Amino Acid and Dipeptide Functionalized Polyolefins

Timothy E. Hopkins and Kenneth B. Wagener*

The George and Josephine Butler Polymer Laboratory, Department of Chemistry, University of Florida, P.O. Box 117200, Gainesville, Florida 32611-7200

Received November 8, 2002; Revised Manuscript Received January 21, 2003

ABSTRACT: N-protected amino acid and dipeptide branched, chiral polyolefins have been prepared using acyclic diene metathesis polycondensation chemistry. The polymerizations were performed in THF using Grubbs' second-generation catalyst. The polymers bearing CBz-protected amino acids and dipeptides are semicrystalline with melt transitions of up to 150 °C, whereas the polymers bearing BOC-protected amino acids and dipeptides are primarily amorphous with the exception of the di-BOC-protected lysine polymer, which is semicrystalline.

Introduction

The synthesis of polymers containing amino acid and peptide moieties is a subject of much interest, since a high degree of amino acid functionality and chirality can lead to polymers with enhanced solubility and the ability to form secondary structures such as α-helices and β-sheets.[1,2] Possible applications include drug-delivery agents, chiral recognition stationary phases, asymmetric catalysts, metal ion absorbents, and biocompatible materials.[3,4] In the 1960s, Pino and co-workers used amino acids to create chiral polymers; however, the lack of readily available enantiopure amino acids limited further enhancement of this initial research.[4] Recently, advances in the areas of chiral separation and synthesis have produced a variety of inexpensive and enantiopure protected amino acids and small peptides.[2] These advances have enabled the preparation of a new generation of amino acid-based biomaterials.[2]

Endo and co-workers have synthesized a variety of amino acid and peptide branched acrylamides via radical polymerizations.[5,6] A peptide moiety composed of L-leucine, L-alanine, and α-aminoisobutyric acid units, which is known to form a helix, was coupled to methacrylic acid and polymerized to yield a polymer demonstrating the same CD spectrum as the monomer when polymerized using dichlorobenzene as the solvent.[1] Thus, Endo and co-workers reported the polymer maintained a linear backbone structure with α-helix-shaped branches. Similar work by North et al. involved the synthesis of a variety of serine-based amino acid branched polymers by radical polymerization, which differ from those of Endo and co-workers since the amino acid functionality is attached to the acrylate through the alcohol of the serine side chain.[7] In addition, monomers bearing dipeptides and tripeptides attached through the acid and amine of the serine unit, respectively, were prepared.[8]

Grubbs et al.[9] and North et al.[10] have used ring-opening metathesis chemistry (ROMP) to make poly(norbornenes) bearing amino acid and peptide branched polymers. The Grubbs group has extended this work to include the synthesis of polymers bearing the biologically active peptide arginine−glycine−aspartic acid (RGD).[11] A simple copolymerization of a norbornene bearing RGD with a norbornene bearing penta(ethylene oxide) yielded a water-soluble polymer capable of binding to fibronectin; the RGD-based copolymer has potential for a variety of biomedical applications.[11]

We now describe the synthesis of amino acid and peptide branched polymers using simple polycondensation chemistry, acyclic diene metathesis (ADMET).[12] Previously, we reported that ADMET could be used to synthesize linear amino alcohol containing polymers as well as polymers containing branched amino acids.[13] The polymers are strong, film-forming materials possessing moduli of up to 220 MPa with up to 260% elongation. These polymers are intended to be durable materials possessing hydrophilic surfaces, properties that could prove useful for biomedical applications where biologically compatible materials are desired, e.g., coatings for artificial implants. In addition, the attachment of amino acids onto a polyolefin backbone could be advantageous for biomaterial applications, since the resulting polymer backbones are not biodegradable.

Experimental Section

Chemicals. Chemicals were purchased from the Aldrich Chemical Co., unless otherwise noted. Diethyl ether and THF were used as received from Fisher Scientific, unless it is stated that dry solvents were used, which were obtained from the Aldrich keg system and dried over Al_2O_3 or by distillation of the solvent over Na/K. 11-Bromo-1-undecene, which was purchased from Fluorochem, 5-bromo-1-pentene, and ethyl formate were refluxed over CaH for 12 h and distilled prior to use. Methylene chloride and chloroform were used as purchased from Fisher, unless it is noted that the solvent was dry; then the solvents were refluxed and distilled over CaH. Triethylamine was purchased from Aldrich and purified by distillation over CaH. Methanol was used from Fisher as received; however, when dry methanol was required, it was used as purchased from an Aldrich sure seal bottle. Anhydrous DMF (99.8%) was used as purchased in an Aldrich sure seal container equipped with an Aldrich Schlenk cap. The second-generation Grubbs' Ru catalyst (tricyclohexylphosphine[1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene][benzylidene]ruthenium(IV) dichloride) was used exclusively and was synthesized as described previously by Grubbs et al.[14] The protected amino acids and dipeptides were used as purchased from Bachem, except CBz alanine−valine, di-CBz lysine, and di-CBz cysteine, which were purchased from Sigma-Aldrich.

Instrumentation. All ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on a Varian Associates Gemini 300, Varian Associates VXR 300, or a Varian Associates Mercury 300 spectrometer. All chemical shifts were referenced

* Corresponding author: e-mail wagener@chem.ufl.edu.

10.1021/ma021668w CCC: $25.00
Published on Web 03/13/2003

to TMS (0.00 ppm) for ^{1}H NMR and to $CDCl_3$ (77.23 ppm) or DMSO-d_6 (39.51 ppm) for ^{13}C NMR.

Gel permeation chromatography (GPC) of the unsaturated ADMET polymers was performed using two 300 mm Polymer Laboratories 5 μm mixed-C columns. The instrument consists of a Rainin SD-300 pump, a Hewlett-Packard 1047-A RI detector, a TC-45 Eppendorf column heater set to 35 °C, and a Waters U6K injector. The solvent used was THF at a flow rate of 1 mL/min, and the samples were dissolved in ACS grade THF (5−8 mg/mL) and filtered before injection. Retention times were calibrated to narrow polystyrene standards purchased from Polymer Laboratories (Amherst, MA).

Fourier transform infrared (FT-IR) spectrometry was performed using a Bio-Rad FTS-40A spectrometer. The polymers were analyzed by dissolving a small amount of sample into CH_2Cl_2 and allowing the solution to evaporate on a salt plate, and the solid monomers were ground up with IR grade KBr into a homogeneous mixture and analyzed using a KBr pellet formed from the mixture.

Differential scanning calorimetry (DSC) was performed using a Perkin-Elmer DSC 7 at a heating rate of 10 °C/min using indium and *n*-octane as calibration standards. Heats of fusion were referenced against indium. The samples were scanned three times to remove recrystallization differences between samples and the results reported came from the third scan. The results are listed in tabular form as well as within the text as T_m (melting peak) and T_g (glass transition).

Characterization. Strenuous purification was only performed on the final monomers reported herein. Only ^{1}H NMR and ^{13}C NMR spectra are reported for the precursors (**3a**, **3b**, and **3c**) to these monomers. The alcohols (**1a**, **1b**, and **1c**) and ketones (**2a**, **2b**, and **2c**) were only isolated in crude form, so no characterization data is given. All of the monomers were fully characterized by ^{1}H NMR, ^{13}C NMR, IR, EI/HRMS, and elemental analysis. The polymers were characterized by ^{1}H NMR, ^{13}C NMR, IR, GPC, and DSC, and only the characterization for the high molecular weight polymers is reported.

Monomer Synthesis. Synthesis of 1-Pent-4-enyl-hex-5-enylamine (3a). Magnesium (4.89 g, 0.20 mol) was added to a 500 mL three-neck flask equipped with a reflux condenser and an addition funnel, and the reaction vessel was backfilled three times with Ar and flamed out after the second backfill. Dry ether (100 mL) was added, followed by the dropwise addition of 5-bromo-1-pentene (25.0 g, 19.9 mL, 0.17 mol) in 60 mL of dry diethyl ether at such a rate as to maintain a gentle reflux. After the addition was complete, a heating mantle was placed under the reaction vessel, and the solution was refluxed for 2 h. Ethyl formate (5.64 g, 0.076 mol) in 20 mL of dry diethyl ether was added dropwise to the cooled reaction mixture (0 °C), and the solution was allowed to warm slowly to room temperature and refluxed for an additional 12 h. Hydrochloric acid (1 M, 100 mL) was added, and the solution was extracted with ether (3 × 25 mL), washed with 1 M HCl (1 × 30 mL), and washed with brine (3 × 20 mL). The solution was dried over $MgSO_4$, followed by evaporation of the solvent to yield 13.6 g of the crude alcohol (**1a**).

To a 1 L round-bottom flask equipped with an addition funnel was added pyridinium chlorochromate (PCC) (26.0 g, 0.12 mol), celite (26.0 g), and methylene chloride (100 mL) followed by the addition of crude **1a** (13.6 g, 0.080 mol) in methylene chloride (20 mL). The reaction was stirred over 4 h, followed by the addition of diethyl ether (200 mL) and filtering through a pad of silica gel. The solvent evaporation yielded 13.0 g of the crude ketone (**2a**).

