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Heterogeneous Copper(I)-Catalyzed Cascade Addition–Oxidative Cyclization of Nitriles with 2-Aminopyridines or Amidines: Efficient and Practical Synthesis of 1,2,4-Triazoles

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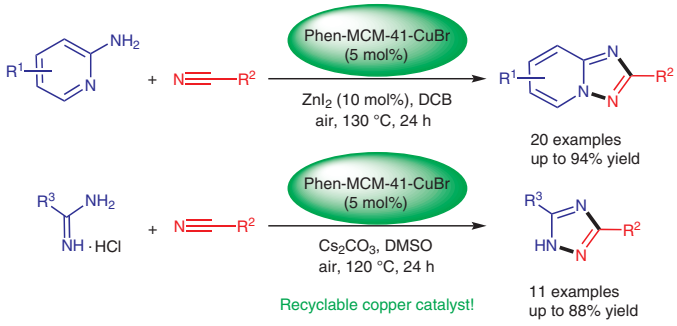

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Abstract The heterogeneous cascade addition-oxidative cyclization of nitriles with 2-aminopyridines or amidines was achieved in 1,2-dichlorobenzene or DMSO at 120–130 °C by using a 1,10-phenanthroline-functionalized MCM-41-supported copper(I) complex [Phen-MCM-41-CuBr] as the catalyst and air as the oxidant. The approach was used to generate a wide variety of 1,2,4-triazole derivatives in mostly high yields. This heterogeneous copper(I) catalyst could be easily prepared in a two-step procedure from commercially or readily available and inexpensive reagents and it exhibited higher catalytic activity than the CuBr/1,10-Phen system. Phen-MCM-41-CuBr was also easy to recover and was recyclable up to eight times with almost consistent activity.

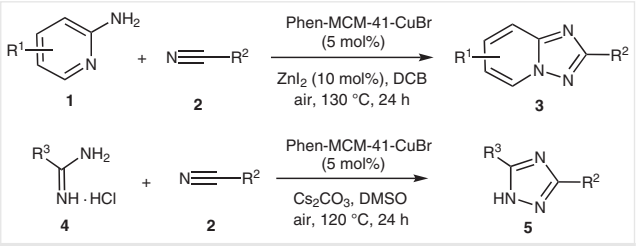
Key words copper, 1,2,4-triazole, oxidative cyclization, heterogeneous catalysis, cascade reaction

1,2,4-Triazoles, as highly important structural motifs, have found broad applications in medicinal and agricultural chemistry fields as well as in materials science.[1] The compounds exhibit a wide variety of biological activities, including antifungal, antibacterial, anticancer, antimicrobial, anti-inflammatory, antiviral, antidepressant, and anticonvulsant behavior.[2] 1,2,4-Triazole scaffolds are found in many biologically active molecules[3] and valuable pharmaceuticals, including maraviroc, triazolam, sitagliptin, and deferasirox.[4] 1,2,4-Triazoles have also been widely used as ligands in transition-metal complexes and metal-organic frameworks, exhibiting tremendous application prospects.[5] Based on the high importance of this scaffold and on its applications in a variety of fields, various synthetic methods have been developed for the synthesis of 1,2,4-triazole derivatives.[1a,6] The most commonly investigated pathways involve the intramolecular and intermolecular condensation reactions of nitrogen-containing compounds.[7] In addition, copper-mediated or alumina-promoted synthesis of 1,2,4-triazoles have been reported.[8] However, most of the existing methods suffer from some drawbacks in one or another respect, such as multistep synthetic procedures, lower yields, a limited substrate scope, or inferior regioselectivity. Therefore, it is highly desired to develop a simple and practical approach to 1,2,4-triazole derivatives from readily available starting materials.

Recently, copper-catalyzed construction of 1,2,4-triazoles from readily available starting materials has attracted considerable interest because of the high efficiency and low cost of copper catalysts.[9] However, in almost all cases, homogeneous copper catalysts with higher loadings (typically 5–20 mol%) were used to achieve high yields, and they are difficult to separate from the reaction mixture and they are not recyclable. These problems are of particular environmental and economic concerns in large-scale syntheses and in industry. Moreover, homogeneous catalysis might cause copper contamination of the desired product because 1,2,4-triazoles are strong ligands for transition metals and could coordinate with copper to form stable complexes.[5c–e] Immobilization of the existing homogeneous copper catalysts on various supports appears to be a logical solution to these problems; the use of immobilized catalysts could enable facile separation, recovery, and reusability of the copper catalysts, thus minimizing copper contamination of the desired product and reducing the amount of waste generated from reaction workup.[10] In recent years, some supported copper complexes have been successfully used for the construction of carbon–carbon[11] and carbon–heteroatom[12] bonds as highly efficient and recyclable catalysts, but the heterogeneous copper-catalyzed synthesis of 1,2,4-triazoles from readily available starting materials has received little attention. Recently, Zhao and co-workers reported an efficient heterogeneously catalyzed addition–oxidative cyclization between 2-aminopyridines or amidines and ni-

triles for the synthesis 1,2,4-triazoles using air as the oxidant and copper-zinc supported on Al_2O_3-TiO_2 as the catalyst.[13]

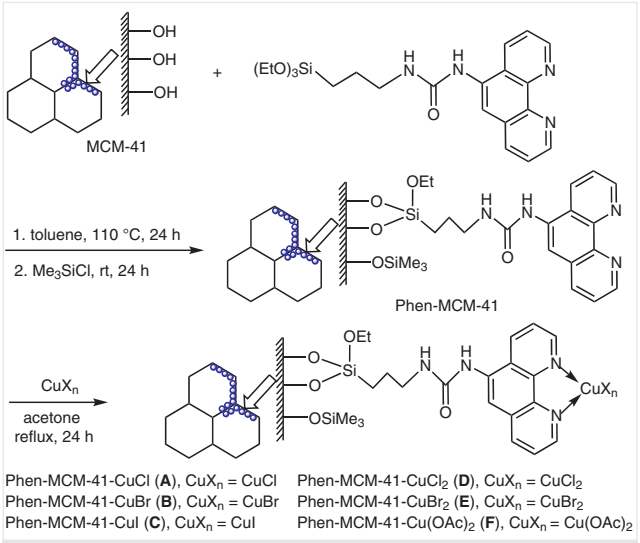
Mesoporous silica MCM-41 has recently emerged as an ideal support for immobilization of homogeneous catalysts because of its unique properties such as extremely high surface area, homogeneity of the pores, large pore volume and high thermal stability in comparison with other solid supports.[14] In addition, nano-sized catalysts can serve as efficient bridges and fill the gap between homogeneous and heterogeneous catalysts.[15] To date, Pd,[16] Rh,[17] Mo,[18] and Au[19] complexes immobilized on MCM-41 have been successfully applied in organic synthesis as recyclable nanocatalysts. Recently, we reported the first synthesis of 1,10-phenanthroline-functionalized MCM-41-supported copper(I) complex [Phen-MCM-41-CuI] and found that it is a highly efficient and recyclable heterogeneous catalyst for the decarboxylative cross-coupling of potassium polyfluorobenzoates with aryl halides and the C–O coupling between aryl iodides and aliphatic alcohols.[20] To further expand our Cu(I)-MCM-41 chemistry toolbox,[11c,d,12f,h,20] herein we report a heterogeneous copper-catalyzed cascade addition-oxidative cyclization of nitriles with 2-aminopyridines or amidines leading to 1,2,4-triazole derivatives by using an 1,10-phenanthroline-functionalized MCM-41-supported copper(I) complex [Phen-MCM-41-CuBr] as the catalyst and air as the oxidant (Scheme 1).



