

Efficient Heck Reactions Catalyzed by Palladium(0) and -(II) Complexes **Bearing N-Heterocyclic Carbene and Amide Functionalities**

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A palladium(0) NHC complex $Pd^{0}(LH^{1})_{2}(MA)$ (MA = maleic anhydride) was prepared from the amide-imidazolium salt $[LH^1H^2]Cl$ ($H^1 = NH$ proton; H^2 NCHN proton). The X-ray diffraction studies confirmed that a η^2 -MA ligand and two monodentate NHC ligands with the H¹ protons remaining intact are coordinated. These NH protons are involved in intra- or intermolecular hydrogen bonds stabilizing the solid-state structure. Degradation of $Pd(LH^1)_2(MA)$ in air leads to the formation of the chelate complex *trans*-Pd^{II}L₂ and other unidentified products. Negative-ion electrospray mass spectrometry revealed some intriguing Pd(0) species, including a 14-electron [Pd⁰L]⁻ species that bears only a bidentate NHC/amido ligand. The anionic amido group imparts a high electron density on a palladium center, as shown by X-ray photoelectron study. The palladium-(0) precatalyst is highly efficient in catalyzing Heck reactions with activated aryl chlorides in ionic liquid. For deactivating aryl chlorides and bulky aryl bromides, *cis*-Pd^{II}L₂ is more effective. A range of Heck-coupled products can be prepared by $Pd^{0}(LH^{1})_{2}(MA)$ and *cis*- $Pd^{II}L_{2}$. The latter complex also successfully mediates one-pot sequential Heck/Heck and Suzuki/Heck coupling reactions with 4-bromochlorobenzene as substrate.

Introduction

The palladium-catalyzed Heck reaction is a powerful tool to prepare arylated alkenes in fine chemical synthesis.¹⁻⁴ There are many catalyst systems that can be used to catalyze the cross-coupling reactions, but typically reactive aryl halides (bromides and iodides) and activated alkenes are required as coupling reactants.¹⁻⁴ Aryl chlorides are more attractive substrates for industrial applications because of their low cost and availability.⁵⁻⁷ However, these substrates, especially deactivated aryl chlorides, are reluctant to undergo catalytic reactions due to their strong C–Cl bonds. 5^{-8} Efforts have been made to meet the challenge, including the search

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for new effective ligands⁹⁻¹⁴ and ligand-free catalyst systems.^{15,16} Trialkylphosphines furnish by far most reactive catalyst systems for the activation of deactivated aryl chlorides and hindered/electronically deactivated coupling partners.¹⁷ However, the preparation of these ligands and their derivatives typically involves substances of poor air-stability and are, in general, expensive. Hence, the development of lowcost phosphine-free catalyst systems for the challenging substrates is more desirable for industrial applications, and such molecular catalyst systems are still relatively few.^{14,18} Lately, N-heterocyclic carbenes (NHCs) are attracting attention because of their versatility in various C–C coupling reactions.^{19–26} Although many reports have already shown

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that palladium complexes with NHC ligands performed well in Heck reactions with a variety of aryl bromides and activated aryl chlorides, their reactivity with deactivated aryl chlorides is somewhat limited.²⁷⁻³⁷ Beller et al. demonstrated that palladium(0) complexes with IMes were effective catalyst systems for the Heck reactions of activated and nonactivated aryl chlorides.¹⁸ However, their uses for deactivated aryl chlorides were not mentioned.

Nickel(II)³⁸ and palladium(II)^{39,40} complexes derived from $[LH^{1}H^{2}]$ Cl have been reported by us (Chart 1). Palladium(II) complexes with similar ligand frameworks have also been published by others.^{41–44} This NHC ligand system, derived from cheap starting materials,³⁹ contains a NH (H¹) proton that upon deprotonation forms an anionic bidentate carbene/ amide ligand, L. Such anionic amide functionality can impart higher electron density on a palladium center and thus can enhance the oxidative addition of a C-Cl bond.¹⁴ On the other hand, defined palladium(0) precatalysts are desirable for more active and productive catalysts compared to the commonly applied in situ generated, undefined catalyst systems.⁴⁵

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Scheme 1. Synthesis of Palladium(0) NHC Complexes



While the applications of palladium(II) NHC precatalysts in various C-C coupling reactions are ubiquitous in the literature, the use of preformed palladium(0) NHC complexes is relatively rare. $^{18,29,46-58}$ On the basis of all these thoughts, we hope to develop new palladium(0) complexes derived from [LH¹H²]Cl for the Heck reactions. Our results illustrate that palladium(0) precatalysts bearing the combination of NHC and amido functionalities indeed deliver highly promising catalytic performances in Heck reactions of activated aryl chlorides with alkenes. However, for challenging substrates of deactivated aryl chlorides and hindered/electronically deactivated coupling partners, palladium(II) precatalysts of L are more efficient. Since deprotonation of H¹ protons leads to anionic Pd(0)L species, negative-ion electrospray mass spectrometry was carried out to give insight into active species derived from the palladium(0) precursors.

Results and Discussion

Preparation of Palladium(0) Carbene Complexes. The new palladium complexes 3a,b were synthesized by treatment of the ligand precursors **1a**,**b** with the known palladium precursor 2^{59} in the presence of K₂CO₃ at ambient temperature (Scheme 1). After thorough washing with methanol, yellow solids of 3a and 3b were obtained with decent yields of 50% and 57%, receptively. These compounds are air-stable in solid forms. However, they are air-sensitive in solution with

