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Synthesis of *N*-heterocyclic carbene-PdCl-[(2-Pyridyl)alkyl carboxylate] complexes and their catalytic activities towards arylation of (benzo)oxazoles with aryl bromides

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ABSTRACT

Four well-defined *N*-heterocyclic carbene-PdCl-[(2-Pyridyl)alkyl carboxylate] complexes have been conveniently synthesized through bridge-cleavage reactions of $[Pd(\mu\text{-}Cl)(Cl)(NHC)]_2$ with (2-pyridyl) alkyl carboxylic acids [2-(pyridin-2-yl)acetic acid and 3-(pyridin-2-yl)propanoic acid]. The new complexes have been fully characterized by NMR, elemental analysis, HR-MS and X-ray single-crystal diffraction. The catalytic performance of the complexes was screened and the obtained palladium (II) complexes shown effective catalytic activities for direct arylation of (benzo)oxazoles with aryl bromides. Moreover, the 2-(pyridin-2-yl)acetate stabilized NHC–Pd complexes were more efficient than the 3-(pyridin-2-yl)propanoate stabilized NHC–Pd analogues. Further studies exhibited that 2-(pyridin-2-yl) acetate, as ancillary ligand, could easily decarboxylate and transform into 2-methylpyridine in the reaction condition.

1. Introduction

Since Herrmann demonstrated that *N*-heterocyclc carbene (NHC) palladium complexes possess high thermal stability and are suitable for use in catalysis, considerable effort has been extended to the synthesis of various NHC–Pd complexes that lead to high catalytic activities [1]. Thus NHCs have played an important role in homogeneous catalysis and coordination chemistry, partially replacing the well-known tertiary phosphine ligands [2]. Among them, a particularly successful family of well-defined Pd(II) complexes was reported by Organ: $(NHC)PdCl_2$(3-chloropyridine), the mixed coordination of NHCs with monodentate pyridyl ligand was developed, which exhibited high catalytic activities and robust ability [3]. Extensive studies suggest that the catalytic performance of their complexes was affected greatly by the properties of the NHCs, however, the coordination of the ancillary ligand also affects the catalytic activities [4]. Therefore, modification of the pyridyl moieties by other *N*-donors have emerged great interest in order to increase the catalytic performance of the NHC–Pd complexes [5]. In the majority of coordination chemistry, the *N*-atoms of pyridines and *O*-atoms of carboxylates were widely engage in coordination with transition metal ions. Recently, Jin and Lu have reported the heteroleptic palladium (II) complexes containing both NHCs and 2-pyridine carboxylate ligand, which shown high catalytic activities for Buchwald-Hartwig amination [6]. It is well-known that the catalytic activities of the well-defined NHC–Pd complexes mainly depend on the balance of the ancillary ligand disassociating from the [NHC–Pd^0] complex and further re-coordinating to it in solution [4a,7]. The decreased strength of the Pd–N bond could lead to easier activation of the complex [4a,4d]. As a result, we envisioned that by introducing of an electron-withdrawing group (COO^-) can decrease the charge density of pyridine ring, furthermore, by increasing the distance between the *N*-atom of pyridine and the *O*-atom of carboxylate can adjust the coordination of the *N,O*-bidentate ligand. Thus the incorporation of the [N,O] chelate ligands into the NHC–Pd(II) complex might fine tune the electronic and steric properties of the coordination sphere of the NHC–Pd complexes, which facilitates ancillary ligand dissociation and recoordination in the catalytic process, and accelerated formation of the active [$(NHC)Pd^0$] species. As part of our ongoing project aimed to explore new types of well-defined NHC–Pd complexes, herein, we introduced the semi-rigid ligands [2-(pyridin-2-yl)acetate and 3-(pyridin-2-yl)propanoate] into the coordination with NHC–Pd complexes and preliminarily examined their catalytic activities for direct arylation of (benzo)oxazoles with aryl halides.

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2. Experimental section

2.1. General remarks

All reactions were carried out under air atmosphere. Dimeric compounds [Pd(μ-Cl)(Cl)(IPr)]$_2$ and [Pd(μ-Cl)(Cl)(SIPr)]$_2$ [IPr = *N,N′*-bis-(2,6-diisopropylphenyl)imidazol-2-ylidene; SIPr = *N,N′*-bis-(2,6-diisopropylphenyl)imidazolidin-2-ylidene] were prepared according to literature method [8]. NMR spectra were performed in $CDCl_3$ with tetramethylsilane (TMS) as an internal standard and recorded on a Bruker Avance NMR spectrometer. High-resolution mass spectra were recorded on Agilent 6550 iFunnel Q-TOF MS System. The C, H, and N analyses were performed with a Vario El III elementar.

2.2. General procedure for preparation of (NHC)PdCl[(2-(pyridin-2-yl)acetate] complexes 1a and 1b

In air, a round bottom flask was charged with [Pd(μ-Cl)(Cl)(NHC)]$_2$ (0.2 mmol, 225 mg), 2-pyridylacetic acid hydrochloride (0.4 mmol, 70 mg), KO^{t}Bu (1.0 mmol, 112 mg) and THF (2.0 mL). After stirring for 6 h at room temperature, the mixture was condensed under vacuum. The solid residue was filtered by flash chromatography on short silica gel with CH_2Cl_2 and recrystallized from *n*-hexane/CH_2Cl_2 to provide the desired products.

2.3. General procedure for preparation of (NHC)PdCl[(3-(pyridin-2-yl)propionate] complexes 1c and 1d

The synthesis of **1c** and **1d** were performed following the same procedure employed for the preparation of **1a** and **1b**, starting from [Pd(μ-Cl)(Cl)(NHC)]$_2$ (0.2 mmol, 225 mg), 3-(2-pyridyl)propionic acid (0.4 mmol, 61 mg), KO^{t}Bu (0.5 mmol, 56 mg) and THF (2.0 mL) to give the desired products.

