# **RSC Advances**



View Article Online

View Journal | View Issue

## PAPER

Check for updates

Cite this: RSC Adv., 2017, 7, 54277

## Palladium/silver reagent-promoted aryl phosphorylation: flexible synthesis of substituted-3-benzylidene-2-(2-(diphenylphosphoryl)-aryl)isoindolin-1-one<sup>+</sup>

Peng Shi,<sup>a</sup> Qing Wang,<sup>a</sup> Xiao Zeng,<sup>b</sup> Yingsheng Zhao<sup>b</sup>\*<sup>a</sup> and Runsheng Zeng<sup>b</sup>\*<sup>a</sup>

A novel Pd(OAc)<sub>2</sub>/Ag<sub>2</sub>CO<sub>3</sub>-catalyzed coupling reaction was investigated. Substituted 3-benzylidene-2-

arylisoindolin-1-ones were reacted with diphenylphosphine oxide to afford 3-arylidene-2-(2-

Received 3rd October 2017 Accepted 20th November 2017

DOI: 10.1039/c7ra10902d

rsc.li/rsc-advances

### Introduction

Nitrogen-containing heterocycles are a series of notable compounds known for their bioactivity in nature.<sup>1</sup> In particular, isoindolin-1-ones such as I and II are the core structural motifs of several compounds of medicinal value (Fig. 1). 3-Methyleneisoindolin-1-ones are known for their use as anaesthetic and sedative drugs.<sup>2</sup> As these compounds have a double bond and phenyl cycle we have tried to find a catalytic system for direct phosphorylation of substituted 3-benzylidene-2-arylisoindolin-1-one.

Diphenylphosphine oxide has become a research focus in the field of organic synthesis due to its unique biological

(diphenylphosphoryl)aryl)isoindolin-1-ones. The reaction proceeded at 25 °C in an air atmosphere in the absence of base and ligands. Our results indicate that the diphenylphosphine oxide free radical tends to attack the aryl rather than the double bond in this reaction. activities.<sup>3</sup> In 1982, Hirao and co-workers reported the first palladium-catalyzed phosphorylation of aryl iodides.<sup>4</sup> Since

palladium-catalyzed phosphorylation of aryl iodides.<sup>4</sup> Since then, a series of formations of Csp<sup>2</sup>–P bonds by cross-coupling has been published in the last thirty years. The coupling partners, included aryl triflates, tosylate, diaryliodonium salts, diazonium salts, boronic acids, triarylbismuths, phenylhydrazine and so on.<sup>5</sup> Moreover, direct radical phosphorylation of benzene derivatives<sup>6</sup> and heterocycle<sup>7</sup> with diethyl phosphate has been successfully developed by using Mn(OAc)<sub>3</sub> as an oxidant (Scheme 1a). There were also studies of the manganesecatalyzed reactions of H-phosphinates.<sup>8</sup> Recently, palladiumcatalyzed direct phosphorylation reaction of arene and heteroarenes has been established (Scheme 1b).<sup>9,10</sup> On the other hand, Ag system has been used for the synthesis of direct phosphorylation reaction (Scheme 1c).<sup>11</sup> Visible light promoted C–P



Fig. 1 Bioactive and drug compounds containing isoindolin-1-one motifs.

<sup>a</sup>Key Laboratory of Organic Synthesis of Jiangsu Province, College of Chemistry Chemical Engineering and Materials Science, Soochow University, Suzhou, Jiangsu 215123, China. E-mail: yszhao@suda.edu.cn; zengrunsheng@suda.edu.cn

<sup>b</sup>Department of Chemistry, National University of Singapore, Singapore

† Electronic supplementary information (ESI) available. See DOI: 10.1039/c7ra10902d



Scheme 1

functionalization has been rapidly developed (Scheme 1d).<sup>12</sup> As part of our research on the transition metal-catalyzed C–P bond formation, this communication reports the first example of a coupling reaction of 3-benzylidene-2-arylisoindolin-1-one with diphenylphosphine oxide catalyzed by  $Pd(OAc)_2/Ag_2CO_3$  (Scheme 1e).

