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(IPr)Pd(pydc) (pydc = pyridine-2,6-dicarboxylate) – A highly active precatalyst for the sterically hindered C–N coupling reactions

Yan-Jing Li, Jin-Ling Zhang, Xiao-Jian Li, Yu Geng, Xiao-Hua Xu*, Zhong Jin*

State Key Laboratory and Institute of Elemento-Organic Chemistry, Nankai University, Tianjin 300071, PR China

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ABSTRACT

A new class of well-defined NHC–Pd complexes incorporating a pyridine-2-carboxylate or pyridine-2,6-dicarboxylate ligand has been synthesized. These novel complexes exhibited prominent catalytic activity in the sterically hindered C–N coupling reactions at elevated temperature, but relatively inferior reactivity at low temperature. The distinctly different reactivity of these NHC–Pd complexes was presumed to be associated with their unique structures of ancillary ligands.

1. Introduction

The use of *N*-heterocyclic carbenes (NHCs) as supporting ligands in the palladium-mediated homogeneous catalysis has witnessed an impressive progress over the past decade [1,2]. To date, a great number of the structurally diverse NHC-containing palladium complexes have been prepared and characterized. These prevailing NHC–Pd complexes have proven to be exceedingly versatile and robust precatalysts in the widespread C–C, C–heteroatom bond-formation reactions [3]. Due to stronger σ-donor property of NHCs [4], air- and moisture-stability, easy handling, and ready structure modification, well-defined monoligated NHC–Pd(II) complexes [2f,2g,2l] have shown superior catalytic reactivity relative to the bulky tertiary phosphine/Pd systems [5], especially in the field of Pd-catalyzed cross-coupling reactions. Generally, they consist of an accurate 1:1 ratio of Pd/NHC (Scheme 1) that avoid the use of excess costly ligand and, more important, usually exhibit enhanced reactivity associated with easy activation to a highly active low-coordinate [LPd^0] species [6].

The catalytic activity of these NHC–Pd complexes significantly related to the NHC and other ancillary ligands around Pd center. In a series of investigation, Nolan, Glorius, and Organ have demonstrated that the reactivity profile of NHC–Pd complexes related substantially to the steric nature of *N*-substituent groups R in the NHC backbone [7–10]. Meanwhile, except for the dominant NHC ligand, other ancillary ligands around the palladium center also play a very crucial role to their catalytic performance. By replacement of the allyl group with the cinnamyl group in (NHC)Pd(allyl)Cl complexes, in 2006 Nolan developed a new class of precatalysts with enhanced catalytic activity which probably resulted from an accelerated activation step from the corresponding NHC–Pd(II) complex to the active [(NHC)Pd^0] species [11]. Conversely, a dramatic reduction of catalytic activity was discovered by Organ when using more electrophilic 2,6-lutidine instead of 3-chloropyridine in the precatalysts of PEPPSI family [10]. A balance of the pyridine ligand detaching from and reattaching to the [NHC–Pd^0] complex in solution was thus implied. Moreover, Nolan discovered in the type of (NHC)Pd(acac)Cl (acac = acetylacetonato) complexes that various substituted patterns in the acac group would give rise to the distinctly different reactivity [12]. Recently, we also observed that the steric and electronic nature of the sal (sal = salicylaldimine) ligand in the (NHC)Pd(sal)Cl complexes showed a significant effect on their catalytic performance [13]. Incorporating the electron-withdrawing group(s) into *N*-substituted aryl group in the sal unit would led to the extremely increased reactivity in the amination reactions of aryl chlorides. More recently, Navarro reported a new family of complexes (NHC)PdCl$_2$(tea) using intermediate σ-donor capability triethylamine (tea) as a "throw-away" neutral ligand [14]. These complexes exhibited higher catalytic activity at lower temperature than the corresponding 3-chloropyridine counterparts.

* Corresponding authors. Tel.: +86 22 2350 1785; fax: +86 22 2350 3691.
E-mail address: zjin@nankai.edu.cn (Z. Jin).

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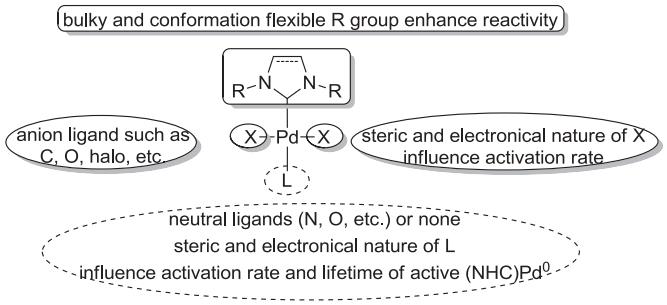


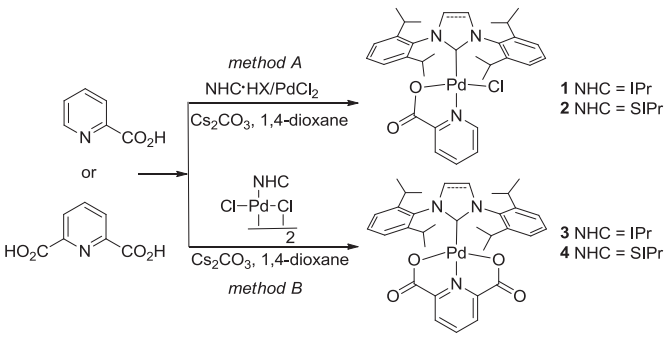
Scheme 1. Well-defined monoligated NHC–Pd(II) complexes.

