


 Cite this: *Chem. Commun.*, 2025, 61, 2333

 Received 16th December 2024,  
Accepted 7th January 2025

DOI: 10.1039/d4cc06585a

rsc.li/chemcomm

## Three-step click assembly using trivalent platforms bearing azido, ethynyl, and fluorosulfonyl groups†

 Takahiro Yasuda, Gaku Orimoto and Suguru Yoshida \*

**Divergent synthesis of triazoles was achieved using newly designed platform molecules possessing azide, alkyne, and fluorosulfonyl moieties. Consecutive conjugations by the sulfur(vi) fluoride exchange and following consecutive triazole formations allowed us to prepare a wide variety of bis(triazole)s by virtue of selective transformations. One-pot triple-click assembly of easily accessible modules led to the facile synthesis of middle-molecular-weight triazoles with various functional moieties.**

Triple click assembly using trivalent platforms has gained attention from a wide range of research fields including pharmaceutical sciences, peptide chemistry, and chemical biology (Fig. 1A).<sup>1–4</sup> Although a variety of trivalent platforms have been developed so far, it is not easy to realize efficient click assembly using platforms bearing azide and alkyne moieties due to the challenging selective triazole formation without deprotection steps (Fig. 1B and C).<sup>3</sup> Divergent synthesis of highly functionalized molecules using platforms bearing azide and alkyne moieties is awaited. We herein describe new trivalent platforms with azide, alkyne, and fluorosulfonyl moieties, allowing us to accomplish efficient triple-click assembly (Fig. 1D).

During our studies in click chemistry,<sup>4</sup> we planned to develop new trivalent platforms **4** for triple click assembly involving sequential triazole formations (Fig. 2). Considering recent great achievements in triazole formations in terms of efficiency and selectivity,<sup>5</sup> a wide variety of bis(triazole)s are expected to be prepared by sequential triazole formations and the sulfur–fluoride exchange (SuFEx) reaction<sup>6</sup> using new platforms **4** possessing azide, alkyne, and fluorosulfonyl moieties. Thus, we started synthesizing new trivalent platforms **4a–4c** from azides bearing *N*-Boc amino groups. Synthesis of trivalent platform **4a** was achieved from azide **1a** through *N*-propargylation with **2**,

deprotection of the Boc group, and 1,4-addition to ethenesulfonyl fluoride (**3**) (Fig. 2A). However, gradual decomposition of trivalent platform **4a** was observed after the purification with silica gel probably due to the side reactions involving intramolecular triazole formation.<sup>7</sup> In contrast, trivalent platforms **4b** and **4c** with long linkers were significantly stable under ambient conditions (Fig. 2B). The synthesis of **4b** was accomplished from azide **1b** by *N*-propargylation, deprotection, and the introduction of 2-(fluorosulfonyl)ethyl group. We also accomplished the preparation of **4c** from **4b** via the reduction of the azido group, condensation with **6**, deprotection, and 1,4-addition. Since trivalent platforms **4b** and **4c** show good stability at room temperature, we found that long linkers prevent decomposition through the intramolecular reaction between the azide and alkyne moiety.

Then, the SuFEx reaction of trivalent platform **4b** enabled us to conjugate a range of functionalized alcohols (Fig. 3A).<sup>6</sup> For example, treatment of **4b** with phenol (**7a**) in the presence of cesium carbonate in acetonitrile afforded phenyl sulfonate **8a** in good yield, in which azide and alkyne moieties were tolerated under the basic conditions. We also succeeded in the synthesis of **8b** and **8c** in high yields without damaging hydroxy, amino, and methoxycarbonyl groups. Moreover, perfluoroalkyl ester **8d** was prepared efficiently by the SuFEx reaction with *n*-C<sub>5</sub>F<sub>11</sub>CH<sub>2</sub>OH, where side products were not observed through the substitution of the alkyl sulfonate moiety.

The versatility in the second step was demonstrated by diverse transformations of azide **8a** (Fig. 3B). The copper-catalyzed azide–alkyne cycloaddition (CuAAC) with 1-ethynyl-1*H*-benzimidazole (**9a**) proceeded smoothly to furnish triazole **10a** in good yield leaving the alkyne moiety intact.<sup>8</sup> Selective triazole formation was realized due to the higher reactivity of ynamide **9a** than that of the ethynyl group of **4b** under the CuAAC conditions. Triazole **10b** was efficiently synthesized from azide **8a** and alkynyl sulfide **9b** by the iridium-catalyzed conditions, in which the regioisomer was not detected.<sup>9</sup> Triazole formation of azide **8a** with dimethyl acetylenedicarboxylate (**9c**) also occurred at room temperature.<sup>10</sup> Cycloalkyne **9d** rapidly reacted with azide **8a** to furnish triazole **10d** in an

Department of Biological Science and Technology, Faculty of Advanced Engineering, Tokyo University of Science, 6-3-1 Niijuku, Katsushika-ku Tokyo 125-8585, Japan.

