ORGANOMETALLICS

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[Pd(IPr*)(3-Cl-pyridinyl)Cl_2]: A Novel and Efficient PEPPSI Precatalyst

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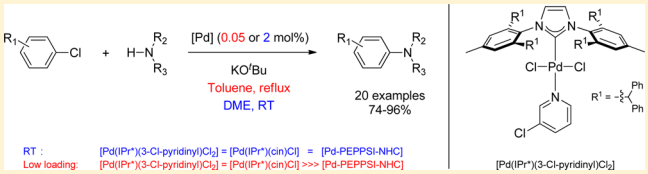
Supporting Information

ABSTRACT: The preparation of the novel, well-defined [Pd(IPr*)(3-Cl-pyridinyl)Cl_2] complex is described. The steric parameters of the ligand as well as its reactivity in the Buchwald–Hartwig amination were directly compared to other [Pd(NHC)(3-Cl-pyridinyl)Cl_2] and [Pd(IPr*)(LX)Cl)] precatalysts (LX = cinnamyl or acac). The title complex exhibits similar catalytic activity to [Pd(NHC)(3-Cl-pyridinyl)Cl_2] congeners (NHC = IPr and SIPr) at room temperature. However, it also showed improved reactivity at low catalyst loading and high temperature (as low as 0.025 mol %). On the other hand, it proved to be as efficient as the previously reported [Pd(IPr*)(cinnamyl)Cl] complex, pointing to the most likely existence of a similar catalytically active species.



INTRODUCTION

Well-defined [Pd-NHC] (NHC = N-heterocyclic carbene) complexes stabilized by ancillary nitrogen ligands have recently demonstrated remarkable activities in palladium-catalyzed cross-coupling reactions. Some notable examples (Figure 1)

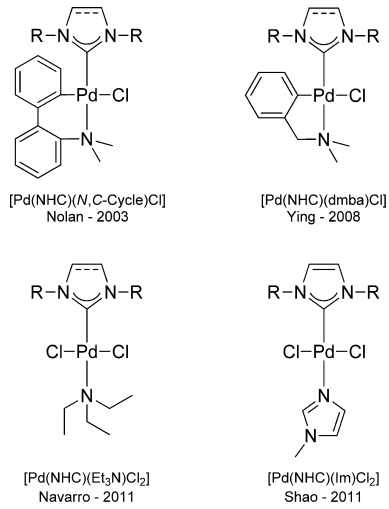


Figure 1. [Pd-NHC] precatalysts stabilized by ancillary nitrogen ligands.

are the N,C-palladacycles described by Nolan,[1] the [Pd(NHC)-(dmba)Cl] complexes (dmba = *N*,*N*-dimethylbenzylamine) reported by Ying,[2] the [Pd(NHC)(Et_3N)Cl_2] precatalysts developed by Navarro,[3] the [Pd(NHC)(Im)Cl_2] complexes reported by Shao,[4] and the [Pd(NHC)(3-Cl-pyridinyl)Cl_2] also called [Pd-PEPPSI-NHC] precatalysts introduced by Organ[5] (PEPPSI = pyridine-enhanced precatalyst preparation stabilization and initiation, Figure 2).[6]

Due to a combination of versatility and efficiency, the latter family appears the most popular family of nitrogen-stabilized

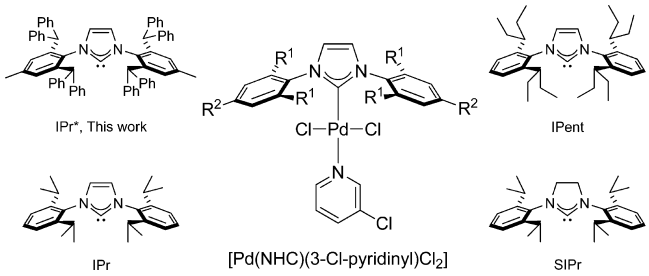


Figure 2. Some [Pd(NHC)(3-Cl-pyridinyl)Cl_2] precatalysts.

