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N-Heterocyclic Carbene−Palladium(II)-1-Methylimidazole Complex Catalyzed Amination between Aryl Chlorides and Amides

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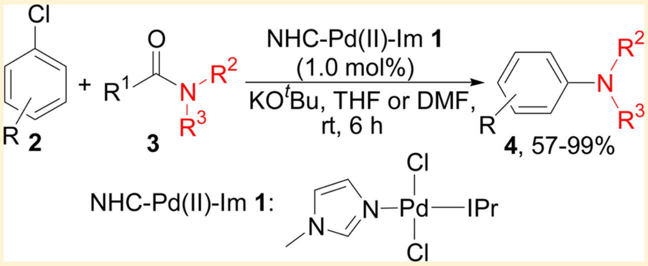
Supporting Information

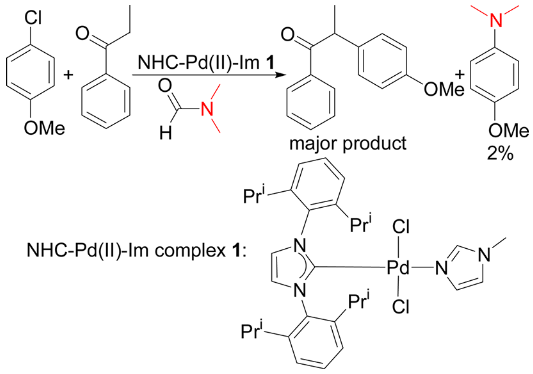
ABSTRACT: We report herein that amides are excellent *N*-sources in the NHC−Pd(II)−Im complex **1** catalyzed amination of aryl chlorides. In the presence of KO^{t}Bu, various aryl chlorides and amides can react smoothly to give the corresponding aminated products in moderate to almost quantitative yields at room temperature within 6 h.



INTRODUCTION

N-Heterocyclic carbenes (NHCs) and their metal complexes have attracted increasing attention during the past years, and they have been proven to be efficient catalysts in the formation of carbon−carbon and carbon−heteroatom bonds.[1] During the past years, we have been engaged in the development of novel NHC−metal complexes and their applications in organic synthesis.[2,3] For example, we have previously shown that NHC−Pd(II)−Im complex **1** was an effective catalyst in the α-arylation reaction between ketones and aryl chlorides using tetrahydrofuran (THF) or *N,N*′-dimethylformamide (DMF) as the solvent, respectively.[3c] It was in the latter cases that we unexpectedly observed small amounts of the aminated product. For instance, GC analysis of the crude reaction mixture of the attempted NHC−Pd(II)−Im complex **1** catalyzed reaction of 4-methoxyphenyl chloride with 1-phenylpropan-1-one showed that the α-arylation product was the major one along with a small amount of *N,N*-dimethyl-4-methoxyphenylamine (2%) (Scheme 1).

Scheme 1. Unexpected Amination Reaction



In fact, a common solvent such as DMF has previously been utilized as a NMe_2 source in the formation of C−N bonds. However, all of the reported methods have some obvious disadvantages, such as only aryl halides possessing strongly electron-withdrawing groups can react under harsh reaction conditions such as high temperature (80−250 °C) and long reaction time.[4]

Realizing the need to develop a general and alternative method for the synthesis of aniline derivatives under mild conditions,[5,6] we then focused on the study of the scope and limitations of the amination of aryl chlorides using amides as the *N*-sources in the presence of NHC−Pd(II)−Im complex **1**. Herein, we wish to report these results in detail.

RESULTS AND DISCUSSION

Initial examinations were carried out using 3-methoxyphenyl chloride **2a** (0.8 mmol) and DMF **3a** (2.0 equiv) as the substrates in the presence of NHC−Pd(II)−Im complex **1** (1.0 mol %) in THF (1.0 mL) at room temperature for 6 h to evaluate the bases. It was found that the bases used drastically affect the reaction. For example, a high yield of product **4a** was obtained when KO^{t}Bu was used as the base (Table 1, entry 7), and in the presence of all other bases such as NaO^{t}Bu, KOH, NaOH, K_2CO_3, Na_2CO_3 and $KHCO_3$, no reaction or only a trace of product **4a** was observed (Table 1, entries 1−6). The solvent effects were also investigated, and THF was the best choice over DMF (82%) (Table 1, entry 8) and Et_2O (41%) (Table 1, entry 9). In addition, only a trace of product or no reaction was observed when other solvents such as toluene, CH_3CN, dioxane, ^{i}PrOH, or DMSO were used (Table 1, entries 10−14). Furthermore, whether THF or DMF was used

