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## Click Chemistry

## Alumina-Supported Copper Iodide: An Efficient and Recyclable Catalyst for Microwave-Assisted Synthesis of 1,4-Disubstituted 1,2,3-Triazoles via Three-Component Reaction in Water

Sandip G. Agalave,<sup>[a]</sup> Shrikant G. Pharande,<sup>[a]</sup> Swapna M. Gade,<sup>[b]</sup> and Vandana S. Pore<sup>\*[a]</sup>

**Abstract:** A one-pot procedure for the synthesis of 1,4-disubstituted 1,2,3-triazoles by a three-component reaction of allyl or benzyl halides, sodium azide, and terminal alkynes over a neutral alumina-supported copper iodide catalyst has been developed. The products were isolated by simple filtration followed by washing of the catalyst with acetone. The products were obtained in almost pure form in up to 98% yield (TON 495). The catalyst can be recycled for more than eight subsequent reactions. The halides are directly converted into triazoles via in situ formation of azides and thus han-

dling of hazardous azides can be avoided. The broad scope of this protocol is shown by the synthesis of a variety of diversely substituted 1,2,3-triazoles and also two-component azide-alkyne click reaction. The key features of this procedure are the use of water as a solvent, recyclability of the catalyst up to eight runs without appreciable loss of activity, and high yields of products. The catalyst has been fully characterized by FTIR, solid-state NMR and EDX spectroscopy, ESEM, TGA, and XRD.

## Introduction

The copper(I)-catalyzed 1,3-dipolar cycloaddition of azides and alkynes (CuAAC)<sup>[1]</sup> constitutes a substantial improvement over the classical Huisgen-type thermal 1,3-dipolar cycloaddition.<sup>[2]</sup> Homogeneous catalysts have a number of advantages such as high selectivity, better yield, and easy optimization of catalytic systems by modification of ligands and metals. This "Click reaction" has become the "gold standard" of click chemistry due to its reliability, specificity, and biocompatibility and has played a significant role as a rapid and versatile strategy for conjugating two molecular fragments under very mild reaction conditions. 1,2,3-Triazoles have received considerable interest because of their useful applications in several fields of synthesis, materials science, and medicinal chemistry.<sup>[3]</sup> Their application in labeling molecules of interest in complex biological samples without interference with any other chemical functionalities makes this reaction very attractive.<sup>[4]</sup> The use of microwave (MW) irradiation has been found to improve the efficiency of

the azide/alkyne click reaction.<sup>[5]</sup> Ultrasonication (US) has been used to promote the CuAAC reaction as well.<sup>[6]</sup>

Organic azides are toxic and hazardous in nature and, hence, their handling is very unsafe. Isolation and purification of certain alkyl azides prepared from corresponding alkyl halides is very difficult and problematic. Preparation of aryl azides from aromatic amines is not so straightforward. Thus a one-pot procedure involving the reaction of azides, generated in situ from the corresponding halides, and alkynes for the synthesis of triazoles is highly desirable. A number of such one-pot procedures catalyzed by various supported copper catalysts such as nanoferrite-glutathione-copper, CuFe<sub>2</sub>O<sub>4</sub>, Cu-Fe nanoparticles, Cu nanoparticles on activated carbon and alumina, CuSO<sub>4</sub>-cyclodextrin, Cu<sup>I</sup>/amino acids ionic liquids, Cu<sup>I</sup> in an ionic liquid-water system, montmorillonite supported Cu<sup>0</sup> nanoparticles, Cu<sup>II</sup> on nanosilica triazine dendrimer, etc. have been reported.<sup>[7]</sup> Recently there is a review article which summarizes important contributions of CuAAC-based multicomponent reactions and their applications in polymer science.<sup>[8]</sup>

Preparation of these catalysts is either tedious or they require longer reaction times. Formation of the undesired homocoupled product of the alkyne restricts the use of a Cu<sup>I</sup> salt in this reaction.<sup>[9]</sup> The other drawbacks of homogeneous copper salts are copper contamination in the product, and recovery and reuse of them. Removal of trace amounts of catalyst from the end product is essential since metal contamination is highly regulated, especially by the pharmaceutical industry. Even with the extensive and careful use of various techniques, such as distillation, chromatography, or extraction, removal of trace amounts of catalyst remains a challenge. To overcome these problems various supports such as polymers,<sup>[10]</sup> zeo-

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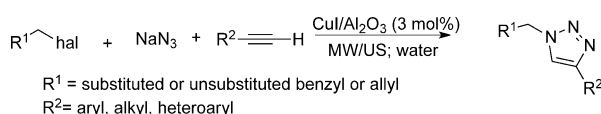
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lites,<sup>[11]</sup> activated carbon,<sup>[12]</sup> silica,<sup>[13]</sup> chitosan,<sup>[14]</sup> porous glass,<sup>[15]</sup> etc., to form the corresponding heterogeneous copper catalyst, have been used. There is a report on alumina-supported copper hydroxide for 1,3-dipolar cycloadditions of organic azides to terminal alkynes.<sup>[16]</sup> Recently Ranu and co-workers have used CuSO<sub>4</sub> on alumina under ball milling for one-pot synthesis of 1,2,3-triazoles in the absence of solvent or additive.<sup>[17]</sup> They obtained the best yield using 10 mol% of catalyst (400 mg) for the completion of the reaction for the representative reaction of benzyl bromide, sodium azide, and phenyl acetylene.

It is reported that in most of the copper-catalyzed cycloaddition reactions for the synthesis of 1,2,3-triazole, copper(II) is reduced with some reducing agents such as sodium ascorbate. In supported copper(II)-catalyzed reactions the copper(II) species is reduced to a copper(I) species in the pretreatment, which then acts as catalyst.<sup>[16]</sup> The degree of reduction of the copper(II) species increases with an increase in the pretreatment period.

We report here a neutral alumina-supported Cu<sup>I</sup> catalyst for the simple, one-pot, three-component reaction of benzyl halides/allyl bromides, sodium azide, and alkynes under microwave/ultrasonication conditions (Scheme 1). The catalyst is fully characterized by FTIR, solid-state NMR and energy dispersive X-ray (EDX) spectroscopy, environmental scanning electron microscopy (ESEM), thermogravimetric analysis (TGA), and x-ray diffraction (XRD).



