Ligand Effects of 2-(2-Pyridyl)benzazole−Pd Complexes on the X-ray Crystallographic Structures, ^{1}H NMR Spectra, and Catalytic Activities in Mizoroki−Heck Reactions

Satoshi Haneda, Zhibin Gan, Kazuo Eda, and Masahiko Hayashi*

Department of Chemistry, Graduate School of Science, Kobe University, Nada, Kobe, 657-8501, Japan

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A series of $PdCl_2$ complexes were synthesized using four 2-(2-pyridyl)benzazoles, namely 2-(2-pyridyl)benzimidazole (**1a**), 2-(2-pyridyl)benzoxazole (**2a**), 2-(2-pyridyl)benzothiazole (**3a**), and 2-(2-pyridyl)-*N*-methylbenzimidazole (**4a**). Their structures were analyzed using single X-ray crystallography, whereas the extent of the ligand dissociation were determined in solution by ^{1}H NMR spectroscopy. Among the catalysts, 2-(2-pyridyl)benzimidazole−$PdCl_2$ (**1b**) complex exhibited the highest catalytic activity toward the Mizoroki−Heck reaction: the diminished catalytic activities of 2-(2-pyridyl)benzoxazole−$PdCl_2$ (**2b**) and 2-(2-pyridyl)benzothiazole−$PdCl_2$ (**3b**) can be attributable to the ease of their ligand dissociation.

Introduction

Among the various benzazole derivatives, 2-(2-pyridyl)benzazoles have gained much attention due to their ability to chelate as ligands in Pt and Pd complexes. As an example, Pt(II)−2-(2-pyridyl)benzimidazole has been investigated in relation to the cytotoxicity of cisplatin. Furthermore, 2-(2-pyridyl)benzimidazole analogues have shown antitumor activity. In 2001, Krebs and co-workers reported on the synthesis of Pt and Pd complexes with ligands such as 2-(2-pyridyl)benzimidazole, 2-(2-pyrazyl)-5,6-dimethylimidazole, 2-(2-pyrazyl)-5,6-dimethylimidazole, bis(pyridine-2-yl)methane, and (2,2′-dipyridyl)propylamine along with their reactivities toward nucleobases and their cytotoxities as anticancer agents.[1] In 2005, Sordo and co-workers also reported on the synthesis and study of the cytotoxicity of 2-(2-pyridyl)benzimidazole complexes of Pd(II) and Pt(II).[2] Furthermore, 2-(2-pyridyl)benzoxazole and 2-(2-pyridyl)benzothiazole have also been shown as useful ligands of Pd complexes.[3] In 2005, Kapturkiewicz and co-workers also reported on the syntheses, along with the electrochemical and spectroscopic properties, of 2-(2-pyridyl)-*N*-methylbenzimidazole, 2-(2-pyridyl)benzoxazole, and 2-(2-pyridyl)benzothiazole complexes of Re(I)tricarbonyl$^+$.[4] To the best of our knowledge, however, structural studies in solution and catalytic studies in coupling reaction such as the Mizoroki−Heck reaction of 2-(2-pyridyl)benzazole complexes of Pd(II) in solution have yet to be reported.

Our laboratories have been investigating Pd complexes and their catalytic properties toward coupling reactions in the formation of carbon−carbon bonds. Recent studies involve Mizoroki−Heck reactions that are composed of two *N*-coordinated ligands. Subsequently, our interests have shifted toward reactions that are catalyzed by Pd complexes of bidentate nitrogen ligands.[7] In the case of 2-(2-pyridyl)benzazoles, the bidentate ligand can be described as electron-donating due to the two nitrogen atoms of the benzazoles and pyridine moieties. Accordingly, substitution of the heteroatom in the benzazoles would presumably affect its electron density and its ability to donate electrons, which in turn should affect its catalytic activity in Mizoroki−Heck reactions.

Since the first report in 1971, Mizoroki−Heck reactions have been widely used for the construction of carbon−carbon bonds.[8] For such reactions, phosphine and related compounds are often used as ligands. Recently, electron-rich and bulky alkylphosphines, such as P(*t*-Bu)$_3$, have been developed as highly effective

* Corresponding author. Tel.: +81-78-803-5687. Fax: +81-78-803-5688. E-mail: mhayashi@kobe-u.ac.jp.

