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Nitrosocarbonyl Hetero-Diels–Alder Cycloaddition: A New Tool for Conjugation

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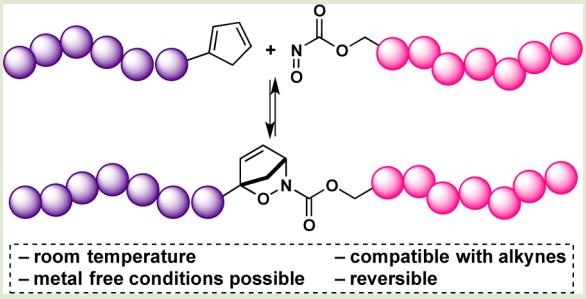
Supporting Information

ABSTRACT: It is demonstrated that nitrosocarbonyl hetero-Diels–Alder chemistry is an efficient and versatile reaction that can be applied in macromolecular synthesis. Polyethylene glycol functionalized with a hydroxamic acid moiety undergoes facile coupling with cyclopentadiene-terminated polystyrene, through a copper-catalyzed as well as thermal hetero-Diels–Alder reaction. The mild and orthogonal methods used to carry out this reaction make it an attractive method for the synthesis of block copolymers. The resulting block copolymers were analyzed and characterized using GPC and NMR. The product materials could be subjected to thermal retro [4 + 2] cycloaddition, allowing for the liberation of the individual polymer chains and subsequent recycling of the diene-terminated polymers.

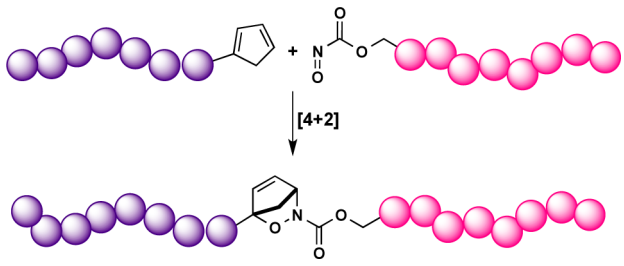


Chemical strategies that rely on "click-like" reactions to engineer well-defined macromolecules with increasing complexity and functionality have expanded significantly in the past decade.[1] As a result, a number of methods are available to chemists to carry out efficient conjugation chemistry for the synthesis of block copolymers and other more complex architectures.[2] Among these, the most widely used reaction is the copper-catalyzed Huisgen 1,3-dipolar cycloaddition,[3] owing to its high selectivity and efficiency. Other classes of well-studied click reactions include organometallic coupling reactions[4] as well as thiol–ene,[5] oxime condensation,[6] and Diels–Alder cycloaddition.[7]

Even though tremendous progress has been made in macromolecular conjugation, there still remains a need for the development of orthogonal, efficient, and mild conjugation chemistries. The Diels–Alder cycloadditions have several attractive features that make them ideal to address challenges associated with current methodology in this area. For example, the reaction can proceed in the absence of a catalyst, which is appealing for biological and macromolecular settings that are sensitive to trace metal contaminates.[8] In addition, Diels–Alder cycloadditions are thermally reversible, which offers the ability to incorporate self-healing and surface modification properties into the material.[9] Lastly, the reaction parameters (i.e., temperature and reaction time) can be tuned by making simple modifications to the diene or dienophile partners, thus increasing the versatility and potential synthetic utility.[10] Recently, Barner-Kowollik[11] and co-workers have shown that the judicious choice of diene and dienophile can be used to overcome the previous requirement of temperature in excess of 100 °C and lengthy reaction times (up to 120 h) encountered with the furan–maleimide[12] and anthracene–maleimide[13] systems. By using more reactive coupling partners, such as dithioesters commonly used as RAFT polymerization initiators and cyclopentadienyl-functionalized polymers, the hetero-Diels–Alder (HDA) polymer coupling reaction can be conducted at ambient temperature and pressure.[11] This approach has enabled the HDA cycloaddition to be used for the construction of block copolymers,[14] stars,[14a] surface functionalization,[15] reversibly cross-linked functional polymers,[16] as well as conjugations in an aqueous environment.[11b]

Our laboratory has been interested in developing nitrosocarbonyl chemistry to expand the synthetic utility of this valuable electrophilic synthon beyond the current state-of-the-art.[17] In this context, we envisioned that an in situ generated nitrosocarbonyl compound could serve as a new and versatile dienophile for conjugation chemistry (Scheme 1). Nitrosocarbonyl intermediates are exceptionally reactive electrophiles with a rich history in the HDA reactions of small molecules.[18] In a related, but distinctly different, approach,

