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Communication

Introducing Ugi Reaction into Polymer Chemistry as a Green Click Reaction to Prepare Middle-Functional Block Copolymers

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Multicomponent reactions (MCRs) and click reactions have a number of significant features in common, such as modularity, high efficiency and atom economy. Some MCRs can thus be considered as a new type of click reaction: multicomponent click reaction. The well-known Ugi reaction has been utilized as a green click reaction to efficiently stitch two different polymer chains together under very benign conditions (25 °C, catalyst free). The mid-functional block copolymers and miktoarm star copolymers which are normally difficult to be synthesized have thus been facilely prepared, indicating the promising potential of Ugi reaction in polymer chemistry to prepare sophisticated structural copolymers.

The notion of 'click chemistry' was first defined by K. B. Sharpless in 2001 to describe some modular, highly efficient and atom economic chemical reactions that create easily purified products with no or only harmless byproducts, such as water[1]. The exploration and discovery of 'clickable feature' of reactions, especially 'old' reactions, represent the persistent pursuit of chemists to ideal reactions. Several 'old' reactions have thus been reappraised and rediscovered as 'click reactions', such as well-known azide-alkyne Huisgen cycloaddition[2], thiol-ene/yne free-radical addition[3, 4], (hetero) Diels-Alder[5] and thiol-isocyanate coupling reactions[6], etc.. Although they are well-known reactions in organic chemistry, abovementioned 'click reactions' still fascinate researchers from material science[7-11], polymer chemistry[12-19] and life science[20, 21] and trigger the recent research wave in those areas due to their outstanding reliability and efficiency.

During our research of multicomponent reactions (MCRs), we found some MCRs naturally possess 'clickable feature'. MCRs are defined as reactions in which three or more compounds react together to form a highly selective, single product that contains most of the atoms from the starting materials[22, 23]. MCRs are naturally modular, highly efficient and atom economic, very similar with click reactions.

With further understanding mechanism and continual optimizing reaction conditions, some MCRs, such as Biginelli, Ugi and Mannich reactions, can now occur smoothly under very mild conditions to form almost single products with only water as the byproduct. Thus, we believe some MCRs are possible to be recognized as 'click reactions' under proper reaction conditions (**Scheme 1**).

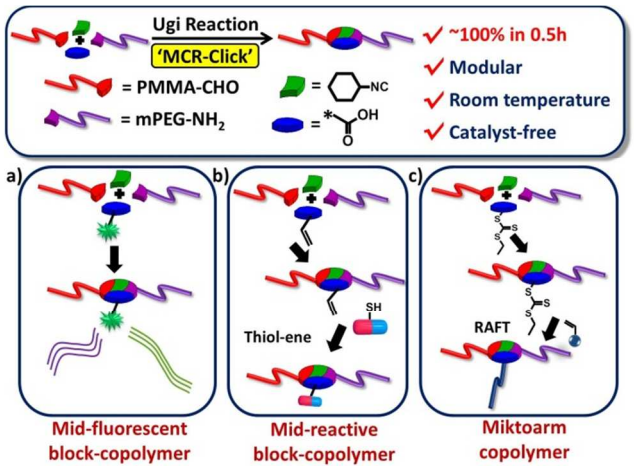
Scheme 1. The significant features in common between MCR and 'Click' reaction.

In our previous work, the three-component Biginelli reaction has been rediscovered as a 'clickable MCR' and utilized in polymer chemistry and chemical biology, demonstrating the new vitality of this 'old' reaction (> 120 years) when people discover its 'clickable feature'[24]. However, there are still some drawbacks of Biginelli reaction, such as using less components (only three), catalyst (normally Lewis acid) and unusual starting materials (urea and β-dione), which more or less limit the application of this new click reaction by researchers from wider ranges.

