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ARTICLE

Rapid, Selective, and Reversible Nitroxide Radical Coupling (NRC) Reactions at Ambient Temperature

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ABSTRACT: High activation of polystyrene with bromine end groups (PSTY-Br) to their incipient radicals occurred in the presence of Cu(I)Br, Me_6TREN, and DMSO solvent. These radicals were then trapped by nitroxide species leading to coupling reactions between PSTY-Br and nitroxides that were ultrafast and selective in the presence of a diverse range of functional groups. The nitroxide radical coupling (NRC) reactions have the attributes of a "click" reaction with near quantitative yields of product formed, but through the reversibility of this reaction, it has the added advantage of permitting the exchange of chemical functionality on macromolecules. Conditions were chosen to facilitate the disproportionation of Cu(I)Br to the highly activating nascent Cu(0) and deactivating Cu(II)Br_2 in the presence of DMSO solvent and Me_6TREN ligand. NRC at room temperature gave near quantitative yields of macromolecular coupling of low molecular weight polystyrene with bromine chain-ends (PSTY-Br) and nitroxides in under 7 min even in the presence of functional groups (e.g., $-\equiv$, $-$OH, $-$COOH, $-NH_2$, $=$O). Utilization of the reversibility of the NRC reaction at elevated temperatures allowed the exchange of chain-end groups with a variety of functional nitroxide derivatives. The robustness and orthogonality of this NRC reaction were further demonstrated using the Cu-catalyzed azide/alkyne "click" (CuAAC) reactions, in which yields greater than 95% were observed for coupling between PSTY-N_3 and a PSTY chain first trapped with an alkyne functional TEMPO (PSTY-TEMPO-$\equiv$).

Introduction

Coupling reactions that are simple, selective in the presence of other chemical functional groups, wide in scope, generate near quantitative yields, and produce nontoxic byproducts are termed "click chemistry".[1] There are many examples of the use of such reactions in both small molecule[2−4] and macromolecular modifications to create new engineered materials.[1,5−9] The most widely used "click" reaction for the preparation of complex polymer architectures,[10−17] including dendrimers, stars, miktoarm stars, and polymer grafts, is the Cu-catalyzed azide/alkyne (CuAAC) reaction.[7,18,19] More recently, other types of rapid "click" reactions have been developed; for example, UV-induced thiol−ene coupling reactions between thiols and alkenes[20,21] and thiobromo coupling.[22] Barner-Kowollik and co-workers[23−26] synthesized polymeric stars through the highly efficient hetero-Diels−Alder (HDA) cycloaddition ("click") reaction.

A new reversible coupling strategy termed atom transfer nitroxide radical coupling (ATNRC)[27−34] has the attributes of a "click" reaction. This reaction involves formation of a carbon-centered radical by an atom transfer reaction with Cu(I)Br and trapping of this radical with a persistent nitroxide radical at close to diffusion-controlled rates. The unique aspect of this reaction is its reversibility, in which the product alkoxyamine can readily be converted to the starting incipient radical and parent nitroxide at elevated temperatures (>100 °C when TEMPO-type nitroxides are used).[35−37] This methodology has been used to synthesize degradable and reversibly coupled linear multiblock copolymers, block and graft copolymers in the presence of a 10-fold molar excess of copper species per halide end group.[33] The rate-determining step in the coupling reaction is the speed (k_{act}) at which the halide end groups on the polymer chains convert (or are activated) to the carbon-centered radical via atom transfer reactions with Cu(I) species.

We aimed to optimize the ATNRC process by exploiting reaction conditions that significantly enhance k_{act}. The use of tris[2-(dimethylamino)ethyl]amine (Me_6TREN) has been shown to accelerate the ATRP of acrylates at room temperature in bulk.[38,39] Percec and co-workers[40,41] showed that Cu(I)Br disproportionated rapidly to Cu(0) and Cu(II)Br_2 in the presence of Me_6TREN and DMSO solvent, leading to ultrafast and well-controlled acrylate polymerizations at room temperature. They postulated that Cu(0) was the activating copper species and termed this process single electron transfer (SET). In this work, we utilized the significant rate enhanced activation of linear polystyrene chains with halide chain ends (PSTY-Br) in the presence of Me_6TREN and DMSO. The incipient radicals were then trapped by a variety of nitroxides (Scheme 1). These coupling reactions in the presence of a trinitroxide core were extremely fast, giving 3-arm stars in under 7 min at room temperature (Scheme 2). Exploiting the decoupling reaction of the alkoxyamine at elevated temperatures, we could exchange one nitroxide for another functional nitroxide. This type of coupling/decoupling reaction represents a "building block"-type approach. Conversion of the polymer halide chain end to a variety of functional groups was possible through NRC reactions with functional nitroxides (Scheme 3). Such rapid and selective coupling reactions with reversibility are rare in organic and polymer chemistry.

Experimental Section

Materials. The following reagents/solvents were used as received: silica gel 60 (230−400 mesh) ATM (SDS), TLC plates (silica gel 60 F254), anisole (Fluka, 98%), sodium chloride

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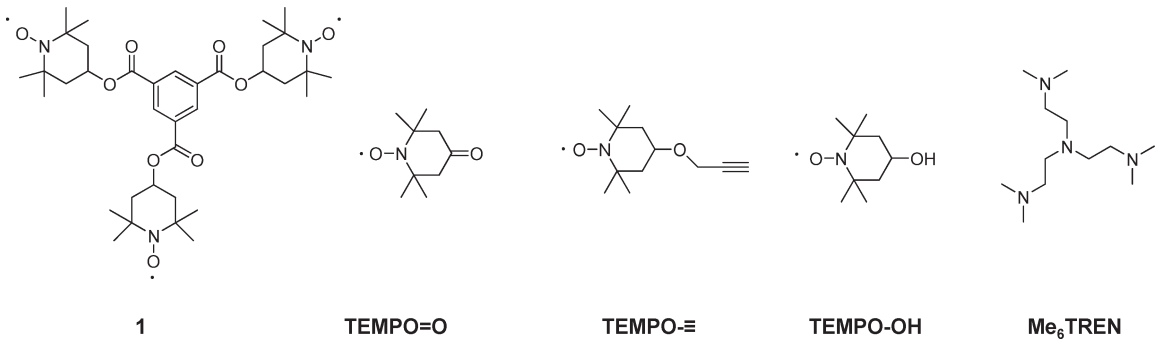
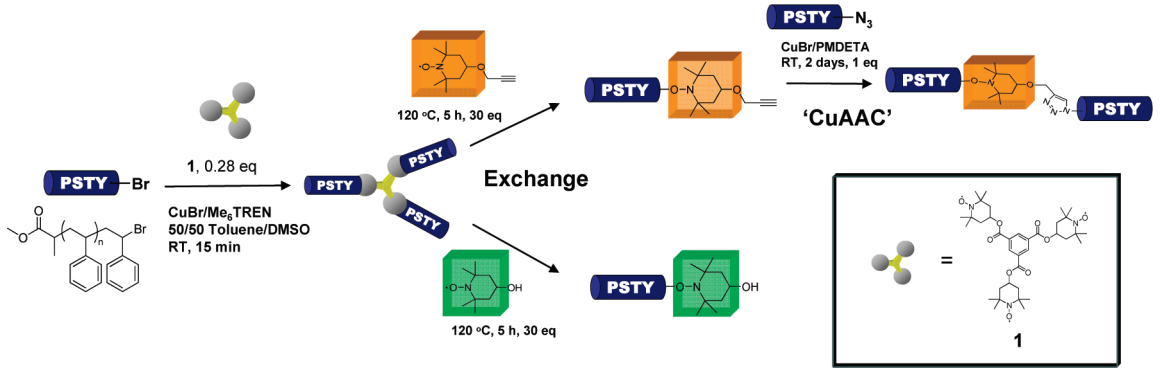
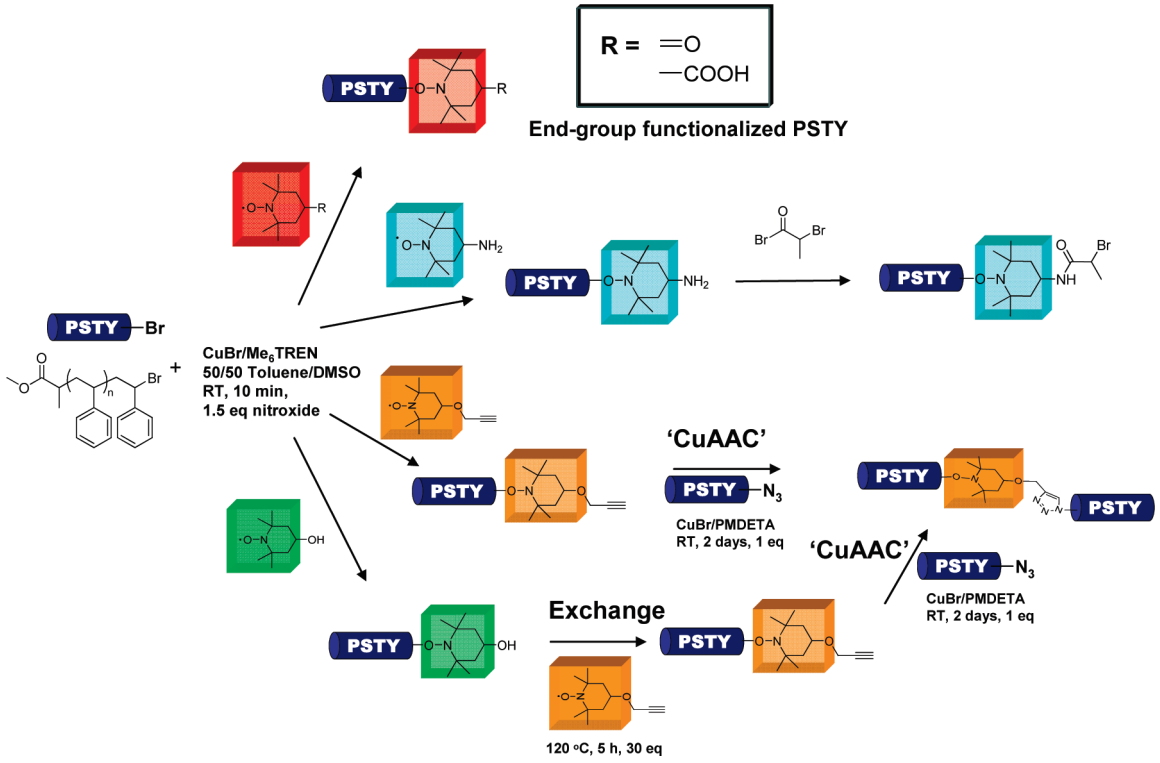
Scheme 1. Various Functional Nitroxides Used in the Nitroxide Coupling Reactions (NRC) and Structure of Tris(2-(dimethylamino)ethyl)amine (Me_6TREN)



