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## Modular synthesis of triazoles from 2-azidoacrylamides having a nucleophilic amino group†

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Assembling methods using 2-azidoacrylamides having a nucleophilic amino group are disclosed. Divergent transformations of the amine-type trivalent platform were accomplished with a wide variety of electrophiles to obtain a broad range of 2-azidoacrylamides involving a fluorosulfonyl group-containing trivalent platform. Consecutive click conjugations including triazole formation, thiol-ene-type 1,4-addition, and SuFEx reactions realized the efficient assembly of easily available simple modules.

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### Introduction

Facile methods to assemble simple modules onto platform molecules having a number of functional groups for click chemistry are of great significance for the preparation of multifunctional compounds in broad research fields such as pharmaceutical science and chemical biology.<sup>1–4</sup> Since click reactions have been in the construction of a vast chemical library and in the synthesis of chemical probes bearing reporter groups, various trivalent platform molecules for consecutive click reactions have been developed so far and an efficient consecutive click assembly using compact platforms is awaited (Fig. 1A).<sup>5,6</sup>

We recently succeeded in the synthesis of 2-azidoacrylamides **1** bearing an alkyne or a tertiary azido moiety as compact trivalent platforms (Fig. 1B).<sup>6d</sup> While 1,4-adducts were not obtained when nucleophiles including thiols and amines were treated with 2-azidoacrylamides **1**, 1,4-addition of nucleophiles proceeded efficiently using 2-(1,2,3-triazol-1-yl)acrylamides **2** synthesized from azides **1** by the copper-catalyzed azide-alkyne cycloaddition (CuAAC) reaction with alkynes, clearly showing increased electrophilicity by triazole formation. We herein designed a compact 2-azidoacrylamide platform **5** possessing a sulfonyl fluoride moiety for the sulfur(vi) fluoride exchange (SuFEx) reaction, which is an emerging click

reaction<sup>7,8</sup> (Fig. 1C). To achieve the synthesis of trivalent platform **5**, we conceived a challenging and efficient synthetic route by hydroamination of ethenesulfonyl fluoride (**4**)<sup>9</sup> with biphilic 2-azidoacrylamides **3** having an electrophilic *exo*-methylene moiety and a nucleophilic free-amino group, paying attention to the inferior electrophilicity of 2-azidoacrylamides **1** compared to that of triazole-substituted acrylamides **2**. Since diverse transformations using a free amino group have been established so far, we also expected that amine-type platform **3** can serve as a useful platform to assemble simple modules.

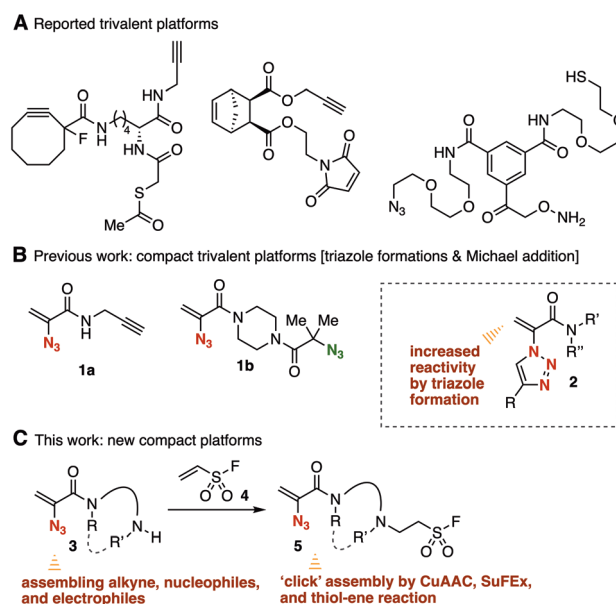


Fig. 1 (A) Trivalent platform molecules. (B) Previous study. (C) This work.

