Modular Synthesis of Tripeptide Analogs with An Aminobitriazole Skeleton Using Diynyl Benziodoxolone as a Trivalent Platform

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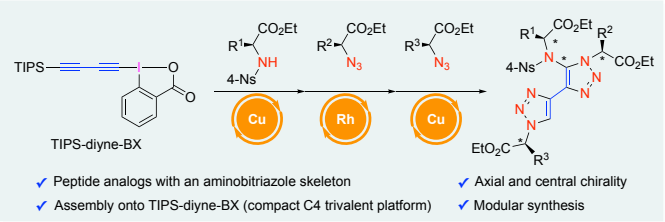
Supporting Information Placeholder



ABSTRACT: A new synthesis method of tripeptide analogs with an aminobitriazole skeleton was proposed. The method involves assembling three amino acid-derived modules at the amino group site and onto a triisopropylsilyl diynyl benziodoxolone by copper-catalyzed electrophilic diynylation of amino acid-derived sulfonamides, chemoselective azide–alkyne cycloadditions with amino acid-derived azides, and deprotection. Various complex aminobitriazoles substituted with pyrene, nucleoside, and *N*-acetylglucosamine were also synthesized. The produced aminobitriazoles have multiple centers and a C–N axial chirality.

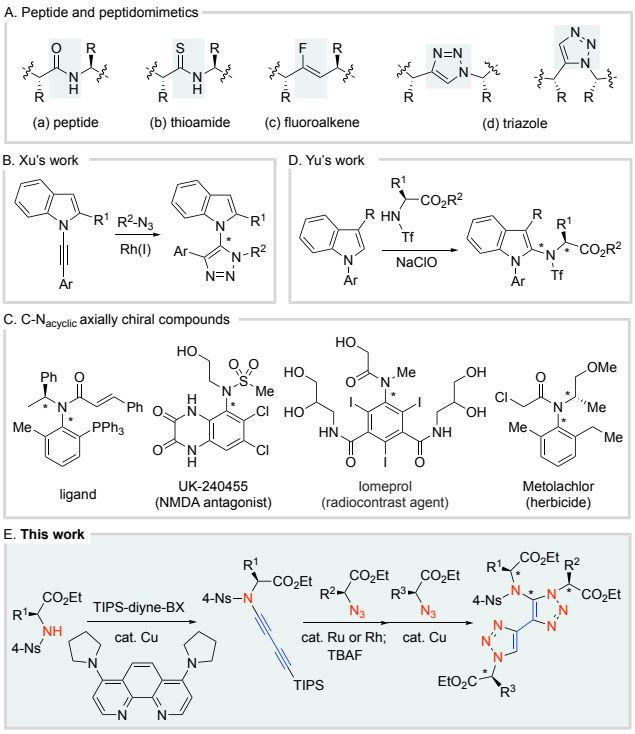
Peptides are important for the development of various functional molecules for different products such as medications and agrichemicals (Scheme 1A-a). However, native peptides exhibit poor absorption and low proteolytic stability. To improve these characteristics, numerous peptidomimetics and other moieties have been developed to replace peptide bonds (Scheme 1A-b, c).[1] Triazole is an essential heterocyclic pharmacophore in the development of bioactive molecules such as anticancer, antiviral, and antibiotic agents.[2] The copper-catalyzed azide–alkyne cycloaddition (CuAAC) is an efficient method for synthesizing 1,4-disubstituted 1,2,3-triazoles.[3] Other transition metals (Ru, Rh, Ir, and Ni)-catalyzed AACs have been reported for the synthesis of 1,5-disubstituted-1,2,3-triazoles.[4] 1,2,3-Triazole-based peptidomimetics, e.g., triazolamer, have emerged as promising lead compounds for the development of various bioactive compounds using AAC (Scheme 1A-d).[5] Furthermore, AAC has been used for the assembly of functional molecules through multiclick reactions to produce complex functionalized molecules.[6]

