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Authors

Bailey, Sophia J
Discekici, Emre H
Barbon, Stephanie M
et al.

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Norbornadiene Chain-End Functional Polymers as Stable, Readily Available Precursors to Cyclopentadiene Derivatives

Sophia J. Bailey,
Department of Chemistry and Biochemistry, University of California, Santa Barbara, Santa Barbara, California 93106, United States

Emre H. Discekici,
Department of Chemistry and Biochemistry and Materials Department and Materials Research Laboratory, University of California, Santa Barbara, Santa Barbara, California 93106, United States

Stephanie M. Barbon,
California NanoSystems Institute, University of California, Santa Barbara, Santa Barbara, California 93106, United States

Shay N. Nguyen,
Department of Chemistry and Biochemistry, University of California, Santa Barbara, Santa Barbara, California 93106, United States

Craig J. Hawker,
Department of Chemistry and Biochemistry, California NanoSystems Institute, and Materials Department and Materials Research Laboratory, University of California, Santa Barbara, Santa Barbara, California 93106, United States

Javier Read de Alaniz
Department of Chemistry and Biochemistry and California NanoSystems Institute, University of California, Santa Barbara, Santa Barbara, California 93106, United States

Abstract

A novel method for facile postpolymerization functionalization of synthetic polymers using terminal norbornadiene (NBD) building blocks is presented. Incorporation of the NBD functionality streamlines the synthesis of a wide array of block polymers utilizing multistep click chemistry strategies. Previously, the use of NBD-functionalized initiators produced polymers that underwent a cascade of Diels–Alder (DA) reactions to unveil a reactive cyclopentadiene (Cp) chain end. When coupled with a maleimide-bearing counterpart, a highly efficient DA cycloaddition with the terminal Cp can occur. To extend this concept to a range of polyacrylates and commercially available poly(ethylene glycol) systems, we developed a novel NBD acid

Corresponding Author Javier Read de Alaniz – javier@chem.ucsb.edu.

Supporting Information

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Further information regarding synthetic procedures, characterization, instrumentation, and data (PDF)

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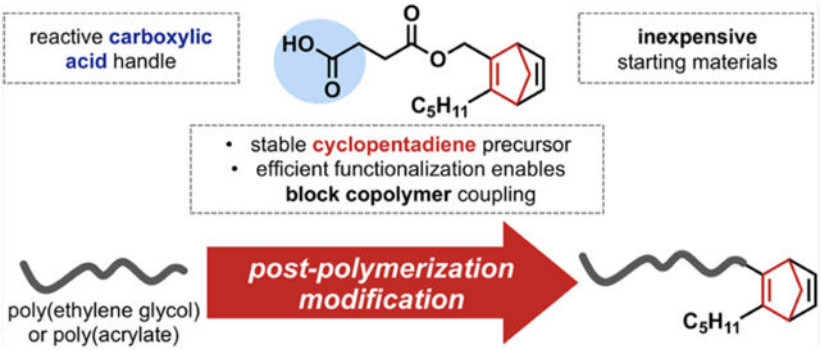
building block for postpolymerization functionalization. Employing this process, we have demonstrated straightforward access to a library of block polymers that leverage this NBD click platform.

Graphical Abstract



INTRODUCTION

Chain-end-functionalized polymers are regarded as highly versatile synthetic materials that enable unique applications throughout materials science from self-assembly to surface functionalization.[1,2] Of these, polymers bearing functionality that leverage click chemistry are the most sought after because they enable the user-friendly construction of more complex and functional polymer architectures with high efficiency, modularity, and orthogonality.[3] Typical methods to incorporate “clickable” functionalities onto polymer chain-ends include (1) the use of functional initiators, (2) in situ termination, and (3) introduction of functional units using postpolymerization processes.[1]

The search for user-friendly combinations of specificity, stability, and compatibility with a range of polymer systems continues to motivate ongoing research to expand the click chemistry toolbox. The copper-catalyzed azide–alkyne cycloaddition (CuAAC) developed by Sharpless and co-workers in 2002[4] has proven to be an invaluable method for conjugation of high-molecular weight polymers,[5] dendrimers [6], and biomolecules.[7] Beyond having all the characteristics associated with the click concept, direct incorporation of azide units through simple postpolymerization processes has enabled this strategy to be widely adopted.[8] Although this method offers efficient functionalization and subsequent click chemistry, the potential hazards associated with azides require that specific safety precautions be exercised. Furthermore, subsequent click reactions using the azide–alkyne platform, such as CuAAC and strain-promoted azide–alkyne cycloaddition (SPAAC),[9] can have significant drawbacks: metal catalysts used in the traditional CuAAC are incompatible with many systems because of copper toxicity, whereas the synthesis of highly strained alkynes used in the SPAAC process are often costly, time-consuming, and difficult to scale.