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## Results and discussion

### Synthesis of 2-azidoacrylamides having free amino groups

First, we succeeded in the synthesis of 2-azidoacrylamide **3a** having a free secondary amino group (Fig. 2A). Treatment of 2-acrylamide **6a** with trifluoroacetic acid in dichloromethane efficiently provided amine **3a** after aqueous workup under basic conditions. Although gradual decomposition of amine **3a** was observed at room temperature under argon, we fortunately isolated **3a** with good purity after the aqueous workup without further purification.<sup>10</sup>

A wide range of amines **3b–3e** bearing 2-azidoacrylamide moieties were prepared from 2-azidoacrylic acid (**7**) and amines having *tert*-butoxycarbonyl (Boc) amide moieties in good yields (Fig. 2B). For example, tertiary amide **3b** possessing a primary amino group was synthesized through condensation with 4-(*tert*-butoxycarbonylamino)piperazine using PyBOP<sup>11</sup> followed by the treatment with trifluoroacetic acid in high yield. The synthesis of secondary amides **3c** and **3d** having a primary amino group was achieved. We found that gradual decomposition of primary amine **3d** occurred at room temperature under argon,<sup>12</sup> showing similar stability to secondary amine **3a**. Also, acrylanilide **3e** was synthesized *via* the condensation between 2-azidoacrylic acid (**7**) and 4-(*tert*-butoxycarbonylamino)aniline in moderate yield.

### Transformations of 2-azidoacrylamides having free amino groups

Transformations of amine **3a** with various electrophiles enabled us to synthesize a broad range of 2-azidoacrylamides

**9a–9i** in moderate to good yields (Fig. 3). We accomplished the acetylation of amine **3a** with acetic anhydride to provide amide **9a** in good yield. Synthesis of amide **9b** was achieved by the condensation between amine **3a** and carboxylic acid **8b** using PyBOP without damaging the 2-azidoacrylic amide moiety. Carbamate **9c** was successfully prepared from amine **3a** and isocyanate **8c** under basic conditions. We also succeeded in the guanidination of amine **3a** with 1-amidinopyrazole hydrochloride (**8d**) yielding guanidine **9d** quantitatively. Sulfonamide **9e** was also prepared from amine **3a** using sulfonyl chloride **8e**. Triazination of amine **3a** with cyanuric chloride (**8f**) proceeded smoothly to provide triazine **9f** in moderate yield. Also, we synthesized amine **9g** by the reductive amination of amine **3a** with aldehyde **8g** using sodium triacetoxyborohydride as a reductant leaving the electrophilic 2-azidoacrylic amide moiety untouched. Arylation of amine **3a** with benzyne generated *in situ* from *o*-silylphenyl triflate **8h** keeping

