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Palladium/silver reagent-promoted aryl phosphorylation: flexible synthesis of substituted-3-benzylidene-2-(2-(diphenylphosphoryl)-aryl)-isoindolin-1-one[†]

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A novel $\text{Pd}(\text{OAc})_2/\text{Ag}_2\text{CO}_3$ -catalyzed coupling reaction was investigated. Substituted 3-benzylidene-2-arylisoindolin-1-ones were reacted with diphenylphosphine oxide to afford 3-arylidene-2-(2-(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.

Introduction

Nitrogen-containing heterocycles are a series of notable compounds known for their bioactivity in nature.¹ 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.² 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

activities.³ In 1982, Hirao and co-workers reported the first palladium-catalyzed phosphorylation of aryl iodides.⁴ Since then, a series of formations of $\text{Csp}^2\text{-P}$ 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.⁵ Moreover, direct radical phosphorylation of benzene derivatives⁶ and heterocycle⁷ with diethyl phosphate has been successfully developed by using $\text{Mn}(\text{OAc})_3$ as an oxidant (Scheme 1a). There were also studies of the manganese-catalyzed reactions of H-phosphinates.⁸ Recently, palladium-catalyzed direct phosphorylation reaction of arene and heteroarenes has been established (Scheme 1b).^{9,10} On the other hand, Ag system has been used for the synthesis of direct phosphorylation reaction (Scheme 1c).¹¹ Visible light promoted C-P

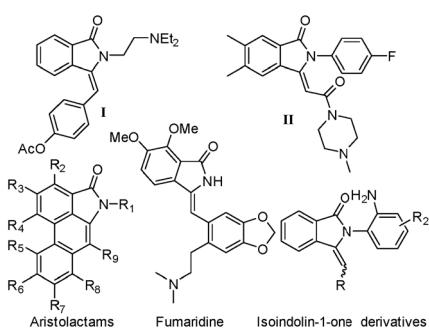
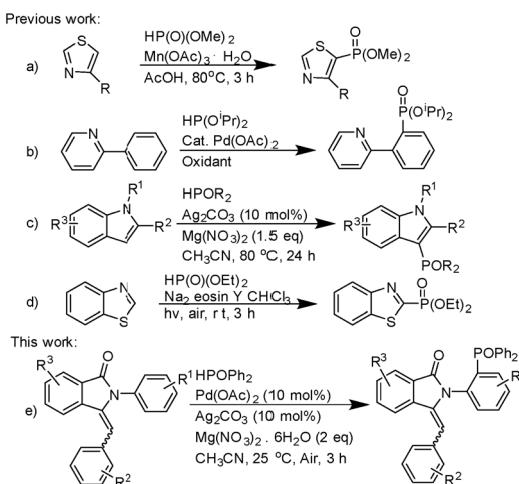


Fig. 1 Bioactive and drug compounds containing isoindolin-1-one motifs.

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Scheme 1

functionalization has been rapidly developed (Scheme 1d).¹² 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-arylisooindolin-1-one with diphenylphosphine oxide catalyzed by $\text{Pd}(\text{OAc})_2/\text{Ag}_2\text{CO}_3$ (Scheme 1e).

Results and discussion

When the model reaction of 3-benzylidene-2-phenylisoindolin-1-one (**1a**) with diphenylphosphine oxide (**2**) was performed in CH_3CN in the presence of oxidants such as TBHP, DTBP, $\text{Mn}(\text{OAc})_3$ and AgNO_3 , no desired products were obtained (Table 1, entries 1, 2, 3 and 5). After the addition of 10 mol% Ag_2CO_3 and $\text{Mg}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$, the reaction proceeded smoothly to afford the desired product, 3-benzylidene-2-(diphenylphosphoryl)phenylisoindolin-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 $\text{Pd}(\text{OAc})_2$ as the catalyst

