An N-C-N Pincer Palladium Complex as an Efficient Catalyst Precursor for the Heck Reaction

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Abstract: The Heck reaction of iodobenzene and methyl acrylate took place smoothly in NMP at 140 °C in the presence of 1 mol ppb of the pincer palladium complex [4-*tert*-butyl-2,6-bis{(3*R*,7a*S*)-2-phenylhexahydro-1*H*-pyrrolo[1,2-*c*]imidazole-1-on-3-yl}-phenyl]chloropalladium to give methyl cinnamate which corresponds to 520×10^6 TON and 6500/sec TOF.

Keywords: aryl halides; cinnamates; Heck reaction; palladacycle catalyst; pincer complex

The palladium-catalyzed arylation and alkenylation of olefins, the so-called Heck reaction, is a versatile synthetic tool for carbon-carbon bond formation. Various Pd^{II} and Pd^0 complexes have been investigated for use as catalyst precursors promoting the Heck reaction. Among the most active ones reported to date are phosphorus-, nitrogen-, and sulfur-containing carbopalladacycles[1] with pincer palladium complexes (Figure 1) being recognized as one of the most active classes of catalyst precursors for this reaction.[2,3] We report here a new N-C-N pincer palladium complex **4** which was found to promote the Heck reaction of aryl iodides with methyl acrylate with extraordinarily high catalytic activity, corresponding to a total turnover number (TON) and turnover frequency (TOF) of 520×10^6 and 6500/sec, respectively.

[4-*tert*-Butyl-2,6-bis{(3*R*,7a*S*)-2-phenylhexahydro-1*H*-pyrrolo[1,2-*c*]imidazole-1-on-3-yl}phenyl]chloropalladium (**4**) is a novel pincer palladium complex having hexahydro-1*H*-pyrrolo[1,2-*c*]imidazolone groups[4] as *trans*-chelating donor groups at the 2,6-positions of the anionic aromatic ligand moiety, which we have recently designed and prepared with a view toward use in several palladium-catalyzed transformations, including asymmetric catalysis.[5] The pincer complex **4** was readily prepared in high yield starting with 4-*tert*-butyl-2,6-diformylphenyl trifluoromethanesulfonate (**5**) *via* oxidative complexation with Pd^0 and condensation with proline anilide, as shown in Scheme 1. As part of our effort to develop their wide utility, we explored the basic catalytic ability of pincer complexes to promote the Heck reaction.

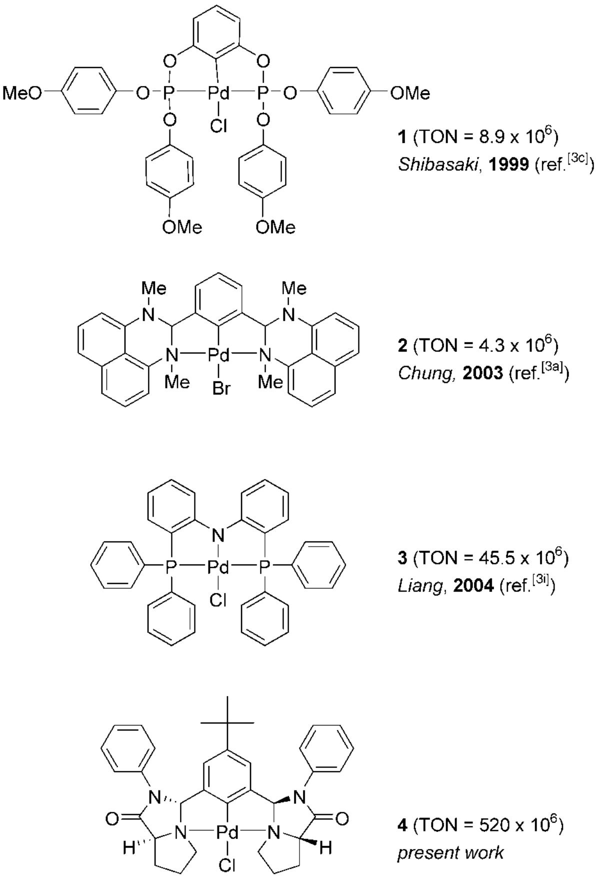
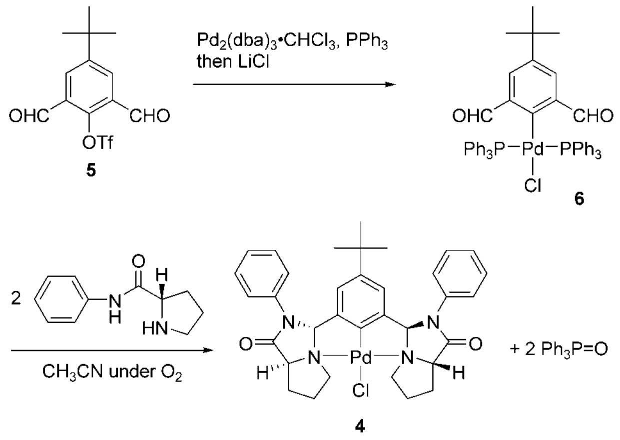
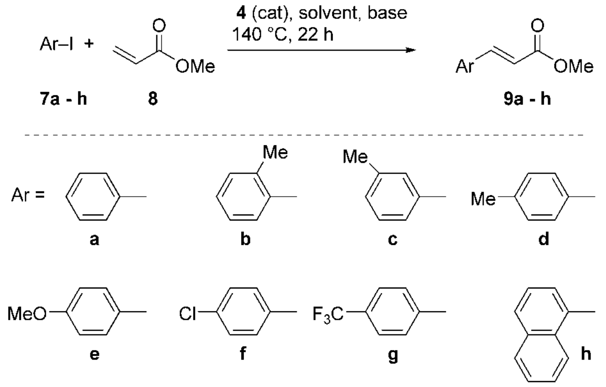


