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N-Heterocyclic Carbene–Palladium(II)–4,5-Dihydrooxazole Complexes: Synthesis and Catalytic Activity toward Amination of Aryl Chlorides

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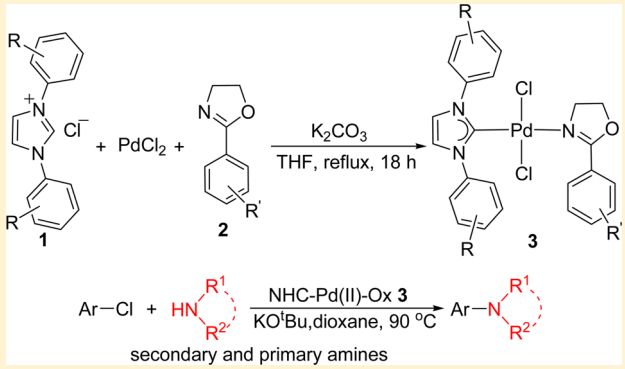
Supporting Information

ABSTRACT: A series of novel N-heterocyclic carbene–palladium(II)–4,5-dihydrooxazole (NHC-Pd^{II}-Ox) complexes **3** were successfully synthesized from commercially available imidazolium salts **1**, $PdCl_2$, and 4,5-dihydrooxazoles **2** in a one-step process, and these complexes showed efficient catalytic activity toward the amination of aryl chlorides. Both secondary and primary amines were tolerated under the same reaction conditions. Under the optimal reaction conditions, the expected coupling products were obtained in moderate to high yields.



INTRODUCTION

During the past few years, the palladium-catalyzed amination reaction has become one of the most important and frequently applied methods for the formation of C–N bonds.[1] Among the electrophiles, aryl chlorides are the most desirable in view of cost, robustness, and availability, although their reactivity is relatively low.[2] Until now, a variety of phosphine ligands were developed for this purpose, such as Buchwald's biaryl phosphines,[3] Hartwig's ferrocene-based phosphines,[4] Beller's N-substituted heteroaryl phosphines,[5] etc.[6] However, all tertiary phosphine ligands mentioned were used as free ligands with palladium salts; thus, usually addition of excess ligands was necessary in comparison to palladium salts. Recently, in addition to air-sensitive tertiary phosphine ligands, several air-stable N-heterocyclic carbene (NHC)–palladium complexes have been developed which have a strict NHC/Pd ratio and have proven to be good catalysts in the amination reactions of aryl chlorides.[7]

The activity of NHC-Pd catalysts is dependent largely on the properties of the NHC. Their steric bulk enables stabilization of the active Pd(0) species and favors reductive elimination, while the strong σ-donor character facilitates the oxidative addition of aryl halides.[8] In addition to the NHC moiety, the "throwaway" ligands which are attached to the metal center can also affect the catalytic activity.[7s,t] We were therefore interested in the development of easily synthesized and highly reactive NHC-Pd complexes bearing a bulky, strongly donating NHC and an efficient "throwaway ligand. Recently, Shao and co-workers have developed well-defined NHC-Pd^{II}-1-methylimidazole complexes, which can be easily prepared from commercially available imidazolium salts, $PdCl_2$, and 1-methylimidazole from a one-step process in good yields, and found them to be efficient catalysts in amination reactions.[7j,l,r] However, these complexes need different systems for the arylation of primary and secondary amines.[7j,r] Considering that, in addition to the NHC moieties, the ancillary throwaway ligands also played important roles in the catalytic activity of the NHC-Pd complexes, in this paper, we thus report the facile synthesis of a series of N-heterocyclic carbene–palladium(II)–4,5-dihydrooxazole complexes (NHC-Pd^{II}-Ox) and their catalytic activities toward amination reactions of aryl chlorides with secondary and primary amines in low catalyst loading in the same catalytic system. Herein, we report these results in detail.

RESULTS AND DISCUSSION

First, according to Shao's previously reported procedure,[7r] NHC-Pd^{II}-Ox complexes **3** were easily obtained in 67–86% yields from commercially available imidazolium salts **1**, $PdCl_2$, and 4,5-dihydrooxazoles **2** in a one-step process (Table 1).

Complexes **3** were air and moisture stable, and were fully characterized by ^{1}H and ^{13}C NMR spectroscopy, MS, HRMS, and elemental analysis. Crystals of **3a,d** suitable for X-ray diffraction were grown in a mixture of ethyl acetate and petroleum ether, and their structures were unambiguously determined by X-ray diffraction (Figures 1 and 2). Both complexes showed slightly distorted square planar geometry for the central palladium atom, with the two chloride anions

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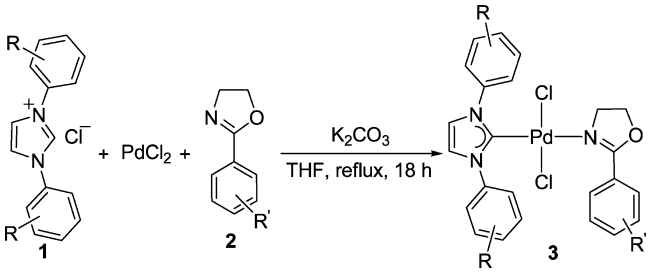
Table 1. Synthesis of NHC-Pd^{II}-Ox Complexes 3



entry[a]	1 (R)	2 (R′)	3, yield (%)[b]
1	**1a** (o,o′-^{i}Pr$_2$)	**2a** (H)	**3a**, 72
2	**1b** (o,o′-Me$_2$)	**2a**	**3b**, 86
3	**1c** (o,p,o′-Me$_3$)	**2a**	**3c**, 84
4	**1a**	**2b** (*p*-Me)	**3d**, 67
5	**1a**	**2c** (*p*-OMe)	**3e**, 70
6	**1a**	**2d** (*p*-F)	**3f**, 68

[a]All reactions were carried out using **1** (1.1 mmol), $PdCl_2$ (1.0 mmol), **2** (2.0 mmol), and K_2CO_3 (1.1 mmol) in THF (5.0 mL) under reflux for 18 h. [b]Isolated yields.

