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Pd-Catalyzed *ortho* Selective C–H Acyloxylation and Hydroxylation of Pyridotriazoles

Deepa Rawat,[a] Rahul Kumar[a] and Subbarayappa Adimurthy*[a]

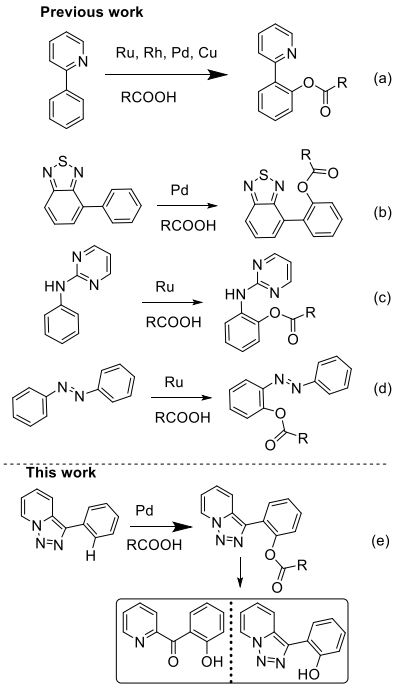
Abstract. An efficient protocol for the palladium-catalyzed direct *ortho* C−H acyloxylation of 3-phenyl-pyridotriazoles is described. The reaction was facilitated by $PhI(OAc)_2$ (PIDA) as an oxidant and with carboxylic acids as acyloxylation reagents. The reaction is highly selective for mono acyloxylation of pyridotriazoles with various acids such as aliphatic, branched, cyclic including adamantine carboxylic acids. When acetic anhydride employed as acylation reagent, an interesting product 2-oxo-1-phenyl-1-(pyridin-2-yl)propyl acetates were obtained through the ring opening of pyridotriazoles. The key strategy is the employment of pyridotriazoles as a modifiable heterocycle; acyloxylation followed by the hydrolysis in one pot to yield the potential drug intermediates (2-hydroxyphenyl)pyridin-2-yl)methanone in good yields.

Introduction

Selective C–H functionalization heterocycles represents a promising approach for the synthesis of complex molecules as they play a crucial role in various fields including pharmaceuticals, agrochemicals and material science.[1] The rapid and efficient synthesis of such complex molecules has been a long-standing interest and challenging in organic chemistry. Particularly, pyridine-fused heterocycles such as imidazo[1,2-a]pyridines, imidazo[1,5-a]pyridines, imidazo[1,2-a]pyrazines, indolizines, imidazo[2,1-a]isoquinolines, pyrazolo[1,5-a]pyridines and pyrido[1,2-a]indoles are important intermediates in both medicinal chemistry and drug development.[2] Despite the wide range of biological activity of such complex molecules,[2h-j] it is important to note that, the hydrophilic groups (such as sulphonyl, sulphonamide, acyloxy and hydroxy groups) present in such molecules enhance the drug discovery due to the fact that, they act rapidly and with site selective to treat diseases.[3] Therefore, the concept of introducing a functional handle onto heterocyclic system is considered to be a powerful tool for accessing such molecules with increased biological activity or suitable for subsequent derivatization.[4]

In this context, the selective acyloxylation of 2-arylpyridines have witnessed the efforts made by various groups with transition metal catalysts including palladium, ruthenium and rhodium.[5] In addition, *ortho* sp^2(C-H) acyloxylation and acylation of arenes with various directing groups have been also reported.[6,7] In the last few decades, transition-metal-catalyzed direct C−H bond acylation under the assistance of a directing group has emerged as a reliable and valuable tool for the synthesis of various ketones.

Although a number of approaches for the acyloxylation of 2-arylpyridines[5] and other directing groups[6,7] have been developed (Scheme 1 a-d), the acyloxylation of pyridotriazoles have never been attempted. Transition-metal-catalyzed denitrogenative transannulation of pyridotriazole is one of the most significant achievements in synthetic chemistry.[8] Because, triazole derivatives are well-known precursors to generate metal carbenoid species. These metal carbenoids react with various nucleophiles to generate corresponding fused heterocycles.[8,9] As a part of our program on the development of denitrogenative transannulation of pyridotriazoles,[10] we envisioned that, aliphatic carboxylic acids may serve as better acyloxylation reagents to obtain acyloxy substituted pyridotriazoles and their subsequent conversion to 2-([1,2,3]triazolo[1,5-a]pyridin-3-yl)phenol (Scheme 1e).



Scheme 1. *ortho*-Acyloxylation of arenes with directing groups.