Scheme 1 Heterogeneous copper(I)-catalyzed synthesis of 1,2,4-triazoles

A series of 1,10-phenanthroline-functionalized MCM-41-supported copper(I) or (II) complexes [Phen-MCM-41-CuX_n] were prepared according to our previous procedure as shown in Scheme 2.[20b] First, the mesoporous MCM-41 was condensed with 1-(1,10-phenanthrolin-5-yl)-3-(3-(triethoxysilyl)propyl)urea[21] in toluene, followed by silylation with Me_3SiCl to generate the 1,10-phenanthroline-functionalized MCM-41 [Phen-MCM-41]. The latter was then reacted with various copper salts in acetone to afford a series of the Phen-MCM-41-CuX_n complexes as light-green powders.

In our initial screening experiments, the cascade reaction of 2-aminopyridine **1a** with benzonitrile **2a** was investigated to optimize the reaction conditions; the results are summarized in Table 1. The reaction was first carried out in

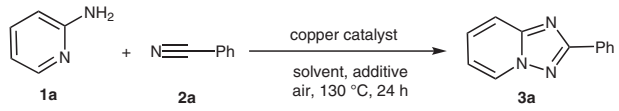


Scheme 2 Preparation of the Phen-MCM-41-CuX_n complexes

1,2-dichlorobenzene (DCB) at 130 °C with Phen-MCM-41-CuCl [**A**] (5 mol%) as the catalyst under an air atmosphere. The reaction was stopped 24 hours later, and 2-phenyl[1,2,4]triazolo[1,5-*a*]pyridine **3a** was obtained in 38% yield after flash chromatography (Table 1, entry 1). To our delight, the addition of 10 mol% ZnI_2 improved the reaction efficacy significantly, and the desired product **3a** was isolated in 81% yield (entry 2).[22] Other zinc salts such as $ZnBr_2$ and $ZnCl_2$ were less effective than ZnI_2 (entries 3 and 4). To further increase the yield, various supported copper catalysts were tested, and a significant catalyst effect was observed. When Phen-MCM-41-CuBr [**B**] was used as the catalyst, the yield of **3a** could be increased to 85%, while other copper catalysts such as Phen-MCM-41-CuI [**C**], Phen-MCM-41-$CuCl_2$ [**D**], Phen-MCM-41-$CuBr_2$ [**E**], and Phen-MCM-41-$Cu(OAc)_2$ [**F**] afforded lower yields (entries 5–9); Phen-MCM-41-CuBr [**B**] was thus the best choice (entry 5). The reaction also worked well in toluene (entry 10), but the use of polar DMSO or DMF as the solvent resulted in a dramatic decrease in the yield (entries 11 and 12). The reaction did not occur in the absence of any copper catalyst, which revealed the special catalytic role of copper in this transformation (entry 13). When a homogeneous CuBr (5 mol%)/1,10-Phen (5 mol%) catalytic system was used, the desired product **3a** was isolated in 81% yield (entry 14), which indicated that this heterogeneous Phen-MCM-41-CuBr [**B**] system exhibited a slightly higher catalytic activity than the homogeneous CuBr (5 mol%)/1,10-Phen (5 mol%) system. When 1-(1,10-phenanthrolin-5-yl)-3-(3-(triethoxysilyl)propyl)urea was used as the ligand instead of 1,10-Phen, a slightly decreased yield (78%) was also observed (entry 15). The slightly higher activity of this heterogeneous catalytic system over the homogeneous analogues may be mainly due to the efficient site isolation and the op-

timal dispersion of the active sites on the inner channel walls of the MCM-41 support with ultra-high surface area. Finally, the amount of copper catalyst was also screened. The use of 2.5 mol% of Phen-MCM-41-CuBr resulted in a decreased yield and required a longer reaction time (entry 16), whereas increasing the amount of copper catalyst could shorten the reaction time, but did not improve the yield significantly (entry 17). Therefore, the optimized conditions for this cascade reaction are the use of Phen-MCM-41-CuBr (5 mol%) as catalyst and ZnI_2 (10 mol%) as additive in DCB at 130 °C for 24 hours under atmospheric air (Table 1, entry 5).

Table 1 Optimization of the Reaction Conditions[a]