As part of our ongoing project aimed to explore new types of well-defined NHC–Pd complexes with improved catalytic profiles, we envision incorporation of a pyridine-2-carboxylate (pyc) or pyridine-2,6-dicarboxylate (pydc) [15] anion ligand into the NHC–Pd(II) complex to form a new class of [O,N] or [O,N,O] chelate NHC–Pd complexes. Organ and co-workers have discovered in the PEPPSI catalyst family that, as an ancillary ligand, substituted pyridine played an extremely important role in the activation of precatalyst [10]. 2,6-Lutidine instead of 3-chloropyridine retarded greatly the disassociation rate of ancillary ligand. We also observed in the (NHC)Pd(sal)Cl complexes that the decreased strength of the Pd–N bond led to easier activation of the complex [13]. As a result, the presence of electron-withdrawing carboxylate group(s), decreasing greatly the charge density of pyridine ring, may cause a weakened N–Pd coordination which facilitates disassociation of ancillary ligand from the Pd center and accelerated formation of the active [(NHC)Pd^0] species.

2. Results and discussion

2.1. Synthesis of (NHC)Pd(pyc)Cl and (NHC)Pd(pydc) complexes

We therefore commenced synthesizing well-defined NHC–Pd complexes **1**–**4** (Scheme 2). Initially, using the protocol analogous to Organ's procedure [16], these NHC–Pd complexes were prepared from salts NHC·HX and $PdCl_2$ in a straightforward one-pot procedure (*method A*). For picolinate-containing complexes **1** and **2**, modest to good yields were obtained under the standard reaction conditions. However, with the sterically encumbered pyridine-2,6-dicarboxylic acid, reaction only gave the desired precatalysts **3** and **4** in poor yields along with remarkable degraded Pd black. As a result, an alternative, more efficient synthetic method was pursued for improving yields. To our delight, through straightforward cleavage of the [NHC–$PdCl_2$] dimers with two equivalents of 2-picolinic acid or pyridine-2,6-dicarboxylic acid in the presence of a base (*method B*), the desired NHC–Pd complexes **1**–**4** could also be obtained in satisfied yields [17]. The requisite [NHC–$PdCl_2$] dimers could be conveniently prepared from $Pd(OAc)_2$ [8], $(PhCN)_2PdCl_2$ [18], or [Pd(η^3-allyl)Cl]$_2$ [19]. The structures of all four complexes were fully characterized by means of elemental analysis, ^{1}H and ^{13}C NMR spectroscopy, and ESI-MS. These complexes commonly exhibit high air- and moisture-stability, allowing for indefinite storage and easy handling on the benchtop.



Scheme 2. Synthesis of NHC–Pd complexes **1**–**4**.

2.2. X-ray crystal structures of (NHC)Pd(pyc)Cl and (NHC)Pd(pydc) complexes

Suitable crystals for single-crystal diffraction analyses of (NHC)Pd(pyc)Cl and (NHC)Pd(pydc) complexes **1**–**4** were obtained by slow diffusion of *n*-pentane into dichloromethane solution (Figs. 1 and 2). Selected bond lengths and angles for compounds **1** and **3** were listed in the captions for figure, respectively. The crystal structures revealed unambiguously a [O,N] bidentate chelate coordination in complexes **1** and **2**, and a slightly distorted square-plane geometry around the palladium center. Like the precatalysts of the PEPPSI family [9,10,16], the neutral σ-donating pyridine nitrogen atom is located *trans* to the NHC ligand, while the carboxylate oxygen anion is situated in the *cis* to the NHC ligand in a direction opposite the chloride anion. While in complexes **3** and **4**, a unique [O,N,O] tridentate *trans*-chelating planar configuration was observed. From the crystal X-ray diffraction data, due to induction by [O,N,O] tridentate chelating coordination of pyridine-2,6-dicarboxylate, the distances of the Pd–$C_{carbene}$ bonds in complexes **3** and **4** are 2.005 Å and 1.996 Å in solid crystals, respectively, which are obviously larger than those of complexes **1** and **2** (1.963 Å for **1** and 1.970 Å for **2**, respectively). In addition, the Pd–$C_{carbene}$ bonds of complexes **3** and **4** are also comparatively longer than those of NHC–Pd complexes [(IPr)$PdCl_2]_2$ dimer [18b] and (IPr)Pd(3-chloropyridine)Cl_2 [10] (1.9553 Å and 1.962 Å, respectively). Generally, the longer Pd–$C_{carbene}$ bond facilitated oxidative addition of [(NHC)Pd^0] species to the sterically encumbered electrophile

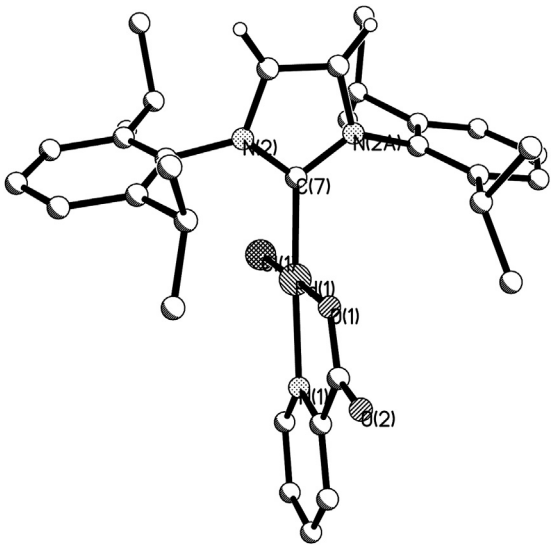


Fig. 1. Crystal structure of complex **1** with thermal ellipsoids drawn at the 50% probability level and most H atoms (except those in the backbone of NHC) and co-crystallizing solvent molecules have been omitted for clarity. Selected bond lengths (Å) and angles (°): Pd(1)–C(7) 1.963(2), Pd(1)–O(1) 2.0219(17), Pd(1)–N(1) 2.067(2), Pd(1) –Cl(1) 2.2773(7); O(1)–Pd(1)–N(1) 81.59(8), O(1)–Pd(1)–Cl(1) 178.39(5), C(7)–Pd(1)–O(1) 89.84(8), N(1)–Pd(1)–Cl(1) 96.80(6), N(2)–C(7)–N(2A) 105.39(19), O(1) –Pd(1)–N(1) 81.59 (8).