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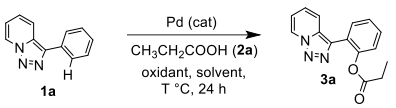
Results and Discussion

Initially, we examined the optimization of conditions for the selective acyloxylation of pyridotriazole **1a** with propionic acid **2a** in the presence of 3 mol % of $Pd(OAc)_2$ at 120°C temperature in a sealed tube, and no reaction was observed up to 24 h (Table 1, entry 1). When the same reaction was performed with the

Table 1. Screening of conditions



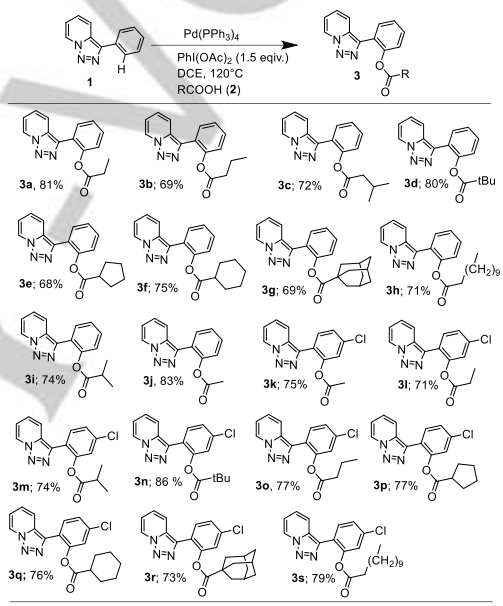
S.No.	2a	Catalyst (3 mol%)	Oxidant (1.5 eqiv.)	Solvent	Temp.°C	Yield % 3a
1	0.5 ml	$Pd(OAc)_2$		-	120	nr
2	0.5 ml	$Pd(OAc)_2$	$PhI(OAc)_2$	-	120	24
3	2	$Pd(OAc)_2$	$PhI(OAc)_2$	DCB	120	33
4	2	$Pd(OAc)_2$	$PhI(OAc)_2$	CH_3CN	120	20
5	2	$Pd(OAc)_2$	$PhI(OAc)_2$	H_2O	120	nr
6	2	$Pd(OAc)_2$	$PhI(OAc)_2$	Toluene	120	25
7	2	$Pd(OAc)_2$	$PhI(OAc)_2$	DMSO	120	nr
8	2	$Pd(OAc)_2$	$PhI(OAc)_2$	THF	120	30
9	2	$Pd(OAc)_2$	$PhI(OAc)_2$	DCE	120	47
10	2	PdI_2	$PhI(OAc)_2$	DCE	120	32
11	2	$Pd(CH_3CN)_2(Cl)_2$	$PhI(OAc)_2$	DCE	120	30
12	2	$Pd(OTf)_2$	$PhI(OAc)_2$	DCE	120	37
13	2	$Pd(PPh_3)_4$	$PhI(OAc)_2$	DCE	120	55
14	**3**	**$Pd(PPh_3)_4$**	**$PhI(OAc)_2$**	**DCE**	**120**	**81**
15[b]	3	$Pd(PPh_3)_4$	$PhI(OAc)_2$	DCE	120	25
16[c]	3	$Pd(PPh_3)_4$	$PhI(OAc)_2$	DCE	120	20
17	3	$Pd(PPh_3)_4$	$PhI(OAc)_2$	DCE	90	36
18	3	$Pd(PPh_3)_4$	$PhI(OAc)_2$	DCE	rt	nr
19	3	---	$PhI(OAc)_2$	DCE	120	nr
20	3	$Pd(PPh_3)_4$	$PhI(OAc)_2$	DCE	140	79

Reaction condition: **1a** (0.2 mmol), **2a** (0.6 mmol), $Pd(PPh_3)_4$ (3 mol %), $PhI(OAc)_2$ (1.5 eqiv.), solvent (1mL), 120°C, sealed tube, isolated yields.[a]$PhI(OAc)_2$, 1.0 eqiv. [b]$Pd(PPh_3)_4$ 1 mol %.

Addition of $PhI(OAc)_2$ (PIDA) as oxidant[11] the desired product **3a** was isolated in 24% yield (Table 1, entry 2). Performing the reaction in dichlorobenzene (DCB) as solvent, the yield of **3a** was increased to 33% (Table 1, entry 3). Screening of different solvents showed that, dichloroethane is the best among the (CH_3CN, THF, Toluene, DMSO, and H_2O) solvents for the reaction (Table 1, entries 4-9). Different catalysts were also considered and the results showed that [$Pd(PPh_3)_4$] was more effective than the other catalysts (Table 1, entries 10–13). The yield of the desired product **3a** was increased to 81%, when 3.0 equivalents of **2a** was employed (w.r.t. **1a**) (entry 14). While decreasing the amount of oxidant, catalyst and temperature, the yield of the desired product was also reduced (Table 1, entries 15-18), and no reaction was observed without catalyst (Table 1, entry19). Further, no improvement in yield was observed, while increasing the reaction temperature to 140 ℃ (Table 1, entry 20). The best yield of **3a** was obtained under the conditions of entry 14; these parameters were set as optimal for further acyloxylation of pyridotriazole with different carboxylic acids (Table 2).

