A Convenient Synthesis of 1,4,5-Trisubstituted 1,2,3-Triazoles via 1,3-Dipolar Cycloaddition/Coupling of Alkynes, Phenylboronic Acids, and Sodium Azide Catalyzed by Cu(I)/Cu(II)

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Abstract: A series of 1,4,5-trisubstituted 1,2,3-triazoles was prepared simply and conveniently via 1,3-dipolar cycloaddition/coupling reaction of terminal alkynes, phenylboronic acids and sodium azide in 1,4-dioxane–water using CuI/$CuSO_4$ as catalyst.

Key words: triazole, cycloaddition/coupling, phenylboronic acid, copper catalyst, alkyne

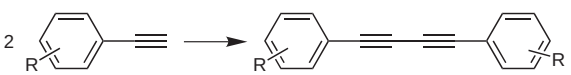
1,2,3-Triazoles have received significant attention as biologically important heterocycles. They possess many interesting antibacterial,[1] antiallergic,[2] anti-HIV activity,[3] and antineoplastic activity.[4] Additionally, they have been applied widely in herbicides, fungicides, and dyes etc.[5] The typical procedure for preparing 1,2,3-triazoles is via 1,3-dipolar cycloaddition of azides and alkynes proposed by Huisgen, yet this reaction often affords a mixture of 1,4- and 1,5-disubstituted isomers.[6] Recently, alternative methods that improve regioselectivity have been developed. For example, Sharpless, Fokin, and co-workers developed Cu(I)-catalyzed cycloaddition of azides with terminal alkynes to synthesize 1,4-disubstituted 1,2,3-triazole.[7] They also reported the regioselective synthesis of 1,5-disubstituted 1,2,3-triazoles and 1,4,5-trisubstituted 1,2,3-triazoles via the addition of bromomagnesium acetylides to azides.[8] Yamamoto and co-workers described the synthesis of triazoles using a palladium catalyst[9] or a Pd(0)–Cu(I) bimetallic catalyst.[10] Very recently, Porco Jr. and co-workers described a 1,3-dipolar cycloaddition/coupling reaction catalyzed by $Cu(MeCN)_4PF_6$ for the synthesis of 1,2,3-triazoles.[11]

Although organic azides are generally safe compounds, those of low molecular weight are sometimes unstable and difficult to handle.[12] Thus, methodologies that avoid the isolation of organic azides are desirable. Click chemistry is a useful way of making diverse collections of triazoles, and is showing a growing impact on drug discovery.[13] Fokin reported the synthesis of triazoles by a convenient one-pot procedure from a variety of available aromatic and aliphatic halides without isolating the potentially unstable organic azide intermediates.[14]

It was reported that phenylboronic acids can be converted into the corresponding halides via a displacement reaction.[15] In this communication, we report an efficient and safe one-pot procedure for the regioselective formation of 1,4,5-trisubstituted 1,2,3-triazoles via Cu(I)/Cu(II)-catalyzed 1,3-dipolar cycloaddition/coupling reaction of terminal alkynes, phenylboronic acids and sodium azide.

We first conducted experiments to define the requirements for solvent systems using CuI as catalyst. Reactions were performed in various solvents containing water including acetone, MeCN, DMF, DMSO, EtOH, MeOH, THF, *t*-BuOH, and 1,4-dioxane (entries 1–12 in Table 1). Initial studies showed that the reaction could be performed in almost all these solvent systems; however, the 1,4-dioxane–water (2:1) solvent system turned out to be the best. As shown in Table 1, $CuSO_4$ showed no catalytic activity for cycloaddition/coupling of **1a**, **2a** and **3**, but a mixture of $CuSO_4$ and CuI exhibited slightly better catalytic activity (entries 13 and 14 in Table 1).

