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Modified (NHC)Pd(allyl)Cl (NHC = *N*-Heterocyclic Carbene) Complexes for Room-Temperature Suzuki−Miyaura and Buchwald−Hartwig Reactions

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Abstract: A series of (NHC)Pd(R-allyl)Cl complexes [NHC: IPr = *N*,*N*′-bis(2,6-diisopropylphenyl)imidazol-2-ylidene, SIPr = *N*,*N*′-bis(2,6-diisopropylphenyl)-4,5-dihydroimidazol-2-ylidene; R = H, Me, *gem*-Me_2, Ph] have been synthesized and fully characterized. When compared to (NHC)Pd(allyl)Cl, substitution at the terminal position of the allyl scaffold favors a more facile activation step. This translates into higher catalytic activity in the Suzuki−Miyaura and Buchwald−Hartwig reactions, allowing for the coupling of unactivated aryl chlorides at room temperature in minutes. In the Suzuki−Miyaura reaction, aryl triflates, bromides, and chlorides react with boronic acids using very low catalyst loading. In the *N*-aryl amination reaction, a wide range of substrates has been coupled efficiently; primary-, secondary-, alkyl-, or aryl-amines react in high yields with unactivated, neutral, and activated aryl chlorides and bromides. In both reactions, extremely hindered substrates such as tri-*ortho*-substituted biaryls and tetra-*ortho*-substituted diarylamines can be produced without loss of activity. Finally, the present catalytic system has proven to be efficient with as low as 10 parts-per-million (ppm) of precatalyst in the Buchwald−Hartwig reaction and 50 ppm in the Suzuki−Miyaura reaction.

Introduction

Palladium-catalyzed cross-coupling reactions have witnessed tremendous advances in the last 20 years and are now extensively used both on industrial and laboratory scales. Among cross-coupling reactions, the Suzuki−Miyaura reaction,[1,2] has emerged as a most practical synthetic method for biaryl compounds that are found in a wide variety of natural products,[3] as well as in chiral reagents and chiral phases for chromatography and chiral liquid crystals.[4] As an added advantage, the organoboron reagents used as reactants in the Suzuki−Miyaura reaction are inert to water and oxygen, generally thermally stable, and tolerant toward various functional groups. Both the boron-containing reagents and generated byproducts of the Suzuki−Miyaura reaction display low toxicity.[5]

On the other hand, increasingly popular since its discovery,[6] the palladium-catalyzed *N*-aryl amination (or Buchwald−Hartwig reaction) has now its place among the widely used arsenal of cross-coupling reactions.[7] Despite the existence of copper- and nickel-catalyzed versions of this reaction,[8,9] palladium remains the metal of choice for this transformation. This is due principally to the higher efficiency of palladium complexes in aryl amination, benefiting from developments in related palladium-catalyzed cross-coupling reactions.[10]

To reach a high degree of efficiency in cross-coupling reactions, studies have mainly focused on the development of new ligands, notably phosphorus-containing ligands. Indeed, even though ligandless systems are known,[11] the ancillary ligation dictates catalytic performance.[12] Strongly bound to the palladium center, σ-donor ligands such as phosphines properly tune the metal electronic properties and minimize palladium

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precipitation (palladium black).[13] Among the plethora of ligands developed for Pd-catalyzed cross-coupling reactions, bulky electron-rich phosphines such as trialkylphosphines[14] or biarylphosphines[15] have met with great success. The enhanced catalytic activity of this new generation of ligands, used in combination with Pd(II) or Pd(0), has been attributed to the formation of a highly active monoligated [PdL] species.[16] Nevertheless, because of the lack of well-defined phosphine-containing systems, the tertiary phosphine is used as free ligand in conjugation with a palladium(II) or palladium(0) source. Therefore, to maintain a catalytically efficient ligand/palladium ratio, an excess of expensive ligand (bulky electron-rich ligands from the last generation are more expensive than common palladium sources[17]) is required.

To circumvent the aforementioned drawbacks associated with *in situ* generated catalytic systems, we have developed several straightforward and convenient syntheses of well-defined, air- and moisture-stable NHC-bearing palladium(II) (NHC = *N*-heterocyclic carbene[18,19]) complexes that allow a strict control of the ligand/palladium ratio.[20] As it has been demonstrated that a ratio close to 1 generally enhances the catalytic activity,[13−15,21] we have focused our efforts on mono-carbene palladium complexes. Taking advantage of the NHC properties[22] and relying on previous studies conducted with allyl-Pd complexes,[23] we have designed new (NHC)Pd(R-allyl)Cl complexes. These precatalysts, possessing a modified allyl moiety, can be easily activated at room temperature, leading to an increased concentration of catalytically active Pd(0) species. This catalytic system