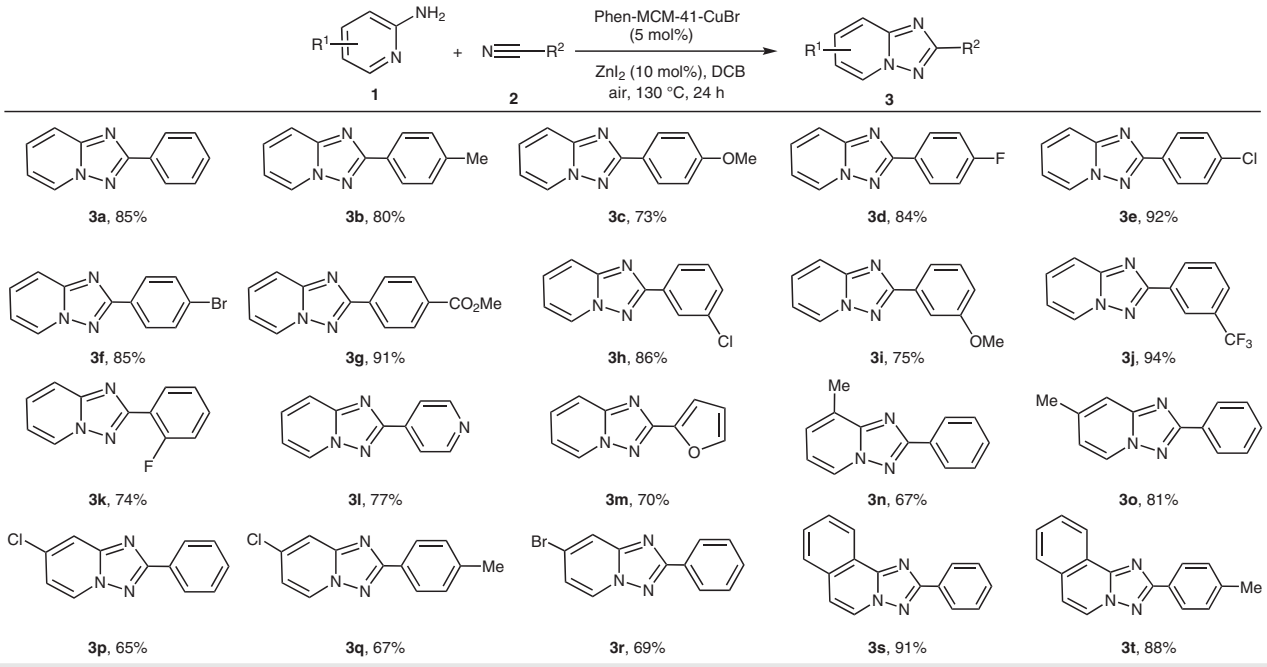
Entry	Copper catalyst (mol%)	Solvent	Additive (10 mol%)	Yield (%)[b]
1	**A** (5)	DCB	–	38
2	**A** (5)	DCB	ZnI_2	81
3	**A** (5)	DCB	$ZnBr_2$	47
4	**A** (5)	DCB	$ZnCl_2$	39
5	**B** (5)	DCB	ZnI_2	85
6	**C** (5)	DCB	ZnI_2	69
7	**D** (5)	DCB	ZnI_2	73
8	**E** (5)	DCB	ZnI_2	77
9	**F** (5)	DCB	ZnI_2	79
10	**B** (5)	toluene	ZnI_2	74
11	**B** (5)	DMSO	ZnI_2	40
12	**B** (5)	DMF	ZnI_2	32
13	–	DCB	ZnI_2	0
14	CuBr/Phen (5)	DCB	ZnI_2	81
15	CuBr/L (5)	DCB	ZnI_2	78
16[c]	**B** (2.5)	DCB	ZnI_2	67
17[d]	**B** (10)	DCB	ZnI_2	86

[a] Reaction conditions: 2-aminopyridine (0.6 mmol), benzonitrile (0.5 mmol), solvent (1.5 mL), under atmospheric air. L = 1-(1,10-phenanthrolin-5-yl)-3-(3-(triethoxysilyl)propyl)urea.
[b] Isolated yield.
[c] For 36 h.
[d] For 15 h.

With the optimum reaction conditions in hand, we next investigated the scope of the heterogeneous copper(I)-catalyzed synthesis of 1,2,4-triazolo[1,5-*a*]pyridines; the results are listed in Scheme 3. The cascade reactions of various *para*-substituted benzonitriles **2b–g** bearing either electron-donating or electron-withdrawing groups with 2-aminopyridine **1a** proceeded smoothly under the optimized conditions to provide the corresponding 1,2,4-triazolo[1,5-*a*]pyridine derivatives **3b–g** in 73–92% yields. These results indicate that the electronic nature of the substituents on the aromatic ring of the benzonitrile substrate has limited influence on this heterogeneous copper-catalyzed cascade reaction. But the reactivity of electron-deficient benzonitriles was higher than that of electron-rich derivatives, and 4-methoxybenzonitrile **2c** with a strong electron-donating group gave the desired product **3c** in only 73% yield. The *meta*-substituted benzonitriles **2h–j** were also suitable substrates and produced the expected products **3h–j** in 75–94% yields, but electron-rich 3-methoxybenzonitrile **2i** displayed lower reactivity and furnished **3i** in 75% yield. The sterically hindered 2-fluorobenzonitrile **2k** also exhibited a lower reactivity and gave the desired product **3k** in only 74% yield. In addition to aryl nitriles, heteroaryl nitriles such as 4-cyanopyridine **2l** and 2-cyanofuran **2m** were also compatible with the standard conditions and afforded the target products **3l** and **3m**, respectively, in good yields. However, when aliphatic nitriles such as acetonitrile or benzyl cyanide were used as substrates, the reaction did not work.

We next examined the substrate scope of 2-aminopyridines. The reaction of 2-amino-3-methylpyridine (**1b**) with benzonitrile **2a** gave 8-methyl-2-phenyl[1,2,4]triazolo[1,5-*a*]pyridine (**3n**) in somewhat reduced yield (67%) due to the steric hindrance. However, 2-amino-4-methylpyridine (**1c**) displayed good reactivity and the reaction with **2a** provided the corresponding 7-methyl-2-phenyl[1,2,4]triazolo[1,5-*a*]pyridine (**3o**) in 81% yield. In addition, halo-substituted 2-aminopyridines such as 2-amino-4-chloropyridine (**1d**) and 2-amino-4-bromopyridine (**1e**) also reacted well in this transformation and generated the corresponding halo-substituted 1,2,4-triazolo[1,5-*a*]pyridines **3p–r** in 65–69% yields. The lower yields probably reflect lower nucleophilicity of 2-aminopyridines **1d** and **1e** because of the electron-withdrawing nature of halogen. Notably, 1-aminoisoquinoline **1f** was also compatible with the standard conditions and the reaction with benzonitrile furnished 2-phenyl-[1,2,4]triazolo[5,1-*a*]isoquinoline (**3s**), which is known as a potent nonhormonal antifertility agent,[9b] in 91% yield. The reaction also worked well with 4-methylbenzonitrile **2b** and gave the target product **3t** in 88% yield. The present method thus provides a novel, highly efficient and practical procedure for the construction of triazoloheterocycles from readily available starting materials.

