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Synthesis of hybrid block copolymers *via* integrated ring-opening metathesis polymerization and polymerization of NCA†

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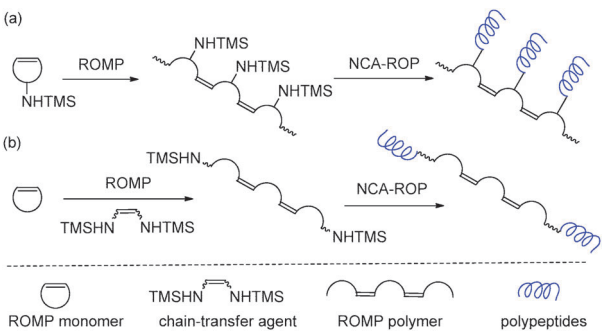
Linear hybrid block copolymers with well controlled molecular weights and narrow polydispersities were synthesized *via* ring-opening metathesis polymerization (ROMP) followed by ring-opening polymerization of amino acid *N*-carboxyanhydrides.

Hybrid copolymers, which contain segments with distinct structures and properties, are useful materials in various applications such as novel plastics,[1,2] polymeric catalysis,[3,4] smart materials,[5–7] self-assembly,[8–14] and bionanotechnology.[15–21] They can be prepared through conjugation of hybrid polymeric segments or polymerization with corresponding initiators. The latter approach is particularly attractive as the hybrid polymers with tuneable molecular weights (MWs) and narrow polydispersities (PDIs) of each block may be readily achieved *via* controlled polymerizations. In parallel to the studies of utilizing AB-type dual initiator to facilitate two distinct, controlled polymerizations from the initiators A and B of the same centre,[22] there is also significant interest in preparing linear hybrid copolymers *via* controlled, sequential polymerizations, using a mono-initiator for the synthesis of the first polymeric block followed by transformation of the active chain end of the resulting first block using chain transfer agents (CTAs) or terminating agents (TAs) to a macromolecular initiator with a desired terminal group for the synthesis of a second polymer block.[23–27] Here, we report the utilization of the CTA approach to synthesize polypeptide-*b*-poly(oxa)-norbornene hybrid copolymers, *via* controlled ring-opening metathesis polymerization (ROMP) followed by ring-opening polymerization of amino-acid *N*-carboxyanhydrides (NCAs).

We recently reported the integration of ring-opening polymerization (ROP) of NCAs[22,28–30] and ROMP[31–33] to prepare polypeptide-grafted brush-like polymers in a one-pot fashion (Scheme 1a).[34] The strategy involves the ROMP of a norbornene monomer containing *N*-trimethylsilyl (*N*-TMS) amine followed by the controlled ROP of NCAs mediated by the pendent *N*-TMS amine group, a method we developed recently.[29,34–36] We reasoned that the excellent compatibility between *N*-TMS amines and ROMP catalysts could also be utilized to prepare linear hybrid block polymers by using an *N*-TMS amine functionalized *cis*-alkene as CTA.[37] Consequently, the *N*-TMS terminal groups, which are amenable for NCA polymerization yet compatible with olefin metathesis catalyst, can be transferred to the polyolefin chain ends, making the synthesis straightforward with no need to protect the amine group (Scheme 1b).

CTA (**2**) was designed as a symmetrical, *N*,*N*′-bis(TMS)-diamine functionalized *cis*-olefin (Scheme 2) instead of an *N*-TMS amine functionalized terminal alkene because the former usually leads to a higher degree of chain-end functionalization than the latter.[25,38–40] **2** was synthesized in a few steps from inexpensive, commercially available starting materials, and fully characterized by ^{1}H-NMR and ^{13}C-NMR (see ESI†). To test whether **2** can act as a CTA and give complete end-capping of ROMP polymers, Grubbs catalyst **1** was mixed with **2** (5–6 equiv.) and stirred for 1 h to ensure complete carbene exchange, yielding a *N*-TMS bearing ruthenium catalyst (Step 1, Scheme 2). The colour gradually turned brown from green, indicating the olefin exchange and the formation of **S3**. The ROMP monomer **M1** (30 equiv.) was then added directly to the **S3** solution and the polymerization proceeded rapidly (Step 2, Scheme 2). We expected that an *N*-TMS amine terminated ROMP polymer (**S4**, Scheme 2) with an active chain-end would be generated from **S3**. Since the ROMP of **M1** was several orders of magnitude faster than the cross-metathesis of **2**,[20,24] the chain termination of the ROMP polymer by excess **2** (Scheme 2, Step 3) would happen



Scheme 1 (a) Synthesis of polypeptide-containing brush-like copolymers using an *N*-TMS amine bearing ROMP monomer; (b) synthesis of linear hybrid block copolymers *via* an *N*-TMS amine functionalized chain-transfer agent.