To a 1 L round-bottom flask was added **2a** (12.96 g, 0.078 mol), dry methanol (200 mL), ammonium acetate (60 g, 0.78 mol), $NaCNBH_3$ (25 g, 0.40 mol), and crushed 4 Å molecular sieves (one scoopula tip) under N_2 and refluxed for 48 h. The crushed molecular sieves were filtered via Büchner filtration, and deionized water (200 mL) was added to the filtrate, followed by extraction with diethyl ether (3 × 50 mL). The organic layer was washed with 1 M NaOH (2 × 50 mL) and brine (2 × 30 mL) and dried over $MgSO_4$. The solution was concentrated to a viscous brown oil, which was purified by flash column chromatography using a 3:1:1 (hexane:ethyl acetate:methanol) mobile phase yielding the desired product **3a** (9.28 g) for an overall yield of 73%. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 1.15−1.70 (m, 8H), 2.01−2.15 (br, 4H), 2.65−2.76 (br, 1H), 4.90−5.10 (m, 4H), 5.75−5.90 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 25.87, 34.29, 37.84, 51.45, 114.95, 139.19.

Synthesis of 1-Undec-10-enyl-dodec-11-enylamine (3b). **3b** was synthesized as described above using 11-bromo-1-undecene (25.0 g, 0.106 mol) instead of 5-bromo-1-pentene. When purified as above using flash column chromatography, an overall yield of 48% (13.0 g) was obtained. However, it was found that a quick purification of the product can be performed by placing the crude amine on a plug of silica gel and washing with 3:1 hexanes:ethyl acetate until the starting materials are no longer present by TLC. Removal of the amine by washing the plug of silica gel with methanol (∼1 L) gave **3b** in similar yields. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 1.15−1.45 (br, 32 H), 2.05 (q, br, 4H), 2.65−2.75 (br, 1H), 4.88−5.05 (m, 4H), 5.72−5.38 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 26.39, 29.20, 29.41, 29.76, 29.84, 29.90, 30.07, 34.08, 38.02, 51.50, 114.36, 139.50.

Synthesis of 1-Dec-9-enyl-undec-10-enylamine (3c). Synthesis was performed using a modified procedure by Zantour and co-workers.[15] To a 500 mL three-neck round-bottom flask equipped with a reflux condenser and an addition funnel was added 10-undecenoyl chloride (0.100 mol, 20.27 g, 21.48 mL) and dry diethyl ether (150 mL). The solution was cooled to 0 °C, and triethylamine (0.180 mol, 18.21 g, 25.09 mL) was added dropwise, instantly forming white triethylammonium chloride salts. The reaction mixture was warmed to room temperature and stirred for 24 h, followed by Büchner filtration of the salts and evaporation to yield the liquid intermediate lactone. Deionized water (100 mL) and NaOH (2.10 mol, 8.80 g) were added, and the mixture was refluxed for 6 h. The solution was acidified with 1 M HCl and extracted with diethyl ether (3 × 40 mL), and the combined organic layers were washed with 1 M HCl (2 × 20 mL), saturated $NaHCO_3$ (2 × 20 mL), and brine (2 × 20 mL). After drying over $MgSO_4$ and recrystallizing from MeOH, the pure ketone (**2c**) (12.58 g, 82%) was obtained. The ^{1}H NMR and ^{13}C NMR were in agreement with those reported previously.[15,17]

The ketone **2c** (11.30 g, 36.9 mmol) was converted to the amine **3c** (8.00 g, 70%) using the same methodology as described above. The overall yield for the two steps was 52%. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 1.18−1.62 (br, 28H), 2.04 (q, 4H), 2.80−2.94 (m, br, 1H), 4.03−4.54 (br, 2H), 4.88−5.07 (m, 4H), 5.71−5.91 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 26.52, 29.34, 29.54, 29.88, 30.01, 30.20, 34.21, 38.18, 51.61, 114.46, 139.48.

General Coupling Procedure of the Amino Acid/ Dipeptides to 3a/3b/3c. The amino acid/ dipeptide and 1-hydroxybenzotriazole (HOBt) (2.5 equiv to amino acid) were added to a 100 mL round-bottom flask. To the flask, equipped with a septum, a stir bar, and under argon, was added 1,3-diisopropylcarbodiimide (DIC) (1.2 equiv to amino acid) and dry THF (just enough to dissolve the compounds). The reaction vessel was equipped with a reflux condenser and stirred 1 h at room temperature, followed by the addition of **3a**/**3b**/**3c** (1.1 equiv to amino acid). The reaction mixture was then refluxed for 12 h for the amino acids and 24 h for the dipeptides. The insoluble urea was removed via gravity filtration, and THF was evaporated to yield a crude white solid. The product was purified with three successive recrystallizations using ethanol/ water or methanol/water (ethanol was used for the monomers that melt above the boiling point of ethanol); the product was dissolved in hot ethanol/ methanol, and water was added until the solution became cloudy. The pure product was then collected by vacuum filtration through a Kontes filtration apparatus and dried under vacuum (10^{-2} mmHg) for 48 h.

Synthesis of [(*S*)-3-Methyl-1-(1-pent-4-enyl-hex-5-enyl-carbamoyl)butyl]carbamic Acid *tert*-Butyl Ester (4a). The pure product **4a** was obtained in 78% yield with a melting point range of 117−119 °C. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 0.85−0.95 (m, 6H), 1.27−1.55 (br, 18H), 1.58−1.72 (br, 2H), 2.05 (q, br, 4H), 3.82−3.92 (br, 1H), 3.95−4.06 (m, 1H), 4.86−

5.03 (m, 5H), 5.65−5.83 (m, 2H), 5.88 (d, br, 1H).^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 22.51, 22.96, 24.99, 25.21, 25.28, 25.51, 28.51, 33.71, 33.76, 34.82, 34.88, 41.07, 49.09, 53.55, 114.91, 138.67, 138.70, 156.00, 172.27. FTIR (KBr pellet, cm^{-1}): 3344, 3279, 3083, 2979, 2936, 2869, 1688, 1649, 1561, 1522, 1455, 1392, 1367, 1321, 1294, 1248, 1176, 1121, 1048, 1023, 995, 910, 875, 792, 753, 633. Anal. Calcd for $C_{22}H_{40}N_2O_3$: C, 69.43; H, 10.59; N, 7.36. Found: C, 69.38; H, 10.61; N, 7.49. EI/HRMS [M + 1]: Calcd for $C_{22}H_{40}N_2O_3$: 380.3039 g/mol. Found: 380.3117 g/mol.

Synthesis of [(*S*)-3-Methyl-1-(1-undec-10-enyl-dodec-11-enylcarbamoyl)butyl]carbamic Acid *tert*-Butyl Ester (4b). The pure product **4b** was obtained in 39%[16] yield with a melting point range of 75−76 °C. ^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ 0.84 (m, 6H), 1.05−1.43 (br, 42H), 1.46−1.64 (br, 2H), 1.98 (q, br, 4H), 3.56−3.71 (br, 1H), 3.88 (q, br, 1H), 4.87−5.03 (br, 4H), 5.68−5.85 (m, 2H), 6.70 (d, br, 1H), 7.34 (d, br, 1H). ^{13}C NMR (75 MHz, DMSO-d_6, ppm): δ 25.23, 26.22, 26.27, 28.74, 29.39, 29.59, 29.82, 29.94, 30.02, 30.06, 30.08, 30.13, 30.18, 34.21, 34.27, 35.67, 35.73, 35.77, 35.80, 49.65, 114.51, 139.65, 172.17, 174.63. FTIR (KBr pellet, cm^{-1}): 3336, 3291, 2924, 2854, 1690, 1654, 1526, 1468, 1391, 1368, 1326, 1246, 1175, 1055, 913. Anal. Calcd for $C_{34}H_{64}N_2O_3$: C, 69.43; H, 10.59; N, 7.36. Found: C, 69.38; H, 10.61; N, 7.49. EI/HRMS [M + 1]: Calcd for $C_{34}H_{64}N_2O_3$: 548.4917 g/mol. Found: 548.4995 g/mol.

Synthesis of [(*S*)-1-(1-Pent-4-enyl-hex-5-enylcarbamoyl)ethyl]carbamic Acid *tert*-Butyl Ester (5a). The pure product **5a** was obtained in 76% yield with a melting point range of 77−78 °C. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 1.27−1.69 (br, 20H), 2.05 (q, br, 4H), 3.82−3.95 (br, 1H), 3.99−4.14 (m, 1H), 4.86−5.03 (m, 5H), 5.65−5.83 (m, 2H), 5.88 (d, br, 1H).^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 25.26, 25.30, 28.53, 33.76, 33.78, 34.88, 34.90, 49.18, 114.95, 138.69, 172.38. FTIR (KBr pellet, cm^{-1}): 3340, 3306, 3076, 2981, 2938, 2859, 1688, 1654, 1542, 1522, 1459, 1391, 1370, 1323, 1250, 1167, 1071, 1052, 1031, 999, 910, 856, 754, 701, 674. Anal. Calcd for $C_{19}H_{34}N_2O_3$: C, 67.42; H, 10.12; N, 8.28. Found: C, 67.41; H, 10.17; N, 8.44. EI/HRMS [M + 1]: Calcd for $C_{19}H_{34}N_2O_3$: 338.2569 g/mol. Found: 338.2648 g/mol.