Therefore, we hope to combine more elements to construct higher level clickable MCRs using common reactants under greener conditions. A famous four-component MCR, Ugi reaction, has therefore entered our insight. Ugi reaction was invented in 1959 as a four-component reaction, which is a condensation reaction among an aldehyde/ketone, an amine, a carboxylic acid and an isocyanide to give an α-aminoacyl amide derivative[25, 26]. The Ugi reaction is inherent atom economic (all atoms are compressed into a single product with only a molecule of water as byproduct), highly efficient (almost quantitative), and facile for operation (usually complete within minutes without external additive catalyst). Therefore, Ugi reaction has possibility to be developed as a four component green click reaction.

Ugi reaction has been not only most widely used in combinatorial chemistry[27, 28] and pharmaceutical industry[29, 30], but

also successfully utilized in polymer chemistry and material science[31]. For example, Meier's group used the Ugi reaction and other MCRs to prepare functional monomer and subsequent functional polymer[32-34]. Herein, we reconsider Ugi reaction as a click reaction and introduce it into polymer chemistry to conduct reactions between polymers to prepare polymers with sophisticate structures. Ugi reaction has been employed to quantitatively stitch two different polymer chains like traditional click reactions to get copolymers efficiently. Moreover, the multicomponent nature of Ugi reaction makes it possible to facilely incorporate more functions to the product. Through using functional acids (one of Ugi reaction elements), middle functionalized copolymer and miktoarm copolymer which are normally difficult to be prepared through traditional synthetic strategy and normal two-component click reactions have been successfully synthesized, demonstrating the unique charm of this new clickable MCR (**Scheme 2**).



Scheme 2. 'Clickable' features of the Ugi reaction and its application for copolymer synthesis. a) Mid-fluorescent block copolymer. b) Mid-reactive block copolymer and subsequent modification through thiol-ene click reaction. c) Miktoarm star copolymer by the collaboration of Ugi-type polymer conjugation and RAFT polymerization.

It is a great challenge in polymer chemistry to prepare polymers with complex macromolecular architecture since polymer properties can be therefore enriched via covalent linkage of two or more different polymers. In many cases, reaction between different polymer chain-ends is the general choice to prepare block copolymers which possess new functions comparing with the original homopolymers. However, the coupling reaction between polymer chain-ends is normally inefficient due to the intrinsic steric hindrance of polymer chain, resulting in the onerous purification of unreacted polymers to finally get the target copolymers. Click reactions are the solution to this thorny problem because of their high efficiency and almost quantitative yields[35], some copolymers have been successfully prepared through click reactions[36-38]. In the current research, Ugi reaction has been employed for copolymer synthesis, and we are pleased to find that Ugi reaction can also stitch two different polymer chains together almost quantitatively like traditional two-component click reactions under even milder conditions (25 °C, catalyst free, ~ 0.5 h). And middle-functional copolymer has been facilely prepared through this multicomponent click reaction. Compared with end-functional polymers, the middle-functional polymer has some unique features. For example, in the protein PEGylation, the mid-functionalized PEGs were found to mask the protein surface more effectively due to the "umbrella-like effect", providing better encapsulation and leading to longer protein circulation half-life times[39, 40]. Also, steric hindrance of the mid-chain (polymer) functionality may potentially be used to enhance selectivity toward functionality on the protein surface, leading to higher bioactivity conservation[41-43].

A benzaldehyde terminated poly(methyl methacrylate) (PMMA-CHO, M_{nNMR} ~ 8800, M_{nGPC} ~ 24200, PDI: 1.08) through atom transfer radical polymerization (ATRP) and a phenylamine terminated methoxypolyethylene glycol (mPEG-NH_2, M_n ~ 5000, M_{nGPC} ~ 28000, PDI: 1.03) were prepared, respectively, and used as parent polymers. Commercially available cyclohexyl isocyanide was chosen as the isocyanide component and different carboxylic acids were used to add various functions to the achieved block copolymers. Gel permeation chromatography (GPC) and ^{1}H NMR were utilized to monitor the polymer conjugation process.

