ChemComm

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: J. Zhang, M. Wu, J. Fan, Q. Xu and M. Xie, *Chem. Commun.*, 2019, DOI: 10.1039/C9CC03893K.

ROYAL SOCIETY OF CHEMISTRY

rsc.li/chemcomm

ROYAL SOCIETY OF CHEMISTRY View Article Online
DOI: 10.1039/C9CC03893K

Journal Name

COMMUNICATION

Selective C-H Acylation of Indoles with α-Oxocarboxylic Acids at the C4 Position by Palladium Catalysis

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

Jitan Zhang*, Manyi Wu, Jian Fan, Qiaoqiao Xu, and Meihua Xie*

The first Pd-catalyzed direct C-H acylation of indoles at the C4 position with α-oxocarboxylic acids using a ketone directing group is described. This reaction exhibits high regioselectivity and accomplishes with a wide scope and functional group tolerance to afford diverse acylated indoles in moderate to good yields. The control experiments evidence the generation of acyl radicals via $K_2S_2O_8$ promoted decarboxylation of α-oxocarboxylic acids and the involvement of a Pd^{II}/Pd^{IV} catalytic cycle. Importantly, the synthetically useful selectivity observed might be applied to prepare the indole derivatives with anti-tumor activity as tubulin inhibitors.

The past decade has witnessed the emergence of C-H functionalizations as an attractive alternative to traditional coupling protocols for the construction of functional molecules which maintains the expediency associated with simple cross-coupling reactions, yet with greater atom and step economy.[1] However, modulating the regioselective outcome of catalytic transformation with multiple C-H bonds remains a challenging task. Especially, the subtle difference from each other in activation barrier makes it appealing to be able to gain highly, even completely, site or regioselectivity.[2] In this context, indoles that possess six C-H bonds have received significant attention for the regioselective C-H bond functionalization for the past several years.[3] Generally, the natural reactivity of indoles suggested that metalation would take place preferentially at the C3 position.[4] To overcome this inherent selectivity, substrate modifications, such as installation of directing groups, have been widely utilized to drive the reaction to the desired regiochemical route. Seminal efforts for this research topic revealed that diverse transformations of indoles at C2,[5] C6[6] and C7[7] positions could be achieved successfully with the assistance of functional groups installed on *N* atom. Despite extensive progress in this field, the selective functionalization of C4 C-H bond is still on its early stage,[8] and the diverse transformations remain relatively unexplored. Therefore, the development of new protocols for the direct and regioselective C4 C-H bond functionalization of indoles would be highly appealing.

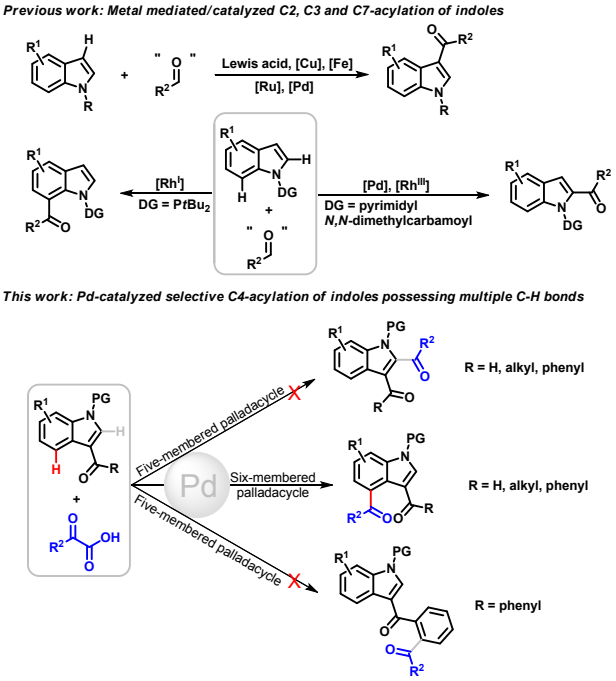


Fig. 1 Acylation of indoles via C-H bond activation.