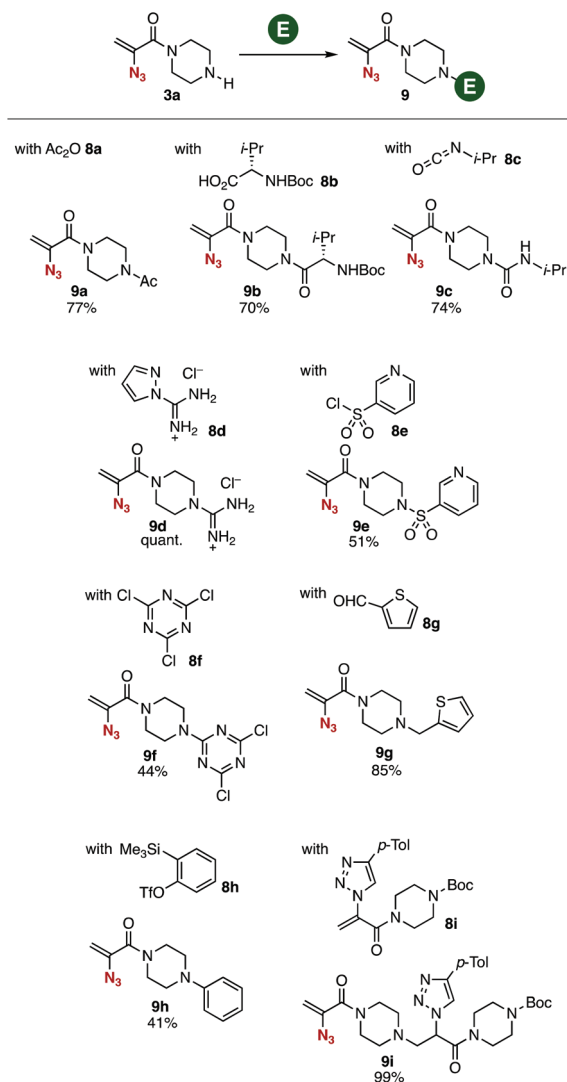


Fig. 3 Synthesis of various 2-azidoacrylamides **9**. See the ESI† for details.

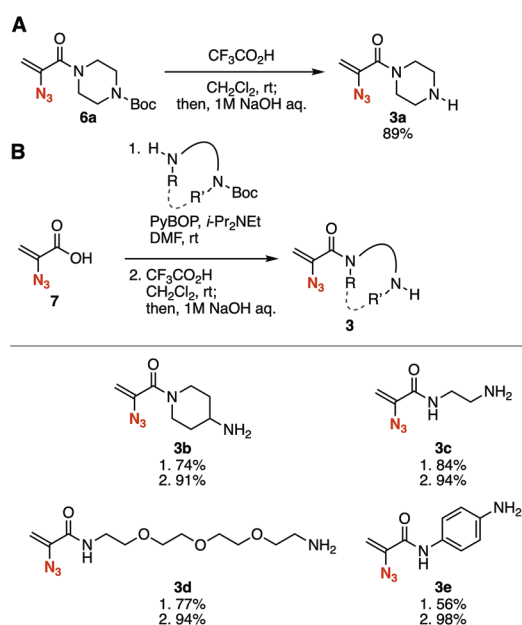


Fig. 2 Synthesis of amines **3**. (A) Deprotection of the Boc moiety of **6a**. (B) Synthesis of various amines **3** from 2-azidoacrylic acid (**7**). PyBOP = (benzotriazol-1-yloxy)(trispyrrolidino)phosphonium hexafluorophosphate. See the ESI† for details.



the azido group unreacted, although azides generally react with benzyne to afford benzotriazoles.<sup>13</sup> Furthermore, we realized the 1,4-addition of amine **3a** with 2-(triazolyl)acrylamide **8i**, which was prepared from 1-(2-azidoacryl)-4-(*tert*-butoxycarbonyl)piperazine (**6a**) and 4-tolylacetylene by the CuAAC reaction<sup>14</sup> in our previous study.<sup>6d</sup> This result clearly showed that a wide variety of 2-azidoacrylamides can be prepared by sequential transformations using 2-azidoacrylamide-type platforms and alkynes in a modular synthetic manner.

Subsequent transformations of 2-azidoacrylamides **9** led to the efficient assembly of simple modules (Fig. 4). The CuAAC reaction of azide **9g** with alkyne **10a** efficiently took place affording 1,2,3-triazole **11** in a quantitative yield. We then achieved the synthesis of amine **13** by the 1,4-addition of 2-(triazolyl)acrylamide **11** with *n*-butylamine (**12**) in high yield. These results indicated that diverse 2-(triazolyl)acrylamides can be synthesized from 2-azidoacrylamide **3a**, electrophiles, alkynes, and nucleophiles in three steps.

