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Andre H. St. Amant
University of California, Santa Barbara

Emre H. Discekici
University of California, Santa Barbara

Sophia J. Bailey
University of California, Santa Barbara

Manuel S. Zayas
University of California, Santa Barbara

Jung-Ah Song
University of California, Santa Barbara

See next page for additional authors

Authors

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Norbornadienes: Robust and Scalable Building Blocks for Cascade "Click" Coupling of High Molecular Weight Polymers

Andre H. St. Amant[†,§], **Emre H. Discekici**[†,‡,§], **Sophia J. Bailey**[†], **Manuel S. Zayas**[†], **Jung-Ah Song**[‡], **Shelby L. Shankel**[†], **Shay N. Nguyen**[†], **Morgan W. Bates**[‡], **Athina Anastasaki**[‡], **Craig J. Hawker**[*,†,‡,⊥], **Javier Read de Alaniz**[*,†]

[†]Department of Chemistry and Biochemistry, Santa Barbara, California 93106, United States
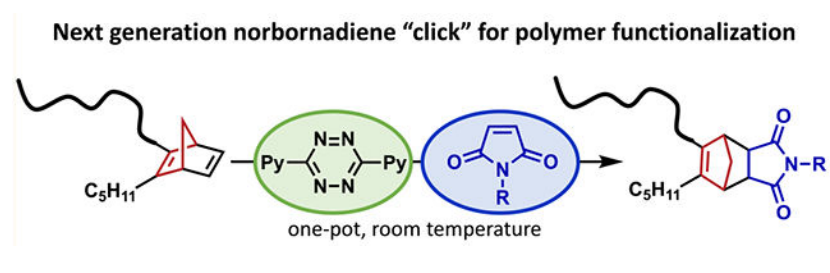
[‡]Materials Research Laboratory, Santa Barbara, California 93106, United States

[⊥]Materials Department, University of California, Santa Barbara, California 93106, United States

Abstract

Herein, we report the development of a scalable and synthetically robust building block based on norbornadiene (NBD) that can be broadly incorporated into a variety of macromolecular architectures using traditional living polymerization techniques. By taking advantage of a selective and rapid deprotection with tetrazine, highly reactive "masked" cyclopentadiene (Cp) functionalities can be introduced into synthetic polymers as chain-end groups in a quantitative and efficient manner. The orthogonality of this platform further enables a cascade "click" process where the "unmasked" Cp can rapidly react with dienophiles, such as maleimides, through a conventional Diels—Alder reaction. Coupling proceeds with quantitative conversions allowing high molecular weight star and dendritic block copolymers to be prepared in a single step under ambient conditions.

Graphical Abstract

Next generation norbornadiene "click" for polymer functionalization

one-pot, room temperature

INTRODUCTION

The concept of "click" chemistry, first introduced by Sharpless and co-workers in 2001, is based on the philosophy that chemical reactions should be modular, simple, high yielding, and orthogonal.[1] These essential characteristics have had a profound impact across the broader chemical sciences, transforming scientific disciplines ranging from bioconjugation to functional polymer synthesis.[2,3] A range of postpolymerization modification strategies have emerged from the concept of click chemistry, enabling the synthesis of polymers with a diverse array of functionalities and architectures.[4,5] Among these strategies, the copper-catalyzed azide–alkyne click (CuACC) represents one of the most highly utilized click platforms in polymer synthesis, driven by the synthetic availability of alkyne and azide building blocks.[6] However, a longstanding drawback for traditional CuAAC-based systems is the presence of metal catalysts. This challenge was mitigated by the development of copper-free or strain-promoted azide–alkyne click (SPACC) chemistry; based on cyclooctyne derivatives,[7] the inherent strain in the cyclooctyne ring dramatically increases the rate of the uncatalyzed reaction,[8] enabling rapid room-temperature coupling to azides. However, the long-term instability of dibenzoazacyclooctyne systems (DIBAC) (storage at −20 °C),[9] the difficulties in scalability, and prohibitively high cost[10,11] render general use in functional polymer synthesis challenging. As such, SPAAC has been mostly limited to small-scale systems such as dendritic[12] or biological applications.[13]

