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CuI/Et_2NH-Catalyzed One-Pot Highly Efficient Synthesis of 1,4-Disubstituted 1,2,3-Triazoles in Green Solvent Glycerol

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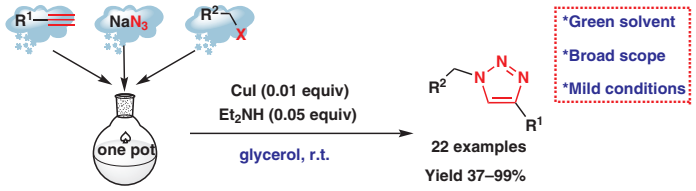

R^1 = XC_6H_4 (X = 4-Et, 4-MeO, 3-MeO, 4-F, 2-F), pyridin-2-yl, pyridin-3-yl, thiophen-2-yl, cyclohexan-1-ol, cyclopropyl, Et_3Si, Ph

R^2 = XC_6H_4 (X = 4-Me, 3-Me, 3-CH_3O, 4-O_2N, 3-Cl, 4-F, penta-F, 3-CF_3O), cyclopropylmethyl, Bu, Ph

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Abstract A concise one-pot three-component reaction of organic halides, terminal acetylenes, and sodium azide provided an efficient route for the synthesis of 1,2,3-triazoles. A variety of 1,2,3-triazoles were prepared in good to excellent yields with green solvent glycerol. This procedure used CuI and diethylamine, which are two easily available reagents as the new catalytic system at room temperature.

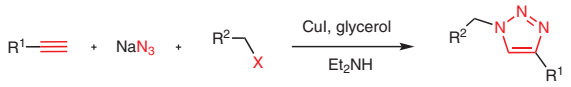
Keywords green solvent, glycerol, copper(I) iodide, diethylamine, triazoles, one-pot synthesis

In the past decades, 1,2,3-triazole derivatives were unique nitrogen-containing heterocyclic scaffolds and attracted much attention[1] as they have been widely used in the fields of biochemical science,[2] material chemistry,[3] medicinal chemistry,[4] and synthetic organic chemistry.[5,1d] Therefore, the development of new, rapid, and efficient protocols for the synthesis of 1,2,3-triazoles has drawn extensive attention. Several methods have been developed for the preparation of these compounds;[6] without controversy, Cu-catalyzed click chemistry of organic azide with terminal alkyne is the most efficient method.[7,1d] This click reaction has many remarkable advantages, including good functionality tolerance, mild reaction conditions, exclusive regioselectivity, operational simplicity, and high yields. Organic azides are currently safe compounds, but those of low molecular weight can be environmentally sensitive, hence, difficult to handle.[8] A number of methodologies were developed by using a three-component reaction of organic halides, terminal acetylenes, and sodium azide in order to avert the isolation of organic azides.[9] Unfortunately, most of these methods for synthesizing 1,2,3-triazoles could not avoid the use of expensive and toxic organic solvents such as DMF, THF, and DMSO.[10]

From green chemistry perspective, one of the vital points in realizing a 'green chemical' process involves the use of a safe, non-toxic, and cheap solvent, especially in numerous industrial processes.[11] Indeed, water is the first solvent of choice, yet the low solubility of most organic and organometallic compounds in water limits its applications. Some researchers successfully synthesized 1,2,3-triazoles using water as the solvent. However, the success of these methods correlated closely with the assistance of microwave,[12] surfactants,[13] or nanometer catalyst.[14] All of these treatments make the reaction much more complicated. Like water, glycerol is also naturally available, highly hydrophilic, environmentally friendly, and inexpensive. These advantages make it an ideal candidate from the environmental and economic standpoint.[15] In recent years, chemists have achieved many classical chemical reactions using glycerol as the solvent.[16] However, to the best of our knowledge, there were no attempts to apply glycerol as solvent in the synthesis of 1,2,3-triazoles so far.

In addition, the new methods for the synthesis of 1,2,3-triazoles developed in recent years were largely due to the preparation of novel catalysts and ligands, which were generally difficult to obtain because of their tricky synthetic routes.[17] A suitable catalytic system should not only make the reaction more convenient but also make the reaction easier to spread and apply in the practical applications. Therefore, the development of an alternative concise, and practical strategy method is still desirable and essential.

Reported here (Scheme 1) is a mild and experimentally simple three-component catalytic reaction pathway for the synthesis of 1,4-disubstituted 1,2,3-triazoles, which uses glycerol as solvent and readily available CuI as catalyst. This approach exhibits wide substrate scope and ambient reaction condition and can be easily used for large-scale preparation.



