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## (DHQD)<sub>2</sub>PHAL ligand-accelerated Cu-catalyzed azide–alkyne cycloaddition reactions in water at room temperature

Abdul Aziz Ali,<sup>a</sup> Mitali Chetia,<sup>a</sup> Prakash J. Saikia<sup>b</sup> and Diganta Sarma<sup>\*a</sup>

Herein, we have described, a 'Click Chemistry' protocol for the rapid synthesis of 1,2,3-triazoles in water. (DHQD)<sub>2</sub>PHAL has been found to be an excellent accelerating ligand for the copper(I)-catalyzed azide–alkyne cycloaddition reaction under air. The procedure is simple, efficient, environmentally-friendly and the products were isolated in excellent yields with high purity.

Water is the solvent of nature; it attracts enormous attention due to its important additional benefits: it is cheap, nonflammable, nontoxic, and an environmentally benign solvent. Water has unique physical and chemical properties such as a high dielectric constant, optimum oxygen solubility to maintain aquatic life forms, high cohesive energy density compared with most organic solvents and has a network of hydrogen bonds which can influence the reactivity of substrates.<sup>1</sup> This unique nature of water is also essential for most biochemical reactions in living systems.<sup>2</sup> From the viewpoint of international consensus on green chemistry, it is desirable to use water instead of organic solvents as a reaction solvent.<sup>3</sup> Therefore, the design and development of environmentally benign chemical processes is often regarded as a goal for synthetic chemists.

The 1,2,3-triazoles are N-heterocyclic compounds which do not occur in nature, although the synthetic molecules that contain 1,2,3-triazole units show a spacious applications ranging from industrial applications to a large number found in pharmaceutical compounds.<sup>4</sup> The 1,2,3-triazole has the beneficial properties like high chemical stability (generally inert to severe hydrolytic, oxidizing, and reducing conditions, even at high temperature), strong dipole moment (4.8–5.6 Debye), aromatic character, and hydrogen bond accepting ability.<sup>5</sup>

Several synthetic methods have been developed for the preparation of 1,2,3-triazole derivatives. Among them, Huisgen 1,3-dipolar azide–alkyne cycloaddition is the most general

approaches for the preparation of five membered heterocycles<sup>6</sup> which proceeds very slowly even at high temperatures, and gives a mixture of 1,4- and 1,5-disubstituted 1,2,3-triazoles. In 2002, the groups of Meldal<sup>7</sup> and Sharpless<sup>8</sup> independently discovered that copper(I) was an excellent catalyst for the regioselective preparation of 1,4-substituted 1,2,3 triazoles. Since then copper-catalyzed azide–alkyne 1,3-dipolar cycloaddition (CuAAC) reaction has been termed as a "click reaction" and numerous applications of the click reaction have been reported in the field of organic synthesis, drug discovery, polymer chemistry, fluorescent imaging, molecular biology, and materials science.<sup>9–12</sup>

The development of copper(I) catalytic systems for CuAAC reactions has been found in numerous literature. Due to the known instability of simple copper(I) salts, the active species are often generated *in situ* from a copper(II) salt and a reducing agent (most often sodium ascorbate). These systems can be enormously efficient, but they are inherently limited to water-tolerant substrates.<sup>13</sup> It has been found that certain Cu-binding ligands accelerate the CuAAC reaction up to several thousand times over the ligand-free process.<sup>14</sup> The CuAAC reaction has been proven to be accelerated by Cu(I) species supported by nitrogen,<sup>15</sup> sulfur,<sup>16</sup> N-heterocyclic carbenes NHC,<sup>17,18</sup> polydentate ligands,<sup>19</sup> simple monodentate phosphine complexes – Cu(P(OEt)<sub>3</sub>)<sub>3</sub>I,<sup>20</sup> Cu(PPh<sub>3</sub>)<sub>3</sub>Br,<sup>21,22</sup> and Cu(PPh<sub>3</sub>)<sub>2</sub>OAc,<sup>23</sup> monodentate phosphoramidite<sup>24</sup> and thioethers,<sup>25</sup> and histidine derivatives.<sup>26</sup> The use of ligands in this context protects the copper(I) center from oxidation or disproportionation and enhances its catalytic activity allowing for smoother reaction conditions or broader applicability. Although most of these ligands help speeding up the reaction, but still fall short of the requisite reaction times for labelling of biological targets with short-lived radioisotopes. Others shortcomings involve high catalyst loadings, tricky synthetic route, long reaction time, use of organic solvent *etc.*