A more cost-effective and scalable metal-free click platform for polymer synthesis is the Diels–Alder (DA) cycloaddition reaction. DA systems have been utilized across numerous applications ranging from polymer cross-linking,[14,15] nanoparticle,[16] surface functionalization,[17] and preparation of antibody–drug conjugates.[18] Furan or anthracene-based dienes, in combination with maleimide dienophiles, are arguably the most commonly utilized building blocks for DA cycloaddition couplings in polymer synthesis (Figure 1a).[19] However, despite their orthogonality, scalability, and wide-spread availability, polymeric materials prepared by DA cycloadditions are plagued with certain fundamental limitations. For example, the propensity for furan–maleimide DA adducts to undergo retro-Diels–Alder (rDA) reactions renders them unsuitable for applications requiring elevated temperatures.[20] Furthermore, the DA cycloaddition of anthracene–maleimide suffers from the necessity for elevated temperatures and long reaction times to achieve high coupling efficiency.[21]

To overcome these challenges, an attractive alternative is to significantly increase the reactivity of the diene or dienophile. Du Prez and co-workers reported the use of triazolinedione (TAD) compounds as "spring-loaded" dienophiles which react with dienes at room temperature within minutes.[22] The high reactivity of TAD compounds offers an elegant method for functionalizing polymers when less reactive dienes are required. In contrast, the reactivity of the diene can be increased through the use of cyclopentadiene (Cp) derivatives.[23,24] Recognizing the potential of Cp as a polymer click platform, Barner-Kowollik and co-workers developed synthetic routes to access Cp-functionalized polymers for conjugation with maleimides,[25] electron-deficient dithioesters,[26-28] and carbon nanoparticles.[29,30] For stable backbones such as polystyrene or poly(ethylene glycol), nucleophilic substitution using ionic cyclopentadienyl salts (NaCp,[26] LiCp,[31] or Me$_2$AlCp[32]) allows for the efficient synthesis of Cp-functionalized chain-end derivatives. In

the case of reactive backbones, such as polyesters, an alternative substitution strategy using nickelocene (NiCp$_2$) has been developed.[27,33,34] Despite the success of these strategies, the ability to incorporate Cp has been limited to chain ends via postpolymerization strategies due to the general instability[24] of Cp and its high reactivity toward electron-deficient vinyl monomers.[35]

Identifying the limitations of general click strategies and the associated promise of cyclopentadiene (Cp) derivatives as a highly efficient coupling platform, we report the development of norbornadiene (NBD) building block as a "masked" Cp unit that can be used for the synthesis of high molecular weight triblock and star copolymers. Our interest in NBD derivatives is driven by their scalability (derived from inexpensive starting materials such as dicyclopentadiene) and compatibility with a wide variety of polymerization techniques such as reversible addition–fragmentation chain transfer (RAFT), atom-transfer radical polymerization (ATRP), and ring-opening polymerization (ROP). A key insight in this study is the use of a cascade sequence of DA reactions to quantitatively couple the NBD units with dienophiles such as functional maleimides.[36] This "unmasking" of the NBD group is mediated by small-molecule tetrazine derivatives through an initial inverse-DA reaction, leading to the in situ generation of Cp functionalities that can then undergo efficient conjugation with maleimide-functionalized materials (Figure 1b). This novel cascade platform is metal free, air tolerant, and quantitative for even demanding systems such as the coupling of high molecular weight, chain-end-functionalized linear polymers. This allows well-defined block copolymers to be prepared on multigram scale that are difficult to synthesize using traditional polymerization strategies.

RESULTS AND DISCUSSION

Initial studies on the scalable synthesis of an NBD derivative employed the commodity chemical dicyclopentadiene (**1**) and methyl 2-octynoate (**2**), an inexpensive and innocuous flavoring agent ($30 per kg). When **1** and **2** are heated neat in a pressure vessel at 200 °C, the resulting methyl ester can be isolated via distillation and subsequently reduced with DIBAL to furnish the NBD alcohol **3**[37] on a 50 g scale in a typical laboratory setting (Scheme 1). The simplicity of this process coupled with the availability of alkyne derivatives allows a range of other NBD derivatives to be prepared. A notable example includes the reaction of **1** with propargyl alcohol which affords the unsubstituted NBD alcohol directly.[38] Significantly, it was observed that the NBD derivatives were stable and could be stored at room temperature under ambient conditions with no observable degradation or instability over 6+ months. In addition, a variety of functionalization reactions can be performed on the NBD building block to give functional initiator units for subsequent polymerization reactions (Figures S23-S30). For example, the alcohol **3** can be esterified to give the RAFT chain transfer agent, **4**, the ATRP initiator, **5**, or the difunctional bis(MPA) ROP initiator, **6**, in high yields.