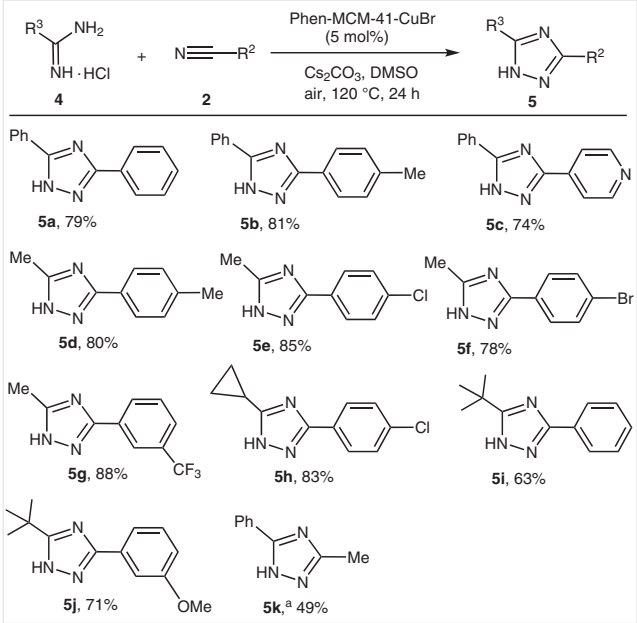
The efficiency of the heterogeneous copper(I)-catalyzed cascade addition-oxidative coupling process for triazoloheterocycles prompted us to explore the construction of 1*H*-1,2,4-triazoles from amidines and nitriles. In contrast to the preparation of 1,2,4-triazolo[1,5-*a*]pyridines, the use of ZnI_2 in DCB proved to be unsuitable for the preparation of 1*H*-1,2,4-triazoles. To our delight, the addition of Cs_2CO_3 in DMSO as the solvent resulted in the successful generation of the corresponding 1*H*-1,2,4-triazoles from amidines **4** and nitriles **2** (Scheme 4). The reactions of benzamidine **4a**



Scheme 3 Heterogeneous copper(I)-catalyzed synthesis of 1,2,4-triazolo[1,5-*a*]pyridines. *Reagents and conditions*: **1** (0.6 mmol), **2** (0.5 mmol), ZnI_2 (0.05 mmol), Phen-MCM-41-CuBr (5 mol%), DCB (1.5 mL), at 130 °C for 24 h under atmospheric air. Isolated yields are given.

with benzonitriles **2a** or **2b** afforded 1*H*-1,2,4-triazoles **5a** and **5b** in good yields. The reaction also worked well with a heteroaryl nitrile, 4-cyanopyridine **2l**, and gave the target product **5c** in 74% yield. In terms of amidines, not only aryl amidines but also primary, secondary, and tertiary alkyl amidines could be employed to synthesize 1*H*-1,2,4-triazoles. For example, the reactions of acetimidamide **4b** with electron-rich or electron-deficient benzonitriles **2b**, **2e**, **2f**, and **2j** proceeded smoothly to give the corresponding 1*H*-1,2,4-triazoles **5d–g** in 78–88% yields. Cyclopropanecarboximidamide **4c** displayed a similar reactivity to acetimidamide **4b** and the reaction with **2e** afforded the corresponding 5-cyclopropyl-substituted triazole **5h** in 83% yield. Pivalimidamide **4d** also reacted well in this transformation, thus giving the corresponding 5-(*tert*-butyl)-substituted triazoles **5i** and **5j** in good yields. Aliphatic nitriles could also be employed as substrates, but the reactivity was clearly lower than with aromatic nitriles. For example, the reaction of benzamidine **4a** with acetonitrile afforded the target product **5k** in only 49% yield.

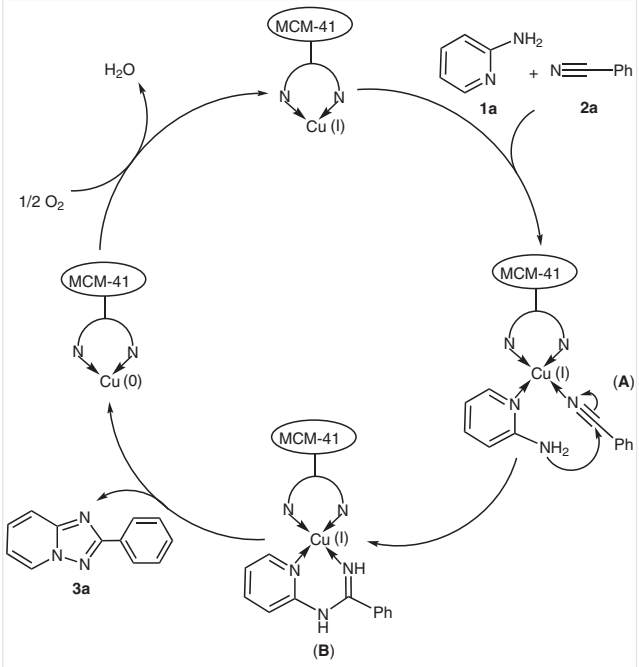
To determine whether the observed activity is derived from the Phen-MCM-41-CuBr catalyst or leached copper species in solution, the heterogeneity of Phen-MCM-41-CuBr was tested by hot filtration.[23] For this, the reaction of benzamidine **4a** with benzonitrile **2a** was carried out for 5 hours to obtain an approximately 30% conversion of **2a**. The catalyst was then removed by filtration of the reaction mixture at 120 °C and the catalyst-free filtrate was allowed to react further at 120 °C for 20 hours. In this case, no increase



Scheme 4 Heterogeneous copper(I)-catalyzed synthesis of 1*H*-1,2,4-triazoles. *Reagents and conditions*: **4** (0.75 mmol), **2** (0.5 mmol), Cs_2CO_3 (1.5 mmol), Phen-MCM-41-CuBr (5 mol%), DMSO (1.5 mL), at 120 °C for 24 h under atmospheric air. Isolated yield are given. [a] MeCN/DMSO (1:3) was used as the solvent.

in conversion of **2a** was observed, indicating that leached copper species from Phen-MCM-41-CuBr (if any) are not responsible for the observed conversion. Furthermore, analysis on the filtered solution by ICP-AES indicated that no Cu metal was detected. These results demonstrated that the catalyst was stable during the cascade cyclization reaction and that this procedure catalyzed by Phen-MCM-41-CuBr is unambiguously heterogeneous in nature.

A plausible mechanism for the heterogeneous copper(I)-catalyzed synthesis of triazole derivatives is shown in Scheme 5.[9b,f,g] First, nucleophilic attack of 2-aminopyridine **1a** on nitrile **2a** promoted by the Phen-MCM-41-CuBr complex occurs by forming an MCM-41-anchored four-nitrogen coordinated copper(I) complex intermediate **A**. The latter intermediate might provide an MCM-41-anchored cyclic copper(I) complex intermediate **B** after amino attacks the carbon of cyano and subsequent proton-transfer process. Next, intermediate **B** undergoes a copper-induced intramolecular oxidative cyclization to produce the desired triazolopyridine **3a** and reduced copper species [Phen-MCM-41-Cu(0)]. Finally, the reduced copper species is oxidized by molecular oxygen of air to regenerate Phen-MCM-41-CuBr and complete the catalytic cycle. The mechanism for producing the 1,2,4-triazoles **5** from amidines **4** and nitriles **2** might resemble that shown in Scheme 5.



