Precise Control of Single Unit Monomer Radical Addition with a Bulky Tertiary Methacrylate Monomer Toward Sequence-Defined Oligo- or Poly(methacrylate)s via the Iterative Process

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ARTICLE

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Iterative single unit monomer radical addition with a bulky tertiary methacrylate monomer, adamantyl and isopropyl pendant methacrylate (IPAMA), under ATRP condition was studied in detail toward syntheses of sequence-defined oligo- or poly(methacrylate)s in higher yields. An inroduction of activated ester for alkyl halide or the adduct was effective to improve the accuracy on the single unit addition of IPAMA without forming unfavorable products. Thus, a cycle consisting of 4 steps, "radical addition", "transformation", "selective cleavage", and "active esterification", was established to realize the circumstance for effective single unit monomer addition and the iterative process along with pendant modification. The cycle was actually repeated to synthesize 2 units adduct in high yield.

Introduction

With the establishment of reversible deactivation radical polymerization (RDRP)[1] allowing control of molecular weight as the occasion, "sequence" or the order/position of repeating monomer units has attracted attention as the structural factor for more precise synthetic polymers in the last decade.[2-7] For nature polymers, i.e., DNA and proteins, sequence is an essential structural factor determining higher order structures, leading to smart and effective functions much superior to artificial counterparts. Herein, crucial is control over order of the pendant groups (i.e., nucleobases and amino acid residues) regularly dangling from main chain composed of a single type of repeating units. In this regard, synthetic copolymers consisting of same monomer derivatives carrying various side chains such as (meth)acrylates, styrenes, and acrylamides has similarly to the natural polymers. However, chain-growth mechanism for syntheses of such copolymers is inherently unsuitable for sequence control, and the difficulty is more marked with same monomer derivatives. Thus, polymer chemists are aware sequence control for same kinds of repeating units is extremely challenging unless some iterative addition process is developed.

Development of RDRP has enabled us to control chain length or molecular weight as well as the terminal groups for vinyl polymers. The deactivation process contributes to temporal conversion of growing active (radical) species into dormant, leading to suppression of irreversible chain transfer and termination reactions. For example, in the case with atom transfer radical polymerization (ATRP) or metal-catalyzed living radical polymerization,[8, 9] a halogen is provided from higher oxidant metal complex to deactivate radical species, and the resultant carbon-halogen bond can be reversibly activated via the one-electron redox of the catalyst.

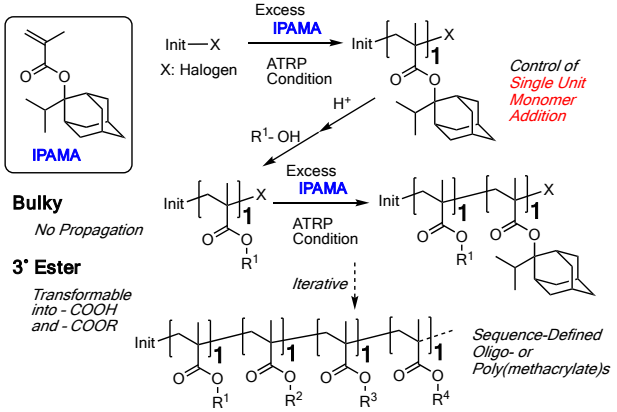

Fig. 1 Iterative single unit monomer addition with IPAMA to construct sequence-defined oligo-or poly(methacrylate)s

The RDRP feature that growing chains can continue to grow without irreversible termination would be required even for sequence control. However, some additional regulation is necessary to overcome the problem that distributed adducts are generated due to the chain growth mechanism. In this context, we have proposed using a special methacrylate monomer carrying an extremely bulky and transformable pendant to control single monomer addition and repeat it.[10] Specifically, adamantly and isopropyl pendant tertiary (3˚) methacrylate (IPAMA) was found to be the special monomer meeting the demand. The pendant is too bulky to react with itself for propagation but the monomer can react with alkyl halide to yield the single unit adduct capped by halogen under

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optimized ATRP condition. The tertiary ester pendant in the resultant adduct is transformed into carboxylic acid via cleavage with a strong protonic acid, and the resultant acidic pendant can be esterified with 1˚ or 2˚ alcohol (R^n–OH) giving a less bulky methacrylate unit. The 1˚ or 2˚ ester is tolerance to the acidic condition for the later cleavage process. For the resultant single methacrylate unit adduct, the chance arises to undergo the radical addition with IPAMA. If the single unit adduct is quantitatively synthesized for the initiator or halogen-capped product, the methodology would allow construction of sequence-defined oligo-or poly(methacrylate)s in high yield.

