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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.

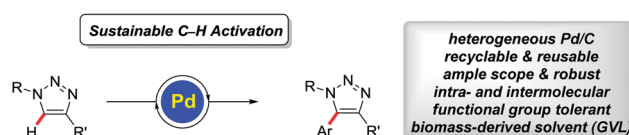


Fig. 1 Sustainable heterogeneous C–H arylation in GVL.

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).

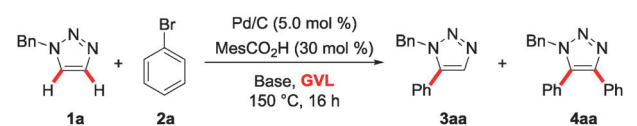
With the optimized reaction conditions in hand, we initially probed the catalyst's versatility in the C–H arylation of *N*-alkyl-substituted 1,2,3-triazoles **1a–1d** in GVL (Scheme 1). Thus, both

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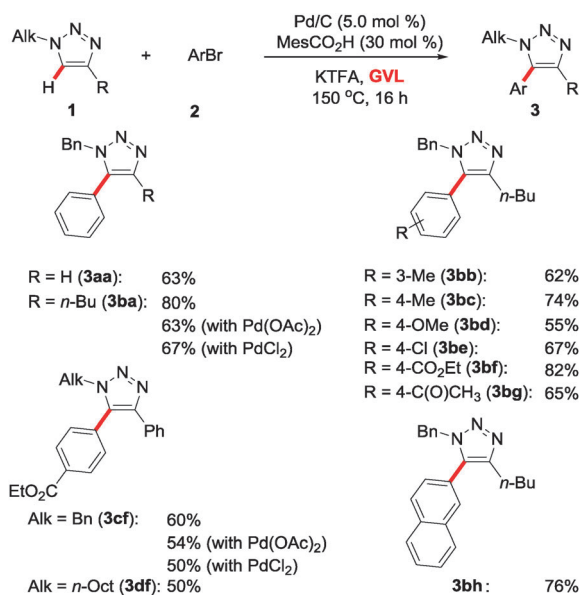
† Electronic supplementary information (ESI) available: Experimental procedures, characterization data, and ¹H and ¹³C NMR spectra for products. See DOI: 10.1039/c6cc03468c



Table 1 Optimization of palladium-catalyzed C–H arylations in GVL^a


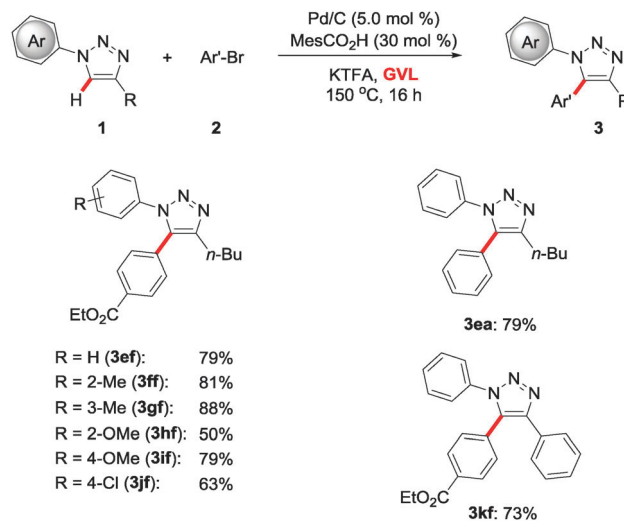
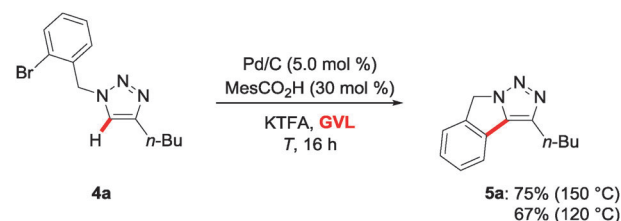
Entry	Base	3aa ^b (%)	4aa ^b (%)
1	NEt ₃ ^c	—	—
2	CS ₂ CO ₃ ^c	—	—
3	K ₂ CO ₃ ^c	70	8
4	NH ₄ OAc	—	—
5	Na ₂ CO ₃	45	5
6	KHCO ₃	78	14
7	K ₂ CO ₃	82 (55)	16 (4)
8	KOAc	66 (42)	16 (4)
9	KTFA	86 (63)	14 (8)

^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 ¹H NMR conversion with CH₂Br₂ as internal standard, yields of isolated products are given in parentheses. ^c 130 °C.