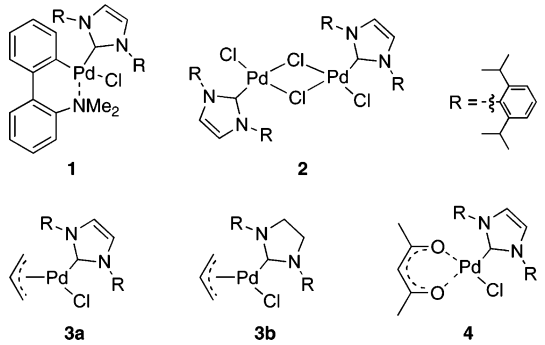

Figure 1. Structures of (NHC)Pd(II) precatalysts efficient in Suzuki−Miyaura and/or Buchwald−Hartwig reactions.

therefore permits the Suzuki−Miyaura and the Buchwald−Hartwig reactions of a wide range of unactivated aryl chlorides even at room temperature in extremely short reaction times.

Results and Discussion

Recently, we reported on a new class of complexes combining the highly σ-donating and sterically demanding properties of NHCs with the stability imparted by a palladacycle framework (Figure 1). Complex **1** displays excellent performance in the Suzuki−Miyaura cross-coupling of aryl chlorides with arylboronic acids in technical grade 2-propanol at room temperature.[20b] From an economic and industrial point of view, these conditions are very appealing, especially since the system involves the use of an inexpensive and environmentally friendly solvent without the need for predrying or purification.

The system also allowed for the coupling of sterically hindered, unactivated aryl chlorides with sterically hindered boronic acids under very mild conditions leading to di- and tri-*ortho*-substituted biaryls in high yields. The only drawbacks linked with the use of **1** were associated with harsh synthetic conditions and low yields of the dimer precursor complex. Furthermore, slow addition of the aryl chloride was required when performing the coupling to avoid dehalogenation of the aryl chlorides which could prove (in certain examples) a significant competing side reaction.[24]

In the course of our studies aimed at exploring new catalytic systems displaying high efficiency in the Buchwald−Hartwig reaction, we have previously reported on various types of well-defined NHC-bearing palladium(II) complexes; a palladacycle **1**,[20c] a dimer **2**,[20a] an allyl-palladium **3**[23] and very recently an acac-palladium **4**[25] (Figure 1). These enable the Buchwald−Hartwig reaction to be performed using aryl chlorides as coupling partners. As the use of Pd(II) precatalysts implies an activation/reduction step leading to an active Pd(0) species, this activation pathway holds important information related to catalyst performance optimization (as previously observed with palladacycle **1** in the Suzuki−Miyaura coupling). Therefore, differences in the architecture of a precatalyst result in different activation pathways. We have postulated that in the case of the (NHC)Pd(allyl)Cl (**3**), the activation mode occurs through a nucleophilic attack at the allyl moiety or through a chloride/

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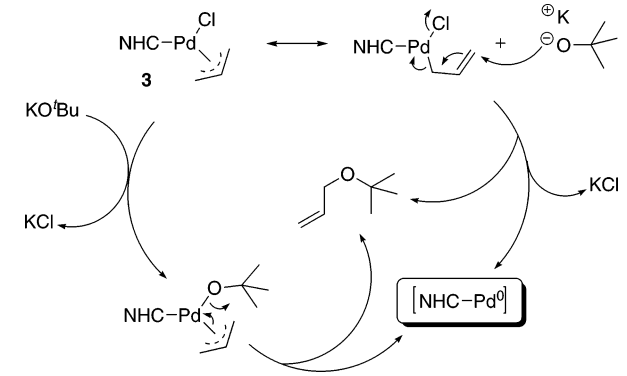
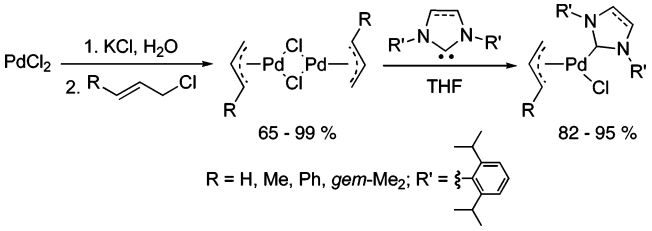
Scheme 1. Proposed Activation Pathways for **3**



Scheme 2. Synthesis of (NHC)Pd(R-allyl)Cl Complexes



alkoxide σ-metathesis followed by reductive elimination, liberating in both cases a [(NHC)Pd(0)] species (Scheme 1).[26,27]