The reaction of 3-phenyl[1,2,3]triazolo[1,5-a]pyridine **(1a)** with a various carboxylic acids, such as long chain, branched, secondary, tertiary and cyclic including adamantane-1-carboxylic acid, reacted smoothly and gave good yields (63−83%) of the desired products **3a−3j**. One of the product **3d** was further confirmed by single-crystal XRD. The reaction of 3-(4-chlorophenyl)-[1,2,3]triazolo[1,5-a]pyridine **1b** was reacted with the above carboxylic acid derivatives and afforded the desired products **(3k−3s)** in good to excellent yields (71−86%) under the optimised conditions. It may be noted that chloro substituted pyridotriazole derivatives **3k−3s** were well tolerated, and these products could be further useful in traditional cross-coupling reactions.

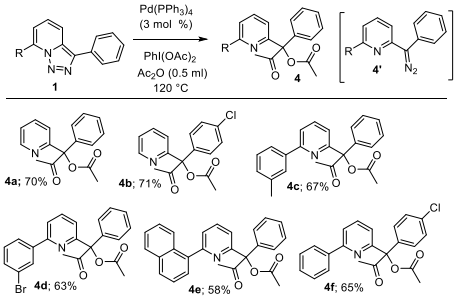
Table 2. Substrate scope for acyloxylation pyridotriazoles[a]



[a]Reaction conditions: **1a** (0.2 mmol), **2** (0.6 mmol), $Pd(PPh_3)_4$ (3 mol %), 24.0 h, DCE (1.0 mL), isolated yields.

For our curiosity, we hypothesized to employ acetic anhydride in place of carboxylic acid it may serve as both solvent as well as acylation reagent. Accordingly **1a** was subjected to the optimised conditions without external solvent (Table 3).

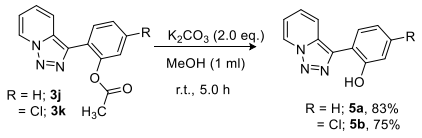
Table 3. Conversion of pyridotriazoles to 2-oxo-1-aryl-1-(pyridinyl)propyl acetates



Reaction conditions: **1a** (0.2 mmol), **Ac_2O**, (5.0 mmol), $Pd(PPh_3)_4$ (3 mol %), PIDA (1.5 eqiv.), 24 .0 h, isolated yields.

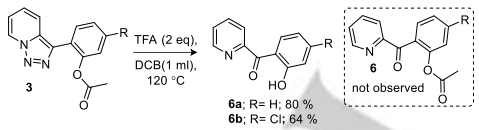
Surprisingly we observed the formation of interesting product 2-oxo-1-phenyl-1-(pyridin-2-yl)propyl acetate **4a** in 70% isolated yield. This reaction may proceeds through the formation of intermediate 2-(diazo(phenyl)methyl)pyridine **4′**, by ring opening of **1** under these conditions. With the encouraging result of **4a**, and the importance of substituted pyridines in chemo sensor applications[12] we further subjected various aryl and naphthyl substituted pyridotriazoles to the same conditions, and obtained the corresponding products **4b−4f** in good yields.

Further we observed that, the direct access to the hydroxylated pyridines and pyridotriazole derivatives were not available in the literature, however, they have been isolated from natural products through multistep procedure.[13] In this context, we subjected the products **3j** and **3k** to the hydrolysis using potassium carbonate in methanol as solvent[14] and obtained 2-([1,2,3]triazolo[1,5-a]pyridin-3-yl)phenol **5a** and 2-([1,2,3]triazolo[1,5-a]pyridin-3-yl)-5-chlorophenol **5b** in 83% and 75% yield respectively (Scheme 2).



Scheme 2

Based on our previous understanding on the ring opening of pyridotriazoles under Lewis acid catalysis,[10b,c] we further subjected the product **3i** and **3k** using trifluoro acetic acid (TFA) and 1,2-dichlorobenzene as solvent to get the 2-picolinoylphenyl acetates **6**, instead, we observed the formation of pyridotriazole ring opening and simultaneous hydrolysed products (2-hydroxyphenyl)(pyridin-2-yl)methanone **6a** and (4-chloro-2-hydroxyphenyl)(pyridin-2-yl)methanone **6b** in 80% and 64% yields respectively (Scheme 3).

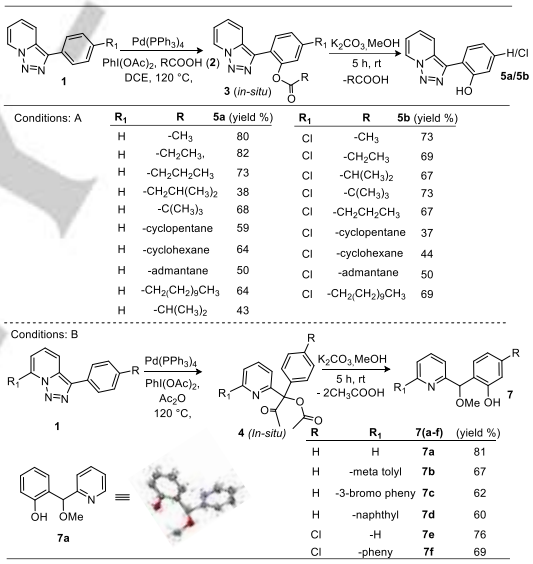


Scheme 3.