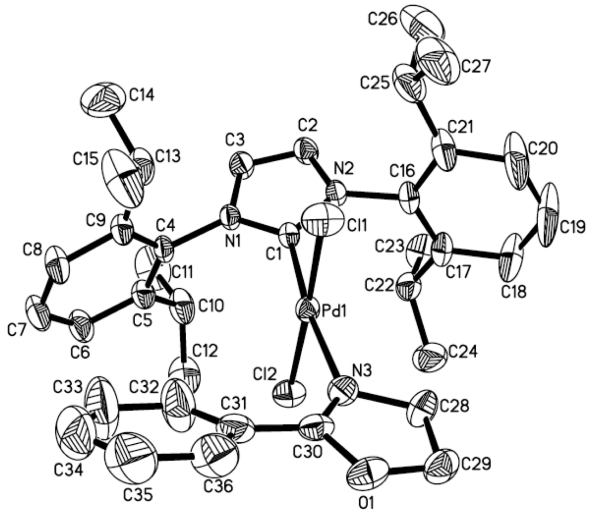


Figure 1. Molecular structure of **3a**. Hydrogens have been omitted for clarity. Selected bond lengths (Å) and angles (deg): Pd(1)−C(1) = 1.959(2); Pd(1)−N(3) = 2.0847(19); Pd(1)−Cl(1) = 2.2918(7); Pd(1)−Cl(2) = 2.3029(7); C(1)−Pd(1)−N(3) = 172.93(9); C(1)−Pd(1)−Cl(1) = 88.92(6); C(1)−Pd(1)−Cl(2) = 92.44(6); N(3)−Pd(1)−Cl(1) = 89.36(6); N(3)−Pd(1)−Cl(2) = 89.58(6); Cl(1)−Pd(1)−Cl(2) = 177.12(3).

perpendicular to the plane of the NHC ligands and the 4,5-dihydrooxazoles trans to it.

The Pd−$C_{carbene}$ and Pd−N bond lengths in complexes **3a,d** are nearly identical. In addition, both are similar to those of other well-defined NHC-Pd^{II} complexes with N-containing compounds such as 1-methylimidazole,[7r] triethylamine,[7t] and 3-chloropyridine[9] as the ancillary ligands and are slightly shorter than that using diethylamine[7s] as the ancillary ligand (Table 2). In addition, the percent buried volumes ($\%V_{Bur}$)[10] for all of these complexes have been calculated using the web application Samb*V*ca.[11] As can be seen from Table 2, similar buried volumes were found for these six complexes mentioned, implying similar structures of these complexes in the solid state.

The catalytic properties of complexes **3** in the Buchwald−Hartwig amination reaction were then tested. Initially, using

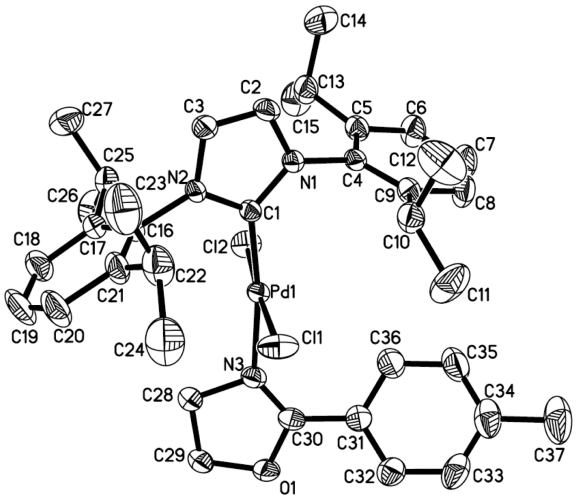


Figure 2. Molecular structure of **3d**. Hydrogens have been omitted for clarity. Selected bond lengths (Å) and angles (deg): Pd(1)−C(1) = 1.955(3); Pd(1)−N(3) = 2.084(3); Pd(1)−Cl(1) = 2.2940(18); Pd(1)−Cl(2) = 2.2983(17); C(1)−Pd(1)−N(3) = 172.14(11); C(1)−Pd(1)−Cl(1) = 89.32(10); C(1)−Pd(1)−Cl(2) = 91.57(10); N(3)−Pd(1)−Cl(1) = 89.90(9); N(3)−Pd(1)−Cl(2) = 89.64(9); Cl(1)−Pd(1)−Cl(2) = 176.84(4).

Table 2. Comparison of Pd−$C_{carbene}$ and Pd−N Bond Lengths and Percent Buried Volumes of Various NHC-Pd^{II} Complexes

entry	complex[a]	Pd−$C_{carbene}$ (Å)	Pd−N (Å)	$\%V_{Bur}$[b]
1	**3a**	1.959(2)	2.085(2)	35.6
2	**3d**	1.955(3)	2.084(3)	35.2
3[c]	(IPr)Pd(3-Cl-pyridine)Cl$_2$	1.969(3)	2.137(2)	34.3
4	(IPr)Pd(Et$_2$NH)Cl$_2$	1.987(2)	2.118(2)	35.3
5	(IPr)Pd(Et$_3$N)Cl$_2$	1.968(4)	2.205(4)	35.0
6	(IPr)Pd(Im)Cl$_2$	1.954(5)	2.088(4)	34.4