### Synthesis of 2-azidoacrylamides having sulfonyl fluoride moieties

The conjugate addition of amines with ethenesulfonyl fluoride (**4**) realized the preparation of novel trivalent platforms having an azido, an alkene, and a sulfonyl fluoride group (Fig. 5). Treatment of amine **3a** with **4** in the presence of triethylamine provided trivalent platform **5a** in an excellent yield leaving three clickable functional groups intact (Fig. 5A). We also accomplished the synthesis of dialkylated amine **5b** from primary amine **3d** with **4** in moderate yield (Fig. 5B). These

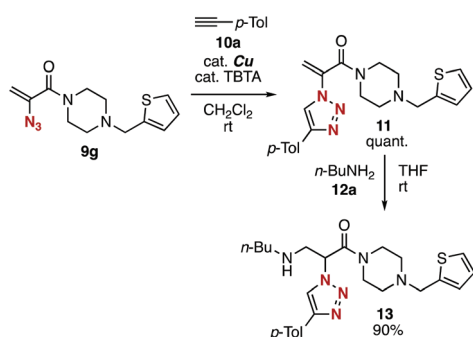


Fig. 4 Synthesis of 2-(triazolyl)amide **13**. TBTA = tris((1-benzyl-4-triazolyl)methyl)amine. See the ESI† for details.

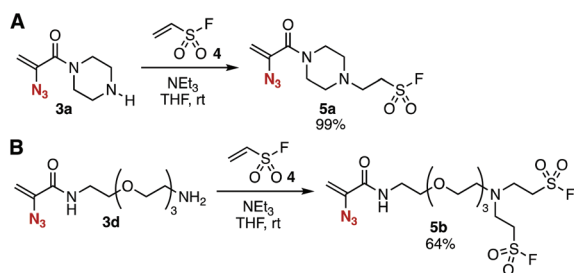


Fig. 5 Synthesis of sulfonyl fluorides **5**. (A) Synthesis of **5a**. (B) Synthesis of **5b**.

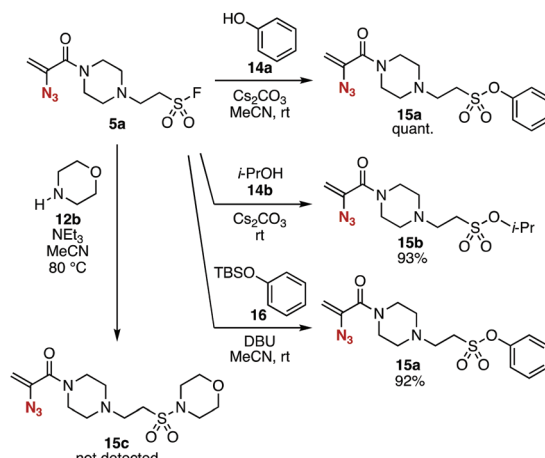


Fig. 6 SuFEx reactions of **5a**. See the ESI† for details.

results suggested that amine-type trivalent platforms will help in the synthesis of a wide variety of clickable platform molecules with electrophiles bearing functional groups for the click chemistry despite the poor stability of amines **3**.

We succeeded in the synthesis of various 2-azidoacrylamides by the SuFEx reactions of sulfonyl fluoride **5a** (Fig. 6).<sup>7,8</sup> For example, sulfonyl fluoride **5a** efficiently reacted with phenol (**14a**) under basic conditions to furnish phenyl sulfonate **15a** quantitatively without reacting with the 2-azidoacrylamide moiety. Treatment of sulfonyl fluoride **5a** with cesium carbonate in 2-propanol (**14b**) afforded isopropyl sulfonate **15b** in high yield. We also achieved the synthesis of phenyl sulfonate **15a** by the reaction of silyl ether **16** in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) keeping the electrophilic 2-azidoacrylamide moiety unreacted. Unfortunately, synthesizing sulfonyl amide **15c** from sulfonyl fluoride **5a** and amine **12b** resulted in failure probably due to undesired side reactions such as 1,4-addition.

