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Rapid and Highly Efficient Functionalization of Polymer Bromide End-Groups by SET-NRC

Zhongfan Jia,* Craig A. Bell, and Michael J. Monteiro

Australian Institute for Bioengineering and Nanotechnology, University of Queensland, Brisbane QLD 4072, Australia

Supporting Information

Synthetic polymers with chemical and biological functional end-groups have attracted considerable attention in recent years due to their broad applications in the construction of complex polymer architectures,[1] macromonomers,[2,3] bioconjugates,[4−6] polymeric therapy,[7] functional surfaces,[8,9] inorganic−organic hybrid materials, and nanotechnology.[10,11] In this work, we wanted to demonstrate the efficient, orthogonal, and rapid one-step method to functionalize polymer chain-ends with a diverse range of functionalities. The first group included glycidyl ether, styryl, acrylate, and methacrylate functionalities that form macromonomers and have the potential to lead to polymer brushes with high grafting densities,[12] multiarm star polymers,[13] and single molecule nanorings.[14] The second group included "click"-type moieties for further reactions using Cu(I)-catalyzed azide/alkyne cycloaddition (CuAAC), alkene or alkyne thiol−ene or thiol−yne reactions.[15] The third group included active esters for postfunctionalization attachment of biomolecules.[16] The last and fourth group included fluorophores as probes for imaging and attaching targeting-specific moieties for biorecognition.[6,17]

The most used living radical polymerization (LRP) techniques, including reversible addition−fragmentation transfer (RAFT) polymerization,[18] atom transfer radical polymerization (ATRP),[19] and single electron transfer-living radical polymerization (SET-LRP),[20,21] produces polymer chains with dithioester or trithiocarbonate (for RAFT) or halide (ATRP and SET-LRP) end-groups. The RAFT end-groups can be transformed by first converting it to a thiol via an aminolysis reactions and then reacting the thiol with other functional thiols (disulfide formation)[22−24] or with functional acrylates or methacrylates via an *in situ* Michael addition reaction.[25−27] In ATRP or SET-LRP, the halide chain-ends can be converted to azides for CuAAC reactions with alkyne functional small molecule compounds or polymers, leading toward functional polymers[19,28] and complex structures.[29,30] In addition, thio−bromo "click" reactions introduced by Percec et al.[31,32] and atom transfer nitroxide radical coupling (ATNRC) reactions by Matyjaszewski[19,33,34] and Huang[35−37] provide another strategy for chemical modification of polymers. In addition, a chemically diverse range of ATRP initiators have been used to modify one end of a polymer chain.[38,39] However, there are only a few reports for a universal and efficient one-step postpolymerization method.[40−42] These reports demonstrate the introduction of a wide variety of chemical functionalities to polymer chain-ends (i.e., with halide end-groups) made by either ATRP or SET-LRP that are reversible and in which the functional end-group can be exchanged for another with little or no side reactions.

Our group recently reported a rapid SET-NRC method using the catalyst Cu(I)Br/Me_6TREN in DMSO to synthesize three-arm polystyrene (PS) star in only a few minutes at ambient temperature.[40] The three-arm PS stars could be degraded to its linear species by heating and capping the end-groups with functionalities ranging from ketones, amines, hydroxyl, and carboxylic acid groups. Kinetic simulations showed that the SET-NRC coupling was highly efficient with little or no side reactions, indicating that the NRC reaction was specific and can be used in orthogonal reactions.[42] In this work, we further exemplify the speed, orthogonal, and versatile nature of the SET-NRC reaction with the reaction of a wide range of reactive and nonreactive functional nitroxides onto polystyrene (PS) and poly(*tert*-butyl acrylate) (P^tBA) chain-ends (Scheme 1). The functional nitroxide library was prepared from the single parent nitroxide, HTEMPO. The resulting polymers were fully characterized to determine the efficiency of the NRC reaction and the presence of side reactions (if any).

