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Microwave-Assisted or Cu–NHC-Catalyzed Cycloaddition of Azido-Disubstituted Alkynes: Bifurcation of Reaction Pathways

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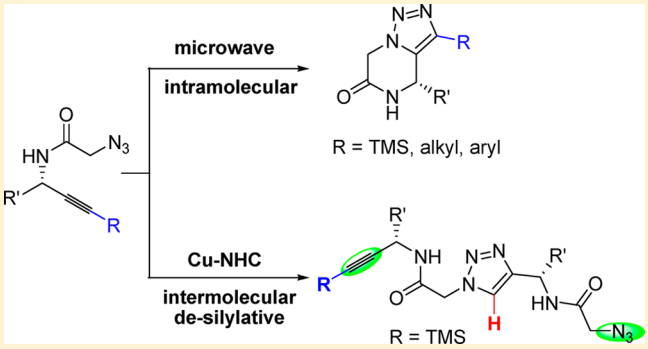
Supporting Information

ABSTRACT: Microwave irradiation promoted the intramolecular cycloaddition of 2-azidoacetamides derived from α-chiral propargylic amines, affording 1,4,5-trisubstituted triazoles **4** bearing a chiral aminomethyl side chain at C5. In contrast, for the same substrates **3a–k**, Cu(I)–NHC complexes catalyzed the intermolecular cycloaddition in an unexpected desilylative fashion, leading to 1,4-disubstituted triazoles **5**. This demonstrates that 1-silyl alkynes can be employed as substrates for CuAAC with a suitable coupling partner.



1,2,3-Triazole is a well-known pharmacophore possessing a wide spectrum of interesting biological activities.[1] The thermal 1,3-dipolar cycloaddition of azides to alkynes to form 1,2,3-triazoles (Huisgen reaction) was first documented in 1893 and studied in greater detail in the late 1950s and the 1960s.[2] However, this reaction in general has low regioselectivities for even terminal alkynes. The copper-catalyzed variant of this transformation (CuAAC), first reported in 2002,[3] marked the emergence of "click chemistry"[4] and has since found widespread applications in medicinal chemistry, materials science, and chemical biology.[5] A complementary ruthenium-catalyzed approach (RuAAC) exhibits the opposite regioselectivity.[6] With the recent advances in N-hetereocyclic carbene (NHC) chemistry,[7] a few Cu–NHC complexes have been reported to catalyze azide cycloaddition to terminal alkynes.[8] While the CuAAC of terminal alkynes enjoys excellent regioselectivity for the 1,4-disubstituted adducts, unsymmetric internal alkynes remain difficult substrates because of low reactivity and problematic regioselectivity control. In this regard, several groups have recently reported Huisgen reactions of well-designed internal alkynes with unambiguous regioselectivity by taking advantage of intramolecular reaction.[9] Additionally, Schubert and co-workers reported that 1-trimethylsilyl-substituted alkynes are excellent substrates favoring the formal 1,5-regioselective intermolecular AAC under thermal conditions.[10] However, the scope of CuAAC of unsymmetrically disubstituted alkynes is still limited to 1-halo- and 1-metallo (Al, Bi)-substituted alkynes.[11] As part our ongoing interest in novel Cu–NHC complexes for organic synthesis,[12] we designed a series of disubstituted alkynes with a pendant azide function and explored their reactivity under both microwave dielectric heating and Cu–NHC catalysis. This enabled us to compare the scope and limitations of the two sets of conditions for unsymmetrically disubstituted alkynes and to determine whether the 1,5-regioselectivity of 1-silylated alkynes also holds for CuAAC.

The substrates were based on synthetically versatile α-chiral propargylic amines[13] because of their ready availability, high enantiopurity, and structural diversity. The preparation was straightforward. After removal of the *N*-sulfinyl group, amidation with azidoacetic acid[14] produced the desired azido alkynes in good yields (Scheme 1). The γ- and α-groups of the propargylic amines constitute the C4 and C5 substituents of the triazole.

Substrates **3** were first subjected to Cu-free microwave-assisted cyclization at 160 °C (power = 200 W, maximum internal pressure = 200 psi). The Huisgen cycloaddition proceeded smoothly to form 1,4,5-trisubstituted triazoles **4** in very good to excellent isolated yields (>85% in most cases;

Scheme 1. Synthesis of Azido Internal Alkynes

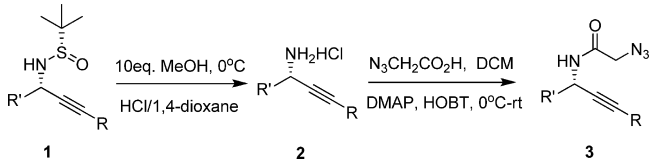


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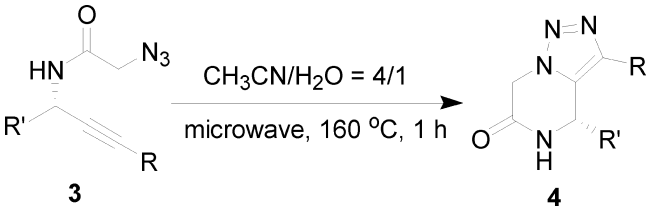
Table 1). Conventional heating at the same temperature proved ineffective, and the starting material was recovered unchanged.

Table 1. Intramolecular Cycloaddition of Azido Alkynes 3 under Microwave Irradiation



3 4

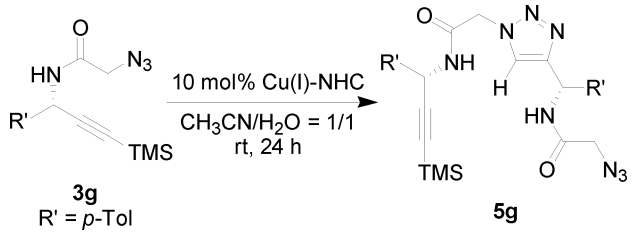
entry	R′	R	product	yield (%)[a]
1	2-propyl	TMS	**4a**	95
2[b]	2-propyl	TMS	**4a**	NR
3	cyclohexyl	TMS	**4b**	97
4	cyclopropyl	TMS	**4c**	96
5	1-adamantyl	TMS	**4d**	85
6	benzyl	TMS	**4e**	90
7	(*E*)-PhCH=CH	TMS	**4f**	87
8	4-Me-phenyl	TMS	**4g**	93
9	4-MeO-phenyl	TMS	**4h**	94
10	pyridin-3-yl	TMS	**4i**	75[c]
11	furan-2-yl	TMS	**4j**	88
12[d]	*N*-Boc-indol-3-yl	TMS	**4k**	85
13[e]	4-MeO-phenyl	phenyl	**4l**	80
14[e]	4-MeO-phenyl	cyclopropyl	**4m**	75

[a]Isolated yields. [b]Upon oil bath heating to 160 °C for 4 h, **3a** was recovered (>90%). [c]Yield after desilylation. [d]The indole *N*-Boc protection was simultaneously removed because of its lability. [e]The reaction time was 3 h.

