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Sequence-controlled and sequence-defined polypeptoids *via* the Ugi reaction: synthesis and sequence-driven properties

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Polypeptoids are peptidomimetic polymers, and their origin can be traced back to the early 1990s. The facile synthesis of sequence-controlled and sequence-defined polypeptoids still faces many challenges. Very recently, the Ugi reaction has been introduced into polypeptoid chemistry. In this mini review, the recent progress in the application of the Ugi reaction for the synthesis of sequence-controlled polypeptoids is summarized. The influence of the sequence structure on polypeptoid properties is presented. Moreover, the future development of the Ugi reaction for the synthesis of sequence-controlled and sequence-defined polypeptoids is discussed.

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1 Introduction

In the last century, the decoding of gene and protein sequences was undoubtedly a great and far-reaching scientific research achievement.^{1–3} Nucleic acids and polypeptides, which are ubiquitous in organisms, maintain the normal operation of organisms, and also determine the diversity, complexity and adaptability of biological organisms. The sequence of biological macromolecules is precisely defined in nature, such

as DNA, RNA and proteins.^{4,5} Their precise sequences drive specific functions, such as molecular recognition, biocatalysis and information storage/transport.⁶ After billions of years of biological evolution, nature has developed a set of sophisticated and precise sequence regulations for biomacromolecules. The synthesis of proteins through ribosomes is a well-known example.^{7,8} Sequence-defined polymers are synthesized from templates with different chemical structures. This is a process in which the nucleotide sequence of an mRNA template on ribosomes is translated into an amino acid sequence. Synthesizing ribosome-like catalysts is still in the infant stage of current chemical tools; however, inspired by the biological macromolecules, the synthesis of sequence-con-

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trolled and sequence-defined polymers has attracted enthusiasm, and scientists are eager to design and define precise polymers to simulate and transcend the functions of natural macromolecules.⁹ In recent years, a large number of sequence-controlled synthesis strategies have been developed, including the template method,¹⁰ kinetic control,¹¹ orthogonal reaction¹² and reconstitution.¹³ Unfortunately, the effective synthesis method still faces great challenges.¹⁴

Producing polymers and realizing sequential control by step-wise synthesis are considered as a practicable way. Merrifield pioneered this strategy to synthesize peptides on solid substrates.^{15,16} After that, the strategy evolved into the synthesis of DNA, RNA and oligomers with diverse organic structures which can combine to various resins.¹⁷ An iterative synthesis,^{18–20} especially a one-by-one iterative method chiefly carried out on a solid support (such as polystyrene resin), is a typical step-wise synthesis.^{21,26} Scientists have developed generous current methods to improve iteration efficiency and simplify processes, and the successful examples include triazene-based polymers,²² poly(alkoxyamine amide)s,²³ oligothioether-amides,²⁴ and thiolactone aminolysis.²⁵

Compared with homopolymers, block copolymers or random copolymers, sequence-controlled and sequence-defined polymers allow a higher level of control over structures and related properties. At present, a series of biological functions have been simulated by sequence-controlled and sequence-defined polymers, for example, the mechanical properties of biological tissues are simulated by folding and self-assembly and biocatalysis and information transmission are realized by molecular recognition; however, the heredity of organisms is mostly in the theoretical stage.^{27,28} As an example, sequence-controlled oligopeptides can self-assemble into various nanostructures,²⁹ including fibers, tapes, ribbons, vesicles and tubes, and they can be further developed into biocompatible polymers, conductive polymers and other multiple applications. Artificial protein analogues with controllable sequences have attracted extensive interest. Meijer designed enzyme analogues to regulate a monomer sequence through controlled radical polymerization and single-strand folding in water to achieve special properties.³⁰ Seeman also demonstrated that complementary DNA strands can be extended to polymers, nanoparticles and nanocrystals.³¹

The self-assembly of synthetic polymers not only is greatly affected by the sequence, but also changes the thermodynamic properties and other macroscopic properties of the polymers, such as the solubility,³² charge density and duration of polyelectrolytes^{33,34} and the mesophase and semi-crystalline phase of special polymers.^{35,36} Zuckermann studied the effect of a sequence-controlled fragment on the phase behavior of polypeptoid–polystyrene block copolymers; a change of the sequence structure leads to an order–disorder transition.³⁶

Polypeptoids are a kind of pseudo-peptidic polymer, serving as a bridge between biomaterials and synthetic polymers^{37–39} (Fig. 1). Small changes in these skeletons have been shown to have a significant impact on overcoming the shortcomings of polypeptides, such as the stability towards