E-mail: s-yoshida@rs.tus.ac.jp

† Electronic supplementary information (ESI) available: Experimental procedures, characterization for new compounds including NMR spectra. See DOI: <https://doi.org/10.1039/d4cc06585a>



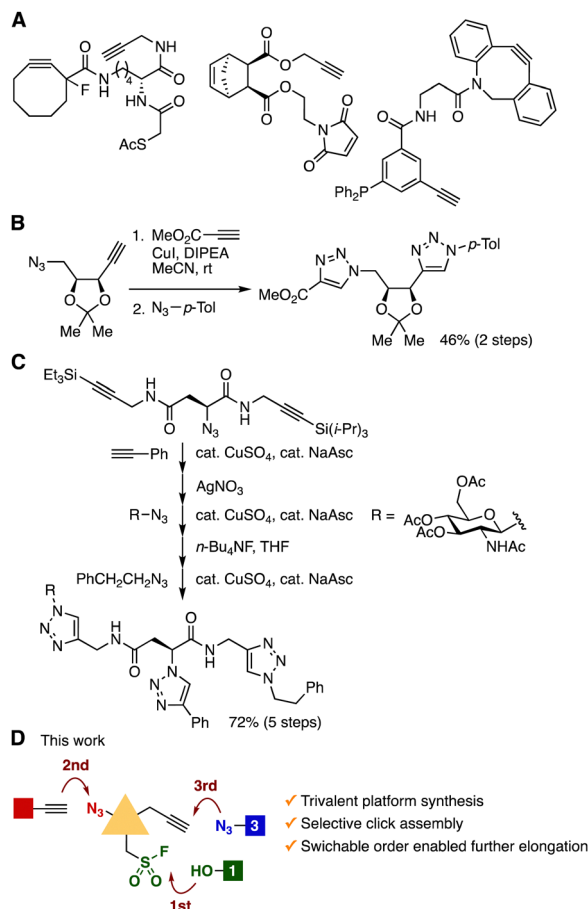


Fig. 1 (A) Examples of trivalent platforms. (B) Bis(triazole) synthesis by Kalippan. (C) Tris(triazole) synthesis by Aucagne. (D) This work.

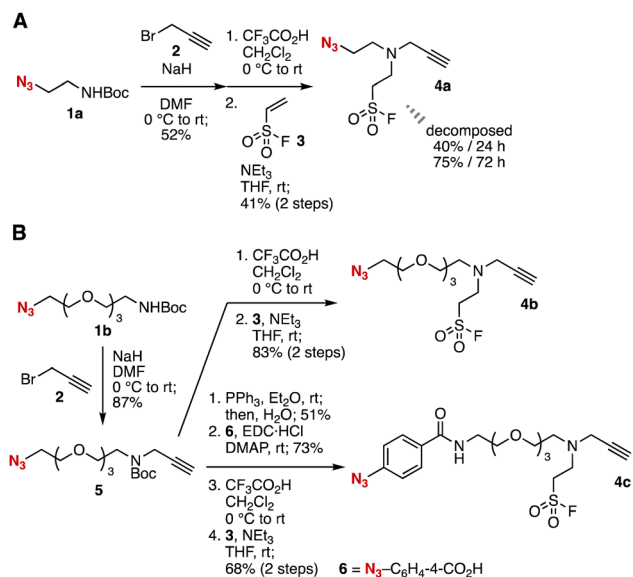


Fig. 2 (A) Synthesis of **4a**. (B) Synthesis of **4b** and **4c**.

excellent yield through the strain-promoted azide-alkyne cycloaddition (SPAAC).<sup>11,12</sup> Furthermore, the Bertozzi-Staudinger ligation of azide **8a** using phosphine **11a** allowed us to