Very bulky 1-adamantyl or heterocyclic R′ groups were all tolerated, except in the case of **3i**, where the silyl group was partially cleaved because of its decreased stability in the presence of the basic pyridine ring (entry 10). It is notable that substrates **3a–k** required only 1 h of microwave irradiation, while the reaction time for the azido alkynes used in Taddei's study was three times longer.[9a] This suggests that placement of a substituent at the α-carbon of the propargylic amine rather than at the α-position of the carbonyl resulted in a more favorable conformation placing the azido group and the alkyne in proximity of each other to facilitate the cyclization. Replacing the silyl group with either an aromatic group (phenyl) or an alkyl group (cyclopropyl) still afforded satisfactory yields, although a longer reaction time was necessary (entries 13 and 14). Products **4** have the potential for further modifications such as hydrolytic ring opening, reduction of the lactam, and stereoselective α-alkylation. Moreover, the TMS group on the triazole ring can be easily converted to halides and used for subsequent cross-coupling.[15]

Then the reaction of azido alkynes **3** using Cu–NHC catalysis was examined at room temperature (Table 2). Different types of NHC precursors, including those widely represented in the literature (**6–8**; Figure 1) and the benzoimidazole-based compounds recently reported by our group (**9–11**), were screened using **3g** as a model substrate. It was found that the complex formed by the NHC derived from **9** exhibited the highest catalytic activity in 50% aqueous acetonitrile (Table 2, entry 5), while other Cu–NHC complexes were less effective. In anhydrous solvents such as MeCN, THF, *tert*-butanol, and DMF, no product was formed.

Table 2. Screening of Cu(I)–NHC Catalysts



3g R' = *p*-Tol **5g**

entry	NHC precursor	yield (%)[a]
1	none	11
2	**6**	40
3	**7**	45
4	**8**	38
5	**9**	81
6	**10**	30
7	**11**	10
8[b]	**9**	NR
9[c]	**9**	66

[a]Isolated yields. [b]In MeCN. [c]In 1:1 *t*-BuOH/H_2O.

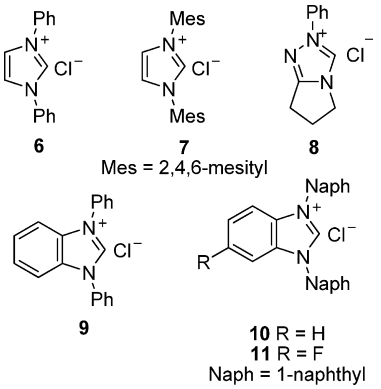


Figure 1. NHC precursors screened for the cycloaddition reaction.

Other mixed solvent systems such as 1:1 *t*-BuOH/H_2O afforded lower yields (entry 9). Under the optimal conditions, a single isolable product was obtained in a satisfactory yield of 81% after 24 h at rt. NMR and MS analysis revealed that the isolated product **5g** was formed via an intermolecular reaction with formal 1,4-regioselectivity (as confirmed by HMBC experiments), opposite to that of the thermal AAC of silyl alkynes.[10] Furthermore, it is interesting that the TMS group supposed to be on the heterocycle was absent, while the terminal TMS of the unreacted alkyne was intact. The spontaneous loss of TMS during an AAC reaction, without the assistance of desilylation reagents, has not been reported to date. In all cases with Cu–NHC catalysis, no intramolecular reaction product was detected by either TLC or LC–MS. It is also notable that further reaction of **5g**, which possesses both azide and alkyne functions, to form oligomers or polymers was minimal without resorting to high-dilution conditions. Unfortunately, the accelerating effect of carboxylic acids[16] in CuAAC cannot be exploited in the present protocol, as HOAc could decompose the Cu–NHC catalyst. The use of a Lewis acid ($ZnCl_2$) alone or with an NHC was also unproductive.

This protocol was then extended to other azido alkynes **3**, and the results are summarized in Table 3. A series of 1,4-disubstituted 1,2,3-triazoles **5** carrying alkyne and azide functions on the side chains were obtained (Table 3, entries

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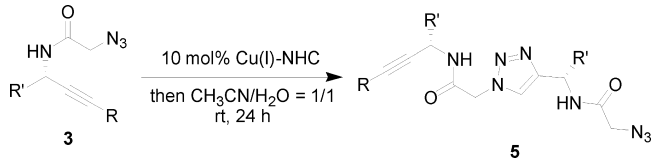
Table 3. Intermolecular CuAAC of 1-Silylated Alkynes 3



3 5

entry	R′	R	conversion (%)[a]	product	yield (%)[b]
1	2-propyl	TMS	73	**5a**	69
2	cyclohexyl	TMS	70	**5b**	65
3	benzyl	TMS	70	**5e**	68
4	(*E*)-PhCH=CH	TMS	75	**5f**	72
5	4-Me-phenyl	TMS	85	**5g**	81
6	4-MeO-phenyl	TMS	84	**5h**	79
7	furan-2-yl	TMS	78	**5j**	75
8	4-MeO-phenyl	phenyl	NR	–	–
9	4-MeO-phenyl	cyclopropyl	NR	–	–
10	4-Me-phenyl	H	100	polymer	–

[a]Based on recovered **3**. [b]Isolated yields.

1−7). Although the reaction did not go to completion in 24 h (65−85% conversion), the yields based on reacted starting material were excellent (>90%). In all cases, the triazole ring did not bear a TMS group. Unfortunately, when the terminal silyl group was replaced by a carbogenic group, the cycloaddition did not proceed, and the starting material was recovered (entries 8 and 9). Interestingly, for an analogous terminal alkyne substrate (desilylated **3g**), polymer formation was observed immediately (entry 10).[17] Therefore, compound **5** represents a class of triazole-based bifunctional molecules that is not readily accessible via the conventional AAC of terminal alkynes.

In order to gain some insight into the mechanism for the CuAAC of 1-silyl alkynes, several control experiments were carried out (Scheme 2). When 1 equiv of benzyl azide was reacted with **3g**, only 5% of the product was 1-benzyl triazole **12**, while 95% was the normal product **5g** (eq 1). In view of the fact that the intrinsic reactivities of azidoacetamide and benzyl azide toward a terminal alkyne under Cu−NHC catalysis are virtually the same (eq 2), this and the polymerization of terminal alkyne (Table 3, entry 10) essentially ruled out free terminal alkyne (formed by either Cu-catalyzed or simple base-induced hydrolysis) as the key intermediate as well as the presence of a desilylation step prior to CuAAC. Another possible mechanism is that the amide carbonyl group may participate in the reaction to facilitate removal of the TMS group for the formation of copper acetylide species without involving a free terminal alkyne. In order to test this possibility, reactions 3 and 4 were conducted. The results showed that the reaction between benzyl azide and 1-(trimethylsilyl)-phenylacetylene was very sluggish under our CuAAC conditions. However, the reaction of *N*-benzyl-2-azidoacetamide with the same alkyne afforded the triazole in a good yield (70%) in 24 h. Moreover, when the very bulky and hydrolytically stable 1-triisopropylsilyl group was employed to cap the alkyne, a moderate yield of 58% could still be achieved. This provides strong evidence that the adjacent functional group of the azide plays an important role in promoting the cleavage of the terminal silyl group regardless of its size. To further illustrate this possibility, eq 5 showed that when the azide and the carbonyl group were separated with more methylene units, the reaction was significantly less efficient than using 2-azidoacetamide. This could occur because the corresponding transition states became slack and less favorable. Therefore, we speculate that a cyclic transition state was involved as a result of the dative interaction of the amide carbonyl with the silyl group (eq 6). Without this neighboring group, the formation of copper acetylide species could rely only on the assistance of water, and this process is apparently not efficient.

