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### **Graphical Abstract**

Solvent-free one-pot synthesis of 1,2,3-triazole derivatives by 'Click' reaction of alkyl halides or aryl boronic acids, sodium azide and terminal alkynes over Cu/Al<sub>2</sub>O<sub>3</sub> surface under ball-milling

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An efficient solvent-free synthesis of 1,2,3-triazole derivatives has been achieved by 'Click' reaction over Cu/Al<sub>2</sub>O<sub>3</sub> surface under ball- milling.

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### **ARTICLE TYPE**

# Solvent–free one–pot synthesis of 1,2,3-triazole derivatives by 'Click' reaction of alkyl halides or aryl boronic acids, sodium azide and terminal alkynes over Cu/Al<sub>2</sub>O<sub>3</sub> surface under ball-milling

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A one-pot procedure for the synthesis of 1,2,3-triazole derivatives by a three-component coupling of alkyl (benzyl) halides or aryl boronic acids, sodium azide and terminal alkynes over cooper(II) sulfate supported on <sup>10</sup> alumina (Cu/Al<sub>2</sub>O<sub>3</sub>) under ball-milling in absence of any solvent and additive, has been developed. The product was isolated by simple washing of the crude reaction residue with ethanol followed by evaporation of solvent. No chromatographic purification is required. The catalyst is recycled for subsequent reactions. The azides are produced in situ and thus this procedure avoids the handling of hazardous azides. This protocol offers a broad scope for an access to a variety of diversely substituted 1,2,3-triazoles. The use of no hazardous organic solvent, <sup>15</sup> ball-milling, cost efficiency, recyclability of the catalyst up to eight runs without appreciable loss of activity and high yields of products make this procedure greener.

### 1. Introduction

1,2,3-Triazoles have received considerable interest because of their useful applications as pharmaceutical 20 agents, agrochemicals, dyes, corrosion inhibitors, photostabilizers and photographic materials.<sup>1</sup> The classical method for their synthesis involved thermal 1,3-dipolar cycloaddition of organic azides with alkynes.<sup>2</sup> However, this procedure was associated 25 with elevated temperature, low yields and lack of selectivity. Thus to overcome these drawbacks an improved procedure involving Cu(I)-catalyzed azidealkyne 1,3-dipolar cycloaddition was reported,<sup>3</sup> which provided high regioselectivity, room <sup>30</sup> temperature reaction and enlarged scope. Because of

their thermodynamic instability and initiation of <sup>40</sup> undesired alkyne-alkyne coupling, the direct use of Cu(I) salts was restricted.<sup>4</sup> Instead, in situ reduction of Cu(II) salts,<sup>3a,3d</sup> oxidation of Cu(0) metal,<sup>2c-2i,</sup> copper(II)/copper(0) comproportionation,<sup>5</sup> were encouraged. Nevertheless, various nitrogen- or 45 phosphorus-based ligands have been employed to protect the metal centre and enhancing its catalytic activity.<sup>6</sup> To check the contamination of metal with the end product and improve the recovery and reuse of Cu-catalyst, heterogeneous copper salt supported <sup>50</sup> on activated carbon,<sup>7</sup> polymers,<sup>8</sup> zeolites,<sup>6</sup> and silica,<sup>10</sup> have received significant attention in recent times.

The handling of organic azides are not safe because of their toxic and hazardous nature. Although 55 alkyl azides are prepared easily by the displacement reaction of alkyl halides and sodium azide, their isolation and purification are problematic in certain cases. On the other hand, the preparation of aryl azides from aromatic amines is not so 60 straightforward. Thus a one-pot procedure involving reaction of in situ generated azides from the corresponding precursors, and alkynes for the

