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Synthesis of 3-methyleneisoindolin-1-ones via palladium-catalyzed C–Cl bond cleavage and cyclocarbonylation of *ortho*-chloro ketimines

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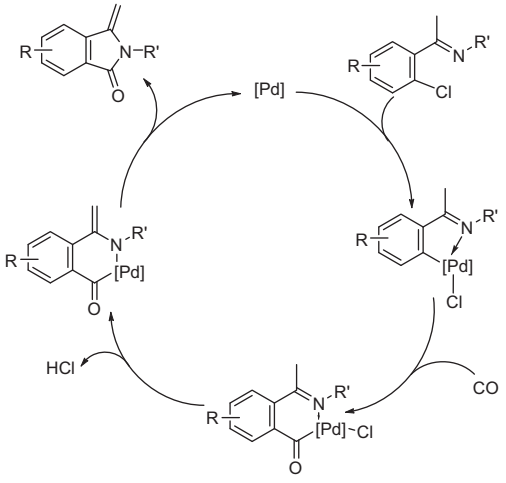
ABSTRACT

$PdCl_2(PCy_3)_2$-catalyzed cyclocarbonylative coupling of *ortho*-chloro arylketimines with CO has been investigated to develop an efficient method for the synthesis of isoindolin-1-ones. The developed synthetic method has the advantages of having easily available starting materials, high atom-economy, and high selectivity.

Catalytic activation of the C–Cl bond of aryl chlorides and its application in the C–C bond formation is one of the interesting and challenging research topics in organic synthesis,[1] since such type of transformation has a higher atom-efficiency by comparison with the use of aryl iodides and bromides. Also, aryl chlorides are typically cheaper and more commercially available aryl halides with a lower toxicity than that of aryl iodides and bromides. With the purpose of developing high-atom efficient C–C bond formation procedures, our previous work[2] disclosed that $PdCl_2(PCy_3)_2$ was an efficient catalyst in the Sonogashira[2a,b] and Heck[2c,d] cross-coupling reactions of aryl chlorides.

3-Methyleneisoindolin-1-one is core structural unit in some natural products,[3,4] such as fumaridine[3a] (Scheme 1). Also, it is a valuable component for the construction of numerous valuable polyheterocycles,[4,5] including some natural products, such as lennoxamine,[4g] aristoyagonine,[4e] and aristolactam alkaloids.[4a,d] Some synthetic 3-methyleneisoindolin-1-ones also show outstanding biological activities.[4c,6] For example, **A** is a good muscarinic receptor ligand.[6a] The double bond in methyleneisoindolinone facilitates it for π-conjugated extend structures,[7] such as **B**,[7a] a promising building block for organic optoelectronic materials.

A variety of synthetic routes to isoindolin-1-ones have been developed,[8,9] including several examples using aryl iodides or bromides as substrates.[8] However, there is no report on the construction of this type of skeleton via the C–Cl bond cleavage. Most recently, Lloyd–Jones and Booker–Milburn, as well as Wang developed an elegant approach for the synthesis of 3-methyleneisoindolin-1-ones via Pd-catalyzed C–H activation of benzamides and coupling with alkenes.[10] However, the substrates are limited to



Scheme 1. Proposed mechanism.

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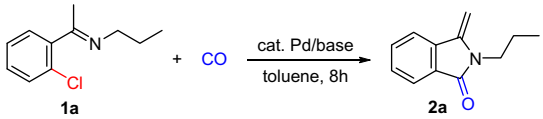
Table 1
Optimization of reaction conditions[a]



1a 2a

Entry	Catalyst	Base	CO(atm)	Yield[b] (%)
1	$PdCl_2(PPh_3)_2$ (3)	Cs_2CO_3	10	Trace
2	$PdCl_2(PCy_3)_2$ (3)	Cs_2CO_3	10	81
3	$PdCl_2$(dppe)(3)	Cs_2CO_3	10	Trace
4	$PdCl_2(PCy_3)_2$ (3)	K_2CO_3	10	72
5	$PdCl_2(PCy_3)_2$ (3)	Na_3PO_4	10	54
6	$PdCl_2(PCy_3)_2$ (3)	Bu_3N	10	<10
7	$PdCl_2(PCy_3)_2$ (3)	Pyrrolidine	10	50
8	$PdCl_2(PCy_3)_2$ (3)	Cs_2CO_3	5	89
9	$PdCl_2(PCy_3)_2$ (3)	Cs_2CO_3	1	Trace
10[c]	$PdCl_2(PCy_3)_2$ (3)	Cs_2CO_3	10	28
11	**$PdCl_2(PCy_3)_2$** (1)	**Cs_2CO_3**	5	95(84)[d]
12	$PdCl_2(PCy_3)_2$ (0.5)	Cs_2CO_3	10	41