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

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

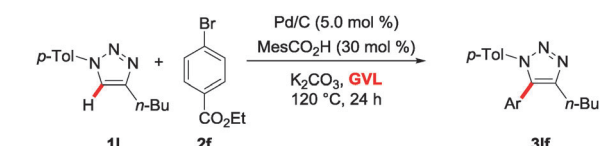
Scheme 2 C–H arylation of *N*-arylated triazoles **1** in GVL.

Scheme 3 Intramolecular C–H arylation in GVL.

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.

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).

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

Table 2 Recovery and reuse of palladium catalyst^a


Run	1st	2nd	3rd
3lf (%)	90	90	90
Pd-leaching ^b (ppm)	5.5	4.1	3.6

^a Reaction conditions: **1l** (0.30 mmol), **2f** (0.45 mmol), Pd/C (5.0 mol%), MesCO₂H (30 mol%), K₂CO₃ (0.60 mmol), GVL (2.0 mL), 120 °C, 24 h.
^b By ICP-MS analysis.³⁷



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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References

- 1 Illustrative reviews on 1,2,3-triazoles: (a) K. D. Hanni and D. A. Leigh, *Chem. Soc. Rev.*, 2010, **39**, 1240–1251; (b) M. Meldal and C. W. Tornøe, *Chem. Rev.*, 2008, **108**, 2952–3015; (c) Y. L. Angell and K. Burgess, *Chem. Soc. Rev.*, 2007, **36**, 1674–1689; (d) H. C. Kolb and K. B. Sharpless, *Drug Discovery Today*, 2003, **8**, 1128–1137, and references cited therein.
- 2 Illustrative reviews on syntheses and applications of 1,2,3-triazoles: (a) E. Haldon, M. C. Nicasio and P. J. Pérez, *Org. Biomol. Chem.*, 2015, **13**, 9528–9550; (b) F. Alonso, Y. Moglie and G. Radivoy, *Acc. Chem. Res.*, 2015, **48**, 2516–2528; (c) A. Qin, Y. Liu and B. Z. Tang, *Macromol. Chem. Phys.*, 2015, **216**, 818–828; (d) D. Astruc, L. Liang, A. Rapakousiou and J. Ruiz, *Acc. Chem. Res.*, 2012, **45**, 630–640; (e) A. H. El-Sagheer and T. Brown, *Chem. Soc. Rev.*, 2010, **39**, 1388–1405; (f) A. Qin, J. W. Y. Lam and B. Z. Tang, *Chem. Soc. Rev.*, 2010, **39**, 2522–2544; (g) H. Nandivada, X. Jiang and J. Lahann, *Adv. Mater.*, 2007, **19**, 2197–2208, and references cited therein.
- 3 R. Huisgen, *Angew. Chem.*, 1963, **75**, 604–637.
- 4 V. V. Rostovtsev, L. G. Green, V. V. Fokin and K. B. Sharpless, *Angew. Chem., Int. Ed.*, 2002, **41**, 2596–2599.
- 5 C. W. Tornøe, C. Christensen and M. Meldal, *J. Org. Chem.*, 2002, **67**, 3057–3064.
- 6 J. E. Hein and V. V. Fokin, *Chem. Soc. Rev.*, 2010, **39**, 1302–1315.
- 7 M. Meldal and C. W. Tornøe, *Chem. Rev.*, 2008, **108**, 2952–3015.
- 8 For recent progress, see: (a) W. Wang, X. Peng, F. Wei, C.-H. Tung and Z. Xu, *Angew. Chem., Int. Ed.*, 2016, **55**, 649–653; (b) S. Ding, G. Jia and J. Sun, *Angew. Chem., Int. Ed.*, 2014, **126**, 1908–1911; (c) B. T. Worrell, J. E. Hein and V. V. Fokin, *Angew. Chem., Int. Ed.*, 2012, **51**, 11791–11794.
- 9 B. M. Trost, *Acc. Chem. Res.*, 2002, **35**, 695–705.
- 10 P. A. Wender, V. A. Verma, T. J. Paxton and T. H. Pillow, *Acc. Chem. Soc.*, 2008, **41**, 40–49.
- 11 Representative reviews on C–H activation: (a) J. G. Kim, K. Shin and S. Chang, *Top. Organomet. Chem.*, 2016, **55**, 29–51; (b) C. Borie, L. Ackermann and M. Nechab, *Chem. Soc. Rev.*, 2016, **45**, 1368–1386; (c) O. Daugulis, J. Roane and L. D. Tran, *Acc. Chem. Res.*, 2015, **48**, 1053–1064; (d) Y. Segawa, T. Maekawa and K. Itami, *Angew. Chem., Int. Ed.*, 2015, **54**, 66–81; (e) N. Kuhl, N. Schroeder and F. Glorius, *Adv. Synth. Catal.*, 2014, **356**, 1443–1460; (f) S. A. Girard, T. Knauber and C.-J. Li, *Angew. Chem., Int. Ed.*, 2014, **53**, 74–100; (g) J. Wencel-Delord and F. Glorius, *Nat. Chem.*, 2013, **5**, 369–375; (h) K. M. Engle, T.-S. Mei, M. Wasa and J.-Q. Yu, *Acc. Chem. Res.*, 2012, **45**, 788–802; (i) T. Satoh and M. Miura, *Chem. – Eur. J.*, 2010, **16**, 11212–11222; (j) T. W. Lyons and M. S. Sanford, *Chem. Rev.*, 2010, **110**, 1147–1169; (k) L. Ackermann, R. Vicente and A. Kapdi, *Angew. Chem., Int. Ed.*, 2009, **48**, 9792–9826; (l) X. Chen, K. M. Engle, D.-H. Wang and J.-Q. Yu, *Angew. Chem., Int. Ed.*, 2009, **48**, 5094–5115; (m) R. G. Bergman, *Nature*, 2007, **446**, 391–393, and references cited therein.