Atropisomeric molecules are an important class of stereogenic compounds. In recent years, these compounds have been attracting considerable attention owing to the atropisomerism arising from the restricted rotation of a C–N bond in their structure.[7,8] Recently, asymmetric click reactions of internal alkynes have been reported for the synthesis of C–N axial chirality (Scheme 1B).[8a] Among the C–N atropisomeric molecules, acyclic amide-containing molecules have attracted considerable attention owing to their unique structure, making them useful in various applications such as synthetic chemistry, materials science, as well as medicinal and agricultural activities (Scheme 1C).[9,10] Numerous synthetic approaches, including kinetic resolution and desymmetrization, electrophilic amination, C–H functionalization, N-functionalization, and annulation, have been developed for the synthesis of C–N atropisomeric molecules.[9,10] However, few $C_{\text{five membered}}$–N_{acyclic} axially chiral compounds were reported to date because of the low rotational barrier caused by the high rotational freedom of the C–N axis and the small size of the five-membered ring. Yu's group synthesized C–N atropisomer with a carbon-centered chirality through atroposelective coupling of indoles with amino acid-derived sulfonamides at the C2 position (Scheme 1D).[10d]

Recently, alkynyl benziodoxolone attracted significant interest because it can be used for electrophilic alkynylation under mild conditions.[11-13] Owing to the importance of 1,3-butadiyne in medicinal chemistry and materials science and because of our interest in developing hypervalent iodine compounds,[14,15] we recently reported a diversity-oriented synthetic method for ynamides based on copper-catalyzed *N*-diynylation of sulfonamide with triisopropylsilyl diynyl benziodoxolone (TIPS-diyne-BX) to give 1,3-butadiynamides, important C4-building blocks, deprotection of the TIPS group, and late-stage chemoselective CuAAC sequence.[13a,16-18] Based on our previous studies, we hypothesized that copper-catalyzed diynylation of amino acid-derived sulfonamide and transition metal-catalyzed azide–alkyne cycloaddition with amino acid-derived azides would result in assembling three amino acid modules onto TIPS-diyne-BX,

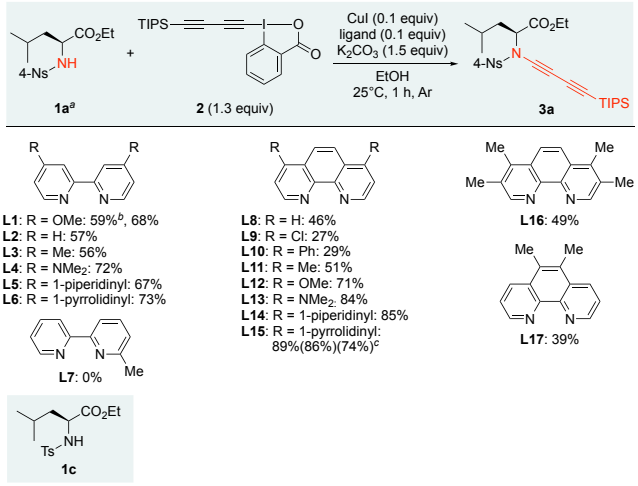
which works as a compact C4 trivalent platform, to produce unique tri-peptidemimetics bonded at the amino group site (Scheme 1E).

