Sequential conjugation methods based on triazole formation and related reactions using azides

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The recent remarkable progress in azide chemistry has realized sequential conjugation methods with selective 1,2,3-triazole formation. On the basis of the diverse reactivities of azides and azidophiles, including terminal alkynes and cyclooctynes, various selective reactions to furnish triazoles and a wide range of platform molecules, such as diynes, diazides, triynes, and triazides, have been developed so far for bis- and tris(triazole) syntheses. This review highlights recent transformations involving selective triazole formation, allowing the efficient preparation of unsymmetric bis- and tris(triazole)s using diverse platform molecules.

Introduction

Azides are recognized as reliable compounds to conjugate with several types of azidophiles, such as terminal alkynes and cycloalkynes. In particular, copper-catalyzed azide–alkyne cycloaddition (CuAAC) and strain-promoted azide–alkyne cycloaddition (SPAAC) have been utilized as “click reactions” for connecting two molecules in broad disciplines, including the pharmaceutical sciences, chemical biology, and materials science (Fig. 1). These reliable methods for forming a 1,2,3-triazole ring have enabled the preparation of a wide range of compounds involving functionalized proteins.

In 2002, Sharpless’s group and Meldal’s group independently reported that a catalytic amount of copper(I) salt efficiently facilitated the [3 + 2] cycloaddition reaction between azides and terminal alkynes. This catalytic reaction realizes the selective synthesis of a wide range of 1,4-triazoles, leaving diverse functional groups unreacted. When cyclooctynes were treated with azides, the triazole formation took place smoothly without copper catalysis. The SPAAC reaction reported by Bertozzi and coworkers in 2004 served in the chemical modification of proteins. Various cycloalkynes have so far been developed for efficient conjugation with azides.

The diversity of synthesizable triazoles has been expanded by the development of sequential triazole formation and related reactions. Sequential reactions using platform molecules, such as diynes, triynes, diazides, and triazides, have allowed for the modular synthesis of bis- and tris(triazole)s from simple modules.

This review summarizes recent sequential conjugation methods based on triazole formation and related chemistry using azides. In particular, various platform compounds bearing two or more clickable moieties are highlighted in terms of their azido- or alkyne-type selectivities.

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Suguru Yoshida received his Ph.D. in 2009 from Kyoto University under the supervision of Prof. Koichiro Oshima. After a postdoctoral fellowship in the group of Prof. Katsuhiko Tomooka at Kyushu University and the group of Prof. Marcus Tius at the University of Hawaii in Manoa, he became Assistant Professor at Tokyo Medical and Dental University (TMDU), Japan, working with Prof. Takamitsu Hosoya in 2010 and was promoted to Associate Professor in 2015. His research interests include new methods in synthetic organic chemistry. He received the Chemical Society of Japan Award for Young Chemists (2017) and the Thieme Chemistry Journal Award (2019).
Multi(triazole) syntheses via selective reactions of diynes or related compounds

One-pot bis(triazole) synthesis using a peptide platform with two types of alkynyl groups, i.e. an ethynyl group and a trimethylsilyl-protected alkynyl moiety, was developed by Aucagne and Leigh in 2006 (Fig. 2A). Indeed, the copper-catalyzed reaction of diyne 1 with azide 2 proceeded selectively at the terminal alkynyl moiety. The subsequent Ag(I)-mediated desilylation and chemoselective triazole formation catalyzed by copper catalysis with azide 3 provided bis(triazole) 4 in high yield. The unsymmetrical bis(triazole) synthesis through selective triazole formation using 1-trimethylsilyl-1,3-butadiyne (5) was reported by Fiandanese and coworkers in 2009 (Fig. 2B). The Cu(II) catalyzed azide–alkyne cycloaddition between diyne 5 and benzyl azide (6) and subsequent Cu(I)-promoted triazole formation with n-decyl azide (7) in the presence of tetrabutylammonium fluoride yielded bis(triazole) 8 in good yield. In 2010, Aizpurua, Fratila, and coworkers reported the efficient preparation of bis(triazole) 13 by selective desilylation of 1,4-bis(trimethylsilyl)-1,3-butadiyne (9) with methyllithium followed by a first CuAAC reaction with azide 10, desilylation with cesium fluoride, and a second CuAAC reaction with azide 12 (Fig. 2C). Simpson et al. also developed a bis(triazole) synthesis from TIPS-protected 1,3-diyne 14 in a one-pot manner (Fig. 2D).