Compounds **4** were converted to unnatural amino acids **13** in very good yields upon microwave-assisted acid hydrolysis (Scheme 3). These products may find application in the study of conformationally constrained peptides and medicinal chemistry.

In summary, the [3 + 2] cycloaddition of a series of azidoacetamides derived from α-chiral propargylic amines was investigated. Microwave irradiation promoted intramolecular cycloaddition to afford 1,4,5-trisubstituted triazoles bearing a chiral aminomethyl side chain at C5, while Cu(I)−NHC complexes catalyzed intermolecular desilylative AAC of azido 1-silyl alkynes at rt, leading to 1,4-disubstituted triazoles **5** without the heterocyclic TMS group. Intramolecular reaction products were not detected under the present CuAAC protocol, while analogous terminal alkynes underwent facile polymerization. The controllable reaction pathways offer good opportunities for building molecular diversity from readily available chiral propargylic amines. The use of 1-silyl alkynes as substrates for CuAAC will also enhance the application of this reaction in organic synthesis.

EXPERIMENTAL SECTION

General Methods. All commercially available reagents were used without purification unless otherwise noted. Acetonitrile was refluxed with sodium under argon before use. Column chromatography was performed using silica gel (300−400 mesh). Visualization of the compounds was accomplished with UV light (254 nm) and iodine. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ operating at 400 and 100 MHz, respectively. Proton chemical shifts are reported relative to the residual proton signals of the deuterated solvent [$CDCl_3$ (7.26 ppm) or DMSO-d_6 (2.50 and 3.33 ppm)] or TMS. Carbon chemical shifts were internally referenced to the deuterated solvent signals in $CDCl_3$ (77.00 ppm) or DMSO-d_6 (40.0 ppm). Data are represented as follows: chemical shift (multiplicity, coupling constant in hertz, integration). Multiplicities are denoted as follows: bs = broad singlet, s

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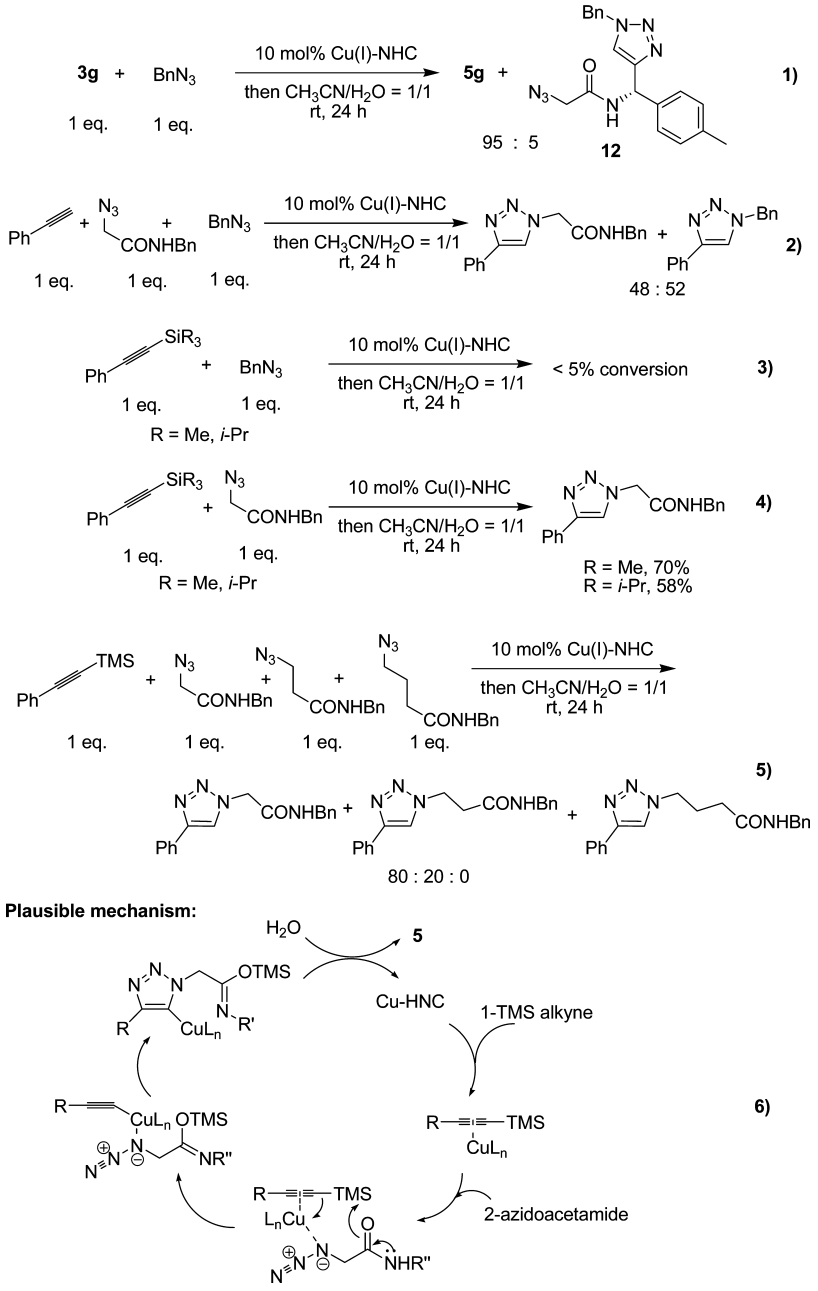
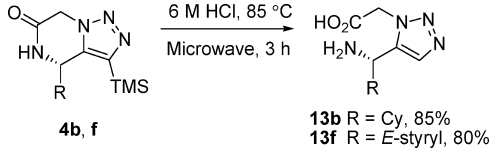
Scheme 2. Control Experiments and a Plausible Mechanism for the Desilylative CuAAC



Scheme 3. Hydrolysis of 4 to Amino Acids



= singlet, d = doublet, t = triplet, m = multiplet. High-resolution mass spectra were recorded on a liquid chromatograph−mass spectrometer (LCMS-IT-TOF). Microwave-assisted reactions were carried out using a focused microwave unit (Biotage Initiator). The reaction temperatures during microwave heating were measured with an internal infrared sensor.

Synthetic Procedures. *General Procedure for the Synthesis of Azido Alkynes* ***3****: (S)-2-Azido-N-(4-methyl-1-(trimethylsilyl)pent-1-yn-3-yl)acetamide (****3a****).* In a dry flask, compound **1** (1 equiv) was dissolved in a small amount of dioxane and methanol (10 equiv). A 2 M HCl solution in dioxane (2 equiv) was added dropwise at 0 °C. The solution was maintained at 0 °C for 1 h, and the solvent was removed under vacuum. The residue was washed with 2:1 hexane/ether, and the resulting solid was filtered and used directly for the next step without further purification. Crude **2a** (650 mg, 3.8 mmol) and DMAP (235 mg, 1.9 mmol) were mixed in methylene chloride in a flask, and the mixture was cooled to 0 °C. HOBt (520 mg, 3.8 mmol) and azidoacetic acid (390 mg, 3.8 mmol) were added, and the mixture was allowed to warm to rt and maintained for 1 h. DCC (950 mg, 4.6 mmol) was added, and the reaction mixture was stirred at rt overnight. The solvent was removed under vacuum, and the crude product was purified by silica gel chromatography (eluent: 15:1 hexane/ethyl acetate) to give **3a** as a colorless oil (700 mg, 72.3%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.56 (d, J = 8.8 Hz, 1H), 4.49−4.45 (m, 1H), 3.89−3.79 (m, 2H), 1.82−1.77 (m, 1H), 0.94 (d, J = 6.8 Hz, 3H), 0.90 (d, J = 6.8 Hz, 3H), 0.15 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.2, 105.0, 87.8, 50.8, 47.4, 32.9,19.2, 18.4, 0.4. HRMS (ESI-TOF) calcd for $C_{11}H_{20}N_4NaOSi$ [M + Na]$^+$ 275.1299, found 275.1297.