Figure 1. Representative examples of pincer palladium complexes catalyzing the Heck reaction. Reported turnover numbers (TONs) for the Heck reaction of aryl iodide are given in parentheses.

First, we examined several solvents and bases for the Heck reaction of iodobenzene (**7a**) with methyl acrylate (**8**) in the presence of the pyrroloimidazolone palladium pincer complex **4** (Scheme 2). Representative results are summarized in Table 1. It was found that the combination of sodium bicarbonate ($NaHCO_3$) as base and 1-methyl-2-piperidone (NMP) as solvent is essential to afford efficient reaction conditions for the Heck reaction with the pincer catalyst **4**. Thus, the reaction of iodobenzene (**7a**) with methyl acrylate (**8**) was carried out in



Scheme 1. Preparation of the pincer palladium complex **4**.



Scheme 2. The Heck reaction.

Table 1. The Heck reaction of iodobenzene (**7a**) and methyl acrylate (**8**).[a]

Entry	**4** (mol %)	Solvent	Base	Yield [%] of **9a** [b]
1	0.1	NMP	NaHCO$_3$	84
2[c]	0.1	NMP	NaHCO$_3$	83
3	0.0001	NMP	NaHCO$_3$	87
4	none	NMP	NaHCO$_3$	–
5	0.1	DMF	NaHCO$_3$	19
6	0.1	mesitylene	NaHCO$_3$	8
7	2.0	NMP	Na$_2$CO$_3$	70
8	2.0	NMP	K$_2$CO$_3$	76
9	2.0	NMP	NaOAc	44
10	2.0	NMP	*i*-Pr$_2$EtN	42
11	2.0	NMP	*n*-Bu$_3$N	19

[a] All reactions were carried out at 140 °C for 22 h.
[b] Isolated yield.
[c] Carried out in air.

NMP in the presence of 1.1 mol equivs. of NaHCO$_3$ and 0.1 mol % of pincer complex **4** at 140 °C for 22 h to give an 84% isolated yield of methyl cinnamate (**9a**) (Table 1, entry 1). It is noteworthy that the Heck reaction took place under aerobic conditions to give 83% yield of **9a** (entry 2). The reaction of **7a** and **8** proceeded smoothly with only 1 mol ppm of the pincer catalyst **4** under otherwise similar conditions to give an 87% isolated yield of the cinnamate **9a** (entry 3). The cinnamate **9a** was not detected by GC-MS analysis at all in the control experiment carried out without the pincer palladium **4** (entry 4). The Heck reaction performed in *N,N*-dimethylformamide (DMF) and mesitylene gave 19% and 8% of the cinnamate **9a**, respectively (entries 5 and 6), whereas the Heck reaction gave 84% yield of **9a** in NMP (entry 1). The reaction efficiency is also strongly affected by the base employed. Thus, the yields of methyl cinnamate (**9a**) were lower in the reactions using more basic and less basic inorganic bases, including sodium carbonate, potassium carbonate, and sodium acetate (Na$_2$CO$_3$: 70%, K$_2$CO$_3$: 76%, NaOAc: 44%) (entries 7–9) even with 2 mol % of the pincer complex **4**. Organic bases such as diisopropylethylamine and tributylamine also gave lower yields, 42% and 19%, respectively, of the Heck product under otherwise similar conditions (entries 10 and 11).