We next examined the cycloaddition/coupling some of phenylboronic acids and terminal alkynes under the optimum conditions. As can be seen from Table 2, the phenylethyne substrates, 4-nitrophenylethyne (**2c**) and 4-acetylphenylethyne (**2d**), bearing an electron-withdrawing group in phenyl ring failed to react with phenylboronic acids and sodium azide to produce **4** (entries 3, 4, 8, and 11 in Table 2). 4-Methoxyphenylethyne (**2a**) and phenylethyne (**2b**) reacted with substrates **1a**, **1b**,**1c** and **1d**, and the corresponding products **4a**, **4d**, **4f**, **4i** and **4b**, **4e**, **4g**, **4j** were isolated in 63%, 68%, 78%, 57% and 55%, 65%, 74%, 52% yields, respectively (entries 1, 2, 6, 7, 9, 10, 13, and 14 in Table 2).[16] Thus, electron-rich phenylethynes gave better results in this reaction. Alkyl ethyne can also give product **4** (entries 5 and 12 in Table 2).[16] Phenylboronic acid substrates bearing an electron-withdrawing group usually led to higher yields (e.g., entries 1, 6, 9, and 13 in Table 2).[16] By-product diyne was observed in all reactions, thus the moderate isolated yields were likely due to competing Glaser coupling (diyne formation, Equation 1).[17]



Equation 1 Diyne formation

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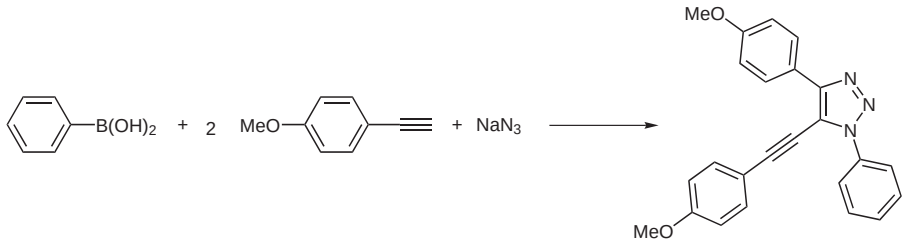
Table 1 Synthesis of 1,2,3-Triazole **4a** in Various Solvent Systems and Catalysts[a]

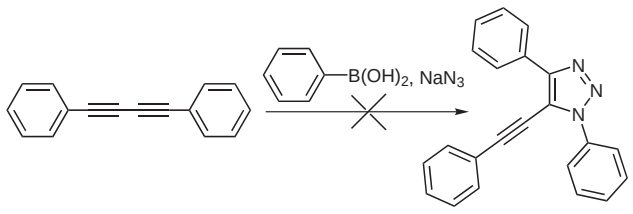


1a **2a** **3** **4a**

Entry	Catalyst[b]	Solvent	Time (h)	**4**, Yield[c] (%)
1	**I**	acetone–H_2O (2:1)	24	44
2	**I**	MeCN–H_2O (2:1)	5	42
3	**I**	DMF–H_2O (2:1)	24	trace[d]
4	**I**	DMSO–H_2O (2:1)	24	trace[d]
5	**I**	EtOH–H_2O (2:1)	24	30
6	**I**	MeOH–H_2O (2:1)	24	43
7	**I**	THF–H_2O (2:1)	24	42
8	**I**	*t*-BuOH–H_2O (2:1)	24	17
9	**I**	1,4-dioxane–H_2O (2:1)	24	55
10	**I**	1,4-dioxane–H_2O (1:1)	24	51
11	**I**	1,4-dioxane–H_2O (1:2)	24	42
12	**I**	1,4-dioxane	24	13
13	**II**	1,4-dioxane–H_2O (2:1)	24	none
14	**III**	1,4-dioxane–H_2O (2:1)	12	63

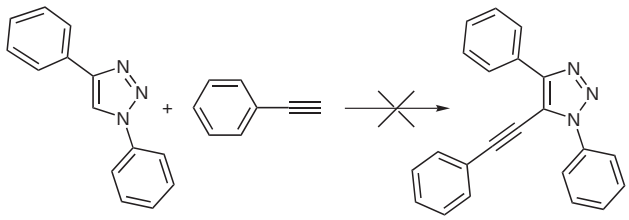
[a] All reactions were performed with **1a** (1 equiv), **2a** (2.2 equiv) and **3** (1.5 equiv) under conditions as indicated.
[b] **I**: CuI (10%), **II**: $CuSO_4 \cdot 5H_2O$ (20%), **III**: CuI (10%), $CuSO_4 \cdot 5H_2O$ (20%).
[c] Isolated yield after column chromatography on silica gel.
[d] Detected by TLC.

