#### Letter

# Copper Aluminate Spinel in Click Chemistry: An Efficient Heterogeneous Nanocatalyst for the Highly Regioselective Synthesis of Triazoles in Water

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Received: 01.10.2019 Accepted after revision: 03.10.2019 Published online: 04.11.2019 DOI: 10.1055/s-0039-1690719; Art ID: st-2019-u0382-I

Abstract An expeditious protocol for the one-pot synthesis of 1,4disubstituted ( $\beta$ -hydroxy)-1,2,3-triazoles in an aqueous medium has been developed using copper aluminate nanoparticles. This heterogeneous catalytic system was found to drive a multicomponent click reaction between organic azides (generated in situ from epoxides or halides) and terminal aliphatic or aromatic alkynes in up to 96% yield without the need for a reducing agent. Structurally diverse 1,2,3-triazoles were synthesized in good to excellent yields, and the catalyst could be easily separated by simple filtration, recycled, and reused in six subsequent cycles.

Key words click chemistry, copper catalysis, triazoles, epoxides, azides, alkynes

The discovery of the azide-alkyne Huisgen 1,3-dipolar cycloaddition has led to the 1,2,3-triazole scaffold becoming important in synthetic chemistry.<sup>1</sup> This importance of 1,2,3-triazoles arises from a number of their properties, such as their chemical stability to high temperatures or to oxidizing, reducing, or hydrolyzing conditions; their aromatic nature; their high dipole moment (<5 D); and their capacity to form hydrogen bonds.<sup>2,3</sup> Although 1,2,3-triazoles are not formed in nature, synthetic compounds containing this structure have shown interesting biological properties.<sup>4</sup> In addition to this range of characteristics, 1,2,3-triazoles are outstanding mimetic of the amide bond in bioconjugation reactions; moreover, they have a wide range of applications in various other fields, such as polymer and dendrimer chemistry, biochemistry, and materials chemistry.<sup>2,5,6</sup> The original Huisgen reaction of terminal alkynes with aliphatic azides proceeds at high temperatures and with prolonged reaction times to give both 1,5and 1,4-disubstituted 1,2,3-triazoles. The modified Huisgen 1,3-dipolar cycloaddition reaction fulfills the criteria for a

click-chemistry reaction as itemized by Sharpless in 2001, giving a high yield, few byatalysis, and sensor materialsproducts, and easily purified products and displaying high regio- and stereospecificity.<sup>3,7</sup> Two revolutionary modifications based on copper- and ruthenium-catalyzed azidealkyne cycloaddition reported in 2002<sup>8</sup> and 2005,<sup>9</sup> respectively, not only reduced the reaction time and temperature, but also gave the desired 1,4-disubstituted and 1,5-disubstituted triazoles, respectively.

Despite the considerable progresses in homogeneous copper-catalyzed azide-alkyne cycloaddition (CuAAC) in recent years, there are some inherent shortcomings associated with these catalytic systems in industry. These include the formation of homocoupling byproducts in the case of copper halide-catalyzed reaction and the contamination of the target products by copper. The latter is particularly important in the pharmaceutical industry and it results in the need to recover and remove the catalyst<sup>10,11</sup> because, for pharmaceutical applications, the content of metal contaminants should not exceed 15 ppm. For example, even in the case of 0.01 mol% of a copper catalyst, about 25 ppm of metal contaminants can be detected in the products from a CuAAC reaction.<sup>10</sup> Hence, there are ongoing efforts to achieve CuAAC reactions by heterogeneous catalysis using materials such as silica, polymers, zeolites, or activated carbon as supports.<sup>6,11,12</sup>

Because of its prominent features such as its benign and inexpensive composition, high thermal stability, high mechanical stability, low surface acidity, and hydrophobicity, spinel copper aluminate (CuAl<sub>2</sub>O<sub>4</sub>) has become a subject of current research in the fields of materials science, catalysis, photocatalysis, and sensor materials.<sup>13</sup> However, spinel copper aluminate and its composites have rarely been used as heterogeneous copper catalysts in organic synthesis, and there are just few reports on a synthesis of imidazol[1,2] pyridines,<sup>14</sup> a solvent-free synthesis of xanthanedione de-