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synthesis of triazoles is highly desirable. A number of such one-pot procedures catalyzed by different Cuderivatives have been reported recently.<sup>11</sup> These catalysts include nanoferite-glutathione-copper under <sup>5</sup> microwave irradiation,<sup>11a</sup> copper nanoparticles on activated carbon,<sup>11b,11c</sup> CuFe<sub>2</sub>O<sub>4</sub> nanoparticles,<sup>11d</sup> ionic liquid supported Cu(I),<sup>11e</sup> Cu(I)/aminoacids ionic liquids,<sup>11f</sup> CuSO<sub>4</sub>/cyclodextrin,<sup>11g</sup> and bimetallic Cu-Fe nanoparticles.<sup>11h</sup>

<sup>10</sup> Recently, ball-milling (intense mechanical grinding) has emerged as a powerful tool for effecting a chemical reaction in a greener way.<sup>12</sup> A variety of reactions such as homocoupling of terminal alkynes,<sup>13</sup> Sonogashira,<sup>14</sup> Michael,<sup>15</sup> aldol reaction<sup>16</sup> <sup>15</sup> among others<sup>17</sup> have been performed efficiently by this technique. We have recently developed an efficient means of trans-esterification by ball-milling without any catalyst and solvent<sup>18</sup> and now we report a simple one-pot three-component reaction of <sup>20</sup> benzyl/alkyl halides, sodium azide, alkyne on the surface of alumina-supported Cu(II) catalyst<sup>19</sup> under ball-milling without any additive and solvent (Scheme 1).



Recently, a Cu- catalyzed reaction of benzyl azide and phenylacetylenes under ball-milling has also <sup>30</sup> been reported.<sup>20</sup>

### 2. Results and discussion

The supported Cu-catalyst was prepared by stirring an aqueous solution of CuSO<sub>4</sub>.5H<sub>2</sub>O (1 g, 4 mmol) and basic alumina (15 g) for 2 h at room <sup>35</sup> temperature followed by evaporation of water and drying. The copper content in the fresh catalyst was found to be 18.78 mg/g (as detected by ICP-MS).

To optimize the reaction conditions a series of experiments were carried out under varying <sup>40</sup> catalyst loading and time for a representative reaction of benzyl bromide, sodium azide and phenyl acetylene on the surface of alumina-supported Cu(II) under ball-milling at 600 rpm. It was found that the View Article Online best yield was obtained using 10 mol% of catalyst 45 (400 mg) and running the operation for 60 min. (Table 1, entry 3). No product was obtained in absence of catalyst under ball-milling in identical conditions (Table 1, entry 6). The reaction also did not initiate at all at room temperature under 50 conventional stirring using a magnetic stirrer for 24 h.

In a typical experimental procedure, a mixture of benzyl halide (bromide or chloride), phenylacetylene and sodium azide over a surface of alumina-supported Cu(II)-catalyst was subjected to <sup>55</sup> ball-milling at 600 rpm for 1 h (TLC). Elution of the reaction residue by ethanol followed by evaporation of solvent provided the pure product.

Table 1 Standardisation of reaction conditions

Br	+ <u>Cu/Al</u> 600 r	$_{2}O_{3}$ , NaN <sub>3</sub>	N <sup>N</sup> N		
Entry	Catalyst (mol%)	Time ( min.)	Yield [%] <sup>a</sup>		
1	2	60	51		
2	5	60	72		
3	10	60	96 <sup>b</sup>		
4	10	30	62		
5	10	45	80		
6 0 60 0 (a) Yield of isolated pure products (by <sup>1</sup> H and <sup>13</sup> C-NMR). (b) best condition.					

A wide range of diversely substituted phenylacetylenes were reacted with a mixture of benzyl bromides/chlorides and sodium azide by this <sup>75</sup> procedure to produce the corresponding 1,4disubstituted-1,2,3-triazoles. The results are summarized in Table 2. The substitution of electron withdrawing and electron donating groups on the phenyl ring of phenyl acetylenes did not have any <sup>80</sup> appreciable influence on the outcome of the reaction (Table 2, entries 4 and 6). The reaction went Table 2 Cu/Al<sub>2</sub>O<sub>3</sub> catalyzed one-pot azide preparation and cycloaddition of alkyl halides with terminal alkyne