- 12 A review: L. Ackermann and H. K. Potukuchi, *Org. Biomol. Chem.*, 2010, **8**, 4503–4513.
- 13 L. Ackermann, H. K. Potukuchi, D. Landsberg and R. Vicente, *Org. Lett.*, 2008, **10**, 3081–3084.
- 14 R. Jeyachandran, H. K. Potukuchi and L. Ackermann, *Beilstein J. Org. Chem.*, 2012, **8**, 1771–1777.
- 15 S. Chuprakov, N. Chernyak, A. S. Dudnik and V. Gevorgyan, *Org. Lett.*, 2007, **9**, 2333–2336.
- 16 M. Iwasaki, H. Yorimitsu and K. Oshima, *Chem. – Asian J.*, 2007, **2**, 1430–1435.
- 17 L. Ackermann, R. Vicente and R. Born, *Adv. Synth. Catal.*, 2008, **350**, 741–748.
- 18 L. Ackermann, A. Althammer and S. Fenner, *Angew. Chem., Int. Ed.*, 2009, **48**, 201–204.
- 19 L. Ackermann and R. Vicente, *Org. Lett.*, 2009, **11**, 4922–4925.
- 20 F. Wei, H. Li, C. Song, Y. Ma, L. Zhou, C.-H. Tung and Z. Xu, *Org. Lett.*, 2015, **17**, 2860–2863.
- 21 J. M. Schulman, A. A. Friedman, J. Pantelev and M. Lautens, *Chem. Commun.*, 2012, **48**, 55–57.
- 22 B. T. Liégault, D. Lapointe, L. Caron, A. Vlassova and K. Fagnou, *J. Org. Chem.*, 2009, **74**, 1826–1834.
- 23 For examples of directed ruthenium-catalyzed C–H arylations of 1,2,3-triazoles, see: (a) C. Tirler and L. Ackermann, *Tetrahedron*, 2015, **71**, 4543–4551; (b) X. G. Li, K. Liu, G. Zou and P. N. Liu, *Eur. J. Org. Chem.*, 2014, 7878–7888; (c) L. Ackermann, R. Vicente, H. K. Potukuchi and V. Pirovano, *Org. Lett.*, 2010, **12**, 5032–5035; (d) L. Ackermann, P. Novák, R. Vicente, V. Pirovano and H. K. Potukuchi, *Synthesis*, 2010, 2245–2253; (e) L. Ackermann, R. Born and R. Vicente, *ChemSusChem*, 2009, **2**, 546–549; (f) L. Ackermann, R. Vicente and A. Althammer, *Org. Lett.*, 2008, **10**, 2299–2302.
- 24 D. Prat, A. Wells, J. Hayler, H. Sneddon, C. R. McElroy, S. Abou-Shehad and P. J. Dunn, *Green Chem.*, 2016, **18**, 288–296.
- 25 L. Ackermann, *Acc. Chem. Res.*, 2014, **47**, 281–295.
- 26 L. Ackermann, *Synlett*, 2007, 507–526.
- 27 R. Cano, A. F. Schmidt and G. P. McGlacken, *Chem. Sci.*, 2015, **6**, 5338–5346.
- 28 S. Santoro, S. Kozhushkov, L. Ackermann and L. Vaccaro, *Green Chem.*, 2016, **18**, 3471–3493.
- 29 A. J. Reay and I. J. S. Fairlamb, *Chem. Commun.*, 2015, **51**, 16289–16307.
- 30 L. Djakovitch and F.-X. Felpin, *ChemCatChem*, 2014, **6**, 2175–2187.
- 31 For examples of palladium-catalyzed heterogeneous C–H functionalizations: (a) V. Pascanu, F. Carson, M. V. Solano, J. Su, X. Zou, M. J. Johansson and B. Martin-Matute, *Chem. – Eur. J.*, 2016, **22**, 3729–3737; (b) Z. Shu, W. Li and B. Wang, *ChemCatChem*, 2015, **7**, 605–608; (c) J. Chen, L. He, K. Natta, H. Neumann, M. Beller and X.-F. Wu, *Adv. Synth. Catal.*, 2014, **356**, 2955–2959; (d) D.-T. D. Tang, K. D. Collins, J. B. Ernst and F. Glorius, *Angew. Chem., Int. Ed.*, 2014, **53**, 1809–1813; (e) D.-T. D. Tang, K. D. Collins and F. Glorius, *J. Am. Chem. Soc.*, 2013, **135**, 7450–7453, and references cited therein. An early report: (f) N. Nakamura, Y. Tajima and K. Sakai, *Heterocycles*, 1982, **19**, 235–245.
- 32 For recent examples, see: (a) D. Rasina, A. Kahler-Quesada, S. Ziarelli, S. Warratz, H. Cao, S. Santoro, L. Ackermann and L. Vaccaro, *Green Chem.*, 2016, DOI: 10.1039/C6GC01393; (b) G. G. Strappaveccia, E. Ismalaj, C. Petrucci, D. Lanari, A. Marrocchi, M. Drees, A. Facchetti and L. Vaccaro, *Green Chem.*, 2015, **17**, 365–372; (c) G. G. Strappaveccia, L. Luciani, E. Bartolini, A. Marrocchi, F. Pizzo and L. Vaccaro, *Green Chem.*, 2015, **17**, 1071–1076, and cited references.