A fluorescent carboxylic acid was used for Ugi-type polymer conjugation (**Scheme 2a**). In this case, the mPEG-NH_2 and PMMA-CHO were treated with cyclohexyl isocyanide and the fluorescent carboxylic acid (molar ratio: NH_2/CHO/COOH/NC = 1/1/5/10) in methanol/acetonitrile mixture (v/v: 1/1) (**Figure 1a**). The GPC curves of the parent polymers, mPEG-NH_2 and PMMA-CHO, show peaks at 8.11 min and 8.15 min, respectively (**Figure S1**). After 0.5 h, the parent polymers, mPEG-NH_2 and PMMA-CHO, disappeared entirely

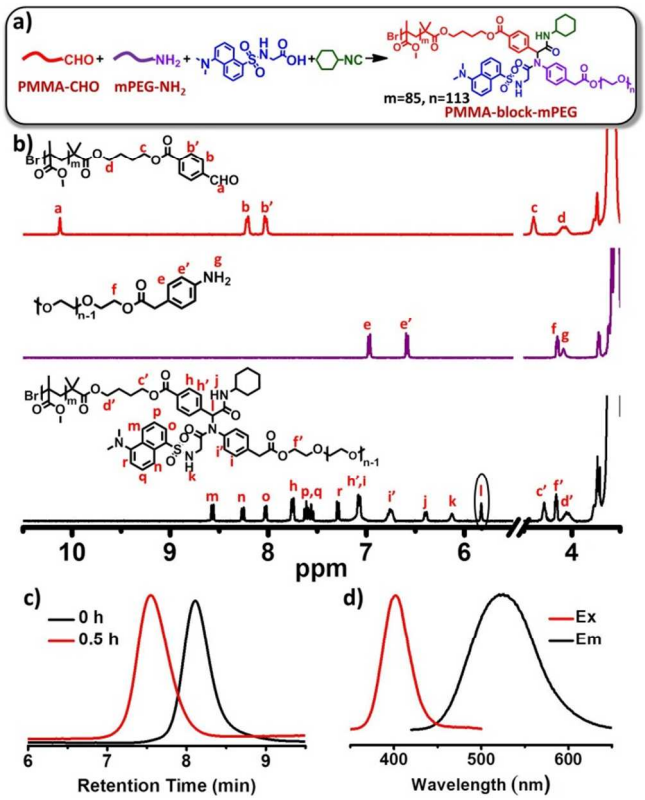


Figure 1. The coupling of two polymers via Ugi reaction to get mid-fluorescent block copolymer. a) Reaction conditions: [mPEG-NH_2]/[PMMA-CHO]/[carboxylic acid]/[isocyanide] = 1/1/5/10, MeOH/CH_3CN (v/v, 1/1) as solvent, 25 °C, 0.5 h. b) ^{1}H NMR spectra

(CD_3CN-d3, 400 MHz, portion) of the parent polymers and the purified daughter copolymer (top to bottom: PMMA-CHO, mPEG-NH_2, PMMA-*b*-mPEG). c) GPC tracing of the Ugi-type conjugation process. d) Fluorescence spectrum of the daughter copolymer.