(DHQD)<sub>2</sub>PHAL or hydroquinidine-1,4-phthalazinediyl diether (Fig. 1) is a phthalazine class of ligand and it was first introduced by Sharpless *et al.* for asymmetric dihydroxylation of alkenes.<sup>27</sup> This reagent is readily available and air stable

<sup>a</sup>Department of Chemistry, Dibrugarh University, Dibrugarh-786004, Assam, India. E-mail: dsarma22@gmail.com; dsarma22@dibru.ac.in

<sup>b</sup>Analytical Chemistry Division, CSIR-North East Institute of Science & Technology, Jorhat-785006, Assam, India

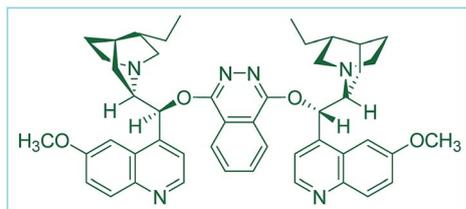


Fig. 1 (DHQD)<sub>2</sub>PHAL ligand.

polydentate ligand. Considering the virtues of ligands, we describe here a (DHQD)<sub>2</sub>PHAL stabilized copper(i) catalyst, without the requirement of immobilization on a polymeric or an inorganic support, for the synthesis of 1,2,3-triazoles in aqueous media at room temperature.

## Results and discussion

We initialized our studies with the cycloaddition of benzyl azide with phenylacetylene as model reaction under standard cycloaddition conditions. The reaction of benzyl azide and phenyl acetylene catalyzed by copper sulphate in presence of sodium ascorbate and (DHQD)<sub>2</sub>PHAL ligand in a mixture of water : *t*-BuOH (1 : 1) solvent system afforded 1,2,3-triazoles in 50% yields (Table 1, entry 1). Optimization studies revealed that the CuAAC reaction could be performed with moderate yields using various copper sources (Table 1, entries 2–7). Interestingly, when CuI (1 mol%) was used as the catalyst the reaction proceeded smoothly under air to afford 1-benzyl-4-phenyl-1,2,3-triazole regioselectively in 75% yields (Table 1, entry 8). Our

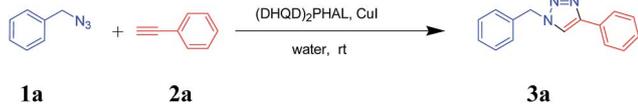
results were well supported by earlier findings. F. Li and T. S. A. Hor reported the use of copper coordinated nitrogen tetradentate ligands for CuAAC reaction.<sup>19</sup> They performed the azide–alkyne cycloaddition reactions in presence of one equivalent each of CuI and ligand in MeCN : water (1 : 1 ratio) solvent system for 10 h at room temperature to achieve almost quantitative yields. Wang *et al.* developed a ‘on water’ protocol for copper catalyzed cycloaddition of water-insoluble aliphatic/aryl azides and alkynes at room temperature using 10 mol% catalyst (CuBr) and 50 mol% ligand (PhSMe).<sup>16</sup> B. L. Feringa and his research group described the accelerating nature of monodentate phosphoramidite ligands for CuAAC reaction yielding a wide variety of functionalized 1,4-disubstituted-1,2,3-triazoles.<sup>24</sup> Their methodology involved the CuAAC reaction carried out in presence of 1 mol% copper sulphate (in presence of sodium ascorbate) and 1.1 mol% ligand in DMSO : water (1 : 3 ratio) solvent system.