A straightforward one-step etherification or esterification syntheses produced the functional nitroxide library (Scheme 1A) from the parent HTEMPO. The ease of purification of the resulting compounds by column chromatography was due to the bright orange color of the product and its very different polarity from the starting HTEMPO. The range of nitroxides synthesized include (**a**) glycidyl ether, (**b**) styryl, (**c**) acrylate, (**d**) methacrylate, (**e**) alkyne, (**f**) dialkyne, (**g**) tosylate, (**h**) active ester, (**i**) biotin, and (**j**) pyrene group (Scheme 1C). Characterization of these compounds by ESI-MS and elemental analysis showed excellent agreement between the found and calculated molecular weight. Characterization by ^{1}H NMR for products **a**, **g**, **h**, **i**, and **j** was made possible by the *in situ* reduction of the nitroxide radical to a hydroxyl amine with a catalytic amount of ammonium formate and palladium on carbon (Pd/C).[43] Compounds with double or triple bonds (**b**, **c**, **d**, **e**, and **f**) readily reduce in the presence of ammonium formate and Pd/C and precluded their analysis by NMR (Supporting Information).

Conventional ATRP produced polymers **1** (PS-Br) and **2** (P^tBA-Br) with a low poydispersity index (PDI) of 1.10. A 20% equivalent of Cu(II)Br_2 to Cu(I)Br in combination with stopping the reaction around 50% conversion ensured the low PDI and high chain-end functionality. The Br end-groups were converted into azides and "clicked" via the CuAAC reaction

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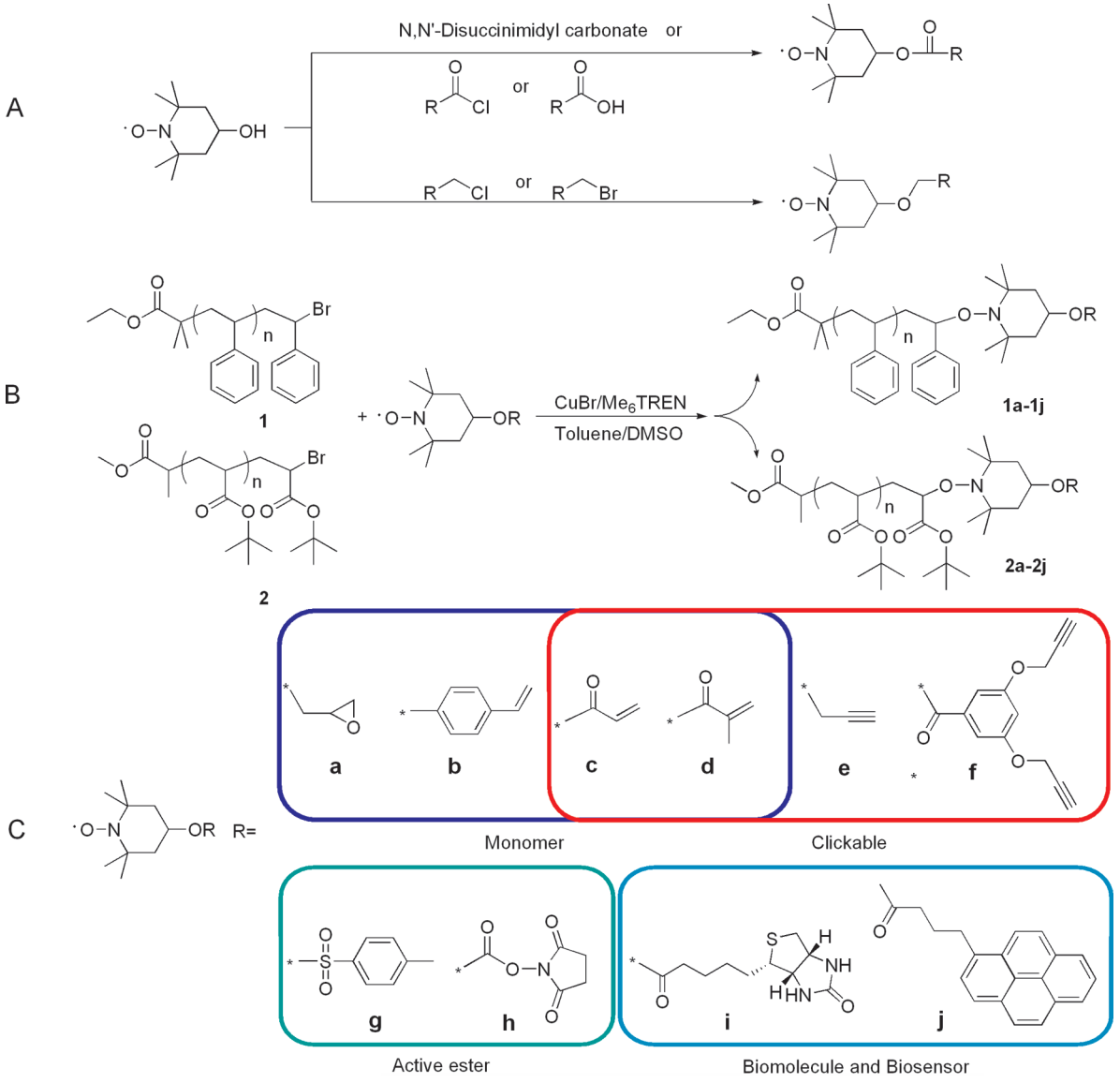
Scheme 1. End-Group Modification of PS-Br and P^{t}BA-Br with Nitroxide Radical Derivatives by SET-NRC[a]



