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Note

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Copper-catalyzed One-pot Synthesis of 1,3-Enynes from 2-Chloro-*N*-(quinolin-8-yl)acetamides and Terminal Alkynes

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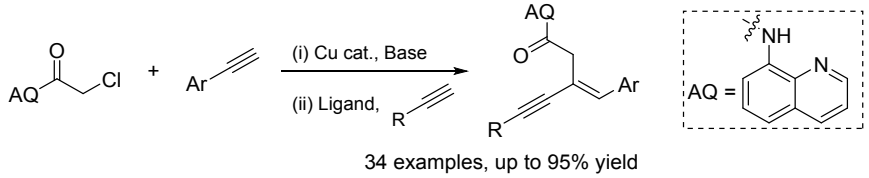


34 examples, up to 95% yield

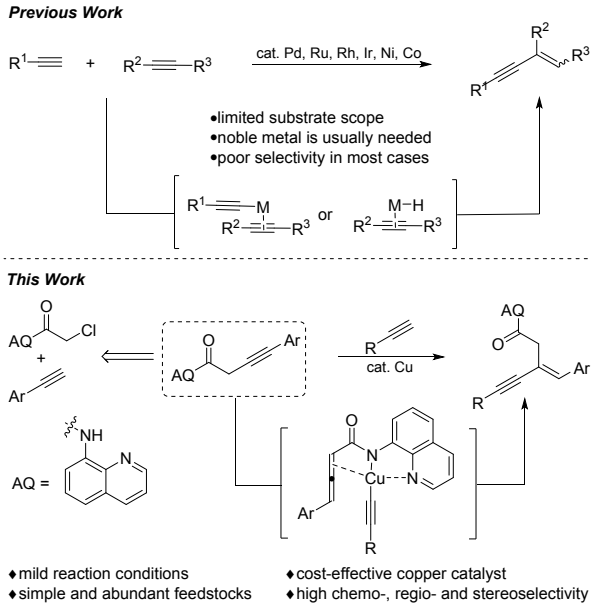
ABSTRACT: A method for the chemo-, regio-, and stereoselective one-pot synthesis of 1,3-enynes is described. The reaction of 2-chloro-*N*-(quinolin-8-yl)acetamides with terminal alkynes proceeds smoothly in the presence of a copper catalyst at room temperature to produce (*E*)-1,3-enynes in satisfactory to excellent yields. The mechanism study reveals that the cross-dimerization of internal alkynes generated in situ with terminal alkynes proceeds via allene intermediates. The directing group 8-aminoquinoline plays a key role in the current selective synthesis of (*E*)-1,3-enynes.

1,3-Enynes are valuable synthons in the field of organic chemistry and can be used for the synthesis of natural products, pharmaceuticals, and functional materials.[1] Numerous synthetic methods, including the name reaction (Wittig and Horner–Wadsworth–Emmons reactions),[2] the transition metal-catalyzed cross-coupling reaction,[3] the reaction involving metal carbene,[4] and the dimerization of alkynes,[5-8] have been developed to synthesize 1,3-enynes. Among these methods, the dimerization of alkynes has attracted considerable attention due to its perfect atomic economy. However, the competitive homo-dimerization of the terminal alkyne frequently occurs in the cross-dimerization of internal alkynes with terminal alkynes. The internal alkyne bearing an electron-withdrawing group[7] or the terminal alkyne having a bulky alkylsilyl group[8] is utilized for target cross-dimerization, which proceeds via the carbometalation or the hydrometallation of internal alkyne, to inhibit a side reaction (Scheme 1, previous work). These starting materials are not readily available, resulting in the narrow substrate scope of cross-dimerization. Therefore, the development of a new method for the synthesis of 1,3-enynes by using readily available and inexpensive starting materials and a cost-effective catalyst is highly desirable.

In the course of our research on alkyne chemistry,[9] we succeeded in the chemo-, regio-, and stereoselective one-pot tandem synthesis of 1,3-enynes by using simple and readily available terminal alkynes and a Cu catalyst (Scheme 1, this work). In the current work,

the cross-dimerization of internal alkynes generated in situ with terminal alkynes proceeded via allene intermediates. The results are reported in this paper.

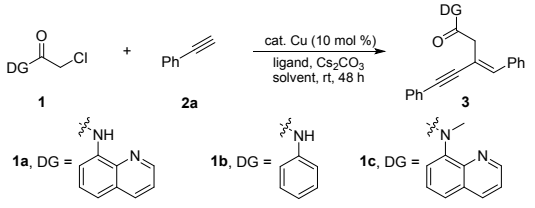
Scheme 1. Cross-dimerization between Terminal and Internal Alkynes



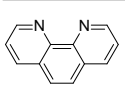
In our initial studies, the reaction of 2-chloro-*N*-(quinolin-8-yl)acetamide (**1a**) with phenylacetylene (**2a**) was selected as a model to optimize the reaction conditions. The results are shown in Table 1. The model reaction was first tested using different Cu catalysts, including Cu(I) and Cu(II) salts, in toluene at room temperature in the presence of Cs_2CO_3 and 1,10-phenanthroline (**L1**) (entries 1–5). Results indicated that CuI possessed relatively higher catalytic activity than others. The desired product, (*E*)-3-benzylidene-5-phenyl-*N*-(quinolin-8-yl)pent-4-ynamide (**3a**) with 73% yield was obtained (entry 3). The ligand was subsequently screened using CuI as the catalyst in

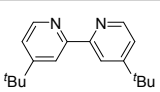
toluene. No reaction or only 9% yield of **3a** was observed when 4,4′-di-*tert*-butyl-2,2′-bipyridine (**L2,** entry 6) and bathocuproine (**L3,** entry 7) instead of **L1** were examined. The solvent was finally screened using CuI and **L1** as catalyst and ligand, respectively. Among the solvents tested, dichloromethane (DCM) was the best (entries 3, 8–10). The yield of **3a** increased with decreasing amount of DCM (entries 10–12). This observation suggested that the relatively high concentration of the starting materials was favorable for the target reaction. The yield of **3a** increased to 91% by reducing the base loading (entry 13). 2-Chloro-*N*-phenylacetamide (**1b,** entry 14) and 2-chloro-*N*-methyl-*N*-(quinolin-8-yl)acetamide (**1c,** entry 15) were used instead of **1a** to examine the effect of directing groups (DG). Only a small amount of the desired product **3ab** was obtained when **1b** was used as the starting material (entry 14). The desired product **3ac** was not formed when **1c** was examined (entry 15). These results suggested that 8-aminoquinoline (AQ) was necessary as a powerful DG to promote the target reaction. Therefore, the subsequent cross-dimerization of various terminal alkynes was conducted in the presence of CuI (10 mol %), **L1** (20 mol %), and Cs_2CO_3 (1.2 equiv.) in DCM at room temperature for 48 h.

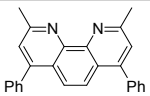
Table 1. Screening of Reaction Conditions[a]



Entry	Catalyst	Ligand	Solvent (mL)	Yield (%)[b]
1	CuCl	L1	Toluene (2)	69
2	CuBr	L1	Toluene (2)	54
3	CuI	L1	Toluene (2)	73
4	$CuCl_2$	L1	Toluene (2)	67
5	$Cu(OAc)_2$	L1	Toluene (2)	71
6	CuI	L2	Toluene (2)	0
7	CuI	L3	Toluene (2)	9
8	CuI	L1	CH_3CN (2)	0
9	CuI	L1	THF (2)	41
10	CuI	L1	DCM (2)	74
11	CuI	L1	DCM (4)	63
12	CuI	L1	DCM (1)	86
13[c]	CuI	L1	DCM (1)	91
14[c,d]	CuI	L1	DCM (1)	9
15[c,e]	CuI	L1	DCM (1)	0


L1


L2

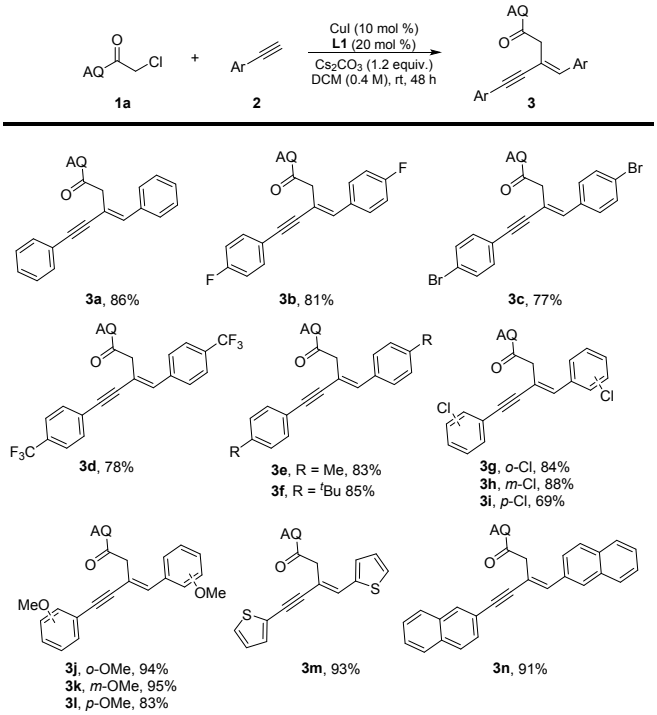

L3

[a]Reaction conditions: **1a** (0.4 mmol), **2a** (1.2 mmol), Cu catalyst (0.04 mmol, 10 mol %), ligand (0.08 mmol, 20 mol %), and Cs_2CO_3 (0.8 mmol) in solvent at room temperature (rt) under N_2 atmosphere for 48 h. [b]Determined through ^1H NMR spectroscopy by using CH_2Br_2 as an internal standard. [c]0.48 mmol Cs_2CO_3 was used as a base. [d]**1b** was used instead of **1a**. [e]**1c** was used instead of **1a**.

The substrate scope of terminal alkynes was initially examined using the optimized conditions (Scheme 2). The reactions of aryl acetylenes bearing electron-withdrawing groups (F, Br, and CF_3) on the *para*-positions of benzene rings proceeded smoothly to provide the corresponding 1,3-enyne products **3b**–**3d** with 77%–81% yields. The X-ray crystallography of **3d** confirmed that the stereostructure of the 1,3-enyne product was an *E*-isomer. The reactions of *para*-methyl phenylacethylene (**2e**) and *para*-*tert*-butyl phenylacetylene (**2f**) also proceeded smoothly to furnish 1,3-enyne products **3e** and **3f**

with 83% and 85% yields, respectively. These results indicated that the reactivity of terminal arylalkynes was not significantly influenced by the electronic property of the substituent linked on the benzene ring. The Cl atom and the MeO group linked on different positions (*ortho*-, *meta*-, and *para*-positions) of the benzene ring did not strongly influence the reactivity of terminal arylalkynes. The desired 1,3-enyne products **3g**–**3l** with 69%–88% yields were obtained. The heterocycle- and fused aromatic ring-containing terminal alkynes **2m** and **2n**, respectively, were finally examined. The desired products **3m** and **3n** were obtained in excellent yields (93% and 91%, respectively).