Encouraged by the high activity of our catalytic system, we then next performed the CuAAC reaction of benzyl azide and phenyl acetylene in presence of CuI catalyst in different solvent systems (Table 1, entries 9–16). Unlike earlier literature reports, the reaction proceeded in excellent yields (90%) under aqueous conditions (Table 1, entry 10). Taking into account the interest of environmental concerns and economic considerations, all CuAAC reactions were performed under aqueous conditions. As water was found to be the best solvent for the reaction under this reaction condition, we next investigated catalyst loading (Table 2, entries 1–3) and gratifyingly, upon lowering the catalyst concentration to 0.5 mol% the reaction still proceeded within 10 min giving 88% yields (Table 2, entry 2). Therefore, a

Table 1 Solvent and catalyst optimization studies<sup>a</sup>

| Entry | Copper source                        | Solvent                                  | Time (min) | Yield <sup>b</sup> (%) |
|-------|--------------------------------------|--|------------|------------------------|
| 1     | CuSO <sub>4</sub> + sodium ascorbate | H <sub>2</sub> O/ <i>t</i> -BuOH (1 : 1) | 60         | 50                     |
| 2     | CuCl                                 | H <sub>2</sub> O/ <i>t</i> -BuOH (1 : 1) | 60         | 55                     |
| 3     | Cu(OAc)                              | H <sub>2</sub> O/ <i>t</i> -BuOH (1 : 1) | 60         | 65                     |
| 4     | CuOTf                                | H <sub>2</sub> O/ <i>t</i> -BuOH (1 : 1) | 60         | 60                     |
| 5     | Cu powder                            | H <sub>2</sub> O/ <i>t</i> -BuOH (1 : 1) | 60         | 50                     |
| 6     | CuCN                                 | H <sub>2</sub> O/ <i>t</i> -BuOH (1 : 1) | 60         | 48                     |
| 7     | CuBr                                 | H <sub>2</sub> O/ <i>t</i> -BuOH (1 : 1) | 60         | 55                     |
| 8     | CuI                                  | H <sub>2</sub> O/ <i>t</i> -BuOH (1 : 1) | 20         | 75                     |
| 9     | CuI                                  | THF                                      | 60         | 70                     |
| 10    | CuI                                  | H <sub>2</sub> O                         | 5          | 90                     |
| 11    | CuI                                  | DMSO                                     | 40         | 65                     |
| 12    | CuI                                  | DMF                                      | 60         | 68                     |
| 13    | CuI                                  | Acetone                                  | 50         | 65                     |
| 14    | CuI                                  | Toluene                                  | 60         | 50                     |
| 15    | CuI                                  | DCM                                      | 60         | 52                     |
| 16    | CuI                                  | H <sub>2</sub> O                         | 60         | 0 <sup>c</sup>         |

<sup>a</sup> Reagents and reaction conditions: **1a** (1 mmol), **2a** (1.1 mmol), catalyst (1 mol%) and ligand (1 mol%) in the given solvent was stirred at room temperature in open air otherwise stated. <sup>b</sup> Isolated yields after reduced pressure distillation. <sup>c</sup> Absence of ligand.

Table 2 CuAAC with different loading of catalyst<sup>a</sup>


| Entry | CuI (mol%) | Time (min) | Yield <sup>b</sup> (%) |
|-------|------------|------------|------------------------|
| 1     | 1          | 10         | 90                     |
| 2     | 0.5        | 10         | 88                     |
| 3     | 2          | 10         | 91                     |

<sup>a</sup> Reagents and reaction conditions: **1a** (1 mmol), **2a** (1.1 mmol), and catalyst CuI (0.5–2 mol%), and ligand (1 mol%) in water. <sup>b</sup> Isolated yields.

catalyst loading of 0.5 mol% appeared to be optimal with respect to yields and short reaction times. Significantly, under these optimized conditions, no undesirable byproduct could be detected. However, in absence of ligand, no triazole formation was observed under this reaction condition, highlighting the key role of the ligand (Table 1, entry 16).