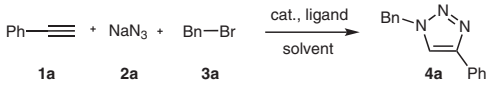
R^1 = XC_6H_4 (X = 4-Et, 4-MeO, 3-MeO, 4-F, 2-F), pyridin-2-yl, pyridin-3-yl, thiophen-2-yl, cyclohexan-1-ol, cyclopropyl, Et_3Si, Ph

R^2 = XC_6H_4 (X = 4-Me, 3-Me, 3-CH_3O, 4-O_2N, 3-Cl, 4-F, penta-F, 3-CF_3O), cyclopropylmethyl, Bu, Ph

Scheme 1 Our strategy for the construction of 1,4-disubstituted 1,2,3-triazoles

Taking into account this promising green solvent glycerol, a systematic screening of catalyst systems was carried out. Phenylacetylene (**1a**), sodium azide (**2a**), and benzyl bromide (**3a**) were selected as model reaction to optimize the conditions (Table 1). First, we purposely screened inexpensive and commercially available copper catalysts, including CuBr, $CuSO_4$ + sodium ascorbate, CuI, etc. at room temperature (Table 1, entries 1–4). To our delight, using copper catalyst independently could reach a fairly high yield and the catalytic effect of CuI was the best (89%). The structure of product **4** was analyzed by ^{1}H NMR, ^{13}C NMR and mass spectrometry and compared with the reported characterization data. Further research showed that catalytic quantity of nitrogen-containing ligands had an effective influence on the catalytic efficiency of CuI. Specifically, diethylamine raised the yield and shortened the reaction time; the highest yield was 98% (entries 5–10). Control experiments suggested that CuI was essential for this transformation (entries 11, 12). At last, to find the most suitable solvent for this catalytic system, other solvents such as EtOH, acetic ether and THF were used (entries 13–20). The results showed that glycerol had the best reaction efficiency in our experiments. Eventually, we determined the final reaction conditions that used catalyst CuI and ligand diethylamine in solvent glycerol at room temperature.

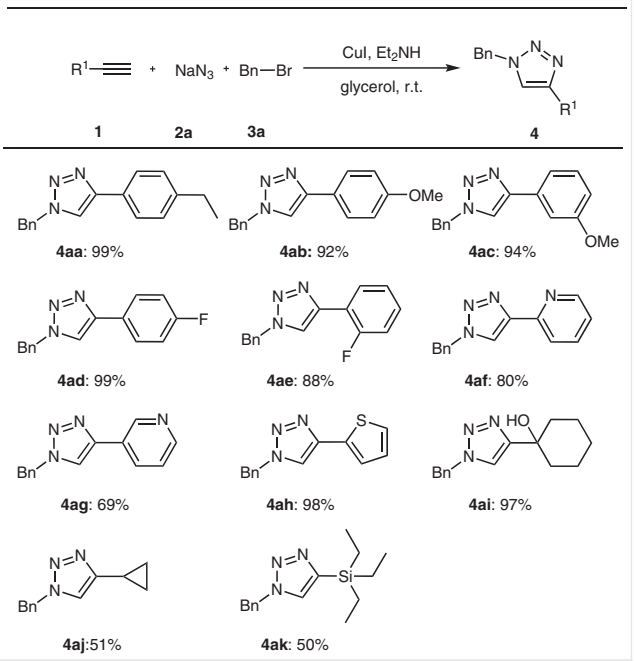
Table 1 Optimization of Reaction Conditions[a]



Entry	Catalyst	Ligand	Solvent	Yield (%)[b]	Time (h)
1	$CuSO_4$	–	glycerol	74	7
2	$CuSO_4$ + sodium ascorbate	–	glycerol	69	8
3	$CuSO_4$ + Cu	–	glycerol	74	8
4	CuI	–	glycerol	89	7
5	CuI	ethylenediamine	glycerol	19	24
6	CuI	Et_3N	glycerol	82	6
7	CuI	pyridine	glycerol	84	6
8	CuI	DMAP	glycerol	86	6
9	CuI	Et_2NH	glycerol	98	3
10	CuI	propane-1,3-diamine	glycerol	18	24
11	–	–	glycerol	–	–
12	–	Et_2NH	glycerol	–	–
13	CuI	Et_2NH	EtOH	80	10
14	CuI	Et_2NH	acetic ether	–	–
15	CuI	Et_2NH	CH_2Cl_2	79	12
16	CuI	Et_2NH	THF	23	24
17	CuI	Et_2NH	MeCN	69	12
18	CuI	Et_2NH	acetone	68	10
19	CuI	Et_2NH	H_2O	73	10
20	CuI	Et_2NH	–	69	10

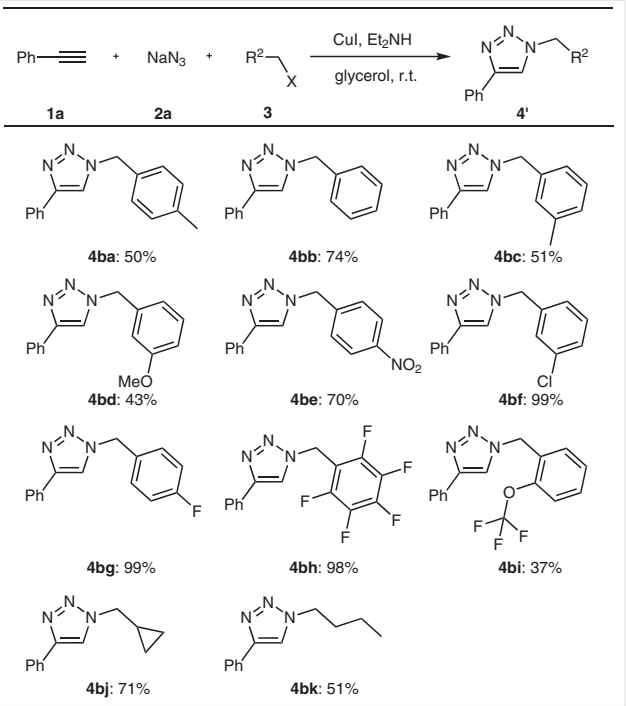
[a] Reaction conditions: **1a** (0.24 mmol), **2a** (0.24 mmol), **3a** (0.20 mmol), and cat. (0.002 mmol), ligand (0.01 mmol), solvent (1 mL). All reactions were carried out under N_2 atmosphere and monitored by HPLC until completion of the reaction.
[b] Isolated yield.