Synthesis of [(*S*)-1-(1-Dec-9-enyl-undec-10-enylcarbamoyl)ethyl]carbamic Acid *tert*-Butyl Ester (5b). The pure product **5b** was obtained in 75% yield with a melting point range of 68−69 °C. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 1.15−1.55 (br, 40H), 2.02 (q, br, 4H), 3.78−3.93 (br, 1H), 4.00−4.18 (br, 1H), 4.88−5.08 (br, 5H), 5.70−5.92 (br, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 26.02, 28.53, 29.13, 29.32, 29.65, 29.67, 29.71, 29.73, 29.77, 29.80, 34.03, 35.48, 49.50, 114.33, 139.45, 172.18. FTIR (KBr pellet, cm^{-1}): 3333, 3301, 2983, 2925, 2854, 1691, 1656, 1549, 1526, 1468, 1391, 1369, 1325, 1268, 1251, 1174, 1069, 1055, 1031, 992, 908, 858, 792, 757, 721, 701, 654. Anal. Calcd for $C_{29}H_{54}N_2O_3$: C, 72.75; H, 11.37; N, 5.85. Found: C, 72.80; H, 11.55; N, 5.85. EI/HRMS [M + 1]: Calcd for $C_{29}H_{54}N_2O_3$: 478.4134 g/mol. Found: 478.4134 g/mol.

Synthesis of [(*S*)-1-(1-Dec-9-enyl-undec-10-enylcarbamoyl)ethyl]carbamic Acid Benzyl Ester (5c). The pure product **5c** was obtained in 74% yield with a melting point range equal of 83−84 °C. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 1.12−1.55 (br, 31H), 2.02 (q, br, 4H), 3.78−3.92 (br, 1H), 4.09−4.25 (m, 1H), 4.84−5.05 (m, 4H), 5.10 (s, 2H), 5.29−5.42 (br, 1H), 5.66 (d, br, 1H), 5.72−5.89 (br, 2H).^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 26.03, 29 (m), 34.03, 35.37, 35.41, 49.66, 50.88, 67.21, 114.35, 128.24, 128.45, 128.78, 139.44, 171.73. FTIR (KBr pellet, cm^{-1}): 32.82, 3081, 2982, 2925, 2854, 1696, 1653, 1557, 1536, 1467, 1323, 1261, 1169, 1072, 1057, 994, 909, 787, 734, 696. Anal. Calcd for $C_{32}H_{52}N_2O_3$: C, 74.95; H, 10.22; N, 5.46. Found: C, 74.91; H, 10.35; N, 5.46. EI/HRMS [M + 1]: Calcd for $C_{32}H_{52}N_2O_3$: 512.3978 g/mol. Found: 512.3978 g/mol.

Synthesis of [(*S*)-1-(1-Undec-10-enyl-dodec-11-enylcarbamoyl)ethyl]carbamic Acid *tert*-Butyl Ester (5d). The pure product **5d** was obtained in 22%[16] yield with a melting point range of 80−81 °C.^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 1.15−1.55 (br, 44H), 2.03 (q, br, 4H), 3.77−3.92 (br, 1H), 4.00−4.16 (br, 1H), 4.89−5.07 (br, 5H), 5.73−5.90 (br, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 26.02, 28.53, 29.16, 29.34, 29.69, 29.77, 34.02, 35.49, 49.51, 114.31, 139.46, 172.16. FTIR (KBr pellet, cm^{-1}): 3332, 3295, 2924, 2854, 1690, 1656, 1549, 1526, 1468, 1391, 1369, 1325, 1248, 1174, 1070, 1054, 913. Anal. Calcd for $C_{31}H_{58}N_2O_3$: C, 73.47; H, 11.54; N, 5.53. Found: C, 73.53; H, 11.60; N, 5.27. EI/HRMS [M + 1]: Calcd for $C_{34}H_{64}N_2O_3$: 506.4447 g/mol. Found: 506.4522 g/mol.

Synthesis of [(*S*)-5-Benzyloxycarbonylamino-5-(1-undec-10-enyl-dodec-11-enylcarbamoyl)pentyl]carbamic Acid Benzyl Ester (6a). The pure product **6a** was obtained in 47%[16] yield with a melting point range of 111−113 °C. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 1.15−1.91 (br, 37H), 1.95−2.13 (br, 1H), 2.23 (q, br, 4H), 3.25−3.44 (br, 2H), 3.96−4.12 (br, 1H), 4.18−4.33 (br, 1H), 4.91−5.07 (br, 1H), 5.08−5.24 (br, 4H), 5.30 (s, br, 4H), 5.56−5.71 (br, 1H), 5.89 (d, br, 1H), 5.93−6.09 (m, 2H), 7.49−7.60 (br, 10H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 22.66, 25.97, 29 (m), 33.91, 34.12, 35.37, 40.41, 49.59, 55.00, 66.71, 114.29, 128 (m), 138.63, 156.49, 171.11. FTIR (KBr pellet, cm^{-1}): 3316, 3278, 2926, 2854, 1691, 1650, 1535, 1467, 1266, 1247, 1153, 1080, 1054, 1024, 911, 696. Anal. Calcd for $C_{45}H_{69}N_3O_5$: C, 73.83; H, 9.50; N, 5.74. Found: C, 73.48; H, 9.59; N, 5.65. EI/HRMS [M + 1]: Calcd for $C_{34}H_{64}N_2O_3$: 731.5237 g/mol. Found: 731.5315 g/mol.

Synthesis of [(*S*)-5-tert-Butoxycarbonylamino-5-(1-undec-10-enyl-dodec-11-enylcarbamoyl)pentyl]carbamic Acid *tert*-Butyl Ester (6b). The pure product **6b** was obtained in 87% yield with a melting point range of 82−84 °C. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): 1.17−1.68 (br, 50H), 1.74−1.92 (m, 2H), 2.05 (q, 4H), 3.10 (q, br, 2H), 3.78−3.91 (br, 1H), 3.97 (q, br, 1H), 4.55−4.66 (br, 1H), 4.86−5.05 (m, 4H), 5.06−5.18 (br, 1H), 5.72−5.89 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 22.91, 26.07, 28.53−29.92 (m), 32.05, 34.03, 35.39, 35.43, 49.53, 114.32, 139.45, 156.35, 172.38. FTIR (KBr pellet, cm^{-1}): 3375, 3342, 3302, 2981, 2926, 2855, 1690, 1653, 1530, 1450, 1391, 1367, 1279, 1250, 1176, 910, 637. Anal. Calcd for $C_{19}H_{34}N_2O_3$: C, 70.54; H, 11.08; N, 6.33. Found: C, 70.57; H, 11.16; N, 6.12. EI/HRMS [M + 1]: Calcd for $C_{19}H_{34}N_2O_3$: 663.5550 g/mol. Found: 663.5628 g/mol.

Synthesis of Thiocarbonic Acid *O*-Benzyl Ester *S*-[2-benzyloxycarbonylamino-2-(1-undec-10-enyl-dodec-11-enylcarbamoyl)ethyl] Ester (7). The pure product **7** was obtained in 29%[16] yield with a melting point range of 129−130 °C. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 1.15−1.54 (br, 32H), 2.07 (q, br, 4H), 3.13−3.38 (m, 2H), 3.79−3.91 (br, 1H), 4.40 (q, br, 1H), 4.88−5.05 (m, 4H), 5.06−5.18 (m, 2H), 5.18−5.29 (m, 2H), 5.68 (d, br, 1H), 5.73−5.89 (m, 2H), 5.93 (d, br, 1H), 7.35 (s, 10H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 26.06, 29 (m), 33.50, 34.04, 35.24, 49.96, 55.59, 67.46, 69.79, 114.35, 128 (m), 135.03, 136.33, 139.44, 156.52, 169.29, 171.72. FTIR (KBr pellet, cm^{-1}): 3278, 2923, 2853, 1712, 1693, 1650, 1561, 1534, 1276, 1241, 1159, 1047, 994, 908, 746, 697. Anal. Calcd for $C_{42}H_{62}N_2O_5S$: C, 71.35; H, 8.84; N, 3.96. Found: C, 71.20; H, 8.83; N, 3.90. EI/HRMS [M + 1]: Calcd for $C_{42}H_{62}N_2O_5S$: 706.4379 g/mol. Found: 706.4458 g/mol.