Scheme 2. Synthetic Strategies for the Formation of 3-Arm Star Using the NRC Reaction, Decoupling and Exchange with Functional Nitroxides, and a CuAAC Reaction To Demonstrate the Orthogonal Nature of the Reaction Method



Scheme 3. Synthetic Strategies for the Preparation of Chain-End Functional Polystyrene



(Univar, 99.9%), methanol (Univar, AR grade), sodium hydrogen carbonate (Merck, AR grade), *n*-hexane (Scharlau, 96%), acetonitrile (Lab-Scan, HPLC grade), hydrogen peroxide 30% w/w (Univar, AR grade), sodium hydride (Aldrich, 60 wt % in mineral oil), propargyl bromide (Aldrich, 80 wt % in toluene), 1,3,5-benzene tricarbonyl trichloride (Aldrich, 98%), 2,2,6,6-tetramethyl-4-piperidinol (Aldrich, 98%), 2,2,6,6-tetramethyl-4-piperidone (Aldrich, 95%), 4-carboxy-TEMPO (TEMPO-COOH)

(Aldrich, 97%), 4-amino-TEMPO (TEMPO-NH_2) (Aldrich, 97%), chloroform ($CHCl_3$, Pronalys, 99%), dichloromethane (DCM, Labscan, AR grade), diethyl ether (Et_2O, Pronalys, AR grade), tetrahydrofuran (THF, HPLC grade, Lichrosolv, 99.8%), toluene (HPLC, LABSCAN, 99.8%), dimethyl sulfoxide (DMSO, LABSCAN, 99.8%), triethylamine (TEA, Fluka, purum), methyl 2-bromopropionate (MBP, Aldrich, 98%), cuprous bromide (Cu(I)Br, Aldrich, 99.999%), cupric bromide (Cu(II)Br_2, Aldrich, 99%), *N,N,N′,N′,N″*-pentamethyldiethylenetriamine (PMDETA, Aldrich, 99%), and 2-bromopropionyl bromide (BPB, Aldrich, 97%). Me_6TREN was synthesized using the previously described method of Ciampolini et al.[42] The syntheses of 4-hydroxy-2,2,6,6-tetramethylpiperidin-1-yloxyl (TEMPO-OH), 2,2,6,6-tetramethylpiperidon-1-yloxyl (4-oxo-TEMPO), and 2,2,6,6-tetramethyl-4-(prop-2-ynyloxy)piperidine-1-yloxyl (TEMPO-≡)[43] are described in the Supporting Information.

Styrene (STY, Aldrich, 99%, 10−15 ppm 4-*tert*-butyl catechol inhibitor) was purified from inhibitor by passage through a column of activated basic alumina (Aldrich, Brockmann I, standard grade, ~150 mesh, 58 Å).

Techniques. *Size Exclusion Chromatography* (*SEC*). All polymer samples were dried under vacuum for 2 days at 25 °C prior to analysis. The dried polymer was dissolved in tetrahydrofuran (THF, Labscan, 1 mg mL^{-1}), and the resulting solution was filtered using a 0.45 μm PTFE syringe filter. Analysis of the molecular weight distributions of the polymers was accomplished using a Waters 2695 separations module, fitted with a Waters 410 refractive index detector maintained at 35 °C, a Waters 996 photodiode array detector, and two Ultrastyragel linear columns (7.8 × 300 mm) arranged in series. These columns were maintained at 40 °C for all analyses and are capable of separating polymers in the molecular weight range of 500−4 million g mol^{-1} with high resolution. All samples were eluted at a flow rate of 1.0 mL min^{-1}. Calibration was performed using narrow molecular weight PSTY standards (PDI ≤ 1.1) ranging from 500 to 2 million g mol^{-1}. Data acquisition was performed using Empower software, and molecular weights were calculated relative to polystyrene standards.

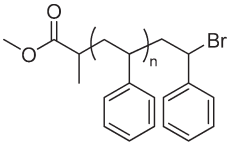
^{1}H Nuclear Magnetic Resonance (*NMR*) *Spectroscopy*. All NMR spectra were recorded on a Bruker DRX 400 MHz spectrometer.

Attenuated Total Reflectance-Fourier Transform Spectroscopy (*ATR-FTIR*). ATR-FTIR spectra were obtained using a horizontal, single bounce, diamond ATR accessory on a Nicolet Nexus 870 FT-IR. Spectra were recorded between 4000 and 500 cm^{-1} for 32 scans at 4 cm^{-1} resolution with an OPD velocity of 0.6289 cm s^{-1}. Solids were pressed directly onto the diamond internal reflection element of the ATR without further sample preparation.

Matrix-Assisted Laser Desorption Ionization−Time-of-Flight (*MALDI-ToF*) *Mass Spectrometry*. MALDI-ToF MS spectra were obtained using an Applied Biosystems MALDI Voyager DE-STR equipped with a nitrogen laser (337 nm, 3 ns pulse, 20 Hz maximum firing rate) with a mass range of 500−300 000 Da. All spectra were recorded in reflectron mode. *trans*-2-[3-(4-*tert*-Butylphenyl)-2-methylpropenylidene]malononitrile (DCTB; 20 mg mL^{-1} in THF) was used as the matrix and Ag(CF_3COO) (2 mg mL^{-1} in THF) as the cation source. Samples were prepared by cospotting the matrix (20 μL), Ag(CF_3COO) (2 μL), and polymer (20 μL, 1 mg mL^{-1} in THF) solutions on the target plate.

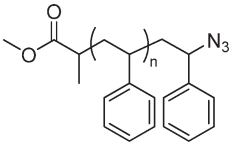
Synthesis of Trinitroxide, Tris(4-hydroxy-2,2,6,6-tetramethylpiperidin-1-yloxyl)benzene-1,3,5-tricarboxylate (***1***). 1,3,5-Benzenetricarbonyl trichloride (0.66 g, 2.5 × 10^{-3} mol) was dissolved in dry toluene (12.4 mL) under argon. A solution of TEMPO-OH (1.92 g, 1.11 × 10^{-2} mol) and dry triethylamine (5.12 mL, 3.68 × 10^{-2} mol) in dry toluene (20 mL) was added dropwise to the stirring acid chloride solution. After stirring at room temperature under argon for 48 h, the solvent was removed under reduced pressure. The resulting oil was suspended in H_2O (100 mL), and the ensuing mixture was vigorously extracted with Et_2O (4 × 120 mL). The combined organic phase was washed with 2 M H_2SO_4 (3 × 30 mL) and dried over Na_2SO_4. Removal of the solvent under reduced pressure gave an orange/red solid, which was purified by flash chromatography (50/50 EtOAc/hexane) to give the triester **1** as a peach orange solid (1.07 g, 64%). R_f (50% EtOAc/hexane) 0.48; MS (MALDI) M − Na^+ Calcd m/z 695.4. Found: m/z 694.7. The presence of the paramagnetic nitroxide moieties precluded direct analysis by NMR. Consequently, **1** was reduced to the corresponding hydroxylamine with phenylhydrazine. ^{1}H NMR ($CDCl_3$): δ 1.17 (s 18H, CH_3CNO), δ 1.19 (s 18H, CH_3CNO), 1.72 (m, 6H, CHCH_2C), 1.94 (m, 6H, CHCH_2C), 5.23 (m, 3H, COOCHCH$_2$), 6.80 (m, phenylhydrazine), 7.23 (m, phenylhydrazine), 7.34 (s, benzene), 8.66 (s, 3H, ArH). The ^{1}H NMR spectrum contains resonances due to excess phenylhydrazine and its oxidation product, benzene. Excess TEMPO-OH was recovered by saturating the aqueous phase with NaCl and extracting with Et_2O (3 × 150 mL). The organic phase was dried over Na_2SO_4 and evaporated under reduced pressure to recover the TEMPO-OH as an orange/red solid.