2.3.1. (IPr)PdCl[(2-(pyridin-2-yl)acetate] (1a)

The procedure yielded 242 mg (91%) of the product **1a** as a yellow powder. ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm) = 8.44 (dd, *J* = 5.5 and 1.0 Hz, 1H, *o*-C*H*-pyridyl), 7.54–7.51 (m, 3H, *m,p*-C*H*-pyridyl), 7.39 (d, *J* = 7.5 Hz, 4H, *m*-C*H*-aniline), 7.17 (s, 2H, NC*H*=C*H*N), 7.05 (t, *J* = 7.5 Hz, 1H, *p*-C*H*-aniline), 7.03 (t, *J* = 7.5 Hz, 1H, *p*-C*H*-aniline), 3.49 (s, 2H, CH_2COO$^-$), 3.00 (br, 4H, C*H*(CH$_3$)$_2$), 1.46 (d, *J* = 6.5 Hz, 12H, CH(CH_3)$_2$), 1.13 (br, 12H, CH(CH_3)$_2$). ^{13}C–{^{1}H} NMR ($CDCl_3$, 125 MHz) δ (ppm) = 171.9 (*C*OO$^-$), 156.4, 156.3 (*C*$_{carbene}$), 150.8, 146.6, 138.6, 134.6, 130.3, 124.8, 124.2, 124.1, 122.4, 49.7 (*C*H$_2$COO$^-$), 28.7 (*C*H(CH$_3$)$_2$), 26.3 (CH(*C*H$_3$)$_2$). HR-MS (ESI): calcd for $C_{34}H_{43}ClN_3O_2Pd$ [M + H$^+$]$^+$ 666.2079; found 666.2098. Anal. Calc. for (IPr)PdCl [2-(pyridin-2-yl)acetate] ($C_{34}H_{42}ClN_3O_2Pd$): C, 61.26; H, 6.35; N, 6.30%. Found: C, 61.55; H, 6.15; N, 6.17%.

2.3.2. (SIPr)PdCl[(2-(pyridin-2-yl)acetate] (1b)

The procedure yielded 245 mg (92%) of the pure product **1b** as a yellow powder. ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm) = 8.37 (d, *J* = 5.5 Hz, 1H, *o*-C*H*-pyridyl), 7.53 (t, *J* = 7.5 Hz, 2H, *p*-C*H*-pyridyl), 7.47–7.44 (m, 2H, *m*-C*H*-pyridyl), 7.34 (d, *J* = 7.5 Hz, 4H, *m*-C*H*-aniline), 7.02 (t, *J* = 7.5 Hz, 2H, *p*-C*H*-aniline), 4.13 (d, *J* = 6.5 Hz, 2H, NCH_2CH_2N), 4.08 (d, *J* = 6.0 Hz, 2H, NCH_2CH_2N), 3.57 (sept, *J* = 6.5 Hz, 2H, C*H*(CH$_3$)$_2$), 3.29 (sept, *J* = 6.5 Hz, 2H, C*H*(CH$_3$)$_2$), 3.24 (s, 2H, CH$_2$COO$^-$),1.52 (br, 12H, CH(CH_3)$_2$), 1.29 (d, *J* = 6.5 Hz, 6H, CH(CH_3)$_2$), 1.24 (d, *J* = 6.0 Hz, 6H, CH(CH_3)$_2$). ^{13}C–{^{1}H} NMR ($CDCl_3$, 125 MHz) δ (ppm) = 187.1 (C$_{carbene}$), 171.9 (*C*OO$^-$), 156.3, 150.8, 147.8, 147.7, 138.6, 134.8, 129.5, 124.6, 124.4, 124.2, 122.3, 53.6 (NCH_2CH_2N), 49.2 (*C*H$_2$COO$^-$), 28.9 (*C*H(CH$_3$)$_2$), 28.8 (*C*H(CH$_3$)$_2$), 26.9 (CH(CH$_3$)$_2$), 26.8 (CH(CH$_3$)$_2$), 24.1 (CH(CH$_3$)$_2$), 23.3 (CH(*C*H$_3$)$_2$). HR-MS (ESI): calcd for $C_{34}H_{45}ClN_3O_2Pd$ [M + H$^+$]$^+$ 668.2235; found 668.2241. Anal. Calc. for (SIPr)PdCl [2-(pyridin-2-yl)acetate] ($C_{34}H_{44}ClN_3O_2Pd$): C, 61.08; H, 6.63; N, 6.28%. Found: C, 61.37; H, 6.97; N, 6.01%.

2.3.3. (IPr)PdCl[(3-(pyridin-2-yl)propionate] (1c)

The procedure yielded 232 mg (85%) of the pure product **1c** as a yellow powder. ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm) = 8.15 (d, *J* = 5.5 Hz, 1H, *o*-C*H*-pyridyl), 7.57 (m, 2H, *m*-C*H*-pyridyl), 7.50 (t, *J* = 7.5 Hz, 1H, *p*-C*H*-pyridyl), 7.43 (d, *J* = 8.0 Hz, 4H, *m*-C*H*-aniline), 7.18 (s, 2H, NC*H*=C*H*N), 6.98 (t, *J* = 8.0 Hz, 2H, *p*-C*H*-aniline), 3.30 (s, 2H, CH_2COO$^-$), 3.06 (br, 4H, C*H*(CH_3)$_2$), 2.08 (t, *J* = 6.5 Hz, 2H, CH_2CH$_2$COO$^-$), 1.46 (d, *J* = 6.5 Hz, 12H, CH(CH_3)$_2$), 1.13 (d, *J* = 4.5 Hz, 12H, CH(CH_3)$_2$). ^{13}C–{^{1}H} NMR ($CDCl_3$, 125 MHz) δ (ppm) = 176.7 (*C*OO$^-$), 161.6, 156.1 (C$_{carbene}$), 151.0, 138.4, 134.9, 130.2, 124.6, 124.1, 124.0, 122.5, 107.9, 37.9 (*C*H$_2$COO$^-$), 34.2 (*C*H$_2$CH$_2$COO$^-$), 28.8 (CH(CH3)2), 26.4 (CH(CH_3)$_2$), 22.9 (CH(CH_3)$_2$). HR-MS (ESI): calcd for $C_{35}H_{45}ClN_3O_2Pd$ [M + H$^+$]$^+$ 681.6340; found 681.6352. Anal. Calc. for (IPr)PdCl [(3-(pyridin-2-yl)propionate] ($C_{35}H_{44}ClN_3O_2Pd$): C, 61.76; H, 6.52; N, 6.17%. Found: C, 61.48; H, 6.24; N, 6.55%.