The Diels–Alder (DA) cycloaddition has also been used extensively throughout materials science as a means of clicking polymers together to form complex architectures,[10-12] dynamic networks,[13,14] or for surface functionalization[15] through an efficient, orthogonal,

and catalyst-free reaction. Typically, a trade-off between stability and efficiency is encountered when choosing dienes and dienophiles for polymer functionalization. Stable functionalities such as furan (or anthracene) allow for simplified and efficient incorporation onto polymers using functional initiators or postpolymerization methods, as well as prolonged storage stability. However, these derivatives suffer from long reaction times and high temperatures for efficient coupling.[10] More reactive units, such as cyclopentadiene (Cp)[16] and triazolinediones (TADs)[17] offer significantly improved reaction rates;[18] however, the high reactivity of Cp and TAD requires that the functional unit be incorporated at a later stage or in situ to avoid unwanted isomerization or dimerization upon storage.[19]

As a complement to these DA technologies, our groups recently reported an inexpensive and highly efficient DA click conjugation platform that utilizes NBD as a dormant form of Cp.[20] NBD can be rapidly converted to Cp in an on-demand manner upon treatment with dipyridyl-tetrazine (DpTz).[21,22] The resulting Cp reacts at near-diffusion controlled rates through a DA cycloaddition process with an appropriate dienophile at room temperature. This new approach overcomes the instability encountered when using a highly reactive diene, while allowing for efficient and rapid polymer conjugation (minutes to hours). This initial work relied on the use of NBD-functional initiators to access high molar mass polymers derived from ring-opening polymerization (ROP), reversible addition/fragmentation chain transfer polymerization, and atom transfer radical polymerization (ATRP).[20] Although high-molecular weight polymers could be prepared by ROP, polymers prepared by ATRP were limited to low conversions and molecular weights. At higher conversions, loss of control was observed likely due to undesired reactivity of the NBD unit with free radicals.[23] We hypothesized that the use of a postpolymerization functionalization strategy would allow for the introduction of NBD functionality into polymer systems that may not be compatible with controlled radical polymerization methods and consequently further expanding the utility of this approach to commercially available polymers such as PEG (Figure 1).

Herein, we report the development of a readily available, functional NBD building block for postpolymerization derivatization of a range of poly(acrylate) and PEG backbones. From these corresponding materials, in situ generation of Cp units and subsequent conjugation with a range of maleimide-functionalized materials is achieved. This cascade click approach is metal-free, air-tolerant, and quantitative. Furthermore, in contrast to prior applications of Cp[19,24-26] where Cp-containing polymers suffer from instability preventing long-term storage,[24] NBD-functionalized polymers can be stored under ambient conditions for months (12+) with no observable degradation or unwanted reactivity.

RESULTS AND DISCUSSION

To demonstrate that NBD-based building blocks with an appropriate functional group handle can serve as a general strategy for postpolymerization processes, we first developed a robust and scalable synthesis of two carboxylic acid-bearing NBD derivatives, **4** and **5** (Figure 2a). Previously reported methyl ester NBD[20] (**3**) serves as the precursor for both derivatives, which can be prepared on large (10+ g) scales. NBD **4** was accessed in one step via hydrolysis, whereas **5** can be prepared in two synthetic steps from **3**: first reduction of the

methyl ester by diisobutylaluminium hydride (DIBAL) followed by base catalyzed ring opening of succinic anhydride to produce **5** in near quantitative yield. To evaluate the ability to liberate the desired Cp reactive unit, NBD **4** and **5** were treated with 1.5 equiv of DpTz in deuterated chloroform at room temperature and monitored by ^{1}H NMR (Figure 2b-d). Of note, in situ formation of the Cp unit was observed for derivative **5** within 10 min, and complete conversion to **5a** was achieved in just over 2 h (Figure 2d). The proximity of the electron-withdrawing group on compound **4** inhibited the efficiency of the DA cascade with tetrazine, and the rate of deprotection to **4a** was reduced. After 6 h, unreacted **4** was still observed by ^{1}H NMR (Figure 2c). This highlights the importance of increasing the electron density of the NBD unit to enable an efficient inverse demand DA with tetrazine which is critical for the in situ formation of the Cp unit and the general deprotection strategy.

The development of a robust synthetic route to **5** allowed exploration of direct nucleophilic substitution of bromine-terminated poly(acrylates) (Figure 3). For incorporation of NBD functionality onto poly(acrylates), we chose to initially study the base-catalyzed nucleophilic substitution of the terminal bromine as a viable approach. The use of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as a catalyst in the direct substitution of terminal bromine with carboxylic acids is well established, having been used with (meth)acrylic acids, to produce well-defined macromonomers.[27,28] Using this strategy, we envisioned that NBD units might be easily incorporated at the chain-end of a variety of poly(acrylate) backbones. Treatment of **P1a**, poly(cyclohexyl acrylate), with a premixed solution of acid **5** (4 equiv) and DBU (4.1 equiv) in ethyl acetate (EtOAc) provided near quantitative NBD functionalization after stirring for 60 h at room temperature. Significantly, no precautions were taken to exclude water or oxygen which further increases the utility of the strategy (Figure 3a-c). As highlighted in Figure 3b, following treatment of poly(cyclohexyl acrylate) (**P1a**) with the DBU/**5** solution and precipitation in methanol, resonances corresponding to the alkene protons of NBD are observed at 6.75 ppm. Integration of these resonances indicate >95% incorporation of NBD. To further confirm successful substitution of bromine for NBD, matrix-assisted laser desorption/ionization time of flight (MALDI-TOF) mass spectroscopy was used. Comparison of the MALDI-TOF spectra of **P1a** and **P2a** show a shift in molecular weight corresponding to the loss of bromine and gain of the terminal NBD unit with the observed molecular weights in agreement with calculated values (Figure 3c).