Synthesis of PSTY-Br. Styrene (15.39 g, 0.1480 mol), PMDETA (0.351 mL, 1.68 × 10^{-3} mol), methyl 2-bromopropionate (0.374 mL, 3.36 × 10^{-3} mol), and Cu(II)Br_2/PMDETA complex (0.1332 g, 3.36 × 10^{-4} mol) were added to a Schlenk flask and purged by bubbling with argon for 20 min with vigorous stirring. The contents were stirred for an extra hour under argon to solublize Cu(II)Br_2/PMDETA. Cu(I)Br (0.241 g, 1.68 × 10^{-3} mol) was added under a positive argon flow, and the contents were bubbled with argon for a further 5 min. The reaction vessel was then sealed and placed in an oil bath at 80 °C, and the reaction mixture was stirred. The reaction was terminated by quenching in ice followed by exposure to air. The contents were diluted with dichloromethane and passed through activated basic alumina. The solvent was removed under reduced pressure, and the residue dissolved in a minimal amount of dichloromethane. The polymer was precipitated in 10× volume of MeOH. The resulting white precipitate was collected by vacuum filtration and dried under vacuum (M_n = 2540, PDI = 1.11).



PSTY-Br

Synthesis of PSTY-N_3. NaN_3 (156 mg, 2.40 × 10^{-3} mol) was added to a stirring solution of PSTY-Br (M_n = 2540, PDI = 1.11, 600 mg, 2.36 × 10^{-4} mol) in DMF (3 mL). The reaction mixture was stirred for 16 h at 25 °C. The polymer was precipitated in 10× volume MeOH, recovered by vacuum filtration and washed exhaustively with water and MeOH. The azide-functionalized polymer was dried under vacuum (M_n = 2540, PDI = 1.14).

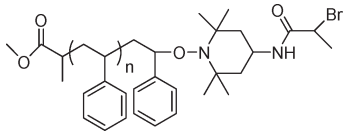


PSTY-N_3

NRC Functionalization of PSTY-Br. PSTY-Br (M_n = 2540, PDI = 1.11, 100 mg, 3.94 × 10^{-5} mol), TEMPO-X (where X = −OH, −≡, −COOH, =O, $-NH_2$) (6.25 × 10^{-5} mol) and Me_6TREN (11.5 mg, 5.0 × 10^{-5} mol) were placed in a 10 mL Schlenk flask and dissolved in 50:50 v/v toluene:DMSO (0.8 mL). Oxygen was removed from the solution by purging with argon (15 min). Cu(I)Br (7.17 mg, 5.0 × 10^{-5} mol) was then added under a positive argon flow. The reaction vessel was sealed and placed in an oil bath at 25 °C with stirring for 10 min. The contents were then diluted with dichloromethane and passed through an activated

basic alumina column. The solvent was removed under reduced pressure, and the residue was dissolved in a minimal amount of dichloromethane. The polymer was precipitated in 10× volume MeOH. The resulting white precipitate was collected by vacuum filtration and dried under vacuum. In the case of PSTY-TEMPO-COOH the purification method was modified due to interaction of the COOH groups with alumina. The PSTY-TEMPO-COOH reaction mixture was diluted with dichloromethane and extracted three times with acidified water (containing a few drops of 2 M HCl). The organic phase was dried with anhydrous Na_2SO_4, and the solvent was removed under reduced pressure. The polymer was precipitated in 10× volume MeOH. The resulting white precipitate was collected by vacuum filtration and dried under vacuum. PSTY-TEMPO-OH (M_n = 2870, PDI = 1.11), PSTY-TEMPO-≡ (M_n = 2870, PDI = 1.11), PSTY-TEMPO-COOH (M_n = 450, PDI = 2.72: this large PDI and apparent low M_n was due to preferential binding of the polymer to the SEC columns), PSTY-TEMPO=O (M_n = 2710, PDI = 1.14), PSTY-TEMPO-NH_2 (M_n = 2170, PDI = 1.30).

PSTY-TEMPO-NHC(O)CH(CH₃)Br. PSTY-TEMPO-NH_2 (M_n = 2170, PDI = 1.30, 45 mg, 1.8×10^{-5} mol) was dissolved in dry THF (0.5 mL), and triethylamine (2.73 mg, 2.7×10^{-5} mol) was added. The contents were cooled to 0 °C in an ice bath, and 2-bromopropionyl bromide (2.83 μL, 2.7×10^{-5} mol) was added dropwise with stirring. The ice bath was removed, and the reaction mixture was stirred for 16 h at 25 °C. The polymer was precipitated in 10× volume MeOH and recovered by vacuum filtration. The polymer was dried under vacuum (M_n = 3330, PDI = 1.14).



3-Arm Star Formation via NRC. PSTY-Br (M_n = 2540, PDI = 1.11, 120 mg, 4.73×10^{-5} mol), trinitroxide **1** (9.25 mg, 1.38×10^{-5} mol), and Me_6TREN (9.50 mg, 4.13×10^{-5} mol) were placed in a 10 mL Schlenk flask and dissolved in 50:50 v/v toluene:DMSO (1 mL). Oxygen was removed from the solution by purging with argon (15 min). Cu(I)Br (5.92 mg, 4.13×10^{-5} mol) was then added under a positive argon flow. The reaction vessel was sealed and placed in an oil bath at 25 °C for 10 min, and the reaction mixture was stirred. The contents were diluted with dichloromethane and passed through activated basic alumina. The solvent was removed under reduced pressure, and the residue was dissolved in a minimal amount of dichloromethane. The polymer was precipitated in 10× volume MeOH. The resulting white precipitate was collected via vacuum filtration and dried under vacuum (M_n = 6890, PDI = 1.24).

Nitroxide Exchange of PSTY-TEMPO-OH with TEMPO-≡. PSTY-TEMPO−OH (M_n = 2830, PDI = 1.10, 60 mg, 2.45×10^{-5} mol) and TEMPO-≡ (50.4 mg, 2.40×10^{-4} mol) were placed in a Schlenk flask equipped with a Teflon screw cap and dissolved in toluene (0.6 mL). Oxygen was removed from the solution by purging with argon (15 min). The flask was then sealed under argon and placed in an oil bath at 120 °C with stirring for 5 h. The reaction mixture was quenched by cooling in an ice bath. The solvent was removed under air flow, and the residue was dissolved in a minimal amount of dichloromethane. The polymer was precipitated in 10× volume MeOH. The resulting white precipitate was collected via vacuum filtration and dried under vacuum (M_n = 3060, PDI = 1.12).

Nitroxide Exchange of 3-Arm Star with TEMPO-≡ or TEMPO-OH. Three-arm star (M_n = 6890, PDI = 1.24, 60 mg, 6.52×10^{-6} mol) and TEMPO-≡ (41.1 mg, 1.96×10^{-4} mol) or TEMPO-OH (33.8 mg, 1.96×10^{-4} mol) were placed in a Schlenk flask equipped with a Teflon screw cap and dissolved in toluene (0.6 mL). Oxygen was removed from the solution by purging with argon (15 min). The flask was sealed under argon and placed in an oil bath at 120 °C with stirring for 5 h. The reaction mixture was quenched by cooling in an ice bath. The solvent was removed under air flow, and the residue was dissolved in a minimal amount of dichloromethane. The polymer was precipitated in 10× volume MeOH. The resulting white precipitate was collected via vacuum filtration and dried under vacuum (M_n = 3330, PDI = 1.14).

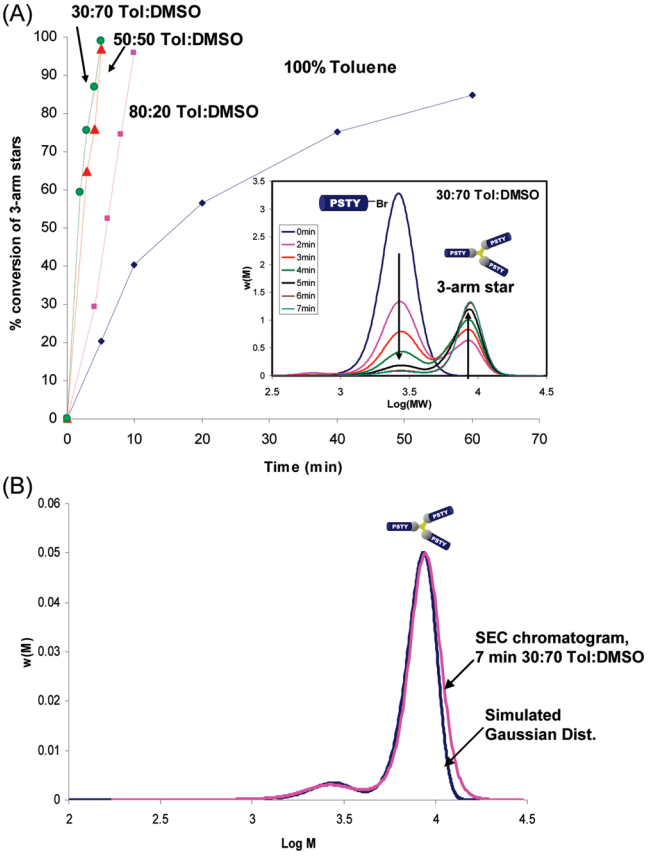


Figure 1. NRC reaction of PSTY-Br and **1** to form 3-arm stars at room temperature. (A) Conversion vs time for a range of toluene to DMSO ratios. Reaction conditions: [PSTY-Br] = 0.0473 M, [**1**] = 0.0138 M, [Cu(I)Br] = 0.0413 M, [Me_6TREN] = 0.0413 M, solvent = 1 mL. (B) Gaussian simulation of SEC trace after the reaction in 30:70 toluene: DMSO.