### Letter

Table 1	Characterization Data for CuAl <sub>2</sub> O <sub>4</sub> Nanoparticles
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Analysis	Results
BET surface area	23.873 m <sup>2</sup> .g <sup>-1</sup>
Pore volume	0.1539 cm <sup>3</sup> ·g <sup>-1</sup> (BJH adsorption: cumulative volume of pores)
Pore size	25.308 nm (pore size distribution)
XRD	monophasic spinel cubic (Fd-3m with a lattice size of 8.064 Å; JCPDS 33-0448) $^{18}$
TG	after loss of $H_2O$ , the catalyst showed stability at least to 1000 °C under air.
SEM	irregularly shaped grains, along with some uniform globular nanocrystals
EDX	Cu: 53.11, Al: 5.31; O: 27.80 (mass %)
TEM	20–30 nm

rivatives,<sup>13e</sup> and a catalytic oxidation of benzylic alcohols.<sup>15</sup> Consequently, an investigation of the application of spinel copper aluminate in organic synthesis is of considerable interest. As an extension of our researches on the development of heterogeneous catalytic systems,<sup>16</sup> we present the first report of a highly regioselective synthesis of 1,4-disubstituted ( $\beta$ -hydroxy)-1,2,3-triazoles from alkynes and organic azides, generated in situ under ecofriendly conditions, with catalysis by spinel CuAl<sub>2</sub>O<sub>4</sub> nanoparticles. Moreover, the reaction does not require any solid support or sacrificial reducing agent. This method not only provides simpler experimental procedures but also bypasses safety issues associated with the handling of the potentially explosive azides.

First, CuAl<sub>2</sub>O<sub>4</sub> was prepared according by a simple and efficient reported procedure based on a modified Pechini sol-gel method.<sup>17</sup> The resulting catalyst was fully characterized by Fourier-transform infrared spectroscopy (FTIR), Xray diffraction (XRD), field-emission scanning electron microscopy (FESEM), transmission electron microscopy (TEM), energy-dispersive X-ray analysis (EDX), Brunauer– Emmett–Teller (BET) and Barrett–Joyner–Halenda (BJH) analyses, X-ray photoelectron spectroscopy (XPS), and thermogravimetric analysis (TG) [see Supporting Information (SI)]. After evaluating varied calcination conditions, we found that calcination at 950 °C for 10 hours was optimal, and the relevant characterization data for the resulting catalyst are summarized in Table 1.

To determine the optimal conditions for the CuAAC reaction, the catalytic activities of spinel  $CuAl_2O_4$  nanoparticles were examined in a model reaction of ethynylbenzene (**1a**), benzyl bromide (**2a**), and sodium azide without any reducing agent. The results are summarized in Table 2.

Although the reaction did not proceed well in aprotic organic solvents, even under reflux conditions (Table 2, entries 1–3), the protic solvents ethanol and *tert*-butanol gave 75 and 78% yields of product **3a**, respectively (entries 4 and 5). These results show that the progress of the reaction depends on the nature of the solvent. Fortunately, an aqueous medium not only afforded a higher yield (84%), but also reduced the reaction time from 3 hours to 1 (entry 6). To our

delight,  $H_2O$  turned out to be the best medium for the reaction and it gave an 89% yield of product **3a** after 45 minutes (entry 7). Increasing the reaction temperature to 90 °C resulted in an excellent 97% yield of **3a** (entry 8). Finally, the effect of the catalyst loadiction and higher yields were obtaineng on the reaction yield was investigated. Increasing the amount of the catalyst to 10 mg (entry 9) had no significant effect on the product yield, whereas decreasing the amount of catalyst to 2.5 mg decreased the yield to 79% (entry 10). Only an 8% yield of **3a** was obtained when no catalyst was present (entry 11). Having established the optimal conditions [CuAl<sub>2</sub>O<sub>4</sub> (5 mg), H<sub>2</sub>O, 90 °C], we explored the scope and limitations of this catalytic system in CuAAC re-