Scheme 5 Plausible mechanism for the heterogeneous copper(I)-catalyzed synthesis of triazole derivatives

The lifetime of the catalyst and its level of reusability are important factors for the practical application of a heterogeneous catalytic system. Under the standard reaction conditions, the stability and recyclability of Phen-MCM-41-CuBr was evaluated in the reaction of 2-aminopyridine (**1a**) with 3-(trifluoromethyl)benzonitrile (**2j**); the results are illustrated in Figure 1. After completion of the first reaction, the reaction mixture was diluted with ethyl acetate. Filtration of the reaction mixture followed by washing of the resulting solid with water and acetone allowed the easy recovery of the Phen-MCM-41-CuBr catalyst. The recovered copper catalyst was used in the next run of the same reaction process and could be recycled up to seven times with almost consistent activity. In addition, ICP-AES analysis was performed on the recovered catalyst after eight consecutive runs, the copper content was found to be 0.69 mmol·g^{-1}, which was almost the same copper content as that of the fresh Phen-MCM-41-CuBr. In our opinion, the excellent catalytic behavior of Phen-MCM-41-CuBr should be attributed to the efficient site isolation, to the optimal dispersion of the active sites on the inner channel walls, and to strong interaction between bidentate 1,10-phenanthroline ligand and the copper center anchored on the MCM-41.

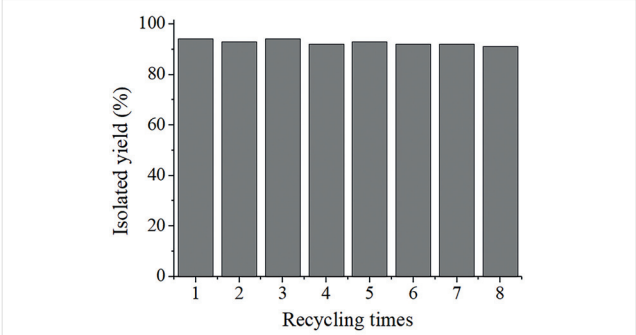


Figure 1 Recycle of heterogeneous copper catalyst

In conclusion, we have developed a general, efficient and practical method for the synthesis of 1,2,4-triazole derivatives through the heterogeneous copper(I)-catalyzed cascade addition-oxidative cyclization reaction of nitriles with 2-aminopyridines or amidines by using molecular oxygen (air at 1 atm) as the oxidant, which produces water as the sole byproduct. The reactions generated a wide variety of 1,2,4-triazoloheterocycles and 1*H*-1,2,4-triazoles in mostly good to excellent yields and were applicable to various nitriles and a wide range of 2-aminopyridines or amidines. Furthermore, the present method offers the advantages of recyclability of the copper catalyst with consistent activity, and the copper catalyst can be easily recovered by a simple filtration and recycled up to eight times, thereby making this approach economically and environmentally more acceptable.

All chemicals were reagent grade and used as purchased. All solvents were dried and distilled prior to use. Phen-MCM-41-CuCl [**A**], Phen-MCM-41-CuBr [**B**], Phen-MCM-41-CuI [**C**], Phen-MCM-41-$CuCl_2$ [**D**], Phen-MCM-41-$CuBr_2$ [**E**], and Phen-MCM-41-$Cu(OAc)_2$ [**F**] were pre-

pared according to our previous procedure,[20b] the copper contents were determined to be 0.72, 0.70, 0.73, 0.67, 0.71, and 0.69 mmol·g^{-1}, respectively. The products were purified by flash chromatography on silica gel. Mixtures of EtOAc and hexane was generally used as eluent. ^{1}H NMR spectra were recorded with a Bruker Avance 400 MHz spectrometer with TMS as internal standard in $CDCl_3$, CD_3OD or DMSO-d_6 as solvent. ^{13}C NMR spectra (100 MHz) were recorded with a Bruker Avance 400 MHz spectrometer in $CDCl_3$, CD_3OD or DMSO-d_6 as solvent. Melting points were determined without correction. Copper content was determined with an inductively coupled plasma atom emission Atomscan 16 (ICP-AES, TJA Corporation). HRMS spectra were recorded with a Q-Tof spectrometer with micromass MS software using electrospray ionization (ESI).

Heterogeneous Copper-Catalyzed Synthesis of 1,2,4-Triazolopyridines 3a–t; General Procedure

A 5 mL reaction tube was charged with Phen-MCM-41-CuBr (36 mg, 0.025 mmol), 2-aminopyridine **1** (0.6 mmol), nitrile **2** (0.5 mmol), ZnI_2 (16 mg, 0.05 mmol), and 1,2-dichlorobenzene (1.5 mL) under an air atmosphere. The reaction tube was sealed and placed in an oil bath at r.t. The reaction mixture was stirred at 130 °C for 24 h. After cooling to r.t., the reaction mixture was diluted with EtOAc (10 mL) and filtered. The supported copper catalyst was washed with water (2 × 5 mL) and acetone (2 × 5 mL), and reused in the next run. The filtrate was concentrated in vacuo and the residue was purified by flash column chromatography on silica gel (hexane/EtOAc, 3:2) to provide the desired product **3**.

2-Phenyl[1,2,4]triazolo[1,5-*a*]pyridine (3a)[7g]

Yield: 83.1 mg (85%); white solid; mp 134–135 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.59 (d, *J* = 6.8 Hz, 1 H), 8.31–8.28 (m, 2 H), 7.75 (d, *J* = 8.8 Hz, 1 H), 7.55–7.46 (m, 4 H), 7.00–6.96 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.2, 151.7, 130.8, 130.1, 129.5, 128.7, 128.3, 127.3, 116.4, 113.6.

2-(*p*-Tolyl)-[1,2,4]triazolo[1,5-*a*]pyridine (3b)[7f]

Yield: 83.4 mg (80%); white solid; mp 167–168 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.57 (d, *J* = 6.8 Hz, 1 H), 8.18 (d, *J* = 8.0 Hz, 2 H), 7.73 (d, *J* = 8.8 Hz, 1 H), 7.47 (t, *J* = 8.0 Hz, 1 H), 7.30 (d, *J* = 8.0 Hz, 2 H), 6.97 (t, *J* = 7.0 Hz, 1 H), 2.42 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.3, 151.7, 140.2, 129.4, 129.3, 128.3, 128.0, 127.3, 116.3, 113.4, 21.5.

2-(4-Methoxyphenyl)-[1,2,4]triazolo[1,5-*a*]pyridine (3c)[9b]

Yield: 82.2 mg (73%); white solid; mp 134–135 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.57 (d, *J* = 6.8 Hz, 1 H), 8.23 (dd, *J* = 6.8, 2.0 Hz, 2 H), 7.72 (d, *J* = 9.2 Hz, 1 H), 7.50–7.46 (m, 1 H), 7.03–6.95 (m, 3 H), 3.88 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.2, 161.3, 151.7, 129.4, 128.8, 128.2, 123.4, 116.2, 114.1, 113.3, 55.3.