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*(S)-2-Azido-N-(1-cyclohexyl-3-(trimethylsilyl)prop-2-yn-1-yl)-acetamide (**3b**).* A colorless oil (800 mg, 71%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.54 (d, J = 8.4 Hz, 1H), 4.49−4.45 (m, 1H), 3.88−3.79 (m, 2H), 1.83−1.6 (m, 5H), 1.46−1.42 (m, 1H), 1.26−0.96 (m, 5H), 0.15 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.1, 105.3, 87.7, 50.9, 46.6, 42.2, 29.2, 28.8, 26.3, 25.8, 25.7, 0.4. HRMS (ESI-TOF) calcd for $C_{14}H_{24}N_4NaOSi$ $[M + Na]^+$ 315.1612, found 315.1607.

*(S)-2-Azido-N-(1-cyclopropyl-3-(trimethylsilyl)prop-2-yn-1-yl)-acetamide (**3c**).* A colorless oil (660 mg, 69%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.70 (d, J = 8.4 Hz, 1H), 4.50−4.46 (m, 1H), 3.88−3.78 (m, 2H), 1.15−1.06 (m, 1H), 0.51−0.29 (m, 4H), 0.14 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.0, 104.4, 86.9, 50.9, 44.3, 15.5, 3.3, 2.6, 0.4. HRMS (ESI-TOF) calcd for $C_{11}H_{18}N_4NaOSi$ $[M + Na]^+$ 273.1142, found 273.1130.

*N-((S)-1-((3S,5S,7S)-Adamantan-1-yl)-3-(trimethylsilyl)prop-2-yn-1-yl)-2-azidoacetamide (**3d**).* A colorless oil (800 mg, 61%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.41 (d, J = 9.2 Hz, 1H), 4.35 (d, J = 9.6 Hz, 1H), 3.86 (s, 2H), 1.97 (s, 3H), 1.68−1.50 (m, 12H), 0.16 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.5, 104.4, 88.4, 51.1, 50.9, 38.3, 37.1, 36.8, 28.1, 0.1. HRMS (ESI-TOF) calcd for $C_{18}H_{28}N_4NaOSi$ $[M + Na]^+$ 367.1925, found 367.1929.

*(S)-2-Azido-N-(1-phenyl-4-(trimethylsilyl)but-3-yn-2-yl)acetamide (**3e**).* A yellow oil (800 mg, 69%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.67 (d, J = 8.4 Hz, 1H), 7.31−7.23 (m, 5H), 4.78−4.73 (m, 1H), 3.85−3.72 (m, 2H), 2.90−2.88 (m, 2H), 0.1 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.0, 137.4, 130.0, 128.5, 127.1, 105.9, 88.0, 51.0, 43.2, 41.4, 0.2. HRMS (ESI-TOF) calcd for $C_{15}H_{20}N_4NaOSi$ $[M + Na]^+$ 323.1299, found 323.1284.

*(S,E)-2-Azido-N-(1-phenyl-5-(trimethylsilyl)pent-1-en-4-yn-3-yl)-acetamide (**3f**).* An orange-yellow solid (800 mg, 67%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.91 (d, J = 8.0 Hz, 1H), 7.47−7.27 (m, 5H), 6.73−6.69 (m, 1H), 6.27−6.22 (m, 1H), 5.45−5.41 (m, 1H), 3.94−3.84 (m, 2H), 0.19 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.0, 136.1, 131.5, 129.2, 128.6, 127.1, 126.6, 104.0, 88.9, 50.9, 43.0, 0.3. HRMS (ESI-TOF) calcd for $C_{16}H_{20}N_4NaOSi$ $[M + Na]^+$ 335.1299, found 335.1294.

*(S)-2-Azido-N-(1-(p-tolyl)-3-(trimethylsilyl)prop-2-yn-1-yl)-acetamide (**3g**).* A light-yellow oil (850 mg, 74%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.09 (d, J = 8.4 Hz, 1H), 7.31 (d, J = 8.0 Hz, 2H), 7.20 (d, J = 8.0 Hz, 2H), 5.84 (d, J = 8.4 Hz, 1H), 3.92−3.80 (m, 2H), 2.30 (s, 3H), 0.17 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.0, 137.6, 136.4, 129.6, 127.2, 105.0, 88.6, 50.8, 44.5, 21.1, 0.3. HRMS (ESI-TOF) calcd for $C_{15}H_{20}N_4NaOSi$ $[M + Na]^+$ 323.1299, found 323.1292.

*(S)-2-Azido-N-(1-(4-methoxyphenyl)-3-(trimethylsilyl)prop-2-yn-1-yl)acetamide (**3h**).* A light-yellow oil (800 mg, 69%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.07 (d, J = 8.0 Hz, 1H), 7.35 (d, J = 8.8 Hz, 2H), 6.95 (d, J = 8.4 Hz, 2H), 5.82 (d, J = 8.4 Hz, 1H), 3.91−3.75 (m, 2H), 3.35 (s, 3H), 0.17 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.9, 159.4, 131.3, 128.6, 114.4, 105.1, 88.5, 55.6, 50.8, 44.2, 0.3. HRMS (ESI-TOF) calcd for $C_{15}H_{20}N_4NaO_2Si$ $[M + Na]^+$ 339.1248, found 339.1237.

*(S)-2-Azido-N-(1-(pyridin-3-yl)-3-(trimethylsilyl)prop-2-yn-1-yl)-acetamide (**3i**).* A white solid (600 mg, 54%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.25 (d, J = 8.0 Hz, 1H), 8.65 (d, J = 0.2 Hz, 1H), 8.55−8.53 (m, 1H), 7.82 (d, J = 8.0 Hz, 1H), 7.46−7.43 (m, 1H), 5.97 (d, J = 8.4 Hz, 1H), 3.96−3.85 (m, 2H), 0.18 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.2, 149.5, 148.7, 135.1, 135.0, 124.1, 103.8, 50.9, 42.9, 31.1, 0.2. HRMS (ESI-TOF) calcd for $C_{10}H_9N_5NaO$ $[M + Na]^+$ 238.0699, found 238.0686.

*(R)-2-Azido-N-(1-(furan-2-yl)-3-(trimethylsilyl)prop-2-yn-1-yl)-acetamide (**3j**).* A yellow oil (700 mg, 66%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.18 (d, J = 8.4 Hz, 1H), 7.67 (s, 1H), 6.45−6.40 (m, 2H), 5.94 (d, J = 8.0 Hz, 1H), 3.92−3.82 (m, 2H), 0.17 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.1, 150.9, 143.8, 111.0, 108.1, 102.2, 88.1, 50.7, 39.0, 0.2. HRMS (ESI-TOF) calcd for $C_{12}H_{16}N_4NaO_2Si$ $[M + Na]^+$ 299.0935, found 299.0928.