 Table 2
 Screening of the Solvent and Temperature in a Copper-Catalyzed Azide–Alkyne Huisgen 1,3-Dipolar Cycloaddition<sup>a</sup>

Ph-C	≡CH <sub>+</sub> PhCH₂Br +	NaN <sub>3</sub> CuAl <sub>2</sub> C	D <sub>4</sub> NPs (mg) ►	N <sup>,N</sup> ,N-CH <sub>2</sub> Ph
	a Za			Ja
Entry	Solvent	Temp (°C)	Time	Yield (%)
1	CH₃CN	reflux	3 h	36
2	THF	reflux	3 h	17
3	$CH_2CI_2$	reflux	3 h	22
4	t-BuOH	reflux	3 h	75
5	EtOH	reflux	3 h	78
6	EtOH-H <sub>2</sub> O (1:1)	80	1 h	84
7	H <sub>2</sub> O	80	45 min	89
<b>8</b> °	H <sub>2</sub> O	90	45 min	97
$9^{d}$	H <sub>2</sub> O	90	45 min	98
10 <sup>e</sup>	H <sub>2</sub> O	90	45 min	79
11 <sup>f</sup>	H <sub>2</sub> O	90	45 min	8

 $^a$  Reaction conditions: benzyl bromide (1 mmol), ethynylbenzene (1.1 mmol), NaN\_3 (1.2 mmol), CuAl\_2O\_4 (5.0 mg), solvent (3 mL).

Isolated yield.

<sup>c</sup> Optimal conditions.

<sup>d</sup> With 10 mg of catalyst.

e With 2.5 mg of catalyst.

<sup>f</sup> With no catalyst.

## Syn lett Letter D. Khalili et al. Table 3 One-Pot CuAl<sub>2</sub>O<sub>4</sub> NPs-Catalyzed Synthesis of 1,2,3-Triazoles from Halides<sup>a</sup> N<sup>-N</sup>N-R<sup>2</sup> CuAl<sub>2</sub>O<sub>4</sub> NPs (5 mg) $R^1-C\equiv CH + R^2X +$ NaN<sub>3</sub> <u>\_\_</u> H<sub>2</sub>O, 90 °C RÍ 3 1 2 .N N N CN **3a**, 95%, <sup>b</sup> 45 min; X = Br 89%, 1.5 h; X = Cl **3b**, 87%, 1.5 h; X = Br 80%, 3 h; X = Cl **3c**, 92%, 1 h; X = Cl NO<sub>2</sub> **3d**, 83%, 1.5 h; X = Br 76%, 4 h; X = Cl **3f**, 96%, 2.5 h; X = Br 3e, 85%, 1 h; X = Br **3g**, 95%,<sup>c</sup> 1 h; X = Br 89%, 1 h; X = Cl **3h**, 85%, 2.5 h; X = Br **3i**, 83%, 2.5 h; X = Br 79%, 3.5 h; X = Cl<sup>c</sup> CN **3k**, 94%, 1.5 h; X = Br **3I**, 89%, 1.5 h; X = Br **3j**, 81%, 3 h; X = Br CN **3o**, 94%, 2 h; X = Br **3m**, 90%, 1.5 h; X = Br **3n**, 94%, 2 h; X = Br **3p**, 95%, 2 h; X = Br 90%, 2 h; X = Cl **3r**, 88%, 1.5 h; X = Br 83%, 2 h; X = Cl 3q, 86%, 2 h; X = Br

С

**3s**, 79%, 3 h; X = Br 74%, 3 h; X = Cl

<sup>a</sup> Reaction condition: alkyl or benzylic halide (1 mmol), terminal alkyne (1.1 mmol), NaN<sub>3</sub> (1.2 mmol), CuAl<sub>2</sub>O<sub>4</sub> (5.0 mg), H<sub>2</sub>O (3 mL), 90 °C.