and a new peak corresponding to the daughter PMMA-*b*-mPEG copolymer appeared at higher molecular weight position with narrow PDI (peak ~ 7.66 min, M_{nGPC} ~ 43800, PDI: 1.08. **Figure 1c**), indicating almost all the parent polymers were locked together to generate the copolymer. ^{1}H NMR results also showed the complete disappearance of characteristic -CHO peak of PMMA-CHO after 0.5 h (**Figure S2**), confirming the almost complete Ugi reaction in such short time. The excess carboxylic acid and isocyanide was easily removed after dialysis (MWCO: 3500 D, DMSO, 24 h), and the ^{1}H NMR spectrum of the purified PMMA-*b*-mPEG copolymer (**Figure 1b**) illustrated the Ugi building blocks (CHO & NH_2) at two parent polymer chain ends disappeared while the characteristic -NCHCO- peak of the Ugi structure (~ 5.83 ppm) can be clearly observed. The integral ratio between -NCHCO- and ester methylene ($I_{5.83}/I_{4.29}$) is 0.50 (theoretical value = 0.5), indicating the complete Ugi reaction between parent polymer chain ends. Meanwhile, the characteristic peaks of the fluorescent moiety in the carboxylic acid can also be clearly observed in the purified copolymer (~ 7.25-8.60 ppm), confirming the successful polymer-polymer coupling via four-component Ugi reaction among mPEG-NH_2, PMMA-CHO, carboxylic acid and isocyanide. Moreover, the copolymer has an excitation wavelength at 400 nm and an emission wavelength at 525 nm (**Figure 1d**), indicating the fluorescent group has been successfully located in the middle of the block copolymer. Control experiment was also carried out between mPEG-NH_2, PMMA-CHO and carboxylic acid, and only partial copolymer (~ 50 %) formed through Schiff's base (the precusor of Ugi reaction) (**Figure S3, S4**), further suggesting the simultaneously present four elements are crucial for the Ugi-type copolymer synthesis.

Mid-reactive (co)polymers are different from the linear counterparts to cover larger area on material/protein surface, leading to better protection[44-46]. However, even through traditional two-component click reaction, it is difficult to synthesize mid-reactive (co)polymers because of the unavoidable laborious organic synthesis to implant other reactive groups. In the current work, mid-reactive block copolymer can also be facilely prepared through the Ugi reaction by using carboxylic acid containing other reactive-group. As a model, a carboxylic acid with vinyl group was used as the carboxylic acid component in the polymer conjugation, and a mid-vinyl PMMA-*b*-mPEG was therefore simply achieved (**Figure 2a**). GPC and ^{1}H NMR were also employed to monitor the process.

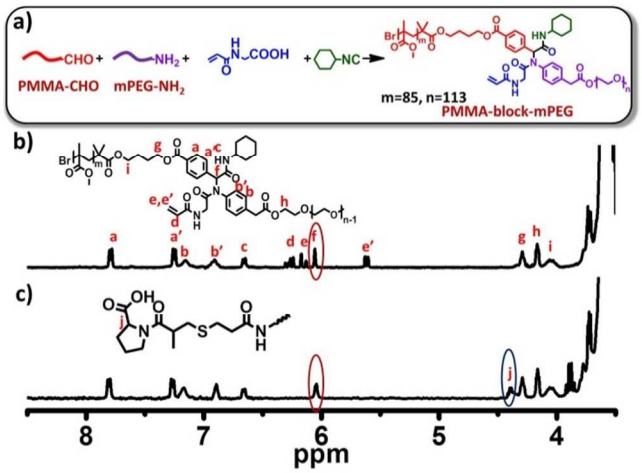


Figure 2. The synthesis of mid-vinyl block copolymer and the subsequent thiol-ene click modification. a) Reaction conditions: [mPEG-NH_2]/[PMMA-CHO]/[carboxylic acid]/[isocyanide] = 1/1/5/10, MeOH/CH_3CN (v/v: 1/1) as solvent, 25 °C, 0.5h. b) ^{1}H NMR spectra (CD_3CN-d3, 400 MHz, portion) of the purified copolymers after Ugi-type polymer conjugation. c) ^{1}H NMR spectra (CD_3CN-d3, 400 MHz, portion) of the purified copolymer-Captopril after thiol-ene click reaction.