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Scheme 2. Proposed Decomposition Pathway of 3a



the need of protection under nitrogen atmosphere. The two new compounds are $Pd(LH^{1})_{2}(MA)$ (MA = maleic anhydride), which are characterized by ${}^{1}H$ and ${}^{13}C{}^{1}H$ NMR spectroscopy, elemental analyses, and X-ray structural studies. $Pd(tmiy)_2(MA)^{29}$ (tmiy = 1,3,4,5-tetramethylimidazol-2-ylidene) and Pd(IMes)(MA)₂ (IMes = 1,3-bis(2,4,6trimethylphenyl)imidazol-2-ylidene) are relevant compounds published in the literature.⁵⁶ A comparison of $Pd(LH^1)_2$ -(MA) with Pd(IMes)(MA)₂ clearly indicates the small steric bulk of the LH¹ ligand such that in the former complex two of the NHC ligands can coordinate to the palladium center. The successful formation of palladium carbene complexes is indicated by the absence of proton signals at ca. 9.4 ppm due to the NCHN protons on their ligand precursors. The ligands on 3a and 3b are coordinated in a monodentate rather than chelating fashion, as the NH protons are still observed at ca. 10.2 ppm. The large coordination-induced shifts (CIS) for the protons of maleic anhydride, $\Delta\delta(H) =$ -3.42 and -3.51 ppm for **3a** and **3b**, respectively, are very similar to those in $Pd(tmiy)_2(MA)$ (tmiy = 1,3,4,5-tetramethylimidazol-2-ylidene)²⁹ and Pd(py)₂(MA),⁶⁰ reflecting a similar electron-rich palladium center in 3a,b. Three downfield ¹³C peaks in the range 165-188 ppm were observed in their respective spectra, corresponding to the carbene and the two different carbonyl carbons. The assignments of these signals were assisted by acquiring the HMBC spectra (see Figure 1S for the HMBC spectrum of 3a in the Supporting Information). In each case, the presence of correlation peaks from the two methylene groups of protons to the most downfield signal unambiguously established that the carbene signals for 3a and 3b are at 187.9 and 186.9 ppm, respectively. The chemical shift of these signals is comparable to that of 185.5 ppm in Pd(tmiy)₂(MA).²⁴

Complexes **3a**,**b** are unstable in solution, especially under air. Thus an attempted recrystallization of 3a in dichloromethane without N₂ protection resulted in the isolation of colorless crystals after ca. 4-5 days, the structure of which was revealed by X-ray crystallography as trans Pd(II) chelate complex 4a (Scheme 2). The kinetic product, cis-4a, had already been prepared and structurally characterized by us elsewhere.³⁹ Noteworthy, palladium peroxo complexes have been isolated when monodentate NHC palladium(0) complexes were exposed to air.^{47,52} The formation of **4a** can be postulated via a similar transient peroxo intermediate, and subsequent proton exchange between the amido groups and peroxo ligand furnishes the formation of a chelate ring. In fact, during the preparation of **3a,b** in Scheme 1, the ¹H NMR spectroscopy of the reaction mixture always indicated the presence of a minute amount of cis-4a,b, which was easily removed by washing with methanol. Attempts to isolate trans-4a in large quantity by stirring a dichloromethane solution of



Electrospray Ionization Mass Spectrometry (ESI-MS). In order to understand the behavior of 3a,b and hopefully observe short-lived reactive intermediates in solution, we performed ESI-MS studies (Table 1). The soft ionization technique allows few fragmentation products, and the ions are transferred from solution to the gas phase in a smooth manner that is ideal for observation of short-lived molecular ions.⁶¹ The positive-ion mass spectra of **3a**,**b** show the absence of molecular peaks, but major positive ions corresponding to a chelate Pd(II) complex, $[PdL_2 + H]^+$, were detected. Thus species A, which are $[4a + H]^+$ and $[4b + H]^+$, are observed at m/z = 787.1 and 687.2, respectively. Interestingly, species **B**, due to the decarbonylation from species **A**, were also observed. The negative-ion ESI-MS studies, contrastingly, exhibit only Pd(0) species. The $[M - H]^-$ peaks were observed at m/z = 884.9 and 784.9 for **3a** and **3b**, respectively. In each case, the base peak is due to species \mathbf{D} , which is a Pd(0) species bearing one chelating carbene ligand and maleic anhydride. Consistent with the observation from the positive-ion mode, decarbonylation products E were also indentified. Importantly, small amounts of intriguing species F, which are Pd(0) species bearing only one chelating carbene ligand, were observed in both spectra. Deprotonation of the amido NH and decoordination of maleic anhydride lead to this anionic, 14-electron $[Pd^0L]^-$ species, which is probably an active species in C-C coupling reactions conducted under basic conditions. The experimental isotopic patterns of all m/z peaks match well with their theoretical patterns.

Crystallographic Studies. All the new palladium complexes described in this paper have been successfully structurally characterized. Figures 2 and 3 display their thermal ellipsoid plots. Crystallographic data and selected bond distance and angles are listed in Tables 2 and 3, respectively. The Pd atoms in 3a and 3b adopt distorted square-planar coordination geometry. In each case, the sum of the four bond angles about the Pd atom equals 360°. However, the C-Pd-C angles from carbenes are wider than the ideal 90° (**3a**: 95.28(14)°; **3b**: 97.5(2)°). Intriguingly, the two Pd-carbene distances in each complex are unequal in length. For example in 3a, one is 2.043(4) Å, whereas the other one is longer, at 2.070(3) Å. The Pd-carbene distances in 3a and 3b are within the normal range of relevant Pd(0) – carbene structures.^{46–54} In each case, the maleic anhydride is close to perpendicular to the square coordination plane. The corresponding interplanar angles in 3a and 3b are $77.32(12)^{\circ}$ and $81.99(16)^{\circ}$, respectively.

A key feature in the molecular structures of 3a and 3b is the presence of classical NH····O=C hydrogen bonds. In the molecular structure of 3a, there are two intramolecular NH····O=C hydrogen bonds (Table 1S in Supporting Information).

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	3a		3b	
Proposed species	$m/z \exp$.	m/z calcd.	$m/z \exp$.	m/z calcd.
$\begin{bmatrix} & & & & \\ & & & & \\ & & & & \\ & & & & $	787.1 (100%)	787.2	687.0 (100%)	687.2
$\begin{bmatrix} N \\ P \\ P \\ P \\ N \\ N \\ N \\ N \\ B \\ \end{bmatrix}^{*} \text{ or } \begin{bmatrix} N \\ N \\ P \\ P \\ P \\ N \\ N \\ N \\ N \\ N \\$	759.3 (75%)	759.2	659.2 (98%)	659.2
	884.9 (9%)	885.2	784.9 (15%)	785.2
$\begin{bmatrix} & & & & \\ & & & & \\ & & & & \\ & & & & $	544.3 (100%)	544.1	494.5 (100%)	494.0
	516.5 (23%)	516.1	466.5 (24%)	466.0
$\begin{bmatrix} & & & \\ & & & & \\ & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & $	446.4 (9%)	446.1	396.5 (5%)	396.0

^{*a*} Relative abundance in parentheses. The site for the proton in species C is ambiguous.



