HETEROCYCLES, Vol. 95, No. 2, 2017, pp. 1121-1131. © 2017 The Japan Institute of Heterocyclic Chemistry
Received, 26th September, 2016, Accepted, 9th November, 2016, Published online, 14th February, 2017
DOI: 10.3987/COM-16-S(S)83

CATALYTIC INTRAMOLECULAR [2+2+2] CYCLOADDITION OF PEPTIDE-TETHERED BRANCHED TRIYNES FOR THE SYNTHESIS OF CYCLIC PEPTIDES

Shuhei Obinata,[1] Yu-ki Tahara,[1] Kyalo Stephen Kanyiva,[2] and Takanori Shibata*[1,3]

[1] Department of Chemistry and Biochemistry, School of Advanced Science and Engineering, Waseda University, 3-4-1 Okubo, Shinjuku, Tokyo 169-8555, Japan; [2] International Center for Science and Engineering Programs (ICSEP), Waseda University, 3-4-1 Okubo, Shinjuku, Tokyo 169-8555, Japan; [3] JST, ACT-C, 4-1-8 Honcho, Kawaguchi, Saitama 332-0012, Japan; E-mail: tshibata@waseda.jp

Dedicated to Prof. Dr. Masakatsu Shibasaki for the celebration of his 70th birthday

Abstract – Rhodium-catalyzed intramolecular [2+2+2] cycloaddition of peptide-tethered branched triynes gave cyclic peptides in moderate to excellent yields. This is a new catalytic protocol for the synthesis of cyclic peptides containing various amino acids.

INTRODUCTION

Transition metal-catalyzed [2+2+2] cycloaddition of alkynes is a reliable and atom-economical method for the synthesis of multi-substituted aromatic compounds.[1] It can be categorized into three types by substrates: intermolecular reaction of three alkynes, semi-intermolecular reaction of a diyne and a monoyne, and intramolecular reaction of a triyne. The semi-intermolecular cycloaddition of 1,n-diynes is useful for the construction of bicyclic compounds, however, most of them are the reactions of 1,6-diynes with monoynes, which efficiently provide five-membered ring fused bicyclic compounds, and those of 1,n-diynes (n > 8) are quite limited, which provide more than seven-membered ring fused bicyclic products. In contrast, the intramolecular [2+2+2] cycloaddition of linear triynes, where 1,6-diyne and monoyne moieties are connected by a long tether, could realize the formation of medium- to large-sized ring-containing compounds. For example, Oshima reported a Rh-catalyzed cyclotrimerization in the

biphasic reaction media.[2] Tanaka disclosed the enantioselective synthesis of ortho- and metacyclophanes by the reaction of the linear triynes.[3] On the other hand, we developed a highly enantioselective reaction of branched triynes, where nitrogen-tethered 1,6-diyne and alkynyl moieties are connected by the nitrogen atom of 2-aminophenol and obtained planar-chiral tripodal cyclophanes with excellent ee.[4] Due to the rigid structure of *ortho*-phenylene moiety at the branched point, large ring system of [15]cyclophane could also be constructed in acceptable yield without high dilution conditions. Recently, we further achieved the enantioselective reaction of triynes branched by α-amino acid moiety,[5] which provided a new strategy for the asymmetric synthesis of aminoindan carboxylic acid (Aic) derivatives.[6] We focused on the high tolerability of functional groups in this protocol and considered an intramolecular cycloaddition of peptide-tethered triynes for the synthesis of cyclic peptides.

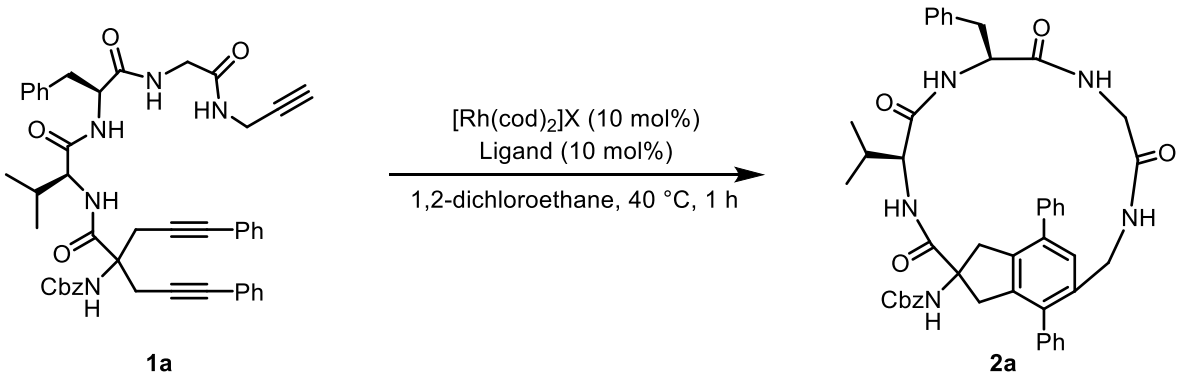
Cyclic peptides are important molecules in modern drug discovery, because their conformational restriction makes them more tolerant to peptitases and interactive to target proteins different from linear peptides.[7] Regarding the facile synthesis of cyclic peptides, transition metal-catalyzed reaction has attracted much attention as an alternative method to conventional intramolecular condensation of linear peptides with a stoichiometric amount of condensation reagents. Pd-Catalyzed Heck reaction,[8] Sonogashira coupling,[9] cycloisomerization,[10] Suzuki-Miyaura coupling,[11] and carbonylative coupling[12] are successful examples. Cu-Catalyzed azide-alkyne cycloadditions have also be reported.[13] Recently, Ru-catalyzed olefin metathesis and Pd-catalyzed C-H activation and amination were used as fascinating approaches.[14-16] Herein we disclose a new catalytic approach using [2+2+2] cycloaddition for the synthesis of cyclic peptides.