Using the efficient reaction conditions (NMP/NaHCO$_3$/140 °C) identified above, various aryl halides were examined for the Heck reaction with acrylates in the presence of 1 mol ppm of the pincer palladium complex **4** (Table 2). Thus, the reactions of the *ortho*-, *meta*-, and *para*-iodotoluenes (**7b–d**) with 1.2 equivs. of methyl acrylate (**8**) were catalyzed by 1.0 mol ppm of the pincer palladium complex **4** at 140 °C in NMP to give 89, 88, and 87% isolated yields of the Heck products **9b**, **9c**, and **9d**, i.e., the turnover numbers (TONs) for the palladium catalyst were 888 × 10^3, 882 × 10^3, and 873 × 10^3, respectively (Table 2, entries 1–3). Excellent TONs were also achieved in the reaction of the aryl halides having electron-donating as well as electron-withdrawing substituents. The observed TONs in the reactions of *para*-iodoanisole (**7e**), *para*-chloroiodobenzene (**7f**), and *para*-(trifluoromethyl)iodobenzene (**7g**) affording **9e**, **9f**, and **9g** were 430 × 10^3, 775 × 10^3, and 910 × 10^3, respectively, to demonstrate the wide substituent tolerance of this reaction system (entries 4–6). The reactions with naphthyl iodide (**7h**) or butyl acrylate (**8′**) gave the corresponding Heck products **9h** or **9a′** in 51 or 60% isolated yield (entries 7 and 8).

The high catalytic potential of the pincer palladium complex **4** prompted us to explore the minimization of the catalyst loading to promote the Heck reaction. The reaction of iodobenzene (**7a**) with methyl acrylate (**8**) took place in the presence of 1.0 mol ppb of the pincer complex **4** under otherwise similar conditions to give a 52% isolated yield of methyl cinnamate (**9a**) along with 46% of the recovered starting aryl substrate with which a TON of 519.6 × 10^6 and a TOF of > 6500 TOF/sec were achieved.

Recently, it has been proposed that palladium nanocluster species were generated *in situ* from PCP pincer palladium complexes to catalyze the Heck reaction

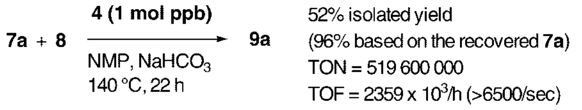
Table 2. The Heck reaction of aryl iodides and methyl acrylate.[a]

Entry	ArI	Product	Yield [%][b]	TON
1	**7b**	**9b**	89	888,000
2	**7c**	**9c**	88	881,700
3	**7d**	**9d**	87	872,500
4	**7e**	**9e**	43 (43)	430,000
5	**7f**	**9f**	78 (6)	775,000
6	**7g**	**9g**	91	910,100
7	**7h**	**9h**	51 (37)	506,700
8[c]	**7a**	**9a′**	60 (30)	600,000

[a] All reactions were carried out in the presence of the pincer palladium complex and $NaHCO_3$ at 140 °C for 22 h. ArI (mol)/**8** (mol)/[Pd] (mol)/base (mol) = 1.0/1.2/0.000001/1.1.

[b] Isolated yield. SM recovered (%) in parentheses.

[c] *n*-Butyl acrylate (**8′**) was used instead of methyl acrylate.



Scheme 3. The Heck reaction with 1 mol ppb of **4**.

with extremely high TON and TOF.[6,7] Although the detailed mechanism of the present Heck reaction with the NCN pincer **4** is not yet clear,[8] an induction period was observed in the preliminary kinetic study (time-conversion profile) of the reaction of **7a** and **8** to show good agreement with the profile of the PCP pincer palladium catalysis.[7]

A novel NCN pincer palladium complex bearing pyrroloimidazolone groups was found to catalyze the Heck reaction with high catalytic activity, i.e., the TON and the TOF were up to 519.6×10^6 and *ca.* 6500 TOF/sec, respectively. The catalytic efficiency achieved for the Heck reaction of various iodoarenes is among the highest reported so far. Mechanistic studies on this catalytic process are currently underway and will be reported in due course.

