C–H arylations of 1,2,3-triazoles by reusable heterogeneous palladium catalysts in biomass-derived γ-valerolactone†

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C–H arylations were accomplished with a user-friendly heterogeneous palladium catalyst in the biomass-derived γ-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.

Fully functionalized 1,2,3-triazoles constitute key structural motifs in various applied areas, such as medicinal chemistry, bioorganic chemistry, and material sciences, among others. The copper(i)-catalyzed azide–alkyne 1,3-dipolar cycloaddition (CuAAC) has emerged as the most valuable tool for the preparation of 1,2,3-triazoles with high levels of regiocontrol. However, the CuAAC approach is largely 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- and step-economical preparation of heterocyclic compounds. 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. Hence, copper- and palladium-based catalysts were shown to enable the site-selective C–H arylation of 1,2,3-triazoles. 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. Within our program directed towards sustainable C–H activation technology, we have developed the first triazole C–H arylation by the aid of a recyclable heterogeneous catalyst (Fig. 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 γ-valerolactone (GVL) – available from renewable lignocellulosic biomass – as an environmentally-sound medium in direct C–H arylation.

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 MesCO2H as the cocatalyst and with K2CO3 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), K2CO3 and KTFA furnished optimal results (entries 7 and 9), with a slightly improved efficacy at a higher reaction temperature (entries 3 and 7).

With the optimized reaction conditions in hand, we initially probed the catalyst’s versatility in the C–H arylation of N-allyl-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.

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 regio-selectively 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 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.

The heterogeneous catalyst was not restricted to intermolecular C–H arylation 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).

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

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**Table 1** Optimization of palladium-catalyzed C–H arylation in GVL

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>3aa (%)</th>
<th>4aa (%)</th>
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<tbody>
<tr>
<td>1</td>
<td>NEt₃</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>2</td>
<td>Cs₂CO₃</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>3</td>
<td>K₂CO₃</td>
<td>70</td>
<td>8</td>
</tr>
<tr>
<td>4</td>
<td>NH₄Ac</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>5</td>
<td>Na₂CO₃</td>
<td>45</td>
<td>5</td>
</tr>
<tr>
<td>6</td>
<td>KHC₃O₃</td>
<td>78</td>
<td>14</td>
</tr>
<tr>
<td>7</td>
<td>K₂CO₃</td>
<td>82 (55)</td>
<td>16 (4)</td>
</tr>
<tr>
<td>8</td>
<td>KOAc</td>
<td>66 (42)</td>
<td>16 (4)</td>
</tr>
<tr>
<td>9</td>
<td>KTFA</td>
<td>86 (63)</td>
<td>14 (8)</td>
</tr>
</tbody>
</table>

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

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

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

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**Table 2** Recovery and reuse of palladium catalyst

<table>
<thead>
<tr>
<th>Run</th>
<th>1st</th>
<th>2nd</th>
<th>3rd</th>
</tr>
</thead>
<tbody>
<tr>
<td>3lf (%)</td>
<td>90</td>
<td>90</td>
<td>90</td>
</tr>
<tr>
<td>Pd-leaching (ppm)</td>
<td>5.5</td>
<td>4.1</td>
<td>3.6</td>
</tr>
</tbody>
</table>

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*a Reaction conditions: 1a (0.25 mmol), 2a (0.75 mmol), Pd/C (5.0 mol%), MesCO₂H (30 mol%), base (3 equiv.), GVL (1.0 mL), 150 °C, 16 h. \(^b\) \(^c\) \(^d\) **Communication ChemComm**

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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.\textsuperscript{37} This observation indicated only minor leaching,\textsuperscript{38} that is within the specifications for active pharmaceutical ingredients produced by palladium-catalyzed processes.\textsuperscript{39}

Our findings were further in line with a hot-filtration test and mercury poisoning studies,\textsuperscript{37} which provided strong support for a heterogeneous mode of action. Likewise, the three-phase test suggested that no active homogeneous palladium species were formed.\textsuperscript{37}

In summary, we have developed the first C–H arylation of 1,2,3-triazoles by a heterogeneous catalyst in environmentally-sound γ-valerolactone (GVL)\textsuperscript{40} 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.\textsuperscript{41}

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37 For detailed information, see the ESI.


40 Under otherwise identical reaction conditions, a C–H arylation under air led to less effective catalysis.