[a]IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene. [b]$\%V_{bur}$ calculated for Pd−$C_{carbene}$ = 2.00 Å. [c]Reference 7m.

chlorobenzene (1.0 mmol) and morpholine (1.2 mmol) as the substrates, a number of bases such as KO^{t}Bu, NaO^{t}Bu, LiO^{t}Bu, NaOH, KOH, Na_2CO_3, K_2CO_3, and Cs_2CO_3 were tested in the presence of **3a** (0.5 mol %) in dioxane at 90 °C, and it was found that the reaction can proceed smoothly only when KO^{t}Bu was used (Table 3, entry 1; see also the Supporting Information). Other solvents such as toluene, DME, THF, and DMF were also tested, and dioxane was the best one (Table 3, entries 1−5). The catalytic activity of complexes **3b−f** was also investigated. Complexes **3a,d−f**, in which the carbene carbon chemical shift was more downfield ($\delta(C_{carbene})$ 156.5−157.3 ppm) in comparison to the shifts for their analogues **3b,c** ($\delta(C_{carbene})$ 154.4 and 154.6 ppm; see the Supporting Information for more details), implying a stronger σ-donation effect, were more efficient for the amination reaction (Table 3, entries 6−10), consistent with our previous investigations.[12] In addition to the NHC moiety (NHC = IPr in Table 3, entries 1 and 8−10), the throwaway 4,5-dihydrooxazole ligands also have some effect on the reactions. For instance, better yields can be achieved when complexes **3** with electron-neutral or -rich substituents attached to the phenyl groups of 4,5-dihydrooxazoles were used (Table 3, entries 1, 8, and 9) in comparison to the yield for a complex with an electron-poor group (Table 2, entry 10).

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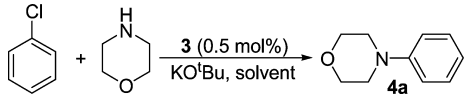
Table 3. Optimization for the NHC-Pd^{II}-Ox (3) Catalyzed Coupling of Chlorobenzene with Morpholine

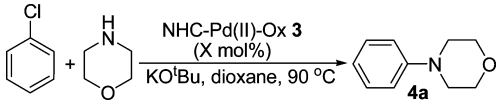


entry[a]	3	solvent	yield (%)[b]
1	**3a**	dioxane	95
2	**3a**	toluene	86
3	**3a**	DME	17
4	**3a**	THF	46
5	**3a**	DMF	31
6	**3b**	dioxane	10
7	**3c**	dioxane	5
8	**3d**	dioxane	95
9	**3e**	dioxane	93
10	**3f**	dioxane	74

[a]All reactions were carried out using chlorobenzene (1.0 mmol), morpholine (1.2 mmol), base (1.3 mmol), **3** (0.5 mol %), and solvent (1.5 mL) at 90 °C for 1 h. [b]Isolated yields.

The comparison of the catalytic activities of complexes **3a,d,e** was further carried out with different catalyst loadings (0.5, 0.1, 0.05, and 0.025 mol %) in dioxane at 90 °C. The results are shown in Table 4. As can be seen from Table 4, similarly high

Table 4. Evaluation of NHC-Pd^{II}-Ox Complexes 3a,d,e with Different Catalyst Loadings



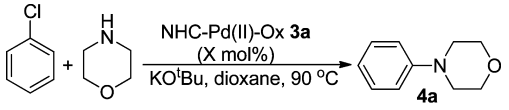
entry[a]	3	[X]	time (h)	yield (g, %)[b]
1	**3a**	0.5	1	0.1547, 95
2	**3a**	0.1	12	0.8144, 99
3	**3a**	0.05	12	1.4592, 90
4	**3a**	0.05	24	1.6000, 98
5	**3a**	0.025	12	0.5909, 18
6	**3a**	0.025	24	0.6686, 21
7	**3d**	0.5	1	0.1546, 95
8	**3d**	0.1	12	0.8100, 99
9	**3d**	0.05	12	1.4314, 88
10	**3d**	0.05	24	1.6140 , 99
11	**3d**	0.025	12	0.3770, 12
12	**3d**	0.025	24	0.6182, 19
13	**3e**	0.5	1	0.1520, 93
14	**3e**	0.1	12	0.8118, 99
15	**3e**	0.05	12	1.2370, 77
16	**3e**	0.05	24	1.3546, 83
17	**3e**	0.025	12	0.2940, 9
18	**3e**	0.025	24	0.3139, 10

[a]All reactions were carried out using chlorobenzene (1.0 equiv), morpholine (1.2 equiv), base (1.3 equiv), and **3** (3.6 mg, 0.005 mmol) at 90 °C. [b]Isolated yields.

yields can be achieved within 1 h when the catalyst loading of complexes **3a,d,e** was 0.5 mol % (Table 4, entries 1, 7, and 13). However, when the catalyst loading was lowered to 0.1 mol %, a longer time (12 h) was necessary to achieve similarly high yields for the three complexes (Table 4, entries 2, 8, and 14). When the catalyst loading was further lowered to 0.05 mol %, similarly higher yields can still be achieved using complexes **3a,d** within 12 or 24 h (Table 4, entries 3, 4 and 9, 10), while inferior results were observed for complex **3e** (Table 4, entries 15 and 16). In the presence of 0.025 mol % of the catalysts, all three complexes showed much lower catalytic activity even when the reactions were performed for 24 h (Table 4, entries 5, 6, 11, 12, 17, and 18). Furthermore, when the temperature was lowered from 90 to 80 °C in the presence of complex **3a** (0.5 mol %), the corresponding amination product **4a** was obtained in a slightly lower yield within 1 h (90%). From the above results, we may draw the conclusion that the NHC-Pd^{II}-Ox complexes **3** are very efficient in the amination of aryl chlorides even with 0.05 mol % catalyst loading, although at longer times.