With the optimized reaction conditions in hand, the substrate scope was investigated next. The substituents of aromatic alkynes were first evaluated as shown in Scheme 2, most of them performed smoothly and the corresponding triazoles were obtained in moderate to excellent yields. Based on the results, it is quite clear that the efficiency of the click reaction is rarely dependent on the electronic nature of the substrates (**4aa–ae**). The three heterocyclic acetylene compounds reacted smoothly and generated target compounds in good to excellent yields (**4af**, **4ag**, **4ah**); the obtained products such as **4af** was potential bidentate ligand for complex formation and catalysis. The 1-ethynylcyclohexan-1-ol generated the desired product **4ai** in excellent yield. Notably, aliphatic alkynes were also successfully converted into the desired products with moderate yields (**4aj**, **4ak**).



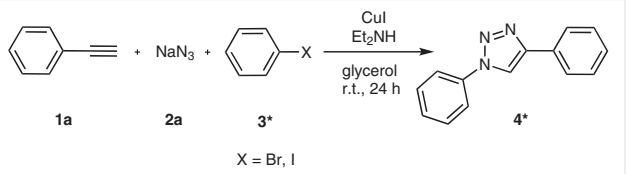
Scheme 2 Substrate scope of alkynes. *Reagents and conditions*: **1** (0.24 mmol), **2a** (0.24 mmol), **3a** (0.20 mmol), catalyst (0.002 mmol), ligand (0.01 mmol), solvent (1 mL). All reactions were carried out under N_2 atmosphere and monitored by HPLC until completion. Isolated yields are shown.

The scope of substituents in respect to organic halides was investigated next as shown in Scheme 3. The substituted benzyl bromides with electron-withdrawing groups performed better than the ones with electron-donating groups (**4bf–bh** vs **4ba**). The substituted benzyl chlorides (X = Cl) were also investigated, and the reactions afforded the corresponding compounds smoothly in moderate yields (**4bb–be**). As for **4bi**, it turned out that steric hindrance significantly affected the reaction efficiency. The use of alkyl bromides gave moderate yields (**4bj**, **4bk**).



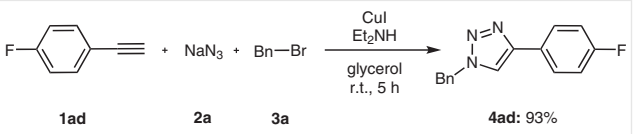
Scheme 3 Substrate scope of organic halides. *Reagents and conditions*: **1a** (0.24 mmol), **2a** (0.24 mmol), **3** (0.20 mmol), catalyst (0.002 mmol), and ligand (0.01 mmol), solvent (1 mL). All reactions were carried out under N_2 atmosphere and monitored by HPLC until completion. Isolated yields are shown. Target compounds **4bb–be** and **4bi** were synthesized from benzyl chlorides, the rest of the compounds were synthesized from organic bromides.

In addition, some reactions were designed using bromobenzene and iodobenzene under standard conditions; however, they did not generate the target compounds. We speculate that phenyl azides are difficult to generate from benzene halides by nucleophilic substitution, which makes the target compound difficult to generate (Scheme 4).



Scheme 4 Synthesis of target compound from halobenzene

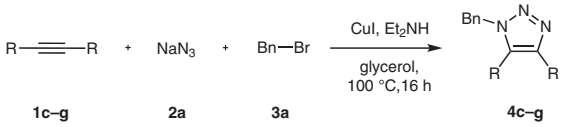
In order to demonstrate the practical application of this method, a gram-scale reaction was designed with 5.04 mmol **1a**, 5.04 mmol **2a**, and 4.2 mmol **3a** under the standard conditions. The corresponding compound 1-benzyl-4-(4-fluorophenyl)-1*H*-1,2,3-triazole (**4ad**) was obtained in 0.99 g (93%). This is a good demonstration for its synthetic value in organic synthesis (Scheme 5).



Scheme 5 Gram-scale preparation of **4ad**

In addition, our catalytic system was active with internal alkynes at the elevated temperature as well, as shown in Table 2. Thus, electron-rich and electron-poor internal aromatic alkynes could react with other substrates to provide the desired products **4e–f**. Heterocyclic aromatic alkynes also provided the desired compound catalyzed by our catalyst system (**4d**). However, aliphatic alkynes did not react with other substrates (**4g**).

Table 2 Synthesis of 1,4,5-Trisubstituted 1,2,3-Triazoles from Internal Alkynes[a]

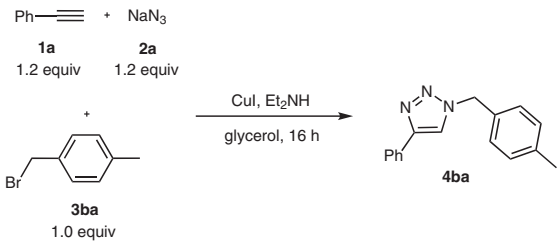


Product	R	Yield (%)[b]
4c	Ph	31
4d	2-thienyl	23
4e	4-FC_6H_4	25
4f	4-$MeOC_6H_4$	20
4g	*n*-Pr	–

[a] Reaction conditions: **1c–g** (0.24 mmol), **2a** (0.24 mmol), **3a** (0.20 mmol), CuI (0.002 mmol), Et_2NH (0.01 mmol), glycerol (1 mL). All reactions were carried out under N_2 atmosphere and monitored by HPLC until completion.
[b] Isolated yield.

