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Construction of sequence-defined polytriazoles using IrAAC and CuAAC reactions

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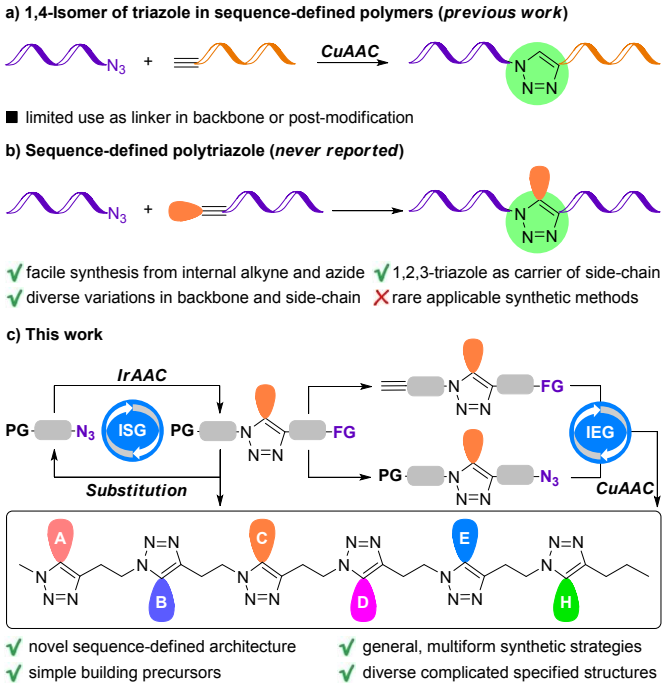
Here we report the first synthesis of sequence-defined polytriazoles, in which different side groups are sequentially anchored to the C-5 position of 1,2,3-triazole rings. By using efficient synthetic strategies based on IrAAC and CuAAC, different monodisperse polytriazoles with up to ~5.3 kDa and 31-mer were constructed. Structural characterizations via NMR, SEC, MALDI-TOF-MS, tandam MS and FTICR-MS evidenced the formation of polytriazoles with desired specified sequence and exact chain length.

1,2,3-Triazole is one stable skeleton towards enzymatic degradation and environmental variables.[1] Since the introduction of copper-catalyzed azide alkyne cycloaddition (CuAAC),[2] 1,2,3-triazole has evolved as one important substructure in robust polymer and functional material syntheses.[3] Mimicking nature to build sequence-regulated polymers is extremely attractive on account of their promising applications in multitudinous areas, such as data storage, drug development, catalysis and molecular recognition.[4] Diverse strategies involving CuAAC have been established for the creation of sequence-defined polymers with 1,2,3-triazole units. For instance, fabrications of biopolymer analogues with unnatural triazole-linked backbones were realized via CuAAC-based iterative monomer additions.[5] The group of Niu developed the orthogonal CuAAC and SuFEx protocol for synthesis of monodispersed sequence-defined polymers.[6] CuAAC also proved to be one ideal basis for the establishment of iterative exponential growth (IEG) and strategies.[7] One emblematic example is the IEG plus side-chain functionalization (IEG$^+$) strategy reported by Johnson, which allows subsequent side-chain functionalizations after each cycle.[7b] In most of above cases, as well as the examples of using CuAAC in post-modification[8] and cyclization[9] of sequence-defined polymers, however, 1,2,3-triazole is limited as a connector that provides its C-1 and C-4 position to link different components (Scheme 1a). Controllable installation of different groups in the C-5 position of this ring, which could be achieved through absolute regioselective cycloaddition of azide with internal alkyne, will allow the construction of sequence-controlled polytriazoles (Scheme 1b). In consideration of the unique properties of 1,2,3-triazole[1,10] and theoretically unlimited variations in the backbone and side-chain, sequence-programmable polytriazole skeletons would be promising in novel functional material developments.



Scheme 1 1,2,3-Triazole in sequence-defined polymers.