Figure 1. Experimental isotopic pattern at m/z 446.4 in the mass spectrum of **3a** (white). The theoretical isotopic pattern is shown in black.

One of them is between an amido NH on the carbene ligand and a C=O on the maleic anhydride with N····O contact distance of 2.963(4) Å and NH····O contact angle of 160.0°. The other hydrogen bond between the two carbene ligands is slightly stronger, reflecting a shorter N····O contact distance of 2.902(4) Å but a similar contact angle of 160.3°. In contrast to **3a**, due to the difference in the relative orientation of the two unsymmetrical carbene ligands (see also Figure 2S in Supporting Information), only one intramolecular NH··· O=C hydrogen bond exists in **3b**. It links the two carbene ligands with a N···O contact distance of 2.916(6) Å and a NH···O contact angle of 164.0°. The other NH hydrogen bond donor links with the C=O on the maleic anhydride in an intermolecular fashion, forming a dimeric structure (see Table 2S and Figure 3S in Supporting Information). The overall stability of **3a** and **3b** in the solid state can be attributed to the presence of such intramolecular forces.

Complex **4a** is situated in a special position with inversion site symmetry in the monoclinic unit cell $P2_1/c$. The Pd atom adopts a distorted square-planar environment with *trans* ligand coordination. The bite angle of the ligand is 85.7° , which is similar to those in *cis*-**4a** (see Table 3).³⁹ The Pd-C distance of 2.006(7) Å is, however, longer than that in the *cis* isomer (1.972(2) Å), indicating the stronger *trans* influence of the carbene than the amido group. Consistently, the Pd-N distances in the *cis* form are long (2.0851(19) and 2.0818(17) Å), whereas that in the *trans* form is shorter (2.040(6) Å).

The arylated alkene products from the Heck reactions, (E)-1,2,3-trimethoxy-5-styrylbenzene (8) and (E)-1,3,5-triisopropyl-2-styrylbenzene (9), were also successfully structurally characterized by X-ray diffraction studies. Figure 4 displays their molecular structures. The interplanar angle between the two aromatic rings in the trimethoxy compound



Figure 2. Molecular structures of **3a** (left) and **3b** (right) with 50% probability ellipsoids for non-H atoms. Hydrogen atoms except those involved in intramolecular hydrogen bonding have been omitted for clarity. Hydrogen bonds are shown with broken lines.

Table 2. Crystallographic Data of 3a, 3b, trans-4, 8, and 9

3b • 0.5C ₄ H ₈ O	trans-4	8	9
d $C_{40}H_{36}N_6O_5Pd \cdot C_4H_8O$	C44H36N6O2Pd	C17H18O3	C ₂₃ H ₃₀
859.25	787.19	270.31	306.47
monoclinic	monoclinic	monoclinic	monoclinic
C2/c	$P2_{1}/c$	$P2_1/c$	$P2_{1}/c$
30.870(4)	11.4007(19)	9.2272(4)	9.9567(3)
9.9302(12)	16.954(3)	12.3242(5)	11.2769(3)
27.134(3)	9.7297(15)	13.7756(7)	17.4701(5)
90	90	90	90
94.039(6)	109.090(4)	113.227(4)	100.638(3)
90	90	90	90
8297.2(17)	1777.3(5)	1439.56(11)	1929.84(10)
150(2)	150(2)	110(2)	110(2)
8	2	4	4
8696	3531	3089	4150
542	241	184	317
0.0646	0.0641	0.0358	0.0390
0.1405	0.2373	0.0533	0.0894
	$\begin{array}{c c} \textbf{3b} \cdot 0.5 C_4 H_8 O \\ \hline \textbf{d} & C_{40} H_{36} N_6 O_5 P d \cdot C_4 H_8 O \\ 859.25 \\ monoclinic \\ C2/c \\ 30.870(4) \\ 9.9302(12) \\ 27.134(3) \\ 90 \\ 94.039(6) \\ 90 \\ 8297.2(17) \\ 150(2) \\ 8 \\ 8696 \\ 542 \\ 0.0646 \\ 0.1405 \\ \end{array}$	$\begin{array}{c c} \textbf{3b} \cdot 0.5 C_4 H_8 O & trans-\textbf{4} \\ \hline \textbf{d} & C_{40} H_{36} N_6 O_5 P d \cdot C_4 H_8 O & C_{44} H_{36} N_6 O_2 P d \\ 859.25 & 787.19 & \\ monoclinic & monoclinic \\ C2/c & P2_1/c & \\ 30.870(4) & 11.4007(19) \\ 9.9302(12) & 16.954(3) & \\ 27.134(3) & 9.7297(15) & \\ 90 & 90 & \\ 94.039(6) & 109.090(4) & \\ 90 & 90 & \\ 8297.2(17) & 1777.3(5) & \\ 150(2) & 150(2) & \\ 8 & 2 & \\ 8696 & 3531 & \\ 542 & 241 & \\ 0.0646 & 0.0641 & \\ 0.1405 & 0.2373 & \\ \end{array}$	$\begin{array}{c c c c c c c c c c c c c c c c c c c $

 ${}^{a}R_{1} = \sum (||F_{o}| - |F_{c}|) / \sum |F_{o}|. {}^{b}wR_{2} = [\sum (|F_{o}|^{2} - |F_{c}|^{2})^{2} / \sum (F_{o}^{2})]^{1/2}.$



Figure 3. Molecular structures of *trans*-**4a** with 50% probability ellipsoids for non-H atoms. Hydrogen atoms have been omitted for clarity.

is 14.7(1)°, which is comparable to that of $16.92(3)^{\circ}$ in (*E*)-1,2,3-trimethoxy-4-styrylbenzene.⁶² In sharp contrast, due to the presence of steric bulkiness of the two *o*-isopropyl groups, the two aromatic rings in **9** are close to orthogonal to each other with an interplanar angle of $82.6(1)^{\circ}$.

