Polymer Chemistry

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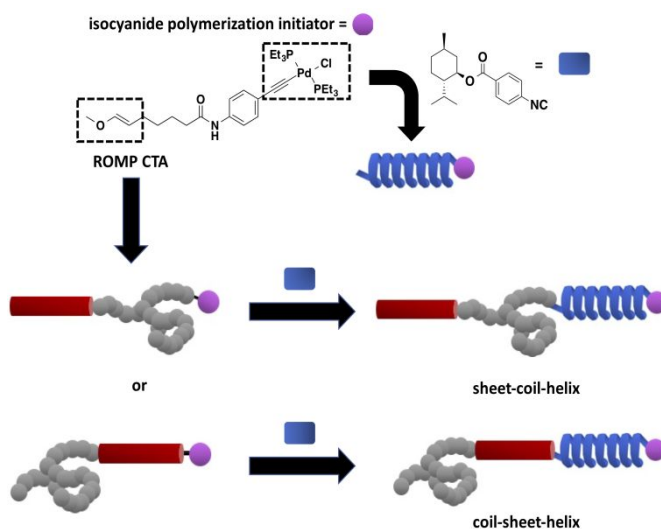Scott K. Pomarico,[a] Diane S. Lye,[a] Elizabeth Elacqua*[b] and Marcus Weck*[a]

Abstract. We report a synthetic route to construct architecturally well-defined triblock copolymers, in particular copolymers featuring secondary structures that form sheet-coil-helix and coil-sheet-helix motifs, through a macroinitiation strategy that combines sequential ring-opening metathesis polymerization (ROMP) with palladium-mediated isocyanide polymerization. Throughout the triblock copolymer fabrication, the individual blocks retained their secondary structures as evidenced by circular dicroism (CD) and fluorescence spectroscopies. Our strategy introduces a facile way to create complex ABC triblock copolymers that contain architecturally-diverse backbones, whilst retaining the ability to control sequence: sheet-coil-helix or coil-sheet-helix.

Nature's design of proteins features intricate building blocks comprised of distinct secondary structure elements including sheets, helices, and coils. The combination of these diverse topologies within the larger macrostructure endows the protein with function. Synthetic copolymers containing structural segments analogous to the ones found in Nature's biomacromolecules have garnered interest in the fields of polymer and materials science.[1-9] Copolymers that result from the combination of synthetic polymers with secondary structures are able to act as mimics, on a basic level, of some of the common domains found in proteins. Numerous examples of diblock and triblock copolymers composed of helices, sheets, and coils have been reported.[1-2, 9-14] However, a covalent system that combines sheet, helix, and coil blocks in one linear system has not yet been realized, owing to synthetic challenges that are presented when working with the monomers needed to form these three discrete secondary structures. Specifically, the desired monomers are not polymerizable using a single polymerization method. The present work introduces a new methodology that combines controlled polymerization methods, thereby creating two specific covalent triblock motifs (Scheme 1).

The synthesis of the triblock copolymers featuring three different architecturally well-defined building blocks, namely coils, sheets, and helices, can be performed using a supramolecular sequencing technique that involves the targeted assembly of mixed telechelic polymers.[13] Methods to engineer *covalent* triblock copolymers featuring such motifs, however, have not been realized. To date, only triblocks that possess two secondary structural elements (an ABA copolymer, for example) using a copolymerization methodology have been reported.[1-2, 5-6, 9] In order to achieve well-defined block copolymers, the chosen monomers need to be compatible and polymerizable using the same method (e.g., radical vs. ring-opening vs. cationic).

Techniques to string together synthetically-*incompatible*

Scheme 1. Strategy to synthesize covalent sheet-coil-helix (red-grey-blue) and coil-sheet-helix (grey-red-blue) triblock copolymers. Sequential ROMP is first performed to synthesize sheet-coil and coil-sheet diblock copolymers. A dual-functional CTA (Pd-CTA) is then added to terminate the polymerizations creating the diblock macroinitiators.

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Finally, the palladium-mediated polymerization of the isocyanide monomer takes place to form the final ABC and BAC triblock copolymers.

polymer blocks are limited to post-polymerization ligation[15-16] or macroinitiation.[17-18] Post-polymerization ligation allows for two or more distinct polymers to be covalently linked by taking advantage of azide-alkyne[15-16,19-20]/cyclooctyne[21] click reactions, as well as other strategies[15,19,22] that facilitate polymer termini functionalization.