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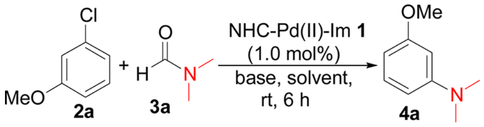
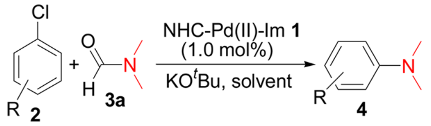
Table 1. Optimization for the Reaction Conditions

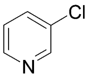


entry[a]	base	solvent	yield (%)
1	NaO^{t}Bu	THF	10
2	KOH	THF	10
3	NaOH	THF	9
4	K_2CO_3	THF	NR
5	Na_2CO_3	THF	NR
6	$KHCO_3$	THF	NR
7	KO^{t}Bu	THF	95
8	KO^{t}Bu	DMF	82
9	KO^{t}Bu	Et_2O	41
10	KO^{t}Bu	toluene	6
11	KO^{t}Bu	CH_3CN	3
12	KO^{t}Bu	dioxane	8
13	KO^{t}Bu	^{i}PrOH	NR
14	KO^{t}Bu	DMSO	2
15[b]	KO^{t}Bu	THF	NR
16[b]	KO^{t}Bu	DMF	NR

[a]Reaction conditions: **2a** (0.8 mmol), **3a** (2.0 equiv), base (4.0 equiv), **1** (1.0 mol %), solvent (1.0 mL), rt, 6 h. [b]No catalyst was added.

Table 2. NHC-Pd(II)-Im 1 Catalyzed Reaction of Aryl Chlorides 2 with DMF 3a



entry[a]	2 (R)	conditions	yield (%)
1	**2b** (4-OMe)	**A**	**4b**, 91
2	**2b**	**B**	**4b**, 97
3	**2c** (4-Me)	**A**	**4c**, 10
4	**2c**	**B**	**4c**, 72
5	**2d** (3-Me)	**A**	**4d**, 5
6	**2d**	**B**	**4d**, 61
7	**2e** (4-H)	**A**	**4e**, 8
8	**2e**	**B**	**4e**, 99
9[b]	**2f** (4-F)	**A**	**4f**, 70
10	**2f**	**B**	**4f**, 57
11	**2g** (4-CN)	**A**	**4g**, 70
12	**2g**	**B**	**4g**, 4
13[c]	**2h** (2-OMe)	**A**	**4h**, 77
14	**2h**	**B**	**4h**, 5
15	**2i** 	**A**	**4i**, 96
16	**2i**	**B**	**4i**, 4

[a]Unless otherwise specified, the reaction conditions were as follows: **2** (0.8 mmol), KO^{t}Bu (4.0 equiv), rt, 6 h and (A) **3a** (2.0 equiv), THF (1.0 mL) or (B) **3a** (1.0 mL). [b]The reaction was carried out in refluxing THF. [c]The time was 24 h.

as the solvent, no reaction occurred in the absence of the NHC−Pd(II)−Im complex **1** (Table 1, entries 15 and 16).

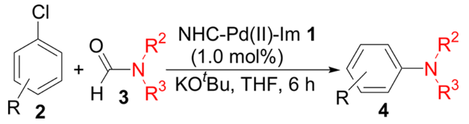
With the optimal reaction conditions in hand, we then investigated the generality using a variety of aryl chlorides **2** and DMF **3a** as the substrates. In these cases, two different catalytic systems as shown in Table 1, entries 7 and 8, were examined, respectively. As can be seen from Table 2, the different catalytic systems drastically affect the most reactions. For example, when 4-methoxyphenyl chloride **2b** was used as the substrate, comparable yields were achieved (Table 2, entries 1 and 2). For 4-methylphenyl chloride **2c**, 3-methylphenyl chloride **2d**, and chlorobenzene **2e**, moderate to high yields of the corresponding aminated products **4** can be achieved when DMF acts as both the reagent and solvent (conditions **B**) (Table 2, entries 4, 6, and 8), while almost no reaction occurred when THF was used as the solvent (conditions **A**) (Table 2, entries 3, 5, and 7). However, for 4-cyanophenyl chloride **2g**, 2-methoxyphenyl chloride **2h**, and a heteroaryl chloride such as 3-pyridinyl chloride **2i**, moderate to high yields can be observed when THF was used as the solvent (conditions **A**) (Table 2, entries 11, 13, and 15), and almost no reaction took place when DMF was used as the solvent (conditions **B**) (Table 2, entries 12, 14, and 16). At this stage, the solvent effect is still unclear.