For the reaction, we initially reasoned that the product **4** may be formed by an initial Glaser coupling and subsequent 1,3-dipolar cycloaddition. However, treatment of 1,4-diphenylbuta-1,3-diyne with sodium azide and phenylboronic acid led to no reaction (Equation 2). Treatment of disubstituted triazole with alkyne in the presence of CuI and $CuSO_4 \cdot 5H_2O$ led to no reaction, either (Equation 3). Proposed mechanism for the catalytic cycle is shown in Scheme 1.



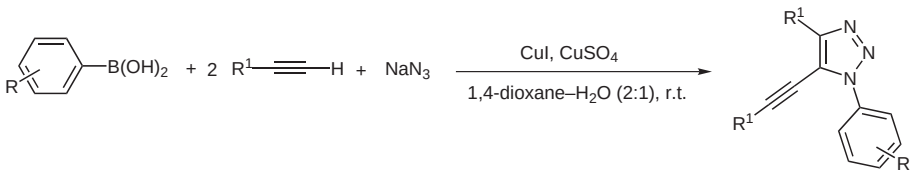
Equation 2

The structures of compounds **4a**–**j** were fully identified by their IR, ^{1}H NMR, and ^{13}C NMR spectra. The X-ray crystal structure of **4b** further confirmed their structures (Figure 1).[18]

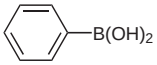
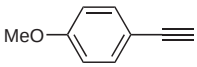
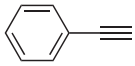
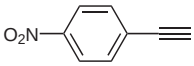
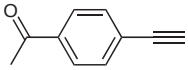
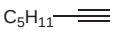
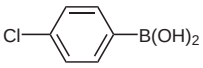
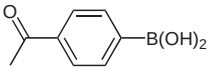
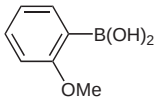


Equation 3

Table 2 Synthesis of 1,4,5-Trisubstituted 1,2,3-Triazole **4** from Various Alkynes, Phenylboronic Acids and Sodium Azide[a]



1a–d **2a–e** **3** **4a–j**

Entry	Phenylboronic acid **1**	Terminal alkyne **2**	Time (h)	Yield[b] (%) of **4**
1	 **1a**	 **2a**	12	**4a**, 63
2	**1a**	 **2b**	12	**4b**, 55
3	**1a**	 **2c**	24	–
4	**1a**	 **2d**	24	–
5	**1a**	 **2e**	12	**4c**, 40
6	 **1b**	**2a**	12	**4d**, 68
7	**1b**	**2b**	12	**4e**, 65
8	**1b**	**2c**	24	–
9	 **1c**	**2a**	12	**4f**, 78
10	**1c**	**2b**	12	**4g**, 74
11	**1c**	**2d**	24	–
12	**1c**	**2e**	12	**4h**, 45
13	 **1d**	**2a**	12	**4i**, 57
14	**1d**	**2b**	12	**4j**, 52

[a] All reactions were performed with **1a** (1 equiv), **2** (2.2 equiv) and **3** (1.5 equiv) under conditions as indicated.
[b] Isolated yield after column chromatography on silica gel.

In conclusion, a novel and direct method for synthesizing 1,4,5-trisubstituted 1,2,3-triazoles directly from a variety of phenylboronic acids, sodium azide, and some terminal alkynes has been developed. The procedure does not require isolating of the azide intermediates and it has a series of advantages, such as, it is safe, efficient, convenient, easy operating and environmentally benign.