RESULTS AND DISCUSSION

As a model substrate, we chose tripeptide-tethered branched triyne **1a** where 1,6-diyne and alkyne moieties are connected by a Val-Phe-Gly tripeptide tether, and examined intramolecular [2+2+2] cycloaddition using cationic rhodium catalysts and various diphosphine ligands at 40 °C in 1,2-dichloroethane (DCE) (Table 1). When the Rh catalyst consisting of BARF (tetrakis(3,5-bis(trifluoromethyl)phenyl)borate) as a counter anion and (*S*)-tolBINAP ((*S*)-2,2'-bis(di-*p*-tolylphosphino)-1,1'-binaphthyl) as a ligand was used, the reaction proceeded to give the desired cyclic peptide **2a** in moderate yield with high diastereoselectivity (Entry 1). We further screened other counter anions of the rhodium complex, and trifluoromethanesulfonate (OTf) gave the best yield and diastereoselectivity among them (Entries 1-3).[17] We next tuned the diphosphine ligands: whereas (*S*)-BINAP gave poorer diastereoselectivity than (*S*)-tolBINAP (Entry 4), higher yield and diastereoselectivity were achieved by more bulky (*S*)-xylBINAP (Entry 5). When we examined (*R*)-tolBINAP as an opposite enantiomer, only a diastereomer was detected and it was the same as the

cycloadduct derived from (*S*)-tolBINAP (Entry 6). These results mean that the stereoselectivity was controlled by the chiral peptide tether, not by chiral Rh catalysts.[18] Finally, achiral ligand BIPHEP (2,2'-bis(diphenylphosphino)-1,1'-biphenyl) also induced almost perfect diastereoselectivity (Entry 7).

Table 1. Screening of counter anions and ligands for Rh catalyst



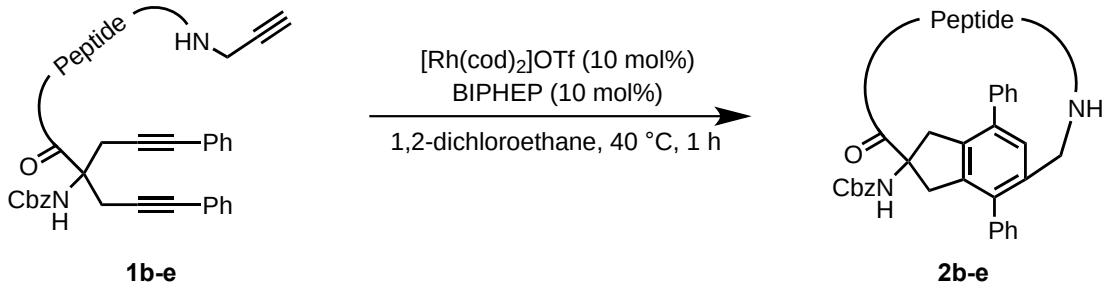
1a **2a**

Entry[a]	X	Ligand	Yield (%)	dr[b]
1	BARF	(*S*)-tolBINAP	55	10:1
2	BF_4	(*S*)-tolBINAP	63	12:1
3	OTf	(*S*)-tolBINAP	69	13:1
4	OTf	(*S*)-BINAP	65	6:1
5	OTf	(*S*)-xylBINAP	75	20:1
6	OTf	(*R*)-tolBINAP	62	>20:1
7	OTf	BIPHEP	75	>20:1

[a] Triyne was added dropwise to a solution of the Rh catalyst over 1 h.
[b] Diastereomeric ratio was determined by integration of ^{1}H-NMR spectra.

Under the reaction conditions of entry 7 in Table 1, we screened triynes with various tethers (Table 2). The reaction of triyne **1b** having a dipeptide tether smoothly proceeded to give **2b** quantitatively (Entry 1). The reaction of triyne **1c** and **1d** possessing Phe-Val-Gly and Gly-Val-Phe tripeptide tethers, respectively, proceeded to give the corresponding cyclic peptides **2c** and **2d** in moderate to good yield (Entries 2 and 3). The cycloaddition of triyne **1e** with a tetrapeptide tether also proceeded, but the yield of the desired cyclic peptide **2e** was low due to the formation of unidentified by-products (Entry 4). In each entry, excellent to almost perfect diastereoselectivity was achieved.

