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, -N- (*N*-carboxyanhydrides, NCA) 3 : -

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1977 Abuchowski [2] (PEG) . Maynard[9] Chilkoti[10] Barner-Kowollik[11] PEG . PEG (ATRP)

[5]. [6]. PEG

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[7, 8].

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- (RAFT)

l’ grafting-from Ł β

[12] α- (IFN-α) C ATRP

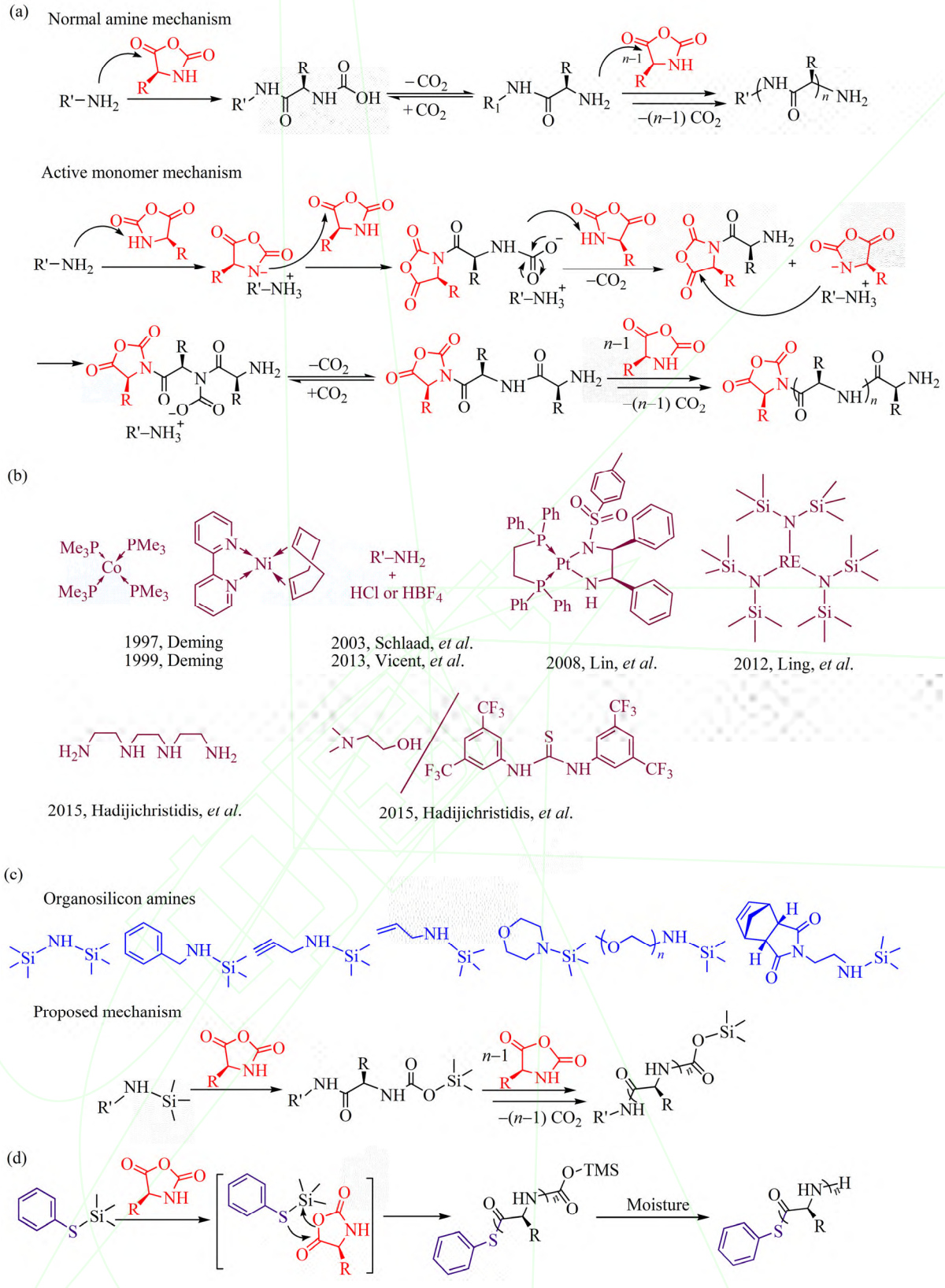

Fig. 1 (a) Two general ring-opening polymerization (ROP) mechanisms of *α*-amino acid NCAs; (b) Examples of reported initiation systems successfully used in controlled ROP of NCAs; (c) Structures of organosilicon amines and proposed mechanisms; (d) PhS-TMS mediated NCA polymerization (Adapted with permission from Ref.[41]; Copyright (2016) American Chemical Society)

(طي1(b)). [35] NCA

(inimer) NCA.