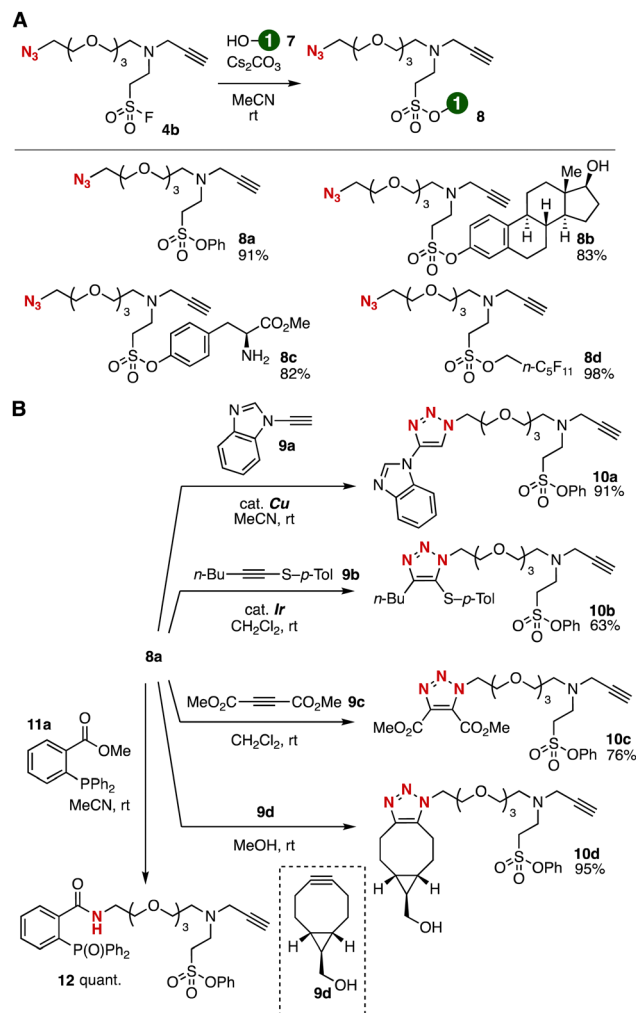


Fig. 3 (A) SuFEx reaction of **4b**. (B) Transformations of azide **8a**. (C) Transformations of alkyne **10a**. See the ESI,† for details.

prepare amide **12** quantitatively.<sup>13</sup> Since various selective transformations of azide **8a** resulted in the synthesis of **10a–10d** and **12** without damaging the alkyne moiety, a wide variety of modules will participate in the click conjugation.



A broad range of third transformations enabled us to synthesize diverse triazoles from alkyne **10a** (Fig. 3C). Indeed, CuAAC reaction of alkyne **10a** efficiently proceeded with azide **13a** to provide bis(triazole) **14a** in good yield without damaging amine, triazolylimidazole, and sulfonyl ester moieties.<sup>5</sup> We also synthesized amidine **15** from alkyne **10a** with tosyl azide (**13b**) catalyzed by copper iodide.<sup>14</sup> Moreover, alkyne **10a** efficiently reacted with tetrazine **16** in toluene at 110 °C to afford pyridazines **17** and **17'** in moderate selectivity.<sup>15</sup> In contrast, the pyridazine formation did not proceed when conducting the reaction in HFIP at 40 °C according to our previous study. We also achieved the preparation of arylalkyne **19** by the Sonogashira coupling of alkyne **10a** and aryl iodide **18**. Thus, a wide range of modules can be assembled onto trivalent platform **4b** by the SuFEx reaction followed by various transformations such as sequential CuAAC reactions. It is worth noting that consecutive triazole formations were accomplished selectively at the azide and alkyne moieties of trivalent platforms **4**, allowing us to construct a vast chemical library from simple modules.

The triple-click assemblies using trivalent platforms **4b** and **4c** were achieved in a one-pot manner (Fig. 4). For instance, the SuFEx reaction with phenol (**7a**), SPAAC reaction with cycloalkyne **9d**, and CuAAC reaction with benzyl azide (**13a**) occurred in one-pot when using acetonitrile as a solvent (Fig. 4A). Selective transformations of not only alkyl azide **4b** but also aromatic azide **4c**<sup>16</sup> were realized in a one-pot fashion through the SuFEx and twice triazole formations, where tris(triazole)-type ligand THPTA<sup>17</sup> was added in the second triazole formation (Fig. 4B). Thus, the one-pot assembly of functional modules **7**, **9**, and **13** onto trivalent platforms **4** enabled us to prepare highly functionalized bis(triazoles). In particular, HaloTag ligand, fluorescent dansyl, and biotin moieties were uneventfully conjugated onto platform **4b** in a one-pot manner without damaging various functional groups (Fig. 5).