Acknowledgment

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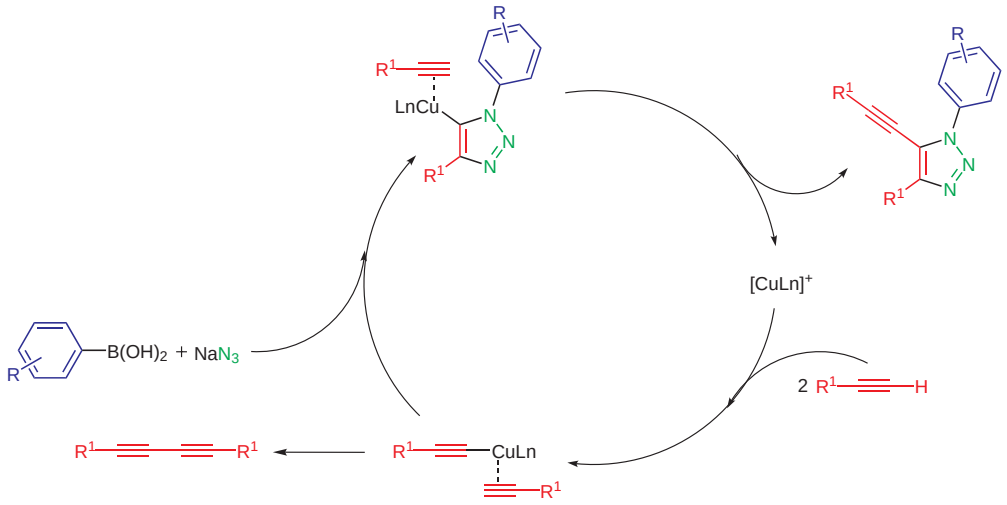

Scheme 1 Proposed mechanism

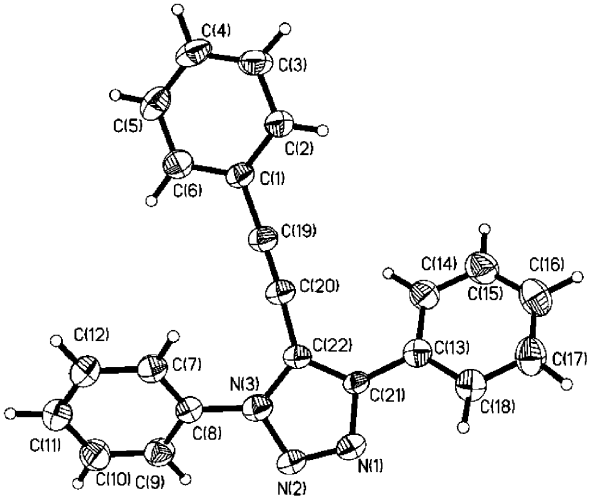

Figure 1 X-ray crystal structure of 1,4-diphenyl-5-(2-phenylethynyl)-1*H*-1,2,3-triazole (**4b**)

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(16) **Synthesis of 4-(4-Methoxyphenyl)-5-[2-(4-methoxyphenyl)ethynyl]-1-phenyl-1*H*-1,2,3-triazole (4a); Typical Procedure**: A mixture of **1a** (50.0 mg, 0.41 mmol), **2a** (118.9 mg, 0.90 mmol), sodium azide (**3**; 40.3 mg, 0.62 mmol), CuI (7.8 mg, 0.041 mmol) and $CuSO_4 \cdot 5H_2O$ (20.5 mg, 0.082 mmol) in 1,4-dioxane (10 mL) and H_2O (5 mL) was stirred overnight. Then, the reaction mixture was diluted with H_2O (20 mL) and was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated. The residue was purified by column chromatography (PE–EtOAc, 10:1) to afford **4a** (98.5 mg, 63%) as a white solid; mp 86–88 °C. IR (KBr):

2216 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.83 (s, 3 H), 3.87 (s, 3 H), 6.89 (d, *J* = 9.3 Hz, 2 H), 7.03 (d, *J* = 8.7 Hz, 2 H), 7.40 (d, *J* = 8.7 Hz, 2 H), 7.50–7.60 (m, 3 H), 7.88 (d, *J* = 8.1 Hz, 2 H), 8.21 (d, *J* = 9.3 Hz, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 55.3 (CH_3), 55.4 (CH_3), 75.4 (C), 102.0 (C), 113.6 (C), 114.1 (CH), 114.3 (CH), 116.3 (C), 122.9 (C), 123.7 (CH), 127.8 (CH), 129.2 (CH), 129.7 (CH), 133.0 (CH), 136.7 (C), 148.1 (C), 160.0 (C), 160.6 (C). EI–MS: *m*/*z* = 381 [M$^+$], 353 [M – N_2]$^+$. Anal. Calcd for $C_{24}H_{19}N_3O_2$: C, 75.57; H, 5.02; N, 11.02. Found: C, 75.50; H, 4.99; N, 10.98.