2.3.4. (SIPr)PdCl[(3-(pyridin-2-yl)propionate] (1d)

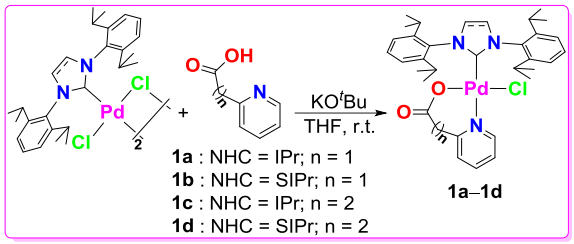
The procedure yielded 235 mg (86%) of the pure product **1d** as a yellow powder. ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm) = 8.06 (d, *J* = 5.5 Hz, 1H, *o*-C*H*-pyridyl), 7.49–7.47 (m, 3H, *m,p*-C*H*-pyridyl), 7.37 (d, *J* = 7.5 Hz, 4H, *m*-C*H*-aniline), 6.95 (t, *J* = 7.5 Hz, 2H, *p*-C*H*-aniline), 4.11 (d, *J* = 9.0 Hz, 4H, NCH_2CH_2N), 3.51 (br, 2H, C*H*(CH$_3$)$_2$), 3.38 (br, 2H, C*H*(CH$_3$)$_2$), 3.14 (br, 2H, CH_2CH$_2$COO$^-$), 2.00 (t, *J* = 6.5 Hz, 2H, CH_2COO$^-$), 1.52 (d, *J* = 6.0 Hz, 12H, CH(CH_3)$_2$), 1.28 (d, *J* = 6.5 Hz, 6H, CH(CH_3)$_2$), 1.24 (d, *J* = 6.5 Hz, 6H, CH(CH_3)$_2$). ^{13}C–{^{1}H} NMR ($CDCl_3$, 125 MHz) δ (ppm) = 186.5 (C$_{carbene}$), 176.9 (*C*OO$^-$), 161.4, 150.9, 147.9, 147.7, 138.3, 135.0, 129.4, 124.5, 124.3, 123.9, 122.4, 53.5 (NCH_2CH_2N), 34.0 (*C*H$_2$COO$^-$), 28.8 (*C*H(CH$_3$)$_2$), 27.0 (*C*H$_2$CH$_2$COO$^-$), 26.9 (*C*H(CH$_3$)$_2$), 23.7 (CH(CH_3)$_2$), 23.4 (CH(*C*H$_3$)$_2$). HR-MS (ESI): calcd for $C_{35}H_{47}ClN_3O_2Pd$ [M + H$^+$]$^+$ 682.2392; found 682.2407. Anal. Calc. for (SIPr)PdCl [(3-(pyridin-2-yl)propionate] ($C_{35}H_{46}ClN_3O_2Pd$): C, 61.58; H, 6.79; N, 6.16%. Found: C, 61.35; H, 6.52; N, 6.43%.

2.4. General procedure for the arylation of (benzo)oxazoles with aryl bromides

The direct arylation reactions were carried out under aerobic conditions. In the parallel reaction, aryl bromide (0.5 mmol), (benzo)oxazoles (0.75 mmol), LiO^{t}Bu (1.0 mmol) and the NHC-PdCl-[(2-pyridyl)alkyl carboxylate] complex (1% mol) and DMF (2.0 mL) were introduced in a reaction tube. The reaction mixture was stirred for 12 h at 130 °C. After completion of the reaction, the reaction mixture was cooled to room temperature and then evaporated under vacuum. The residue was subjected to purification *via* column chromatography with petroleum ether–EtOAc (20:1) as eluent to give the products.

2.5. General procedure for preparation of (NHC)PdCl$_2$[(2-methylpyridine] complexes 2a and 2b

In air, a round bottom flask was charged with [Pd(μ-Cl)(Cl)(NHC)]$_2$ (0.2 mmol, 225 mg), 2-pyridylacetic acid hydrochloride (0.4 mmol, 70 mg), K_2CO_3 (1.0 mmol, 138 mg) and THF (2.0 mL). The reaction mixture was stirred for 6 h at 70 °C. After completion of the reaction, the reaction mixture was cooled to room temperature and then evaporated under vacuum. The solid residue was filtered by flash chromatography on short silica gel with CH_2Cl_2 and recrystallized from *n*-hexane/CH_2Cl_2 to provide the desired products.



Scheme 1. Synthesis route for the well-defined NHC–Pd complexes **1a–1d**: [Pd(μ-Cl)(Cl)(NHC)]$_2$, (2-Pyridyl)alkyl carboxylic acid, KO^{t}Bu, THF, r.t., 6 h.