*(S)-tert-Butyl 3-(1-(2-Azidoacetamido)-3-(trimethylsilyl)prop-2-yn-1-yl)-1H-indole-1-carboxylate (**3k**).* A yellow oil (1.036 g, 60%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.11 (d, J = 8.4 Hz, 1H), 8.10 (d, J = 8.4 Hz, 1H), 7.69 (s, 1H), 7.60 (d, J = 8.0 Hz, 1H), 7.40−7.36 (m, 1H), 7.30−7.26 (m, 1H), 6.10 (d, J = 8.0 Hz, 1H), 3.94−3.81 (m, 2H), 1.63 (s, 9H), 0.20 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.2, 149.2, 135.7, 128.0, 125.4, 124.6, 123.3, 120.1, 119.1, 115.4, 103.9, 88.2, 84.6, 50.9, 37.6, 28.1, 0.2. HRMS (ESI-TOF) calcd for $C_{21}H_{27}N_5NaO_3Si$ $[M + Na]^+$ 448.1775, found 448.1766.

*(S)-2-Azido-N-(1-(4-methoxyphenyl)-3-phenylprop-2-yn-1-yl)-acetamide (**3l**).* A white solid (860 mg, 70%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.16 (d, J = 8.4 Hz, 1H), 7.49−7.40 (m, 7H), 6.97 (d, J = 8.8 Hz, 2H), 6.03 (d, J = 8.4 Hz, 1H), 3.94−3.84 (m, 2H), 3.76 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.0, 159.4, 131.9, 131.6, 129.3, 129.2, 128.7, 122.4, 114.5, 88.8, 84.0, 55.7, 51.0, 44.2. HRMS (ESI-TOF) calcd for $C_{18}H_{16}N_4NaO_2$ $[M + Na]^+$ 343.1165, found 343.1154.

*(S)-2-Azido-N-(3-cyclopropyl-1-(4-methoxyphenyl)prop-2-yn-1-yl)acetamide (**3m**).* A white solid (760 mg, 70%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.95 (d, J = 8.4 Hz, 1H), 7.32 (d, J = 8.8 Hz, 2H), 6.92 (d, J = 8.8 Hz, 2H), 5.72−5.69 (m, 1H), 3.88−3.77 (m, 2H), 3.74 (s, 3H), 1.40−1.34 (m, 1H), 0.82−0.77 (m, 2H), 0.63−0.59 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.7, 159.3, 132.2, 128.5, 114.3, 87.8, 74.5, 55.6, 50.9, 43.8, 8.3. HRMS (ESI-TOF) calcd for $C_{15}H_{16}N_4NaO_2$ $[M + Na]^+$ 307.1165, found 307.1167.

*General Procedure for Cu-Free Microwave-Assisted AAC: (S)-4-Isopropyl-3-(trimethylsilyl)-4,5-dihydro[1,2,3]triazolo[1,5-a]pyrazin-6(7H)-one (**4a**).* Compound **3a** (126 mg, 0.5 mmol) was dissolved in acetonitrile (20 mL) and water (5 mL). This solution was heated by microwave irradiation to 160 °C and maintained at this temperature for 1 h. The solvent was removed under vacuum. This gave sufficiently pure **4a** as a white solid (120 mg, 95%). Mp 176−177 °C. $[\alpha]_D^{25}$ = +68.3 (c 0.23, MeOH). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.81 (d, J = 3.2 Hz, 1H), 5.15−5.00 (m, 2H), 4.59−4.58 (m, 1H), 1.99−1.95 (m, 1H), 1.01 (d, J = 7.2 Hz, 3H), 0.62 (d, J = 6.8 Hz, 3H), 0.30 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.3, 139.6, 137.9, 53.5, 48.7, 37.0, 19.8, 15.8, −0.4. MS (ESI) m/z 253.1 $[M + H]^+$. HRMS (ESI-TOF) calcd for $C_{11}H_{21}N_4OSi$ $[M + H]^+$ 253.1479, found 253.1470.

*(S)-4-Cyclohexyl-3-(trimethylsilyl)-4,5-dihydro-[1,2,3]triazolo[1,5-a]pyrazin-6(7H)-one (**4b**).* A white solid (142 mg, 97%). Mp 213−214 °C. $[\alpha]_D^{25}$ = +61.8 (c 0.17, MeOH). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.81 (d, J = 3.2 Hz, 1H), 5.12−4.99 (m, 2H), 4.54 (s, 1H), 1.77−1.59 (m, 5H), 1.32−0.92 (m, 6H), 0.31 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.2, 139.6, 137.6, 53.2, 48.8, 46.9, 29.9, 26.3, 26.1, 26.0, 25.8, −0.4. MS (ESI) m/z 293.2 $[M + H]^+$. HRMS (ESI-TOF) calcd for $C_{14}H_{25}N_4OSi$ $[M + H]^+$ 293.1792, found 293.1785.

*(S)-4-Cyclopropyl-3-(trimethylsilyl)-4,5-dihydro-[1,2,3]triazolo-[1,5-a]pyrazin-6(7H)-one (**4c**).* A white solid (120 mg, 96%). Mp 151−152 °C. $[\alpha]_D^{25}$ = +50.2 (c 0.20, MeOH). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.79 (d, J = 3.6 Hz, 1H), 5.23−5.00 (m, 2H), 4.49−4.47 (m, 1H), 1.26−1.19 (m, 1H), 0.51−0.49 (m, 4H), 0.46 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.2, 139.7, 137.6, 50.0, 48.8, 19.0, 2.8, 2.3, −0.3. MS (ESI) m/z 251.1 $[M + H]^+$. HRMS (ESI-TOF) calcd for $C_{11}H_{19}N_4OSi$ $[M + H]^+$ 251.1323, found 251.1318.

*(4S)-4-((1R,3R,5S)-Adamantan-1-yl)-3-(trimethylsilyl)-4,5-dihydro-[1,2,3]triazolo[1,5-a]pyrazin-6(7H)-one (**4d**).* This was further purified by silica gel chromatography (eluent: 5:1 hexane/acetone) to give a white solid (152 mg, 85%). Mp 297−298 °C. $[\alpha]_D^{25}$ = +78.4 (c 0.18, MeOH). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.85 (d, J = 4.0 Hz, 1H), 5.13−4.96 (m, 2H), 4.07 (d, J = 4.4 Hz, 1H), 1.96 (s, 3H), 1.65−1.44 (m, 12H), 0.33 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.8, 141.4, 135.2, 57.7, 49.9, 38.4, 36.5, 28.0, 0.1. MS (ESI) m/z 345.2 $[M + H]^+$. HRMS (ESI-TOF) calcd for $C_{18}H_{29}N_4OSi$ $[M + H]^+$ 345.2105, found 345.2106.

