DOI: 10.1002/ejoc.201001043

Oxidation of Alkylcatecholboranes with Functionalized Nitroxides for Chemical Modification of Cyclohexene, Perallylated Polyglycerol and of Poly(butadiene)

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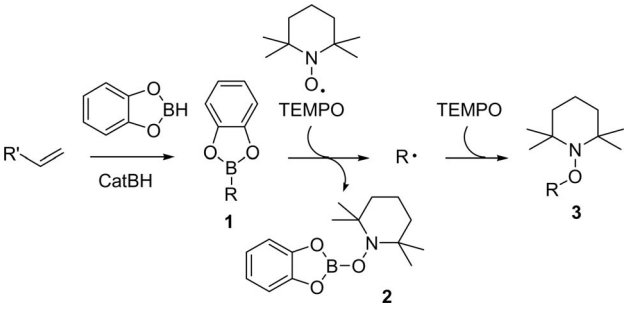
Keywords: Polymers / Hydroboration / Polymer modification / Boron / Radicals / Nitroxides

The present communication reports on the synthesis of alkoxyamines by hydroboration of olefins with catecholborane and subsequent oxidation by using nitroxides. Oxidation occurs via a radical process and the intermediately formed C-radicals are trapped by the nitroxides to form the corresponding alkoxyamines. If functionalized nitroxides are used, the method allows incorporation of interesting functional moieties via this approach. The novel method is applied for chemical modification of cyclohexene as a test substrate. More importantly, it is also shown that the reaction sequence can be used for chemical modification of macromolecules containing multiple double bonds. This is documented by successful functionalization of poly(butadiene) and of perallylated polyglycerol.

Introduction

There are two reasons for introducing boryl substituents into polymers: a) boron atoms alter the physical properties of a polymer,[1] and b) boron substituents can be used as reactive functional groups that are readily replaced/substituted for further chemical modification of the polymers by oxidation, C–C coupling or other reactions. B-containing polymers have successfully been prepared by polymerization of boron-containing monomers.[1–4] In addition, borylated polymers are accessible by introducing the boryl substituents into an existing polymer via chemical modification of the polymer backbone or its side chains. Along this line, direct transition-metal-catalyzed C–H borylation has been achieved.[5] Moreover, lithiated polymers react with B-electrophiles to give borylated polymers,[1,6] and silylated polystyrene has been reported to react with BBr_3 in an electrophilic aromatic substitution to yield B-substituted polystyrene.[7] Most obviously, hydroboration can be used for the transformation of polymers containing alkene moieties into the corresponding B-containing polymers.[8]

Alkylcatecholboranes have been applied as precursors for generation of C-radicals upon reaction with TEMPO (2,2,6,6-tetramethylpiperidine-*N*-oxyl radical).[9,10,11] In these reactions, one equivalent of the nitroxide reacts with a B-alkylcatecholborane **1** in a formal homolytic substitution at boron to the boric ester **2** and the corresponding C-centered radical, which is subsequently trapped by TEMPO to form alkoxyamine **3** (Scheme 1). In the present communication we report on the application of this reaction for the introduction of various functional moieties into cyclohexene as a test olefin as well as into macromolecules containing multiple double bonds. The sequence comprises catecholborane (CatBH)-mediated hydroboration followed by nitroxide oxidation to give the corresponding alkoxyamines. The mild process should allow the use of olefins with nitroxides containing various interesting functional groups.



Scheme 1. Transformation of olefins into TEMPO-derived alkoxyamines.

