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## COMMUNICATION

C–H Arylations of 1,2,3-Triazoles by Reusable Heterogeneous Palladium Catalysts in Biomass-Derived  $\gamma$ -Valerolactone
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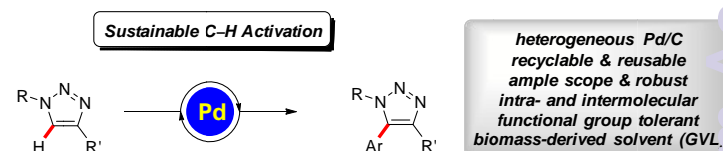
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**C–H arylations were accomplished with a user-friendly heterogeneous palladium catalyst in the biomass-derived  $\gamma$ -valerolactone (GVL) as an environmentally-benign reaction medium. The user-friendly protocol was characterized by ample substrate scope and high functional group tolerance in the C–H arylation of 1,2,3-triazoles, and the palladium catalyst could be recycled and reused in the C–H activation process.**

## Introduction

Fully functionalized 1,2,3-triazoles<sup>1</sup> constitute key structural motifs in various applied areas, such as medicinal chemistry, bioorganic chemistry, and material sciences, among others.<sup>2</sup> The copper(I)-catalyzed azide-alkyne 1,3-dipolar cycloaddition<sup>3</sup> (CuAAC)<sup>4, 5</sup> has emerged as the most valuable tool for the preparation of 1,2,3-triazoles with high levels of regio control.<sup>6, 7</sup> However, the CuAAC approach is largely<sup>8</sup> limited to terminal alkynes and, hence, fails short in providing general access to fully trisubstituted triazoles. In recent years, catalyzed C–H activations have been identified as a transformative platform for the atom-<sup>9</sup> and step-economical<sup>10</sup> preparation of heterocyclic compounds.<sup>11</sup> Particularly, the nexus of CuAAC and C–H functionalization technology proved instrumental for the efficient assembly of fully decorated 1,2,3-triazoles with excellent levels of positional selectivity.<sup>12</sup> Hence, copper-<sup>13, 14</sup> and palladium-based<sup>15–22</sup> catalysts were shown to enable the site-selective C–H arylation of 1,2,3-triazoles.<sup>23</sup> Despite these undisputable advances, C–H arylations on 1,2,3-triazoles were thus far solely accomplished with homogeneous catalysts, rendering a recycling and reuse of the metal catalysts challenging, while, at the same time, leading to considerable amounts of undesired metal impurities in the target products. Moreover, the catalyzed C–H functionalizations of 1,2,3-triazoles were predominantly performed in dipolar aprotic solvents, such as dimethylformamide (DMF), *N*-

methylpyrrolidin-2-one (NMP) and *N,N*-dimethylacetamide (DMA). Unfortunately, these solvents face considerable environmental and safety issues, which is of particular relevance for the practitioner in academia and industries.<sup>24</sup> Within our program directed towards sustainable C–H activation technology,<sup>25, 26</sup> we have developed the first triazole C–H arylation by the aid of a recyclable heterogeneous<sup>27–31</sup> catalyst (Figure 1). Thus, a versatile palladium catalyst was effectively reused in the C–H activation of synthetically meaningful 1,2,3-triazoles. Importantly, we herein also describe the use of bio-based  $\gamma$ -valerolactone (GVL)<sup>32, 33</sup> – available from renewable lignocellulosic biomass<sup>–34, 35</sup> as an environmentally-sound medium in direct C–H arylation.



**Figure 1.** Sustainable heterogeneous C–H arylation in GVL.

## Results and Discussion

At the outset of our studies, we optimized reaction conditions for the envisioned palladium-catalyzed C–H arylation of triazole **1a** with aryl bromide **2a** in the biomass-derived GVL as the solvent (Table 1). The C–H arylation occurred smoothly by means of palladium on charcoal catalysis in the presence of the carboxylic acid MesCO<sub>2</sub>H as the cocatalyst<sup>36</sup> and with K<sub>2</sub>CO<sub>3</sub> as the base, thereby delivering the desired product **3aa** (entries 1–3). The C–H functionalization proceeded with excellent positional selectivity, and only trace amounts of the diarylated product **4aa** were detected (entry 3). Among a representative set of bases (entries 3–9), K<sub>2</sub>CO<sub>3</sub> and KTFM furnished optimal results (entries 7 and 9), with a slightly improved efficacy at a higher reaction temperature (entries 3 and 7).