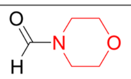
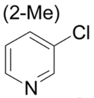
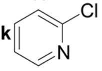
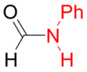
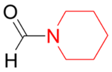
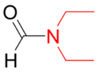
Subsequently, a broad scope of aryl chlorides **2** and formamides **3** were examined under the optimal reaction conditions (Table 1, entry 7). First, the reactions between a variety of aryl chlorides **2** and morpholine-4-carbaldehyde **3b** were carried out. As can be seen from Table 3, all reactions performed very well to give the corresponding aminated products **4j−s** in high to almost quantitative yields (Table 3, entries 1−10). The electronic effect of the substituents on the aryl chlorides did not affect the reactions. For example, whether electron-donating groups such as MeO- and Me- or electron-withdrawing group such as F- were attached on the aryl chlorides, similar high to almost quantitative yields were achieved. Sterically hindered substituents such as 2-MeO (**2h**) and 2-Me (**2j**) groups on the aryl chlorides also have less effect on the reactions (Table 3, entries 7 and 8). 3-Pyridinyl chloride **2i**, as well as its analogue 2-pyridinyl chloride **2k**, was also good reaction partner to give products **4r** and **4s** in almost quantitative yields, respectively (Table 3, entries 9 and 10). For some other formamides such as *N*-phenylformamide **3c**, piperidine-1-carbaldehyde **3d**, and *N*,*N*-diethylformamide **3e**, all of them reacted with aryl chlorides smoothly to give the desired aminated products **4t−x** in good to almost quantitative yields (Table 3, entries 11−15).

Besides formamides **3a−e**, some other amides such as *N*,*N*-dimethylacetamide **3f** and *N*,*N*-dimethylbenzamide **3g** were also tested in the reactions with various aryl chlorides under the optimal conditions. As can be seen from Table 4, all reactions also performed well to give the aminated products **4** in good to almost quantitative yields. The reaction involving heteroaryl chloride such as 3-pyridinyl chloride **2i** also works well to give product **4i** in 84% yield (Table 4, entry 4).

On the basis of previous investigations,[7] a plausible mechanism for this type of NHC−Pd(II)−Im complex **1** catalyzed amination reaction was shown in Scheme 2. First, in the presence of KO^{t}Bu, amides **3** will be decomposed to intermediates **I** and **II**. Meanwhile, aryl chlorides **2** proceed oxidative addition to Pd^0, giving intermdiate **IV**. Then intermediate **II** undergoes transmetalation process with intermediate **IV** to give intermediate **V**. Finally, reductive elimination of intermediate **V** will afford the final products **4** and regenerate Pd^0 catalyst to furnish the catalytic cycle. In the meantime, intermediate **I** will be transformed to intermediate **III**.[8] The formation of intermediate **III** was further confirmed by GC−MS when *N*,*N*-dimethylbenzamide **3g** was used as the amination reagent (see the Supporting Information for more details).

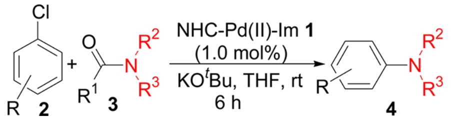
Table 3. NHC-Pd(II)-Im 1 Catalyzed Reaction of Aryl Chlorides 2 with Formamides 3

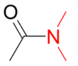
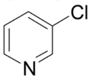
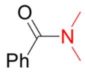


entry[a]	2 (R)	3	yield (%)
1	**2a** (3-OMe)	**3b** 	**4j**, 98
2	**2b** (4-OMe)	**3b**	**4k**, 92
3	**2c** (4-Me)	**3b**	**4l**, 99
4	**2d** (3-Me)	**3b**	**4m**, 98
5	**2e** (H)	**3b**	**4n**, 99
6	**2f** (4-F)	**3b**	**4o**, 97
7[b]	**2h** (2-OMe)	**3b**	**4p**, 95
8	**2j** (2-Me)	**3b**	**4q**, 95
9	**2i** 	**3b**	**4r**, 99
10	**2k** 	**3b**	**4s**, 99
11[b]	**2a**	**3c** 	**4t**, 92
12[b]	**2b**	**3c**	**4u**, 83
13	**2a**	**3d** 	**4v**, 98
14	**2b**	**3d**	**4w**, 92
15[c]	**2a**	**3e** 	**4x**, 86

[a] Unless otherwise specified, all reactions were carried out using **2** (0.8 mmol), **3** (2.0 equiv), KO^{t}Bu (4.0 equiv), and **1** (1.0 mol %) in THF (1.0 mL) at rt for 6 h. [b] The reaction was carried out in refluxing THF. [c] The temperature was 50 °C.