Given the prevalence of acylated indoles in medicinal chemistry and pharmaceutical industries,[9] considerable attention has been paid to the establishment of the synthetic methodologies. By taking advantages of C-H activation strategies, some precedent catalytic systems have been disclosed in this research area (Fig. 1).[10] For instance, Li and co-workers reported a rhodium-catalyzed oxidative C2-acylation of indoles with aldehydes via a selective C-H activation.[11a] Subsequently, Zhu[11b] and Noël[11c] also demonstrated the C-H acylation of indoles at the C2-position with different acylated reagents by palladium and photoredox catalysis, respectively.

Key Laboratory of Functional Molecular Solids (Ministry of Education), Anhui Key Laboratory of Molecular Based Materials, College of Chemistry and Materials Science, Anhui Normal University, Wuhu 241002, China.

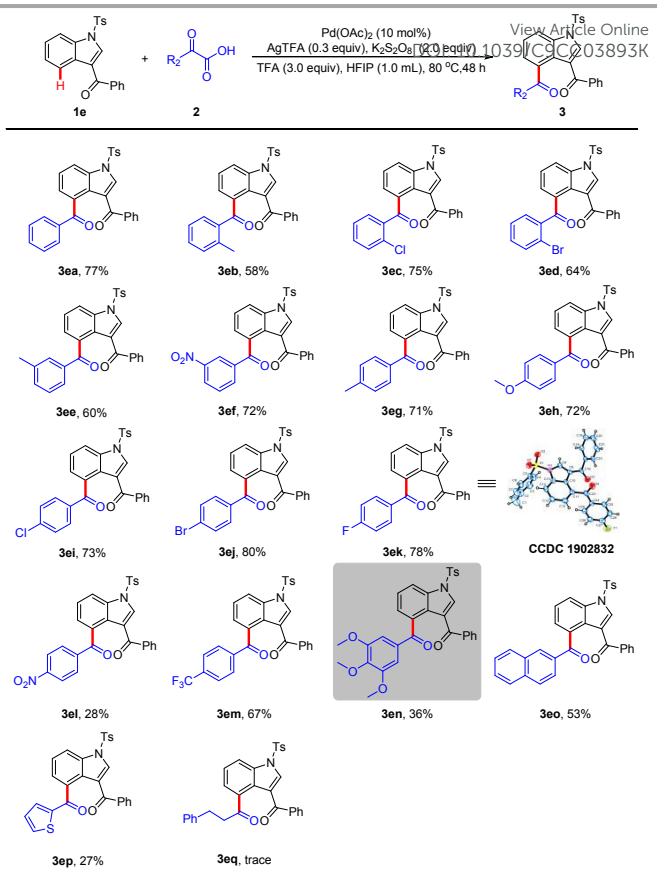
E-mail: zhangjt@ahnu.edu.cn; xiemh@mail.ahnu.edu.cn

Electronic Supplementary Information (ESI) available. Experimental procedures and characterization data for new compounds. See DOI: 10.1039/x0xx00000x

Very recently, Shi group[12] described a Rh(I)-catalyzed C7-selective acylation with anhydrides by C-H activation. To the best of our knowledge, there has been no example for the catalytic C4 C-H acylation of indoles,[13] although a series of C4-acylated indoles exhibit excellent antiproliferative activity as inhibitors of tubulin polymerization.[14] Undoubtedly, the installation of an auxiliary group at C3-position might be a readily accessible and practical strategy to achieve C4 C-H activation via a six-membered metallacycle. Nevertheless, the potential cleavage of other C-H bonds involving five-membered metallacycles makes this set a remarkable challenge. Inspired by Yu's work on the direct C–H acylation of aromatic ketones[15] and as our efforts to selective C-H activation chemistry, we herein discuss the first Pd-catalyzed straight-forward acylation of indoles at the inert C4 position via decarboxylative C-H bond functionalization with readily available α-oxocarboxylic acids[16] as acylated reagents. This process exhibits high regioselectivity among multiple C-H bonds of the indole substrates and good tolerance of various functional groups.