As expected, the conjugation process was completed in 0.5 h at 25 °C (**Figure S5**). The excess carboxylic acid and isocyanide were easily removed after dialysis, and the characteristic peaks of the Ugi structure (-NCHCO-, 6.06 ppm) can be clearly observed in the purified block copolymer in ^{1}H NMR spectrum while the vinyl moiety in the carboxylic acid was incorporated in the copolymer structure (**Figure 2b**). The integral ratio between the -NCHCO-, vinyl group and ester methylene ($I_{6.06}/I_{5.62}/I_{4.29}$) is 1/1/2 (theoretical value: 1/1/2), indicating the integrity of vinyl group during Ugi reaction and the complete formation of copolymer. The vinyl group in the middle of copolymer is still reactive for further modification. Captopril, an angiotensin-converting enzyme (ACE) inhibitor used for the treatment of hypertension and some types of congestive heart failure, was chosen as the model of functional small molecules to react with the mid-vinyl copolymer. Captopril and mid-vinyl block copolymer were linked together efficiently through light-catalyzed thiol-ene click reaction to achieve copolymer-Captopril conjugate (UV 365 nm, 25 °C, 4 h). After facile removing the excess Captopril through dialysis, the ^{1}H NMR spectrum of the purified product illustrated the vinyl group completely disappeared while the characteristic -NCHCOOH- peak of Captopril appeared in the purified copolymer (**Figure 2c**, 4.39 ppm). The integral ratio between -NCHCOOH- and the ester methylene ($I_{4.39}/I_{4.29}$) is 0.50 (theoretical value: 0.5), indicating the complete addition of Captopril to the mid-vinyl copolymer. The GPC curves of copolymer-Captopril conjugate and vinyl-copolymer had negligible change, indicating the thiol-ene reaction is inoffensive to the polymer main chain (**Figure S6**).

Miktoarm star polymers are polymers where three or more different polymer arms are linked on the core[47-49]. The special structure of miktoarm star polymers leads to their distinctive aggregation behavior, and the applications of miktoarm star polymers in drug delivery, diagnostic assays, nanopatterned structures, and photonics often result in interesting results[50-52]. Some methods have been tried to synthesize miktoarm star

polymers, mainly through the combination of different polymerization approaches ranging from ring-opening, living radical and anionic polymerization, etc.[48, 53-55]. Herein, we also prepared a miktoarm star polymer easily through the Ugi-type polymer conjugation and the subsequent reversible addition-fragmentation chain transfer (RAFT) polymerization. Carboxylic acid containing trithiocarbonate group, a chain transfer agent (CTA) for RAFT process, was used as the carboxylic acid component in the Ugi-type conjugation (**Figure 3a**),

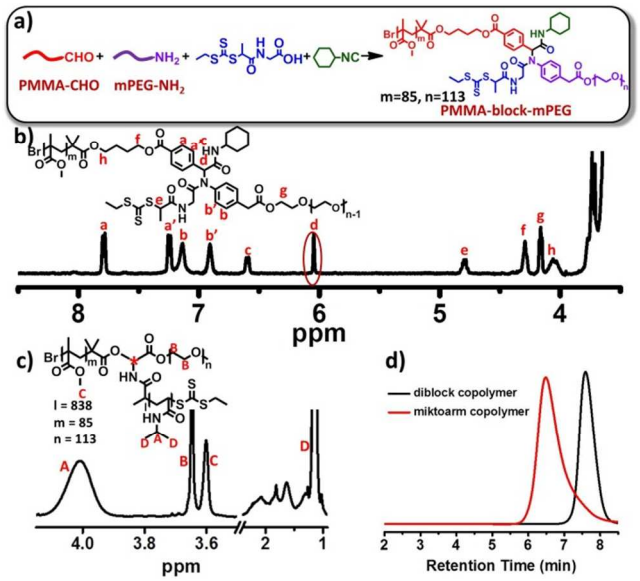


Figure 3. The synthesis of mid-CTA copolymer via Ugi reaction and subsequent RAFT polymerization to get miktoarm star copolymer. a) Reaction conditions: [mPEG-NH_2]/[PMMA-CHO]/[carboxylic acid]/[isocyanide] = 1/1/5/10, MeOH/CH_3CN (v/v: 1/1) as solvent, 25 °C, 0.5 h. b) ^{1}H NMR spectra (CD_3CN-d3, 400 MHz, portion) of the purified mid-CTA copolymer. c) ^{1}H NMR spectra ($CDCl_3$-d, 400 MHz, portion) of the purified miktoarm star copolymers after RAFT polymerization. d) GPC curves of the diblock copolymer (black) and the miktoarm star copolymer (red).