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ligands.[9] In view of the recent advances in the field of palladacycles,[10] *N*-heterocyclic carbenes have also been utilized as ligands.[11] Dai and co-workers have focused on the development of amide-based phosphines as the P,O-ligands for coupling reactions.[12] Čermák and co-workers have reported on diphosphinoazine Pd(II) complexes which feature a novel tridentate ligand for Mizoroki−Heck reactions with high TON and TOF (h^{-1}).[13] Additionally, there have been various attempts to improve the Mizoroki−Heck reaction by activating aryl chloride using Pd compounds such as $(CH_3CN)_2PdCl_2-PPh_4Cl$,[14] $Pd(OAc)_2$ with excess $P(OEt)_3$,[15] and heterogeneous Pd/C[16] as catalysts.[17]

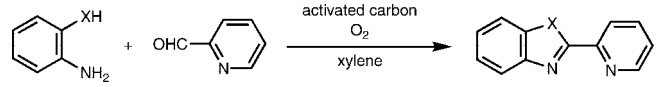
Herein, we report on the structural analyses of a series of 2-(2-pyridyl)benzazole−$PdCl_2$ complexes using X-ray crystallography and in solution (DMSO-d_6) using ^{1}H NMR spectroscopy. Furthermore, their catalytic activities toward the Mizoroki−Heck reaction in the presence of base (K_2CO_3) are also presented.

Results and Discussion

Synthesis of 2-(2-Pyridyl)benzazole Ligands (1a, 2a, and 3a). We followed our recently developed general and efficient synthetic methodology for 2-arylbenzazoles.[18] Applying for this method, three *N,N′*-bidentate ligands, specifically 2-(2-pyridyl)benzimidazole (**1a**), 2-(2-pyridyl)benzoxazole (**2a**), and 2-(2-pyridyl)benzothiazole (**3a**), were prepared by the reaction between 2-pyridylaldehyde and the corresponding amine (2-aminophenol, 1,2-phenylenediamine, and 2-aminobenzenethiol, respectively) in a ratio of 1:1 in the presence of 50 wt % activated carbon relative to substrate. The results are shown in Table 1. In all cases, the desired products were obtained in good yields following recrystallization (82−86%).

In previous methods, the synthesis of 2-(2-pyridyl)benzazoles involves the condensation between pyridine-2-carboxylic acid and 2-aminophenol, 1,2-phenylenediamine, or 2-aminobenzenethiol in the presence of polyphosphoric acid at 180−200 °C.[19] In contrast to such harsh conditions, our method, which involves a simple activated carbon−O_2 system is straightforward and economical. The *N*-methylation from **1a** to **4a** was carried out according to the reported method.[20]

Table 1. Preparation of 2-(2-Pyridyl)benzimidazole, Benzoxazole, and Benzothiazole[a]



entry	X	time/h	yield[b]
1	NH	5	82
2	O	4	86
3	S	24	82

[a] All reactions were carried out in xylene at 120 °C. [b] Isolated yield after recrystallization.

X-ray Crystallography. Pd complexes **1b**, **2b**, and **3b** for X-ray crystallography analysis were prepared as follows: Upon heating a mixture of **1a**, **2a**, or **3a** and $PdCl_2$ at 50 °C for 3 h in DMF, the resulting solids were collected by filtration and then dissolved in DMSO at 60−70 °C to afford crystalline 2-(2-pyridyl)benzimidazole−$PdCl_2$ (**1b**, prisms), 2-(2-pyridyl)-benzoxazole−$PdCl_2$ (**2b**, needles), and 2-(2-pyridyl)benzothiazole−$PdCl_2$ (**3b**, needles), respectively. The results of the X-ray crystallographic analysis of **1b**, **2b**, and **3b** are prepared in Figure 1 (ORTEP views) and Table 2 (data). In general, as shown in Figure 1, all three complexes in the solid state exist as a plain four-coordinated Pd complex. In fact, however, the bond length of Pd−N(1) (nitrogen atom coordinated to Pd in benzazole moiety) of **1b** [2.025(5) Å] is shorter and thus stronger than that of **2b** [2.040(7) Å] or **3b** [2.070(2) Å]. In contrast, the bond lengths of Pd−N(2) (nitrogen atom of pyridine) among the three complexes were comparable [(2.054(6) Å in **1b**, 2.064(7) Å in **2b**, and 2.042(2) Å in **3b**)]. The order of the average of bond lengths [Pd—N(1) + Pd—N(2)]/2, for the three complexes, **1b** (2.040 Å) < **2b** (2.052 Å) < **3b** (2.056 Å) is consistent with the resistance to dissociation of the ligand, as observed in the ^{1}H NMR spectra (discussed in detail below). We considered the valance of the two bonds Pd−N(1) over Pd−N(2) to be critical in stabilizing each complex.