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(a) Isolated yields of pure products (by <sup>1</sup>H and <sup>13</sup>C-NMR)

- (b) This denotes the earlier reference of the corresponding product  $% \left( \mathbf{b}^{\prime}\right) =\left( \mathbf{b}^{\prime}\right) \left( \mathbf{b}^{\prime}\right)$
- uniformly for all *o*-, *m*-, and *p* substituted phenylacetylenes (Table 2, entries 4, 2, and 5). The <sup>25</sup> 1,4-diethynylbenzene produced the corresponding bis-triazole derivatives (Table 2, entry 8). The heteroaryl substituted acetylene, 3-ethynylthiophene underwent clean reaction to produce 1-benzyl-4-(thiophen-3-yl)-1,2,3-triazole (Table 2, entry 7). The <sup>30</sup> alkyl acetylenes such as propargyl alcohol (Table 2, entry 11), hexyne (Table 2, entry 12) and ethyl propiolate (Table 2, entry 13) also participated in this reaction to provide the corresponding products. The reaction of cinnamyl bromide by this procedure
- <sup>35</sup> furnished the 1-cinnamyl-4-phenyl-1,2,3-triazole in relatively low yield (70%) (Table 2, entry 14). The

alkyl halides such as cyclohexyl bromides <sup>60</sup> and di-iodo methane also react with phenylacetylene without any difficulty to produce the corresponding triazoles (Table 2, entries 9 and 10).

Unfortunately, the aryl halides failed to undergo this one-pot reaction to produce the corresponding triazoles. We then focussed our attention on using aryl boronic acids in place of aryl halides to open an access to the very valuable 1-aryl-1,2,3-triazoles. Our investigation towards optimization of reaction conditions revealed that best vyield was obtained using 10 mol% of catalyst in presence of one equivalent of K<sub>2</sub>CO<sub>3</sub> (Table 3, entry

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3). Following this procedure phenylacetylene and 3thienylacetylene (heteroaryl) underwent reactions with phenyl, substituted phenyl, alkenyl and heteroaryl boronic acids to provide the corresponding s triazoles. The results are reported in Table 4.

Table 3 Standardisation of reaction conditions of one-pot aryl azide preparation and cycloaddition with terminal alkyne

B(	1. Cu/Al <sub>2</sub> O <sub>3</sub> K <sub>2</sub> CO <sub>3</sub> , Nal OH) <sub>2</sub> 600 rpm, 6 <u>1 h</u> 2. Ph— 600 rpm, 1	$ \begin{array}{c} \overset{\text{B}}{\overset{\text{N}_{3}}{\overset{\text{ball}}{\underset{}{\overset{}{\underset{}{}{}{}{\overset$	
Entry	Catalyst (mol%)	K <sub>2</sub> CO <sub>3</sub> (equiv.)	Yield [%] <sup>a</sup>
1	10	0	42
2	0	1	0
3	10	1	91 <sup>b</sup>
4	0	0	0
5	10	3	90
(a) Yiel <sup>13</sup> C- (b) besi	d of isolated p NMR). t condition.	ure products (by <sup>1</sup> H	I and

<sup>20</sup> The participation of aryl boronic acids in the synthesis of triazoles by this route using Cu-catalysts in H<sub>2</sub>O and other solvents was reported earlier too.<sup>21</sup> However, to the best of our knowledge no report of this reaction under ball-milling on a supported Cu-25 catalyst in absence of any solvent is known. In addition, the reactions of alkyl- and heteroaryl boronic acids were not addressed earlier.