and the conjugation proceeded smoothly in 0.5 h (**Figure S7**), same as previous reactions. The characteristic peaks of the Ugi structure (6.05 ppm) and the CTA group (4.79 ppm) can be clearly observed in the ^{1}H NMR spectrum of the purified block copolymer (**Figure 3b**). The integral ratio ($I_{6.05}/I_{4.79}$) is 1.01 (theoretical value: 1), indicating the integrity of trithiocarbonate moiety during Ugi reaction. N-isopropylacrylamide was then used as the monomer for subsequent RAFT polymerization with the mid-CTA block copolymer as the macromolecular CTA ($[M]_0/[CTA]$: 1500). The polymerization was performed in toluene at 70 °C. When the monomer conversion reached ~ 50% in 1 h, the polymerization was quenched, and the polymer was purified by precipitation in cold ether. The purified polymer has narrow PDI and obviously increased molecular weight (M_{nGPC} ~ 196700, PDI: 1.30) (**Figure 3d**). From the ^{1}H & ^{13}CNMR spectra of the purified polymer, the characteristic peaks of the three polymer arms: PEG, PMMA and PNIPAAm are clearly visible, indicating the successfully synthesis of the miktoarm star copolymer (**Figure 3c, Figure S9**).

Conclusions

Through the highly efficient Ugi reaction under benign condition (catalyst free, room temperature (25 °C), ~ 0.5 h), a series of functional copolymers have been successfully synthesized: 1) mid-fluorescent block copolymer; 2) mid-reactive block copolymer; 3) miktoarm star copolymer. All these results suggest Ugi reaction can not only behave like traditional two-component click reactions to efficiently stitch two different polymers together to quantitatively generate copolymers, but also facilely implant new functions to the products due to its unique multicomponent nature. The Ugi reaction might be considered as a multicomponent green click reaction, and we believe such an elegant green click reaction will play important roles in the area of polymer chemistry. The applications of this new click reaction in other fields such as material science and chemical biology are under our research.

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Notes and references

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Electronic Supplementary Information (ESI) available: Detailed experimental description and GPC curves of series of middle functional copolymers etc. See DOI:10.1039/b000000x/

1. H. C. Kolb, M. Finn and K. B. Sharpless, *Angew. Chem. Int. Ed.*, 2001, **40**, 2004-2021.
2. P. Wu, A. Feldman, A. Nugent, C. Hawker, A. Scheel, B. Voit, J. Pyun, J. Fréchet, K. Sharpless and V. Fokin, *Angew. Chem. Int. Ed*, 2004, **43**, 3928-3932.
3. D. Konkolewicz, A. Gray-Weale and S. b. Perrier, *J. Am. Chem. Soc.*, 2009, **131**, 18075-18077.
4. C. E. Hoyle and C. N. Bowman, *Angew. Chem. Int. Ed.*, 2010, **49**, 1540-1573.
5. B. Gacal, H. Durmaz, M. Tasdelen, G. Hizal, U. Tunca, Y. Yagci and A. Demirel, *Macromolecules*, 2006, **39**, 5330-5336.
6. J. Shin, H. Matsushima, J. W. Chan and C. E. Hoyle, *Macromolecules*, 2009, **42**, 3294-3301.
7. R. K. Iha, K. L. Wooley, A. M. Nystro□m, D. J. Burke, M. J. Kade and C. J. Hawker, *Chem. Rev.*, 2009, **109**, 5620-5686.
8. W. H. Binder and R. Sachsenhofer, *Macromol. Rapid Commun.*, 2008, **29**, 952-981.
9. W. H. Binder and R. Sachsenhofer, *Macromol. Rapid Commun.*, 2007, **28**, 15-54.
10. J. F. Lutz, *Angew. Chem. Int. Ed.*, 2007, **46**, 1018-1025.
11. G. Chen, L. Tao, G. Mantovani, V. Ladmiral, D. P. Burt, J. V. Macpherson and D. M. Haddleton, *Soft Matter*, 2007, **3**, 732-739.
12. C. J. Hawker, V. V. Fokin, M. Finn and K. B. Sharpless, *Aust. J. Chem.*, 2007, **60**, 381-383.
13. Y. Zhang, C. Fu, C. Zhu, S. Wang, L. Tao and Y. Wei, *Polym. Chem.*, 2013, **4**, 466-469.
14. L. M. Campos, K. L. Killops, R. Sakai, J. M. Paulusse, D. Damiron, E. Drockenmuller, B. W. Messmore and C. J. Hawker, *Macromolecules*, 2008, **41**, 7063-7070.
15. N. V. Tsarevsky, B. S. Sumerlin and K. Matyjaszewski, *Macromolecules*, 2005, **38**, 3558-3561.
16. G. Chen, L. Tao, G. Mantovani, J. Geng, D. Nyström and D. M. Haddleton, *Macromolecules*, 2007, **40**, 7513-7520.