Scheme 1. Modular synthesis of tripeptide analoges with aminobitriazole skeleton



First, we investigated the reaction conditions of the electrophilic diynylation reaction conducted in our previous study using leucine-derived p-toluenesulfonamide (**1c**) as the substrate.[13a] In this case, a moderate yield (59%) of the corresponding diynamide **3c** was obtained probably owing to the low acidity of **1c** (Scheme 2, **L1**). Thus, leucine-derived 4-nitrobenzenesulfonamide (**1a**), which has higher acidity of the sulfonamide moiety, was used as a substrate instead of **1c**, achieving an improved yield (68%) (**L1**). Next, we further optimized the reaction conditions while using **1a**. In this reaction, an alkynyl-Cu(III) intermediate might be formed (Scheme S1, ESI†).[13a,19] Therefore, the effect of electron-rich ligands on stabilizing the Cu(III) intermediate was examined. As expected, a better yield was obtained when electron-rich bipyridine ligands were used (**L2**–**L7**), and an even higher yield was obtained when electron rich 1,10-phenanthrolines was used (**L8**–**L17**). Among the examined ligands, 4,7-di-1-pyrrolidinyl-1,10-phenanthroline (**L15**), which is a highly electron-rich ligand, achieved the highest yield of **3a**.[20] The catalyst, base, and solvent were then examined to determine the optimized reaction conditions to be: **1a** (0.1 mmol), **2** (1.3 equiv.), CuI (0.1 equiv.), **L15** (0.1 equiv.), and K_2CO_3 (fine powder: 1.5 equiv.) in EtOH mixed under stirring at 25°C for 1 h. Conducting the reaction under these conditions resulted in a **3a** isolated yield of 86% (Table S2, ESI†). Moreover, **3a** was synthesized at the 1 mmol scale and achieved good yield (74%), demonstrating the scalability of the reaction.

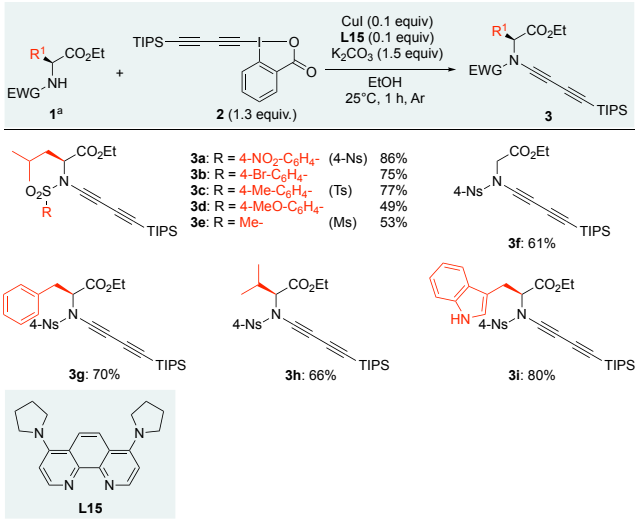
Scheme 2. Study of reaction conditions.



[a]Reaction conditions: **1a** (0.1 mmol), **2** (1.3 equiv), CuI (0.1 equiv), ligand (0.1 equiv), K_2CO_3 (1.5 equiv), EtOH (5 mL), 25°C, 1 h, argon. ^{1}H NMR yields. Numbers in parentheses are isolated yield. [b]**1c** was used as substrate. **3c** (59%) was obtained as product instead of **3a**. [c]1mmol scale.

Based on these optimized reaction conditions, the substrate was investigated (Scheme 3). First, we investigated sulfonyl group-containing substrates. Good yields of the corresponding products were obtained when 4-bromobenzenesulfonamide and p-toluenesulfonamide were used (**3b**, **3c**). In contrast, moderate yields were obtained when the less acidic 4-methoxybenzenesulfonamide and methanesulfonamide were used (**3d**, **3e**). Next, various amino acid derivatives were examined. Glycine, phenylalanine, valine, and tryptophan derivatives achieved moderately high to high yields of the corresponding products (**3f**–**3i**).

Scheme 3. Electrophilic diynylation of amino acid-derived sulfonamides

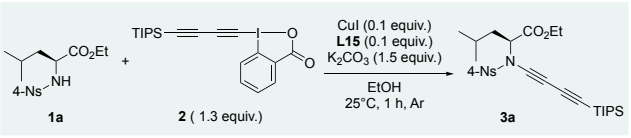


[a]Reaction conditions: **1** (0.1 mmol), **2** (1.3 equiv), CuI (0.1 equiv), ligand (**L15**) (0.1 equiv), K_2CO_3 (1.5 equiv), EtOH, 25°C, 1 h, argon. Isolated yields.