Sequential triple-triazole-formation methods have been accomplished through selective desilylation (Fig. 3). For example, the synthesis of tris(triazole) 17 using triazacyclophane-scaffold 16 was achieved by Liskamp et al. in 2014 (Fig. 3A). Indeed, a first CuAAC reaction with an azide followed by Ag(I)-mediated selective deprotection of the TES group proceeded efficiently. Then, a second CuAAC, desilylation of the TIPS group with TBAF, and a third CuAAC resulted in the convergent synthesis of tris(triazole) 17 bearing three cyclic peptide moieties. In 2015, Jiráček and coworkers developed a versatile trifunctional scaffold 18 with three alkynyl groups; an ethynyl group and TES- and TIPS-protected alkynyl moieties, which enabled a solid-phase triple-click synthesis (Fig. 3B). Stepwise triple-click functionalization of a peptide-type triyne platform 19 was also accomplished by Vrabel et al. in 2018.

Bis(triazole) syntheses using diynes without silyl protective groups have also been achieved through selective triazole for-
Tanimoto and coworkers developed a unique azide–alkyne cycloaddition between azides and propargyl propiolic amide through cationic intermediates [Fig. 4C]. Since the cationic intermediates generated from diyne 29 and azide 6 can react with azides, bis(triazole) synthesis was accomplished in moderate yield. Furthermore, an elegant four-component coupling by sequential triazole formation and subsequent amination has been achieved using diyne 29, azides 6 and 30, and allylamine (Fig. 4C).

Since aryn e intermediates spontaneously react with azides without catalysis to efficiently provide benzotriazoles, we developed an efficient bis(triazole) synthesis using arynes that contain a terminal alkyne moiety (Fig. 5A). Indeed, treatment of o-iodoaryl triflate 32 with a silylmetal Grignard reagent in the presence of azides followed by a CuAAC reaction furnished bis(triazole)s 33a and 33b in good yields. The aryne–azide cycloaddition and following azide–alkyne cycloaddition catalyzed by ruthenium afforded bis(triazole) 34a with a 1,5-triazole moiety. Furthermore, the synthesis of tris(triazole) 39 was achieved from o-iodoaryl triflate 35 and azides 36–38 by aryne–azide cycloaddition, a first CuAAC, Ag(i)-mediated desilylation, and a second CuAAC (Fig. 5B).

Bis(triazole) synthesis using a platform with an ethynyl group and a cyclooctyne moiety was accomplished (Fig. 6). Dual labeling of biomolecules using diyne 40 through SPAAC and CuAAC was reported by Kele, Wolfbeis, and coworkers in 2009 (Fig. 6A). The SPAAC reaction between cyclooctyne 40 and azide 36 furnishes N-alkylated cyclooctyne 37, which is then functionalized with CuAAC and Ag(i)-catalyzed deprotection to afford bis(triazole) 38a (Fig. 6B).
and azide 41 took place smoothly without catalysis, and subsequent CuAAC reaction at the remaining ethynyl group efficiently furnished a regiosomeric mixture of bis(triazole)s 43. In 2011, Boons et al. reported that the selective bis(triazole) synthesis allowed for a dendrimer-type multi(triazole) synthesis using platform with ethynyl groups and a cycloalkyne moiety by a SPAAC reaction and following CuAAC reaction efficiently providing multi(triazole) 46 (Fig. 6B).21 In 2014, we reported a novel method to prepare bis(triazole) 49 using diyne 47 through transient protection of the cyclooctyne moiety toward the click reaction with azides (Fig. 7A).22 In 2016, Dudley and co-worker developed a novel platform 50 bearing a cyclononyne and terminal alkyne moieties (Fig. 7B).25 The SPAAC reaction of the cyclononyne moiety of 50 with azide 6 took place efficiently with gentle heating. Transient protection of the cycloalkyne moiety by complexation with copper enabled the selective CuAAC reaction of platform 50 at the ethynyl group followed by SPAAC with azide 53 to afford bis(triazole) 54 in good yield.