Table 2. Reaction of triynes with various peptide-tethers

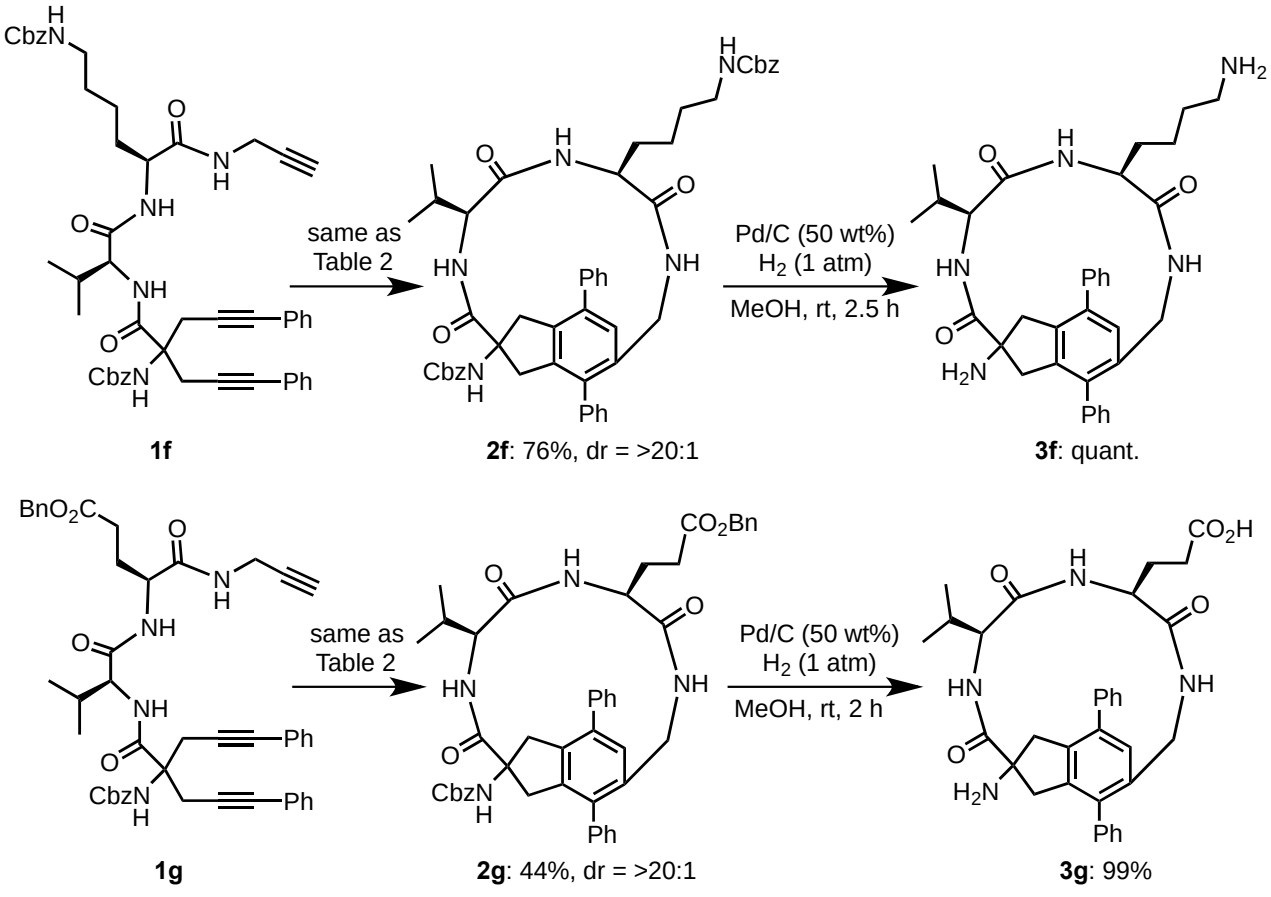


1b-e **2b-e**

Entry[a]	Triyne	Peptide	Yield (%)	dr[b]
1	**1b**	Val-Phe	>99 (**2b**)	>20:1
2	**1c**	Phe-Val-Gly	65 (**2c**)	10:1
3	**1d**	Gly-Val-Phe	59 (**2d**)	>20:1
4	**1e**	Val-Phe-Ala-Gly	24 (**2e**)	>20:1

[a] Triyne was added dropwise to a solution of the Rh catalyst over 1 h.
[b] Diastereomeric ratio was determined by integration of ^{1}H-NMR spectra.

In place of peptide-tethered triynes consisted of only neutral amino acids, we tried the reaction of triynes **1f** and **1g**, which contained basic and acidic amino acid moieties, respectively (Scheme 1). The reaction



Scheme 1. Synthesis of cyclic peptides containing basic or acidic amino acid moiety

of triyne **1f** possessing Val-Lys(Cbz) dipeptide tether smoothly proceeded to the desired cyclic peptide **2f** in good yield. The reaction of triyne **1g** with Val-Glu(OBn) dipeptide tether was sluggish and three hours were required for the reaction to complete, but the cyclic peptide **2g** was obtained in moderate yield. The Cbz and benzyl groups of cycloadducts **2f** and **2g** were readily removed by the conventional reductive treatment, and unprotected cyclic peptides **3f** and **3g** were obtained quantitatively.

In conclusion, we have developed the Rh-catalyzed intramolecular [2+2+2] cycloaddition of peptide-tethered branched triynes. The present reaction provides a new protocol for the catalytic synthesis of cyclic peptides, and moderate to excellent yield was achieved along with almost perfect diastereoselectivity.

EXPERIMENTAL

General. All reactions were examined under an argon atmosphere in oven-dried glassware with a magnetic stirring bar. Dehydrated 1,2-dichloroethane was purchased from Wako Pure Chemical Industries Ltd. (Wako) and degassed by argon bubbling before use. Other reagents were purchased from Wako, Kanto, TCI, or Aldrich and were used without further purification. Flash column chromatography was performed with silica gel (Kanto Chemical Co., Inc. 60 N). Preparative thin-layer chromatography (PTLC) was performed with silica gel-precoated glass plates (Merck 60 GF254) prepared in our laboratory. NMR spectra were measured with JEOL ECX500 (^{1}H NMR, 495.13 MHz; ^{13}C NMR, 124.5 MHz) using TMS as an internal standard, $CDCl_3$ and CD_3OD were used as solvents. High-resolution mass spectra (HRMS) were measured with an electrospray ionization (ESI)-orbitrap mass spectrometer.

Val-Phe-Gly-tethered triyne (1a): a yellow solid; mp 107 °C; ^{1}H NMR ($CDCl_3$) δ 7.52-7.12 (m, 22H), 7.07 (s, 1H), 6.96 (s, 1H), 6.18 (s, 1H), 5.24 (d, *J* = 12.2 Hz, 1H), 5.10 (d, *J* = 12.2 Hz, 1H), 4.84-4.70 (m, 1H), 4.13-4.05 (m, 1H), 4.05-3.96 (m, 3H), 3.96-3.89 (m, 1H), 3.49 (d, *J* = 13.4 Hz, 1H), 3.36 (d, *J* = 7.8 Hz, 1H), 3.32 (d, *J* = 7.8 Hz, 1H), 3.17-3.02 (m, 2H), 2.95-2.83 (m, 1H), 2.16 (t, *J* = 2.5 Hz, 1H), 2.13-2.04 (m, 1H), 0.75 (d, *J* = 6.8 Hz, 3H), 0.58 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR δ 172.9, 172.0, 171.5, 169.3, 156.7, 137.6, 135.3, 131.9, 128.9, 128.9, 128.8, 128.7, 128.7, 128.6, 128.5, 128.5, 128.0, 128.0, 126.8, 122.7, 122.2, 86.1, 85.1, 83.6, 82.8, 79.8, 71.3, 67.9, 61.2, 54.9, 43.4, 36.6, 29.2, 29.2, 29.1, 27.7, 26.2, 19.4, 17.2; HRMS (ESI) *m/z* calcd for $C_{47}H_{47}N_5NaO_6$ ([M+Na]): 800.3409. Found: 800.3419. $[\alpha]^{35}_D$ 34.2 (*c* 1.13, $CHCl_3$).