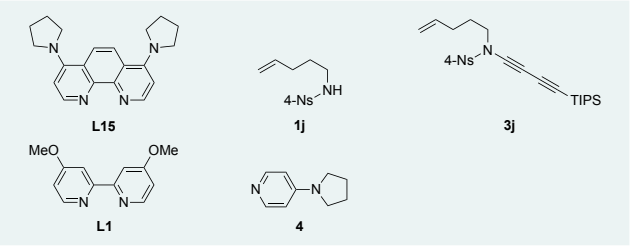
Next, several control experiments were performed to gain a mechanistic insight into the reaction. In the absence of a catalyst, base, and ligand, the reaction hardly proceeded (Table 1, Entries 2–4), indicating that these components are necessary for a successful reaction. The reaction achieved good yield under dark

conditions (Entry 5). Furthermore, in the presence of 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO), 2,6-di-tert-butyl-p-cresol, and 1,1-diphenylethylene as radical inhibitors, the reaction achieved good yields (Entries 6–8). Moreover, the *N*-diynylation of **1j** proceeded to achieve a 44% yield of **3j** with no cyclized products (Entry 9).[16c] These results indicate that the radical mechanism is not a major path in this reaction. In addition, using **4** did not improve the product yield. Thus, **L15** probably works as a ligand to stabilize the diyne-Cu(III) intermediate and not as a base (Scheme S1, ESI†).[13a,19]

Table 1. Control experiments.



entry	changed from the standard condition	yield (%)[a]
1	-	89 (86)
2	without CuI	0
3	without **L15**	13
4	without K_2CO_3	0
5	in the dark	76
6	with TEMPO	(69)
7	with BHT	76
8	with 1,1-diphenylethylene	82
9[b]	-	(44)
10	**L1** was used instead of **L15**, with **4** (0.1 equiv.)	64
11	**4** (0.2 equiv.) was used instead of **L15**	0

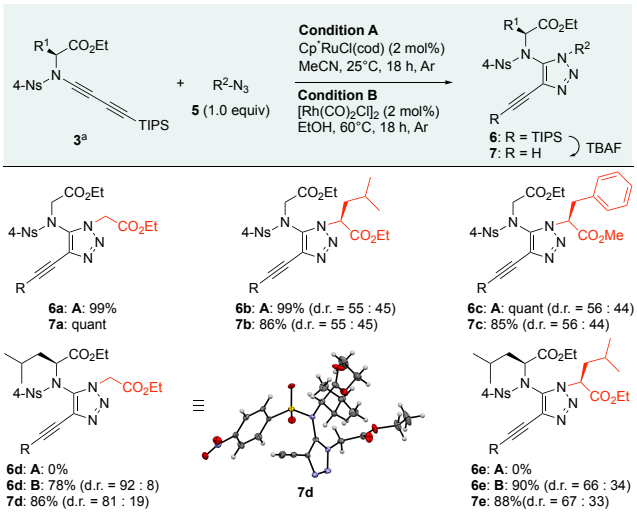


[a]Reaction conditions: **1a** (0.1 mmol), **2** (1.3 equiv), catalyst (0.1 equiv), ligand (0.1 equiv), base (fine powder: 1.5 equiv) in EtOH at 25℃ for 1 h. ^{1}H NMR yields. Number in parentheses is isolated yield. [b]**1j** was used as substrate instead of **1a**. **3j** (44%) was obtained as product instead of **3a**.

Next, we examined the reaction conditions for chemoselective AAC conducted at the ynamide moiety site.[18b] Under Condition A (Cp*RuCl(cod) in MeCN at 25°C), glycine-derived diynamide **3f** reacts with glycine-derived azide **5a** to give a high yield of **6a** (Scheme 4, Condition A; Table S3, ESI†).[21] When leucine- and phenylalanine-derived azide were used, they achieved high yields of the corresponding products with a low diastereomeric ratio (**6b**, **6c**). However, using leucine-derived diynaide **3a** did not result in the desired products (**6d** or **6e**) under Condition A. In contrast, $[Rh(CO)_2Cl]_2$ achieved good yields of **6d** and **6e** at 60°C at moderate to good diastereomeric ratio (**6d**, d.r. = 92 : 8; **6e**, d.r. = 66 : 34)(Scheme 4, Condition B; Table S4, ESI†).[18b] Moreover, the deprotection of the TIPS group with tetrabutylammonium fluoride proceeded, giving high yields (Scheme 4; **7a**–**7e**).[22] The diastereomeric ratio of **7d** (d.r. = 81 : 19) was lower than that of **6d** (d.r. = 92 : 8). Furthermore, the diastereomeric ratio of **7b** and **7d** changed depending on the deuterated solvent, indicating that the C–N bond of **7b** and **7d** rotates at 25°C (**7b**: from d.r. = 58 : 42 in THF-d_8 to 52 : 48 in CD_3OD; **7d**: from d.r. = 81 : 19 in $CDCl_3$ to 76 : 24 in DMSO-d_6) (Table S7 and S9, ESI†). Furthermore, the diastereomeric ratio of **7d** did not change after heating in DMSO-d_6 (Table S8, ESI†). No improvement of the diastereomeric ratio was observed when (S)-(-)-tol-BINAP was used as a ligand (Scheme S2, ESI†).[8a]