### Results and discussion

When the model reaction of 3-benzylidene-2-phenylisoindolin-1one (**1a**) with diphenylphosphine oxide (**2**) was performed in CH<sub>3</sub>CN in the presence of oxidants such as TBHP, DTBP, Mn(OAc)<sub>3</sub> and AgNO<sub>3</sub>, no desired products were obtained (Table 1, entries 1, 2, 3 and 5). After the addition of 10 mol% Ag<sub>2</sub>CO<sub>3</sub> and Mg(NO<sub>3</sub>)<sub>2</sub>·6H<sub>2</sub>O, the reaction proceeded smoothly to afford the desired product, 3-benzylidene-2-(2-(diphenylphosphoryl)phenyl) isoindolin-1-one (**3a**) in 60% yield (Table 1, entry 4).

Further investigations of palladium catalysts, the yield of 3a was improved to 78% when we used Pd(OAc)<sub>2</sub> as the catalyst

 Table 1
 Optimization of the reaction conditions<sup>a</sup>

(Table 1, entries 7). On the other hand, when we use Ag(OAc) in place of Ag<sub>2</sub>CO<sub>3</sub>, the reaction afforded the desired product in a lower yield (Table 1, entry 9). By screening polar solvents such as DMF, THF, i-PrOH, and a representative nonpolar solvent, toluene (Table 1, entries 10–13), we found that CH<sub>3</sub>CN works best for the reaction. Apart from the above-mentioned factors, the effects of catalyst loading, reaction temperature, time and molecular sieves were also investigated, and the optimal reaction conditions were determined to be room temperature reaction for 3 h in air atmosphere, with the addition of 10 mol% Pd(OAc)<sub>2</sub> and 10 mol% Ag<sub>2</sub>CO<sub>3</sub> as catalyst, Mg(NO<sub>3</sub>)<sub>2</sub>·6H<sub>2</sub>O as promoter and CH<sub>3</sub>CN as solvent (Table 1, entries 14–23).

With the promising results obtained in the model reaction, we subsequently examined the substrate scope of 3benzylidene-2-arylisoindolin-1-one under the optimized reaction conditions (10 mol% Pd(OAc)<sub>2</sub> and 10 mol% Ag<sub>2</sub>CO<sub>3</sub> as catalyst, and Mg(NO<sub>3</sub>)<sub>2</sub>·6H<sub>2</sub>O as promoter in CH<sub>3</sub>CN at 25 °C, for 3 h in air atmosphere). As shown in Table 2, electron-