With optimized parameters in hand, exploration of the scope of the catalyst system for CuAAC reaction was performed in water at room temperature without the exclusion of air with a variety of organic azides and acetylenes. The results are exemplified in Table 3 (entries 1–12). All reactions proceeded

Table 3 Copper(i) catalysed azide–alkyne cycloaddition of a variety of azides and alkynes in water at room temperature<sup>a</sup>

| Entry | Azide | Alkyne | Product   | Time (min) | Yield <sup>b</sup> (%) |
|-------|-------|--------|-----------|------------|------------------------|
| 1     |       |        | <b>3a</b> | 5          | 88                     |
| 2     |       |        | <b>3b</b> | 30         | 82                     |
| 3     |       |        | <b>3c</b> | 15         | 85                     |
| 4     |       |        | <b>3d</b> | 20         | 87                     |
| 5     |       |        | <b>3e</b> | 25         | 82                     |
| 6     |       |        | <b>3f</b> | 30         | 84                     |
| 7     |       |        | <b>3g</b> | 30         | 82                     |
| 8     |       |        | <b>3h</b> | 25         | 86                     |
| 9     |       |        | <b>3i</b> | 20         | 90                     |
| 10    |       |        | <b>3j</b> | 30         | 92                     |
| 11    |       |        | <b>3k</b> | 25         | 90                     |
| 12    |       |        | <b>3l</b> | 20         | 87                     |

<sup>a</sup> All reactions were carried out using azide (1 mmol), alkynes (1.1 mmol), CuI (0.5 mol%), and (DHQD)<sub>2</sub>PHAL (0.01 mmol) in H<sub>2</sub>O (2 mL) at room temp. <sup>b</sup> Isolated yields.

smoothly giving excellent isolated yields of the corresponding triazoles after simple extraction and crystallization, irrespective of the substitution either on the starting azides or on the alkynes. The results indicated that benzyl (entries 1, 6 and 9, Table 3), aryl (entries 2–4, 7–8, and 10–12, Table 3), and alkyl azides (entry 5, Table 3) generated the 1,4-disubstituted 1,2,3-triazoles in excellent yields. Of the alkynes, aromatic (entries 1–5, Table 3) and aliphatic alkynes (entries 6–8, Table 3) – all worked efficiently toward this click conversion and the hydroxyl-functionalized alkyne (entries 9–12, Table 3) was also a good coupling partner resulting in 87–92% yields of the desired triazoles.

## Conclusions

In conclusion, we have successfully developed a quick, versatile, highly efficient and environmentally friendly catalytic system for CuAAC reactions in water. This protocol provides a wide scope for the synthesis of desired 1,4-disubstituted-1,2,3-triazoles in excellent yields within a few minutes by using (DHQD)<sub>2</sub>PHAL as an accelerating ligand at room temperature. The operational ease of this protocol and the purity of the recovered products make it attractive for tremendous applications in various research fields.

## Experimental

All reactions were carried out in oven dried glassware under atmospheric conditions otherwise noted. Reagents and solvents were obtained from commercial suppliers and used without further purification. All reported yields are isolated yields. Thin layer chromatography (TLC) was carried out using aluminium sheets pre-coated with silica gel 60F<sub>254</sub> (Merck) and was visualized under 254 nm UV light. <sup>1</sup>H NMR (300 MHz), <sup>13</sup>C NMR (100 MHz) were measured on a Bruker Avance 400 MHz spectrometer. Chemical shifts are reported in parts per million (ppm,  $\delta$ ) downfield from residual solvents peaks and coupling constants are reported as Hertz (Hz). Splitting patterns are designated as singlet (s), doublet (d), triplet (t), quartet (q), broad (br) *etc.*, splitting patterns that could not be interpreted or easily visualized are designated as multiplet (m). ESI-MS spectra were recorded on an Agilent 6510 ESI-QTOF LC/MS mass spectrometer. Melting points were measured with a Büchi B-540 melting point apparatus.

