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Acid-mediated Synthesis of Fully Substituted 1,2,3-Triazoles: Multicomponent Couplings, Mechanistic Study, Synthesis of Serine Hydrolase Inhibitor and Its Derivatives

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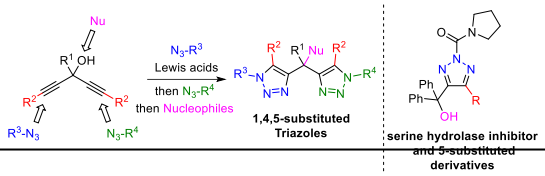

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Acid-mediated Synthesis of Fully Substituted 1,2,3-Triazoles: Multicomponent Coupling Reactions, Mechanistic Study, Synthesis of Serine Hydrolase Inhibitor and Its Derivatives

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ABSTRACT

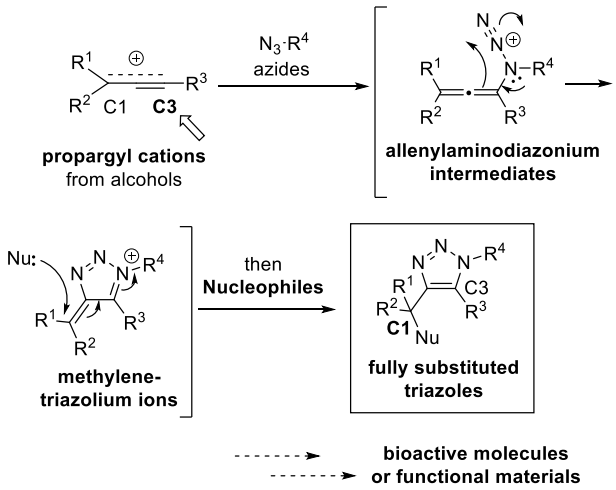
We describe the full details of multicomponent coupling reactions in acid-mediated synthesis of fully substituted 1,2,3-triazoles syntheses, and their applications to bioactive molecule synthesis. For substitution with wide range of nucleophiles, selection of acids or activating reagents was important, and various types of multicomponent coupling reactions were demonstrated, allowing functionalization with alcohols, amines, thiol, azide, and carbon nucleophiles. Four-component couplings including double triazolations were also tested. The efficiency of this method was demonstrated by the synthesis of serine hydrolase inhibitor and its novel substituted derivatives.

1. Introduction

Organic azides are important functional compounds that facilitate the introduction of amino groups, chemical bond rearrangements, and C–H insertions via nitrenes.[1] Because of the specific reactivity and various applications, organic azides have been well studied in the fields of synthetic organic chemistry and natural product synthesis.[1b]

In recent years, azide–alkyne cycloadditions (AAC) under Cu-catalyzed (CuAAC) and Cu-free conditions have been extensively developed to produce 1,2,3-1*H*-triazoles;[2] many studies have reported their numerous applications, especially in chemical biology,[2,3] ligand/material design,[4] pharmaceuticals,[5] and new reactions of triazoles as the synthetic precursors.[6] However, triazole syntheses by CuAAC and metal-activated AAC are mostly limited to terminal alkynes, and one-pot or cascade transformation of triazole compounds have been requested toward synthesis of multifunctional molecules in short steps.

The reactions of organic azides with carbocations have been well studied (Schmidt–Aubé reaction).[1a,7] However, the reactions of organic azides with delocalized carbocations such as allyl/propargyl cations have rarely been studied. Recently, we investigated the reactions of organic azides with allyl cations, smoothly affording cyclic unsaturated imines under moderate temperature conditions, and this method enabled the synthesis of



Scheme 1. Triazole synthesis with propargyl cations, organic azides, and additional nucleophiles.

the unstable iminium venom alkaloid of Costa Rican ants.[8] Based on the research,[8a] we previously reported novel triazole synthesis with propargyl cations (Scheme 1).[9] In this reactions, organic azides can attack at both the C1 and C3 positions of propargyl cations as shown in Scheme 1, and it has been reported that the

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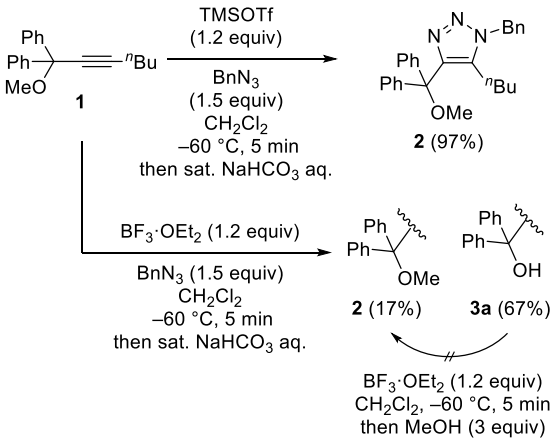
attacks at the C1 positions simply proceeded by the Schmidt reaction to produce the corresponding ynimines.[10] On the other hand, if the attack of azides can be controlled, then the C–N bond formation at the C3 position would produce allenylaminodiazonium compounds—a type of allenylazides.[11] We anticipated that these unstable species could immediately be transformed to cyclic triazolium intermediates possessing exo-methylene units, to which nucleophiles could be reacted. Because fully substituted and functionalized triazoles are difficult to prepare by CuAAC, our approach could provide an efficient synthetic method for promising compounds for developing novel bioactive molecules and functional materials.[12,13] Herein we report the full detail of the three/four-component coupling reactions of acid-mediated triazole synthesis via carbocations and applications to the syntheses of serine hydrolase inhibitor and its derivatives, which are difficult to prepare by CuAAC.

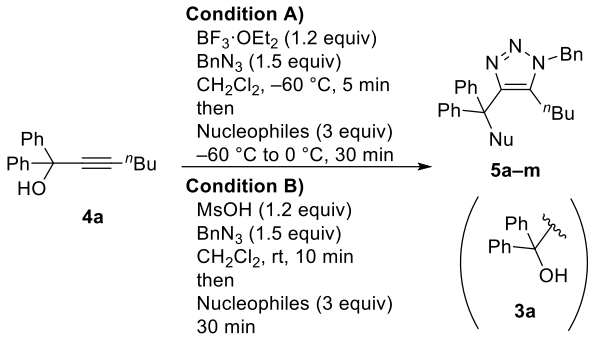
2. Results and discussions

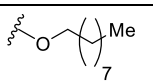
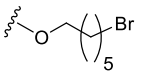
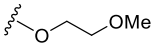
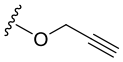
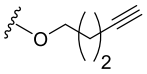
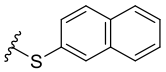
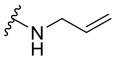
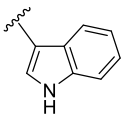
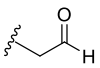
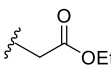
In previous paper, we mainly disclosed introduction of hydroxy group into the triazole products in one-pot by quenching with aqueous media as nucleophiles.[9] However, considering the proposed reaction mechanism (Scheme 1), the products could be functionalized using other additional nucleophiles instead of a hydroxy group. Although we have already demonstrated a few examples of three-component couplings including intramolecular substitution, the true source of hydroxy groups is unclear. Thus, before testing the generality of multicomponent coupling reactions, we reinvestigated the origin of the hydroxy group (Scheme 2). The treatment of methyl ether **1** with stoichiometric amount of trimethylsilyl trifluoromethanesulfonate (TMSOTf),[9] which were used in previous work, only afforded the triazole possessing methoxy group **2** at both –90 and –60 °C, even after quenching with an aqueous medium. However, boron trifluoride etherate ($BF_3{\cdot}OEt_2$) gave hydroxy compound **3a** as the major product. This indicates that the origin of the hydroxy group depends on the acid used, and the resulting silanols or silyl ethers may be the source of hydroxy groups in the case of TMSOTf. With $BF_3{\cdot}OEt_2$, the benzylic position was successfully substituted by external water. This indicates that $BF_3{\cdot}OEt_2$ is a suitable acid for the substitution of triazolium intermediates with additional nucleophiles probably because hydroxy group donation activity of the resulting boronates or borinates are limited. For introduction of hydroxy groups, TMSOTf seems to be better reagent. Methyl ether **2** was not obtained from **3a** by acid treatments in the presence of methanol. Thus, the functionalization of the benzylic position should be performed as one-pot reactions.