[Pd-NHC] complexes. In a recent review and with the development of [Pd(IPent)(3-Cl-pyridinyl)Cl_2], Organ highlighted that bulky, yet flexible NHC ligands were able to circumvent various limitations of cross-coupling reactions (IPent =1,3-bis(2,6-di(pentan-3-yl)phenyl)imidazol-2-ylidene).[7] Very recently, our group also showed similar trends using the [Pd(IPr*)(cinnamyl)Cl][8] and [Pd(IPr*)(acac)Cl][9] complexes (IPr* = 1,3-bis(2,6-bis(diphenylmethyl)-4-methylphenyl)imidazo-2-ylidene). This *bulky-yet-flexible* concept was first stated by Glorius,[10] and one of our "workhorse NHC ligands", namely IPr (IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene) is also an example of this concept.[11] We wished to examine the reactivity of a complex combining the properties of the IPr* ligand[12] and the activation pathway of the PEPPSI precatalysts. Since there is still no report on the synthesis of IPent·HCl in the literature,[5e,13] the preparation of [Pd(IPr*)(3-Cl-pyridinyl)Cl_2] **1** may very well represent an interesting, readily available alternative to [Pd(IPent)(3-Cl-pyridinyl)Cl_2]. Herein, we report the preparation of complex **1** as well as its catalytic activity in the Buchwald–Hartwig amination reaction.[14] A direct comparison with the previously described and well-

Received: July 30, 2012

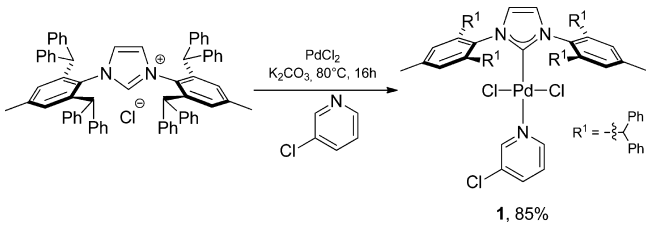
   dx.doi.org/10.1021/om300725f | *Organometallics* XXXX, XXX, XXX–XXX

established [Pd(NHC)(3-Cl-pyridinyl)Cl_2] (NHC = IPr and SIPr; SIPr = 1,3-bis(2,6-diisopropylphenyl)-4,5-dihydroimidazol-2-ylidene) and [Pd(IPr*)(cinnamyl)Cl] is also presented.

RESULTS AND DISCUSSION

Complex **1** was prepared using the methodology developed by Organ.[5a] The IPr*·HCl salt was mixed with $PdCl_2$ in the presence of a large excess of potassium carbonate at 80 °C for 16 h in neat 3-chloropyridine. After recrystallization, complex **1** was obtained as an air- and moisture-stable off-white powder in a very good isolated yield (Scheme 1, 85%). Crystals suitable

Scheme 1. Synthesis of the [Pd(IPr*)(3-Cl-pyridinyl)Cl_2] Precatalyst 1



for X-ray diffraction were grown by slow diffusion of hexane into a saturated $CDCl_3$ solution of the complex (Figure 3).[15] The complex adopts the expected slightly distorted square-planar geometry.

The Pd1−C1 and Pd1−N72 bond lengths are comparable to other [Pd(NHC)(3-Cl-pyridinyl)Cl_2] derivatives.[3b,5e,h,16] To evaluate the sterics of the NHC ligands around the palladium center, the percent buried volume (% V_{Bur})[17] of each of these has been calculated using the web application Sambvca.[18] The results have been summarized in Table 1. Unsurprisingly, with a buried volume of 43.1%, IPr* is one of the biggest ligands for the series of [Pd(NHC)(3-Cl-pyridinyl)Cl_2] complexes, bulkier than IPent and comparable to other [Pd-IPr*] complexes. Surprisingly, in this series, SIPr appears to be bulkier than IPent. This result can be explained by the highly distorted