Such single monomer addition has been investigated by some groups. Moad et al. utilized kinetic parameters with reversible addition-fragmentation chain-transfer (RAFT) polymerization to demonstrate synthesis of a dimer of *N*-isopropylacrylamide (NIPAM) and styrene, but the overall yield was low (about 30%).[11] Junkers et al. synthesized sequence-defined oligoacrylates by repeating equimolar addition of acrylate monomer and purification of the single unit adduct on the basis of RAFT and photo-induced ATRP.[12-15] This methodology is simpler but faces the yield issue due to necessity of isolating the single unit adduct from dispersed product at each reaction. Recently, Xu and Boyers et al. have reported the single monomer addition via photo-induced electron transfer (PET)-RAFT system.[16-19] Crucial is the selective activation by organic photoredox catalyst or selective cross-over propagation based on comonomer reactivity ratios.

Although our methodology is rational in principle to realize defined sequence, a problem to be solved also remains: the single unit monomer radical addition of IPAMA is partially imperfect in the strict sense resulting in a small amount of unfavorable product (vide infra). The process for removal of the side product might cause low yield of the ideal single unit adduct. A high yield in one cycle as much as possible is required, because it is accumulated via the iterative process. Thus, in this work, we focused on the radical addition of IPAMA with a halogen compound or the adduct in detail to improve the efficiency of the single unit addition. Consequently, we found that an electronic effect of the alkyl halide is important to control the radical addition of the bulky monomer. One more step was necessary to change the electron density of halogen terminal, but the efficiency of single unit addition was improved.

Results and discussion

The radical addition with IPAMA was studied in more detail (Fig. 2). Here, dodecyl 2-chloro-2-phenylacetate (DCPA) was used as the alkyl halide or the initiator (A), because the type of phenyl acetate halide allowed better efficient radical generation due to the lower bond energy than the simple methacrylate-based halide.[20] The long alkyl chain ($C_{12}H_{25}$-) was introduced to detect the product by SEC. The radical addition reaction of 10 equivalent of IPAMA with DCPA was performed with Cp*/bisphosphine monoxide-based ruthenium catalyst upon heating (80˚C)[10, 21] and the reaction was monitored by ^{1}H NMR. The resultant products over time were analyzed by SEC.

As shown in Fig. 2B, IPAMA was initially consumed after the solution was heated, but the conversion was saturated at around 10%: further consumption was not observed even after a long interval. For the SEC analysis (Fig.2C), the relative intensity of the peak from alkyl halide were gradually decreased, whereas a higher molecular weight (MW) peak likely from the single unit adduct was observed. Finally the peak was mainly observed and the alkyl halide peak disappeared. However, another minor peak of higher molecular (dotted line square) was also observed. The product was purified by preparative SEC for removal of lower molecular weight compounds (e.g., the excess IPAMA and catalyst residues) (Fig. S1 for the SEC curve after the purification) and the higher MW product was analyzed by ^{1}H NMR. The spectrum nearly supported ideal structure of the single unit adduct, but the integration ratio from the IPAMA side chain to the initiator moiety was inconsistent with the ideal value for assuming the 1 unit adduct was formed [Fig. 2D: the ideal integration of the methyl protons (*h*) is 6.0 for the methylene protons (2H) in the DCPA unit]. Considering the integration ratio and the minor peak of higher MW in the SEC analysis, a bimolecular coupling reaction between DCPA was likely accompanied and a small amount of the coupled product was contained.

