N-Heterocyclic Carbene-Palladium(II)-1-Methylimidazole Complex Catalyzed α-Arylation of Oxindoles with Aryl Chlorides and Aerobic Oxidation of the Products in a One-Pot Procedure

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NHC-Pd(II)-Im complex 1 was found to be an effective catalyst for the α -arylation of unprotected oxindoles with aryl chlorides to give products 4 in 44–98% yields under a N₂ atmosphere. Furthermore, if the reactions were first performed under conditions identical to those for the α -arylation reaction for 12 h and then exposed to air for another 3 h, 3-aryl-3-hydroxy-2-oxindoles 5 can be obtained in 49–84% yields in a one-pot procedure.

During the past years, palladium-catalyzed α -arylation reactions of carbonyl compounds have become versatile methods for the formation of new carbon–carbon bonds.¹ Among them, since its first discovery, the palladiumcatalyzed direct α -arylation of oxindoles has proven to be an important reaction and has attracted considerable attention² because the 3-substituted oxindole derivatives are frequently found in many natural products and compounds with biological activity.³ Meanwhile, the 3-substituted 3-hydroxy-oxindoles are also attractive due to their prevalence in many alkaloid natural compounds and compounds with pharmaceutical and biological activity.⁴ However, the previously reported palladium-catalyzed α -arylation of oxindoles is still hampered as a practical method mainly due to the following reasons: (1) expensive, air-sensitive, electron-rich, and sterically hindered phosphine ligands are mandatory to facilitate such a transformation; (2) some require high catalyst loadings; (3) some require the preprotection of the free N-H of oxindoles. Therefore, development of an alternative method for the α -arylation of oxindoles still remains a challenge. During the past two decades, N-heterocyclic carbenes (NHCs) and their metal complexes have attracted much attention because of their significant advantages over their phosphine counterparts in air, thermal, and moisture stability. Consequently, NHC-Pd complexes have proven to be effective catalysts in the formation of carbon-carbon

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and carbon-heteroatom bonds.⁵ Despite the progress of NHC-Pd complexes in organic synthesis, however, to the best of our knowledge, NHC-Pd complex catalyzed α -arylation of oxindoles has not been reported to date. Therefore, on the basis of our success in the well-defined and easily prepared N-heterocyclic carbene-Pd(II)-1methylimidazole [NHC-Pd(II)-Im] complex 1 catalyzed carbon-carbon and carbon-nitrogen bond formation reactions using aryl chlorides as the substrates,⁶ and as a continuation of our investigations on the α -arylation reaction of ketones,^{6a} herein, we wish to report the first example of phosphine-free, NHC-Pd complex catalyzed α -arylation of oxindoles with aryl chlorides and the further unprecedented aerobic oxidation of the corresponding products to 3-aryl-3-hydroxy-oxindoles in a one-pot procedure.

Using oxindole 2a (1.3 mmol) and chlorobenzene 3a (1.0 mmol) as the substrates, NHC-Pd(II)-Im complex 1 (1.0 mol %) as the catalyst, and toluene (2.0 mL) as the solvent, we initially compared a variety of bases for this reaction performed at 100 °C for 12 h. Typical results are shown in Table 1. It was found that the bases drastically affected the reaction. For example, a moderate yield (78%)of product 4a can be achieved when KO^tBu was used as the base (Table 1, entry 1), while, in the presence of all other bases such as NaO^tBu, Cs₂CO₃, NaOH, KOH, K₂CO₃, and Na₂CO₃, no reaction occurred (Table 1, entries 2–7). The solvents also drastically affected the reaction. For example, almost no reaction occurred when other solvents such as DMSO, DMF, THF, dioxane, and CH₃CN were used, respectively (Table 1, entries 8-12). It seems that the vield cannot be further increased even if the reaction was performed in refluxing toluene for 12 h (Table 1, entry 13).

With the optimal reaction conditions in hand, we then first explored the scope and limitations of this reaction using oxindole **2a** and various aryl chlorides **3** as the substrates under identical conditions (Table 2). As can be seen from Table 2, all reactions performed well to give the desired products **4** in moderate to high yields at 100 °C or reflux, respectively. Substituents on the aryl chlorides have some effect on the reactions. For example, sterically hindered substrates such as 2-methylphenyl chloride **3d** and 2,6-dimethylphenyl chloride **3e** can give the corresponding products **4d** and **4e** in very high yields, respectively (Table 2, entries 3 and 4); however, when 2-methoxyphenyl chloride **3i** was used as the substrate, only a moderate yield of product **4i** was obtained (Table 2, entry 8). Heteroaryl chlorides such as 3-pyridinyl chloride Table 1. Optimization for the Reaction Conditions



$entry^a$	base	solvent	yield/% ^b
1	KO ^t Bu	toluene	78
2	NaO ^t Bu	toluene	NR
3	Cs_2CO_3	toluene	NR
4	NaOH	toluene	NR
5	KOH	toluene	NR
6	K_2CO_3	toluene	NR
7	Na_2CO_3	toluene	NR
8	KO ^t Bu	DMSO	NR
9	$KO^{t}Bu$	DMF	NR
10	$KO^{t}Bu$	THF	<5
11	KO ^t Bu	dioxane	<5
12	KO ^t Bu	CH_3CN	NR
13^c	KO ^t Bu	toluene	79

^{*a*} Unless otherwise specified, all reactions were carried out using **2a** (1.3 mmol), **3a** (1.0 mmol), **1** (1.0 mol %), base (4.0 equiv), and solvent (2.0 mL) at 100 °C for 12 h. ^{*b*} Isolated yields. ^{*c*} The reaction was performed in refluxing toluene for 12 h.





entry ^a	3 (R)	temp/ºC	yield/% ^b
1	3b (4-Me)	reflux	4b ,80
2	3c (3-Me)	reflux	4c , 90
3	3d (2-Me)	reflux	4d , 95
4	3e (2,6-Me ₂)	reflux	4e , 98
5	3f (4-F)	100	4f , 79
6	3g (4-OMe)	100	4g , 86
7	3h (3-OMe)	100	4h , 81
8	3i (2-OMe)	100	4 i, 66
9	3j	reflux	4j , 87

^{*a*} All reactions were carried out using **2a** (0.65 mmol), **3** (0.5 mmol), **1** (1.0 mol %), KO'Bu (4.0 equiv), and toluene (1.0 mL) at 100 °C or refluxing for 12 h. ^{*b*} Isolated yields.