The assembly order using trivalent platform **4b** was switchable (Fig. 6A). First, the CuAAC reaction with picolyl azide **13d** took place selectively at the alkyne moiety leaving azide and sulfonyl fluoride moieties untouched.<sup>18</sup> Second, the remaining azido group of **21** efficiently reacted with alkyne **9e** in the presence of a catalytic amount of copper complex and THPTA

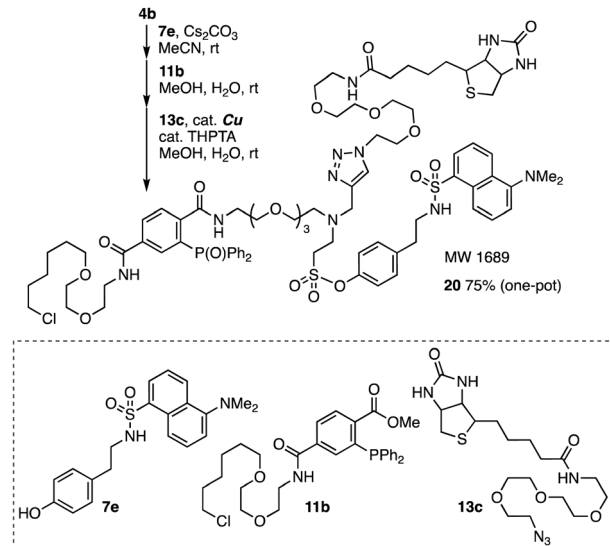


Fig. 5 One-pot assembly of **7e**, **11b**, and **13c**.

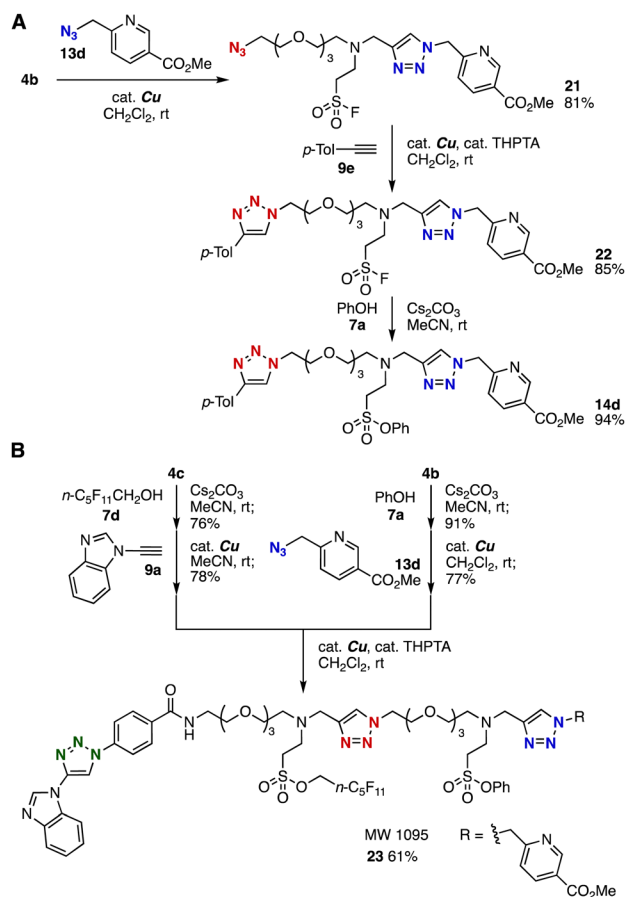


Fig. 6 (A) Synthesis of **14d**. (B) Synthesis of tris(triazole) **23**. See the ESI,<sup>†</sup> for details.