Scheme 2. Investigation of the origin of hydroxy group

Table 1. Scope of nucleophiles



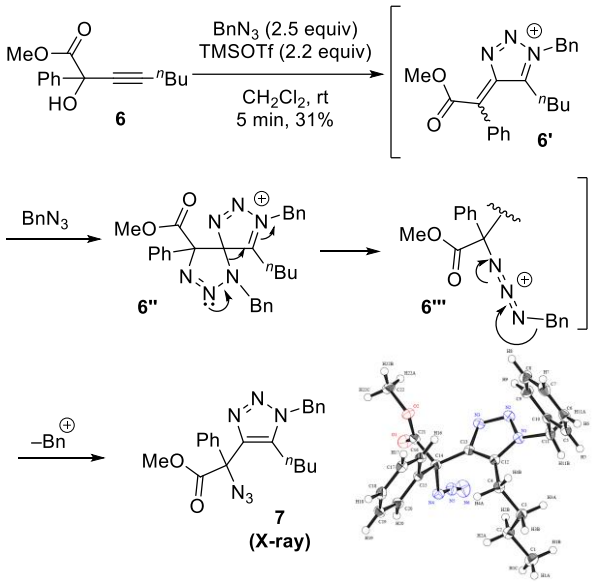
Entry	Nucleophiles and Products		Yield (%)[a]	
			Cond. A	Cond. B
1		**5a**	82 (10)	69 (trace)
2		**5b**	73 (11)	58 (11)
3		**5c**	76 (12)	63 (0)
4		**5d**	74 (12)	53 (trace)
5		**5e**	77 (10)	61 (0)
6		**5f**	81 (7)	62 (0)
7		**5g**	78 (11)	55 (0)
8		**5h**	77 (12)	60 (0)
9[b]		**5i**	85 (10)	70 (0)
10		**5j**	65 (0)	42 (0)
11[c]		**5k**	69 (3)	54 (trace)
12[d]		**5l**	55 (35)	43 (25)
13[e]		**5m**	68 (20)	55 (14)

[a] Isolated yields of **5a–m** and **3a** (in parentheses). [b] Azidotrimethylsilane was used as the nucleophile. [c] Allyltributyltin was used as the nucleophile. [d] Ethyl vinyl ether was used as the nucleophile. [e] 1-Ethoxy-1-trimethylsilyloxyethylene was used as the nucleophile.

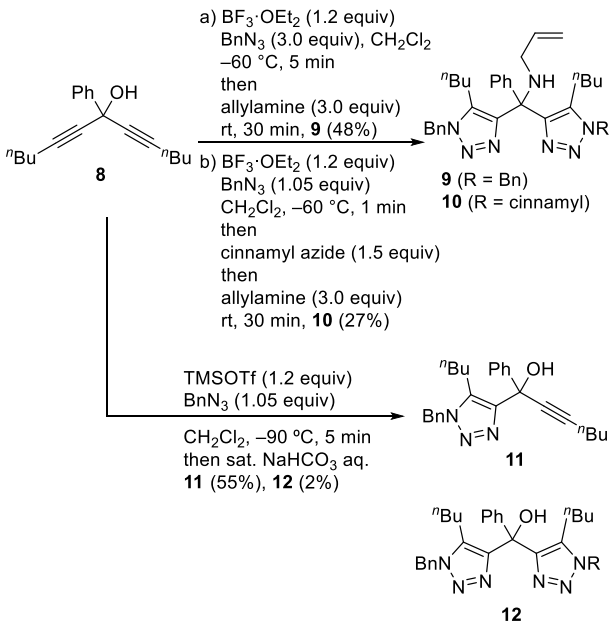
Based on these results, three-component coupling reactions with various nucleophiles were investigated to functionalize the benzylic position with $BF_3{\cdot}OEt_2$ (Table 2, Condition A). In order to avoid quenching reaction by moisture, the reactions were performed under nitrogen gas atmosphere. The reactions with primary alcohols afforded the desired ether products (**5a**–**e**) in good yields (entries 1–5). Although the reactions with secondary alcohols failed to afford the coupling products, naphthalenethiol,

and diethylamine were successfully introduced to the products similar to allylamine (entries 6–8). Azido product **5i** was also obtained in a good yield from azidotrimethylsilane (entry 9). Not only heteroatom nucleophiles, but also carbon nucleophiles were investigated to form quaternary carbon centers. Indole gave desired coupling compound **5j** selectively (entry 10). The allyl group was successfully introduced with allyltributyltin (entry 11), while allylsilanes did not afford **5k**. The C–C bonds could also be formed by silyl enol ethers to afford aldehyde **5l** and ethyl ester **5m** (entries 12 and 13). Addition of molecular sieves did not improve the results.

To achieve these three-component coupling reactions at ambient temperature, the same reactions were investigated with methanesulfonic acid (MsOH) (Table 1, Condition B),[9] and the desired coupling products were successfully obtained in 40 min. Interestingly, although the product yields were slightly lower than those obtained under condition A, lesser amount of by-product **3a** were generated. Considering the generation of **3a** in Scheme 2, boronic acids or borates were still active as nucleophiles, and water molecule generated by MsOH was relatively weeker nucleophiles than those acids.



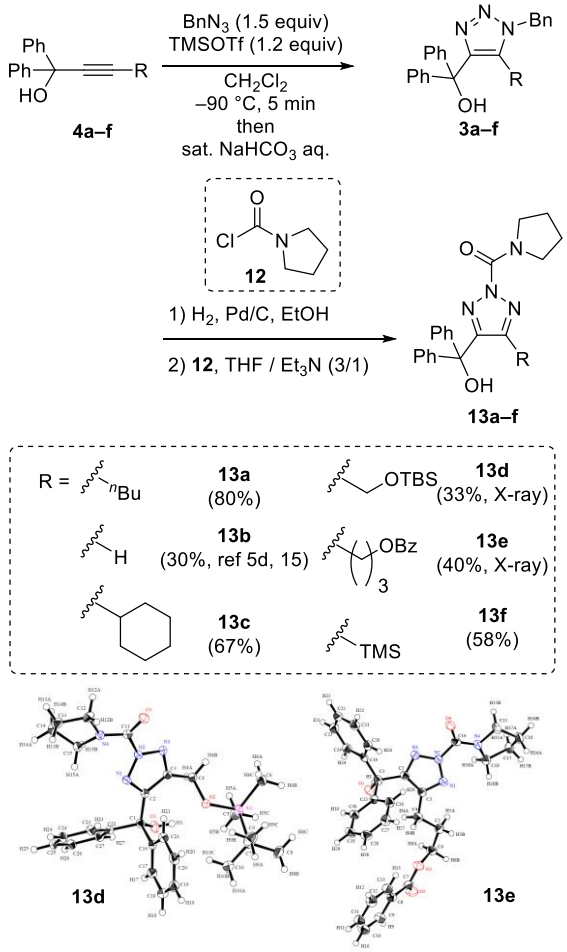
Scheme 3. Azidation of benzylic position with organic azide.



Scheme 4. Four-component coupling reactions, and control of triazolation.