With optimized conditions in hand, we next explored the generality of this approach on a library of poly(acrylate) polymers possessing different pendant groups—cyclic, hydrophobic, hydrophilic, and fluorinated—prepared by photo-induced ATRP (**P1a–f**).[29-32] Full synthetic details for the synthesis of poly(cyclohexyl acrylate) (**P1a**), poly(cyclodecyl acrylate) (**P1b**), poly(octadecyl acrylate) (**P1c**), poly(*tert*-butyl acrylate) (**P1d**), poly(PEG acrylate) (**P1e**), and poly(octafluoropentyl acrylate) (**P1f**) are provided in the Supporting Information. The **P1a–f** library of polymers was successfully functionalized with **5** using the optimized DBU catalyzed conditions to afford **P2a–f** (Figure 3a). Of note, the rate of substitution could also be increased by heating the solution at 50 °C, which reduced the reaction time to 48 h for substitution onto **P1a**. Furthermore, the limitations previously encountered using NBD functional initiators are easily overcome with this postpolymerization approach, allowing for the preparation of high-molecular weight (35

kDa+) NBD-functionalized poly(acrylates) (**P2c**). After functionalization, these monofunctional derivatives could be easily purified from excess starting materials and small-molecule byproducts by precipitation or dialysis. Successful functionalization of the poly(acrylates) was confirmed by ^{1}H NMR spectroscopy with the appearance and integration of unique resonances corresponding to the NBD unit, indicating high chain-end fidelity (see Supporting Information for full details).

To further illustrate the power of this postfunctionalization approach, we sought to broaden the process to quantitative functionalization of terminal hydroxy groups for commodity polymers. Driven by the utility of PEG-based polymers in biomaterials and the availability of maleimide-derived functional materials such as antibody–drug conjugate pay-load,[33-35] dyes, and bioactive small molecules, we initially focused on PEG-based systems. Using *N,N*′-dicyclohexylcarbodiimide (DCC) as the coupling agent, NBD-functionalized PEG was prepared from commercially available PEG monomethyl ether (**P3**, M_n = 5000 g mol^{-1}). Coupling could be accomplished within 24 h upon treatment with excess **5** (2 equiv), DCC, and catalytic 4-dimethylaminopyridine (DMAP) (Figure 4a). ^{1}H NMR spectroscopy following precipitation of **P4** in cold ethanol showed the expected resonances corresponding to successful NBD incorporation with integration values, confirming >95% functionalization (Figure 4b).

To demonstrate the versatility of these functionalized polymeric building blocks, we sought to prepare block copolymers via the NBD click platform. It is worth noting that these Cp precursor materials could be stored under ambient conditions for extended periods (12+ months) with no observable degradation, allowing large quantities to be prepared and fully characterized, followed by storage and later use in NBD click reactions. With these NBD-functionalized materials in hand, several maleimide-bearing counterparts were prepared. The utility of the maleimide unit in Michael additions and DA cycloadditions has driven the establishment of a range of synthetic approaches for the preparation of functional maleimide derivatives.[36-38] As an illustrative example, a protected maleimide initiator was used in the polymerization of methyl methacrylate under metal-free ATRP conditions;[36,39] then, it was subsequently heated at 110 °C to deprotect the maleimide and afford an α-functionalized poly(methyl methacrylate) (mal-PMMA, **P5**, Figures 5 and S36-S38). To perform NBD-based click coupling, **P2a** and **P5** were dissolved in deuterated chloroform with **P2a** in slight excess (1.14 equiv) (Figure 5a). Following dissolution, DpTz (2.28 equiv) was added and the reaction was allowed to proceed at room temperature while monitoring reaction completion by ^{1}H NMR. After 24 h, the disappearance of the maleimide resonances of **P5** indicated quantitative clicking to **P2a** (Figure S46). The excess DpTz was quenched with norbornene before the block copolymer (PCHA-*b*-PMMA, **P6**) was precipitated in methanol, then hexanes, to remove excess small molecules and **P2a**. Analysis by size-exclusion chromatography (SEC) confirmed a shift to higher molecular weight material which indicates successful diblock formation (Figure 5b). Furthermore, analysis by SEC and ^{1}H NMR corroborates that any unreacted **P2a** was successfully removed by precipitation (Figures 5b and S47).