**Scheme 1.** One-pot reaction in a microwave catalyzed by CuI on Al<sub>2</sub>O<sub>3</sub>.

The advantages of this catalyst over previous reports are that preparation is very easy and it can be prepared in very short time, the single desired product is formed, there is no copper contamination in the product, the catalyst can be recovered and reused for at least eight cycles without appreciable loss of activity, and water has been used as green solvent. The use of microwave conditions also lowers the reaction time considerably, the three-component protocol of this system obviates the necessity to isolate potentially explosive organic azides, and the catalyst can be used for the synthesis of highly active antifungal molecules by two-component azide-alkyne click reaction.

## Results and Discussion

Supported reagent neutral alumina-CuI was easily prepared from potassium iodide and copper sulfate. A freshly filtered solution of CuI (0.190 g, 1 mmol) was stirred rapidly with neutral alumina (1 g). Water (20 mL) was added to this stirred mixture over a period of 1 h and the reaction mixture was stirred at room temperature for 24 h, so as to slowly precipitate the CuI on to the alumina support. The supported catalyst was filtered

through sintered glass funnel and it was then washed several times with water, and ethanol. The catalyst was dried under vacuum at room temperature for 6 h. The copper content in the fresh catalyst was found to be 4.2% (16.916 mg g<sup>-1</sup>, as detected by inductively coupled plasma atomic emission spectroscopy, ICP).

To optimize the reaction conditions, various copper catalysts and two supports (silica and neutral alumina) were used for a representative reaction of benzyl bromide, sodium azide, and phenyl acetylene (Table 1). During this optimization study, CuI supported on neutral alumina was found to be very superior in terms of reaction rate, isolated yield, and selectivity.

**Table 1.** Screening of various copper catalysts for the click reaction.

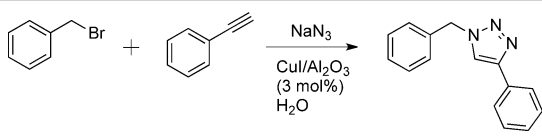
Entry	Catalyst	Microwave <sup>[a]</sup>		Ultrasonication <sup>[b]</sup>	
		t [min]	Yield [%]	t [min]	Yield [%]
1	alumina-CuI (30 mg)	6	98	15	96
2	alumina-CuSO <sub>4</sub> (30 mg)	16	86	30	50
3	SiO <sub>2</sub> -CuI (30 mg)	12	90	15	86
4	SiO <sub>2</sub> -CuSO <sub>4</sub> (30 mg)	40	85	45	80
5	Cu(0) (15 mg)	28	84	43	83
6	CuCl (15 mg)	34	86	45	82
7	Cu(OAc) <sub>2</sub> (22 mg)	27	83	48	80
8	CuSO <sub>4</sub> (10 mg)	50	30	45	80

[a] 100W, 70 °C, 0 psi; [b] 50 °C, 25 KHz.

By using this catalyst, the reaction was completed within six minutes under microwave irradiation and within 15 minutes under ultrasonication, as compared with the other catalysts as shown in Table 1. We used water as a green solvent for these reactions and found that the reaction gave high yields and regioselectivity. By using the best catalyst among all the catalysts mentioned in Table 1 (neutral alumina-supported CuI) to optimize the other reaction conditions, the reaction was carried out under microwave irradiation at 100W and 70 °C at 0 psi in an oil bath at 50 °C, under ultrasonication at 50 °C and 25 KHz, and also at room temperature under magnetic stirring (Table 2) for a representative reaction of benzyl bromide, sodium azide, and phenyl acetylene.

A series of experiments were carried out under varying catalyst loading and time. It was found that the best yield was obtained using 3 mol% of catalyst and six minutes under micro-

**Table 2.** Comparison of reaction conditions.

		
Entry	Conditions	t
1	MW, 100 W, 70 °C, 0 psi	6 min
2	oil bath 50 °C	5 h
3	ultrasonication 50 °C, 25 KHz	15 min
4	room temp	12 h

wave irradiation at 100W and 70 °C at 0 psi. It is important that the reaction did not proceed in the absence of catalyst.

In a typical experimental procedure, a mixture of benzyl bromide, phenyl acetylene, and sodium azide (1 mmol each) over a surface of neutral alumina-supported CuI-catalyst (3 mol %) in water was subjected to microwave irradiation (100 W, 70 °C at 0 PSI) for six minutes with turnover number (TON) 495 (moles of converted substrate (0.98)/moles of metal (0.00198)=494.94; for turnover frequency (TOF) (0.98/0.00198)/360 (six mins))=1.37 s<sup>-1</sup> (×3600=4949.49 h<sup>-1</sup>). After completion of the reaction (monitored by TLC) the reaction mixture was filtered and the catalyst was washed with acetone. The filtrate was concentrated and the product was crystallized from ethanol/water mixture giving 98% yield with turnover number 495.

A wide range of diversely substituted alkynes were reacted with a mixture of benzyl halides and sodium azide by this procedure to produce the corresponding 1,4-disubstituted-1,2,3-triazoles. The results are summarized in Table 3. The substitution on the phenyl ring of phenyl acetylenes or benzyl bromide did not have any appreciable influence on the outcome of the reaction (Table 3, entries 3, 4, 9–13). Alkynes such as propargyl alcohol (Table 3, entry 7) and prop-2-yn-1-ylcyclohexane (Table 3, entry 6) also participated in this reaction to provide the corresponding products. The reactions of allyl bromide furnished the desired 1,2,3-triazoles in relatively high yield (Table 3, entry 8 and 9) without any difficulty. In almost all cases, the reactions proceeded smoothly to completion within 6–15 minutes and the products were isolated in excellent yields and high purity. 1-Bromooctane was found to be less reactive among other halides used. In this case, a complex reaction mixture formed and the expected product could not be isolated. The reaction of unreactive alkynes such as 1-hexyne, 1-octyne, and cyclohexyl alkyne with benzyl bromide and sodium azide under the same reaction condition furnished a complex reaction mixture. Unfortunately, aromatic halides such as bromobenzene and chlorobenzene failed to undergo this one-pot reaction to produce the corresponding triazoles.

