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Combining Orthogonal Chain End Deprotections and Thiol-Maleimide Michael Coupling: Engineering Discrete Oligomers through Iterative Growth Strategy

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Abstract: *For the first time, we combined orthogonal maleimide and thiol deprotections together with thiol-maleimide coupling to synthesize discrete oligomers/macromolecules on gram scale with molecular weight up to 27.4 kDa (128mer, 7.9 g) via iterative exponential growth strategy with degree of polymerization (DP) at* 2^n*-1. By using the same chemistry, a "readable" sequence-defined oligomer and a discrete cyclic topology were also created. Furthermore, uniform dendrons were fabricated via either sequential growth (DP =* 2^n*-1) or double exponential dendrimer growth approach (DP =*2^{2^n}*-1) with significantly accelerated growth rate. This work offered a versatile, efficient and metal-free platform for construction of discrete oligomers with vast designability and high growth rate, which would greatly facilitate sophisticated structure-property research as well as applications of precise polymer-based materials.*

It is well-documented that the property/function of polymers strongly relies on their molecular weight, topology and sequence distribution.[1] Nature creates a variety of biopolymers, such as DNA[2] and proteins[3] with precisely-defined chain lengths, functional sequence, and topologies. Since most artificial polymers are polydisperse with various chemical structures and molecular weights at the molecular level, the research on structure-property relationship is mainly limited to an ambiguous and statistical manner.[4] Therefore, it is of great interest for synthesis of discrete oligomers with uniform chain lengths (*i.e.*, monodisperse molecular weight), monomer unit sequences, and topologies to advance more comprehensive and accurate study of the structure-property relationship.[5] Driven by this challenge, indeed, chemists have made enormous efforts to synthesize discrete oligomers with diverse directions and approaches. Within these pioneering work,[6] iterative sequential,[7] or exponential[8] growth through terminal deprotections/transformations and end-to-end couplings,[9] is commonly used for preparations of discrete oligomers. When building discrete oligomers, the efficient orthogonal chain terminal deprotections together with end-to-end coupling reaction are highly desirable for high degree of polymerization (DP) and scalable preparation. A number of coupling reactions, such as Suzuki coupling reaction,[8b] Sonogashira reaction,[9a] Stille reaction,[9b] Buchwald reaction,[8e] Wittig reaction,[9c] copper catalyzed azide-alkyne cycloaddition (CuAAC) reaction,[8d, 8i, 8k, 8l] Glaser coupling reaction,[10] esterification,[11] amidation,[9d] and etherification[8c, 9e] *etc.*, have been utilized in precision synthesis of oligomers. Among them, metal-catalyzed coupling reactions are frequently used owing to the versatility, effectiveness and sometimes "click-like" manner.[7g, 8d, 8i, 8k] However, metal ions may increasingly accumulate after many cycles and contaminate target products. This might yield inaccurate measurements when investigating the structure-property relationship of the discrete oligomers, limiting their potential for future applications.

Herein, for the first time, we combined the orthogonal chain end deprotections and thiol-maleimide Michael coupling together as a versatile approach for the iterative synthesis of a variety of discrete oligomers, including linear, dendron and cyclic oligomers. The thiol-maleimide Michael coupling is a well-known and important member of the "click" reactions.[12] The maleimide group can be readily protected by furan group, which can be quantitatively deprotected by retro Diels-Alder reaction upon heating to 110 °C or above.[13] On the other hand, thiol group[14] was protected by the judiciously selected acetyl group, which can withstand high temperature up to 110 °C and release a reactive thiol group in quantitative yield under acidic (or basic) environment or by using acetyl chloride.[15] Surprisingly, no previous report combined the deprotections of maleimide and thiol at two terminals for the subsequent thiol-maleimide coupling in polymers and/or oligomers synthesis. This work unprecedentedly developed a metal-free, mild and user-friendly chemistry, *i.e.*, combining orthogonal maleimide and thiol group deprotections together with the thiol-maleimide coupling reaction, to prepare discrete oligomers, which are ideal models for accurately investigating the polymer's structure-property relationship and provide potential applications in bio-related or smart polymeric materials with molecular level precision.

In all the iterative chain growth of this study, the highly efficient retro Diels-Alder reaction was used to remove the furan protecting group on the maleimide group, and a hydrolysis reaction was used to remove the acetyl group on the thiol for the subsequent coupling reactions. As depicted in Figure 1a, the precursor monomer (US-G1) was first synthesized with furan-protected maleimide and acetyl-protected thiol (Scheme S1) for linear oligomers synthesis. Then, repeating the orthogonal deprotections of two ends followed by thiol-maleimide Michael coupling cycles (Scheme S2), the linear oligomer's chain length propagated exponentially with DP= 2^n-1 to generate 2mer (536.7 Da), 4mer (963.3 Da), 8mer (1,816.5 Da), 16mer (3,522.8 Da), 32mer (6,935.6 Da), 64mer (13,761.0 Da) and 128mer (27,411.9 Da) (Scheme S3-S8). Importantly, the chemistry for these discrete oligomers can be scalable, and dozens of grams of these linear oligomers were obtained.