Scheme 1. New Tool for Conjugate Formation



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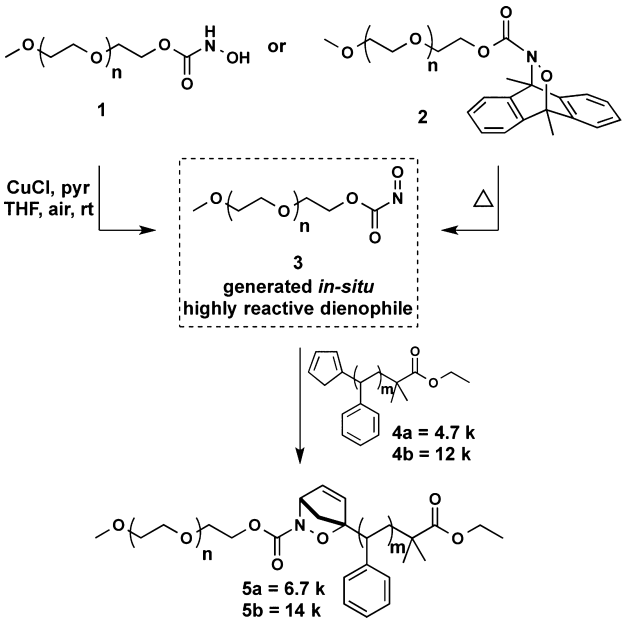
Tillman, Wang, and others have independently used nitroso compounds to facilitate the efficient coupling of two end-halogenated polymers.[19] However, to the best of our knowledge, application of the nitroso HDA reaction has not been explored in the synthesis of macromolecules.

This direct extension of small-molecule chemistry to polymer synthesis can prove to be highly challenging; however, we were motivated to expand the tools available to facilitate efficient and straightforward access to well-defined macromolecular structures using the nitrosocarbonyl HDA cycloaddition. Herein, the successful development of an efficient coupling strategy for block copolymer synthesis based on nitrosoformate dienophiles is demonstrated (Scheme 2). This approach offers a viable

Scheme 2. General Strategy for Conjugate Formation



alternative to the valuable thiocarbonyl hetero-Diels–Alder reaction, pioneered by Barner–Kowollik and co-workers, for polymer–polymer coupling. The reaction can be conducted at ambient temperature and pressure when catalyzed by Cu(I) salts or at 65 °C in the absence of a catalyst. Furthermore, by taking advantage of the reversible nature of the nitroso HDA cycloaddition at elevated temperatures, heat can be used as a mild stimulus to regenerate the cyclopentadiene-functionalized polymer, which can then be refunctionalized in a quantitative fashion.

To showcase the potential of a new synthetic strategy for the synthesis of functional polymeric materials and complex macromolecular architectures, the preparation of block copolymers has served as an excellent test vehicle. As a result, the synthesis of PEG–PS block copolymers was sought as a model case for evaluating the feasibility of nitroso HDA as a coupling/functionalization strategy (Scheme 2). To test the potential of this strategy, the hydroxamic acid functionalized PEG polymer **1** (mPEG-HA) was synthesized in a straightforward fashion using readily available monomethylated polyethylene glycol (mPEG). Ease of synthesis and characterization were the main factors with the decision to use the PEG system for the synthesis of mPEG-HA beginning with activation of the terminal alcohol via carbonyldiimidazole (*N*,*N*-CDI), followed by treatment with hydroxylamine in the presence of imidazole. Utilizing this approach mPEG-HA could be synthesized on a multigram scale in an inexpensive manner, and electrospray ionization mass spectrometry was used to characterize the new polymer end-group composition with a high degree of accuracy and sensitivity. The successful synthesis of **1** was confirmed by ^{1}H NMR and MALDI-MS spectroscopic methods with essentially complete introduction of the desired hydroxamic acid group (see SI Figure 1). Concurrently, ∼5k and ∼12k cyclopentadienyl (Cp) end-capped polystyrene polymers **4a** and **4b** were prepared according to known methods.[20] The terminal cyclopentadiene affords the benefits of ease of installation and acceleration of the coupling reaction as compared to open-chain diene analogues.

To validate our approach using nitrosoformate as a suitable dienophile for polymer–polymer conjugations with Cp-functional polymers, we began our studies with conditions similar to those developed for the small molecule HDA reaction. Using 20 mol % CuCl, 5 mol % pyridine, and air as the terminal oxidant, mPEG-HA polymer **1** was allowed to react with 5.5 equiv of cyclopentadiene.[17b] To our gratification the reaction proceeded to complete conversion at ambient temperature and pressure. It is worth noting that the only oxidative byproduct produced in this conjugation reaction is water. The resulting oxazine-capped polymer **6** could be easily isolated by precipitation and was characterized by ^{1}H NMR spectroscopy (Figure 1).