### Sequential conjugation using trivalent platform **5a**

Sequential conjugation of trivalent platform **5a** was achieved with alkyne **10a** and amine **12a** to provide 3-amino-2-triazolyl amide **18** having the sulfonyl fluoride moiety (Fig. 7). Indeed,

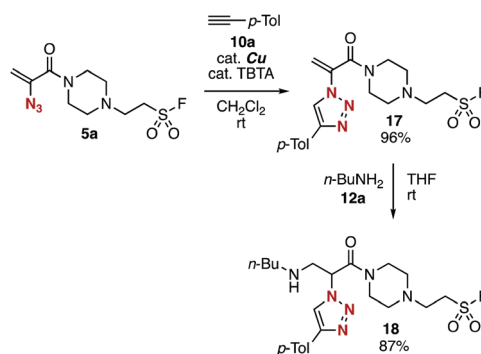


Fig. 7 Modular synthesis of **18**.



triazole formation of azide **5a** with alkyne **10a** catalyzed by tetrakis(acetonitrile)copper and TBTA occurred smoothly to yield **17** in an excellent yield. Then, we successfully prepared amine **18** by efficient conjugate addition using *n*-butylamine (**12a**) at room temperature without damaging the amine-susceptible fluorosulfonyl group. These results clearly showed that the 2-azidoacrylamide moiety can react with alkynes and nucleophiles prior to the SuFEx reaction.

The successful synthesis of 2-triazolylamide **21** by three component assembly indicated the good diversifiable reactivity of trivalent platform **5a** (Fig. 8). The CuAAC reaction of phenyl sulfonate **15a** followed by the thiol-ene reaction<sup>15</sup> with **20** promoted by a base took place efficiently to provide 2-triazolylamide **21** in high yield (Fig. 8A). Moreover, the three component assembly onto platform **5a** with phenol (**14a**), alkyne **10a**, and

thiol **20** was achieved by the consecutive click reactions in a one-pot fashion (Fig. 8B).

### Synthesis of bis(triazole) **24**

To showcase the divergent potential of platforms **3** and **5**, we then examined a synthesis of diamide **24** from simple modules (Fig. 9). First, the treatment of amine-type platform **3a** with 2-(triazolyl)acrylamide **19** synthesized from trivalent platform **5a**, silyl ether **16**, and alkyne **10a** provided diamide **22** in good yield. Second, CuAAC reaction of diamide **22** proceeded smoothly without damaging amino, triazolyl, and phenoxysulfonyl groups. Third, amine **24** was synthesized efficiently as a mixture of diastereomers by the conjugate addition of *n*-butylamine (**12a**) with 2-(triazolyl)acrylamide **23**. The good reactivity of 2-(triazolyl)acrylamide **23** as a Michael acceptor will allow us to repeat the conjugation using amine-type platforms **3** to synthesize multi(triazole)s in an iterative manner. Diamide **24** was prepared from trivalent platforms **3a** and **5a**, alkynes **10a** and **10b**, amine **12a**, and silyl ether **16** in 5 steps. Since alkynes, phenols, silyl ethers, and nucleophiles for 1,4-addition are easily available, the efficient modular synthetic method will be used for synthesizing diverse multi(triazole)s in an iterative manner from simple modules.

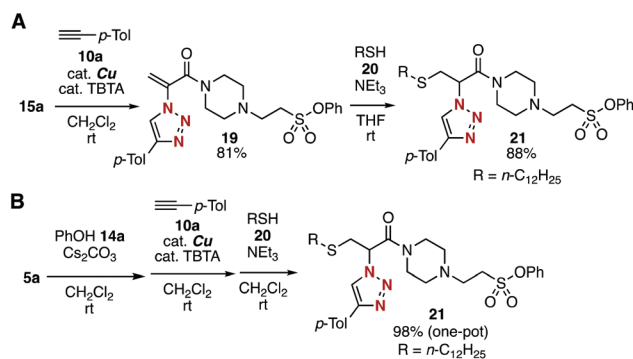


Fig. 8 Modular synthesis of **21**. (A) Synthesis of **21** via isolated intermediates. (B) One-pot synthesis of **21** from **5a**.

