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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

Zheng-Kang Xiao, Hui-Ying Yin, and Li-Xiong Shao*

College of Chemistry and Materials Engineering, Wenzhou University, Chashan University Town, Wenzhou, Zhejiang Province 325035, People's Republic of China

Shaolix@wzu.edu.cn

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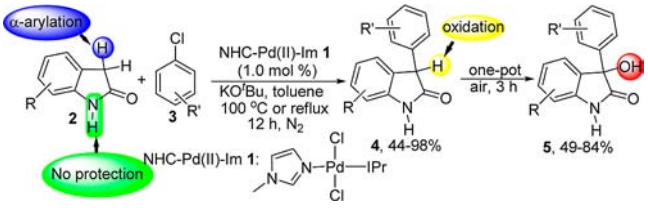
ABSTRACT



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 N_2 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 palladium-catalyzed direct α-arylation of oxindoles has proven to be an important reaction and has attracted considerable attention[2] 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

(1) For recent reviews on the α-arylation reaction, please see: (a) Bellina, F.; Rossi, R. *Chem. Rev.* **2010**, *110*, 1082–1146. (b) Johansson, C. C. C.; Colacot, T. J. *Angew. Chem., Int. Ed.* **2010**, *49*, 676–707.

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(4) For recent selected reviews, please see: (a) Trost, B. M.; Brennan, M. K. *Synthesis* **2009**, 3003–3025. (b) Peddibhotla, S. *Curr. Anal. Chem. Curr. Bioact. Compd.* **2009**, *5*, 20–38. (c) Badillo, J. J.; Hanhan, N. V.; Franz, A. K. *Curr. Opin. Drug Discovery Dev.* **2010**, *13*, 758–776.

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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)-1-methylimidazole [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.

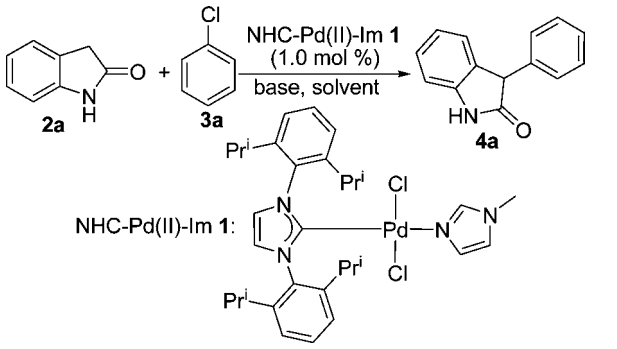
Using oxindole **2a** (1.3 mmol) and chlorobenzene **3a** (1.0 mmol) as the substrates, NHC-Pd(II)-Im complex **1** (1.0 mol %) as the catalyst, and toluene (2.0 mL) as the solvent, we initially compared a variety of bases for this reaction performed at 100 °C for 12 h. Typical results are shown in Table 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^{t}Bu was used as the base (Table 1, entry 1), while, in the presence of all other bases such as NaO^{t}Bu, Cs_2CO_3, NaOH, KOH, K_2CO_3, and Na_2CO_3, 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 CH_3CN were used, respectively (Table 1, entries 8–12). It seems that the yield 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

(5) For reviews on the NHC-Pd complexes catalyzed coupling reactions, please see: (a) Hillier, A. C.; Grasa, G. A.; Viciu, M. S.; Lee, H. M.; Yang, C.-L.; Nolan, S. P. *J. Organomet. Chem.* **2002**, *653*, 69–82. (b) Kantchev, E. A. B.; O'Brien, C. J.; Organ, M. G. *Angew. Chem., Int. Ed.* **2007**, *46*, 2768–2813. (c) Marion, N.; Nolan, S. P. *Acc. Chem. Res.* **2008**, *41*, 1440–1449. (d) Würtz, S.; Glorius, F. *Acc. Chem. Res.* **2008**, *41*, 1523–1533. (e) Fortman, G. C.; Nolan, S. P. *Chem. Soc. Rev.* **2011**, *40*, 5151–5169. (f) Valente, C.; Çalimsiz, S.; Hoi, K. H.; Mallik, D.; Sayah, M.; Organ, M. G. *Angew. Chem., Int. Ed.* **2012**, *51*, 3314–3332.

(6) For some selected examples, please see: (a) Xiao, Z.-K.; Shao, L.-X. *Synthesis* **2012**, 711–716. (b) Wang, Z.-Y.; Chen, G.-Q.; Shao, L.-X. *J. Org. Chem.* **2012**, *77*, 6608–6614. (c) Chen, W.-X.; Shao, L.-X. *J. Org. Chem.* **2012**, *77*, 9236–9236. (d) Lin, X.-F.; Li, Y.; Li, S.-Y.; Xiao, Z.-K.; Lu, J.-M. *Tetrahedron* **2012**, *68*, 5806–5809.