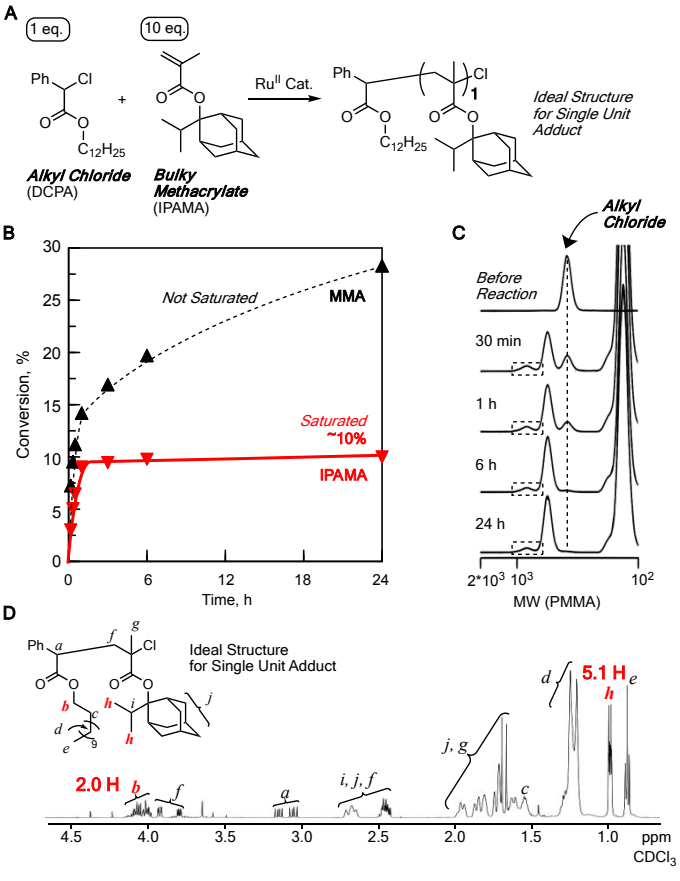

Fig. 2 Radical addition of IPAMA with DCPA: $[IPAMA]_0/[DCPA]_0/[[Cp^*Ru(\mu_3\text{-}Cl)]_4]_0/[BPMO\ ligand]_0$ = 200/20/1.0/8.0 mM in toluene at 80˚C. (A) Scheme; (B) time-conversion; (C) SEC curves of the products; (D) ^{1}H NMR spectrum of the product. BPMO ligand: 1,2-bis(diphenylphosphino)ethane monoxide.

Suppression of the the unfavourable coupling reaction was studied by changing reaction conditions, i.e., catalyst, concentration, temperature (Fig. S2), but the unfavourable peak did not disappear perfectly. We then decided to replace the dodecyl ester of the chloride with an activated ester[22] in anticipation that the coupling reaction between the corresponding electron deficient radical species could be avoided. *N*-Hydroxy-5-norbornene-2,3-dicarboxyimide (NHND)-based ester[23] was selected among various types of activated ester, because the relatively high molecular weight is suited for SEC analysis. Thus, NHND-CPA was designed as the new initiator. Fig.3 shows ^{1}H NMR spectrum of NHND-CPA in comparison with DCPA. The lower shift of the methine proton neighboring chlorine than DCPA indicated the electron withdrawing effect of the NHND-based ester. Such an activated ester can be transformed into alkyl ester or amide via the reaction with alcohol or amine. Thus, the concept to repeat the cycle via post modification is still available, although one more step in one cycle is required (see below).

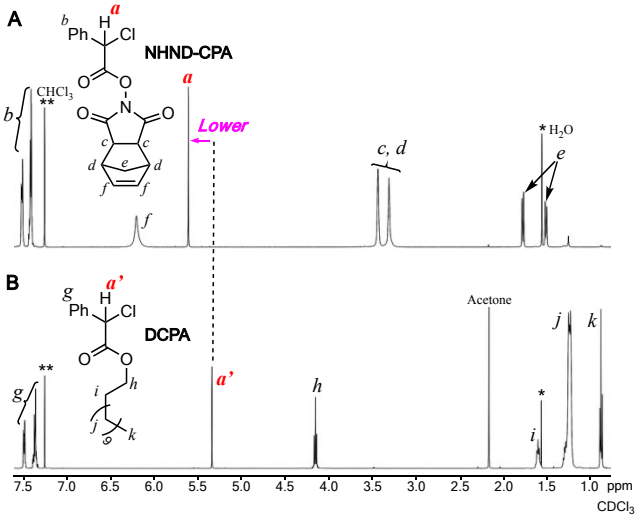

Fig. 3 ^{1}H NMR spectrum of NHND-CPA (A) and DCPA (B) (r.t., $CDCl_3$)