X-ray Photoelectron Spectroscopy (XPS). The electronic property of the palladium(0) complex **3b** and the palladium-(II) complex *cis*-**4b** was probed by XPS. The binding energies of Pd electrons in the core $3d_{3/2}$ and the $3d_{5/2}$ orbitals in **3b** are 340.7 and 335.4 eV, which compare favorably with those of 340.5 and 335.1 eV in Pd(0). Intriguingly, the corresponding binding energies in *cis*-**4b** are 341.7 and 336.6 eV, which are close to those in elemental Pd(0)⁶³ and thus very low for a Pd(II) atom,⁶⁴ reflecting the strong electron-donating effect of the anionic amido groups. These low binding energies in

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⁽⁶⁴⁾ Boekman, F.; Gogoll, A.; Pettersson, L. G. M.; Bohman, O.; Siegbahn, H. O. G. Organometallics **1992**, 11, 1784.

Table 3. Selected Bond Distances (Å) and Angles (deg) of 3a, 3b, trans-4a, and cis-4a^a

3a 3b		trans-4a	<i>cis</i> - 4a ³⁹
Pd1—C1, 2.043(4) Pd1—C23, 2.070(3) Pd1—C45, 2.114(4)	Pd1—C1, 2.049(5) Pd1—C19, 2.066(5) Pd1—C39, 2.102(5)	Pd1—C1, 2.006(7) Pd1—N3, 2.040(6)	Pd1—C1, 1.972(2) Pd1—C23, 1.972(2) Pd1—N3, 2.0851(19) Pd1—N3, 2.081(19)
Pd1—C40, 2.115(3) C1—Pd1—C23, 95.28(14) C1—Pd1—C46, 110.33(14) C23—Pd1—C45, 114.03(14) C45—Pd1—C46, 40.08(14) C1—Pd1—C46, 150.41(14)	Pd1—C40, 2.110(5) C1—Pd1—C19, 97.5(2) C1—Pd1—C39, 110.3(2) C19—Pd1—C40, 112.7(2) C39—Pd1—C40, 39.68(19) C1—Pd1—C40, 149.8(2)	C1—Pd1—N3, 85.7(2)	Pd1—N6, 2.0818(17) C1—Pd1—N3, 86.45(8) C23—Pd1—N6, 84.50(8) C1—Pd1—C23, 95.50(9) N3—Pd1—N6, 93.46(7) C1—Pd1—N6, 177.70(8) C23_Pd1_N2_177.01(0)
^{<i>a</i>} Symmetry code = $1-x$, $2-y$, $2-z$.	C19—Fu1—C39, 151.9(2)		C25—ru1—i\\5, 177.01(9)
		CG CT CS CO	

Figure 4. Left: molecular structure of 8 with 50% probability ellipsoids for non-H atoms. Right: molecular structure of 9 with 50% probability ellipsoids for non-H atoms.

Table 4. Heck Reaction of 4-Chloroacetophenone and Styrene^a

 \sim

		O CI + 0.5 mol% [Pd] cat. NaOAc, 110-140 °C 5 + 0 5'				
entry	cat.	temp, °C	solvent	yield, % (5:5')		
1	3a	120	organic	36 (92:8)		
2	3b	120	organic	40 (92:8)		
3	cis-4b	120	organic	13 (100:0)		
4	3b	110	IL	94 (94:6)		
5	3b	120	IL	> 99 (93:7)		
6	3b	120	IL	92 $(96:4)^{b}$		
7	3b	140	IL	98 (94:6)		
8	cis-4b	120	IL	0		
9	trans-4b	120	IL	0		
10	cis-4b	140	IL	96 (93:7)		
11	trans-4b	140	IL	> 99 (93:7)		

^{*a*} 1.0 mmol of 4-chloroacetophenone, 1.4 mmol of styrene, 1.1 mmol of NaOAc, 5 mL of DMA or 2 g of TBAB, 0.5 mol % [Pd] cat., 110–140 °C, 2 h. Yields and regioselectivity determined by NMR using 1,3,5-trimethoxybenzene as internal standard. ^{*b*} Isolated yield with regioselectivity determined by NMR.

cis-Pd^{II}L₂ are, in fact, similar to those of 342.0 and 336.7 eV in *cis*-Pd^{II}(LH¹)(PCy₃)Cl₂, possessing a strong electron-donating PCy₃ ligand.⁴⁰ For comparison, the binding energies in Pd(II) complexes with a bidentate carbene of abnormal binding are much higher, at ca. 348.0 and 342.6 eV.⁶⁵

Catalytic Studies. The catalytic performances of complexes **3a,b** in Heck reactions of aryl halides with alkenes were studied. The reaction between 4-chloroacetophenone and styrene was chosen as the benchmark for initial investigation (Table 4). We screened the reactions in the commonly used highly polar organic solvent *N*,*N*-dimethylacetamide

(65) Heckenroth, M.; Kluser, E.; Neels, A.; Albrecht, M. Angew. Chem., Int. Ed. 2007, 46, 6293.

(DMA) and the ionic liquid tetra-*n*-butylammonium bromide (TBAB), which is a solid at ambient temperature but a liquid at high temperature. The green solvent not only offers the advantages of low vapor pressure, high boiling point, cheap price, availability, and recyclability but also shortens the workup time, as the procedure to remove high-boiling solvent is replaced by a simple extraction procedure. Reports have demonstrated that palladium-catalyzed coupling reactions can be performed effectively in ionic liquids.^{18,66,67} It is worthy to mention that ionic liquids were also employed as

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(67) Wang, R.; Zeng, Z.; Twamley, B.; Piekarski, M. M.; Shreeve, J. n. M. *Eur. J. Org. Chem.* 2007, 2007, 655.