Synthesis of {(*S*)-1-[(*S*)-2-Methyl-1-(1-undec-10-enyl-dodec-11-enylcarbamoyl)propylcarbamoyl]ethyl}-carbamic Acid Benzyl Ester (8). The pure product **8** was obtained in 46%[16] yield with a melting point range of 135−136 °C. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 0.912 (m, 6H), 1.06−1.55 (br, 33H), 2.02 (q, br, 4H), 2.31−2.57 (br, 2H), 3.47 (q, br, 2H), 3.75−3.93 (br, 1H), 4.15 (t, 1H), 4.86−5.15 (br, 6H), 5.45−5.57 (m, br, 1H), 5.67−5.89 (br, 3H), 6.46 (d, br, 1H), 7.33 (s, br, 5H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 18.48, 19.50, 26.10, 29 (m), 31.32, 34.01, 35.13, 35.31, 36.23, 37.50, 49.77, 59.16, 66.18, 114.33, 128.19, 128.24, 128.68, 136.81, 139.40, 170.70. FTIR (KBr pellet, cm^{-1}): 3280, 3080, 2926, 2854, 1690, 1638, 1542, 1468, 1386, 1272, 1151, 1024, 994, 911, 723, 696. Anal. Calcd for $C_{36}H_{67}N_3O_4$: C, 73.20; H, 10.24; N, 6.57. Found: C, 73.05; H, 10.28; N, 6.30. EI/HRMS [M + 1]: Calcd for $C_{39}H_{65}N_3O_4$: 639.4975 g/mol. Found: 639.5053 g/mol.

Synthesis of {(*S*)-3-Methyl-1-[(*S*)3-methyl-1-(1-undec-10-enyl-dodec-11-enylcarbamoyl)butylcarbamoyl]butyl}-carbamic Acid Benzyl Ester (9). The pure product **9** was obtained in 95% yield with a melting point range of 68−71 °C. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 0.917 (m, 12H), 1.17−

1.79 (br, 47H), 2.03 (q, 4H), 3.75−3.91 (br, 1H), 3.97−4.14 (br, 1H), 4.31−4.43 (m, 1H), 4.86−5.04 (br, 5H), 5.72−5.89 (m, 2H), 5.97−6.10 (br, 1H), 6.47−6.62 (br, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 22.70, 23.14, 24.98, 26.03, 26.11, 28.49, 29 (m), 34.03, 35.18, 35.45, 41.07, 49.58, 52.22, 53.49, 114.31, 139.45, 171.24, 172.67. FTIR (KBr pellet, cm^{-1}): 3290, 3080, 2926, 2854, 1693, 1646, 1532, 1468, 1438, 1391, 1368, 1324, 1292, 1270, 1241, 1175, 1121, 1052, 1021, 993, 966, 912, 875, 792, 747, 720, 667, 570. Anal. Calcd for $C_{40}H_{75}N_3O_4$: C, 72.57; H, 11.42; N, 6.35. Found: C, 72.30; H, 11.61; N, 6.02. EI/HRMS [M + 1]: Calcd for $C_{40}H_{75}N_3O_4$: 661.5758 g/mol. Found: 661.5835 g/mol.

Polymer Synthesis. General Synthesis. The monomer was added to a 50 or 100 mL Schlenk tube equipped with a stir bar and a glass stopcock and dried by heating the vessel in an oil bath at 50 °C under full vacuum (10^{-3} mmHg) for 24 h. After 24 h the reaction vessel was backfilled with Ar, and the second-generation Grubbs' Ru catalyst (100:1/monomer: catalyst) was added, while maintaining a positive Ar flow throughout the system. A septum was placed in the top of the vessel equipped with a syringe needle to allow the Ar to flow through the system and out through a bubbler. A minimal amount of dry THF, just enough to dissolve the polymer, was added via syringe, and the reaction mixture was allowed to stir for 120 h. Dry THF was added periodically, due to the loss of THF by evaporation, as to keep the polymer in solution. Solution ADMET is difficult to monitor because the ethylene released is not as easily observed as in the case for bulk ADMET polymerizations. After 120 h, the reaction was sampled and tested for total conversion by ^{1}H NMR (monitoring terminal olefin disappearance). If incomplete conversion was observed, the mixture was stirred for an additional 48 h. Once it was evident that the polymerization had reached high conversion, the mixture was dissolved in THF or $CHCl_3$ and precipitated into cold methanol, unless otherwise noted. The polymers were then dissolved and solvent cast onto a Teflon plate to yield a thin film.

Characterization of 10b. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 0.77−0.95 (br, 6H), 1.03−1.50 (br, 42H), 1.51−1.69 (br, 2H), 1.80−2.01 (br, 4H), 3.71−3.87 (br, 1H), 3.88−4.05 (br, 1H), 4.79−5.10 (br, 1H), 5.19−5.30 (br, 2H), 5.72−6.06 (br, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 22.48, 23.05, 24.88, 28.43, 28.88−31.88 (m), 32.87, 35.48, 41.27, 49.36, 49.57, 130.55, 155.99, 172.11. FTIR (KBr pellet, cm^{-1}): 3285, 2976, 2955, 2854, 1689, 1649, 1526, 1465, 1456, 1437, 1391, 1366, 1320, 1289, 1249, 1174, 1119, 1046, 1023, 967, 921, 875, 800, 721.

Characterization of 11b. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 1.09−1.58 (br, 40H), 1.84−2.07 (br, 4H), 3.78−3.94 (br, 1H), 4.06−4.26 (br, 1H), 5.25−5.52 (br, 3H), 6.06−6.34 (br, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 18.74, 26.07, 27.40, 28.53, 29 (m), 32.78, 35.14, 35.50, 49.46, 50.36, 79.95, 130.53, 155.75, 172.33. FTIR (KBr pellet, cm^{-1}): 3424, 3328, 3055, 2984, 2931, 2856, 1705, 1669, 1519, 1497, 1455, 1425, 1392, 1368, 1324, 1266, 1167, 1094, 1067, 1027, 971, 897, 855, 744, 705.

Characterization of 11c. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 0.96−1.61 (br, 31H), 1.81−2.09 (br, 4H), 3.70−3.95 (br, 1H), 4.12−4.40 (br, 1H), 5.09 (s, br, 2H), 5.25−5.45 (br, 2H), 5.65−5.92 (br, 1H), 6.08−6.44 (br, 1H), 7.34 (br, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 19.38, 26.11, 29 (m), 32.84, 35.33, 35.45, 49.62, 50.84, 67.03, 128.11, 128.37, 128.74, 130.13, 130.59, 136.46, 156.20, 172.06. FTIR (KBr pellet, cm^{-1}): 3422, 3341, 3056, 2988, 2930, 2857, 1718, 1673, 1503, 1454, 1423, 1266, 1068, 972, 897, 743, 705.

Characterization of 11d. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 0.99−1.61 (br, 44H), 1.48−2.07 (br, 4H), 3.72−3.91 (br, 1H), 3.98−4.19 (br, 1H), 5.02−5.25 (br, 1H), 5.26−5.43 (br, 2H), 5.84−6.13 (br, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 18.70, 26.07, 28.54, 29 (m), 32.81, 35.49, 49.51, 130.55, 172.33. FTIR (KBr pellet, cm^{-1}): 3425, 3056, 2986, 2930, 2857, 1707, 1673, 1497, 1456, 1423, 1369, 1265, 1167, 1024, 897, 740, 705.

Characterization of 12a. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 0.96−1.71 (br, 37H), 1.73−2.05 (br, 5H), 3.01−3.23 (br, 2H), 3.72−3.93 (br, 1H), 3.99−4.19 (br, 1H), 4.79−5.17 (br, 5H), 5.22−5.44 (br, 2H), 5.47−5.75 (br, 1H), 5.78−6.15 (br, 1H), 7.31 (s, 10H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 22.62, 26.12, 29 (m), 32.38, 32.82, 35.30, 40.53, 49.67, 55.16, 66.84, 67.20, 128.27, 128.72, 130.57, 136.41, 156.84, 171.33. FTIR (KBr pellet, cm^{-1}): 3423, 3314, 3057, 2989, 2930, 2856, 1719, 1685, 1648, 1519, 1456, 1423, 1266, 1137, 1028, 973, 897, 742, 704.

Characterization of 12b. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 1.02−1.70 (br, 50H), 1.71−2.22 (m, 6H), 2.97−3.19 (br, 2H), 3.75−3.91 (br, 1H), 3.90−4.07 (br, 1H), 4.59−4.71 (br, 1H), 5.10−5.48 (br, 3H), 5.91−6.19 (br, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 22.91, 26.09, 27.43, 28.53, 28.65, 29 (m), 32.06, 32.11, 32.81, 35.43, 40.06, 49.54, 79.30, 80.09, 130.07, 130.52, 156.00, 156.36, 171.77. FTIR (KBr pellet, cm^{-1}): 3426, 3334, 3056, 2985, 2930, 2857, 1708, 1673, 1510, 1457, 1424, 1393, 1368, 1267, 1171, 1047, 1021, 971, 897, 864, 743, 705.