As an extension of three component procedure, the supported alumina-CuI catalyst system was applied to azide-alkyne click reaction (Table 3, entries 14–16) to obtain highly active antifungal compounds. By using this system a bis-β-lactam (Table 3, entry 14) was obtained in comparable yield to the earlier report, whereas compounds containing two 1,2,3-triazoles (Table 3, entries 15 and 16) were obtained in slightly higher yield than our earlier report.<sup>[18]</sup>

Copper is known to coordinate with 1,2,3-triazole, hence, we checked the copper content in the reaction product. No Cu metal was detected in the reaction solvent after completion of the reaction (ICP analysis). This confirms the fact that alumina provides enough binding sites on the surface to minimize deterioration and metal leaching, and facilitates efficient catalyst recycling. The catalyst was recovered by simple filtration through a sintered glass bed (G-4), washing with acetone, and then drying under vacuum for 2 h before reuse.

## Recyclability

The catalyst was recycled up to eight runs for the cycloaddition reaction without any appreciable loss of activity. After eight consecutive reactions, the recovered Al<sub>2</sub>O<sub>3</sub>-CuI was found to contain 3.8% (w/w) of Cu based on ICP analysis (Figure 1).

The heterogeneity of the catalyst was evaluated by Sheldon test.<sup>[19]</sup> The reaction between benzyl bromide and phenyl acetylene was carried out according to the procedure mentioned in the Table 3. The catalyst was removed after two minutes when the reaction was 55 % completed. The reaction was continued in the microwave oven without the catalyst for two minutes. It was found that reaction almost stopped (56% completion). At this stage the catalyst was reintroduced in the reaction mixture and the reaction was continued till completion of the reaction (98%, total eight minutes). This clearly shows the heterogeneous nature of the catalyst, which does not leach into the reaction mixture.

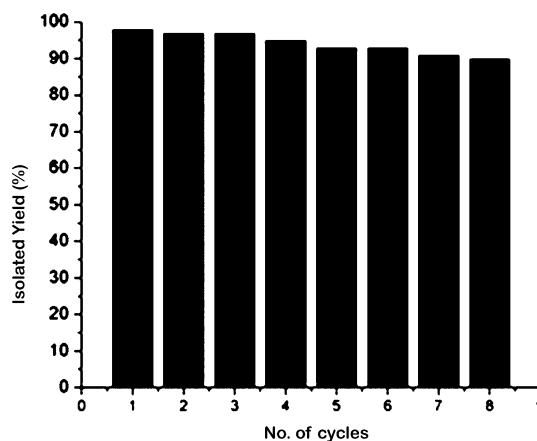


Figure 1. Recyclability chart.

## XRD

The XRD pattern of CuI/Al<sub>2</sub>O<sub>3</sub> is presented in Figure 2. The obtained XRD pattern contains the following diffraction peaks, which are correlated to hkl indices (Table 4). The XRD pattern of the catalyst has significant peaks of cuprite, aluminum oxide, and CuI phases present in the catalyst. Sharp peaks of copper iodide confirm the crystalline nature of the product. The diffraction features when compared with JCPDF files (Table 4) revealed that CuI is in cubic phase (83-1132).<sup>[20]</sup>

## Thermogravimetric Analysis

The thermal behavior of the CuI/Al<sub>2</sub>O<sub>3</sub> catalyst was investigated by TGA. As shown in Figure 3, the catalyst slowly loses weight at 100 °C (8.06%), which could be assigned to the loss of absorbed water from the surface of the sample. The second zone of weight loss was because of iodine loss from CuI supported on Al<sub>2</sub>O<sub>3</sub>. This weight loss (10.07%) is in the range of 300–576 °C.<sup>[19]</sup> Further thermal decomposition of the catalyst occurred between 576–800 °C, which may be due to the forma-

**Table 3.** CuI/Al<sub>2</sub>O<sub>3</sub>-catalyzed one-pot reaction of alkyl halides with terminal alkynes and sodium azide.



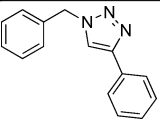


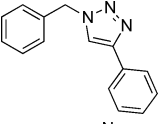

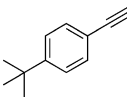
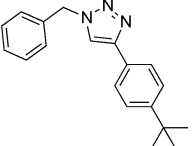

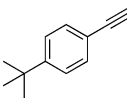
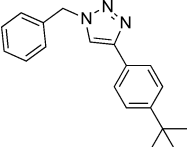


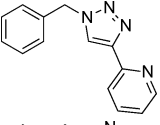

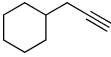
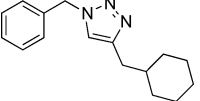


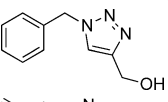


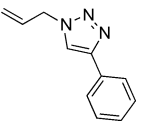

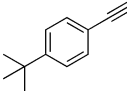
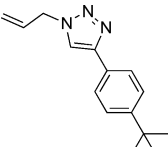


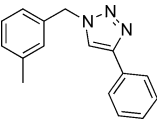

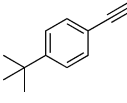
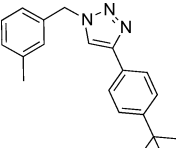


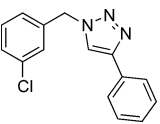
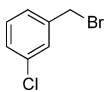
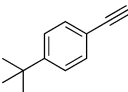
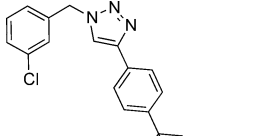
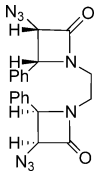
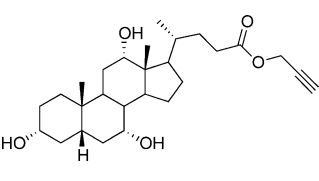
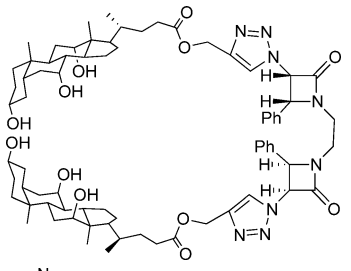
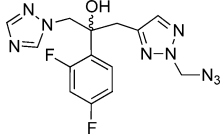