Using the previously established metal-free ATRP conditions, a library of block polymers was prepared by combining maleimide and NBD-functionalized polymers in the presence of

DpTz (Figure 6). To further expand the polymer coupling partners, a second maleimide-functionalized polymer (mal-PEG, **SP3**) was prepared in a similar fashion to the NBD-functionalized analog, using **P3**, DCC and DMAP (Figures S44 and S45). From this material, poly(acrylate)-*b*-PEG copolymers were prepared (**P8–P9**, Figure 6). Likewise, the NBD-functionalized PEG (**P4**) was used to prepare a PEG-*b*-poly(methacrylate) copolymer (**P13**) by clicking with a maleimide-functionalized poly(hexyl methacrylate) (**SP1**, Figure 6). In all cases examined, the NBD click method provides efficient and practical access to block copolymers bearing hydrophobic, hydrophilic, and fluorinated groups.

Finally, to demonstrate that this strategy can also be extended to triblock formation, a bifunctional poly(dodecyl acrylate) (**SP4**) was prepared by light-induced ATRP of the protected maleimide initiator followed by substitution of the terminal bromine with **5** (Figures S63-S65). From this bifunctional material, a triblock terpolymer was prepared in two sequential clicks. In the first click, **SP5**^{20} was treated with DpTz and the appearance of the Cp was monitored by ^{1}H NMR (Figure S66). Upon complete deprotection to the desired Cp-PLA (**SP6**), the excess DpTz was quenched to prevent undesired deprotection of the NBD unit upon addition of **SP4**. The intermediate diblock, **P14**, was purified and characterized (Figures 6 and S67, S68) before subjecting the material to a subsequent deprotection followed by click reaction with **SP3** to afford the triblock PLA-*b*-PDA-*b*-PEG with a final M_n of 33,000 g mol^{-1} and dispersity of 1.14 (**P15**, Figures 6 and S69, S70).

CONCLUSIONS

In conclusion, we have developed a general procedure for the introduction of NBD and associated Cp units to the chain-ends of a variety of polymer backbones. Key to the success of this strategy is the synthetically simple and stable NBD derivative (**5**) which possesses a carboxylic acid group suitable for efficient postpolymerization functionalization of poly(acrylates) and PEG. The functionalization conditions disclosed offer high reaction efficiency and orthogonality leading to polymeric building blocks with high chain-end fidelity. Unlike previously reported functionalization through NBD-bearing initiators, this strategy offers a facile route to Cp-terminated materials that circumvents any unwanted reactivity of the NBD unit in radical polymerizations. Furthermore, we demonstrate that this straightforward functionalization of synthetic and commercially available polymers offers a streamlined route to create a library of diverse block copolymers from stable precursors. We envision that the ability to functionalized preformed polymer chains with a stable Cp precursor will propel the utility of the DA click platform throughout materials science. Further investigations in the functionalization of materials with NBD and subsequent applications of this powerful click platform are currently underway.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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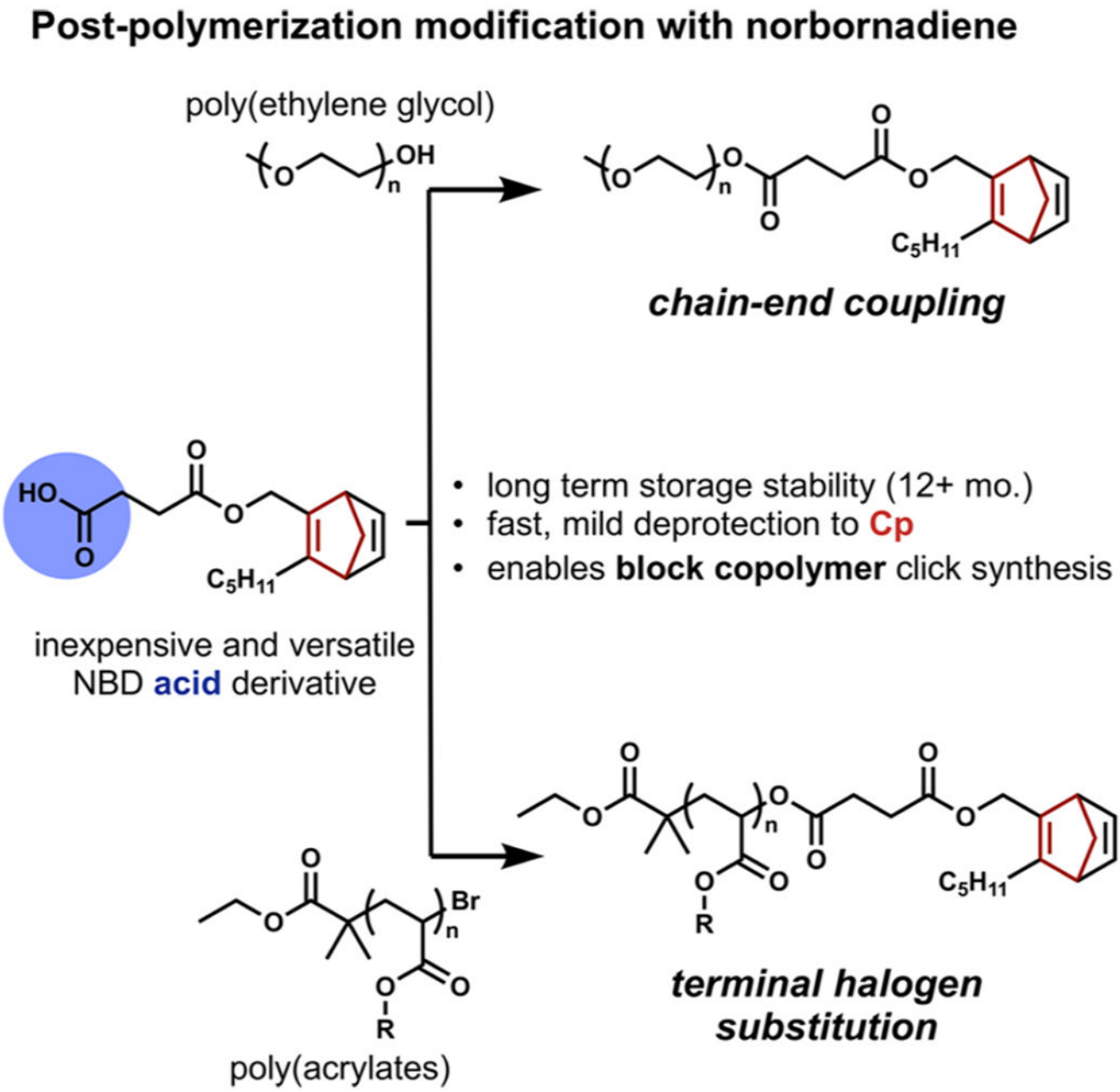