**3t**, 87%, 2 h; X = Br 84%, 2 h; X = Cl

HC

<sup>b</sup> Isolated yields are reported.

<sup>c</sup> The reaction was performed in a sealed tube.

actions (Table 3). Notably, to bypass the difficulties and dangers associated with the synthesis and handling of organic azides, these were generated in situ by treating NaN<sub>3</sub> with organic halides. Several benzylic or alkyl halides and terminal alkynes were examined under the optimum conditions, and these gave a wide range of structurally diverse 1,4-disubstituted triazoles. Generally, electron-donating or electron-withdrawing groups on the benzylic halides had only slightly effects on the reactivity, and all the reactants showed acceptable activity. Nevertheless, electron-donating groups slightly favored the reaction and higher yields were obtained (**3a-f**).<sup>19</sup> Primary and secondary alkyl bromides or chlorides were also used in the nucleophilic substitution followed by 1,3-dipolar cycloaddition to give products **3g-i**. Various terminal aliphatic alkynes, such as 1benzyl-4-(prop-2-yn-1-yloxy)benzene and 1-(prop-2-yn-1-yloxy)naphthalene also reacted with high efficiency in the presence of only 5.0 mg of  $CuAl_2O_4$  to give products **3k**- **r**. Attempts to use simple aliphatic alkynes as substrates were successful and gave the desired products **3s** and **3t** in good yields.

To examine the possibility of broadening the scope of the method, we examined the replacement of halides with epoxides to give  $\beta$ -hydroxy-1,2,3-triazoles. The catalytic performance of the CuAl<sub>2</sub>O<sub>4</sub> nanoparticles was tested under the same optimized conditions that were used in the synthesis of the 1,4-disubstituted 1,2,3-triazoles. As shown in Table <sup>4,[20</sup> several epoxides were tolerated and gave the desired products **5a–j** in good to excellent yields.

Notably, the ring-opening of the epoxide occurred preferentially depending on the presence of an alkyl or aryl group at the position  $\alpha$  to the oxygen, so that the regioselective reaction gave two types of product. In this context, the use of styrene oxide as a precursor gave the primary  $\beta$ -hydroxy triazole **5a** in excellent yield. An aliphatic epoxide gave the target product **5b** with equal reactivity to aromatic epoxides, but with the opposite regioselectivity. The reaction conditions were found to tolerate sterically more-hin-



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<sup>a</sup> Reaction condition: epoxide (1 mmol), terminal alkyne (1.1 mmol), sodium azide (1.2 mmol), CuAl<sub>2</sub>O<sub>4</sub> (5.0 mg) in water (3 ml) at 90 °C. <sup>b</sup> Isolated vields are reported.

dered bicyclic epoxide, such as cyclohexene oxide, which gave the *N*-cyclohexyltriazole **5c** in 90% isolated yield. The current procedure was also found to be effective for 2-phenoxyoxirane, 2-butoxyoxirane, and 2-allyloxyoxirane, which gave high yields of the corresponding target products **5d–f**, with the same regioselectivity pattern as that of alkyl-substituted oxiranes. Moreover, replacement of ethynylbenzene by nonactivated aliphatic terminal alkynes incorporating a 4-benzylphenoxy or 2-naphthyloxy motif gave the corresponding products **5g–i** in good to high yields. The reaction of 2-methyl-3-butyn-2-ol as a simple aliphatic alkyne gave the triazole **5j** in 80% yield.

From the industrial and environmental viewpoints, the stability and reusability of catalyst systems are important features. We therefore used our model reaction (Table 1) to examine the recyclability of the catalyst system. After each cycle, the reaction mixture was filtered to separate the catalyst, which was washed with  $H_2O$  and EtOH then dried in a vacuum oven at 70 °C for reuse in a subsequent cycle. Notably, the catalytic system retained its efficiency during six consecutive cycles (Table 5). After each run, an inductively coupled plasma analysis was carried out to determine the amount of catalyst leaching. As shown in Table 5, only negligible amounts of copper leached from the catalyst surface during each cycle.

