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Reusable Pd@PEG Catalyst for Aerobic Dehydrogenative C–H/C–H Arylations of 1,2,3-Triazoles

Francesco Ferlin,[a][b] Santhivardhana Reddy Yetra,[a] Svenja Warratz,[a] Luigi Vaccaro,[b] and Lutz Ackermann*[a]

Abstract: Dehydrogenative C–H arylations of 1,2,3-triazoles were accomplished with the aid of a reusable palladium catalyst in PEG. The widely applicable oxidative palladium-catalysis enabled the synthesis of fully decorated 1,2,3-triazoles with a broad functional group tolerance and ample substrate scope. The sustainability of the aerobic C–H arylation was reflected by the use of PEG as green reaction medium and demonstrated by recycling studies of the catalyst and the reaction medium.

1,2,3-Triazoles are structural motifs found in several molecules endowed with specific properties, which feature applications in various applied fields of pharmaceutical industries and materials sciences.[1] As a consequence, there is continued strong demand for the development of synthetic methods that provide an efficient access to fully decorated 1,2,3-triazoles. Thus, hetero-fused triazoles have received considerable attention for their applications in drug discovery and chemical biology.[2]
During the last two decades transition metal-catalyzed functionalizations of otherwise inert C−H bonds have been identified as atom-economic tools to assemble complex organic molecules with a wide range of different functionalities.[3] Recently, the dehydrogenative double C−H bond activation catalyzed by metal catalyst based on palladium,[4] and ruthenium,[5] among others,[6] have attracted considerable attention because these methods avoid the tedious lengthy synthesis of prefunctionalized starting materials thus, providing a streamlining of molecular syntheses. However, industrial applications of these homogeneous precious metal catalysts remain challenging due to the tedious procedures for their separation from the reaction media. In fact, this step is associated with the production of waste and consequently a drawback in terms of chemical and environmental costs. From a green chemistry perspective, the development of recyclable and reusable[7] catalysts that allow for efficient and selective oxidative C−H arylations of a wide range of substrates is of major interest.

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In order to satisfy both recyclability and environmental concerns, an efficient approach is to immobilize a homogeneous catalyst in a liquid phase by dissolving it into a non-volatile and non-miscible liquid, such as ionic liquids[8] or poly(ethylene glycols) (PEGs).[9] This strategy combines the benefits of homogeneous catalysis with the possibility to recover and reuse not only the catalyst but also the reaction medium. Although ionic liquids[10] provide notable advantages, the tedious preparation of ionic liquids is a main disadvantage and their environmental safety is still debated as especially the first generation of ionic liquids are critical in terms of toxicity.[11] It should be kept in mind, that the reaction media constitutes the largest part of the waste generated in chemical productions.[12] Therefore, a farsighted choice of the reaction medium plays a pivotal role in establishing sustainable chemical methodologies.[13] Here, PEGs can play a key role for substituting toxic and/or flammable solvents.[14] PEGs have a negligible vapour pressure, are commercially available, inexpensive, thermally stable, recoverable, and nontoxic, hence serving as efficient reaction media for environmentally-friendly and safe chemical reactions.[15] In recent years, PEGs have been successfully utilized as reaction media for palladium-catalyzed direct arylations of 1,2,3-triazoles with aryl bromides,[9d] with facile recyclability of solvents and palladium catalysts. However, to the best of our knowledge no palladium-catalyzed intramolecular C–H arylation under oxidative conditions have been reported to date using PEG as solvent. Within our program on sustainable C–H activation,[16] we now report on the application of a catalyst comprising $Pd(OAc)_2$, $Cu(OAc)_2 \cdot H_2O$,[17] PEG, and O_2 as an effective and reusable catalyst for the intramolecular oxidative C–H arylation of 1,2,3-triazoles. Notable features of our strategy include (*i*) a robust and versatile methodology for aerobic C–H activation (*ii*) PEG as green and recyclable reaction medium as well as (*iii*) reusable palladium complexes as the catalyst.