2-(4-Fluorophenyl)-[1,2,4]triazolo[1,5-*a*]pyridine (3d)[7g]

Yield: 89.5 mg (84%); white solid; mp 173–174 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.56 (d, *J* = 6.8 Hz, 1 H), 8.27 (dd, *J* = 8.4, 1.6 Hz, 2 H), 7.72 (d, *J* = 8.8 Hz, 1 H), 7.48 (t, *J* = 8.0 Hz, 1 H), 7.17 (t, *J* = 8.6 Hz, 2 H), 6.97 (t, *J* = 6.8 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.1 (d, $^1J_{C-F}$ = 248.0 Hz), 163.3, 151.7, 129.5, 129.3 (d, $^3J_{C-F}$ = 8.4 Hz), 128.3, 127.1, 116.3, 115.7 (d, $^2J_{C-F}$ = 21.7 Hz), 113.6.

2-(4-Chlorophenyl)-[1,2,4]triazolo[1,5-*a*]pyridine (3e)[7g]

Yield: 105.6 mg (92%); white solid; mp 220–221 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.59 (d, *J* = 6.8 Hz, 1 H), 8.23 (d, *J* = 8.4 Hz, 2 H), 7.75 (d, *J* = 9.2 Hz, 1 H), 7.53 (t, *J* = 8.0 Hz, 1 H), 7.47 (d, *J* = 8.8 Hz, 2 H), 7.03 (t, *J* = 6.8 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.3, 151.7, 136.1, 129.7, 129.4, 129.0, 128.6, 128.4, 116.5, 113.8.

2-(4-Bromophenyl)-[1,2,4]triazolo[1,5-*a*]pyridine (3f)[7g]

Yield: 116.5 mg (85%); white solid; mp 229–230 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.58 (d, *J* = 6.0 Hz, 1 H), 8.16 (d, *J* = 7.6 Hz, 2 H), 7.75 (d, *J* = 8.4 Hz, 1 H), 7.63 (d, *J* = 8.0 Hz, 2 H), 7.52 (t, *J* = 7.4 Hz, 1 H), 7.02 (t, *J* = 6.0 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.3, 151.7, 131.9, 129.8, 129.7, 128.9, 128.4, 124.5, 116.5, 113.8.

Methyl 4-([1,2,4]Triazolo[1,5-*a*]pyridin-2-yl)benzoate (3g)

Yield: 115.2 mg (91%); white solid; mp 184–185 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.62 (d, *J* = 6.8 Hz, 1 H), 8.37 (d, *J* = 8.0 Hz, 2 H), 8.17 (d, *J* = 8.0 Hz, 2 H), 7.78 (d, *J* = 8.8 Hz, 1 H), 7.54 (t, *J* = 7.8 Hz, 1 H), 7.05 (t, *J* = 6.8 Hz, 1 H), 3.95 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.8, 163.2, 151.8, 135.0, 131.4, 130.0, 129.8, 128.4, 127.2, 116.7, 114.0, 52.2.

HRMS (ESI): *m*/*z* $[M]^+$ calcd for $C_{14}H_{11}N_3O_2$: 253.0851; found: 253.0847.

2-(3-Chlorophenyl)-[1,2,4]triazolo[1,5-*a*]pyridine (3h)[7g]

Yield: 98.7 mg (86%); white solid; mp 177–178 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.60 (d, *J* = 6.8 Hz, 1 H), 8.30 (s, 1 H), 8.19–8.15 (m, 1 H), 7.76 (d, *J* = 9.2 Hz, 1 H), 7.55–7.50 (m, 1 H), 7.45–7.42 (m, 2 H), 7.05–7.01 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.0, 151.7, 134.8, 132.6, 130.1, 130.0, 129.7, 128.4, 127.5, 125.4, 116.6, 113.9.

2-(3-Methoxyphenyl)-[1,2,4]triazolo[1,5-*a*]pyridine (3i)[7g]

Yield: 84.5 mg (75%); white solid; mp 106–108 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.57 (d, *J* = 6.4 Hz, 1 H), 7.89 (d, *J* = 7.2 Hz, 1 H), 7.84 (s, 1 H), 7.74 (d, *J* = 8.8 Hz, 1 H), 7.47 (t, *J* = 7.6 Hz, 1 H), 7.40 (t, *J* = 7.8 Hz, 1 H), 7.01 (d, *J* = 7.6 Hz, 1 H), 6.96 (t, *J* = 6.4 Hz, 1 H), 3.91 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.1, 159.9, 151.6, 132.1, 129.7, 129.5, 128.3, 119.8, 116.8, 116.4, 113.6, 111.8, 55.4.

2-(3-(Trifluoromethyl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridine (3j)[9b]

Yield: 123.7 mg (94%); white solid; mp 164–165 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.61 (d, *J* = 6.8 Hz, 1 H), 8.58 (s, 1 H), 8.48 (d, *J* = 8.0 Hz, 1 H), 7.78 (d, *J* = 8.8 Hz, 1 H), 7.72 (d, *J* = 8.0 Hz, 1 H), 7.62 (t, *J* = 7.8 Hz, 1 H), 7.57–7.52 (m, 1 H), 7.05 (t, *J* = 7.0 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.9, 151.8, 131.7, 131.3 (q, $^2J_{C-F}$ = 32.4 Hz), 130.4, 129.9, 129.2, 128.4, 126.6 (q, $^3J_{C-F}$ = 3.6 Hz), 124.3 (q, $^3J_{C-F}$ = 3.9 Hz), 124.0 (q, $^1J_{C-F}$ = 270.8 Hz), 116.6, 114.0.

2-(2-Fluorophenyl)-[1,2,4]triazolo[1,5-*a*]pyridine (3k)[9b]

Yield: 78.9 mg (74%); white solid; mp 171–172 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.67 (d, *J* = 6.8 Hz, 1 H), 8.26 (td, *J* = 7.6, 1.6 Hz, 1 H), 7.80 (d, *J* = 9.2 Hz, 1 H), 7.56–7.51 (m, 1 H), 7.48–7.43 (m, 1 H), 7.32–7.22 (m, 2 H), 7.06–7.01 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.8 (d, $^1J_{C-F}$ = 257.3 Hz), 160.8 (d, $^3J_{C-F}$ = 4.9 Hz), 151.1, 131.5 (d, $^2J_{C-F}$ = 8.5 Hz), 131.0 (d, $^3J_{C-F}$ = 2.6 Hz), 129.7, 128.5, 124.3 (d, $^3J_{C-F}$ = 3.6 Hz), 118.9 (d, $^2J_{C-F}$ = 11.1 Hz), 116.8, 116.6, 113.8.