Although post-polymerization ligation is used prominently in the syntheses of covalent diblock copolymers featuring two different secondary structures, it often suffers from non-quantitative yields, and it is usually difficult to remove unfunctionalized chains;[16,19] these characteristics provide a significant bottleneck for the synthesis of ABC triblock copolymers. In contrast, a macroinitiation approach ensures full linkage of the polymer blocks.[17-18] Through the unification of two strategies, namely ROMP and macroinitiation, we are able to circumvent challenges with post-polymerization modification methods, while polymerizing synthetically-incompatible monomers, to realize architecturally well-defined triblock copolymers in high yields with a high degree of control.

Our design is based on the successive ROMP of sheet- and coil-forming monomers, followed by palladium-mediated polymerization of a helical-forming monomer allowing for the facile synthesis of covalent coil-sheet-helix (ABC) and sheet-coil helix (BAC) copolymers (Scheme 2). After the initial sheet or coil-forming monomer is polymerized through ROMP, the second monomer is introduced and polymerized, leading to a diblock comprised of sheet and coil structures. Polymerization is then terminated by a chain-transfer agent (CTA)[17] that features an isocyanide polymerization initiator.[23-25] The resulting telechelic diblock copolymers, each containing coil-

sheet and sheet-coil blocks, then function as macroinitiators for the polymerizations of P-helix forming monomers.[26] This combination of sequential copolymerization and macroinitiation enables three different polymer chains, synthesized through two separate polymerization types, ROMP and palladium-mediated isocyanide polymerization, to be linked covalently with high fidelity. The resulting covalent triblock copolymers feature defined blocks; the structure of each relying on monomer choice alone.

Synthesis of the targeted covalent triblocks (Scheme S1 and S2) starts with sequential ROMP of norbornene octyl ester (NBC8), a coil-forming monomer,[27] and a substituted [2.2]paracyclophane-1,9-diene (pCpd), a monomer that yields a rigid, conjugated polymer backbone resembling a sheet-like architecture.[12-13, 28-29] A monomer-to-initiator ([M]$_0$/[I]$_0$) of 100 was targeted for the polymerizations of the NBC8 monomer. For the sheet-forming pCpd block, a monomer-to-initiator ratio of 50 was chosen as pCpd polymerization leads to two repeat units per monomer.

The covalent coil-sheet macroinitiator was obtained through ROMP of the norbornene octyl ester using Grubbs' 2nd generation initiator (G2). After 45 minutes, pCpd was added to the reaction mixture, and the temperature was raised to 68 °C to initiate the polymerization. Monomer consumption was monitored through ^{1}H NMR spectroscopy by comparing the poly(norbornene) backbone peak integrations at 5.0 – 5.5 ppm to the signals at 3.5 – 4.3 ppm that correspond to the poly(p-phenylene vinylene) side-chains (Figure S1). Upon complete monomer consumption, ROMP was terminated by the addition of the bifunctional, palladium-containing CTA (Pd-CTA); this allowed for the incorporation of the isocyanide initiator onto every diblock copolymer chain end. To synthesize the sheet-coil diblock macroinitiator, the sequential polymerization
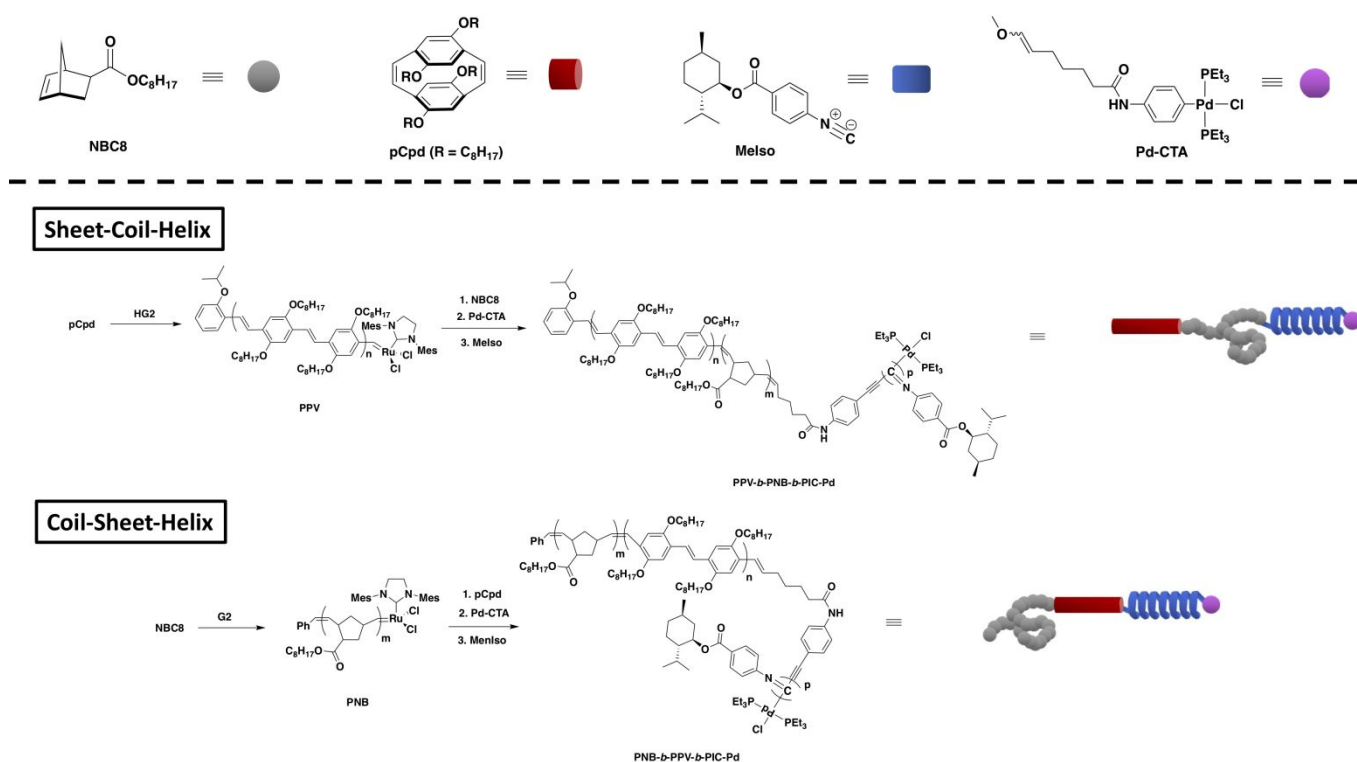
Scheme 2. Strategy to synthesize sheet-coil-helix and coil-sheet-helix triblock copolymers. The three monomers and palladium-containing CTA used to form these structures are shown at the top (NBC8, pCpd, MeIso, Pd-CTA).