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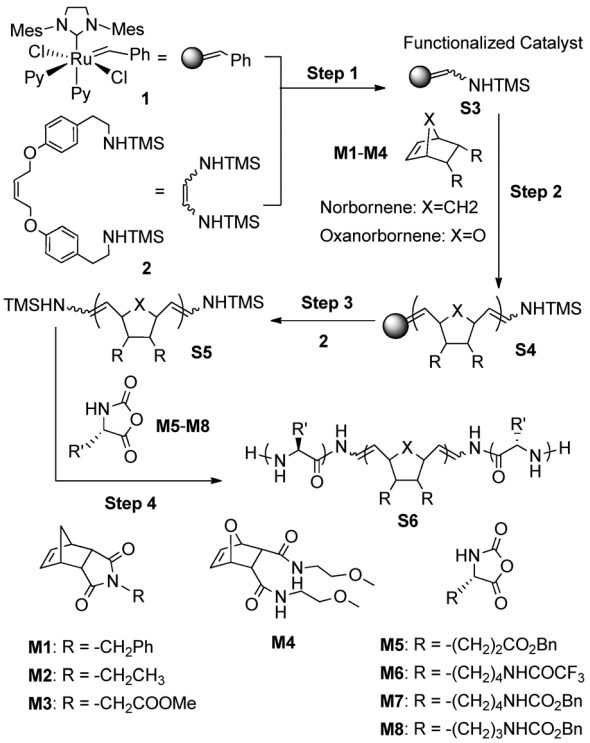


Scheme 2 Structures of the Grubbs-catalyst (**1**), CTA (**2**), ROMP monomers (**M1–M4**) and NCA monomers (**M5–M8**) used in the study, and the scheme of the synthesis of polypeptide-*b*-poly(oxa)norbornene-*b*-polypeptide triblock polymers. Py = pyridine; Bn = benzyl; Mes = 2,4,6-trimethylphenyl.

only after the monomer **M1** was completely consumed, and thus resulted in *N*-TMS amine groups on both ends of the resulting ROMP polymer (**S5**, Scheme 2). **S5** was isolated by precipitation in dry hexane in a glove-box and analysed by ^{1}H-NMR. The *N*-TMS amine group was successfully detected with >99% end-capping efficiency (see ESI†). For the polymerization mediated at a monomer/initiator (M/I) ratio of 30 : 1, gel permeation chromatography (GPC) analysis showed a monomodal peak with an M_n value of 7.5 × 10^3 g mol^{-1}, which was close to the expected MW (8.1 × 10^3 g mol^{-1}), and a narrow PDI (1.02, **P1**, Table 1). Another polymerization performed under the same condition at an **M1**/initiator ratio of 100 : 1 yielded **P2** with a MW identical to the expected value and a narrow PDI of 1.02 (Table 1; Fig. 1).

To study whether the *N*-TMS amine situated at the terminus of the ROMP polymers is still reactive, we quenched **P1** with di-*tert*-butyl dicarbonate ((Boc)$_2$O). Complete *trans*-functionalization from *N*-TMS amine to *N*-Boc was confirmed by ^{1}H-NMR (see ESI†). After confirming the activity of **P1**'s *N*-TMS amine, we went on to synthesize a series of polypeptide-*b*-polynorbornene-*b*-polypeptide copolymers (**S6**, Scheme 2) by treating **S5** with various NCAs (**M5–M8**). A triblock copolymer **P6** (Table 1) was successfully obtained by mixing NCA monomer **M5** and **P1** at 100 : 1 M/I ratio in anhydrous DMF. The GPC analysis of the resulting mixture showed a monomodal peak with an M_n value close to the theoretical value and a narrow PDI of 1.12. The MW obtained from the ^{1}H-NMR spectrum of **P6** agreed well with the M_n obtained from GPC (see ESI†). Similarly, **P2**-initiated

Table 1 Characterization of poly(oxa)norbornene polymers and polypeptide-poly(oxa)norbornene-polypeptide triblock copolymers

Polymer	Monomer	Initiator	M/I[a]	Conv. of monomer (ROMP/PP(%))[b]	M_n (M_n*)[c] ($\times 10^3$ g mol^{-1})	PDI[d]
P1	**M1**	**1** + **2**	30 : 1	>99/-	7.5 (8.1)	1.02
P2	**M1**	**1** + **2**	100 : 1	>99/-	25.8 (25.8)	1.02
P3	**M3**	**1** + **2**	75 : 1	>99/-	19.9 (18.1)	1.02
P4	**M2**	**1** + **2**	100 : 1	>99/-	19.1 (19.5)	1.05
P5	**M1** + **M4**	**1** + **2**	(100 + 25) : 1	>99/-	33.3 (33.2)	1.06
P6	**M5**	**P1**	100 : 1	>99/>99	28.5 (29.5)	1.12
P7	**M5**	**P2**	100 : 1	>99/>99	50.2 (47.7)	1.03
P8	**M5**	**P2**	200 : 1	>99/>99	68.1 (69.6)	1.03
P9	**M6**	**P2**	100 : 1	>99/>99	49.5 (48.2)	1.03
P10	**M8**	**P3**	100 : 1	>99/>99	47.8 (44.8)	1.02
P11	**M5**	**P4**	100 : 1	>99/>99	47.6 (41.2)	1.13
P12	**M7**	**P5**	300 : 1	>99/>96	113.6 (111.4)	1.07

[a] M/I = monomer/initiator ratio. [b] Conversion of monomer of the ring-opening metathesis polymerization (ROMP)/the ring-opening polymerization of NCA for the synthesis of polypeptide (PP). [c] M_n = molecular weight measured by GPC; M_n* = molecular weight expected. [d] Polydispersity index (M_w/M_n).