Results and Discussion

We first tested the reaction of cyclohexylcatecholborane, readily prepared by treating cyclohexene in CH_2Cl_2 with catecholborane (CatBH) in the presence of catalytic amounts of *N*,*N*-dimethylacetamide,[12] with different TEMPO derivatives to afford the corresponding alkoxyamines. This reaction was reported by Renaud to occur in a good yield with the parent TEMPO as an oxidant/C-radical trapping reagent.[13] We used 12 different nitroxides

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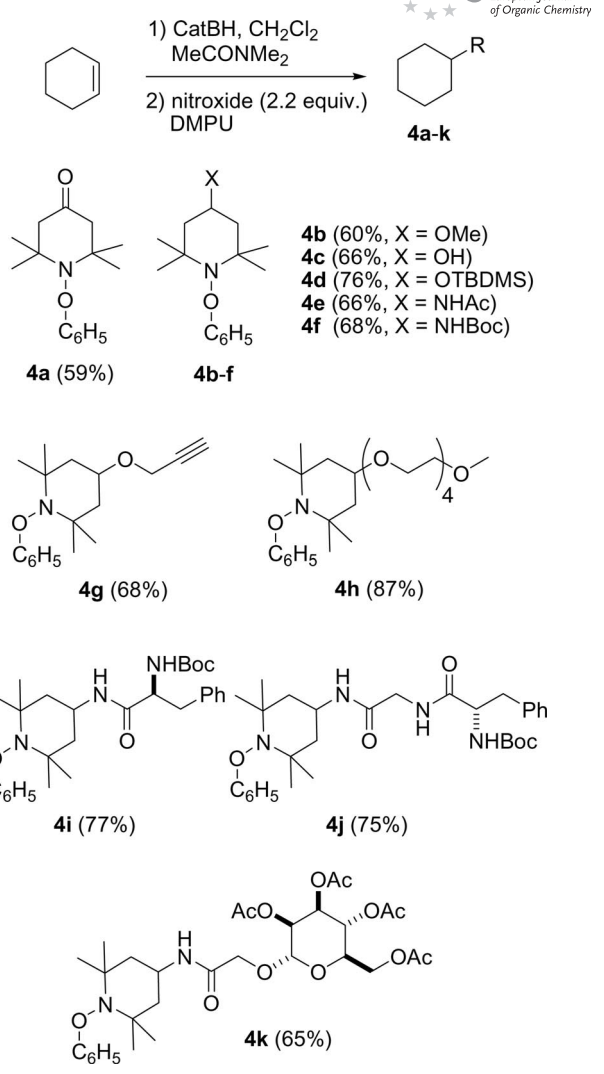
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201001043.

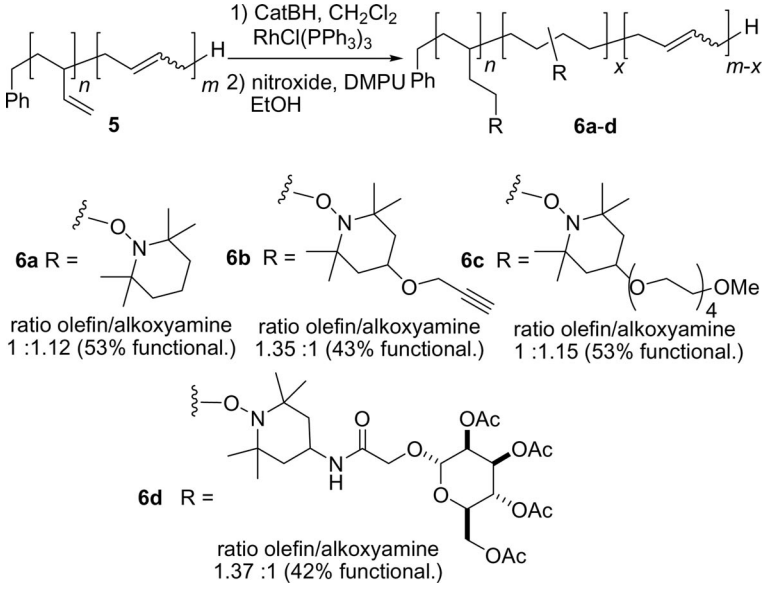
in these studies. Experimental details on the synthesis of TEMPO derivatives that are not commercially available can be found in the Supporting Information. Oxidation was best conducted by adding the nitroxide (2.2 equiv.) to the in situ generated boron compound **1** (R = C_6H_{11}) in the presence of 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU) to provide alkoxyamines **4a**–**k** in moderate to good yields (Scheme 2). By using the 4-oxo-TEMPO derivative as an oxidant, the targeted alkoxyamine **4a** was obtained in 59% isolated yield. 4-hydroxy-TEMPO and its protected derivatives afforded the corresponding trapping products **4b**–**d** in up to 76% yield. Importantly, more valuable groups such as a small PEG-tail (see **4h**) or a propargyl group, ready for subsequent click chemistry (see **4g**), can be introduced by this approach.