The newly synthesized halide initiator (NHND-CPA) was used for the ruthenium-catalyzed radical reaction with 10 eq. of IPAMA (Fig. 4). The saturated conversion at 10% (Fig. 4A) and the peak shift in SEC analysis (Fig. 4B) were observed similar to with DCPA, indicating progress of the single unit monomer addition. Importantly, no coupling peak was observed in the SEC trace. The quantitative formation of the single unit adduct was proved by ^{1}H NMR spectrum (Fig. 4C): the integration ratio of the methyl protons of IPAMA unit (*h*, 6H) to those of olefin protons from NHND moiety (*d*, 2H) was exactly 3:1. H-H COSY 2D NMR and ESI-MS spectrum also corresponded to formation of the single unit adduct (Fig. S3 and S4).

Thus, the activated ester-based halide was found to be effective to control the single unit addition with IPAMA. To always realize such reaction circumstance in the iterative cycle, the steps in a cycle were modified as shown in Fig. 5A. Namely, after control of single unit addition, the penultimate NHND-based unit was transformed into an alkyl methacrylate unit via transformation, and afterwards the terminal IPAMA unit was selectively cleaved under acidic condition to convert into a

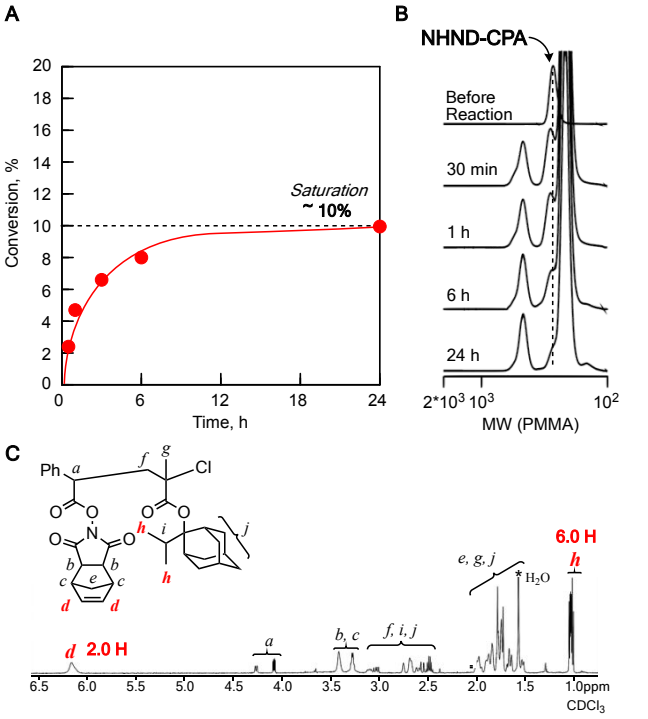

Fig. 4 Radical addition of IPAMA with NHND-CPA: $[IPAMA]_0/[NHND\text{-}CPA]_0/[[Cp^*Ru(\mu_3\text{-}Cl)]_4]_0/[BPMO\ Ligand]_0$ = 200/20/1.0/8.0 mM in toluene at 80˚C. (A) time-conversion (B) SEC curves of the products (C) ^{1}H NMR spectrum of the product.

methacrylic acid unit. Finally, NHND was introduced via esterification to form the activated ester-based halide terminal that is effective to control next single unit radical addition with IPAMA. The step number in a cycle is one more than conventional (Fig. 5B), but the process is also advantageous that the circumstance of the radical addition is always identical in