Complexes of type **3** present the advantage of being very straightforwardly synthesized, even on multigram scale, from commercially available allyl palladium chloride dimer.[28] Nevertheless, they still required activation at 70 °C to perform effectively in aryl amination.[29] To overcome this sluggish activation step, we focused on the design of a more labile framework (such as the palladacycle) that would be closely related to the (NHC)-Pd(allyl)Cl system, since it can be easily synthesized. Keeping in mind that substitution on the allyl moiety decreases the overall stability of the palladium complex by increasing steric bulk around the metal center and by decreasing the back-bonding from the metal to the olefin,[30] we thought that modification of this site could facilitate the activation pathway. This also renders the allyl scaffold less tightly bound to the palladium center and more prone to nucleophilic attack or to reductive elimination, depending on which activation pathway is considered. As a result, we focused our studies on the effect of substitution at the allyl moiety in the generation of the active species [(NHC)-Pd(0)] and synthesized a series of modified (NHC)Pd(allyl)Cl (**3)** with general formulas (NHC)Pd(R-allyl)Cl.

Synthesis of (IPr)Pd(R-allyl)Cl Complexes. The syntheses of the new complexes were very straightforward and involved the simple fragmentation of the corresponding [Pd(R-allyl)Cl]$_2$ dimer by IPr or SIPr carbene in dry THF (Scheme 2).[24a] The palladium dimers were either purchased from commercial sources or easily prepared from $PdCl_2$ and (R-allyl)chloride following the literature.[31] The reaction involving a free NHC and the appropriate dimer was followed by evaporation of the solvent, trituration of the complex, and filtration in air. This led to the desired complexes in very good yields (≥82%).

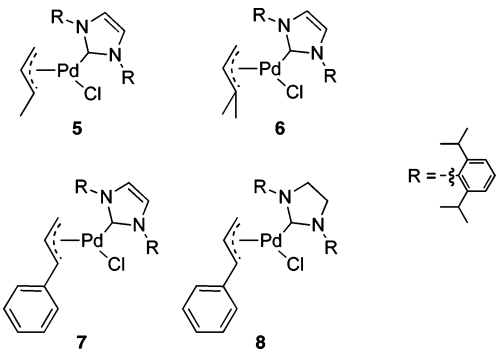


Figure 2. Structures of complexes **5**, **6**, **7**, and **8**.

Following this procedure on a 2 mmol scale, we synthesized and fully characterized four derivatives of the commercially available (IPr)Pd(allyl)Cl (**3a**):[32] (IPr)Pd(crotyl)Cl (crotyl = 3-methylallyl) (**5**), (IPr)Pd(prenyl)Cl (prenyl = 3,3-dimethylallyl) (**6**), (IPr)Pd(cinnamyl)Cl (cinnamyl = 3-phenylallyl) (**7**) and (SIPr)Pd(cinnamyl)Cl (**8**) (Figure 2).

As in the case of **3a**−**b**, these new complexes are air- and moisture-stable and can be stored indefinitely on the shelf in air.[33] Single crystals suitable for X-ray diffraction of **5**−**8** were obtained from concentrated solutions of CH_2Cl_2/hexanes. Ball-and-stick representations of the X-ray diffraction study results for **5**−**7** are presented in Figure 3.

A comparison of selected bond distances is shown in Table 1.[34] For a more accurate discussion on the effect of terminal substitution on the allyl moiety, we will consider IPr-bearing complexes (**3a**, **5**, **6**, and **7**) separately from the SIPr-bearing complexes (**3b** and **8**). While the Pd−C(1) distances remain fairly constant, the Pd−C(3) distances become longer upon terminal substitution at the allyl moiety. Strikingly, when compared to that in **3a** the increase of dissymmetry in **6** and **7** is 405 and 80% respectively.[35] As previously mentioned, both electronic and steric factors appear to play a role in this increase of dissymmetry in the coordination of the allyl moiety: terminal phenyl substitution is less electron donating than methyl substitution,[36] but the elongation of the Pd−C(3) distance in **7** is even larger than the one observed in **6**.

As for **5**−**7**, single crystals of **8**, suitable for X-ray diffraction, were obtained from a concentrated CH_2Cl_2/hexanes mixture. Ball-and-stick representations of the X-ray diffraction study results for **3b** and **8** are presented in Figure 4.