Furthermore, the relative ratio of the bond lengths [Pd−N(1)]/[Pd−N(2)] (**1b**, 0.986: **2b**, 0.988: **3b**, 1.014), which is inversely correlated to the relative strengths, indicates that the contribution of Pd−N(1) relative to Pd−N(2) is greatest for **1b** followed by **2b** and then **3b**.

^{1}H NMR Analysis of Pd Complexes of 1b, 2b, and 3b. Using the same samples that were used for X-ray crystallography, the ^{1}H NMR spectra of ligands **1a**, **2a**, and **3a** and their $PdCl_2$ complexes, **1b**, **2b**, and **3b** were obtained in DMSO-d_6 as shown in Figure 2. The new peaks that were assignable to $PdCl_2$ complexes **1b**, **2b**, and **3b** are indicated in red. Differences between the spectra of ligands **1a**, **2a**, and **3a** (upper three) and those of the corresponding $PdCl_2$ complexes **1b**, **2b**, and **3b** (lower three) are shown as the black peaks in the lower spectra. These peaks indicate the degree of ligand dissociation as 0% (**1b**), 20% (**2b**), and 50% (**3b**). Presumably, the degree of ligand dissociation is related to the bond strengths: longer bond distances in average [**1b** (2.040 Å) < **2b** (2.052 Å) < **3b** (2.056 Å)] correspond to weaker bond

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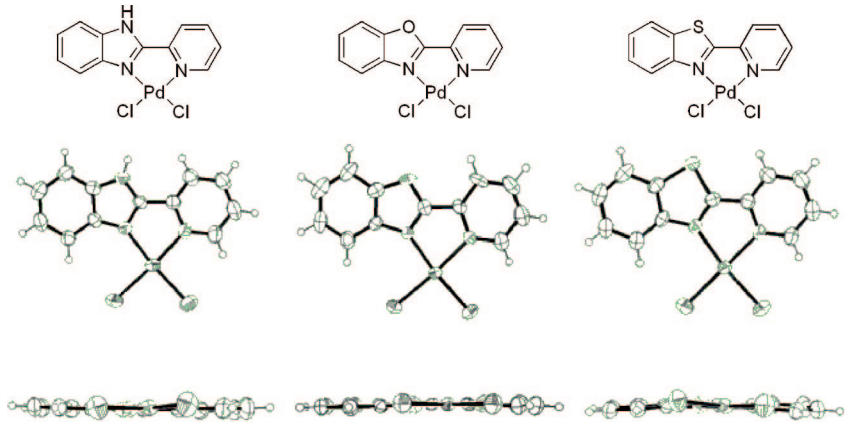


Figure 1. ORTEP drawing of palladium complexes **1b**, **2b**, and **3b** (50% thermal ellipsoids).