Cu-Catalyzed Huisgen 1,3-Cycloaddition Reaction of PSTY-TEMPO-≡ with PSTY-N_3. A typical reaction was performed as follows: PSTY-N_3 (M_n = 2540, PDI = 1.14, 8.89 mg, 3.27×10^{-6} mol), PSTY-TEMPO-≡ (M_n = 2870, PDI = 1.11, 10.0 mg, 3.27×10^{-6} mol), and PMDETA (3.03 mg, 1.75×10^{-5} mol) were placed in a 10 mL Schlenk flask and dissolved in DMF (0.44 mL). Oxygen was removed from the solution by purging with argon (15 min). Cu(I)Br (2.5 mg, 1.75×10^{-5} mol) was then added under a positive argon flow. The reaction vessel was sealed and placed in an oil bath at 25 °C with stirring for 48 h. The reaction mixture was sampled and analyzed by SEC (M_n = 5100, PDI = 1.14).

Results and Discussion

In this work, we use Cu(I)Br, which rapidly undergoes disproportionation to the highly active nascent Cu(0) in the presence of Me_6TREN ligand and DMSO solvent,[40,41,44–46] to produce high radical fluxes, leading to ultrafast coupling reactions with nitroxide compounds (i.e., NRC).

The coupling time between polystyrene with bromine end groups (PSTY-Br) and trinitroxide, **1**, to form highly pure 3-arm

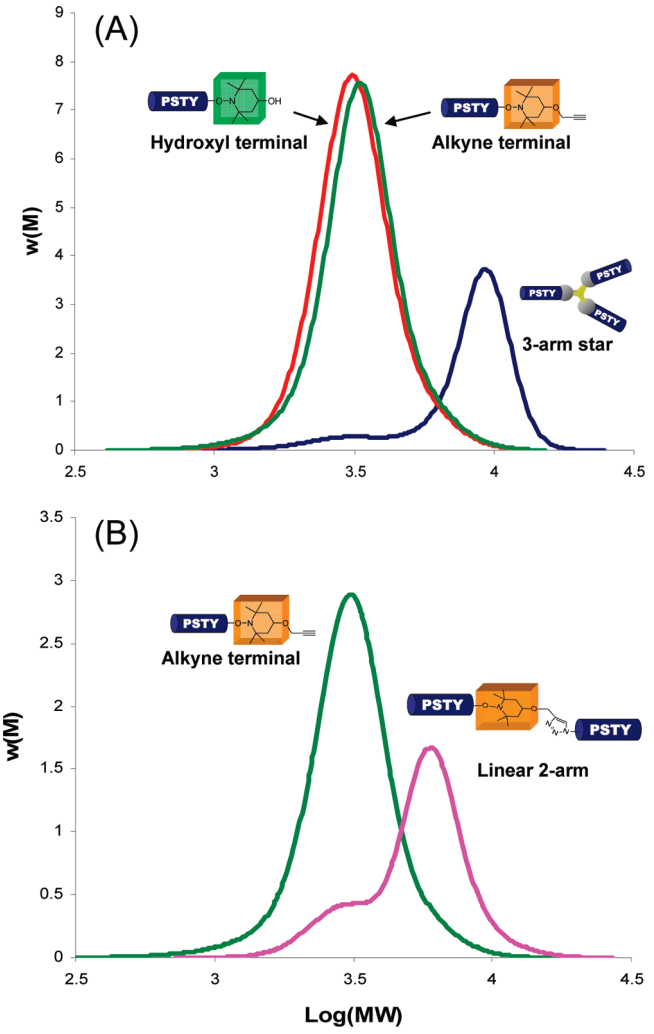


Figure 2. SEC chromatograms of (A) exchange reaction of 3-arm star (formed in 50:50 toluene:DMSO at RT) with TEMPO-≡ or TEMPO-OH and (B) CuAAC reaction of PSTY-TEMPO-≡ (M_n = 3100, PDI = 1.16) with PSTY-N_3 (M_n = 2500, PDI = 1.11) in DMF at RT for 2 days to form a 2-arm polymer.

Table 1. SEC and ^{1}H NMR Data for NRC and Exchange Reactions

	M_n (SEC)	PDI (SEC)	M_n (NMR)[a]
PSTY-Br	2540	1.11	2720
3-arm star → PSTY-T−OH	3070	1.14	2570
3-arm star → PSTY-T-≡	3090	1.16	2610
PSTY-TEMPO−OH	2870	1.11	2680
PSTY-T−OH → PSTY-T-≡	3060	1.12	2780
PSTY-TEMPO-≡	2870	1.11	2680
PSTY-TEMPO=O	2710	1.14	2550
PSTY-TEMPO−COOH	450	2.72	2690
PSTY-TEMPO-NH_2	2170	1.30	2760
PSTY-TEMPO-NHC(O)CH(CH_3)Br	3330	1.14	2900

[a] The molecular weights of the nitroxide and initiator were added. M_n values were determined by comparing the integration between protons **g** and **a**.

stars was less than 7 min at room temperature (Scheme 2). Figure 1A shows the rate of formation of 3-arm stars over a range of toluene to DMSO ratios. The inset in Figure 1A shows SEC chromatograms (scaled to weight) for the loss of PSTY-Br and formation of the 3-arm star (which has a molecular weight 3 times greater than linear PSTY-Br) at a toluene to DMSO ratio of 30:70. When the NRC reaction (0.87 equiv of Cu(I)Br and Me_6TREN, 0.28 equiv of **1**, and 1 equiv of PSTY-Br) was carried out at room

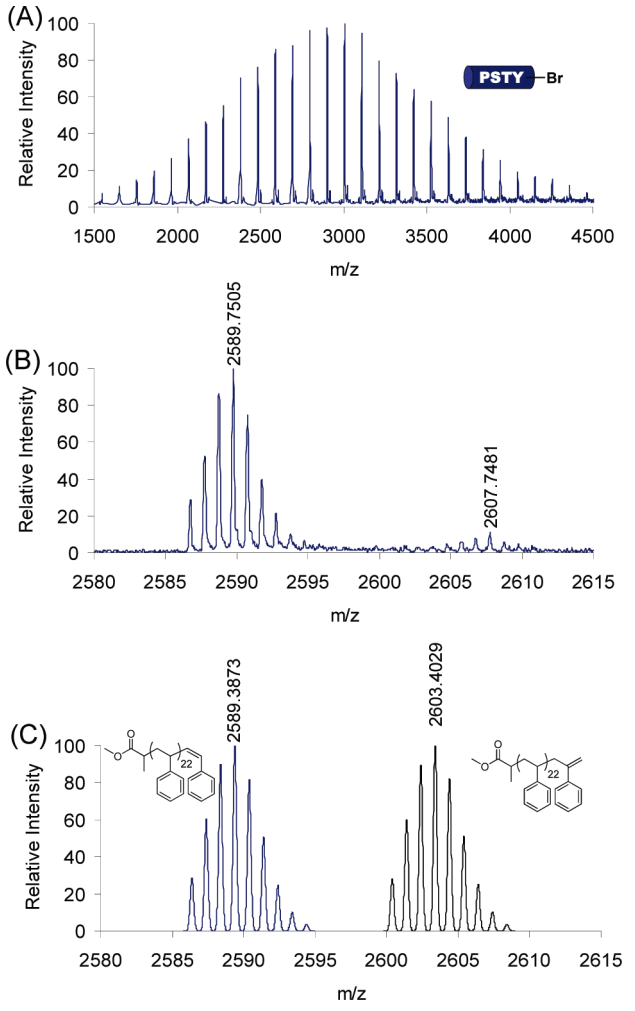


Figure 3. MALDI-ToF mass spectrometry of PSTY-Br (M_n = 2500, PDI = 1.11) with Ag salt as cationization agent from a DCTB matrix in reflectron mode: (A) full molecular weight distribution, (B) isotopic resolution of peaks, and (C) theoretical isotopic pattern of fragmentation products as described by Ladaviere et al.[47]

temperature in 100% toluene, the reaction was slow, reaching 85% yield by SEC after 65 min. It can be seen that the reaction rate increased with the greater ratio of DMSO to toluene, most probably due to the increased concentration of the highly active nascent Cu(0) formed by disproportionation of Cu(I) species in the presence of DMSO. We could not use 100% DMSO in our reactions as PSTY-Br and **1** immediately precipitate out of solution. However, even the reactions with a small amount of DMSO (20 wt %) showed a significant rate enhancement so that very high conversions were reached in under 7 min. The efficiency of the coupling reaction was determined by simulating the molecular weight distribution (MWD) of the product with Gaussian distributions of starting polymer and all possible products, including dead polymer species and polymer chains with free nitroxides attached. The simulation gave a good fit with the experimental weight distribution (Figure 1B), including the 3-arm star in greater than 91 mol %, starting PSTY-Br (6 mol %, which was used in 1.2 times excess to **1**), negligible amounts of **1** with either a single PSTY arm or two PSTY arms attached, and 3 mol % of dead PSTY-PSTY formed through bimolecular radical coupling.