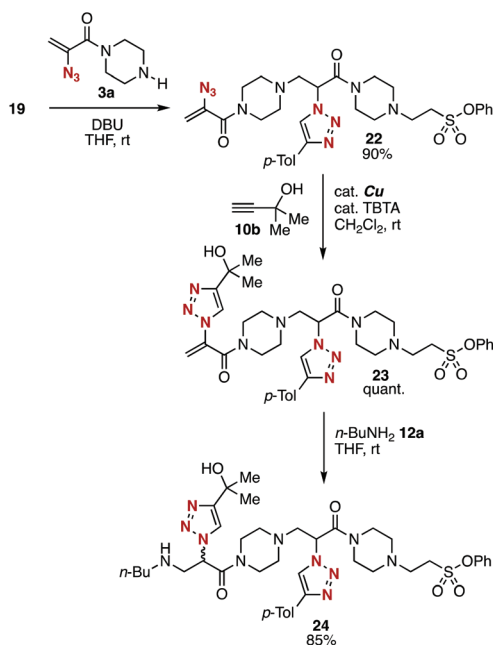


Fig. 9 Modular synthesis of multi(triazole) **24**.

## Conclusions

In summary, we synthesized novel trivalent platforms **5** having azido, alkene, and fluorosulfonyl groups through 2-azidoacrylamides having a free amino group. A wide variety of triazoles were synthesized from trivalent platforms **5** and simple modules by click reactions. Since diverse multi(triazole)s can be prepared in a modular synthetic manner, the combinatorial chemistry using trivalent platforms will be used in constructing a vast chemical library of mid-sized multi(triazole)s. Further studies on the transformations of trivalent platforms **3** and **5** involving the scope and limitations are ongoing in our laboratory.

## Conflicts of interest

There are no conflicts to declare.