Table 1. Comparison of Bond Lengths and Percent Buried Volumes of Various [Pd-NHC] Complexes[a]

complex	Pd1−C1 (Å)	Pd1−N_{Pyr} (Å)[b]	% V_{Bur}[c]
[Pd(IMes)(3-Cl-pyridinyl)Cl_2]	1.962 (4)	2.117 (3)	34.2
[Pd(IEt)(3-Cl-pyridinyl)Cl_2]	1.971 (3)	2.109 (2)	34.8
[Pd(IPr)(3-Cl-pyridinyl)Cl_2]	1.969 (3)	2.137 (2)	34.3
[Pd(SIPr)(3-Cl-pyridinyl)Cl_2]	1.990 (3)	2.108 (3)	39.3
[Pd(IPent)(3-Cl-pyridinyl)Cl_2]	1.974 (3)	2.097 (3)	37.9
[Pd(IPr*)(3-Cl-pyridinyl)Cl_2]	1.974 (6)	2.132 (6)	43.1
[Pd(IPr**)(pyridinyl)Cl_2][d]	1.973 (3)	2.096 (3)	44.9[e]
[Pd(IPr*)(cin)Cl]	2.038 (6)		44.6
[Pd(IPr*)(acac)Cl]	2.019 (10)		42.2

[a]All % V_{Bur} and all bond distances have been calculated using cif files obtained from the CCDC. [b]Distance between the palladium and nitrogen atom of the pyridinyl moiety for [Pd-PEPPSI-NHC] complexes. [c]% V_{Bur} calculated for Pd−C1 = 2.00 Å. [d]Despite [Pd(IPr**)(pyridinyl)Cl_2] bearing a pyridine ligand instead of 3-chloropyridine, we consider that this small modification would not change significantly the % V_{Bur} and that the comparison is accurate. [e]Our value is slightly different from the one described in the literature[16] (% V_{Bur} = 46.2) because H atoms were excluded from the calculation.

structure that SIPr assumes around the metal center in the solid state.[3b]

The reactivity of the new complex **1** in aryl amination was next investigated and directly compared to the commercially available [Pd(NHC)(3-Cl-pyridinyl)Cl_2] precatalysts. The reaction between 4-chlorotoluene and morpholine was chosen to compare the catalytic activity of the different complexes. Potassium *tert*-butoxide (KO^tBu) and 1,2-dimethoxyethane (DME) were selected as the base/solvent combination (as described by Organ),[5d] and a catalyst loading of 1 mol % was used to achieve the cross-coupling at room temperature (Scheme 2).

The study of the evolution of the reaction over 6 h revealed similar catalytic activity for the three different complexes. However, upon closer inspection, **1** was discovered to give the highest conversion over 6 h (91% against 81% and 80%