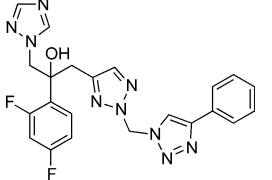
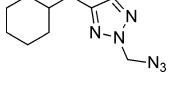
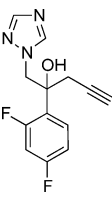
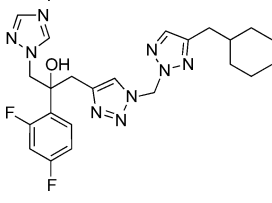
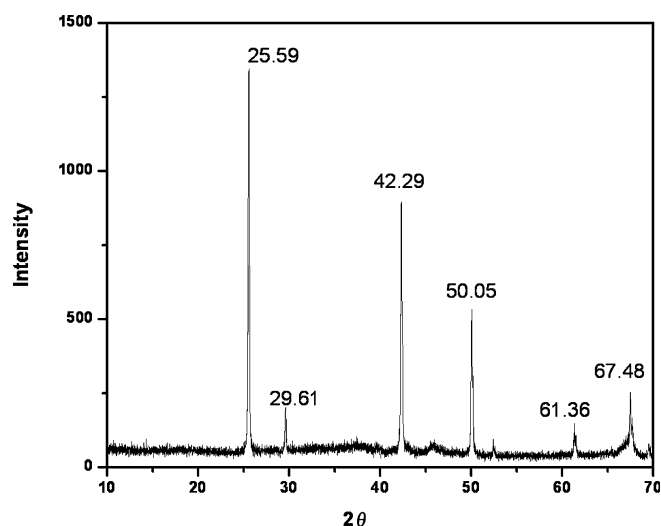
Entry	Halide	Alkyne	Product	t [min]	Yield <sup>[a]</sup> [%]	Ref <sup>[b]</sup>
1				6	98	[7a]
2				8	92	[7a]
3				7	96	[22a]
4				7	90	[23a]
5				7	95	[7a]
6				12	91	–
7				9	90	[7a]
8				7	92	[7a]
9				9	91	–
10				11	92	[23b]
11				11	95	–
12				10	94	[23c]

Table 3. (Continued)

Entry	Halide	Alkyne	Product	t [min]	Yield <sup>[a]</sup> [%]	Ref <sup>[b]</sup>
13				10	91	–
14 <sup>[c]</sup>				13	90	[18a]
15 <sup>[c]</sup>				11	70	[18b]
16 <sup>[c]</sup>				13	72	[18b]

[a] Isolated yield of pure product; [b] earlier reference of the corresponding product; [c] reaction conditions: DMF/H<sub>2</sub>O(4:1), catalyst (3 mol%).

Figure 2. XRD pattern of Cu/Al<sub>2</sub>O<sub>3</sub>.

tion of CuO/Al<sub>2</sub>O<sub>3</sub>. This TGA clearly indicates that the thermal stability of the Cu/Al<sub>2</sub>O<sub>3</sub> catalyst is good, which meets demands for potential applications in organic synthesis and catalysis.

Table 4. Diffraction features compared with JCPDF files.				
2θ	Matrix and morphology			JCPDF; reference
	Al <sub>2</sub> O <sub>3</sub>	Cu <sub>2</sub> O	CuI	
25.59	(012)	–	111	821468, 831132; [20]
29.61	–	(110)	200	782076, 831132; [20]
42.29	–	(200)	220	782076, 831132; [20]
50.05	–	–	311	851326, 831132; [20]
52.45	–	–	222	831132; [20]
61.36	–	(220)	400	782076, 831132; [20]
67.48	(512)	–	420	861410, 831132; [20]

## ESEM

The morphology of the neutral alumina-supported CuI catalyst was carried out by environmental scanning electron microscopy. The ESEM images of the samples were taken at an accelerating voltage of 15 kV. The morphology of the particles is very uniformly spherical (Figure 4).

The elemental composition of the catalyst was measured from the EDX spectrum associated with this ESEM by following the same experimental procedure. EDX analysis on various regions confirmed the presence of copper on the support, with

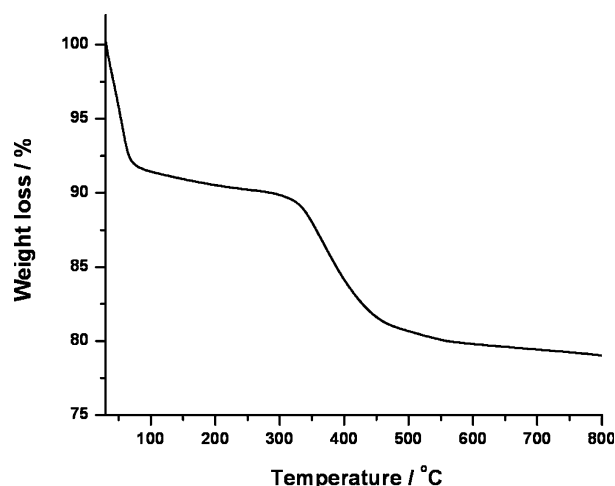


Figure 3. TGA curves of CuI/Al<sub>2</sub>O<sub>3</sub>.

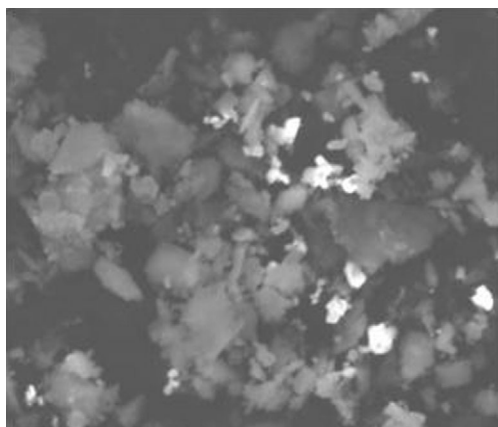


Figure 4. ESEM image of CuI/Al<sub>2</sub>O<sub>3</sub>.

