# Triazole-Directed Pd-Catalyzed C($sp^2$)−H Oxygenation of Arenes and Alkenes

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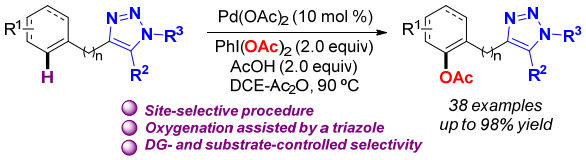
*Supporting Information Placeholder*

**ABSTRACT:** Selective Pd-catalyzed C($sp^2$)−H oxygenation of 4-substituted-1,2,3-triazoles is described. Unlike previous metal-catalyzed C−H functionalization events, which preferentially occur at the activated heterocyclic C−H bond, the regioselective oxygenation of the arene/alkene moiety is now achieved featuring an unconventional role of such simple triazole scaffold as a modular and selective directing group.




Owing to its high metabolic stability, hydrogen bonding capability and amide bioequivalence, 1,2,3-triazole core is a privileged structure of wide presence in a vast array of relevant compounds in distinct research areas such as crop protection, medicinal chemistry and material sciences.[1] One of the most practical methods for the assembly of 1,2,3-triazoles is widely referred to as a "*click process*" involving a Cu-catalyzed azide-alkyne [3+2] cycloaddition (CuAAC) to furnish 1,4-disubstituted triazoles.[2] However, despite their widespread important applications and the existence of modular syntheses, 1,2,3-triazoles have been overlooked in organic chemistry and their powerful and unique properties have not yet been exploited.

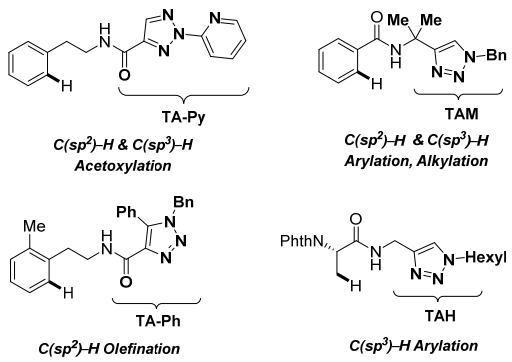
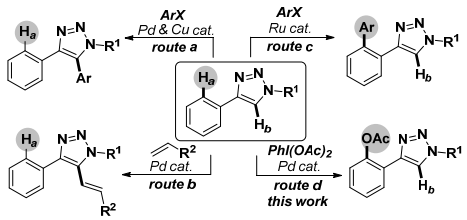



**Figure 1. Triazole-containing bidentate directing groups in C−H activation events**

Metal-catalyzed C−H functionalizations are established methods in synthetic chemists' toolbox.[3] The common approach implies the use of a directing group (DG), which by coordination to a metal catalyst enables the selective activation of a proximal C−H bond through a cyclometallation process.[4] Despite the availability of a plethora of DGs, expanding the scope to other versatile motifs remains a critical challenge in modern chemistry. In this regard, Ackermann,[5a-c] Shi[5d-e] and Ding[5f] have recently introduced the use of novel triazole-containing systems as effective bidentate DGs in the field of C−H activation (Figure 1). Although impressive progress achieved, the use of alternative and simple triazole derivatives easily installed within the arene ring in a straightforward fashion and acting as monodentate DGs would be of utmost synthetic practical value.

**Scheme 1. Metal-catalyzed C−H functionalization processes using 4-phenyl-1,2,3-triazoles**

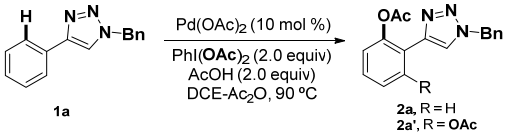



4-Aryl-1,2,3-triazoles resulting from the atom-economical CuAAC stand out as ideal substrates to develop novel C−H functionalization events. If successful, such methods would represent unprecedented, yet powerful, techniques for the chemoselective late-stage derivatization of "*click compounds*". However, competitive functionalization of the heterocyclic core poses a major drawback. Indeed, metal-catalyzed arylations and alkenylations selectively occurring at the acidic C−H bond are well-documented (Scheme 1, *route a-b*).[6] Our approach involves a distinct binding mode of the metal catalyst within the triazole and further activation of a specific C−H bond in the arene while leaving intact the $C_5$−H bond (Scheme 1, *route d*). Whereas ruthenium complexes have allowed