order was reversed, and the ROMP was initiated by the use of a Hoveyda-Grubbs' 2nd generation catalyst (HG2).[30]

The resulting coil-sheet and sheet-coil macroinitiators were purified by precipitation. ^{31}P NMR spectroscopy of the macroinitiators demonstrated that both polymeric systems were functionalized with Pd-end groups and contained only one Pd species (Figures S2 and S9). GPC analysis of the diblocks confirmed successful block copolymer formation with a monomodal trace, and an increase in molecular weight (Figures S6 and S13 and Table 1). Molar ratios of the coil-sheet and sheet-coil macroinitiators were determined by ^{1}H NMR spectroscopic end-group analysis (Figures S1 and S8). For calculations associated with the subsequent polymerizations of the menthol-isocyanide monomer, these ^{1}H NMR spectroscopy results were utilized.

The pure **PNB-*b*-PPV-Pd** and **PPV-*b*-PNB-Pd** macroinitiators were then used to polymerize the menthol-based phenyl isocyanide monomer (MeIso) (Scheme 2). Isocyanide polymerizations were conducted with $[M]_0/[I]_0$ of 100. The isocyanide underwent polymerization over the course of 16 hours at 55 °C to achieve the final triblock copolymers containing architecturally well-defined building blocks, namely sheet-coil-helix and coil-sheet-helix.

After purification, GPC analyses yielded dispersities of 1.51 and 1.30 for the **PNB-*b*-PPV-*b*-PIC-Pd** and **PPV-*b*-PNB-*b*-PIC-Pd** triblocks respectively (Table 1), and peak shifts to lower retention times, corresponding to increases in molecular weight after the helical blocks were added, were seen (Figures S6 and S13). ^{31}P NMR spectroscopic analysis of the block copolymers revealed that a single phosphorus signal is maintained at δ = 17.9 ppm, suggesting that the palladium moiety remained intact after initiation of the isocyanide monomer and purification (Figures S5 and S12). This demonstrates the robustness of the palladium-containing macroinitiator and our macroinitiation methodology in general.

Fluorescence and circular dichroism (CD) spectroscopies were conducted to characterize whether each block had retained its secondary structure. Fluorescence spectroscopy revealed that the coil-sheet-helix and sheet-coil-helix block copolymers retained the intrinsic fluorescence of the PPV block (Figures 1a and 2a respectively). In each iteration, both before and after macroinitiation of the isocyanide monomer, the strong signal at 546 nm in the emission spectra demonstrated that the sheet-like structure of the PPV block remained intact, despite the presence of the PNB block, which could affect the polymer's natural tendency to organize into stacked structures.