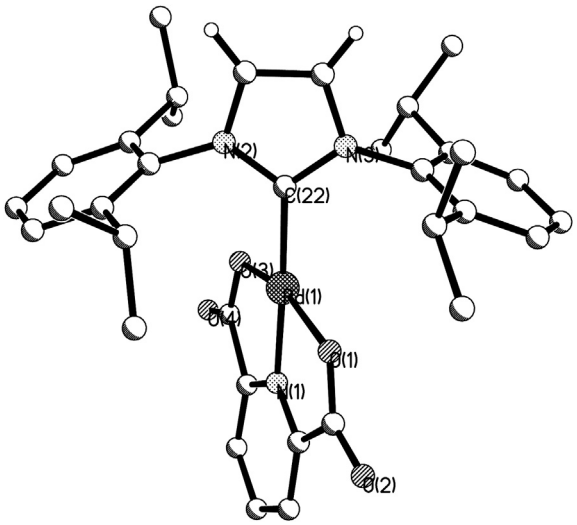


Fig. 2. Crystal structure of complex **3** with thermal ellipsoids drawn at the 50% probability level and most H atoms (except those in the backbone of NHC) and co-crystallizing solvent molecules have been omitted for clarity. Selected bond lengths (Å) and angles (°): Pd(1)–C(22) 2.005(2), Pd(1)–O(1) 2.0398(16), Pd(1)–O(3) 2.0407(15), Pd(1)–N(1) 1.9430(18); O(1)–Pd(1)–N(1) 80.71(7), O(3)–Pd(1)–N(1) 80.48(7), O(1)–Pd(1)–O(3) 161.16(6), C(22)–Pd(1)–N(1) 177.19(8), N(2)–C(22)–N(3) 104.98(19).

substrates because of the decreased steric propelment from the bulky NHC ligand.

2.3. Catalytic studies of (NHC)Pd(pyc)Cl and (NHC)Pd(pydc) complexes in Buchwald–Hartwig cross-coupling reactions

With these complexes in hand, their catalytic activities in Buchwald–Hartwig coupling reactions were subsequently investigated. In initial experiments using mesityl chloride and morpholine as the coupling partners, NaO*t*Bu and 1,4-dioxane were identified to be the optimal base and solvent for the coupling reactions. At the beginning, coupling reactions were performed at 50 °C using the conditions for PEPPSI catalysts reported by Organ and co-workers [20]. However, relative to the control dimer $[(IPr)PdCl_2]_2$ and PEPPSI family derivative $(IPr)PdCl_2$(3-chloropyridine) (IPr-PEPPSI), all four complexes exhibited the inferior reactivity under the reaction conditions (Fig. 3). To our surprise, when the coupling reactions were carried out at elevated temperature (100 °C), an obviously different reactivity between complexes **1**–**4** and the control catalysts was observed (Fig. 4).

Under the optimized conditions, a significant difference in catalytic performance between complexes **1**–**4** was also observed (Table 1). Compared to complexes **1** and **2**, complexes **3** and **4** showed obviously superior reactivity. In all cases, unsaturated NHC palladium complexes were more effective catalysts than their saturated counterparts [21]. Amongst them, (IPr)Pd(pydc) **3** was found to be the most active catalyst for the coupling reactions. For example, coupling reaction employing complex **3** as a catalyst afforded the corresponding *N*-mesityl morpholine in an isolated yield of 93% within mere 20 min (entry 3, Table 1).

Furthermore, complex **3** was also found to show the predominant reactivity in the coupling of a variety of aliphatic amines with the sterically encumbered aryl chlorides (Table 2). Generally, using complex **3** at 1.0 mol % catalyst loading, the sterically congested aryl chlorides were capable of coupling with various cyclic and acyclic aliphatic amines in high yields within no more than 1 h. Unfortunately, piperidine proved less reactive relative to morpholine under the present system (entry 3, Table 2). In addition, coupling with mono-protected *N*-tosyl piperizine also afforded the desired product in a decreased yield even at a longer reaction time, which probably resulted from the low solubility of protected amine substrate in 1,4-dioxane (entries 5 and 10, Table 2).

The sterically congested *N*,*N*-diarylamines have recently proven mild and extremely active dehydrative agents for ester condensation process [22]. (IPr)Pd(pydc) **3** was also found to be the highly active catalyst for coupling of the sterically demanding aryl chlorides with aromatic amines (Table 3). As illustrated, most of the sterically crowded diarylamines could be obtained in excellent yields within no more than 30 min. In general, coupling reactions were more sensitive to the bulkiness of aryl chloride substrates than that of aromatic amines. With more bulky aryl chlorides, such as 2,6-diisopropylphenyl chloride, a longer reaction time was required for complete conversion (entries 11 and 12, Table 3). Notably, using complex **3** as a catalyst, 1,1′-biphenyl-2,2′-diamine is also capable of coupling with the sterically congested aryl chlorides