triazole-assisted direct arylations to selectively proceed at the arene (Scheme 1, *route c*),[7] Pd-catalyzed processes remain virtually unexplored. In this respect, Shi and co-workers have recently developed elegant Pd-catalyzed C−H acetoxylations by triazole assistance.[5e] Although structurally complex 1,2,3-triazole-4-carboxylic acid derivatives are required (Figure 1), easy cleavage of the DG can be performed. Following our interest in the field of C−H functionalization,[8] we describe herein an alternative, novel Pd-catalyzed triazole-directed oxygenation of arenes[9,10] which features a unique tool to enable the build-up of molecular diversity combined with a facile assembly of the required heterocyclic substrates via click chemistry.

We initiated our studies with **1a** as the model substrate.[11] After careful optimization, we were pleased to observe that using $Pd(OAc)_2$, $PhI(OAc)_2$ and AcOH in DCE/$Ac_2O$ provided a mixture of acetoxylated arenes **2a**/**2a'** in 78% isolated overall yield and not even traces of the acetoxylation of the heterocyclic core were detected (Table 1, entry 1). As expected, the reaction did not proceed in the absence of either metal (entry 2) or oxidant (entry 3) and the addition of both AcOH and $Ac_2O$ was crucial for the process to occur in high yields (entries 5-6).[12] It is worth noting that the yield was not improved either at higher temperature (entry 8) or by adding pyridine derivatives which are known to enhance the rate of Pd-catalyzed C−H acetoxylations.[13]

**Table 1. Pd-catalyzed C($sp^2$)−H acetoxylation of 1a**[a]

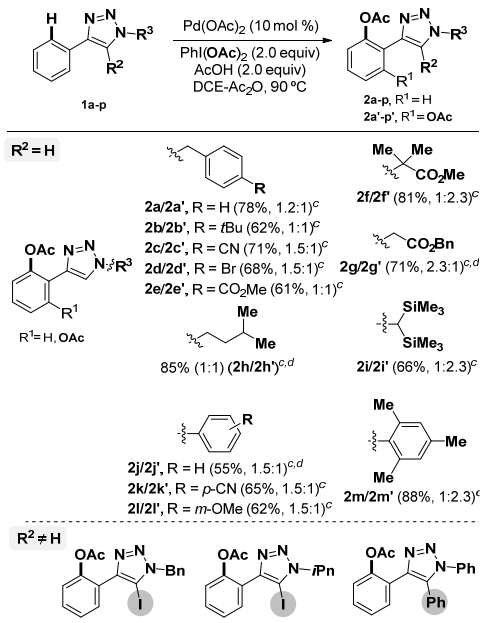



| entry | change from standard conditions | yield (%)[b] |
|---|---|---|
| 1 | none | 78 (1.2:1)[c] |
| 2 | without $Pd(OAc)_2$ | 0 |
| 3 | without $PhI(OAc)_2$ | 0 |
| 4 | under air | 60 (1.1:1)[c] |
| 5 | without $Ac_2O$ | 27 (1.1:1)[c] |
| 6 | *p*TsOH·$H_2O$ instead of AcOH | traces |
| 7 | $K_2S_2O_8$ instead of $PhI(OAc)_2$ | traces |
| 8 | 110 °C instead of 90 °C | 79 (1.1:1)[c] |
| 9 | 5 mol % of $Pd(OAc)_2$ instead of 10 mol % | 61 (1.1:1)[c] |

[a] Reaction conditions: **1a** (0.25 mmol), $Pd(OAc)_2$ (10 mol %), $PhI(OAc)_2$ (2.0 equiv), AcOH (2.0 equiv), DCE/$Ac_2O$ (1:1, 1 mL) at 90 °C for 24 h. [b] Yield of isolated product after column chromatography. [c] Ratio of mono- *vs* diacetoxylated product (**2a**/**2a'**).