[a] The reaction was carried out in DMSO/toluene mixture (1/1, v/v) at 25 °C for 10 min. Me_6TREN = tris(2-(dimethylamino)ethyl)amine.

with alkyne functional (bio)molecules or polymers in a two-step process.[15] Boyer and Davis[44] also report the two-step transformation of Br end-groups to a variety of functional groups using methanethiolsulfonyl functionality as the intermediate. One-step modifications of polymers **1** and **2** in this paper were performed by directly reacting all nitroxide derivatives via the SET-NRC reaction. This eliminates the two-step process and reduces the potential for loss of chain-end functionality usually found with each consecutive reaction step. Using DMSO and Me_6TREN as the solvent and ligand significantly increases the rate of disproportionation of Cu(I)Br to nascent Cu(0) and Cu(II)Br_2. Transfer of the Br end-groups by the active Cu(0) to produce a high polymeric radical flux leads to ultrafast NRC reactions at ambient temperatures with little or no radical side reactions (i.e., little or no bimolecular radical termination). A small excess of each nitroxide ensured quantitative functionalization, and the remaining nitroxide was removed by repeated precipitation.

Reactive functionalities introduced onto the polymer chain-end must be suitably protected to avoid side reactions and low capping efficiencies. In this study, despite of the experimental conditions being suitable for either radical reactions with the monomer-type nitroxides (**b**−**d**) or Glaser coupling reaction of alkyne nitroxide (**e**, **f**), no such side-reactions were observed. The functionalized polymers after SET-NRC were first characterized by SEC. Table 1 shows that the molecular weight of the functionalized polymers increased by 100−700 in accord with the molecular weight of the nitroxide compound. All the chain-end-modified polymers produced unimodal SEC traces (Figures S23 and S24) with narrow polydispersity indexes. The SET-NRC coupling reactions with chromophoric groups on the nitroxides were further detected using a photodiode array detector attached to the SEC. The UV spectra of **1f** and **2f** recorded at the peak elution time showed an absorbance at 305 nm characteristic of the phenyl ring on the dialkyne-TEMPO (**f**), and the spectra of

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Table 1. Polymer Characterization of PS-Br, P^{t}BA-Br, and Their Corresponding End-Group-Modified Products