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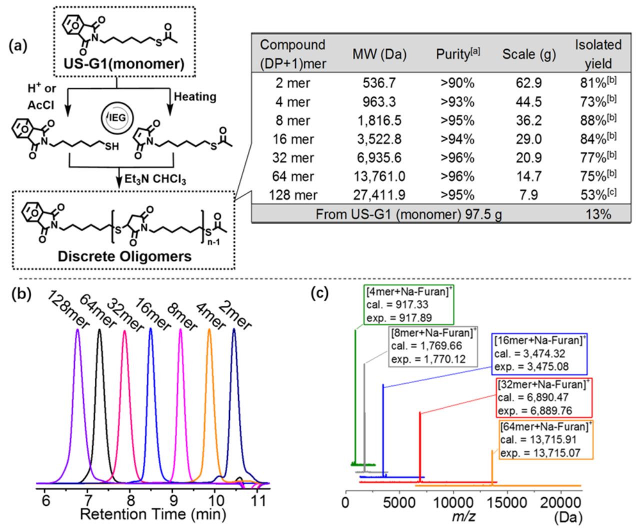
For example, 7.9 g of 128mer was afforded with 13.3% isolated yield over 21 steps from the starting monomer (US-G1, 97.5 g), demonstrating the high-efficiency of this approach.



Compound (DP+1)mer	MW (Da)	Purity[a]	Scale (g)	Isolated yield
2 mer	536.7	>90%	62.9	81%[b]
4 mer	963.3	>93%	44.5	73%[b]
8 mer	1,816.5	>95%	36.2	88%[b]
16 mer	3,522.8	>94%	29.0	84%[b]
32 mer	6,935.6	>96%	20.9	77%[b]
64 mer	13,761.0	>96%	14.7	75%[b]
128 mer	27,411.9	>95%	7.9	53%[c]
From US-G1 (monomer) 97.5 g				13%

Figure 1. (a) Synthetic route of the discrete oligomers *via* iterative exponential growth (IEG). [a]The purity of each generation was confirmed by combining ^{1}H NMR, SEC trace and MALDI-TOF mass spectrum. [b]Purification was performed by silica gel column chromatography except that [c]128mer was purified by fractional precipitation in anhydrous methanol; The isolated yields were calculated over 3 successive steps (*i.e.* terminal maleimide deprotection, terminal thiol deprotection, and intermolecular thiol-maleimide coupling) in each cycle. (b) SEC traces of 2mer, 4mer, 8mer, 16mer, 32mer, 64mer, and 128mer; (c) MALDI-TOF mass spectra of 4mer, 8mer, 16mer, 32mer, and 64mer.

The molecular structure of each linear oligomer was further validated by size exclusion chromatography (SEC, SEC traces of crude oligomers without purification were shown in Figure S7 in Supporting Information) and matrix-assisted laser desorption ionization time-of-flight (MALDI-TOF) mass spectrometry (Figures 1b and 1c). Unimodal and symmetrical SEC traces as well as the single-peak signal agreeing with the calculated value of the molecular mass ([M+Na-Furan]$^+$) for each oligomer in MALDI-TOF mass spectrum confirmed the uniformity of these structures. MALDI-TOF mass spectrum of 128mer by reflection mode could not be obtained, and the linear mode resulted in fragmentations due to its high MW and low ionization efficiency (Figure S8). Figure 2 showed the ^{1}H NMR spectra of the discrete oligomers from 2mer to 128mer. The resonances for the protons from furan protected chain terminal could be easily identified at 6.50 (a) and 5.26 (b) ppm. The protons of the acetyl protected group at the other chain end were identified at 2.25 (e) ppm. Based on the integrations of 3.70 (d), 3.12 (c) and 2.48 (c) ppm arising from the protons of the succiminide thioethers and the protons (e) of acetyl, the DP of each oligomer was calculated. The results from ^{1}H NMR were in agreement with those from MALDI-TOF mass spectrum. These convincing results enabled the orthogonal deprotections and subsequent thiol-maleimide Michael coupling as an accessible, robust and scalable platform for the precise preparation of uniform linear oligomers. In addition to linear oligomers, cyclic ones were also successfully prepared by the intramolecular ring closure *via* thiol-maleimide Michael coupling under high dilution (about 1.1×10^{-4} M) (Scheme S16). Detailed characterizations, *i.e.*, NMR, SEC and mass spectrometry, were carried out to confirm the cyclic structure (Figure S32). The successful fabrication of monodisperse cyclic oligomer would enable reliable property comparisons between the analogous cyclic and linear oligomers, since the research on the cyclic polymer have been the subject of increased study because their cyclic topology imparts upon them unique physical properties.[16]