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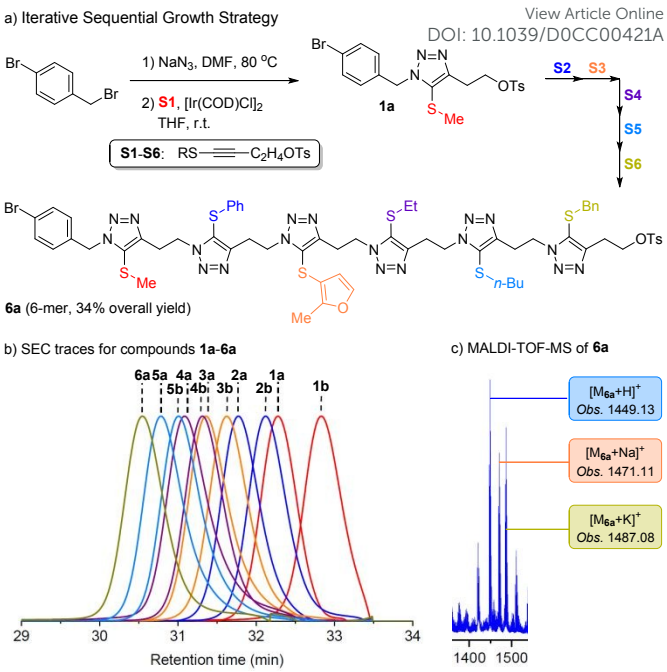
We herein first reported the construction of sequence-defined polytriazole architecture by using iridium-catalyzed azide-thioalkyne cycloaddition (IrAAC)[11] and CuAAC (Scheme 1c). A simple two-step iterative method involving IrAAC and azide substitution was first used to synthesized sequence-specified oligomers in up to gram scale. Construction of polytriazoles with longer chain-length through CuAAC-based IEG strategy was further realized due to the sluggishness of internal 1-silylalkynes in IrAAC. Notably, the H atom at C-5 position of the formed 1,4-disubsituted triazole ring here is one important side-chain variation. More complicated sequence could be accessed by cross-coupling of different sequence-regulated oligomers under CuAAC condition. The newly introduced sequence-defined polytriazole skeleton, together with these efficient synthetic strategies described here, are expected to benefit the field of sequence-controlled polymers and further applications in diverse areas.

The iterative sequential growth (**ISG**) synthesis is the primary strategy for building sequence-defined polymers since its first use for peptide synthesis by Merrifield.[12] The excellent adaptability of IrAAC to different solvents encouraged us to start our investigations by designing a solution-phase iterative-growth approach that can significantly simplify and accelerate the synthetic procedure (Figure S5, Scheme 2a). Six different thioalkynes involving OTs group (**S1**-**S6**) were conveniently prepared from simple commercially available disulphides and 3-butynol in two steps (Figure S1). The initial azide substrate could be selected accordingly to satisfy further multitudinous utilizations of the synthesized sequence-regulated oligomers. In our case, to demonstrate the good selectivity and tolerance of IrAAC, one benzyl azide bearing a Csp^2-Br (**A1**, Figure S3) was chosen as a representative. With 2 mol % of $[Ir(COD)Cl]_2$, the click reaction of thioalkyne **S1** and azide **A1** proceeded smoothly to completion within 2 hours, affording the desired monomer **1a** in 93% isolated yield via silica gel flash column chromatography (entry 1, Table S1). The sequence-defined hexamer **6a** (α-Br-**ABCDEF**-ω-OTs) was obtained by running five more cycles of the simple two-step iterative method involving IrAAC and azide substitution in an overall yield of 34%. The subsequent extension of the sequence-defined structures was successfully evidenced by ^{1}H NMR spectra (Figure S10) and mass spectrometry characterizations (Figures S100-S110), with an average of over 90% isolated yield in each step (Table S1). The size exclusion chromatography (SEC) traces of the monomer units **1a** and **1b**, and the oligomers **2a**-**5b** up to the final monodisperse sequenced-defined 6-mer **6a** not only verifies the iterative chain growth after each cycle, but also showed the variation of molecular weight in each cycle (Scheme 2b). The obtained matrix-assisted laser desorption ionization-time-of-flight mass spectrum (MALDI-TOF-MS) of purified sequence-defined 6-mer **6a** showed multiple charged peaks, all of which are in excellent agreement with calculated molecular mass (Scheme 2c). In addition, the consistence of experimental and theoretical isotopic pattern of **6a** also clearly demonstrated the successful synthesis of the sequence-defined hexamer and its monodispersity (Figure S7).