Characterization of 13. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 1.00−1.91 (br, 32H), 2.01−2.36 (br, 4H), 3.27−3.66 (m, 2H), 3.93−4.18 (br, 1H), 4.48−4.77 (br, 1H), 5.30 (s, br, 2H), 5.42 (s, br, 2H), 5.50−5.71 (br, 2H), 5.97−6.23 (br, 1H), 6.25−6.59 (br, 1H), 7.53 (s, br, 10H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 26.09, 29 (m), 32.87, 35.27, 49.97, 67.45, 69.81, 128 (m), 130.57, 135.01, 136.28, 139.44, 169.28, 171.70. FTIR (KBr pellet, cm^{-1}): 3414, 2397, 3056, 2988, 2929, 2856, 1716, 1677, 1504, 1457, 1423, 1266, 1146, 1048, 971, 897, 740, 705.

Characterization of 14. ^{1}H NMR (300 MHz, DMSO-d_6, 140 °C, ppm): δ 0.78−0.98 (br, 6H), 1.13−1.54 (br, 33H), 2.83−2.11 (br, 4H), 2.31−2.46 (br, 2H), 3.20−3.38 (br, 2H), 3.57−3.81 (br, 1H), 4.06−4.23 (br, 1H), 5.04 (s, br, 2H), 5.27−5.47 (br, 2H), 6.46−6.66 (br, 1H), 7.01−7.13 (br, 1H), 7.33 (s, br, 5H). ^{13}C NMR (75 MHz, DMSO-d_6, ppm): No spectra were obtained due to only partial solubility of the polymer in hot DMSO-d_6. FTIR (KBr pellet, cm^{-1}): 3575, 3506, 3300, 2975, 2856, 1726, 1654, 1535, 1460, 1365, 1241, 1070, 911.

Characterization of 15. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 0.75−1.02 (br, 12H), 1.03−1.77 (br, 47H), 1.84−2.06 (br, 4H), 3.73−3.91 (br, 1H), 3.98−4.24 (br, 1H), 4.28−4.53 (m, 1H), 4.98−5.53 (br, 3H), 6.08−6.58 (br, 2H), 6.66−7.14 (br, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 18.15, 22.45, 23.08, 23.16, 24.98, 26.07, 27.04, 27.43, 28.53, 29 (m), 30.54, 32.83, 35.14, 35.45, 41.25, 49.58, 52.27, 53.44, 80.27, 124.73, 125.74, 130.10, 130.55, 155.98, 171.39, 172.80. FTIR (KBr pellet, cm^{-1}): 3422, 2397, 3056, 2928, 2857, 1694, 1645, 1521, 1465, 1441, 1391, 1368, 1266, 1169, 1120, 1047, 1023, 970, 897, 874, 743, 706.

Results and Discussion

Monomer Synthesis. The synthesis of the amino acid and dipeptide branched dienes needed for this research is easily accomplished using standard peptide coupling chemistry to attach amino acid or peptide functionality to amine branched dienes. The amine branched dienes **3a** and **3b** were prepared in three steps, giving an overall yield of up to 73% (Figure 1). The synthesis was achieved without strenuous purification of the intermediates—only simple acid/base extractions were performed. Alcohols **1a** and **1b** were prepared by the Grignard reaction of 5-bromo-1-pentene and 11-bromo-1-undecene, respectively, with ethyl formate.

Oxidation of **1a** and **1b** with pyridinium chlorochromate (PCC) gives the ketones **2a** and **2b**, respectively, in nearly quantitative yields, which can be subjected to reductive amination using ammonium acetate as the amine source, sodium cyanoborohydride as the reducing agent, and crushed molecular sieves to help drive the reaction to completion to give **3a** and **3b**. Purification by flash chromatography using a 3:1:1 ethyl acetate: hexanes:methanol mobile phase yielded the pure amines. An alternative and faster purification was achieved by placing the crude amine on a silica gel plug, followed by successive washing with 3:1 hexane:ethyl acetate until no starting materials were detected by TLC. Methanol was then used to remove the pure amines **3a** and **3b** from the silica gel, and the structures were

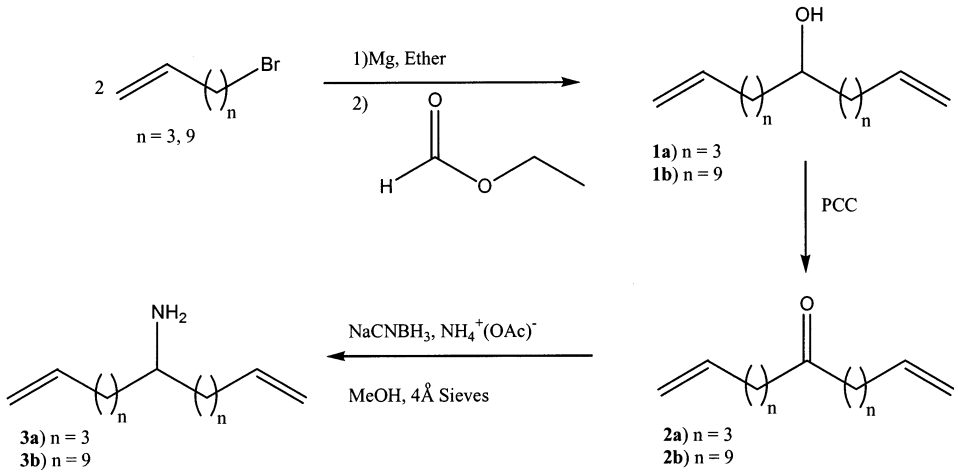

Figure 1. Synthesis of the amine branched dienes **3a** and **3b**.

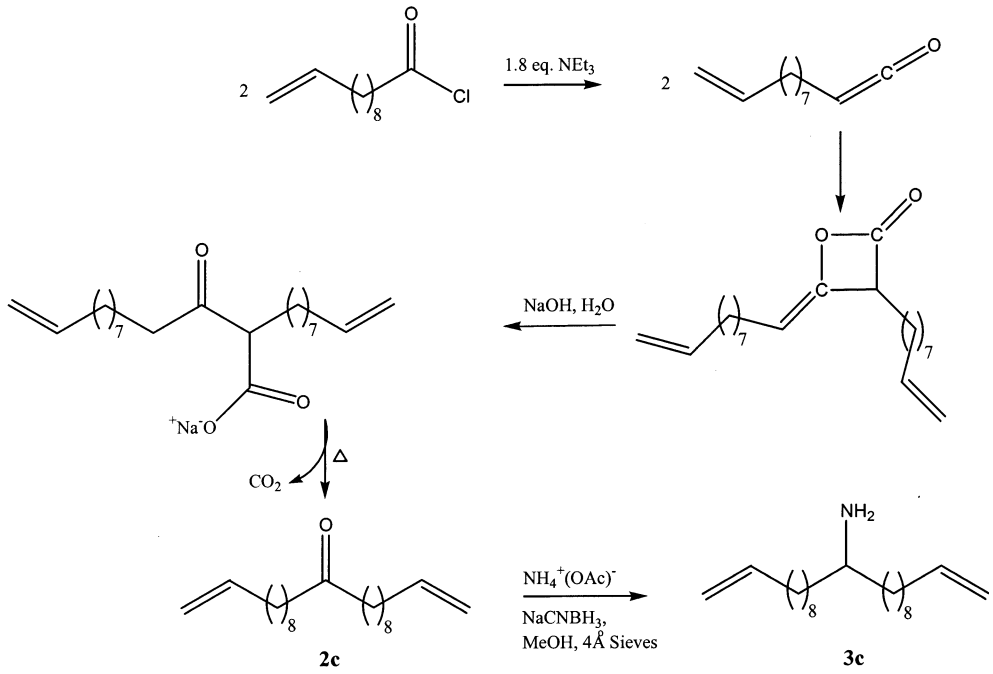

Figure 2. Previously published mechanism of ketone **2c**[15] and synthesis of the amine branched diene **3c**.

verified by ^{1}H NMR and ^{13}C NMR. This quick purification technique was possible because of the vast differences in polarity between the starting materials and the final product. Similar yields were achieved for both methods; however, lower yields were achieved for **3b** than for **3a**, which could be attributed to steric differences.

The amine **3c** was not synthesized by the method described for **3a** and **3b** due to the lack of readily available starting material 10-bromo-1-decene. For this reason Watson et al.[17] and Zantour et al.[15] have published different syntheses for the ketone **2c** from derivatives of the inexpensive starting material 10-undecenoic acid. Watson's method involves the Claisen condensation reaction of ethyl 10-undecenoate, followed by dealkoxycarbonylation to give **2c** in moderate yields with difficult purification.[17] In Zantour's method, 10-undecenoyl chloride is reacted with 1.8 equiv of triethylamine to form a ketene, followed by the ketene coupling reaction to form the intermediate β-lactone (Figure 2). Refluxing the intermediate in a sodium hydroxide solution opens the lactone, allowing decarboxylation to occur forming the ketone **2c** in high yields (82%) with easy purification (Figure 2).[15] The ketone **2c** is then converted to the amine **3c** using the same methodology employed for the synthesis of amines **3a** and **3b** for an overall yield of 52%.