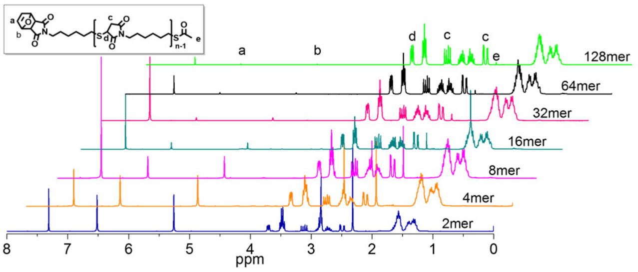


Figure 2. ^{1}H NMR spectra of 2mer, 4mer, 8mer, 16mer, 32mer, 64mer, and 128mer in $CDCl_3$ (Bruker, 300 MHz, TMS).

The above efficient chemistry, *i.e.*, orthogonal chain terminal deprotections together with thiol-maleimide coupling reaction, was also employed for the synthesis of sequence-defined oligomers. An example was demonstrated here, wherein two precursor monomers were each incorporated with naphthyl (FS-PI-3, Scheme S10) and alkene groups (FS-PII-8, Scheme S12). Dimers of FS-PI (Scheme S11) and FS-PII (Scheme S13) were obtained *via* one IEG cycle from corresponding monomers, respectively. FS-PI-MA (removal of furan of FS-PI) and FS-PII-SH (removal of acetyl of FS-PII) were coupled *via* thiol-maleimide Michael type addition to afford FS-L (Figure 3a and Scheme S14). Then, FS with definite unit sequence was successfully constructed by click coupling of US-G4-SH with FS-L-MA (Figure 3a and Scheme S15). The sequence-defined oligomer FS was rigorously characterized by MALDI-TOF mass spectrometry (upper inset in Figure 3b) and ^{1}H NMR (Figure S23). Since sulfur-carbon bonds of the succinimide thioether unit formed in this thiol-maleimide Michael coupling were relatively weak, the information stored in the sequence-defined oligomer was able to be “read” or decoded *via* a tandem mass spectrometry (MS/MS)-based sequencing methodology with potential applications for data storage and anti-counterfeiting technologies.[7d, 7j, 17] The decoding of the as-prepared sequence-defined discrete oligomers was implemented on the tandem MALDI-TOF/TOF (*i.e.*, MS/MS). The fragmentations of FS affording the US-G1 unit (unit MW = 213Da), FS-PII (unit MW = 304 Da) and FS-PI (unit MW = 343 Da) were clearly identified (Figure 3b). Some fragmentations of the corresponding cleavage owing to the high energy of laser were also reasonably assigned (Figure S24).

The versatility and robustness of the above chemistry for building discrete oligomers was further demonstrated by constructing different generations of topological oligomers, *i.e.*, dendrons. In this study, the succinimide thioether groups in US-G2 from thiol-maleimide Michael addition reaction was facilely reduced to regenerate the vinyl double bonds, through an addition-elimination process using N-chlorosuccinimide (DT-1, Scheme S17). [18] Subsequent thiol-maleimide Michael coupling on maleimide thioether group with thiol-deprotected US-G1-SH afforded DT-G1 with one branching point (Figure 4a and Scheme S18). Starting from DT-G1, the uniform oligomer-based dendrons of DT-G2 and DT-G4 were constructed *via* double exponential dendrimer growth (DEDG) strategy[19] with DP $=2^{2^n}$-1 (Figure 4a and Schemes S19 and S21) by repetitive orthogonal deprotections and thiol-maleimide Michael additions. Meanwhile, through sequential growth strategy[20] with DP = 2^n-1, dendron of DT-G3 was prepared from DT-