1,4-Diphenyl-5-(2-phenylethynyl)-1*H*-1,2,3-triazole (4b): white solid; mp 105–107 °C. IR (KBr): 2215 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.38–7.60 (m, 11 H), 7.88 (d, *J* = 8.4 Hz, 2 H), 8.28 (d, *J* = 7.5 Hz, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 76.4 (C), 102.0 (C), 116.8 (C), 121.4 (C), 123.8 (CH), 126.5 (CH), 128.6 (CH), 128.7 (CH), 128.7 (CH), 129.2 (CH), 129.4 (CH), 129.6 (CH), 130.1 (C), 131.4 (CH), 136.5 (C), 148.5 (C). EI–MS: *m*/*z* = 321 [M$^+$], 293 [M –N_2]$^+$. Anal. Calcd for $C_{22}H_{15}N_3$: C, 82.22; H, 4.70; N, 13.08. Found: C, 82.16; H, 4.71; N, 13.04.

5-(Hept-1-ynyl)-4-pentyl-1-phenyl-1*H*-1,2,3-triazole (4c): liquid. IR (KBr): 2236 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.87–0.94 (m, 6 H), 1.26–1.42 (m, 8 H), 1.53–1.60 (m, 2 H), 1.76–1.81 (m, 2 H), 2.45 (t, *J* = 7.0 Hz, 2 H), 2.79 (t, *J* = 7.6 Hz, 2 H), 7.44–7.53 (m, 3 H), 7.78 (d, *J* = 6.9 Hz, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.87 (CH_3), 13.94 (CH_3), 19.6 (CH_2), 22.1 (CH_2), 22.3 (CH_2), 25.4 (CH_2), 27.7 (CH_2), 28.5 (CH_2), 30.9 (CH_2), 31.4 (CH_2), 66.9 (C), 103.1 (C), 118.7 (C), 123.3 (CH), 128.8 (CH), 129.0 (CH), 136.8 (C), 151.2 (C). EI–MS: *m*/*z* = 309 [M$^+$], 281 [M – N_2]$^+$. Anal. Calcd for $C_{20}H_{27}N_3$: C, 77.63; H, 8.79; N, 13.58. Found: C, 77.56; H, 8.77; N, 13.55.

1-(4-Chlorophenyl)-4-(4-methoxyphenyl)-5-[2-(4-methoxyphenyl)ethynyl]-1*H*-1,2,3-triazole (4d): white solid; mp 150–152 °C. IR (KBr): 2214 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.84 (s, 3 H), 3.87 (s, 3 H), 6.91 (d, *J* = 9.0 Hz, 2 H), 7.02 (d, *J* = 8.7 Hz, 2 H), 7.41 (d, *J* = 9.0 Hz, 2 H), 7.54 (d, *J* = 8.7 Hz, 2 H), 7.84 (d, *J* = 9.0 Hz, 2 H), 8.20 (d, *J* = 9.3 Hz, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 55.3 (CH_3), 55.4 (CH_3), 75.2 (C), 102.4 (C), 113.3 (C), 114.1 (CH), 114.4 (CH), 116.2 (C), 122.7 (C), 124.8 (CH), 127.8 (CH), 129.4 (CH), 133.1 (CH), 135.1 (C), 135.2 (C), 148.3 (C), 160.0 (C), 160.7 (C). EI–MS: *m*/*z* = 415 [M$^+$], 387 [M – N_2]$^+$. Anal. Calcd for $C_{24}H_{18}ClN_3O_2$: C, 69.31; H, 4.36; N, 10.10. Found: C, 69.27; H, 4.32; N, 10.08.