POPh<sub>2</sub> + HPOPh<sub>2</sub> Conditions 2 Solvent Yeild<sup>b</sup> Entry Catalyst (%) Oxidant (%) Temperature TBHP(10)  $25 \ ^{\circ}C$ CH<sub>3</sub>CN N.D 1 DTBP(10) 2  $25 \ ^{\circ}C$ CH<sub>3</sub>CN N.D 3 25 °C CH<sub>3</sub>CN  $Mn(OAc)_3$ N.D 4  $Ag_2CO_3(10)$ 25 °C CH<sub>3</sub>CN 60% 5  $AgNO_3(10)$  $25 \ ^{\circ}C$ CH<sub>3</sub>CN N.D 6  $Pd(PPh_3)_4(10)$  $25 \ ^{\circ}C$ CH<sub>3</sub>CN  $Ag_2CO_3(10)$ 38% 7  $Pd(OAc)_2(10)$  $Ag_2CO_3(10)$  $25 \ ^{\circ}C$ CH<sub>3</sub>CN 78% 8  $PdCl_2(10)$  $Ag_2CO_3(10)$ 25 °C CH<sub>3</sub>CN 72% 9  $Pd(OAc)_2(10)$ Ag(OAc)10 25 °C CH<sub>3</sub>CN 48% 10  $Pd(OAc)_2(10)$  $Ag_2CO_3(10)$  $25 \ ^{\circ}C$ THF 32% 11  $Pd(OAc)_2(10)$  $Ag_2CO_3(10)$  $25 \ ^{\circ}C$ DMF 36% 12  $Pd(OAc)_2(10)$  $Ag_2CO_3(10)$  $25 \ ^{\circ}C$ i-PrOH 40% 13  $Pd(OAc)_2(10)$  $Ag_2CO_3(10)$  $25 \ ^{\circ}C$ Toluene 30%  $Pd(OAc)_2(5)$ 14  $Ag_2CO_3(10)$ 25 °C CH<sub>3</sub>CN 48% $Pd(OAc)_2(20)$ CH<sub>3</sub>CN 65% 15  $Ag_2CO_3(10)$ 25 °C  $Pd(OAc)_2(10)$ CH<sub>3</sub>CN 16<sup>6</sup>  $Ag_2CO_3(10)$ 25 °C 20%  $Pd(OAc)_2(10)$  $0 \ ^{\circ}C$ 17  $Ag_2CO_3(10)$ CH<sub>3</sub>CN 10%  $Pd(OAc)_2(10)$ CH<sub>3</sub>CN 18  $Ag_2CO_3(10)$ 40 °C 72% 19  $Pd(OAc)_2(10)$  $Ag_2CO_3(10)$  $60 \ ^{\circ}C$ CH<sub>3</sub>CN 20%  $20^d$  $Pd(OAc)_2(10)$  $Ag_2CO_3(10)$ 25 °C CH<sub>3</sub>CN 30%  $21^e$  $Pd(OAc)_2(10)$  $25 \ ^{\circ}C$ CH<sub>3</sub>CN 58%  $Ag_2CO_3(10)$  $Pd(OAc)_2(10)$  $22^{f}$  $Ag_2CO_3(10)$ 25 °C CH<sub>3</sub>CN 76%  $23^g$  $Pd(OAc)_2(10)$  $Ag_2CO_3(10)$  $25 \ ^{\circ}C$ CH<sub>3</sub>CN 35%  $23^h$  $Pd(OAc)_2(10)$  $Ag_2CO_3(10)$ 25 °C CH<sub>3</sub>CN 66%  $23^i$  $Pd(OAc)_2(10)$  $Ag_2CO_3(10)$  $25 \ ^{\circ}C$ CH<sub>3</sub>CN 75%

<sup>*a*</sup> Reaction condition: **1a** (0.2 mmol), HPOPh<sub>2</sub> (0.4 mmol), Pd(OAc)<sub>2</sub>, (0.02 mmol), Ag<sub>2</sub>CO<sub>3</sub> (0.02 mmol), Mg(NO<sub>3</sub>)<sub>2</sub>·6H<sub>2</sub>O (0.4 mmol), solvent (2 ml), at 25 °C in air atmosphere, 3 h. <sup>*b*</sup> Yields are given for isolated products. <sup>*c*</sup> Without Mg(NO<sub>3</sub>)<sub>2</sub>·6H<sub>2</sub>O. <sup>*d*</sup> HPOPh<sub>2</sub> (0.2 mmol) was added. <sup>*e*</sup> HPOPh<sub>2</sub> (0.6 mmol) was added. <sup>*f*</sup> Molecular sieves (0.1 g) was added. <sup>*g*</sup> 1 h. <sup>*h*</sup> 2 h. <sup>*i*</sup> 4 h.

**Table 2**Scope studies of 3-benzylidene-2-(2-(diphenyl-phosphoryl)phenyl)isoindolin-1-one $^a$ 



<sup>*a*</sup> Reaction condition: 1 (0.2 mmol), HPOPh<sub>2</sub> (0.4 mmol), Pd(OAc)<sub>2</sub>, (0.02 mmol), Ag<sub>2</sub>CO<sub>3</sub> (0.02 mmol), Mg(NO<sub>3</sub>)<sub>2</sub>  $\cdot$  6H<sub>2</sub>O (0.4 mmol), CH<sub>3</sub>CN (2 ml), at 25 °C in air atmosphere, 3 h. Yield of isolated products are given.