Scheme 2. Scope of Terminal Alkynes[a,b]

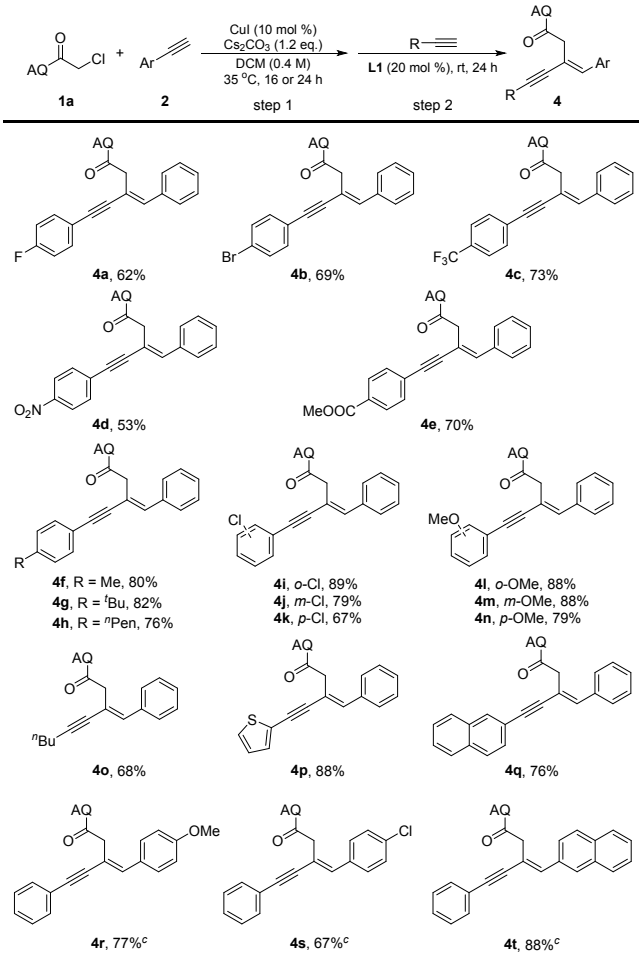


[a]Reaction conditions: **1a** (0.4 mmol), **2** (1.2 mmol), CuI (10 mol %), **L1** (20 mol %), and Cs_2CO_3 (0.48 mmol) in DCM (1 mL) at room temperature (rt) under N_2 atmosphere for 48 h. [b]Isolated yields.

Encouraged by the success in the one-pot synthesis of 1,3-enyne from the reaction of **1a** with a terminal alkyne, we synthesized 1,3-enyne by using two different terminal alkynes (Scheme 3). We conducted the reaction in two steps to avoid the undesired homo-dimerization of terminal alkyne. The Sonogashira-type coupling reaction of **1a** with the first terminal alkyne was completed within 16 or 24 h, and the mixture was added with the second terminal alkyne and ligand **L1**. Then, the resulting mixture was stirred at room temperature for 24 h. The tandem reaction of **1a**, **2a**, and a second terminal arylalkyne, including **2b**–**2d**, **2o**, and **2p** bearing electron-withdrawing groups (F, Br, CF_3, NO_2, and COOMe) on the *para*-position of the benzene rings also proceeded smoothly to provide 1,3-enyne products **4a**–**4e** with 53%–73% yields. The 1,3-enyne products **4f**–**4h** were obtained in relatively high yields (76%–82%) when the terminal alkynes **2e**, **2f**, and **2q** bearing electron-donating groups (Me, ^{t}Bu, and ^{n}Pen) on the *para*-position of benzene rings were utilized as the second terminal alkynes. Terminal alkynes with Cl or OMe on the *ortho*-, *meta*-, and *para*-positions of the benzene rings were found suitable as second terminal alkynes in the one-pot tandem reaction. The 1,3-enyne products **4i**–**4n** with 67%–89% yields were obtained. The subsequent investigation revealed that the aliphatic terminal alkyne and the heterocycle- and fused aromatic ring-containing terminal alkynes were also suitable substrates for the current one-pot tandem reaction. The desired products **4o**–**4q** were obtained in 68%–88% yields. Finally, we changed the first terminal alkyne **2a** to **2i**, **2l** and **2n**, and used **2a** as the

second terminal alkyne. Tandem reactions also proceeded smoothly to produce the desired 1,3-enynes **4r**–**4t** with 67%–88% yields.

Scheme 3. Synthesis of 1,3-Enyne by using Two Different Terminal Alkynes[a,b]

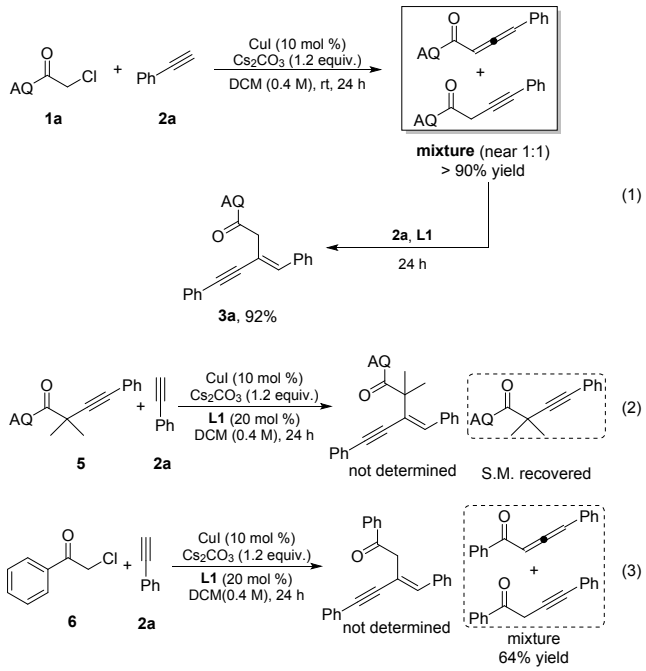


[a]Reaction conditions: Step 1) **1a** (0.4 mmol), **2** (0.4 mmol), CuI (0.04 mmol, 10 mol %), and Cs_2CO_3 (0.48 mmol) in DCM (1 mL) at 35 ºC under N_2 atmosphere for 16 h; Step 2) The reaction mixture was added with another terminal alkyne (0.8 mmol) and 1,10-phenanthroline (0.08 mmol, 20 mol %) and stirred at room temperature (rt) under N_2 atmosphere for 24 h. [b]Isolated yields. [c]The reaction was carried out for 24 h in Step 1. See SI for details.

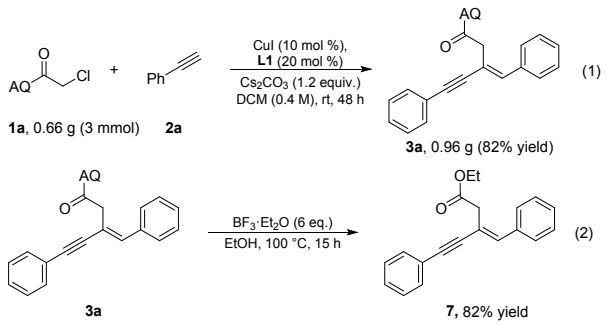
Control experiments were conducted to gain insight into the mechanism (Scheme 4). A mixture of alkyne and allene was obtained when **1a** and **2a** were reacted without a ligand.

This mixture can be completely transformed to the corresponding 1,3-enyne compound **3a** just by the addition of ligand **L1** (92% yield, Scheme 4, Eq. 1). This result suggested that a ligand was necessary for cross-dimerization. No desired product was detected when the internal alkyne **5** was treated under standard conditions (Scheme 4, Eq. 2) because alkyne **5** cannot isomerize to allene isomer due to the absence of α-H. Also, no desired product was detected when α-Cl acetophenone (**6**) was treated under standard conditions (Scheme 4, Eq. 3). This result revealed that an appropriate DG played an essential role in the catalytic cycle.

Scheme 4. Control Experiments



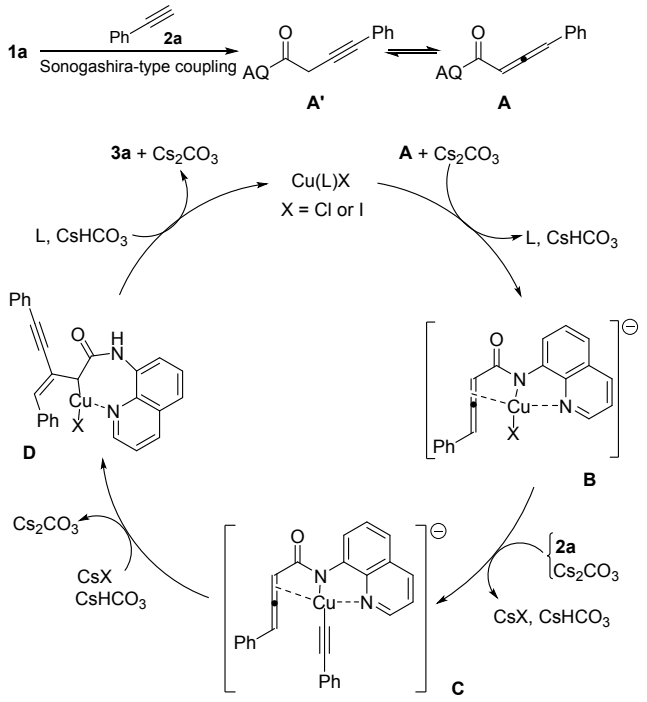
Scheme 5. Gram-scale Synthesis and Product Derivatization



Substrate **1a** was scaled up to 3 mmol to verify the usefulness of the current cross-dimerization reaction. Treating 3 mmol (0.66 g) **1a** at standard conditions resulted in a slightly decreased yield (0.96 g, 82% yield; Scheme 5, Eq. 1) compared with the small-scale reaction was observed. The DG AQ was removed by alcoholysis with ethanol in the presence of $BF_3{\cdot}Et_2O$. The product, ethyl-(*E*)-3-benzylidene-5-phenylpent-4-ynoate (**7**), with 82% yield was obtained. This product can be used for further manipulation to produce useful compounds[10] (Scheme 5, Eq. 2).