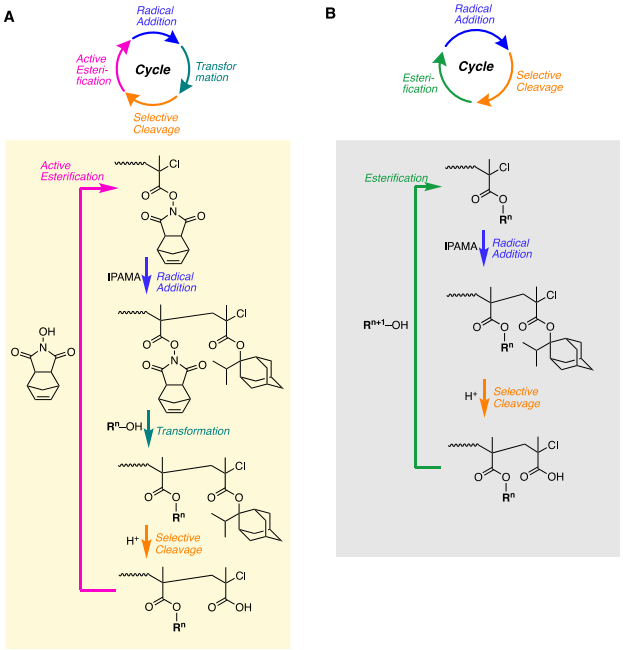

Fig. 5 A new cycle with activated ester (A) in comparison with the previous cycle (B).

the iterative process (i.e., the reaction between NHND-terminal halide and IPAMA).

Thus, one cycle consisting of 4 steps, i.e., "radical addition", "transformation", "selective cleavage", and "active esterification", was actually performed, and the structure of the product obtained at each step was characterized by ^{1}H NMR (Fig. 6). For the transformation of the IPAMA-adduct, dodecyl alcohol was used in conjunction with 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) as the base. The peak from double bond of the NHND pendant perfectly disappeared, and instead peaks from the dodecyl ester pendant (*k*, *m*, *n*) appeared with the reasonable integration ratios for the quantitative transformation. The transformation product was fully supported with the assistance of H–H COSY 2D NMR (Fig. S5). Interestingly the peaks from methine proton neighbouring to phenyl group clearly shifted to higher field (*a'* vs *a''*) via the transformation due to change in electronic environment. The split of single peak (a) into two peaks (*a'* and *a''*) was due to the formation of two diastereoisomers caused by the chiral carbon neighbouring to chlorine atom. Then the product was treated with trifluoroacetic acid (TFA) for cleavage of the IPAMA unit. Consequently, the peak from isopropyl methyl protons vanished, while the peaks from dodecyl ester pendant survived quantitatively, indicating the quantitative and selective cleavage. Finally, NHND was reacted with the methacrylic acid adduct to convert into activated ester-based halide terminal.

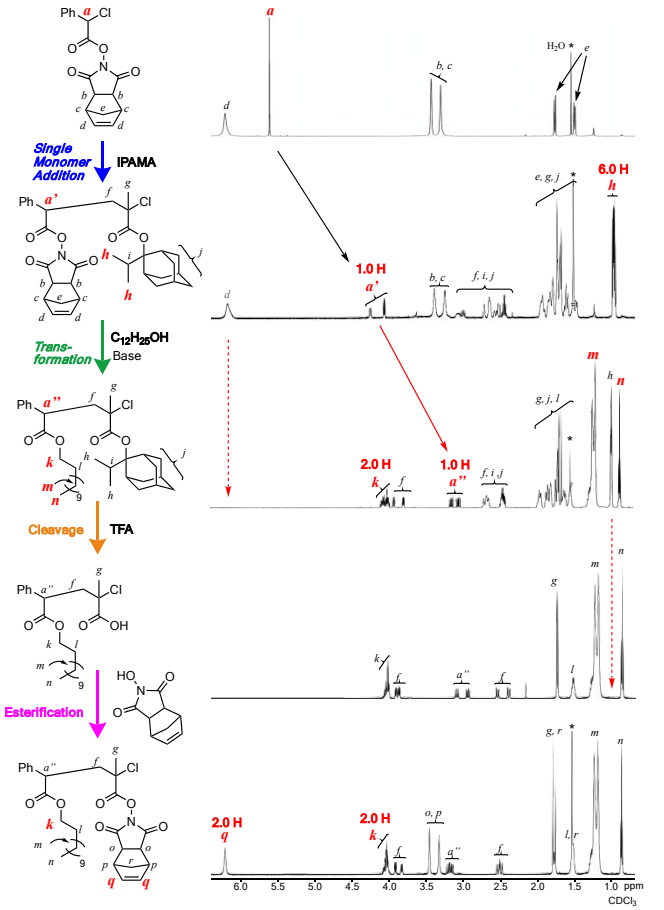

Fig. 6 Structural analyses by ^{1}H NMR for the products after all the steps. See supporting information for reaction conditions.

