures and/or aggregates form on the solid support during the synthesis of β-sheet forming peptides. Aggregation reduces the efficiency of coupling the next amino acid by limiting access to the nucleophile. We reasoned that similar types of aggregation could be occurring during polymerization of our norbornene pendent peptide monomers and be limiting access of the monomer to the catalyst reaction center. Although the peptide sequences we utilized do not show a propensity for β-sheet formation in solution, tethering of the peptides to the polymer backbone might induce β-sheet formation between neighboring peptides in the growing polymer chain. In turn, this sheet formation would lead to insolubility and precipitation, thus removing the catalyst from solution and further reaction. This phenomenon would explain why introduction of a triglycine linker between the norbornene and monomer did not improve polymerization efficiency, as the triglycine is also able to form β-sheet with a neighboring oligopeptide

The issues of secondary structure and aggregation may be resolved by the use of structure-altering solvents such as trifluoroethanol,[9] and/or the addition of lithium salts. Seebach[10] and co-workers have shown that LiCl and other forms of inorganic salts can influence the solubility of peptides in nonpolar organic solvents. Lansbury[11] and Hilvert[12] have shown that this idea can be applied to improve coupling reactions and cleavage reactions, respectively, in peptide chemistry.

Peptide **2** was chosen for optimization of the reaction conditions. This peptide and peptides **1**, **3**, and **4** were synthesized in good overall yields by solution-phase peptide chemistry, using TBTU, HOBt, and DIEA in CH_2Cl_2. The monomers were purified by flash column chromatography and characterized by ^{1}H and ^{13}C NMR spectroscopy.

Polymerization reactions were carried out in different solvent conditions that included TFE, LiCl, and 1 N HCl,

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TABLE 2. Norbornyl Oligopeptides Synthesized with LiCl[a]

entry	monomer	catalyst	$[M]_o/[C]_o$[b]	av *n* (DP)[b]	% yield[c]	polymer
1	**1**	**5a**	50/1	50	79	**6**
2	**2**	**5a**	25/1	25	68	**7a**
3	**2**	**5a**	50/1	50	79	**7b**
4	**3**	**5a**	50/1	45	64	**8**
5	**4**	**5a**	50/1	48	73	**9**
6	**1**	**5b**	50/1	50	88	**6**

[a] General reaction conditions: CH_2Cl_2:MeOH (3:1), 6 M LiCl, rt, 4 h, $[M]_o/[C]_o = 0.3$ M. [b] Calculated from ^{1}H NMR spectrum. [c] Isolated yield after purification and deprotection.

as well as the original solvent used, CH_2Cl_2/MeOH (3:1). Upon completion of the polymerization reactions, the solvent was removed and the product was washed with water if LiCl was used in the reaction. Polymers were redissolved in CH_2Cl_2 and isolated by precipitation with cold Et_2O. Unreacted monomer was removed by repeated washing with Et_2O. The oligopeptide polymers were then deprotected with TFA, using water and triisopropylsilane as scavengers. The polymers were fully reduced by the addition of TCEP and precipitated with 1 N HCl for storage. The $[M]_o/[C]_o$ ratios ranged from 25/1 to 50/1 (Table 1, entries 8−14). The results of the polymerization reactions clearly indicate that aggregation must have been the cause of early chain termination as the addition of LiCl leads to the formation of polymers with DPs that correlate to the $[M]_o/[C]_o$ in the reaction mixture. Polymerization in TFE did not occur, because of the low solubility of the monomer in the solvent. As the LiCl results were promising, the use of other solvent mixtures that included TFE was not investigated.

We then explored whether the addition of LiCl to polymerization reactions was of general utility. We performed ROMP of three other norbornyl oligopeptides, **1**, **3**, and **4**. Polymers of the expected lengths ($n = 25-50$) were obtained in excellent isolated yields ranging from 64 to 79% (Table 2). We compared catalyst **5b** to **5a** and found that polymer chain extension was equally efficient and proceeded in slightly higher yield (Table 2, entries 1 and 6). Thus, our optimized reaction conditions work with norbornyl oligopeptides with high functionality to give polymers of high substituent density, regardless of sequence or catalyst.