Drawing inspiration from small-molecule reports[39,40] and the pioneering development of additive-free polymer functionalization based on norbornene–tetrazine coupling chemistry by Dove, Du Prez, and O'Reilly,[41] we identified norbornadiene (NBD) as a masked Cp precursor. Together with the synthetic accessibility demonstrated above, we envisaged that

the high ring strain (32.3 kcal/mol)[42] would allow for a cascade of selective cycloaddition reactions when used in conjunction with tetrazine.[43-45] This highly efficient process proceeds through an initial inverse electron-demand DA (IEDDA) reaction that releases N_2, followed by a retro-DA (rDA), to yield pyridazine[46] and Cp as products.[39,40] This strategy therefore permits the facile incorporation of Cp into a range of materials through the initial introduction of NBD units.

To demonstrate the versatility of **3** as a stable, masked Cp unit, end-functionalized polylactide (PLA) **P1** (Figure 2a) was prepared using the base-catalyzed ROP of D,L-lactide and **3** as an initiator. Significantly, the resulting polymer was determined to have a degree of polymerization of ~500 (M_n = 42 000 g/mol and $Đ$ = 1.04), which compares favorably with the theoretical DP of 440 and illustrates the compatibility of the NBD unit under basic conditions. Additionally, ^{1}H NMR spectroscopy shows the unique signals for the alkene present in the NBD units and confirms the efficient introduction of NBD at the end of the high molecular weight PLA chain.

The ability to liberate reactive Cp units was then demonstrated through sequential "demasking" of the NBD group followed by rapid, DA cycloaddition with readily available maleimide dienophiles containing a range of functionality (e.g., dye, biomolecule, and photoswitch). From a practical point of view, one advantage of this approach is that the maleimide group lies dormant until the Cp group is revealed leading to a metal-free and room-temperature "cascade click" functionalization process.[36] The orthogonality of these cycloaddition processes combined with the user-friendly nature of the reaction setup addresses a number of challenges that exist in the synthesis of complex macromolecular architectures by coupling of polymeric building blocks. To validate the efficient conjugation via a cascade click sequence, a solution of **P1** in CDCl$_3$ was treated with the commercially available tetrazine (DpTz, 2.4 equiv) and N-(1-pyrenyl)maleimide (PyrM, 1.2 equiv) at room temperature with no precaution to exclude water or oxygen. As highlighted by Figure 2a, the cascade process proceeds through an initial inverse electron-demand DA (IEDDA) reaction with DpTz (**7**) at the unsubstituted olefin of NBD (**P1** to **P1a**). Upon release of N_2 from **P1a** a subsequent rDA reaction occurs to yield an in situ generated terminal Cp unit (**P1b**) which undergoes a DA reaction with the functionalized maleimide (**8**) to give the desired pyrene-functionalized **P2**. Following purification by precipitation, **P2** was obtained in quantitative yield with SEC characterization before and after functionalization, confirming no change in the molar mass distribution. Significantly, incorporation of pyrene was determined to be >95% by both ^{1}H NMR and UV–vis spectroscopy, calibrating against known concentrations of PyrM (Figures 2d and S31-34). Similar reactivity was observed for a range of PLA molecular weights and for maleimides bearing more complex biotin or azobenzene functionalities (Figures S35, S36, S39, and S40). The ability to employ a wide range of functional starting materials and high (>40 000 kDa) molecular weight polymers highlights the efficiency of NBD as a building block with this cascade click strategy representing a viable alternative to both CuAAC and SPAAC.[47]

The facile introduction of reactive Cp units to the chain ends of polymeric systems now opens up the intriguing possibility of coupling stable, end-functionalized polymers to give high molecular weight block copolymers and other complex macromolecular architectures.