Lu Cheng[36] 2007 (HMDS) NCA

(طي1(c)). NCA [37].

TMS

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[38~40].

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PhS-TMS NCA

(PhS-TMS) NCA [41] (طي1(d)).

S—Si

PhS-TMS NCA

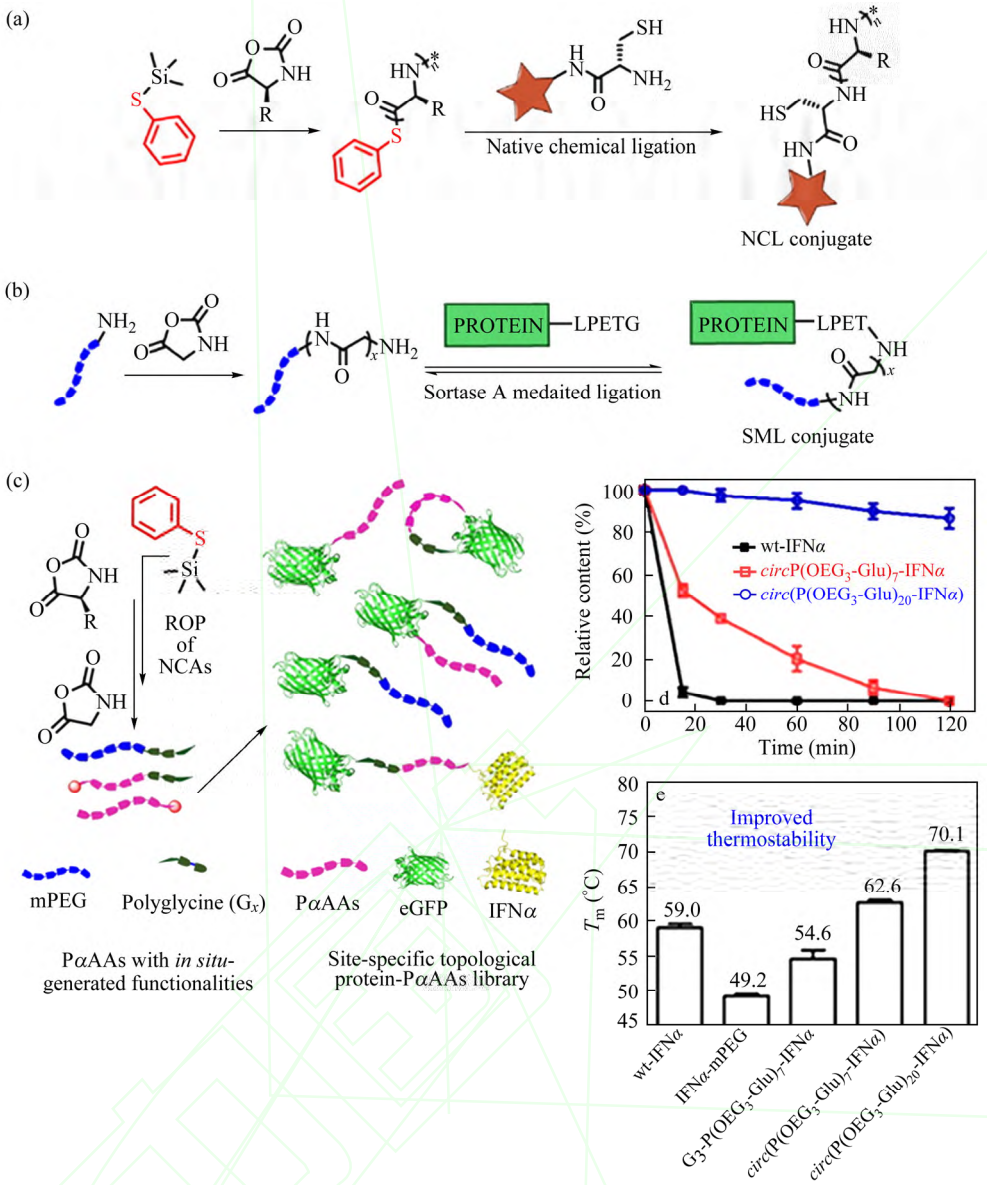

Fig. 2 (a) Synthesis of poly(*α*-amino acid)s (P*α*AAs) by PhS-TMS-mediated controlled ring of NCAs (A thioester was installed to the C-terminus of the P*α*AA and serves as a chemical handle for NCL reaction); (b) A polyglycine (G_x) nucleophile generated by ROP of glycine NCA as a substrate for SML reaction; Combinatory application of NCL and SML facilely generated various protein-polymer conjugates with novel topology (c), which exhibited excellent protease resistance (d) and thermostability (e) (Adapted with permission from Ref.[44]; Copyright (2016) American Chemical Society)

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modifications, PTM)