Val-Phe-tethered triyne (1b): a pale yellow solid; mp 94 °C; ^{1}H NMR ($CDCl_3$) δ 7.41-7.26 (m, 15H), 7.25-7.11 (m, 7H), 6.74 (d, *J* = 5.3 Hz, 1H), 5.75 (s, 1H), 5.28 (d, *J* = 12.2 Hz, 1H), 5.14 (d, *J* = 12.2 Hz, 1H), 4.90-4.80 (m, 1H), 4.25-4.16 (m, 1H), 4.14-4.07 (m, 1H), 3.99-3.89 (m, 1H), 3.65-3.54 (m, 1H), 3.47 (d, *J* = 17.6 Hz, 1H), 3.34 (d, *J* = 17.5 Hz, 1H), 3.17 (d, *J* = 17.6 Hz, 1H), 3.07 (d, *J* = 17.5 Hz, 1H),

2.93-2.82 (m, 1H), 2.21 (t, *J* = 2.5 Hz, 1H), 2.18-2.07 (m, 1H), 0.71 (d, *J* = 7.0 Hz, 3H), 0.43 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR δ 172.4, 171.0, 170.5, 156.4, 138.0, 135.3, 131.9, 131.8, 128.9, 128.9, 128.7, 128.6, 128.5, 128.4, 128.2, 126.6, 122.7, 122.1, 86.1, 85.1, 83.5, 82.7, 79.9, 71.2, 68.0, 61.4, 60.8, 54.2, 36.9, 29.3, 28.9, 27.7, 26.5, 19.5, 16.7 (two pairs of peaks at the aromatic region are overlapped); HRMS (ESI) *m/z* calcd for $C_{45}H_{44}N_4NaO_5$ ([M+Na]): 743.3196. Found: 743.3204. $[\alpha]^{35}_D$ 30.7 (*c* 1.13, $CHCl_3$).

Phe-Val-Gly-tethered triyne (1c): a pale yellow solid; mp 105 °C; ^{1}H NMR ($CDCl_3$) δ 7.75-7.25 (m, 15H), 7.24-6.87 (m, 9H), 5.73 (s, 1H), 5.16-4.93 (m, 1H), 4.73 (d, *J* = 12.1 Hz, 1H), 4.65-4.51 (m, 1H), 4.34-4.21 (m, 1H), 4.15-3.93 (m, 3H), 3.90-3.72 (m, 1H), 3.42-2.82 (m, 6H), 2.41-2.24 (m, 1H), 2.15 (t, *J* = 2.5 Hz, 1H), 0.90 (d, *J* = 6.9 Hz, 3H), 0.83 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 172.0, 171.9, 171.8, 169.2, 156.0, 135.3, 135.2, 131.8, 129.2, 129.1, 129.0, 128.8, 128.8, 128.7, 128.6, 128.5, 128.4, 128.1, 127.5, 122.7, 122.2, 86.0, 85.0, 83.6, 82.6, 79.9, 71.1, 67.9, 61.2, 60.2, 55.6, 43.3, 36.6, 29.0, 28.0, 25.8, 19.4, 17.8 (a pair of peaks at the alkyl region are overlapped); HRMS (ESI) *m/z* calcd for $C_{47}H_{47}N_5NaO_6$ ([M+Na]): 800.3409. Found: 800.3419. $[\alpha]^{35}_D$ 127.6 (*c* 1.11, $CHCl_3$).

Gly-Val-Phe-tethered triyne (1d): a pale yellow solid; mp 200 °C; ^{1}H NMR (CD_3OD) δ 7.14 (m, 20H), 5.25-5.09 (m, 2H), 4.69-4.62 (m, 1H), 4.01 (d, *J* = 7.2 Hz, 1H), 3.98-3.92 (m, 2H), 3.87 (d, *J* = 17.1 Hz, 1H), 3.35-3.32 (m, 3H), 3.31-3.24 (m, 2H), 3.12 (d, *J* = 17.1 Hz, 1H), 2.97-2.85 (m, 1H), 2.44-2.36 (m, 1H), 2.14-1.99 (m, 1H), 0.85 (d, *J* = 6.8 Hz, 3H), 0.79 (d, *J* = 6.8 Hz, 3H) (five NH protons could not be assigned); ^{13}C NMR (CD_3OD) δ 175.3, 174.9, 172.6, 162.9, 156.4, 136.9, 136.6, 131.5, 131.4, 129.0, 128.2, 128.2, 128.1, 127.9, 127.7, 127.7, 127.3, 127.3, 126.5, 123.2, 123.2, 84.1, 83.5, 83.4, 71.1, 66.7, 61.4, 60.3, 54.7, 43.2, 41.0, 40.4, 39.9, 37.4, 29.6, 28.3, 25.9, 18.2, 17.8; HRMS (ESI) *m/z* calcd for $C_{47}H_{47}N_5NaO_6$ ([M+Na]): 800.3410. Found: 800.3419. $[\alpha]^{36}_D$ -27.6 (*c* 1.07, MeOH).

Val-Phe-Ala-Gly-tethered triyne (1e): a white solid; mp 231 °C; ^{1}H NMR ($CDCl_3$) δ 7.45-7.27 (m, 21H), 7.25-7.10 (m, 3H), 6.95 (d, *J* = 3.5 Hz, 1H), 5.85 (s, 1H), 5.24 (d, *J* = 12.1 Hz, 1H), 5.04 (d, *J* = 12.1 Hz, 1H), 4.63-4.53 (m, 2H), 4.17-4.02 (m, 2H), 4.02-3.98 (m, 1H), 3.98-3.87 (m, 2H), 3.52 (dd, *J* = 14.8, 3.1 Hz, 1H), 3.38 (dd, *J* = 17.4, 3.3 Hz, 2H), 3.12 (d, *J* = 17.4 Hz, 1H), 3.06-3.00 (m, 1H), 3.00-2.90 (m, 1H), 2.13 (t, *J* = 2.5 Hz, 1H), 2.02-1.88 (m, 1H), 1.52 (d, *J* = 7.3 Hz, 3H), 0.72 (d, *J* = 7.0 Hz, 3H), 0.61 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 173.5, 173.0, 172.5, 172.0, 169.4, 156.6, 137.5, 135.0, 131.8, 131.8, 129.2, 128.9, 128.9, 128.7, 128.6, 128.6, 128.5, 128.0, 122.4, 121.8, 86.6, 85.5, 82.8, 82.3, 80.3, 70.8, 68.2, 61.9, 61.1, 56.4, 49.5, 43.2, 36.0, 29.2, 28.8, 27.8, 26.3, 19.2, 17.5, 17.1 (two pairs of peaks at the aromatic region are overlapped); HRMS (ESI) *m/z* calcd for $C_{50}H_{52}N_6NaO_7$ ([M+Na]): 871.3779. Found: 871.3790. $[\alpha]^{36}_D$ 8.3 (*c* 1.05, MeOH).