We commenced our investigations with the C4 C-H acylation of 1-(1-tosyl-1*H*-indol-3-yl)ethanone (**1a**) using 2-oxo-2-phenylacetic acid (**2a**) as a coupling partner (more details, see Optimization of Reaction Conditions and Table S1 in the Supporting Information). Gratifyingly, the C4-acylated product **3aa** was obtained in 47% yield when the reaction underwent with $Pd(OAc)_2$ (10 mol%), AgOAc (0.2 equiv), $K_2S_2O_8$ (2 equiv), and TFA (3 equiv) using HFIP as the optimal solvent that always has beneficial effect on C-H activation[17] (Table S1, entry 1). Various Ag salts were explored and superior catalytic efficiency was obtained when AgTFA was utilized to the reaction mixture (Table S1, entries 2-4, and Supporting Information). Other oxidants such as $Na_2S_2O_8$, $(NH_4)_2S_2O_8$, or Oxone were not able to give a better result (Table S1, entries 5-7). The reactivity could not be improved under argon atmosphere (Table S1, entry 8). Additional optimization revealed that an increase of AgTFA loading to 0.3 equiv could lead to a higher yield in 65% (Table S1, entry 9). While MsOH and $TsOH{\cdot}H_2O$ were not effective to this reaction, AcOH and PivOH afforded the desired product just in depressed yields (Table S1, entries 10-13). We next examined the impact of the auxiliary groups on the reaction efficiency (details in supporting information). We found that the choice of the protecting group on indole was crucial, as N-H indole could generate the desired product in low yields. The extensive screening gave the best choice phenyl(1-tosyl-1*H*-indol-3-yl)methanone, and the corresponding product could be isolated in 77% yield. Notably, all the reaction above gave high regioselectivity at the C4 position, even for the indole substrate with multiple reactive sites on the heterocyclic and aromatic rings.

The reaction proved to be general for a variety of α-oxocarboxylic acids to afford C4 C-H acylated indoles in moderate to good yields, and the results were summarized in Scheme 1. The regioselectivity of decarboxylative acylation was consistent with that of the model reaction. A number of functional groups on the aromatic ring of α-oxocarboxylic acids

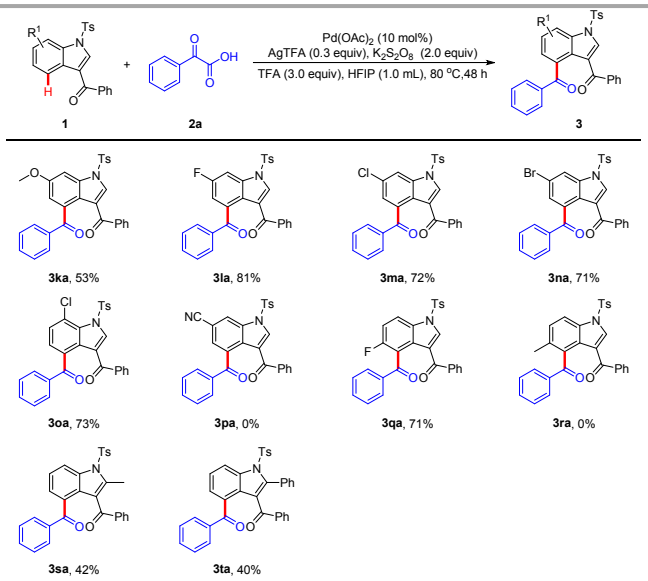


[a]Reaction conditions: **1e** (0.2 mmol), **2** (0.3 mmol), $Pd(OAc)_2$ (0.02 mmol), AgTFA (0.06 mmol), $K_2S_2O_8$ (0.4 mmol), TFA (3.0 equiv), HFIP (1.0 mL), Air, 80 °C, 48 h. [b] Isolated yield by flash column chromatography.

Scheme 1 Substrate scope of α-oxocarboxylic acids [a,b]

were tolerated, including methyl, methoxyl, halogen, nitro and trifluoromethyl groups (**3ea**-**3em**). No obvious electronic and steric effects were observed, albeit a low yield was obtained with 2-(4-nitrophenyl)-2-oxoacetic acid (**3el**). Interestingly, 2-oxo-2-(3,4,5-trimethoxyphenyl)acetic acid could also participate in this reaction to afford the corresponding product (**3en**) which might further be transformed to the free (NH)-indole with biological activities.[14a] Furthermore, 2-(naphthalen-2-yl)-2-oxoacetic acid gave a moderate yield (**3eo**). However, heteroaromatic carboxylic acids led to a lower yield (**3ep**), whereas aliphatic carboxylic acid nearly had no reactivity (**3eq**). Finally, X-ray crystallographic analysis of **3ba** (CCDC 1903234) and **3ek** (CCDC 1902832) further confirmed the structure of these C4-acylated indoles.