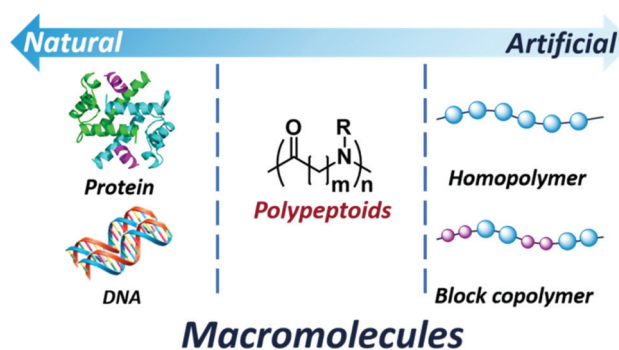


Fig. 1 Polypeptoids build a bridge between natural and artificial macromolecules.

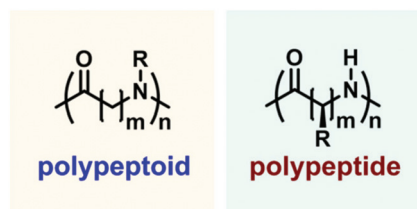


Fig. 2 Structures of a polypeptoid and polypeptide.

enzymes⁴⁰ (Fig. 2). Polypeptoids can be employed as effective siRNA transfection reagents,⁴¹ diagnostic reagents,⁴² pulmonary surfactant mimics,⁴³ antibacterial agents, *etc.*⁴⁴ Sequence-controlled polypeptoids with high biomimetic properties provide a broad range of opportunities for the development of robust artificial materials in the future. This is mainly because polypeptoids have the advantages of chemical diversity, secondary structures and biocompatibility.^{45–47}

It is well known that there are two strategies for the synthesis of polypeptoids: solid-phase synthesis and ring-opening polymerization (ROP) of *N*-substituted α -amino acid-*N*-carboxyanhydrides (NNCAs).⁴⁸ The solid-phase submonomer approach was developed by Zuckermann *et al.* in 1992.³⁹ Since each monomer is individually tunable, an infinite variety of polymer sequences can be designed and synthesized.⁴⁹ As for ring-opening polymerization (ROP) of *N*-substituted α -amino acid-*N*-carboxyanhydrides (NNCAs), although it overcomes the issues of low polymerization degree and molecular weight (M_w) in solid phase synthesis, it cannot synthesize polypeptoids with controllable sequences.⁵⁰

Inspired by the above challenges, the Ugi reaction is considered to be a good method.^{51–55} The Ugi reaction was first reported by the German chemist Ivar Karl Ugi in 1959.⁵⁶ In the development of a multicomponent reaction, this reaction was only used for crosslinking sodium alginate.⁵⁷ Wessjohann synthesized selenocysteine containing peptoids and peptide-peptoid conjugates.⁵⁸ In 2014, Meier polymerized dicarboxylic acid and diamine with isocyanides and aldehydes through the Ugi reaction to obtain polyamides.^{59,60} Then, sequence-defined peptoid oligomers were obtained by Meier *et al.* In 2016, Tao



Fig. 3 (A) General formula of the Ugi reaction. (B) Synthesis of poly(γ -, δ - and ϵ -peptide)s through the Ugi reaction.⁴⁵

et al. introduced the Ugi reaction, which was a four-component reaction involving stoichiometric amounts of acid, amine, isocyanide, and aldehyde, into polypeptide synthesis⁴⁵ (Fig. 3A). The reaction between aldehyde and amine produces an imine, which is protonated by the carboxylic acid component. The imine is attacked by isocyanides, and carboxylic acids help to form the corresponding intermediates. Finally, the amino amide product is formed after rearrangement. They successfully obtained and poly(γ -, δ - and ϵ -peptide)s by the Ugi reaction of amino acids under mild conditions⁴⁵ (Fig. 3B). Subsequently, they reported the preparation of alternating polypeptides through the Ugi reaction, and realized the synthesis of sequence-controlled polypeptides by the Ugi reaction.⁶¹ Among the few reviews dedicated to this topic, Tao *et al.* documented polypeptide preparation *via* the Ugi reaction.^{45,61,62} As a result, this mini review is not meant to offer a comprehensive review of the research activities in this field. It focuses on the recent development in the synthetic approaches to access sequence-controlled polypeptides and highlights the sequence-driven properties that are fundamental topics in the polymer science area.