Val-Lys(Cbz)-tethered triyne (1f): a pale yellow solid; mp 184 °C; ^{1}H NMR ($CDCl_3$) δ 7.47-7.21 (m, 21H), 7.21-7.09 (m, 1H), 6.91 (s, 1H), 5.95 (s, 1H), 5.21-5.09 (m, 2H), 5.05 (s, 2H), 4.95 (s, 1H), 4.51-4.37 (m, 1H), 4.27-4.17 (m, 1H), 4.17-4.06 (m, 1H), 3.98-3.85 (m, 1H), 3.51-3.25 (m, 2H), 3.17 (t, *J*

= 15.0 Hz, 1H), 3.14-3.00 (m, 3H), 2.40-2.23 (m, 1H), 2.19 (t, *J* = 2.5 Hz, 1H), 2.11-1.91 (m, 2H), 1.53-1.24 (m, 4H), 0.89 (d, *J* = 7.0 Hz, 3H), 0.82 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 172.4, 171.6, 170.9, 156.5, 156.3, 136.7, 135.6, 131.9, 131.9, 128.9, 128.8, 128.8, 128.6, 128.6, 128.5, 128.4, 128.1, 128.1, 128.0, 122.7, 122.3, 85.9, 85.0, 83.7, 83.0, 79.9, 71.2, 67.7, 66.6, 61.4, 60.6, 53.2, 40.8, 30.7, 29.8, 29.3, 29.2, 27.6, 26.4, 23.3, 19.6, 17.4; HRMS (ESI) *m/z* calcd for $C_{50}H_{53}N_5NaO_7$ ([M+Na]): 858.3286. Found: 858.3837. $[\alpha]^{36}_D$ 59.5 (*c* 1.07, $CHCl_3$).

Val-Glu(OBn)-tethered triyne (1g): a pale yellow solid; mp 101 °C; ^{1}H NMR ($CDCl_3$) δ 7.47-7.39 (m, 1H), 7.39-7.22 (m, 20H), 7.17-7.01 (m, 1H), 6.83 (d, *J* = 5.7 Hz, 1H), 5.78 (s, 1H), 5.18-5.00 (m, 4H), 4.55-4.45 (m, 1H), 4.22 (dd, *J* = 5.7, 4.1 Hz, 1H), 4.13 (ddd, *J* = 17.5, 5.3, 2.6 Hz, 1H), 3.93 (ddd, *J* = 17.5, 5.3, 2.6 Hz, 1H), 3.53-2.99 (m, 4H), 2.59-2.26 (m, 4H), 2.19 (t, *J* = 2.5 Hz, 1H), 2.14-1.95 (m, 1H), 0.89 (d, *J* = 7.0 Hz, 3H), 0.78 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 172.8, 172.4, 170.8, 170.8, 156.4, 135.8, 135.5, 131.9, 131.9, 128.8, 128.8, 128.6, 128.6, 128.5, 128.5, 128.4, 128.3, 128.3, 128.2, 122.7, 122.2, 86.1, 85.0, 83.7, 82.9, 79.8, 71.2, 67.9, 66.5, 61.3, 60.6, 52.9, 31.4, 29.2, 29.1, 27.8, 26.5, 26.3, 19.6, 17.3; HRMS (ESI) *m/z* calcd for $C_{48}H_{48}N_4NaO_7$ ([M+Na]): 815.3406. Found: 815.3415. $[\alpha]^{36}_D$ 85.9 (*c* 0.82, $CHCl_3$).

Typical procedure for the Rh-catalyzed cycloaddition: BIPHEP (10 mol%, 2.6 mg) and $[Rh(cod)_2]OTf$ (10 mol%, 2.3 mg) were placed in a dried schlenk tube, which was then evacuated and backfilled with argon (×3). To the reaction vessel was added 1,2-dichloroethane (0.5 mL). While stirring the solution at room temperature for 5 min, hydrogen gas was introduced, and the solution was further stirred for 30 min at room temperature. After removal of the solvent and hydrogen gas under reduced pressure, argon gas was introduced. 1,2-Dichloroethane (0.5 mL) was added and the reaction vessel was immersed in an oil bath of 40 °C for 5 min. Then, triyne **1** (0.05 mmol) in 1,2-dichloroethane (2.5 mL) was added dropwise via syringe pump over 1 h. After the reaction finished, the solvent was removed under reduced pressure, and the crude products were purified by preparative TLC to give analytically pure cycloadduct **2**. The diastereomeric ratio was determined by integration of ^{1}H-NMR spectra.

Val-Phe-Gly-tethered cycloadduct (2a): a pale yellow solid; mp 202 °C; ^{1}H NMR ($CDCl_3$) δ 7.47-7.06 (m, 22H), 6.31 (s, 1H), 6.24-5.95 (m, 2H), 5.75 (s, 1H), 5.06 (s, 2H), 4.67-4.49 (m, 1H), 4.23-3.88 (m, 5H), 3.79 (t, *J* = 7.5 Hz, 1H), 3.34-3.19 (m, 1H), 3.14-2.97 (m, 1H), 2.97-2.77 (m, 3H), 2.00 (s, 1H), 0.77 (brs, 3H), 0.73 (brs, 3H); ^{13}C NMR ($CDCl_3$) δ 173.2, 170.6, 170.2, 168.8, 155.1, 141.7, 139.7, 138.9, 138.8, 137.4, 136.5, 135.0, 134.0, 130.5, 129.6, 129.3, 128.9, 128.6, 128.5, 128.5, 128.1, 128.0, 127.9, 127.9, 127.7, 67.1, 66.5, 58.1, 57.4, 43.5, 42.7, 42.1, 40.7, 37.2, 33.1, 18.8, 17.3 (two pairs of peaks at the aromatic region are overlapped); HRMS (ESI) *m/z* calcd for $C_{47}H_{47}N_5NaO_6$ ([M+Na]): 800.3408. Found: 800.3419. $[\alpha]^{33}_D$ 24.9 (*c* 1.46, $CHCl_3$).