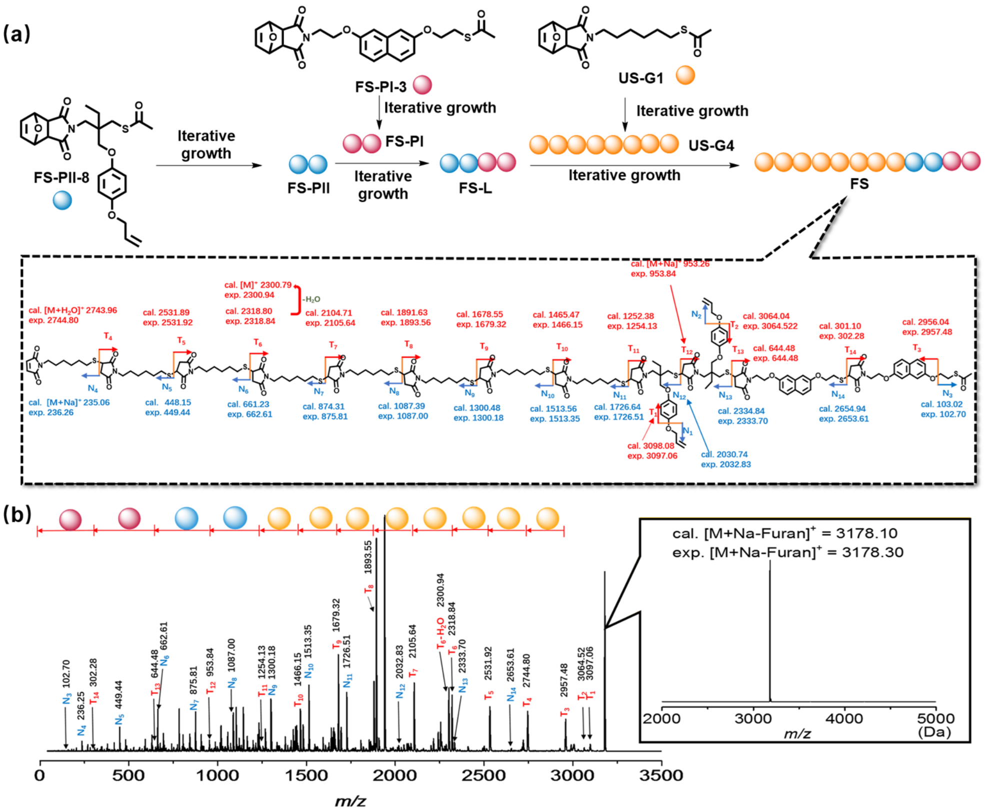


Figure 3. (a) Synthetic route of the sequence-defined oligomer FS. (b) Full interpretation of the MALDI–TOF/TOF mass spectrum of FS fragments using the LIFT mode (Upper inset: MALDI-TOF mass spectrum of FS acquired in the first TOF unit using Na salt as the cationization agent and DCTB as the matrix).

G2 and DT-G1 (Figure 4a and Scheme S20). The resulting dendron topologies were characterized by SEC (Figure 4b), MALDI-TOF mass spectrometry (Figure 4c) and ^{1}H NMR (Figures S28-S30). The data of analysis clearly demonstrated the precise constructions of these topologies. It is noteworthy that these dendron topologies were merely originated from one starting monomer, US-G1, no other reactant was needed besides the catalysts or reducing agents. More importantly, DEDG approach paved an avenue towards highly-branched dendrons in a significantly accelerated manner.