The reaction also occurred quantitatively, which was supported by the appearance of the peak derived from double bond protons of the NHND pendant. Note that the isolation yield for each step in the cycle was over 95%. Most probably, the reaction yield is almost 100%.

The obtained NHND-ester pendant adduct was used as the initiator for the 2nd radical addition of IPAMA (Fig. 7). When the reaction was performed at 80˚C similar to the 1st radical addition, a slightly higher conversion (10.7%) was observed than the saturated value (10%) assuming control of single unit addition. In addition, unknown peaks was observed at lower molecular weight than the starting initiator (Fig. S6). The trend was more remarkable at 100˚C. Probably, some side reactions, such as decomposition of the initiator, took place at such higher temperature. However, when the reaction temperature was decreased to 60˚C, the conversion was saturated at 10% (Fig. 7B) and the unfavourable peaks were not observed in SEC (Fig. 7C). Indeed, ^{1}H NMR spectrum of the product totally supported formation of the ideal adduct consisting of three kinds of ester pendant, i.e., dodecyl (*e*), NHND (*b*), and isopropyl (*n*) (Fig 7D).

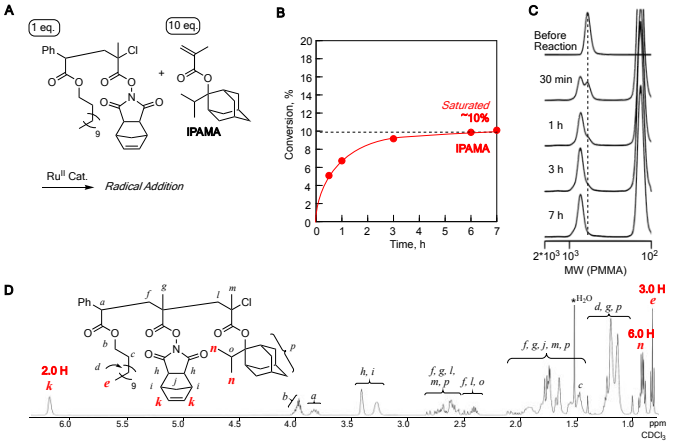

Fig. 7 2nd radical addition reaction of IPAMA with the chlorine-capped product obtained by 1st cycle: (A) scheme, (B) time-conversion, (C) SEC curves, (D) ^{1}H NMR spectrum for the product after the reaction in 7 hours. See supporting information for reaction conditions.

The NHND-ester pendant in the middle unit was transformed into methyl ester, i.e., MMA unit via the reaction with methanol in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).[24] The transformation was characterized by ^{1}H NMR (Fig. 8). The peak (*k*) from olefin protons in the NHND pendant perfectly disappeared, and instead the methoxy proton peaks (*h*) were observed with the reasonable integration ratio for the quantitative transformation. The resultant spectrum was very complicated due to existence of some chiral carbons. The formation of the methyl pendant product was fully supported with the assistance of H–H COSY 2D NMR (Fig S7).

The MMA-converted product after the transformation underwent selective cleavage under acidic condition, followed by active esterification with NHND for the IPAMA unit, similar to the 1st cycle. These reaction also proceeded quantitatively to give the corresponding product (see Figure S8 for ^{1}H NMR

and Figure S9 for ESI-MS), which are ready for the next radical addition in the 3rd cycle.

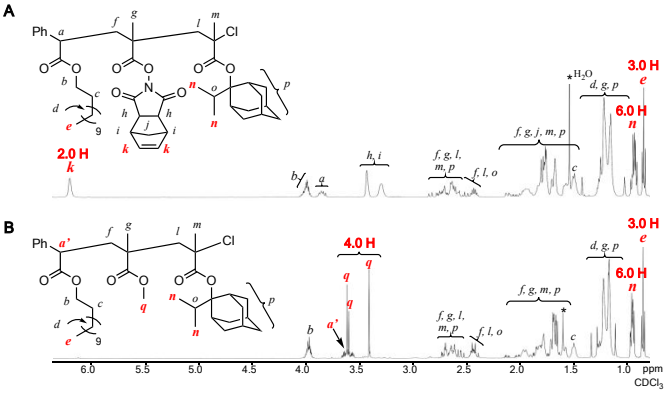

Fig. 8 Structural analyses by ^{1}H NMR for the products in the 2nd cycle: (A) after radical addition of IPAMA; (B) after transformation with methanol.