### Synthesis of azide

All azides were synthesized according to the reported procedure.<sup>28</sup>

**A typical CuAAC procedure for the preparation of 1,2,3-triazole.** To a mixture of CuI (0.95 mg, 0.5 mol%), (DHQD)<sub>2</sub>PHAL (7.7 mg, 0.01 mmol) and azide (1 mmol) in deionised water (2 mL), alkyne (1.1 mmol) was added at room temperature. The resultant mixture was stirred continuously until the reaction system solidified completely. Then ethyl acetate (20 mL) was added to dissolve the crude product. The organic layer was washed with H<sub>2</sub>O, 0.25 N HCl (10 mL) and brine, and dried over

anhydrous Na<sub>2</sub>SO<sub>4</sub>. Removal of the solvent yielded a residue, which was washed with petroleum ether (50 mL) to furnish the product triazoles.

**1-Benzyl-4-phenyl-1H-1,2,3-triazole (3a).** White solid, mp 128–130 °C, 88% yield. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.80 (d, *J* = 7.35 Hz, 2H), 7.66 (s, 1H), 7.42–7.29 (m, 5H), 5.57 (s, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 148.2, 134.6, 130.4, 129.1, 128.8, 128.2, 128.0, 125.7, 119.5, 54.2. MS (ESI) *m/z*: 236 [M + H]<sup>+</sup>, cal. 236.3.

**1-(4-Diphenyl)-1H-1,2,3-triazole (3b).** Pale yellow solid, mp 183–184 °C, 82% yield. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 8.19 (s, 1H), 7.92 (d, *J* = 7.34 Hz, 2H), 7.80 (d, *J* = 7.73 Hz, 2H), 7.64–7.19 (m, 6H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 148.9, 137.2, 130.6, 129.5, 129.1, 128.8, 126.2, 120.6, 118.4; MS (ESI) *m/z*: 222 [M + H]<sup>+</sup>, cal. 222.3.

**1-(4-Bromophenyl)-4-phenyl-1H-1,2,3-triazole (3c).** White solid, mp 231–233 °C, 85% yield. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 8.17 (s, 1H), 7.91–7.35 (m, 9H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 149.1, 133.3, 136.4, 130.4, 129.4, 129.0, 126.3, 122.8, 122.3, 117.7. MS (ESI) *m/z*: 301 [M + H]<sup>+</sup>, cal. 301.2.

**1-(4-Chlorophenyl)-4-phenyl-1H-1,2,3-triazole (3d).** Yellow solid, mp 225–227 °C, 87% yield. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 8.17 (s, 1H), 7.92 (d, *J* = 7.5 Hz, 2H), 7.77 (d, *J* = 8.6 Hz, 2H), 7.54–7.36 (m, 5H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 135.6, 134.4, 129.8, 128.8, 128.4, 125.7, 121.5, 117.2. MS (ESI) *m/z*: 257 [M + H]<sup>+</sup>, cal. 256.7.

**1-Octyl-4-phenyl-1H-1,2,3-triazole (3e).** White solid, mp 74–76 °C, 82% yield. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.84 (d, *J* = 7.3 Hz, 2H), 7.74 (s, 1H), 7.44–7.29 (m, 3H), 4.40 (t, *J* = 7.2 Hz, 2H), 1.96 (t, *J* = 7.0 Hz, 2H), 1.34–1.26 (m, 10H), 0.89 (t, *J* = 6.9 Hz, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 147.5, 130.6, 129.0, 128.7, 127.9, 125.5, 119.3, 50.3, 31.5, 30.2, 28.9, 28.8, 26.3, 22.4, 13.9. MS (ESI) *m/z*: 258 [M + H]<sup>+</sup>, cal. 258.4.