*(S)-4-Benzyl-3-(trimethylsilyl)-4,5-dihydro-[1,2,3]triazolo[1,5-a]-pyrazin-6(7H)-one (**4e**).* This was further purified by silica gel chromatography (eluent: 5:1 hexane/acetone) to give a light-yellow solid (135 mg, 90%). Mp 206−207 °C. $[\alpha]_D^{25}$ = +169.1 (c 0.15, MeOH). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.75 (d, J = 3.6 Hz, 1H), 7.28−7.19 (m, 3H), 6.74−6.72 (m, 2H), 5.14−5.11 (m, 1H), 4.70 (d, J = 17.2 Hz, 1H), 3.29 (d, J = 17.6 Hz, 1H), 3.15−3.10 (m, 1H), 2.99−2.95 (m, 1H), 0.37 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.8, 139.7, 137.1, 134.9, 130.5, 128.7, 127.6, 49.0, 48.0, 43.8, −0.4. MS

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(ESI) m/z 301.1 $[M + H]^+$. HRMS (ESI-TOF) calcd for $C_{15}H_{21}N_4OSi$ $[M + H]^+$ 301.1479, found 301.1483.

*(S,E)-4-Styryl-3-(trimethylsilyl)-4,5-dihydro-[1,2,3]triazolo[1,5-a]-pyrazin-6(7H)-one (**4f**).* This was further purified by silica gel chromatography (eluent: 5:1 hexane/acetone) to give an orange-yellow solid (136 mg, 87%). Mp 197−198 °C. $[\alpha]_D^{25}$ = +94.3 (c 0.21, MeOH). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.96 (d, J = 3.2 Hz, 1H), 7.46−7.29 (m, 5H), 6.65 (d, J = 15.6 Hz, 1H), 6.35−6.29 (m, 1H), 5.43−5.40 (m, 1H), 5.17−5.06 (m, 2H), 0.25 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.3, 140.5, 136.7, 136.0, 132.2, 129.3, 128.8, 128.1, 127.1, 51.0, 48.5, −0.5. MS (ESI) m/z 313.1 $[M + H]^+$. HRMS (ESI-TOF) calcd for $C_{16}H_{21}N_4OSi$ $[M + H]^+$ 313.1479, found 301.1466.

*(S)-4-(p-Tolyl)-3-(trimethylsilyl)-4,5-dihydro-[1,2,3]triazolo[1,5-a]-pyrazin-6(7H)-one (**4g**).* A white solid (140 mg, 93%). Mp 199−200 °C. $[\alpha]_D^{25}$ = +124.1 (c 0.19, MeOH). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.07 (d, J = 2.4 Hz, 1H), 7.18 (d, J = 8.0 Hz, 2H), 7.08 (d, J = 8.0 Hz, 2H), 5.83 (s, 1H), 5.34−5.11 (m, 2H), 2.29 (s, 3H), 0.01 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.5, 140.4, 138.4, 138.4, 137.4, 129.8, 128.2, 52.5, 48.3, 21.2, −1.0. MS (ESI) m/z 301.1 $[M + H]^+$. HRMS (ESI-TOF) calcd for $C_{15}H_{21}N_4OSi$ $[M + H]^+$ 301.1479, found 301.1480.

*(S)-4-(4-Methoxyphenyl)-3-(trimethylsilyl)-4,5-dihydro-[1,2,3]-triazolo[1,5-a]pyrazin-6(7H)-one (**4h**).* A white solid (149 mg, 94%). Mp 171−172 °C. $[\alpha]_D^{25}$ = +136.9 (c 0.19, MeOH). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.05 (s, 1H), 7.12 (d, J = 8.8 Hz, 2H), 6.92 (d, J = 8.4 Hz, 2H), 5.83 (s, 1H), 5.33−5.10 (m, 2H), 3.74 (s, 3H), −0.01 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.4, 159.8, 140.4, 137.6, 133.4, 129.6, 114.6, 55.7, 52.2, 48.3, 31.1, −1.0. MS (ESI) m/z 317.1 $[M + H]^+$. HRMS (ESI-TOF) calcd for $C_{15}H_{21}N_4O_2Si$ $[M + H]^+$ 317.1428, found 317.1419.

*(S)-4-(Pyridin-3-yl)-4,5-dihydro-[1,2,3]triazolo[1,5-a]pyrazin-6(7H)-one (**4i**).* This was further purified by silica gel chromatography (eluent: 2:1 hexane/acetone) to give a light-yellow oil (108 mg, 75%). $[\alpha]_D^{25}$ = +67.6 (c 0.19, MeOH). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.11 (s, 1H), 8.65 (s, 1H), 8.58 (s, 1H), 7.78 (d, J = 8.0 Hz, 1H), 7.54 (s, 1H), 7.45−7.42 (m, 1H), 6.09 (s, 1H), 5.31−5.11 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.4, 150.1, 148.9, 135.3, 132.1, 130.2, 49.7, 48.5. MS (ESI) m/z 216.1 $[M + H]^+$. HRMS (ESI-TOF) calcd for $C_{10}H_{10}N_5O$ $[M + H]^+$ 216.0880, found 216.0877.

*(R)-4-(Furan-2-yl)-3-(trimethylsilyl)-4,5-dihydro-[1,2,3]triazolo-[1,5-a]pyrazin-6(7H)-one (**4j**).* This was further purified by silica gel chromatography (eluent: 5:1 hexane/acetone) to give a light-yellow solid (121 mg, 88%). Mp 160−161 °C. $[\alpha]_D^{25}$ = +85.5 (c 0.24, MeOH). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.17 (d, J = 3.2 Hz, 1H), 7.64 (d, J = 0.8 Hz, 1H), 6.47−6.42 (m, 2H), 6.03 (d, J = 3.2 Hz, 1H), 5.23−5.14 (m, 2H), 0.15 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.3, 152.0, 144.0, 140.6, 135.2, 111.3, 108.7, 48.5, 46.1, 31.1, −0.9. MS (ESI) m/z 277.1 $[M + H]^+$. HRMS (ESI-TOF) calcd for $C_{12}H_{17}N_4O_2Si$ $[M + H]^+$ 277.1115, found 227.1103.

*(S)-4-(1H-Indol-3-yl)-3-(trimethylsilyl)-4,5-dihydro-[1,2,3]triazolo-[1,5-a]pyrazin-6(7H)-one (**4k**).* This was further purified by silica gel chromatography (eluent: 5:1 hexane/acetone) to give an orange-yellow solid (138 mg, 85%). Mp 256−257 °C. $[\alpha]_D^{25}$ = +116.2 (c 0.10, MeOH). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.19 (s, 1H), 8.95 (d, J = 2.0 Hz, 1H), 7.39−7.31 (m, 2H), 7.10−6.89 (m, 3H), 6.16 (d, J = 1.6 Hz, 1H), 5.35−5.14 (m, 2H), −0.16 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.6, 140.3, 138.1, 136.9, 125.5, 125.1, 122.0, 119.6, 118.7, 114.1, 112.3, 48.2, 46.0, −1.1. MS (ESI) m/z 326.1 $[M + H]^+$. HRMS (ESI-TOF) calcd for $C_{16}H_{20}N_5OSi$ $[M + H]^+$ 326.1432, found 326.1426.