Conclusions

As shown above, the introduction of activated ester pendant for the chloride initiator allowed efficient radical addition of the bulky methacrylate. One more step is required to realize the reaction circumstance in the iterative cycle for construction of sequence-defined oligo- or poly(methacrylate)s, but the progress of single unit radical addition without unfavourable side reactions is particularly significance in this strategy. Fig 9 summarizes yields for all the cycles in 1st and 2nd cycles demonstrated in this work. Note that the high values are yields of actual isolated products after purification for removal of excess reactants (IPAMA, alcohol) and catalysts etc. The reaction yields are probably close to 100% in all the steps, though the purification process could be a bottleneck for the large scale synthesis. For more practical process, introduction of some supporter (solid resign or soluble polymer chain carrying cleavable spacer[25]) would be required, which is now under investigation.

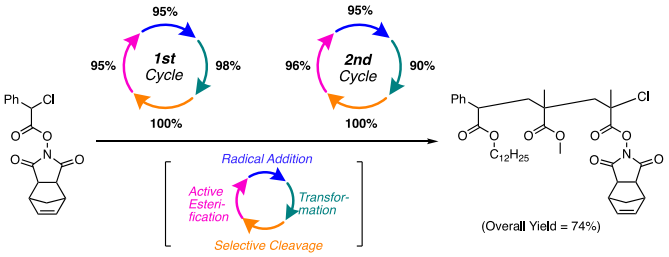

Fig. 9 Yields for all the steps in 1st and 2nd cycle.

Conflicts of interest

There are no conflicts to declare".

Acknowledgements

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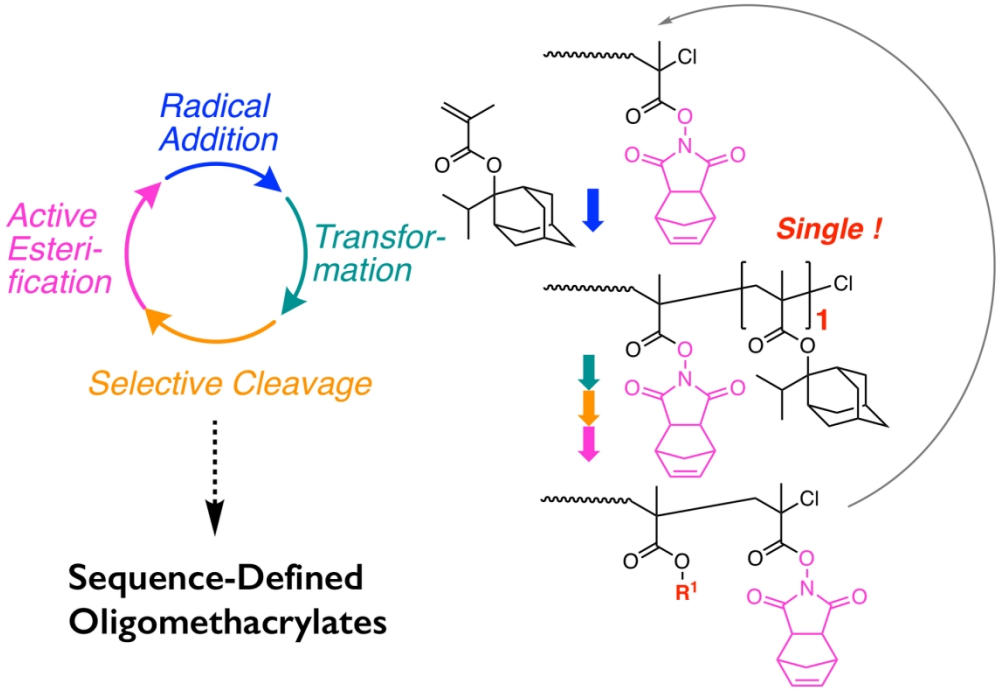

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