#### Paper

withdrawing substituent such as F and Cl groups on the paraposition of arylamine ring of substituted 3-benzylidene-2arylisoindolin-1-one (1) facilitated the reaction to afford the arylphosphonates (3) in good yields (Table 2, 3d and 3e). On the contrary, election-donating groups such as alkyl and methoxy were unfavorable for the reaction and led to lower yields (Table 2, 3b and 3c). Substituted groups such as  $CH_3$  and Cl on the meta-position of arlyamine ring are both given good yields (Table 2, 3f and 3g). We also investigated the substituent  $R^2$  on the benzylidene and the substituent  $R^3$  on the isoindolin-1-one, the results indicate that the reaction affords the arylphosphonates (3) in moderate to good yields (Table 2, 3k, 3l, 3m, 3n, 3o, 3p, 3q, 3r and 3s). In order to understand the reaction mechanism, following control experiments were carried out. We repeated the reaction in the presence of radical quencher 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO) and none of 3a was obtained (Scheme 2a). The result suggested that the diphenylphosphine oxide free radical was probably generated during the reaction. Furthermore, neither aliphatic amine nor benzylamine substrate produced the corresponding products (Scheme 2b and c). These results indicated that the reaction is only suitable for arylamine substrates which have enough electron cloud density.

As the phosphorylation always took place on the *ortho*position of aniline in the above experiments, we wondered



Scheme 2 Control experiments.



Scheme 3 Proposed reaction mechanism

whether the reaction would proceed if the aniline had substituent groups at the *ortho*-position. Hence, we did further reactions (Scheme 2d–f). Surprisingly, the diphenylphosphine oxide free radical will attack the double bond instead of aniline with a moderate yield. These results further indicated that this reaction has a high regioselectivity that the diphenylphosphine oxide free radical would prioritize its attack on the *ortho*-position of aniline rather than the *para*-position of aniline or the double bond. On the basis of the mechanistic studies and experimental results, a plausible mechanism is proposed in Scheme 3.

Initially,  $Pd(OAc)_2$  reacted with the substrate (1a) to form a six-membered palladacycle (C) in presence of  $Mg(NO_3)_2$ , and generated HNO<sub>3</sub> through C-H activation. The diphenylphosphine oxide (2) was excited by Ag(1) (A) to generate the key intermediate P-centered radical (B), which then underwent addition with palladacycle (C) to form  $Pd^{III}$  intermediate **D**.<sup>13</sup> Thereafter, the radical intermediate **D** was oxidized by HNO<sub>3</sub> to produce the  $Pd^{IV}$  intermediate **E**. **E** underwent reductive elimination to afford the product (3a) together with the regeneration of  $Pd(OAc)_2$  which could complete the palladium catalytic cycle. Finally, Ag(0) was also oxidized to Ag(1) by HNO<sub>3</sub> to complete the silver catalytic cycle.

## Conclusions

In summary, we have developed a novel catalytic system for direct phosphorylation of substituted 3-benzylidene-2arylisoindolin-1-one *via* a radical pathway. The reaction has a high regioselectivity that diphenylphosphine oxide free radical is prone to attacking aryl rather than a double bond. The method has a broad scope and offers a good yield. The corresponding products are potentially useful in drug discovery.

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

We gratefully acknowledge financial support from the Prospective Study Program of Jiangsu (BY2015039-08), the National Natural Science Foundation of China (No. 21572149), and the Priority Academic Program Development of Jiangsu Higher Education Institutions.