A comparison of the solid-state structures of (SIPr)Pd(allyl)-Cl (**3b**) and (SIPr)Pd(cinnamyl)Cl **8** revealed that substitution

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(32) (IPr)Pd(allyl)Cl (**3**) is commercially available from Strem Chemicals for small quantities (hundreds of mg) and from Umicore AG for larger quantities.
(33) As a testimony to their stability, samples of **7** and **8** retrieved from our laboratories in New Orleans showed no decomposition after being subjected for 2 months to harsh environmental conditions (90/95 °F, high humidity and high level of volatile chemicals) imposed by Hurricane *Katrina*.
(34) Owing to the slightly lower quality of structural data for (IPr)Pd(crotyl)-Cl, **5**, (despite repeated attempts) higher error factors preclude a bond length discussion involving **5**; it is of note that an increase of the dissymmetry of the allyl moiety is observed with increased steric substitution at the allylic terminal position.
(35) Calculation for the increase of dissymmetry: $\{[(Pd-C(3))-(Pd-C(1))]^{R-allyl}-[(Pd-C(3))-(Pd-C(1))]^{allyl}\}/[(Pd-C(3))-(Pd-C(1))]^{allyl}$.
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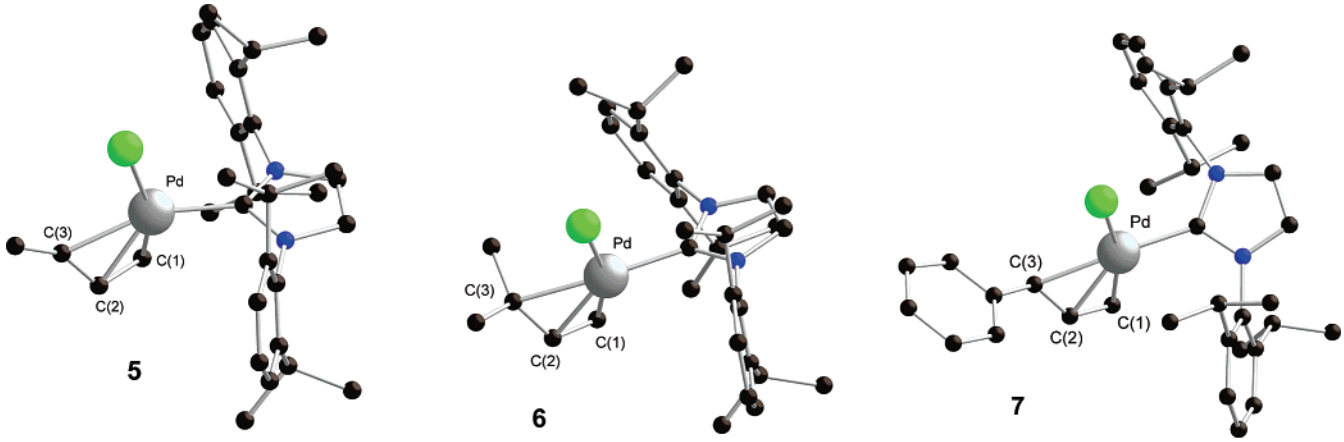
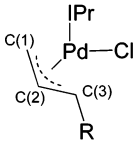


Figure 3. Ball-and-stick representations of (IPr)Pd(crotyl)Cl (**5**), (IPr)Pd(prenyl)Cl (**6**), and (IPr)Pd(cinnamyl)Cl (**7**) (hydrogens are omitted for clarity).

Table 1. Selected Bond Distances for **3a** and **5**−**7**



(Å)	IPr Pd-Cl **3a**	IPr Pd-Cl **5**	IPr Pd-Cl **6**	IPr Pd-Cl Ph **7**
Pd-C(1)	2.098(6)	2.147(18)	2.095(4)	2.082(9)
Pd-C(2)	2.124(7)	2.122(18)	2.137(5)	2.136(10)
Pd-C(3)	2.210(6)	2.209(16)	2.252(5)	2.284(9)

of the allyl moiety by a phenyl group increases the distances between the palladium center and the three bound carbon atoms of the allyl scaffold (Table 2).

We previously noticed that even though the allyl group is symmetrical, in the (SIPr)Pd(allyl)Cl the carbon *trans* to the chlorine atom, C(1), is closer to the palladium center than the carbon *trans* to the SIPr, C(3). This dissymmetry is increased by 68% in the new complex **8**.[35] Regardless of which of the pathways for the allyl elimination is preferred,[37] the observed elongation of the Pd−C(3) distances appears to correlate with an easier activation process, leading to a [(IPr)−Pd(0)] species. To determine if this feature allowed for a more facile activation step leading to a more active catalytic system, we tested the complexes in the Suzuki−Miyaura and the Buchwald−Hartwig cross-coupling reactions.

Study of the Activity of (NHC)Pd(R-allyl)Cl Complexes in the Suzuki−Miyaura Reaction. It was worth examining whether the observed structural insights could lead to an improved activation and result in an increase in the amount of active Pd species in solution on test substrates. A comparison of the performance of four Pd-allyl complexes in the Suzuki−Miyaura reaction of 4-chlorotoluene and phenylboronic acid at room temperature is shown in Table 3. Only the substituted allyl complexes **5**−**7** allowed for the coupling to proceed in high yield at room temperature, even when sterically hindered substrates were tested (Table 4). Complex **3a** afforded no more than a 40% yield for the coupling of 2,6-dimethylphenyl chloride with 1-naphthaleneboronic acid at room temperature, despite extending reaction time to several hours.