Initially, we found it necessary to add 1 equiv (to $[C]_o$) of HCl to the polymerization reaction to activate catalyst **5a**[8] or to employ the more active dihydroimidazolylidene catalyst **5b.**[7] However, with the LiCl modification, the HCl was not necessary, and in fact, slowed the reaction rate, in addition to decreasing the polymerization efficiency (Table 1, entries 12 and 13). This reduction is presumably due to decomposition of the catalyst. Moreover, faster initiation and higher catalyst stability alone were insufficent for production of longer high-density polymers; LiCl was again required for **5b**-catalyzed polymerization (Table 1, entry 6; Table 2, entry 6). Both catalysts **5a** and **5b** yielded polymers of the desired lengths; however, the dihydroimidazolylidene catalyst provided a slightly higher yield. These results suggest that disrupting aggregation is the predominant factor in achieving polymerization of norbornyl oligopeptides and that catalyst stability plays a minor although important role in these polymerizations.

In summary, we have demonstrated that the addition of 6 M LiCl to ROMP reactions using norbornyl monomers with pendent oligopeptides that are catalyzed by Ru catalysts significantly improves the catalytic reaction. Extended polymers with high substituent density and of the expected length are obtained ($n = 25-50$). This methodology should significantly expand the variety of polymers that may be prepared by ROMP and be of general use with norbornyl oligopeptides of any sequence.

Experimental Methods

Materials and Methods. CH_2Cl_2 was freshly distilled from CaH; CF_3CH_2OH, CH_3OH, and Et_2O were used without further purification. LiCl was oven-dried and stored over P_2O_5 before use. All reactions were carried out under an N_2 or Ar atmosphere in oven-dried glassware. Moisture and oxygen-sensitive reagents were handled in an N_2-filled drybox. 5-Norbornene-*exo*-carboxylic acid was synthesized according to the literature.[13]

Analytical thin-layer chromatography (TLC) was performed on precoated silica gel plates ($60F_{254}$), and flash chromatography on silica gel-60 (230−400 mesh). TLC spots were detected by UV light and by staining with phosphomolybdic acid (PMA). Peptides were purified by flash column chromatography on silica gel-60. Spectra were recorded in $CDCl_3$ unless otherwise noted. Chemical shifts are quoted in parts per million (ppm) and ^{1}H NMR data are assumed to be first order. The purity of the peptides was assessed by reversed-phase HPLC (C18, 2 column volume linear gradient of 30% CH_3CN/H_2O to 40% CH_3CN/H_2O, followd by an 8 column volume linear gradient of 40% CH_3CN/H_2O to 95% CH_3CN/H_2O). The purity of polymers was assessed by aqueous-phase gel-filtration chromatography (BioSep-SEC-S 2000), using 50 mM potassium phosphate, pH 7. The identity of the peptides was confirmed by MALDI/TOF mass spectroscopy with use of α-hydroxycinnamic acid as a matrix. Peptides were analyzed by analytical HPLC and polymers were analyzed by analytical GFC immediately before use to confirm that the cysteines had not oxidized to form disulfide dimer.

Peptide Synthesis. (a) General Procedure for Amino Acid Coupling. A typical amino acid coupling was carried out in dry CH_2Cl_2 with TBTU/HOBt (1.1 equiv/0.37 equiv) and DIEA (1.6 equiv). Each reaction was carried out under Ar at a final concentration of 0.7 M in the amine compound, and a 1.1-fold excess of the carboxylic acid component. Upon completion of the reaction, the mixture was diluted with CH_2Cl_2 and washed with 1 N HCl and 5% $NaHCO_3$, and the organic layer was dried with Na_2SO_4. The solvent was rotary evaporated. The peptide was purified by flash chromatography eluting with 10% acetone/CH_2Cl_2 or 20% EtOAc/CH_2Cl_2.

(b) General Procedure for Cbz Hydrogenation. A methanolic solution of Cbz-protected peptide (0.3 M) and 10% Pd-C (0.05 equiv) was stirred under an H_2 atmosphere for 2 h. The catalyst was removed by filtration and the amine used without further purification.

(c) General Procedure for Fmoc Removal. A solution of Fmoc-protected peptide in dry CH_2Cl_2 (0.5 M) was treated with octanethiol (0.1 equiv) and a catalytic amount of DBU (0.001 equiv).[14] The reaction was stirred at rt for 16 h. The solvent was concentrated and the product was purified by flash column chromatography eluting with a step gradient ranging from 2% to 50% EtOAc/CH_2Cl_2.