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Table 3. NHC-Pd(II)-Im 1 Catalyzed Reactions of Oxindoles 2 with Aryl Chlorides 3



^{*a*} Unless specified otherwise, all reactions were carried out using **2** (0.65 mmol), **3** (0.5 mmol), **1** (1.0 mol %), KO'Bu (4.0 equiv), and toluene (1.0 mL) at 100 °C or reflux for 12 h. ^{*b*} Isolated yields. ^{*c*} **2b/3j** = 0.75/0.5 mmol.

3d

3e

3a

3h

3a

3b

3g

3j was also a suitable partner to give product **4j** in 87% yield (Table 2, entry 9).

Furthermore, a variety of oxindoles 2 and aryl chlorides 3 were subjected to the optimal reaction conditions to test the generality. As can be seen from Table 3, all reactions also took place smoothly to give the desired products 4 in moderate to high yields. It seems that substituents on both of the substrates tested have no obvious effect in these cases. For instance, whether electron-rich or -poor groups were attached on the oxindoles 2 or aryl chlorides 3, all reactions worked well. Sterically hindered substituents such as 2-Me and 2,6-Me₂ on the aryl chlorides 3 did not significantly affect the reactions (Table 3, entries 4 and 5). However, such substituents on the oxindoles 2 affected the reactions to some extent. For instance, for the reactions involving 5,7-dimethyloxindole 2d, the corresponding products 4ab-4ad were formed only in 44-55% yields, respectively, maybe due to the steric hindrance (Table 3, entries 17-19).

To our pleasure, when the reactions between oxindoles 2 and aryl chlorides 3 were first carried out under identical conditions shown in Tables 1-3 for 12 h and then the

4w, 86

4x. 92

4z. 91

4aa, 78

4ab. 44

4ac, 44 **4ad**, 55

100

100

100

100

100

100

100

2	3		5 H O
entry ^a	2 (R')	3 (R)	yield/% ^b
1	2a (H)	3a (H)	5a , 72
2	2a	3b (4-Me)	5b , 80
3	2a	3c (3-Me)	5c , 71
4	2a	3d (2-Me)	5d , 49
5	2a	3f (4-F)	5e , 68
6	2a	3g (4-OMe)	5f , 84
7	2a	3h (3-OMe)	5g , 76
8	2a	3i (2-OMe)	5h , 56
		CI	
9	2a	3j 🛛 🔰	5 i, 72
10	2b (5-Me)	3a ^N	5j , 73
11	2b	3b	5k , 74
12	2b	3c	5I , 78
13	2b	3f	5m , 69
14	2b	3g	5n , 79
15	2b	3h	50 , 74
16	2c (5-F)	3a	5p , 62
17	2b	3b	5q , 73
18	2b	3c	5r , 63

Table 4. NHC-Pd(II)-Im 1 Catalyzed Reactions of Oxindoles 2

1) NHC-Pd(II)-Im 1

100 or 110 °C, 12 I

KO^tBu, toluene

with Arvl Chlorides 3 To Form Products 5

CI

^{*a*} All reactions were carried out using **2** (0.65 mmol), **3** (0.5 mmol), **1** (1.0 mol %), KO'Bu (4.0 equiv), and toluene (1.0 mL) at 100 °C or reflux under N₂ for 12 h, and then the mixture was stirred under air for another 3 h. ^{*b*} Isolated yields.

reaction mixture was further exposed to air for another 3 h, 3-aryl-3-hydroxy oxindoles **5** can be formed in accepatable to good yields (Table 4). Substituents on the aryl chlorides have some effect on these reactions. For example, when 2-methylphenyl chloride **3d** and 2-methoxyphenyl chloride **3i** were used as the substrates, somewhat lower yields of products **5d** (49%) and **5h** (56%) were obtained, probably due to the steric hindrance of the substrates (Table 4, entries 4 and 8). Moreover, when 2,6-dimethylphenyl chloride **3e** was utilized, only the normal α -arylated product **4o** was obtained in 87% yield, and none its oxidized product was detected.

In conclusion, to the best of our knowledge, we report in this paper the first example of a phosphine-free, easily prepared and highly active NHC-Pd(II) complex catalyzed α -arylation of oxindoles with aryl chlorides. Furthermore, the normal α -arylated products can be further transformed to the oxidized products, the 3-aryl-3-hydroxy-oxindoles, under ambient conditions at room temperature in a onepot procedure. Both reactions can tolerate a variety of substrates such as both oxindoles and aryl chlorides, which thus will enrich the chemistry of NHC-Pd(II) complexes

13

14

15

16

17

18

19

20

2c

2c

2c

2d

2d

2d (5,7-Me₂)

in organic synthesis and make the α -arylation reaction of oxindoles more practical.

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Supporting Information Available. General procedure for the formation of compounds 4 and 5 and their ¹H and ¹³C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.