Having demonstrated the feasibility of our approach, we next prepared a representative set of 4-phenyl-1,2,3-triazoles through CuAAC to evaluate the influence of the nature of the heterocyclic motif on the *ortho*-acetoxylation. As depicted in Table 2, a variety of triazoles including those bearing both aliphatic and aromatic motifs were found effective DGs to afford the corresponding oxygenated products as separable mixtures of mono- and diacetoxylated isomers in good to high yields (up to 88% yield). Remarkably, a variety of functional groups such as cyano (**2c**,**2k**), ester (**2e**,**2f**,**2g**), bromide (**2d**), ether (**2l**), and silicon groups (**2i**) were perfectly accommodated. Intriguingly, sterical hindrance played a crucial role in selectivity; whereas diacetoxylation was significantly enhanced when using triazoles bearing sterically demanding

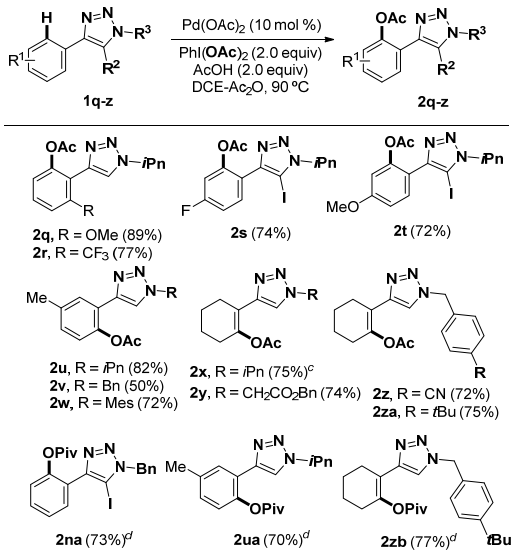
**Table 2. Influence of the nature of triazole ring on the Pd-catalyzed C($sp^2$)−H acetoxylation of arenes**[a,b]




[a] As for Table 1, entry 1. [b] Yield of isolated product after column chromatography, average of at least two independent runs. [c] Ratio of mono- *vs* diacetoxylated product. [d] 110 °C.

substituents on the N1 atom (**2f'**,**2i'**,**2m'**), the introduction of a bulky substituent such as iodine in the heterocyclic moiety ($C_5$−I) resulted in the exclusive formation of monoacetoxylated arenes (**2n**,**2o**) in excellent yields. Apparently, the iodine atom could block the free-rotation of the arene thus positioning the directing triazole unit away from the second *ortho* C−H bond. As an added benefit from using such 5-iodo-1,2,3-triazoles as DGs, the resulting products constitute versatile synthetic intermediates in the cross-coupling arena. In striking contrast, the introduction of a less sterically demanding phenyl group resulted in a total loss of selectivity towards the mono-acetoxylation and the corresponding oxygenated product was obtained as a separable mixture of isomers (**2p**/**2p'**). Remarkably, in all cases analyzed C($sp^2$)−H acetoxylation exclusively occurred at the *ortho*-position of the arene moiety leaving intact the heterocyclic C($sp^2$)−H bond.[14] We next evaluated the preparative scope of our method. To our delight, both DG and substrate controlled selectivity was achieved and this transformation was found highly efficient for the exclusive monoacetoxylation of a wide range of substrates (Table 3). The use of 5-iodotriazoles facilitated the selective *ortho*-oxygenation of substituted arenes (**2s**, **2t**) upon a DG controlled reaction pathway. Notably, substrate controlled selectivity was also observed even with simple triazoles ($R^2$ = H); *ortho*-substituents did not hamper the process and indeed allowed the oxygenation to occur in high yields (**2q**,**2r**).[15] Likewise, *meta*-substituted substrates displayed excellent regioselectivity producing the corresponding acetoxylated products as single regioisomers (**2u-w**), where oxygenation preferentially proceeded at the less hindered *ortho*-position. Remarkably, comparatively less explored vinylic C−H bonds smoothly underwent the oxygenation process to furnish the desired products (**2x-z**, **2za**) in high yields.