Scheme 3. One-Pot Sequential Palladium-Catalyzed Cross-Coupling Reactions

Heck/Heck coupling reactions catalyzed by 3 mol% of cis-4b



Suzuki/Heck coupling reactions catalyzed by 3 mol% of cis-4b





Figure 5. Time-yield curves of 3b and *cis*-4b in the Heck reaction between 4-chloroacetophenone and styrene.

solvent in Heck reactions catalyzed by palladium nanoparticles.^{15,68} Entries 1 and 2 show that 36-40% yields of 4-acetylstilbene can be achieved in 2 h using 0.5 mol % of palladium(0) precatalysts at 120 °C with DMA as solvent. Complex 3b is slightly more efficient than **3a**. Bis(bidentate) palladium(II) complex *cis*-**4b** reported by us earlier³⁹ affords a poor 13% yield at 120 °C (entry 3). Its ineffectiveness can be attributed to the insufficient formation of active Pd(0) species from cis-4b at such low temperature. Replacing the organic solvent with TBAB leads to a substantial increase in product yields. For example, complex **3b** gives a yield of only 40% in DMA (entry 2), but a quantitative yield was obtained in 2 h using the ionic liquid as solvent (entry 5). As shown by entries 4, 5, and 7, the optimal temperature for the catalytic reaction is 120 °C. Entries 8 and 9 confirmed that both cis- and trans-4b were ineffective even in ionic liquid at this temperature. To our surprise, excellent yields of 96% and 99% were obtained by raising the reaction temperature to 140 °C (entries 10 and 11). This reflects that the conversion of the precatalyst $Pd^{II}L_2$ into an active Pd^0 species, such as $[Pd^0L]^-$ (species **F**), is facile at a higher temperature, leading to the resulting activity. The time—yield curves for **3b** and *cis*-**4b** over a period of 2 h were obtained in order to shed light on their behavior in catalyst activation. Figure 5 clearly shows that the catalyst activation of the palladium(0) complex is much faster than the palladium(II) complex. For palladium(0) complex **3b**, catalytic activity starts instantaneously, giving a ca. 85% yield in the initial 20 min, whereas there is a long activation period of 1 h for the bischelate Pd(II) complex *cis*-**4b** to form active catalytic species.

31: 58%

As demonstrated above, a low loading of 3b as precatalyst (0.5 mol %) was sufficient to obtain 4-acetylstilbene almost quantitatively in 2 h with the activated substrate 4-chloroacetophenone. However, these conditions were not suitable with challenging substrates including hindered aryl bromides and nonactivated and deactivated aryl chlorides. Instead, we found that robust palladium(II) complex cis-4b outperforms palladium(0) complex 3b in utilizing these substrates. The substrate scope of cis-4b with hindered aryl bromides was explored in Table 5. A general condition was established involving 3 mol % of cis-4b at 140 °C in 12 h, and the catalyst system is capable of delivering good trans product yields with a range of challenging aryl bromide substrates. For example, the catalyst system can utilize the deactivating substrate 5-bromo-1,2,3-trimethoxybenzene to synthesize 8 in 72% yield (entry 3). Hindered aryl bromides with two o-substitutents can also be coupled effectively (entries 4/5 and 10/11). In particular, a decent 52% yield of 9 can be achieved from the very bulky 1-bromo-2,4,6triisopropylbenzene (entry 4). Both of the coupled products 8 and 9 were successfully characterized by X-ray diffraction studies (vide supra). Complex **3b** is not suitable for bulky aryl bromides, as illustrated in entry 5, showing that (E)-2,4,6trimethylstilbene (10) was obtained from 2-bromomesitylene in only 22% yield, whereas cis-4b delivered a high 81% yield. (E)-3,4,5,4'-Tetramethoxystilbene (11), designated as DMU-212, is attracting interest recently because it has emerged as a strong candidate for antitumor applications.⁶⁹ Entry 6 shows

⁽⁶⁸⁾ Ye, C.; Xiao, J.-C.; Twamley, B.; LaLonde, A. D.; Norton, M. G.; Shreeve, J. n. M. *Eur. J. Org. Chem.* **2007**, 2007, 5095.

⁽⁶⁹⁾ Cross, G. G.; Eisnor, C. R.; Gossage, R. A.; Jenkins, H. A. Tetrahedron Lett. 2006, 47, 2245.

		II	NaOAc, TB 12 h, 140 º(AB Ar	
entry	mol % cat.	Ar–Br	alkene	product	yield, %
1	0.5	Br OMe			71
2	0.5	OMe Br		OMe 7	87
3	3.0	MeO MeO OMe		MeO MeO OMe	72
4	3.0	Br		y	52
5	3.0	Br		10	81 (22 ^b)
6	3.0	MeO MeO OMe	OMe	MeO MeO MeO MeO MeO MeO MeO MeO MeO MeO	56
7	0.5	Br OMe		OMe 12	58
8	0.5	OMe Br		CO ₂ ⁿ Bu OMe 13	80
9	3.0	MeO MeO OMe		MeO CO ₂ ⁿ Bu MeO 14	57
10	3.0	Br		СО ₂ "Ви 15	54
11	3.0	Br		CO ₂ "Bu	76

Ar-Br + R $\frac{0.5 \text{ or } 3 \text{ mol}\% [Pd] \text{ cat.}}{NaOAc, TBAB}$ Ar

^{*a*} 1.0 mmol of aryl bromide, 1.4 mmol of alkene, 1.1 mmol of NaOAc, 2 g of TBAB, 0.5 or 3 mol % *cis*-4b unless otherwise stated, 140 °C, 12 h, isolated yields. ^{*b*} 3 mol % 3b as precatalyst.

that it can be prepared in 56% yield with a mere 3 mol % Pd precatalyst loading, which is much more cost-effective than the reported procedure, which requires a 40 mol % of Pd loading.⁶⁹

The catalyst system of *cis*-**4b** is also effective for a range of aryl chlorides (Table 6). A comparison between entry 1 and 2 clear reflects the higher effectiveness of *cis*-**4b** than **3b**. Entries 2 and 3 indicate that the *trans* and *cis* isomers of *cis*-**4b** give the same product yield. For activating aryl chlorides, a 0.5 mol % of **3b** or *cis*-**4b** loading is sufficient to afford high isolated yields of coupled products (90–98%) in 2 or 12 h (entries 9, 10, 14–16). For nonactivated chlorobenzene as substrate, a 0.5 mol % of *cis*-**4b** affords stilbene (**20**) and (*E*)-3-phenylacrylic acid *n*-butyl ester (**25**) in 71% and 55%, respectively (entries 8 and 13). For deactivated substrates, a higher loading of 1.5-3 mol % of *cis-4b* is needed to deliver decent yields of coupled products (42-72%) (entries 4, 6, 7, 11, 12). For example, 4-methoxystilbene (17) can be obtained in 72% yield from 4-chloroanisole in 12 h with a 1.5 mol % of Pd loading (entry 4).