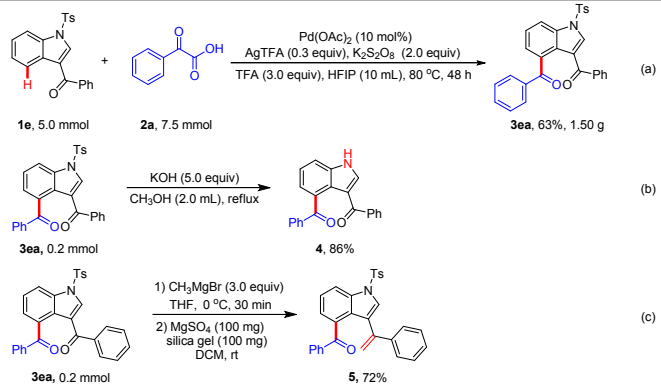
Next, the scope of indoles was also examined. As showed in Scheme 2, a number of functional groups on the indoles could be tolerated, rendering the desired products in moderate to good yields (**3ka**-**3oa**, **3qa**, **3sa** and **3ta**). However, 3-benzoyl-1-tosyl-1*H*-indole-6-carbonitrile and (5-methyl-1-tosyl-1*H*-indol-3-yl)(phenyl)methanone failed to give the acylated product, indicating that the reactivity of indoles was sensitive to the electronic characters and steric hindrance (**3pa** and **3ra**). In addition, it should be noted that the low yields obtained in this catalytic system was mainly due to the incomplete reaction.



[a]Reaction conditions: **1** (0.2 mmol), **2a** (0.3 mmol), $Pd(OAc)_2$ (0.02 mmol), AgTFA (0.06 mmol), $K_2S_2O_8$ (0.4 mmol), TFA (3.0 equiv), HFIP (1.0 mL), Air, 80 °C, 48 h. [b] Isolated yield by flash column chromatography.

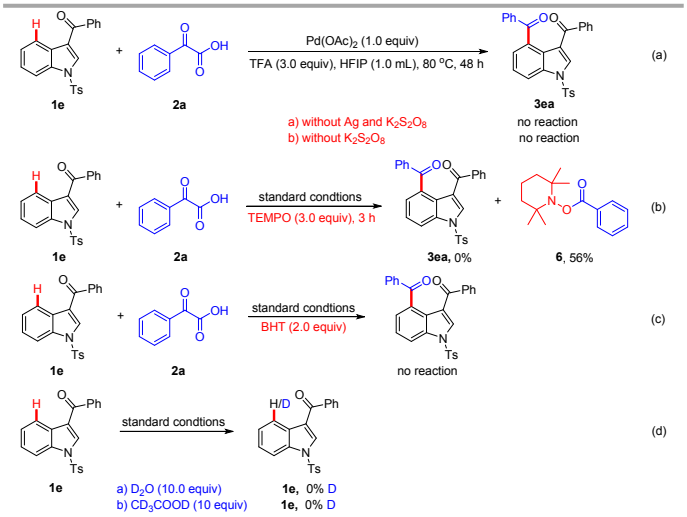
Scheme 2 Substrate scope of indoles [a,b]

In order to demonstrate the practical utility of the developed protocol, firstly, a gram-scale experiment with phenyl(1-tosyl-1*H*-indol-3-yl)methanone (**1e**) and 2-oxo-2-phenylacetic acid (**2a**) was carried out. With the standard conditions, 1.50 g (63%) of isolated product **3ea** could be obtained (Scheme 3a). And the Ts group could be removed easily in the presence of potassium hydroxide to give the N-H indole **4** in 86% yield (Scheme 3b). Besides, the sequential treatment of **3ea** with CH_3MgBr and $MgSO_4$ in mild reaction conditions would realize the formation of a functional alkene **5**, which might be transformed furtherly to 1,1-diarylalkane with simple operation (Scheme 3c).[18] And the selective reaction of one ketone over other with excess Grignard reagent might be mainly due to the larger steric hindrance in aryl-aryl ketone comparing with that in aryl-pyrrolyl ketone.



