## Palladium-catalyzed acetoxylation of sp $^3$ C–H bonds using molecular oxygen $\ddagger$

Huanfeng Jiang,\* Huoji Chen, Azhong Wang and Xiaohang Liu

Received 9th April 2010, Accepted 1st July 2010 DOI: 10.1039/c0cc00841a

Molecular oxygen as oxidant to promote palladium-catalyzed acetoxylation of sp<sup>3</sup> C–H bonds to afford  $\alpha$ -oxygenated products is reported.

Transition metal-catalyzed C–H bond functionalization has attracted much interest in recent years.<sup>1</sup> A particularly appealing aspect of this area is the Pd-catalyzed reactions of sp<sup>3</sup> C–H bonds, such as acetoxylation,<sup>2</sup> halogenation,<sup>3</sup> amination,<sup>4</sup> sulfonylation,<sup>5</sup> and arylation.<sup>1e</sup> These reactions are usually performed using PhI(OAc)<sub>2</sub>, IOAc, MeCO<sub>3</sub>*t*-Bu or *t*-BuO<sub>2</sub>H as oxidant. Still, the development of such reactions with safe and environmentally friendly oxidants remains challenging.

Oxygen would be environmentally preferred due to its abundance and ultimate "greenness", and is emerging as an effective oxidant in palladium catalysis.<sup>6,7</sup> More recently, we have described a new Pd-catalyzed selective difunctionalization of alkenes.<sup>8</sup> The results prompted us to investigate the reactivity and selectivity of unactivated sp<sup>3</sup> C–H bonds by using molecular oxygen as the sole oxidant, which represents a central challenge in the field. In this communication, we will report our preliminary results.

Treatment of 2-ethylpyridine (1a) using 5 mol% of Pd(OAc)<sub>2</sub>, 1 equiv. of KI in 3 mL HOAc under 8 atm of O<sub>2</sub> at 100 °C for 24 h afforded  $\alpha$ -oxygenated product (2a) in only 10% GC yield and the  $\beta$ -oxygenated product was not detected in this process.<sup>2b</sup> This result made us very interested in screening suitable reaction conditions for the  $\alpha$ -oxygenated product. On examining the additive KI, we noted that it is essential to promote this catalytic oxidation although inferior results were obtained at different temperature (Table 1, entries 1-4). Inspired by this finding, we searched for another additive to replace KI, and we were pleased to find that the breakthrough was achieved when CuI was employed, and 1a underwent acetoxylation smoothly to give 2a in 71% GC and 63% isolated yield (Table 1, entry 5). Further investigation on other Cu salts led to inferior results, which indicated that the selection of CuI is crucial to this reaction (Table 1, entries 7-9). The presence of Pd is also critical for the success of this reaction (Table 1, entry 10). Pd(OAc)<sub>2</sub> is superior to any other Pd catalysts so far tested (Table 1, entry 5 vs. entries 12-14). Moreover, a lower yield of 2a was obtained when the reaction was run under 1 atm of pressure of  $O_2$  (Table 1, entry 15).

Under the optimized conditions, various substrates were examined, and the results are summarized in Table 2. The

Guangzhou City, Guangdong Province 510640, China.

E-mail: jianghf@scut.edu.cn

**Table 1** Optimization of reaction conditions for the palladium-<br/>catalyzed acetoxylation of 2-ethylpyridine $^{a}$ 



Entry	O <sub>2</sub> (atm)	Cat.	Additive	$T/^{\circ}\mathbf{C}$	Conversion (%)	Yield <sup>b</sup> (%)
1	8	Pd(OAc) <sub>2</sub>	KI	100	10	10
2	8	$Pd(OAc)_2$	_	100	0	0
3	8	$Pd(OAc)_2$	KI	120	30	30
4	8	$Pd(OAc)_2$	KI	140	50	17
5	8	Pd(OAc) <sub>2</sub>	CuI	120	71	71 (63)
6	8	$Pd(OAc)_2$	CuI	140	31	31
7	8	$Pd(OAc)_2$	CuCl	120	25	25
8	8	$Pd(OAc)_2$	CuCl <sub>2</sub>	120	Trace	Trace
9	8	$Pd(OAc)_2$	$Cu(OAc)_2$	120	Trace	Trace
10	8		Cul	120	0	0
11	8		_	120	0	0
12	8	PdCl <sub>2</sub>	CuI	120	37	37
13	8	$Pd_2(dba)_3$	CuI	120	Trace	Trace
14	8	Pd/C	CuI	120	Trace	Trace
15	1	$Pd(OAc)_2$	CuI	120	Trace	Trace
a Daga	tion oon	ditional All m	an ationa man	manfan	mad with 1a (1	(maga a 1)