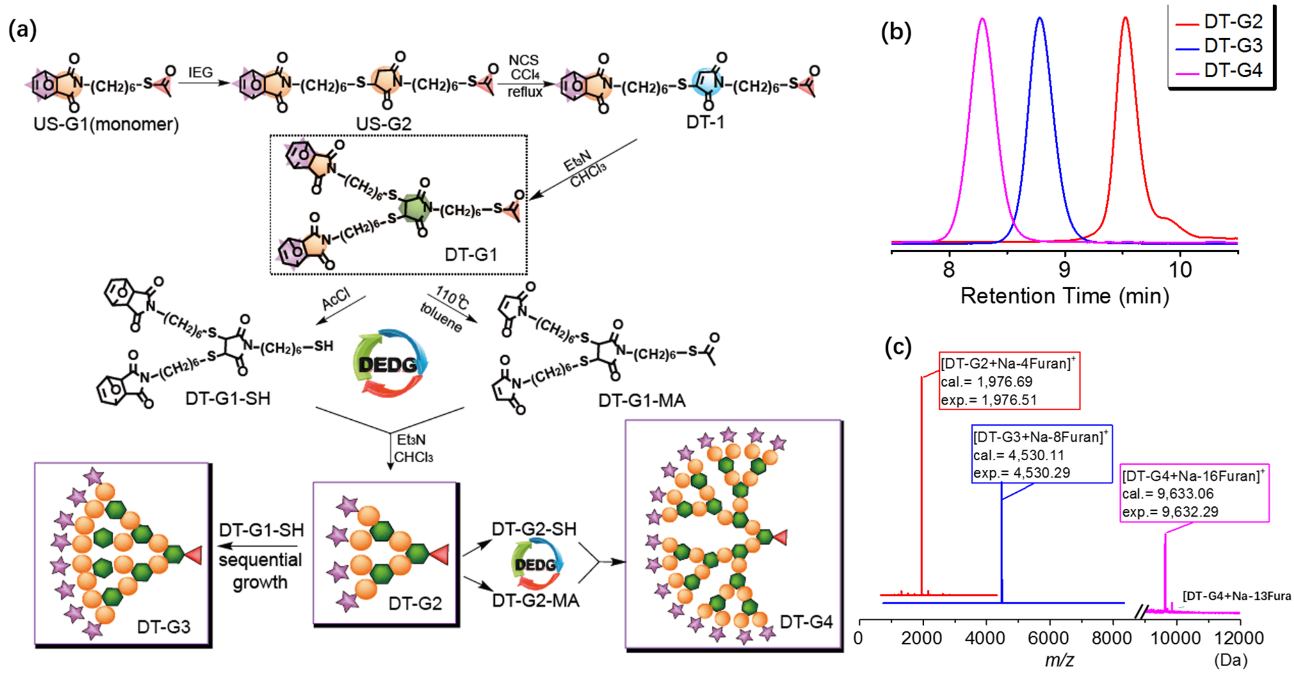


Figure 4. (a) Synthetic route of dendrons DT-G2, DT-G3 and DT-G4, NCS: N-chlorosuccinimide; (b) SEC spectra and (c) MALDI-TOF mass spectra of DT-G2, DT-G3 and DT-G4 (DT-G4 was destroyed during testing in MALDI-TOF mass spectrometry due to its high MW, the full spectrum with fragmentation peaks is shown in Figure S31 in Supporting Information).

As demonstrated, the above chemistry afforded an array of discrete oligomers, which are perfect samples for accurately exploring structure-property relationship. Especially, the study of the physical properties of discrete oligomers with similar chemical structure but different MWs or topologies is a fundamental topic in polymer science area. As demonstrated here, the variation of glass transition temperature (T_g) with inverse MW of these discrete oligomers, including linear and topological ones, was analyzed based on Flory-Fox equation[21] as in Figure 5. For both uniform linear oligomers and dendrons, the T_g gradually increases with increasing the MW (Figure 5a and 5b). Importantly, the correlation between the MW and T_g matched with Flory-Fox equation, and the T_g was close to the predicted $T_{g\infty}$ when MW reached up to 10,000 Da (Figure 5c). In addition, the linear oligomers and dendrons ones show almost the same linear correlation plot, denoting that both $T_{g\infty}$ and empirical parameter K of Flory-Fox equation are almost the same values in linear and topological ones with the same chemical structure, although the concentration of end groups in each molecules is different in oligomers and dendrons, respectively. Furthermore, the DSC results indicate that oligomers with polydisperse MWs obtained from step-growth polymerization *via* thiol-maleimide coupling exhibit much broader glass transition[8f] and lower T_g, as compared with the discrete oligomers having similar MWs (Figure S9). These differences might probably be attributed to the existence of low-MW fractions in the polydisperse samples, according to Flory-Fox equation.[21] Deep insights and comprehensive understanding requires detail study, providing us further motivations for developing effective chemistry towards discrete oligomers.

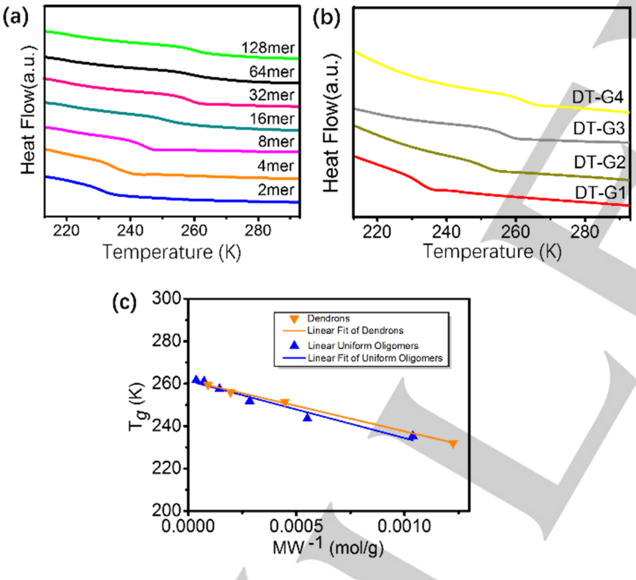


Figure 5. (a) The glass transition temperature of discrete oligomers and (b) dendrons. (c) Flory–Fox analysis of *Tg vs.* MW^{-1} for uniform linear oligomers and dendrons.