	PS-R				P^{t}BA-R			
-R	M_n[a]	PDI[b]	functionality (%)[c]	conv (%)[d]	M_n[a]	PDI[b]	functionality (%)[c]	conv (%)[d]
Br	1700	1.11	95.4		2080	1.10	96.3	
a	2190	1.07	94.8	99.4	2190	1.09	96.0	99.7
b	2200	1.09	93.2	97.7	2300	1.09	92.8	96.4
c	2230	1.07	94.5	99.1	2290	1.11	94.7	98.3
d	2160	1.07	91.5	95.6	2260	1.10	91.4	94.9
e	2240	1.08	91.7	96.1	2230	1.10	95.1	98.8
f	2400	1.07	95.1	99.7	2510	1.08	94.3	97.8
g	2080	1.08	89.0	93.3	2260	1.09	94.0	97.6
h	2060	1.08	88.0	92.2	2300	1.09	90.0	93.4
i	1780	1.09	90.0	94.3	2110	1.13	92.7	96.3
j	2140	1.08	95.2	99.8	2340	1.09	95.0	98.7

[a] Molecular weights from SEC in THF are based on PS standards. [b] Polydispersity index. [c] End-group functionality calculated from ^{1}H NMR spectra based on the integration ratio of protons from initiator to the functional end-group. [d] End-group transformation efficiency based on the -Br functionalities of PS or P^{t}BA prior to NRC functionalization.

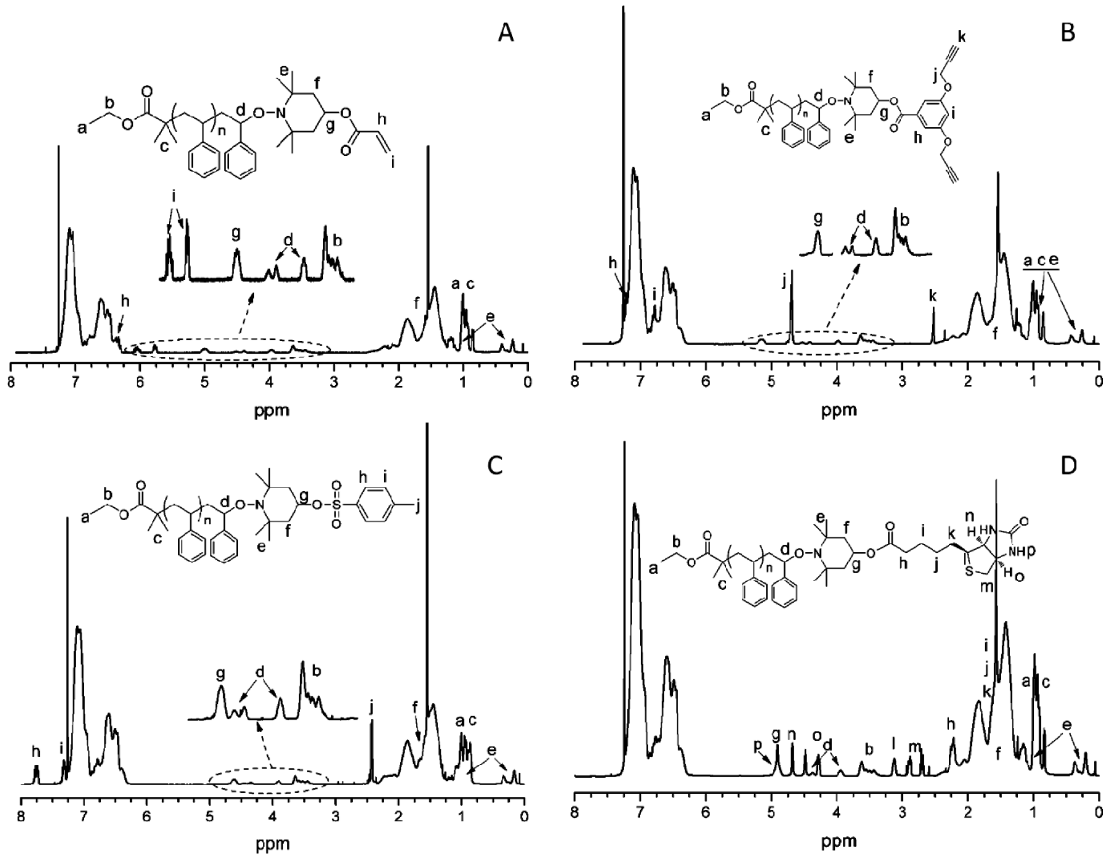

Figure 1. Typical ^{1}H NMR spectra of each groups of functional PS chain-end (A) **1c**, (B) **1f**, (C) **1g**, and (D) **1i**.