2.5.1. (IPr)PdCl$_2$(2-methylpyridine) (2a)

The procedure yielded 221 mg (84%) of the pure product **2a** as a yellow powder. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) = 8.22 (d, J = 5.2 Hz, 1H, C*H*-pyridyl), 7.53 (t, J = 7.6 Hz, 2H, *p*-C*H*-aniline), 7.40–7.38 (m, 5H), 7.15 (s, 2H, NC*H*=C*H*N), 6.96–6.91 (m, 2H), 3.19 (br, 4H, C*H*(CH$_3$)$_2$), 2.55 (s, 3H, C*H*$_3$-Pyridine), 1.46 (d, J = 4.8 Hz, 12H, CH(C*H*$_3$)$_2$), 1.11 (d, J = 6.4 Hz, 12H, CH(C*H*$_3$)$_2$). ^{13}C–{^{1}H} NMR ($CDCl_3$, 100 MHz) δ (ppm) = 159.4 ($C_{carbene}$), 157.3, 150.4, 147.0, 136.8, 130.1, 125.3, 124.8, 124.0, 123.8, 121.4, 28.8 (*C*H(CH3)2), 26.4 (CH(*C*H$_3$)$_2$), 25.0 (*C*H$_3$-Pyridine), 22.9 (CH(*C*H$_3$)$_2$). HR-MS (ESI): calcd for $C_{33}H_{44}Cl_2N_3Pd$ [M + H$^+$]$^+$ 658.1947; found 658.1959. Anal. Calc. for (IPr)PdCl$_2$(2-methylpyridine) ($C_{33}H_{44}Cl_2N_3Pd$): C, 60.14; H, 6.58; N, 6.38%. Found: C, 60.43; H, 6.87; N, 6.21%.

2.5.2. (SIPr)PdCl$_2$(2-methylpyridine) (2b)

The procedure yielded 212 mg (80%) of the pure product **2b** as a yellow powder. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) = 8.13 (d, J = 4.8 Hz, 1H, C*H*-pyridyl), 7.46 (t, J = 7.6 Hz, 2H, *p*-C*H*-aniline), 7.36–7.38 (m, 5H), 6.92–6.87 (m, 2H), 4.12 (s, 4H, NC*H*$_2$C*H*$_2$N), 3.61 (sept, J = 6.8 Hz, 4H, C*H*(CH$_3$)$_2$), 2.40 (s, 3H, C*H*$_3$-Pyridine), 1.53 (br 12H, CH(C*H*$_3$)$_2$), 1.25 (d, J = 6.8 Hz, 12H, CH(C*H*$_3$)$_2$). ^{13}C–{^{1}H} NMR ($CDCl_3$, 100 MHz) δ (ppm) = 188.3 ($C_{carbene}$), 159.4, 150.3, 148.2, 136.8, 129.3, 125.2, 124.5, 124.2, 121.4, 53.7 (NC*H*$_2$C*H*$_2$N), 28.8 (*C*H(CH$_3$)$_2$), 27.0 (CH(*C*H$_3$)$_2$), 24.7 (*C*H$_3$-Pyridine), 23.8 (CH(*C*H$_3$)$_2$). HR-MS (ESI): calcd for $C_{33}H_{45}Cl_2N_3Pd$ [M + H$^+$]$^+$ 659.2025; found 659.2041. Anal. Calc. for (SIPr)PdCl$_2$(2-methylpyridine) ($C_{33}H_{44}Cl_2N_3Pd$): C, 59.96; H, 6.86; N, 6.36%. Found: C, 60.21; H, 7.04; N, 6.19%.

2.6. X-ray crystallography

Data collection was performed on a Bruker-AXS SMART CMOS area detector diffractometer at 296 K using ω rotation scans with a scan width of 0.5° and Mo-Kα radiation (λ = 0.71073 Å). Multi-scan corrections were applied using SADABS [9]. Structure solutions and refinements were performed with the *SHELX-2014* package [10]. All non-hydrogen atoms were refined anisotropically by full-matrix least-squares on F^2. The hydrogen atoms to carbon were included in idealized geometric positions with thermal parameters equivalent to 1.2 times those of carbon atoms. CCDC 1841674–1841679 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* https://www.ccdc.cam.ac.uk/structures/.

3. Results and discussion

3.1. Synthesis and characterization of the complexes

As shown in Scheme 1, reactions of [Pd(μ-Cl)(Cl)(NHC)]$_2$ with (2-pyridyl)alkyl carboxylic acids in the presence of KO^{t}Bu in THF at room temperature afforded the (NHC)PdCl[(2-pyridyl)alkyl carboxylate] complexes **1a–1d** in good yields. The compounds were

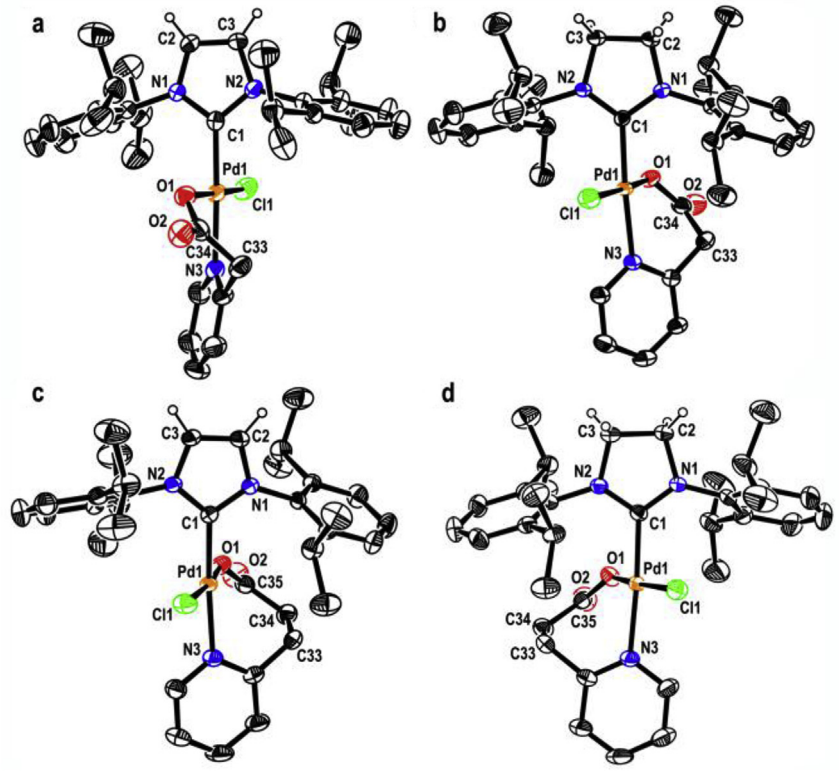


Fig. 1. ORTEP diagrams of complexes **1a–1d** with thermal displacement parameters drawn at 30% probability. Parts of the hydrogen atoms and solvent molecules have been omitted for clarity.