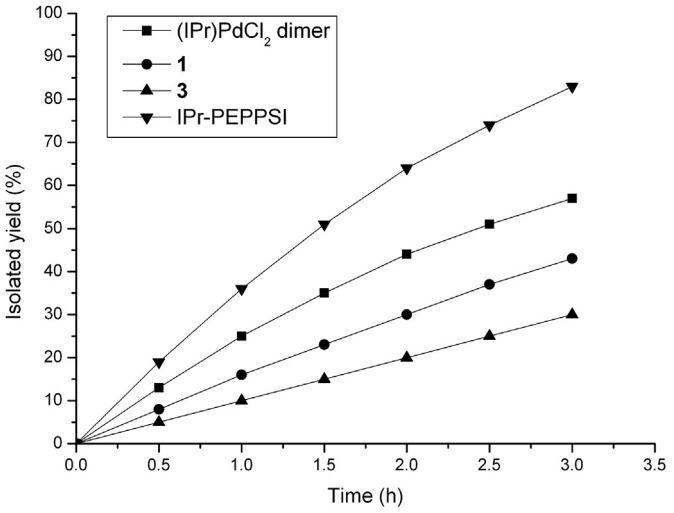


Fig. 3. Coupling reactions between mesityl chloride and morpholine at 50 °C with $[(IPr)PdCl_2]_2$ dimer, IPr-PEPPSI, complexes **1** and **3** at 1.0 mol % catalyst loading (for $[(IPr)PdCl_2]_2$ dimer, 0.5 mol % catalyst was used).

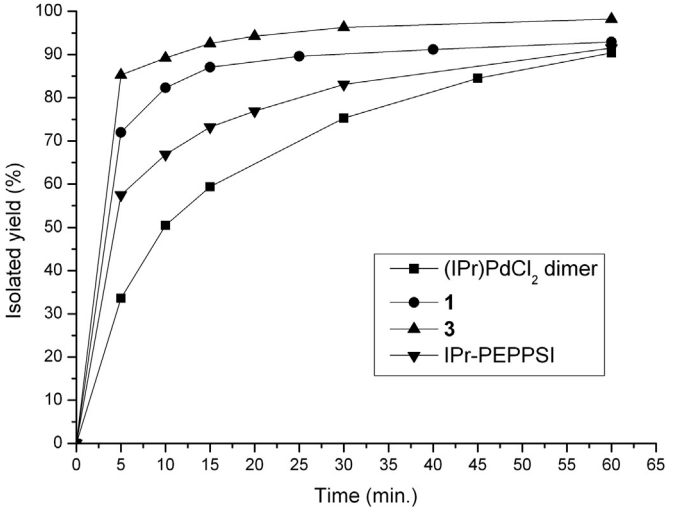
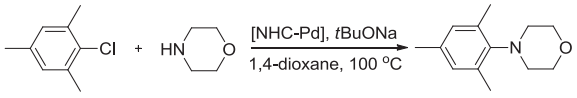


Fig. 4. Coupling reactions between mesityl chloride and morpholine at 100 °C with $[(IPr)PdCl_2]_2$ dimer, IPr-PEPPSI, complexes **1** and **3** at 1.0 mol % catalyst loading (for $[(IPr)PdCl_2]_2$ dimer, 0.5 mol % catalyst was used).

Table 1
Buchwald–Hartwig coupling catalyzed by complexes **1**–**4**.[a]



Entry	NHC–Pd complex	Time (min)	Yield (%)[b]
1	**1**	20	86
2	**2**	20	79
3	**3**	20	93
4	**4**	20	88
5[c]	$[(IPr)PdCl_2]_2$	20	62
6	IPr-PEPPSI	20	75

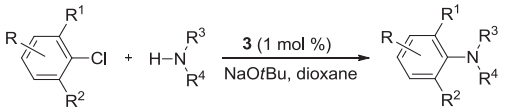
[a] Reaction conditions: mesityl chloride (1 mmol), morpholine (1.1 mmol), NHC–Pd complex (1 mol %), NaO*t*Bu (1.5 mmol), 1,4-dioxane (3 mL), *T* 100 °C.
[b] Isolated yield on average of two runs.
[c] 0.5 mol % of $[(IPr)PdCl_2]_2$ dimer.

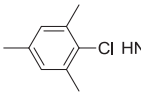
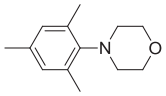
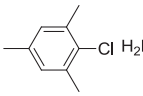
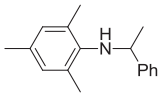
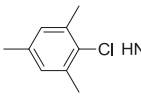
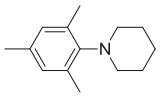
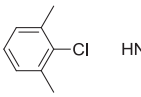
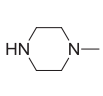
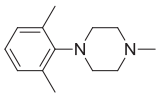
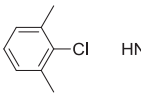
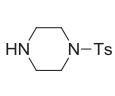
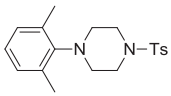
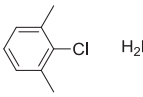
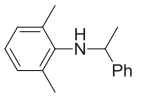
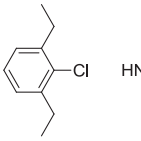
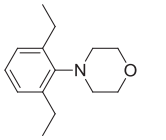
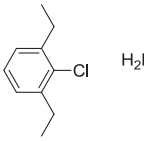
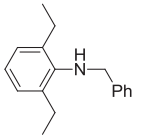
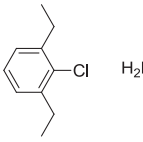
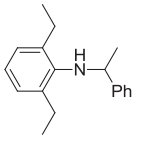
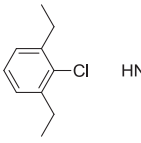
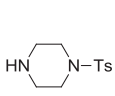
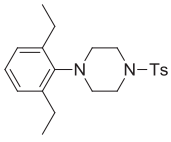
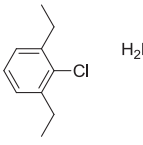
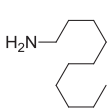
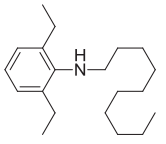
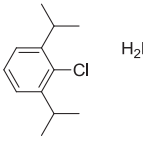
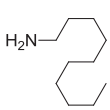
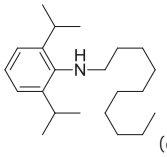
to provide the corresponding *N,N′*-diaryl substituted derivatives (entries 13 and 14, Table 3), which have proven the essential building blocks of a new class of secondary phosphine oxides (SPOs) preligands developed recently by us [23].