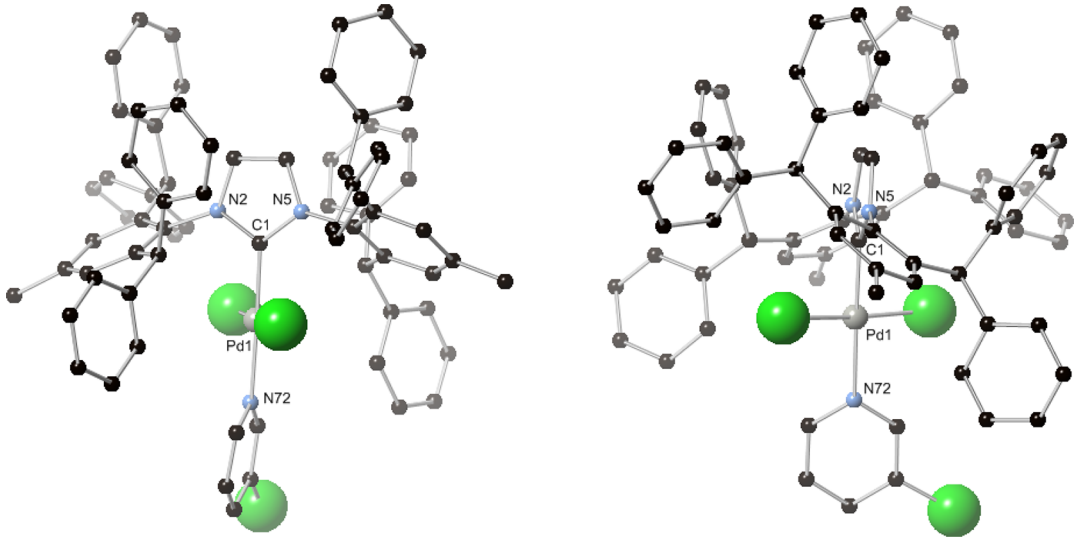
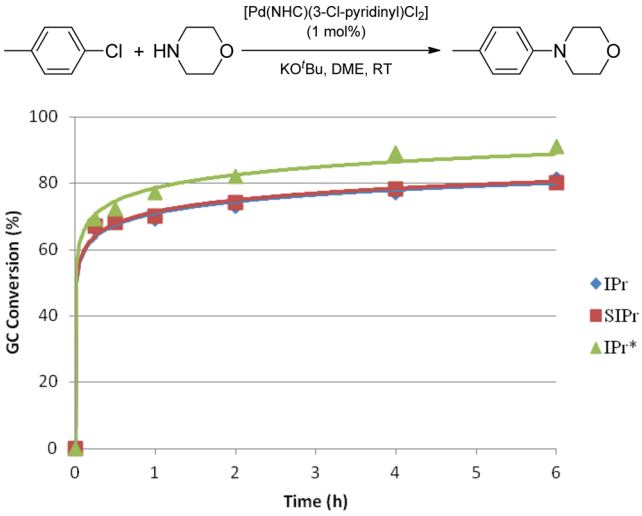


Figure 3. Two different views of the graphical representation of **1**. Hydrogen atoms have been omitted for clarity. Selected bond distances (Å) and angles (deg): Pd1−C1 1.974(6), Pd1−N72 2.132(6), Pd1−Cl1 2.3114(18), Pd1−Cl2 2.303(2), C1−Pd1−Cl2 89.27(16), N72−Pd1−Cl2 92.84(18), C1−Pd1−Cl1 87.43(16), N72−Pd1−Cl1 90.47(18).

dx.doi.org/10.1021/om300725f | Organometallics XXXX, XXX, XXX−XXX

Scheme 2. Comparison of the Reactivity of Some [Pd(NHC)(3-Cl-pyridinyl)Cl_2] Precatalysts at Room Temperature[a]

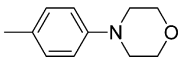
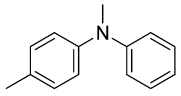
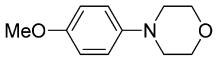
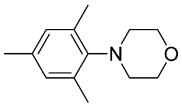
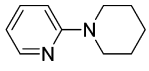


[a]Reagents and conditions: 4-Chlorotoluene (1.0 mmol), morpholine (1.1 mmol), KO^{t}Bu (1.1 mmol), **1** (1 mol %), DME (1.0 mL), 25 °C. Conversion to coupling product based on starting material determined by GC, average of at least two separate runs.

respectively for [Pd(IPr)(3-Cl-pyridinyl)Cl_2] and [Pd(SIPr)(3-Cl-pyridinyl)Cl_2]). A short scope of the amination process using several chlorides and amines was finally conducted at room temperature (Table 2). Results were found to be globally similar to those described in the literature using [Pd(NHC)(3-Cl-pyridinyl)Cl_2] precatalysts[5d] and the recently reported [Pd(IPr*)(cin)Cl] complex.[8a] Notably, primary amines were found to not react at room temperature using **1** as it was observed using [Pd(IPr)(3-Cl-pyridinyl)Cl_2] or [Pd(IPr*)(cin)Cl].[8a]