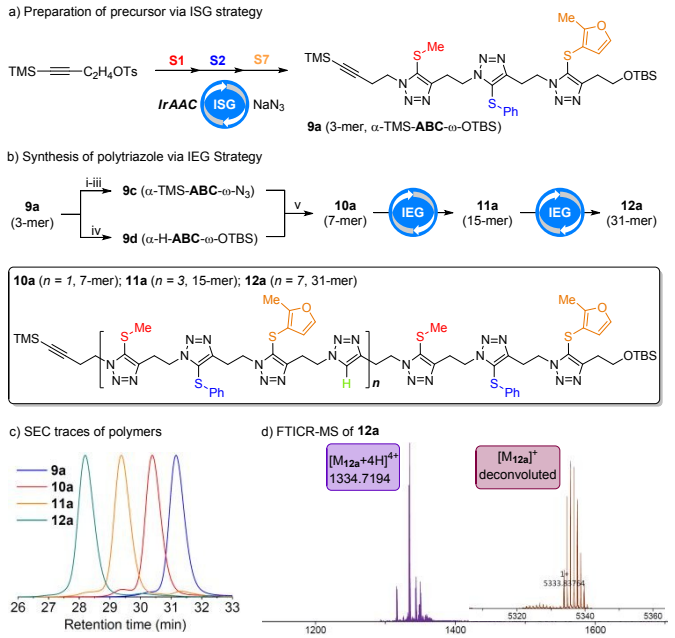


Scheme 2 Synthesis of sequence-defined polytriazoles through iterative sequential growth strategy. Compounds **1b**-**5b** were azidation derivatives from related compounds **1a**-**5a**.

We further explored the construction of long-chain polymers by connecting sequence-regulated oligomers together in minimal synthetic steps. Ever since the initial demonstration by Whiting in 1982,[13] iterative exponential growth (**IEG**) has proved to be one powerful strategy for extending chain lengths in precise synthesis of molecularly defined polymers.[14] Here we employed the IEG strategy relying on CuAAC reaction for our investigation, as the sluggishness of silyl-protected alkynes in IrAAC allows the synthesis of orthogonally protected monomers or oligomers from IrAAC for the CuAAC-based IEG process. CuAAC was first introduced into this field by Drockenmuller,[15] and successively developed for sequence-defined polymer syntheses by Johnson,[7a,7b] Monterio,[7c] etc. Nevertheless, the contribution of the newly formed 1,2,3-triazole rings via CuAAC is limited as linkages in these cases. And to some extent, they might influence the tacticity of the sequence-regulated backbones. By contrast, the 1,4-isomers from CuAAC could play as crucial components in sequence-defined polytriazoles. Notably, in consideration of this, the chain length of the polymer derived from *n* species after one IEG cycle will not be *2n*, but *2n+1*.

To promote the reaction efficiency in both IrAAC and CuAAC, a new type of orthogonally protected α-TMS-ω-OTBS building block was designed for this IEG process, in which the TMS group could be easily deprotected under basic conditions, while the TBS group at the end could be selectively removed under acidic conditions to release the hydroxyl group, one precursor for azide group (Figure S6). Starting from a simple α-TMS-ω-N_3 substrate (**A2**, Figure S4), a 3-mer of α-TMS-ω-OTBS (**9a**, α-TMS-**ABC**-ω-OTBS) was built for this protocol by using the previously developed ISG method in 5 steps (70% overall yield, Scheme 3a).

The monoprotected azide trimer **9c** (α-TMS-**ABC**-ω-N_3) was obtained from **9a** via subsequent deprotection, tosylation and azidation in a total of 83% isolated yield (Table S2). In parallel, the TMS-protective group in **9a** was facilely put off to generate the monoprotected alkyne 3-mer **9d** (α-H-**ABC**-ω-OTBS) in quantitative yield. Under one CuAAC reaction condition (10% of CuBr, 20% of PMDETA, DMF, 50 °C), trimers **9c** and **9d** were connected to afford heptamer **10a** (α-TMS-**ABCHABC**-ω-OTBS) in 77% isolated yield after purification by silica gel chromatography. Heptamer **10a** was then split into two parts for the independent synthesis of 7-mers **10c** (α-TMS-**ABCHABC**-ω-N_3) and **10d** (α-H-**ABCHABC**-ω-OTBS), which are coupling partners for the construction of 15-mer **11a** (α-TMS-(**ABCH**)$_3$**ABC**-ω-OTBS). Running one more iteration of this process successfully produced 31-mer **12a** (α-TMS-(**ABCH**)$_7$**ABC**-ω-OTBS) from **11a** in 53% yield.



Scheme 3 Synthesis of sequence-defined polytriazoles through iterative exponential growth Strategy. Experimental conditions: (i) AcCl, MeOH, room temperature; (ii) TsCl, Et_3N, DMAP, DCM, room temperature; (iii) NaN_3, DMF, 80 °C; (iv) K_2CO_3, MeOH, room temperature; (v) CuBr, PMDETA, DMF, 50 °C.