In addition, the medium-scale reactions between chlorobenzene (100 mmol) and morpholine (120 mmol) were also carried out in the presence of complex **3a** under identical conditions (Scheme 1). **4a** can be obtained in almost

Scheme 1. Medium-Scale Reactions between Chlorobenzene and Morpholine in the Presence of Complex 3a



[X]	time (h)	yields
0.5	3	99%
0.05	12	84%

quantitative yield in the presence of 0.5 mol % of complex **3a** within 3 h, and a good yield can also be achieved in the presence of 0.05 mol % of complex **3a** within 12 h, implying the high catalytic activity of complex **3a** toward medium-scale reactions even at very low catalyst loading (Scheme 1).[13]

Under the optimal conditions, a series of aryl chlorides and morpholine were first used as the substrates to test the generality of the reactions. As can been seen from Table 5, all reactions proceed smoothly to give the corresponding aminated products in good to high yields. The relative positions of substituents in the aryl chlorides have hardly any influence on the coupling reactions. For example, almost identical results were observed when *o*-, *m*-, and *p*-chlorotoluene were used (**4b−d**). Only a 65% yield of **4e** was obtained for the reaction involving *o*-chloroanisole, probably due to the coordination of the *o*-oxygen atom to the metal center, while higher yields of products **4f** (98%) and **4g** (92%) could be obtained when *m*- and *p*-chloroanisoles were used. Heterocyclic chloroarenes were also good substrates to give **4m,n** in high yields. A sterically hindered substrate such as 2,6-dimethylchlorobenzene was also suitable, and **4i** was obtained in 79% yield. In addition, dimethylamino (*p* and *m*) and vinyl (*p*) substituted aryl chlorides were also tolerated to give the corresponding aminated products **4j−l** in high yields.

Encouraged by these results, other amines such as piperidine, pyrrolidine, *N*-methylbenzylamine, *N*-methylaniline, and piperazine with various aryl chlorides were also tested. For the reactions of piperidine with aryl chlorides, good to high yields of products **5a−h** were achieved. On extension of the scope to pyrrolidine, **6a,b** were formed only in moderate yields. *N*-Methylbenzylamine and *N*-methylaniline were also involved, giving products **7a−d** and **8a−f** in good to high yields. The protocol was further extended to piperazine, and the diaminated product **9** was obtained in 98% yield.

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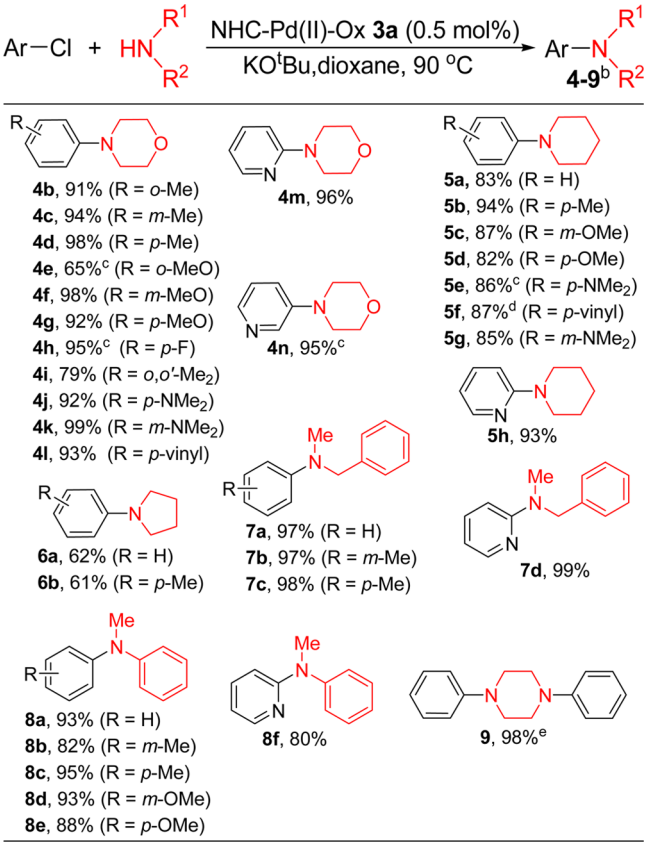
Table 5. NHC-Pd^{II}-Ox Complex 3a Catalyzed Coupling of Aryl Chlorides with Secondary Amines[a]



[a]Unless otherwise specified, all reactions were carried out using aryl chlorides (1.0 mmol), secondary amines (1.2 mmol), KO^{t}Bu (1.3 mmol), **3a** (0.5 mol %), and dioxane (1.5 mL) at 90 °C for 1 h. [b]Isolated yields. [c]The reaction time was 3 h. [d]The reaction time was 6 h. [e]Chlorobenzene (2.0 mmol) and KO^{t}Bu (2.6 mmol) were used.