Table 2. Scope of the Amination Reaction at Room Temperature[a]

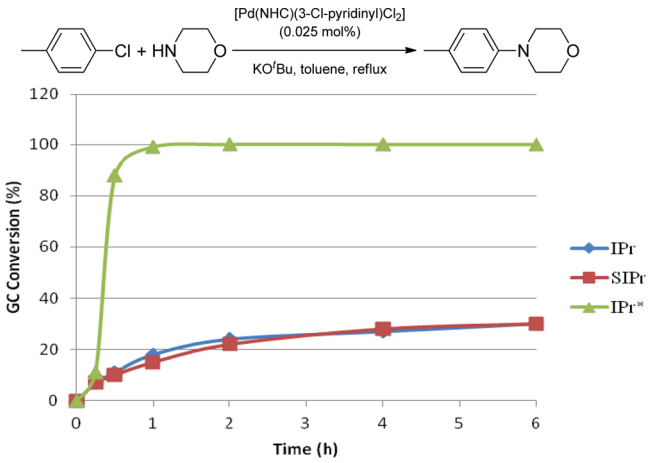
(Het)ArCl + RR'NH —**1** (2 mol %), KO^{t}Bu, DME, RT→ (Het)ArNRR'

Entry	Product	Time[b]	Yield (%)[c]
1		24	94
2		18	87
3		18	92
4		24	93
5		18	78

[a]Reagents and conditions: (Het)ArCl (1.0 mmol), RR′NH (1.1 mmol), KO^{t}Bu (1.1 mmol), **1** (2 mol %), DME (1.0 mL), 25 °C. [b]Reaction times have not been optimized. [c]Isolated yields after chromatography on silica gel, average of two runs.

The comparison of the different [Pd(NHC)(3-Cl-pyridinyl)-Cl_2] precatalysts was next investigated at low catalyst loading. After optimization of the reaction conditions, by examining the reactivity of various base/solvent combinations, the best result was found using KO^{t}Bu in refluxing toluene.[19] To perform a meaningful comparison, a low catalyst loading of 0.025 mol % was used. In this case, the study of the evolution of the reaction over 6 h revealed a significantly different catalytic behavior of the various precatalysts (Scheme 3). After a short induction period of 15 min, **1** permitted the completion of the reaction in approximately 1 h. On the other hand, [Pd(IPr)(3-Cl-pyridinyl)Cl_2] and [Pd(SIPr)(3-Cl-pyridinyl)Cl_2] showed a significantly lower reaction rate and led to poor conversions after 6 h (30%) and even after 24 h (50%). This result shows one more time the efficiency of precatalysts bearing bulky yet flexible ligands such as IPr*. To the best of our knowledge, this is the first example of the use of a [Pd-PEPPSI-NHC] complex at such a low catalyst loading to perform any cross-coupling reaction.

Scheme 3. Comparison of the Reactivity of Some [Pd(NHC)(3-Cl-pyridinyl)Cl_2] Precatalysts at Low Catalyst Loading[a]



[a]Reagents and conditions: 4-Chlorotoluene (1.0 mmol), morpholine (1.1 mmol), KO^{t}Bu (1.1 mmol), **1** (0.025 mol %), toluene (1.0 mL), reflux. Conversion to coupling product based on starting material determined by GC, average of at least two separate runs.

The scope of the reaction was further investigated at low catalyst loading and was directly compared to our previous investigations with [Pd(IPr*)(cin)Cl].[8a] The results were found to be similar, allowing the coupling of nonactivated (Table 3, entries 1−5, 9−13), deactivated (Table 3, entries 6−8, 15−16), and heteroaryl (Table 3, entries 14−16) chlorides with a wide range of amines, globally in excellent yields (74−96%). As previously reported, an increase in temperature favors the coupling of primary amines, which was not possible at room temperature.[8a] These observations highlight that despite two different activation pathways, the precatalysts [Pd(IPr*)(3-Cl-pyridinyl)Cl_2] (**1**) and [Pd(IPr*)(cin)Cl] probably lead to the formation of the same [Pd^0-IPr*] active species in the reaction medium.