To showcase the potential of this new strategy, a PLA-*b*-PEO-*b*-[G-4 dendron] triblock copolymer (**P5**) was prepared in a single step by coupling of a chain-end-functionalized PLA-NBD ((**P3**), M_n = 21 800) derivative with a maleimide-terminated PEO-*b*-[G-4 dendron] (**P4**), Figure 3. Significantly, only a minor excess of **P4** (1.5 equiv) was required to drive the reaction to completion with SEC showing the expected increase in molecular weight for the desired triblock copolymer and no detectable **P3** (Figure S48).

To further illustrate the power of this cascade click approach for the synthesis of complex macromolecular architectures, we took inspiration from dendrimer and star copolymer targets. The NBD-containing diol **6** was subjected to standard lactide ROP conditions to obtain a two-armed B_2 precursor (**P6**, Figure 4a) where a masked Cp unit is located at the midpoint of the PLA chain. This allows access to high molar mass AB_2 miktoarm star polymers when coupled with linear maleimide-terminated polymers. Maleimide-terminated poly(*n*-butyl methacrylate) (PnBMA) **P7**[48] synthesized using metal-free ATRP[49] serves as the conjugation partner ($M_{n(SEC)}$ 9600 g/mol, $Đ$ = 1.26) with the corresponding AB_2 PnBMA-*b*-(PLA)$_2$ miktoarm star copolymer **P8** obtained after room-temperature reaction under ambient conditions (Figure 4a). It is important to note that excess **P7** was removed by simple precipitation of the crude reaction mixture into a 1:1 v/v methanol:isopropanol solution. SEC-RI analysis confirmed the efficient coupling and successful formation of a high molecular weight AB_2 miktoarm block copolymer (Figure 4b). ^{1}H NMR analysis of **P8** corroborated a quantitative incorporation of P*n*BMA and PLA blocks (Figure S53) based on the stoichiometric reaction between chain ends and the estimated molecular weight of each precursor. Small-angle X-ray scattering (SAXS) provided additional evidence for efficient conjugation and the absence of unreacted homopolymer. After annealing **P8** at 120 °C for 4 h, multiple Bragg reflections corresponding to well-ordered lamellae were observed with a characteristic length scale (q^* = 0.25 nm^{-1}, d = 25 nm) defined by the self-assembly of the neat and symmetric AB_2 block polymer ($f_{PLA} \approx 0.5$). As an additional demonstration of the modularity of this platform, a second AB_2 miktoarm star (**S-P12**) was prepared using polymer precursors of different molar masses, targeting a $f_{PLA} \approx 0.7$ AB_2 miktoarm (Figures S55 and S56). Upon annealing, the miktoarm block copolymer also exhibited microphase separation, forming hexagonally packed cylinders as evidenced by SAXS (Figure S57). The ability to quickly and efficiently link polymer precursors promotes a more facile avenue to tune chemical composition and volume fraction of blocks through this "mix and match" approach. We envision that this strategy will enable easy access to a range of polymeric architectures or potentially afford new opportunities in reactive compatibilization of polymer blends.

CONCLUSION

We demonstrate a cascade click strategy for the facile preparation of high molecular weight macromolecular architectures. On the basis of synthetically accessible and chemically robust norbornadiene (NBD) building blocks, masked Cp units can be introduced into a range of polymeric systems. The general compatibility of the NBD building block with common polymerization techniques (i.e., RAFT, ATRP, ROP) is illustrated, highlighting the versatility and orthogonality of NBD. Importantly, upon addition of DpTz, quantitative

deprotection of NBD to form Cp is observed via a rapid cascade of DA reactions, and in the presence of a variety of functional maleimide derivatives, in situ coupling then occurs via a traditional DA cycloaddition. This metal-free process is highly efficient and requires no heating or precaution for an air- or moisture-free environment. Importantly, it is amenable across an array of functional maleimides, making this strategy accessible to the broader scientific community.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