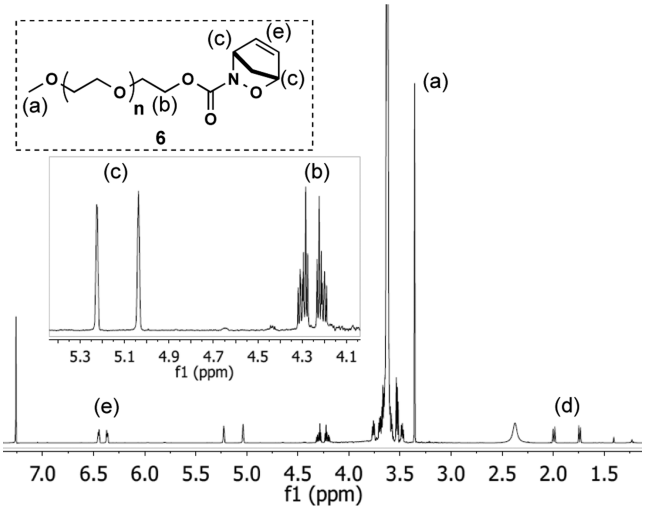


Figure 1. ^{1}H NMR spectrum of 2k mPEG-HA after reaction with cyclopentadiene showing full functionalization.

Encouraged by this result, we next investigated the synthesis of the mPEG-*b*-PS copolymer under the copper-catalyzed aerobic oxidation conditions. The coupling reaction between 2k mPEG-HA **1** (1.5 equiv) and 4.7k PS-Cp **4a** via the HDA cycloaddition was performed in THF at ambient temperature using our optimized reaction conditions.[17b] After 24 h, complete conversion of **4a** was observed, and the block copolymer was isolated by flash chromatography on silica gel or by trituration in methanol–water (1:1), which removed any unreacted mPEG-HA.

Figure 2 shows an overlay of GPC traces of the 4.7k PS-Cp (**4a**) and the new coupling product **5a** indicating successful diblock formation. ^{1}H NMR analysis of the block copolymer product also confirmed the construction of the oxazine with

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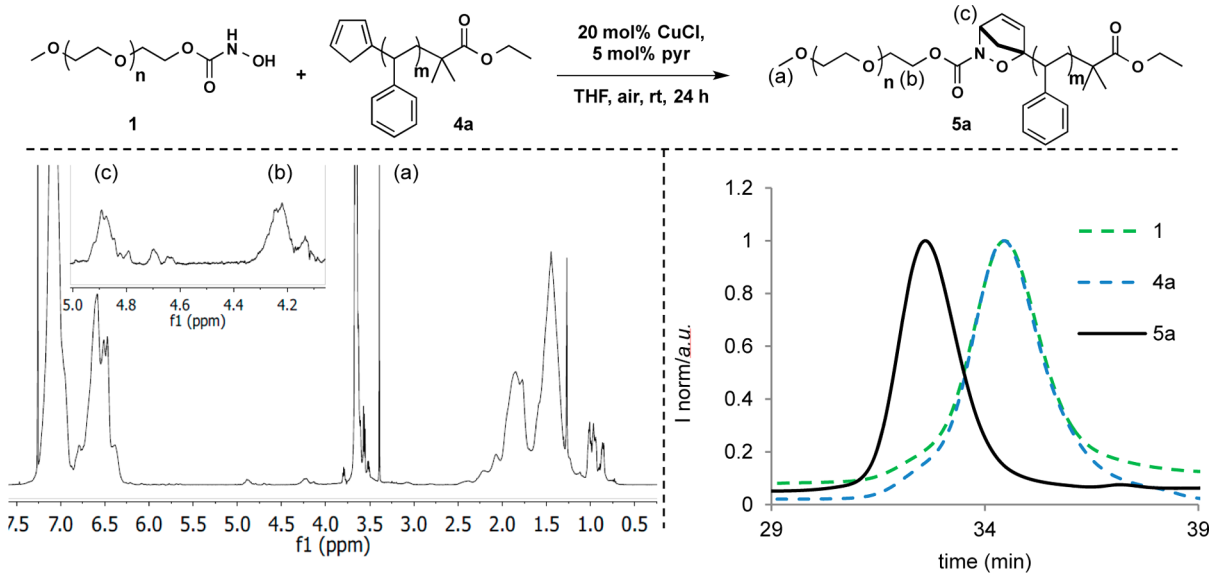

Figure 2. Top: Reaction scheme for aerobic copper-catalyzed synthesis of nitroso-DA block copolymer, **5a**. Bottom left: ^{1}H NMR spectrum of PS-*b*-mPEG (**5a**) in $CDCl_3$ with expansion of the 4−5 ppm region. Bottom right: Overlay of GPC traces showing the formation of the PS-*b*-mPEG (**5a**) through mild oxidative coupling, compared to the starting 4.7k PS-Cp (**4a**) and 2k PEG-HA (**1**).

similar results being observed for the coupling of 12k PS-Cp (**4b**) and 2k mPEG-HA (**1**).