Along the ether tether, we could also show that the amino group can be used for conjugation of interesting functionalities to the nitroxide component. Thus, acetyl and Boc-protected 4-amino-TEMPO worked well in this oxidation/trapping sequence (see **4e**,**f**). Moreover, with Boc-phenylalanine-conjugated amino-TEMPO the desired alkoxyamine **4i** (77%) was obtained and a similar result was achieved with a dipeptide conjugated TEMPO derivative to give alkoxyamine **4j** in 75% yield. Protected sugar derivatives can be conjugated to give olefins via this route as documented by the successful preparation of the mannose derivative **4k**.

We then decided to apply the hydroboration/oxidation sequence to macromolecules containing multiple double bonds as a novel method for conjugation of interesting moieties to polymers for preparation of functionalized macromolecules. Chemical modification of polymers by using click-type chemistry has recently gained increased attention.[14] Towards this end, we chose poly(butadiene) **5** (M_n = 1800 g/mol, PDI = 1.34, according to ^{1}H NMR: ratio 1,2- vs. 1,4-addition, 1.8:1) and perallylated polyglycerol **7**, that

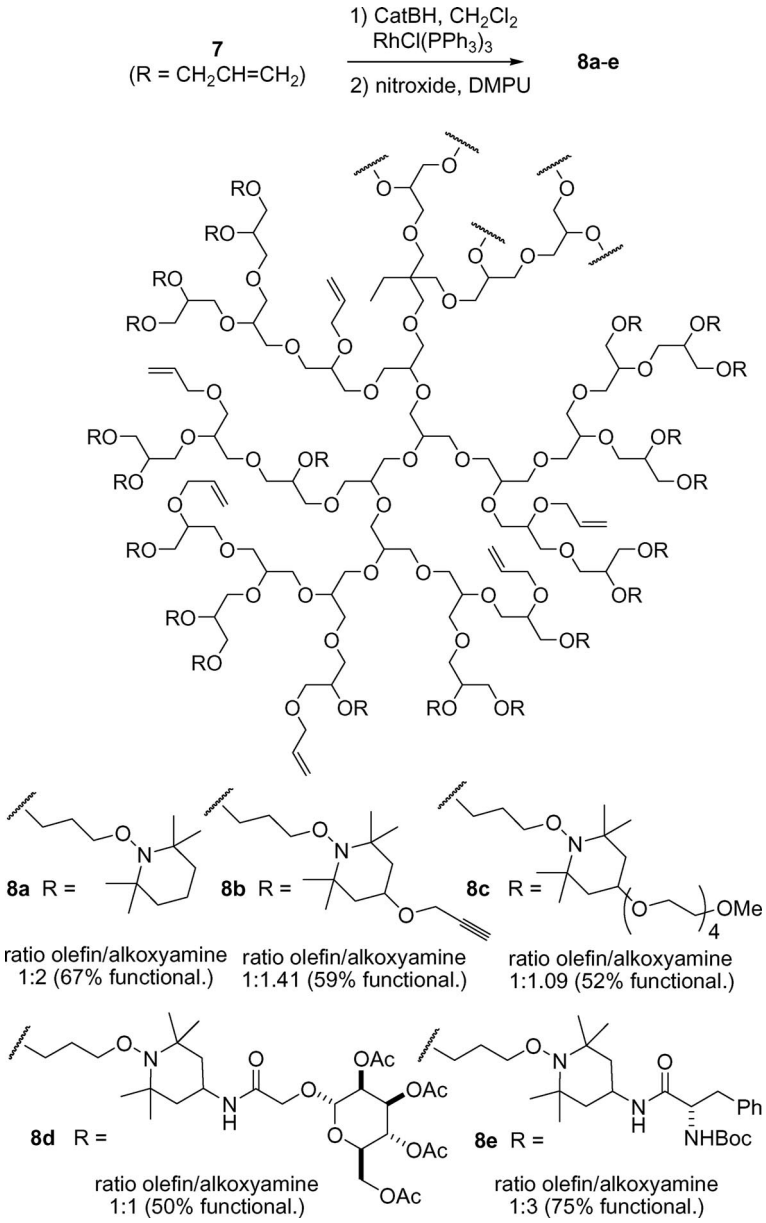


Scheme 2. Oxidation of cyclohexylcatecholborane with various nitroxides.