Nolan and co-workers have demonstrated elegantly that enhanced catalytic activity in the NHC–Pd complexes could be achieved by accelerating the corresponding activation step from NHC–Pd^{II} complex to active [(NHC)Pd^0] species [11]. From the crystal X-ray diffraction data of complexes **3** and **4**, there are two adjacent acute angles (N(1)–Pd(1)–O(1) and N(1)–Pd(1)–O(3) angles) in the molecular structures of complexes **3** and **4** (80.71° and 80.79°, respectively) (Scheme 3), which caused an increased ring strain in each cycle around the Pd center. As a result, high reactivity of complexes **3** and **4** probably attributed to the increased ring strain, which caused an accelerated activation step from the corresponding NHC–Pd^{II} complex to the [NHC–Pd^0] species at elevated temperature, whereas at low temperature complexes **3** and **4** were relatively inert toward activation by base due to the firmly [O,N,O] chelating *δ*-coordination. In addition, considering that all of these NHC–Pd(II) complexes were transformed into the same [(NHC)Pd^0] species in solution, their dramatically different reactivity were probably associated with effect of other ancillary ligand. As a result, a balance of the pyridine-2,6-dicarboxylate ligand detaching from and reattaching to the [NHC–Pd^0] complex in solution was not completely excluded yet [10,14]. When pyridine-2,6-dicarboxylate ligand reattached to the Pd^0 center, except for stabilizing the [NHC–Pd^0] species and lengthening the lifetime of catalyst, it also probably induced a longer $C_{carbene}$–Pd bond.

Using an *in situ* trapping experiment carried out in the presence of PPh_3, the activation of Pd(II) to Pd(0) for the complex **3** was investigated with various bases used at 50 °C and 100 °C, respectively (Fig. 5). Regardless of the activation route, a complex was formed when NaO*t*Bu was used as a base (Fig. 5(b) and (c)). The existence of such a complex was confirmed by observation of the formation of known (IPr)Pd(PPh_3) (^{31}P NMR 33.4 ppm) [24]. As illustrated in Fig. 5, the activation rate of the precatalyst **3** at 100 °C (Fig. 5(c)) was obviously faster than that at 50 °C (Fig. 5(b)). Although the exact activation pathway was not known at this stage, a mechanism proposed originally by Hartwig is probably involved, in which the alkoxide base acts as an initiator and leads to the formation of an alkoxidepalladium species [25]. Relatively, the use of Cs_2CO_3 instead of NaO*t*Bu did not give rise to the desired NHC–Pd^0 species at the same condition (Fig. 5(d)). Furthermore, the catalytic effect of ancillary ligand was studied by ligand exchanging experiments (Scheme 4). When additional 1 mol % PPh_3 was present in the coupling reaction between mesityl chloride and

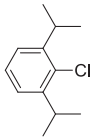
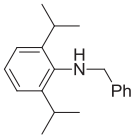
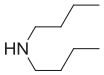
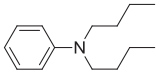
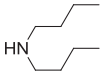
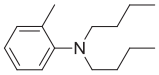
Table 2
Cross-coupling of the sterically hindered aryl chlorides with aliphatic amines.[a]



Entry	ArCl	Amine	Product	Time (min)	Yield (%)[b]
1				20	93
2				15	92
3				20	65
4				30	95
5				30	58 (86)[c]
6				15	91
7				60	90[d,e]
8				25	91
9				40	90
10				120	37 (75)[c]
11				30	90
12				45	96

(*continued on next page*)

Table 2 (*continued*)

Entry	ArCl	Amine	Product	Time (min)	Yield (%)[b]
13				60	86
14				15	95
15				20	87

[a] Reaction conditions: aryl chloride (1 mmol), amine (1.1 mmol), **3** (1 mol %), NaO*t*Bu (1.5 mmol), 1,4-dioxane (3 mL), *T* 100 °C.
[b] Isolated yield on average of two runs.
[c] Yield was reported in the parentheses using 1,4-dioxane (10 mL) for 120 min.
[d] 2 mol % of complex **3** were used.
[e] 2 mmol morpholine were used.

morpholine, only trace amount coupling product was obtained under the aforementioned standard conditions (Scheme 4). In contrast, by adding 1 mol % pyridine-2,6-dicarboxylic acid, increased yield (91%) was achieved in the coupling reaction catalyzed by $[(IPr)PdCl_2]_2$ dimer.

3. Conclusion

In conclusion, we have developed a new class of well-defined NHC–Pd complexes incorporating pyridine-2-carboxylate or pyridine-2,6-dicarboxylate as an ancillary ligand. Among them, complex (IPr)Pd(pydc) **3** showed an obviously enhanced catalytic potential in the Buchwald–Hartwig reactions of the sterically hindered coupling substrates at elevated temperature. Further applications of this type of air-stable NHC–Pd complexes for other cross-coupling reactions are currently underway.

4. Experimental section

4.1. General comments

All cross-coupling reactions were carried out in dry Ar_2 using the standard Schlenk technique unless indicated. All solvents were dried according to the common methods prior to use. Aryl chlorides were used as received from commercial availability or prepared via the classical Sandmeyer reactions from the corresponding aryl amines. Aliphatic and aryl amines were used as received from commercial availability. ^1H and ^{13}C Nuclear Magnetic Resonance (NMR) spectra were recorded on a Bruker AV400 spectrometer at ambient temperature in $CDCl_3$ (Cambridge Isotope Laboratories, Inc). ESI mass spectra were recorded on Thermo Finnigan LCQ Advantage spectrometers. Elemental analyses were performed on a Perkin–Elmer 240C analyzer. Melt points of compounds were recorded with uncorrected thermometers. Flash column chromatography was performed on silica gel 60 (230–400 mesh).