Generation of three-component coupling products indicated the presence of methylenetriazolium intermediates or carbocations of triazole (Scheme 1). Other evidence of the methylenetriazolium intermediates was obtained from **6** (Scheme 3). When electron-withdrawing methoxycarbonyl group was placed instead of one of the phenyl groups on the C1 position, **6** was converted into triazole **7** at ambient temperature, possessing an azide on C1 position. Because these types of azido triazoles were not found in other cases, the azide group of **7** may be introduced by the [3 + 2] cycloaddition of an additional benzyl azide to unsaturated ester moiety of triazolium intermediate **6'**.

To further develop the one-pot functionalization of triazoles by multicomponent coupling reactions, double [3 + 2] triazolation reactions were investigated (Scheme 4). Based on the previous successful results, we conducted four-component coupling reactions consisted by double [3 + 2] reactions followed by substitutions with nucleophiles. When allylamine was used as the nucleophile, the reactions successfully afforded the desired products **9** and **10** in moderate yields along with trace amount of Meyer-Schuster rearrangement product, hydroxy-substituted compound, and unidentified polymeric materials. In these cases, introduction of carbon nucleophiles like indole were unsuccessful, and hydroxylated compunds were produced. For introduction of hydroxyl groups, use of TMSOTf was efficient in double triazolation reactions.[9] Notably, the triazole synthesis could be controlled to afford monotriazole **11** by reducing the amount of



Scheme 5. Synthesis of serine hydrolase inhibitor urea and 5-substituted derivatives.

organic azide and the use of TMSOTf (2% of bistriazole **12** was obtained).

To demonstrate the efficiency of our method for bioactive molecule synthesis, we carried out the synthesis of triazole urea **13b** reported as a serine hydrolase inhibitor by Cravatt *et al.*[5d] and its 5-substituted derivatives (Scheme 5). Serine hydrolases have been used as the targets of clinical drugs to treat various diseases such as diabetes and Alzheimer's disease.[14] However, the biochemical activities of these enzymes are yet to be understood. For this reason, it is important to produce efficient synthetic methods to prepare selective inhibitors of these enzymes and preparation of its derivatives as candidates of more active drug molecules. 1,4,5-Trisubstituted triazoles **3a,c–f** and 1,4-disubstituted **3b** were prepared from appropriate propargyl alcohols with TMSOTf followed by quenching with aqueous media.[9] The obtained *N*-benzyltriazoles were deprotected by hydrogenolysis, and the obtained unprotected triazoles were coupled with carbamoyl chloride **12** to afford serine hydrolase inhibitor triazole urea **13b** and its 5-substituted derivatives **13a,c–f**. In all cases, desired 2*H*-triazole ureas **13a–f** were obtained regioselectively. Since it is difficult to prepare triazole ureas **13a,c–f** obtained from internal alkynes by CuAAC, our method could prove to be an efficient way to explore the property and activity of fully substituted triazole molecules. The NMR data of the synthesized inhibitor molecule **13b** were identical to those provided.[15]

3. Conclusion

We have developed regioselective rapid azide–alkyne cycloaddition to produce fully substituted 1*H*-1,2,3-triazoles. via propargyl cations derived from the corresponding alcohols. Various types of multicomponent coupling reactions, including double triazolations and functionalizations of triazoles with additional nucleophiles in one-pot, were demonstrated. The presence of methylenetriazolium intermediates was indicated. The synthesized triazoles were successfully converted to serine hydrolase inhibitor triazole urea and its derivatives. Our method can provide new preparation method of highly substituted triazoles and exploration of their uses in synthetic organic chemistry and pharmaceutical research.

4. Experimental Section

^{1}H and ^{13}C NMR were recorded on a JEOL JNM-ECP500 spectrometer (500 MHz for ^{1}H NMR, 126 MHz for ^{13}C NMR). Chemical shifts are reported as δ values in ppm and calibrated by residual solvent peak (CDCl3: δ 7.26 for ^{1}H NMR, δ 77.00 for ^{13}C NMR, CD_2Cl_2: δ 5.32 for ^{1}H NMR, δ 53.80 for ^{13}C NMR, CD_3OD: δ 49.00 for ^{13}C NMR) or tetramethylsilane (δ 0 for ^{1}H NMR). Abbreviations are following: s (singlet), d (doublet), t (triplet), q (quartet), br (broad peak), m (complex multiplet). Infrared spectra were measured on a JASCO FT/IR-4200 spectrometer. Mass spectra were recorded on a double-focusing mass spectrometer JEOL JMS-700 MStaion [EI (70 eV), CI, FAB and ESI]. X-ray crystallography was performed on Rigaku R-AXIS RAPID/S imaging plate diffractometer. Flash column chromatography was performed by MERCK Silica gel 60. The progress of reactions was monitored by silica gel thin layer chromatography plates (MERCK TLC Silicagel 60 F254). Phosphomolybdic acid ethanol solution, ninhydrin-acetic acid butanol solution and anisaldehyde-acetic acid-sulfuric acid ethanol solution were used as TLC stain. All reagents were purchased from Sigma-Aldrich, Wako pure chemical industries, Ltd, TCI (Tokyo Chemical Industry, Co. Ltd), Kanto Chemical Co. Inc., and Nakalai Tesque. Used Dehydrated solvents — tetrahydrofuran, dichloromethane and toluene— were purchased from Kanto Chemical, Wako pure chemical industries, Ltd, and Nakalai Tesque. Sodium azide purchased from Nakalai Tesque was carefully handled, and transferred with plastic spatulas. Regiochemistry of all synthesized triazoles were determined by NOE experiment or X-ray crystallographic analysis. For analytical data and NMR spectra that are not shown in this article, see previous report.[9]

*4.1. 1,1-Diphenyl-1-methoxyhept-2-yne (**1**)*

To a stirred solution of sodium hydride (39.4 mg, 0.983 mmol) in THF (3 mL) at 0 ºC under nitrogen atmosphere was added **4a** (200 mg, 0.757 mmol) in THF (1 mL) dropwise and stirred for 30 min at the same temperature. After 30 min, iodomethane (0.141 mL, 2.27 mmol) was then added at same temperature and the mixture was warmed up to room temperature. After 2h, reaction mixture was quenched with water. The mixture was diluted with ethyl acetate and washed with water and brine. Then the collected organic layer was dried over magnesium sulfate and concentration *in vacuo* followed by silica gel column chromatography (ethyl acetate/hexane = 1/5) to give **1** (187.7 mg, 46%).; Colorless oil; R_f value 0.76 (ethyl acetate/hexane = 1/5); IR (NaCl, neat) ν_{max} 2933, 1488, 1449, 1082, 763, 698 cm^{-1}; ^{1}H NMR(500 MHz, $CDCl_3$) δ 7.56–7.54 (m, 4H), 7.31–7.27 (m, 4H), 7.24–7.20 (m, 2H), 3.33 (s, 3H), 2.38 (t, 2H, *J* = 7.0 Hz), 1.60 (tt, 2H, *J* = 7.5, 7.0 Hz), 1.47 (tq, 2H, *J* = 7.0, 7.5 Hz), 0.94 (t, 3H, *J* = 7.5 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.9, 128.0, 127.3, 126.6, 90.4, 80.9, 79.4, 52.2, 30.8, 22.0, 18.6, 13.6; LRMS (EI) 278 (M^+,27%), 247 (60), 221 (57), 201 (100); HRMS (EI) calcd for $C_{20}H_{22}O$ (M^+) 278.1670, found 278.1668.