On the basis of previous reports[11] and the experimental results, a plausible mechanism is illustrated in Scheme 6. Initially, a Sonogashira-type coupling reaction between **1a** and terminal alkyne **2a** occurred in the presence of CuI and Cs_2CO_3 to produce a tautomer of allene **A** and internal alkyne **A′**. Then, the Cu catalyst coordinated to **A** in the presence of Cs_2CO_3 to generate a chelated Cu complex **B**, which reacted with **2a** in the presence of Cs_2CO_3 to generate intermediate **C**. The intermediate **C** subsequently underwent intramolecular regio- and stereoselective carbocupration to generate intermediate **D**. Finally, the protonolysis of intermediate **D** occurred to yield the desired product **3a** and regenerate the Cu catalyst.

Scheme 6. Proposed Mechanism



In summary, a convenient and efficient method for the chemo-, regio-, and stereoselective synthesis of 1,3-enynes was developed in this work. The Cu-catalyzed one-pot tandem reaction of 2-chloro-*N*-(quinolin-8-yl)acetamides and terminal alkynes proceeded smoothly at mild reaction conditions to produce (*E*)-1,3-enynes in satisfactory to excellent yields. The wide availability of the simple terminal alkynes, cost effectivity of Cu catalyst, mild reaction conditions, good functional group tolerance, and experimental simplicity rendered the current method highly useful for the synthesis of (*E*)-1,3-enynes.

EXPERIMENTAL SECTION

General Information.

Solvents were used without further drying. ^{1}H and ^{13}C NMR spectra were recorded on either a Bruker Avance II-400 spectrometer (400 MHz for ^{1}H, 100 MHz for ^{13}C) or a Bruker Avance III-500 spectrometer (500 MHz for ^{1}H, 125 MHz for ^{13}C); $CDCl_3$ and TMS were used as a solvent and an internal standard, respectively. Chemical shifts are reported in ppm downfield (δ) from TMS, the coupling constants J are given in Hz. The peak patterns are indicated as follows: s, singlet; d, doublet; t, triplet; dd, doublet of doublets; m, multiplet; q, quartet. TLC was carried out on SiO_2 (silica gel 60 F254, Merck) and the spots were located with UV light. Flash chromatography was carried out on SiO_2 (silica gel 60, 200-300 mesh). IR spectra were recorded on a NEXUS FT-IR spectrometer. High resolution mass spectra were recorded on either a Q-TOF mass spectrometry or a GC-TOF mass spectrometry. The starting materials were purchased from Energy Chemicals Co. Ltd.

Procedure 1: Synthesis of 2-Chloro-N-(quinolin-8-yl)acetamide (1a).[12a] A reaction flask was charged with a mixture of 8-aminoquinoline (1.5 g, 10.35 mmol) and dichloromethane (60 mL) at 0 ºC. Then 4 mL of dry Et_3N and 1.5 mL of chloroacetyl chloride were dropped to the solution over a few minutes. The reaction mixture was stirred at 0 ºC for 3 h. The resultant mixture was evaporated under a reduced pressure to remove the solvent. The product 1a was purified via silica gel chromatography (eluent:

petroleum ether/ethyl acetate = 5:1). Yield: 81%, Yellow solid (1.85 g, 81% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.85 (bs, 1H), 8.82 (d, J = 4.9 Hz, 1H), 8.72 (dd, J = 4.0, 4.8 Hz 1H) 8.12 (d, J = 9.0 Hz, 1H), 7.53−7.48 (m, 2H), 7.43 (dd, J = 8.2, 4.2 Hz, 1H), 4.30 (s, 2H).

Procedure 2: Synthesis of 2-Chloro-*N*-methyl-*N*-(quinolin-8-yl)acetamide (1c).[12a,b] A reaction flask was charged with a mixture of 8-aminoquinoline (0.65 g, 4.5 mmol), CH_3I (0.85 g, 6 mmol), K_2CO_3 (0.63 g, 4.5 mmol), and DMF (15 mL). After the reaction mixture was stirred at room temperature for 24 h, 10 mL of H_2O was added. The reaction mixture was extracted with EtOAc (3×10 mL) and the combined organic phases were dried over Na_2SO_4. The organic phases were evaporated under a reduced pressure to remove the solvent. The product *N*-methylquinolin-8-amine was purified via silica gel chromatography (eluent: petroleum ether/ethyl acetate = 5:1). Yield: 60% (0.43 g).

A reaction flask was charged with a mixture of *N*-methylquinolin-8-amine (0.32 g, 2 mmol) and dichloromethane (12 mL) at 0 ºC. Then 1 mL of dry Et_3N and 0.3 mL of chloroacetyl chloride were dropped to the solution over a few minutes. The reaction mixture was stirred at 0 ºC for 3 h. The resultant mixture was evaporated under a reduced pressure to remove the solvent. The product **1c** was purified via silica gel chromatography (eluent: petroleum ether/ethyl acetate = 5:1). Yield: 76% (0.356 g). Brown solid, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.97 (d, J = 3.9 Hz, 1H), 8.24 (d, J = 8.1 Hz, 1H), 7.89 (d, J = 8.2 Hz, 1H), 7.72−7.70 (m, 1H), 7.63−7.59 (m, 1H), 7.50 (dd, J = 4.1, 8.2 Hz, 1H), 3.75 (s, 2H), 3.44 (s, 3H). ^{13}C{^{1}H}NMR (DMSO, 100 MHz) δ 160.9, 147.3,

147.0, 132.5, 131.1, 129.7, 127.4, 123.4, 123.2, 118.2, 56.0, 29.1. IR (neat): 2951, 2915, 2848, 1463, 1376, 1151, 939, 718, (cm^{-1}); HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{12}H_{12}ClN_2O$ 235.0638; found 235.0640.

Procedure 3: Synthesis of 2,2-Dimethyl-4-phenyl-*N*-(quinolin-8-yl)but-3-ynamide (5).[12a,c] A reaction flask was charged with a mixture of 8-aminoquinoline (0.65 g, 4.5 mmol) and dichloromethane (30 mL) at 0 ºC. Then 2 mL of dry Et_3N and 0.85 mL of 2-bromo-2-methylpropionyl bromide were dropped to the solution over a few minutes. The reaction mixture was stirred at 0 ºC for 3 h. The resultant mixture was evaporated under a reduced pressure to remove the solvent. The product 2-bromo-2-methyl-*N*-(quinolin-8-yl)propanamide was purified via silica gel chromatography (eluent: petroleum ether/ethyl acetate = 5:1). Yield: 84% (1.11 g). White solid, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 11.06 (bs, 1H), 8.89 (dd, J = 1.5, 4.2 Hz, 1H), 8.76 (dd, J = 3.0, 6.0 Hz, 1H), 8.19 (dd, J = 1.5, 8.3 Hz, 1H), 7.60−7.55 (m, 2H), 7.50 (dd, J = 4.2, 8.3 Hz, 1H), 2.17 (s, 6H); ^{13}C{^{1}H}NMR ($CDCl_3$, 100 MHz) δ 170.3, 148.6, 138.9, 136.3, 134.3, 128.0, 127.2, 122.1, 121.7, 116.3, 61.7, 32.4.

A reaction flask was charged with a mixture of 2-bromo-2-methyl-*N*-(quinolin-8-yl)propanamide (2 mmol, 0.59 g), phenylacetylene (2a, 3 mmol), CuBr (0.2 mmol, 10 mol%), 1,10-phenanthroline (0.4 mmol, 20 mol%), Cs_2CO_3 (4 mmol, 2 equiv.), and toluene (4.0 mL) under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 24 h. The resultant mixture was evaporated under a reduced pressure to remove the solvent. The product

2,2-dimethyl-4-phenyl-*N*-(quinolin-8-yl)but-3-ynamide (**5**) was purified via silica gel chromatography (eluent: petroleum ether/ethyl acetate = 10:1). Yield: 79% (0.497 g). Colorless oil, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 11.48 (bs, 1H), 8.85 (dd, J = 1.1, 7.3 Hz, 1H), 8.72 (dd, J = 1.4, 4.2 Hz, 1H), 8.14 (dd, J =1.3, 8.3 Hz, 1H), 7.76−7.73 (m, 2H), 7.58−7.50 (m, 2H), 7.45−7.40 (m, 4H), 1.74 (s, 6H). ^{13}C{^{1}H}NMR ($CDCl_3$, 100 MHz) δ 172.4, 148.2, 139.1, 136.3, 134.6, 131.8, 128.3, 128.3, 128.0, 127.4, 123.0, 121.8, 121.6, 116.3, 91.9, 85.8, 40.8, 27.7.

Procedure 4: Copper-Catalyzed One-Pot Synthesis of 1,3-Enynes Using One Kind of Terminal Alkyne. A reaction flask was charged with a mixture of 2-chloro-*N*-(quinolin-8-yl)acetamide (**1a**, 0.4 mmol), terminal alkyne (**2**, 1.2 mmol, 3.0 equiv.), CuI (0.04 mmol, 10 mol%), 1,10-phenanthroline (**L1**, 0.08 mmol, 20 mol%), Cs_2CO_3 (0.48 mmol, 1.2 equiv.), and DCM (1.0 mL) under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 48 h. The resultant mixture was evaporated under a reduced pressure to remove the solvent. The product **3** was purified via silica gel chromatography (eluent: petroleum ether/ethyl acetate = 10:1).

(E)-3-Benzylidene-N,5-diphenylpent-4-ynamide (**3ab**) Colorless oil (12.1 mg, 9% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.83 (bs, 1H), 7.53−7.48 (m, 4H), 7.41−7.35 (m, 4H), 7.34−7.30 (m, 6H), 7.25 (s, 1H), 7.11 (dd, J = 7.4, 7.4 Hz, 1H), 3.58 (s, 2H). ^{13}C{^{1}H}NMR ($CDCl_3$, 100 MHz) δ 167.6, 140.3, 137.7, 135.3, 131.6, 129.0, 128.9, 128.8, 128.5, 128.4, 124.5, 122.5, 120.0, 116.6, 91.1, 90.9, 41.5.

(E)-3-Benzylidene-5-phenyl-N-(quinolin-8-yl)pent-4-ynamide (**3a**). Colorless oil (133.7 mg, 86% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.46 (bs, 1H), 8.85 (d, J = 7.5 Hz, 1H), 8.45 (d, J = 4.2 Hz, 1H), 8.06 (d, J = 8.2 Hz, 1H), 7.53−7.45 (m, 6H), 7.39 (dd, J = 7.6, 7.6 Hz, 2H), 7.33−7.23 (m, 6H), 3.71 (s, 2H); ^{13}C{^{1}H}NMR ($CDCl_3$, 100 MHz) δ 164.5,

144.4,136.0, 134.9, 132.4, 131.9, 131.0, 128.1, 125.3, 124.9, 124.6, 124.5, 124.4, 124.2, 123.6, 119.4, 118.0, 117.8, 113.4, 113.0, 87.7, 87.1, 38.4. IR (neat): 3340, 3053, 2922, 1683, 1525, 1486, 1424, 1326, 825, 790, 754, 690, (cm^{-1}); HRMS (EI) *m/z*: $[M]^+$calcd for $C_{27}H_{20}N_2O$ 388.1587; found 388.1569.