## Notes and references

- 1 A. K. Mailyan, J. A. Eickhoff, A. S. Minakova, Z. Gu, P. Lu and A. Zakarian, *Chem. Rev.*, 2016, **116**, 4441.
- 2 (a) L. Li, M. Wang, X. J. Zhang, Y. W. Jiang and D. W. Ma, Org. Lett., 2009, 11, 1309; (b) V. Rys, A. Couture, E. Deniau and P. Grandclaudon, Tetrahedron, 2003, 59, 6615; (c) H. Fuwa and M. Sasaki, Org. Biomol. Chem., 2007, 5, 1849; (d) Y. L. Choi, J. K. Kim, S. U. Choi, Y. K. Min, M. A. Bae, B. T. Kim and J. N. Heo, Bioorg. Med. Chem. Lett., 2009, 19, 3036.
- 3 (a) P. Schultz and R. A. Lerner, Acc. Chem. Res., 1993, 26, 391;
  (b) J. D. Stewart, L. J. Liotta and S. J. Benkovic, Acc. Chem. Res., 1993, 26, 396;
  (c) R. J. Cox, M. B. Mayo Martín and A. T. Hadfield, Chem. Commun., 2001, 18, 1710;
  (d) R. R. Breaker, G. R. Gough and P. T. Gilham, Biochemistry, 1993, 32, 9125.
- 4 T. Hirao, T. Masunaga and N. Yamada, *Bull. Chem. Soc. Jpn.*, 1982, 55, 909.
- 5 (a) J. Yang, J. Xiao, T. Chen and L. B. Han, J. Organomet. Chem., 2016, 820, 120; (b) J. Xu, P. Zhang, Y. Gao, Y. Chen, G. Tang and Y. Zhao, J. Org. Chem., 2013, 78, 8176; (c) R. Berrino, S. Cacchi, G. Fabrizi, A. Goggiamani and P. Stabile, Org. Biomol. Chem., 2010, 8, 4518; (d) R. Q. Zhuang, Z. S. Cai, G. Tang, M. J. Fang and Y. F. Zhao, Org. Lett., 2011, 13, 2110; (e) T. Fu, H. Qiao, Z. Peng, G. Hu, X. Wu, Y. Gao and Y. Zhao, Org. Biomol. Chem., 2014, 12, 2895; (f) M. Andaloussi, J. Lindh, J. Savmarker, P. J. Sjoberg and M. Larhed, Chem.-Eur. J., 2009, 15, 13069; (g) T. Wang, S. Sang, L. Liu, H. Qiao, Y. Gao and Y. Zhao, J. Org. Chem., 2014, 79, 608; (h) X. H. Zhang, H. Z. Liu, X. M. Hu, G. Tang, J. Zhu and Y. F. Zhao, Org. Lett., 2011, 13, 3478; (i) T. Satoh and M. Miura, Chem. Lett., 2007, 36, 200; (j) H. Y. Zhang, M. Sun, Y. N. Ma, Q. P. Tian and S. D. Yang, Org. Biomol. Chem., 2012, 10, 9627; (k) C. S. Demmer, N. Krogsgaard-Larsen and L. Bunch, Chem. Rev., 2011, 111, 7981; (l) Y. L. Zhao, G. J. Wu, Y. Li, L. X. Gao and F. S. Han, Chem.-Eur. J., 2012, 18, 9622; (m) S. Y. Chen, R. S. Zeng, J. P. Zou and O. T. Asekun, J. Org. Chem., 2014, 79, 1449; (n) N. Iranpoor, H. Firouzabadi, K. R. Moghadam and S. Motavalli, RSC Adv., 2014, 4, 55732; (o) J. Li, X. Bi,

H. Wang and J. Xiao, *RSC Adv.*, 2014, **4**, 19214; (*p*) H. Luo, H. Liu, X. Chen, K. Wang, X. Luo and K. Wang, *Chem. Commun.*, 2017, **53**, 956; (*q*) Y. Luo and J. Wu, *Organometallics*, 2009, **28**, 6823; (*r*) R. S. Shaikh, S. J. S. Düsel and B. König, *ACS Catal.*, 2016, **6**, 8410; (*s*) K. Xu, F. Yang, G. Zhang and Y. Wu, *Green Chem.*, 2013, **15**, 1055.