Figure 1.

Postpolymerization functionalization using a carboxylic acid bearing norbornadiene (NBD) derivative allows for preparation of stable poly(ethylene glycol) (PEG) and poly(acrylate) click building blocks.

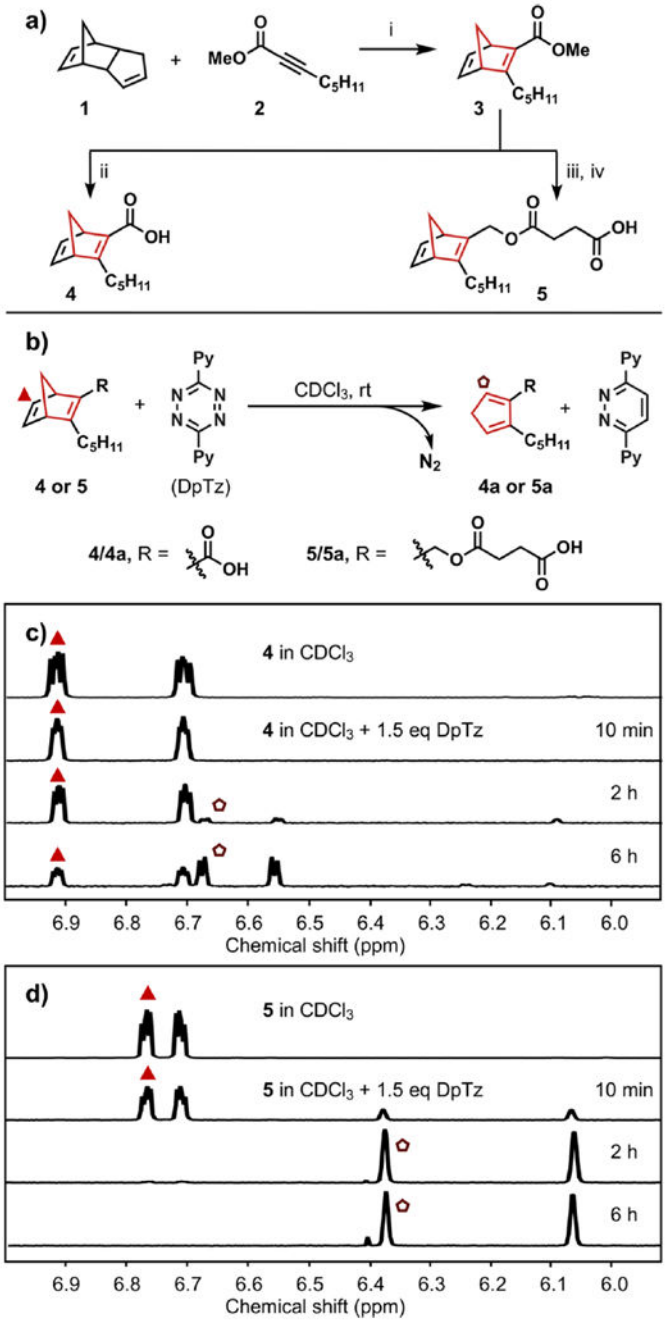

Figure 2.

(a) Synthesis of NBD acids for polymer modification. (i) neat, pressure vessel, 200 °C, 5 h, 50%, (ii) NaOH, MeOH, H_2O, reflux, 15 h, then HCl, 66%, (iii) DIBAL, tetrahydrofuran, 0 °C, 30 min, 71%, and (iv) succinic anhydride, Et_3N, DMAP, DCM, rt, 1 h, 97%. (b) Scheme of NBD deprotection to Cp. (c) ^{1}H NMR overlays monitoring the deprotection of **4** to **4a**. (d) ^{1}H NMR overlays monitoring the deprotection of **5** to **5a**.