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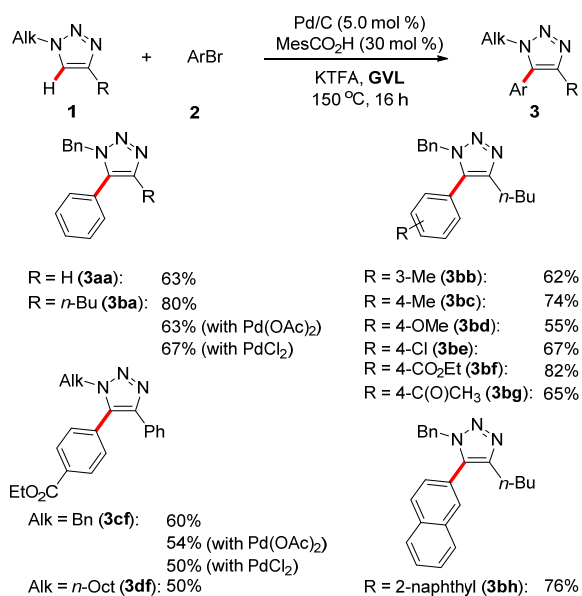
† Electronic Supplementary Information (ESI) available: Experimental procedures, characterization data, and <sup>1</sup>H and <sup>13</sup>C NMR spectra for products. See DOI: 10.1039/b000000x

**Table 1.** Optimization of palladium-catalyzed C–H arylations in GVL.<sup>a</sup>

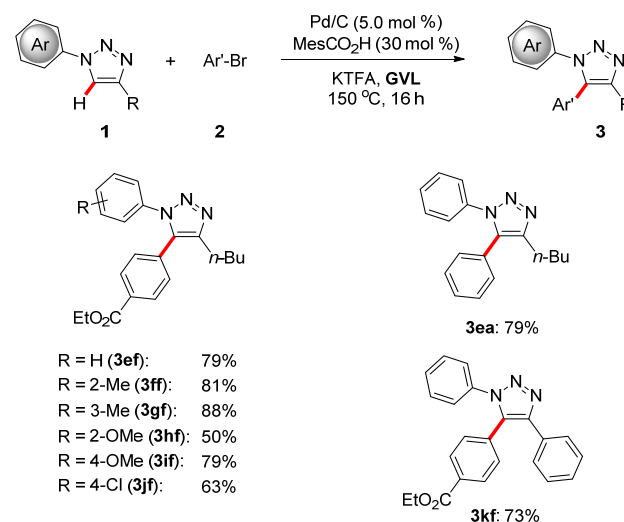
Entry	Base	<b>3aa</b> (%) <sup>b</sup>	<b>4aa</b> (%) <sup>b</sup>
1	NEt <sub>3</sub> <sup>c</sup>	---	---
2	Cs <sub>2</sub> CO <sub>3</sub> <sup>c</sup>	---	---
3	K <sub>2</sub> CO <sub>3</sub> <sup>c</sup>	70	8
4	NH <sub>4</sub> OAc	---	---
5	Na <sub>2</sub> CO <sub>3</sub>	45	5
6	KHCO <sub>3</sub>	78	14
7	<b>K<sub>2</sub>CO<sub>3</sub></b>	<b>82 (55)</b>	<b>16 (4)</b>
8	KOAc	66 (42)	16 (4)
9	<b>KTFA</b>	<b>86 (63)</b>	<b>14(8)</b>

[a] Reaction conditions: **1a** (0.25 mmol), **2a** (0.75 mmol), Pd/C (5.0 mol %), MesCO<sub>2</sub>H (30 mol %), base (3 equiv), GVL (1.0 mL), 150 °C, 16 h. [b] <sup>1</sup>H NMR conversion with CH<sub>2</sub>Br<sub>2</sub> as internal standard, yields of isolated products are given in parentheses. [c] 130 °C.