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## Notes and references

- J. Lahann, *Click Chemistry for Biotechnology and Materials Science*, John Wiley & Sons, West Sussex, 2009.
- For reviews of sequential click reactions, see: (a) A.-C. Knall and C. Slugovc, *Chem. Soc. Rev.*, 2013, **42**, 5131; (b) Z.-J. Zheng, D. Wang, Z. Xu and L.-W. Xu, *Beilstein J. Org. Chem.*, 2015, **11**, 2557; (c) S. Yoshida, *Org. Biomol. Chem.*, 2020, **18**, 1550; (d) D. Sato, Z. Wu, H. Fujita, J. S. Lindsey, D. Sato, Z. Wu, H. Fujita and J. S. Lindsey, *Organics*, 2021, **2**, 161.
- For recent examples of sequential click reactions, see: (a) I. E. Valverde, A. F. Delmas and V. Aucagne, *Tetrahedron*, 2009, **65**, 7597; (b) B. C. Sanders, F. Friscourt, P. A. Ledin, N. E. Mbuu, S. Arumugam, J. Guo, T. J. Boltje, V. V. Popik and G.-J. Boons, *J. Am. Chem. Soc.*, 2011, **133**, 949; (c) J. Dommerholt, O. van Rooijen, A. Borrmann, C. F. Guerra, F. M. Bickelhaupt and F. L. van Delft, *Nat. Commun.*, 2014, **5**, 5378; (d) P. R. Werkhoven, H. van de Langemheen, S. van der Wal, J. A. W. Kruijtzter and R. M. J. Liskamp, *J. Pept. Sci.*, 2014, **20**, 235; (e) M. Robert, J. Vallée, P. Majkut, D. Krause, M. Gerrits and C. P. R. Hackenberger, *Chem. – Eur. J.*, 2015, **21**, 970; (f) R. R. Ramsubhag and G. B. Dudley, *Org. Biomol. Chem.*, 2016, **14**, 5028; (g) D. A. Sutton, S.-H. Yu, R. Steet and V. V. Popik, *Chem. Commun.*, 2016, **52**, 553; (h) N. Münster, P. Nikodemiak and U. Koert, *Org. Lett.*, 2016, **18**, 4296; (i) D. Svatunek, N. Houszka, T. A. Hamlin, F. M. Bickelhaupt and H. Mikula, *Chem. – Eur. J.*, 2019, **25**, 754.
- For our recent studies on click chemistry, see: (a) S. Yoshida, T. Kuribara, H. Ito, T. Meguro, Y. Nishiyama, F. Karaki, Y. Hatakeyama, Y. Koike, I. Kii and T. Hosoya, *Chem. Commun.*, 2019, **55**, 3556; (b) K. Adachi, T. Meguro, Y. Sakata, K. Igawa, K. Tomooka, T. Hosoya and S. Yoshida, *Chem. Commun.*, 2020, **56**, 9823; (c) N. Makio, T. Kuribara, K. Adachi, Y. Hatakeyama, T. Meguro, Y. Sakata, K. Igawa, K. Tomooka, T. Hosoya and S. Yoshida, *Chem. Commun.*, 2020, **56**, 11449; and references therein.
- For recent examples of sequential click reactions using trivalent platforms, see: (a) V. Vaněk, J. Pícha, B. Fabre, M. Buděšínský, M. Lepšík and J. Jiráček, *Eur. J. Org. Chem.*, 2015, 3689; (b) B. Fabre, J. Pícha, V. Vaněk, M. Buděšínský and J. Jiráček, *Molecules*, 2015, **20**, 19310; (c) B. Fabre, J. Pícha, V. Vaněk, I. Selicharová, M. Chrudinová, M. Collinsová, L. Žáková, M. Buděšínský and J. Jiráček, *ACS Comb. Sci.*, 2016, **18**, 710; (d) A.-C. Knall, M. Hollauf, R. Saf and C. Slugovc, *Org. Biomol. Chem.*, 2016, **14**, 10576; (e) T. Yokoi, H. Tanimoto, T. Ueda, T. Morimoto and K. Kakiuchi, *J. Org. Chem.*, 2018, **83**, 12103; (f) T. Yokoi, T. Ueda, H. Tanimoto, T. Morimoto and K. Kakiuchi, *Chem. Commun.*, 2019, **55**, 1891; (g) K. Maegawa, H. Tanimoto, S. Onishi, T. Tomohiro, T. Morimoto and K. Kakiuchi, *Org. Chem. Front.*, 2021, **8**, 5793.