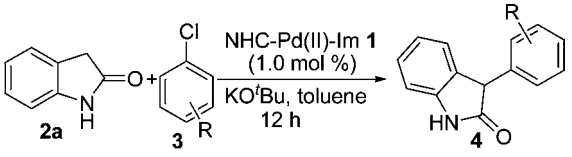
Table 1. Optimization for the Reaction Conditions

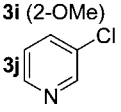


entry[a]	base	solvent	yield/%[b]
1	KO^{t}Bu	toluene	78
2	NaO^{t}Bu	toluene	NR
3	Cs_2CO_3	toluene	NR
4	NaOH	toluene	NR
5	KOH	toluene	NR
6	K_2CO_3	toluene	NR
7	Na_2CO_3	toluene	NR
8	KO^{t}Bu	DMSO	NR
9	KO^{t}Bu	DMF	NR
10	KO^{t}Bu	THF	<5
11	KO^{t}Bu	dioxane	<5
12	KO^{t}Bu	CH_3CN	NR
13[c]	KO^{t}Bu	toluene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

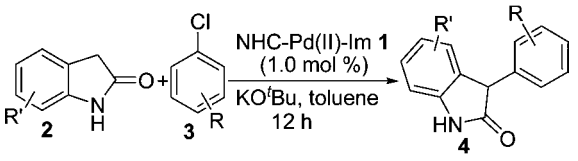
Table 2. NHC-Pd(II)-Im **1** Catalyzed Reactions of Oxindole **2a** with Aryl Chlorides **3**

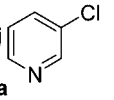


entry[a]	**3** (R)	temp/°C	yield/%[b]
1	**3b** (4-Me)	reflux	**4b**,80
2	**3c** (3-Me)	reflux	**4c**, 90
3	**3d** (2-Me)	reflux	**4d**, 95
4	**3e** (2,6-Me$_2$)	reflux	**4e**, 98
5	**3f** (4-F)	100	**4f**, 79
6	**3g** (4-OMe)	100	**4g**, 86
7	**3h** (3-OMe)	100	**4h**, 81
8	**3i** (2-OMe)	100	**4i**, 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^{t}Bu (4.0 equiv), and toluene (1.0 mL) at 100 °C or refluxing for 12 h. [b] Isolated yields.

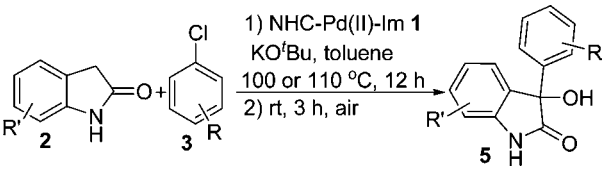
Table 3. NHC-Pd(II)-Im **1** Catalyzed Reactions of Oxindoles **2** with Aryl Chlorides **3**

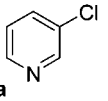


entry[a]	**2** (R')	**3** (R)	temp/°C	yield/%[b]
1	**2b** (5-Me)	**3a** (H)	100	**4k**, 89
2	**2b**	**3b** (4-Me)	100	**4l**, 79
3	**2b**	**3c** (3-Me)	100	**4m**, 74
4	**2b**	**3d** (2-Me)	reflux	**4n**, 88
5	**2b**	**3e** (2,6-Me$_2$)	reflux	**4o**, 89
6	**2b**	**3f** (4-F)	100	**4p**, 76
7	**2b**	**3g** (4-OMe)	100	**4q**, 85
8	**2b**	**3h** (3-OMe)	100	**4r**, 77
9[c]	**2b**	**3j** 	reflux	**4s**, 75
10	**2c** (5-F)	**3a**	100	**4t**, 86
11	**2c**	**3b**	100	**4u**, 80
12	**2c**	**3c**	100	**4v**, 80
13	**2c**	**3d**	100	**4w**, 86
14	**2c**	**3e**	100	**4x**, 92
15	**2c**	**3g**	100	**4z**, 91
16	**2c**	**3h**	100	**4aa**, 78
17	**2d** (5,7-Me$_2$)	**3a**	100	**4ab**, 44
18	**2d**	**3b**	100	**4ac**, 44
19	**2d**	**3g**	100	**4ad**, 55

[a] Unless specified otherwise, all reactions were carried out using **2** (0.65 mmol), **3** (0.5 mmol), **1** (1.0 mol %), KO^{t}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.

Table 4. NHC-Pd(II)-Im **1** Catalyzed Reactions of Oxindoles **2** with Aryl Chlorides **3** To Form Products **5**



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
9	**2a**	**3j** 	**5i**, 72
10	**2b** (5-Me)	**3a**	**5j**, 73
11	**2b**	**3b**	**5k**, 74
12	**2b**	**3c**	**5l**, 78
13	**2b**	**3f**	**5m**, 69
14	**2b**	**3g**	**5n**, 79
15	**2b**	**3h**	**5o**, 74
16	**2c** (5-F)	**3a**	**5p**, 62
17	**2b**	**3b**	**5q**, 73
18	**2b**	**3c**	**5r**, 63

[a] All reactions were carried out using **2** (0.65 mmol), **3** (0.5 mmol), **1** (1.0 mol %), KO^{t}Bu (4.0 equiv), and toluene (1.0 mL) at 100 °C or reflux under N_2 for 12 h, and then the mixture was stirred under air for another 3 h. [b] Isolated yields.

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-Me$_2$ 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 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 one-pot 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

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 ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.