Table 1 Optimization of the reaction conditions^a

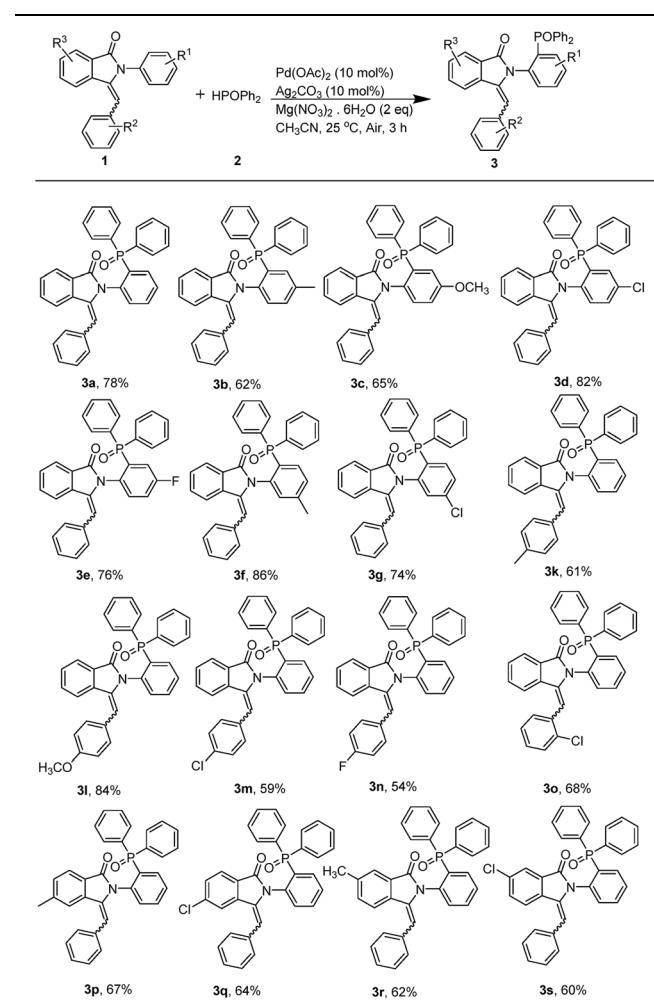
Entry	Catalyst (%)	Oxidant (%)	Temperature	Solvent	Yield ^b
1		TBHP(10)	25 °C	CH_3CN	N.D
2		DTBP(10)	25 °C	CH_3CN	N.D
3		$\text{Mn}(\text{OAc})_3$	25 °C	CH_3CN	N.D
4		Ag_2CO_3 (10)	25 °C	CH_3CN	60%
5		AgNO_3 (10)	25 °C	CH_3CN	N.D
6	$\text{Pd}(\text{PPh}_3)_4$ (10)	Ag_2CO_3 (10)	25 °C	CH_3CN	38%
7	$\text{Pd}(\text{OAc})_2$ (10)	Ag_2CO_3 (10)	25 °C	CH_3CN	78%
8	PdCl_2 (10)	Ag_2CO_3 (10)	25 °C	CH_3CN	72%
9	$\text{Pd}(\text{OAc})_2$ (10)	$\text{Ag}(\text{OAc})$ 10	25 °C	CH_3CN	48%
10	$\text{Pd}(\text{OAc})_2$ (10)	Ag_2CO_3 (10)	25 °C	THF	32%
11	$\text{Pd}(\text{OAc})_2$ (10)	Ag_2CO_3 (10)	25 °C	DMF	36%
12	$\text{Pd}(\text{OAc})_2$ (10)	Ag_2CO_3 (10)	25 °C	i-PrOH	40%
13	$\text{Pd}(\text{OAc})_2$ (10)	Ag_2CO_3 (10)	25 °C	Toluene	30%
14	$\text{Pd}(\text{OAc})_2$ (5)	Ag_2CO_3 (10)	25 °C	CH_3CN	48%
15	$\text{Pd}(\text{OAc})_2$ (20)	Ag_2CO_3 (10)	25 °C	CH_3CN	65%
16 ^c	$\text{Pd}(\text{OAc})_2$ (10)	Ag_2CO_3 (10)	25 °C	CH_3CN	20%
17	$\text{Pd}(\text{OAc})_2$ (10)	Ag_2CO_3 (10)	0 °C	CH_3CN	10%
18	$\text{Pd}(\text{OAc})_2$ (10)	Ag_2CO_3 (10)	40 °C	CH_3CN	72%
19	$\text{Pd}(\text{OAc})_2$ (10)	Ag_2CO_3 (10)	60 °C	CH_3CN	20%
20 ^d	$\text{Pd}(\text{OAc})_2$ (10)	Ag_2CO_3 (10)	25 °C	CH_3CN	30%
21 ^e	$\text{Pd}(\text{OAc})_2$ (10)	Ag_2CO_3 (10)	25 °C	CH_3CN	58%
22 ^f	$\text{Pd}(\text{OAc})_2$ (10)	Ag_2CO_3 (10)	25 °C	CH_3CN	76%
23 ^g	$\text{Pd}(\text{OAc})_2$ (10)	Ag_2CO_3 (10)	25 °C	CH_3CN	35%
23 ^h	$\text{Pd}(\text{OAc})_2$ (10)	Ag_2CO_3 (10)	25 °C	CH_3CN	66%
23 ⁱ	$\text{Pd}(\text{OAc})_2$ (10)	Ag_2CO_3 (10)	25 °C	CH_3CN	75%