*4.2. 1-Benzyl-5-butyl-4-(methoxydiphenylmethyl)-1H-1,2,3-triazole (**2**)*

To a mixture of propargyl ether **1** (34.7 mg, 0.125 mmol) and benzyl azide (24.9 mg, 0.187 mmol) in dichloromethane (1.5 mL) under nitrogen atmosphere, TMSOTf (27 μL, 0.150 mmol) was added at room temperature dropwise. After five minutes, the reaction was quenched with saturated sodium bicarbonate aqueous solution, and was washed with brine. Then the collected organic layer was dried over magnesium sulfate followed by concentration *in vacuo* and silica gel column chromatography (ethyl acetate/hexane = 1/5) to afford **2** (49.8 mg, 97%) as a colorless oil.; R_f value 0.19 (ethyl acetate/hexane = 1/4); IR (NaCl, neat) ν_{max} 2927, 2855, 1456, 1070, 744, 703 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (d, 4H, *J* = 7.0 Hz),7.19–7.10 (m, 7H), 7.03 (tt, 2H, *J* = 7.5, 7.0 Hz), 6.98 (d, 2H, *J* = 7.0 Hz), 5.33 (s, 2H), 2.91 (s, 3H), 1.96 (t, 2H, *J* = 8.0 Hz), 0.83–0.74 (m, 4H), 0.50 (t, 3H, *J* = 7.0 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 146.1, 143.9, 136.9, 135.3, 128.9, 128.1, 127.8, 127.6, 126.9, 126.8, 82.6, 51.9, 51.8, 29.8, 22.8, 22.6, 13.4; LRMS (EI) LRMS (EI) 411(M^+,7%), 381(35), 105(12), 91(100); HRMS (EI) calcd for $C_{27}H_{29}N_3O$ (M^+) 411.2311, found 411.2314.

4.3. General procedures of three-component coupling reactions

(Condition A) To a solution of **4a** (1 equiv), benzyl azide (1.5 equiv) in dichloromethane (0.1 M to alcohols) under nitrogen atmosphere, boron trifluoride diethyl etherate (1.2 equiv) was added at –60 °C dropwise. Then nucleophile reagent (3 equiv) was added at the same temperature and the mixture was warmed up to 0 °C. After 30 min, the reaction was quenched with saturated sodium bicarbonate aqueous solution, and was washed with brine. Then the collected organic layer was dried over magnesium sulfate followed by concentration *in vacuo* and silica gel column chromatography to afford three-component coupling products.; **(Condition B)** To a solution of **4a** (1 equiv), benzyl azide (1.5 equiv) in dichloromethane (0.1 M to alcohol) under nitrogen atmosphere, methanesulfonic acid (1.2 equiv) was added at 0 °C dropwise. Then nucleophiles (3 equiv) were added at the

same temperature and the mixture was warmed up to 0 °C. After 30 min, the mixture was treated as same as above to obtain three-component coupling products.

4.3.1. *1-Benzyl-5-butyl-4-((nonyloxy)diphenylmethyl)-1H-1,2,3-triazole (**5a**)*

(Condition A) **5a** (85.9 mg, 82%) and **3a** (7.7 mg, 10%) from **4a** (53.0 mg, 0.200 mmol) [silica gel purification (ethyl acetate/hexane = 1/30 to 1/20 to 1/10)]. (Condition B) **5a** (72.2 mg, 69%) and trace amount of **3a** from **4a** (53.0 mg, 0.200 mmol).; Colorless oil ; R_f value 0.38 (ethyl acetate/hexane = 1/5); R_f value 0.38 (ethyl acetate/hexane = 1/5); IR (NaCl, neat) ν_{max} 2927, 2855, 1457, 1070, 704 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.59 (d, 4H, *J* = 7.0 Hz), 7.33–7.25 (m, 7H), 7.17 (dd, 2H, *J* = 6.0, 7.5 Hz), 7.11 (d, 2H, *J* = 6.0 Hz), 5.47 (s, 2H,) 3.09 (t, 2H, *J* = 7.0 Hz), 2.07 (t, 2H, *J* = 8.0 Hz), 1.54 (tt, 2H, *J* = 7.0, 8.0 Hz), 1.28–1.22 (m, 12H), 0.96–0.86 (m, 7H),0.65 (t, 3H, *J* = 7.0 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 146.6, 144.4, 136.9, 135.4, 128.8, 128.1, 127.8, 127.5, 126.9, 126.7, 81.8, 63.7, 51.8, 31.9, 29.9, 29.52, 29.46, 29.2, 26.3, 22.9, 22.7, 22.6, 14.1, 13.5; HRMS (ESI) calcd for $C_{35}H_{45}N_3ONa$ $[M+Na]^+$ 546.34603, found 546.34558.

4.3.2. *1-Benzyl-4-(((6-bromohexyl)oxy)diphenylmethyl)-5-butyl-1H-1,2,3-triazole (**5b**)*

(Condition A) **5b** (81.5 mg, 73%) and **3a** (8.7 mg, 11%) from **4a** (53.0 mg, 0.200 mmol) [silica gel purification (ethyl acetate/hexane = 1/15 to 1/10)]. (Condition B) **5b** (64.8 mg, 58%) and trace amount of **3a** from **4a** (53.0 mg, 0.200 mmol).; Colorless oil ; R_f value 0.29 (ethyl acetate/hexane = 1/5); IR (NaCl, neat) ν_{max} 2933, 2868, 1456, 1071, 896, 704 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.58 (d, 4H, *J* = 8.0 Hz), 7.34–7.25 (m, 7H), 7.17 (dd, 2H, *J* = 7.5, 6.5 Hz), 7.12 (d, 2H, *J* = 6.5 Hz), 5.47 (s, 2H), 3.35 (t, 2H, *J* = 7.0 Hz), 3.11 (t, 2H, *J* = 6.5 Hz), 2.04 (t, 2H, *J* = 8.0 Hz), 1.80 (tt, 2H, *J* = 7.0, 6.5 Hz), 1.55 (tt, 2H, *J* = 6.5, 7.0 Hz), 1.35 (m, 4H), 0.96–0.86 (m, 4H), 0.65 (t, 3H, *J* = 7.0 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 146.4, 144.3, 136.9, 135.3, 128.8, 128.1, 127.8, 127.4, 126.9, 126.7, 81.8, 63.4, 51.8, 33.8, 32.7, 29.9, 29.7, 27.9, 25.5, 22.8, 22.7, 13.4; LRMS (EI) ; HRMS (ESI) calcd for $C_{32}H_{38}BrN_3ONa$ $[M+Na]^+$ 582.20959, found 582.20950.

4.3.3. *1-Benzyl-5-butyl-4-[(2-methoxyethoxy)diphenylmethyl]-1H-1,2,3-triazole (**5c**)*

(Condition A) **5c** (105.7 mg, 76%) and **3a** (14.3 mg, 12%) from **4a** (80.5 mg, 0.196 mmol) [silica gel purification (ethyl acetate/hexane = 1/60 to 1/50 to 1/40 to 1/30 to 1/20 to 1/10)]. (Condition B) **5c** (57.9 mg, 63%) from **4a** (52.9 mg, 0.201 mmol).; Colorless oil; R_f value 0.18 (ethyl acetate/hexane = 1/4); IR (NaCl, neat) ν_{max} 2955, 2929, 1449, 1080, 705 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.60 (d, 4H, *J* = 8.0 Hz), 7.26–7.34 (m, 7H), 7.18 (dd, 2H, *J* = 7.5, 7.0 Hz), 7.14 (d, 2H, *J* = 7.5 Hz), 5.46 (s, 2H), 3.49 (t, 2H, *J* = 4.0 Hz), 3.30–3.31 (m, 5H), 2.13 (m, 2H), 0.89–1.02 (m, 4H), 0.67 (t, 3H, *J* = 7.0 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 146.5, 143.8, 137.0, 135.3, 128.9, 128.1, 127.8, 127.7, 127.0, 126.8, 82.3, 72.0, 62.9, 58.7, 51.8, 30.0, 22.9, 22.7, 13.5; LRMS (EI) 455 (3%, M^+), 381 (26), 91 (100); HRMS (EI) calcd for $C_{29}H_{33}N_3O_2$ (M^+) 455.2573, found 455.2573.