**1-Benzyl-4-butyl-1H-1,2,3-triazole (3f).** White solid, mp 64–66 °C, 84% yield. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.41–7.21 (m, 6H), 5.50 (s, 2H), 2.73 (t, *J* = 7.5 Hz, 2H), 1.68–1.58 (m, 2H), 1.42–1.30 (m, 2H), 0.93 (t, *J* = 7.5 Hz, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 148.2, 134.9, 128.2, 128.4, 127.2, 120.4, 53.6, 31.4, 25.2, 22.3, 14.7. MS (ESI) *m/z*: 216 [M + H]<sup>+</sup>, cal. 216.3.

**4-Butyl-1-phenyl-1H-1,2,3-triazole (3g).** Colorless liquid, 82% yield. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.73 (d, *J* = Hz, 2H), 7.53–7.39 (m, 3H), 7.27 (s, 1H), 2.83–2.78 (t, 2H), 1.77–1.67 (m, 2H), 1.49–1.37 (m, 2H), 0.98 (t, *J* = 7.2 Hz, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 151.3, 130.5, 128.5, 127.9, 126.6, 119.4, 50.1, 32.4, 19.7, 14.4. MS (ESI) *m/z*: 202 [M + H]<sup>+</sup>, cal. 202.3.

**1-(4-Bromo-phenyl)-4-butyl-1H-[1,2,3]triazole (3h).** White solid, mp 69–71 °C, 86% yield. <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 8.61 (s, 1H), 7.88 (d, *J* = 8.8 Hz, 2H), 7.80 (d, *J* = 8.8 Hz, 2H), 2.72 (t, *J* = 7.4 Hz, 2H), 1.70–1.60 (m, 2H), 1.43–1.35 (m, 2H), 0.94 (t, *J* = 7.3 Hz, 3H); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>): δ 148.8, 136.4, 133.1, 122.1, 121.3, 127.82, 120.5, 55.3, 31.3, 25.1, 22.1, 14.1. MS (ESI) *m/z*: 281 [M + H]<sup>+</sup>, cal. 281.2.

**(1-Benzyl-1H-1,2,3-triazol-4-yl) methanol (3i).** White solid, mp 75–78 °C, 90% yield. <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 8.02 (s, 1H), 7.40–7.31 (m, 5H), 5.57 (s, 2H), 4.52 (s, 2H), 2.50 (br, 1H); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>): δ 148.7, 136.6, 129.1, 128.5, 128.3, 123.2, 55.5, 53.1. MS (ESI) *m/z*: 190 [M + H]<sup>+</sup>, cal. 190.2.

**(1-Phenyl-1H-[1,2,3]triazol-4-yl)-methanol (3j).** White solid, mp 115–118 °C, 92% yield. <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 8.68 (s, 1H), 7.92 (d, *J* = 7.8 Hz, 2H), 7.61–7.45 (m, 3H), 4.64 (d, *J* = 5.2 Hz, 2H), 2.50 (br, 1H); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>): δ 149.6, 137.2, 130.3, 128.9, 121.4, 120.4, 55.4. MS (ESI) *m/z*: 176 [M + H]<sup>+</sup>, cal. 176.2.

**[1-(4-Chloro-phenyl)-1H-[1,2,3]triazol-4-yl]-methanol (3k).** Yellowish solid, mp 146–148 °C, 90% yield. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 8.01 (s, 1H), 7.68 (d, *J* = 8.5 Hz, 2H), 7.50 (d, *J* = 8.5 Hz, 2H) 4.88 (s, 2H), 2.35 (br, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): 148.7, 135.5, 134.6, 129.9, 121.7, 56.2. MS (ESI) *m/z*: 211 [M + H]<sup>+</sup>, cal. 210.6.

**[1-(4-Bromo-phenyl)-1H-[1,2,3]triazol-4-yl]-methanol (3l).** Yellowish solid, mp 135–137 °C, 87% yield. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 8.00 (s, 1H), 7.72–7.59 (m, 4H), 4.89 (s, 2H), 2.14 (br, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): 148.2, 136.8, 134.3, 130.9, 121.3, 54.6. MS (ESI) *m/z*: 255 [M + H]<sup>+</sup>, cal. 255.1.

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