To elucidate the solid-state structure of the 5-aminotriazole, a suitable single crystal of **7d** grown from chloroform/hexane at −30°C was subjected to X-ray crystallographic analysis (CCDC 2342916; Scheme 4; Fig. S1-S3, Table S5–S6, ESI†). The absolute configuration of **7d** was determined to be (Sa, S). **7d** exhibited a planar geometry around the nitrogen atom of leucine owing to a root-mean-square deviation of 0.055Å (N1, C1, C3, and S1) calculated based on the least-square plane method and the sum of the nitrogen-centered bond angles (Σ°N1 = 357.8°). The torsion angle (C2, C1, N1, and S1) was −84.7°, indicating that the plan was orthogonal to the triazole ring. The acetylenic hydrogen H1…N4' distance was 2.311 Å, which was shorter than their combined van der Waals radii (2.75 Å), and the C5–H1…N4' bond exhibited a nearly linear conformation with an angle of 165.18°, indicating that triazole works as a hydrogen bonding acceptor (Fig. S2, ESI†). Furthermore, the π···π interaction between the alkyne and benzene ring of the 4-Ns group probably stabilizes the major isomer (distance ≈ 3.3 Å) (Fig. S3, ESI†).

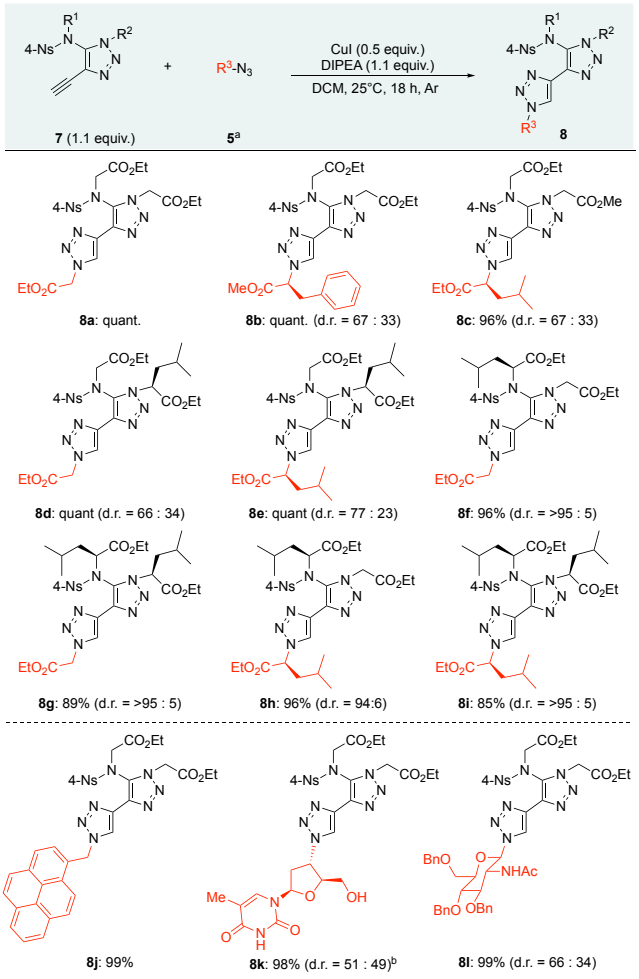
Scheme 4. AAC with diynamides and deprotection