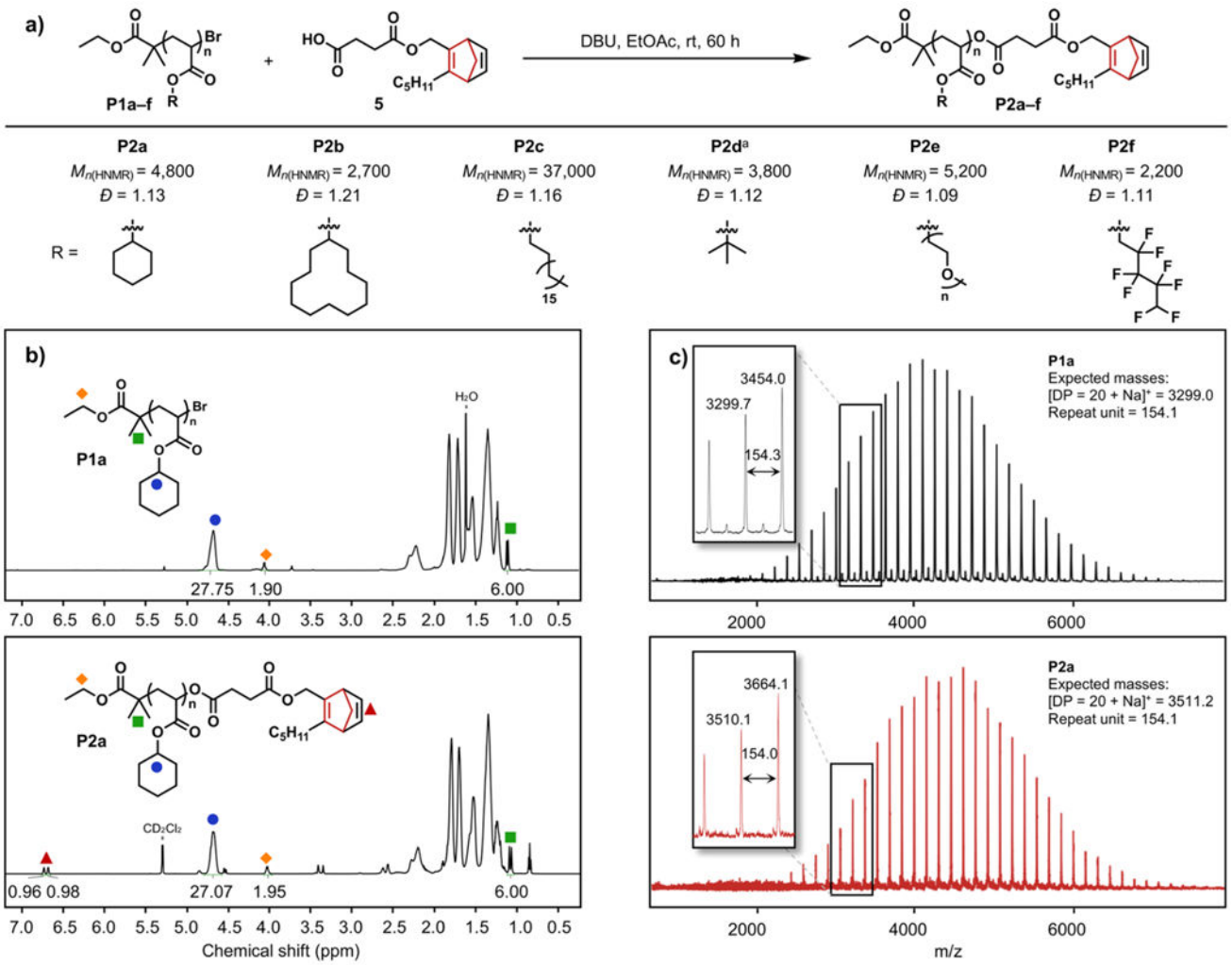

Figure 3.

(a) General reaction for substitution of the NBD unit onto polymers prepared by ATRP. [a]Functionalization performed in acetonitrile. (b) ^{1}H NMR of **P1a** and **P2a** in deuterated dichloromethane (DCM). (c) MALDI-TOF spectra of **P1a** and **P2a** agree with expected masses corresponding to functionalization of the ω-chain-end with NBD.