^a Reaction condition: **1a** (0.2 mmol), HPOPh_2 (0.4 mmol), $\text{Pd}(\text{OAc})_2$, (0.02 mmol), Ag_2CO_3 (0.02 mmol), $\text{Mg}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$ (0.4 mmol), solvent (2 ml), at 25 °C in air atmosphere, 3 h. ^b Yields are given for isolated products. ^c Without $\text{Mg}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$. ^d HPOPh_2 (0.2 mmol) was added. ^e HPOPh_2 (0.6 mmol) was added. ^f Molecular sieves (0.1 g) was added. ^g 1 h. ^h 2 h. ⁱ 4 h.

(Table 1, entries 7). On the other hand, when we use $\text{Ag}(\text{OAc})$ in place of Ag_2CO_3 , 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_3CN 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% $\text{Pd}(\text{OAc})_2$ and 10 mol% Ag_2CO_3 as catalyst, $\text{Mg}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$ as promoter and CH_3CN as solvent (Table 1, entries 14–23).

With the promising results obtained in the model reaction, we subsequently examined the substrate scope of 3-benzylidene-2-arylisooindolin-1-one under the optimized reaction conditions (10 mol% $\text{Pd}(\text{OAc})_2$ and 10 mol% Ag_2CO_3 as catalyst, and $\text{Mg}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$ as promoter in CH_3CN at 25 °C, for 3 h in air atmosphere). As shown in Table 2, electron-

Table 2 Scope studies of 3-benzylidene-2-(diphenylphosphoryl)phenylisoindolin-1-one^a