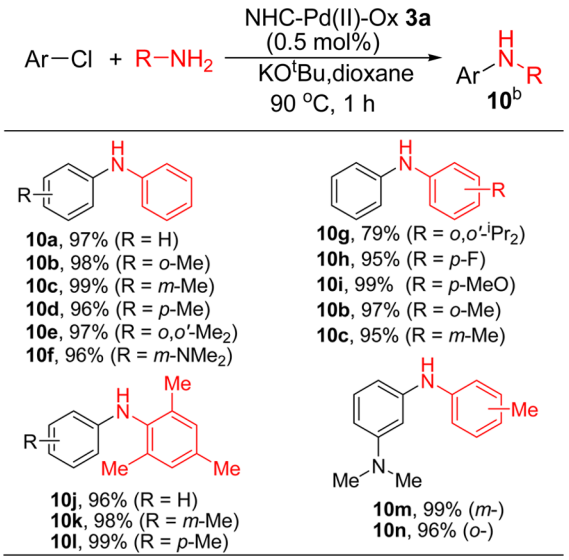
Primary amines, which are less reactive substrates in the previously reported NHC-Pd systems, were also tested under the same reaction conditions. To our delight, all reactions took place smoothly to give the monoaminated products **10** in good to high yields (Table 6). A sterically hindered chloroarene such as 2,6-dimethylchlorobenzene gave the corresponding aminated product **10e** in 97% yield. Sterically hindered amines were also tolerated to give products **10b**,**g**,**j**−**l**,**n** in high yields.

Finally, it was found that alkyl amines were also suitable in the NHC-Pd^{II}-Ox complex **3a** catalyzed aminations under the optimal reaction conditions. For example, when cyclohexylamine was used, **11a**,**b** were formed in 87% and 83% yields, respectively (Scheme 2). When acyclic amines such as benzylamine and *n*-octylamine were used as substrates, the *mono*-aminated products **12a** and **13a** along with the *bis*-aminated products **12b** and **13b** were observed, with the monoaminated products being the major species in both cases (Scheme 2).

CONCLUSIONS

In conclusion, we have reported the preparation and characterization of novel types of NHC-Pd^{II}-Ox complexes **3** and found that the complexes showed high catalytic activity in the amination of aryl chlorides. In addition to secondary amines, a series of primary amines were also coupled successfully with aryl chlorides under the same catalytic system. Reactions on a 100 mmol scale also performed very well even in the presence of 0.05 mol % of catalyst. The protocol represents a general, practical, and scalable approach to various functionalized amines.

Table 6. NHC-Pd^{II}-Ox Complex 3a Catalyzed Coupling of Aryl Chlorides with Primary Amines[a]



[a]All reactions were carried out using aryl chlorides (1.0 mmol), primary amines (1.2 mmol), KO^{t}Bu (1.3 mmol), **3a** (0.5 mol %), and dioxane (1.5 mL) at 90 °C for 1 h. [b]Isolated yields.

EXPERIMENTAL SECTION

General Remarks. NMR spectra were recorded at 300/500 MHz (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 given in Hz. The organic solvents used were dried by standard methods. The mass analyzer type for the high-resolution mass spectra (HRMS) is quadrupole (for ESI). Other commercially obtained reagents were used without further purification. Flash column chromatography was performed on silica gel (300−400 mesh).

General Procedure for the Synthesis of NHC-Pd^{II}-Ox Complexes 3. Under an N_2 atmosphere, a mixture of imidazolium salts **1** (1.1 mmol), $PdCl_2$ (1.0 mmol), K_2CO_3 (1.1 mmol), and 4,5-dihydrooxazoles **2** (2.0 mmol) was stirred in anhydrous THF (5.0 mL) under reflux for 18 h. Then the solvent was removed under reduced pressure, and the residue was purified by flash chromatography on silica gel (CH_2Cl_2) to give the pure NHC-Pd^{II}-Ox complexes **3** as yellow solids.

General Procedure for the NHC-Pd^{II}-Ox Complex 3a Catalyzed Amination of Aryl Chlorides. Under an N_2 atmosphere, NHC-Pd^{II}-Ox complex **3a** (0.5 mol %), KO^{t}Bu (1.3 equiv), dioxane (1.5 mL), amines (1.2 mmol), and aryl chlorides (1.0 mmol) were successively added into a Schlenk reaction tube. The mixture was stirred vigorously at 90 °C for 1 h. Then the solvent was removed under reduced pressure and the residue was purified by flash column chromatography (SiO_2) to give the pure products.

The products **4a**,[14] **4b**,[7r] **4c**,[15] **4d**,[14] **4e**,[16] **4f**,[7r] **4g**,[15] **4h**,[7q] **4i**,[17] **4j**,[18] **4k**,[19] **4l**,[20] **4m**,[7r] **4n**,[7r] **5a**,[7r] **5b**,[7r] **5c**,[7r] **5d**,[7r] **5e**,[21] **5f**,[22] **5h**,[7r] **6a**,[7r] **6b**,[23] **7a**,[7r] **7b**,[7r] **7c**,[7r] **7d**,[7r] **8a**,[7r] **8b**,[24] **8c**,[7g] **8d**,[7r] **8e**,[7r] **8f**,[7r] **9**,[7u] **10a**,[25] **10b**,[7j] **10c**,[7j] **10d**,[25] **10e**,[25] **10f**,[26] **10g**,[7j] **10h**,[27] **10i**,[7j] **10j**,[7j] **10k**,[7h] **10l**,[7h] **11a**,[7j] **11b**,[28] **12a**,[7j] **12b**,[29] **13a**,[30] and **13b**[7j] are known compounds and were fully determined according to the authentic samples.