The higher activity of *cis*-**4b** compared with **3b** with challenging substrates can be explained by the continuous supply of active Pd(0) species from the robust Pd(II) *cis*-**4b**. In contrast, the instantaneously high concentration of Pd(0) active species from Pd(0) **3b** may lead to fast coupling activity with activated aryl chlorides, but such high concentration is favorable to catalyst deactivation when prolong heating is needed for

Table 6. Heck Reactions of Aryl Chlorides^a

	R ¹	CIR ² <u>0</u> + ∬	.5-3 mol% [Pd] cat. NaOAc, TBAB 2 or 12 h,140 °C	R ¹ + trans		2 ²
entry	cat. (mol %)	Ar–Cl	alkene	product	time, h	yield, % (trans:gem)
1	3b (0.5)	MeO		Me0 17	12	9 (95:5)
2	<i>cis</i> -4b (0.5)	MeO			12	65 (91:9)
3	trans-4b (0.5)	MeO			12	66 (92:8)
4	<i>cis-</i> 4b (1.5)	MeO			12	72 (91:9)
5	<i>cis</i> -4b (0.5)	Me		Me 18	12	54 (94:6)
6	<i>cis-</i> 4b (1.5)	Me			12	68 (94:6)
7	<i>cis-</i> 4b (3.0)	Me		Me 19	12	42 (100:0)
8	<i>cis</i> -4b (0.5)	CI		20	12	71 (93:7)
9	3b (0.5)	NC		NC 21	2	90 (100:0)
10	<i>cis</i> -4 b (0.5)	O H			12	97 (100:0)
11	<i>cis</i> -4b (3.0)	MeO	∕⊂O ₂ ″Bu	MeO 23	12	48 (100:0)
12	<i>cis-4b</i> (3.0)	Me		Me 24	12	50 (100:0)
13	<i>cis</i> -4b (0.5)	CI		CO ₂ "Bu 25	12	55 (100:0)
14	3b (0.5)	NC		NC 26	2	93 (100:0)
15	3b (0.5)	o Me		CO ₂ ⁿ Bu Me	2	94 (100:0)
16	cis- 4b (0.5)	O CI		СО ₂ ⁿ Ви Н	12	98 (100:0)

^{*a*} 1.0 mmol of aryl chloride, 1.4 mmol of alkene, 1.1 mmol of NaOAc, 2 g of TBAB, 0.5–3 mol % [Pd] cat., 140 °C, 2 or 12 h, isolated yields with regioselectivity determined by NMR.

challenging substrates, which eventually leads to poorer product yields. The catalyst system derived from L is capable of utilizing deactivated aryl chlorides, reflecting its higher efficient than the palladium(0) IMes system reported in the literature.¹⁸ genaration.⁷⁰ So far only a few examples using a single precatalyst in the sequential C–C coupling have been reported and the aryl dihalides were limited to those containing Br and I.^{70,71}

One-pot sequential cross-coupling reactions of aryl dihalides are attracting interests because of the possibilities of obtaining difunctionalized arenes in a single step with less waste

(70) Zhang, X.; Liu, A.; Chen, W. Org. Lett. 2008, 10, 3849.

⁽⁷¹⁾ Flaherty, D. P.; Dong, Y.; Vennerstrom, J. L. *Tetrahedron Lett.* **2009**, *50*, 6228.

The use of cheaper 4-bromochlorobenzene has been demonstrated in a recent report for sequential Heck/Heck but not Suzuki/Heck coupling reactions.¹⁵ We found that *cis*-4b performs well in both the sequential Heck/Heck coupling reactions and Suzuki/Heck coupling reactions to generate the desired products using 4-bromochlorobenzene as substrate (Scheme 3). Thus (E)-butyl 3-(4-styrylphenyl)acrylate (29) and 1-methoxy-4-(4-styrylstyryl)benzene (30) can be obtained in 64 and 51% yields, respectively, from the Heck/Heck coupling reactions. We reported that cis-4b is a precatalyst for Suzuki coupling reactions capable of utilizing aryl bromides but not chlorides. Thus cis-4b can generate 4-chlorobiphenyl via Suzuki coupling chemoselectively and the subsequent coupling with styrene generates the desirable product, (E)-4-styrylbiphenyl (31), in 58% yield. Consistently, the reverse of the coupling sequence leads to the isolation of (E)-1-chloro-4-styrylbenzene only. Thus our system is markedly more effective than that reported by Chen et al. in which the more reactive 4-bromoiodobenzene had to be used in the sequential Heck/Suzuki coupling sequence.70

Conclusions

We prepared palladium(0) complexes **3a**,**b** based on the amido-functionalized NHC ligands. As revealed by the ESI-MS study, facile deprotonation of the NH proton and decoordination of one carbene ligand allow the formation of an anionic electron-rich species F, which is postulated as an active species in coupling reactions. The anionic amide functionality imparts a higher electron density on the palladium center as indicated by the XPS study. Hence, palladium(0) complex **3b** is highly effective in catalyzing Heck coupling reactions with activated aryl chlorides in TBAB ionic liquid. However, for electron-deactivating aryl chlorides and bulky aryl bromides, palladium(II) complex cis-4b becomes more efficient. The prolong heating required for demanding substrates is not favorable for the palladium(0) precatalyst. The robustness of the palladium(II) precatalyst may allow a constant supply of Pd(0) active species over a long period of time. Favorably, the combination of 3b and cis-4b enables the access of a wide range of coupled products from challenging substrates. Complex cis-4b is also promising in one-pot sequential Heck/Heck and Suzuki/Heck coupling reactions to generate unsymmetrical substituted arenes from cheap 4-bromochlorobenzene. In view of the generality and simple, practical, and green operating procedure, the catalyst systems of 3b and cis-4b are expected to find wide interests.