- 6 T. Kagayama, A. Nakano, S. Sakaguchi and Y. Ishii, *Org. Lett.*, 2006, **8**, 407.
- 7 X. J. Mu, J. P. Zou, Q. F. Qian and W. Zhang, *Org. Lett.*, 2006, 8, 5291.
- 8 (a) O. Berger and J. L. Montchamp, *Chem.-Eur. J.*, 2014, 20, 12385; (b) S. H. Kim, S. H. Kim, C. H. Lim and J. N. Kim, *Tetrahedron Lett.*, 2013, 54, 1697; (c) S. O. Strekalova, K. M. N. Khrizanforov, T. V. Gryaznova, V. V. Khrizanforova and Y. H. Budnikova, *Russ. Chem. Bull.*, 2016, 65, 1295.
- 9 C. G. Feng, M. Ye, K. J. Xiao, S. Li and J. Q. Yu, *J. Am. Chem. Soc.*, 2013, **135**, 9322.
- 10 (a) Y. Kuninobu, T. Yoshida and K. Takai, J. Org. Chem., 2011,
  76, 7370; (b) M. Xia, M. M. Huang, J. Y. Zhang, C. Y. Wang and Y. J. Wu, Org. Lett., 2013, 15, 6266; (c) C. B. Xiang,
  Y. J. Bian, X. R. Mao and Z. Z. Huang, J. Org. Chem., 2012,
  77, 7706; (d) C. Hou, Y. Ren, R. Lang, X. Hu, C. Xia and
  F. Li, Chem. Commun., 2012, 48, 5181; (e) C. Li, T. Yano,
  N. Ishida and M. Murakami, Angew. Chem., Int. Ed., 2013, 52, 9801.
- (a) C. B. Xiang, Y. J. Bian, X. R. Mao and Z. Z. Huang, J. Org. Chem., 2012, 77, 7706; (b) B. Wan, H. Wang, X. Li and F. Wu, Synthesis, 2012, 44, 941; (c) H. J. Zhang, W. Lin, Z. Wu, W. Ruan and T. B. Wen, Chem. Commun., 2015, 51, 3450; (d) S. H. Kim, K. H. Kim, J. W. Lim and J. N. Kim, Tetrahedron Lett., 2014, 55, 531; (e) W. B. Sun, J. F. Xue, G. Y. Zhang, R. S. Zeng, L. T. An, P. Z. Zhang and J. P. Zou, Adv. Synth. Catal., 2016, 358, 1753.
- 12 P. Peng, L. Peng, G. Wang, F. Wang, Y. Luo and A. Lei, *Org. Chem. Front.*, 2016, 3, 749.
- 13 (a) D. Kalyani, K. B. McMurtrey, S. R. Neufeldt and M. S. Sanford, J. Am. Chem. Soc., 2011, 133, 18566; (b) C. Qian, D. Lin, Y. Deng, X. Q. Zhang, H. Jiang, G. Miao, X. Tang and W. Zeng, Org. Biomol. Chem., 2014, 12, 5866; (c) H. Song, D. Chen, C. Pi, X. Cui and Y. Wu, J. Org. Chem., 2014, 79, 2955; (d) P. Das, D. Saha, D. Saha and J. Guin, ACS Catal., 2016, 6, 6050; (e) C. Premi, A. Dixit and N. Jain, Org. Lett., 2015, 17, 2598; (f) Y.-F. Liang, X. Li, X. Wang, Y. Yan, P. Feng and N. Jiao, ACS Catal., 2015, 5, 1956; (g) D. Zhang, X. Cui, Q. Zhang and Y. Wu, J. Org. Chem., 2015, 80, 1517; (h) P. Y. Lee, P. Liang and W. Y. Yu, Org. Lett., 2017, 19, 2082.