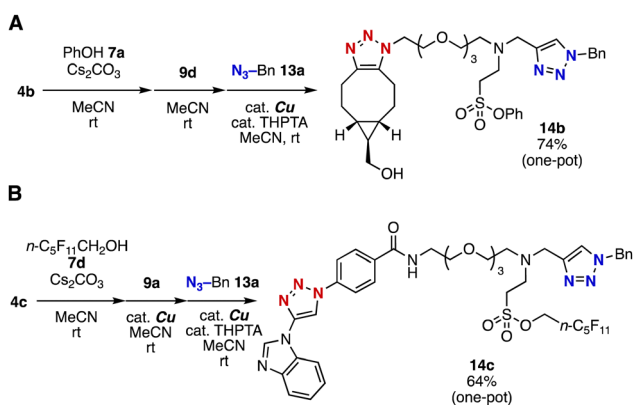


Fig. 4 (A) One-pot synthesis of **14b**. (B) One-pot synthesis of **14c**.

without damaging the fluorosulfonyl group. Due to the good functional group tolerance, a wide variety of sulfonyl fluorides would be accessible by the sequential triazole formations.<sup>4b,4c,19</sup> Third, we succeeded in the SuFEx reaction of the resulting



sulfonyl fluoride **22** to furnish bis(triazole) **14d** in an excellent yield.

The significant modular synthesis of tris(triazole) **23** was achieved using trivalent platforms **4b** and **4c** with **7a**, **7d**, **9a**, and **13d** (Fig. 6B). Indeed, the SuFEx reaction of **4c** with alcohol **7d** followed by selective CuAAC reaction with 1-ethynyl-1*H*-benzimidazole (**9a**) occurred with the remaining azido group. The resulting alkyne efficiently reacted with an azide prepared by the selective CuAAC reaction of **8a** and azide **13d**, to provide middle-molecular-weight tris(triazole) **23**. Thus, the switchable order of trivalent platforms enabled the click assembly of six modules, serving in the synthesis of highly functionalized molecules by sequential click reactions.

In summary, we have developed divergent synthetic methods for middle-molecular-weight triazoles using newly designed trivalent platforms with azide, alkyne, and fluorosulfonyl moieties. The key to successful selective triazole formations lies in choosing the preferred alkynes or azides under appropriate conditions. One-pot triple-click assembly of easily accessible modules onto the trivalent platforms enabled us to synthesize a broad range of triazoles. Our research group is undertaking further studies such as applications to iterative multi(triazole) synthesis using trivalent platforms.

This work was supported by JSPS KAKENHI Grant Number 23K179200 (S.Y.) and Asahi Glass Foundation (S.Y.).

## Data availability

The data supporting this article have been included as part of the ESI.†

## Conflicts of interest

There are no conflicts to declare.