**Table 3. Pd-catalyzed C($sp^2$)−H *ortho*-oxygenation of arenes and alkenes**[a,b]

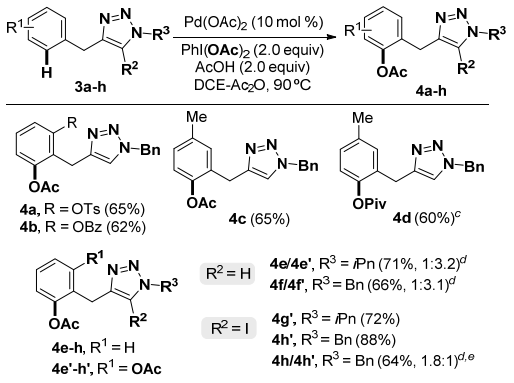



[a] As for Table 1, entry 1. [b] Yield of isolated product after column chromatography, average of at least two independent runs. [c] 110 °C. [d] $PhI(OPiv)_2$ (2.0 equiv), PivOH (2.0 equiv) in DCE (1 mL).

Gratifyingly, Pd-catalyzed *ortho*-pivaloxylation was successfully achieved to yield **2na**, **2ua** and **2zb** under similar reaction conditions by switching the oxidant and acid to $PhI(OPiv)_2$ and PivOH, respectively.[16] It is worth highlighting that the selective introduction of pivaloxy group is of great synthetical importance owing to its broad opportunities in Ni-catalyzed cross-coupling events.[17] Next we turned our attention to examine the feasibility of the Pd-catalyzed oxygenation process to substrates with a longer tether between the arene and the triazole. As shown in Table 4, 4-benzyl-1,2,3-triazoles **3e** and **3f** provided the corresponding acetoxylated products **4e** and **4f** as separable mixtures of mono- and difunctionalized products. Importantly, the introduction of both *ortho*- and *meta*-substituents into the arene ring enabled the selective monooxygenation process to occur in good yields (**4a-d**). Strikingly, the use of 5-iodo derivatives **3g** and **3h** resulted in a selectivity switch to furnish exclusively diacetoxylated products **4g'** and **4h'**, respectively, in high yields; reducing the amount of $PhI(OAc)_2$ provided monoacetoxylated **4h** as the major compound. We hypothesized that the triazole motif could bind to the Pd center via the presumable formation of a more flexible 6-membered palladacycle and hence the iodine atom may not block the free rotation of the benzyl group as when using a phenyl ring. As a result, previous selectivity towards monoacetoxylation (Table 2, **2n-2o**) is not observed and selective diacetoxylation is achieved instead, which remains unclear to rationalize at this stage. As depicted on Table 3-4, the chemoselectivity of our method is illustrated by the fact that a variety of groups such as ester (**2y, 4b**), cyano (**2z**), ether (**2q**,**2t**), fluoride (**2r**, **2s**) sulfonate (**4a**) and iodo (**2s**, **2t**, **2na**) are tolerated.

Finally, the synthetic usefulness of the developed method was illustrated by the conversion of some of the acetoxylated products into other valuable functionalities. As shown in Scheme 2, acetoxylated arene **2a** was easily converted under mild reaction conditions into the phenol derivative **7**, which

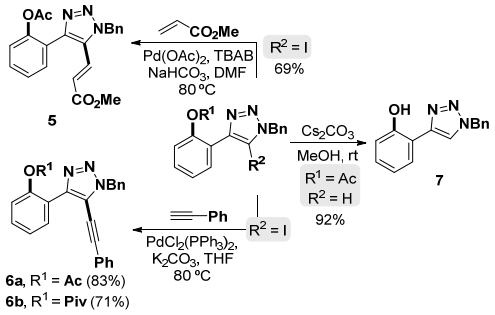
**Table 4. Pd-catalyzed C($sp^2$)−H *ortho*-acetoxylation of arenes 3a-d**[a,b]