Val-Phe-tethered cycloadduct (2b): a white solid; mp 145 °C; ^{1}H NMR ($CDCl_3$) δ 7.65-7.11 (m, 22H), 6.08 (s, 1H), 6.01-5.85 (m, 1H), 5.71 (s, 1H), 5.01 (s, 2H), 4.74-4.55 (m, 1H), 3.94-3.81 (m, 1H), 3.76 (dd, *J* = 13.3, 3.2 Hz, 1H), 3.72-3.57 (m, 1H), 3.56-3.08 (m, 6H), 1.89 (s, 1H), 0.74 (brs, 3H), 0.56 (d, *J* = 4.8 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 172.9, 172.6, 170.6, 155.8, 141.2, 139.0, 138.1, 138.1, 137.8, 136.7, 136.2, 135.8, 135.7, 129.1, 128.9, 128.7, 128.6, 128.4, 128.3, 128.2, 128.0, 127.9, 127.6, 127.1, 68.1, 66.9, 62.9, 61.2, 44.7, 42.4, 40.2, 35.0, 31.8, 29.8, 18.6 (two pairs of peaks at the aromatic region are overlapped); HRMS (ESI) *m/z* calcd for $C_{45}H_{44}N_4NaO_5$ ([M+Na]): 743.3196. Found: 743.3204. $[\alpha]^{33}_D$ -126.9 (*c* 1.71, $CHCl_3$).

Phe-Val-Gly-tethered cycloadduct (2c): a pale brown solid; mp 169 °C; ^{1}H NMR ($CDCl_3$) δ 7.51-7.26 (m, 20H), 7.23-7.00 (m, 3H), 6.69 (s, 1H), 6.42 (s, 1H), 6.20 (s, 1H), 5.15-5.05 (m, 2H), 4.62-4.52 (m, 1H), 4.41-4.30 (m, 1H), 4.26-4.02 (m, 4H), 3.46 (dd, *J* = 17.2, 3.5 Hz, 1H), 3.36-3.17 (m, 2H), 2.92 (d, *J* = 15.9 Hz, 1H), 2.65-2.52 (m, 1H), 2.45-2.31 (m, 1H), 1.62-1.49 (m, 1H), 0.78 (d, *J* = 6.7 Hz, 3H), 0.54 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 172.7, 170.7, 170.6, 168.4, 154.7, 148.4, 142.3, 139.7, 139.1, 139.1, 137.9, 136.9, 136.6, 134.0, 130.5, 129.8, 129.2, 128.5, 128.5, 128.1, 128.0, 128.0, 127.8, 127.7, 127.6, 66.4, 66.1, 63.0, 54.8, 43.6, 42.9, 42.8, 40.9, 37.9, 29.3, 19.2, 19.0 (two pairs of peaks at the aromatic region are overlapped); HRMS (ESI) *m/z* calcd for $C_{47}H_{47}N_5NaO_6$ ([M+Na]): 800.3409. Found: 800.3419. $[\alpha]^{34}_D$ 73.1 (*c* 1.27, $CHCl_3$).

Gly-Val-Phe-tethered cycloadduct (2d): a white solid; mp 190 °C; ^{1}H NMR ($CDCl_3$) δ 7.53-7.28 (m, 14H), 7.20-7.07 (m, 7H), 6.81 (s, 1H), 6.67 (s, 1H), 6.24-5.91 (m, 3H), 5.04 (s, 2H), 4.53-4.43 (m, 1H), 4.43-4.30 (m, 2H), 3.95-3.82 (m, 3H), 3.62-3.52 (m, 2H), 3.41-3.28 (m, 1H), 3.06-2.84 (m, 2H), 2.60 (d, *J* = 15.3 Hz, 1H), 1.80-1.66 (m, 1H), 0.59-0.51 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 173.5, 170.6, 169.5, 169.4, 154.7, 141.9, 139.6, 139.5, 139.3, 139.1, 138.4, 138.1, 137.7, 136.3, 134.8, 130.9, 129.5, 128.8, 128.7, 128.7, 128.6, 128.3, 128.2, 127.8, 126.8, 66.6, 66.4, 62.3, 55.7, 43.6, 43.4, 41.2, 40.2, 36.2, 29.3, 18.7, 17.8 (two pairs of peaks at the aromatic region are overlapped); HRMS (ESI) *m/z* calcd for $C_{47}H_{47}N_5NaO_6$ ([M+Na]): 800.3411. Found: 800.3419. $[\alpha]^{34}_D$ -39.0 (*c* 1.19, $CHCl_3$).

Val-Phe-Ala-Gly-tethered cycloadduct (2e): a pale yellow solid; mp 300 °C (decomp.); ^{1}H NMR ($CDCl_3$) δ 7.76-7.61 (m, 1H), 7.52-7.26 (m, 15H), 7.25-7.16 (m, 3H), 7.15-7.02 (m, 2H), 6.77-6.61 (m, 2H), 6.56 (s, 1H), 6.05 (d, *J* = 7.7 Hz, 1H), 5.79 (s, 1H), 5.39 (s, 1H), 5.11-4.99 (m, 2H), 4.81-4.62 (m, 1H), 4.30 (ddd, *J* = 17.2, 13.9, 4.3 Hz, 2H), 4.17-4.09 (m, 1H), 4.02-3.83 (m, 2H), 3.75-3.44 (m, 4H), 3.10 (d, *J* = 15.2 Hz, 1H), 2.88-2.71 (m, 1H), 2.72-2.55 (m, 1H), 2.25 (br, 1H), 1.21 (d, *J* = 7.2 Hz, 3H), 0.79 (d, *J* = 6.5 Hz, 3H), 0.64 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 173.5, 171.6, 171.3, 170.9, 168.2, 156.0, 140.0, 139.4, 139.3, 138.2, 137.4, 136.7, 135.9, 135.7, 130.3, 129.7, 129.1, 129.0, 128.9, 128.7, 128.6, 128.5, 128.4, 128.4, 128.1, 127.8, 127.8, 127.7, 67.1, 66.3, 59.1, 53.4, 51.3, 43.1, 42.9, 42.4, 38.9, 30.5, 29.8, 19.2, 16.9, 16.4; HRMS (ESI) *m/z* calcd for $C_{50}H_{52}N_6NaO_7$ ([M+Na]): 871.3779. Found:

871.3790. $[\alpha]^{36}_{D}$ -7.76 (*c* 0.52, $CHCl_3$).