Scheme 3 Gram-scale reaction and transformation of product **3ea**

To gain more insight into the reaction mechanism, some control experiments were carried out. When the reaction was performed with 1.0 equiv $Pd(OAc)_2$ in the absence of $K_2S_2O_8$, no reaction took place at all (Scheme 4a). This result indicates that $K_2S_2O_8$ might serve as the promoter for the generation of acyl radical intermediate, which has been evidenced by the outcome of radical control experiments (Scheme 4b and 4c). The H/D exchange experiment was also conducted, by suggesting the initial C-H cleavage irreversible (Scheme 4d). In respect of the reason for the regioselectivity at the C4 position, we hypothesize that a six-membered palladacycle might be helpful for reducing the chelate ring strain derived from the two double bonds on the cycle, whereas a five-membered palladacycle would experience greater ring strain.[19]



Scheme 4 Control experiments

On the basis of our observations and analogous literature precedents,[15,20] a plausible reaction mechanism was proposed (see in the Supporting Information). While the formation of a six-membered palladacycle **A** (see Mechanistic Studies in the Supporting Information), the decarboxylic process promoted by $Ag/K_2S_2O_8$ generated an acyl radical species **B** which was trapped by TEMPO to form the compound **6**. Then the oxidative coupling of intermediate **B** and Pd^{II} complex **A** resulted in the formation of intermediate **C**, which might be further oxidized to Pd^{IV} complex **D**. Finally, a reductive elimination took place, releasing the desired product **3** and regenerating the Pd^{II} catalyst.

In summary, the first C4 C-H acylation of indoles by palladium catalysis has been developed with the aid of a carbonyl directing group. The reaction proceeds with high regioselectivity for the indole coupling partner and is compatible with a wide variety of functional groups. Moreover, the synthetic value of this transformation is proved by the straightforward access to analogues of bioactive indoles and the easily accessible transformations of the product. Additional mechanistic studies to fully rationalize the observed selectivity and broad synthetic applications of this catalytic system are currently pursued in our laboratory.

Funding from Natural Science Foundation of China (No. 21702237, and 21272004) is acknowledged.

Conflicts of interest

There are no conflicts of interest to declare.

Notes and references

1 For selected reviews, see: (a) P. Gandeepan, T. Müller, D. Zell, G. Cera, S. Warratz and L. Ackermann, *Chem. Rev.,* 2019,

119, 2192; (b) Y. Yang, J. Lan and J. You, *Chem. Rev.,* 2017, **117**, 8787; (c) Y. Wei, P. Hu, M. Zhang and W. Su, *Chem. Rev.,* 2017, **117**, 8864; (d) F. Wang, S. Yu and X. Li, *Chem. Soc. Rev.,* 2016, **45**, 6462; (e) T. Gensch, M. N. Hopkinson, F. Glorius and J. Wencel-Delord, *Chem. Soc. Rev.,* 2016, **45**, 2900; (f) Z. Chen, B. Wang, J. Zhang, W. Yu, Z. Liu and Y. Zhang, *Org. Chem. Front.,* 2015, **2**, 1107; (g) C. S. Yeung and V. M. Dong, *Chem. Rev.,* 2011, **111**, 1215; (h) R. Giri, B.-F. Shi, K. M. Engle, N. Maugel and J.-Q. Yu, *Chem. Soc. Rev.,* 2009, **38**, 3242.