To gain insight into the reaction mechanism, several control experiments were carried out (Table 3). The results showed that CuI was essential for this reaction; however,

Table 3 Control Experiments for Reaction Mechanism Study[a]



Entry	CuI (equiv)	Et_2NH (equiv)	Yield (%)[b]
1	1.0	–	7
2	0.01	–	23
3	0.01	0.05	50
4	0.01	1.0	48
5	0.01	2.0	51

[a] Reaction conditions: **1a** (0.24 mmol), **2a** (0.24 mmol), **3ba** (0.20 mmol), catalyst (0.002 mmol), ligand (0.01 mmol), solvent (1 mL). All reactions were carried out under N_2 atmosphere and monitored by HPLC until completion.
[b] Isolated yield.

increasing the quantity of CuI reduced the yield of the reaction. Catalytic quantity of ligand (diethylamine) could obviously improve the catalytic efficiency of CuI, but increasing the quantity of diethylamine had no obvious effect on the reaction. According to the above results, we may conjecture that diethylamine mainly acted as a ligand of CuI but not as base to the reaction. To verify our hypothesis, CuI and diethylamine were mixed for 10 minutes under an N_2 atmosphere, then the remaining diethylamine was removed under high vacuum conditions for 1 hour (Figure 1 **A**, **B**). At the end, we used the residue as catalyst to synthesize **4ba**, this showed almost the same result compared to the optimized reaction condition. Another experiment without diethylamine demonstrated this result, thus CuI showed a suspended state in glycerol (Figure 1 **D**). The introduction of diethylamine could effectively improve the solubility of CuI

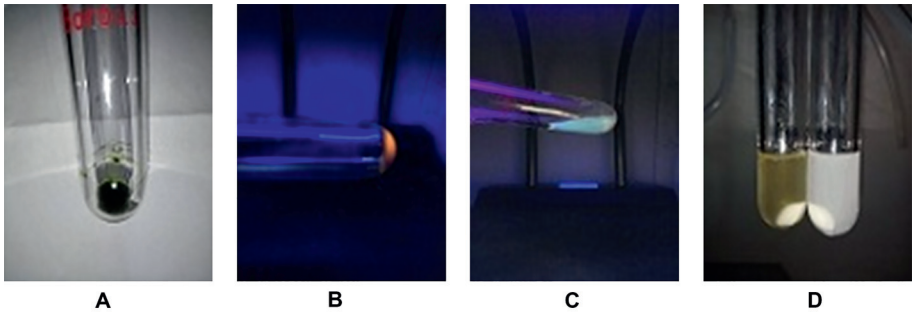
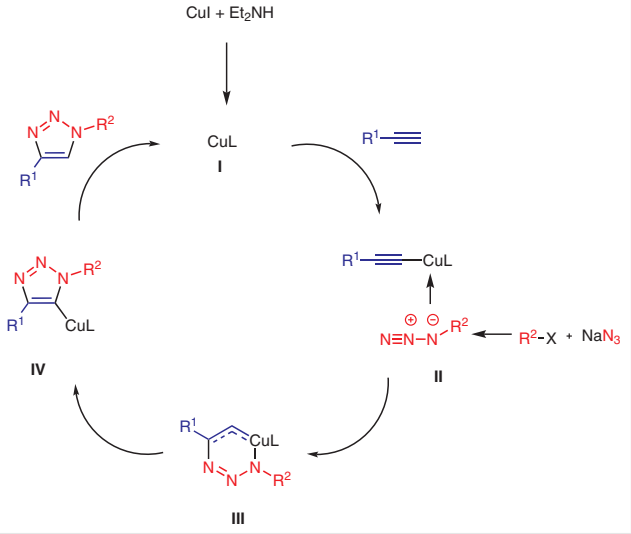


Figure 1 A : Schlenk tube containing CuI and diethylamine without vacuum; **B**: Schlenk tube containing CuI and diethylamine under vacuum for 1 h, and then observed under 365 nm UV; **C**: Contents of Schlenk tube **B** was mixed with glycerol and stirred for 10 min, and then observed under 365 nm UV; **D**: The left Schlenk tube containing CuI, diethylamine, and glycerol was stirred for 10 min. The right Schlenk tube containing CuI and glycerol was stirred for 10 min.

by forming the copper-diethylamine complex (Figure 1 **B**, **C**), which may be an important reason to increase the catalytic efficiency.