Experimental Section

General Remarks

All manipulations were carried out under a nitrogen atmosphere unless otherwise noted. Nitrogen gas was dried by passage through P_2O_5. NMR spectra were recorded on a JEOL JNM-AL400 spectrometer (400 MHz for ^1H, 100 MHz for ^{13}C, 162 MHz for ^{31}P), JEOL JNM-AL500 spectrometer (500 MHz for ^1H, 125 MHz for ^{13}C), or JEOL JNM-LA500 spectrometer (500 MHz for ^1H, 125 MHz for ^{13}C). Chemical shifts are reported in δ ppm referenced to an internal tetramethylsilane standard for ^1H NMR. Chemical shifts of ^{13}C NMR are given relative to $CDCl_3$ as an internal standard (δ = 77.0). The ^{31}P NMR data are reported relative to external 85% H_3PO_4. ^1H, ^{13}C, and ^{31}P NMR spectra were recorded in $CDCl_3$ at 25 °C unless otherwise noted. FAB mass spectra were recorded on a JEOL JMS-777V spectrometer; 3-nitrobenzyl alcohol was used as the matrix. Melting points were determined using a Yanaco micro melting point apparatus MP-J3 and are uncorrected. Optical rotations were measured on a JASCO P-1020 polarimeter. Commercially available reagents were used without any purification.

4-*tert*-Butyl-2,6-diformylphenyl Trifluoromethanesulfonate (5)

To a solution of 5-*tert*-butyl-1,3-diformyl-2-hydroxybenzene[9] (1.72 g, 8.34 mmol) and pyridine (1.20 mL, 14.8 mmol) in 50 mL of CH_2Cl_2 was added trifluoromethanesulfonic anhydride (1.80 mL, 10.7 mmol) dropwise at 0 °C over 10 min. The reaction mixture was warmed to room temperature and stirred for 30 min. The solution was cooled to 0 °C and quenched with 40 mL of 1.5 M HCl. After separation, the aqueous phase was extracted twice with CH_2Cl_2 (30 mL) and the combined extract was dried over Na_2SO_4. The organic phase was passed through a short plug of silica gel, which was then washed with CH_2Cl_2 (100 mL). The filtrates were concentrated under reduced pressure and the resulting crude solid was recrystallized from hexane to give the title compound as a white crystalline solid; yield: 2.63 g (93%); mp 69–70 °C. MS (EI): $m/z = 338$ ($[M]^+$); ^1H NMR ($CDCl_3$, 500 MHz): δ = 1.35 (s, 9H, CH_3), 8.22 (s, 2H, Ar*H*), 10.24 (s, 2H, C*H*O); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ = 31.1 [$C(CH_3)_3$], 35.5 [$C(CH_3)_3$], 118.4 (q, $^1J_{CF} = 320$ Hz, O_3SCF_3), 129.2 (Ar*C* attached to CHO), 132.4 (Ar*C*), 147.0 (Ar*C* attached to *t*-Bu), 153.2 (Ar*C* attached to OTf), 185.3 (*C*HO); anal. calcd. for $C_{13}H_{13}F_3O_5S$: C 46.15, H 3.87, S 9.48; found: C 45.89, H 3.87, S 9.64.

trans-(4-*tert*-Butyl-2,6-diformylphenyl)chlorobis(triphenylphosphine)palladium (6)

4-*tert*-Butyl-2,6-diformylphenyl trifluoromethanesulfonate (**5**; 2.03 g, 6.00 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ (3.11 g, 3.00 mmol), and triphenylphosphine (3.15 g, 12.0 mmol) were dissolved in 60 mL of CH_2Cl_2, which was stirred at room temperature for 4 h. After the solvent was removed, the residue and LiCl (2.73 g, 64 mmol) were suspended in a mixture of acetone (50 mL) and water (10 mL). The reaction mixture was stirred at room temperature for 10 h and concentrated under reduced pressure. The residue was dissolved in 100 mL of $CHCl_3$, which was washed with water (50 mL × 2) and brine (50 mL), and dried over Na_2SO_4. The solvent was removed under vacuum and the resulting solid was recrystallized from MeCN to afford **6** as yellow crystals; yield: 4.71 g (92%); mp 226–229 °C (dec.); MS (FAB): $m/z = 819$ ($[M-Cl]^+$); ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.16 (s, 9H, CH_3), 7.15 (s, 2H, Ar*H*), 7.22 (t, 12H, $^3J_{HH} = 7.6$ Hz, *m*-Ph*H*), 7.30 (t, 6H, $^3J_{HH} = 7.2$ Hz, *p*-Ph*H*), 7.50 (dd, 12H, *o*-Ph*H*), 10.40 (s, 2H, C*H*O); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ = 31.3 [$C(CH_3)_3$], 34.1 [$C(CH_3)_3$], 127.9 (virtual t, $|^2J_{CP} + {}^4J_{CP}| = 5.3$ Hz, *o*-Ph*C*), 129.7 (virtual t, $|^1J_{CP} + {}^3J_{CP}| = 23.9$ Hz, *ipso*-Ph*C*), 129.9 (*p*-