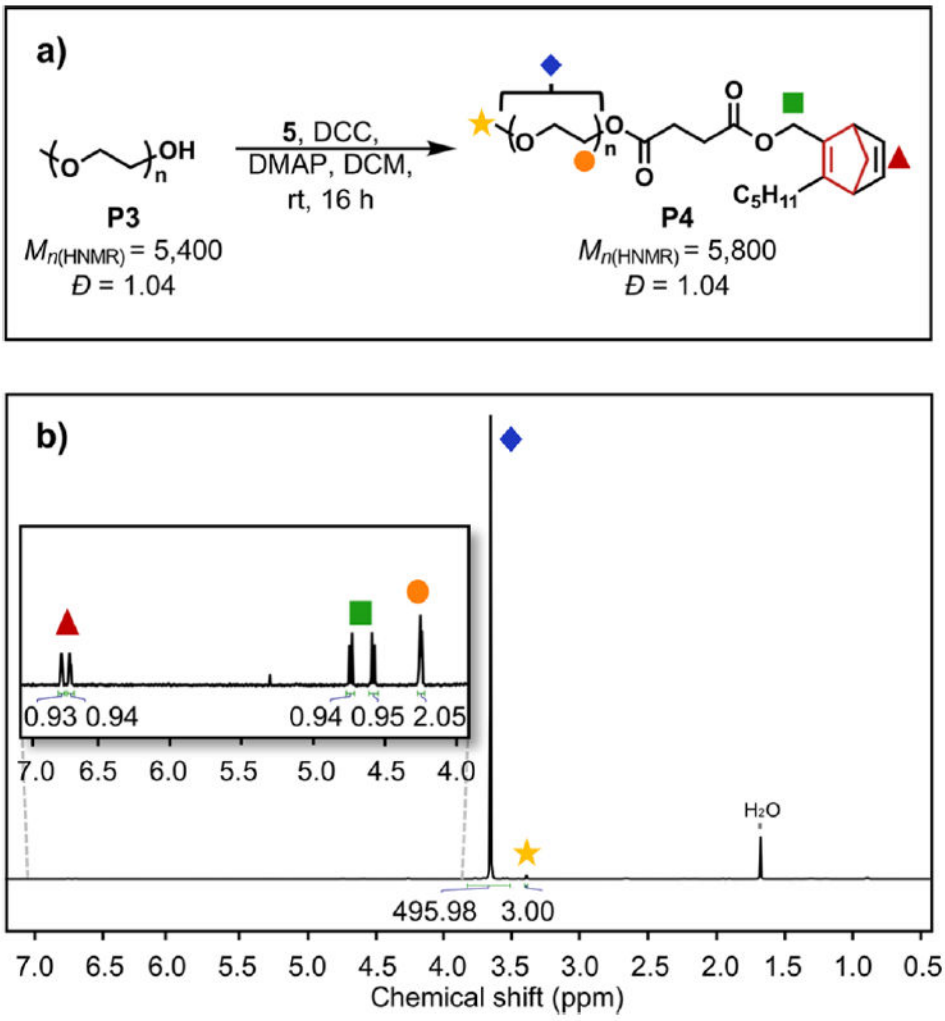

Figure 4.

(a) Functionalization of PEG chain-end with NBD. (b) ^{1}H NMR of **P4** showing expected resonances corresponding to the NBD unit.

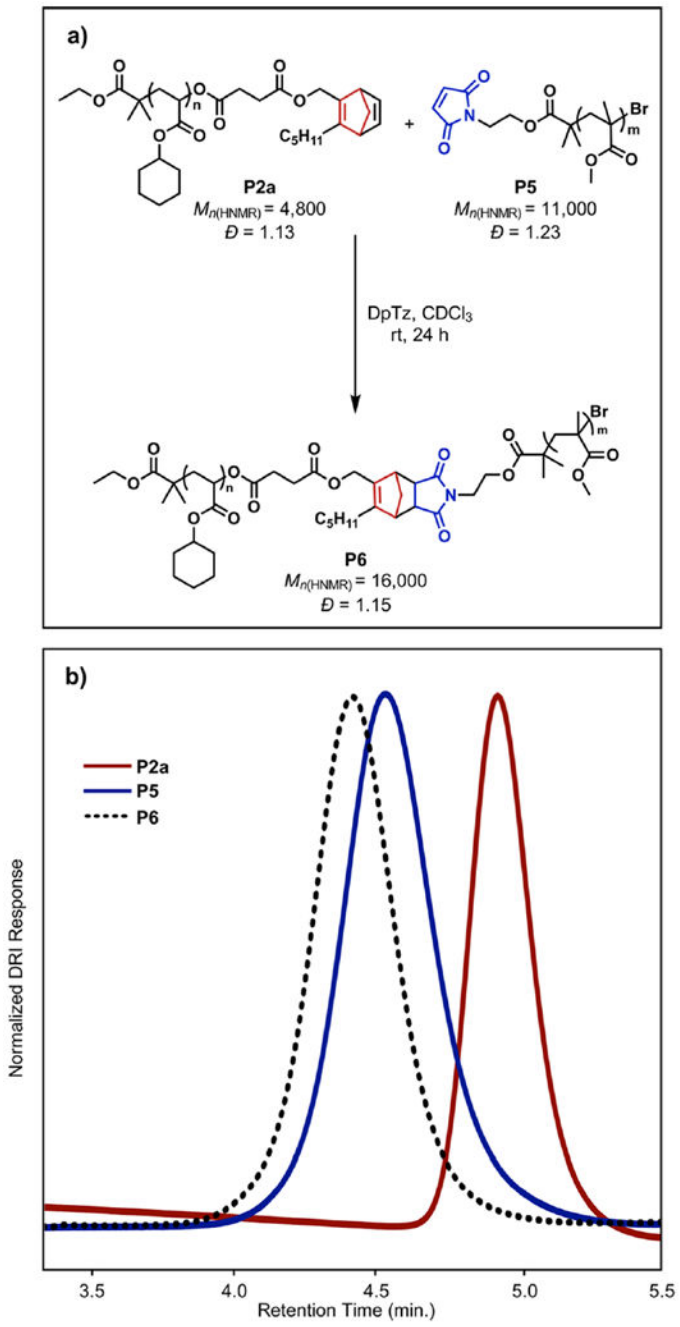

Figure 5.