Table 2. Crystal Data and Collection Parameters for Complexes 1b, 2b, and 3b

	complex **1b**	complex **2b**	complex **3b**
formula	$C_{12}H_9Cl_2N_3Pd{\bullet}C_2H_6OS$	$C_{12}H_8Cl_2N_2OPd{\bullet}{}^1/_3C_2H_6OS$	$C_{12}H_8Cl_2N_2PdS$
formula weight	450.65	399.55	389.56
T (K)	293(2)	296(2)	298(2)
radiation	Mo Kα (λ = 0.71073 Å)	Mo Kα (λ = 0.71073 Å)	Mo Kα (λ = 0.71073 Å)
crystal system	triclinic	orthorhombic	monoclinic
space group	PÎ	*Pbca*	$P2_1/c$
unit cell dimensions (Å)	a = 8.743(2), α = 103.763(4)°	a = 18.284(2)	a = 11.1776(17)
	b = 9.519(3), β = 109.476(5)°	b = 20.762(3)	b = 15.931(2), β = 105.854(3)°
	c = 11.584(3), γ = 101.362(4)°	c = 21.564(3)	c = 7.3544(11)
V (Å^3)	841.7(4)	8186.3(19)	1259.8(3)
Z	2	24	4
D (calcd) (Mg/m^3)	1.778	1.945	2.054
F000	448	4704	760
μ (Mo Kα) (mm^{-1})	1.547	1.796	2.042
crystal size (mm^3)	0.38 × 0.15 × 0.15	0.33 × 0.10 × 0.05	0.25 × 0.08 × 0.06
θ range (deg)	1.97–27.05	1.76–27.34	1.89–27.35
index ranges	$-6\le h\le 11$, $-12\le k\le 12$, $-14\le l\le 8$	$-23\le h\le 23$, $-15\le k\le 26$, $-24\le l\le 26$	$-11\le h\le 13$, $-20\le k\le 20$, $-9\le l\le 6$
no. of reflections	total: 3217	total: 41004	total: 6744
measured	unique: 3217	unique: 8446	unique: 2549
	(R_{int} = 0.0267)	(R_{int} = 0.0874)	(R_{int} = 0.0318)
structure solution	direct method	direct method	direct method
refinement	full-matrix least-squares on F^2	full-matrix least-squares on F^2	full-matrix least-squares on F^2
no. of variables	201	525	163
GOF	1.07	1.018	1.075
R_1	0.0642	0.0657	0.0261
wR_2	0.1806	0.1527	0.0708

Table 3. Selected Bond Length of the Complexes 1b, 2b, and 3b[a]

	1b	**2b**	**3b**
Pd−N(1)	2.025(5)	2.040(7)	2.070(2)
Pd−N(2)	2.054(6)	2.064(7)	2.042(2)
average[b]	2.040	2.052	2.056
Pd−N(1)/Pd−N(2)	0.986	0.988	1.014

[a] Distance (Å). [b] [Pd−N(1) + Pd−N(2)]/2.

strength, which in turn correspond to higher degrees of ligand dissociation [**1b** (0%) < **2b** (20%) **3b** (50%)].

Overall, the observed results are consistent with those derived from calculating the electron density of each nitrogen atom (N1 and N2) of **1a**, **2a**, and **3a** (optimized using B3LYP/LANL2DZ level), as listed in Table 4. According to the results given in Table 4, the highest electron density for the N(1) atom was exhibited by **1a** (−0.023 e) (versus 0.012 e for **3a**).

Mizoroki−Heck Reaction Catalyzed by Pd Complexes 1b, 2b, and 3b. Under typical conditions, the Mizoroki−Heck reactions between 4-bromotoluene and *tert*-butyl acrylate were carried out in DMF at 120 °C with K_2CO_3 as a base. The use of isolated and characterized $PdCl_2$ complexes, **1b**, **2b**, and **3b** as catalysts (1 mol %) resulted in yields of 97%, 83%, and 75%, respectively (Table 5).

Considering the low catalytic activity of only $PdCl_2$ in Mizoroki−Heck reactions, ligand dissociation would presumably result in similar low yields for our Mizoroki−Heck reactions. Conventional conditions for the Mizoroki−Heck reaction involve bases such as K_2CO_3 and Cs_2CO_3; in our case, the presence of a base (K_2CO_3) caused a shift in the ^{1}H NMR spectra of those that contain an NH moiety (ligand **1a** and Pd complex **1b**). Accordingly, for the reaction catalyzed by **1b**, the orange color of the reaction mixture remained unchanged during the course of the reaction, whereas for the reaction catalyzed by **3b**, precipitation of Pd black (due to the dissociation of benzothiazole ligand) was observed.