In summary, a versatile, efficient and metal-free chemistry, *i.e.*, combining orthogonal deprotections of maleimide and thiol groups together with thiol-maleimide Michael coupling, was developed for precisely fabricating discrete oligomers. This efficient coupling chemistry allows the generation of an unprecedentedly broad library of discrete oligomers with a range of linear, cyclic, and dendron architectures. We anticipated that these precisely-defined oligomers would enable accurate investigation on the structure-property relationships and advance potential applications of exquisite polymer-based functional materials.

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Keywords： thiol-maleimide Michael type addition • discrete oligomer • iterative growth • dendrimer • sequence defined

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[1] J. F. Lutz, J. M. Lehn, E. W. Meijer, K. Matyjaszewski, *Nature Reviews Materials* **2016**, *1*, 16024.
[2] G. M. Church, Y. Gao, S. Kosuri, *Science* **2012**, *337*, 1628.
[3] K. A. Dill, J. L. MacCallum, *Science* **2012**, *338*, 1042-1046.
[4] K. Müllen, *Nature Reviews Materials* **2016**, *1*. DOI: 10.1038/natrevmats.2015.13
[5] B. van Genabeek, B. F. de Waal, B. Ligt, A. R. Palmans, E. Meijer, *ACS Macro. Lett.* **2017**, *6*, 674-678.
[6] a) J. Lawrence, S. H. Lee, A. Abdilla, M. D. Nothling, J. M. Ren, A. S. Knight, C. Fleischmann, Y. Li, A. S. Abrams, B. V. Schmidt, M. C. Hawker, L. A. Connal, A. J. McGrath, P. G. Clark, W. R. Gutekunst, C. J. Hawker, *J. Am. Chem. Soc.* **2016**, *138*, 6306-6310; b) J. Xu, C. Fu, S. Shanmugam, C. J. Hawker, G. Moad, C. Boyer, *Angew. Chem. Int. Ed.* **2017**; DOI: 10.1002/anie.201610223; c) B. Oschmann, J. Lawrence, M. W. Schulze, J. M. Ren, A. Anastasaki, Y. Luo, M. D. Nothling, C. W. Pester, K. T. Delaney, L. A. Connal, A. J. McGrath, P. G. Clark, C. M. Bates, C. J. Hawker, *ACS Macro. Lett.* **2017**, 668-673; d) S. C. Solleder, R. V. Schneider, K. S. Wetzel, A. C. Boukis, M. A. R. Meier, *Macromol. Rapid Commun.* **2017**, *38*. DOI: 10.1002/marc.201600711
[7] a) R. B. Merrifield, *J. Am. Chem. Soc.* **1963**, *85*, 2149-2154; b) B. Merrifield, *Bioscience reports* **1985**, *5*, 353-376; c) C. M. Gothard, N. A. Rao, J. S. Nowick, *J. Am. Chem. Soc.* **2007**, *129*, 7272-7273; d) G. Cavallo, A. Al Ouahabi, L. Oswald, L. Charles, J. F. Lutz, *J. Am. Chem. Soc.* **2016**, *138*, 9417-9420; e) S. Pfeifer, Z. Zarafshani, N. Badi, J. F. Lutz, *J. Am. Chem. Soc.* **2009**, *131*, 9195-9197; f) V. Duvigneaud, C. Ressler, J. M. Swan, C. W. Roberts, P. G. Katsoyannis, S. Gordon, *J. Am. Chem. Soc.* **1953**, *75*, 4879-4880; g) S. Muthana, H. Yu, H. Cao, J. Cheng, X. Chen, *J. Org. Chem.* **2009**, *74*, 2928-2936; h) G. Lu, S. Lam, K. Burgess, *Chem. Commun.* **2006**, 1652-1654; i) N. G. Angelo, P. S. Arora, *J. Am. Chem. Soc.* **2005**, *127*, 17134-17135; j) N. Zydziak, W. Konrad, F. Feist, S. Afonin, S. Weidner, C. Barner-Kowollik, *Nat. Commun.* **2016**, *7*, 13672.