Experimental Section

General Information. All manipulations were performed under a dry nitrogen atmosphere using standard Schlenk techniques. Solvents were dried with standard procedures. Starting chemicals were purchased from commercial source and used as received. Compounds $1,^{38} 2,^{59}$ and *cis-4b*³⁹ were prepared according to literature procedures. ¹H, and ¹³C{¹H} NMR spectra were recorded at 300.13 and 75.48 MHz, respectively, on a Bruker AV-300 spectrometer. Elemental analyses were performed on a Thermo Flash 2000 CHN-O elemental analyzer. ESI-MS was carried out on a Finnigan/Thermo Quest MAT 95XL mass spectrometer at National Chung Hsing University (Taiwan). X-ray photoelectron spectroscopy was performed on a ESCA

PHI 1600 system using Mg K α radiation (hv = 1253.6 eV) at National Tsing Hua University (Taiwan).

Synthesis of 3a. To a 50 mL Schlenk flask containing complex 2 (0.10 g, 0.268 mmol), 1a (0.20 g, 0.537 mmol), and potassium carbonate (0.074 g, 0.537 mmol) was added dry DMF (8 mL). The mixture was allowed to stir for 5 h at ambient temperature. The solvent was completely removed under vacuum. The residue was dissolved in dichloromethane. The organic layer was then washed twice with water. After drying with anhydrous magnesium sulfate, the solvent was completely removed under vacuum. The residue was washed with diethyl ether and subsequently with methanol. The airstable yellow solid was then filtered on a frit and dried under vacuum. Yield: 0.12 g (50%); mp 195.2-196.4 °C (dec); ¹H NMR (300 MHz, DMSO-d₆, 25 °C, TMS): δ 3.58 (s, 2H, CCH=CHC), 5.09 (s, 4H, CH₂C=O), 5.48 (AB quartet, ${}^{2}J(H,$ H) = 7.5 Hz, $\Delta \nu$ = 24.0 Hz, 4H, NpCH_aH_b), 6.82 (s, 2H, imi-*H*), 6.99 (t, ${}^{3}J(H,H) = 7.2$ Hz, 2H, *p*-Ph-*H*), 7.11–7.19 (m, 6H, Ph-*H* and Np-*H*), 7.23 (s, 2H, imi-*H*), 7.31 (t, ${}^{3}J(H,H) = 7.5$ Hz, 2H, Np-*H*), 7.37–7.48 (m, 8H, Ph-*H* and Np-*H*), 7.78 (d, ${}^{3}J$ (H, H) = 4.2 Hz, 2H, Np-*H*), 7.86 (d, ${}^{3}J$ (H,H) = 3.8 Hz, 2H, Np-*H*), 7.86 (d, ${}^{3}J$ (H,H) = 3.8 Hz, 2H, Np-*H*), 7.95 (d, ${}^{3}J$ (H,H) = 4.1 Hz, 2H, Np-*H*), 10.20 (s, 2H, N*H*); ¹³C{¹H} NMR (75 MHz, DMSO- d_6 , 25 °C, TMS): δ 38.6 (CCH = CHC), 51.9 (NpCH₂), 53.7 (CH₂C=O), 119.6 (CH), 121.2 (CH), 123.7 (CH), 125.6 (CH), 126.2 (CH), 126.8 (CH), 126.9 (CH), 128.6 (CH), 128.7 (CH), 128.9 (CH), 130.9 (CH), 132.6 (CH), 133.5 (CH), 138.8 (O=CNHC), 166.1 (CH₂-C=O), 173.9 (CHCO=O), 187.9 (NCN); elemental analysis calcd (%) for C₄₈H₄₀N₆O₅Pd: C, 64.97; H, 4.54; N, 9.47; found: C, 64.68; H, 4.55; N, 9.03%; Crystals suitable for X-ray crystallography were obtained by vapor diffusion of dried diethyl ether into a dried THF solution of the solid mixture under nitrogen.

Synthesis of 3b. The preparation was similar to that of 1. Complex 2 (0.20 g, 0.537 mmol), 1b (0.35 g, 1.07 mmol), and potassium carbonate (0.15 g, 1.07 mmol) were used. A pale vellow crystal was obtained. Yield: 0.24 g (57%); mp 163.8-167.8 °C (dec); ¹H NMR (300 MHz, DMŠO-*d*₆, 25 °C, TMS): δ 3.49 (s, 2H, CCH = CHC), 4.96–5.07 (m, 8H, CH₂C=O and PhCH₂), 7.03-7.28 (m, 20H, imi-H and Ph-H), 7.47 (d, $^{3}J(H,H) = 3.9$ Hz, 4H, o-Ph-H), 10.17 (s, 2H, NH); $^{13}C{^{1}H}$ NMR 75 MHz, DMSO- d_6 , 25 °C, TMS): δ 38.1 (CCH = CHC), 53.2 (PhCH₂), 53.4 (CH₂C=O), 119.3 (CH), 121.21 (CH), 123.4 (CH), 123.5 (CH), 127.3 (CH), 128.2 (CH), 128.6 (CH), 137.2 (CH), 138.5 (O = CNHC), 165.8 (CH₂C=O), 173.5 (CHCO = O), 186.9 (NCN). analysis calcd (%) for C₄₀-H₃₆N₆O₅Pd: C, 61.05; H, 4.61; N, 10.69; found: C, 61.28; H, 5.08; N, 10.21%; Crystals suitable for X-ray crystallography were obtained by vapor diffusion of dried diethyl ether into a dried dichloromethane solution of the solid mixture under nitrogen.

Synthesis of *trans*-4a. Crystals suitable for X-ray crystallography were grown in ca. 4-5 days by slow evaporation of a dichloromethane solution of 3a in air.