4.3.4. *1-Benzyl-5-butyl-4-((pent-4-yn-1-yloxy)diphenylmethyl)-1H-1,2,3-triazole (**5e**)*

(Condition A) **5e** (71.8 mg, 77%) and **3a** (8.1 mg, 10%) from **4a** (53.0 mg, 0.200 mmol) [silica gel purification (ethyl acetate/hexane = 1/10 to 1/4)]. (Condition B) **5e** (57.1 mg, 61%) and trace amount of **3a** from **4a** (52.8 mg, 0.200 mmol); Colorless oil ; R_f value 0.29 (ethyl acetate/hexane = 1/5); IR (NaCl, neat) ν_{max} 3448, 3303, 2956, 2871, 1449, 1071, 705 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.59 (d, 4H, *J* = 8.0 Hz), 7.33–7.25 (m, 7H), 7.18–7.12 (m, 4H), 5.46 (s, 2H), 3.22 (t, 2H, *J* = 6.5 Hz), 2.81 (t, 2H, *J* = 7.5 Hz), 2.03 (t, 2H, *J* = 8.5 Hz), 1.78–1.73 (m, 3H), 0.95–0.86 (m, 4H), 0.63 (t, 3H, *J* = 7.0 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 146.2, 144.2, 137.0, 135.3, 128.9, 128.1, 127.8, 127.4, 126.9, 126.7, 83.8, 81.8, 68.4, 62.0, 51.8, 29.9, 29.0, 22.8, 22.6, 15.5, 13.4; HRMS (ESI) calcd for $C_{31}H_{33}N_3ONa$ $[M+Na]^+$ 486.25213, found 486.25226.

4.3.5. *1-Benzyl-5-butyl-4-((naphthalen-2-ylthio)diphenylmethyl)-1H-1,2,3-triazole (**5f**)*

(Condition A) **5f** (87.8 mg, 81%) and **3a** (5.2 mg, 7%) from **4a** (53.0 mg, 0.200 mmol) [silica gel purification (ethyl acetate/hexane = 1/10 to 1/5)]. (Condition B) **5f** (62.7 mg, 62%) from **4a** (52.8 mg, 0.200 mmol).; Colorless oil; R_f value 0.28 (ethyl acetate/hexane = 1/5); IR (NaCl, neat) ν_{max} 3054, 2975, 1495, 1455, 728, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.76 (d, 1H, *J* = 8.0 Hz), 7.57 (d, 1H, *J* = 7.5 Hz), 7.54–7.53 (m, 2H), 7.48–7.43 (m, 6H), 7.32–7.22 (m, 10H), 7.04 (d, 2H, *J* =7.5 Hz), 5.49 (s, 2H), 2.18 (t, 2H, *J* = 8.5 Hz), 0.97 (tq, 2H, *J* = 7.5, 8.0 Hz), 0.73 (m, 2H), 0.64 (t, 3H, *J* = 7.5 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ147.1, 142.9, 135.9, 135.1, 133.9, 133.0, 132.3, 131.5, 131.1, 129.4, 128.7, 128.0, 127.7, 127.6, 127.4, 127.2, 126.9, 126.7, 126.1, 125.9, 64.0, 52.0, 29.0, 23.3, 22.7, 13.3; HRMS (ESI) calcd for $C_{36}H_{33}N_3SNa$ $[M+Na]^+$ 562.22929, found 562.22952.

4.3.6. *N-((1-Benzyl-5-butyl-1H-1,2,3-triazol-4-yl)diphenylmethyl)prop-2-en-1-amine (**5h**)*

(Condition A) **5h** (68.2 mg, 77%) and **3a** (9.4 mg, 12%) from **4a** (53.8 mg, 0.204 mmol) [silica gel purification (ethyl acetate/hexane = 1/10 to 1/4)]. (Condition B) **5h** (53.4 mg, 60%) from **4a** (53.6 mg, 0.200 mmol).; Colorless oil; R_f value 0.29 (ethyl acetate/hexane = 1/5); IR (NaCl, neat) ν_{max} 3320, 2957, 2870, 1491, 1456, 728, 704 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.45 (d, 4H, *J* = 7.0 Hz), 7.32–7.23 (m, 7H), 7.18 (dd, 2H, *J* = 7.0, 6.5 Hz), 7.10 (d, 2H, *J* = 7.0 Hz), 5.91 (ddt, 1H, *J* = 17.0, 10.5, 5.0 Hz), 5.43 (s, 2H), 5.18 (dd, 1H, *J* = 17.0, 1.5 Hz), 5.01 (dd, 1H, *J* = 10.5, 1.5 Hz), 2.92 (d, 2H, *J* = 5.0 Hz), 2.18 (t, 2H, *J* = 8.5 Hz), 2.07 (s, 1H, NH), 0.98 (td, 2H, *J* = 7.5, 7.0 Hz), 0.81–0.75 (m, 2H), 0.64 (t, 3H, *J* = 7.0 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.3, 144.4, 137.0, 135.3, 135.1, 128.8, 128.3, 128.0, 127.7, 126.8, 126.5, 114.9, 66.6, 51.8, 46.6, 29.8, 22.9, 22.7, 13.4; HRMS (ESI) calcd for $C_{29}H_{32}N_4Na$ $[M+Na]^+$ 459.2525, found 459.2524.

4.3.7. *1-Benzyl-5-butyl-4-(1,1-diphenylbut-3-en-1-yl)-1H-1,2,3-triazole (**5k**)*

(Condition A) **5k** (57.9 mg, 69%) and **3a** (2.1 mg, 3%) from **4a** (53.0 mg, 0.200 mmol) [silica gel purification (ethyl acetate/hexane = 1/15 to 1/10 to 1/4)]. (Condition B) **5k** (39.1 mg, 54%) with trace amount of **3a** from **4a** (45.5 mg, 0.172 mmol).; White solid; R_f value 0.28 (ethyl acetate/hexane = 1/5); m.p. 128.9–130.1 °C; IR (NaCl, neat) ν_{max} 3081, 2959, 1466, 907, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.43–7.38(m, 3H), 7.34–7.31 (m, 4H), 7.28–7.24 (m, 6H), 7.20 (t, 2H, *J* = 7.0 Hz), 6.02 (tdd, 1H, *J* = 17.0, 6.5, 7.5 Hz), 5.53 (s, 2H), 4.97–4.92 (m, 2H), 3.63 (d, 2H, *J* = 6.5 Hz), 1.90 (m, 2H), 0.89 (tt, 2H, *J* = 7.5, 7.5 Hz), 0.62 (t, 3H, *J* = 7.5 Hz), 0.51–0.45 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.1, 144.6, 136.2, 135.4, 135.3, 128.9, 128.8, 128.1, 127.7, 126.8, 126.2, 117.0, 52.1, 51.8, 47.1, 29.1, 23.1, 22.7, 13.4; HRMS (ESI) calcd for $C_{29}H_{31}N_3Na$ $[M+Na]^+$ 444.24157, found 444.23930.

4.3.8. *3-(1-Benzyl-5-butyl-1H-1,2,3-triazol-4-yl)-3,3-diphenylpropanal (**5l**)*

(Condition A) **5l** (45.8 mg, 55%) and **3a** (27.6 mg, 35%) from **4a** (52.4 mg, 0.198 mmol) [silica gel purification (ethyl acetate/hexane = 1/10 to 1/5 to 1/4)]. (Condition B) **5l** (28.3 mg, 43%) and **3a** (15.6 mg, 25%) from **4a** (41.2 mg, 0.156 mmol).; Colorless oil; R_f value 0.14 (ethyl acetate/hexane = 1/5); IR (NaCl, neat) ν_{max} 2957, 2858, 1715, 1455, 1023, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.84 (t, 1H, *J* = 2.5 Hz), 7.56–7.51 (m, 3H), 7.49–7.41 (m, 6H), 7.35 (d, 2H, *J* = 7.0 Hz), 7.25 (d, 4H, *J* = 8.5 Hz), 5.65 (s, 2H), 3.80 (d, 2H, *J* = 2.5 Hz), 1.96 (t, 2H, *J* = 8.5 Hz), 0.95 (qt, 2H, *J* = 7.5, 7.5 Hz), 0.71 (t, 3H, *J* = 7.5 Hz), 0.59–0.53 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 202.5, 148.0, 143.8, 135.8, 135.1, 129.0, 128.5, 128.4, 128.3, 127.0, 126.99, 55.2, 52.0, 49.7, 29.3, 23.0, 22.7, 13.3; HRMS (ESI) calcd for $C_{28}H_{29}N_3ONa$ $[M+Na]^+$ 446.22083, found 446.22063.