Scheme 3. Chemical functionalization of poly(butadiene) **5**.

is readily prepared from commercially available polyglycerol (M_n = 6000 g/mol, PDI < 1.5),[15] as substrates. We found that the catecholborane-mediated hydroboration of these systems was best conducted by using $RhCl(PPh_3)_3$ as catalyst. By applying ^1H NMR spectroscopy we found that the initial hydroboration of poly(butadiene) occurred highly preferentially at the vinylic olefins, the internal olefins were converted to a smaller extent. Since hydroboration under the applied conditions on small molecular weight olefins occurs with perfect regiocontrol, we assume that the terminal olefins were transformed with high regiochemistry. However, hydroboration of the internal olefins likely occurred without any regiocontrol as indicated in Scheme 3. The intermediately formed hydroboration product was then converted into the poly(alkoxyamine) without any prior purification in a one pot process by treatment with a nitroxide in the presence of DMPU.[13] The poly(alkoxyamines)-formed were eventually purified by dialysis (see SI for details). We found that only a small amount of **6** was lost during purification. By ^1H NMR analysis we determined the ratio of unreacted olefinic protons to characteristic protons of the conjugated alkoxyamine in **6** (for ^1H NMR spectra, see the SI). We were pleased to find that our two step sequence worked also on a more complex substrate such as **5**. By using TEMPO as oxidant/trapping reagent, we isolated **6a** with a ratio of 1:1.12 of remaining olefins to alkoxyamines. A slightly lower degree of functionalization was achieved with the propargylated OH-TEMPO as a trapping reagent (see **6b**). The PEG-tail did not change reaction outcome to a large extent since a similar result as compared with the TEMPO-trapping experiment was obtained (see **6c**). We could also show that a protected sugar derivative was conjugated to poly(butadiene) by this method (see **6d**).



Scheme 4. Chemical functionalization of perallylated polyglycerol **7**.

Since all hydroborations were performed under identical conditions the varying degree of functionalization needs some comments. To destroy excess catecholborane that was used for the initial hydroboration we always added a small amount of EtOH. It was recently shown that MeOH complexed to a borane might become a quite good radical reducing reagent.[16] Therefore, we currently believe that the EtOH present in combination with a CatB-Lewis acid might act as a reducing reagent and thereby might reduce the degree of alkoxyamine functionalization in our reactions.[17] It was not possible to identify the reduction product due to peak overlap.

Finally, we applied the hydroboration/oxidation/nitroxide trapping cascade to the modification of perallylated polyglycerol **7**.[15] Experiments were conducted in analogy to those performed on **5** and results are summarized in Scheme 4. Degree of functionalization was estimated by ^{1}H NMR analysis as described above for poly(butadiene). Five different nitroxides were used in these studies. The oxidation/trapping sequence provided dendritic type architectures decorated with various interesting functionalities. Hence, a propargyl substituent was successfully introduced via this approach onto **7** (see **8b**) and also pegylation of perallylated polyglycerol was possible (see **8c**). More importantly, decoration of **7** with biologically interesting groups such as protected sugars (see **8d**) and protected phenylalanine (see **8e**) could be achieved clearly documenting the potential of our approach. It is important to note that experiments are easy to conduct without the need for any special equipment.

Conclusions

In summary, we showed that hydroboration with catecholborane followed by oxidation by using a functionalized nitroxide leads to the corresponding C-radical which is immediately trapped by the nitroxide to provide a functionalized alkoxyamine. The reaction sequence tolerates various interesting functionalities that are propargyl ethers, free hydroxy groups, PEG tails and protected amines. Along this line it was shown that protected sugars and also amino acids can be conjugated to olefins via this novel approach. Importantly, this method can be applied for the chemical modification of poly(butadiene) and of perallylated polyglycerol to give the corresponding functionalized macromolecules.