2 For selected examples, see: (a) L. Ping, D. S. Chung, J. Bouffard and S.-G. Lee, *Chem. Soc. Rev.,* 2017, **46**, 4299; (b) R. Boyaala, R. Touzani, T. Roisnel, V. Dorcet, E. Caytan, D. Jacquemin, J. Boixel, V. Guerchais, H. Doucet and J.-F. Soulé, *ACS Catal.,* 2019, **9**, 1320; (c) D. Ding, G. Zhu and X. Jiang, *Angew. Chem. Int. Ed.,* 2018, **57**, 9028; (d) K. Hirano and M. Miura, *Chem. Sci.,* 2018, **9**, 22; (e) Z. Zhang, K. Tanaka and J.-Q. Yu, *Nature,* 2017, **543**, 538; (f) S. Yamada, K. Murakami and K. Itami, *Org. Lett.,* 2016, **18**, 2415; (g) R. B. Bedford, S. J. Durrant and M. Montgomery, *Angew. Chem. Int. Ed.,* 2015, **54**, 8787; (h) N. Kuhl, M. N. Hopkinson, J. Wencel-Delord and F. Glorius, *Angew. Chem. Int. Ed.,* 2012, **51**, 10236.

3 For selected reviews, see: (a) S. Cacchi and G. Fabrizi, *Chem. Rev.,* 2011, **111**, 215; (b) J. A. Leitch, Y. Bhonoah and C. G. Frost, *ACS Catal.,* 2017, **7**, 5618; (c) M. Petrini, *Chem-Eur. J.,* 2017, **23**, 16115; (d) M. Bandini and A. Eichholzer, *Angew. Chem., Int. Ed.,* 2009, **48**, 9608.

4 For selected examples, see: (a) S. G. Modha and M. F. Greaney, *J. Am. Chem. Soc.,* 2015, **137**, 1416; (b) Y. Li, T. Yan, K. Junge and M. Beller, *Angew. Chem., Int. Ed.,* 2014, **53**, 10476; (c) M. V. Leskinen, K.-T. Yip, A. Valkonen andP. M. Pihko, *J. Am. Chem. Soc.,* 2012, **134**, 5750; (d) J.-C. Wu, R.-J. Song, Z.-Q. Wang, X.-C. Huang, Y.-X. Xie and J.-H. Li, *Angew. Chem., Int. Ed.,* 2012, **51**, 3453; (e) Y. Zhu and V. H. Rawal, *J. Am. Chem. Soc.,* 2012, **134**, 111; (f) W. Wu and W. Su, *J. Am. Chem. Soc.,* 2011, **133**, 11924.

5 (a) F. Pesciaioli, U. Dhawa, J. C. A. Oliveira, R. Yin, M. John and L. Ackermann, *Angew. Chem. Int. Ed.,* 2018, **57**, 15425; (b) D. Zhao, J. H. Kim, L. Stegemann, C. A. Strassert and F. Glorius, *Angew. Chem., Int. Ed*., 2015, **54**, 4508; (c) M. Moselage, N. Sauermann, S. C. Richter and L. Ackermann, *Angew. Chem., Int. Ed.,* 2015, **54**, 6352; (d) H. Ikemoto, T. Yoshino, K. Sakata, S. Matsunaga and M. Kanai, *J. Am. Chem. Soc.,* 2014, **136**, 5424; (e) D.-G. Yu, T. Gensch, F. Azambuja, S. Vásquez-Céspedes and F. Glorius, *J. Am. Chem. Soc.,* 2014, **136**, 17722; (f) F. Xie, Z. Qi, S. Yu and X. Li, *J. Am. Chem. Soc.,* 2014, **136**, 4780; (g) M. Nishino, K. Hirano, T. Satoh and M. Miura, *Angew. Chem., Int. Ed.,* 2012, **51**, 6993; (h) Z. Ding and N. Yoshikai, *Angew. Chem., Int. Ed.,* 2012, **51**, 4698; (i) L. Jiao and T. Bach, *J. Am. Chem. Soc.,* 2011, **133**, 12990; (j) A. DeAngelis, V. W. Shurtleff, O. Dmitrenko and J. M. Fox, *J. Am. Chem. Soc.,* 2011, **133**, 1650.

6 (a) Y. Yang, R. Li, Y. Zhao, D. Zhao and Z. Shi, *J. Am. Chem. Soc.,* 2016, **138**, 8734; (b) Y. Feng, D. Holte, J. Zoller, S. Umemiya, l. R. Simke, P. S. Baran, *J. Am. Chem. Soc.,* 2015, **137**, 10160; (c) G. Yang, P. Lindovska, D. Zhu, J. Kim, P. Wang, R.-Y. Tang, M. Movassaghi and J.-Q. Yu, *J. Am. Chem. Soc.,* 2014, **136**, 10807.