All of the amino acid branched dienes were prepared using simple textbook peptide coupling chemistry (Figure 3). The three-spacer BOC-L-leucine branched diene (**4a**) and the three-spacer BOC-L-alanine branched diene (**5a**) were synthesized by coupling **3a** with the corresponding BOC-protected amino acids by the standard peptide coupling method using the 1-hydroxybenzatriazole (HOBt)/1,3-diisopropylcarbodiimide (DIC) method. Purification was achieved by three successive recrystallizations from CH_3OH/water, yielding the pure products **4a** and **5a** in 78% and 76%, respectively.

The nine-spacer di-CBz-L-lysine branched diene (**6a**) and the nine-spacer di-CBz-L-cysteine branched diene (**7**) were prepared by coupling **3b** with the corresponding CBz-protected amino acid using the HOBt/DIC method and purified by the recrystallization method described above to yield **6** in 47% and **7** in 29%. The nine-spacer BOC-L-alanine branched diene (**5b**), nine-spacer BOC-L-leucine branched diene (**4b**), and nine-spacer BOC-L-

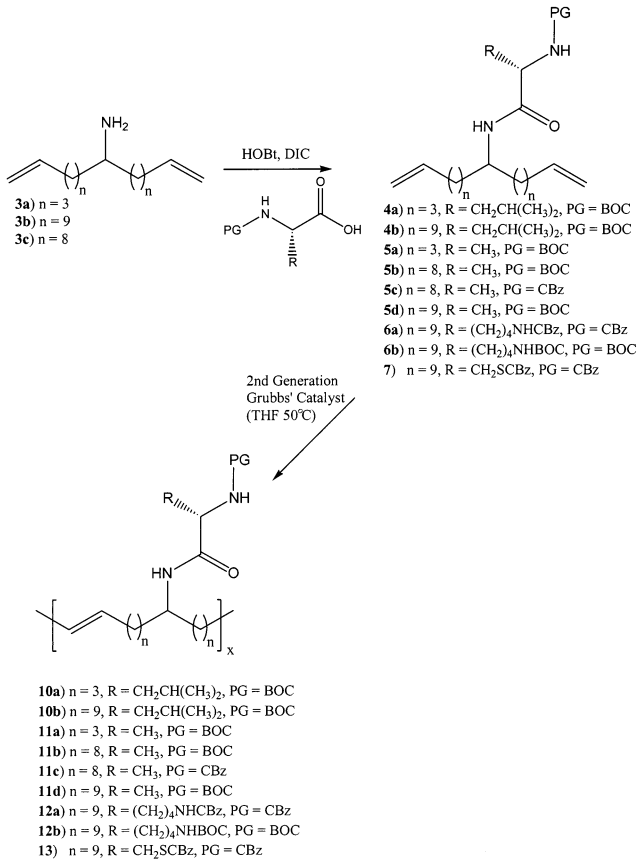

Figure 3. Synthesis and polymerization of the amino acid branched dienes.

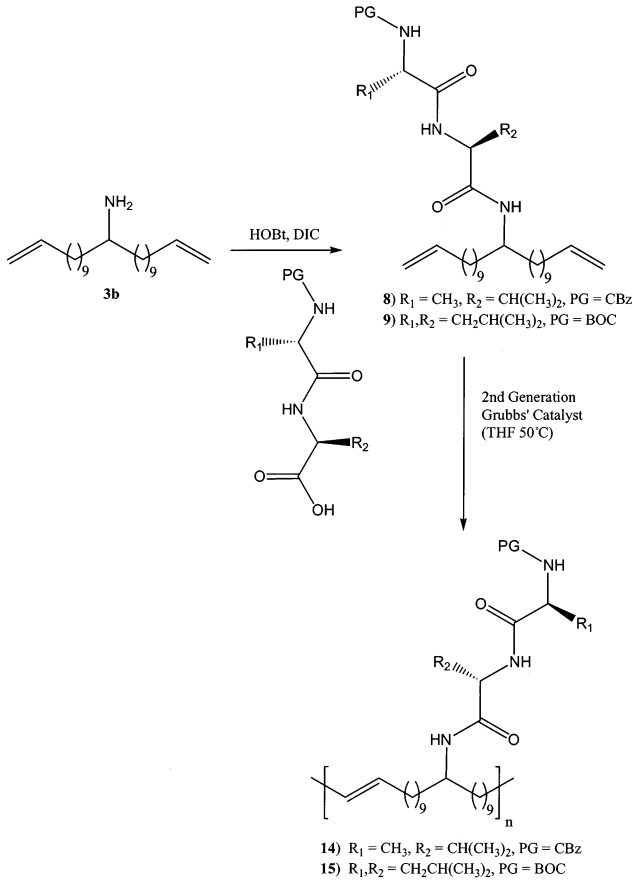

Figure 4. Synthesis and polymerization of the dipeptide branched dienes.

lysine branched diene (**6b**) were prepared by coupling the BOC-protected amino acids with **3b** using the HOBt/DIC method and purified as described above to give the pure dienes in 22% for **5d**, 39% for **4b**, and 87% for **6b**. The BOC- and CBz-protected eight-spacer L-alanine branched dienes (**5b** and **5c**) were prepared by reacting the corresponding protected amino acids with **3c** using the above methodology to yield the pure monomers **5b** and **5c** in 75% and 74%, respectively. The dipeptide branched dienes **8** and **9** were prepared by coupling the protected dipeptides with **3b** using the HOBt/DIC coupling method and purified as described above, yielding 46% and 95% for **8** and **9**, respectively (Figure 4).

Some observations were made during the synthesis of the monomers. It appears that a longer reaction time (up to 48 h for the protected dipeptides), performing the reaction at THF reflux conditions, and using 2.5 equiv of HOBt gave the best reaction yields. Also, CH_2Cl_2, $CHCl_3$, and THF were used as solvents for the amino acid synthesis, but the latter was used preferably due to the ease of availability of the pure dry solvent in our laboratory,[18] the high yields obtained, and the increased solubility of the HOBT and amino acids/dipeptides in this solvent. Purification was best achieved by filtration of the insoluble urea and evaporation of the solvent, followed by three recrystallizations from ethanol/water or methanol/water depending on the mp of the monomers. It was found that three recrystallizations resulted in pure compounds by elemental analysis, NMR, and HRMS; moreover, the yields were improved if extractions were not performed to remove the HOBt and soluble urea due to emulsions that formed during the extraction process.

Table 1. [a]

polymer	$\bar{M}_n$[a] (g/mol)	PDI[a]	T_m[b] (°C)	T_g[b] (°C)
10b	20 000	1.96	*c*	34
11b	37 000	1.85	*c*	7
11c	21 000	1.89	46[e]	*d*
11d	13 000	2.11	*c*	18
12a	25 000	1.92	96	*d*
12b	11 000	1.92	60	*d*
13	14 000	1.76	110	*d*
14	12 000	2.61	150	*d*
15	7 500	1.78	*c*	40

[a] $\bar{M}_n$ values were calculated by GPC vs polystyrene standards. [b] Data obtained using a Perkin-Elmer DSC 7. [c] No T_m observed over the scanned range of −80 to 190 °C. [d] No T_g observed over the scanned range of −80 to 190 °C. [e] The T_m reported is that of the solvent crystallized sample; no T_m was observed from the melt crystallized sample.

Polymer Synthesis. ADMET is a simple condensation polymerization that allows for precise branch and/or functionality placement along the polymer backbone by monomer design. ADMET is commonly performed in the bulk; however, since the monomers were all solids, the polymerization methodology chosen was that previously published using a small amount of solvent with an argon purge to aid in the removal of ethylene.[13]

There appears to be a solvent effect associated with this chemistry. For instance, when monomer **6a** was polymerized using $CHCl_3$ as the solvent only oligomeric products were observed, whereas the monomer was successfully polymerized to **12a** ($\bar{M}_n$ of 25 000 g/mol) using THF as the solvent (Table 1). The low conversion in $CHCl_3$ is likely due to complexation of the catalyst to the amino acid functionality of the dienes;[13,19] there-

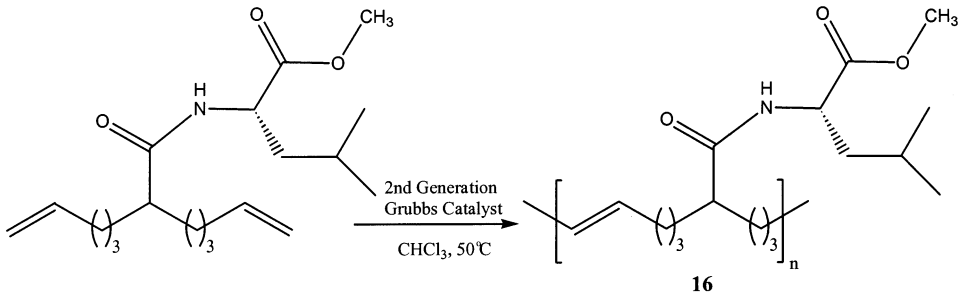

Figure 5. Synthesis of the previously published polymer **16**.[13]