(E)-3-(4-Fluorobenzylidene)-5-(4-fluorophenyl)-N-(quinolin-8-yl)pent-4-ynamide (**3b**). White solid (137.8 mg, 81% yield), mp 197–200 °C. ^1H NMR ($CDCl_3$, 400 MHz) δ 10.41 (bs, 1H), 8.84 (d, J = 6.9 Hz, 1H), 8.50 (s, 1H), 8.14 (d, J = 8.2 Hz, 1H), 7.57−7.45 (m, 6H), 7.40−7.38 (m, 1H), 7.21 (s, 1H), 7.09 (dd, J = 8.4, 8.4 Hz, 2H), 6.99 (dd, J = 8.4, 8.4 Hz, 2H), 3.67 (s, 2H); $^{13}C\{^1H\}$NMR ($CDCl_3$, 100 MHz) δ 168.1, 162.5 (d, $^1J_{C\text{-}F}$ = 248.7 Hz), 162.5 (d, $^1J_{C\text{-}F}$ = 247.4 Hz), 148.2, 138.6, 138.5, 136.3, 134.5, 133.7 (d, $^3J_{C\text{-}F}$ = 8.2 Hz), 131.7 (d, $^4J_{C\text{-}F}$ = 3.3 Hz), 130.8 (d, $^3J_{C\text{-}F}$ = 8.0 Hz), 127.9, 127.4, 121.8, 121.6, 119.1 (d, $^4J_{C\text{-}F}$ = 3.7 Hz), 116.9, 116.7, 115.7 (d, $^2J_{C\text{-}F}$ = 21.4 Hz), 115.6 (d, $^2J_{C\text{-}F}$ = 21.9 Hz), 90.8, 89.7, 42.0. IR (neat): 3338, 2921, 1675, 1539, 1506, 1486, 1330, 1230, 1159, 831, 786, 759 (cm^{-1}); HRMS (EI) *m/z*: $[M]^+$ calcd for $C_{27}H_{18}N_2OF_2$ 424.1387; found 424.1376.

(E)-3-(4-Bromobenzylidene)-5-(4-bromophenyl)-N-(quinolin-8-yl)pent-4-ynamide (**3c**). White solid (167.8 mg, 77% yield), mp 213–215 °C. ^1H NMR ($CDCl_3$, 400 MHz) δ 10.37 (bs, 1H), 8.83 (dd, J = 1.58, 7.2 Hz, 1H), 8.52 (dd, J = 1.6, 4.2 Hz, 1H), 8.13 (dd, J = 1.6, 8.3 Hz, 1H), 7.56−7.50 (m, 4H), 7.42−7.38 (m, 5H), 7.33 (d, J = 8.5 Hz, 2H), 7.17 (s, 1H), 3.66 (s, 2H); $^{13}C\{^1H\}$NMR ($CDCl_3$, 100 MHz) δ 167.8, 148.2, 138.8, 138.5, 136.3, 134.5, 134.3, 133.2, 131.8, 131.5, 130.6, 127.9, 127.4, 122.7, 122.5, 121.9, 121.9, 121.6, 117.7, 116.7, 92.2, 90.1, 42.0. IR (neat): 3340, 2922, 1677, 1537, 1485, 1427, 1331, 1011, 817, 789, 758, 693 (cm^{-1}); HRMS (EI) *m/z*: $[M]^+$ calcd for $C_{27}H_{18}N_2OBr_2$ 543.9786; found 543.9793.

(E)-N-(Quinolin-8-yl)-3-(4-(trifluoromethyl)benzylidene)-5-(4-(trifluoromethyl)phenyl)pent-4-ynamide (**3d**). White solid (164.4 mg, 78% yield), mp 187–190 °C. ^1H NMR (500 MHz, Chloroform-d) δ 10.34 (bs, 1H), 8.84 (dd, J = 1.5, 7.3 Hz, 1H), 8.53 (dd, J = 1.6, 4.2 Hz, 1H), 8.14 (dd, J =1.6, 8.3 Hz, 1H), 7.69–7.65 (m, 4H), 7.58–7.50 (m, 6H),7.39 (dd, J = 4.2, 8.3 Hz, 1H), 7.31 (s, 1H), 3.69 (s, 2H); $^{13}C\{^1H\}$NMR (125 MHz, CDCl3) δ 167.5, 148.1, 139.0, 138.8, 138.5, 136.3, 134.4, 132.0, 130.2 (q, $^2J_{C\text{-}F}$ = 32.5 Hz), 130.1 (q, $^2J_{C\text{-}F}$ = 32.4 Hz), 129.3, 128.0, 127.4, 126.6, 125.6 (q, $^3J_{C\text{-}F}$ = 3.7 Hz), 125.2 (q, $^3J_{C\text{-}F}$ = 3.7 Hz), 123.9 (q, $^1J_{C\text{-}F}$ = 270.6 Hz), 124.0 (q, $^1J_{C\text{-}F}$ = 270.5 Hz), 122.0, 121.7, 119.0, 116.8, 92.9, 90.0, 41.9. IR (neat): 3339, 2923, 1684, 1617, 1525, 1487, 1325, 1168, 1112, 1067, 841, 829, 793 (cm^{-1}); HRMS (EI) *m/z*: $[M]^+$ calcd for $C_{29}H_{18}N_2OF_6$ 524.1323;

found 524.1329.

(E)-3-(4-Methylbenzylidene)-N-(quinolin-8-yl)-5-(p-tolyl)pent-4-ynamide (**3e**). White solid (138.0 mg, 83% yield), mp 140−142 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.48 (bs, 1H), 8.85 (d, J = 7.4 Hz, 1H), 8.49 (d, J = 4.1 Hz, 1H), 8.10 (d, J = 8.3 Hz, 1H), 7.55−7.47 (m, 2H), 7.42−7.38 (m, 4H), 7.35 (dd, J = 4.2, 8.3 Hz, 1H), 7.25 (s, 1H), 7.21−7.19 (m, 2H), 7.10−7.08 (m, 2H), 3.71 (s, 2H), 2.35 (s, 3H), 2.34 (s, 3H); ^{13}C{^{1}H}NMR ($CDCl_3$, 100 MHz) δ 168.5, 148.2, 139.5, 138.7, 138.4, 138.1, 136.1, 134.7, 132.9, 131.7, 129.3, 129.0, 129.0, 127.9, 127.3, 121.7, 121.5, 120.1, 116.7, 116.4, 91.0, 90.8, 42.2, 21.6, 21.3. IR (neat): 3340, 2921, 1683, 1526, 1486, 1424, 1327, 1164, 816, 791, 757, 583 (cm^{-1}); HRMS (EI) *m/z*: $[M]^+$ calcd for $C_{29}H_{24}N_2O$ 416.1889; found 416.1878.

(E)-3-(4-(tert-Butyl)benzylidene)-5-(4-(tert-butyl)phenyl)-N-(quinolin-8-yl)pent-4-ynamid e (**3f**). White solid (170.6 mg, 85% yield), mp 172−174 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.51 (bs, 1H), 8.86 (dd, J = 1.2, 7.4 Hz, 1H), 8.42 (dd, J = 1.6, 4.2 Hz, 1H), 8.08 (dd, J = 1.6, 8.3 Hz, 1H), 7.54−7.41 (m, 8H), 7.33−7.29 (m, 3H), 7.25 (s, 1H), 3.73 (s, 2H), 1.31 (s, 9H), 1.30 (s, 9H); ^{13}C{^{1}H}NMR ($CDCl_3$, 100 MHz) δ 168.5, 151.6, 151.2, 148.2, 139.4, 138.7, 136.1, 134.8, 132.9, 131.5, 128.8, 127.9, 127.3, 125.6, 125.2, 121.6, 121.4, 120.2, 116.7, 116.5, 91.0, 90.8, 42.4, 34.8, 34.7, 31.3, 31.2. IR (neat): 3327, 2962, 1686, 1526, 1486, 1424, 1327, 1267, 826, 791, 756, 563 (cm^{-1}); HRMS (EI) *m/z*: $[M]^+$ calcd for $C_{35}H_{36}N_2O$ 500.2828; found 500.2817.

(E)-3-(2-Chlorobenzylidene)-5-(2-chlorophenyl)-N-(quinolin-8-yl)pent-4-ynamide (**3g**). White solid (154.2 mg, 84% yield), mp 91−92 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.38 (bs, 1H), 8.83 (d, J = 7.1 Hz, 1H), 8.49 (d, J = 3.2 Hz, 1H), 8.10 (d, J = 8.1 Hz, 1H), 7.76 (d, J = 7.4 Hz, 1H), 7.55−7.48 (m, 3H), 7.44−7.41 (m, 2H), 7.37−7.25 (m, 4H), 7.31−7.14 (m, 2H), 3.65 (s, 2H); ^{13}C{^{1}H}NMR ($CDCl_3$, 100 MHz) δ 167.9, 148.1, 138.6, 137.2, 136.2, 136.1, 134.6, 133.9, 133.8, 133.4, 130.8, 129.6, 129.6, 129.4, 129.2, 127.9, 127.3, 126.9, 126.3, 122.9, 121.8, 121.6, 1188, 116.7, 95.4, 88.2, 42.0. IR (neat): 3339, 2923, 1683, 1525, 1486, 1425, 1328, 1053, 826, 791, 753, 693 (cm^{-1}); HRMS (EI) *m/z*: $[M]^+$ calcd for $C_{27}H_{18}N_2OCl_2$ 456.0796; found 456.0807.

(E)-3-(3-Chlorobenzylidene)-5-(3-chlorophenyl)-N-(quinolin-8-yl)pent-4-ynamide (**3h**). White solid (161.6 mg, 88% yield), mp 148−150 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.34 (bs, 1H), 8.84 (d, J = 6.8 Hz, 1H), 8.60 (s, 1H), 8.14 (d, J = 8.0 Hz, 1H), 7.57−7.48 (m, 5H), 7.42−7.40 (m, 1H), 7.36−7.26 (m, 4H), 7.22−7.19 (m, 2H), 3.68 (s, 2H);

$^{13}C\{^{1}H\}$NMR ($CDCl_3$, 100 MHz) δ 167.6, 148.3, 138.7, 138.5, 137.2, 136.3, 134.5, 134.5, 134.1, 131.6, 129.9, 129.9, 129.5, 129.0, 128.7, 128.3, 128.0, 127.3, 127.1, 124.6, 121.9, 121.7, 118.3, 116.8, 91.9, 89.8, 42.0. IR (neat): 3343, 2921, 1682, 1558, 1538, 1486, 1327, 886, 823, 788, 679, 586 (cm^{-1}); HRMS (EI) *m/z*: $[M]^+$ calcd for $C_{27}H_{18}N_2OCl_2$ 456.0796; found 456.0802.