1j and **2j** showed the characteristic absorbance peaks at 276 and 343 nm attributed to pyrene group (Figures S47 and S48).

Analysis of the polymer chain-ends after SET-NRC by ^{1}H NMR allowed the determination of chain-end functionality, which was then used to calculate the SET-NRC coupling efficiency. Typical ^{1}H NMR spectra given in Figure 1 show the high functionalization of PS after the SET-NRC reaction (all other ^{1}H NMR spectra for other PS and P^{t}BA componds are given in the Supporting Information). Characteristic proton peaks for the functionalization of PS-Br with four functional nitroxides were as follows: the double bond protons for **1c** were found at 5.77 and 6.06 ppm (Figure 1A), the alkyne and methylene protons of di-alkyne functionalized PS chain-end **1e** (Figure 1B) were found at 2.52 and 4.70 ppm, the methyl and phenyl protons of tosylate functionalized PS **1g** (Figure 1C) were found at 2.44 and 7.76 ppm, the methylene protons of biotin functionalized PS **1i** (Figure 1D) were found between 2.71 and 2.88 ppm. The NMR showed no evidence of any side reactions, supporting the highly efficient

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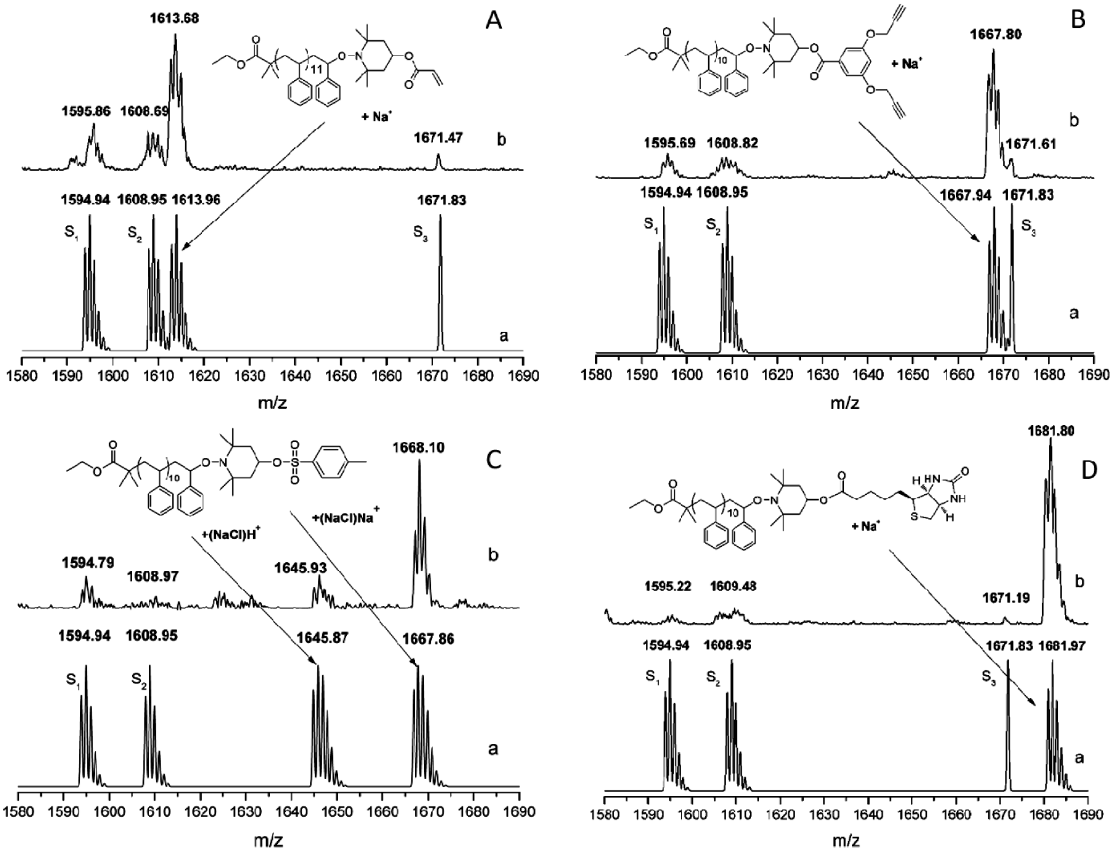