[a]Reaction conditions: Condition A: **3** (0.25–1.0 mmol), **5** (1.0 equiv), Cp*RuCl(cod) (2 mol%), MeCN (2 mL), 25°C, 18 h, argon. Condition B: **3** (1.0 mmol), **5** (1.0 equiv), $[Rh(CO)_2Cl]_2$ (2 mol%), EtOH (2 mL), 60°C, 18 h, argon. Deprotection: **6** (0.25–1.0 mmol), TBAF (2.0 equiv), AcOH (3.0 equiv), THF, rt, 10 min. Isolated yields. Diastereomeric ratio was determined by ^{1}H NMR of isolated products.

Next, we conducted the CuAAC with terminal alkyne (Scheme 5).[13a] CuAAC of **7a** with glycin-, phenylalanine-, and leucine-derived azide achieved high yields of the corresponding aminobitriazole (**8a–c**, respectively) with moderate diastereomeric ratio (d.r. = 67 : 33 for **8b** and **8c**). High yields of **8d** and **8e** were obtained with higher diastereomeric ratios (**8d**: d.r. = 66 : 34; **8e**: d.r. = 77 : 23) when **7b** (d.r. = 55 : 45) was used. Furthermore, aminobitriazoles synthesized from leucine-derived sulfonamide (**7d**, **7e**) exhibited high diastereomeric ratios (**8f-8i**: d.r. = ≧94 : 6). In addition, various complex molecules-derived aminobitriazoles were synthesized with high yields through the reaction of **7a** and various azides with pyrene, nucleoside, and *N*-acetylglucosamine (**8j**–**8l**). Moreover, **8k** and **8l** exhibited low diastereomeric ratios (**8k**: d.r. = 51 : 49; **8l**: d.r. = 66 : 34).

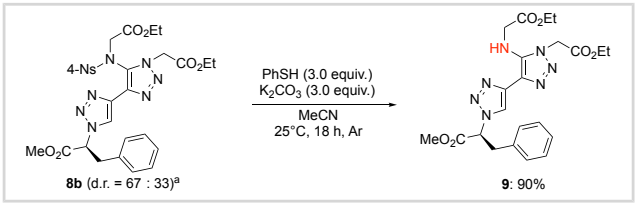
Scheme 5. CuAAC with terminal alkynes



[a]Reaction conditions: **7** (1.1 equiv), **5** (0.1 mmol), CuI (0.5 equiv.), DIPEA (1.1 equiv.), DCM (2 mL), 25°C, 18 h, argon, Isolated yields. Diastereomeric ratio was determined by ^{1}H NMR of isolated products. [b]Diastereomeric ratio was determined by ^{13}C NMR of isolated products.

Finally, the 4-nitrobenzenesulfonyl group of **8b** was deprotected with thiophenol to obtain a high yield of amine **9**, which has no diastereomer (Scheme 6).

Scheme 6. Deprotection of 4-Ns group



[a]Reaction conditions: **8b** (0.1 mmol), PhSH (3.0 equiv), K_2CO_3 3.0 equiv), MeCN (2 mL), 25°C, 18 h, argon. Isolated yield.

In conclusion, a synthetic method of a new class of tripeptide analogs with an aminobitriazole skeleton was developed. Aminobitriazoles, which have multiple centers and C–N axial chirality, were constructed by assembling three amino acid-derived modules at the amino group site and onto a TIPS-diyne-BX through (1) copper-catalyzed electrophilic diynylation of amino acid-derived sulfonamides, (2) chemoselective azide–alkyne cycloaddition with amino acid-derived azide, and (3) deprotection. Triisopropylsilyl diynyl benziodoxolone acts as a trivalent platform for the assembly of the functional modules to produce various aminobitriazoles with amino acid, pyrene, nucleoside, and *N*-acetylglucosamine substituents.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures, characterization data, and NMR spectra (PDF)

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Notes

Any additional relevant notes should be placed here.

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