Ph*C*), 132.4 (Ar*C*), 134.1 (virtual t, $|^3J_{CP}+^5J_{CP}|=6.3$ Hz, *m*-Ph*C*), 140.9 (Ar*C* attached to CHO), 146.7 (Ar*C* attached to *t*-Bu), 172.4 (t, $^2J_{CP}=6.2$ Hz, Ar*C* attached to Pd), 194.7 (*C*HO); ^{31}P{^{1}H} NMR (CDCl$_3$, 162 MHz): δ = 22.5 (s); anal. calcd. for $C_{48}H_{43}ClO_2P_2Pd \cdot CH_3CN$: C 66.97, H 5.17, N 1.56; found: C 67.04, H 5.17, N 1.53.

[4-*tert*-Butyl-2,6-bis{(3*R*,7a*S*)-2-phenylhexahydro-1*H*-pyrrolo[1,2-*c*]imidazole-1-on-3-yl}phenyl]chloropalladium (4)

Palladium complex **6** (1.71 g, 2.00 mmol) and L-proline anilide (3.80 g, 20 mmol) were suspended in 60 mL of MeCN. The suspension was refluxed under O_2 atmosphere for 94 h (turned to a clear solution) and allowed to cool to room temperature. After removal of the solvent, the crude product was treated with MeOH and ether. The resulting yellow powder was filtered, washed with ether, and dried under vacuum to give **4**-Cl; yield: 1.33 g (98%); mp 263–265 °C (dec.); MS (FAB): *m/z* = 639 ([M – Cl]$^+$); $[\alpha]_D^{24}$: –161 (*c* 1.0, CH$_2$Cl$_2$); ^{1}H NMR (CDCl$_3$, 500 MHz): δ = 0.70 (s, 9H, C*H*$_3$), 1.81 (m, 2H), 2.17 (m, 2H), 2.39 (m, 2H), 2.60 (m, 2H), 3.56 (m, 2H), 4.23 (m, 2H), 5.13 (dd, 2H, $^3J_{HH}=9.7$ Hz, $^3J_{HH}=1.9$ Hz, bridge-head C*H*), 5.87 (s, 2H), 6.15 (s, 2H), 7.20 (d, 4H, $^3J_{HH}=7.6$ Hz, *o*-Ph*H*), 7.32 (t, 2H, $^3J_{HH}=7.5$ Hz, *p*-Ph*H*), 7.41 (t, 4H, $^3J_{HH}=7.8$ Hz, *m*-Ph*H*); ^{13}C{^{1}H} NMR (CDCl$_3$, 125 MHz): δ = 23.5 (*C*H$_2$ in pyrroloimidazolone ring), 29.2 (*C*H$_2$ in pyrroloimidazolone ring), 30.7 [C(*C*H$_3$)$_3$], 34.2 [*C*(CH$_3$)$_3$], 63.6 (N-*C*H$_2$), 71.3 (bridge-head *C*H), 94.4 (N-*C*H-N), 121.5 (*p*-Ph*C*), 126.6 (*o*-Ph*C*), 128.0 (Ar*C*), 129.5 (*m*-Ph*C*), 134.9 (*ipso*-Ph*C*), 144.6 (Ar*C* attached to pyrroloimidazolone ring), 146.7 (Ar*C* attached to *t*-Bu), 150.0 (Ar*C* attached to Pd), 170.2 (*C*=O); anal. calcd. for $C_{34}H_{37}ClN_4O_2Pd$: C 60.45, H 5.52, N 8.29; found: C 60.30, H 5.74, N 8.03.

General Procedure for the Heck Reactions

To a suspension of NaHCO$_3$ (1.1 equivs.) in NMP (1.0 mL/1.0 mmol of aryl halide) were added aryl halide (1.0 equiv.), methyl acrylate (1.2 equivs.) and the catalyst **4** (as a 0.1 mM solution in NMP). The reaction mixture was heated at 140 °C for 22 h and allowed to cool to room temperature. Then the reaction mixture was diluted with water, and the product was extracted three times with ether. The combined extracts were dried over Na$_2$SO$_4$. The organic phase was concentrated under reduced pressure and the crude product was purified by silica gel column chromatography (eluent: hexane/EtOAc = 100/1), giving the desired product. CAS Registry numbers of the Heck products: **9a**, 1754-62-7; **9a′**, 52392-64-0; **9b**, 130451-86-4; **9c**, 95416-56-1; **9d**, 20754-20-5; **9e**, 3901-07-3; **9f**, 20754-21-6; **9 g**, 20754-22-7; **9 h**, 22837-81-6.

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