[a] As for Table 1, entry 1. [b] Yield of isolated product after column chromatography, average of at least two independent runs. [c] $PhI(OPiv)_2$ (2.0 equiv), PivOH (2.0 equiv) in DCE (1 mL). [d] Ratio of mono- *vs* diacetoxylated product. [e] $PhI(OAc)_2$ (1.0 equiv).

could show potential activity as a novel N,O-bidentate ligand in metal catalysis.[18] Furthermore, 5-iodo oxygenated compounds **2n** and **2na** smoothly underwent Pd-catalyzed Heck and Sonogashira couplings to efficiently yield 1,4,5-trisubstituted-1,2,3-triazoles **5** and **6a-b**, respectively.[19] Although a detailed mechanistic picture clearly requires further studies, based on previous results[9d,15a] a mechanism featuring a typical chelation-controlled C−H activation step with concomitant formation of a palladacycle may be operative. The resulting Pd(II) species would be likely oxidized to form a Pd(IV) intermediate,[20] which would eventually undergo a C−O bond forming reductive elimination to furnish the targeted oxygenated product.

**Scheme 2. Synthetic versatility of the oxygenated compounds**




In summary, we have disclosed an unprecedented triazole-directed Pd-catalyzed C($sp^2$)−H acetoxylation/pivaloxylation of arenes and certain alkenes. The key feature relies on the use of simple triazoles prepared in a straightforward fashion upon click chemistry as practical directing groups. Our C($sp^2$)−O bond forming process is distinguished by its wide group tolerance, site-selectivity and DG and substrate controlled regioselectivity. As a result, this C−H oxygenation procedure complements existing methodologies and represents a rare example of post-synthetic C−H functionalization of 4-substituted-1,2,3-triazoles. Further investigations aimed at promoting other related events assisted by simple triazole motifs derived from click chemistry as well as mechanistic studies are currently underway in our laboratories.

## ASSOCIATED CONTENT

### Supporting Information

Experimental procedures and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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### Notes

The authors declare no competing financial interests.

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11. Related 2-phenyl-1,2,3-triazoles have been recently used to perform Pd-catalyzed *ortho*-alkoxylation events, see: (a) Shi, W.; Shi, Z. *Chin. J. Chem.* **2014**, *32*, 974. (b) Shi, S.; Kuang, C. *J. Org. Chem.* **2014**, *79*, 6105. Remarkably, triazole **1a** remained unreactive under those conditions evidencing hence the key importance of the triazole substitution pattern.
12. $Ac_2O$ has been proposed to be crucial for the regeneration of active Pd(II) catalyst in other Pd(II)/Pd(IV) acetoxylations, see: (a) Giri, R.; Liang, J.; Lei, J.-G.; Li, J.-J.; Wang, D.-H.; Chen, X.; Naggar, I. C.; Guo, C.; Foxman, B. M: Yu, J.-Q. *Angew. Chem. Int. Ed.* **2005**, *44*, 7420. (b) Ref. 10a.
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14. Although merely speculative, the regioselectivity towards the acetoxylation reaction may be related to the more feasible formation of the required palladacycle under acidic conditions, whereas C−H functionalization of the more acidic heterocyclic position generally occurs under basic conditions.
15. In certain reported protocols the presence of *ortho*-substituents was found detrimental for the reaction to occur, see for example: (a) Huang, C.; Chernyak, N.; Dudnik, A. S.; Gevorgyan, V. *Adv. Synth. Catal.* **2011**, *353*, 1285. (b) Chernyak, N.; Dudnik, A. S.; Huang, C.; Gevorgyan, V. *J. Am. Chem. Soc.* **2010**, *132*, 8270.
16. Importantly, in these cases $Ac_2O$ had to be removed from the reaction media to avoid competitive *ortho*-acetoxylation which could be attributed to the *in situ* formation of more reactive $PhI(OAc)_2$ by a reasonable ligand exchange on the hypervalent iodine species, see: (a) Narayan, R.; Manna, S.; Antonchic, A. P. *Synlett* **2015**, *26*, 1785. (b) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2008**, *108*, 5299 and references cited therein.
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