Upon introduction of the helical block through palladium-mediated isocyanide polymerization, the CD spectroscopic data (Figure 1b and Figure 2b) of both **PNB-*b*-PPV-*b*-PIC-Pd** and **PPV-*b*-PNB-*b*-PIC-Pd** showed the emergence of a strong positive Cotton Effect at 364 nm. This indicates that a right-handed helical structure formed after isocyanide polymerization from the sheet-coil and coil-sheet PPV- and PNB-based macroinitiators. Before addition of the isocyanide monomer, no signal was visible (Figures 2b and 3b, red and blue traces). These CD results clearly demonstrate that the structural integrity of the helical block was maintained throughout the formation of both sheet-coil-helix and coil-sheet-helix triblock copolymers, which aligns with expectations based on our previous studies of analogous supramolecular systems.[12-13]

In conclusion, we have introduced a straightforward synthetic methodology to engineer covalent triblock copolymers comprised of sheet, coil, and helical blocks. Our strategy involves the engineering of a sheet-coil or coil-sheet polymer by sequential ROMP and termination with a CTA that contains an isocyanide polymerization initiator. An isocyanide monomer, known to form static right-handed helices, is then added to the PPV- and PNB-based macroinitiators to form the final sheet-coil-helix and coil-sheet-helix ABC and BAC copolymers; the successful formation of which was confirmed using GPC and ^{1}H NMR spectroscopy. Through fluorescence and

Table 1 Polymer characterization data for **PNB-*b*-PPV-Pd**, **PNB-*b*-PPV-*b*-PIC-Pd**, **PPV-*b*-PNB-Pd**, and **PPV-*b*-PNB-*b*-PIC-Pd**.

Polymer	$[M]_0/[I]_0$	$Đ$[a]	M_n[a]	M_w[b]
PPV-b-PNB-Pd	50, 100	1.47	25,500	65,000
PPV-b-PNB-b-PIC-Pd	50, 100, 100	1.30	39,000	-----[c]
PNB-b-PPV-Pd	100, 50	1.14	16,000	82,000
PNB-b-PPV-b-PIC-Pd	100, 50, 100	1.51	45,500	-----[c]

[a]$Đ$ and M_n were determined by GPC (CHCl$_3$, poly(styrene) standards); [b]M_w was determined by ^{1}H NMR spectroscopic end-group analysis; [c]unable to measure accurately for the poly(isocyanide) backbone from ^{1}H NMR spectroscopy.
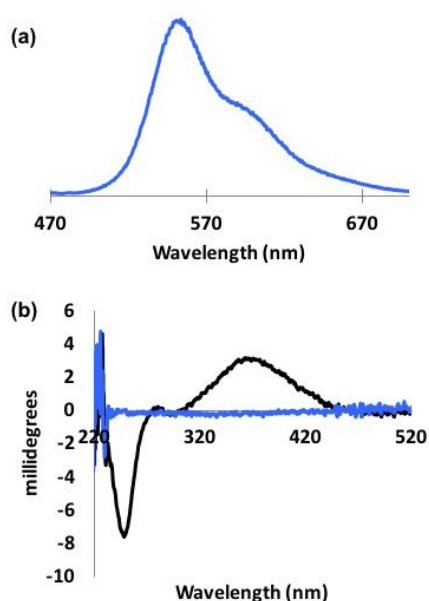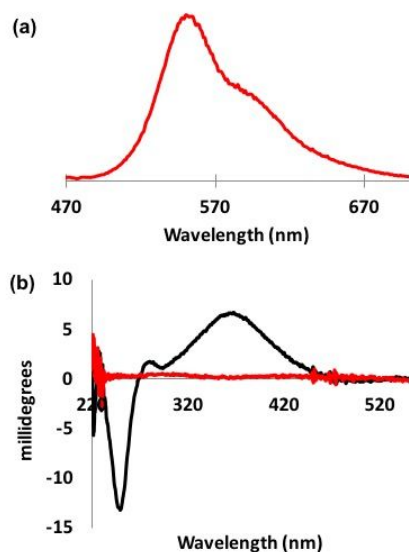
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CD spectroscopies, we observed that the individual block shapes were maintained throughout the synthesis and purification steps.

The present study provides a new methodology to covalently link three distinct structures together with high fidelity whilst retaining control over sequence. This work can

be extended to the formation of a diverse array of tri- and multiblock copolymers. The diblock macroinitiators can be used to polymerize or copolymerize poly(isocyanide) monomers containing different side-chains, or to copolymerize isocyanide monomers with monomers of other types.[24] Alternatively, the versatile Pd-CTA can be modified with various functional groups to perform a role in other polymerization techniques. For example, a primary alcohol can be incorporated onto the palladium compound to act as an initiator for ring-opening polymerization (ROP) of lactides.[31] With these potential uses in mind, future work will focus on the engineering of triblock copolymers with different motifs, as well as performing morphological and materials studies on these copolymer systems.

Acknowledgements

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A new methodology towards architecturally well-defined covalent triblock copolymers is presented.