<sup>a</sup> Reaction conditions: All reactions were performed with **1a** (1 mmol), Pd catalyst (5 mol%), and additive (1 equiv.) in 3 mL of HOAc for 24 h. <sup>b</sup> Determined by GC. Number in parentheses is isolated yield.

substrate scope was tested by using a variety of pyridines and pyrazines; the acetoxylation afforded the  $\alpha$ -oxygenated products in modest to excellent yields. Reactions of substrates **1b**, **1d**, **1f** and **1h** could produce  $\alpha$ -oxygenated products at lower temperature, however high temperature produced the  $\alpha$ -oxidized by-products [2-formylpyridine, 2-benzoylpyridine, 2-(4-chlorobenzoyl)pyridine and 2-formylpyrazine] (Table 2, entries 2, 4, 6, 8). Substrate 1k, which contains multiple possible sites for directed C-H activation, showed high selectivity for functionalization of 2° α-C-H bonds in lieu of those at 1° carbon centers (Table 2, entry 11). A small amount of diacetate (2lb) was obtained by the reaction of substrate 1l (Table 2, entry 12). Notably, all employed substrates revealed extremely high selectivity for acetoxylation at the  $\alpha$ -C-H bonds. In this system, we also detected the  $\alpha$ -iodinated and α-oxidized by-products.

The exact mechanism for the product formation is not clear at the present stage. To clarify whether or not the reaction involves  $\beta$ -hydride elimination to produce 1-hetaryl olefin with subsequent addition of AcOH across the olefin double bond a control reaction (Scheme 1, A) was carried out with 2-vinylpyridine under the optimized conditions; no acetate product

College of Chemistry, South China University of Technology,

<sup>†</sup> Electronic supplementary information (ESI) available: Experimental details. See DOI: 10.1039/c0cc00841a

**Table 2** Palladium-catalyzed acetoxylation of 2-substituted pyridinesand pyrazines $^{a}$ 



<sup>*a*</sup> Reaction conditions: substrate (1 mmol), 5 mol% of Pd(OAc)<sub>2</sub>, 1 equiv. CuI in 3 mL AcOH, 120 °C, 24 h. <sup>*b*</sup> Isolated yield. <sup>*c*</sup> Reaction temperature: 70 °C. <sup>*d*</sup> Reaction temperature: 40 °C. <sup>*e*</sup> Determined by <sup>1</sup>H NMR.

was found. Another control reaction (Scheme 1, B) was carried out with stoichiometric Pd(OAc)<sub>2</sub> as catalyst, and a lower yield



Scheme 1 Control experiments.

of acetate product was detected without  $O_2$ . Due to these results, an alternative  $Pd^{II}/Pd^0$  cycle result is less probable.

On the basis of the results that we obtained in this paper and in the previous one,<sup>9</sup> it is possible that intermediates I and II are involved in the reaction, which were further converted into the acetate products.<sup>10</sup>



In summary, we have successfully developed a Pd-catalyzed acetoxylation of sp<sup>3</sup> C–H bonds using oxygen as the sole oxidant to afford  $\alpha$ -oxygenated product, which avoids the environmentally hazardous by-products obtained with other oxidants. Further studies on the mechanism, the scope of the reaction, and the potential for asymmetric induction in the acetoxylation process are in progress.

We thank the National Natural Science Foundation of China (Nos. 20625205, 20772034 and 20932002) and Doctoral Fund of Ministry of Education of China (20090172110014) for financial support.