Compound **3a**: yellow solid (511.9 mg, 0.72 mmol). ^{1}H NMR (500 MHz, TMS, $CDCl_3$): δ 8.32 (d, J = 7.5 Hz, 2H, H_{Ar}), 7.59−7.58 (m, 2H, H_{Ar}), 7.43−7.37 (m, 5H, H_{Ar}), 7.12−7.09 (m, 4H, H_{Ar}+2NC*H*=),

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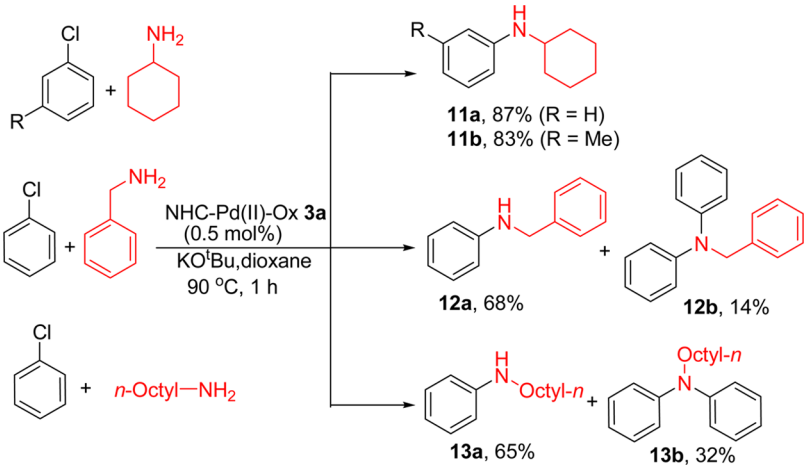
Scheme 2. NHC-Pd^{II}-Ox Complex 3a Catalyzed Amination of Aryl Chlorides with Alkyl Amines



4.30 (t, J = 10.0 Hz, 2H, OCH_2), 3.94 (t, J = 10.0 Hz, 2H, NCH_2), 3.16−3.11 (m, 4H, 4CHMe$_2$), 1.38 (br, 12H, 2CHMe_2), 1.09 (d, J = 7.0 Hz, 12H, 2CHMe_2). ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.8 (NCO), 156.9 ($C_{carbene}$), 147.1 (NC=), 135.2 (C_{Ar}), 131.8 (C_{Ar}), 130.1 (C_{Ar}), 129.7 (C_{Ar}), 128.0 (C_{Ar}), 125.0 (C_{Ar}), 124.9 (C_{Ar}), 123.9 (C_{Ar}), 67.4 (OCH_2), 54.1 (NCH_2), 28.7 (CHMe$_2$), 26.4 (CH_3), 22.9 (CH_3). HRMS (ESI): calcd for $C_{36}H_{45}Cl_2N_3NaOPd$ [M + Na]$^+$, 734.1874; found, 734.1837. Anal. Calcd for $C_{36}H_{45}Cl_2N_3OPd\cdot{}^1/_2CH_3CO_2Et$: C, 60.28; H, 6.52; N, 5.55. Found: C, 60.16; H, 6.32; N, 5.81. IR (neat): ν 2961, 2359, 1643, 1461, 1414, 1381, 1252, 1109, 944, 932, 801, 756, 725 cm^{-1}.

Compound **3b**: yellow solid (515.2 mg, 0.86 mmol). ^{1}H NMR (300 MHz, TMS, $CDCl_3$): δ 8.36 (d, J = 7.8 Hz, 2H, H_{Ar}), 7.46−7.40 (m, 3H, H_{Ar}), 7.31 (d, J = 7.2 Hz, 4H, H_{Ar}), 7.22 (t, J = 7.2 Hz, 2H, H_{Ar}), 7.11 (s, 2H, 2NCH=), 4.32 (t, J = 9.6 Hz, 2H, OCH_2), 3.91 (t, J = 9.6 Hz, 2H, NCH_2), 2.40 (s, 12H, 4CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.8 (NCO), 154.6 ($C_{carbene}$), 137.6 (NC=), 137.0 (C_{Ar}), 132.1 (C_{Ar}), 129.7 (C_{Ar}), 129.4 (C_{Ar}), 128.4 (C_{Ar}), 127.9 (C_{Ar}), 124.9 (C_{Ar}), 123.8 (C_{Ar}), 67.4 (OCH_2), 54.0 (NCH_2), 19.2 (CH_3). HRMS (ESI): calcd for $C_{28}H_{29}Cl_2N_3NaOPd$ [M + Na]$^+$, 622.0619; found, 622.0644. Anal. Calcd. for $C_{28}H_{29}Cl_2N_3OPd\cdot{}^1/_2CH_3CO_2Et$: C, 55.87; H, 5.16; N, 6.52. Found: C, 56.05; H, 5.24; N, 6.43. IR (neat): ν 2357, 1655, 1638, 1472, 1410, 1371, 1259, 1216, 1106, 1022, 945, 928, 785, 706 cm^{-1}.

Compound **3c**: yellow solid (526.7 mg, 0.84 mmol). ^{1}H NMR (300 MHz, TMS, $CDCl_3$): δ 8.39 (d, J = 7.2 Hz, 2H, H_{Ar}), 7.48−7.43 (m, 1H, H_{Ar}), 7.27−7.20 (m, 2H, H_{Ar}), 7.12−7.07 (m, 6H, H_{Ar} + 2NCH=), 4.33 (t, J = 9.6 Hz, 2H, OCH_2), 3.95 (t, J = 9.6 Hz, 2H, NCH_2), 2.45 (s, 6H, 2CH_3), 2.36 (s, 12H, 4CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.8 (NCO), 154.4 ($C_{carbene}$), 139.0 (NC=), 136.6 (C_{Ar}), 135.2 (C_{Ar}), 132.0 (C_{Ar}), 129.8 (C_{Ar}), 129.1 (C_{Ar}), 127.8 (C_{Ar}), 125.0 (C_{Ar}), 123.9 (C_{Ar}), 67.4 (OCH_2), 54.0 (NCH_2), 21.2 (CH_3), 19.1 (CH_3). HRMS (ESI): calcd. for $C_{30}H_{33}Cl_2N_3NaOPd$ [M + Na]$^+$: 650.0933; found: 650.0899. Anal. Calcd for $C_{28}H_{29}Cl_2N_3OPd\cdot CH_3CO_2Et$: C, 56.95; H, 5.76; N, 5.86. Found: C, 56.84; H, 5.74; N, 5.87. IR (neat): ν 2319, 1643, 1483, 1411, 1375, 1331, 1262, 1229, 1106, 1030, 945, 929, 857, 776, 710 cm^{-1}.