4.2. General procedure for preparation of complexes **1** and **2** (method A)

In air, to a Schlenk tube that closed with a screw cap fitted with a septum and was equipped with a magnetic stir bar were added in turn NHC·HCl (1.1 mmol, 468 mg), $PdCl_2$ (1.0 mmol, 177 mg), Cs_2CO_3 (5 mmol, 1.63 g), and 2-nicotinic acid (1.1 mmol, 136 mg). The tube was then caped with a rubber septum and evacuated and backfilled with argon. This sequence was repeated three times. 1,4-Dioxane (10 mL) was injected through the septum. The mixture was then stirred at a pre-heated oil bath (80 °C) for 20 h. The reaction mixture was cooled to room temperature and CH_2Cl_2 (25 mL) added. After filtration via a short pad of celite, the filtrate was condensed under vacuum and the residue was purified by flash chromatography on silica gel to provide the desired **1**and **2**.

Complex **1**: Yellow solid, yield 65%. M.p. > 280 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 8.55 (d, 1H), 7.80 (t, 2H), 7.49 (t, 2H), 7.34 (m, 5H), 7.18 (s, 2H), 2.95 (m, 4H), 1.41 (d, 12H), 1.13 (d, 12H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.8, 157.2, 151.2, 146.8, 146.5, 139.2, 134.5, 130.4, 126.7, 126.2, 125.2, 124.1, 28.6, 26.2, 22.9. Anal. Calcd for $C_{33}H_{40}ClN_3O_2Pd$: C, 60.74; H, 6.18; N, 6.44. Found: C, 60.67; H, 6.10; N, 6.38. MS (ESI): *m*/*z* 652 ($M^+ + H$).

Complex **2**: Yellow solid, yield 56%. M.p. > 280 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 8.51 (d, 1H), 7.78 (t, 2H), 7.40 (t, 2H), 7.28 (m, 5H), 4.11 (s, 4H), 3.44 (m, 4H), 1.40 (d, 12H), 1.12 (d, 12H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 187.6, 172.7, 151.2, 147.7, 146.4, 139.2, 134.6, 129.6, 126.6, 126.2, 124.5, 53.7, 28.7, 26.6, 23.8. Anal. Calcd for $C_{33}H_{42}ClN_3O_2Pd$: C, 60.55; H, 6.47; N, 6.42. Found: C, 60.66; H, 6.49; N, 6.46. MS (ESI): *m*/*z* 654 ($M^+ + H$).

4.3. General procedure for preparation of complexes **3** and **4** (method B)

In air, to a Schlenk tube that closed with a screw cap fitted with a septum and was equipped with a magnetic stir bar were added in turn $[(NHC)PdCl_2]_2$ dimer (0.5 mmol, 568 mg), Cs_2CO_3 (2.6 mmol, 848 mg), and pyridine-2,6-dicarboxylate (2.5 mmol, 418 mg). The tube was then caped with a rubber septum and evacuated and backfilled with argon. This sequence was repeated three times. 1,4-Dioxane (10 mL) was injected through the septum. The mixture was then stirred at a pre-heated oil bath (80 °C) for 20 h. The reaction mixture was cooled to room temperature and CH_2Cl_2 (25 mL) added. After filtration via a short pad of celite, the filtrate was condensed under vacuum and the residue was purified by flash chromatography on silica gel to provide the desired **3** and **4**.

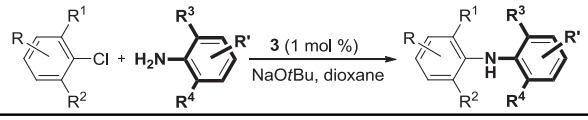
Complex **3**: Yellow solid, yield 85%. M.p. > 280 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 7.95 (t, 1H), 7.70 (d, 2H), 7.51 (t, 2H), 7.36 (m, 4H), 7.22 (s, 2H), 2.70 (m, 4H), 1.39 (d, 12H), 1.16 (d, 12H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.9, 164.0, 147.9, 146.6, 140.4, 134.1, 130.5, 127.0, 125.2, 124.2, 28.7, 25.6, 23.1. Anal. Calcd for $C_{34}H_{39}N_3O_4Pd$: C, 61.86; H, 5.96; N, 6.37. Found: C, 61.67; H, 5.90; N, 6.38. MS (ESI): *m*/*z* 660 ($M^+ + H$).