The 3-arm star alkoxyamine formed after 15 min was decoupled and exchanged with two functional TEMPO nitroxides (Scheme 2). Figure 2A shows the SEC chromatograms (scaled to weight) of the starting 3-arm star alkoxyamine before and after exchange with a 30-fold excess of either an alkyne functional

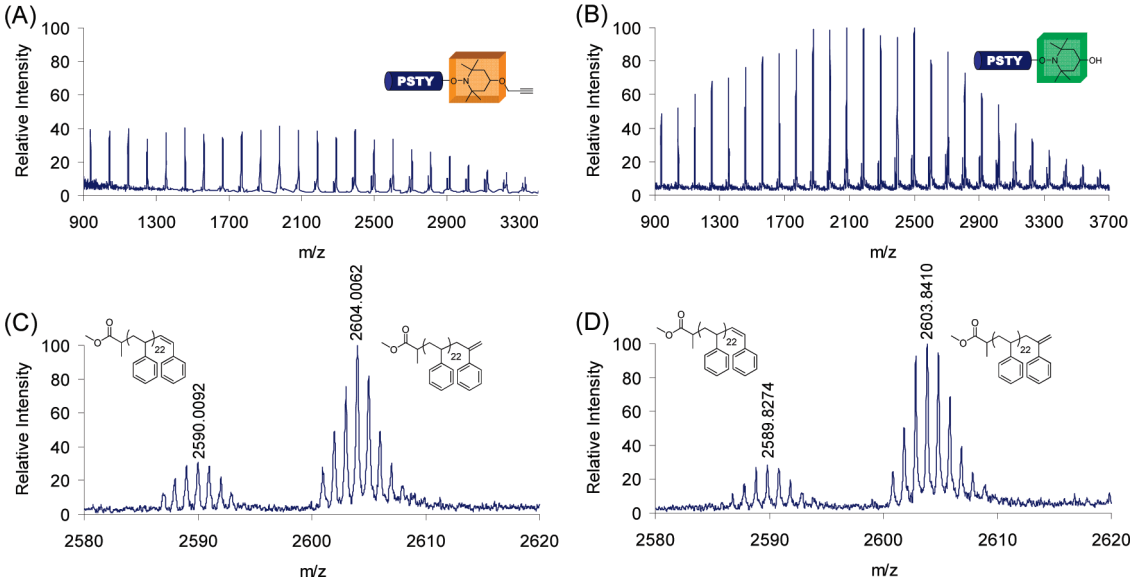
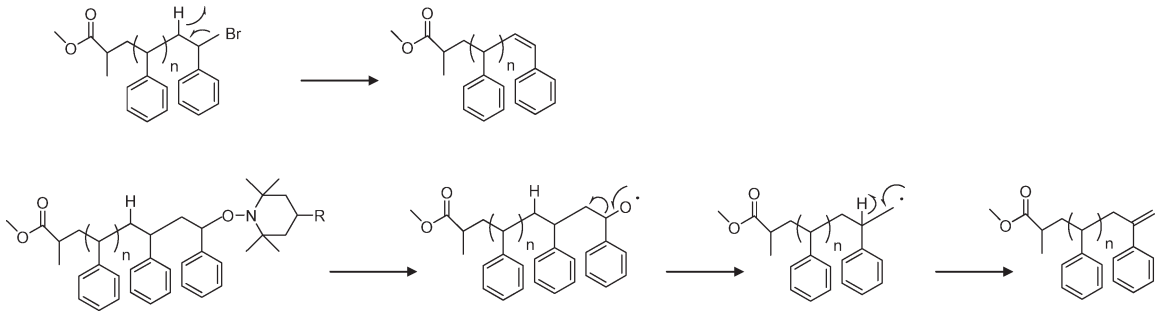


Figure 4. MALDI-ToF mass spectrometry of (A) PSTY-TEMPO-≡ and (B) PSTY-TEMPO-OH after exchange reactions with 3-arm stars, utilizing Ag salt as cationization agent from a DCTB matrix in reflectron mode. Isotopic resolution of (C) PSTY-TEMPO-≡ and (D) PSTY-TEMPO-OH peaks.

Scheme 4. Proposed Mechanism for the Fragmentation of Polymer End Groups during MALDI-ToF Analysis



TEMPO (TEMPO-≡) or hydroxy-TEMPO (TEMPO-OH) to form linear PSTY alkoxyamines. A 30-fold excess was used to kinetically eliminate side reactions from decoupling and consequent bimolecular termination. The MWD data after the exchange reaction to form PSTY-TEMPO-≡ (M_n = 3090, PDI = 1.16) or PSTY-TEMPO−OH (M_n = 3070, PDI = 1.11) were similar to the starting PSTY-Br (M_n = 2540, PDI = 1.11). The M_n values after the exchange reaction calculated by ^{1}H NMR were in good agreement with those determined by SEC (Table 1). These SEC traces showed loss of all of the 3-arm star, suggesting near quantitative exchange with the functional TEMPO. Further characterization of these PSTY chains by MALDI-ToF mass spectrometry provided insight into the efficiency of the nitroxide exchange process.

The MALDI-ToF mass spectrum in Figure 3A shows the full molecular weight distribution of the starting polymer PSTY-Br, which gave a similar MWD to the SEC trace in Figure 1 (inset). A magnified region between 2580 and 2615 showed one major peak and two weak overlapping peaks, each exhibiting isotopic resolution (Figure 3B). The major peak was consistent with the theoretical isotopic pattern from PSTY with a chain-end group of −CH=CH(Ph), resulting from the formal loss of HBr during the mass spectrometry analysis (Figure 3C). Our conditions, utilizing AgTFA as the cationization salt, were similar to those used by Ladavière et al.[47] in which identical isotopic patterns were observed, with the major peak after fragmentation of PSTY-Br corresponding to PSTY-CH=CH(Ph) (Scheme 4). The lower m/z portion of the overlapping weak signals in Figure 3B can be attributed to PSTY with a chain-end group of −C(Ph)=CH_2 (Figure 3C). The assignment of the higher m/z portion at approximately +18 m/z with respect to the major peak is unknown but may be related to instrumental conditions. Very similar observations were made by Ladavière et al.[47] Using other matrices and cationization salts gave poor peak resolution and reproducibility. Figure 4 shows the MALDI-ToF mass spectra for the alkyne and hydroxyl terminal PSTY chains obtained after exchange with the 3-arm star. The molecular weight distributions were similar to the SEC chromatograms in Figure 2, and the isotopic pattern of the main peak was consistent with the structure PSTY-C(Ph)=CH_2 with a small amount of PSTY-CH=CH(Ph), which is the reverse to that observed for the MALDI-ToF analysis of PSTY-Br. Schulte et al.[48] postulated that end-group degradation of poly(*N*-isopropylacrylamide)-TEMPO from the MALDI resulted in a −C(CONHCH-$(CH_3)_2$)=CH_2 chain end. Scheme 4 shows the degradation mechanism based on their postulate but for polystyrene-TEMPO.[47] The high intensity of the PSTY-C(Ph)=CH_2 signal observed in the MALDI-ToF spectrum provides strong evidence for near quantitative exchange of the functional nitroxides with the 3-arm alkoxyamine star.

The use of Cu(I)Br/Me_6TREN in DMSO allows for rapid activation and coupling between PSTY-Br and a trifunctional nitroxide to form 3-arm stars in near quantitative yields. Decoupling of this 3-arm star and subsequent exchange with either an alkyne or hydroxyl functionalized nitroxide also occurred with near quantitative yields. To further quantify the efficiency of the NRC reaction (see Scheme 2), PSTY-TEMPO-≡ was "clicked"