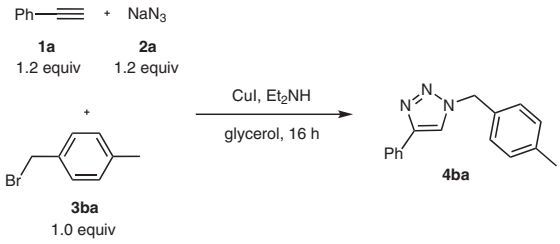
Based on these experimental results and previous reports,[7b] a possible mechanism for this cascade reaction is outlined in Scheme 6. Most likely, the initial step here is the formation of the copper complex **I** from CuI and Et_2NH; meanwhile, organic azide **II** is formed from the organic halide and sodium azide by nucleophilic substitution. Then, copper(I) acetylide is generated from copper complex **I** and the alkyne. Subsequently, copper(I) acetylide attacks organic azides and gives six-membered copper metallacycle **III**. Finally, ring contraction affords copper(I) triazolide complex **IV**, from which the target product is produced by the release of the catalyst.



Scheme 6 Proposed mechanism for complex **I**-catalyzed cycloaddition of terminal alkynes[7b]

The most important feature of our work is that CuI/Et_2NH-catalyzed synthesis of target compounds in green solvent glycerol. Compared with other protic solvents (water, ethanol), glycerol shows excellent results, and it is likely to be due to the unique solubility of organic compounds. This hypothesis was tested and verified by experiments. Phenylacetylene (**1a**), sodium azide (**2a**), and 4-methylbenzyl bromide (**3ba**) were selected as reaction substrates, and component solvent in different proportions of water (poor solubility of organic substrate) and *tert*-butyl alcohol (good solubility of organic substrate) were selected as solvents. It can be seen that the yield of the reaction varies greatly by changing the proportion of the solvent. In particular, when the ratio of *tert*-butyl alcohol and water is 1:2, the yield of the reaction is obviously improved. This shows that the solubility of the organic substrate in the solvent has great effect on the result of the reaction (Table 4).

Table 4 Effect of Solvent on the Reaction[a]



Entry	*t*-BuOH (mL)	H_2O (mL)	Yield (%)[b]
1	1	–	30
2	0.66	0.33	28
3	0.5	0.5	21
4	0.33	0.66	45
5	–	1	33

[a] Reaction conditions: **1a** (0.24 mmol), **2a** (0.24 mmol), **3ba** (0.20 mmol), catalyst (0.002 mmol), and ligand (0.01 mmol), in solvent. All reactions were carried out under N_2 atmosphere and monitored by HPLC until completion.
[b] Isolated yield.

In conclusion, we have developed a new method for the synthesis of 1,4-disubstituted 1,2,3-triazoles with the catalyst system of CuI/Et_2NH using a three-component reaction of organic halides, terminal acetylenes, and sodium azide. This protocol provides a simple, cheap, atom- and step-efficient access to 1,4-disubstituted 1,2,3-triazoles. The attractive features of the reaction involve green solvent glycerol, excellent functional group tolerance, and mild reaction conditions.

^1H NMR spectra were recorded at 400 MHz, and ^{13}C NMR spectra were recorded at 100 MHz (Bruker). ^1H NMR chemical shifts (δ) are reported in ppm relative to TMS with the solvent signal as the internal standard ($CDCl_3$ at 7.26 ppm). ^{13}C NMR chemical shifts are reported in ppm from TMS with the solvent resonance as the internal standard ($CDCl_3$ at 77.00 ppm). HPLC analysis used Agilent 1260 HPLC. Flash column chromatography was carried out using silica gel. High-resolution mass spectra were obtained with an AB Triple TOF 5600 Plus system. Reactions were monitored by TLC and visualized with ultraviolet light. IR spectra were recorded on a Nicolet 6700 on a KBr beamsplitter.

1,2,3-Triazoles; General Procedure

A mixture of alkyne (0.24 mmol), NaN_3 (16 mg, 0.24 mmol), and halide (0.20 mmol) were stirred in glycerol (1.0 mL) in the presence of CuI (0.38 mg, 0.002 mmol) and Et_2NH (0.73 mg, 0.01 mmol) at r.t. in a Schlenk tube under N_2. The progress of the reaction was monitored by HPLC until the reaction was complete. H_2O (10 mL) was added to the mixture and extracted with acetic ether (3 × 20 mL). The combined organic layers were dried (anhyd Na_2SO_4) and concentrated. The residue was subjected to flash column chromatography on silica gel (petroleum ether/acetic ether) to afford the corresponding compound **4**.

1-Benzyl-4-(4-ethylphenyl)-1*H*-1,2,3-triazole (4aa)

Reaction time: 5.5 h; white solid; yield: 52.3 mg (99%); mp 118–119 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.71 (d, *J* = 8.2 Hz, 2 H), 7.62 (s, 1 H), 7.42–7.36 (m, 3 H), 7.33–7.28 (m, 2 H), 7.23 (d, *J* = 7.9 Hz, 2 H), 5.57 (s, 2 H), 2.66 (q, *J* = 7.6 Hz, 2 H), 1.24 (t, *J* = 7.6 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.30, 144.44, 134.73, 129.14, 128.76, 128.30, 128.05, 127.89, 125.72, 119.19, 54.25, 28.67, 15.49.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{17}N_3$: 264.1495; found: 264.1511.

1-Benzyl-4-(4-methoxyphenyl)-1*H*-1,2,3-triazole (4ab)

Reaction time: 5 h; yellow solid; yield: 49.0 mg (92%); mp 143–145 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.75–7.69 (m, 2 H), 7.57 (s, 1 H), 7.42–7.35 (m, 3 H), 7.35–7.28 (m, 2 H), 6.96–6.90 (m, 2 H), 5.56 (s, 2 H), 3.83 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.60, 148.11, 134.77, 129.14, 128.75, 128.05, 127.01, 123.28, 118.67, 114.21, 55.32, 54.21.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{15}N_3O$: 266.1288; found: 266.1281.