7 (a) X. Qiu, P. Wang, D. Wang, M. Wang, Y. Yuan and Z. Shi, *Angew. Chem. Int. Ed.,* 2019, **58**, 1504; (b) A. J. Borah and Shi, Z. *J. Am. Chem. Soc.,* 2018, **140**, 6062; (c) J. A. Leitch, C. L. McMullin, M. F. Mahon, Y. Bhonoah and C. G. Frost, *ACS Catal.,* 2017, **7**, 2616; (d) L. Xu, C. Zhang, Y. He, L. Tan, D. Ma, *Angew. Chem. Int. Ed.,* 2016, **55**, 321; (e) Y. Kim, J. Park and S. Chang, *Org. Lett.,* 2016, **18**, 1892; (f) Y. Yang, X. Qiu, Y. Zhao, Y. Mu and Z. Shi, *J. Am. Chem. Soc.,* 2016, **138**, 495; (g) Z. Song, R. Samanta and A. P. Antonchick, *Org. Lett.,* 2013, **15**, 5662; (h) T. Nishikata, A. R. Abela, S. Huang and B. H. Lipshutz, *J. Am. Chem. Soc.,* 2010, **132**, 4978; (i) D. W. Robbins, T. A. Boebel and J. F. Hartwig, *J. Am. Chem. Soc.,* 2010, **132**, 4068; (j) S. Paul, G. A. Chotana, D. Holmes, R. C. Reichle, R. E. Maleczka and M. R. Smith, *J. Am. Chem. Soc.,* 2006, **128**, 15552; (k) C. G. Hartung, A. Fecher, B. Chapell and V. Snieckus, *Org. Lett.,* 2003, **5**, 1899.

8 (a) C. N. Kona, Y. Nishii and M. Miura, *Org. Lett.,* 2018, **20**, 4898; (b) J. Lv, B. Wang, K. Yuan, Y. Wang and Y. Jia, *Org. Lett.,* 2017, **19**, 3664; (c) X. Chen, G. Zheng, Y. Li, G. Song and X. Li *Org. Lett.,* 2017, **19**, 6184; (d) H. Chen, C. Lin, C. Xiong, Z. Liu and Y. Zhang, *Org. Chem. Front.,* 2017, **4***,* 455; (e) V. Lanke and K. R. Prabhu, *Chem. Commun.,* 2017, **53**, 5117; (f) A. J. Borah and Shi, Z. *Chem. Commun.,* 2017, **53**, 3945; (g) T. Zhou, B. Li and B. Wang, *Chem. Commun.,* 2017, **53**, 6343; (h) S. Maity, U. Karmakar and R. Samanta, *Chem. Commun.,* 2017, **53**, 12197; (i) V. Lanke, K. R. Bettadapur and K. R. Prabhu, *Org. Lett.,* 2016, **18**, 5496; (j) X. Liu, G. Li, F. Song, and J. You, *Nat. Commun.,* 2014, **5***, 5030*; (k) Q. Liu, Q. Li, Y. Ma and Y. Jia, *Org. Lett.,* 2013, **15**, 4528.

9 (a) Y. S. Wu, M. S. Coumar, J. Y. Chang, H. Y. Sun, F. M. Kuo, C. C. Kuo, Y. J. Chen, C. Y. Chang, C. L. Hsiao and J. P. Liou, *J. Med. Chem.,* 2009, **52**, 4941; (b) R. Romagnoli, P. G. Baraldi, T. Sarkar, M. D. Carrion, C. L. Cara, O. Cruz-Lopez, D. Preti, M. A. Tabrizi, M. Tolomeo, S. Grimaudo, A. Di Cristina, N. Zonta, J. Balzarini, A. Brancale, H. P. Hsieh and E. Hamel, *J. Med. Chem.,* 2008, **51**, 1464; (c) M. L. Barreca, S. Ferro, A. Rao, L. De Luca, M. Zappala, A. M. Monforte, Z. Debyser, M. Witvrouw and A. Chimirri, *J. Med. Chem.,* 2005, **48**, 7084.