Table 1
Selected bond lengths [Å] and angles [°] for complexes **1a**–**1d**.

	1a	1b	1c	1d
Pd1–C1	1.968(5)	1.940(4)	1.965(4)	1.975(5)
Pd1–N3	2.094(4)	2.062(4)	2.079(4)	2.098(4)
Pd1–O1	2.034(3)	2.022(3)	2.017(3)	2.047(4)
Pd1–Cl1	2.2714(16)	2.2633(15)	2.2615(14)	2.2821(18)
C1–Pd1–O1	91.27(16)	89.94(14)	89.84(15)	89.91(19)
O1–Pd1–N3	87.82(16)	88.82(14)	91.94(13)	91.64(17)
C1–Pd1–Cl1	87.87(14)	89.11(12)	88.49(12)	88.74(15)
N3–Pd3–Cl1	92.96(14)	92.39(11)	90.19(11)	90.22(13)
PdCONCl/carbene dihedral angle	79.76	68.35	67.44	69.67

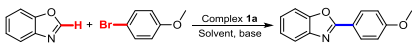
fully characterized by ^{1}H, ^{13}C NMR, HR-MS and elemental analysis. The ^{1}H NMR spectra of complexes **1a**–**1d** in $CDCl_3$ reveals the complete disappearance of the proton signals of carboxylic acids and the stoichiometric proton signals of NHCs with (2-pyridyl)alkyl carboxylates. In addition, the ^{13}C NMR spectra revealed the appearance of diagnostic carbene carbon peaks (156.3 and 156.1 ppm for IPr-bearing complexes **1a** and **1c**; 187.1 and 186.5 ppm for SIPr-bearing complexes **1b** and **1d**) and the carbonyl carbon peaks at a range of 171.9–176.9 ppm. All of the complexes were further characterized by high-resolution mass spectrometry.

Furthermore, the crystals of complexes **1a**–**1d**, which were grown in the mixture of dichloromethane and *n*-hexane, have been subjected to single crystal X-ray diffraction to determine the crystal structures. The solid-state molecular structures of the complexes are depicted in Fig. 1 and selected bond lengths and angles are listed in Table 1. As commonly observed for Pd(II)-complexes, all NHC-PdCl-[(2-pyridyl)alkyl carboxylate] complexes feature slightly distorted square-planar Pd centers and the adjacent bite angles around the Pd centers are close to 90°. The coordination spheres contain the NHCs, the bidentate *N,O*-donors of (2-pyridyl)alkyl carboxylates and the respective chlorides. The neutral σ-donating pyridine nitrogen atom is located *trans* to NHCs, while the carboxylate oxygen is situated *cis* to NHCs and in a direction opposite to the chloride. In order to satisfy the square-planar geometry of the central planes around the Pd centers, the (2-pyridyl) alkyl carboxylates are twisted and the six or seven-membered chelate ring are non-coplanar and show the bent geometry. The slightly distorted square-planar coordination planes of the Pd centers are approximately perpendicular to the carbene ring planes with the dihedral angles are 79.76, 68.35, 67.44 and 69.67°, respectively. The Pd–C bond distances in IPr-bearing complexes (1.968(5) Å for **1a** and 1.965(4) Å for **1c**) are similar with the analogous distances in their corresponding SIPr-bearing analogues (1.940(4) Å for **1b** and 1.975 (5) Å for **1d**). Generally, the Pd–C bonds distances indicated the single bond character, which is in good accordance with their σ-donor properties. Among the obtained complexes, complex **1d** has the slightly longer distances of Pd–C [1.975 (5) Å], Pd–N [2.098 (4) Å], and Pd–O [2.047 (4) Å] bonds, as well as the Pd–Cl bond [2.2821(18) Å] and were similar with those found in (IPr)PdCl(pyridine-2-carboxylate) [6]. The Pd–C bond distances were between the obtained complexes [1.940(4)–1.975(5) Å)] and the Pd-PEPPSI-(NHC) complexes (1.969(3) Å for {(IPr)$PdCl_2$(3-chloropyridine) [3a], 1.990 (3) Å for (SIPr)PdCl2(3-chloropyridine) [4a]} have no evident differences. However, due to the chelation of the bidentate *N,O*-donors and *trans* arrangement of the *N*-donors and the NHCs, the Pd–N bond distances [2.062(4)–2.098(4) Å)] are significantly shorter than the Pd-PEPPSI-(NHC) complexes.

3.2. Direct arylation of (benzo)oxazoles with aryl halides

Arylated (benzo)oxazoles are important structural scaffolds found in natural products, bioactive compounds and pharmaceuticals [11]. There is a considerable attention in the development of practical methods for the construction of these compounds [12]. Recently the transition metal-catalyzed direct C–H bond arylation of (benzo)oxazoles with aryl halides emerged as a straight forward approach for the synthesis of these compounds [13]. In most cases, excessive tertiary phosphine ligands with the Pd–complexes were used as efficient catalysts for the reaction. Due to the stronger σ-donor electronic ability and fine-tuning steric, NHCs were considered as simple phosphane mimics in organometallic chemistry. However, so far, only a few examples of well-defined NHC–Pd complexes catalyzed arylation of (benzo)oxazoles using aryl halides have been described [14]. With the isolation and characterization of this series of (NHC)PdCl [(2-pyridyl)alkyl carboxylate] complexes, we were able to test and compare their catalytic activities in the arylation of (benzo)oxazoles with aryl halides. As an initial experiment, a model reaction of benzoxazole with 4-bromoanisole was tested in the presence of 1.0 mol % of complex **1a** as precatalyst and 2 equiv of K_2CO_3 as base in *N,N*-dimethylformamide (DMF) at 130 °C for 24 h, to our delight, the arylation product, 2-(4-methoxyphenyl)benzoxazole was isolated in 47% yield (Table 2, entry 1). This preliminary result encouraged us to further optimize the reaction conditions. In most cases, C–H activation of azoles was

Table 2
Influence of the reaction conditions for complex **1a** catalyzed arylation of benzoxazole with 4-bromoanisole[a].