An added advantage of complexes **5**−**7** is that the slow addition of the chloride is no longer required. This already overcomes a drawback encountered in our palladacyclic-NHC system. In the present system, only trace amounts of the undesired dehalogenation byproducts were observed. Complex **7** was routinely used instead of **6** from this point on because of the relative lower cost of the corresponding allyl chloride precursor.[38]

Room-Temperature Suzuki−Miyaura Coupling Reactions of Aryl Bromides and Triflates. The system is compatible with the use of unactivated aryl bromides and triflates, more reactive substrates than the corresponding chlorides (Table 5).[1a,39] Aryl triflates are a very attractive alternative to aryl halides since they can be easily synthesized from readily available phenols.[40]

Both aryl bromides and triflates can be coupled using as little as 0.05 mol% of **7** in very short reaction times and at room temperature. Assembly of multiple *ortho* substitutions (entry 4) does not appear to be problematic in this system. The reaction depicted in entry 5 produced a linear tri-aryl containing motif in acceptable yields at room temperature but proceeded in excellent yields (>90%) when the temperature was raised to 60 °C for 1 h.

Room-Temperature Suzuki−Miyaura Coupling Reactions of Aryl Chlorides. Aryl chlorides are very attractive halides due to their low cost and avaibility in a wide diversity. Their use in cross-coupling reactions was initially judged to be limited because of the strength of the C−Cl bond.[41] However, in 1998 unactivated chlorides were reported for the first time to couple with boronic acids in good yields.[42] Since then, a large variety of systems have been reported to overcome this reactivity limitation.[1] These now commonly used substrates usually require elevated temperatures and catalyst loading on about 1 mol%.

(37) Prof. Irina P. Beletskaya (Moscow State University) kindly pointed out reduction of Pd(II) to Pd(0) by the boronic acid as another plausible activation pathway for our complexes in the case of the Suzuki−Miyaura reaction. Although we have carried out experiments to examine whether the two mentioned mechanisms occur for the activation of **3a** (ref 23a) and we can presume the same mechanism to be at play for **5**−**8**, however, we cannot totally rule out reduction by the boronic acid for these new complexes. Experiments addressing this possibility are currently ongoing.

(38) According to the Aldrich catalog 2004−2005, cinnamyl chloride (by 100 g) and prenyl chloride (by 25 g) cost respectively $94.2/mol and $398.7/mol.

(39) For the initial general methods to couple bromides and triflates at room temperature, see: (a) Wolfe, J. P.; Singer, R. A.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9550−9561. (b) Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020−4028.

(40) Echavarren, A. M.; Stille, J. K. *J. Am. Chem. Soc.* **1987**, *109*, 5478−5486.

(41) For a review in palladium-catalyzed coupling reactions of aryl chlorides: Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176−4211.

(42) (a) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **1998**, *37*, 3387−3388. (b) Old, D. W.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 9722−9723.

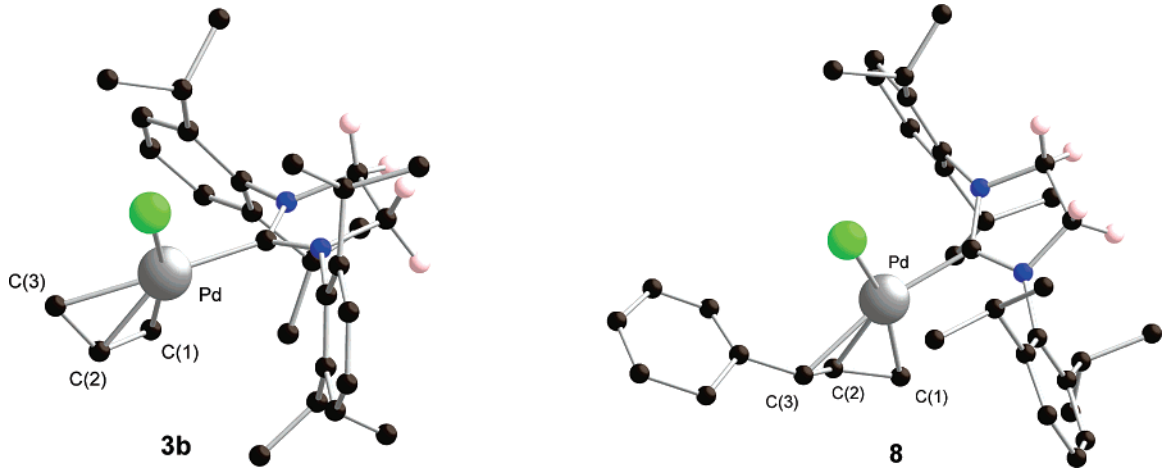
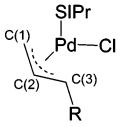


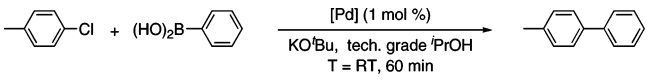
Figure 4. Ball-and-stick representations of (SIPr)Pd(allyl)Cl (**3b**) and (SIPr)Pd(cinnamyl)Cl (**8**) (most hydrogens are omitted for clarity).