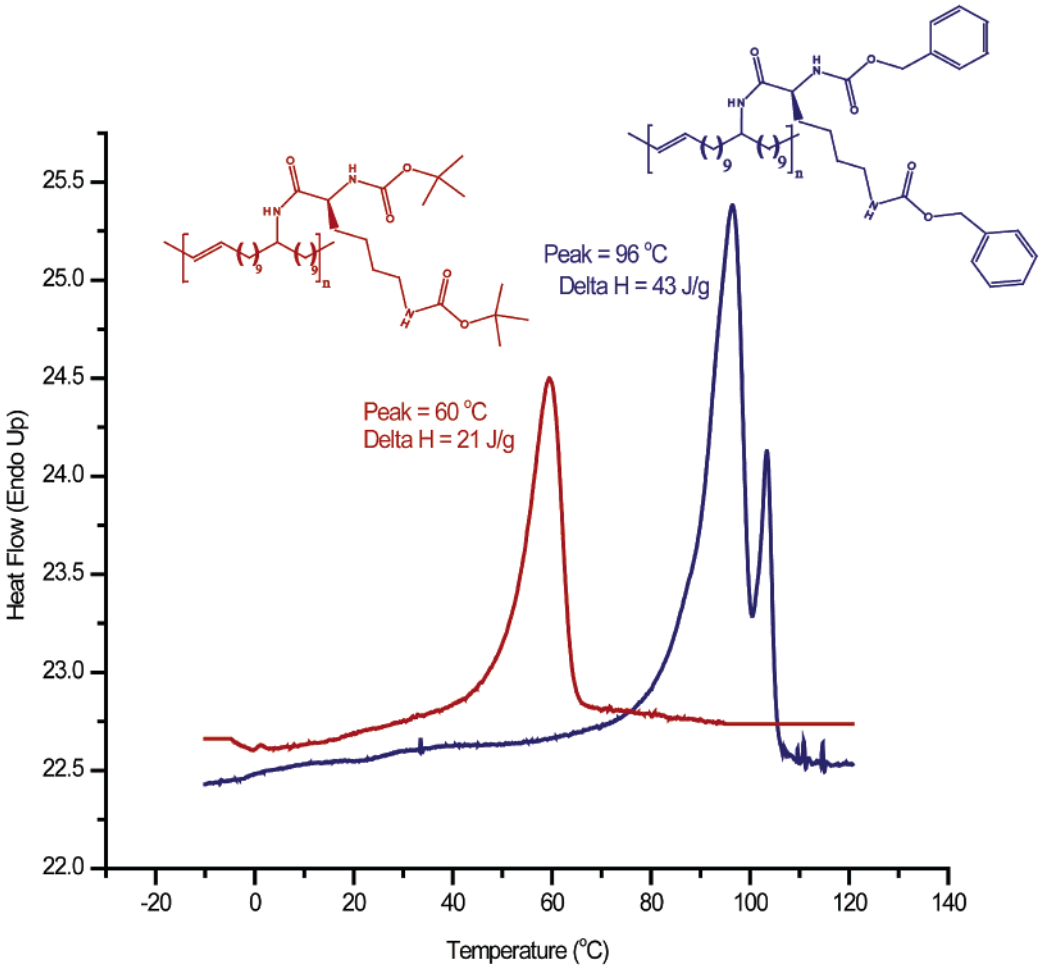

Figure 6. Comparison of the melt transitions of polymers **12a** and **12b**.

fore, THF appears to prevent complexation between the monomer and catalyst. This is the first known example of THF being used as a solvent for ADMET polymerization. As shown in Table 1, monomers **4b**, **5b**, **5c**, **5d**, and **6b** were successfully polymerized using this methodology to form polymers **10b**, **11b**, **11c**, **11d**, and **12b** with M_n's equal to 21 000, 37 000, 21 000, 13 000, and 11 000, respectively (Table 1). Further, no terminal olefin resonances were observed in the ^{1}H NMR for these polymers, which is a phenomenon observed for high molecular weight ADMET polymers.

To compare these polymers with those reported in a previous communication,[13] monomers **4a** and **5a** with three methylene spacers between the olefin and the amino acid branch were synthesized. The three-spacer-L-leucine methyl ester branched diene **16**, which was reported previously, was successfully polymerized using $CHCl_3$ as the solvent (Figure 5); however, the polymerization of **4a** in THF and **5a** in THF or $CHCl_3$ resulted in only oligomer formation in all cases. One major difference is evident when comparing these monomers: the location of the amine and carbonyl group relative to the diene. We reported previously that the amide carbonyl prevented or limited the polymerization of linear amino alcohol containing dienes when the carbonyl was two or three carbons from the diene, which was due to intermolecular complexation of the nucleophilic amide carbonyl with the catalyst.[13] In this case, we believe the molecular orientation of monomers **4a** and **5a** also allows for complexation to occur between the monomer functionality and catalyst, resulting in only oligomer formation.

Monomer **7**, bearing a cysteine branch, has a CBz protected sulfur—a functional group never before polymerized by ADMET. This amino acid was of particular interest since the unprotected sulfur could be used to

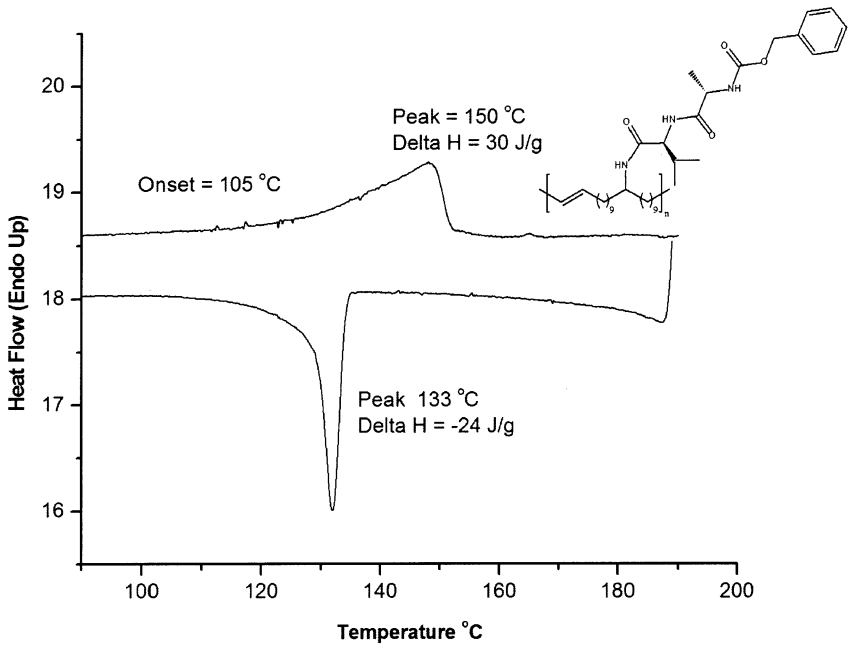

Figure 7. DSC trace of polymer **14**.

make cross-linked materials.[20] The monomer was successfully polymerized to yield **13** with a $\bar{M}_n$ of 14 000 g/mol.

The successful polymerization of dipeptide branched monomers will lead toward the synthesis of monomers bearing longer peptides, which could have specific biological properties. Therefore, we attempted to polymerize the dipeptide monomer **8** to polymer **14** using THF as the solvent. The polymer was relatively insoluble in THF; however, stirring 10 mg in 2 mL of THF overnight allowed for successful GPC molecular weight determination (12 000 g/mol).[21] Polymerization of the dipeptide monomer **9** yielded **15**, which was shown to be a high polymer by the lack of terminal olefin resonances in the ^{1}H NMR spectrum and had a GPC molecular weight of 7500 g/mol.[22] Polymer **15** could not be purified by precipitation in cold methanol, since it was slightly soluble in methanol and could not be precipitated even with the addition of water. Purification was achieved instead by dissolving the polymer in CH_2Cl_2 and adding 25 equiv of 1 M tris(hydroxymethyl)-phophine (THP) in isopropyl alcohol, a procedure which removes catalyst residues.[23]

Thermal Characterization. Differential scanning calorimetry (DSC) measurements were completed to determine whether the samples were amorphous or semicrystalline in nature. The BOC-protected polymers **10b**, **11b**, and **11d** are amorphous with glass transitions at 34, 7, and 18 °C, respectively, where the lack of crystallinity likely is due to the presence of the bulky BOC protecting groups. Polymers **11c** and **12a** each possess CBz protecting groups and are semicrystalline with melting points of 46 and 96 °C, respectively. Surprisingly, polymer **12b**, which has two BOC protecting groups per repeat unit, also is semicrystalline with a T_m of 60 °C. Why is polymer **12b** semicrystalline? We expected an amorphous polymer, as is the case for the analogous polymers **10b**, **11b**, and **11d**, since the presence of two BOC protecting groups per repeat unit in **12b** should inhibit crystallization. This unexpected crystallinity could be explained by the added polarity of the amino acid branch in polymer **12b**, which has two hydrogen-bonding sites per repeat unit. Figure 6 compares the DSC spectra for polymers **12a** and **12b**, which differ only in protecting group strategy. These DSC spectra demonstrate that although the BOC protecting groups do not prevent crystallization, they do affect the thermal properties of the resulting polymers. The possibility that polarity of the side branch has an impact on the semicrystalline nature of the polymer is further supported by the analysis of the cysteine branched polymer **13**, which is semicrystalline with a T_m of 110 °C.