Table 5	Recovery Studies in the Model Reaction (Table 2, Entry 8) Cat-
alyzed by	the Same Recovered Spinel CuAl <sub>2</sub> O <sub>4</sub> NPs

Run	1	2	3	4	5	6
Yield of <b>3a</b> (%)	95	95	94	93	92	89
Cu leaching (%)	0.09	0.16	0.18	0.21	0.22	0.31

A TEM image of the recovered catalyst after the sixth reaction run indicated that the CuAl<sub>2</sub>O<sub>4</sub> NPs had agglomerated to form large clusters (see SI, Figure 7). We surmised that, in the catalytic cycle, NaN<sub>3</sub> can change the valence state of Cu in  $CuAl_2O_4$  and that this might be responsible for the observed activity.<sup>21,22</sup> To verify this hypothesis and to gain insight into the possible reaction mechanism, we used XPS to investigate the oxidation state of the Cu in the fresh catalyst (see SI, Figure 5) and the CuAl<sub>2</sub>O<sub>4</sub> catalyst treated with sodium azide. The Cu 2p core-level spectrum (Figure 1a) showed two main peaks at 934.6 and 953.1 eV, which were assigned to Cu  $2p_{3/2}$  and Cu  $2p_{1/2}$ , respectively. This result confirmed the presence of Cu (II) (see SI). As shown in Figure 1b, when CuAl<sub>2</sub>O<sub>4</sub> was treated with sodium azide, in addition to the binding energy peaks at 934.8 and 953.0 eV, two additional sets of binding energy peaks at 932.7 and 954.3 eV were also observed, which clearly indicated that Cu<sup>2+</sup> was partially reduced to Cu<sup>+</sup>.<sup>21,23</sup>



Figure 1 High-resolution narrow X-ray photoelectron spectra (XPS) for (a) fresh  $CuAl_2O_4$ , and (b)  $CuAl_2O_4$  treated with sodium azide

A deconvolution of the Cu 2p envelop of the catalyst treated with NaN<sub>3</sub> showed that Cu<sup>2+</sup> and Cu<sup>+</sup> accounted for 44% and 56% of copper species, respectively. As proven by XPS analysis, after the generation of Cu<sup>+</sup> species, the CuAAC proceeds according to a reaction mechanism proposed previously by Sharpless and co-workers (Scheme 1).<sup>24</sup>



Scheme 1 The proposed reaction mechanism

In summary,  $CuAl_2O_4$ , as a heterogeneous catalyst, effectively induced multicomponent one-pot reactions of sodium azide with terminal aromatic or aliphatic alkynes and halides or epoxides to give 1,4-disubstituted 1,2,3-triazoles. The reactions proceeded in water, an acceptable green solvent, without any additives, and a wide range of structurally diverse precursors could be used under the optimized conditions. This CuAAC reaction involves the generation of organic azides in situ by using low-cost sodium azide, which avoids the need to isolate hazardous organic azides,

## Letter

reduces waste generation, and simplifies operational procedures. The recovered catalyst showed a high activity over six experimental runs.

#### **Funding Information**

Financial support from the Shiraz University research council is gratefully acknowledged.

### Acknowledgment

The authors thank Mr. Mehdi Koohgard for his kind assistance.

#### **Supporting Information**

Supporting information for this article is available online at https://doi.org/10.1055/s-0039-1690719.