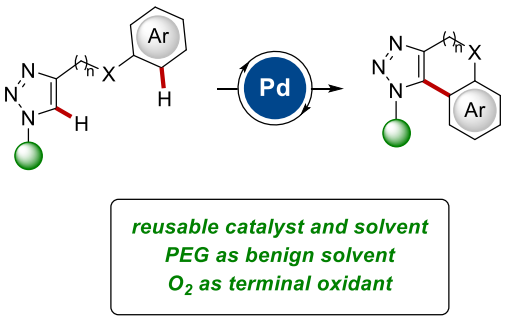

Figure 1. C–H Arylation of 1,2,3-triazoles.

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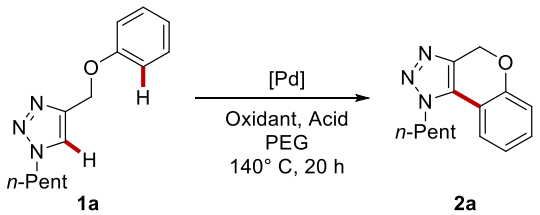
At the outset of our studies, we probed the intramolecular C–H arylation of triazole **1a**. The influence of the PEG's molecular weight and the palladium source was tested (Table 1, entry 1-3). High molecular weight PEG-20000 and $Pd(OAc)_2$ emerged as the best solvent and catalyst, respectively, with pivalic acid providing optimal performance (entries 5-7 and Table S2 in the Supporting Information).

Table 1. Optimization studies for the dehydrogenative C–H arylation of triazole **1a**.[a]



1a **2a**

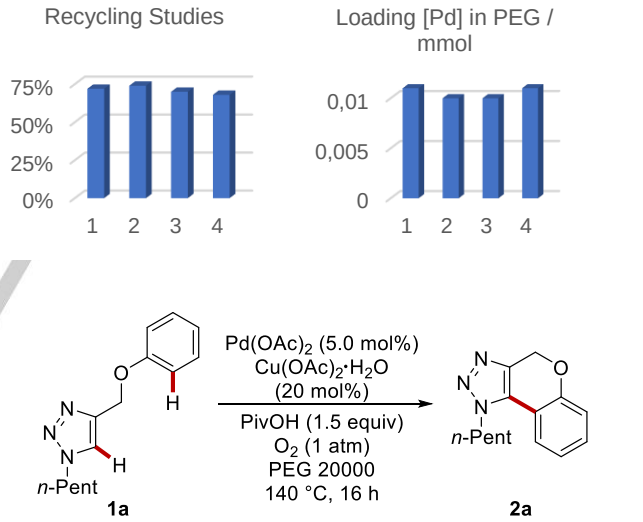
Entry	PEG MW	[Pd]	Oxidant	Acid	Yield (%)[b]
1	2000	$Pd(OAc)_2$ (5 mol%)	$Cu(OAc)_2{\cdot}H_2O$ (1.0 equiv)	PivOH (5.0 equiv)	47
2	20000	$Pd(OAc)_2$ (5 mol%)	$Cu(OAc)_2{\cdot}H_2O$ (1.0 equiv)	PivOH (5.0 equiv)	58
3	20000	$Pd(OAc)_2$ (5 mol%)	$Cu(OAc)_2{\cdot}H_2O$ (20 mol %)/O_2	PivOH (5.0 equiv)	52
4	20000	$Pd(OAc)_2$ (5 mol%)	AgOAc (20 mol %)/O_2	PivOH (1.5 equiv)	29
5	20000	$Pd(OAc)_2$ (5 mol%)	$Cu(OAc)_2{\cdot}H_2O$ (20 mol %)/O_2	$MesCO_2H$ (5.0 equiv)	36
6	20000	$Pd(OAc)_2$ (5 mol%)	$Cu(OAc)_2{\cdot}H_2O$ (20 mol %) /O_2	PivOH (0.5 equiv)	43
7	**20000**	**$Pd(OAc)_2$ (5 mol%)**	**$Cu(OAc)_2{\cdot}H_2O$ (20 mol %) /O_2**	**PivOH (1.5 equiv)**	**72**
8	20000	$Pd(OAc)_2$ (5 mol%)	$Cu(OAc)_2{\cdot}H_2O$ (20 mol %) /air	PivOH (1.5 equiv)	62
9	20000	$Pd(OAc)_2$ (5 mol%)	$Cu(OAc)_2{\cdot}H_2O$ (1.0 equiv)	---	22
10	20000	---	$Cu(OAc)_2{\cdot}H_2O$ (20 mol %)/O_2	PivOH (1.5 equiv)	-

[a] Reaction conditions: **1a** (0.5 mmol), [Pd], Oxidant, Acid, PEG (500 mg), 140 °C, 20 h. [b] Isolated yield.