Hydroxypyridine derivatives are important precursors[15] for the drug 5-aminolevulinic acid that is used in cancer therapy.[16] Due to the biological importance of these hydroxylated pyridine derivatives,[17] and based on the encouraging results of scheme 2 and 3, we prepared some of the pyridine derivatives directly from pyridotriazoles with the above optimized conditions followed by hydrolysis in one pot procedure (Table 4), rather than subjecting the isolated products **3** and **4** separately. As can be seen from the products of table 4 (conditions A), the best yields (82% and 73%) of hydrolysed products **5a** and **5b** were obtained when propionic acid and acetic acid were used as acyloxylation reagents compared to other carboxylic acid derivatives. Under the conditions of **B**, table 4, the unsubstituted pyridotriazoles provided good yield (81%) of hydrolysis product 2-(methoxy(pyridin-2-yl)methyl)phenol **7a** in one pot procedure. The structure of the product **7a** was further confirmed by single-crystal XRD analysis.[18] Other substituents such as *meta*-tolyl, 3-Br-phenyl, naphthyl, and phenyl on the pyridotriazole also afforded the corresponding products **7b−7f** in moderate to good yields (60-81%) under the optimised conditions (Table 4, conditions B).

For the conditions B; no external solvent was used, instead, 5.0 mmol of acetic anhydride was employed. Development of direct methods for the synthesis of desired products by reducing the number of steps is of prime importance in synthetic chemistry, as these molecules are useful for industrial applications. By this method not only reduces the cost of the process, but also it is step economical. To see the feasibility of the process two products **5a** and **7a** were performed at a gram scale under the optimized conditions (Scheme 4). Although this route to the formation of hydroxy derivatives was only realized for a particular class of substrates, pyridotriazoles, it represents a major developmental strategy to obtain hydroxy derivatives of pyridines via acyloxylation of pyridotriazoles followed by hydrolysis.

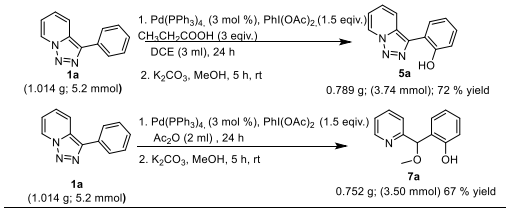
Table 4. Direct conversion of pyridotriazoles to **5** and **7** via hydrolysis[a]



[a]Reaction conditions A: **1** (0.2 mmol), **2** (RCOOH, 0.6 mmol), $Pd(PPh_3)_4$ (3 mol %), $PhI(OAc)_2$ (1.5 eqiv.), DCE (1 mL), 24 h, followed by the addition of K_2CO_3 (2.0 eqiv.), MeOH (1 mL), isolated yields.
[a]Reaction conditions B: **1** (0.2 mmol), Ac_2O (5.0 mmol), $Pd(PPh_3)_4$ (3 mol %), $PhI(OAc)_2$ (1.5 eqiv.), 24 h, followed by the addition of K_2CO_3 (2 eqiv.), MeOH (1 mL), isolated yields.

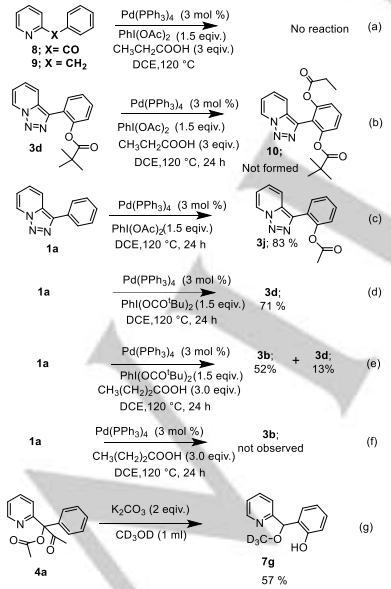
To gain insights into the reaction mechanism of present transformation, some experiments were performed (Scheme 5). Initially 2-benzoylpyridine **8** and 2-benzylpyridine **9** were subjected to the optimized conditions in place of **1a**, but these reaction fail to afford desire product **3a** (eq. a). These two reactions indicate that the nitrogen atom of triazole ring is essential for the regioselective acyloxylation.[5-7]

Further to check the regioselectivity, one of the substrate 2-([1,2,3]triazolo[1,5-a]pyridine-3-yl)phenyl pivalate **3d** was subjected to the same reaction conditions, the formation of desired product **10** was not observed (Scheme 5, eq. b). This experiment indicates that, the present transformation is highly desirable for selective mono acyloxylation of pyridotriazoles.