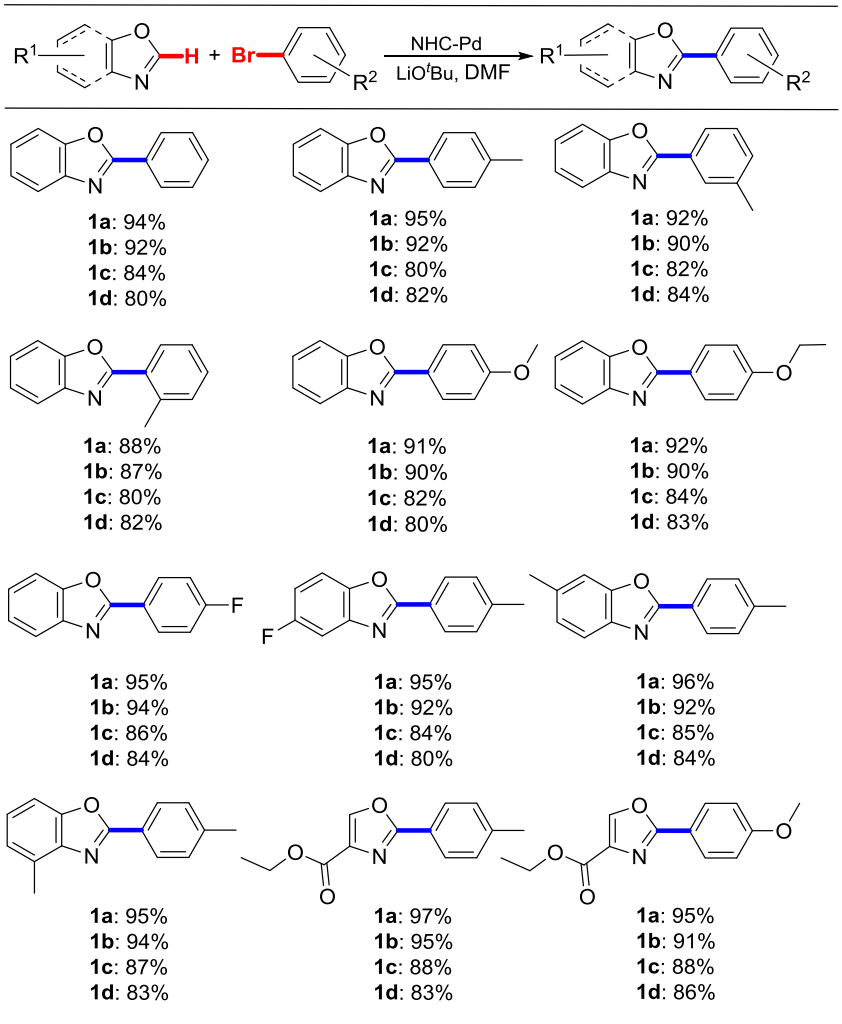


Entry	[Pd] [%]	Solvent	Base	Yield[b] (%)
1	**1a** (1.0%)	DMF	K_2CO_3	47
2	**1a** (1.0%)	DMF	LiO^tBu	92
3	**1a** (1.0%)	DMF	NaO^tBu	84
4	**1a** (1.0%)	DMF	KO^tBu	77
5	**1a** (1.0%)	CH_3CN	LiOMe	70
6	**1a** (1.0%)	DMF	NaOMe	75
7	**1a** (1.0%)	DMF	KOMe	75
8	**1a** (1.0%)	DMF	NaOH	60
9	**1a** (1.0%)	DMF	KOH	65
10	**1a** (1.0%)	DMF	Cs_2CO_3	55
11	**1a** (1.0%)	DMAc	LiO^tBu	88
12	**1a** (1.0%)	NMP	LiO^tBu	85
13	**1a** (1.0%)	1,4-dioxane	LiO^tBu	75
14	**1a** (1.0%)	toluene	LiO^tBu	65
15[c]	**1a** (1.0%)	DMF	LiO^tBu	50
16[d]	**1a** (1.0%)	DMF	LiO^tBu	91
17[e]	**1a** (1.0%)	DMF	LiO^tBu	72
18[d]	**1a** (0.5%)	DMF	LiO^tBu	65

[a] Reaction conditions: benzoxazole (0.75 mmol), 4-bromoanisole (0.50 mmol), NHC–Pd **1a** (1.0% mol), base (1.0 mmol), solvent (2.0 mL) at 130 °C for 24 h.
[b] Isolated yield.
[c] The reaction was performed at 100 °C for 24 h.
[d] The reaction was performed at 130 °C for 12 h.
[e] The reaction was performed at 130 °C for 6 h.