2 Synthesis of alternating polypeptides

Alternating polypeptides are one of the simplest sequence-controlled and sequence-defined artificial copolymers. In recent years, the oligomeric peptoids with alternating sequences have been extensively explored. Zuckermann *et al.* synthesized peptoids which can self-assemble into highly ordered and free floating nanosheets with an alternating arrangement of hydrophobic and ionic monomers.⁶³ Franzyk *et al.* reported the syn-

thesis of alternating peptoids that have both stability toward enzymatic degradation and activity against multidrug-resistant bacteria.^{64,65}

In 2018, Tao *et al.* utilized the Ugi reaction in a one-pot procedure for the synthesis of alternating polypeptides⁶² (Fig. 4A). Employing the AA'BB'-type monomers lysine methyl ester, *N*-Boc-glutamic acid, isobutyraldehyde, and *tert*-butyl isocyanide as reactants in the Ugi polymerization, the alternating polypeptides can be easily obtained in a one-pot process, with a molecular weight of 15.1 kg mol⁻¹ and a dispersity of 2.2. The monofunctional components should be excessive to ensure the complete consumption of the two amino acids. In addition, they found that the yield and molecular weight increased first and then decreased along the increase of the monomer concentration, which can be interpreted as the high viscosity of the system at a very high concentration. It is gratifying that when the structure of aldehydes or isocyanides is changed, the alternating polypeptides with different side groups can be obtained in 86% yield. The structures of all the polypeptides were confirmed by ¹H, ¹³C, and COSY NMR spectroscopy.

Debuigne *et al.* successfully carried out the Ugi reaction using β -alanyl-L-histidine or glycylglycine as the difunctional substrate, affording a library of structurally diverse polypeptides featuring a high degree of peptide-peptoid alternating sequences. The principle for the choice of reactants is that the distance between amine and carboxylic acid groups is enough to prevent the cyclization of the 6-membered ring *via* an intramolecular side reaction. Different types of aldehydes (*e.g.*, formaldehyde and isobutyraldehyde) and isocyanides were employed as building blocks.⁶⁶

3 Synthesis of sequence-controlled polypeptides

Sequence-controlled polymers refer to polymers with defined monomer positions along the polymer chain. The Ugi reaction can contribute to a great extent for the synthesis of sequence-controlled polypeptides.

In 2019, Tao *et al.* combined amino acid building blocks and iterative Ugi reactions for the synthesis of sequence-controlled polypeptides (Fig. 4B).⁶¹ Importantly, the amino acid building block plays a crucial role in the Ugi reaction. An active amino group together with a *tert*-butyl ester protected carboxylic acid function that can undergo efficient deprotection consists of the building block. Subsequently, the amino acid building block reacted with other molecules (*e.g.*, acetic acid), benzaldehyde, and *tert*-butyl isocyanide. The deprotection and Ugi reaction cycle was iterated, and trifluoroacetic acid (TFA) was used for deprotection. After 10 cycles, a 10-mer peptoid sequence was obtained. For purification methods, column chromatography and rotary evaporation were used. By adjusting the aldehydes or isocyanates with different side groups in each cycle, they obtained polypeptides with