In order to guarantee both recyclability and catalytic efficacy we further optimized the stoichiometry and the reaction time. However, among a variety of terminal oxidants, $Cu(OAc)_2{\cdot}H_2O$ enabled more effective oxidative C–H arylations (entries 4-9 and Table S2 in the Supporting Information). Particularly notable results were obtained when using an oxidant consisting of molecular oxygen and $Cu(OAc)_2{\cdot}H_2O$, allowing for high yields of isolated product **2a** and reducing the amount of pivalic acid needed (Table 1, entry 7). Notably, the dehydrogenative coupling did not occur in the absence of the palladium catalyst (entry 10).

As shown in Table 2, the optimal reaction conditions (Table 1, entry 7) proved to be ideal for the recyclability of the palladium catalyst with only a slight decrease in the catalytic efficacy. We also tested the stability and durability of the palladium catalysis in its use for consecutive runs (Table 2). Therefore, we reused the Pd/PEG mixture and solely added catalytic amounts of copper acetate, pivalic acid and the starting materials. Thus, for at least four consecutive reactions similar results were obtained. Although results are relevant for a small scale laboratory experiment, we explored the loss in efficiency of the system. Therefore, to better understand the effective palladium loading of our catalytic system we have analysed the solid materials (PEG/Pd) isolated by precipitation after the reaction by ICP-AES. We were able to thus show that the loading of palladium basically remained unchanged (Table 2).

Table 2. Recovery and reuse of catalytic system with ICP-AES measurements for the palladium loading.



1a **2a**

Run	Yield (%)	Loading of Pd in PEG
1	72 %	0.011 mmol (0.2% w/w)
2	74 %	0.010 mmol (0.2% w/w)
3	70 %	0.010 mmol (0.2% w/w)
4	68 %	0.011 mmol (0.2% w/w)

[a] Reaction conditions: **1a** (1.0 mmol), $Pd(OAc)_2$ (5.0 mol %), $Cu(OAc)_2{\cdot}H_2O$ (20 mol %), PivOH (1.5 equiv), PEG 20000 (1 g), O_2 (1 atm), 140 °C, 16 h. For each consecutive run: **1a** (1.0 mmol), $Cu(OAc)_2{\cdot}H_2O$ (20 mol %), PivOH (1.5 equiv), O_2 (1 atm), 140 °C, 16 h.

With the optimized conditions in hand, we explored the substrate scope of the palladium-catalyzed C–H activation (Scheme 1). Hence, diversely decorated 1,2,3-triazolo-fused-

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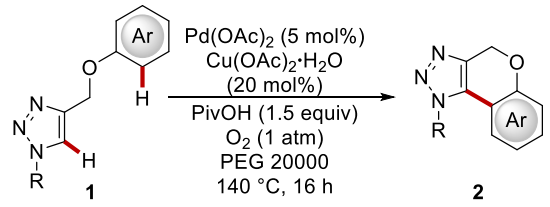
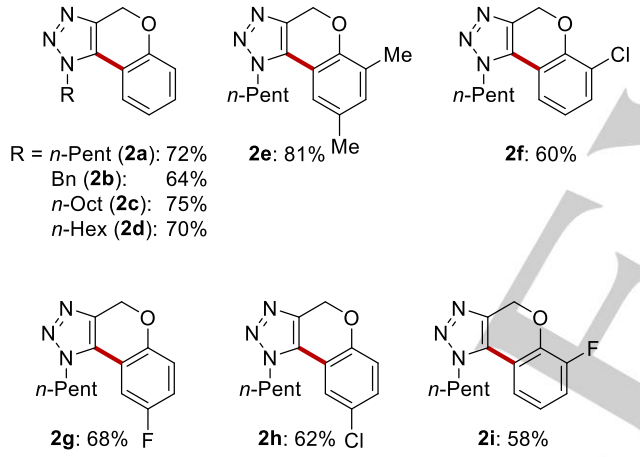
chromenes were regioselectively synthesized in good yields, even when bearing sensitive halogen-substituents. Remarkably, the palladium catalyst also proved applicable to the synthesis of sterically hindered tetra-*ortho*-substituted biaryl **2e**.