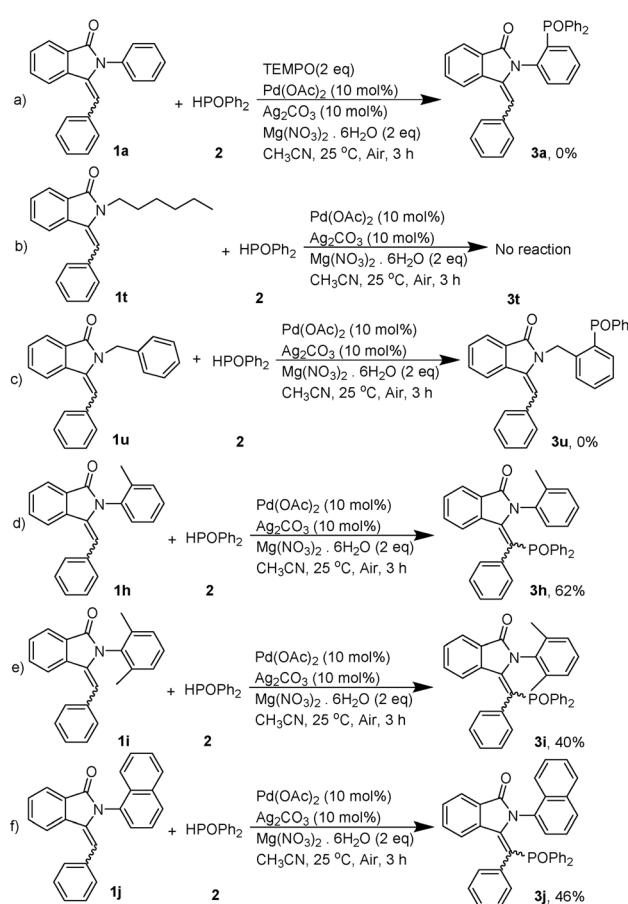


^a Reaction condition: **1** (0.2 mmol), HPOPh_2 (0.4 mmol), $\text{Pd}(\text{OAc})_2$, (0.02 mmol), Ag_2CO_3 (0.02 mmol), $\text{Mg}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$ (0.4 mmol), CH_3CN (2 ml), at 25 °C in air atmosphere, 3 h. Yield of isolated products are given.

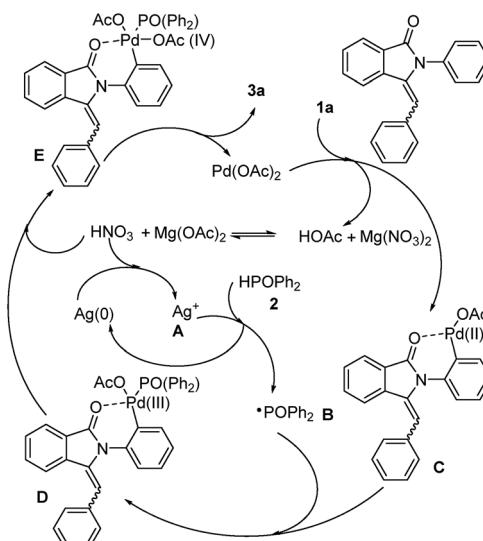


withdrawing substituent such as F and Cl groups on the *para*-position of arylamine ring of substituted 3-benzylidene-2-arylisooindolin-1-one (**1**) facilitated the reaction to afford the arylphosphonates (**3**) in good yields (Table 2, **3d** and **3e**). On the contrary, electron-donating groups 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 arylamine 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, $\text{Pd}(\text{OAc})_2$ reacted with the substrate (**1a**) to form a six-membered palladacycle (**C**) in presence of $\text{Mg}(\text{NO}_3)_2$, and generated HNO_3 through C-H activation. The diphenylphosphine oxide (**2**) was excited by $\text{Ag}(\text{i})$ (**A**) to generate the key intermediate P-centered radical (**B**), which then underwent addition with palladacycle (**C**) to form Pd^{III} intermediate **D**.¹³ Thereafter, the radical intermediate **D** was oxidized by HNO_3 to produce the Pd^{IV} intermediate **E**. **E** underwent reductive elimination to afford the product (**3a**) together with the regeneration of $\text{Pd}(\text{OAc})_2$ which could complete the palladium catalytic cycle. Finally, $\text{Ag}(\text{0})$ was also oxidized to $\text{Ag}(\text{i})$ by HNO_3 to complete the silver catalytic cycle.

Conclusions

In summary, we have developed a novel catalytic system for direct phosphorylation of substituted 3-benzylidene-2-arylisooindolin-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.



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