Table 2. Selected Bond Distances from **3b** and **8**



(Å)	SIPr Pd-Cl **3b**	SIPr Pd-Cl Ph **8**
Pd-C(1)	2.118(6)	2.136(10)
Pd-C(2)	2.132(7)	2.137(8)
Pd-C(3)	2.203(6)	2.279(10)

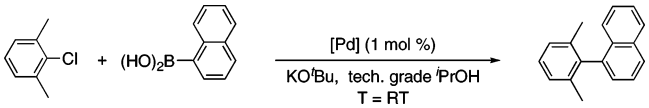
Table 3. Effect of Substitution at the Allyl Moiety on Precatalyst Performance in the Suzuki−Miyaura Coupling of a Simple Substrate[a]



entry	[Pd]	yield (%)[b]
1	(IPr)Pd(allyl)Cl **3a**	12
2	(IPr)Pd(crotyl)Cl **5**	86
3	(IPr)Pd(prenyl)Cl **6**	90
4	(IPr)Pd(cinnamyl)Cl **7**	90

[a] Reaction conditions: aryl chloride (1 mmol), boronic acid (1.05 mmol), [Pd] (1 mol %), KO^{t}Bu (1.1 mmol), tech. grad ^{i}PrOH (1 mL). [b] GC yields, average of two runs.

Table 4. Effect of Substitution at the Allyl Moiety on Precatalyst Performance in the Suzuki−Miyaura Coupling of a Hindered Substrate[a]

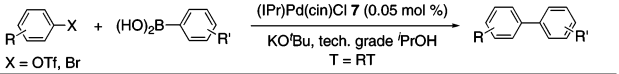


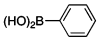
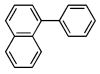
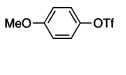
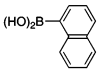
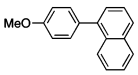
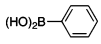
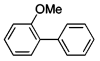
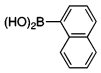
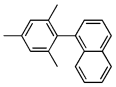
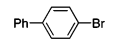
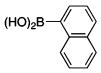
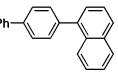
entry	[Pd]	time (min)	yield (%)[b]
1	(IPr)Pd(crotyl)Cl **5**	45	91
2	(IPr)Pd(prenyl)Cl **6**	25	95
3	(IPr)Pd(cinnamyl)Cl **7**	25	94

[a] Reaction conditions: aryl chloride (1 mmol), boronic acid (1.05 mmol), [Pd] (1 mol %), KO^{t}Bu (1.1 mmol), tech. grade ^{i}PrOH (1 mL). [b] GC yields, average of two runs.

In Table 6 are listed the coupling reactions of a series of aryl chlorides with a variety of boronic acids, carried out at room temperature with a catalyst loading of 0.05 mol %. This loading is the lowest reported to date for reactions leading to di- (entries 5, 8) and tri-*ortho*-substituted (entries 6, 7) biaryls at room

Table 5. Suzuki−Miyaura Coupling of Unactivated Aryl Bromides and Triflates at Room Temperature[a]



entry	Ar-X	Ar'-B(OH)$_2$	product	time (h)	yield (%)[b]
1				2.5	88
2				2.5	85
3				3.5	95
4				3.5	89
5				3 6	55 61

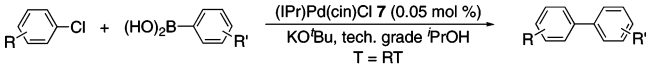
[a] Reaction conditions: aryl bromide or triflate (1 mmol), boronic acid (1.05 mmol), (IPr)Pd(cin)Cl (**7**) (0.05 mol %), KO^{t}Bu (1.1 mmol), tech. grade ^{i}PrOH (1 mL). [b] Isolated yields, average of two runs.