Experimental Section

Materials: Catecholborane (from Alfa Aesar, 97%) was distilled under reduced pressure before use. THF was freshly distilled from K, CH_2Cl_2 was distilled from P_2O_5. All solvents for extraction and flash chromatography were distilled before use. Poly(butadiene) (Acros, $M_n \approx 1800$ g mol^{-1}, PDI ≈ 1.34, according to ^{1}H NMR: ratio 1,2- vs. 1,4-addition, 1.8:1) and polyglycerol (Hyperpolymers GmbH, $M_n \approx 6000$ g mol^{-1}, PDI < 1.5, ca. 13.3 mmol g^{-1} of OH) were used as received. All other chemicals were used as received. Flash column chromatography (FC) was carried out on Merck silica gel 60 (40–63 μm) with an argon pressure of about 0.6–1.0 bar. Dialysis was performed in chloroform using a benzoylated cellulose membrane (MWCO 2000, Sigma).

Characterization: ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX 300 (^{1}H: 300 MHz; ^{13}C: 75 MHz), a Bruker AV 400 (^{1}H: 400 MHz; ^{13}C: 100 MHz) or a Varian 500 INOVA (^{1}H: 500 MHz) spectrometer at room temperature. ESI-MS (*m*/*z*) and HRMS (*m*/*z*) were performed on a Bruker MicroTof. Melting points were determined on a Stuart SMP10 and are uncorrected. Infrared spectra were recorded on a Digilab Varian 3100 FT-IR Excalibur Series.

Representative Example for the Alkoxyamination of Cyclohexene: According to a procedure described by Renaud et al.,[9] catecholborane (95 μL, 0.90 mmol, 2.0 equiv.) was added at 0 °C to a solution of cyclohexene (46 μL, 0.45 mmol) and *N*,*N*-dimethylacetamide (4 μL, 0.05 mmol, 10 mol-%) in CH_2Cl_2 (0.8 mL) and the mixture was heated in a sealed tube to 60 °C for 3 h. EtOH (26 μL, 0.45 mmol, 1.0 equiv.) was added slowly at 0 °C and the solution was stirred for 15 min at room temperature. After the addition of DMPU (54 μL, 0.45 mmol, 1.0 equiv.) and 4-oxo-TEMPO (169 mg, 0.990 mmol, 2.2 equiv.) the reaction was stirred overnight at room temperature. The reaction mixture was filtered through a plug of silica gel (MTBE as eluent). The filtrate was concentrated under reduced pressure and the residue was purified by FC.

Representative Example for the Alkoxyamination of Poly(butadiene): According to a procedure described by Renaud et al.,[9] catecholborane (53 μL, 0.50 mmol, 2.0 equiv.) was added at 0 °C to a solution of poly(butadiene) **5** (24 mg, approximately 0.25 mmol of double bonds) and $RhCl(PPh_3)_3$ (5 mg, 5 μmol, 2 mol-%) in CH_2Cl_2 (0.8 mL) and the mixture was stirred for 3 h at room temperature. EtOH (15 μL, 0.25 mmol, 1.0 equiv.) was added slowly at 0 °C and the solution was stirred for 15 min at room temperature. After the addition of DMPU (30 μL, 0.25 mmol, 1.0 equiv.) and TEMPO (86 mg, 0.55 mmol, 2.2 equiv.) the reaction was stirred overnight at room temperature. The reaction mixture was filtered through a plug of celite (CH_2Cl_2 as eluent). The filtrate was concentrated under reduced pressure and the residue was purified by dialysis.

Supporting Information (see also the footnote on the first page of this article): Experimental details, compound characterization data, copies of the NMR spectra.

Acknowledgments

The Deutsche Forschungsgemeinschaft (DFG) is acknowledged for funding our research (Stu 9/1).

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Received: July 22, 2010
Published Online: September 17, 2010