(E)-3-(4-Chlorobenzylidene)-5-(4-chlorophenyl)-N-(quinolin-8-yl)pent-4-ynamide (**3i**). White solid (126.2 mg, 69% yield), mp 217–220 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.38 (bs, 1H), 8.84 (d, *J* = 7.0 Hz, 1H), 8.52 (d, *J* = 3.2 Hz, 1H), 8.14 (d, *J* = 8.2 Hz, 1H), 7.57−7.48 (m, 4H), 7.42−7.36 (m, 5H), 7.26 (d, *J* = 8.3 Hz, 2H), 7.20(s, 1H), 3.67 (s, 2H); $^{13}C\{^{1}H\}$NMR ($CDCl_3$, 100 MHz) δ 167.8, 148.2, 138.7, 138.5, 136.3, 134.5, 134.5, 134.2, 133.9, 133.0, 130.3, 128.9, 128.6, 127.9, 127.4, 121.8, 121.6, 121.5, 117.6, 116.7, 92.0, 89.9, 42.0. IR (neat): 3337, 2923, 1675, 1536, 1486, 1425, 1329, 1094, 822, 787, 757, 687 (cm^{-1}); HRMS (EI) *m/z*: $[M]^+$ calcd for $C_{27}H_{18}N_2OCl_2$ 456.0796; found 456.0798.

(E)-3-(2-Methoxybenzylidene)-5-(2-methoxyphenyl)-N-(quinolin-8-yl)pent-4-ynamide (**3j**). Colorless oil (169.0 mg, 94% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.49 (bs, 1H), 8.86 (d, *J* = 7.5 Hz, 1H), 8.40 (s, 1H), 8.09 (d, *J* = 8.1 Hz, 1H), 7.55 (d, *J* = 7.4 Hz, 1H), 7.55−7.43i (m, 3H), 7.39 (s, 1H), 7.33−7.23 (m, 3H), 6.99 (dd, *J* = 7.4, 7.4 Hz, 1H), 6.90−6.79 (m, 3H), 3.82 (s, 3H), 3.67 (m, 5H); $^{13}C\{^{1}H\}$NMR ($CDCl_3$, 100 MHz) δ 168.8, 160.1, 157.1, 148.1, 136.0, 135.3, 134.9, 133.7, 130.3, 129.7, 129.6, 127.9, 127.3, 124.7, 121.5, 121.4, 120.5, 120.3, 117.3, 116.6, 110.6, 110.5, 95.4, 87.1, 55.6, 55.4, 42.5. IR (neat): 3343, 2932, 1682, 1526, 1486, 1463, 1425, 1247, 1025, 827, 792, 754 (cm^{-1}); HRMS (EI) *m/z*: $[M]^+$ calcd for $C_{29}H_{24}N_2O_3$ 448.1787; found 448.1777.

(E)-3-(3-Methoxybenzylidene)-5-(3-methoxyphenyl)-N-(quinolin-8-yl)pent-4-ynamide (**3k**). White solid (170.2 mg, 95% yield), mp 130−133 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.45 (bs, 1H), 8.85 (dd, *J* = 1.5, 7.4 Hz, 1H), 8.50 (dd, *J* = 1.6, 4.2 Hz, 1H), 8.11 (dd, *J* = 1.6, 8.3 Hz, 1H), 7.56−7.48 (m, 2H), 7.37 (dd, *J* = 4.2, 8.2 Hz, 1H), 7.31 (dd, *J* = 7.9, 7.9 Hz, 1H), 7.26 (d, *J* = 1.6 Hz, 1H), 7.20 (dd, *J* = 7.9, 7.9 Hz, 1H), 7.13−7.09 (m, 3H), 7.02−7.01 (m, 1H), 6.87 (dd, *J* = 2.5, 8.2 Hz, 1H), 3.84 (s, 3H), 3.73 (s, 2H), 3.72 (s, 3H); $^{13}C\{^{1}H\}$NMR ($CDCl_3$, 100 MHz) δ 168.2, 159.7, 159.3, 148.3, 139.8, 136.9, 136.1, 134.7, 129.6, 129.3, 127.9, 127.3, 124.4, 121.7, 121.5, 121.5, 117.3, 116.7, 116.5, 115.1, 114.4, 114.0, 91.1, 90.8, 55.4, 55.2, 42.3. IR (neat): 3341, 2924, 1684, 1525, 1486, 1425, 1326, 1044, 826, 789, 757, 686 (cm^{-1}); HRMS (EI) *m/z*: $[M]^+$ calcd for $C_{29}H_{24}N_2O_3$ 448.1787; found 448.1777.

(E)-3-(4-Methoxybenzylidene)-5-(4-methoxyphenyl)-N-(quinolin-8-yl)pent-4-ynamide (**3l**). White solid (148.8 mg, 83% yield), mp 112−114 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.52 (bs, 1H), 8.85 (dd, J = 1.4, 7.4 Hz, 1H), 8.47 (dd, J = 1.6, 4.2 Hz, 1H), 8.09 (dd, J = 1.6, 8.3 Hz, 1H), 7.55−7.43 (m, 6H), 7.34 (dd, J = 4.2, 8.2 Hz, 1H), 7.18 (s, 1H), 6.94−6.91 (m, 2H), 6.83−6.81 (m, 2H), 3.80 (s, 3H), 3.79(s, 3H), 3.71 (s, 2H); ^{13}C{^{1}H}NMR ($CDCl_3$, 100 MHz) δ 168.6, 159.6, 159.4, 148.2, 138.7, 138.7, 136.1, 134.8, 133.2, 130.5, 128.5, 127.9, 127.3, 121.6, 121.5, 116.7, 115.4, 115.3, 114.0, 113.9, 90.6, 90.4, 55.3, 55.3, 42.3. IR (neat): 3323, 2927, 1682, 1604, 1525, 1424, 1327, 1251, 1031, 827, 792, 669 (cm^{-1}); HRMS (EI) *m/z*: $[M]^+$ calcd for $C_{29}H_{24}N_2O_3$ 448.1787; found 448.1779.

(E)-N-(Quinolin-8-yl)-5-(thiophen-2-yl)-3-(thiophen-2-ylmethylene)pent-4-ynamide (**3m**). Yellow oil (148.8 mg, 93% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.42 (bs, 1H), 8.81 (d, J = 7.4 Hz, 1H), 8.55 (d, J = 4.0 Hz, 1H), 8.07 (d, J = 8.1 Hz, 1H), 7.52−7.45 (m, 2H), 7.36−7.30 (m, 4H), 7.25 (d, J = 5.1 Hz, 1H), 7.22 (d, J = 3.6 Hz, 1H), 7.05 (dd, J = 4.2, 4.4 Hz, 1H), 6.96 (dd, J = 4.2, 4.5 Hz, 1H), 3.87 (s, 2H); ^{13}C{^{1}H}NMR ($CDCl_3$, 100 MHz) δ 167.3, 148.3, 138.7, 138.6, 136.1, 134.5, 132.2, 132.0, 129.7, 127.9, 127.7, 127.6, 127.5, 127.3, 127.1, 123.2, 121.7, 121.5, 116.6, 114.0, 95.5, 84.6, 42.5. IR (neat): 3322, 3103, 2923, 1683, 1525, 1485, 1423, 1327, 1161, 826, 791, 700 (cm^{-1}); HRMS (EI) *m/z*: $[M]^+$ calcd for $C_{23}H_{16}N_2OS_2$ 400.0704; found 400.0696.

(E)-5-(Naphthalen-2-yl)-3-(naphthalen-2-ylmethylene)-N-(quinolin-8-yl)pent-4-ynamide (**3n**). White solid (178.4 mg, 91% yield), mp 138−140 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.53 (bs, 1H), 8.91 (d, J = 7.6 Hz, 1H), 8.45 (d, J = 4.2 Hz, 1H), 8.08−8.05 (m, 2H), 8.01 (s, 1H), 7.90−7.63 (m, 7H), 7.57−7.57 (m, 2H), 7.48−7.45 (m, 6H), 7.28 (dd, J = 4.2, 8.2 Hz, 1H), 3.84 (s, 2H); ^{13}C{^{1}H}NMR ($CDCl_3$, 100 MHz) δ 168.3, 148.2, 139.9, 138.7, 136.2, 134.7, 133.3, 133.2, 133.0, 132.9, 132.8, 131.7, 128.6, 128.5, 128.5, 128.2, 127.9, 127.9, 127.8, 127.8, 127.6, 127.4, 126.8, 126.7, 126.6, 126.5, 126.4, 121.7, 121.5, 120.5, 117.5, 116.8, 91.9, 91.5, 42.4. IR (neat): 3347, 3053, 2922, 1683, 1526, 1485, 1424, 1326, 1264, 823, 791, 745, 475 (cm^{-1}); HRMS (EI) *m/z*: $[M]^+$ calcd for $C_{35}H_{24}N_2O$ 488.1889; found 488.1884.

Procedure 5: Copper-Catalyzed One-Pot Synthesis of 1,3-Enynes Using Two Kinds of Terminal Alkynes. A reaction flask was charged with a mixture of 2-chloro-*N*-(quinolin-8-yl)acetamide (**1a**) (0.4 mmol), a first-step alkyne (**2a**, **2i**, **2l**, and **2n**) (0.4 mmol, 1.0 equiv.), CuI (0.04 mmol, 10 mol%), Cs_2CO_3 (0.48 mmol, 1.2 equiv.), and DCM (1.0 mL) under nitrogen atmosphere. After the reaction mixture was stirred at

35 ºC for 16 or 24 h, the flask was cooled to room temperature. 1,10-Phenanthroline (**L1**, 0.08 mmol, 20 mol%) and a second-step alkyne (**2**, 0.8 mmol, 2.0 equiv.) were added into the mixture under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 24 h. The resultant mixture was evaporated under a reduced pressure to remove the solvent. The product **4** was purified via silica gel chromatography (eluent: petroleum ether/ethyl acetate = 10:1).