4.3.9. *Ethyl 3-(1-benzyl-5-butyl-1H-1,2,3-triazol-4-yl)-3,3-diphenylpropanoate (**5m**)*

Used 1-ethoxy-1-trimethyl-silyloxyethylene was prepared according to known procedure.[16] (Condition A) **5m** (63.1 mg, 68%) and **3a** (15.3 mg, 20%) from **4a** (52.5 mg, 0.199 mmol) [silica gel purification (ethyl acetate/hexane = 1/80 to 1/70 to 1/50 to 1/30 to 1/20 to 1/4)]. (Condition B) **5m** (38.7 mg, 55%) and **3a** (8.1 mg, 14%) from **4a** (39.7 mg, 0.150 mmol).; Colorless oil; R_f value 0.14 (ethyl acetate/hexane = 1/5); IR (NaCl, neat) ν_{max} 2957, 2870, 1742, 1151, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.33–7.28 (m, 3H), 7.25–7.22 (m, 4H), 7.21–7.15 (m, 6H), 7.10 (d, 2H, *J* = 7.0 Hz), 5.42 (s, 2H), 3.95 (q, 2H, *J* = 7.0 Hz), 3.78 (s, 2H), 1.84 (t, 2H, *J* = 8.5 Hz), 1.06 (t, 3H, *J* = 7.0 Hz), 0.77 (qt, 2H, *J* = 7.0, 7.5 Hz), 0.51 (t, 3H, *J* = 7.5 Hz), 0.37–0.30 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.8, 148.0, 144.2, 135.4, 135.2, 128.9, 128.7, 128.1, 127.9, 126.8, 126.5, 60.0, 51.9, 50.8, 46.9, 29.0, 23.3, 22.7, 13.9, 13.4; HRMS (ESI) calcd for $C_{30}H_{34}N_3O_2$ $[M+H]^+$ 468.26510, found 468.26574.

*4.4. Methyl 2-hydroxy-2-phenyloct-3-ynoate (**6**)*

To a stirred solution of 1-hexyne (0.487 mL, 4.26 mmol) in THF (31 mL) at 0 ºC under nitrogen atmosphere was added lithium bis(trimethylsilyl)amide (1.0 M in THF, 4.57 mL, 4.57 mmol) dropwise. After 30 min, methyl benzoylformate (500.0 mg, 3.05 mmol) was then added at the same temperature and the mixture was warmed up to room temperature. After 12 h, reaction mixture was quenched with saturated ammonium chloride aqueous solution. The mixture was diluted with ether and washed with water and brine. Then the collected organic layer was dried over magnesium sulfate and concentration *in vacuo* followed by silica gel column chromatography (ethyl acetate/hexane = 1/ 20 to 1/15) to give **6** (344.8 mg, 46%).; Colorless oil; R_f value 0.29 (ethyl acetate/hexane = 1/5); IR (NaCl, neat) ν_{max} 3496, 3029, 1736, 1256, 1063, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.68 (d, 2H, *J* = 6.5 Hz), 7.39–7.32 (m, 3H), 4.18 (s, 1H, OH), 3.76 (s, 3H), 2.33 (t, 2H, *J* = 7.5 Hz), 1.58 (tt, 2H, *J* = 7.5, 8.0 Hz), 1.46 (tq, 2H, *J* = 8.0, 7.5 Hz), 0.93 (t, 3H, *J* = 7.5 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.7, 139.6, 128.5, 128.2, 126.2, 87.6, 78.1 72.8, 54.0, 30.3, 21.9, 18.4, 13.5; HRMS (CI) calcd for $C_{15}H_{19}O_3$ $[M+H]^+$ 247.1334, found 247.1335.

*4.5. Methyl 2-azido-2-(1-benzyl-5-butyl-1H-1,2,3-triazol-4-yl)-2-phenylacetate (**7**, CCDC 950507)*

To a mixture of propargyl alcohol **6** (68.3 mg, 0.277 mmol) and benzyl azide (55.4 mg, 0.416 mmol) in dichloromethane (2.8 mL) under nitrogen atmosphere, TMSOTf (110.2 µL, 0.610 mmol) was added at room temperature dropwise. After five minutes, the reaction was quenched with saturated sodium bicarbonate aqueous solution, and was washed with brine. Then the collected organic layer was dried over magnesium sulfate followed by concentration *in vacuo* and silica gel column chromatography (ethyl acetate / hexane = 1 / 5) to afford **7** (34.3 mg, 31%) as a colorless solid.; R_f value 0.18 (ethyl acetate/hexane = 1/5); m.p. 158.7–159.4 °C; IR (NaCl, neat) ν_{max} 2957, 2112, 1746, 1241 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.44–7.42 (m, 2H), 7.35–7.30 (m, 6H), 7.11 (d, 2H, *J* = 7.0 Hz), 5.54 (d, 1H, *J* = 16.0 Hz), 5.47 (d, 1H, *J* = 16.0 Hz), 3.89 (s, 3H), 2.19 (m, 1H), 2.02 (m, 1H), 1.06–0.84 (m, 4H), 0.62 (t, 3H, *J* = 7.0 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.8, 143.3, 136.6, 136.2, 134.7, 129.0, 128.5, 128.3, 128.1, 127.4, 126.8, 71.1, 53.6, 52.1, 29.7, 22.5, 22.4, 13.2; HRMS (ESI) calcd for $C_{22}H_{24}N_6NaO_2$ $[M+Na]^+$ 427.1858, found 427.1856.

*4.6. N-(Bis(1-benzyl-5-butyl-1H-1,2,3-triazol-4-yl)(phenyl)methyl)prop-2-en-1-amine (**9**)*

To a mixture of **8** (55.3 mg, 0.206 mmol),[9] benzyl azide (82.3 mg, 0.618 mmol) in dichloromethane (2.1 mL) was added boron trifluoride diethyl ether complex (66.7 µL, 0.247 mmol) at –60 °C. After five minutes, allylamine (36.6 µL, 0.618 mmol) was added at the same temperature, and then warmed up to room temperature. After 30 min, the mixture the reaction was quenched with saturated sodium bicarbonate aqueous solution, and was washed with brine. Then the collected organic layer was dried over magnesium sulfate followed by concentration *in vacuo* and silica gel column chromatography (ethyl acetate/hexane = 1/10 to 1/5 to 1/3) to afford **9** (56.1 mg, 48%).; Colorless oil: R_f value 0.31 (ethyl acetate/hexane = 1/2); IR (NaCl, neat) ν_{max} 3344, 2957, 2870, 1455, 1241, 905, 725, 699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.43 (d, 2H, *J* = 8.5 Hz), 7.30–7.27 (m, 8H), 7.22 (dd, 1H, *J* = 7.5, 8.5 Hz), 7.12–7.10 (m, 4H), 5.90–5.83 (m, 1H), 5.45 (s, 4H), 5.15 (dd, 1H, *J* = 1.5, 17.0 Hz), 4.98 (d, 1H, *J* = 10.5 Hz), 2.95 (d, 2H, *J* = 5.0Hz), 2.37–2.23 (m, 4H), 1.07–1.03 (m, 4H), 0.86–0.76 (m, 4H), 0.68 (t, 6H, *J* = 7.5 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 147.1, 142.8, 136.9, 135.7, 135.4, 128.8, 128.4, 128.1, 127.6, 126.9, 126.8, 114.8, 62.6, 51.8, 46.3, 29.8, 22.9, 22.7, 13.5; HRMS (ESI) calcd for $C_{36}H_{43}N_7Na$ $[M+Na]^+$ 596.34776, found 596.35051.