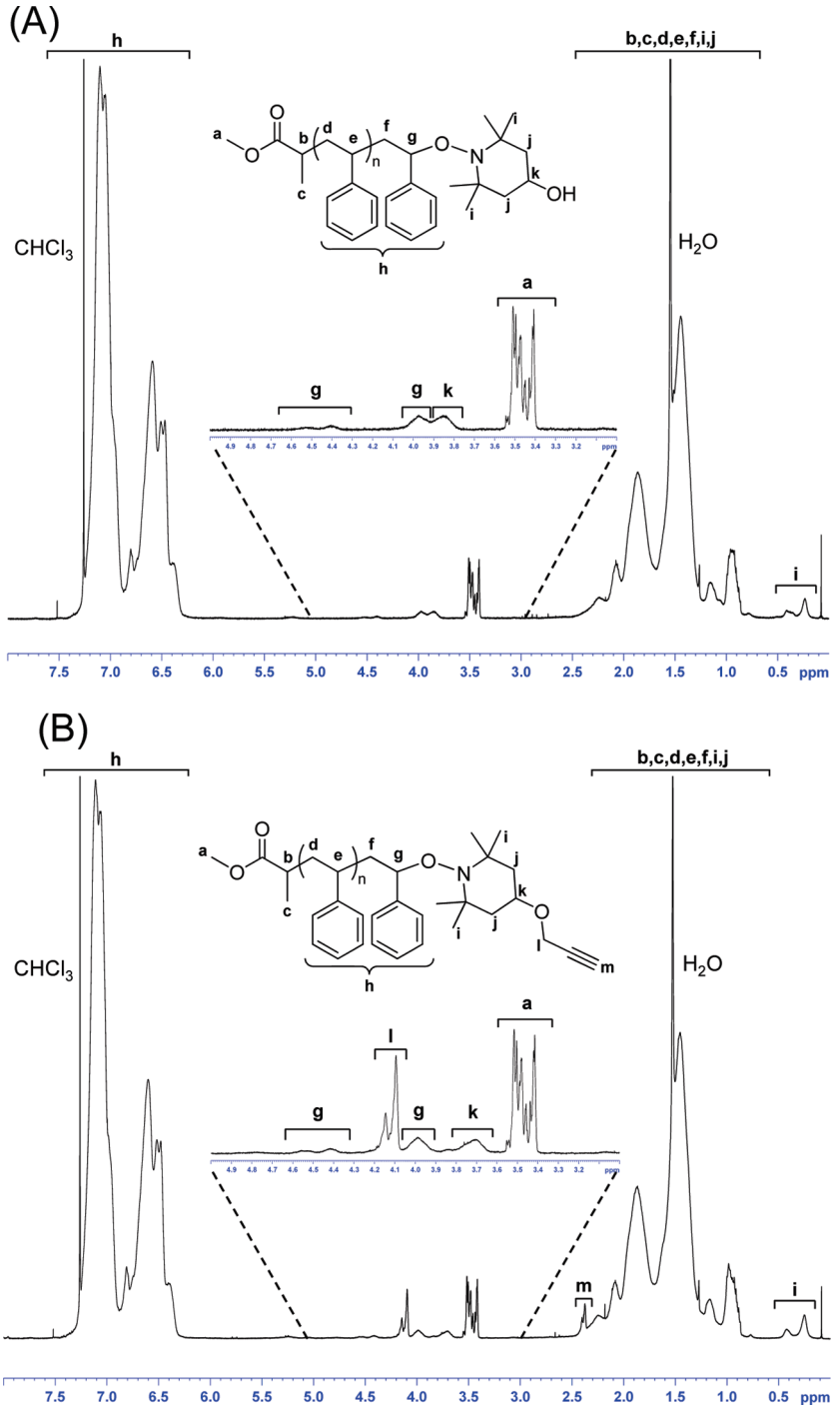


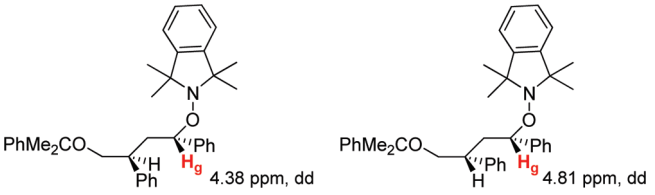
Figure 5. ^{1}H NMR spectra of (A) PSTY-TEMPO-OH and (B) PSTY-TEMPO-≡ after exchange reactions with the 3-arm stars.

with PSTY-N_3, which was formed from the same starting PSTY-Br, using stoichiometric Cu(I)Br/PMDETA catalyst in DMF at room temperature for 2 days. The calculated yield for the 2-arm polymer was found to be greater than 89% (Figure 2B) as determined from the reduction of the peak height of the starting polymer. Calculating the yield based on area led to large errors due to significant overlap between the one-arm and two-arm polymer MWDs (simulations of the Gaussian distributions not shown). This reaction demonstrates the versatility of the NRC reaction, in which orthogonal reactions can occur in near quantitative yields. There are several reasons why 100% yield was not obtained: (i) there was most probably a slight excess of one of the reactants, (ii) the CuAAc reaction did not go to full completion since the reaction was carried out at room temperature, and (iii) toward the end of the reaction the very low concentration of functional groups prohibits quantitative yields.

The polymers PSTY-TEMPO-OH and PSTY-TEMPO-≡ were also characterized by ^{1}H NMR spectroscopy (Figure 5). The ^{1}H NMR spectrum of PSTY-TEMPO-OH in Figure 5A shows the characteristic peaks assigned to the methyl groups on the nitroxide (denoted **i** in Figure 5A), peaks with chemical shifts between 3.4 and 3.6 assigned to the methyl protons **a**, and peaks with chemical shifts between 3.7 and 4.7 ppm assigned to proton **g** adjacent to the nitroxide and **k** alpha to the hydroxyl group on the nitroxide. A similar spectrum was observed for PSTY-TEMPO-≡ with additional peaks at 2.4 ppm assigned to alkyne proton **m** and a broad peak at 3.7 ppm assigned to **k** alpha to the hydroxyl group on the nitroxide. The three broad peaks for **g** were assigned based

on previously reported ^{1}H NMR spectra[49,50] of diastereomers of small molecule model compounds capped with nitroxides and stereochemical effects of phenyl groups two or three units from **g**. As shown in Scheme 5, shielding effects by a phenyl group in the model compound[49,50] can result in chemical shift differences of ~0.5 ppm for proton **g**. The ^{1}H NMR spectra of all nitroxide capped polymers can be found in the Supporting Information. For the polymers with the same nitroxide end group, the ^{1}H NMR spectra were identical regardless of how the polymer was synthesized. These results, together with the high CuAAC "click" efficiency, strongly support high chain-end fidelity through the NRC and nitroxide exchange reactions.

Scheme 5. Literature ^{1}H NMR Spectra of Model Compound Diastereomers[49]



This NRC methodology has also allowed us to functionalize polymer chain ends with desired chemical functionality, ranging from ketones, amines, carboxylic acids, to alcohols, using functional nitroxides. The starting polymer, PSTY-Br, was coupled to a range of functional nitroxides as shown in Scheme 3. The reactions were complete in <10 min at room temperature, and the SEC chromatograms in Figure 6 showed little change from

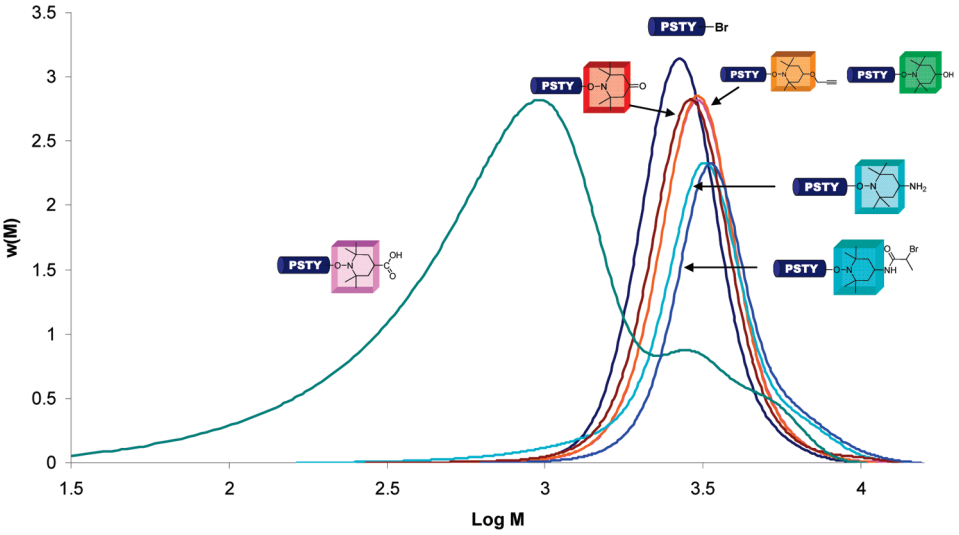


Figure 6. SEC chromatograms for the NRC reaction of PSTY-Br with functional TEMPO nitroxides. Reaction conditions: [PSTY-Br] = 0.0493 M, [TEMPO-X] = 0.0781 M, [Cu(I)Br] = 0.0625 M, [Me_6TREN] = 0.0625 M, 50:50 v/v toluene:DMSO = 0.8 mL.

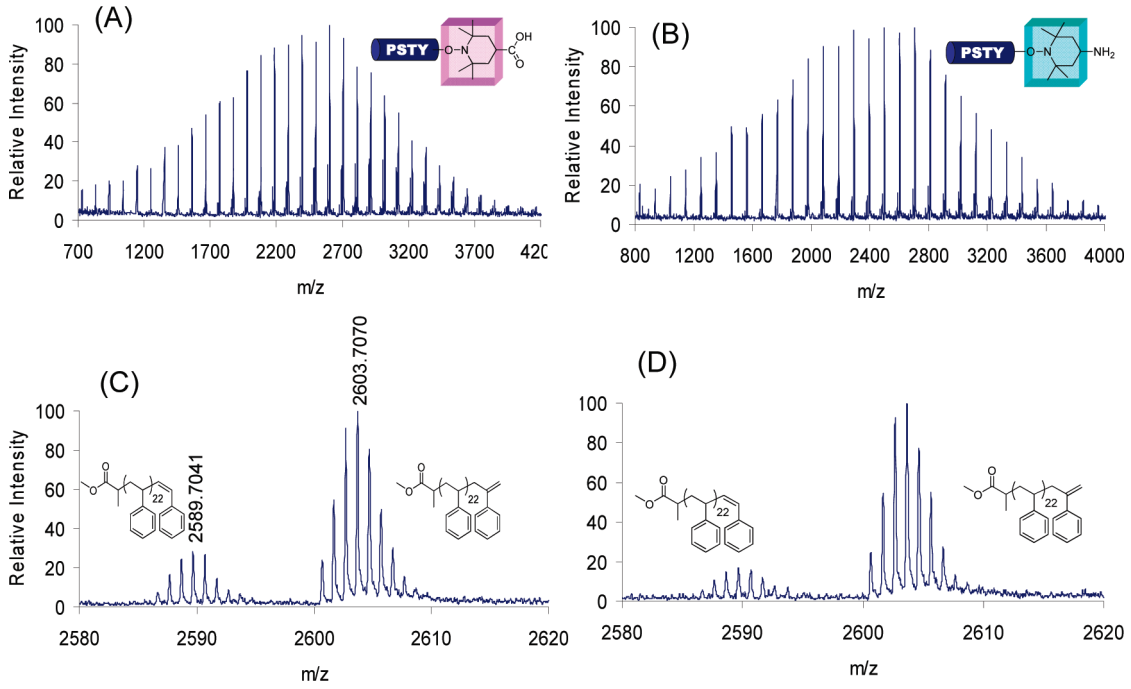


Figure 7. MALDI-ToF mass spectrometry of (A) PSTY-TEMPO-COOH and (B) PSTY-TEMPO-NH_2 after NRC reaction between PSTY-Br and functional TEMPO with Ag salt as cationization agent from a DCTB matrix in reflectron mode. Isotopic patterns of (C) PSTY-TEMPO−COOH and (D) PSTY-TEMPO-NH_2.