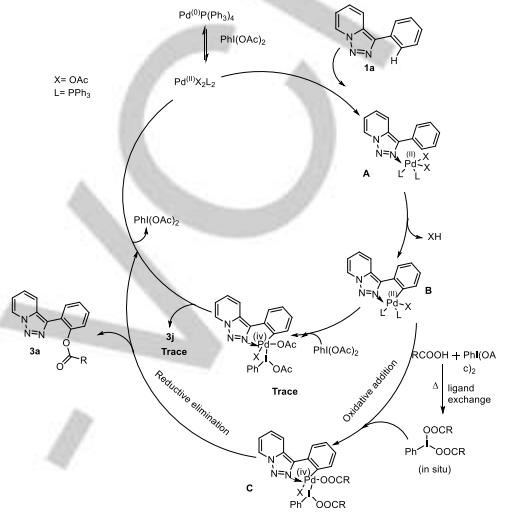
Scheme 4. Gram scale reactions

To see the effect of carboxylic acid, upon subjecting **1a** with the optimised conditions without any carboxylic acid, we obtained 83% yield of product **3j** (Scheme 5, eq. c). It indicate that, the acyl group contributes from $PhI(OAc)_2$ (PIDA) in absence of external carboxylic acid. Further to confirm the source of acyloxylation, **1a** was reacted with $PhI(OCO^tBu)_2$ and the mixture of $PhI(OCO^tBu)_2$ and butanoic acid separately in place of $PhI(OAc)_2$ under the optimized conditions; the desired products **3d** and **3b** were obtained in 71% and 52% yields respectively (Scheme 5, eqs. d & e). In the latter case along with major product **3b**, small amount of **3d** was also observed, it may be due to the stability of carboxylate ($^tBuCOO^-$) ion. The reaction of **1a** under the optimized conditions without PIDA, no product formation was observed (Scheme 5, eq. f). The reactions of equations c - f (Scheme 5) suggest that, PIDA is essential for present transformation and also indicates the exchange of ligand with PIDA (carboxylate derivative), such exchange of ligands were known in the literature.[19] To confirm the source of methoxy group, **4a** was reacted with deuterated methanol (CD_3OD) under the optimized conditions and observed the formation of 2-((methoxy-*d*$_3$)pyridin-2-yl)methyl)phenol **7g** in 57% yield (Scheme 5 eq. g). This reaction indicates that, the methoxy group comes from the methanol during hydrolysis.



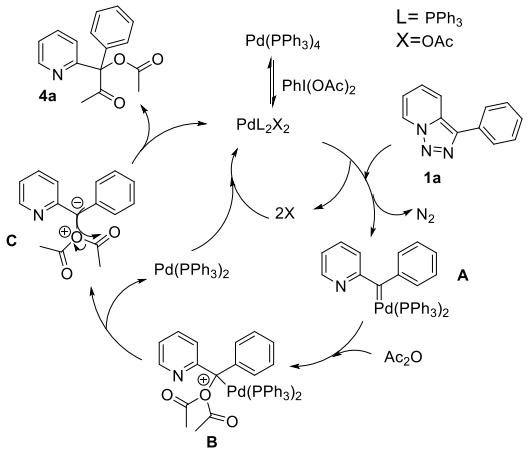
Scheme 5. Control experiments

Based on previous literature and our experiments, a plausible reaction mechanism has been proposed (Scheme 6). Initially $Pd(PPh_3)_4$ oxidized to Pd(II) species by $PhI(OAc)_2$ and coordination of nitrogen atom of **1a** with Pd(II) species affords an intermediate **A**. Subsequently, the cleavage of the *ortho* C−H bond smoothly proceeds and generates a five-membered cyclopalladated(II) intermediate **B**,[7c-e] which undergoes oxidative addition with $PhI(OAc)_2$ to deliver the Pd(IV) intermediate **C**. Followed by its reductive elimination leads the formation of the desired product **3a** with the regeneration of the Pd(II)-catalyst.



Scheme 6. Plausible reaction mechanism for **3a**

Similar reaction mechanism is applicable for the 2-oxo-1-phenyl-1-(pyridin-2-yl)propyl acetate (**4a**) under the present conditions (Scheme 7). Denitrogenation of **1a** with $Pd(PPh_3)_4$ may generate the metallocarbene intermediate **A**.[10a] The insertion of Ac_2O to the intermediate **A** may generates metalated intermediate **B**. Which upon elimination of $(Pd(PPh_3)_2$ generates another intermediate **C**. Due to the positive charge on oxygen of Ac_2O, the negative charge present on the central carbon may attack on electrophilic carbonyl carbon and deliver the desired product **4a**.



Scheme 7. Proposed mechanism for **4a**

Conclusions

We have developed an efficient protocol for the palladium-catalyzed direct *ortho* C−H acyloxylation of 3-phenyl-pyridotriazoles with various carboxylic acids as acyloxylation reagents. The reaction is highly selective for mono acyloxylation of pyridotriazoles with $PhI(OAc)_2$ (PIDA) as an oxidant and aliphatic carboxylic acids such as aliphatic, branched, cyclic including adamantine carboxylic acids. When acetic anhydride was employed as acylation reagent, an interesting product 2-oxo-1-phenyl-1-(pyridin-2-yl)propyl acetates were obtained through the ring opening of pyridotriazoles. We also reported the direct one pot synthesis of (2-hydroxyphenyl)(pyridin-2-yl)methanones via acyloxylation followed by basic hydrolysis. It is interesting to note that, when 2-([1,2,3]triazolo[1,5-a]pyridin-3-yl)phenyl acetate was subjected to acid hydrolysis 2-([1,2,3]triazolo[1,5-a]pyridin-3-yl)phenol was obtained. To validate the feasibility of the process for commercial synthesis, two products were synthesized at gram scale (5.0 mmol) under the optimized conditions.