## Notes and references

- For reviews, see: (a) A. E. Shilov and G. B. Shul'pin, *Chem. Rev.*, 1997, **97**, 2879; (b) V. Ritleng, C. Sirlin and M. Pfefer, *Chem. Rev.*, 2002, **102**, 1731; (c) A. R. Dick and M. S. Sanford, *Tetrahedron*, 2006, **62**, 2439; (d) D. Alberico, M. E. Scott and M. Lautens, *Chem. Rev.*, 2007, **107**, 174; (e) X. Chen, K. M. Engle, D. H. Wang and J. Q. Yu, *Angew. Chem., Int. Ed.*, 2009, **48**, 5094.
- For examples, see: (a) A. R. Dick, K. L. Hull and M. S. Sanford, J. Am. Chem. Soc., 2004, **126**, 2300; (b) L. V. Desai, K. L. Hull and M. S. Sanford, J. Am. Chem. Soc., 2004, **126**, 9542; (c) R. Giri, J. Liang, J. G. Lei, J. J. Li, D. H. Wang, X. Chen, I. C. Naggar, C. Guo, B. M. Foxman and J. Q. Yu, Angew. Chem., Int. Ed., 2005, **44**, 7420; (d) B. V. S. Reddy, L. R. Reddy and E. J. Corey, Org. Lett., 2006, **8**, 3391; (e) D. H. Wang, X. S. Hao, D. F. Wu and J. Q. Yu, Org. Lett., 2006, **8**, 3387.
- 3 For examples, see: (a) R. Giri, X. Chen and J. Q. Yu, Angew. Chem., Int. Ed., 2005, 44, 2112; (b) K. L. Hull, W. Q. Anani and M. S. Sanford, J. Am. Chem. Soc., 2006, 128, 7134.
- 4 For examples, see: H. Y. Thu, W. Y. Yu and C. M. Che, J. Am. Chem. Soc., 2006, **128**, 9048.
- 5 X. Zhao, E. Dimitrijevic and V. M. Dong, J. Am. Chem. Soc., 2009, 131, 3466.
- 6 For reviews for transition metal-catalyzed reactions with oxygen, see: (a) S. S. Stahl, Angew. Chem., Int. Ed., 2004, 43, 3400;

(b) M. S. Sigman and D. R. Jensen, Acc. Chem. Res., 2006, 39, 221;
(c) G. Liu, G. Yin and L. Wu, Angew. Chem., Int. Ed., 2008, 47, 4733.

7 For examples for palladium-catalyzed reactions with oxygen see: (a) R. M. Trend, Y. K. Ramtohul and B. M. Stoltz, J. Am. Chem. Soc., 2005, 127, 17778; (b) H. F. Jiang, Y. X. Shen and Z. Y. Wang, Tetrahedron Lett., 2007, 48, 7542; (c) H. F. Jiang, Y. X. Shen and Z. Y. Wang, Tetrahedron, 2008, 64, 508; (d) A. Wang and H. Jiang, J. Am. Chem. Soc., 2008, 130, 5030; (e) J. Zhang, E. Khaskin, N. P. Anderson, P. Y. Zavalij and A. N. Vedernikov, Chem. Commun., 2008,

3625; (f) A. Z. Wang, H. F. Jiang and Q. X. Xu, Synlett, 2009, (6), 929.

- 8 (a) A. Wang, H. Jiang and H. Chen, J. Am. Chem. Soc., 2009, 131, 3846; (b) A. Wang and H. Jiang, J. Org. Chem., 2010, 75, 2321.
- 9 (a) B. Qian, S. Guo, J. Shao, Q. Zhu, L. Yang, C. Xia and H. Huang, J. Am. Chem. Soc., 2010, **132**, 3650; (b) L. Boisvert, M. C. Denney, S. K. Hanson and K. I. Goldberg, J. Am. Chem. Soc., 2009, **131**, 15802; (c) B. V. Popp, J. E. Wendlandt, C. R. Landis and S. S. Stahl, Angew. Chem., Int. Ed., 2007, **46**, 601.
- 10 Although the role of CuI was not clear at this stage, we believe it promoted the formation of intermediate.