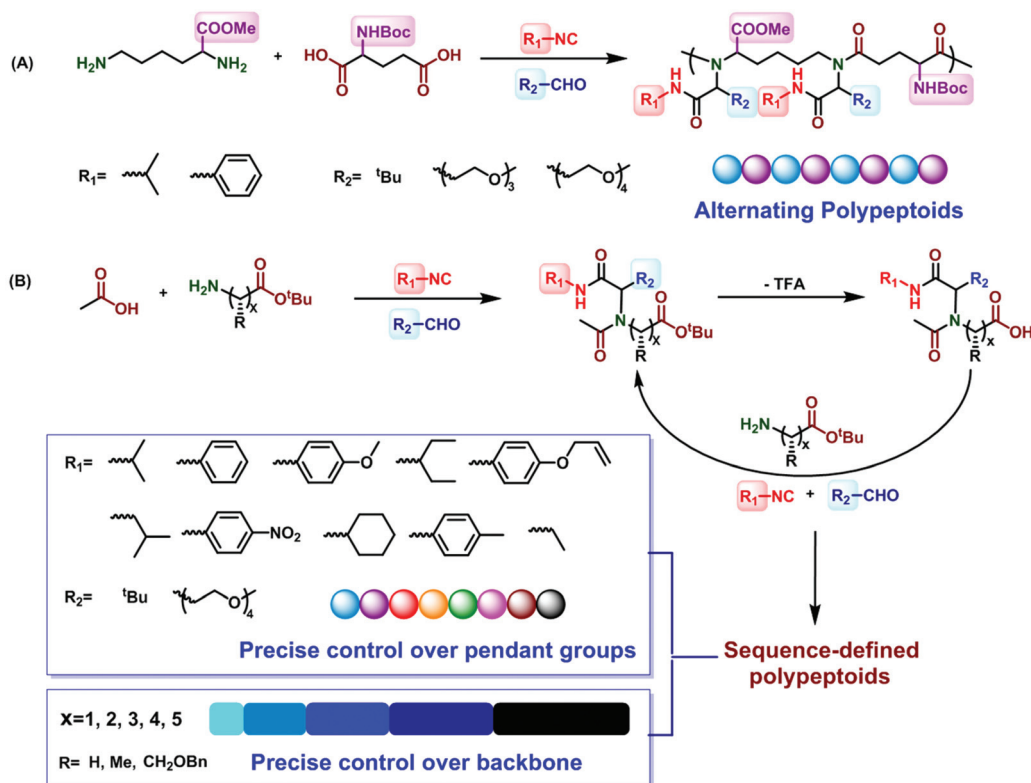


Fig. 4 (A) Preparation of alternating polypeptoids via the Ugi reaction.⁶² (B) Preparation of sequence-controlled polypeptoids based on the iterative Ugi reaction.⁶¹

diverse sequences. Using bis-COOH functionalized PEG as the starting molecule, polypeptoids with a higher M_w value ($M_n \approx 4.1$ kDa) were synthesized.

Tao *et al.* further extended traditional sequence-controlled poly(α -peptoid)s to poly(β -, γ -, δ - and ϵ -peptoid)s. Thus, a 5-mer polypeptoid was constructed (Fig. 5). It is composed of five different amino acid building blocks, which greatly proves the versatility and robustness of the sequence-controlled polypeptoid by the iterative Ugi reaction.

Meier *et al.* also applied the iterative Ugi reaction to the formation of sequence-controlled peptoid oligomers. With stearic acid as the starting molecule, monodisperse four dimers ($M_n =$

1568.5 g mol⁻¹) were obtained by changing the amine components in the Ugi reaction.⁶⁷

In 2018, Becer and coworkers reported an iterative synthesis method combining solid-phase synthesis and the Ugi reaction to form peptides, peptoids or peptide-peptoid hybrids with well-controlled sequences.⁶⁸

4 Sequence-driven properties

A monomer sequence is expected to affect polymer properties and functions. With longer range monomer sequences,

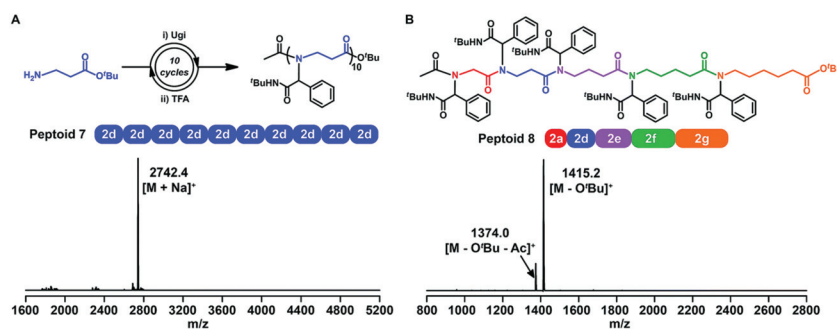


Fig. 5 (A) Synthetic route and MALDI-TOF-MS spectrum of a 10-mer β -peptoid. (B) Chemical structure and MALDI-TOF-MS spectrum of a 5-mer peptoid consisting of all five amino acid building blocks (peptoid 8).⁶¹