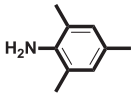
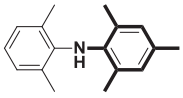
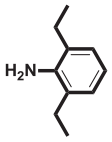
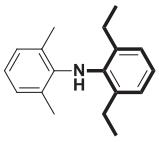
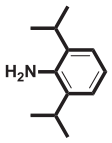
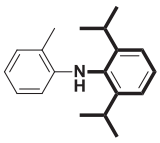
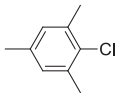
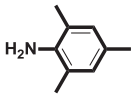
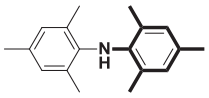
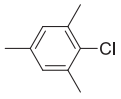
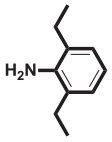
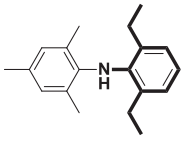
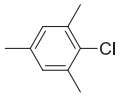
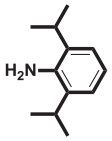
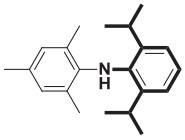
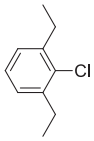
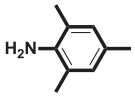
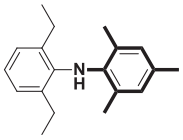
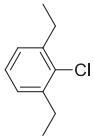
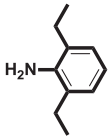
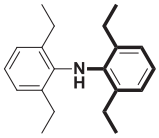
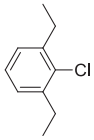
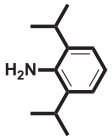
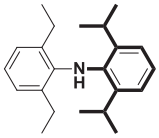
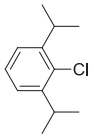
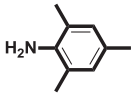
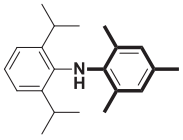
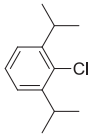
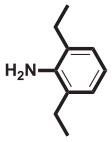
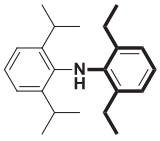
Complex **4**: Yellow solid, yield 83%. M.p. > 280 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 7.93 (t, 1H), 7.70 (d, 2H), 7.43 (t, 2H), 7.30 (m, 4H), 4.13 (s, 4H), 3.23 (m, 4H), 1.44 (d, 12H), 1.30 (d, 12H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 192.9, 171.9, 147.7, 140.4, 134.0, 130.0, 127.0, 124.7, 53.9, 28.8, 26.0, 23.9. Anal. Calcd for $C_{34}H_{41}N_3O_4Pd$: C, 61.67; H, 6.24; N, 6.35. Found: C, 61.67; H, 6.20; N, 6.41. MS (ESI): *m*/*z* 662 ($M^+ + H$).

4.4. General procedure for the Buchwald–Hartwig amination reactions

In air, to a Schlenk tube that closed with a screw cap fitted with a septum and was equipped with a magnetic stir bar were added in turn complex **3** (0.01 mmol, 7 mg), and $NaOBu^t$ (1.5 mmol, 144 mg). The tube was then caped with a rubber septum and evacuated and backfilled with argon. This sequence was repeated three times. Aryl chloride (1.0 mmol) and amine (1.1 mmol) was injected through the septum by syringe, followed by addition of dry 1,4-dioxane (10 mL). The mixture was then stirred at a pre-heated oil bath (100 °C) for the indicated time. The reaction mixture was cooled to room

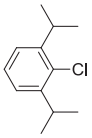
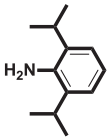
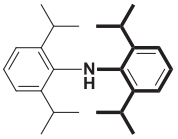
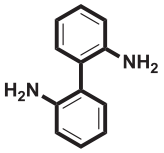
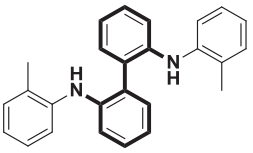
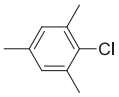
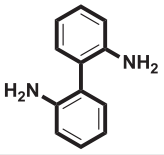
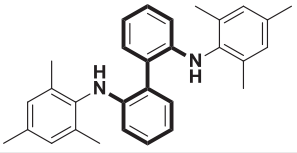
Table 3
Cross-coupling of the sterically hindered aryl chlorides with anilines.[a]



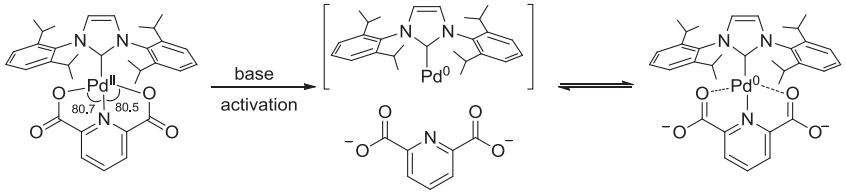
Entry	ArCl	Aniline	Product	Time (min)	Yield (%)[b]
1				10	98
2				10	99
3				10	99
4				10	98
5				15	97
6				15	97
7				15	96
8				20	97
9				25	98
10				20	94
11				60	95[c,d]

(*continued on next page*)

Table 3 (*continued*)

Entry	ArCl	Aniline	Product	Time (min)	Yield (%)[b]
12				60	54[c,d]
13				60	79[e]
14				60	74[e]

[a] Reaction conditions: ArCl (1 mmol), amine (1.1 mmol), complex **3** (1 mol %), NaO*t*Bu (1.5 mmol), 1,4-dioxane (3 mL), *T* 100 °C.
[b] Isolated yield on average of two runs.
[c] 2 mol % of **3** were used.
[d] 2 mmol $ArNH_2$ were used.
[e] 2.0 equiv ArCl per equivalent $ArNH_2$ were used.



Scheme 3. Precatalyst activation and possible balance between (NHC)Pd^0 and ancillary ligand.