Effect of Base (K_2CO_3). The influence of a base (K_2CO_3) was determined using the ^{1}H NMR spectra of Pd complexes **1b**, **2b**, **3b**, and 2-(2-pyridyl)-*N*-methylbenzimidazole−$PdCl_2$ (**4b**), which does not possess an NH proton. In the case of **2a** and **3a**, which lack a proton that can be deprotonated, differences were not observed between their spectra before and after the addition of K_2CO_3. As mentioned above, partial ligand dissociation was observed for complexes **2b** and **3b**: upon addition of K_2CO_3, however, complete dissociation was

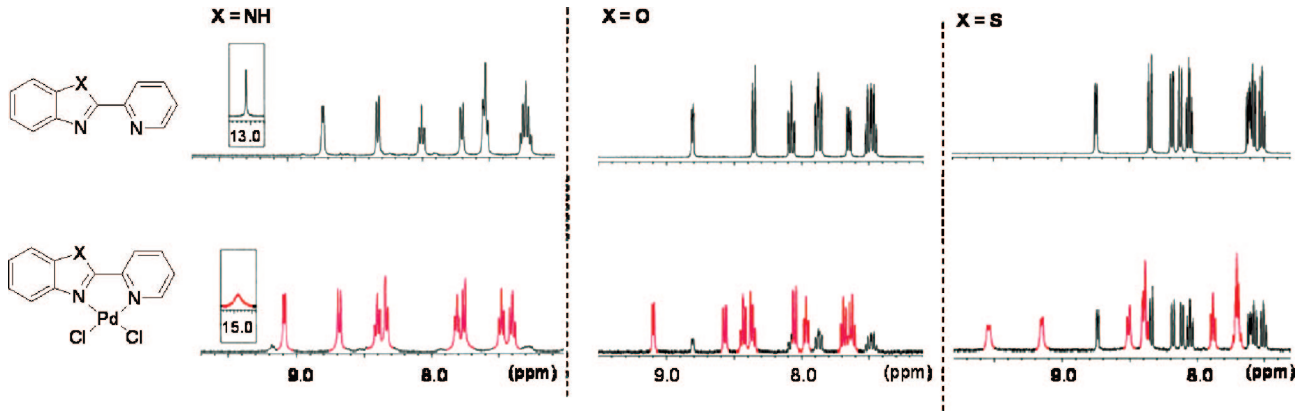
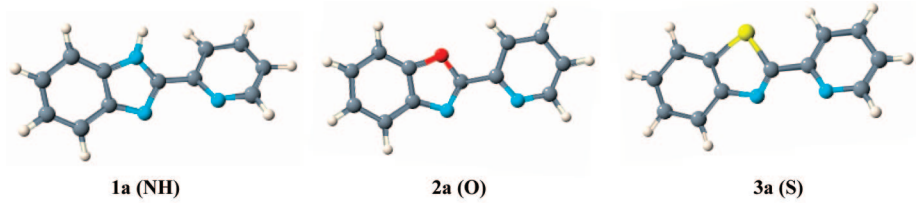


Figure 2. ^{1}H NMR of ligands **1a**, **2a**, and **3a** (upper) and the corresponding $PdCl_2$ complexes **1b**, **2b**, and **3b** (lower).

Table 4. Calculation of Electron Density of 2-(2-Pyridyl)benzazole[a]

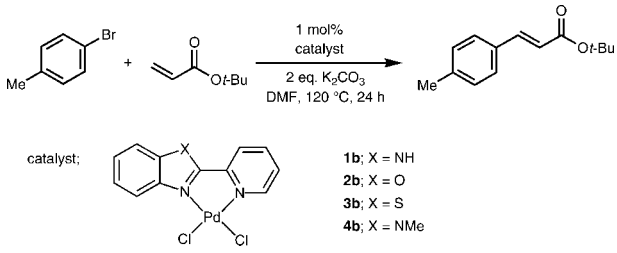


electron density (e)

	1a	2a	3a
N1	−0.023	−0.0010	0.012
N2	0.012	0.001	0.008

[a] Optimized by B3LYP/LANL2DZ.