In general the reactions are clean and high-yielding. Several functional groups such as F, Br, NO<sub>2</sub>, CN, 30 OMe, CO<sub>2</sub>Et, CF<sub>3</sub>, CHO are compatible under the reaction conditions. No rigorous extraction of product by solvent and work up are necessary. A simple washing of the reaction residue by ethanol followed by evaporation of solvent furnished pure product. The 35 ICP-MS measurement of Cu content in both the

products obtained with halogenides and with the boronic acids showed the absence of copper. Chromatographic purification/separation is usually not required. Thus this procedure avoids use of <sup>40</sup> hazardous organic solvent in the whole process. The

Cu/Al<sub>2</sub>O<sub>3</sub> catalyst was recovered and dried after washing with ethanol followed by acetone before reuse. We have found recyclability up to eight runs although there is marginal linear loss of activity of 45 the catalyst due to lower mass recovery in each step (Figure 1).

In comparison to a related procedure reported by Stolle et al earlier,<sup>20</sup> our procedure offers significant green advantages avoiding handling of 50 hazardous and toxic azides involving its in situ generation, use of environment friendly ethanol for isolation of product and recyclability of catalyst.



Fig. 1 Recyclability Chart (Recyclability of the 60 catalyst was tested on the reaction with benzyl bromide and phenylacetylene).

We have observed that in our catalyst,  $Cu/Al_2O_3$ , copper remains in +2 oxidation state in the fresh, intermediate and in the recovered stage, as 65 established by EPR studies (Figure 2). The XPS (Xray Photoelectron Spectroscopy) study of the fresh, intermediate and recovered catalyst also supports the +2 oxidation state of the Cu (Figure 3). Thus we assume that our reaction proceeds via a similar <sup>70</sup> reaction pathway involving Cu<sup>+2</sup> as postulated by Pitchumani et al.<sup>22</sup> Further, we did not detect formation of diynes, usually generated by Cu(I) catalysis during reduction of Cu(II) to Cu(I).

### 3. Experimental

75 IR spectra were recorded on a Shimadzu 8300 FTIR spectrometer. <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra were run on Bruker DPX-300 and DPX-500 instruments. HRMS were acquired on a Microtek Qtof Micro YA 263 spectrometer. All commercial reagents were <sup>80</sup> distilled before use. A PM 100, Retsch GmbH, Germany, ball-milling apparatus was used for all reactions.

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Table 4 Cu/Al<sub>2</sub>O<sub>3</sub> catalyzed one-pot aryl azide preparation and cycloaddition with terminal alkyne

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R	<sup>1</sup> –B(OH) <sub>2</sub>	$Cu/Al_2O_3$ (10n $K_2CO_3$ (1 equi NaN <sub>3</sub> (3-equiv 1 h, 600 rpm	nol%) v.) ∕.) R <sup>1</sup> −N;	$_{3} + {}^{35} R^2 = \frac{1 \text{ h, 600 rpm}}{1 \text{ b, 600 rpm}}$	$R^{1} \sim R^{2}$	
Entry	В	oronic acid	Acetylene	Triazole	Yield [%] <sup>a</sup>	Re
1	ĺ	он В он			91	2
2		он В он			, 90	2
3	H H	он В он			° 88	
4		он В он			, 88	
5	H	O B-OH			87	
6	H	о в-он s	s_		83	
7	$\sim$	ОН			<sup>)</sup> 85	

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### Preparation of Cu/Al<sub>2</sub>O<sub>3</sub> catalyst

Basic alumina (15 g, SRL, India) was added 30 to a well-stirred aqueous solution (30 mL) of CuSO<sub>4</sub>.5H<sub>2</sub>O (1 g, 4 mmol) and the mixture was stirred at 25 °C for 2 h. The excess water was

evaporated on a rotary evaporator under reduced pressure followed by drying under vacuum at 140 °C for 8 h to get the catalyst as a light green powder.