(E)-3-Benzylidene-5-(4-fluorophenyl)-N-(quinolin-8-yl)pent-4-ynamide (**4a**). White solid (101.6 mg, 62% yield), mp 129−131 ºC. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.41 (bs, 1H), 8.85 (d, J = 7.4 Hz, 1H), 8.50 (d, J = 3.9 Hz, 1H), 8.11 (d, J = 8.2 Hz, 1H), 7.55−7.44 (m, 6H), 7.42−7.35 (m, 3H), 7.32−7.27 (m, 2H), 6.97 (dd, J = 8.6, 8.6 Hz, 2H), 3.71 (s, 2H); ^{13}C{^{1}H}NMR ($CDCl_3$, 100 MHz) δ 168.2, 162.5 (d, $^1J_{C\text{-}F}$ = 249.7 Hz), 148.1, 139.8, 138.6, 136.2, 135.6, 134.6, 133.7 (d, $^3J_{C\text{-}F}$ = 8.4 Hz), 129.0, 128.6, 128.2, 127.9, 127.4, 121.7, 121.6, 119.2 (d, $^4J_{C\text{-}F}$ = 3.5 Hz), 117.0, 116.7, 115.5 (d, $^2J_{C\text{-}F}$ = 22.0 Hz), 91.0, 89.6, 42.1. IR (neat): 3348, 2922, 1684, 1597, 1526, 1506, 1326, 1230, 1156, 835, 791, 754 (cm^{-1}); HRMS (EI) *m/z*: $[M]^+$ calcd for $C_{27}H_{19}N_2OF$ 406.1481; found 406.1479.

(E)-3-Benzylidene-5-(4-bromophenyl)-N-(quinolin-8-yl)pent-4-ynamide (**4b**). White solid (128.6 mg, 69% yield), mp 119−121 ºC. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.39 (bs, 1H), 8.85 (d, J = 7.4 Hz, 1H), 8.52 (d, J = 4.0 Hz, 1H), 8.11 (d, J = 8.2 Hz, 1H), 7.55−7.48 (m, 4H), 7.41−7.28 (m, 9H), 3.71 (s, 2H); ^{13}C{^{1}H}NMR ($CDCl_3$, 100 MHz) δ 168.1, 148.2, 140.2, 138.6, 136.2, 135.5, 134.6, 133.2, 131.5, 129.0, 128.7, 128.2, 127.9, 127.4, 122.6, 122.1, 121.8, 121.6, 116.9, 116.7, 92.4, 89.6, 42.0. IR (neat): 3446, 1681, 1526, 1485, 1424, 1385, 1326, 823, 790, 755, 697, (cm^{-1}); HRMS (EI) *m/z*: $[M]^+$ calcd for $C_{27}H_{19}N_2OBr$ 466.0681, 468.0660; found 466.0675, 468.0634.

(E)-3-Benzylidene-N-(quinolin-8-yl)-5-(4-(trifluoromethyl)phenyl)pent-4-ynamide (**4c**). White solid (133.8 mg, 73% yield), mp 122−125 ºC. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.37 (bs, 1H), 8.86 (dd, J = 1.0, 7.3 Hz, 1H), 8.52 (dd, J = 1.4, 4.1 Hz, 1H), 8.12 (dd, J = 1.3, 8.3 Hz, 1H), 7.58−7.49 (m, 8H), 7.43−7.36 (m, 3H), 7.4−7.28 (m, 2H), 3.73 (s, 2H); ^{13}C{^{1}H}NMR ($CDCl_3$, 125 MHz) δ 168.0, 148.1, 140.9, 138.6, 136.3, 135.4, 134.5, 131.9, 129.9 (q, $^2J_{C\text{-}F}$ = 32.6 Hz), 129.0, 128.7, 128.4, 128.0, 127.4, 126.9, 125.1 (q, $^3J_{C\text{-}F}$ = 3.7 Hz), 123.9 (q, $^1J_{C\text{-}F}$ = 270.6 Hz), 121.8, 121.6, 116.7, 93.6, 89.1, 41.9. IR (neat): 3346, 2924, 1685, 1615, 1526, 1486, 1324, 1166, 1125, 1065, 842, 826, 791 (cm^{-1}); HRMS (EI) *m/z*: $[M]^+$ calcd for $C_{28}H_{19}N_2OF_3$ 456.1449; found 456.1448.

(E)-3-Benzylidene-5-(4-nitrophenyl)-N-(quinolin-8-yl)pent-4-ynamide (**4d**). Yellow solid

(92.3 mg, 53% yield), mp 201−203 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.33 (bs, 1H), 8.85 (d, J = 7.1 Hz, 1H), 8.59 (s, 1H), 8.17−8.13 (m, 3H), 7.61−7.54 (m, 6H), 7.43−7.41 (m, 3H), 7.36−7.33 (m, 2H), 3.74 (s, 2H); ^{13}C{^{1}H}NMR ($CDCl_3$, 100 MHz) δ 167.8, 148.1, 146.9, 141.8, 138.5, 136.4, 135.2, 134.4, 132.4, 130.0, 129.1, 128.7, 128.6, 128.0, 127.4, 123.5, 121.9, 121.7, 116.7, 116.5, 96.5, 88.6, 41.7. IR (neat): 3441, 2924, 1683, 1588, 1520, 1486, 1341, 1097, 852, 823, 790, 748 (cm^{-1}); HRMS (EI) *m/z*: $[M]^+$ calcd for $C_{27}H_{19}N_3O_3$ 433.1426; found 433.1423.

Methyl-(E)-4-(3-benzylidene-5-oxo-5-(quinolin-8-ylamino)pent-1-yn-1-yl)benzoate (**4e**). White solid (125.0 mg, 70% yield), mp 127−129 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10. 41 (bs, 1H), 8.85 (dd, J = 1.3, 7.4 Hz, 1H), 8.51 (dd, J =1.6, 4.2 Hz, 1H), 8.11 (dd, J =1.5, 8.3 Hz, 1H), 7.95 (d, J = 8.4 Hz, 2H), 7.55−7.48 (m, 6H), 7.43−7.30 (m, 5H), 3.90 (s, 3H), 3.73 (s, 2H); ^{13}C{^{1}H}NMR ($CDCl_3$, 100 MHz) δ 168.0, 166.5, 148.2, 140.8, 138.6, 136.2, 135.4, 134.6, 131.7, 129.5, 129.4, 129.1, 128.7, 128.4, 127.9, 127.8, 127.3, 121.8, 121.6, 116.8, 116.7, 94.3, 89.9, 52.2, 41.9. IR (neat): 3430, 2924, 1720, 1683, 1600, 1526, 1486, 1435, 1276, 1108, 826, 791, 769 (cm^{-1}); HRMS (EI) *m/z*: $[M]^+$ calcd for $C_{29}H_{22}N_2O_3$ 446.1630; found 446.1621.

(E)-3-Benzylidene-N-(quinolin-8-yl)-5-(p-tolyl)pent-4-ynamide (**4f**). White solid (129.0 mg, 80% yield), mp 128−131 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.47 (bs, 1H), 8.85 (d, J = 7.5 Hz, 1H), 8.49 (d, J = 3.7 Hz, 1H), 8.08 (d, J = 8.2 Hz, 1H), 7.53−7.45 (m, 4H), 7.40−7.37(m, 4H), 7.33 (dd, J = 4.3, 8.3 Hz, 1H), 7.31−7.26 (m, 2H), 7.09−7.07(m, 2H), 3.71 (s, 2H), 2.33 (s, 3H); ^{13}C{^{1}H}NMR ($CDCl_3$, 100 MHz) δ 168.3, 148.2, 139.4, 138.7, 138.5, 136.1, 135.7, 134.7, 131.7, 129.0, 128.6, 128.0, 127.9, 127.3, 121.7, 121.5, 120.1, 117.3, 116.7, 91.0, 90.8, 42.2, 21.6. IR (neat): 3434, 2922, 1682, 1525, 1486, 1424, 1385, 1326, 1164, 816, 791, 753, 700 (cm^{-1}); HRMS (EI) *m/z*: $[M]^+$ calcd for $C_{28}H_{22}N_2O$ 402.1732; found 402.1736.

(E)-3-Benzylidene-5-(4-(tert-butyl)phenyl)-N-(quinolin-8-yl)pent-4-ynamide (**4g**). White solid (145.6 mg, 82% yield), mp 132−135 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.48 (bs, 1H), 8.85 (dd, J = 1.5, 7.5 Hz, 1H), 8.43 (dd, J = 1.7, 4.2 Hz, 1H), 8.08 (dd, J = 1.7, 8.3 Hz, 1H), 7.54−7.50 (m, 3H), 7.48−7.37 (m, 5H), 7.34−7.27 (m, 5H), 3.71 (s, 2H), 1.30 (s, 9H); ^{13}C{^{1}H}NMR ($CDCl_3$, 100 MHz) δ 168.4, 151.7, 148.2, 139.4, 138.6, 136.1, 135.7, 134.7, 131.6, 129.0, 128.6, 128.1, 127.9, 127.3, 125.3, 121.7, 121.5, 120.1, 117.3, 116.7, 91.0, 90.8, 42.2, 34.8, 31.2. IR (neat): 3344, 2962, 1683, 1525, 1486, 1424, 1327, 1265, 1165, 826, 791, 757, 698 (cm^{-1}); HRMS (EI) *m/z*: $[M]^+$ calcd for $C_{31}H_{28}N_2O$ 444.2202;

found 444.2208.

(E)-3-Benzylidene-5-(4-pentylphenyl)-N-(quinolin-8-yl)pent-4-ynamide (**4h**). White solid (139.0 mg, 76% yield), mp 106−109 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.54 (bs, 1H), 8.91 (d, J = 7.5 Hz, 1H), 8.52−8.48 (m, 1H), 8.13 (d, J = 8.2 Hz, 1H), 7.59−7.42 (m, 8H), 7.38−7.31 (m, 3H), 7.15 (d, J = 7.8 Hz, 2H), 3.76 (s, 2H), 2.63 (t, J = 7.6 Hz, 2H), 1.64 (tt, J = 7.2,7.2 Hz, 2H), 1.40−1.32 (m, 4H), 0.94 (t, J = 6.8 Hz, 3H); ^{13}C{^{1}H}NMR ($CDCl_3$, 100 MHz) δ 168.3, 148.2, 143.5, 139.4, 138.7, 136.1, 135.7, 134.7, 131.8, 129.0, 128.6, 128.4, 128.0, 127.9, 127.3, 121.7, 121.5, 120.3, 117.3, 116.7, 91.1, 90.8, 42.2, 35.9, 31.4, 30.9, 22.5, 14.1. IR (neat): 3346, 2925, 1684, 1525, 1486, 1424, 1326, 1262, 825, 753, 699 (cm^{-1}); HRMS (EI) *m/z*: $[M]^+$ calcd for $C_{32}H_{30}N_2O$ 458.2358; found 458.2347.