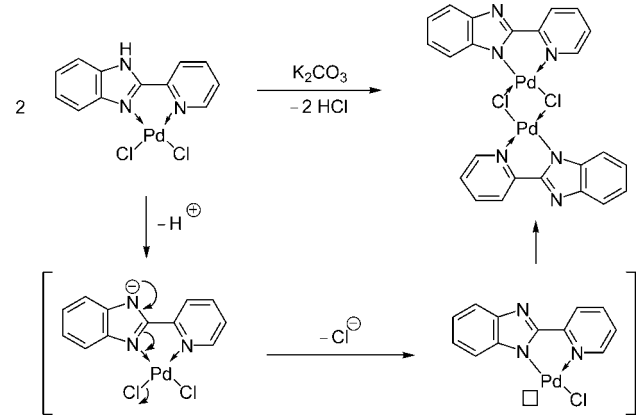
Table 5. Mizoroki−Heck Reaction Catalyzed by Palladium Complexes 1b, 2b, 3b, and 4b



catalyst	yield[a]
1b	97
2b	83
3b	75
4b	61

[a] Isolated yield.

Scheme 1. Proposed Catalytic Species of Pd Complex in Mizoroki−Heck Reaction



observed. In the case of **1a**, treatment with K_2CO_3 gave a new compound after deprotonation, along with formation of a new Pd complex that was different from **1b**. In the case of **4a**, no change was observed after addition of K_2CO_3 to ligand **4a**; in the spectrum of 2-(2-pyridyl)-*N*-methylbenzimidazole−$PdCl_2$ complex (**4b**), no dissociation was observed. In other words, in the case of ligand **4a**, addition of K_2CO_3 has no effect on its spectra. Addition of the base to complex **4b**, however, caused the complex to undergo slight dissociation. It should be mentioned that under similar conditions as described in Table 5, a yield of 61% was obtained for the Mizoroki−Heck reaction catalyzed by **4b** (1 mol %).

Although the actual catalytic species in Mizoroki−Heck reactions remains elusive, the mechanism of the active Pd species **1b** can be proposed as shown Scheme 1. As described above, the presence of an NH group, which can be deprotonated, is critical for catalytic activity. Deprotonation of the NH group may release one of two Cl atoms, which would generate a vacant site on the Pd atom, which, in turn, would cause the formation of a dimeric species. Furthermore, based on the mass spectral data, it is reasonable that an oligomeric Pd species may exist prior to the oxidative addition step.

In summary, four types of 2-(2-pyridyl)benzazole−$PdCl_2$ complexes were synthesized and characterized. Among the four complexes, **1b** was found to be efficient in catalyzing Mizoroki−Heck reactions. Recently, a simple Pd−imidazoline system for the Mizoroki−Heck reaction has been developed.