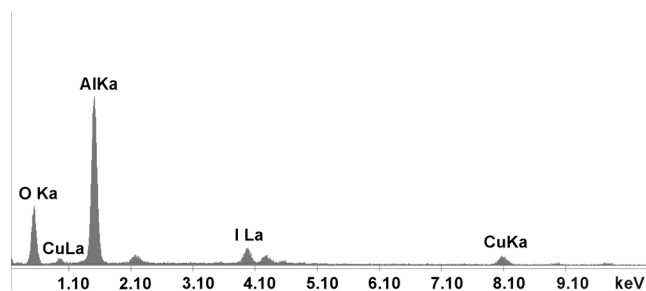


Figure 5. EDX spectra of CuI/Al<sub>2</sub>O<sub>3</sub>.

energy bands of 8.04 (Cu<sub>Kα</sub>) and 0.92 (Cu<sub>Kα</sub>) keV (L line, Figure 5).

#### FT-IR

The FT-IR spectrum of the copper iodide on alumina contains a strong broad peak between 3000–3500 cm<sup>-1</sup> due to O-H stretching vibrations.<sup>[20]</sup> The immobilization of copper iodide

on alumina causes a weak absorption band at around 743 cm<sup>-1</sup>. There is shift of CO absorption on the surface of catalyst from 1635.5 cm<sup>-1</sup> in neutral alumina to 1628 cm<sup>-1</sup> in the neutral alumina-supported CuI catalyst. The electron density around the carbonyl group decreases due to electron donation from the carbonyl group to Cu<sup>+</sup>. The FT-IR spectrum also has a characteristic peak at 610 cm<sup>-1</sup> due to Cu-I stretching vibration.

#### <sup>27</sup>Al MAS NMR

Figure 6 shows a <sup>27</sup>Al MAS NMR spectrum for the present alumina-supported CuI. The alumina has two resonances at δ = 74 and 14.5 ppm with several spinning side bands. The chemical shifts at δ = 74 and 14.5 ppm correspond to four- and six-coordinated aluminum, respectively. The area ratio of six- to four-coordinated aluminum was about 2, which is consistent with the corresponding value of a spinel-type of alumina such as γ-alumina.<sup>[21]</sup> The results indicate that the coordination number of the surface aluminum atoms was unchanged by the deposition of CuI.

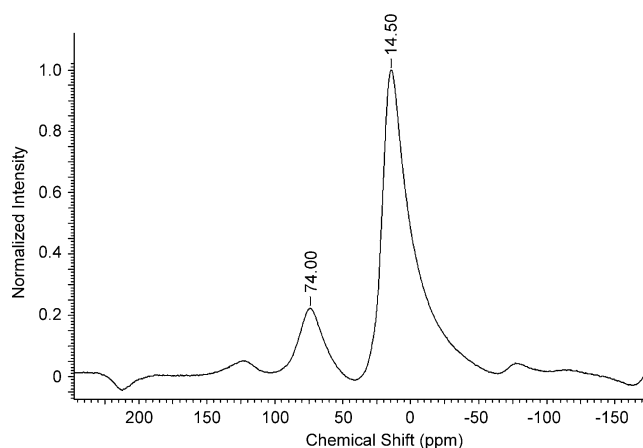


Figure 6. <sup>27</sup>Al MAS NMR spectrum of CuI/Al<sub>2</sub>O<sub>3</sub>.

## Conclusions

In conclusion, a neutral alumina-supported copper catalyst was prepared, fully characterized, and was used for the synthesis of 1,4-disubstituted 1,2,3-triazoles by a three-component reaction of allyl or benzyl halides, sodium azide, and terminal alkynes, and also for the synthesis of highly active antifungal molecules by two-component azide-alkyne click reaction. This simple, heterogeneous catalyst was reused with retention of its high catalytic activity for more than eight cycles using water as green solvent under microwave conditions. Isolation of the desired product by simple filtration in high yields (TON 495), without requiring column chromatography is an additional green attribute of this reaction. The three-component protocol of this system obviates the necessity to isolate potentially explosive organic azides.



## Experimental Section

All the liquid-state 1D NMR spectra ( $^1\text{H}$ ,  $^{13}\text{C}$  NMR) were recorded in  $\text{CDCl}_3$  on an AV-500 MHz Bruker NMR spectrometer. Microwave reactions were carried in a CEM Discover, model number 908010. The FTIR study was carried on a Shimadzu FTIR-8400 spectrophotometer. Scanning electron microscopy was performed on an environmental scanning electron microscope Quanta 200 3D by FEI. Powder X-ray diffraction was carried out on a PANalytical X'pert Pro dual goniometer diffractometer working under 40 kV and 30 mA. The radiation used was  $\text{Cu}_{\text{K}\alpha}$  (1.5418 Å) with a Ni filter, and the data collection was carried out using a flat holder in Bragg-Brentano geometry with a  $1^\circ$  slit at the source and receiving sides. An X'celerator solid-state detector with a scan speed of  $2^\circ \text{min}^{-1}$  was used in the  $2\theta$  range from  $10$  to  $70^\circ$ . HRMS were acquired on a Thermo Scientific Q exactive spectrometer. Thermogravimetric analysis was performed on a TGA-TA5000R instrument at a heating rate  $10^\circ \text{Cmin}^{-1}$  in a nitrogen atmosphere. All commercial reagents were distilled before use.

### Preparation of Cuprous Iodide on Neutral Alumina Catalyst:

The supported reagent neutral alumina-CuI was prepared from potassium iodide and copper sulfate as per the literature procedure.<sup>[22]</sup> CuI was prepared by reacting copper sulfate solution (2.5 g in 15 mL distilled water) with potassium iodide (8.5 g). The brown precipitate, which was immediately formed, was stirred for 15 min at room temperature (liberation of iodine vapors was observed). The precipitate was filtered and it was washed with distilled water. CuI was obtained as a white residue. Freshly filtered CuI (0.190 g, 1 mmol) in distilled water (5 mL) was stirred rapidly with neutral alumina (1 g). Water (20 mL) was added to this stirred mixture over a period of 1 h and the reaction mixture was stirred at room temperature for 24 h, so as to slowly precipitate the CuI on to the alumina support. The supported catalyst was filtered through sintered glass funnel and it was then washed several times with water and ethanol. The catalyst was dried under vacuum at room temperature for 6 h. The copper content in the fresh catalyst was found to be 4.2% (16.916 mg g<sup>-1</sup>, as detected by ICP).