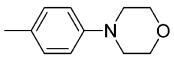
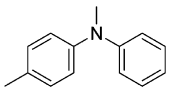
CONCLUSION

In summary, we reported the facile preparation of a new member of the PEPPSI series, namely, [Pd(IPr*)(3-Cl-

dx.doi.org/10.1021/om300725f | Organometallics XXXX, XXX, XXX−XXX

Table 3. Scope of the Aryl Amination Reaction at Low Catalyst Loading[a]

(Het)ArCl + RR'NH —[1 (0.05 mol %), KO^{t}Bu, toluene, reflux]→ (Het)ArNRR'

Entry	Product	Time (h)	Yield (%)[b]
1[c]		1.5	96
2[c]		2	80
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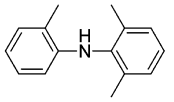
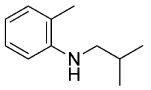
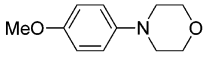
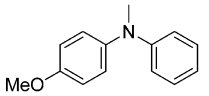
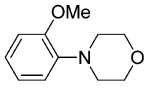
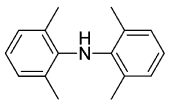
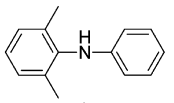
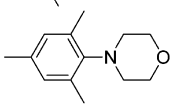
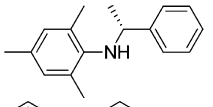
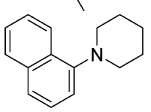
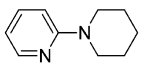
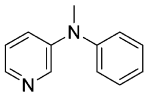
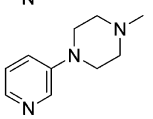
4		2	88
5		2	95
6		2	95
7		3	93
8[d]		2	80
9		2	94
10		2	90
11		2	74
12		2	94
13		2	75
14		2	93
15		2	74
16		2	87

[a]Reagents and conditions: (Het)ArCl (1.0 mmol), RR′NH (1.1 mmol), KO^{t}Bu (1.1 mmol), **1** (0.05 mol %), toluene (1.0 mL), reflux. [b]Isolated yields after chromatography on silica gel, average of two runs. [c]Catalyst loading of 0.025 mol %. [d]Catalyst loading of 0.1 mol %.

pyridinyl)Cl_2] (**1**). The complex proved to be highly active in the Buchwald−Hartwig amination reaction. The comparison in terms of reactivity of **1** with previously reported [Pd(NHC)(3-Cl-pyridinyl)Cl_2] precatalysts showed similar reactivity at room temperature, but a much improved catalytic activity at low catalyst loading and high temperature. Complex **1** also revealed similar reactivity to [Pd(IPr*)(cin)Cl], strongly suggesting that the [Pd^0] active species involved in the reaction is most likely the same in both cases.