10 (a) L. Yu, P. Li and L. Wang, *Chem. Commun.,* 2013, **49**, 2368; (b) S. K. Guchhait; M. Kashyap and H. Kamble, *J. Org. Chem.,* 2011, **76**, 4753; (c) H. Johansson, A. Urruticoechea, I. Larsen and D. S. Pedersen, *J. Org. Chem.,* 2015, **80**, 471; (d) O. Ottoni, A. de V. F. Neder, A. K. B. Dias, R. P. A. Cruz and L. B. Aquino, *Org. Lett.,* 2001, **3**, 1005; (e) W. Wu and W. Su, *J. Am. Chem. Soc.,* 2011, **133**, 11924.

11 (a) B. Zhou, Y. Yang and Y. Li, *Chem. Commun.,* 2012, **48**, 5163; (b) C. Pan, H. Jin, X. Liu, Y. Cheng and C. Zhu, *Chem. Commun.,* 2013, **49**, 2933; (c) U. K. Sharma, H. P. L. Gemoets, F. Schröder, T. Noël and E. V. Van der Eycken, *ACS Catal.,* 2017, **7**, 3818.

12 X. Qiu, P. Wang, D. Wang, M. Wang, Y. Yuan and Z. Shi, *Angew. Chem. Int. Ed.,* 2019, **58**, 1504.

13 J. Kalepu, P. Gandeepan, L. Ackermann and L. T. Pilarski, *Chem. Sci.,* 2018, **9**, 4203.

14 (a) S. Zhang, B. An, J. Li, J. Hu, L. Huang, X. Li and A. S. C. Chan, *Org. Biomol. Chem.,* 2017, **15**, 7404; (b) J.-P. Liou, C.-Y. Wu, H.-P. Hsieh, C.-Y. Chang, C.-M. Chen, C.-C. Kuo and J.-Y. Chang, *J. Med. Chem.,* 2007, **50***,* 4548.

15 P.-Y. Lee, P. Liang and W.-Y. Yu, *Org. Lett.,* 2017, **19**, 2082.

16 For selected examples, see: (a) M. Kim, N. K. Mishra, J. Park, S. Han, Y. Shin, S. Sharma, Y. Lee, E.-K. Lee, J. H. Kwak and I. S. Kim, *Chem. Commun.,* 2014, **50**, 14249; (b) H. Li, P. Li, H. Tan and L. Wang, *Chem.-Eur. J.,* 2013, **19**, 14432; (c) L. J. Gooßen, F. Rudolphi, C. Oppel and N. Rodríguez, *Angew. Chem., Int. Ed*., 2008, **47**, 3043; (d) R. Shang, Y. Fu, J. B. Li, S. L. Zhang, Q. X. Guo and L. Liu, *J. Am. Chem. Soc*., 2009, **131**, 5738; (e) P. Fang, M. Li and H. Ge, *J. Am. Chem. Soc*., 2010, **132**, 11898.

17 J. Sanjosé-Orduna, J. M. S. Toro and M. H. Pérez-Temprano, *Angew. Chem. Int. Ed.,* 2018, **57**, 11369.

18 Z. Wang, F. Ai, Z. Wang, W. Zhao, G. Zhu, Z. Lin and J. Sun, *J. Am. Chem. Soc*., 2015, **137**, 383.

19 W. Liu, J. Zheng, Z. Liu, W. Hu, X. Wang and Y. Dang, *ACS Catal.,* 2018, **8**, 7698.

20 (a) K. Jing, J.-P. Yao, Z.-Y. Li, Q.-L. Li, H.-S. Lin and G.-W. Wang, *J. Org. Chem.* 2017, **82**, 12715; (b) G. Shan, X. Yang, L. Ma, and Y. Rao, *Angew. Chem. Int. Ed.,* 2012, **51**, 13070.

View Article Online
DOI: 10.1039/C9CC03893K

The first catalytic C-H acylation of indoles at the C4 position with α-oxocarboxylic acids by palladium catalysis is described.