17. C. Boyer, M. Whittaker and T. P. Davis, *J. Polym. Sci., Part A: Polym. Chem.*, 2011, **49**, 5245-5256.
18. B. S. Sumerlin, N. V. Tsarevsky, G. Louche, R. Y. Lee and K. Matyjaszewski, *Macromolecules*, 2005, **38**, 7540-7545.
19. G. Gody, C. Rossner, J. Moraes, P. Vana, T. Maschmeyer and S. b. Perrier, *J. Am. Chem. Soc.*, 2012, **134**, 12596-12603.
20. P. De, M. Li, S. R. Gondi and B. S. Sumerlin, *J. Am. Chem. Soc.*, 2008, **130**, 11288-11289.
21. A. Dondoni, *Angew. Chem. Int. Ed.*, 2008, **47**, 8995-8997.
22. R. W. Armstrong, A. P. Combs, P. A. Tempest, S. D. Brown and T. A. Keating, *Acc. Chem. Res.*, 1996, **29**, 123-131.
23. A. Domling, W. Wang and K. Wang, *Chem. Rev.*, 2012, **112**, 3083-3135.
24. C. Zhu, B. Yang, Y. Zhao, C. Fu, L. Tao and Y. Wei, *Polym. Chem.*, 2013, **4**, 5395-5400.
25. I. Ugi, R. Meyr and U. Fetzer, *Angew. Chem*, 1959, **71**, 386.
26. I. Ugi and C. Steinbruckner, *Angew. Chem*, 1960, **72**, 267-268.
27. A. Dömling and I. Ugi, *Angew. Chem. Int. Ed.*, 2000, **39**, 3168-3210.
28. A. Dömling, *Combinatorial Chem. High Throughput Screening*, 1998, **1**, 1-22.
29. L. Weber, *Curr. Med. Chem.*, 2002, **9**, 2085-2093.
30. C. Hulme and V. Gore, *Curr. Med. Chem.*, 2003, **10**, 51-80.
31. L. Wessjohann, M. Henze, O. Kreye and D. Rivera, *WO Patent*, 2011, 134,607.
32. O. Kreye, O. Türünç, A. Sehlinger, J. Rackwitz and M. A. Meier, *Chem. Eur. J.*, 2012, **18**, 5767-5776.
33. O. Kreye, T. Tóth and M. A. Meier, *J. Am. Chem. Soc.*, 2011, **133**, 1790-1792.
34. S. C. Solleder and M. A. Meier, *Angew. Chem. Int. Ed.*, 2014, **53**, 711-714.
35. C. Barner‐Kowollik, F. E. Du Prez, P. Espeel, C. J. Hawker, T. Junkers, H. Schlaad and W. Van Camp, *Angew. Chem. Int. Ed.*, 2011, **50**, 60-62.
36. C. F. Hansell, P. Espeel, M. M. Stamenovic, I. A. Barker, A. P. Dove, F. E. Du Prez and R. K. O'Reilly, *J. Am. Chem. Soc.*, 2011, **133**, 13828-13831.