(d) Norbornene-E(tBu)C(Trt)D(tBu)VT(tBu)-OMe (1). Peptide **1** was prepared in 5 coupling steps to yield 0.75 g (76% overall yield). ^{1}H NMR (250 MHz) δ 7.38 (m, 6H), 7.20 (m, 11H), 6.98 (dd, $J = 8.1$ and 6.3 Hz, 1H), 6.72 (dd, $J = 7.2$ and 3.3 Hz, 1H), 6.47 (dd, $J = 9.0$ and 2.7 Hz, 1H), 6.0 (m, 2H), 4.74 (m,

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1H), 4.43 (dd, J = 8.7 and 1.8 Hz, 1H), 4.19 (m, 3H), 3.92 (m, 1H), 3.65 (s, 3H), 2.78 (m, 5H), 2.49 (m, 2H), 2.27 (m, 1H), 2.02 (m, 3H), 1.83 (m, 2H), 1.60 (m, 2H), 1.41 (d, J = 4.5 Hz, 9H), 1.39 (s, 9H), 1.24 (m, 2H), 1.11 (d, J = 6.3 Hz, 3H), 1.07 (s, 9H), 0.90 (d, J = 6.6 Hz, 3H), 0.87 (d, J = 6.9 Hz, 3H). ^{13}C NMR (250 MHz) δ 18.04, 19.01, 20.82, 26.41, 27.97, 28.26, 30.44, 30.54, 30.77, 32.22, 32.96, 33.05, 36.72, 41.48, 44.39, 46.33, 46.98, 49.72, 51.97, 52.51, 52.61, 54.15, 57.73, 58.86, 73.95, 81.19, 81.31, 126.83, 128.02, 129.45, 135.87, 138.07, 144.15, 169.33, 169.96, 170.56, 170.76, 171.00, 171.36, 173.66, 176.73. MALDI, calcd for (MNa^+) 1132.89, found 1133.96. HPLC purity was 98%.

(e) Norbornene-C(Trt)VD(tBu)E(tBu)T(tBu)-OMe (2). Peptide **2** was prepared in 5 coupling steps to yield 0.92 g (78% overall yield). ^{1}H NMR (600 MHz) δ 7.43 (m, 7H), 7.23 (m, 12H), 6.81 (d, J = 9.6 Hz, 1H), 6.57 (dd, J = 7.8 and 8.4 Hz, 1H), 6.07 (m, 2H), 4.80 (m, 1H), 4.54 (dd, J = 7.8 and 13.8 Hz, 1H), 4.46 (m, 1H), 4.19 (ddd, J = 2.1 and 6.3 Hz, 1H), 4.06 (m, 2H), 3.37 (s, 3H), 2.87 (d, J = 16.8 Hz, 1H), 2.78 (m, 1H), 2.75 (m, 1H), 2.63 (m, 3H), 2.34 (t, J = 7.5 Hz, 2H), 2.17 (m, 2H), 1.92 (m, 2H), 1.86 (dt, J = 3.9 and 11.4 Hz, 1H), 1.79 (dt, J = 4.0 and 12.0 Hz, 1H), 1.58 (dd, J = 7.8 and 8.4 Hz, 1H), 1.41 (d, J = 1.8 Hz, 9H), 1.39 (d, J = 3.0 Hz, 9H), 1.26 (m, 2H), 1.13 (d, J = 6.6 Hz, 3H), 1.10 (s, 9H), 0.91 (dd, J = 7.2 and 7.8 Hz, 3H), 0.84 (dd, J = 3.0 and 3.0 Hz, 3H). ^{13}C NMR (250 MHz,) δ 17.4, 19.3, 20.7, 27.9, 28.2, 29.9, 30.1, 30.4, 31.5, 32.6, 37.0, 41.5, 44.1, 44.2, 46.1, 47.0, 47.4, 49.4, 52.0, 52.5, 52.8, 57.9, 59.4, 67.2, 67.3, 74.0, 80.4, 81.4, 126.9, 128.1, 129.4, 135.7, 135.8, 138.4, 144.3, 170.1, 170.2, 170.7, 170.9, 171.0, 172.5, 176.4, 176.4. MALDI, calcd for (MNa^+) 1132.89, found 1134.87. HPLC purity was 97%.