[8] a) O. I. Paynter, D. J. Simmonds, M. C. Whiting, *J. Chem. Soc.* **1982**, 1165-1166; b) J. S. Schumm, D. L. Pearson, J. M. Tour, *Angew. Chem. Int. Ed.* **1994**, *33*, 1360-1363; c) C. J. Hawker, E. E. Malmstrom, C. W. Frank, J. P. Kampf, *J. Am. Chem. Soc.* **1997**, *119*, 9903-9904; d) S. Binauld, C. J. Hawker, E. Fleury, E. Drockenmuller, *Angew. Chem Int. Ed.* **2009**, *48*, 6654-6658; e) J. P. Sadighi, R. A. Singer, S. L. Buchwald, *J. Am. Chem. Soc.* **1998**, *120*, 4960-4976; f) K. Takizawa, C. Tang, C. J. Hawker, *J. Am. Chem. Soc.* **2008**, *130*, 1718-1726; g) Q. L. Wang, Y. Qu, H. K. Tian, Y. H. Geng, F. S. Wang, *Macromolecules* **2011**, *44*, 1256-1260; h) S. Binauld, D. Damiron, L. A. Connal, C. J. Hawker, E. Drockenmuller, *Macromol. Rapid Commun.* **2011**, *32*, 147-168; i) F. A. Leibfarth, J. A. Johnson, T. F. Jamison, *Proc. Natl. Acad. Sci.* **2015**, *112*, 10617-10622; j) Y. Jiang, M. R. Golder, H. V. Nguyen, Y. Wang, M. Zhong, J. C. Barnes, D. J. Ehrlich, J. A. Johnson, *J. Am. Chem. Soc.* **2016**, *138*, 9369-9372; k) J. C. Barnes, D. J. Ehrlich, A. X. Gao, F. A. Leibfarth, Y. Jiang, E. Zhou, T. F. Jamison, J. A. Johnson, *Nat. Chem.* **2015**, *7*, 810-815; l) F. Amir, Z. Jia, M. J. Monteiro, *J. Am. Chem. Soc.* **2016**, *138*, 16600-16603.
[9] a) D. L. Pearson, J. S. Schumm, J. M. Tour, *Macromolecules* **1994**, *27*, 2348-2350; b) S. Sakurai, H. Goto, E. Yashima, *Org. Lett.* **2001**, *3*, 2379-2382; c) E. Igner, O. I. Paynter, D. J. Simmonds, M. C. Whiting, *J. Chem. Soc., Perkin Trans. 1* **1987**, 2447-2454; d) S. S. Reddy, X. Dong, R. Murgasova, A. I. Gusev, D. M. Hercules, *Macromolecules* **1999**, *32*, 1367-1374; e) K. L. Wooley, C. J. Hawker, J. M. J. Frechet, *Angew. Chem. Int. Ed.* **1994**, *33*, 82-85.
[10] X. Jiang, J. J. Lu, F. Zhou, Z. B. Zhang, X. Q. Pan, W. Zhang, Y. Wang, N. C. Zhou, X. L. Zhu, *Polym. Chem.* **2016**, *7*, 2645-2651.
[11] K. Takizawa, H. Nulwala, J. Hu, K. Yoshinaga, C. J. Hawker, *J. Polym. Sci. Pol. Chem.* **2008**, *46*, 5977-5990.
[12] a) C. E. Hoyle, A. B. Lowe, C. N. Bowman, *Chem. Soc. Rev.* **2010**, *39*, 1355-1387; b) A. B. Lowe, M. Liu, J. A. van Hensbergen, R. P. Burford, *Macromol. Rapid Commun.* **2014**, *35*, 391-404; c) Y. W. Li, H. Su, X. Y. Feng, Z. Wang, K. Guo, C. Wesdemiotis, Q. Fu, S. Z. D. Cheng, W. B. Zhang, *Polym. Chem.* **2014**, *5*, 6151-6162; d) P. Espeel, L. L. Carrette, K. Bury, S. Capenberghs, J. C. Martins, F. E. Du Prez, A. Madder, *Angew. Chem. Int. Ed.* **2013**, *52*, 13261-13264.
[13] a) Z. Liu, C. Dong, X. Wang, H. Wang, W. Li, J. Tan, J. Chang, *ACS appl materials & interfaces* **2014**, *6*, 2393-2400; b) G. Mantovani, F. Lecolley, L. Tao, D. M. Haddleton, J. Clerx, J. J. Cornelissen, K. Velonia, *J. Am. Chem. Soc.* **2005**, *127*, 2966-2973; c) E. B. Murphy, F. Wudl, *Prog. Polym. Sci.* **2010**, *35*, 223-251.
[14] a) G. Battistini, P. G. Cozzi, J. P. Jalkanen, M. Montalti, L. Prodi, N. Zaccheroni, F. Zerbetto, *ACS Nano* **2008**, *2*, 77-84; b) K. Hu, Y. J. Qi, J. Zhao, H. F. Jiang, X. Chen, J. Ren, *Eur. J. Med. Chem.* **2013**, *64*, 529-539.
[15] R. Kota, R. Samudrala, D. L. Mattern, *J. Org. Chem.* **2012**, *77*, 9641-9651.
[16] B. Verbraeken, R. Hoogenboom, *Angew. Chem. Int. Ed.* **2017**, *56*, 7034-7036.