Compound **3d**: yellow solid (488.4 mg, 0.67 mmol). ^{1}H NMR (500 MHz, TMS, $CDCl_3$): δ 8.19 (d, J = 8.0 Hz, 2H, H_{Ar}), 7.59 (br, 2H, H_{Ar}), 7.42 (d, J = 7.0 Hz, 4H, H_{Ar}), 7.11 (s, 2H, 2NCH=), 6.89 (d, J = 8.0 Hz, 2H, H_{Ar}), 4.27 (t, J = 10.0 Hz, 2H, OCH_2), 3.90 (t, J = 10.0 Hz, 2H, NCH_2), 3.14−3.12 (m, 4H, 4CHMe$_2$), 2.35 (s, 3H, CH_3), 1.38 (s, 12H, br, 4CH_3), 1.09 (d, J = 6.5 Hz, 12H, 4CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.9 (NCO), 157.1 ($C_{carbene}$), 147.1 (NC=), 142.1 (C_{Ar}), 135.2 (C_{Ar}), 130.1 (C_{Ar}), 129.7 (C_{Ar}), 128.7 (C_{Ar}), 124.9 (C_{Ar}), 123.9 (C_{Ar}), 122.3 (C_{Ar}), 67.3 (OCH_2), 54.0 (NCH_2), 28.7 (CHMe$_2$), 26.4 (CH_3), 22.9 (CH_3), 21.6 (CH_3). HRMS (ESI): calcd for $C_{37}H_{47}Cl_2N_3NaOPd$ [M + Na]$^+$, 748.2031; found, 748.1983. Anal. Calcd for $C_{37}H_{47}Cl_2N_3OPd$: C, 61.12; H, 6.52; N, 5.78. Found: C, 60.93; H, 6.53; N, 5.68. IR (neat): ν 1643, 1464, 1408, 1371, 1331, 1256, 1099, 944, 914, 887, 799, 773, 751, 735, 723 cm^{-1}.

Compound **3e**: yellow solid (518.0 mg, 0.70 mmol). ^{1}H NMR (300 MHz, TMS, $CDCl_3$): δ 8.34 (d, J = 8.7 Hz, 2H, H_{Ar}), 7.59 (br, 2H, H_{Ar}), 7.44−7.41 (m, 4H, H_{Ar}), 7.12 (s, 2H, 2NCH=), 6.59 (d, J = 8.7 Hz, 2H, H_{Ar}), 4.26 (t, J = 9.6 Hz, 2H, OCH_2), 3.89 (t, J = 9.6 Hz, 2H, NCH_2), 3.84 (s, 3H, OCH_3), 3.15 (br, 4H, 4CHMe$_2$), 1.40 (br, 12H, 4CH_3), 1.09 (d, J = 6.6 Hz, 12H, 4CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.3 (NCO), 162.3 (C_{Ar}), 157.3 ($C_{carbene}$), 147.1 (NC=), 135.2 (C_{Ar}), 131.7 (C_{Ar}), 130.0 (C_{Ar}), 124.9 (C_{Ar}), 123.9 (C_{Ar}), 117.4 (C_{Ar}), 113.3 (C_{Ar}), 67.2 (OCH_2), 55.3 (OCH_3), 53.9 (NCH_2), 28.7 (CHMe$_2$), 26.4 (CH_3), 22.9 (CH_3). HRMS (ESI): calcd for $C_{37}H_{47}Cl_2N_3NaO_2Pd$ [M + Na]$^+$, 764.1980; found, 764.1971. Anal. Calcd for $C_{37}H_{47}Cl_2N_3O_2Pd$: C, 59.80; H, 6.37; N, 5.65. Found: C, 59.76; H, 6.40; N, 5.60. IR (neat): ν 1633, 1600, 1514, 1464, 1411, 1351, 1252, 1176, 1099, 929, 799, 770, 756, 731, 708 cm^{-1}.

Compound **3f**: yellow solid (497.0 mg, 0.68 mmol). ^{1}H NMR (300 MHz, TMS, $CDCl_3$): δ 8.36 (dd, J = 9.0, 5.4 Hz, 2H, H_{Ar}), 7.61 (t, J = 7.8 Hz, 2H, H_{Ar}), 7.42 (d, J = 7.8 Hz, 4H, H_{Ar}), 7.12 (s, 2H, 2NCH=), 6.77 (t, J = 8.7 Hz, 2H, H_{Ar}), 4.30 (t, J = 9.9 Hz, 2H, OCH_2), 3.92 (t, J = 9.9 Hz, 2H, NCH_2), 3.16−3.07 (m, 4H, 4CHMe$_2$), 1.38 (d, J = 6.3 Hz, 12H, 4CH_3), 1.09 (d, J = 6.9 Hz, 12H, 4CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 164.83 (NCO), 164.77 (d, J_{C-F} = 251.5 Hz, C_{Ar}), 156.6 ($C_{carbene}$), 147.1 (NC=), 135.1 (C_{Ar}), 132.2 (d, J_{C-F} = 9.1 Hz, C_{Ar}), 130.2 (C_{Ar}), 125.0 (C_{Ar}), 124.0 (C_{Ar}), 121.3 (d, J_{C-F} = 3.0 Hz, C_{Ar}), 115.2 (d, J_{C-F} = 21.9 Hz, C_{Ar}), 67.6 (OCH_2), 54.1 (NCH_2), 28.7 (CHMe$_2$), 26.4 (CH_3), 22.9 (CH_3). HRMS (ESI): calcd for $C_{36}H_{44}Cl_2FN_3NaOPd$ [M + Na]$^+$, 752.1780; found, 752.1713. Anal. Calcd for $C_{36}H_{44}Cl_2FN_3OPd$: C, 59.14; H, 6.07; N, 5.75. Found: C, 59.13; H, 6.08; N, 5.74. IR (neat): ν 2961, 2855, 1517, 1451, 1381, 1356, 1282, 1239, 1103, 1086, 949, 833, 798, 767, 751, 740, 730, 705 cm^{-1}.