Val-Lys(Cbz)-tethered cycloadduct (2f): a pale yellow solid; mp 165 °C; ^{1}H NMR ($CDCl_3$) δ 7.69-7.02 (m, 22H), 6.56 (s, 1H), 6.12 (s, 1H), 5.86 (s, 1H), 5.12-4.94 (m, 5H), 4.67-4.55 (m, 1H), 3.76-3.54 (m, 3H), 3.45-3.23 (m, 3H), 3.20-3.07 (m, 3H), 2.11-1.80 (m, 3H), 1.80-1.69 (m, 2H), 1.27-1.14 (m, 2H), 0.81 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 172.8, 172.6, 171.3, 156.5, 155.9, 141.1, 139.1, 138.0, 138.0, 137.8, 136.7, 135.8, 135.7, 129.1, 129.0, 128.6, 128.4, 128.2, 128.2, 128.2, 128.1, 128.0, 127.8, 127.6, 127.6, 68.1, 66.9, 66.7, 62.1, 61.0, 44.6, 42.2, 40.8, 32.0, 29.4, 29.0, 23.8, 18.9, 18.8, 14.3; HRMS (ESI) *m/z* calcd for $C_{50}H_{53}N_5NaO_7$ ([M+Na]): 858.3824. Found: 858.3837. $[\alpha]^{35}_{D}$ -92.9 (*c* 2.59, $CHCl_3$).

Val-Glu(OBn)-tethered cycloadduct (2g): a white solid; mp 122 °C; ^{1}H NMR ($CDCl_3$) δ 7.61-7.06 (m, 22H), 6.52-6.38 (m, 1H), 6.09 (br, 1H), 5.76 (s, 1H), 5.02-4.87 (m, 4H), 4.68-4.54 (m, 1H), 3.76-3.51 (m, 4H), 3.36-3.25 (m, 2H), 3.24-3.11 (m, 1H), 2.48-2.23 (m, 4H), 1.97 (br, 1H), 0.85 (brs, 3H), 0.80 (brs, 3H); ^{13}C NMR ($CDCl_3$) δ 172.9, 172.6, 172.4, 170.5, 155.8, 141.1, 139.0, 138.1, 137.9, 137.8, 135.7, 136.0, 135.7, 129.0, 129.0, 128.7, 128.6, 128.6, 128.5, 128.4, 128.3, 128.2 128.0, 127.9, 127.7, 68.1, 66.7, 61.1, 61.0, 61.0, 42.3, 32.0, 30.8, 24.4, 18.9, 18.9, 18.8, 18.8 (two pairs of peaks at the aromatic region are overlapped); HRMS (ESI) *m/z* calcd for $C_{48}H_{48}N_4NaO_7$ ([M+Na]): 815.3406. Found: 815.3415. $[\alpha]^{35}_{D}$ -76.9 (*c* 1.03, $CHCl_3$).

Val-Lys-tethered cyclic peptide (3f): a pale yellow solid; mp 197 °C (decomp.); ^{1}H NMR (MeOD) δ 7.76-7.13 (m, 11H), 4.59 (d, *J* = 13.2 Hz, 1H), 3.74 (d, *J* = 13.2 Hz, 1H), 3.62 (d, *J* = 8.8 Hz, 1H), 3.43 (t, *J* = 8.2 Hz, 1H), 3.32-3.28 (m, 1H), 3.27-3.15 (m, 2H), 3.15-3.04 (m, 2H), 2.85 (t, *J* = 7.6 Hz, 2H), 2.30-2.09 (m, 1H), 2.02-1.84 (m, 2H), 1.72-1.57 (m, 2H), 1.46-1.28 (m, 2H), 0.95-0.78 (m, 6H) (six NH protons could not be assigned); ^{13}C NMR (MeOD) δ 179.8, 176.8, 176.2, 145.3, 143.0, 142.2, 141.9, 141.9, 141.8, 141.4, 139.6, 132.8, 132.3, 132.2, 131.7, 131.5, 131.4, 72.8, 64.9, 64.5, 51.5, 46.0, 44.7, 43.5, 35.8, 32.4, 31.1, 27.3, 22.8, 22.3; HRMS (ESI) *m/z* calcd for $C_{34}H_{42}N_5O_3$ ([M+H]): 568.3281. Found: 568.3282. $[\alpha]^{26}_{D}$ -82.3 (*c* 1.39, MeOH).

Val-Glu-tethered cyclic peptide (3g): a white solid; mp 193 °C (decomp.); ^{1}H NMR (MeOD) δ 7.96-7.12 (m, 11H), 4.65-4.55 (m, 1H), 3.81-3.68 (m, 1H), 3.61 (d, *J* = 8.4 Hz, 1H), 3.57-3.49 (m, 1H), 3.41-3.33 (m, 1H), 3.27-3.11 (m, 3H), 2.46-2.31 (m, 1H), 2.31-2.17 (m, 3H), 2.03-1.86 (m, 1H), 0.96-0.84 (m, 6H) (five NH protons and a CO_2H proton could not be assigned); ^{13}C NMR (MeOD) δ 176.5, 174.0, 172.5, 172.0, 140.8, 139.1, 138.2, 137.9, 137.6, 137.2, 135.9, 128.6, 128.2, 128.2, 127.7, 127.6, 127.4, 67.9, 60.7, 60.5, 46.0, 41.7, 39.5, 31.9, 31.7, 24.8, 18.3, 17.8 (a pair of peaks at the alkyl region are overlapped); HRMS (ESI) *m/z* calcd for $C_{33}H_{37}N_4O_5$ ([M+H]): 569.2759. Found: 569.2758. $[\alpha]^{29}_{D}$ -100.2 (*c* 1.43, MeOH).