(E)-3-Benzylidene-5-(2-chlorophenyl)-N-(quinolin-8-yl)pent-4-ynamide (**4i**). Colorless oil (150.6 mg, 89% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.44 (bs, 1H), 8.85 (d, J = 7.4 Hz, 1H), 8.45 (s, 1H), 8.08 (d, J = 8.3 Hz, 1H), 7.55−7.46 (m, 5H), 7.42−7.38 (m, 2H), 7.35−7.29 (m, 4H), 7.22−7.14 (m, 2H), 3.75 (s, 2H); ^{13}C{^{1}H}NMR ($CDCl_3$, 100 MHz) δ 168.2, 148.1, 140.4, 138.6, 136.1, 136.1, 135.5, 134.6, 133.4, 129.3, 129.2, 129.1, 128.6, 128.3, 127.9, 127.3, 126.4, 123.1, 121.7, 121.6, 117.0, 116.7, 96.4, 87.5, 42.0. IR (neat): 3444, 2923, 1683, 1525, 1486, 1474, 1425, 1386, 1327, 825, 791, 755 (cm^{-1}); HRMS (EI) *m/z*: $[M]^+$ calcd for $C_{27}H_{19}N_2OCl$ 422.1186; found 422.1187.

(E)-3-Benzylidene-5-(3-chlorophenyl)-N-(quinolin-8-yl)pent-4-ynamide (**4j**). White solid (134.0 mg, 79% yield), mp 98−100 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.40 (bs, 1H), 8.86 (dd, J = 1.6, 7.3 Hz, 1H), 8.57 (dd, J = 1.6, 4.2 Hz, 1H), 8.12 (dd, J = 1.6, 8.3 Hz, 1H), 7.56−7.48 (m, 5H), 7.43−7.25 (m, 7H), 7.22−7.18 (m, 1H), 3.71 (s, 2H); ^{13}C{^{1}H}NMR ($CDCl_3$, 125 MHz) δ 168.1, 148.3, 140.4, 138.6, 136.2, 135.4, 134.6, 134.1, 131.6, 129.8, 129.4, 129.0, 128.6, 128.5, 128.3, 128.0, 127.3, 124.8, 121.8, 121.6, 116.8, 116.7, 92.4, 89.2, 42.0. IR (neat): 3340, 3060, 1683, 1590, 1525, 1486, 1424, 1385, 1327, 1165, 788, 752 (cm^{-1}); HRMS (EI) *m/z*: $[M]^+$ calcd for $C_{27}H_{19}N_2OCl$ 422.1186; found 422.1181.

(E)-3-Benzylidene-5-(4-chlorophenyl)-N-(quinolin-8-yl)pent-4-ynamide (**4k**). White solid (113.0 mg, 67% yield), mp 135−136 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.41 (bs, 1H), 8.86 (d, J = 7.3 Hz, 1H), 8.51 (dd, J = 1.2, 4.1 Hz, 1H), 8.12 (dd, J = 1.1, 8.2 Hz, 1H), 7.56−7.49 (m, 4H), 7.42−7.36 (m, 5H), 7.33−7.24 (m, 4H), 3.71 (s, 2H); ^{13}C{^{1}H}NMR ($CDCl_3$, 100 MHz) δ 168.2, 148.2, 140.2, 138.6, 136.3, 135.5, 134.6, 134.3, 133.0, 129.0, 128.7, 128.6, 128.6, 128.2, 127.9, 127.4, 121.8, 121.6, 116.9, 116.7, 92.2, 89.5, 42.0. IR

(neat): 3338, 2926, 1683, 1525, 1487, 1424, 1385, 1326, 1089, 825, 790, 757 (cm^{-1}); HRMS (EI) *m/z*: $[M]^+$ calcd for $C_{27}H_{19}N_2OCl$ 422.1186; found 422.1175.

(E)-3-Benzylidene-5-(2-methoxyphenyl)-N-(quinolin-8-yl)pent-4-ynamide (**4l**). Colorless oil (146.9 mg, 88% yield). ^1H NMR ($CDCl_3$, 400 MHz) δ 10.49 (bs, 1H), 8.85 (d, J = 7.5 Hz, 1H), 8.40 (s, 1H), 8.08 (d, J = 8.3 Hz, 1H), 7.54−7.52 (m, 3H), 7.47−7.45 (m, 2H), 7.39 (dd, J = 7.6, 7.6 Hz, 2H), 7.32−7.24 (m, 4H), 6.86 (t, J = 7.5 Hz, 1H), 6.81 (d, J = 8.3 Hz, 1H), 3.74 (s, 2H), 3.70 (s, 3H); $^{13}C\{^1H\}$NMR ($CDCl_3$, 100 MHz) δ 168.4, 160.1, 148.1, 139.3, 138.7, 136.0, 135.8, 134.8, 133.7, 129.8, 129.0, 128.6, 128.0, 127.9, 127.3, 121.6, 121.5, 120.3, 117.4, 116.7, 112.4, 110.6, 95.4, 87.4, 55.7, 42.3. IR (neat): 3343, 2925, 1682, 1525, 1487, 1425, 1327, 1248, 1024, 826, 792, 753 (cm^{-1}); HRMS (EI) *m/z*: $[M]^+$ calcd for $C_{28}H_{22}N_2O_2$ 418.1681; found 418.1690.

(E)-3-Benzylidene-5-(3-methoxyphenyl)-N-(quinolin-8-yl)pent-4-ynamide (**4m**). Colorless oil (146.8 mg, 88% yield). ^1H NMR ($CDCl_3$, 400 MHz) δ 10.46 (bs, 1H), 8.86 (d, J = 7.4 Hz, 1H), 8.50 (dd, J = 1.2, 4.1 Hz, 1H), 8.09 (dd, J = 1.1, 8.2 Hz, 1H), 7.54–7.47 (m, 4H), 7.40 (dd, J = 7.6, 7.6 Hz, 2H), 7.36–7.29 (m, 3H), 7.19 (dd, J = 7.9, 7.9 Hz, 1H), 7.10 (d, J = 7.6 Hz, 1H), 7.01 (s, 1H), 6.86 (dd, J = 8.2, 2.4 Hz, 1H), 3.72 (s, 2H), 3.70 (s, 3H); $^{13}C\{^1H\}$NMR ($CDCl_3$, 100 MHz) δ 168.3, 159.2, 148.3, 139.9, 138.6, 136.2, 135.6, 134.7, 129.3, 129.0, 128.6, 128.2, 127.9, 127.3, 124.4, 124.1, 121.7, 121.6, 117.1, 116.7, 116.4, 115.1, 91.1, 90.7, 55.2, 42.1. IR (neat): 3336, 2924, 1685, 1525, 1486, 1424, 1326, 1238, 1044, 826, 790, 754 (cm^{-1}); HRMS (EI) *m/z*: $[M]^+$ calcd for $C_{28}H_{22}N_2O_2$ 418.1681; found 418.1670.

(E)-3-Benzylidene-5-(4-methoxyphenyl)-N-(quinolin-8-yl)pent-4-ynamide (**4n**). White solid (132.0 mg, 79% yield), mp 116−118 °C. ^1H NMR ($CDCl_3$, 400 MHz) δ 10.48 (bs, 1H), 8.86 (d, J = 7.4 Hz, 1H), 8.50 (d, J = 3.8 Hz, 1H), 8.10 (d, J = 8.1 Hz, 1H), 7.55−7.47 (m, 4H), 7.45−7.34 (m, 5H), 7.31−7.27 (m, 1H), 7.24 (s, 1H), 6.82 (d, J = 8.6 Hz, 2H), 3.80 (s, 3H), 3.71 (s, 2H); $^{13}C\{^1H\}$NMR ($CDCl_3$, 100 MHz) δ 168.4, 159.7, 148.2, 139.0, 138.6, 136.1, 135.8, 134.7, 133.3, 129.0, 128.6, 128.0, 127.9, 127.3, 121.7, 121.5, 117.3, 116.7, 115.2, 113.9, 90.9, 90.1, 55.3, 42.2. IR (neat): 3338, 2925, 1682, 1601, 1524, 1442, 1326, 1249, 1030, 827, 791, 700 (cm^{-1}); HRMS (EI) *m/z*: $[M]^+$ calcd for $C_{28}H_{22}N_2O_2$ 418.1681; found 418.1676.

(E)-3-Benzylidene-N-(quinolin-8-yl)non-4-ynamide (**4o**). Colorless oil (99.6 mg, 68% yield). ^1H NMR ($CDCl_3$, 400 MHz) δ 10.33 (bs, 1H), 8.85 (dd, J = 1.4, 7.4 Hz, 1H), 8.79 (dd, J = 1.6, 4.2 Hz, 1H), 8.14 (dd, J = 1.6, 8.3 Hz, 1H), 7.56−7.48 (m, 2H), 7.46−7.41 (m,

3H), 7.36 (dd, J = 7.6, 7.6 Hz, 2H), 7.28–7.25 (m, 1H), 7.11 (s, 1H), 3.60 (s, 2H), 2.38 (t, J = 7.1 Hz, 2H), 1.49 (tt, J = 7.0, 7.1 Hz, 2H), 1.36 (tq, J = 7.1, 7.3 Hz, 2H), 0.78 (t, J = 7.3 Hz, 3H); $^{13}C\{^1H\}$NMR ($CDCl_3$, 100 MHz) δ 168.5, 148.1, 138.7, 138.3, 136.2, 135.9, 134.7, 128.8, 128.5, 128.0, 127.7, 127.4, 121.6, 121.5, 117.9, 116.7, 92.1, 82.3, 42.4, 30.7, 22.0, 19.3, 13.5. IR (neat): 3351, 2956, 2930, 1683, 1525, 1486, 1424, 1385, 1326, 826, 791, 752 (cm^{-1}); HRMS (EI) *m/z*: $[M]^+$ calcd for $C_{25}H_{24}N_2O$ 368.1889; found 368.1881.

(E)-3-Benzylidene-N-(quinolin-8-yl)-5-(thiophen-2-yl)pent-4-ynamide (**4p**). Yellow oil (138.6 mg, 88% yield). ^1H NMR ($CDCl_3$, 400 MHz) δ 10.42 (bs, 1H), 8.84 (dd, J = 1.2, 7.4 Hz, 1H), 8.55 (dd, J = 1.5, 4.2 Hz, 1H), 8.09 (dd, J = 1.5, 8.3 Hz, 1H), 7.54−7.46 (m, 4H), 7.41−7.34 (m, 3H), 7.31−7.22 (m, 4H), 6.95 (dd, J = 3.8, 5.0 Hz, 1H), 3.70 (s, 2H); $^{13}C\{^1H\}$NMR ($CDCl_3$, 100 MHz) δ 168.1, 148.3, 139.9, 138.6, 136.1, 135.6, 134.6, 132.3, 129.0, 128.6, 128.2, 127.9, 127.5, 127.3, 127.1, 123.2, 121.7, 121.6, 116.9, 116.7, 95.0, 83.9, 41.8. IR (neat): 3341, 2924, 1683, 1525, 1486, 1424, 1386, 1327, 1162, 826, 791, 754 (cm^{-1}); HRMS (EI) *m/z*: $[M]^+$ calcd for $C_{25}H_{18}N_2OS$ 394.1140; found 394.1142.