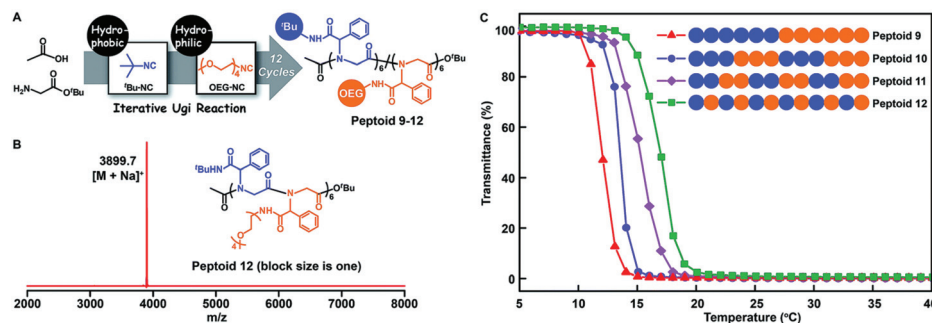


Fig. 6 (A) Illustration of the side-chain sequence-regulated peptoids 9–12 synthesized by iterative Ugi reactions. (B) MALDI-TOF-MS spectrum of 12-mer peptoid 12. (C) Temperature dependence of the transmittance of the aqueous solutions (2 mg mL^{-1}) of sequence-regulated peptoids.⁶¹

diblock, triblock, and even multiblock copolymers have been prepared and are used as functional materials, which have properties quite different from those of homopolymers and random copolymers.⁶⁹

Tao *et al.* prepared a library of polypeptoids with hydrophobic and hydrophilic side chains, which have 12 sequence controllable units (Fig. 6). The arrangement of hydrophobic and hydrophilic units on the skeleton is different, and a variety of sequence controllable polypeptoids are formed by abundant arrangement and combination. The thermo-responsive behavior of these polypeptoids in water was studied at varying temperatures by measuring the light transmittance of the polypeptoid solutions. The sequence-controlled polypeptoids showed sequence-specific properties: the alternating polypeptoid was more soluble than the block polypeptoid, and thus showed higher lower critical solution temperature (LCST).

Tao *et al.* further studied the effect of the backbone structure of polypeptoids on the material properties (Fig. 7A). The structures of these sequence-controlled polypeptoids were verified by MALDI-TOF-MS and SEC tests (Fig. 7B). The solubility of these polypeptoids in mixed solvents of EtOH and H₂O at different temperatures was evaluated by measuring the trans-

mittance of the solution. The polypeptoid with an ABB alternating sequence in the backbone is more soluble than other proteins, and its cloud point is $T_c = 45 \text{ }^\circ\text{C}$, which is lower than that of the corresponding block copolymer ($T_c = 53 \text{ }^\circ\text{C}$) (Fig. 7C). These experiments indicate that not only the side chain sequence but also the backbone sequence has a great influence on the properties of polypeptoids, and the solubility can be gradually adjusted by varying the backbone and side chain monomer sequences.

Sequence-controlled and sequence-defined polypeptoids provide a new channel for artificial nucleic acid delivery. Nowadays, researchers are paying more and more attention to the structure of synthetic materials and biological agents to create new therapeutic methods. Therefore, Tao *et al.* studied whether sequence-controlled polypeptoids can bind to DNA for biomedical applications. Tao *et al.* added the azide function to the polypeptoids (Fig. 8A) by using the Ugi reaction and 3-azidopropan-1-amine. The azide modified polypeptoids were coupled to DNA with a dibenzocyclooctyne (DBCO) group in acetonitrile and PBS, as demonstrated by gel electrophoresis displacement (Fig. 8B). The success of conjugation was verified by MALDI-TOF-MS (Fig. 8C).

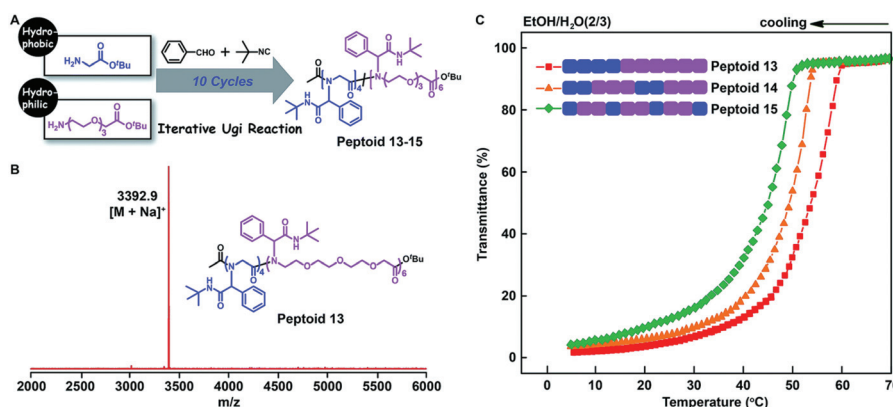


Fig. 7 (A) Illustration of the backbone sequence-regulated peptoids 13–15 obtained by iterative Ugi reactions using glycine *tert*-butyl ester and oligo-ethylene-glycol based amino acid *tert*-butyl ester as building blocks. (B) MALDI-TOF-MS spectrum of 10-mer peptoid 13. (C) Transmittance of the backbone sequence-regulated peptoids 13–15 at varying temperatures in EtOH/H₂O (2/3).⁶¹