ACKNOWLEDGEMENTS

This work was supported by ACT-C from JST (Japan) and Waseda University Grant for Special Research Projects.

REFERENCES AND NOTES

1. (a) M. Lautens, W. Klute, and W. Tam, *Chem. Rev.*, 1996, **96**, 49; (b) S. Saito and Y. Yamamoto, *Chem. Rev.*, 2000, **100**, 2901; (c) T. Shibata and K. Tsuchikama, *Org. Biomol. Chem.*, 2008, **6**, 1317; (d) K. Tanaka, *Chem. Asian J.*, 2009, **4**, 508; (e) Y. Shibata and K. Tanaka, *Synthesis*, 2012, **44**, 323; (f) Transition-Metal-Mediated Aromatic Ring Construction, Part I: [2 + 2 + 2] and Related Cycloaddition Reactions, ed. by K. Tanaka, Wiley, Hoboken, NJ, 2013.
2. H. Kinoshita, H. Shinokubo, and K. Oshima, *J. Am. Chem. Soc.*, 2003, **125**, 7784.
3. (a) K. Tanaka, H. Sagae, K. Toyoda, K. Noguchi, and M. Hirano, *J. Am. Chem. Soc.*, 2007, **129**, 1522; (b) K. Tanaka, H. Sagae, K. Toyoda, and M. Hirano, *Tetrahedron*, 2008, **64**, 831.
4. (a) T. Shibata, T. Uchiyama, and K. Endo, *Org. Lett.*, 2009, **11**, 3906; (b) T. Shibata, T. Uchiyama, H. Hirashima, and K. Endo, *Pure Appl. Chem.*, 2011, **83**, 597; (c) T. Shibata, M. Miyoshi, T. Uchiyama, K. Endo, N. Miura, and K. Monde, *Tetrahedron*, 2012, **68**, 2679.
5. A pioneering work of amino acid-tethered diynes as substrates for [2+2+2] cycloaddition: S. Kotha and E. Brahmachary, *Tetrahedron Lett.*, 1997, **38**, 3561.
6. Y. Tahara, S. Obinata, K. S. Kanyiva, A. Mándi, T. Taniguchi, K. Monde, and T. Shibata, *Eur. J. Org. Chem.*, 2016, 1405.
7. (a) J. N. Lambert, J. P. Mitchell, and K. D. Roberts, *J. Chem. Soc., Perkin Trans. 1*, 2001, 471; (b) E. Marsault, and M. L. Peterson, *J. Med. Chem.*, 2011, **54**, 1961; (c) C. J. White and A. K. Yudin, *Nat. Chem.*, 2011, **3**, 509; (d) A. K. Yudin, *Chem. Sci.*, 2015, **6**, 30; (e) T. Morioka, N. D. Loik, C. J. Hipolito, Y. Goto, and H. Suga, *Curr. Opin. Chem. Biol.*, 2015, **26**, 34.
8. (a) K. Akaji, K. Teruya, M. Akaji, and S. Aimoto, *Tetrahedron*, 2001, **57**, 2293; (b) P. R. Reddy, V. Balraju, G. R. Madhavan, B. Banerji, and J. Iqbal, *Tetrahedron Lett.*, 2003, **44**, 353.
9. (a) A. C. Spivey, J. McKendrick, and R. Srikaran, *J. Org. Chem.*, 2003, **68**, 3575; (b) V. Balraju, D. S. Reddy, M. Periasamy, and J. Iqbal, *J. Org. Chem.*, 2005, **70**, 9626; (c) H. T. Brink, D. T. S. Rijkers, and R. M. J. Liskamp, *J. Org. Chem.*, 2006, **71**, 1817.
10. V. Balraju, R.-V. Dev, D. S. Reddy, and J. Iqbal, *Tetrahedron Lett.*, 2006, **47**, 3569.
11. (a) Y. Jia, M. Michèle, B. Choussy, and J. Zhu, *Org. Lett.*, 2007, **9**, 2401; (b) J. Dufour, L. Neuville, and J. Zhu, *Chem. Eur. J.*, 2010, **16**, 10523; (c) A. Afonso, O. Cussó, L. Feliu, and M. Planas, *Eur. J. Org. Chem.*, 2012, 6204.
12. (a) S. Kamioka, S. Shimizu, T. Doi, and T. Takahashi, *J. Comb. Chem.*, 2008, **10**, 681; (b) T. Doi, S.

Kamioka, S. Shimizu, and T. Takahashi, *Org. Lett.*, 2008, **10**, 817.

13. (a) V. D. Bock, R. Perciaccante, T. P. Jansen, H. Hiemstra, and J. H. van Maarseveen, *Org. Lett.*, 2006, **8**, 919; (b) J. Springer, K. R. de Cuba, S. Calvet-Vitale, J. A. J. Geenevasen, P. H. H. Hermkens, H. Hiemstra, and J. H. van Maarseveen, *Eur. J. Org. Chem.*, 2008, 2592.
14. (a) A. E. Cohrt and T. E. Nielsen, *ACS Comb. Sci.*, 2014, **16**, 71; (b) D. S. Maxwell, D. Sun, Z. Peng, D. V. Martin, B. A. B. Prasad, and W. G. Bornmann, *Tetrahedron Lett.*, 2013, **54**, 5799; (c) S. L. Mangold and R. H. Grubbs, *Chem. Sci.*, 2015, **6**, 4561.
15. (a) H. Dong, C. Limberakis, S. Liras, D. Price, and K. James, *Chem. Commun.*, 2012, **48**, 11644; (b) L. Mendive-Tapia, S. Preciado, J. García, R. Ramón, N. Kielland, F. Albericio, and R. Lavilla, *Nat. Commun.*, 2015, **6**, 7160; (c) L. Mendive-Tapia, A. Bertran, J. García, G. Acosta, F. Albericio, and R. Lavilla, *Chem. Eur. J.*, 2016, **22**, 13114.
16. B. A. Hopkins, G. F. Smith, and N. Sciammetta, *Org. Lett.*, 2016, **18**, 4072.
17. The reaction of methyl-substituted and unsubstituted diynes did not give the corresponding cycloadducts.
18. The absolute configuration could not be determined yet.