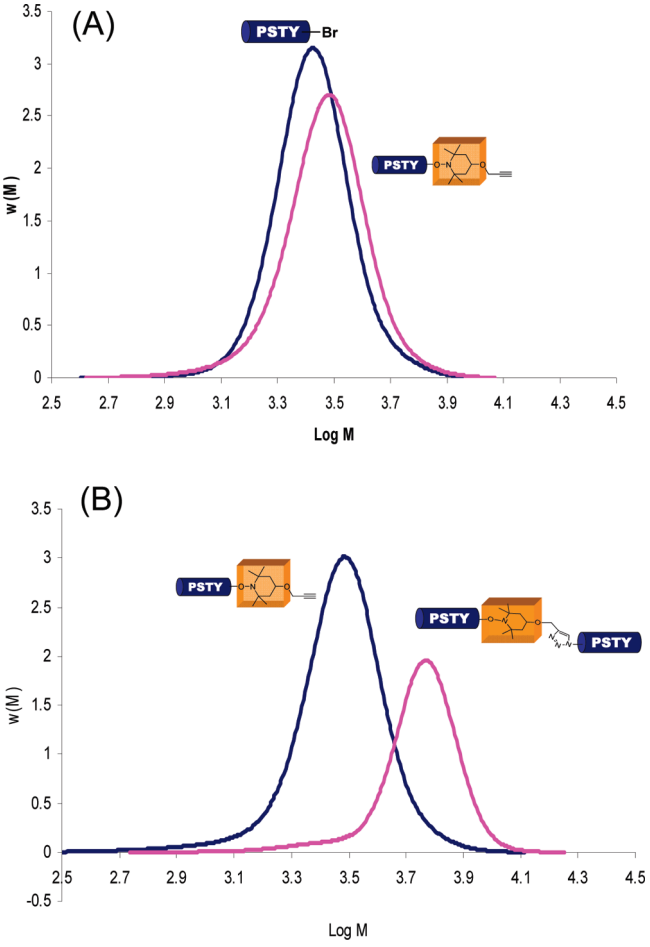


Figure 8. SEC chromatograms for (A) the NRC reaction between PSTY-Br and TEMPO-≡ and (B) the subsequent CuAAC reaction of PSTY-N_3 with PSTY-TEMPO-≡ (formed from A).

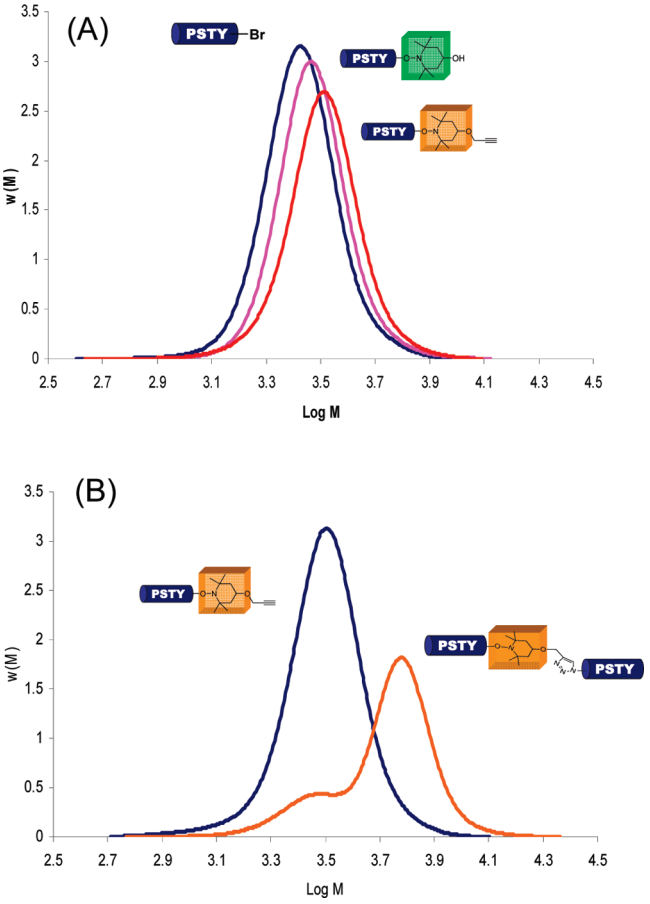


Figure 9. SEC chromatograms for (A) the NRC reaction between PSTY-Br and TEMPO-OH, exchange reaction with TEMPO-≡ to form PSTY-TEMPO-≡, and (B) subsequent CuAAC reaction of PSTY-N_3 with PSTY-TEMPO-≡ (formed from A) after 1.5 days.

that of the starting polymer with the exception of the amine and carboxylic acid chain-end-functionalized polymers (also see MWD data in Table 1). In the latter cases, the large discrepancy between their M_n and PDI values and that for PSTY-Br was postulated to be due to preferential binding of the −COOH and $-NH_2$ end groups to the SEC columns. When PSTY-TEMPO-NH_2 was reacted with excess 2-bromopropionyl bromide to form the resultant amide, the PDI decreased from 1.32 to 1.13, showing that the amide-funtionalized polymer exhibited little or no preferential binding to the columns. The M_n values calculated by ^{1}H NMR after the SET-NRC reaction were in good agreement with those determined by SEC (Table 1). The MALDI-ToF spectra of carboxylic acid and amine terminal PSTY given in Figure 7 showed similar MWDs and isotopic patterns to all the other PSTY with terminal functional nitroxides (see Figure 4 and Supporting Information for all MALDI-ToF spectra). This strongly suggests that the NRC reaction was near quantitative.

The orthogonal nature of this reaction was shown through the CuAAC reaction between the alkyne functional polymer PSTY-TEMPO-≡ and PSTY-N_3 using the same conditions as the CuAAC reaction above (see Scheme 3). Figure 8A shows the SEC chromatogram of PSTY-Br before and after coupling with an alkyne functional nitroxide, and Figure 8B shows the formation of a 2-arm polymer after the CuAAC reaction between PSTY-TEMPO-≡ and PSTY-N_3. The CuAAC reaction was near quantitative (>95%) with little starting PSTY-TEMPO-≡ observed in the SEC chromatogram. This "click" reaction was also used to assess the efficiency for the exchange reaction from PSTY-TEMPO-OH to PSTY-TEMPO-≡. Figure 9A shows the SEC chromatogram of (i) the starting PSTY-Br, (ii) after NRC with TEMPO−OH, and (iii) after the exchange reaction with TEMPO-≡. It can be seen that the "click" reaction of this alkyne functional polymer after 1.5 days resulted in a yield of greater than 86% (Figure 9B), indicating the high efficiency of the exchange reaction. The results from this work demonstrate that the NRC reactions were significantly faster with similar selectivity in the presence of various functional moieties (e.g., amine, ketone, alcohol) than the well-known Cu-catalyzed azide/alkyne "click" reactions at room temperature and are comparable to the ultrafast thiol−ene[20,21,51] and hetero-Diels−Alder (HDA) cycloaddition reactions.[23−25] The most interesting feature of this approach, however, was the reversibility of these reactions and the ability to exchange the various functional nitroxides.

Conclusion

The disproportionation of Cu(I)Br species into nascent Cu(0) and Cu(II)Br_2 species in the presence of DMSO and Me_6TREN ligand was used to significantly accelerate the activation of alkyl halides to their corresponding incipient radicals via a single electron transfer process. These radicals were then coupled (trapped) at close to diffusion-controlled rates with TEMPO nitroxide derivatives to form the resultant alkoxyamines. This NRC reaction was significantly faster and used greatly reduced amounts of Cu(I)Br than previous ATNRC reactions. Functionalization of polymer end groups with TEMPO derivatives (−≡, −OH, −COOH, $-NH_2$, =O) was near quantitative in under 10 min at room temperature using the NRC reaction. Analysis of the end groups by ^{1}H NMR spectroscopy and MALDI-ToF

mass spectrometry showed that the NRC reactions were ultrafast, selective, and highly efficient even in the presence of functional groups attached to the nitroxide. The orthogonality of the NRC reaction was demonstrated using Cu-catalyzed azide/alkyne "click" (CuAAC) reactions, in which yields greater than 95% were observed for coupling between PSTY-N_3 and PSTY-TEMPO-≡. The reversibility of the trapping process (decoupling of the alkoxyamine) at elevated temperatures, to regenerate the nitroxide and carbon-centered radical, was further exploited to exchange the chain end with nitroxides having a different chemical functionality (−≡, −OH) with high efficiency.