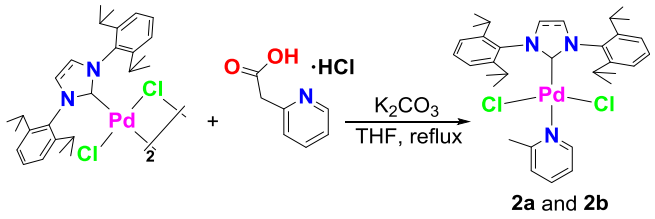
carried out in the presence of strong bases. Herein, the high yields were obtained when LiO^{t}Bu was used as the base instead of K_2CO_3 (Table 2, entry 2). In addition, the replacement of LiO^{t}Bu by two alternative bases (NaO^{t}Bu and KO^{t}Bu) was also gave high yields but less effective than LiO^{t}Bu (Table 2, entries 3–4). Other inorganic bases, such as LiOMe, NaOMe, KOMe, NaOH, KOH and Cs_2CO_3 were also examined for the reaction, and all proved to be inferior as bases, affording the product in low yields (Table 2, entries 5–10). Further screening of solvents revealed that DMF was the optimal solvent. Other polar solvent, such as *N,N*-dimethylacetamide (DMAc), *N*-methyl pyrrolidone (NMP), 1,4-dioxane and toluene, were less effective than that of DMF (Table 2, entries 11–14). In this solvent, decreasing the reaction temperature from 130 °C to 100 °C had detrimental effect on the yield (Table 2, entry 15). Furthermore, when the reaction time was reduced from 24 h to 12 h, no noticeable effect on the yield was observed, but when the reaction time was reduced to 6 h, the yield dropped significantly (Table 2, entries 16–17). The loading of the precatalyst was also examined, in the presence of 1 mol% of **1a** as precatalyst, LiO^{t}Bu as base, DMF as solvent at 130 °C for 12 h, the arylated benzoxazoles was obtained in 91% isolated yield, but when the precatalyst loading was reduced from 1 mol% to 0.5 mol%, the yield decreased to 65% (Table 2, entry 18). Finally, the best result was obtained when the reaction was carried out in DMF in the presence of LiO^{t}Bu at 130 °C for 12 h with the precatalyst loading of 1.0% mol.

After the optimization of the reaction conditions, arylation of (benzo)oxazoles with a variety of aryl bromides catalyzed by complexes **1a–1d** under the optimum reaction condition were carried out and the results are given in Scheme 2. Firstly, several substituted aryl bromides were applied to the arylation reactions with benzoxazole. As shown in Scheme 2, most of the aryl bromides, both with electron-donating substituents, such as 2-Me, 3-Me, 4-Me, 4-OMe and 4-OEt groups, and with electron-withdrawing group, such as 4-F group, on the benzene rings, could react smoothly with benzoxazole to give the corresponding products in good yields. Notably, simple benzoxazoles with various substituents on the heterocyclic (5-F, 6-Me and 4-Me groups) were also employed for the reaction with aryl bromide under the optimized reaction condition. The results indicated that the reaction proceeded smoothly and were tolerated a number of substituted groups. The corresponding 2-aryl substituted benzoxazoles were obtained in good yields. Moreover, the reactions of 4-bromotoluene and 4-bromoanisole with ethyl oxazole-4-carboxylate were highly efficient to generate the corresponding products in high yields, respectively. The reaction showed a good tolerance of different groups on the aromatic ring. However, both complexes gave poor



Scheme 2. Arylation of (benzo)oxazoles with aryl bromides catalyzed by the (NHC)-PdCl-[(2-Pyridyl)alkyl carboxylate] complexes **1a–1d**[a].

[a] Reaction conditions: (benzo)oxazoles (0.75 mmol), aryl bromide (0.50 mmol), LiO^{t}Bu (1.0 mmol), NHC–Pd complex (1.0% mol) in DMF (2.0 mL) at 130 °C for 12 h.



Scheme 3. Synthesis route for the well-defined NHC–Pd complexes **2a** and **2b**: [Pd(μ-Cl)(Cl)(NHC)]$_2$, 2-pyridylacetic acid hydrochloride, K_2CO_3, THF, reflux, 6 h.

yields in reactions with aryl chlorides as substrates. For example, under the same catalytic condition, complexes **1a**–**1d** afford only 27–38% yields for the reaction between 4-chloroanisole and benzoxazole. In this regard, complexes **1a**–**1d** are inferior to the well-defined (IPr)PdCl$_2$(1-methylimidazole) complex, which is more effective with aryl chlorides [14c].

As seen in Scheme 2, complexes **1a**–**1d** were effective in the arylation of (benzo)oxazoles with aryl bromides and the IPr-bearing complexes showed the slightly higher catalytic activities than their SIPr-bearing analogues. Although the superior reactivity of SIPr-bearing complexes compared to IPr-bearing analogues has been previously reported for the coupling reactions using the well-defined NHC–Pd complexes [15], however, this is in contrast to the general trends found in our work. We cannot attribute the reactivity differences to disparities in the electronic and steric properties of the ligands, which have been proven to be very similar [16]. With the results in hand, we believe that in our system, due to the [*N*, *O*] bidentate-chelating coordination of the (2-pyridyl)alkyl carboxylate, the unsaturated IPr–Pd complexes may be favourable when generating the IPr–Pd^0 active catalyst species [6a]. Furthermore, the [2-(pyridin-2-yl)acetate complexes **1a** and **1b** are more active than the 3-(pyridin-2-yl)propanoate stabilized NHC–Pd analogues **1c** and **1d**. According to the previous reports for the well-defined NHC–Pd complexes, higher catalytic activities of **1a** and **1b** appear to be due to an easier departure of the "throw-away" ligand to form the active [(NHC)Pd^0] species or a higher tendency of the "throw-away" ligand to recoordinate to [(NHC)Pd^0] during the activation process [4a,4d]. The coordination and dissociation ability of the ancillary ligand is significantly influence the catalytic activities. Herein, in our system, the ancillary ligands 2-(pyridin-2-yl) acetate and 3-(pyridin-2-yl)propanoate have the similar structure and coordination mode (*N,O*-bidentate chelate ligands). Nevertheless, the decarboxylation of the 2-(pyridin-2-yl)acetate into 2-methylpyridine is easily taken place in the solvent under reflux. Therefore, the complexes **1a** and **1b** possibly have been transformed into the Pd-PEPPSI precatalyst (NHC)PdCl$_2$(2-methylpyridine) under the reaction condition. Due to its easier dissociation from the Pd-centre thus forming the active [(NHC)Pd^0] species or higher tendency to recoordinate to the [(NHC)Pd^0] species, the monodentate 2-methylpyridine stabilized NHC–Pd complexes exhibited more active than 3-(pyridin-2-yl)propanoate stabilized NHC–Pd analogues. In order to obtain more information and to explain the influence factor for the higher catalytic activities of complexes **1a** and **1b**, we tried to identify the catalytically active species present in solution. Unfortunately, we have not separated the [(NHC)Pd^0] intermediate product. In another way, we found that treatment of 2-(pyridin-2-yl)acetic acid hydrochloride with dimeric compounds [Pd(μ-Cl)(Cl)(NHC)]$_2$ in THF under reflux with K_2CO_3 as the base led to the (NHC)PdCl$_2$(2-methylpyridine) complexes, which confirmed our conjecture. As shown in Scheme 3, the reaction of 2-(pyridin-2-yl)acetic acid hydrochloride with 0.5 equivalent of [Pd(μ-Cl)(Cl)(IPr)]$_2$ in THF at 60 °C generated the (IPr)PdCl$_2$(2-methylpyridine) in 84% yield. The structures of the complexes were unequivocally established by the X-ray single-crystal analysis of the crystals (Fig. 2).