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**Fig. 2** X-band EPR spectrum of  $Cu^{+2}$  in (a) fresh catalyst, (b) after  $1^{st}$  run, (c) after  $8^{th}$  run, (d) at intermediate stage after 30 minutes reaction

<sup>15</sup> EPR data: The X-band EPR spectrum of the fresh catalyst shows four well-defined hyperfine lines for a solid sample at nitrogen atmosphere resulting from the coupling of the unpaired electron with the nuclear spin of Cu(II) (Figure 2). The regenerated and <sup>20</sup> intermediate catalyst also show very similar EPR spectrum as observed in the fresh catalyst





<sup>50</sup> **Fig. 3** XPS data of the (a) fresh, (b) intermediate and (c) recovered catalyst

**XPS analysis:** The XPS study of the fresh, intermediate and recovered catalyst at the Cu 2p level <sup>55</sup> showed the 2p3/2 lines at 934.5, 932.7 and 932.4 eV respectively with characteristic shake up features indicating +2 oxidation state of Cu throughout the reaction. A slight variation (higher) in the binding energy of Cu in the fresh catalyst is possibly due to a <sup>60</sup> combined contribution of CuSO<sub>4</sub> and Cu(OH)<sub>2</sub> on the surface of alumina.



Fig. 4 SEM image of Cu/Al<sub>2</sub>O<sub>3</sub> catalyst

**SEM analysis:** The tuned basic Al<sub>2</sub>O<sub>3</sub> supported Cu <sup>75</sup> (II) catalyst are analysed by FESEM (Field Emission Scanning Electron Microscopy) (Fig. 4). The particles show very uniform spherical morphology. Inset pic. shows a selected area scanning.



Fig. 5 EDX spectra of the catalyst

<sup>15</sup> EDX analysis: Energy Dispersive X-ray (EDX) analysis on various regions confirmed the presence of copper on the support, with energy bands of 8.04, 8.90 Kev (K lines) and 0.92 K (L line) (Fig 5).



**Fig. 6** AFM image of the Cu/Al<sub>2</sub>O<sub>3</sub> catalyst (top), AFM topological image of the catalyst (bottom)

**AFM analysis:** The AFM method is used to provide an independent and quantitative measurement of catalyst particle size and morphology. The morphology of the catalyst is clearly seen from the <sup>50</sup> two-dimensional (2 D) and three- dimensional (3 D) AFM images (Figure 6). By achieving a good dispersion of the particles it is assumed that the particles are spherical in nature.

### <sup>55</sup> Representative experimental procedure for the synthesis of 1,4-disubstituted 1,2,3-triazole (Table 2, entry 1)

A mixture of benzyl bromide (171 mg, 1 mmol) and phenylacetylene (102 mg, 1 mmol), NaN<sub>3</sub> (65 mg, 1 60 mmol) and Cu/Al<sub>2</sub>O<sub>3</sub> (400 mg, 10 mol%) was subjected to ball-milling at 600 rpm using a 25 mL stainless steel beaker with six balls (d = 10 mm) of the same material for 60 min. Ball-milling operation was performed using inverted rotation directions, 65 with interval of 10 min. and taking interval break of 30 sec. Extraction of the reaction residue by simple elution with ethanol followed by evaporation of solvent furnished an ivory solid (96 %), mp = 133<sup>o</sup>C; IR (KBr) 3121, 1466, 1356, 1225, 1074, 1049, <sup>70</sup> 766, 729, 692 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, DMSO-d<sub>6</sub>)  $\delta$  5.63 (s, 2H), 7.31-7.43 (m, 8H), 7.82 (d, J = 7.5 Hz, 2H), 8.63 (s, 1H);  $^{13}$ C NMR (125 MHz, DMSO-d<sub>6</sub>)  $\delta$ 52.9, 121.4, 125.0, 127.7, 128.0, 128.6, 128.7, 130.5, 135.8, 146.5. These spectroscopic data are in good 75 agreement with those of an authentic sample of 1benzyl-4-phenyl-1H-1,2,3-triazole.<sup>14d</sup>

This procedure was followed for all the reactions listed in Table 2. All of these triazoles are known compounds and were easily identified by <sup>80</sup> comparison of their spectroscopic data with those previously reported. These data were provided in the Supplementary Information.

The residual catalyst was further washed with ethanol followed by acetone, dried under <sup>85</sup> vacuum and reused.