The dipeptide branched polymers **14** and **15**, having a CBz-protected alanine−valine branch and a BOC-protected leucine−leucine branch, respectively, were also analyzed. Polymer **14** is semicrystalline with a T_m value of 150 °C (Figure 7), whereas polymer **15** is amorphous with a T_g of 40 °C. Interestingly, the T_g found for polymer **15** is similar to that found for the single BOC-protected leucine branched polymer **10b**. The differences in crystallinity can be explained not only by the difference in protecting groups but also by the relatively small alkyl branches, methyl and isopropyl, on the dipeptide of polymer **14**, which should have a smaller effect on the crystallization than the two isobutyl branches on the leucine moieties of polymer **15**.

As is evident by the DSC study, both the nature of the protecting group and the polarity of the amino acid or peptide functionality appear to influence the crystallinity and the T_m of the resulting polymers. The differences in the percentage of mass composition of the amino acid vs polymer backbone, as well as the high T_m values obtained for some of the polymers, demonstrate that it is indeed the amino acid or peptide functionality that is responsible for the semicrystallinity we observe.

Conclusions

Amino acid and dipeptide funtionalized polyolefins have been prepared by ADMET polymerization from monomers synthesized in high yields using simple peptide coupling chemistry. The resulting polymers have T_m values of up to 150 °C, which could lend them

useful for possible biomedical applications, and the crystallinity of the polymers is due to the amino acid or peptide functionality and not the polyolefin backbone. Also, the polarity of the amino acid or peptide branch appears to greatly affect the crystallinity of the sample as well as the T_m values; the higher the polarity of the amino acid or peptide branch, the higher the crystallinity and the higher the T_m.

We believe the ability to use ADMET to polymerize amino acid and peptide containing monomers could lead toward the synthesis of designer biomaterials for specific biological applications. This methodology has the advantage that the amount of functionality as well as the placement of the branch can be completely controlled by either monomer synthesis or simple copolymerization.

Acknowledgment. We thank the National Science Foundation, Division of Materials Research, and the Army Research Office for financial support of this work. We would like to thank Dr. Ravi Orugunty, Mr. Claud Robotham, Prof. Jean M. J. Fréchet, Prof. Dennis Wright, Prof. Eric Enholm, and Dr. James H. Pawlow for helpful comments and discussions during the course of this work. We acknowledge Mr. Brian Cuevas, Mr. Clay Bohn, Prof. Anthony Brennan, and Prof. Eugene Goldberg for help in obtaining initial material property data. We acknowledge Dr. Jason Smith for his help in obtaining thermoanalysis data for the polymers discussed and Mr. John Sworen for his help in the preparation of this manuscript and for helpful discussions during the course of this work. Finally, we are grateful to Dr. Richard Pederson of Materia, Inc., for providing the THP solution required for removal of the catalyst from polymer **15**.

References and Notes

(1) Murata, H.; Sanda, F.; Endo, T. *J. Polym. Sci., Part A: Polym. Chem.* **1998**, *36*, 1679.
(2) Sanda, F.; Endo, T. *Macromol. Chem. Phys.* **1999**, *200*, 2651.
(3) (a) Methenitis, C.; Morcellet, J.; Morcellet, M. *Polym. Bull. (Berlin)* **1984**, *181*, 485. (b) Methenitis, C.; Morcellet, J.; Morcellet, M. *Polym. Bull. (Berlin)* **1984**, *12*, 141.
(4) Pino, P. *Adv. Polym. Sci.* **1965**, *4*, 393.
(5) (a) Murata, H.; Sanda, F.; Endo, T. *Macromolecules* **1996**, *29*, 5535. (b) Katakai, R.; Nakayama, Y. *J. Chem. Soc., Chem. Commun.* **1977**, *22*, 805. (c) Murata, H.; Sanda, F.; Endo, T. *Macromolecules* **1997**, *30*, 2902. (d) Sanda, F.; Ogawa, F.; Endo, T. *Polymer* **1998**, *39*, 5543. (e) Sanda, F.; Kamatani, J.; Handa, H.; Endo, T. *Macromolecules* **1999**, *32*, 2490. (f) Kudo, H.; Sanda, F.; Endo, T. *Macromol. Chem. Phys.* **1999**, *200*, 1232.
(6) (a) Murata, H.; Sanda, F.; Endo, T. *Macromolecules* **1996**, *29*, 5535. (b) Murata, H.; Sanda, F.; Endo, T. *Macromolecules* **1997**, *30*, 2902.
(7) (a) Bush, S. M.; North, M. *Polymer* **1996**, *37*, 4649. (b) Bush, S. M.; North, M. *Polymer* **1998**, *39*, 2991. (c) Bush, S. M.; North, M.; Sellarjah, S. *Polymer* **1998**, *39*, 2991.
(8) Birchall, A. C.; Bush, S. M.; North, M. *Polymer* **2001**, *42*, 375.
(9) (a) Maynard, H. D.; Okada, S. Y.; Grubbs, R. H. *Macromolecules* **2000**, *33*, 6239. (b) Maynard, H. D.; Grubbs, R. H. *Macromolecules* **1999**, *32*, 6917.
(10) Biagini, S. C. G.; Davies, R. G.; Gibson, V. C.; Giles, M. R.; Marshall, E. L.; North, M. *Polymer* **2001**, *42*, 6669.
(11) Maynard, H. D.; Okada, S. Y.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 1275.
(12) (a) Lindmark-Hamburg, M.; Wagener, K. B. *Macromolecules* **1987**, *20*, 2949. (b) Wagener, K. B.; Nel, J. G.; Konzelman, J.; Boncella, J. M. *Macromolecules* **1990**, *23*, 5155. (c) Smith, J. A.; Brzezinska, K. R.; Valenti, D. J.; Wagener, K. B. *Macromolecules* **2000**, *33*, 3781. (d) Watson, M. D.; Wagener, K. B. *Macromolecules* **2000**, *33*, 8963. (e) Watson, M. D.; Wagener, K. B. *Macromolecules* **2000**, *33*, 5411.
(13) (a) Hopkins, T. E.; Pawlow, J. H.; Deters, K. S.; Solivan, S. M.; Davis, J. A.; Koren, D. L.; Gómez, F. J.; Wagener, K. B. *Macromolecules* **2001**, *34*, 7920. (b) Hopkins, T. E.; Pawlow, J. H.; Tep, F.; Wagener, K. B. *Polym. Prepr.* **2002**, *43*, 281.
(14) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953.
(15) Zantour, H.; Pousse, A.; Brini, M. *Bull. Chim. Fr.* **1972**, *12*, 4715.
(16) The reaction conditions were not optimized to obtain the best yield for this reaction, i.e., longer reaction times and reflux temperatures.
(17) Watson, M. D.; Wagener, K. B. *Macromolecules* **2000**, *33*, 3196.
(18) The THF was used directly from the Aldrich Keg system.
(19) (a) Ghosh, A. K.; Cappiello, J.; Shin, D. *Tetrahedron Lett.* **1998**, *39*, 4651. (b) Choi, T. L.; Chatterjee, A. K.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **2001**, *40*, 1277. (c) Wright, D. *Curr. Org. Chem.* **1999**, *3*, 211. (d) Furstner, A.; Langemann, K. *J. Am. Chem. Soc.* **1997**, *119*, 9130. (e) Patton, J. T.; Boncella, J. M.; Wagener, K. B. *Macromolecules* **1992**, *25*, 3862.
(20) Kudo, H.; Sanda, F.; Endo, T. *Macromol. Chem. Phys.* **1999**, *200*, 1232.
(21) Since the polymer was insoluble in $CHCl_3$ and THF, we were unable to perform molecular weight determination by GPC analysis.
(22) GPC data gave a $\bar{M}_n$ of 6500 g/mol; however, initial studies using light scattering on polymer **11c** suggest that this number was off by a factor of 3. Therefore, we believe GPC is not an accurate measure of molecular weight for these systems including polymer **15**.
(23) Maynard, H. D.; Grubbs, R. H. *Tetrahedron Lett.* **1999**, *40*, 4137. Procedure modified by Richard Pederson of Materia, Inc.

MA021668W