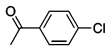
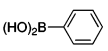
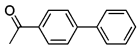
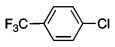
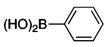
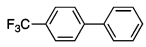
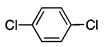
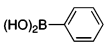
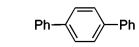
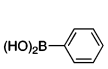
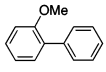
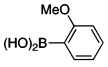
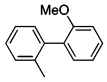
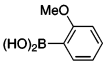
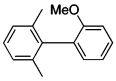
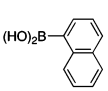
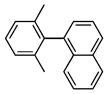
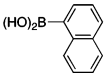
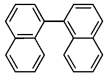
temperature using unactivated aryl chlorides. The present system requires even shorter reaction times than systems using higher catalyst loadings.[43] The same conditions can be applied for the coupling of activated (electron-deficient) aryl chlorides (entries 1, 2). Attempts to decrease the catalyst loading even further for room-temperature reactions led to incomplete conversions. In all cases, no sign of catalyst decomposition (palladium black) was observed.

Suzuki−Miyaura Coupling Reactions of Aryl Halides at Low Catalyst Loadings. Decreasing the amount of palladium necessary to catalyze a process is desirable not only because of cost, but also to facilitate its removal, particularly on industrial scale for questions of product purity, toxicity, and environmental concerns.[44] Table 7 presents the coupling of a series of aryl bromides and chlorides with a variety of arylboronic acids at

(43) Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4685−4696. (b) Walker, S. D.; Barder, T. E.; Martinelli, J. R.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 1871−1876. (c) Altenhoff, G.; Goddard, R.; Lehmann, C. W.; Glorius, F. *Angew. Chem., Int. Ed.* **2003**, *42*, 3690−3693.
(44) Garret, C. E.; Prasad, K. *Adv. Synth. Catal.* **2004**, *346*, 889−900.

Table 6. Suzuki−Miyaura Cross-Coupling of Aryl Chlorides at Room Temperature[a]



entry	Ar-Cl	Ar'-B(OH)$_2$	product	yield (%)[b]
1				96
2				93
3				80[c]
4				85
5				85
6				83
7				94
8				96

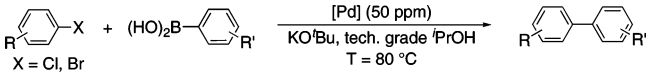
[a] Reaction conditions: aryl chloride (1 mmol), boronic acid (1.05 mmol), (IPr)Pd(cin)Cl (**7**) (0.05 mol %), KO^{t}Bu (1.1 mmol), tech. grade ^{i}PrOH (1 mL), t = 15 h. [b] Isolated yields, average of two runs. [c] Aryl chloride (1 mmol), PhB(OH)$_2$ (2.1 mmol), (IPr)Pd(cin)Cl (**7**) (0.1 mol %), KO^{t}Bu (2.2 mmol), tech. grade ^{i}PrOH (2.5 mL), 7% of the monophenylated product were also isolated.

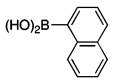
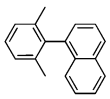
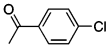
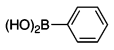
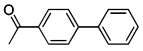
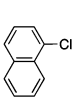
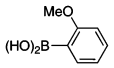
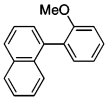
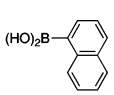
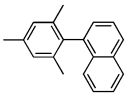
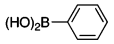
low catalyst loadings. When the temperature was increased, the catalyst loading could be reduced to 50 ppm with no loss of yield, and reactions reached completion in even shorter reaction times.

As expected, the use of the commercially available (IPr)Pd(allyl)Cl (**3a**) at high temperature provided the same results as use of **7** (entry 1),[45] highlighting again that the substitution at the allyl moiety is only useful to activate the catalyst at lower temperatures. In all cases, as well as for the room-temperature reactions, precatalyst solutions were prepared with technical grade 2-propanol and injected into the reaction vials through the septum. It is noteworthy that solutions of **7** in technical grade 2-propanol decomposed slightly over several days, and the same solutions heated at 40 °C for 48 h in air showed little degradation (<5% by ^{1}H NMR). Encouraged by such results, we examined the activity of the substituted-allyl complexes in the Buchwald−Hartwig reaction.

Study of the Activity of (NHC)Pd(R-allyl)Cl Complexes in the Buchwald−Hartwig Reaction. Previous studies conducted in our laboratories with the (SIPr)Pd(allyl)Cl (**3b)** showed that 1,2-dimethoxyethane (DME) and NaO^{t}Bu were the most efficient solvent and base for *N*-aryl amination.[20a] We reexamined these conditions and found that with KO^{t}Bu only 1.1 equiv of base, instead of 1.4, were necessary. Furthermore, we were able to dramatically reduce the amount of solvent from 4 to 1 mL, which had, in fact, an accelerating effect on the reaction.