# Representative experimental procedure for the synthesis of 1,4-diaryl-1,2,3-triazole from aryl boronic acid (Table 4, entry 1)

A mixture of phenylboronic acid (122 <sup>90</sup> mg, 1 mmol), potassium carbonate (138 mg, 1 mmol), NaN<sub>3</sub> (195 mg, 3 mmol) and Cu/ Al<sub>2</sub>O<sub>3</sub> (400 mg, 10 mol%) was subjected to ball-milling at 600

rpm using six balls (d = 10 mm) for 60 min. Then phenylacetylene (102 mg, 1 mmol) was added to the mixture and the mixture was further submitted to ball-milling at the same condition for one hour, as s required for maximum conversion (TLC/NMR). The product was extracted from the reaction mixture by simple filtration through sintered funnel followed by washing with ethyl acetate (30 ml). The ethyl acetate extract was washed with brine, dried and evaporated <sup>10</sup> to leave the crude product which was crystallized from ethanol-hexane mixture to provide a white solid (91%), mp = 168-171 °C; IR (KBr) 3120, 3090, 1605, 1510, 1412, 1220, 1025, 768 cm<sup>-1</sup>, <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.37 (t, J = 7.5 Hz, 1H), 7.46  $_{15}$  (td, J = 2 and 7.5 Hz, 3H), 7.56 (t, J = 8 Hz, 2H), 7.79-7.81 (m, 2H), 7.91-7.93 (m, 2H), 8.19 (s, 1H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>), δ 117.7, 120.7, 126.0, 128.6, 128.9, 129.0, 130.0, 130.4, 137.3, 148.6. These data are in good agreement with the reported 20 values.<sup>20c</sup>

### 3-(4-Phenyl-1H-1,2,3-triazol-yl)benzaldehyde (Table 4, entry 3)

Dirty white solid (88%), mp = 158-160  $^{\text{O}}$ C; IR (KBr) 3140, 3086, 1699, 1595, 1499, 1454, 1236, 1203, <sup>25</sup> 1176, 1014 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  7.36-7.50 (m, 3H), 7.75 (t, *J* = 7.8 Hz, 1H), 7.90-7.98 (m, 3H), 8.15-8.19 (m, 1H), 8.26-8.27 (m, 1H), 8.30 (s, 1H), 10.12 (s, 1H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  117.5, 120.2, 126.0, 126.1, 128.8, 129.1, 130.0, <sup>30</sup> 130.2, 130.9, 137.9, 138.0, 149.0, 190.9; HRMS calcd for C<sub>15</sub>H<sub>11</sub>N<sub>3</sub>O [M+H]<sup>+</sup>: 250.0980, found: 250.0976.

### Ethyl-4-(4-phenyl-1H-1,2,3-triazol-1-yl)benzoate (Table 4, entry 4)

<sup>35</sup> White solid (88%), mp = 165-168  $^{\circ}$ C; IR (KBr) 3121, 3098, 2995, 1715, 1607, 1454, 1435, 1273, 1225, 1174, 1103 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  1.43 (t, *J* = 7 Hz, 3H), 4.42 (q, *J* = 7 Hz, 2H), 7.38 (t, *J* = 7 Hz, 1H), 7.46 (t, *J* = 7.5 Hz, 2H), 7.89-7.95 (m, 4H), <sup>40</sup> 8.22-8.26 (m, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$ 14.4, 61.6, 117.5, 120.0, 126.1, 128.8, 129.1, 130.0, 130.8, 131.5, 140.2, 148.9, 165.6; HRMS calcd for C<sub>17</sub>H<sub>15</sub>N<sub>3</sub>O<sub>2</sub>[M+H]<sup>+</sup>: 294.1242, found: 294.1237.