[a] Unless otherwise noted, reactions were carried out using 1.0 mmol **1a**, catalyst, and 1.1 equiv of base in 1.0 mL of toluene in a 25 mL autoclave with CO at 130 °C for 8 h.
[b] Yields of **2a** are based on GC by using *n*-$C_{22}H_{46}$ as internal standard.
[c] Reactions were carried out at 115 °C.
[d] Isolated yields.

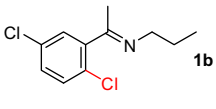
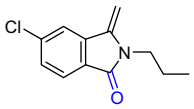
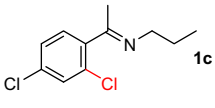
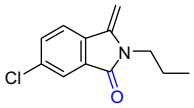
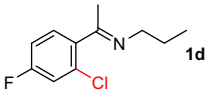
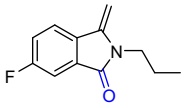
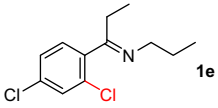
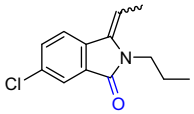
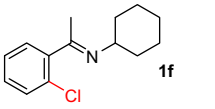
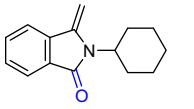
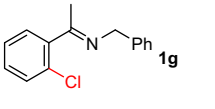
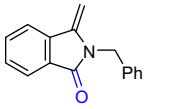
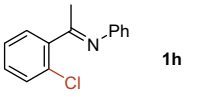
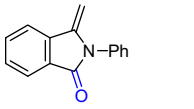
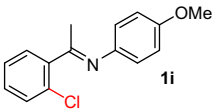
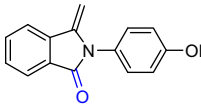
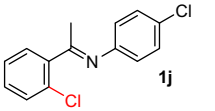
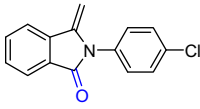
N-methoxybenzamides and active alkenes. Also, the use of stoichiometric benzoquinone as oxidant and acetic acid as solvent makes the reaction still not practical in the view of green chemistry. In continuation of our interest in the C–Cl bond activation[2] and cyclocarbonylation,[11] we became interested in the development of an alternative synthetic strategy toward 3-methyleneisoindolin-1-one derivatives via palladium-catalyzed cyclocarbonylation[12] of *ortho*-chloro ketimines.

As a model reaction, *ortho*-chloro ketimine (**1a**) was employed as the substrate, while a variety of catalysts and bases were employed to optimize the reaction conditions (Table 1). Gas chromatography (GC) was used to give the yield of each entry by using *n*-$C_{22}H_{46}$ as internal standard.

To start our study, three Pd(II) catalysts with different ligands were used with Cs_2CO_3 as base to explore an efficient catalyst system. A common catalyst $PdCl_2(PPh_3)_2$ showed rather low activity (entry 1), while a remarkable yield (81%) of the desired product (**2a**) was obtained by simply replacing the PPh_3 ligand with PCy_3 (entry 2). Catalyst with a bidentate ligand 1,2-bis(diphenylphosphino)ethane (dppe) also showed low activity (entry 3). These results revealed that the Pd(II) catalyst with trialkylphosphine ligand PCy_3 was an efficient catalyst for the C–Cl bond activation, which is comparable with our previous studies.

By using $PdCl_2(PCy_3)_2$ as catalyst, we next surveyed several bases (entries 4–7). Another carbonate K_2CO_3 was also suitable for the reaction besides Cs_2CO_3, but gave a lower yield (72%). Na_3PO_4 displayed much lower efficiency (54%), and organic bases such as Bu_3N and pyrrolidine showed low activity. By using the $PdCl_2(PCy_3)_2/Cs_2CO_3$ catalytic system, we further conducted our optimization by varying other reaction conditions. To our delight, a higher yield (89%) was obtained by reducing the CO pressure to 5 atm (entry 8). However, only trace amount of product was detected when the reaction was conducted under 1 atm CO (entry 9). Decreasing the temperature from 130 °C to 115 °C made the reaction sluggish and gave much lower yield (28%, entry 10). Interestingly, a much satisfactory yield (95%) was obtained by reducing the catalyst loading from 3 mol % to 1.0 mol % (entry 11), may be due to the suppression of the side reactions. However, further reducing the catalyst loading to 0.5 mol % gave disappointing yield (41%, entry 12).