- For our recent studies on sequential click reactions using tri- or tetravalent platforms, see: (a) T. Meguro, Y. Sakata, T. Morita, T. Hosoya and S. Yoshida, *Chem. Commun.*, 2020, **56**, 4720; (b) N. Terashima, Y. Sakata, T. Meguro, T. Hosoya and S. Yoshida, *Chem. Commun.*, 2020, **56**, 14003; (c) H. Takemura, S. Goto, T. Hosoya and S. Yoshida, *Chem. Commun.*, 2020, **56**, 15541; (d) S. Yoshida, Y. Sakata, Y. Misawa, T. Morita, T. Kuribara, H. Ito, Y. Koike, I. Kii and T. Hosoya, *Chem. Commun.*, 2021, **57**, 899; and references therein.
- For reviews of the SuFEx chemistry, see: (a) J. Dong, L. Krasnova, M. G. Finn and K. B. Sharpless, *Angew. Chem., Int. Ed.*, 2014, **53**, 9430; (b) A. S. Barrow, C. J. Smedley, Q. Zheng, S. Li, J. Dong and J. E. Moses, *Chem. Soc. Rev.*, 2019, **48**, 4731; (c) Y.-P. Meng, S.-M. Wang, W.-Y. Fang, Z.-Z. Xie, J. Leng, H. Alsulami and H.-L. Qin, *Synthesis*, 2020, 673.
- For recent examples of the SuFEx chemistry, see: (a) R. Zelli, S. Tommasone, P. Dumy, A. Marra and A. Dondoni, *Eur. J. Org. Chem.*, 2016, 5102; (b) Q. Chen, P. Mayer and H. Mayr, *Angew. Chem., Int. Ed.*, 2016, **55**, 12664; (c) H.-L. Qin, Q. Zheng, G. A. L. Bare, P. Wu and K. B. Sharpless, *Angew. Chem., Int. Ed.*, 2016, **55**, 14155; (d) Q. Zheng, J. Dong and K. B. Sharpless, *J. Org. Chem.*, 2016, **81**, 11360; (e) X. Chen, G.-F. Zha, G. A. L. Bare, J. Leng, S.-M. Wang and H.-L. Qin, *Adv. Synth. Catal.*, 2017, **359**, 3254; (f) H. Wang, F. Zhou, G. Ren, Q. Zheng, H. Chen, B. Gao, L. Klivansky, Y. Liu, B. Wu, Q. Xu, J. Lu, K. B. Sharpless and P. Wu, *Angew. Chem., Int. Ed.*, 2017, **56**, 11203; (g) J. Leng and H.-L. Qin, *Chem. Commun.*, 2018, **54**, 4477; (h) C. J. Smedley, M.-C. Giel, A. Molino, A. S. Barrow, D. J. D. Wilson and J. E. Moses, *Chem. Commun.*, 2018, **54**, 6020; (i) D. Gahtory, R. Sen, S. Pujari, S. Li, Q. Zheng, J. E. Moses, K. B. Sharpless and H. Zuilhof, *Chem. – Eur. J.*, 2018, **24**, 10550; (j) J. Thomas and V. V. Fokin, *Org. Lett.*, 2018, **20**, 3749; (k) X. Zhang, B. Moku, J. Leng, K. P. Rakesh and H.-L. Qin, *Eur. J. Org. Chem.*, 2019, 1763; (l) C. Li, Y. Zheng, K. P. Rakesh and H.-L. Qin, *Chem. Commun.*, 2020, **56**, 8075; (m) M.-C. Giel, C. J. Smedley, E. R. R. Mackie, T. Guo, J. Dong, T. P. Soares da Costa and J. E. Moses, *Angew. Chem., Int. Ed.*, 2020, **59**, 1181; (n) S. Li, G. Li, B. Gao, S. P. Pujari, X. Chen, H. Kim, F. Zhou, L. M. Klivansky, Y. Liu, H. Driss, D.-D. Liang, J. Lu, P. Wu, H. Zuilhof, J. Moses and K. B. Sharpless, *Nat. Chem.*, 2021, **13**, 858.
- (a) B. M. Gladshtein, E. I. Polyanskaya and L. Z. Soborovskii, *Zh. Obshch. Khim.*, 1961, **31**, 855; (b) J. A. Hyatt and J. J. Krutak, *J. Org. Chem.*, 1977, **42**, 169.
- When **3a** was placed at room temperature under argon for 3 days, we observed that 65% of **3a** was decomposed.
- J. Coste, D. Le-Nguyen and B. Castro, *Tetrahedron Lett.*, 1990, **31**, 205.
- When **3d** was placed at room temperature under argon for 3 days, we observed that 66% of **3d** was decomposed.
- F. Shi, J. P. Waldo, Y. Chen and R. C. Larock, *Org. Lett.*, 2008, **10**, 2409.
- (a) C. W. Tornøe, C. Christensen and M. Meldal, *J. Org. Chem.*, 2002, **67**, 3057; (b) V. V. Rostovtsev, L. G. Green, V. V. Fokin and K. B. Sharpless, *Angew. Chem., Int. Ed.*, 2002, **41**, 2596; (c) T. R. Chan, R. Hilgraf, K. B. Sharpless and V. V. Fokin, *Org. Lett.*, 2004, **6**, 2853.
- A. B. Lowe, *Polym. Chem.*, 2014, **5**, 4820.