EXPERIMENTAL SECTION

Synthesis of [Pd(IPr*)(3-Cl-pyridinyl)Cl_2]. In air, a vial equipped with a stirring bar was charged with $PdCl_2$ (248 mg, 1.4 mmol), IPr*·HCl (1462 mg, 1.54 mmol), and K_2CO_3 (967 mg, 7 mmol). 3-Chloropyridine (5.6 mL) was added, and the mixture was stirred at 80 °C during 16 h. After cooling to room temperature, the reaction mixture was diluted in DCM and passed through a pad of silica covered with Celite and eluted with DCM. After evaporation of the solvents, the crude product was recrystallized in a DCM/pentane mixture to remove completely the 3-chloropyridine. The pure complex was finally obtained after filtration and drying under high vacuum as an off-white powder (1.43 g, 85%). ^{1}H NMR (300 MHz, C_6D_6): δ 9.40 (d, J = 2.3 Hz, 1H, H_{Pyr}), 9.01 (dd, J = 5.6 Hz, 1.3 Hz, 1H, H_{Pyr}), 7.91−7.84 (m, 8H, H_{Ar}), 7.16−7.09 (m, 12H, H_{Ar}), 7.07−6.98 (m, 12H, H_{Ar}), 6.92−6.76 (m, 12H + 4H, H_{Ar} + CH), 6.61 (ddd, J = 8.1 Hz, 2.3 Hz, 1.3 Hz, 1H, H_{Pyr}), 6.05 (dd, J = 8.1 Hz, 5.6 Hz, 1H, H_{Pyr}), 5.16 (s, 2H, H_{Im}), 1.74 (s, 6H, CH_3). ^{13}C{^{1}H} NMR (75 MHz, C_6D_6): δ 152.3 (NCN), 150.9 (C_{Pyr}), 149.9 (C_{Pyr}), 145.1 (C_{Ar}), 144.9 (C_{Ar}), 143.0 (C_{Ar}), 139.2 (C_{Ar}), 137.5 (C_{Pyr}), 136.1 (C_{Ar}), 131.2 (C_{Ar}), 130.0 (C_{Ar}), 128.5 (C_{Ar}), 126.7 (C_{Ar}), 126.5 (C_{Ar}), 124.3 (C_{Pyr}), 124.3 (C_{Im}), 51.6 (CH), 21.3(CH_3). Anal. Calcd for $C_{74}H_{60}Cl_3N_3Pd$: C 73.82, H 5.02, N 3.49. Found: C 73.96, H 4.91, N 3.40.

General Procedure for Amination Reactions Using [Pd(IPr*)-(3-Cl-pyridinyl)Cl_2] at Room Temperature. In a glovebox, in a vial equipped with a stirring bar and later sealed with a screw cap fitted with a septum were added KO^{t}Bu (123 mg, 1.1 mmol) and the [Pd(IPr*)(3-Cl-pyridinyl)Cl_2] precatalyst (24.0 mg, 2 mol %). Outside the glovebox, were added the aryl chloride (1.0 mmol), the amine (1.1 mmol), and finally 1 mL of anhydrous DME. The reaction mixture was then stirred (800 rpm) at room temperature (25 °C) for 18−24 h. The solution was then filtered through Celite and eluted with DCM. The filtrate was evaporated in vacuo. The crude product was finally purified by flash chromatography on silica gel. The reported yields are the average of two runs.

General Procedure for Amination Reactions Using [Pd(IPr*)-(3-Cl-pyridinyl)Cl_2] at Low Catalyst Loading. In a glovebox, in a vial equipped with a stirring bar and later sealed with a screw cap fitted with a septum were added KO^{t}Bu (123 mg, 1.1 mmol) and the necessary amount of toluene to bring the total solvent volume to 1 mL. Outside the glovebox were added the aryl chloride (1.0 mmol), the amine (1.1 mmol), and finally a solution of the [Pd(IPr*)(3-Cl-pyridinyl)Cl_2] precatalyst (75−300 μL, 0.025−0.1 mol %, prepared from 12.0 mg of the precatalyst in 3 mL of toluene). The reaction mixture was then stirred (800 rpm) while refluxing the toluene during 1.5−3 h. The solution was then cooled, filtered through Celite, and eluted with DCM. The filtrate was evaporated in vacuo. The crude product was finally purified by flash chromatography on silica gel. The reported yields are the average of two runs.

ASSOCIATED CONTENT

Supporting Information

Crystallographic data for **1**, procedure for the amination reactions, results of optimization reactions, and NMR spectra for complex **1** and cross-coupling products. This material is available free of charge via the Internet at http://pubs.acs.org.

dx.doi.org/10.1021/om300725f | Organometallics XXXX, XXX, XXX−XXX

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We gratefully acknowledge the EC for funding through the seventh framework program SYNFLOW. Umicore AG is thanked for its generous gifts of materials. S.P.N. is a Royal Society Wolfson Research Merit Award holder.

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