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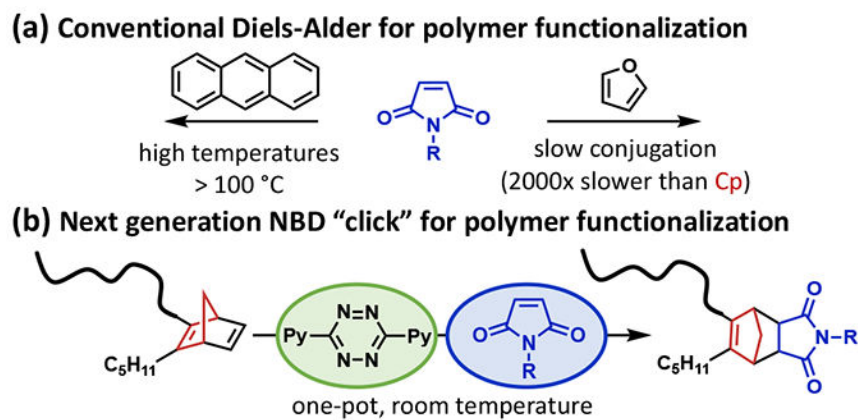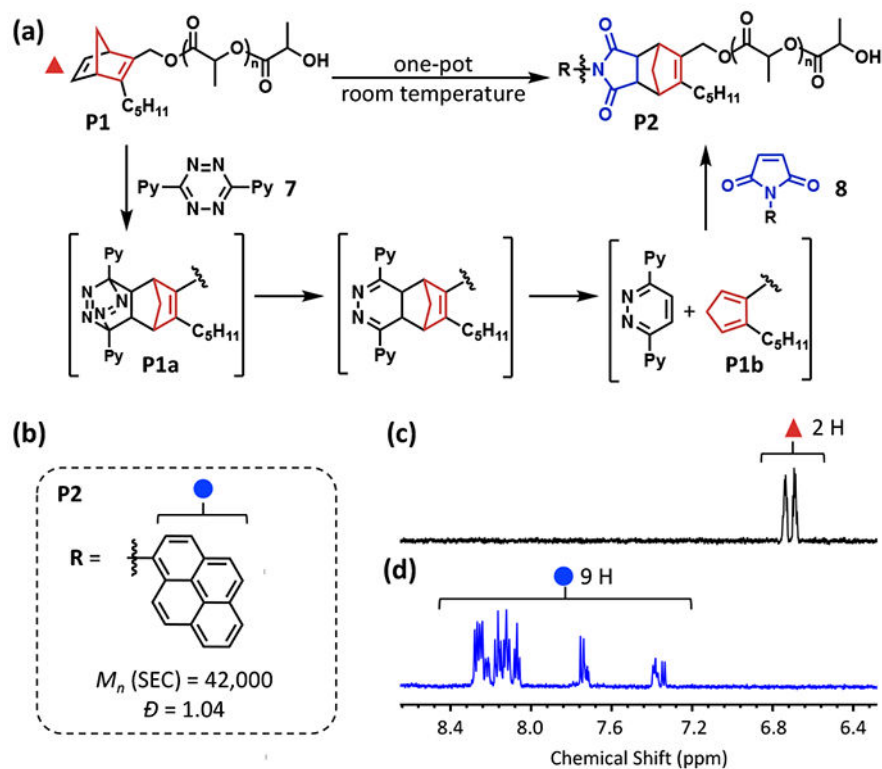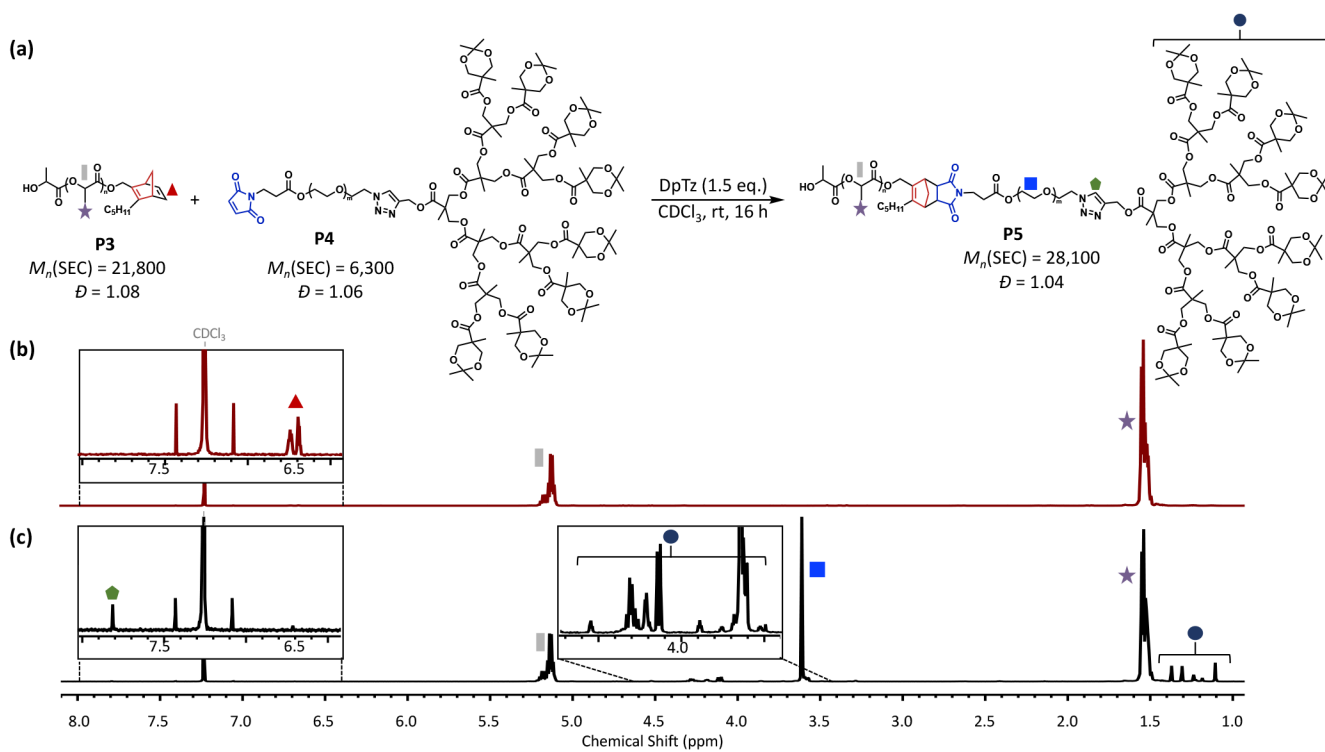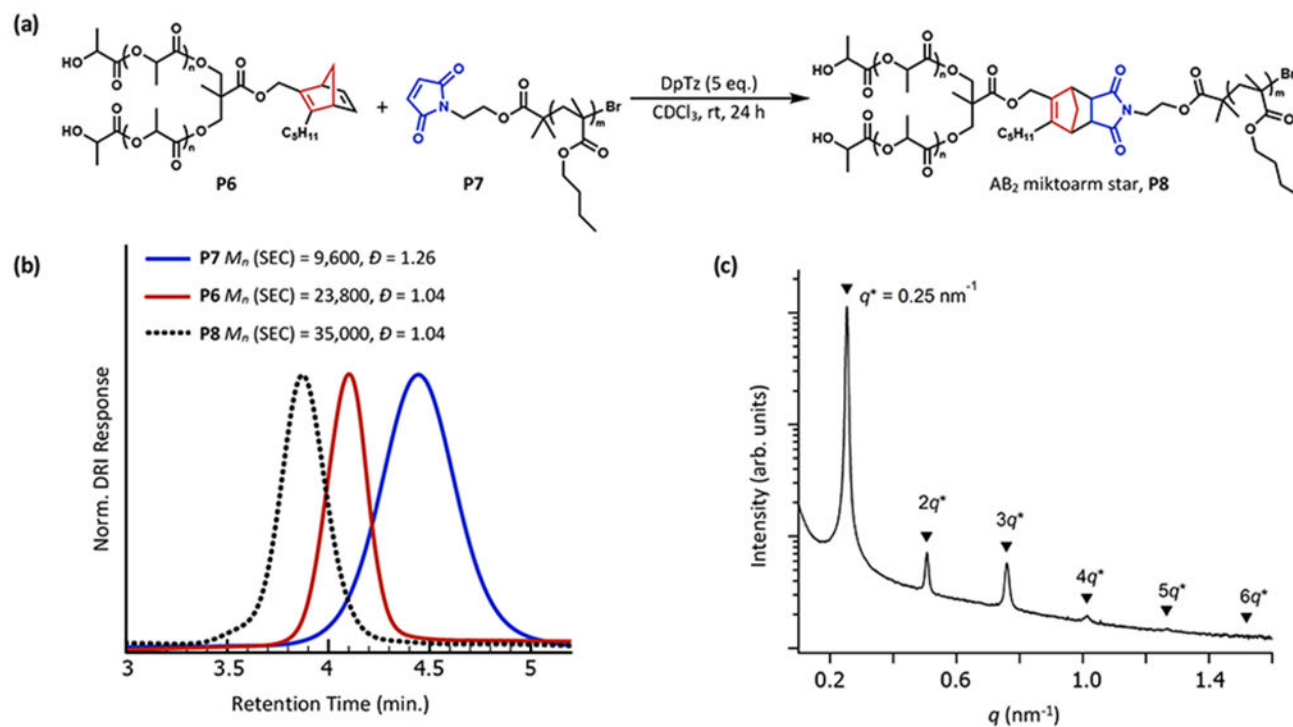
Figure 1.
(a) Current methods for maleimide–polymer conjugation using anthracene or furan. (b)
Strategy reported herein introducing masked Cp into polymers, highlighted by red bonds.