*4.7. N-((1-Benzyl-5-butyl-1H-1,2,3-triazol-4-yl)(5-butyl-1-cinnamyl-1H-1,2,3-triazol-4-yl)(phenyl)methyl)prop-2-en-1-amine (**10**)*

To a mixture of **8** (77.6 mg, 0.289 mmol), benzyl azide (40.4 mg, 0.304 mmol) in dichloromethane (3.0 mL) was added boron trifluoride diethyl ether complex (101.3 µL, 0.376 mmol) at –60 °C. After 1 min, cinnamyl azide (69.0 mg, 0.434 mmol) dissolved in 0.5 mL of dichloromethane was added to the mixture. After five minutes, allylamine (51.3 µL, 0.867 mmol) was added at the same temperature, and then warmed up to room temperature. After 30 min, the mixture the reaction was quenched with saturated sodium bicarbonate aqueous solution, and was washed with brine. Then the collected organic layer was dried over magnesium sulfate followed by concentration *in vacuo* and silica gel column chromatography (ethyl acetate/hexane = 1/12 to 1/10 to 1/5 to 1/3) to afford **10** (45.9 mg, 27%).; Colorless oil; R_f value 0.30 (ethyl acetate/hexane = 1/2); IR (NaCl, neat) ν_{max} 3344, 2957, 2931, 2870, 1456, 1241, 904, 728 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.47 (dd, 2H, *J* = 7.5, 2.0 Hz), 7.39–7.25 (m, 11H), 7.16 (dd, 2H, *J* = 6.5, 1.5 Hz), 6.49 (d, 1H, *J* = 16.0 Hz), 6.33 (td, 1H, *J* =16.0, 6.5 Hz), 5.92 (ddt, 1H, *J* = 17.0, 10.0 Hz), 5.50 (s, 2H), 5.21 (dd, 1H, *J* = 17.0, 2.0 Hz), 5.06–5.02 (m, 3H), 3.01 (d, 2H, *J* = 4.0 Hz), 2.58–2.29 (m, 4H), 1.21–1.15 (m, 2H), 1.09–1.05 (m, 4H), 0.86–0.78 (m, 5H), 0.70 (t, 3H, *J* = 7.5 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 147.2, 146.9, 142.9, 136.9, 135.7, 135.6, 135.3, 133.5, 128.8, 128.6, 128.4, 128.2, 128.1, 127.6, 126.9, 126.8, 126.5, 123.0, 114.8, 62.6, 51.8, 50.2, 46.4, 30.2,

29.8, 22.91, 22.87, 22.76, 22.67, 13.61, 13.55; HRMS (ESI) calcd for $C_{38}H_{45}NaN_7$ $[M+Na]^+$ 622.36341, found 622.36220.

*4.8. 1-(1-Benzyl-5-butyl-1H-1,2,3-triazol-4-yl)-1-phenylhept-2-yn-1-ol (**11**)*

To a mixture of **8** (70.0 mg, 0.261 mmol), benzyl azide (36.5 mg, 0.274 mmol) in dichloromethane (2.6 mL) was added trimethylsilyl trifluoromethanesulfonate (56.6 µL, 0.313 mmol) at –90 °C. After five minutes, the reaction was quenched with saturated sodium bicarbonate aqueous solution, and was washed with brine. Then the collected organic layer was dried over magnesium sulfate followed by concentration *in vacuo* and silica gel column chromatography (ethyl acetate/hexane = 1/15 to 1/5 to 1/2) to afford **11** (57.9 mg, 55%) and **12** (2.1 mg, 2%)[9].; Colorless oil; R_f value 0.29 (ethyl acetate/hexane = 1/5); IR (NaCl, neat) ν_{max} 3352, 2957, 1455, 1003, 733, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.83 (d, 2H, *J* = 7.5 Hz), 7.55 (m, 6H), 7.35 (d, 2H, *J* = 7.0 Hz), 5.67 (d, 1H, *J* = 15.5 Hz), 5.64 (d, 1H, *J* = 15.5 Hz), 4.63 (s, 1H, OH), 2.59–2.61 (m, 1H), 2.52 (td, 2H, *J* = 1.5, 7.0 Hz), 2.41–2.46 (m, 1H), 1.75 (tt, 2H, *J* = 7.5, 7.5 Hz), 1.62 (tq, 2H, *J* = 7.5, 7.5 Hz), 1.24–1.27 (m, 3H), 1.10 (t, 3H, *J* = 7.5 Hz), 0.92–1.02 (m, 1H), 0.89 (t, 3H, *J* = 7.5 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 147.8, 143.5, 134.9, 133.7, 128.9, 128.3, 128.1, 128.0, 127.1, 126.5, 88.2, 80.9, 69.7, 52.0, 30.5, 29.9, 22.6, 22.5, 22.0, 18.6, 13.6, 13.5; HRMS (ESI) calcd for $C_{26}H_{31}N_3NaO$ $[M+Na]^+$ 424.2365, found 424.2365.

4.9. General procedure of synthesis of triazole ureas:

A slurry of 30wt% (based on starting material triazole) of 10% Pd/C in ethanol was added to a stirred solution of 1,4,5-trisubstituted triazoles under nitrogen and the resulting mixture was stirred under an atmosphere of hydrogen gas for 20 h. The reaction mixture was filtered through a plug of celite washing with methanol. The filtrate was evaporated under reduced pressure to give a white solid residue which was used to the next step without further purification. The crude unprotected triazoles (1.2 equiv), pyrrolidine carbonyl chloride **12** (1.0 equiv), and 4-dimethylaminopyridine (0.2 equiv) were dissolved in 5:1 THF/triethylamine (0.1 M based on triazoles), and the mixture was stirred for 10 h at 60 °C. The solvents were removed, and then the crude material was purified by silica gel chromatography to afford triazole ureas.

4.9.1. *(4-Butyl-5-(hydroxydiphenylmethyl)-2H-1,2,3-triazol-2-yl)(pyrrolidin-1-yl)methanone (**13a**)*

121.7mg (0.300mmol, 80%) for two steps from **3a** (220.1 mg, 0.554mmol) [silica gel chromatography (hexane/ethyl acetate = 3:1 to 1:1, dichloromethane/methanol = 40:1)].; White solid; Rf value 0.45 (ethyl acetate/hexane = 1/2); m.p. 168.7–170.4 °C; IR (NaCl, neat) ν_{max} 3333, 2958, 2871, 1694, 1448, 1418, 1264, 1171, 941 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.27–7.19 (m, 10H), 3.67 (s, 1H), 3.64–3.58 (m, 4H), 2.20 (t, 2H, *J* = 8.0 Hz), 1.83 (br, 4H), 1.27 (tt, 2H, *J* = 7.5, 8.0 Hz), 1.07 (tt, 2H, *J* = 7.5, 7.5 Hz), 0.66 (t, 3H, *J* = 7.5 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.2, 148.9, 147.9, 144.4, 128.0, 127.8, 127.5, 77.9, 50.1, 48.6, 30.3, 26.5, 25.5, 24.0, 22.4, 13.6; HRMS (ESI) calcd for $C_{24}H_{28}N_4O_2Na$ $[M+Na]^+$ 427.21099, found 427.21052.