(E)-3-Benzylidene-5-(naphthalen-2-yl)-N-(quinolin-8-yl)pent-4-ynamide (**4q**). White solid (132.6 mg, 76% yield), mp 100−102 °C. ^1H NMR ($CDCl_3$, 400 MHz) δ 10.51 (bs, 1H), 8.88 (dd, J = 1.0, 7.5 Hz, 1H), 8.46 (dd, J = 1.6, 4.2 Hz, 1H), 8.07 (dd, J = 1.5, 8.3 Hz, 1H), 7.98 (s, 1H), 7.79−7.67 (m, 3H), 7.56−7.51 (m, 4H), 7.48−7.39 (m, 5H), 7.32−7.27 (m, 3H), 3.76 (s, 2H); $^{13}C\{^1H\}$NMR ($CDCl_3$, 100 MHz) δ 168.3, 148.2, 139.9, 138.7, 136.2, 135.7, 134.7, 132.9, 132.8, 131.7, 129.1, 128.6, 128.5, 128.2, 127.9, 127.9, 127.8, 127.8, 127.4, 126.7, 126.6, 121.7, 121.5, 120.4, 117.2, 116.7, 91.8, 91.2, 42.2. IR (neat): 3343, 2924, 1683, 1526, 1486, 1424, 1385, 1327, 1264, 1162, 825, 791, 699 (cm^{-1}); HRMS (EI) *m/z*: $[M]^+$ calcd for $C_{31}H_{22}N_2O$ 438.1732; found 438.1727.

(E)-3-(4-Methoxybenzylidene)-5-phenyl-N-(quinolin-8-yl)pent-4-ynamide (**4r**). Colorless oil (129.5 mg, 77% yield). ^1H NMR ($CDCl_3$, 400 MHz) δ 10.50 (bs, 1H), 8.85 (d, J = 7.4 Hz, 1H), 8.43 (d, J = 4.1 Hz, 1H), 8.08 (d, J = 8.2 Hz, 1H), 7.54−7.46 (m, 6H), 7.34−7.28 (m, 4H), 7.21 (s, 1H), 6.93 (d, J = 8.7 Hz, 2H), 3.80 (s, 3H), 3.72 (s, 2H); $^{13}C\{^1H\}$NMR ($CDCl_3$, 100 MHz) δ 168.5, 159.5, 148.2, 139.5, 138.6, 136.1, 134.7, 131.8, 130.6, 128.3, 128.2, 128.2, 127.9, 127.3, 123.3, 121.7, 121.5, 116.7, 115.1, 114.1, 91.9, 90.3, 55.3, 42.3. IR (neat): 3342, 2926, 1682, 1605, 1525, 1487, 1424, 1385, 1327, 1254, 1032, 826, 756 (cm^{-1}); HRMS (EI) *m/z*: $[M]^+$ calcd for $C_{28}H_{22}N_2O_2$ 418.1681; found 418.1675.

(E)-3-(4-Chlorobenzylidene)-5-phenyl-N-(quinolin-8-yl)pent-4-ynamide (**4s**). White solid (113.6 mg, 67% yield), mp 134−137 °C. ^1H NMR ($CDCl_3$, 400 MHz) δ 10.44 (bs, 1H),

8.83 (dd, J = 1.2, 7.4 Hz, 1H), 8.45 (dd, J = 1.4, 4.2 Hz, 1H), 8.10 (dd, J = 1.4, 8.3 Hz, 1H), 7.55−7.48 (m, 6H), 7.37−7.33 (m, 3H), 7.31−7.26 (m, 3H), 7.19 (s, 1H), 3.67 (s, 2H); $^{13}C\{^1H\}$NMR ($CDCl_3$, 100 MHz) δ 168.0, 148.2, 138.6, 138.3, 136.2, 134.6, 134.0, 131.8, 130.3, 128.8, 128.5, 128.3, 127.9, 127.3, 123.0, 121.8, 121.6, 117.8, 116.7, 91.2, 91.1, 42.1. IR (neat): 3344, 2922, 1683, 1526, 1487, 1424, 1327, 1165, 1094, 825, 791, 755 (cm^{-1}); HRMS (EI) *m/z*: $[M]^+$ calcd for $C_{27}H_{19}N_2OCl$ 422.1186; found 422.1193.

(E)-3-(Naphthalen-2-ylmethylene)-5-phenyl-N-(quinolin-8-yl)pent-4-ynamide (**4t**). Yellow oil (154.9 mg, 88% yield). ^1H NMR ($CDCl_3$, 400 MHz) δ 10.49 (bs, 1H), 8.89 (dd, J = 1.1, 7.6 Hz, 1H), 8.44 (dd, J = 1.6, 4.2 Hz, 1H), 8.07 (dd, J = 1.6, 8.3 Hz, 1H), 8.04 (s, 1H), 7.89−7.79 (m, 3H), 7.61 (dd, J = 1.6, 8.5 Hz, 1H), 7.55−7.44 (m, 6H), 7.41 (s, 1H), 7.33−7.26 (m, 4H), 3.80 (s, 2H); $^{13}C\{^1H\}$NMR ($CDCl_3$, 100 MHz) δ 168.3, 148.2, 139.8, 138.6, 136.2, 134.7, 133.3, 133.1, 132.9, 131.9, 128.5, 128.5, 128.4, 128.3, 128.2, 127.9, 127.6, 127.3, 126.8, 126.5, 126.4, 123.2, 121.7, 121.5, 117.4, 116.7, 91.6, 91.1, 42.3. IR (neat): 3346, 2923, 1682, 1604, 1525, 1486, 1424, 1326, 1263, 825, 791, 756 (cm^{-1}); HRMS (EI) *m/z*: $[M]^+$ calcd for $C_{31}H_{22}N_2O$ 438.1732; found 438.1737.

Procedure 6: Control Experiments. A reaction flask was charged with a mixture of 2-chloro-*N*-(quinolin-8-yl)acetamide (**1a**, 0.4 mmol), phenylacetylene (**2a**, 0.4 mmol, 1.0 equiv.), CuI (0.04 mmol, 10 mol%), Cs_2CO_3 (0.48 mmol, 1.2 equiv.), and DCM (1.0 mL) under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 24 h. The resultant mixture was evaporated under a reduced pressure to remove the solvent. The product was purified through a silica gel column (eluent: petroleum ether/ethyl acetate = 10:1). Mixture of allene and internal alkyne: >90% total yield.

A reaction flask was charged with a mixture of allene and internal alkyne (0.4 mmol), phenylacetylene (**2a**, 0.8 mmol, 2 equiv.), CuI (0.04 mmol, 10 mol%), 1,10-phenanthroline (**L1**, 0.08 mmol, 20 mol%), Cs_2CO_3 (0.2 mmol, 0.5 equiv.), and DCM (1.0 mL) under nitrogen atmosphere. The reaction mixture was stirred at room

temperature for 24 h. The resultant mixture was evaporated under a reduced pressure to remove the solvent. The product **3a** was purified via silica gel chromatography (eluent: petroleum ether/ethyl acetate = 10:1). **3a**: 92% yield.

A reaction flask was charged with a mixture of 2,2-dimethyl-4-phenyl-N-(quinolin-8-yl)but-3-ynamide (**5**, 0.4 mmol), phenylacetylene (**2a**, 0.8 mmol, 2 equiv.), CuI (0.04 mmol, 10 mol%), 1,10-phenanthroline (**L1**, 0.08 mmol, 20 mol%), Cs_2CO_3 (0.48 mmol, 1.2 equiv.), and DCM (1.0 mL) under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 24 h. The resultant mixture was evaporated under a reduced pressure to remove the solvent. The residue obtained was separated through a silica gel column (eluent: petroleum ether/ethyl acetate = 10:1). Starting material **5** was recovered.

A reaction flask was charged with a mixture of 2-chloroacetophenone (**6**, 0.4 mmol), phenylacetylene (**2a**, 1.2 mmol, 3 equiv.), CuI (0.04 mmol, 10 mol%), 1,10-phenanthroline (**L1**, 0.08 mmol, 20 mol%), Cs_2CO_3 (0.48 mmol, 1.2 equiv.), and DCM (1.0 mL) under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 24 h. The resultant mixture was evaporated under a reduced pressure to remove the solvent. The residue obtained was separated through a silica gel column (eluent: petroleum ether/ethyl acetate = 10:1). A mixture of allene and internal alkyne was obtained.

Procedure 7: Gram-Scale Reaction. A reaction flask was charged with a mixture of 2-chloro-*N*-(quinolin-8-yl)acetamide (**1a**, 0.66 g, 3 mmol), phenylacetylene (**2a**, 9 mmol,

3.0 equiv.), CuI (0.3 mmol, 10 mol%), 1,10-phenanthroline (**L1**, 0.6 mmol, 20 mol%), Cs_2CO_3 (3.6 mmol, 1.2 equiv.), and DCM (8.0 mL) under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 48 h. The resultant mixture was evaporated under a reduced pressure to remove the solvent. The product **3a** was purified via silica gel chromatography (eluent: petroleum ether/ethyl acetate = 10:1). **3a**: 82% yield (0.956 g).

Procedure 8: Deprotection Reaction.[11a] A reaction flask was charged with a mixture of (*E*)-3-benzylidene-5-phenyl-*N*-(quinolin-8-yl)pent-4-ynamide (**3a**, 0.4 mmol), $BF_3{\cdot}Et_2O$ (2.4 mmol, 6 equiv.), and EtOH (4 mL) under nitrogen atmosphere. The reaction mixture was stirred at 100 ºC for 15 h. The resultant mixture was evaporated under a reduced pressure to remove the solvent. The product **7** was purified via silica gel chromatography (eluent: petroleum ether/ethyl acetate = 20:1). **7**: 82% yield. Colorless oil, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.47 (dd, J =2.9, 6.4 Hz, 2H), 7.39−7.27 (m, 8H), 7.15 (s, 1H), 4.23 (q, J = 7.1 Hz, 2H), 3.47 (s, 2H), 1.29 (t, J = 7.1 Hz, 3H); ^{13}C{^{1}H}NMR ($CDCl_3$, 100 MHz) δ 170.6, 138.9, 135.9, 131.6, 128.7, 128.5, 128.3, 128.3, 127.9, 123.2, 117.2, 90.8, 89.8, 61.1, 38.2, 14.3. IR (neat): 2916, 2848, 1736, 1466, 1371, 1236, 1125, 1019, 935, 875, 718 (cm^{-1}); HRMS (EI) *m/z*: $[M]^+$ calcd for $C_{20}H_{18}O_2$ 290.1307; found 290.1304.

SUPPORTING INFORMATION

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

Optimization studies, mechanistic study data, X-ray data and NMR spectra. (PDF)

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Notes

The authors declare no competing financial interest.

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