The experimental mass spectrometry results of all involved building blocks in this series are highly consistent with their own expected molecular weight (Table S2). The structure and purity of them were further characterized by SEC analysis, all of which showed one single SEC peak to verify their uniform structure. The molecular weight differences of synthetic intermediates in each IEG cycle were clearly tracked by the SEC traces (Figure S8). Gradually lessened retention times were observed when inspecting the SEC traces of building blocks **9a**-**12a** for IEG process at each cycle, indicating the iterative chain extension and increased molecular weight (Scheme 3c). The MALDI-TOF-MS of purified sequence-defined polytriazoles **9a**-**11a** (Figure S9), and the Fourier-transform ion cyclotron resonance mass spectrum (FTICR-MS) of **12a** (Scheme 3d) and **12b** (derived from monodeprotection of **12a**, Figure S129) further evidenced the successfully exponential generation of desired macromolecules.

^{1}H and ^{13}C NMR spectrums of all of building blocks listed in Table S2 are provided for the determination of their structures and purities (Figures S58-S97). The trend of the molecular growth at an exponential rate is explicitly illustrated by checking the integrated intensity changes in their ^{1}H NMR spectrums (Figures 1, S11, S12). With the help of 2D NMR experiments, including NOESY (Figures S62, S67, S70, S77), HSQC (Figure S71), and HMBC (Figure S72), the assignment of hydrogen atom groups from the structure of **9a** to the signals from ^{1}H NMR spectrum of it was facilely accomplished (a, Figure 1). The proton spectrums and structures of **9a**, **10a**, **11a** and **12a** are shown in Figure 1, from which it could be seen that the integrated intensities of the proton resonances (t1, t2, 1, 2, 15 and 16) from the two termini of these sequence-defined oligomers remain unchanged, while the integration values of the protons (3-14) associated with the inner main chain increase exponentially. Meanwhile, the chemical shift value dissimilarities of the protons in the same kind side-chain from different sequence-specified fragments (-**ABCH**- vs -**ABC**-OTs) were observed. Comparison of the integrated intensities of these signals (f1 vs f3, m1 vs m3, m2 vs m4) also offers one solid evidence to prove the iterative exponential growth process.

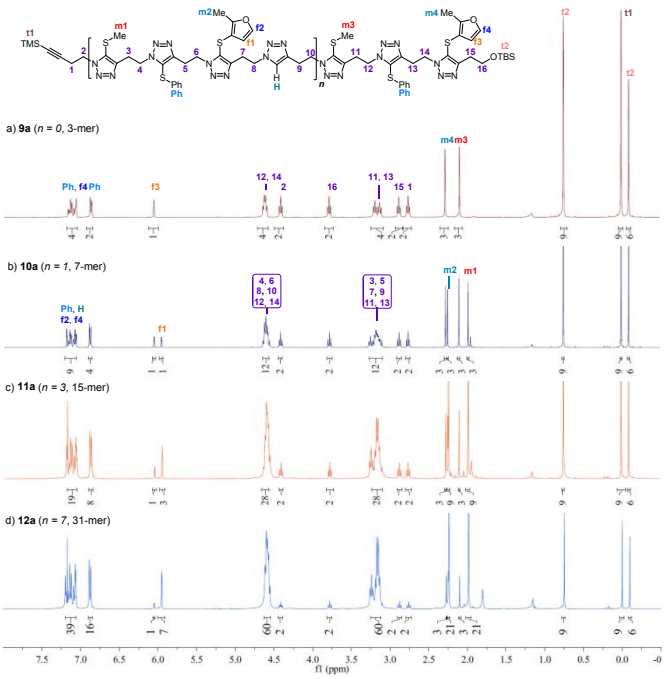
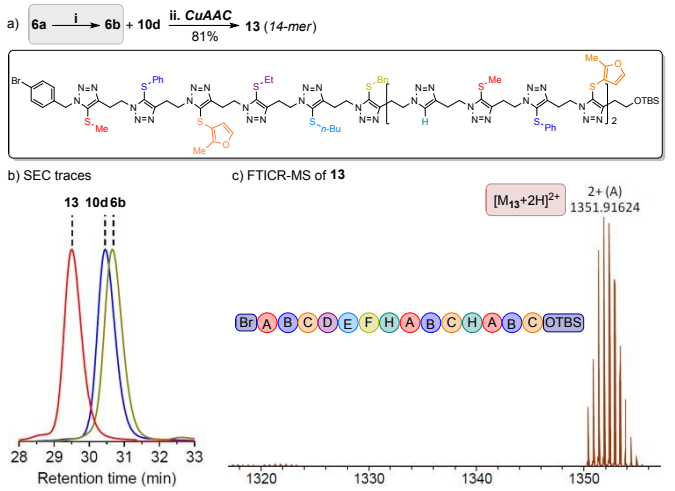