Experimental Section

General procedure for the synthesis of 2-([1,2,3]triazolo[1,5-a]pyridin-3yl)phenyl propionate (3a):

To a reaction tube equipped with a magnetic stir bar, added 3-phenyl-[1,2,3]triazolo[1,5-a]pyridine (1a)(39.0 mg, 0.2 mmol), propionic acid (2a)(45 mg, 0.6 mmol), $Pd(PPh_3)_4$ (6.7 mg, (3 mol%) , $PhI(OAc)_2$ (97 mg,1.5 eqiv) and 1.0 mL of 1,2-dichloroethane. The mixture was heated in an oil bath at 120°C in a closed tube for 24 h. Reaction was monitored by TLC, after completion of the reaction; it was allowed to attain room temperature. Then the mixture was poured into 30 mL of sodium chloride solution. The product was extracted with EtOAc (15 mL X 3) and dried with anhydrous Na_2SO_4. Removal of the solvent under reduced pressure the left out residue was purified by column chromatography using silica gel (20% EtOAc/hexane) to afford 3a(40.7 mg; 81% yield).

General procedure for the synthesis of 2-oxo-1-phenyl-1-(pyridin-2-yl)propyl acetate (4a):

To a reaction tube equipped with a magnetic stir bar, added 3-phenyl-[1,2,3]triazolo[1,5-a]pyridine (**1a**)(39.0 mg, 0.2 mmol), acetic anhydride (0.5 mL, (5.0 mmol), $Pd(PPh_3)_4$ (6.7 mg, (3 mol%) and $PhI(OAc)_2$ (97 mg, 1.5 eqiv). The mixture was heated in an oil bath at 120°C in a closed tube for 24 h. Reaction was monitored by TLC, after completion of the reaction; it was allowed to attain room temperature. Then the mixture was poured into 30 mL of sodium chloride solution. The product was extracted with EtOAc (15 mL X 3) and dried with anhydrous Na_2SO_4. Removal of the solvent under reduced pressure the left out residue was purified by column chromatography using silica gel (20% EtOAc/hexane) to afford **4a**(38 mg; 70% yield).

CCDC 1955145 [for **3d**] and 1958755 [for **7a**] contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

Acknowledgements

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Keywords: *Ortho*-C-H activation, Pyridotriazole, Pd-catalyzed, *ortho* hydroxylation, gram scale.

[1] a) R. D. Taylor, M. MacCoss ,A. D. G. Lawson, *J. Med. Chem.* **2014**, *57*, 5845–5859; b) J. S. Carey, D. Laffan, C. Thomson, M. T. Williams, *Org. Biomol. Chem.* **2006**, *4*, 2337–2347; c) Z. Wang, K. Li, D. Zhao, J. Lan, J. You, *Angew. Chem. Int. Ed.* **2011**, *50*, 5365–5369; d) S. Gamsey, A. Miller, M. M. Olmstead, C. M. Beavers, L. C. Hirayama, S. Pradhan, R. A. Wessling, B. Singaram, *J. Am. Chem. Soc.* **2007**, *129*, 1278–1286.

[2] a) J. A. Joule, K. Mills, *Heterocyclic Chemistry, 4th.ed.,Vol 369*, Blackwell, Oxford, **1990** pp.1993–2000. b) Y. Rival, G. Grassy, G. Michel, *Chem. Pharm. Bull.* **1992**, *40*, 1170–1176; c) M. H. Fisher, A. Lusi, *J. Med. Chem*. **1972**, *15*, 982–985. d) C. Hamdouchi, J. d. Blas, M. d. Prado, J. Gruber, B. A. Heinz, L. Vance, *J. Med. Chem.* **1999**, *42*, 50–59; e) J. J. Kaminsky, A. M. Doweyko, *J. Med. Chem*. **1999**, *40*, 427–736; f) M. Hranjec, M. Kralj, I. Piantanida, M. Sedic, L. Suman, K. Pavelic, G. K.Zamola , *J. Med. Chem*. **2007**, *50*, 5696–5711; g) S. K. Kotovskaya, Z. M. Baskakova, V. N. Charushin, O. N. Chupakhin, E. F. Belanov, N. I. Bormotov, S. M. Balakhnin, O. A. Serova, *Pharm. Chem. J*. **2005**, *39*, 574–578; h) M. Lhassani, O. Chavignon, J. M. Chezal, J. C. Teulade, J. P. Chapat, R. Snoeck, G. Andrei, J. Balzarini, E. D. Clercq, A. Gueiffier, Eur. *J. Med. Chem*. **1999**, *34*, 271–274; i) S. Z. Langer, S. Arbilla, J. Benavides, B. Scatton, *Adv. Biochem. Psychopharmacol.* **1990**, *46*, 61–72; j) K. Mizushige, T. Ueda, K. Yukiiri, H. Suzuki, *Cardiovasc. Drugs Rev*. **2002**, *20*, 163–174.