(f) Norbornene-GGGE(tBu)C(Trt)D(tBu)-OMe (3). Peptide **3** was prepared in 4 coupling steps to yield 0.20 g (68% overall yield). ^{1}H NMR (DMSO, 500 MHz) δ 8.06 (m, 6H), 7.28 (m, 10H), 7.21 (m, 4H), 6.08 (m, 2H), 5.66 (m, 1H), 4.54 (dd, J = 6.6 and 6.6 Hz, 1H), 4.26 (m, 2H), 3.74 (m, 2H), 3.72 (m, 2H), 3.71 (m, 2H), 3.52 (s, 3H), 3.16 (s, 2H), 2.83 (s, 1H), 2.80 (s, 1H), 2.63 (dd, J = 6.6 and 6.0 Hz, 1H), 2.52 (d, J = 6.0 Hz, 1H), 2.48 (s, 1H), 2.36 (m, 2H), 2.18 (m, 2H), 2.11 (dt, J = 8.4 and 4.2 Hz, 1H), 2.03 (m, 2H), 1.83 (m, 1H), 1.77 (m, 1H), 1.71 (m, 1), 1.59 (d, J = 7.8 Hz, 1H), 1.34 (s, H), 1.33 (s, 9H), 1.16 (m, 2H). ^{13}C NMR (DMSO, 250 MHz) δ 27.30, 27.51, 29.76, 30.51, 31.06, 33.30, 36.76, 40.93, 41.93, 42.09, 42.35, 42.85, 45.58, 46.63, 48.56, 51.44, 51.82, 54.44, 65.80, 168.67, 168.77, 169.12, 169.27, 169.59, 170.51, 170.64, 171.49, 175.27. MALDI: calcd for (MK^+) 1063.80, found 1063.73. HPLC purity was 98%.

(g) Norbornene-C(Trt)T(tBu)E(tBu)VD(tBu)-OMe (4). Peptide **4** was prepared in 5 coupling steps to yield 0.40 g (76% overall yield). ^{1}H NMR (600 MHz) δ 7.42 (m, 6H), 7.30 (m, 6H), 7.25 (m, 4H), 6.92 (m, 2H), 6.89 (d, J = 6.6 Hz, 1H), 6.13 (m, 2H), 5.67 (d, J = 4.8 Hz, 1H), 4.82 (m, 1H), 4.37 (m, 1H), 4.27 (m, 2H), 4.13 (m, 1H), 4.00 (m, 1H), 3.72 (s, 3H), 2.87(m, 2H), 2.76 (m, 2H), 2.66 (m, 1H), 2.33 (m, 3H), 2.14 (m, 1H), 1.92 (m, 2H), 1.83 (d, J = 12.0 and 3.3 Hz, 1H), 1.43 (s, 9H), 1.42 (s, 9H), 1.27 (m, 2H), 1.17 (s, 9H), 1.07 (d, J = 6.6 Hz, 3H), 0.95 (d, J = 6.6 Hz, 3H), 0.93 (d, J = 6.6 Hz, 3H). ^{13}C NMR (250 MHz) δ 17.68, 19.05, 19.87, 26.11, 26.51, 27.27, 27.99, 28.44, 30.45, 30.67, 31.90, 33.96, 37.18, 38.54, 41.54, 44.39, 46.21, 47.06, 47.67, 48.53, 49.26, 51.02, 52.47, 52.59, 58.55, 65.39, 66.67, 67.65, 68.05, 74.32, 80.77, 81.73, 126.79, 127.92, 129.39, 135.84, 138.24, 144.23, 169.98, 170.44, 170.59, 170.98, 171.12, 172.58, 175.02, 175.05. MALDI: calcd (MNa^+) 1132.89, found 1133.96. HPLC purity was 96%.