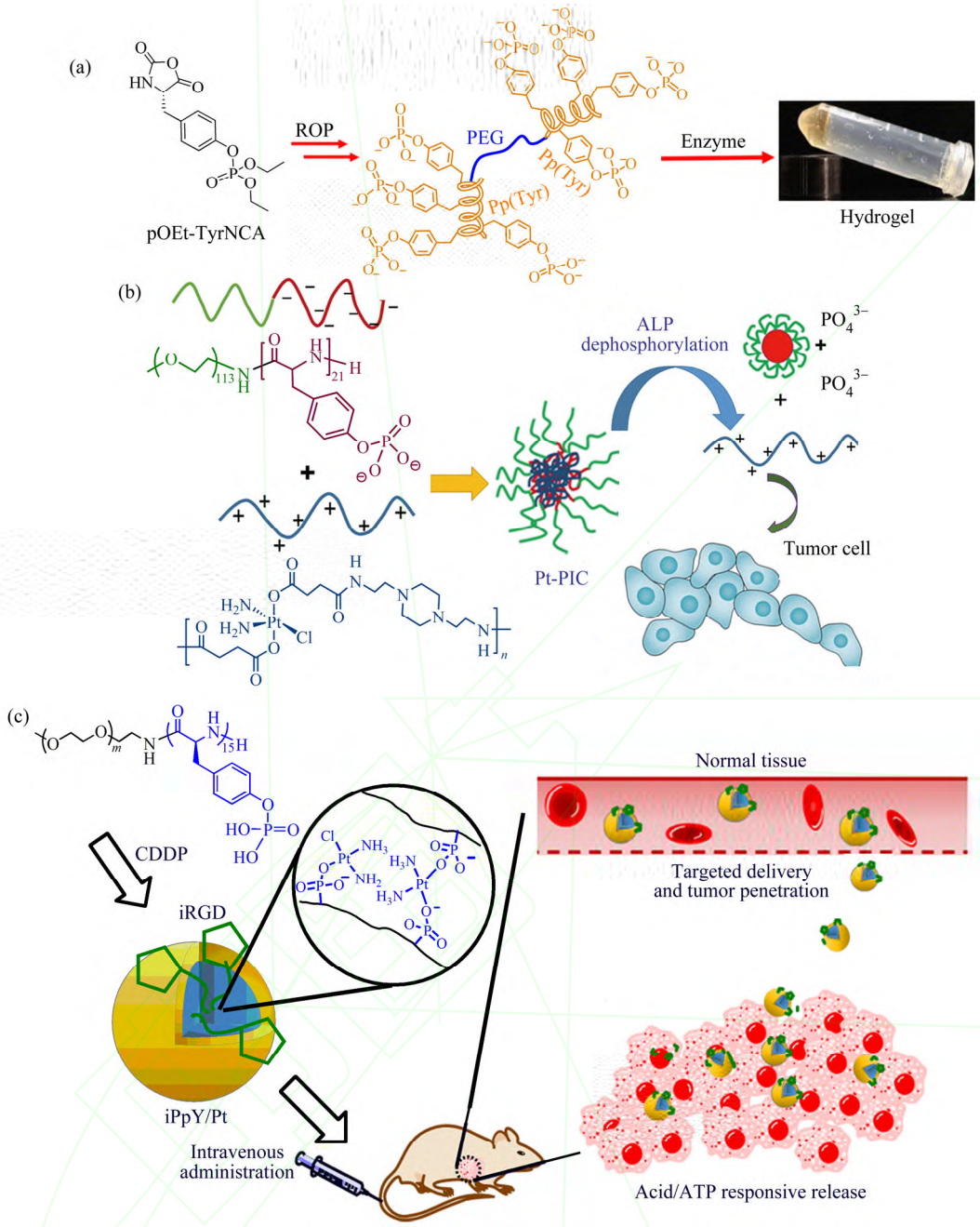

Fig. 3 (a) Synthesis and enzyme-induced hydrogelation of poly(L-phosphotyrosine) (PpY) (Adapted with permission from Ref.[52]; Copyright (2015) American Chemical Society); (b) Schematic illustration of the alkaline phosphatase-triggered dissociation of Pt(IV)-based polyion complex (Pt-PIC) to releases Pt(I) prodrug (Adapted with permission from Ref.