Under otherwise identical conditions, we likewise achieved the synthesis of isoindoline-fused triazoles by dehydrogenative intramolecular cyclization of 4-substituted *N*-benzyl-triazoles (Scheme 2). This transformation was characterized by high functional group tolerance even when an electron-withdrawing group was present in the triazole moiety (compound **4d**).

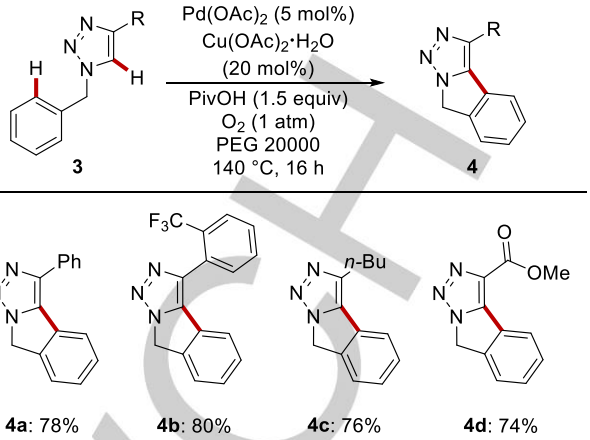
Scheme 1. Scope for the synthesis of triazole-fused chromenes.[a]





[a] Reaction conditions: **1** (0.5 mmol), PEG 20000 (500 mg), $Cu(OAc)_2 \cdot H_2O$ (20 mol %), PivOH (1.5 equiv), O_2 (1 atm), 140 °C, 16 h.

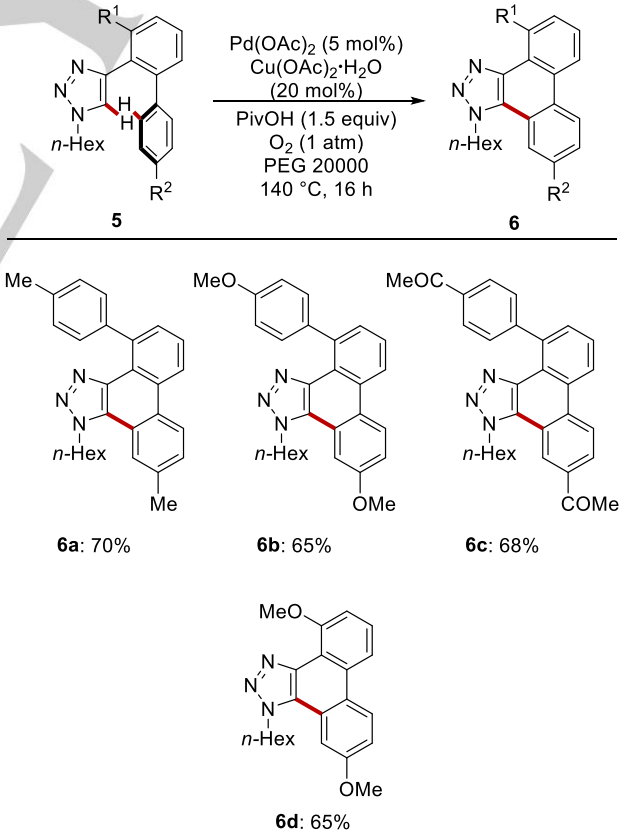
Scheme 2. Scope of isoindoline-fused triazoles.[a]



[a] Reaction conditions: **3** (0.5 mmol), PEG 20000 (500 mg), $Cu(OAc)_2 \cdot H_2O$ (20 mol %), PivOH (1.5 equiv), O_2 (1 atm), 140 °C, 16 h.

We also performed the cyclodehydrogenative arylation to provide step-economical access to substituted phenanthro[9,10-d]triazoles **6** (Scheme 3).