### Representative Experimental Procedure for the Synthesis of 1,4-Disubstituted 1,2,3-Triazoles (Table 3, entry 1).

A mixture of benzyl bromide (171 mg, 1 mmol), phenyl acetylene (102 mg, 1 mmol),  $\text{NaN}_3$  (65 mg, 1 mmol), and  $\text{CuI}/\text{Al}_2\text{O}_3$  (30 mg, 3 mol%) in water (3.5 mL) was subjected to microwave irradiation (100W,  $70^\circ \text{C}$ , 0 psi) for 6 min. The reaction was monitored by TLC. Extraction of the reaction residue by simple elution with ethyl acetate followed by evaporation of the solvent furnished crude product in almost pure form, which was further purified by column chromatography giving a yellowish solid (98%), m.p.  $133^\circ \text{C}$ .  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ , TMS):  $\delta$  = 7.84–7.82 (m, 1H), 7.81–7.79 (m, 1H), 7.68 (s, 1H), 7.44–7.38 (m, 5H), 7.36–7.30 (m, 3H), 5.59 ppm (s, 2H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ , TMS):  $\delta$  = 148.1, 134.6, 130.3, 129.1 (2C), 128.8 (3C), 126.2, 128.0 (2C), 125.7 (2C), 119.5, 54.2 ppm. HRMS (ESI):  $m/z$ : calcd for  $\text{C}_{15}\text{H}_{14}\text{N}_3$  [ $M+H$ ] $^+$ : 236.1182; found: 236.1182. These data are in good agreement with those of an authentic sample of 1-benzyl-4-phenyl-1H-1,2,3-triazole.<sup>[7a]</sup>

The same procedure was used for all the compounds listed in Table 3. All the known triazoles (Entries 1, 2, 3, 4, 5, 7, 8, 10, 12, 14, 15, and 16) were easily identified by comparison of their spectroscopic data with those previously reported (Please see the supporting information).

**1-Benzyl-4-phenyl-1H-1,2,3-triazole (Table 3, entry 1):** Yellowish solid (98%), m.p.  $133^\circ \text{C}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ , TMS):  $\delta$  = 7.84–7.82 (m, 1H), 7.81–7.79 (m, 1H), 7.68 (s, 1H), 7.44–7.38 (m, 5H), 7.36–7.30 (m, 3H), 5.59 ppm (s, 2H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ , TMS):  $\delta$  = 148.1, 134.6, 130.3, 129.1 (2C), 128.8 (3C), 126.2, 128.0 (2C), 125.7 (2C), 119.5, 54.2 ppm. HRMS (ESI):  $m/z$ : calcd for  $\text{C}_{15}\text{H}_{14}\text{N}_3$  [ $M+H$ ] $^+$ : 236.1182; found: 236.1182.

**1-Benzyl-4-(4-(tert-butyl)phenyl)-1H-1,2,3-triazole (Table 3, entry 3)<sup>[23a]</sup>:** White solid (96%), m.p.  $117^\circ \text{C}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ , TMS):  $\delta$  = 7.73 (d,  $J$  = 8.0 Hz, 2H), 7.63 (s, 1H), 7.42 (d,  $J$  = 8.3 Hz, 2H), 7.38–7.35 (m, 2H), 7.29 (d,  $J$  = 7.5 Hz, 1H), 5.57 (s, 2H), 1.33 ppm (s, 9H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ , TMS):  $\delta$  = 151.2, 148.2, 134.7, 129.0 (2C), 128.7, 128.0 (2C), 127.7, 125.7 (2C), 125.4 (2C), 119.2, 54.1, 34.6, 31.2 ppm (3C). HRMS (ESI):  $m/z$ : calcd for  $\text{C}_{19}\text{H}_{22}\text{N}_3$  [ $M+H$ ] $^+$ : 292.1808; found: 292.1807.

**2-(1-Benzyl-1H-1,2,3-triazol-4-yl)pyridine (Table 3, entry 5):** White solid (96%), m.p.  $103^\circ \text{C}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ , TMS):  $\delta$  = 8.54 (d,  $J$  = 4.34 Hz, 1H), 8.16 (d,  $J$  = 7.83 Hz, 1H), 8.06 (s, 1H), 7.41–7.29 (m, 5H), 7.23–7.18 (m, 1H), 5.58 ppm (s, 2H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ , TMS):  $\delta$  = 150.1, 149.2, 148.6, 136.9, 134.2, 129.1, 128.8, 128.2, 122.8, 121.9, 120.2, 54.31 ppm. HRMS (ESI):  $m/z$ : calcd for  $\text{C}_{14}\text{H}_{13}\text{N}_4$  [ $M+H$ ] $^+$ : 237.1135; found: 237.1133.

**1-Benzyl-4-(cyclohexylmethyl)-1H-1,2,3-triazole (Table 3, entry 6):** White solid (91%), m.p.  $91^\circ \text{C}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ , TMS):  $\delta$  = 7.40–7.33 (m, 3H), 7.27–7.23 (m, 2H), 7.17 (s, 1H), 5.50 (s, 2H), 2.56 (d,  $J$  = 6.5 Hz, 2H), 1.78–1.55 (m, 6H), 1.26–1.08 (m, 3H), 0.97–0.88 ppm (m, 2H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ , TMS):  $\delta$  = 147.4, 135.0, 129.0 (2C), 128.5, 127.9 (2C), 121.1, 53.9, 38.0, 33.4, 33.0, 26.3, 26.1 ppm. HRMS (ESI):  $m/z$ : calcd for  $\text{C}_{16}\text{H}_{20}\text{N}_3$  [ $M+H$ ] $^+$ : 254.1652; found: 254.1652.

**(1-Benzyl-1H-1,2,3-triazol-4-yl)methanol (Table 3, entry 7):** White solid (90%), m.p.  $102^\circ \text{C}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ , TMS):  $\delta$  = 7.46 (s, 1H), 7.37–7.33 (m, 3H), 7.27–7.25 (m, 2H), 5.49 (s, 2H), 4.73 (s, 2H), 3.52 ppm (bs, 1H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ , TMS):  $\delta$  = 148.1, 134.4, 129.1 (2C), 128.7, 128.1 (2C), 121.7, 56.1, 54.1 ppm. HRMS (ESI):  $m/z$ : calcd for  $\text{C}_{10}\text{H}_{11}\text{ON}_3$  [ $M+H$ ] $^+$ : 212.0794; found: 212.0793.