[3] a) D. C. Blakemore, L. Castro, I. Churcher, D. C. Rees, A. W. Thomas, D.M. Wilson, A. Wood, *Nature Chemistry.* **2018**, *10*, 383–394; b) P. Martins, J. Jesus, S. Santos, L. R. Raposo, C. R. Rodrigues, P. V. Baptista, A. R. Fernandes, *Molecules.* **2015**, *20*, 16852–16891.

[4] T. Cernak, K. D. Dykstra, S. Tyagarajan, P. Vachal, S. W. Krskab, *Chem. Soc. Rev*. **2016**, *45*, 546–576.

[5] Acyloxylation of 2-aryl pyridines, see: a) W. Wang, F. Luo, S. Zhang, J. Cheng, *J. Org. Chem*. **2010**, *75*, 2415–2418; b) J. M. Racowski, A. R. Dick, M. S. Sanford, *J. Am. Chem. Soc*. **2009**, *131*, 10974–10983; c) F. Wang, Z. Lin, W. Yu, Q. Hu, C. Shua, W Zhang, *RSC Adv*. **2018**, *8*, 16378–16382; d) C. Chen, Y. Pan, H. Zhao, X. Xu, J. Xu, Z. Zhang, S. Xi, L. Xu, H. Li, *Org. Chem. Front*. **2018**, *5*, 415–422; e). Y. J. Biana, C. B. Xianga, Z. M. Chena, Z. Z. Huang, *Synlett.* **2011**, *16*, 2407–2409; f) Z. Ye, W. Wang, F. Luo, S. Zhang, J. Cheng, *Org. Lett*. **2009***, 11*, 3974–3977.

[6] Acyloxylation sp2 (C-H) bonds with amides as directing groups, see: a) Z. Yin, P. Sun, *J. Org. Chem*. **2012**, *77*, 11339–11344; b) S. Zhao, F. J. Chen, B. Liu, B. F. Shi, *Science China Chemistry*. **2015**, *58*, 1302–1309; c) R. Ueno, S. Natsui, N. Chatani, *Org. Lett*. **2018,** *20*, 1062–1065; d) C. Lin, Z. Chen, Z. Liu, Y. Zhang, *Adv. Synth. Catal*. **2018**, *360*, 519–532; e) I. B. Krylov, V. A. Vil, A. O. Terent, *Beilstein J. Org. Chem*., **2015**, *11*, 92–146; f) K. Padala, M. Jeganmohan, *Chem. Commun*. **2013**, *49*, 9651–9653.

[7] Acyloxylation and acetoxylation with other directing groups, see: a) N. Chernyak, A. S. Dudnik, C. Huang, V. Gevorgyan, *J. Am. Chem. Soc.* **2010**, *132*, 8270–8272; b) D. Sarkar, A. V. Gulevich, F. S. Melkonyan, V. Gevorgyan, *ACS Catal*. **2015**, *5*, 6792–6801; c). C. Wang, D. M. Flanigan, L. N. Zakharov, P. R. Blakemore, *Org. Lett.* **2011**, *13*, 4024–4027; d) L. Wang, X. D. Xia, W. Guo, J. R. Chen, W. J. Xiao, *Org. Biomol. Chem.* **2011**, *9*, 6895–6898; e) L. Zhou, W. Lu, *Org. Lett*. **2014**, *16*, 508–511; f) K. Raghuvanshi, K. Rauch, L. Ackermann, *Chem. Eur. J*. **2015**, *21*, 1790–1794; g) T. Okada, K. Nobushing, T. Satoh, M. Miura, *Org. Lett*. **2016**, *18*, 1150–1153; h) F. Wang, Q. Hu, C. Shu, Z. Lin, D. Min, T. Shi, W. Zhang, *Org. Lett*. **2017,** *19*, 3636–3639; i) D. D. Li, Y. X. Cao, G. W. Wang, *Org. Biomol. Chem*. **2015**, *13*, 6958–6964; j) J. Guo, H. He, Z. Ye, K. Zhu, Y. Wu, F. Zhang, *Org. Lett*. **2018**, *20*, 5692–5695; k) E. Kianmehr, S. B. Nasab, *Eur. J. Org. Chem*. **2019**, 1038–1044; l) T. Sarkar, S. Pradhan, T. Punniyamurthy, *J. Org. Chem*. **2018**, *83*, 6444–6453; m) A. R. Dick, K. L.