Table 2
Substrate scope[a]

Entry	Ketimine **1**	Product **2**	
1	 **1b**		**2b**, 72%
2	 **1c**		**2c**, 72%
3	 **1d**		**2d**, 56%
4	 **1e**		**2e**, 31%
5	 **1f**		**2f**, 81%
6	 **1g**		**2g**, 75%
7	 **1h**		**2h**, 83%
8	 **1i**		**2i**, 61%
9	 **1j**		**2j**, 50%

[a] Reactions were carried out using 1.0 mmol of **1**, 1.0 mol % of $PdCl_2(PCy_3)_2$, and 1.1 equiv of Cs_2CO_3 in 1.0 mL of toluene in a 25 mL autoclave with 5.0 atm of CO at 130 °C for 8 h.

With the optimized reaction condition in hand, the generality for the synthesis of isoindolin-1-ones was next examined (Table 2).[13] Dichloro ketimine **1b** and **1c** were used to afford chloro-substituted products **2b** and **2c** in 72% yield. Notably, chloro groups not in the *ortho* position were inert in the system. This selectivity in the C–Cl bond cleavage indicates that the C–Cl bond activation is facilitated by the coordination to Pd using the N atom in the ketimine (vide infra). Fluoro-substituted ketimine **1d** gave the fluoro-having products **2d** in 56%, indicating that the C–F bond remained intact under the reaction conditions. By using **1e** as the substrate, two isomers are expected to be formed, but only one of them was obtained in 31% isolated yield, and unfortunately the stereochemistry of the C=C double bond could not be confirmed by 2D NOESY experiment. Ketimines with bulkier *N*-substitutes or *N*-aryl substitutes were also employed and the reaction proceeded smoothly to afford the corresponding 3-methyleneisoindolin-1-ones **2f**–**j** in moderate to good yields.

A proposed mechanism was shown in Scheme 1, *ortho*-chloro ketimine makes an oxidative addition to the Pd catalyst to afford a five-membered palladacyclic intermediate. Subsequently, CO insertion occurs and a six-membered palladacyclic intermediate

is obtained. At last, a reductive elimination of the intermediate proceeds to yield the product and catalytic species is regenerated. The byproduct hydrochloric acid is absorbed by the added base.

In summary, we have developed a facile route to construct 3-methyleneisoindolin-1-ones from readily available *ortho*-chloro arylketimines. The reaction proceeds efficiently via the C–Cl bond cleavage and the cyclocarbonylation by using the $PdCl_2(PCy_3)_2/Cs_2CO_3$ catalytic system.

A typical experimental procedure for the cyclocarbonylation of **1a** (Table 1, entry 11): To a 25 mL autoclave equipped with a magnetic stirrer, **1a** (194.5 mg, 1.0 mmol), $PdCl_2(PCy_3)_2$ (8.0 mg, 0.01 mmol), Cs_2CO_3 (360.1 mg, 1.1 mmol), and dry toluene (1.0 mL) were added sequentially under nitrogen. The autoclave was sealed and CO was introduced at an initial pressure of 5.0 atm at room temperature. The autoclave was stirred at 130 °C in a heating jacket for 8 h. After the autoclave was cooled to room temperature, CO was released slowly. The reaction mixture was diluted with CH_2Cl_2 (4.0 mL), and then *n*-octadecane (92.5 mg, 0.36 mmol) was added as an internal standard for GC analysis. After GC and GC–MS analyses, volatiles were removed under reduced pressure, and the residue was subjected to silica gel column chromatography with petroleum ether/ethyl acetate (mixture ratio 4:1) as eluent to afford **2a** (156.5 mg, 84%) as a pale yellow oil.

Acknowledgments

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Supplementary data

Supplementary data (general method, characterization data and charts of ^1H, ^{13}C NMR for all products) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.07.017.

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13. The characterization data of the products are reported in Supplementary data.