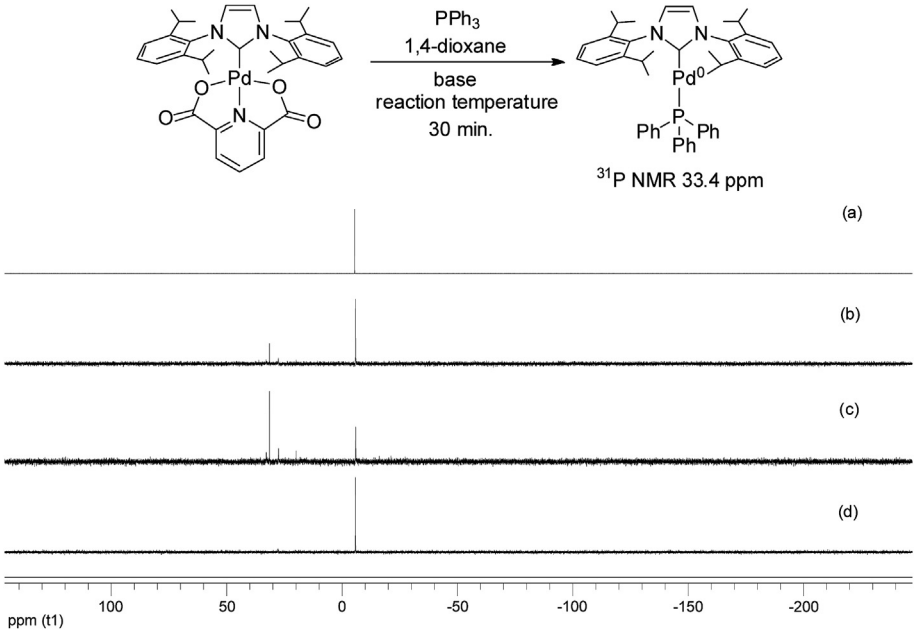
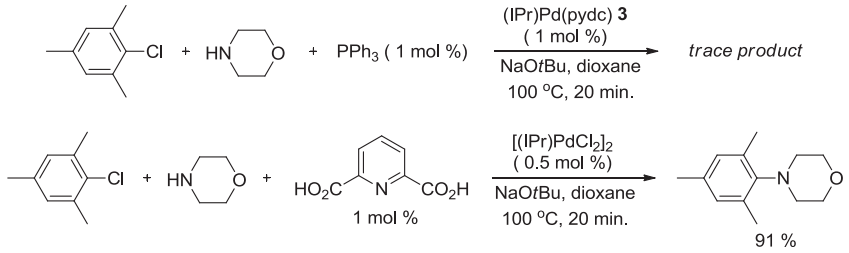


Fig. 5. Generation of Pd(0) species monitored by ^{31}P NMR spectra. (a) ^{31}P NMR spectra of free PPh_3; (b) Base: NaO*t*Bu, reaction temperature: 50 °C; (c) Base: NaO*t*Bu, reaction temperature: 100 °C; (d) Base: Cs_2CO_3, reaction temperature: 100 °C.



Scheme 4. Effect of ancillary ligands on the coupling reaction.

Table 4
Crystallographic data for complexes **1**–**4**.

	1	**2**	**3**	**4**
Chemical formula	$C_{33}H_{40}ClN_3O_2Pd$	$C_{33}H_{42}ClN_3O_2Pd$	$C_{34}H_{39}N_3O_4Pd$	$C_{34}H_{41}N_3O_4Pd$
Space group	*Pnma*	*Pnma*	*P*−1	*P*2(1)2(1)2(1)
Cryst syst	Orthorhombic	Orthorhombic	Triclinic	Orthorhombic
a, Å	16.029(2)	15.965(4)	10.268(2)	13.181(4)
b, Å	21.122(3)	21.221(5)	16.765(3)	14.373(4)
c, Å	10.9821(16)	11.055(3)	17.991(4)	20.024(6)
α, °	90.00	90.00	91.540(5)	90.00
β, °	90.00	90.00	90.425(5)	90.00
γ, °	90.00	90.00	90.179(6)	90.00
Z	4	4	4	4
D_{calc}, g cm^{-3}	1.469	1.462	1.416	1.457
μ(Mo), mm^{-1}	0.89	0.89	0.64	0.81
F(000)	1688	1696	1368	1712
θ range, °	1.9–27.9	1.92–27.87	1.68–27.86	1.74–27.91
No. of reflns. collected	34,483	39,520	35,544	40,028
No. of unique reflns/R_{int}	4565/0.035	4586/0.0487	14,564/0.0466	9074/0.0723
No. of params/restraints	230/0	230/0	773/0	442/0
Final *R* indices [$I > 2\sigma(I)$]	$R_1 = 0.0293$, $wR_2 = 0.0708$	$R_1 = 0.0363$, $wR_2 = 0.0808$	$R_1 = 0.0363$, $wR_2 = 0.0713$	$R_1 = 0.0443$, $wR_2 = 0.0954$
R indices (all indices)	$R_1 = 0.0329$, $wR_2 = 0.0728$	$R_1 = 0.0396$, $wR_2 = 0.0828$	$R_1 = 0.0466$, $wR_2 = 0.0749$	$R_1 = 0.0477$, $wR_2 = 0.0974$
Goodness-of-fit on F^2	1.064	1.111	1.060	1.037
Peak/hole, e Å^{-3}	1.00 and −0.77	1.07 and −0.83	0.69 and −0.98	0.61 and −0.76

temperature and CH_2Cl_2 (25 mL) added. After filtration via a short pad of celite, the filtrate was condensed under vacuum and the residue was purified by flash chromatography on silica gel to provide the desired coupling products. Yields of isolated products were reported in Tables 1–3.

4.5. X-ray diffraction analysis

Suitable crystals of **1**–**4** for X-ray diffraction were obtained by slow diffusion of *n*-pentane into dichloride methane solution. Crystallographic data was collected on a Bruker SMART CCD area detector diffractometer with graphite-monochromated Mo Kα radiation (λ 0.71073 Å). Diffraction measurements were made at room temperature. An absorption correction by SADABS was applied to the intensity data. The structures were solved by Patterson method. The remaining non-hydrogen atoms were determined from the successive difference Fourier syntheses. All non-hydrogen atoms were refined anisotropically except those mentioned otherwise. The hydrogen atoms were generated geometrically and refined with isotropic thermal parameters. The structures were refined on F2 by full-matrix least-squares methods using the SHELXTL-97 program package [26]. The crystal data and structural refinements details are listed in Table 4. CCDC reference numbers are 873328–873331.

Acknowledgment

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Appendix A. Supplementary material

CCDC 873328–873331 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.

Appendix B. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jorganchem.2013.03.021.

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