Hull, M. S. Sanford, *J. Am. Chem. Soc*. **2004**, *126,* 2300–2301; n) L. V. Desai, K. L. Hull, M. S. Sanford, *J. Am. Chem. Soc*. **2004**, *126*, 9542–9543; o) D. Kalyani, M. S. Sanford, Org. Lett. **2005**, *7,* 4149–4152; p) L. V. Desai, H. A. Malik, M. S. Sanford, *Org. Lett.* **2006**, *8*, 1141–1144; q) R. Yi. Zhang, L. Y. Xi, L. Shi, X. Z. Zhang, S. Y. Chen, X. Q. Yu. *Org. Lett*. **2016,** *18*, 4024–4027; r) S. Gu, C. Chen, W. Chen, *J. Org. Chem*. **2009,** *74*, 7203–7206; s) H. M. Guo, W. H. Rao, H.Y. Niu, L. L. Jiang, G. Meng, J. J. Jin, X. N. Yanga, G. R. Qu, *Chem. Commun*. **2011**, *47*, 5608–5610.

[8] a) S. Chuprakov, F. W. Hwang, V. Gevorgyan*, Angew. Chem. Int. Ed.* **2007**, *46*, 4757–4759; b) V. Helan, A. V. Gulevich, V. Gevorgyan, *Chem. Sci.* **2015**, *6*, 1928-1931; c) Y. Shi, V. Gevorgyan, *Chem. Commun*. **2015,** *51*, 17166–17169; d) D. Yadagiri, A. Anbarasan, *Org. Lett*. **2014,** *16*, 2510–2513; e) S. Shin, Y. Park, C.E. Kim, J. Y. Son, P. H. Lee, *J. Org. Chem*. **2015**, *80*, 5859–5869.

[9] a) Y. Yang, J. X. Yu, X. H. Ouyang, J. H. Li, *Org. Lett.* **2017**, *19*, 3982–3985; b) C. Wang, Y. Zhou, X. Bao, *J. Org. Chem.* **2017**, *82*, 3751–3759.

[10] a) A. Joshi, D. Chandra Mohan, S. Adimurthy, *Org. Lett.* **2016,** *18*, 464–457; b) A. Joshi, D. C. Mohan, S. Adimurthy, *J. Org. Chem.*, **2016**, *81*, 9461–9469; c) D. Rawat, C. Ravi, A. Joshi, E. Suresh, K. Jana, B. Ganguly, S. Adimurthy, *Org. Lett.* **2019**, *21*, 2043–2047; d) A. Joshi, S. Rashmi, E. Suresh, K. Jana, B. Ganguly, S. Adimurthy *Chem. Commun*. **2019**, *55*, 10888–10891.

[11] The reaction was screened with other oxidants (TBHP, DTBP, $K_2S_2O_8$, and oxone), but the reaction was unsuccessful under these conditions (not included in the table).

[12] A. G. Fang, J. V. Mello, N. S. Finney, *Tetrahedron.* **2004**, *60* 11075–11087.

[13] S. N. Wang, P. Xu, H. Z. Tang, J. Meng, X. L. Liu, C.Q. Ma, *Environ. Sci. Technol*. **2005**, *39*, 6877–6880.

[14] P. Lennartz, G. Raabe, C. Bolm, *Adv. Synth. Catal*. **2012**, *354*, 3237–3249.

[15] H. Tang, Y. Yao, D. Zhang, X. Meng, L. Wang, H. Yu, L.Ma, P.Xu, *J. Biolog. Chem.* **2011**, *286*, 39179–39187.

[16] Q. Peng, T. Warloe, K. Berg, J. Moan, M. Kongshaug, K.E. Giercksky, J.M. Nesland, *Cancer.* **1997**,*79,* 2282–2308.

[17] a) J. Stankevičiūtė, J. Vaitekūnas, V. Petkevičius, R. Gasparavičiūtė, D. Tauraitė, R. Meškys, *Sci. Rep.* **2016**, *6*, 39129; b) H. Yu, R. P. Hausinger, H. Z. Tang, P. Xu, *J. Biolog. Chem.* **2014**, *289*, 29158–29170. c) Y. Wu, B. Zhou, *Org. Lett.* **2017**,*19*, 3532–3535.

[18] The detailed mechanism for the formation of product **7**, under the present conditions are under progress in our laboratory.

[19] W. Xue, Y.Su, K. H. Wang, R. Zhang, Y. Feng, L. Cao, D. Huang, Y. Hu, *Org. Biomol. Chem*. **2019**, *17*, 6654–6661.

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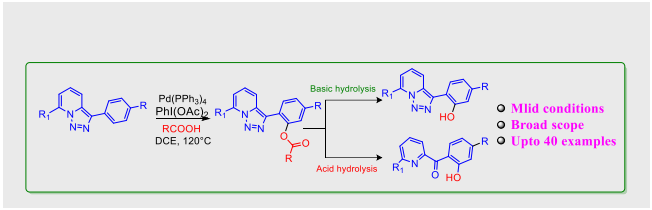

Pd-Catalyzed *ortho* Selective C-H Acyloxylation and Hydroxylation of Pyridotriazoles

Pyridotriazole, Pd-catalyzed, *ortho* hydroxylation

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