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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-triazoles¹ constitute key structural motifs in various applied areas, such as medicinal chemistry, bioorganic chemistry, and material sciences, among others.² The copper(i)-catalyzed azide–alkyne 1,3-dipolar cycloaddition³ (CuAAC)^{4,5} has emerged as the most valuable tool for the preparation of 1,2,3-triazoles with high levels of regio control.^{6,7} However, the CuAAC approach is largely⁸ 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-⁹ and step-economical¹⁰ preparation of heterocyclic compounds.¹¹ 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.¹² Hence, copper-^{13,14} and palladium-based^{15–22} catalysts were shown to enable the site-selective C–H arylation of 1,2,3-triazoles.²³ 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.

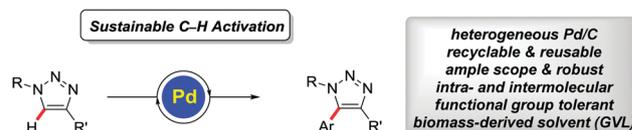


Fig. 1 Sustainable heterogeneous C–H arylation in GVL.

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.²⁴ Within our program directed towards sustainable C–H activation technology,^{25,26} we have developed the first triazole C–H arylation by the aid of a recyclable heterogeneous^{27–31} 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)^{32,33} – available from renewable lignocellulosic biomass^{34,35} – 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 cocatalyst³⁶ 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*-alkyl-substituted 1,2,3-triazoles **1a–1d** in GVL (Scheme 1). Thus, both

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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.³⁷ This observation indicated only minor leaching,³⁸ that is within the specifications for active pharmaceutical ingredients produced by palladium-catalyzed processes.³⁹ Our findings were further in line with a hot-filtration test and mercury poisoning studies,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.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)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.⁴¹

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