Bis(triazole) synthesis using platform 56 with a dicobalt-protected cycloheptyne moiety and an ethynyl group was also achieved by Fouquet, Hermange, and co-worker in 2019 (Fig. 8A).26 Platform 56 was prepared through the Nicholas reac-

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Fig. 6 Multitriazole syntheses by SPAAC followed by CuAAC. (A) Kele and Wolfbeis’s work. (B) Boons’s work. DIPEA = N,N-diisopropylethylamine.
tion of dicobalt-protected alkyne 55. Then, the generation of cycloheptyne by deprotection with trimethylamine N-oxide and SPAAC reaction with benzyl azide took place to afford triazole 57 in moderate yield without damaging the ethynyl group. Bis(triazole) 58 was synthesized by the CuAAC reaction of 57.

Based on the photo-triggered click chemistry developed by Popik, Boons, and coworkers, bis(triazole) synthesis by sequential SPAAC reactions was accomplished using platform 59 by Popik et al. in 2014 (Fig. 8B).28 Indeed, the first SPAAC reaction of diyne 59 followed by photoirradiated removal of carbon monoxide to generate dibenzo-fused cyclooctyne and a subsequent SPAAC reaction efficiently provided bis(triazole) 60.

In 2010, the double-click reaction of Sondheimer–Wang diyne 61 was accomplished by Hosoya, Kii, and coworkers (Fig. 9A).10 The double-click reaction served in the chemical modification of azido proteins with diyne 61 and azides, but selective bis(triazole) synthesis was not easy.11 In 2016, Popik et al. succeeded in a selective bis(triazole) synthesis via the mono-cyclopropene formation of diyne 61 followed by SPAAC reaction with butyl azide and a further SPAAC reaction with benzyl azide through the generation of a cycloalkyne moiety (Fig. 9B).28c

Bis(triazole) synthesis and a thiol–ene reaction using platform 65 enabled the assembly of three modules by reliable conjugation methods (Fig. 10).32 In 2012, Beal and coworkers developed platform 65 with cyclooctyne and terminal alkyne moieties and an acetylthio group. Sequential SPAAC and CuAAC reactions efficiently yielded bis(triazole) 67. Then, removal of the acetyl group followed by a thiol–ene reaction using a maleimide conjugated with bovine serum albumin (BSA) resulted in the dual-modification of the BSA protein.

Multi(triazole) syntheses using platforms with both azido and alkyne moieties

Platform compounds bearing both azido and alkyne moieties have also served in the preparation of bis(triazole)s and tris(tri-
azole)s (Fig. 11). For example, Kaliappan et al. reported that the CuAAC reaction of platform 69 with methyl propiolate (70) and a following CuAAC reaction with p-tolyl azide (71) furnished bis(triazole) 72 in moderate yield by virtue of the higher clickability of methyl propiolate than that of the ethynyl group of platform 69 (Fig. 11A). Platform 73, with both an azido group and TES- and TIPS-protected alkyne moieties, was developed by Aucagne and coworkers in 2009 (Fig. 11B). Indeed, an elegant 5-step transformation was achieved through a first CuAAC with alkyne 74, TES-selective desilylation with silver nitrate, a second CuAAC with azide 75, TIPS-selective desilylation by TBAF, and a third CuAAC with azide 76.