(a) Synthesis of PCHA-*b*-PMMA diblock copolymer. (b) SEC traces showing expected shift to higher molecular weight after NBD click.

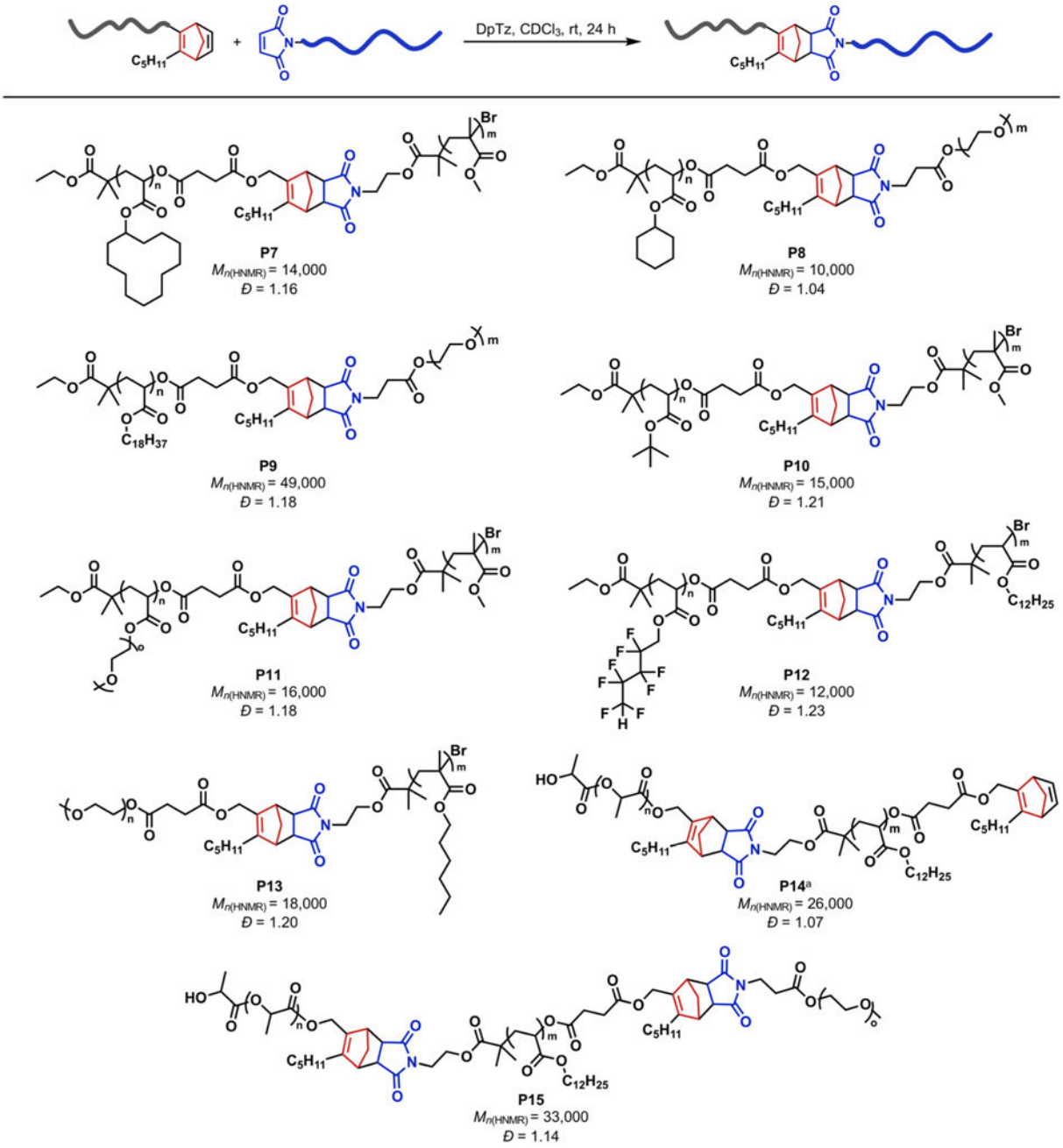

Figure 6.

Scope of the NBD click platform to produce mix-and-match block copolymers. All reactions were performed in deuterated chloroform to allow for monitoring by ^{1}H NMR and confirmation of quantitative clicking before precipitation. [a]Maleimide-poly(dodecyl acrylate)-NBD was added to solution after complete deprotection of poly(lactic acid)-NBD to Cp was observed by ^{1}H NMR and unreacted DpTz was quenched with norbornene.