Having developed a mild copper-catalyzed aerobic nitrosocarbonyl HDA conjugation, we sought to further illustrate the utility of the nitrosocarbonyl HDA polymer coupling strategy by performing the reaction in the absence of a catalyst. The development of polymer transformations that avoid the use of metals still remains a highly sought after goal because metal catalysts can be toxic in biological applications and can cause significant problems in material applications, specifically in the semiconductor industry. To avoid metals all together, we took advantage of the in situ formation of the nitrosocarbonyl compound via a thermal retro-[4 + 2] cycloaddition. This approach has been utilized to reveal the nitroso species in situ when oxidation methods proved incompatible with the desired transformation.[21] For these experiments, we chose 9,10-dimethylanthracene as the sacrificial diene because this thermally labile protecting group can be removed efficiently at moderate temperatures, ∼60−70 °C. To our delight, treatment of **4b** (1 equiv) with **2** (1.25 equiv) at 65 °C for 24 h gave block copolymer **5b** (Figure 3). Importantly, removal of 9,10-dimethylanthracene can be achieved quantitatively upon workup because it is soluble in methanol which is used to precipitate and isolate **5b**. Even though **5b** can also undergo a thermal retro-[4 + 2] cycloaddition, in this case the diene exchange reaction is quantitative as the cyclopentadiene−nitroso-Diels−Alder adduct **5b** requires higher temperatures (90−100 °C) to facilitate the thermal retro-[4 + 2] cycloaddition.

To further investigate the synthetic utility of nitrosocarbonyl compounds for conjugation reactions, the construction of an ABC triblock was carried out. Specifically, we wanted to demonstrate the compatibility of this new conjugation reaction with terminal alkynes, which are commonly used in the traditional copper-catalyzed alkyne−azide click reaction and the thiol−ene reaction. A 3.3k alkyne-terminated polystyrene cyclopentadienide (PS-Cp, **8**) was therefore coupled to mPEG-HA (**1**) under aerobic copper-catalyzed conditions (Figure 4). Following isolation via column chromatography,

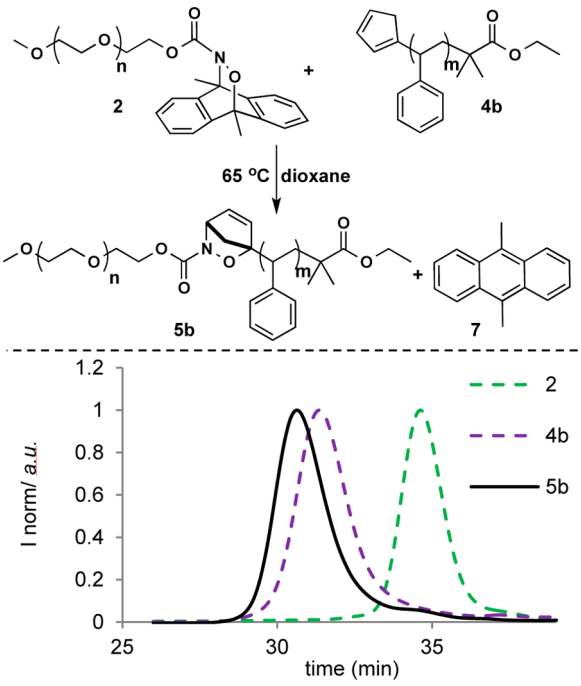

Figure 3. Top: Forming the nitroso-DA block copolymer using the thermal diene-exchange reaction. Bottom: Overlay of GPC traces showing formation of the 14k PS-*b*-mPEG **5b** through thermal coupling, compared to the starting 12k PS-Cp **4b** and **2**.

diblock product **9** was coupled to azide-terminated 5.2k poly(methyl methacrylate) using copper nanoparticle mediated CuAAC with GPC analysis showing the formation of well-defined triblock **11** with excellent selectivity for both copper-catalyzed transformations and confirming the compatibility of the new conjugation reaction with alkyne functional groups.