Moreover, to further examine the structure–activity relationship, we have selected complexes **1a**–**1d** and **2a**, **2b** as models for time-conversion study (Fig. 3). The reaction of benzoxazole with 4-bromoanisole were performed in the presence of 1 mol% of the complex as precatalyst, LiO^{t}Bu as base, DMF as solvent at 130 °C for 12 h and the yields were monitored by GC (with dodecane used as an internal standard). In these conditions, complexes **1a** and **1b** show a similar level of catalytic activity compared with **2a** and **2b**, but a slightly higher activity in comparison with **1c** and **1d**. These results hinted that the well-defined (NHC)PdCl$_2$(2-methylpyridine) complexes should be the precatalysts in the reaction. In addition, as ancillary ligands, the coordination modes significantly influenced the catalytic activities of the well-defined NHC–Pd complexes.

4. Conclusions

In conclusion, a series of heteroleptic palladium complexes containing both NHCs and (2-pyridyl)alkyl carboxylates [2-(pyridin-2-yl)acetate and 3-(pyridin-2-yl)propanoate] were synthesized and fully characterized. The catalytic behaviours of the complexes was investigated in direct arylation of (benzo)oxazoles with aryl bromides. The [NHC)PdCl(2-pyridyl)alkyl carboxylate] complexes were found to be suitable catalysts for arylation of (benzo)oxazoles with aryl bromides. Further studies exhibited that 2-(pyridin-2-yl)acetate stabilized NHC-Pd complexes exhibited more active than 3-(pyridin-2-yl)propanoate stabilized NHC-Pd

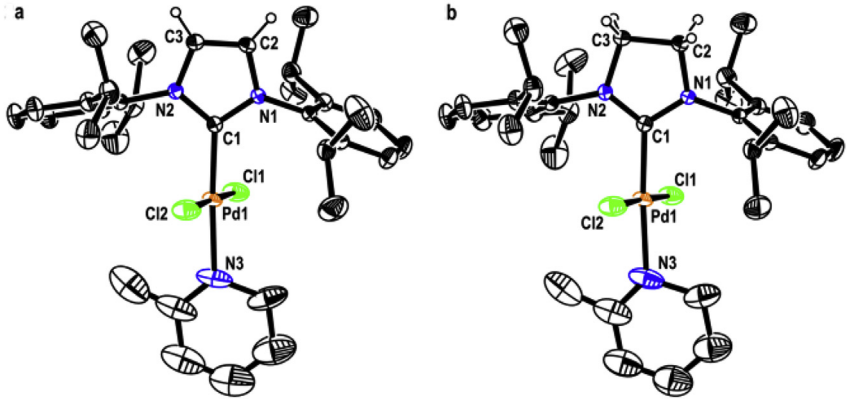


Fig. 2. ORTEP diagrams of **2a** and **2b** with thermal displacement parameters drawn at 30% probability. Parts of the hydrogen atoms have been omitted for clarity.

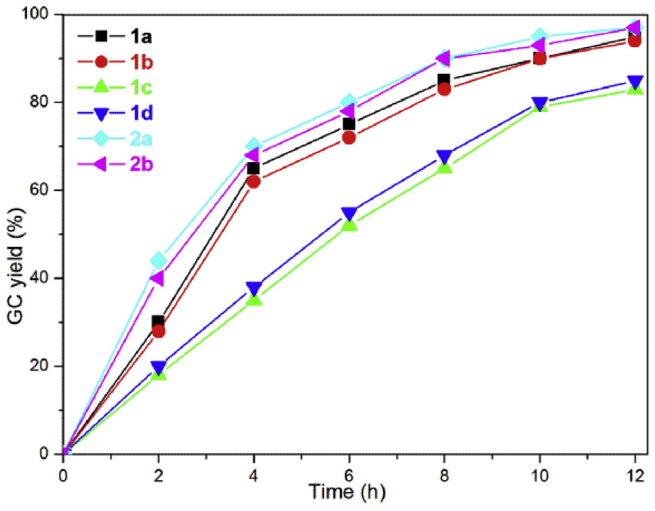


Fig. 3. Activity comparison of complexes **1a–1d, 2a** and **2b** in the arylation of benzoxazole with 4-bromoanisole.

analogues, due to the decarboxylation of the 2-(pyridin-2-yl)acetate into 2-methylpyridine has been taken place in the reaction condition. Studies have elucidated that the monodentate *N*-donor stabilized NHC-Pd complexes shown enhanced catalytic activities than the related bidentate *N,O*-donors stabilized NHC–Pd complexes.

Although there is no real benefit apparently arising from the introduction of a bidentate *N,O*-donors into the coordination with NHC–Pd complexes, we still believe that the catalytic activities of the well-defined NHC—Pd complexes depend on the balance of the ancillary ligand detaching from and re-coordinating to the [NHC-Pd^0] complex in solution. An appropriate bidentate ligand could effective adjust this kind of balance and play an important role in stabilizing the reactive catalytic species. We are carrying out further studies to clarify this point and further modification of the NHC–Pd complexes and their application are in progress in our laboratory.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jorganchem.2018.07.029.

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