*(S)-4-(4-Methoxyphenyl)-3-phenyl-4,5-dihydro-[1,2,3]triazolo-[1,5-a]pyrazin-6(7H)-one (**4l**).* Reaction time: 3 h. This was further purified by silica gel chromatography (eluent: 5:1 hexane/acetone) to give a light-yellow oil (128 mg, 80%). $[\alpha]_D^{25}$ = +137.9 (c 0.38, MeOH). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.21 (d, J = 2.4 Hz, 1H), 7.62−7.60 (m, 2H), 7.37−7.28 (m, 3H), 7.17−7.15 (m, 2H), 6.85−6.82 (m, 2H), 6.22 (d, J = 3.2 Hz, 1H), 5.41−5.18 (m, 2H), 3.69 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.5, 159.6, 141.3, 132.3, 130.7, 129.1, 129.0, 128.4, 128.2, 126.9, 114.6, 55.6, 51.8, 48.9. MS (ESI) m/z 321.1 $[M + H]^+$. HRMS (ESI-TOF) calcd for $C_{18}H_{17}N_4O_2$ $[M + H]^+$ 321.1346, found 321.1344.

*(S)-3-Cyclopropyl-4-(4-methoxyphenyl)-4,5-dihydro-[1,2,3]-triazolo[1,5-a]pyrazin-6(7H)-one (**4m**).* Reaction time: 3 h. This was further purified by silica gel chromatography (eluent: 5:1 hexane/acetone) to give a white solid (107 mg, 75%). Mp 118−119 °C. $[\alpha]_D^{25}$ = +31.1 (c 0.30, MeOH). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.06 (d, J = 2.4 Hz, 1H), 7.27 (d, J = 8.8 Hz, 2H), 6.93 (d, J = 8.4 Hz, 2H), 5.90 (s, 1H), 5.26−5.02 (m, 2H), 3.75 (s, 3H), 0.77−0.73 (m, 1H), 0.63−0.56 (m, 2H), 0.53−0.48 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.0, 159.6, 143.1, 132.5, 129.1, 128.8, 114.6, 55.7, 51.4, 48.6, 7.4, 7.0, 6.0. MS (ESI) m/z 285.1 $[M + H]^+$. HRMS (ESI-TOF) calcd for $C_{15}H_{17}N_4O_2$ $[M + H]^+$ 285.1346, found 285.1347.

*General Procedure for Cu−NHC-Catalyzed AAC: 2-Azido-N-((S)-2-methyl-1-(1-(2-(((S)-4-methyl-1-(trimethylsilyl)pent-1-yn-3-yl)-amino)-2-oxoethyl)-1H-1,2,3-triazol-4-yl)propyl)acetamide (**5a**).* The NHC precursor **9** (15 mg, 0.05 mmol) was dissolved in acetonitrile (3 mL) under nitrogen. To this was added CuCl (5 mg, 0.05 mmol) and sodium *tert*-butoxide (4.8 mg, 0.05 mmol). The mixture was stirred for 3 h at rt. Then **3a** (150 mg, 0.5 mmol) and water (3 mL) were added successively to the reaction mixture, and the resulting solution was stirred at rt for 24 h. After removal of the solvent under vacuum, the crude product was purified by silica gel chromatography (eluent: 5:1 hexane/acetone) to give **5a** as a white solid (149 mg, 69%). Mp 108−109 °C. $[\alpha]_D^{25}$ = +170.8 (c 0.20, MeOH). ^{1}H NMR (400 MHz, CD_3OD) δ 7.91 (s, 1H), 5.18 (s, 2H), 4.97 (d, J = 7.6 Hz, 1H), 4.55 (d, J = 6.0 Hz, 1H), 3.93 (m, 2H), 2.30−2.23 (m, 1H), 1.95−1.86 (m, 1H), 1.04−0.99 (m, 9H), 0.92 (d, J = 6.8 Hz, 3H), 0.18 (s, 9H). ^{13}C NMR (100 MHz, CD_3OD) δ 168.3, 165.4, 124.1, 102.9, 87.9, 51.6, 51.5, 51.4, 32.8, 32.1, 18.3, 17.8, 17.6, 16.8, −1.5. MS (ESI) m/z 433.2 $[M + H]^+$. HRMS (ESI-TOF) calcd for $C_{19}H_{33}N_8O_2Si$ $[M + H]^+$ 433.2490, found 433.2492.

*2-Azido-N-((S)-cyclohexyl(1-(2-(((S)-1-cyclohexyl-3-(trimethylsilyl)prop-2-yn-1-yl)amino)-2-oxoethyl)-1H-1,2,3-triazol-4-yl)methyl)acetamide (**5b**).* A white solid (166 mg, 65%). Mp 158−159 °C. $[\alpha]_D^{25}$ = +82.1 (c 0.17, MeOH). ^{1}H NMR (400 MHz, CD_3OD) δ 7.90 (s, 1H), 5.16 (s, 2H), 4.98 (d, J = 8.0 Hz, 1H), 4.54 (d, J = 6.8 Hz, 1H), 3.91 (m, 2H), 1.92−1.56 (m, 12H), 1.31−0.99 (m, 10H), 0.18 (s, 9H). ^{13}C NMR (100 MHz, CD_3OD) δ 168.2, 165.4, 147.0, 124.2, 103.3, 87.9, 51.5, 51.5, 50.7, 42.4, 41.6, 29.6, 28.9, 28.8, 28.4, 25.9, 25.6, 25.6, 25.5, −1.5. MS (ESI) m/z 513.3 $[M + H]^+$. HRMS (ESI-TOF) calcd for $C_{25}H_{41}N_8O_2Si$ $[M + H]^+$ 513.3116, found 513.3127.

*2-Azido-N-((S)-1-(1-(2-oxo-2-(((S)-1-phenyl-4-(trimethylsilyl)but-3-yn-2-yl)amino)ethyl)-1H-1,2,3-triazol-4-yl)-2-phenylethyl)-acetamide (**5e**).* A white syrup (179 mg, 68%). $[\alpha]_D^{25}$ = +119.7 (c 0.15, MeOH). ^{1}H NMR (400 MHz, CD_3OD) δ 7.77 (s, 1H), 7.31−7.18 (m, 10H), 5.43−5.39 (m, 1H), 5.13−5.03 (m, 2H), 4.88−4.86 (m, 1H), 3.81 (s, 2H), 3.33−3.29 (m, 1H), 3.20−3.14 (m, 1H), 2.97 (d, J = 6.8 Hz, 2H), 0.14 (s, 9H). ^{13}C NMR (100 MHz, CD_3OD) δ 168.0, 165.2, 137.4, 136.6, 129.4, 129.0, 128.0, 127.9, 126.5, 126.3, 123.8, 103.7, 88.2, 51.5, 51.5, 43.5, 41.1, 40.0, −1.6. MS (ESI) m/z 529.2 $[M + H]^+$. HRMS (ESI-TOF) calcd for $C_{27}H_{33}N_8O_2Si$ $[M + H]^+$ 529.2492, found 529.2483.

*2-Azido-N-((S,E)-1-(1-(2-oxo-2-(((S,E)-1-phenyl-5-(trimethylsilyl)-pent-1-en-4-yn-3-yl)amino)ethyl)-1H-1,2,3-triazol-4-yl)-3-phenylallyl)acetamide (**5f**).* A white solid (198 mg, 72%). Mp 115−116 °C. $[\alpha]_D^{25}$ = −20.3 (c 0.20, MeOH). ^{1}H NMR (400 MHz, CD_3OD) δ 7.36 (s, 1H), 7.35−7.31 (m, 4H), 7.29−7.24 (m, 6H), 6.81 (d, J = 15.6 Hz, 1H), 6.69 (d, J = 16.0 Hz, 1H), 6.55−6.49 (m, 1H), 6.25−6.20 (m, 1H), 5.94 (d, J = 6.4 Hz, 1H), 5.49−5.47 (m, 1H), 5.23 (s, 2H), 3.98 (s, 2H), 0.22 (s, 9H). ^{13}C NMR (100 MHz, CD_3OD) δ 168.0, 165.2, 147.2, 136.4, 136.1, 132.2, 132.1, 128.3, 128.2, 127.8, 127.6, 126.3, 126.3, 126.2, 124.9, 124.2, 101.9, 89.0, 56.9, 51.6, 51.5, 43.3, −1.6. MS (ESI) m/z 553.2 $[M + H]^+$. HRMS (ESI-TOF) calcd for $C_{29}H_{32}N_8NaO_2Si$ $[M + Na]^+$ 575.2310, found 575.2296.