Figure 1 ^{1}H NMR spectra of α-TMS-ω-OTBS oligomers ($CDCl_3$, 400 MHz).

Considering that ISG processes are usually time-consuming, and most polymers derived from IEG methods are limited to repetitive sequences, we took a further step to explore the construction of more complicated long chain sequence-defined polymers by cross-coupling short sequences (Scheme 4). The sequence-defined hexamer **6a** could be easily further converted into α-Br-ω-N_3 building block **6b**. Cross-coupling of **6b** (6-mer from **ISG**) and **10d** (7-mer from **IEG**) led to the formation of unsymmetrical 14-mer **13**

(α-Br-**ABCDEF**(**HABC**)$_2$-ω-OTBS) with a more complicated regulated sequence (Scheme 4a). The uniform nature of **13** was verified by the presence of single peak and sharp molecular weight distribution in its SEC trace (Scheme 4b). The observed *m/z* value (1351.92) of the expected molecular ion $[M+2H]^{2+}$ for **13** is consistent with its theoretical *m/z* value of 1351.89 (Scheme 4c). ^{1}H NMR spectrum of **13** (Figure S98) also characterized its structure and purity.



Scheme 4 Coupling of sequence-defined oligomers. (i) NaN_3, DMF, 80 °C; (ii) CuBr, PMDETA, DMF, 50 °C.

Moreover, to learn the potential applications of sequence-defined polytriazoles in data storage,[16] decoding of **6b** was studied by tandem mass spectrometry (MS/MS). The MS/MS spectra of **6b** (Figure S13) verified the intended sequence of the monomers. Due to the weak C-S bond in the side chains, peaks involving the dissociation of one or more side-arms were observed as the majority, all of which were assigned to the fragments with intended orders, further confirming the successful synthesis of sequence-defined polytriazoles (Figure S14).

To sum up, we pioneered the construction of the novel sequence-defined polytriazole architecture, in which different groups were anchored at C-5 position of the 1,2,3-triazole rings as side-chains in regulated sequence. Sequence-regulated macromolecules with up to ~5.3 kDa molecular weight and 31 side groups were smoothly afforded through IrAAC-based ISG protocol combining with CuAAC-based IEG strategy and cross-coupling method. Simple reaction conditions and high yields in these solution-phase processes bring the opportunity of scalable productions. The identity and purity of these newly introduced sequence-regulated polymers was confirmed by characterizations of NMR, SEC, MALDI-MS and FTICR-MS. Research on the application of this newly introduced skeleton in different areas is ongoing.

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Conflicts of interest

There are no conflicts to declare.

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Notes and references

1 (a) W.-Q. Fan and A. R. Katritzky, *Comprehensive Heterocyclic Chemistry II*, 1996, **4**, 1-126; (b) A. C. Tomé, in *Science of Synthesis: Houben-Weyl Methods of Molecular Transformations*, ed. R. C. Storr and T. L. Gillchrist, Thieme, Stuttgart, 2004, vol. 13, pp. 415-601.

2 (a) V. V. Rostovtsev, L. G. Green, V. V. Fokin and K. B. Sharpless, *Angew. Chem., Int. Ed.,* 2002, ***41***, 2596; (b) C. W. Tornøe, C. Christensen and M. Meldal, *J. Org. Chem.,* 2002, ***67***, 3057.

3 For selected reviews, see: (a) A. Qin, J. W. Y. Lam and B. Z. Tang, *Chem. Soc. Rev.*, 2010, **39**, 2522; (b) A. Qin, J. W. Y. Lam and B. Z. Tang, *Macromolecules*, 2010, **43**, 8693; (c) B. Li, D. Huang, A. Qin and B. Z. Tang, *Macromol. Rapid Commun.*, 2018, **39**, 1800098; (d) Y. Shi, J. Z. Sun and A. Qin, *J. Polym. Sci. Pol. Chem.*, 2017, **55**, 616; (e) B. Yao, J. Z. Sun, A. Qin and B. Z. Tang, *J. Inorg. Organomet. Polym.*, 2015, **25**, 37; (f) M. Juríček, P. H. J. Kouwer and A. E. Rowan, *Chem. Commun.*, 2011, **47**, 8740.