**1-Allyl-4-phenyl-1H-1,2,3-triazole (Table 3, entry 8):** White solid (92%), m.p.  $108^\circ \text{C}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ , TMS):  $\delta$  = 7.84 (d,  $J$  = 7.58 Hz, 2H), 7.78 (s, 1H), 7.43 (t,  $J$  = 7.58 Hz, 2H), 7.37–7.32 (m, 1H), 6.12–6.02 (m, 1H), 5.40–5.33 (m, 2H), 5.04–5.02 ppm (m, 2H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ , TMS):  $\delta$  = 131.2, 130.5, 128.8 (2C), 128.1 (2C), 125.7 (2C), 120.2, 119.4, 52.7 ppm. HRMS (ESI):  $m/z$ : calcd for  $\text{C}_{15}\text{H}_{20}\text{N}_3$  [ $M+H$ ] $^+$ : 242.1652; found: 242.1650.

**1-Allyl-4-(4-(tert-butyl)phenyl)-1H-1,2,3-triazole (Table 3, entry 9):** White solid (91%), m.p.  $113^\circ \text{C}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ , TMS):  $\delta$  = 7.76 (d,  $J$  = 8.31 Hz, 2H), 7.73 (s, 1H), 7.45 (d,  $J$  = 8.56 Hz, 2H), 6.11–6.02 (m, 1H), 5.40–5.31 (m, 2H), 5.04–5.0 (m, 2H), 1.34 ppm (s, 9H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ , TMS):  $\delta$  = 151.2, 131.3, 127.5, 126.8, 125.7 (2C), 125.4 (2C), 120.0, 119.1, 52.7, 34.64, 31.2 ppm (3C). HRMS (ESI):  $m/z$ : calcd for  $\text{C}_{19}\text{H}_{22}\text{N}_3$  [ $M+H$ ] $^+$ : 186.1026; found: 186.1026.

**1-(3-Methylbenzyl)-4-phenyl-1H-1,2,3-triazole (Table 3, entry 10)<sup>[23b]</sup>:** White solid (92%), m.p.  $96^\circ \text{C}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ , TMS):  $\delta$  = 7.81 (d,  $J$  = 7.2 Hz, 2H), 7.66 (s, 1H), 7.42–7.37 (t,  $J$  = 7.3 Hz, 2H), 7.34–7.17 (m, 1H), 7.18 (d,  $J$  = 7.6 Hz, 1H), 7.12 (m, 1H), 5.53 (s, 2H), 2.35 ppm (s, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ , TMS):  $\delta$  = 148.1, 139.0, 134.5, 130.5, 129.5, 128.7 (2C), 128.1, 125.6 (2C), 125.1, 119.4, 54.2, 21.3 ppm. HRMS (ESI):  $m/z$ : calcd for  $\text{C}_{16}\text{H}_{16}\text{N}_3$  [ $M+H$ ] $^+$ : 250.1339; found: 250.1337.

**4-(4-(tert-Butyl)phenyl)-1-(3-methylbenzyl)-1H-1,2,3-triazole (Table 3, entry 11):** White solid (95%), m.p.  $103^\circ \text{C}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ , TMS):  $\delta$  = 7.73 (d,  $J$  = 8.2 Hz, 2H), 7.63 (s, 1H), 7.42



(d,  $J=8.2$  Hz, 2H), 7.29–7.24 (m, 1H), 7.17 (d,  $J=7.6$  Hz, 1H), 7.10 (bs, 1H), 5.53 (s, 2H), 2.34 (s, 3H), 1.33 ppm (s, 9H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ , TMS):  $\delta=151.2$ , 148.1, 139.0, 135.0, 129.4, 129.0, 128.6, 127.7, 125.7 (2C), 125.4 (2C), 125.0, 119.2, 54.1, 34.6, 31.2 (3C), 21.32 ppm. HRMS (ESI):  $m/z$ : calcd for  $\text{C}_{20}\text{H}_{24}\text{N}_3$   $[\text{M}+\text{H}]^+$ : 306.1965; found: 306.1965.

**1-(3-Chlorobenzyl)-4-phenyl-1 *H*-1,2,3-triazole (Table 3, entry 12)**<sup>[23c]</sup>: White solid (94%), m.p. 107 °C;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ , TMS):  $\delta=7.82$  (d,  $J=7.33$  Hz, 2H), 7.70 (s, 1H), 7.44–7.40 (t,  $J=7.3$  Hz, 2H), 7.35–7.29 (m, 4H), 7.19 (d,  $J=7.0$  Hz, 1H), 5.55 ppm (s, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ , TMS):  $\delta=148.9$ , 136.6, 135.0, 130.5, 130.3, 129.0, 128.8 (2C), 128.3, 128.0, 126.0, 125.7 (2C), 119.5, 53.5 ppm. HRMS (ESI):  $m/z$ : calcd for  $\text{C}_{15}\text{H}_{13}\text{N}_3\text{Cl}$   $[\text{M}+\text{H}]^+$ : 270.0793; found: 270.0793.

**4-(4-(*tert*-Butyl)phenyl)-1-(3-chlorobenzyl)-1 *H*-1,2,3-triazole (Table 3, entry 13)**: White solid (91%), m.p. 109 °C;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ , TMS):  $\delta=7.74$  (d,  $J=8.5$  Hz, 2H), 7.67 (s, 1H), 7.44 (d,  $J=8.2$  Hz, 2H), 7.34–7.2 (m, 3H), 7.17 (d,  $J=7.0$  Hz, 1H), 5.54 (s, 2H), 1.33 ppm (s, 9H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ , TMS):  $\delta=151.4$ , 148.4, 136.7, 135.0, 130.4, 128.9, 128.0, 127.5, 126.0, 125.7 (2C), 125.4 (2C), 119.2, 53.4, 34.6, 31.2 ppm (3C). HRMS (ESI):  $m/z$ : calcd for  $\text{C}_{19}\text{H}_{21}\text{N}_3\text{Cl}$   $[\text{M}+\text{H}]^+$ : 326.1419; found: 326.1420.