Table 4. NHC-Pd(II)-Im 1 Catalyzed Reaction of Aryl Chlorides 2 with Amides 3



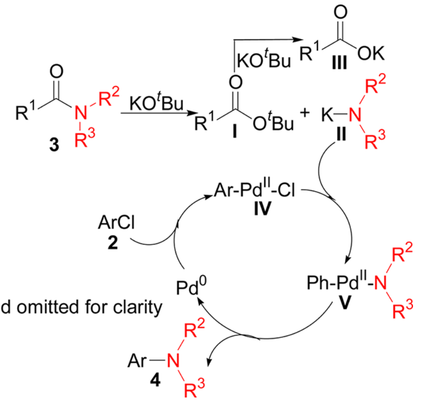
entry[a]	2 (R)	3	yield (%)
1	**2a** (3-OMe)	**3f** 	**4a**, 82
2	**2b** (4-OMe)	**3f**	**4b**, 99
3	**2c** (4-Me)	**3f**	**4c**, 81
4	**2i** 	**3f**	**4i**, 84
5	**2a**	**3g** 	**4a**, 94
6	**2b**	**3g**	**4b**, 84

[a] All reactions were carried out using **2** (0.8 mmol), **3** (2.0 equiv), KO^{t}Bu (4.0 equiv), and **1** (1.0 mol %) in THF (1.0 mL) at rt for 6 h.

CONCLUSIONS

In conclusion, we have found that amides can be used as the *N*-sources in the NHC−Pd(II)−Im complex catalyzed reactions with aryl chlorides. The reactions can tolerate a broad scope of substrates. Under mild conditions, all reactions performed very well to give the corresponding aminated products in moderate to almost quantitative yields, enriching a convenient and alternative method for the amination of aryl chlorides. Furthermore, compared to the direct amination between aryl chlorides and amines catalyzed by NHC−Pd(II)−Im complex,[3a,b] the reactions reported in this paper can be performed under milder conditions to give the aminated products in similar or higher yields.

Scheme 2. Plausible Mechanism



EXPERIMENTAL SECTION

General Remarks. NMR spectra were recorded at 300/500 (for ^{1}H NMR) or 75/125 MHz (for ^{13}C NMR), respectively. ^{1}H NMR and ^{13}C NMR spectra recorded in $CDCl_3$ solutions were referenced to TMS (0.00 ppm) and the residual solvent peak (77.0 ppm), respectively. *J* values are reported in hertz. Organic solvents used were dried by standard methods. Other commercially obtained reagents were used without further purification. Flash column chromatography was performed on silica gel (300−400 mesh).

General Procedure for the NHC−Pd(II)−Im Complex 1-Catalyzed Amination between Aryl Chlorides and Amides. *Conditions A.* Under N_2 atmosphere, KO^{t}Bu (4.0 equiv), NHC−Pd(II)−Im complex **1** (1.0 mol %), THF (1.0 mL), 3-methoxyphenyl chloride **2a** (0.8 mmol), and DMF **3a** (2.0 equiv) were successively added into a Schlenk reaction tube. The mixture was stirred at room temperature for 6 h. The solvent was evaporated in vacuo and then purified by flash column chromatography on silica gel (eluent: PE/EA = 15:1) to give the pure product **4a**.

Conditions B. Under N_2 atmosphere, KO^{t}Bu (4.0 equiv), NHC−Pd(II)−Im complex **1** (1.0 mol %), DMF (1.0 mL), and 3-methoxyphenyl chloride **2a** (0.8 mmol) were successively added into a Schlenk reaction tube. The mixture was stirred at room temperature for 6 h. The reaction mixture was diluted with ethyl acetate, washed with brine, and dried over anhydrous Na_2SO_4. The solvent was evaporated in vacuo and then purified by flash column chromatography on silica gel (eluent: PE/EA = 15:1) to give the pure product **4a**.

All products such as **4a**,[9] **4b**,[9] **4c**,[9] **4d**,[9] **4e**,[10] **4f**,[10] **4g**,[11] **4h**,[9] **4i**,[12] **4j**,[3a] **4k**,[3a] **4l**,[3a] **4m**,[3a] **4n**,[3a] **4o**,[13] **4p**,[9] **4q**,[3a] **4r**,[3a] **4s**,[3a] **4t**,[3b] **4u**,[3b] **4v**,[3a] **4w**,[3a] and **4x**[14] are known compounds and were fully determined according to the authentic samples.

ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H and ^{13}C NMR spectra of compounds **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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