1-Benzyl-4-(3-methoxyphenyl)-1*H*-1,2,3-triazole (4ac)

Reaction time: 4.5 h; white solid; yield: 50.0 mg (94%); mp 74–75 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.65 (s, 1 H), 7.44–7.34 (m, 4 H), 7.33–7.27 (m, 4 H), 6.86 (m, 1 H), 5.55 (s, 2 H), 3.84 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.02, 148.09, 134.68, 131.86, 129.84, 129.16, 128.79, 128.06, 119.73, 118.11, 114.32, 110.70, 55.36, 54.23.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{15}N_3O$: 266.1288; found: 266.1288.

1-Benzyl-4-(4-fluorophenyl)-1*H*-1,2,3-triazole (4ad)

Reaction time: 4.5 h; white solid; yield: 50.3 mg (99%); mp 110–112 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.80–7.73 (m, 2 H), 7.62 (s, 1 H), 7.38 (m, 3 H), 7.31 (m, 2 H), 7.13–7.04 (m, 2 H), 5.56 (s, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.85, 160.39, 146.33, 133.56, 128.15, 127.80, 127.05, 126.44, 126.36, 125.76, 125.73, 118.21, 114.85, 114.63, 53.24.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{12}FN_3$: 254.1088; found: 254.1078.

1-Benzyl-4-(2-fluorophenyl)-1*H*-1,2,3-triazole (4ae)

Reaction time: 3 h; white solid; yield: 44.7 mg (88%); mp 96–97 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.23 (m, 1 H), 7.79 (d, *J* = 3.7 Hz, 1 H), 7.29 (m, 3 H), 7.26–7.13 (m, 4 H), 7.02 (m, 1 H), 5.52 (s, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.38, 156.92, 140.61, 133.65, 128.31, 128.23, 128.10, 127.72, 126.94, 126.77, 126.73, 123.57, 123.54, 121.70, 121.57, 117.58, 117.45, 114.69, 114.47, 53.18.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{12}FN_3$: 254.1088; found: 254.1087.

2-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)pyridine (4af)

Reaction time: 3 h; white solid; yield: 37.9 mg (80%); mp 115–116 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.58–8.50 (m, 1 H), 8.17 (d, *J* = 8.0, 1.1 Hz, 1 H), 8.04 (s, 1 H), 7.76 (m, 1 H), 7.42–7.29 (m, 5 H), 7.20 (m, 1 H), 5.58 (s, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.26, 149.35, 148.75, 136.89, 134.34, 129.18, 128.86, 128.33, 122.86, 121.90, 120.23, 54.40.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{12}N_4$: 237.1135; found: 237.1137.

3-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)pyridine (4ag)

Reaction time: 2.5 h; white solid; yield: 32.7 mg (69%); mp 100–101 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.95 (d, *J* = 2.3 Hz, 1 H), 8.55 (m, 1 H), 8.18 (m, 1 H), 7.76 (s, 1 H), 7.47–7.26 (m, 6 H), 5.60 (s, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.23, 147.01, 145.15, 134.37, 132.99, 129.24, 128.95, 128.13, 126.70, 123.73, 119.86, 54.39.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{12}N_4$: 237.1135; found: 237.1131.

1-Benzyl-4-(thiophen-2-yl)-1*H*-1,2,3-triazole (4ah)

Reaction time: 4 h; white solid; yield: 47.4 mg (98%); mp 118–120 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.57 (s, 1 H), 7.42–7.34 (m, 3 H), 7.35–7.25 (m, 4 H), 7.04 (m, 1 H), 5.54 (s, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.32, 134.53, 132.91, 129.20, 128.87, 128.11, 127.61, 125.07, 124.19, 119.04, 54.29.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{11}N_3S$: 242.0746; found: 242.0746.

1-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)cyclohexan-1-ol (4ai)

Reaction time: 3 h; white solid; yield: 50.1 mg (97%); mp 122–124 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37 (d, *J* = 6.9 Hz, 4 H), 7.30–7.24 (m, 2 H), 5.50 (s, 2 H), 2.29 (s, 1 H), 2.00–1.29 (m, 10 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.00, 134.61, 129.08, 128.69, 128.09, 119.47, 69.53, 54.14, 38.07, 25.32, 21.92.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{19}N_3O$: 258.1601; found: 258.1605.

1-Benzyl-4-cyclopropyl-1*H*-1,2,3-triazole (4aj)

Reaction time: 5 h; white solid; yield: 20.4 mg (51%); mp 44–45 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.27 (d, *J* = 6.7 Hz, 3 H), 7.19–7.13 (m, 2 H), 7.07 (s, 1 H), 5.37 (s, 2 H), 1.83 (m, 1 H), 0.88–0.76 (m, 2 H), 0.76–0.68 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.61, 133.89, 128.00, 127.56, 126.95, 118.60, 52.96, 6.70, 5.69.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{13}N_3$: 200.1182; found: 200.1182.