- 33 For representative contributions, see: (a) P. Pongrácz, L. Kollár and L. T. Mika, *Green Chem.*, 2016, **18**, 842–847; (b) Z. Zhang, *ChemSusChem*, 2016, **9**, 156–171; (c) L. Qi, Y. F. Mui, S. W. Lo, M. Y. Lui, G. R. Akien and I. T. Horváth, *ACS Catal.*, 2014, **4**, 1470–1477; (d) E. I. Gürbüz, J. M. R. Gallo, D. M. Alonso, S. G. Wettstein, W. Y. Lim and J. A. Dumesic, *Angew. Chem., Int. Ed.*, 2013, **52**, 1270–1274, see also: (e) S. G. Wettstein, D. M. Alonso, Y. Chong and J. A. Dumesic, *Energy Environ. Sci.*, 2012, **5**, 8199–8203; (f) Z.-Q. Duan and F. Hu, *Green Chem.*, 2012, **14**, 1581–1583; (g) L. Qi and I. T. Horváth, *ACS Catal.*, 2012, **2**, 2247–2249; (h) I. T. Horváth, H. Mehdi, V. Fábos, L. Boda and L. T. Mika, *Green Chem.*, 2008, **10**, 238–242.
- 34 I. T. Horváth, *Green Chem.*, 2008, **10**, 1024–1028.
- 35 Y. Gu and F. Jérôme, *Chem. Soc. Rev.*, 2013, **42**, 9550–9570.
- 36 L. Ackermann, *Chem. Rev.*, 2011, **111**, 1315–1345.
- 37 For detailed information, see the ESI†.
- 38 (a) R. H. Crabtree, *Chem. Rev.*, 2012, **112**, 1536–1554; (b) M. Pagliaro, V. Pandarus, R. Ciriminna, F. Béland and P. Demma Carà, *ChemCatChem*, 2012, **4**, 432–445.
- 39 (a) C. E. Garrett and K. Prasad, *Adv. Synth. Catal.*, 2004, **346**, 889–900; (b) Specification limits for residues of metal catalysts: <http://www.ema.europa.eu/ema/>.
- 40 Under otherwise identical reaction conditions, a C–H arylation under air led to less effective catalysis.
- 41 (a) Syntheses via C–H Bond Functionalizations, L. Ackermann, A. R. Kapdi, H. K. Potukuchi and S. I. Kozhushkov, in *Handbook of Green Chemistry*, ed. C.-J. Li, Wiley-VCH, Weinheim, 2012, pp. 259–305; (b) L. Vaccaro, D. Lanari, M. Assunta and G. Strappaveccia, *Green Chem.*, 2014, **16**, 3680–3704; (c) J. Sherwood, M. D. Bruyn, A. Constantinou, L. Moity, C. R. McElroy, T. J. Farmer, T. Duncan, W. Raverty, A. J. Hunta and J. H. Clark, *Chem. Commun.*, 2014, **50**, 9650–9652.