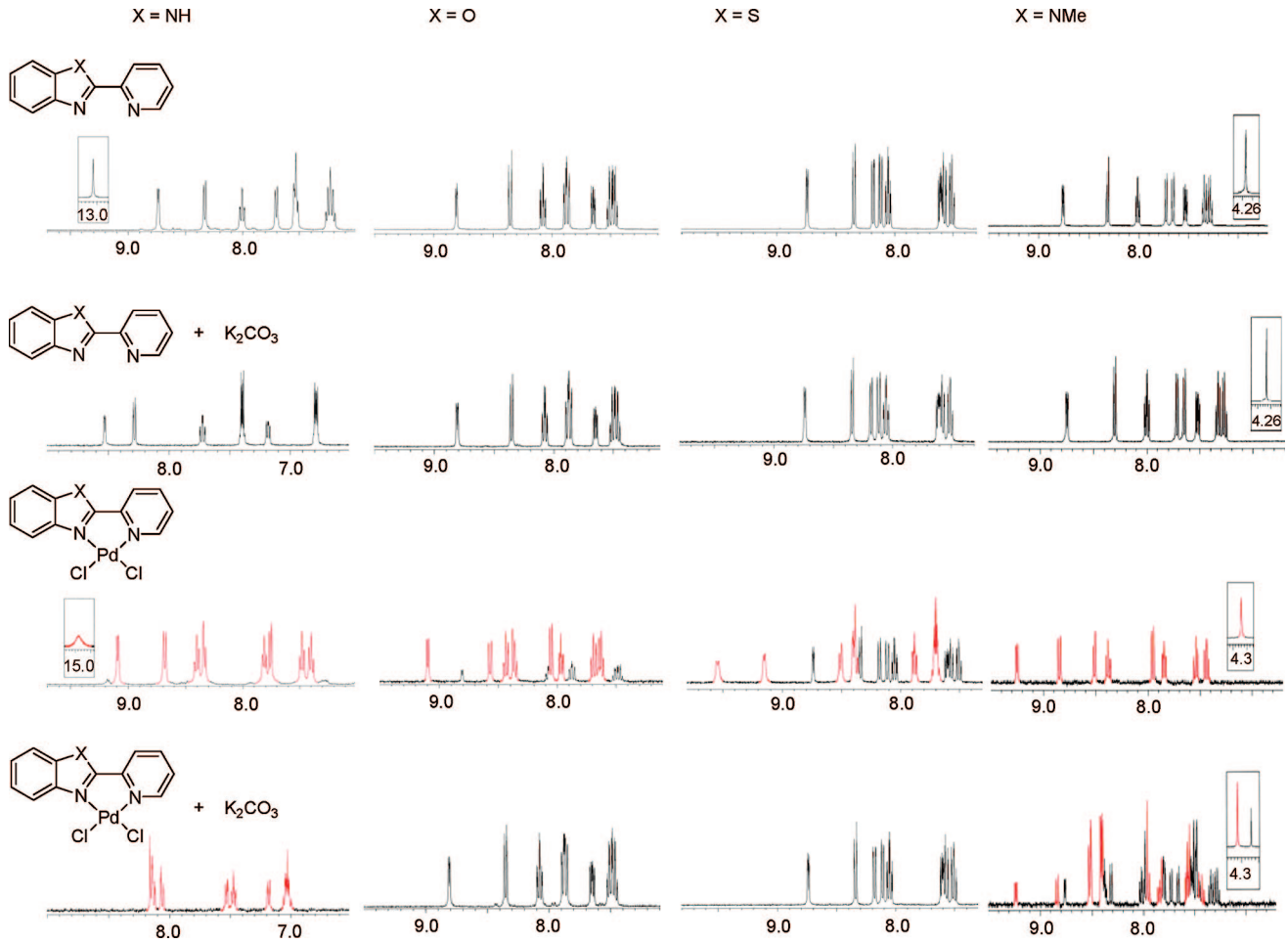


Figure 3. ^{1}H NMR spectra of **1a**, **2a**, **3a**, **4a**, **1b**, **2b**, **3b**, and **4b** (before and after addition of K_2CO_3).

Further investigations of our catalytic system to other coupling reactions are currently in progress.

Experimental Section

General Procedure for Mizoroki−Heck Reaction. A mixture of $PdCl_2$ (3.55 mg, 0.01 mmol), 2-(2-pyridyl)benzazole ligand (0.01 mmol), and K_2CO_3 (2 equiv) in DMF (10.0 mL) was stirred at 50 °C for 1 h, 4-bromotoluene (2 mmol) and olefin (2 mmol) were added, and then the mixture was allowed to stir at 120 °C. After the reaction mixture was allowed to cool to room temperature, the precipitates were removed by filtration, and the products were extracted from the filtrate using diethyl ether. The combined organic layers were dried over anhydrous sodium sulfate, filtered, and evaporated to afford the crude product, which was purified by silica gel column chromatography to give the coupling products.

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Supporting Information Available: Experimental procedure and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) We preliminarily examined the Sonogashira coupling reaction catalyzed by the 2-(2-pyridyl)benzimidazole−$PdCl_2$ complex. That is, when complex **1b** (5 mol%), CuI (12.5 mol %), K_3PO_4 (1.1 equiv) were used, the reaction of 4-iodotoluene and ethynylbenzene proceeded to give the coupling product in 91% yield (in DMF, 110 °C, 4 h).