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Supporting Information Available: Syntheses of 4-hydroxy-2,2,6,6-tetramethylpiperidin-1-yloxyl (TEMPO-OH), 2,2,6,6-tetramethylpiperidon-1-yloxyl (4-oxo-TEMPO), and 2,2,6,6-tetramethyl-4-(prop-2-ynyloxy)piperidine-1-yloxyl (TEMPO-≡); MALDI-ToF, ^{1}H NMR, and ATR-FTIR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2001**, *40* (11), 2004–2021.
(2) Joralemon, M. J.; O'Reilly, R. K.; Matson, J. B.; Nugent, A. K.; Hawker, C. J.; Wooley, K. L. *Macromolecules* **2005**, *38* (13), 5436–5443.
(3) Thibault, R. J.; Takizawa, K.; Lowenheilm, P.; Helms, B.; Mynar, J. L.; Frechet, J. M. J.; Hawker, C. J. *J. Am. Chem. Soc.* **2006**, *128* (37), 12084–12085.
(4) Malkoch, M.; Thibault, R. J.; Drockenmuller, E.; Messerschmidt, M.; Voit, B.; Russell, T. P.; Hawker, C. J. *J. Am. Chem. Soc.* **2005**, *127* (42), 14942–14949.
(5) Luo, X.; Wang, G.; Pang, X.; Huang, J. *Macromolecules* **2008**, *41* (7), 2315–2317.
(6) Jiang, X.; Vogel, E. B.; Smith, M. R.III; Baker, G. L. *Macromolecules* **2008**, *41* (6), 1937–1944.
(7) Binder, W. H.; Sachsenhofer, R. *Macromol. Rapid Commun.* **2007**, *28* (1), 15–54.
(8) O'Reilly, R. K.; Joralemon, M. J.; Hawker, C. J.; Wooley, K. L. *J. Polym. Sci., Part A: Polym. Chem.* **2006**, *44* (17), 5203–5217.
(9) Vestberg, R.; Malkoch, M.; Kade, M.; Wu, P.; Fokin, V. V.; Sharpless, K. B.; Drockenmuller, E.; Hawker, C. J. *J. Polym. Sci., Part A: Polym. Chem.* **2007**, *45* (14), 2835–2846.
(10) Urbani, C. N.; Bell, C. A.; Lonsdale, D.; Whittaker, M. R.; Monteiro, M. J. *Macromolecules* **2008**, *41* (1), 76–86.
(11) Urbani, C. N.; Bell, C. A.; Lonsdale, D. E.; Whittaker, M. R.; Monteiro, M. J. *Macromolecules* **2007**, *40* (19), 7056–7059.
(12) Urbani, C. N.; Bell, C. A.; Whittaker, M. R.; Monteiro, M. J. *Macromolecules* **2008**, *41* (4), 1057–1060.
(13) Urbani, C. N.; Lonsdale, D. E.; Bell, C. A.; Whittaker, M. R.; Monteiro, M. J. *J. Polym. Sci., Part A: Polym. Chem.* **2008**, *46* (5), 1533–1547.
(14) Whittaker, M. R.; Urbani, C. N.; Monteiro, M. J. *J. Am. Chem. Soc.* **2006**, *128* (35), 11360–11361.
(15) Gao, H.; Matyjaszewski, K. *Macromolecules* **2006**, *39* (15), 4960–4965.
(16) Yuan, Y.-Y.; Wang, Y.-C.; Du, J.-Z.; Wang, J. *Macromolecules* **2008**, *41* (22), 8620–8625.
(17) Hua, C.; Peng, S.-M.; Dong, C.-M. *Macromolecules* **2008**, *41* (18), 6686–6695.
(18) Lutz, J.-F. *Angew. Chem., Int. Ed.* **2007**, *46* (7), 1018–1025.
(19) Kluger, C.; Binder, W. H. *J. Polym. Sci., Part A: Polym. Chem.* **2006**, *45* (3), 485–499.
(20) Campos, L. M.; Killops, K. L.; Sakai, R.; Paulusse, J. M. J.; Damiron, D.; Drockenmuller, E.; Messmore, B. W.; Hawker, C. J. *Macromolecules* **2008**, *41* (19), 7063–7070.
(21) Killops, K. L.; Campos, L. M.; Hawker, C. J. *J. Am. Chem. Soc.* **2008**, *130* (15), 5062–5064.
(22) Rosen, B. M.; Lligadas, G.; Hahn, C.; Percec, V. *J. Polym. Sci., Part A: Polym. Chem.* **2009**, *47*, 3931–3939.
(23) Sinnwell, S.; Synatschke, C. V.; Junkers, T.; Stenzel, M. H.; Barner-Kowollik, C. *Macromolecules* **2008**, *41* (21), 7904–7912.
(24) Nebhani, L.; Sinnwell, S.; Inglis, A. J.; Stenzel, M. H.; Barner-Kowollik, C.; Barner, L. *Macromol. Rapid Commun.* **2008**, *29* (17), 1431–1437.
(25) Inglis, A. J.; Sinnwell, S.; Davis, T. P.; Barner-Kowollik, C.; Stenzel, M. H. *Macromolecules* **2008**, *41* (12), 4120–4126.
(26) Inglis, A. J.; Sinnwell, S.; Stenzel, M. H.; Barner-Kowollik, C. *Angew. Chem., Int. Ed.* **2009**, *48*, 2411–2414.
(27) Fu, Q.; Wang, G.; Lin, W.; Huang, J. *J. Polym. Sci., Part A: Polym. Chem.* **2009**, *47* (3), 986–990.
(28) Luo, X.; Wang, G.; Huang, J. *J. Polym. Sci., Part A: Polym. Chem.* **2008**, *47* (1), 59–68.
(29) Fu, Q.; Liu, C.; Lin, W.; Huang, J. *J. Polym. Sci., Part A: Polym. Chem.* **2008**, *46* (20), 6770–6779.
(30) Liu, C.; Pan, M.; Zhang, Y.; Huang, J. *J. Polym. Sci., Part A: Polym. Chem.* **2008**, *46* (20), 6754–6761.
(31) Lin, W.; Fu, Q.; Zhang, Y.; Huang, J. *Macromolecules* **2008**, *41* (12), 4127–4135.
(32) Fu, Q.; Lin, W.; Huang, J. *Macromolecules* **2008**, *41* (7), 2381–2387.
(33) Nicolay, R.; Marx, L.; Hemery, P.; Matyjaszewski, K. *Macromolecules* **2007**, *40* (26), 9217–9223.
(34) Matyjaszewski, K.; Woodworth, B. E.; Zhang, X.; Gaynor, S. G.; Metzner, Z. *Macromolecules* **1998**, *31*, 5955–5957.
(35) Otsuka, H.; Aotani, K.; Higaki, Y.; Takahara, A. *Chem. Commun.* **2002**, 2838–2839.
(36) Otsuka, H.; Aotani, K.; Higaki, Y.; Takahara, A. *J. Am. Chem. Soc.* **2003**, *125*, 4064–4065.
(37) Higaki, Y.; Otsuka, H.; Takahara, A. *Macromolecules* **2004**, *37*, 1696–1701.
(38) Xia, J.; Gaynor, S. G.; Matyjaszewski, K. *Macromolecules* **1998**, *31*, 5958–5959.
(39) Queffelec, J.; Gaynor, S. G.; Matyjaszewski, K. *Macromolecules* **2000**, *33*, 8629–8639.
(40) Percec, V.; Guliashvili, T.; Ladislaw, J. S.; Wistrand, A.; Stjerndahl, A.; Sienkowska, M. J.; Monteiro, M. J.; Sahoo, S. *J. Am. Chem. Soc.* **2006**, *128* (43), 14156–14165.
(41) Percec, V.; Popov, A. V.; Ramirez-Castillo, E.; Monteiro, M.; Barboiu, B.; Weichold, O.; Asandei, A. D.; Mitchell, C. M. *J. Am. Chem. Soc.* **2002**, *124* (18), 4940–4941.
(42) Ciampolini, M.; Nardi, N. *Inorg. Chem.* **1966**, *5*, 41–44.
(43) Reiser, O.; Gheorghe, A.; Matsuno, A. *Adv. Synth. Catal.* **2006**, *348* (9), 1016–1020.
(44) Monteiro, M. J.; Guliashvili, T.; Percec, V. *J. Polym. Sci., Part A: Polym. Chem.* **2007**, *45* (10), 1835–1847.
(45) Lligadas, G.; Rosen, B. M.; Bell, C. A.; Monteiro, M. J.; Percec, V. *Macromolecules* **2008**, *41* (22), 8365–8371.
(46) Lligadas, G.; Rosen, B. M.; Monteiro, M. J.; Percec, V. *Macromolecules* **2008**, *41* (22), 8360–8364.
(47) Ladaviere, C.; Lacroix-Desmazes, P.; Delolme, F. *Macromolecules* **2009**, *42* (1), 70–84.
(48) Schulte, T.; Siegenthaler, K. O.; Luftmann, H.; Letzel, M.; Studer, A. *Macromolecules* **2005**, *38* (16), 6833–6840.
(49) Rizzardo, E.; Serelis, A. K.; Solomon, D. H. *Aust. J. Chem.* **1982**, *35* (10), 2013–2024.
(50) Busfield, W. K.; Jenkins, I. D.; Monteiro, M. J. *Polymer* **1997**, *38* (1), 165–171.
(51) Chan, J. W.; Hoyle, C. E.; Lowe, A. B. *J. Am. Chem. Soc.* **2009**, *131* (16), 5751–5753.