37. A. J. Inglis, S. Sinnwell, M. H. Stenzel and C. Barner‐Kowollik, *Angew. Chem. Int. Ed.*, 2009, **48**, 2411-2414.
38. J. A. Opsteen and J. C. van Hest, *Chem. Commun.*, 2005, **41**, 57-59.
39. J. M. Harris and R. B. Chess, *Nature Reviews Drug Discovery*, 2003, **2**, 214-221.
40. F. Ercole, N. Malic, S. Harrisson, T. P. Davis and R. A. Evans, *Macromolecules*, 2009, **43**, 249-261.
41. J. Ramon, V. Saez, R. Baez, R. Aldana and E. Hardy, *Pharm. Res.*, 2005, **22**, 1375-1387.
42. F. M. Veronese, *Biomaterials*, 2001, **22**, 405-417.
43. C. J. Fee, *Biotechnol. Bioeng.*, 2007, **98**, 725-731.
44. L. Tao, J. Xu, D. Gell and T. P. Davis, *Macromolecules*, 2010, **43**, 3721-3727.
45. L. Tao, J. Liu and T. P. Davis, *Biomacromolecules*, 2009, **10**, 2847-2851.
46. D. Colak, I. Cianga, A. E. Muftuoglu and Y. Yagci, *J. Polym. Sci., Part A: Polym. Chem.*, 2006, **44**, 727-743.
47. H. Iatrou and N. Hadjichristidis, *Macromolecules*, 1992, **25**, 4649-4651.
48. N. Hadjichristidis, *J. Polym. Sci., Part A: Polym. Chem.*, 1999, **37**, 857-871.
49. N. Hadjichristidis, H. Iatrou, M. Pitsikalis and J. Mays, *Prog. Polym. Sci.*, 2006, **31**, 1068-1132.
50. Z. Li, E. Kesselman, Y. Talmon, M. A. Hillmyer and T. P. Lodge, *Science*, 2004, **306**, 98-101.
51. K. Khanna, S. Varshney and A. Kakkar, *Polym. Chem.*, 2010, **1**, 1171-1185.
52. C. Li, Z. Ge, H. Liu and S. Liu, *J. Polym. Sci., Part A: Polym. Chem.*, 2009, **47**, 4001-4013.
53. M. R. Whittaker, C. N. Urbani and M. J. Monteiro, *J. Am. Chem. Soc.*, 2006, **128**, 11360-11361.
54. H. Gao, N. V. Tsarevsky and K. Matyjaszewski, *Macromolecules*, 2005, **38**, 5995-6004.
55. A. Lv, X.-X. Deng, L. Li, Z.-L. Li, Y.-Z. Wang, F.-S. Du and Z. Li, *Polym. Chem.*, 2013, **4**, 3659-3662.

Table of Contents

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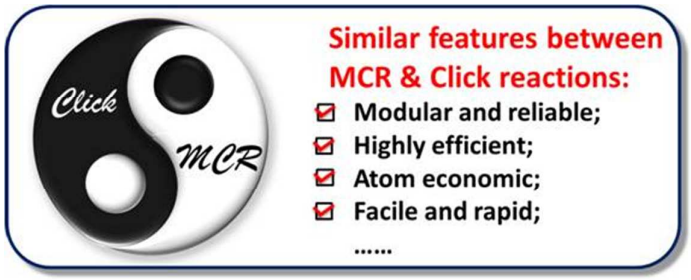

Ugi reaction has been utilized as a new click reaction to facilely synthesize middle-functional copolymers.