One of the distinct advantages of using the nitrosocarbonyl HDA conjugation reaction is the reversibility of the formed adduct. Thermoreversible covalent bonds in polymer chemistry have been utilized in reversible cross-linked gels, self-healing

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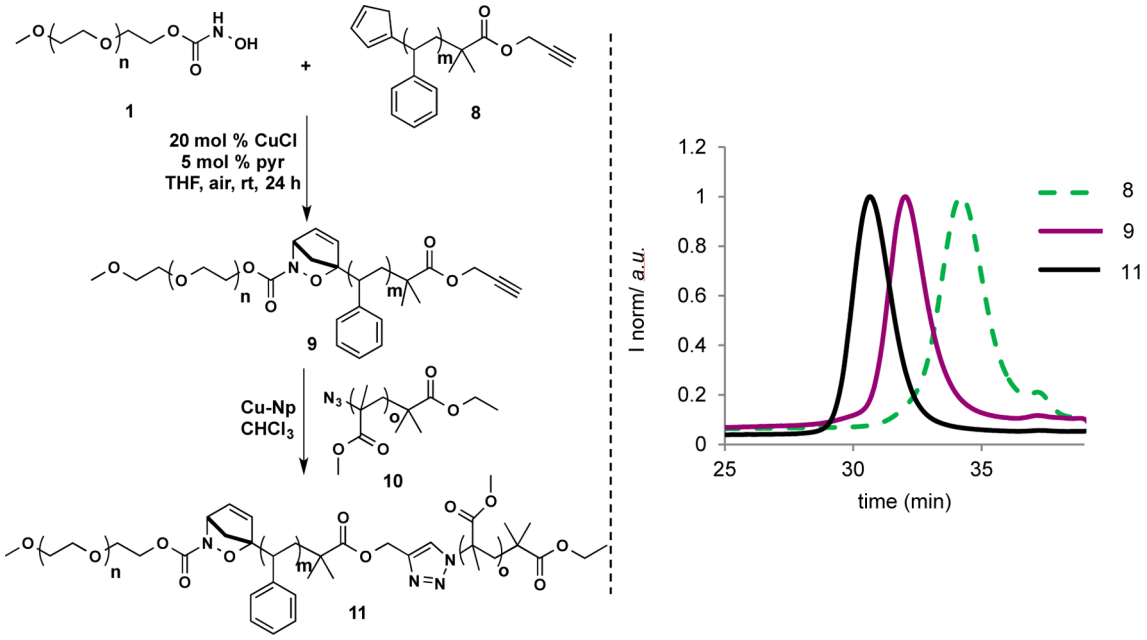

Figure 4. Left: Reaction scheme for aerobic copper-catalyzed synthesis of nitroso-DA diblock copolymer **9**, followed by CuAAC coupling with PMMA-N_3. Right: Overlay of GPC showing the formation of the PS-*b*-PEG diblock through mild oxidative coupling, followed by CuAAC coupling by copper nanoparticles.

polymers, and surface modification.[9a] As a proof of principle, we chose to demonstrate that the nitrosocarbonyl HDA conjugation reaction can be reversible, without compromising the Cp end-group fidelity. To our gratification, exposure of the 14k PS-*b*-PEG block copolymer **5b** to thermal cleavage conditions (95 °C, 24 h) in the presence of benzylamine as a trapping agent for the liberated nitroso-terminated PEG afforded the PS-Cp polymer (**4b**) (see SI Figure 5). Following isolation, **4b** was resubjected to copper-catalyzed oxidative coupling to reform the PS-*b*-PEG (**5b**), thus verifying the integrity of the Cp end group and the ability to "recycle" the HDA functional group. During these studies we discovered that the thermal cleavage reaction must be conducted under an inert atmosphere in degassed solvent to avoid unwanted side reactions of the liberated PS-Cp polymer. Presumably, the PS-Cp polymer reacts with molecular oxygen at these elevated temperatures.

In summary we have shown a unique application of nitrosocarbonyl chemistry in the field of block copolymer preparation. In addition to a mild, copper-catalyzed, aerobic coupling of polystyrene, poly(methyl methacrylate), and poly(ethylene oxide) polymers, we have further shown the ability to carry out this coupling under thermal conditions, in the absence of a metal. As a model case, our synthesis of block copolymers provides a good basis to expect that the nitrosocarbonyl HDA reaction will allow access to more intricate macromolecular structures such as star polymers, dendrimers, and polymer brushes using operationally simple reaction conditions.

■ ASSOCIATED CONTENT

Supporting Information

Experimental conditions and additional figures. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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