1-Benzyl-4-(triethylsilyl)-1*H*-1,2,3-triazole (4ak)

Reaction time: 4 h; light yellow liquid; yield: 27.4 mg (50%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.50 (s, 1 H), 7.38–7.31 (m, 3 H), 7.24 (m, 2 H), 5.56 (s, 2 H), 1.01–0.95 (m, 9 H), 0.85–0.77 (m, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.09, 134.06, 128.61, 127.98, 127.48, 126.86, 52.41, 6.29, 2.46.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{23}N_3Si$: 274.1734; found: 274.1746.

1-(4-Methylbenzyl)-4-phenyl-1*H*-1,2,3-triazole (4ba)

Reaction time: 4 h; white solid; yield: 25.0 mg (50%); mp 95–96 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.82–7.76 (m, 2 H), 7.63 (s, 1 H), 7.43–7.36 (m, 2 H), 733–7.27 (m, 1 H), 7.24–7.14 (m, 4 H), 5.53 (s, 2 H), 2.36 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.11, 137.71, 130.61, 129.56, 128.78, 127.74, 127.10, 127.08, 124.65, 118.34, 53.02, 20.14.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{15}N_3$: 250.1339; found: 250.1333.

1-Benzyl-4-phenyl-1*H*-1,2,3-triazole (4bb)

Reaction time: 5 h; white solid; yield: 39.4 mg (74%); mp 129–130 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.83–7.76 (m, 2 H), 7.66 (s, 1 H), 7.44–7.35 (m, 5 H), 7.31 (m, 3 H), 5.58 (s, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.21, 133.65, 129.50, 128.13, 127.77, 127.13, 127.03, 124.67, 118.44, 53.21.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{13}N_3$: 236.1282; found: 266.1280.

1-(3-Methylbenzyl)-4-phenyl-1*H*-1,2,3-triazole (4bc)

Reaction time: 6 h; light yellow solid; yield: 25.5 mg (51%); mp 96–97 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.80 (d, *J* = 7.5 Hz, 2 H), 7.65 (s, 1 H), 7.39 (t, *J* = 7.3 Hz, 2 H), 7.28 (m, 2 H), 7.20–7.07 (m, 3 H), 5.53 (s, 2 H), 2.34 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.17, 139.01, 134.56, 130.56, 129.51, 129.00, 128.77, 128.75, 128.11, 125.68, 125.12, 119.45, 54.23, 21.32.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{15}N_3$: 250.1339; found: 250.1344.

1-(3-Methoxybenzyl)-4-phenyl-1*H*-1,2,3-triazole (4bd)

Reaction time: 5 h; white solid; yield: 22.9 mg (43%); mp 84–85 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.76–7.70 (m, 2 H), 7.60 (s, 1 H), 7.37–7.29 (m, 2 H), 7.28–7.18 (m, 2 H), 6.83 (m, 2 H), 6.76 (m, 1 H), 5.47 (s, 2 H), 3.71 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.13, 147.20, 135.08, 129.50, 129.20, 127.77, 127.13, 124.67, 119.23, 118.46, 113.24, 112.63, 54.30, 53.16.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{15}N_3O$: 266.1288; found: 266.1283.

1-(4-Nitrobenzyl)-4-phenyl-1*H*-1,2,3-triazole (4be)

Reaction time: 5 h; white solid; yield: 39.4 mg (70%); mp 160–161 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.21 (d, *J* = 8.4 Hz, 2 H), 7.82–7.78 (m, 2 H), 7.76 (s, 1 H), 7.46–7.38 (m, 4 H), 7.33 (t, *J* = 7.4 Hz, 1 H), 5.69 (s, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.69, 148.08, 141.75, 130.08, 128.92, 128.56, 128.50, 125.75, 124.32, 119.78, 53.20.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{12}N_4O_2$: 281.1033; found: 281.1041

1-(3-Chlorobenzyl)-4-phenyl-1*H*-1,2,3-triazole (4bf)

Reaction time: 6 h; white solid; yield: 54.9 mg (99%); mp 165–167 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.85–7.78 (m, 2 H), 7.70 (s, 1 H), 7.46–7.37 (m, 2 H), 7.38–7.29 (m, 4 H), 7.18 (m, 1 H), 5.55 (s, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.45, 136.62, 135.07, 130.46, 130.34, 129.01, 128.84, 128.30, 128.08, 126.05, 125.73, 119.49, 53.52.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{12}ClN_3$: 270.0793; found: 270.0787.

1-(4-Fluorobenzyl)-4-phenyl-1*H*-1,2,3-triazole (4bg)

Reaction time: 5 h; white solid; yield: 49.7 mg (99%); mp 123–125 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.79 (d, *J* = 7.3 Hz, 2 H), 7.66 (s, 1 H), 7.40 (t, *J* = 7.5 Hz, 2 H), 7.35–7.27 (m, 3 H), 7.07 (t, *J* = 8.5 Hz, 2 H), 5.53 (s, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.11, 161.64, 148.31, 130.56, 130.53, 130.39, 129.98, 129.90, 128.83, 128.81, 128.26, 125.72, 119.42, 116.26, 116.05, 53.50.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{12}FN_3$: 254.1088; found: 254.1091

1-[(Perfluorophenyl)methyl]-4-phenyl-1*H*-1,2,3-triazole (4bh)

Reaction time: 5 h; white solid; yield: 63.9 mg (98%); mp 158–160 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.86–7.76 (m, 3 H), 7.41 (m, 2 H), 7.34 (m, 1 H), 5.67 (s, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.48, 130.06, 128.89, 128.47, 125.80, 119.58, 40.90.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_8F_5N_3$: 326.0711; found: 326.0711.