Compound **5g**: pale yellow liquid (173.6 mg, 0.85 mmol). ^{1}H NMR (500 MHz, TMS, $CDCl_3$): δ 7.10 (t, J = 8.0 Hz, 1H, H_{Ar}), 6.35 (dd, J = 8.0, 2.0 Hz, 1H, H_{Ar}), 6.31 (s, 1H, H_{Ar}), 6.27 (dd, J = 8.0, 2.0 Hz, 1H, H_{Ar}), 3.12 (t, J = 5.5 Hz, 4H, CH_2NCH_2), 2.90 (s, 6H, 2NCH_3), 1.72−1.67 (m, 4H, $CH_2CH_2NCH_2CH_2$), 1.57−1.53 (m, 2H, $NCH_2CH_2CH_2$). ^{13}C NMR (125 MHz, $CDCl_3$): δ 153.5 (C_{Ar}), 151.6 (C_{Ar}), 129.3 (C_{Ar}), 106.0 (C_{Ar}), 104.9 (C_{Ar}), 101.9 (C_{Ar}), 51.2 (NCH_2), 40.8 (NCH_3), 26.0 (NCH_2CH_2), 24.4 ($NCH_2CH_2CH_2$). IR (neat): ν 2935, 2849, 2789, 1607, 1504, 1448, 1355, 1232, 1123, 992, 924, 819, 756, 688 cm^{-1}. MS (ESI): 205 [M + H]$^+$. HRMS (ESI): calcd for $C_{13}H_{21}N_2$ [M + H]$^+$, 205.1699; found, 205.1690.

Compound **10m**: thick yellow liquid (222.9 mg, 0.99 mmol). ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.11 (t, J = 8.0 Hz, 2H, H_{Ar}), 6.87 (d, J = 6.5 Hz, 2H, H_{Ar}), 6.70 (d, J = 8.0 Hz, 1H, H_{Ar}), 6.45 (dd, J = 8.0, 1.5 Hz, 1H, H_{Ar}), 6.42 (t, J = 2.0 Hz, 1H, H_{Ar}), 6.33 (dd, J = 8.0, 2.0 Hz, 1H, H_{Ar}), 5.59 (s, 1H, NH), 2.88 (s, 6H, 2NCH_3), 2.27 (CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 151.6 (C_{Ar}), 143.9 (C_{Ar}), 143.5 (C_{Ar}),

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138.9 (C_{Ar}), 129.7 (C_{Ar}), 129.0 (C_{Ar}), 121.3 (C_{Ar}), 118.3 (C_{Ar}), 114.7 (C_{Ar}), 106.9 (C_{Ar}), 105.9 (C_{Ar}), 102.5 (C_{Ar}), 40.5 (NCH_3), 21.4 (CH_3). IR (neat): ν 3378, 3034, 2915, 2789, 1613, 1520, 1298, 1239, 1169, 998, 833, 755, 687 cm^{-1}. MS (ESI): 227 $[M + H]^+$. HRMS (ESI): calcd for $C_{15}H_{19}N_2$ $[M + H]$, 227.1543; found, 227.1547.

Compound **10n**: thick yellow liquid (215.9 mg, 0.96 mmol). ^1H NMR (500 MHz, $CDCl_3$, TMS): δ 7.28 (d, J = 8.0 Hz, 1H, H_{Ar}), 7.18 (d, J = 7.0 Hz, 1H, H_{Ar}), 7.12 (t, J = 8.0 Hz, 2H, H_{Ar}), 6.89 (td, J = 7.0, 1.0 Hz, 1H, H_{Ar}), 6.38−6.35 (m, 3H, H_{Ar}), 5.34 (s, 1H, N*H*), 2.91 (s, 6H, 2NCH_3), 2.26 (CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 151.7 (C_{Ar}), 144.6 (C_{Ar}), 141.7 (C_{Ar}), 130.8 (C_{Ar}), 129.8 (C_{Ar}), 127.7 (C_{Ar}), 126.6 (C_{Ar}), 121.3 (C_{Ar}), 118.4 (C_{Ar}), 106.7 (C_{Ar}), 105.7 (C_{Ar}), 102.2 (C_{Ar}), 40.6 (NCH_3), 17.9 (CH_3). IR (neat): ν 3385, 3027, 2888, 2796, 1905, 1610, 1511, 1255, 1159, 1053, 997, 824, 751, 687 cm^{-1}. MS (ESI): 227 $[M + H]^+$. HRMS (ESI): calcd for $C_{15}H_{19}N_2$ $[M + H]^+$, 227.1543; found, 227.1544.

■ ASSOCIATED CONTENT

Supporting Information

Text, tables, figures, and CIF files giving optimization for the coupling of chlorobenzene with morpholine, the procedure for the 10 g reactions, calculations for $\%V_{Bur}$, spectral data for all compounds, and X-ray data of compounds **3a** (CCDC-882551) and **3d** (CCDC-978383). 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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