[17] a) J. F. Lutz, *Accounts Chem. Res.* **2013**, *46*, 2696-2705; b) H. Colquhoun, J. F. Lutz, *Nat. Chem.* **2014**, *6*, 455-456; c) N. F. Konig, A. Al Ouahabi, S. Poyer, L. Charles, J. F. Lutz, *Angew. Chem. Int. Ed.* **2017**, *56*, 7297-7301.

[18] a) Y. Arai, M. Matsui, T. Koizumi, M. Shiro, *J. Org. Chem.* **1991**, *56*, 1983-1985; b) J. F. Barry, T. W. Wallace, N. D. A. Walshe, *Tetrahedron Lett.* **1993**, *34*, 5329-5330.

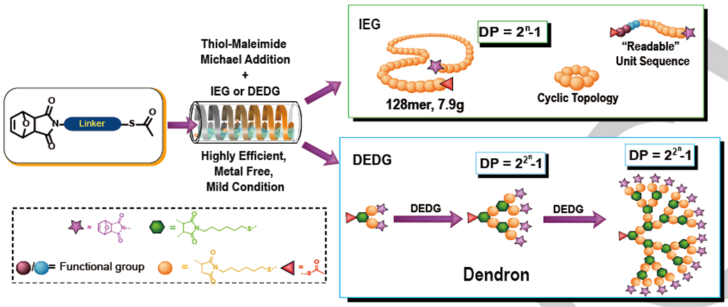
[19] a) T. Kawaguchi, K. L. Walker, C. L. Wilkins, J. S. Moore, *J. Am. Chem. Soc.* **1995**, *117*, 2159-2165; b) J. S. Moore, *Accounts Chem. Res.* **1997**, *30*, 402-413; c) S. M. Grayson, J. M. Frechet, *Chem. Rev.* **2001**, *101*, 3819-3868; d) M. I. Montanez, L. M. Campos, P. Antoni, Y. Hed, M. V. Walter, B. T. Krull, A. Khan, A. Hult, C. J. Hawker, M. Malkoch, *Macromolecules* **2010**, *43*, 6004-6013.

[20] a) C. J. Hawker, J. M. J. Frechet, *J. Am. Chem. Soc.* **1990**, *112*, 7638-7647; b) J. M. J. Frechet, C. J. Hawker, I. Gitsov, J. W. Leon, *J. Macromol. Sci.-Pure and Appl. Chem.* **1996**, *A33*, 1399-1425; c) J. W. Leon, M. Kawa, J. M. J. Frechet, *J. Am. Chem. Soc.* **1996**, *118*, 8847-8859; d) M. Ohta, J. M. J. Frechet, *J. Macromol. Sci.-Pure and Appl. Chem.* **1997**, *A34*, 2025-2046; e) A. W. Freeman, J. M. J. Frechet, *Org. Lett.* **1999**, *1*, 685-687; f) S. L. Gilat, A. Adronov, J. M. J. Frechet, *J. Org. Chem.* **1999**, *64*, 7474-7484; g) A. W. Freeman, L. A. Chrisstoffels, J. M. Frechet, *J. Org. Chem.* **2000**, *65*, 7612-7617; h) L. Brauge, G. Magro, A.M. Caminade, J.-P. Majoral, *J. Am. Chem. Soc.* **2001**, *123*, 6698-6699; i) S. Hecht, J. M. Frechet, *Angew. Chem. Int. Ed.* **2001**, *40*, 74-91; j) V. Maraval, A. M. Caminade, J. P. Majoral, J. C. Blais, *Angew. Chem. Int. Ed.* **2003**, *42*, 1822-1826.

[21] a) J. E. Puskas, Y. H. Chen, K. Kulbaba, G. Kaszas, A. Soleymannezhad, *J. Polym. Sci. Pol. Chem.* **2006**, *44*, 1770-1776; b) A. Stoddart, W. J. Feast, S. P. Rannard, *Soft Matter* **2012**, *8*, 1096-1108; c) K. L. Wooley, C. J. Hawker, J. M. Pochan, J. M. J. Frechet, *Macromolecules* **1993**, *26*, 1514-1519.

COMMUNICATION

A versatile, efficient and metal-free chemistry, combining orthogonal deprotections of maleimide and thiol groups together with thiol-maleimide Michael coupling, was firstly developed for precisely fabricating discrete oligomers.



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