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(20) **1,2,3-Triazoles; General Procedure** 

In a 10 mL round-bottomed flask, the alkyl halide or epoxide (1 mmol), terminal alkyne (1.1 mmol), and NaN<sub>3</sub> (1.2 mmol) were mixed and stirred in H<sub>2</sub>O (3 mL) in the presence of the CuAl<sub>2</sub>O<sub>4</sub> catalyst (0.005g) at 90 °C. When the reaction was complete (TLC; hexane–EtOAc), the catalyst was collected by simple filtration. The filtrate was diluted with H<sub>2</sub>O (5 mL) and extracted with EtOAc (3 × 10 mL). The combined organic phases were washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated under reduced pressure. The resulting residue was purified by column chromatography (silica gel, hexane–EtOAc).

# 4-({4-[(4-Benzylphenoxy)methyl]-1*H*-1,2,3-triazol-1-yl}methyl)benzonitrile (31)

Yellow solid; yield: 372 mg (89%); mp 63–65 °C. IR (KBr): 3031, 2923, 2360, 2240, 1612, 1512, 1458, 1334, 1234, 1110, 1002, 833, 725 cm<sup>-1</sup>. <sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>):  $\delta$  = 4.93 (s, 2 H), 5.58 (s, 2 H), 5.68 (s, 2 H), 6.69 (dd, *J* = 7.5, 2.5 Hz, 2 H), 6.88 (dd, *J* = 10.1, 5.4 Hz, 2 H), 7.27–7.34 (m, 5 H), 7.57 (dd, *J* = 7.5, 2.5 Hz, 2 H), 7.64 (dd, *J* = 7.5, 2.5 Hz, 2 H), 7.75 (s, 1 H). <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>):  $\delta$  = 41.09, 53.37, 58.25, 112.31, 114.80, 123.16, 126.13, 128.20, 128.86, 130.00, 130.16, 132.87, 134.13, 135.04, 139.87, 141.46, 145.08, 156.55.

# 4-[(4-Benzylphenoxy)methyl]-1-(3-fluorobenzyl)-1H-1,2,3-triazole (3m)

Yellow solid; yield: 369 mg (90%); mp 59–61 °C. IR (KBr): 3070, 2916, 2353, 1697, 1512, 1450, 1250, 1049, 732, 694, 594 cm<sup>-1</sup>. <sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>): δ = 3.82 (s, 2 H), 5.07 (s, 2 H), 5.40 (s, 2 H), 6.65 (dd, *J* = 5.3, 2.5 Hz, 1 H), 6.84–6.95 (m, 3 H), 6.97–7.02

(m, 3 H), 7.06–7.11 (m, 4 H), 7.14–7.17 (m, 2 H), 7.45 (s, 1 H).  $^{13}$ C NMR (101 MHz, CDCl<sub>3</sub>):  $\delta$  = 41.14, 53.32, 62.00, 114.71–115.80 (m, 2 C), 126.18, 128.61, 128.97, 130.08, 130.90, 134.07, 137.33, 141.61, 144.68, 156.76, 161.73–164.19 (d, *J* = 248.5 Hz, 1 C). **2-{4-[(4-Benzylphenoxy)methyl]-1H-1,2,3-triazol-1-yl}-1**-

#### phenylethanol (5g)

White solid; yield: 351 mg (83%); mp 64–66 °C. IR (KBr): 3309, 3062, 2916, 2360, 2245, 2098, 1951, 1890, 1604, 1504, 1450, 1342, 1242, 1049, 910, 840 cm<sup>-1</sup>. <sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>):  $\delta$  = 3.89–3.93 (m, 2 H), 4.10–4.22 (m, 1 H), 4.49–4.64 (m, 1 H), 5.13–5.15 (m, 2 H), 5.57–5.65 (m, 1 H), 6.84–6.90 (m, 2 H), 7.16–7.35 (m, 12 H), 7.53–7.56 (m, 1 H). <sup>13</sup>C NMR (101 MHz,

 $CDCl_3$ ):  $\delta$  = 41.11, 61.99, 64.77, 67.30, 114.83, 123.76, 126.12, 127.25, 128.54, 128.90, 128.96, 129.14, 130.02, 134.04, 136.08, 141.50, 144.05, 156.66.

Letter

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