Scheme 3. Synthesis of phenantrene-fused triazoles.[a]



[a] Reaction conditions: **5** (0.5 mmol), PEG 20000 (500 mg), $Cu(OAc)_2 \cdot H_2O$ (20 mol %), PivOH (1.5 equiv), O_2 (1 atm), 140 °C, 16 h.

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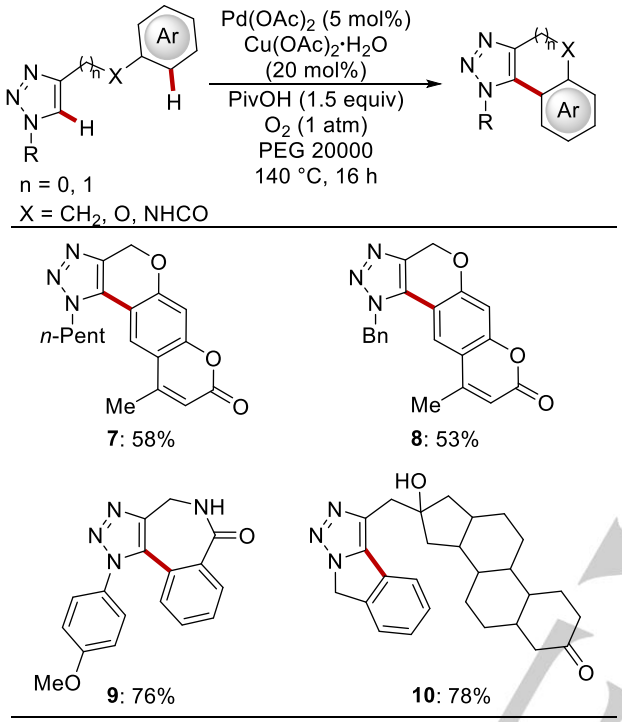
Encouraged by these results we extended our reusable palladium C–H activation to the synthesis of bio-active derivatives (Scheme 4). Thereby, we were able to access heterofused-coumarins **7-8**, azepinone-like **9** and steroid-based triazolo-fused isoindoline **10**.

Scheme 4. Derivatization of bio-active triazole compounds.[a]



[a] Reaction conditions: **substrate** (0.5 mmol), PEG 20000 (500 mg), $Cu(OAc)_2{\cdot}H_2O$ (20 mol %), PivOH (1.5 equiv), O_2 (1 atm), 140 °C, 16 h.

In conclusion, we have reported on the development of an efficient method for the oxidative C–H arylation of 1,2,3-triazoles. Specifically, a catalyst comprising $Pd(OAc)_2$ in PEG enabled the selective cyclodehydrogenative biheteroaryl formation, including the step-economical synthesis of bio-active derivatives in an aerobic fashion. Furthermore, the palladium/PEG system could be recycled and reused four times without significant decrease in catalytic activity. Our reusable homogeneous catalyst avoids the use of volatile and harmful organic solvents as the reaction media. This protocol serves as an efficient and sustainable procedure to allow the preparation of a wealth of triazole-fused heteroarenes.

Acknowledgements

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Keywords: PEG • C–H Activation • Palladium • Oxidation • Arylation

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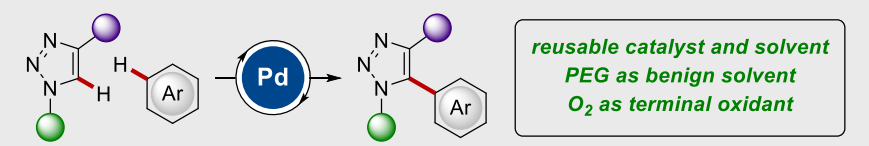

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Reusable Pd@PEG Catalyst for Aerobic Dehydrogenative C–H/C–H Arylations of 1,2,3-Triazoles

Aerobic C–H arylations were accomplished in benign PEG solvent. The easily reusable catalyst $Pd(OAc)_2$ proved highly effective for the intramolecular oxidative C–H arylation of 1,2,3-triazoles, thus, enabling a step-economical synthesis of bio-active derivatives in a sustainable fashion.