2-(Pyridin-4-yl)-[1,2,4]triazolo[1,5-*a*]pyridine (3l)[7g]

Yield: 75.5 mg (77%); white solid; mp 190–192 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.77 (d, *J* = 5.6 Hz, 2 H), 8.63–8.60 (m, 1 H), 8.14 (d, *J* = 5.6 Hz, 2 H), 7.81–7.78 (m, 1 H), 7.58–7.53 (m, 1 H), 7.07 (t, *J* = 6.8 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.9, 151.7, 150.4, 138.3, 130.0, 128.5, 121.3, 116.8, 114.4.

2-(Furan-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridine (3m)

Yield: 64.8 mg (70%); white solid; mp 126–127 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.58 (d, *J* = 6.8 Hz, 1 H), 7.72 (d, *J* = 8.8 Hz, 1 H), 7.62 (d, *J* = 1.6 Hz, 1 H), 7.53–7.48 (m, 1 H), 7.21–7.19 (m, 1 H), 7.02–6.97 (m, 1 H), 6.59–6.57 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.0, 151.3, 146.2, 144.1, 129.9, 128.4, 116.3, 113.8, 111.7, 111.3.

HRMS (ESI): *m*/*z* $[M]^+$ calcd for $C_{10}H_7N_3O$: 185.0589; found: 185.0587.

8-Methyl-2-phenyl[1,2,4]triazolo[1,5-*a*]pyridine (3n)[24]

Yield: 70.1 mg (67%); white solid; mp 100–101 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.39 (d, *J* = 6.4 Hz, 1 H), 8.32–8.28 (m, 2 H), 7.51–7.41 (m, 3 H), 7.17–7.15 (m, 1 H), 6.79 (t, *J* = 7.0 Hz, 1 H), 2.64 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.6, 152.1, 131.1, 129.9, 128.6, 128.1, 127.4, 127.0, 125.8, 113.4, 17.0.

7-Methyl-2-phenyl[1,2,4]triazolo[1,5-*a*]pyridine (3o)[24]

Yield: 84.7 mg (81%); white solid; mp 139–140 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.45 (d, *J* = 6.8 Hz, 1 H), 8.27 (d, *J* = 7.6 Hz, 2 H), 7.52–7.43 (m, 4 H), 6.82 (d, *J* = 6.8 Hz, 1 H), 2.48 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.1, 151.9, 141.0, 130.9, 130.0, 128.7, 127.3, 116.1, 115.0, 21.6.

7-Chloro-2-phenyl[1,2,4]triazolo[1,5-*a*]pyridine (3p)[9b]

Yield: 74.6 mg (65%); white solid; mp 189–190 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.48 (d, *J* = 7.2 Hz, 1 H), 8.27–8.23 (m, 2 H), 7.73 (d, *J* = 2.0 Hz, 1 H), 7.52–7.45 (m, 3 H), 6.96 (dd, *J* = 7.2, 2.0 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.3, 151.9, 136.2, 130.4, 128.8, 128.4, 127.4, 115.5, 115.1.

7-Chloro-2-(*p*-tolyl)-[1,2,4]triazolo[1,5-*a*]pyridine (3q)

Yield: 81.6 mg (67%); white solid; mp 217 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.45 (dd, *J* = 7.2, 0.4 Hz, 1 H), 8.13 (dd, *J* = 6.4, 1.6 Hz, 2 H), 7.70 (d, *J* = 1.6 Hz, 1 H), 7.29 (d, *J* = 8.0 Hz, 2 H), 6.93 (dd, *J* = 7.2, 2.4 Hz, 1 H), 2.41 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.4, 151.8, 140.6, 136.0, 129.5, 128.4, 127.5, 127.3, 115.3, 114.9, 21.5.

HRMS (ESI): *m*/*z* $[M]^+$ calcd for $C_{13}H_{10}ClN_3$: 243.0563; found: 243.0574.

7-Bromo-2-phenyl[1,2,4]triazolo[1,5-*a*]pyridine (3r)

Yield: 94.5 mg (69%); white solid; mp 187–188 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.44 (d, *J* = 7.2 Hz, 1 H), 8.28–8.23 (m, 2 H), 7.93 (d, *J* = 1.6 Hz, 1 H), 7.51–7.47 (m, 3 H), 7.10 (dd, *J* = 7.2, 2.0 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.1, 152.2, 130.4, 128.8, 128.5, 127.4, 123.6, 118.8, 117.6.

HRMS (ESI): *m*/*z* $[M]^+$ calcd for $C_{12}H_8BrN_3$: 272.9902; found: 272.9905.

2-Phenyl[1,2,4]triazolo[5,1-*a*]isoquinoline (3s)[9b]

Yield: 111.6 mg (91%); white solid; mp 152–153 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.72–8.68 (m, 1 H), 8.37–8.31 (m, 3 H), 7.81–7.78 (m, 1 H), 7.72–7.67 (m, 2 H), 7.52–7.44 (m, 3 H), 7.21 (d, *J* = 7.2 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.3, 150.3, 131.4, 131.1, 129.9, 129.8, 128.7, 128.4, 127.2, 124.6, 124.4, 122.3, 114.0.

2-(*p*-Tolyl)-[1,2,4]triazolo[5,1-*a*]isoquinoline (3t)

Yield: 114.1 mg (88%); white solid; mp 198 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.72–8.69 (m, 1 H), 8.33 (d, *J* = 7.2 Hz, 1 H), 8.23 (d, *J* = 8.4 Hz, 2 H), 7.83–7.78 (m, 1 H), 7.72–7.67 (m, 2 H), 7.32 (d, *J* = 7.6 Hz, 2 H), 7.21 (d, *J* = 7.2 Hz, 1 H), 2.43 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.4, 150.2, 139.9, 131.4, 129.8, 129.4, 128.3, 128.2, 127.2, 127.1, 124.6, 124.5, 122.3, 113.8, 21.5.

HRMS (ESI): *m*/*z* $[M]^+$ calcd for $C_{17}H_{13}N_3$: 259.1109; found: 259.1106.

Heterogeneous Copper-Catalyzed Synthesis of 1*H*-1,2,4-Triazoles 5a–j; General Procedure

A 5 mL reaction tube was charged with Phen-MCM-41-CuBr (36 mg, 0.025 mmol), amidine **4** (0.75 mmol), nitrile **2** (0.5 mmol), Cs_2CO_3 (489 mg, 1.5 mmol), and DMSO (1.5 mL) under an air atmosphere. The reaction tube was sealed and placed in an oil bath at r.t. The reaction mixture was stirred at 120 °C for 24 h. After cooling to r.t., the reaction mixture was diluted with EtOAc (10 mL) and filtered. The supported copper catalyst was washed with water (2 × 5 mL) and acetone (2 × 5 mL), and reused in the next run. The filtrate was washed with 5% aqueous $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$ and concentrated in vacuo and the residue was purified by flash column chromatography on silica gel (hexane/EtOAc, 3:2) to provide the desired product **5**.