Figure 2.
(a) One-pot deprotection of NBD and conjugation with maleimide. Note: quenched with norbornene after 4 h. (b) Pyrene chain-end functionality introduced to PLA. ^{1}H NMR of (c) NBD-functionalized PLA, **P1**, and (d) PyrM-functionalized PLA, **P2**, in dichloromethane-d$_2$.

Figure 3.
(a) Chemical schematic for synthesis of triblock copolymer, **P5**, using a sequential deprotection–conjugation strategy between NBD-functionalized PLA (**P3**) and maleimide-terminated PEO-*b*-[G-4 dendron] (**P4**). ^{1}H NMR of (b) NBD-functionalized PLA, **P3**, and (c) triblock **P5** in chloroform-*d*.

Figure 4.
(a) Chemical schematic for one-pot AB$_2$ miktoarm star formation using a sequential deprotection–conjugation strategy between two-arm NBD-functionalized PLA (**P6**) and maleimide-terminated P*n*BMA (**P7**) to yield **P8**. Note: quenched with norbornene after 5 h. (b) SEC-RI overlay of polymer precursors and purified AB$_2$ miktoarm star (**P8**). (c) SAXS data confirming self-assembly of **P8** to a well-ordered lamellar structure.
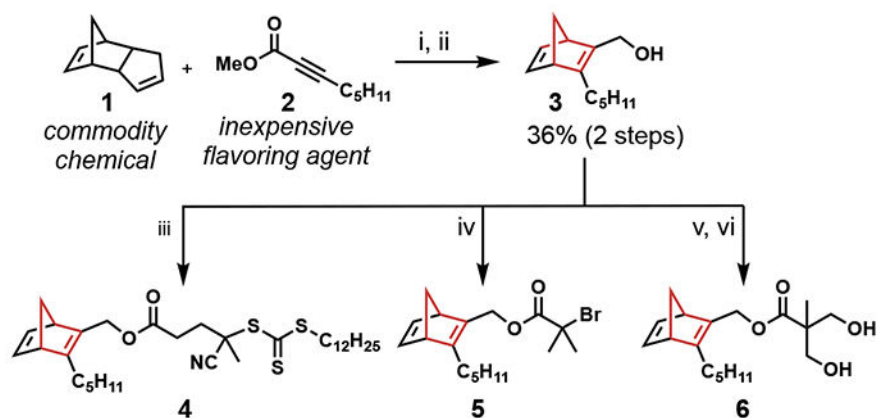
Scheme 1. Synthesis of Norbornadiene Polymer Building Blocks[a]
Conditions: (i) Neat, pressure vessel, 200 °C, 5 h, 50%. (ii) DIBAL, THF, 0 °C, 30 min, 71%. (iii) CDTPA, EDC·HCl, DMAP, DCM, rt, 16 h, 92%. (iv) *a*-Bromoisobutryl bromide, pyridine, THF, 0 °C, 2 h, 72%. (v) 2,2-Bis(*tert*-butyldimethylsiloxymethyl)propionic acid, EDC·HCl, DMAP, DCM, rt, 2 days, 86%. (vi) TBAF, THF, rt, 2 h, 73%.