In 2015, Workentin, Gilroy, and coworkers developed platform 80 bearing an azide and dicobalt-protected cyclooctyne moieties (Fig. 12A). The protection of bicyclononyne 78 with dicobalt octacarbonyl successfully proceeded to a high yield of 79, enabling the formation of carbamate 80 using 2-azidoethylamine without an SPAAC reaction. Subsequent a CuAAC reaction using the azido group followed by alkyne formation by DIC took place efficiently to provide 86, which reacted with azide 87 catalyzed by copper to afford bis(triazole) 88 in excellent yield.

Platform compound 84 with an azido group and alkyne precursor moiety has been developed by Wright, Couty, and coworkers (Fig. 12B). Indeed, the CuAAC reaction of platform 84 with alkyne 74 followed by alkyne formation by DIC took place efficiently to provide 86, which reacted with azide 87 catalyzed by copper to afford bis(triazole) 88 in excellent yield.

Recently, we reported bis(triazole) syntheses using platform compounds with an azido group and an arylene precursor moiety (Fig. 13). In 2015, platform compound 89 bearing both an azido group and an o-silylaryl triflate moiety for arylene generation was prepared through Ir-catalyzed C–H borylation37,38 of o-silylaryl triflate and following deborylationization (Fig. 13A). Since aliphatic azide 6 showed higher reactivity than azide 89 in cycloaddition with arylene intermediate B, bis(triazole) 91 was efficiently prepared by azide–aryne cycloaddition and subsequent CuAAC with alkyne 90. Platform 92 with both an azido group and an o-idoaryl triflate moiety was also developed in 2016 (Fig. 13B). For instance, a CuAAC reaction with terminal alkynes and arylene–aryne cycloaddition with a silylmethyl Grignard reagent as an activator enabled the facile synthesis of bis(triazole)s 93a–93c, leaving various functional groups untouched.

Multi(triazole) syntheses using multi-azido platforms

Azido-type selective reactions have served in multi(triazole) syntheses. In 2012, Zhu et al. found efficient reactions between 2-picolyd azides and terminal alkynes in the presence of a catalytic amount of copper(II) acetate by virtue of significant enhancement in the clickability of the picolyd azido group

Fig. 11 Bis(triazole) syntheses using platforms 69 and 73. (A) Kalippan’s work. (B) Aucagne’s work.

Fig. 12 Bis(triazole) syntheses using platforms 80 and 84. (A) Gilroy and Workentin’s work. (B) Wright and Couty’s work. DIC = diisopropylcarbodiimide.
facilitated by chelation (Fig. 14). On the basis of this remarkable clickability of the 2-picolyl azido group, bis(triazole) was efficiently prepared from diazide by Cu(II)-catalyzed azide–alkyne cycloaddition of 2-picolyl azido group with alkyne followed by Cu(I)-catalyzed cycloaddition of the remaining azido group with alkyne. This method allowed for the stepwise click functionalization of alkyne-installed DNA.

Efficient bis(triazole) syntheses using platform compound with an aromatic and an aliphatic azido group were achieved through triazole formation with nucleophilic species (Fig. 15). In 2011, Belkheira, Pons, Bressy, and coworkers succeeded in efficient bis(triazole) synthesis by an organocatalytic azide–ketone [3 + 2]-cycloaddition reaction. Indeed, triazole was obtained selectively by the reaction between ketone and diazide in the presence of cesium carbonate, and bis(triazole) was successfully prepared in good yield by further cycloaddition with benzyl cyanide using potassium tert-butoxide.

In 2014, Delft, Bickelhaupt, and coworkers reported that electron-deficient aromatic azides showed significantly higher reactivity than aliphatic azides in the SPAAC reaction with bicyclo[6.1.0]non-4-yn (BCN). On the other hand, the clickability of aliphatic azides was higher than that of aromatic azides in the SPAAC reaction with dibenzo-fused azacyclooctyne. These SPAAC reactions enabled selective bis(triazole) formation using diyne, providing bis(triazole) in a quantitative amount.