[53]; Copyright (2017) The Royal Society of Chemistry); (c) Schematic illustration of acid/ATP-responsive cisplatin release using iPpY/Pt micelle (iPpY/Pt was prepared based on phosphate-patinum complexation and equipped with targeting ligand iRGD) (Adapted with permission from Ref.[54]; Copyright (2017) American Chemical Society)

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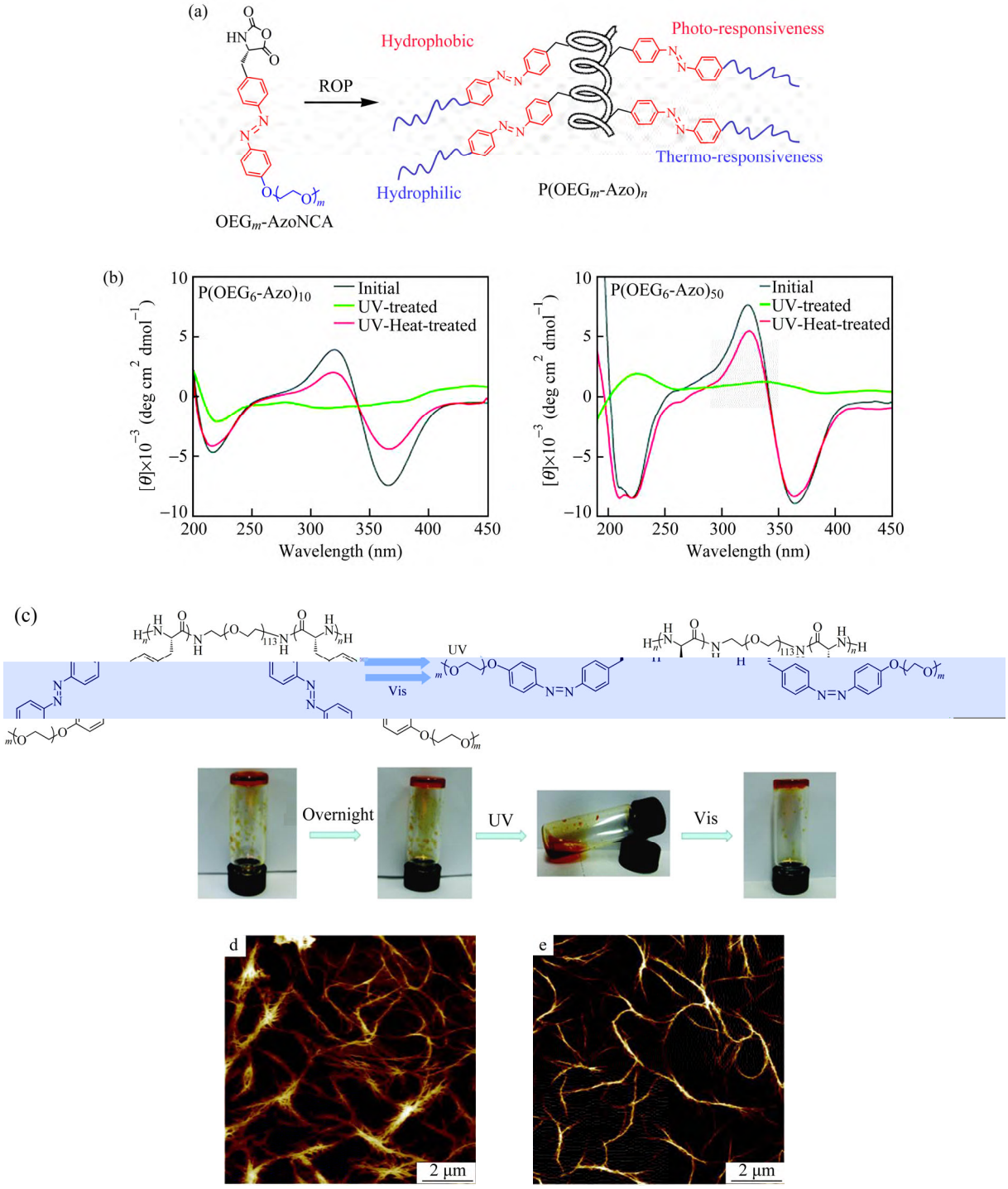