## Notes and references

- For reviews of sequential click reactions, see: (a) D. M. Beal and L. H. Jones, *Angew. Chem., Int. Ed.*, 2012, **51**, 6320; (b) A.-C. Knall and C. Slugovc, *Chem. Soc. Rev.*, 2013, **42**, 5131; (c) Z.-J. Zheng, D. Wang, Z. Xu and L.-W. Xu, *Beilstein J. Org. Chem.*, 2015, **11**, 2557; (d) A. Maruani, D. A. Richards and V. Chudasam, *Org. Biomol. Chem.*, 2016, **14**, 6165; (e) S. Yoshida, *Org. Biomol. Chem.*, 2020, **18**, 1550; (f) D. Sato, Z. Wu, H. Fujita and J. S. Lindsey, *Organics*, 2021, **2**, 161; (g) H. Tanimoto and T. Tomohiro, *Chem. Commun.*, 2024, **60**, 12062.
- 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.
- (a) K. P. Kaliappan, P. Kalanidhi and S. Mahapatra, *Synlett*, 2009, 2162; (b) I. E. Valverde, A. F. Delmas and V. Aucagne, *Tetrahedron*, 2009, **65**, 7597; (c) H. S. G. Beckmann, F. Nie, C. E. Hagerman, H. Johansson, Y. S. Tan, D. Wilcke and D. R. Spring, *Nat. Chem.*, 2013, **5**, 861; (d) M.-L. Winz, E. C. Linder, J. Becker and A. Jäschke, *Chem. Commun.*, 2018, **54**, 11781; (e) K. Hema and K. M. Sureshan, *Acc. Chem. Res.*, 2019, **52**, 3149.
- For examples of recent our studies on sequential click reactions using trivalent platforms, see: (a) H. Takemura, S. Goto, T. Hosoya and S. Yoshida, *Chem. Commun.*, 2020, **56**, 15541; (b) H. Takemura, G. Orimoto, A. Kobayashi, T. Hosoya and S. Yoshida, *Org. Biomol. Chem.*, 2022, **20**, 6007; (c) G. Orimoto and S. Yoshida, *Chem. Commun.*, 2024, **60**, 4545; (d) M. Hamada, G. Orimoto and S. Yoshida, *Chem. Commun.*, 2024, **60**, 7930.
- A. K. Agrahari, P. Bose, M. K. Jaiswal, S. Rajkhowa, A. S. Singh, S. Hotha, N. Mishra and V. K. Tiwari, *Chem. Rev.*, 2021, **121**, 7638.
- 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, 672.
- Intramolecular reactions between azides and alkynes, see: (a) R. Li, D. J. Jansen and A. Datta, *Org. Biomol. Chem.*, 2009, **7**, 1921; (b) Z. Shan, M. Peng, H. Fan, Q. Lu, P. Lu, C. Zhao and Y. Chen, *Bioorg. Med. Chem. Lett.*, 2011, **21**, 1731.
- (a) M. Z. C. Hatit, J. C. Sadler, L. A. McLean, B. C. Whitehurst, C. P. Seath, L. D. Humphreys, R. J. Young, A. J. B. Watson and G. A. Burley, *Org. Lett.*, 2016, **18**, 1694; (b) M. Z. C. Hatit, C. P. Seath, A. J. B. Watson and G. A. Burley, *J. Org. Chem.*, 2017, **82**, 5461; (c) F. Peschke, A. Taladriz-Sender, M. J. Andrews, A. J. B. Watson and G. A. Burley, *Angew. Chem., Int. Ed.*, 2023, **62**, e202313063; (d) R. P. Bunschoten, F. Peschke, A. Taladriz-Sender, E. Alexander, M. J. Andrews, A. R. Kennedy, N. J. Fazakerley, G. C. L. Jones, A. J. B. Watson and G. A. Burley, *J. Am. Chem. Soc.*, 2024, **146**, 13558; (e) F. Peschke, A. Taladriz-Sender, A. J. B. Watson and G. A. Burley, *Bioconjugate Chem.*, 2024, **35**, 1788.
- S. Ding, G. Jia and J. Sun, *Angew. Chem., Int. Ed.*, 2014, **53**, 1877.
- S. K. Khetan and M. V. George, *Can. J. Chem.*, 1967, **45**, 1993.
- J. Dommerholt, S. Schmidt, R. Temming, L. J. A. Hendriks, F. P. J. T. Rutjes, J. C. M. van Hest, D. J. Lefeber, P. Friedl and F. L. van Delft, *Angew. Chem., Int. Ed.*, 2010, **49**, 9422.
- J. C. Jewett and C. R. Bertozzi, *Chem. Soc. Rev.*, 2010, **39**, 1272.
- E. Saxon and C. R. Bertozzi, *Science*, 2000, **287**, 2007.
- D. P. Chauhan, S. J. Varma, A. Vijeta, P. Banerjee and P. Talukdar, *Chem. Commun.*, 2014, **50**, 323.
- (a) C. Yamamoto, M. Suzuki and S. Yoshida, *Bull. Chem. Soc. Jpn.*, 2022, **95**, 1741; (b) C. Yamamoto, K. Numata, M. Suzuki and S. Yoshida, *Org. Chem. Front.*, 2024, **11**, 6159.
- Since aromatic azides also serve in various triazole formations and show unique selectivity in base-catalyzed 1,5-triazole formation, a wide range of triazoles would be accessible using trivalent platform **4c**. See, ref. 1e. For an example of a base-catalyzed reaction, see: S. W. Kwok, J. R. Fotsing, R. J. Fraser, V. O. Rodionov and V. V. Fokin, *Org. Lett.*, 2010, **12**, 4217.
- (a) T. R. Chan, R. Hilgraf, K. B. Sharpless and V. V. Fokin, *Org. Lett.*, 2004, **6**, 2853; (b) X.-M. Liu, A. Thakur and D. Wang, *Biomacromolecules*, 2007, **8**, 2653.
- (a) G.-C. Kuang, H. A. Michaels, J. T. Simmons, R. J. Clark and L. Zhu, *J. Org. Chem.*, 2010, **75**, 6540; (b) Z. Yuan, G.-C. Kuang, R. J. Clark and L. Zhu, *Org. Lett.*, 2012, **14**, 2590.
- (a) X. Zhang, B. Moku, J. Leng, K. P. Rakesh and H.-L. Qin, *Eur. J. Org. Chem.*, 2019, 1763; (b) Z. Li, X. Ren, P. Sun, H. Ding, S. Li, Y. Zhao and K. Zhang, *ACS Macro Lett.*, 2021, **10**, 223.