#### View Article Online 4-Phenyl-1-(thiophen-3-yl)-1H-1,2,3-triazole 45 (Table 4, entry 5)

Dirty white solid (87%), mp = 164-166  $^{\text{O}}$ C, IR (KBr) 3103, 1558, 1456, 1231, 1092, 1074 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  7.34-7.39 (m, 1H), 7.43-7.53 (m, 4H), 7.61 (dd, *J* = 1.5, 3 Hz, 1H), 7.88-7.91 (m, <sup>50</sup> 2H), 8.11 (s, 1H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$ 114.3, 121.0, 126.0, 127.5, 128.6, 129.1, 130.3; HRMS calcd for C<sub>12</sub>H<sub>9</sub>N<sub>3</sub>S [M+H]<sup>+</sup> : 228.0595, found: 228.0591.

# 1,4-Di-(thiophen-3-yl)-1H-1,2,3-triazole (Table 4, 55 entry 6)

Ivory solid (83%), mp = 184-186  $^{\circ}$ C; IR (KBr) 3105, 1229, 1194, 1092 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  7.40-7.42 (m, 1H), 7.46-7.51 (m, 3H), 7.58-7.60 (m, 1H), 7.76 (d, *J* = 2.1 Hz, 1H), 8.00 (s, 1H); <sup>13</sup>C  $^{\circ0}$  NMR (75 MHz, CDCl<sub>3</sub>),  $\delta$  114.3, 117.9, 121.0, 121.8, 126.0, 126.7, 127.5, 131.5; HRMS calcd for C<sub>10</sub>H<sub>7</sub>N<sub>3</sub>S<sub>2</sub> [M+H]<sup>+</sup> : 234.0159, found: 234.0155.

### 1-((*E*)-Pent-1-enyl)-4-phenyl-1H-1,2,3-triazole (Table 4, entry 7)

<sup>65</sup> White solid (85%), mp = 86-90  $^{\circ}$ C; IR (KBr) 3127, 3096, 2957, 2872, 1460, 1234, 1082, 1039 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  0.99 (t, *J* = 7.5 Hz, 3H), 1.52-1.59 (m, 2H), 2.24 (q, *J* = 7.5 Hz, 2H), 6.23-6.29 (m, 1H), 7.16 (d, *J* = 14 Hz, 1H), 7.30-7.36 (m, 1H), 70 7.43 (t, *J* = 7.5 Hz, 2H), 7.84 (d, *J* = 7.5 Hz, 2H), 7.93 (s, 1H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>), 13.7, 22.3, 31.8, 123.4, 124.5, 126.0, 128.5, 129.0, 130.4; HRMS calcd for C<sub>13</sub>H<sub>15</sub>N<sub>3</sub> [M+H]<sup>+</sup> : 214.1344, found: 214.1338.

### 75 4. Conclusion

In conclusion, we have developed a general procedure for the synthesis of 1,4disubstituted-1,2,3-triazoles by a simple one pot three-component reaction of alkyl halide/aryl boronic <sup>80</sup> acid, sodium azide and terminal alkyne on the surface of Cu/Al<sub>2</sub>O<sub>3</sub> catalyst under ball-milling in absence of any solvent and additive. This protocol offers a broad scope for an access to a wide spectrum of diversely substituted 1,2,3-triazoles. The simplicity in

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operation, avoiding the handling of hazardous azides, use of no toxic organic solvent in the entire process, reusability of the catalyst for the more than eight times, no need for chromatographic purification, <sup>5</sup> reaction at ambient temperature under ball-milling, good purity, excellent regioselectivity and high yields of products make this procedure greener and more cost effective.

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### **Graphical Abstract**

<sup>10</sup> Solvent-free one-pot synthesis of 1,2,3triazole derivatives by 'Click' reaction of alkyl halides or aryl boronic acids, sodium azide and terminal alkynes over Cu/Al<sub>2</sub>O<sub>3</sub> surface under ball-milling

<sup>15</sup> Nirmalya Mukherjee, Sabir Ahammed, Sukalyan Bhadra and Brindaban C. Ranu\*



An efficient solvent-free synthesis of 1,2,3triazole derivatives has been achieved by 'Click' <sup>25</sup> reaction over Cu/Al<sub>2</sub>O<sub>3</sub> surface under ballmilling.

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