Figure 2. Typical ESI-MS spectra of each type of functional PS with NaI as salt and DCM/MeOH (1/3, v/v) as solvent (A) **1c** (cone voltage = 100 V), (B) **1f** (cone voltage = 100 V), (C) **1g** (cone voltage = 50 V) (NaCl was possible from the brine which was added to the methanol to help the precipitation of PS), and (D) **1i** (cone voltage = 120 V), where "a" represents theoretical isotopic resolution and "b" recorded isotopic resolution.

SET-NRC reaction. The end-group functionality was calculated based on the integration ratio of methylene protons at 3.63 ppm of PS-Br or methyl protons at 3.62 ppm of P^{t}BA-Br from the ATRP initiator (Figures S1 and S12) to that of typical protons from nitroxide functional groups. Most of the chain-end functionalities ranged from 90 to 95% (Table 1). However, this percentage does not account for the starting halide functionality of PS-Br (95.4%). The NRC efficiency, therefore, showed near-quantitative coupling close to 99%, strongly supporting the "click" attributes of the SET-NRC reaction.

ESI-MS instead of MALDI-TOF was used for the characterization and identification of polymer chain-end. The high energy of the MALDI-TOF caused cleavage of the alkoxyamine linkage.[45] We also found that the cone voltage used in the ESI-MS affected identification and signal strength of the end-group. Notable, was that both the C−Br and the alkoxyamine bonds attached to P^{t}BA had a higher tolerance to increased cone voltages than those of PS products. The end groups were present at lower cone voltages but at the cost of a lower signal strength. Hence, the spectra of all the samples have been recorded using different, suitable cone voltages (Supporting Information).

Figure 2A−D shows the typical ESI-MS spectra of four modified PS (**1c**, **1f**, **1g**, and **1i**), and the ESI-MS spectra for all other compounds are given in the Supporting Information. In all cases, the main peaks matched with the theoretical isotopical resolution, confirming the modification of the polymer chain-end with the functional nitroxides. Some small species were also observed and marked as S_1, S_2, and S_3 (NaI clusters). These fragmentation patterns, similar to the previous studies,[40,45] were identified as species found by cleavage of C−Br bond on PS and cleavage of the alkoxyamine attached to PS after ESI-MS. The chain-ends after cleavage of the PS-Br were the inner double bond structure S1, while cleavage of the alkoxyamine gave both inner and outer bond structures, S1 and S2, of equal intensity. All the ESI-MS spectra showed S1 and S2 of equal intensity (Figures S26−S35), supporting alkoxyamine rather than PS-Br cleavage. These ESI-MS results further support the high chain-end functionally from the NRC reaction (see Supporting Information for all other spectra).

In summary, a library of functional TEMPO-based molecules were synthesized and directly coupled onto polymers, PS-Br and P^{t}BA-Br, using SET-NRC. These SET-NRC reactions were completed in less than 10 min, resulting in polymers with functionalities above 90% and near-quantitative coupling efficiencies of greater than 95%. ^{1}H NMR showed no evidence of side reactions, and ESI-MS showed that all the end-groups matched with their theoretical isotopic resolution patterns. This fast and efficient coupling reaction represents a mild, versatile, orthogonal, and highly practical strategy for the functionalization and construction of a wide range of macromolecules. Our synthetic methodology could have an impact on a diverse range of areas such as bioconjugation, advanced materials, surface modification, sensors, and nanotechnology.

■ ASSOCIATED CONTENT

Supporting Information. Synthesis and characterizations of all the TEMPO derivatives, experimental details of end-group

modification reactions, all the ^{1}H NMR spectra, SEC traces, ESI-MS spectra, and UV−vis spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author
*E-mail: z.jia@uq.edu.au.

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