**((3*S*,3'*S*,4*R*,4'*R*)-Ethane-1,2-diylbis(2-oxo-4-phenylazetidine-1,3-diyl))bis(1 *H*-1,2,3-triazole-1,4-diyl)bis(methylene)(4*R*,4'*R*)-bis(4-((3*R*,5*S*,7*R*,8*R*,9*S*,10*S*,12*S*,13*R*)-3,7,12-trihydroxy-10,13-dimethyl-hexadecahydro-1 *H*-cyclopenta[*a*]phenanthren-17-yl)pentanoate) (Table 3, entry 14)**: White solid (90%); m.p. 167–168 °C;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz, TMS):  $\delta=7.50$  (s, 1H), 7.47 (s, 1H), 7.21 (bs, 10H), 6.16 (d,  $J=4.8$  Hz, 1H), 6.13 (d,  $J=5.0$  Hz, 1H), 5.56 (d,  $J=4.8$  Hz, 2H), 4.97 (s, 4H,  $-\text{OCH}_2$ ), 4.11 (t,  $J=9.3$  Hz, 2H), 3.94 (bs, 2H, CH-12), 3.84 (d,  $J=13.6$  Hz, 2H, CH-7), 3.40 (bs, 2H, CH-3), 3.13 (t,  $J=11.8$  Hz, 2H), 0.94 (s, 6H), 0.86 (d,  $J=7.8$  Hz, 6H), 0.64 ppm (s, 6H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz):  $\delta=173.7$ , 163.4, 142.4, 130.9, 128.8, 128.4, 126.6, 124.0, 72.6, 71.3, 68.7, 67.9, 60.4, 56.5, 46.4, 46.0, 41.1, 39.0, 38.9, 38.6, 34.9, 34.4, 34.2, 30.7, 30.3, 29.6, 27.7, 27.2, 25.9, 22.8, 22.1, 16.8, 12.1 ppm; MS (LCMS):  $m/z$ : 1295  $[\text{M}+\text{H}]^+$ , 1318  $[\text{M}+\text{Na}]^+$ ; elemental analysis: calcd for  $\text{C}_{74}\text{H}_{102}\text{N}_8\text{O}_{12}$ : C 68.60, H 7.94, N 8.65; found: C 68.45, H 7.71, N 8.89.

**2-(2,4-Difluorophenyl)-1-(2-((4-phenyl-1 *H*-1,2,3-triazol-1-yl)methyl)-2 *H*-1,2,3-triazol-4-yl)-3-(1 *H*-1,2,4-triazol-1-yl)propan-2-ol (Table 3, entry 15)**: Yellowish solid (70%),  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta=8.02$  (s, 1H), 7.85 (s, 1H), 7.83 (s, 1H), 7.79 (d,  $J=7.27$  Hz, 2H), 7.44–7.41 (m, 3H), 7.37–7.33 (m, 1H), 7.25–7.20 (m, 1H), 6.76–6.69 (m, 3H), 6.61–6.56 (m, 1H), 4.99 (bs, 1H), 4.77 (d,  $J=14.03$  Hz, 1H), 4.52 (d,  $J=14.03$  Hz, 1H), 3.43 (d,  $J=14.80$  Hz, 1H), 3.17 ppm (d,  $J=14.80$  Hz, 1H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta=163.9$ , 161.4, 159.5, 157.0, 152.0, 148.8, 145.5, 137.0, 129.8, 128.9, 128.6, 125.8, 124.0, 119.2, 111.5, 104.1, 75.0, 64.2, 56.6, 34.4 ppm; HRMS (ESI):  $m/z$ : calcd for  $\text{C}_{22}\text{H}_{20}\text{N}_9\text{O}_2$   $[\text{M}+\text{H}]^+$ : 464.1753; found: 464.1749.

**1-(1-((4-(Cyclohexylmethyl)-2 *H*-1,2,3-triazol-2-yl)methyl)-1 *H*-1,2,3-triazol-4-yl)-2-(2,4-difluorophenyl)-3-(1 *H*-1,2,4-triazol-1-yl)propan-2-ol (Table 3, entry 16)**: Glassy solid (72%) IR:  $\tilde{\nu}=3422$ , 3019, 2927, 1618, 1500, 1215  $\text{cm}^{-1}$ ,  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta=8.09$  (s, 1H), 7.80 (s, 1H), 7.46 (s, 1H), 7.41 (s, 1H), 7.38–7.29 (m, 1H), 6.76–6.65 (m, 2H), 6.62 (d,  $J=2.15$  Hz, 2H), 5.25 (s, 1H), 4.72 (d,  $J=14.27$  Hz, 1H), 4.53 (d,  $J=14.27$  Hz, 1H), 3.44 (d,  $J=13.89$  Hz, 1H), 3.14 (d,  $J=13.89$  Hz, 1H), 2.53 (d, 2H), 1.77–1.71 (m, 3H), 1.70–1.64 (m, 3H), 1.21–1.13 (m, 2H), 1.05–0.85 ppm (m, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta=164.8$ , 160.7, 159.8, 155.7, 149.7, 143.2, 135.2, 129.8, 124.4, 122.5, 111.05, 103.7, 77.2, 74.8, 64.3, 56.8, 37.6, 33.8, 32.8, 32.7, 29.4, 26.0, 25.8 ppm; HRMS (ESI):  $m/z$ : calcd for  $\text{C}_{23}\text{H}_{28}\text{N}_9\text{O}_2$   $[\text{M}+\text{H}]^+$ : 484.2379; found: 484.2380.

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## FULL PAPER

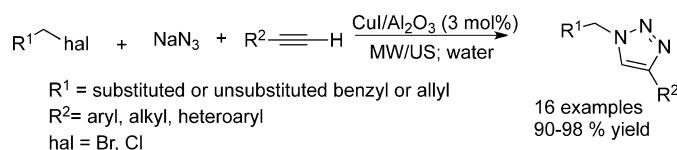
## Click Chemistry

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■■ – ■■



**Alumina-Supported Copper Iodide: An Efficient and Recyclable Catalyst for Microwave-Assisted Synthesis of 1,4-Disubstituted 1,2,3-Triazoles via Three-Component Reaction in Water**



**Azide from that:** A neutral alumina-supported copper catalyst was prepared for the synthesis of 1,4-disubstituted 1,2,3-triazoles by a three-component reaction. It was used for the synthesis of highly active antifungal molecules. This simple

heterogeneous catalyst was reused in water as a green solvent under microwave conditions. The three-component protocol obviates the necessity to isolate potentially explosive organic azides. US = ultrasound.