4.9.2. *(4-(Hydroxydiphenylmethyl)-2H-1,2,3-triazol-2-yl)(pyrrolidin-1-yl)methanone (**13b**)*[5d,15]

17.9 mg (30%) for two steps from **3b** (70.0 mg, 0.206 mmol) [silica gel chromatography (hexane/ethyl acetate = 20:1 to 10:1 to 5/1 to 3/1 to 2/1 to 1/1 to ethyl acetate)].; White solid; R_f value 0.23 (ethyl acetate/hexane = 1/2); m.p. 156.7–157.7 °C; IR (NaCl, neat) ν_{max} 3363, 2917, 1697, 1264, 1058, 699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.56 (s, 1H), 7.33–7.29 (m, 10H), 3.76 (t, 2H, *J* = 6.5 Hz), 3.70 (t, 2H, *J* = 6.5 Hz), 1.96–1.92 (m, 4H); ^1H NMR (500 MHz, CD_2Cl_2) δ 7.61 (s, 1H), 7.35–7.27 (m, 10H), 3.72 (t, 2H, *J* = 6.0 Hz), 3.63 (t, 2H, *J* = 6.0 Hz), 1.95–1.90 (m, 4H); ^1H NMR (500 MHz, CD_3OD) δ 7.84 (s, 1H), 7.37–7.23 (m, 10H), 3.73 (t, 2H, *J* = 6.0 Hz), 3.64 (t, 2H, *J* = 6.0 Hz), 1.94–1.90 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.6, 147.7, 144.9, 135.3, 128.2, 127.8, 127.1, 77.2, 50.1, 48.7, 26.4, 24.0; ^{13}C NMR (126 MHz, CD_2Cl_2) δ 155.8, 147.9, 145.5, 135.4, 128.4, 128.1, 127.4, 77.4, 50.4, 48.9, 26.7, 24.4; ^{13}C NMR (126 MHz, CD_3OD) δ 158.0, 149.6, 147.1, 136.7, 128.9, 128.5, 128.4, 78.0, 51.5, 49.8, 27.4, 25.0; HRMS (ESI) calcd for $C_{20}H_{20}N_4O_2Na$ $[M+Na]^+$ 371.14839, found 371.14822.

4.9.3. *(4-Cyclohexyl-5-(hydroxydiphenylmethyl)-2H-1,2,3-triazol-2-yl)(pyrrolidin-1-yl)methanone (**13c**)*

152.0 mg (0.353 mmol, 67%) for two steps from **3c** (260.0 mg, 0.614 mmol) [silica gel chromatography (hexane/ethyl acetate = 5:1 to 3:1 to 1:1, dichloromethane/methanol = 40:1)].; White solid; R_f value 0.26 (ethyl acetate/hexane = 1/2); m.p. 226.8–227.0 °C; IR (NaCl, neat) ν_{max} 3334, 3061, 2925, 2854, 1694, 1423, 1340, 1260 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.34–7.26 (m, 10H), 3.73 (s, 1H), 3.72 (t, 2H, *J* = 7.0 Hz), 3.68 (t, 2H, *J* = 7.0Hz), 2.17–2.11 (m, 1H), 1.91 (m, 4H), 1.69–1.53 (m, 3H), 1.46–1.37 (m, 4H), 1.16–1.10 (m, 1H), 0.96–0.89 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.1, 151.5, 148.0, 144.5, 128.0, 127.8, 127.7, 78.0, 50.1, 48.6, 35.2, 26.5, 26.3, 25.7, 24.0; HRMS (ESI) calcd for $C_{26}H_{30}N_4O_2Na$ $[M+Na]^+$ 453.22664, found 453.22670.

4.9.4. *(4-(((tert-Butyldimethylsilyl)oxy)methyl)-5-(hydroxydiphenylmethyl)-2H-1,2,3-triazol-2-yl)(pyrrolidin-1-yl)methanone (**13d**, CCDC 1014155)*

39.1 mg (0.079 mmol, 33%) for two steps from **3d** (139.6 mg, 0.287 mmol) [silica gel chromatography (hexane/ethyl acetate = 5:1 to 3:1 to 1:1)].; White solid; R_f value 0.2 (ethyl acetate/hexane = 1/2); m.p. 146.8–147.9 °C; IR (NaCl, neat) ν_{max} 3403, 2928, 2884, 1717, 1410, 1259, 1059, 993 cm^{-1}; ^1H NMR (500 MHz, CD_2Cl_2) δ 7.38–7.36 (m, 4H), 7.33–7.27 (m, 6H), 5.68 (s, 1H), 4.65 (s, 2H), 3.59 (t, 2H, *J* = 6.5 Hz), 3.54 (t, 2H, *J* = 6.5 Hz), 1.90–1.84 (m, 4H), 0.82 (s, 9H), –0.02(s, 6H); ^{13}C NMR (126 MHz, CD_2Cl_2) δ 153.9, 147.9, 146.5, 145.3, 128.1, 127.7, 127.5, 76.9, 58.4, 50.4, 48.9, 26.7, 25.8, 24.4, 18.4, –5.7; HRMS (ESI) calcd for $C_{27}H_{36}N_4O_3SiNa$ $[M+Na]^+$ 515.24544, found 515.24415.

4.9.5. *3-(5-(Hydroxydiphenylmethyl)-2-(pyrrolidine-1-carbonyl)-2H-1,2,3-triazol-4-yl)propyl benzoate (**13e**, CCDC 1014154)*

117.7 mg (0.231 mmol, 40%) for two steps from **3e** (349.3 mg, 0.694 mmol) [silica gel chromatography (hexane/ethyl acetate = 5:1 to 3:1 to 2:1, dichloromethane / methanol = 60:1)].; White solid; R_f value 0.2 (ethyl acetate/hexane = 1/2); m.p. 184.7–185.5 °C; IR (NaCl, neat) ν_{max} 3403, 2928, 2884, 1717, 1410, 1259, 1059, 993 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ7.92 (dd, 2H, *J* = 8.0, 1.0 Hz), 7.53 (td, 1H, *J* = 7.0, 1.0 Hz), 7.39 (tt, 2H, *J* = 7.0, 8.0 Hz), 7.30–7.23 (m, 10H), 4.18 (t, 2H, *J* = 5.5 Hz), 3.63 (s, 1H), 3.64–3.60 (m, 4H), 2.52 (t, 2H, *J* = 7.5 Hz), 1.97–1.81 (m, 2H), 1.89–1.84 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.5, 152.2, 147.81, 147.76, 144.3, 132.9, 130.1, 129.5, 128.3, 128.1, 127.9, 127.4, 77.9, 64.2, 50.1, 48.6, 27.1, 26.5, 24.0, 22.7; HRMS (ESI) calcd for $C_{30}H_{30}N_4O_4Na$ $[M+Na]^+$ 533.21647, found 533.21563.

4.9.6. *(4-(Hydroxydiphenylmethyl)-5-(trimethylsilyl)-2H-1,2,3-triazol-2-yl)(pyrrolidin-1-yl)methanone (**13f**)*

82.1 mg (0.195 mmol, 58%) for two steps from **3f** (164.7 mg, 0.404 mmol) [silica gel chromatography (hexane/ethyl acetate = 5:1 to 3:1 to 2:1 to 1:1)].; White solid; R_f value 0.34 (ethyl acetate/hexane = 1/2); m.p. 168.7–169.4 °C; IR (NaCl, neat) ν_{max} 3350, 2959, 1697, 1252, 1048, 928, 761 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.32–7.28 (m, 10H), 3.66 (t, 2H, *J* = 7.0 Hz), 3.58 (t, 2H, *J* = 7.0 Hz), 2.88 (s, 1H), 1.92–1.84 (m, 4H), 0.22 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.1, 148.6, 148.2, 145.6, 128.0, 127.7, 127.4, 78.7, 49.9, 48.4, 26.4, 24.1, –0.4; HRMS (ESI) calcd for $C_{23}H_{28}N_4O_2SiNa$ $[M+Na]^+$ 443.18792, found 443.18773.

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