4 (a) J.-F. Lutz, *Polym. Chem.,* 2010, **1**, 55; (b) J.-F. Lutz, M. Ouchi, D. R. Liu and M. Sawamoto, *Science,* 2013, **341**, 1238149; (c) J. F. Lutz, T. Y. Meyer, M. Ouchi and M. Sawamoto, *Sequence-controlled polymers: synthesis, self-assembly, and properties*; American Chemical Society, Washington, DC, 2014; (d) J.-F. Lutz, *Sequence-controlled polymers*; Wiley-VCH, Weinheim, 2018.

5 (a) N. G. Angelo and P. S. Arora, *J. Am. Chem. Soc.,* 2005, **127**, 17134; (b) S. Pfeifer, Z. Zarafshani, N. Badi and J.-F. Lutz, *J. Am. Chem. Soc.,* 2009, **131**, 9195; (c) T. T. Trinh, L. Oswald, D. Chan-Seng, L. Charles and J.-F. Lutz, *Chem. Eur. J.,* 2015, **21**, 11961.

6 C. J. Yang, J. P. Flynn and J. Niu, *Angew. Chem., Int. Ed.,* 2018, **57**, 16194.

7 (a) F. A. Leibfarth, J. A. Johnson and T. F. Jamison, *Proc. Natl. Acad. Sci. U. S. A.,* 2015, **112**, 10617; (b) J. C. Barnes, D. J. C. Ehrlich, A. X. Gao, F. A. Leibfarth, Y. Jiang, E. Zhou, T. F. Jamison and J. A. Johnson, *Nat. Chem.,* 2015, **7**, 810; (c) Y. Jiang, M. R. Golder, H. V.-T. Nguyen, Y. Wang, M. Zhong, J. C. Barnes, D. J. C. Ehrlich and J. A. Johnson, *J. Am. Chem. Soc.,* 2016, **138**, 9369; (d) F. Amir, Z. Jia and M. J. Monteiro, *J. Am. Chem. Soc.,* 2016, **138**, 16600; (e) M. R. Golder, Y. Jiang, P. E. Teichen, H. V.-T. Nguyen, W. Wang, N. Milos, S. A. Freedman, A. P. Willard and J. A. Johnson, *J. Am. Chem. Soc.,* 2018, **140**, 1596.

8 N. F. Konig, A. Al Ouahabi, S. Poyer, L. Charles and J.-F. Lutz, *Angew. Chem., Int. Ed.,* 2017, **56**, 7297.

9 Z. Huang, Y. Zhou, Z. Wang, Y. Li, W. Zhang, N. Zhou, Z. Zhang and X. Zhu, *Chinese J. Polym. Sci.,* 2017, **35**, 317.

10 (a) H. C. Kolb and K. B. Sharpless, *Drug Discovery Today*, 2003, **8**, 1128; (b) D. Dheer, V. Singh and R. Shankar, *Bioorg. Chem.,* 2017, **71**, 30.

11 S. Ding, G. Jia and J. Sun, *Angew. Chem. Int. Ed.,* 2014, **53**, 1877.

12 R. B. Merrifield. *J. Am. Chem. Soc.,* 1963, **85**, 2149.

13 O. I. Paynter, D. J. Simmonds and M. C. Whiting, *J. Chem. Soc., Chem. Commun.,* 1982, 1165.

14 S. Binauld, D. Damiron, L. A. Connal, C. J. Hawker and E. Drockenmuller, *Macromol. Rapid Commun.,* 2011, **32**, 147.

15 S. Binauld, C. J. Hawker, E. Fleury and E. Drockenmuller, *Angew. Chem., Int. Ed.,* 2009, **48**, 6654.

16 For selected reviews, see: (a) J. F. Lutz, *Acc. Chem. Res.*, 2013, **46**, 2696; (b) H. Colquhoun and J. F. Lutz, *Nat. Chem.*, 2014, **6**, 455; (c) M. G. T. A. Rutten, F. W. Vaandrager, J. A. A. W. Elemans and R. J. M. Nolte, *Nat. Rev. Chem.*, 2018, **2**, 365.