Catalytic Heck Reaction. In a typical run, a Schlenk tube was charged with aryl halide (1.0 mmol), alkene (1.4 mmol), anhydrous sodium acetate (1.1 mmol), and an appropriate amount of palladium precatalyst (0.5-3 mol %). The flask was thoroughly degassed, added with DMA (5 mL) via a syringe or TBAB (2 g for conventional heating; 1 g for microwave irradiation), and then placed in a preheated oil bath at the appropriate temperature listed in Table 4-6. After the mixture was cooled, in case of using DMA, the solvent was removed completely under high vacuum. The residue was then dissolved in diethyl ether (10 mL). The organic portion was then washed with water $(3 \times 10 \text{ mL})$ and dried over anhydrous MgSO₄. In the case of using TBAB, after the mixture was cooled, the mixture was diluted with water (10 mL) and extracted with ether (3 \times 10 mL). The combined organic portions were dried over anhydrous MgSO₄. After filtration, the solvent was removed completely under vacuum.

Products 5, ⁷² 6–8, ⁷³ 9, ⁷⁴ 10, ⁷⁵ 11, ⁶⁹ 12, ⁷⁶ 13, ⁷⁷ 15, ⁷⁸ 16, ⁷⁶ 17–22, ⁷² 23–26, ⁷⁹ and 27–28⁸⁰ were indentified by comparison of NMR data with those in the literature; yields and regioselectivity were determined by integration ratio using 1,3,5-trimethoxylbenzene as internal standard or after purification with column chromatography on silica gel.

(*E*)-Butyl 3-(3,4,5-trimethoxyphenyl)acrylate (14). A white solid. ¹H NMR (300 MHz, CDCl₃, 25 °C, TMS): δ 0.92 (t, ³*J*(H,H) = 7.5 Hz, 3H, CH₃CH₂), 1.40 (m, 2H, CH₂CH₃), 1.65 (m, 2H, CH₂CH₂CH₂), 3.84 (s, 3H, *p*-OCH₃), 3.85 (s, 6H, *m*-OCH₃), 4.17 (t, ³*J*(H,H) = 6.6 Hz, 2H, OCH₂), 6.31 (d, ³*J*(H,H) = 8.1 Hz, 1H, C=CHCO), 6.71 (s, 2H, Ar-H), 7.56 (d, ³*J*(H,H) = 8.1 Hz, 1H, CCH=CH). ¹³C{¹H} NMR (75 MHz, CDCl₃, 25 °C, TMS): δ 13.7 (CH₂CH₃), 19.1 (CH₂CH₃), 30.7 (CH₂CH₂CH₂), 55.9 (*m*-OCH₃), 60.8 (*p*-OCH₃), 64.3 (OCH₂), 105.0 (Ar-CH), 117.4 (C=CHCO), 129.8 (Ar-C), 139.9 (*p*-COCH₃), 144.4 (CCH=CH), 153.3 (*m*-COCH₃), 166.9 (C=O). HRMS (EI): calcd C₁₆H₂₂O₅ 294.1467; found 294.1458.

Sequential Heck/Heck Coupling. A Schlenk tube was charged with 4-bromochlorobenzene (1.0 mmol), *n*-butyl acrylate or 4-methyoxylstyrene (1.4 mmol), anhydrous sodium acetate (1.1 mmol), *cis*-4b (20.6 mg, 3.0 mmol %), and TBAB (2 g). The mixture was heated at 140 °C for 6 h. It was then allowed to cool to room temperature, styrene (160.9 μ L, 1.4 mmol) was added, and the mixture was heated to 140 °C for another 12 h. The workup procedure was similar to that for the Heck reaction. The residue was then purified by column chromatography on silica gel to give the desired product. Products 29⁷⁰ and 30⁷¹ were characterized by comparison of NMR data with those in the literature.

Sequential Suzuki/Heck Coupling. A Schlenk tube was charged with phenylboronic acid (1.3 mmol), $K_3PO_4 \cdot H_2O$ (2.0 mmol), and TBAB (2 g) and then placed in a preheated oil bath at 100 °C. 4-Bromochlorobenzene (1 mmol) was then added. The mixture was heated at 100 °C for 6 h. It was then allowed to cool to room temperature. 4-Methyoxylstyrene (1.4 mmol) and NaOAc (1.1 mmol) were added, and the mixture was heated

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to 140 °C for another 12 h. The workup procedure was similar to that for the Heck reaction. The residue was then purified by column chromatography on silica gel to give the desired product. Product **31** was characterized by comparison of NMR data with those in the literature.⁸¹

X-ray Diffraction Studies. For compounds 3a, 3b, and trans-4, data were collected at 150(2) K on a Bruker APEX II equipped with a CCD area detector and a graphite monochromator utilizing Mo K α radiation ($\lambda = 0.71073$ Å). The unit cell parameters were obtained by least-squares refinement. Data collection and reduction were performed using the Bruker APEX2 and SAINT software.⁸² Absorption corrections were performed using the SADABS program.⁸³ Compounds 8 and 9 were collected at 110(2) K on an Xcalibur Oxford Diffraction diffractometer equipped with a Sapphire-3 CCD area detector at National Chung Hsing University (Taiwan). Graphite-monochromatized Mo K α radiation was used ($\lambda = 0.71073$ Å). Data collection and reduction were performed using the Oxford Diffraction CrysAlisPro software.⁸⁴ All the structures were solved by direct methods and refined by full-matrix leastsquares methods against F^2 with the SHELXTL software package.⁸⁵ All non-H atoms were refined anisotropically. All H-atoms in 3a, $3b \cdot 0.5C_4H_8O$, trans-4a, and 8 and those on C22 in 9 were fixed at calculated positions and refined with the use of a riding model. H atoms in 9, except those on C22, were located in the electron density map and freely refined. Crystallographic data are listed in Table 1. CCDC-755879 (3a), -755880 (3b · 0.5C₄H₈O), -755881 (trans-4a), -764706 (8), and -764707 (9) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam. ac.uk/data_request/cif.

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Supporting Information Available: Full crystallographic data for all the structures are provided as a CIF file. HMBC spectrum of **3a** and additional crystallographic data and graphics of **3a** and **3b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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