3,5-Diphenyl-1*H*-1,2,4-triazole (5a)[9f]

Yield: 87.4 mg (79%); white solid; mp 190–191 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.09–7.99 (m, 4 H), 7.49–7.38 (m, 6 H).

^{13}C NMR (100 MHz, CD_3OD): δ = 160.6, 131.1, 130.3, 130.0, 127.6.

5-Phenyl-3-(*p*-tolyl)-1*H*-1,2,4-triazole (5b)[9g]

Yield: 95.3 mg (81%); white solid; mp 189 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 14.44 (br, 1 H), 8.13–8.08 (m, 2 H), 8.02–7.96 (m, 2 H), 7.54–7.46 (m, 3 H), 7.37–7.32 (m, 2 H), 2.36 (s, 3 H).

^{13}C NMR (100 MHz, CD_3OD): δ = 159.4, 158.9, 140.1, 129.6, 129.2, 128.5, 126.2, 125.8, 20.1.

4-(5-Phenyl-1*H*-1,2,4-triazol-3-yl)pyridine (5c)[9b]

Yield: 82.2 mg (74%); white solid; mp 241–242 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.73 (d, *J* = 5.6 Hz, 2 H), 8.10 (d, *J* = 8.0 Hz, 2 H), 8.01 (d, *J* = 6.0 Hz, 2 H), 7.60–7.53 (m, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 167.4, 150.9, 137.7, 132.0, 130.7, 129.5, 129.1, 126.7, 120.6.

5-Methyl-3-*p*-tolyl-1*H*-1,2,4-triazole (5d)

Yield: 69.3 mg (80%); white solid; mp 192 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 13.60 (br, 1 H), 7.89 (d, *J* = 8.0 Hz, 2 H), 7.29–7.23 (m, 2 H), 2.40 (s, 3 H), 2.34 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 161.4, 153.8, 138.4, 129.6, 126.1, 21.3, 12.1.

HRMS (ESI): *m*/*z* $[M]^+$ calcd for $C_{10}H_{11}N_3$: 173.0953; found: 173.0948.

3-(4-Chlorophenyl)-5-methyl-1*H*-1,2,4-triazole (5e)[9b]

Yield: 82.3 mg (85%); white solid; mp 174–175 °C.

^{1}H NMR (400 MHz, CD_3OD): δ = 7.83 (d, *J* = 8.4 Hz, 2 H), 7.34 (d, *J* = 8.4 Hz, 2 H), 2.37 (s, 3 H).

^{13}C NMR (100 MHz, CD_3OD): δ = 159.0, 155.3, 135.0, 128.5, 127.4, 10.5.

3-(4-Bromophenyl)-5-methyl-1*H*-1,2,4-triazole (5f)[9b]

Yield: 92.8 mg (78%); white solid; mp 183–185 °C.

^{1}H NMR (400 MHz, CD_3OD): δ = 7.87 (d, *J* = 8.4 Hz, 2 H), 7.60 (d, *J* = 8.4 Hz, 2 H), 2.48 (s, 3 H).

^{13}C NMR (100 MHz, CD_3OD): δ = 159.4, 155.3, 131.6, 129.2, 127.6, 123.2, 10.5.

5-Methyl-3-(3-trifluoromethylphenyl)-1*H*-1,2,4-triazole (5g)[9b]

Yield: 99.9 mg (88%); white solid; mp 170–171 °C.

^{1}H NMR (400 MHz, CD_3OD): δ = 8.30 (s, 1 H), 8.24 (d, *J* = 7.6 Hz, 1 H), 7.71 (d, *J* = 8.0 Hz, 1 H), 7.65 (t, *J* = 7.6 Hz, 1 H), 2.51 (s, 3 H).

^{13}C NMR (100 MHz, CD_3OD): δ = 159.4, 155.2, 131.4, 130.8 (q, $^2J_{C-F}$ = 32.2 Hz), 129.3, 129.2, 125.5 (q, $^3J_{C-F}$ = 3.7 Hz), 124.1 (q, $^1J_{C-F}$ = 271.1 Hz), 122.5 (q, $^3J_{C-F}$ = 3.9 Hz), 10.3.

3-(4-Chlorophenyl)-5-cyclopropyl-1*H*-1,2,4-triazole (5h)[9b]

Yield: 91.2 mg (83%); white solid; mp 202–203 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 13.76 (br, 1 H), 7.95 (dd, *J* = 6.6, 1.8 Hz, 2 H), 7.50 (d, *J* = 8.4 Hz, 2 H), 2.13–2.01 (m, 1 H), 1.06–0.99 (m, 2 H), 0.98–0.92 (m, 2 H).

^{13}C NMR (100 MHz, CD_3OD): δ = 161.4, 135.0, 131.0, 128.8, 128.5, 127.5, 7.2, 6.9.

5-(*tert*-Butyl)-3-phenyl-1*H*-1,2,4-triazole (5i)[9b]

Yield: 63.4 mg (63%); white solid; mp 145–146 °C.

^{1}H NMR (400 MHz, CD_3OD): δ = 7.98 (d, *J* = 6.4 Hz, 2 H), 7.47–7.40 (m, 3 H), 1.42 (s, 9 H).

^{13}C NMR (100 MHz, CD_3OD): δ = 167.3, 159.8, 129.2, 128.5, 128.3, 126.2, 32.0, 28.2.

5-(*tert*-Butyl)-3-(3-methoxyphenyl)-1*H*-1,2,4-triazole (5j)[9b]

Yield: 82.1 mg (71%); colorless oil.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 13.65 (br, 1 H), 7.59 (d, *J* = 7.2 Hz, 1 H), 7.53–7.51 (m, 1 H), 7.39–7.34 (m, 1 H), 6.98–6.93 (m, 1 H), 3.82 (s, 3 H), 1.37 (s, 9 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 165.4, 160.6, 159.9, 133.6, 130.2, 118.7, 114.8, 111.3, 55.6, 32.2, 29.5.

3-Methyl-5-phenyl-1*H*-1,2,4-triazole (5k)[9b]

Yield: 58.5 mg (49%); white solid; mp 162–164 °C.

^{1}H NMR (400 MHz, CD_3OD): δ = 7.87–7.83 (m, 2 H), 7.37–7.31 (m, 3 H), 2.36 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.5, 156.0, 129.6, 128.8, 127.4, 126.4, 12.5.

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Supporting Information

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