CuAAC reaction of the remaining benzylic azido group (Fig. 15A). In 2015, Ramachary et al. reported that benzyl cyanide also reacted with azides to afford triazoles (Fig. 15B). In the case of using diazide, triazole formation took place selectively at the aromatic azido group in the presence of cesium carbonate, and bis(triazole) was successfully prepared in good yield by further cycloaddition with benzyl cyanide using potassium tert-butoxide.

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Bulky tertiary azides also served in selective SPAAC and CuAAC reactions (Fig. 17). In 2016, Koert and coworkers reported that the CuAAC reaction of diazide took place selectively at the primary azido group (Fig. 17A). On the basis of this selective CuAAC reaction and azacyclooctyne-selective triazole formation using diyne, a novel layer-by-layer method was developed. Bis(triazole) synthesis using diazide through two SPAAC reactions was realized by Bickelhaupt, Mikula, and coworkers (Fig. 17B). Indeed, the selective SPAAC reaction of diazide at the primary azido group using dibenzo-fused azacyclooctyne and a subsequent SPAAC reaction at the remaining bulky azido group with BCN provided bis(triazole) in a quantitative amount.

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**Fig. 13** Bis(triazole) syntheses using platforms 89 and 92. (A) Platform 89 with both an azido group and an o-silylaryl triflate moiety. (B) Platform 92 with both an azido group and an o-iodoaryl triflate moiety.

**Fig. 14** Bis(triazole) synthesis using diazide 94.

**Fig. 15** Bis(triazole) syntheses using diazide 100. (A) Belkheira, Pons, and Bressy’s work. (B) Ramachary’s work.
Remarkable clickability of doubly sterically-hindered aromatic azides also realized selective bis(triazole) formation (Fig. 18). In 2011, we found that 2,6-diisopropylphenyl azide showed 76 times higher reactivity than phenyl azide in the SPAAC reaction with dibenzo-fused cyclooctynes due to the steric inhibition of resonance. Thus, a selective SPAAC reaction with cyclooctyne 121 took place efficiently at the doubly sterically hindered aromatic azido group of diazide 120 (Fig. 18A). In 2018, a further enhancement in clickability was achieved using 4-amino-2,6-diisopropylphenyl azides, allowing the selective SPAAC reaction of diazide 124 with dibenzo-fused cyclooctyne 121 (Fig. 18B). Thus, a following CuAAC reaction with alkyne 125 furnished bis(triazole) 126 in excellent yield.

In 2018, we found three types of selectivities in triazole formation, namely SPAAC, Ru-catalyzed azide–alkyne cycloaddition (RuAAC), and base-catalyzed triazole formation with 1,3-dicarbonyl compounds. By competitive experiments using an equimolar mixture of 2,6-diisopropylphenyl azide, phenyl azide, and benzyl azide. On the basis of these findings, we succeeded in a consecutive tris(triazole) synthesis using triazole platform 127 (Fig. 19). Indeed, selective base-catalyzed triazole formation with 1,3-diketone 128 at the unhindered aromatic azido group followed by selective RuAAC with alkyne 125 at the benzylic azido group and SPAAC reaction with cyclooctyne 121 at the remaining 2,6-diisopropylphenyl azido group efficiently provided tris(triazole) 129a (Fig. 19A). Triple-triazole formation was also achieved by SPAAC reaction with 121 at the doubly sterically-hindered aromatic azido group, aromatic azido-selective base-catalyzed cycloaddition with diketone 128, and CuAAC reaction with alkyne 74. A trifunctional chemical probe 129c was as a dual-label-
ing ligand was efficiently developed by assembling three modules onto triazide platform 127 in three steps (Fig. 19B).

A transient protection method realized selective triazole formation using diazide platform 130 (Fig. 20). In 2018, we found that azides were efficiently protected toward SPAAC and CuAAC reactions by phosphazide formation with Amphos (131). Since the formation of phosphazide 132 from diazide 130 selectively proceeded at the aromatic azido group by the addition of an equimolar amount of Amphos (131), we accomplished selective SPAAC and CuAAC reactions of diazide 130 with cyclooctyne 78 and alkyne 134, respectively, at the aliphatic azido group through deprotective removal of Amphos by elemental sulfur.