1-(4-Chlorophenyl)-4-phenyl-5-(2-phenylethynyl)-1*H*-1,2,3-triazole (4e): white solid; mp 95–97 °C. IR (KBr): 2219 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.39–7.57 (m, 10 H), 7.85 (d, *J* = 8.1 Hz, 2 H), 8.26 (d, *J* = 8.4 Hz, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 76.1 (C), 102.4 (C), 116.7 (C), 121.2 (C), 124.9 (CH), 126.5 (CH), 128.7 (CH), 128.7 (CH), 128.9 (CH), 129.5 (CH), 129.8 (CH), 129.9 (C), 131.5 (CH), 135.0 (C), 135.3 (C), 148.7 (C). EI–MS: *m*/*z* = 355 [M$^+$], 327 [M – N_2]$^+$. Anal. Calcd for $C_{22}H_{14}ClN_3$: C, 74.26; H, 3.97; N, 11.81. Found: C, 74.21; H, 3.96; N, 11.77.

1-(4-Acetylphenyl)-4-(4-methoxyphenyl)-5-[2-(4-methoxyphenyl)ethynyl]-1*H*-1,2,3-triazole (4f): white solid; mp 126–128 °C. IR (KBr): 2214, 1685 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.67 (s, 3 H), 3.84 (s, 3 H), 3.87 (s, 3 H), 6.91 (d, *J* = 8.4 Hz, 2 H), 7.03 (d, *J* = 8.4 Hz, 2 H), 7.43 (d, *J* = 8.1 Hz, 2 H), 8.06 (d, *J* = 8.4 Hz, 2 H), 8.16 (d, *J* = 8.1 Hz, 2 H), 8.20 (d, *J* = 8.1 Hz, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.7 (CH_3), 55.3 (CH_3), 55.4 (CH_3), 75.2 (C), 102.7 (C), 113.2 (C), 114.1 (CH), 114.4 (CH), 116.0 (C), 122.5 (C), 123.2 (CH), 127.8 (CH), 129.4 (CH), 133.0 (CH), 137.0 (C), 140.0 (C), 148.5 (C), 160.1 (C), 160.8 (C), 196.8 (C). EI–MS: *m*/*z* = 423 [M$^+$], 395 [M –N_2]$^+$. Anal. Calcd for $C_{26}H_{21}N_3O_3$: C, 73.74; H, 5.00; N, 9.92. Found: C, 73.71; H, 5.02; N, 9.89.

1-(4-Acetylphenyl)-4-phenyl-5-(2-phenylethynyl)-1*H*-1,2,3-triazole (4g): white solid; mp 138–140 °C. IR (KBr): 2215, 1680 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.69 (s, 3 H), 7.41–7.55 (m, 8 H), 8.08 (d, *J* = 8.7 Hz, 2 H), 8.18 (d, *J* = 9.0 Hz, 2 H), 8.28 (d, *J* = 7.8 Hz, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.7 (CH_3), 76.1 (C), 102.7 (C), 108.3 (C), 121.2 (C), 123.4 (CH), 126.6 (CH), 128.73 (CH), 128.77 (CH), 129.0 (CH), 129.5 (CH), 129.83 (C), 129.91 (CH), 131.5 (CH), 137.3 (C), 139.9 (C), 149.1 (C), 196.8 (C). EI–MS: *m*/*z* = 363 [M$^+$], 335 [M – N_2]$^+$. Anal. Calcd for $C_{24}H_{17}N_3O$: C, 79.32; H, 4.72; N, 11.56. Found: C, 79.30; H, 4.69; N, 11.51.