Norbornyl Oligopeptide Polymers. (a) General Polymerization Procedure. Catalyst **5a** or **5b** was weighed in an N_2-filled drybox and dissolved in CH_2Cl_2/CH_3OH (3/1) to give a typical concentration of 0.03 M. Monomers were each dissolved in a minimum amount of CH_2Cl_2/CH_3OH (3/1) and LiCl (6 M) was added to the mixture. The desired portion of catalyst was added via syringe to the reaction bottle under an inert atmosphere. A typical reaction was carried out at an initial monomer concentration of 0.2 to 0.3 M. The reaction was stirred at rt for 3 to 4 h before quenching with ethyl vinyl ether and stirring for an additional 30 min. The solvent was removed and the product was washed with H_2O. Polymers were dissolved in CH_2Cl_2 and precipitated with cold Et_2O. Product was isolated by centrifugation and dried under vacuum in the presence of P_2O_5.

(b) General Deprotection and Reduction Procedure. Polymers were deprotected in a cocktail containing H_2O, TIS, and TFA (2.5, 2.5, 95) for 5 h. The reaction mixtures were concentrated with N_2 and precipitated in cold Et_2O and centrifuged. Polymers were dissolved in H_2O at pH 6 and reduced with excess TCEP for 5 h with stirring at 37 °C. Pure deprotected product was isolated by precipitation with 1 N HCl. Excess TCEP was removed by repeated washing with H_2O. A gray white solid was collected, dried, and stored at −20 °C.

(c) Polymer 6. Yield 41 mg (79%); ^{1}H NMR (D_2O, 600 MHz) δ 7.20 (m), 5.28 (br s), 4.72−3.98 (with max at 4.62, 4.51, 4.40, 4.22, 4.15), 3.69, 3.62 (s), 2.92−2.31 (with max at 2.68, 2.49, 2.43), 2.22−1.66 (with max at 1.78, 1.83, 2.19), 1.60 (m), 1.17 (m), 0.91 (br s). GFC purity was 97%.

(d) Polymer 7a. Yield 26 mg (68%); ^{1}H NMR (D_2O, 600 MHz) δ 7.21 (m), 5.30 (br s), 4.69 (br s), 4.36 (br s), 4.29 (br s), 4.19 (m), 4.28−3.99 (with max at 4.18, 4.15, 4.13), 3.70−3.51 (with max at 3.64, 3.61, 3.50), 3.20 (s), 3.14 (m), 2.81 (br s), 2.63−2.29 (with max at 2.52, 2.40, 2.31), 2.10−1.45 (with max at 2.17, 1.91, 1.78, 1.60), 1.40−1.00 (with max at 1.30, 1.18, 1.11), 0.89 (s). GFC purity was 98%.

(e) Polymer 7b. Yield 20 mg (79%); ^{1}H NMR (D_2O, 600 MHz) δ 7.22 (m), 6.14 (br s), 5.60−5.14 (with max at 5.55, 5.34), 4.60 (br s), 3.72 (m), 3.40 (br s), 2.60 (m) 2.22−1.41(with max at 2.16, 1.97, 1.78, 1.60), 1.40−0.99 (with max at 1.23, 1.10), 0.80 (br s). GFC purity was 96%.

(f) Polymer 8. Yield 15 mg (64%); ^{1}H NMR (D_2O, 600 MHz) δ 5.18 (m), 4.56 (m), 4.40 (m), 4.21 (br s), 3.89 (m), 3.60 (m), 3.60 (m), 3.15 (m), 3.01−2.53 (with max at 2.86, 2.6), 2.45 (s), 2.33 (s), 2.16 (m), 1.91 (m), 1.84 (m), 1.68 (m), 1.59 (m), 1.39−1.03 (with max 1.38, 1.24, 1.20, 1.11). GFC purity was 96%.

(g) Polymer 9. Yield 10 mg (73%) ^{1}H NMR (D_2O, 600 MHz) δ 7 0.20 (m), 5.30 (br s), 5.01 (br s), 4.51 (s), 4.39 (m), 4.28 (br s), 4.09 (m), 3.70 (br s), 3.64 (s), 3.00−2.38 (with max at 2.73, 2.61, 2.55), 2.23−1.72 (with max at 2.18, 1.93, 1.80), 1.59 (m), 1.40−0.91 (with max at 1.09, 1.17), 0.89 (m), 0.79 (br s). GFC purity was 97%.

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Supporting Information Available: Experimental procedures for precursors to compounds **1**−**4** and **6**−**9** and their spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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