Related sequential conjugation methods based on transformations using azides

Azides show diverse reactivities in conjugation reactions with various azidophiles. In 2015, platform compound 136 with a masked-phosphonite and terminal alkyne moieties was developed by Hackenberger and coworkers (Fig. 21). Indeed, sequential conjugation was achieved by CuAAC reaction, removal of borane, and reaction with an azide to form a P–N bond.

Recently, Yan and Ramstöm’s group, Yi and Xi’s group, and our group independently reported the Staudinger reaction affording robust aza-ylides. In 2018, we found that the Staudinger reaction between 2,6-dichlorophenyl azide (141) and triphenylphosphine (140) took place smoothly to provide stable aza-ylide 142 even in the presence of cyclooctyne 121, while the SPAAC reaction of benzyl azide (6) with cyclooctyne 121 proceeded faster than that with phosphine 140 (Fig. 22A). We also demonstrated that aza-ylides formed by the Staudinger reaction between 2,6-dichloroaryl azides and triphenylphosphine derivatives showed significant stability in the presence of biomolecules, enabling the chemical modification of azido-incorporated proteins. We also reported a novel sequential conjugation method using diazide 146 with tri-
phenylphosphine (140) and cyclooctyne 121, providing triazole 147 in high yield by three-component coupling (Fig. 22B).

In 2019, Workentin et al. developed a sequential conjugation method using platform 148 (Fig. 23A). Indeed, the generation of cyclooctyne with an ortho-alkoxycarbonyl-substituted triarylphosphine moiety from 148 enabled the SPAAC reaction with azide 6 followed by a rapid Staudinger reaction with tetrafluorophenyl azide 149, yielding stable aza-ylide 150. In 2019, Yi, Xi, and coworkers developed diazide platform 151 (Fig. 23B). Staudinger reaction of diazide 151 with triphenylphosphine derivative 152 proceeded smoothly to afford a stable aza-ylide followed by an SPAAC reaction with cyclooctyne 118, resulting in efficient sequential conjugation.

Elegant sequential conjugations using triazide 154 have been accomplished by Tanimoto and coworkers (Fig. 23). Indeed, selective transformations of azidomethyl groups into

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Fig. 22  Selective reactions of azides with phosphine 140 and cyclooctyne 121. (A) Competitive experiments using an equimolar mixture of 140 and 121. (B) Three-component reaction between diazide 146, phosphine 140 and cyclooctyne 121.

Fig. 23  Sequential conjugations through stable aza-ylide formation. (A) Workentin’s work. (B) Yi and Xi’s work.

Fig. 24  Sequential three-component assembly using triazide 154. (A) Transformations via two generations of a diazo group. (B) Transformations via oxime and diazo intermediates.
diazomethyl groups enabled sequential cycloadditions to efficiently provide 160 [Fig. 24A]. Furthermore, the selective preparation of oxime was achieved by the transformation of α-azidoacetophenone, leaving two azido groups untouched [Fig. 24B]. Following the synthesis of triazine 162 with 2-pyridyl aldehyde, diazomethane formation, cycloaddition to acrylic acid ester 163, SPAAC reaction with cyclooctyne 121, and conjugation with trans-cyclooctene 164 at the triazine ring realized efficient three-component assembly.

Conclusions

Complicated multi(triazole)s have been prepared by the consecutive syntheses of simple modules onto platform molecules, such as multiazides, through selective triazole formation. However, three (or more) component coupling still remains challenging due to the limited methods available to control triazole formation. Various methods to synthesize multi(triazole)s would be useful in broad disciplines, including materials science, the pharmaceutical sciences, and chemical biology.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This work was supported by JSPS KAKENHI Grant Number 19K05451; the Naito Foundation; the Japan Agency for Medical Research and Development (AMED) under Grant Numbers JP19am0101098 (Platform Project for Supporting Drug Discovery and Life Science Research, BINDS); and the Cooperative Research Project of Research Center for Biomedical Engineering.

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