4-Phenyl-1-[2-(trifluoromethoxy)benzyl]-1*H*-1,2,3-triazole (4bi)

Reaction time: 16 h; light yellow solid; yield: 23.7 mg (37%); mp 94–95 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.82 (d, *J* = 7.6 Hz, 2 H), 7.73 (s, 1 H), 7.42 (t, *J* = 7.4 Hz, 3 H), 7.32 (m, 4 H), 5.68 (s, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.88, 130.41, 130.39, 130.34, 128.84, 128.28, 127.55, 127.47, 125.76, 121.83, 120.69, 120.68, 119.78, 48.41.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{12}F_3N_3O$: 320.1005; found: 320.1020.

1-(Cyclopropylmethyl)-4-phenyl-1*H*-1,2,3-triazole (4bj)

Reaction time: 10 h; white solid; yield: 28.4 mg (71%); mp 80–82 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.90–7.80 (m, 3 H), 7.42 (t, *J* = 7.6 Hz, 2 H), 7.33 (t, *J* = 7.4 Hz, 1 H), 4.25 (s, 2 H), 1.34 (m, 1 H), 0.72 (m, 2 H), 0.47 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.53, 126.55, 124.57, 123.81, 121.47, 114.80, 50.80, 25.46, 6.87.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{13}N_3$: 200.1182; found: 200.1187.

1-Butyl-4-phenyl-1*H*-1,2,3-triazole (4bk)

Reaction time: 10 h; light yellow solid; yield: 20.4 mg (51%); mp 47–48 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.86–7.80 (m, 2 H), 7.74 (s, 1 H), 7.42 (m, 2 H), 7.36–7.30 (m, 1 H), 4.40 (t, *J* = 7.2 Hz, 2 H), 1.93 (m, 2 H), 1.46–1.35 (m, 2 H), 0.97 (t, *J* = 7.4 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.73, 130.75, 128.81, 128.06, 125.69, 119.38, 50.15, 32.32, 19.74, 13.47.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{15}N_3$: 202.1339; found: 202.1347.

1-Benzyl-4,5-diphenyl-1*H*-1,2,3-triazole (4c)

Reaction time: 16 h; white solid; yield: 19.4 mg (31%); mp 99–100 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.58–7.54 (m, 2 H), 7.50–7.39 (m, 3 H), 7.29–7.22 (m, 6 H), 7.15 (d, *J* = 7.0 Hz, 2 H), 7.03 (m, 2 H), 5.41 (s, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.45, 134.28, 132.89, 129.76, 129.08, 128.68, 128.14, 127.67, 127.42, 127.13, 126.78, 126.71, 126.48, 125.71, 51.06.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{17}N_3$: 312.1495; found: 312.1496.

1-Benzyl-4,5-di(thiophen-2-yl)-1*H*-1,2,3-triazole (4d)

Reaction time: 16 h; light yellow solid; yield: 14.9 mg (23%); mp 132–133 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.56 (d, *J* = 5.1 Hz, 1 H), 7.28–7.23 (m, 3 H), 7.21 (d, *J* = 5.1 Hz, 1 H), 7.13 (m, 2 H), 7.06 (m, 2 H), 6.97 (d, *J* = 3.6 Hz, 1 H), 6.94 (m, 1 H), 5.44 (s, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.16, 133.99, 131.54, 130.13, 128.72, 127.67, 127.18, 126.83, 126.37, 126.25, 125.01, 124.51, 124.40, 123.69, 51.22.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{13}N_3S_2$: 324.0624; found: 324.0632.

1-Benzyl-4,5-bis(4-fluorophenyl)-1*H*-1,2,3-triazole (4e)

Reaction time: 16 h; white solid; yield: 17.4 mg (25%); mp 82–83 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.53–7.47 (m, 2 H), 7.26 (m, 3 H), 7.12–7.07 (m, 4 H), 7.03–6.99 (m, 2 H), 6.95 (m, 2 H), 5.39 (s, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.67, 163.62, 162.18, 161.16, 143.98, 135.13, 132.62, 132.11, 132.02, 128.78, 128.45, 128.37, 128.28, 127.39, 126.92, 126.88, 123.57, 123.54, 116.66, 116.44, 115.60, 115.39, 52.18.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{16}F_2N_3$: 348.1307; found: 348.1303.

1-Benzyl-4,5-bis(4-methoxyphenyl)-1*H*-1,2,3-triazole (4f)

Reaction time: 16 h; light yellow liquid; yield: 14.8 mg (20%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.50 (d, *J* = 8.7 Hz, 2 H), 7.28–7.21 (m, 3 H), 7.04 (d, *J* = 8.3 Hz, 4 H), 6.92 (d, *J* = 8.6 Hz, 2 H), 6.80 (d, *J* = 8.7 Hz, 2 H), 5.38 (s, 2 H), 3.85 (s, 3 H), 3.76 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.43, 159.60, 144.75, 134.77, 133.78, 132.96, 129.14, 128.58, 128.32, 127.55, 124.88, 120.26, 116.13, 114.99, 55.95, 55.51, 52.25.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{23}H_{22}N_3O_2$: 372.1707; found: 372.1713.

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Supporting Information

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