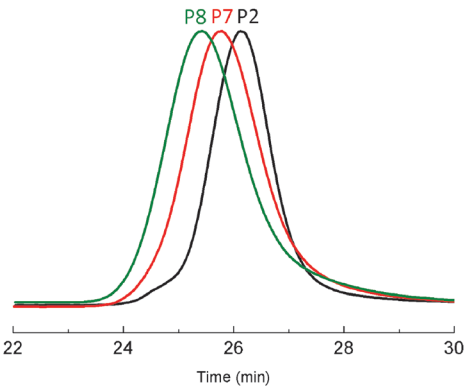
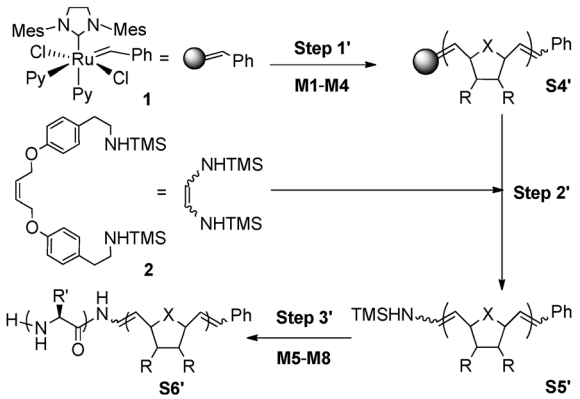


Fig. 1 Overlay of the GPC curves of the ROMP polymer (**P2**) and the triblock copolymers (**P7** and **P8**).

polymerizations of **M5**, which yielded **P7** and **P8** at M/I ratios of 100 : 1 and 200 : 1, respectively (Table 1), also showed remarkable control over molecular weights and PDIs, evidenced by the GPC analysis (Fig. 1). **P7** and **P8** had an obtained MW of 50.2 and 68.1 × 10^3 g mol^{-1}, respectively, which was deviated only 5% and 2% from the expected values (Table 1). Both **P7** and **P8** had very narrow PDIs (1.03).

We then tested the same strategy using several different ROMP monomers (**M2–M4** in Scheme 2) and NCA monomers (**M6–M8** in Scheme 2). Both the ROMP for the synthesis of **P3–P5** and subsequent ROP of NCAs proceeded smoothly and gave a variety of well-defined polypeptide-*b*-poly(oxa)-norbornene-*b*-polypeptide triblock copolymers (**P9–P14**) using different combinations of ROMP and NCA monomers at various M/I ratios (Table 1 and ESI†). The facile synthesis of those block copolymers validated the generality of this controlled, sequential polymerization strategy.

Synthesis of polynorbornene-*b*-polypeptide diblock copolymers were also attempted by following a slightly modified strategy (Scheme 3).[25] ROMP of **M1** was first initiated by **1**



Scheme 3 Structures of the Grubbs-catalyst (**1**), CTA (**2**), and the scheme of the synthesis of polypeptide-*b*-poly(oxa)norbornene diblock polymers. Py = pyridine; Bn = benzyl; Mes = 2,4,6-trimethylphenyl.

(Step 1′, Scheme 3). **2** was added to the solution after the initiation was complete (Step 2′, Scheme 3). The olefin cross-metathesis only occurred at the chain-propagation end as the benzylidene terminus on the other end was too sterically hindered to compete for such a chain transfer reaction.[25,41] Mono-(*N*-TMS amine) functionalized ROMP polymer was obtained (**S5′**, Scheme 3). After the excess **2** was removed, the ROMP polymer was used for the ROP of NCAs to give the polynorbornene-*b*-polypeptide diblock copolymers (**S6′**, Scheme 3). All the diblock polymers synthesized had well-controlled molecular weights and low PDIs (**P17–P18**, Table S1, see ESI†).

In summary, we developed a novel strategy for the facile synthesis of polypeptide-*b*-poly(oxa)norbornene-*b*-polypeptide triblock and polynorbornene-*b*-polypeptide diblock copolymers. By using a symmetrical CTA **2** for ROMP, mono-(*N*-TMS amine) and *N*,*N*′-bis(TMS)diamine terminally functionalized ROMP polymers were generated and utilized to initiate the controlled ROP of NCAs to yield the desired, well-defined hybrid block copolymers. We are currently exploring the properties, self-assembly and biomedical applications of these novel materials.

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