*2-Azido-N-((S)-(1-(2-oxo-2-(((S)-1-(p-tolyl)-3-(trimethylsilyl)prop-2-yn-1-yl)amino)ethyl)-1H-1,2,3-triazol-4-yl)(p-tolyl)methyl)-acetamide (**5g**).* A white solid (214 mg, 81%). Mp 85−86 °C. $[\alpha]_D^{25}$ = −8.6 (c 0.36, MeOH). ^{1}H NMR (400 MHz, CD_3OD) δ 7.73 (s, 1H), 7.36 (d, J = 8.0 Hz, 2H), 7.27 (d, J = 8.0 Hz, 2H), 7.20−7.18 (m, 4H),

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6.32 (s, 1H), 5.86 (s, 1H), 5.19−5.10 (m, 2H), 4.00−3.91 (m, 2H), 2.35 (m, 6H), 0.20 (s, 9H). ^{13}C NMR (100 MHz, CD_3OD) δ 167.9, 165.1, 137.8, 137.4, 136.8, 135.5, 129.0, 129.0, 126.9, 126.6, 124.6, 103.0, 88.7, 51.5, 51.4, 49.5, 45.0, 19.7, −1.6. MS (ESI) m/z 529.2 $[M + H]^+$. HRMS (ESI-TOF) calcd for $C_{27}H_{33}N_8O_2Si$ $[M + H]^+$ 529.2490, found 529.2498.

*2-Azido-N-((S)-(4-methoxyphenyl)(1-(2-(((S)-1-(4-methoxyphenyl)-3-(trimethylsilyl)prop-2-yn-1-yl)amino)-2-oxoethyl)-1H-1,2,3-triazol-4-yl)methyl)acetamide (**5h**).* A white solid (221 mg, 79%). Mp 61−62 °C. $[\alpha]_D^{25}$ = −9.4 (*c* 0.17, MeOH). ^{1}H NMR (400 MHz, CD_3OD) δ 7.73 (s, 1H), 7.40 (d, *J* = 8.4 Hz, 2H), 7.29 (d, *J* = 8.8 Hz, 2H), 6.93−6.90 (m, 4H), 6.30 (s, 1H), 5.85 (s, 1H), 5.18−5.05 (m, 2H), 3.99−3.89 (m, 2H), 3.80−3.79 (m, 6H), 0.20 (s, 9H). ^{13}C NMR (100 MHz, CD_3OD) δ 167.9, 165.0, 159.7, 159.5, 148.2, 131.8, 130.4, 128.3, 128.0, 124.5, 113.8, 113.7, 103.1, 88.7, 54.4, 54.4, 51.5, 51.4, 49.3, 44.7, −1.5. MS (ESI) m/z 561.2 $[M + H]^+$. HRMS (ESI-TOF) calcd for $C_{27}H_{32}N_8NaO_4Si$ $[M + Na]^+$ 583.2208, found 583.2203.

*2-Azido-N-((R)-furan-2-yl(1-(2-(((R)-1-(furan-2-yl)-3-(trimethylsilyl)prop-2-yn-1-yl)amino)-2-oxoethyl)-1H-1,2,3-triazol-4-yl)methyl)acetamide (**5j**).* A light-yellow oil (180 mg, 75%). $[\alpha]_D^{25}$ = +13.9 (*c* 0.33, MeOH). ^{1}H NMR (400 MHz, CD_3OD) δ 7.96 (s, 1H), 7.51−7.49 (m, 2H), 6.47−6.32 (m, 5H), 5.97 (m, 1H), 5.24−5.15 (m, 2H), 3.99−3.91 (m, 2H), 0.20 (s, 9H). ^{13}C NMR (100 MHz, CD_3OD) δ 168.0, 165.2, 151.7, 150.5, 145.6, 142.9, 142.9, 142.6, 124.7, 110.1, 107.6, 107.4, 100.3, 88.1, 51.4, 51.3, 43.9, 39.4, −1.7. MS (ESI) m/z 481.1 $[M + H]^+$. HRMS (ESI-TOF) calcd for $C_{21}H_{25}N_8O_4Si$ $[M + H]^+$ 481.1763, found 481.1766.

*General Procedure for Microwave-Assisted Acid Hydrolysis: (S)-2-(5-(Amino(cyclohexyl)methyl)-1H-1,2,3-triazol-1-yl)acetic Acid (**13b**).* Compound **4b** (55 mg, 0.22 mmol) was added to 6 M aqueous HCl (2.7 mL), and the mixture was heated under microwave conditions at 85 °C for three cycles of 1 h each. The solution was washed with $CHCl_3$ (4 × 3 mL), and the aqueous layer was evaporated under vacuum to give compound **13b** as a light-yellow solid (44.6 mg, 85% yield). Mp 96−97 °C. $[\alpha]_D^{25}$ = +11.1 (*c* 0.75, MeOH). ^{1}H NMR (400 MHz, CD_3OD) δ 7.98 (s, 1H), 5.54−5.39 (AB, J_{AB} = 18.0 Hz, 2H), 4.45 (d, *J* = 9.2 Hz, 1H), 2.04−1.28 (m, 11H). ^{13}C NMR (100 MHz, CD_3OD) δ 168.4, 135.4, 132.1, 49.2 (2C), 41.0, 28.7, 28.6, 25.3, 25.1 (2C). HRMS (ESI-TOF) calcd for $C_{11}H_{18}N_4NaO_2$ $[M + Na]^+$ 261.1322, found 261.1319.

*(S,E)-2-(5-(1-Amino-3-phenylallyl)-1H-1,2,3-triazol-1-yl)acetic Acid (**13f**).* A yellow solid (45.4 mg, 80% yield). Mp 127−128 °C. $[\alpha]_D^{25}$ = +103.4 (*c* 0.30, MeOH). ^{1}H NMR (400 MHz, D_2O) δ 7.91 (s, 1H), 7.46−7.44 (m, 2H), 7.37−7.32 (m, 3H), 6.82 (d, *J* = 16.0 Hz, 1H), 6.32 (dd, *J* = 15.6, 8.0 Hz, 1H), 5.33 (d, *J* = 8.0 Hz, 1H), 5.04 (AB, J_{AB} = 17.6 Hz, 2H). ^{13}C NMR (100 MHz, D_2O) δ 172.2, 136.9, 135.0, 134.7, 132.8, 129.3, 129.0, 127.1, 120.7, 52.1, 47.3. HRMS (ESI-TOF) calcd for $C_{13}H_{14}N_4NaO_2$ $[M + Na]^+$ 281.1009, found 281.1001.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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