1-(4-Acetylphenyl)-4-pentyl-5-(hept-1-ynyl)-1*H*-1,2,3-triazole (4h): liquid. IR (KBr): 2235, 1689 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.88–0.93 (m, 6 H), 1.31–1.39 (m, 8 H), 1.57–1.64 (m, 2 H), 1.76–1.81 (m, 2 H), 2.49 (t, *J* = 6.8 Hz, 2 H), 2.67 (s, 3 H), 2.79 (t, *J* = 7.5 Hz, 2 H), 7.98 (d, *J* = 8.7 Hz, 2 H), 8.11 (d, *J* = 8.1 Hz, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.88 (CH_3), 13.94 (CH_3), 19.6 (CH_2), 22.1 (CH_2), 22.3 (CH_2), 25.3 (CH_2), 26.6 (CH_3), 27.7 (CH_2), 28.5 (CH_2), 31.0 (CH_2), 31.3 (CH_2), 66.7 (C), 104.0 (C), 118.6 (C), 122.8 (CH), 129.3 (CH), 136.8 (C), 140.3 (C), 151.8 (C), 196.8 (C). EI–MS: *m*/*z* = 351 [M$^+$], 323 [M – N_2]$^+$. Anal. Calcd for $C_{22}H_{29}N_3O$: C, 75.18; H, 8.32; N, 11.96. Found: C, 75.11; H, 8.33; N, 11.93.

1-(2-Methoxyphenyl)-4-(4-methoxyphenyl)-5-[2-(4-methoxyphenyl)ethynyl]-1*H*-1,2,3-triazole (4i): white solid; mp 96–98 °C. IR (KBr): 2217 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.81 (s, 3 H), 3.84 (s, 3 H), 3.87 (s, 3 H), 6.84 (d, *J* = 8.7 Hz, 2 H), 7.02 (d, *J* = 8.7 Hz, 2 H), 7.12 (t, *J* = 7.5 Hz, 2 H), 7.28 (d, *J* = 9.3 Hz, 2 H), 7.50 (d, *J* = 7.2 Hz, 2 H), 8.22 (d, *J* = 9.0 Hz, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 55.3 (CH_3), 55.3 (CH_3), 55.9 (CH_3), 75.1 (C), 101.0 (C), 112.2 (CH), 113.8 (C), 114.0 (CH), 114.2 (CH), 118.9 (C), 120.6 (CH), 123.2 (C), 125.4 (C), 127.6 (CH), 128.3 (CH), 131.5 (CH), 133.0 (CH), 146.8 (C), 154.3 (C), 159.8 (C), 160.3 (C). EI–MS: *m*/*z* = 411 [M$^+$], 383 [M – N_2]$^+$. Anal. Calcd for $C_{25}H_{21}N_3O_3$: C, 72.98; H, 5.14; N, 10.21. Found: C, 72.93; H, 5.10; N, 10.20.

1-(2-Methoxyphenyl)-4-phenyl-5-(2-phenylethynyl)-1*H*-1,2,3-triazole (4j): white solid; mp 84–86 °C. IR (KBr): 2219 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.83 (s, 3 H), 7.10–7.52 (m, 12 H), 8.30 (d, *J* = 8.4 Hz, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 55.8 (CH_3), 76.1 (C), 101.0 (C), 112.1 (CH), 119.4 (C), 120.6 (CH), 121.6 (C), 125.1 (C), 125.8 (CH), 126.3 (CH), 128.2 (CH), 128.5 (CH), 128.6 (CH), 129.3 (CH), 130.3 (C), 131.3 (CH), 131.7 (CH), 147.1 (C), 154.2 (C). EI–MS: *m*/*z* = 351 [M$^+$], 323 [M – N_2]$^+$. Anal. Calcd for $C_{23}H_{17}N_3O$: C, 78.61; H, 4.88; N, 11.96. Found: C, 78.55; H, 4.91; N, 11.94.

(17) (a) Siemsen, P.; Livingston, R. C.; Diederich, F. *Angew. Chem. Int. Ed.* **2000**, *39*, 2632. (b) Myers, A. G.; Goldberg, S. D. *Angew Chem. Int. Ed.* **2000**, *39*, 2732.

(18) Crystal data: $C_{22}H_{15}N_3$, *MW* = 321.37, *T* = 294(2) K, λ = 0.71073 Å, monoclinic, space group $P2_1/c$, *a* = 7.6038(2) Å, *b* = 18.6814(6) Å, *c* = 12.1815(4) Å, α = 90.00°, β = 91.356 (2)°, γ = 90.00°, *V* = 1729.89(9) Å^3, *Z* = 4, *D* = 1.234 g/cm^3, μ = 0.074 mm^{-1}, *F*(000) = 672.0. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication CCDC-626008.