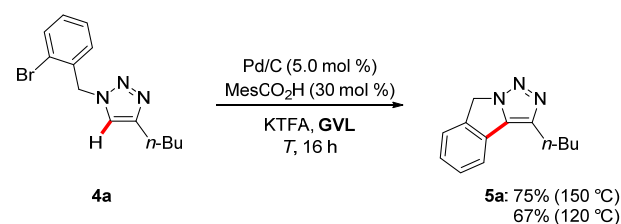
With the optimized reaction conditions in hand, we initially probed the catalyst's versatility in the C–H arylation of *N*-alkyl-substituted 1,2,3-triazoles **1a–1d** in GVL (Scheme 1). Thus, both mono- and 1,4-di-substituted 1,2,3-triazoles **1a,b** were efficiently converted. The triazole **1b** displaying two alkyl-substituents delivered the corresponding products **3bb–3bh** selectively as the sole products. Here, the robust nature of the heterogeneous palladium catalyst was reflected by fully tolerating valuable electrophilic functional groups, such as chloro, ester or enolizable ketone substituents. Likewise, the hindered 2-naphthyl electrophile **2h** was transformed with high catalytic efficacy, as were alkyl-substituted 1,2,3-triazoles **1c,d**.

**Scheme 1.** C–H arylation of *N*-alkyl triazoles **1** in GVL.

Subsequently, we evaluated the power of the Pd/C catalyst in the C–H functionalization of 1,2,3-triazole **1e–1k** bearing *N*-aryl motifs (Scheme 2). Hence, differently decorated arenes were well tolerated by the user-friendly catalyst, enabling the synthesis of regioselectively arylated products **3** with excellent positional control. Substrates **1f–1j** with electron-withdrawing or electron-donating *N*-aryl groups furnished the desired tri-substituted 1,2,3-triazoles **3ef–3jf**, again featuring good functional group tolerance. Thereby, our strategy provided atom-economical access to the selectively tri-arylated 1,2,3-triazole **3kf** as well.

**Scheme 2.** C–H arylation of *N*-arylated triazoles **1** in GVL.

The heterogeneous catalyst was not restricted to intermolecular C–H arylations in GVL. Indeed, the intramolecular C–H functionalization with substrate **4a** proved viable with comparable levels of efficacy, thereby delivering the triazolo[1,5-*a*]isoindole **5a** (Scheme 3).

**Scheme 3.** Intramolecular C–H arylation in GVL.

In consideration of the remarkable efficacy of the versatile palladium C–H activation catalyst, we became attracted to probing its recyclability and reusability. To this end, we developed an effective protocol for the recycle of the heterogeneous palladium catalyst (Table 2), thereby allowing for the robust reuse of the catalyst. It is noteworthy that only a minor amount of palladium was detected by detailed ICP-MS analysis of the crude product.<sup>37</sup> This observation indicated only minor leaching,<sup>38</sup> that is within the specifications for active pharmaceutical ingredients produced by palladium-catalyzed processes.<sup>39</sup> Our findings were further in line with a hot-filtration test and mercury poisoning studies,<sup>37</sup> which provided strong support for a heterogeneous mode of action.

Likewise, the three-phase test suggested that no active homogeneous palladium species were formed.<sup>37</sup>

**Table 2.** Recovery and reuse of palladium catalyst.<sup>[a]</sup>

Run	1 <sup>st</sup>	2 <sup>nd</sup>	3 <sup>rd</sup>
<b>3If (%)</b>	90	90	90
<b>Pd-leaching (ppm)<sup>[b]</sup></b>	5.5	4.1	3.6

[a] Reaction conditions: **1I** (0.30 mmol), **2f** (0.45 mmol), Pd/C (5.0 mol %), MesCO<sub>2</sub>H (30 mol %), K<sub>2</sub>CO<sub>3</sub> (0.60 mmol), GVL (2.0 mL), 120 °C, 24 h. [b] By ICP-MS analysis.<sup>37</sup>

## Conclusions

In summary, we have developed the first C–H arylation of 1,2,3-triazoles by a heterogeneous catalyst in environmentally-sound  $\gamma$ -valerolactone (GVL)<sup>40</sup> as the reaction medium. Thus, a broadly applicable palladium catalyst allowed for inter- as well as intramolecular C–H functionalizations with ample scope. The biomass-derived solvent further set the stage for the efficient reuse of the heterogeneous palladium catalyst in positional selective C–H activations. The use of the biomass-based GVL as environmentally-benign solvent in C–H functionalization technology should prove instrumental for the future development of sustainable processes.<sup>41</sup>

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