Fig. 4 (a) Synthesis of dual photo- and thermal- responsive PαAAs; (b) CD spectra of P(OEG$_6$-Azo)$_{10}$ and P(OEG$_6$-Azo)$_{50}$ in 2,2,2-trifluoroethyl alcohol (the polymers were first irradiated with UV at 365 nm for 5 min, followed by heating at 70 ºC for 60 min) (The online version is colorful.); (c) Photographs of triblock copolymer P(OEG$_6$-Azo)$_7$-PEG-P(OEG$_6$-Azo)$_7$ solution in THF showing reversible UV-Vis triggered gel-sol transition; AFM images of P(OEG$_6$-Azo)$_7$-PEG-P(OEG$_6$-Azo)$_7$ organogel in its original state (d) and after UV irradiation (e) (Adapted with permission from Ref.[71]; Copyright (2016) The Royal Society of Chemistry)

P(OEG

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Efficient Synthesis and Application of Protein-Poly(*α*-amino acid) Conjugates

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Abstract Protein-polymer conjugates are important therapeutics for various diseases. There are currently two major challenges in this field: one is the search of new biodegradable polymers beyond traditional PEGylation, and the other is to develop highly efficient and site-specific conjugation strategy. Poly(*α*-amino acid)s (P*α*AAs) are biodegradable and biocompatible polymers with tunable properties and numerous functions, making them promising candidates for protein modification. In this review, we summarize our recent progresses in protein-P*α*AAs conjugates. Specifically, we discuss our developments in: (1) Recent developments in the controlled ring-opening polymerization (ROP) of *α*-amino acid *N*-carboxyanhydrides (NCAs), including amine-based initiators, organometallic initiators, organosilicon amines initiators and sulfide-based initiators. For instance, trimethylsilyl phenylsulfide (PhSTMS) is a novel initiator for controlled ROP of NCAs. It exhibits higher nucleophilicity than conventional amine-based initiator, and thus affords considerably higher chain initiation rate to ensure a more controlled polymerization. Moreover, this initiator is well-tolerated to various functional groups. (2) *In situ* functionalization of P*α*AAs for site-specific protein conjugation, and construction of various topological structures. Using PhSTMS initiator, it *in situ* generates a reactive phenyl thioester group at one end of the P*α*AAs, which can be used for protein *N*-terminus conjugation *via* native chemical ligation (NCL); moreover, ROP of glycine NCA yields oligoglycine at the other end of P*α*AAs, which can be used for C-terminus protein conjugation *via* sortase-A mediated ligation (SML). More interestingly, combinatory use of the two methods can construct various topological protein-P*α*AA conjugates including the head-to-tail circular conjugates. (3) Development of functional P*α*AAs for potential protein conjugation. Various functional P*α*AAs have been developed as delivery materials or hydrogels. To further expand the arsenal of P*α*AAs for potential modulation of protein functions, P*α*AAs that mimic protein post-translational modifications (PTM) are synthesized; On the other hand, a series of multiple stimuli-responsive P*α*AAs are also produced. These P*α*AAs show interesting enzyme, light, and/or thermal responsiveness, which could be potentially harnessed for modulation of protein functions in the future.

Keywords Protein conjugation, Poly(*α*-amino acid), PTM mimicking, Topology, Stimuli-responsiveness

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