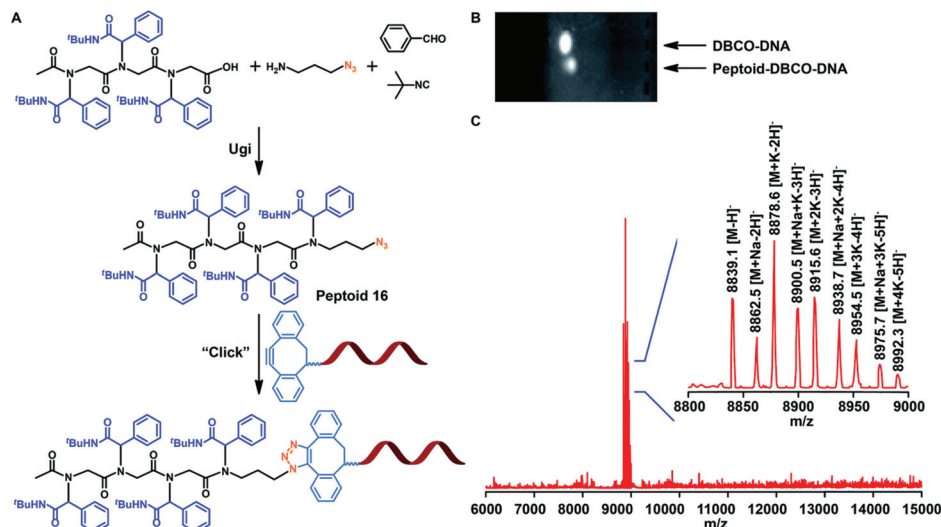


Fig. 8 (A) Conjugation of sequence-controlled peptoid 16 to DNA (DNA : peptoid molar ratio = 1, 24 h reaction in $\text{CH}_3\text{CN}/\text{PBS}$). (B) Gel electrophoresis result for the peptoid–DNA conjugation reaction. (C) MALDI-TOF-MS analysis of DNA conjugates.

5 Conclusions and perspectives

In summary, great progress has been made in the synthesis and sequence-driven properties of polypeptoids, including alternating polypeptoids, and sequence-controlled polypeptoids, *via* the Ugi reaction. Not only traditional sequence-controlled poly(α -peptoid)s, but also poly(β -, γ -, δ - and ϵ -peptoid)s can be obtained with high efficiency. In this review, the effect of the monomer sequence on the polypeptoid properties has also been described. It is clear that sequence-controlled polypeptoids exhibit sequence-oriented properties/functions, which could potentially lead to a ground-breaking paradigm shift for the synthesis of polymer materials.

Because of the excellent performances of the Ugi reaction, it will play a more and more important role in the synthesis of sequence-controlled polypeptoids. The attraction of polypeptoids, of course, is that their designability is beyond current predictions. For instance, polypeptoids possess easily regulated thermodynamic properties. Thus, they can be coupled to biological macromolecules, which is helpful in developing new therapeutic methods.^{70,71} Polypeptoids can form an ideal self-assembly system, which can be assembled hierarchically to simulate proteins and other biological macromolecules. This is a complex space that has not yet been fully explored. The accurate regulation of the sequence structure of polypeptoids will bring broad applications and advanced materials.

Furthermore, how can we synthesize stereo- and sequence-controlled polypeptoids *via* the Ugi reaction? Although the Ugi reaction offers a good result in terms of sequence control, the synthesis of stereo- and sequence-controlled polypeptoids *via* the Ugi reaction remains an unmet challenge. A breakthrough work has been recently reported by Zhang and co-workers evaluating the enantioselective Ugi reaction using asymmetric

phosphoric acid derivatives as catalysts.⁷² One can envision the application of asymmetric phosphoric acid catalysts that can enable the synthesis of stereo- and sequence-controlled polypeptoids. This will provide access to polypeptoids with different microstructures exhibiting different performances and broaden their potential applications.

Conflicts of interest

The authors declare no competing financial interest.

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