Table 7. Suzuki−Miyaura Cross-Coupling of Aryl Bromides and Chlorides at Low Catalyst Loadings[a]



entry	Ar-X	Ar'-B(OH)$_2$	product	[Pd]	time (h)	yield (%)[b]
1				**7**	4	93[c]
				7	3	93
				3a	3	92
2				**3a**	2	93
3				**3a**	3	83
4				**3a**	1	85
5				**3a**	1.5	91

[a] Reaction conditions: aryl halide (1 mmol), boronic acid (1.05 mmol), [Pd] (50 ppm), KO^{t}Bu (1.1 mmol), tech. grade ^{i}PrOH (1 mL). [b] Isolated yields, average of two runs. [c] Catalyst loading 100 ppm, T = 60 °C.

Table 8. Effect of the NHC and the Substitution at the Allyl Moiety at Room Temperature in the Buchwald−Hartwig Reaction[a]

Amine	Ar-Cl	Product	[Pd]	Time	GC Conv. (%)[b]
			(IPr)Pd(all)Cl **3a**	5 h	98
			(SIPr)Pd(all)Cl **3b**	2.5 h	99
			(IPr)Pd(cin)Cl **7**	2 h	100
			(SIPr)Pd(cin)Cl **8**	20 min	100
			(IPr)Pd(all)Cl **3a**	20 h	31[c]
			(SIPr)Pd(all)Cl **3b**	20 h	62[c]
			(IPr)Pd(cin)Cl **7**	5 h	100
			(SIPr)Pd(cin)Cl **8**	5 min	100
			(IPr)Pd(all)Cl **3a**	20 h	73[c]
			(SIPr)Pd(all)Cl **3b**	15 h	90[c]
			(IPr)Pd(cin)Cl **7**	6 h	98
			(SIPr)Pd(cin)Cl **8**	1.5 h	97

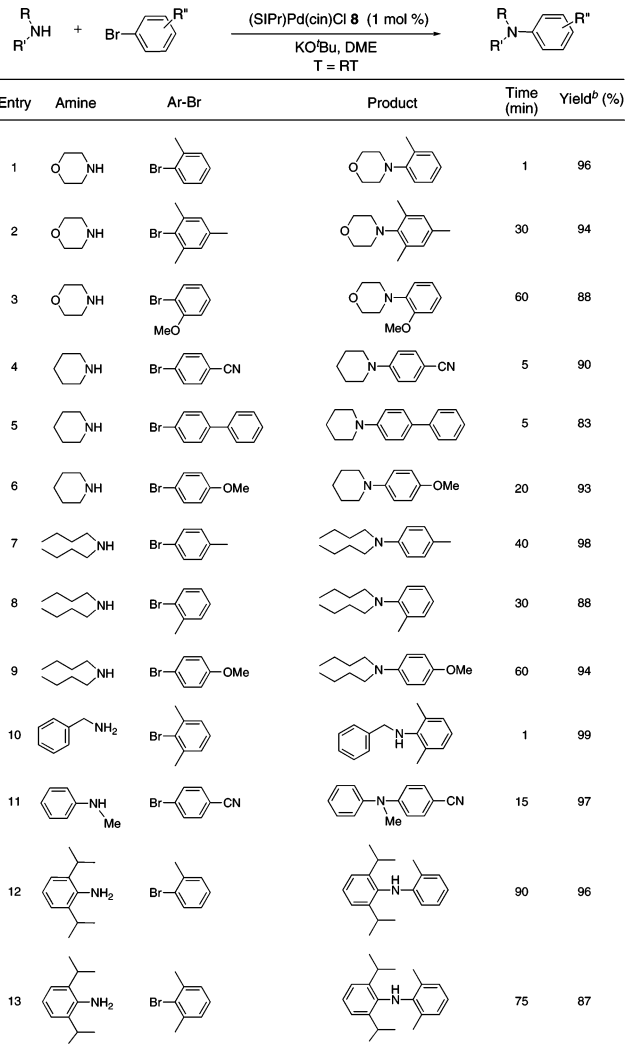
[a] Reaction conditions: aryl chloride (1 mmol), amine (1.1 mmol), [Pd] (1 mol %), KO^{t}Bu (1.1 mmol), DME (1 mL). [b] Average of two runs. [c] No further conversion.

As we,[20a,26] and others,[46] previously reported that SIPr performs better than IPr in the Buchwald−Hartwig amination, we tested the activity of (SIPr)Pd(cinnamyl)Cl (**8**) versus (SIPr)Pd(allyl)Cl **(3b**) along with their IPr counterparts (Table 8). The results, all obtained with challenging substrates, clearly show the tremendous effect of both the ancillary ligand on the palladium center (from IPr to SIPr) and of the substitution at the terminal position of the allyl scaffold (from allyl to cinnamyl). When combined, these two aspects generate a highly efficient precatalyst, (SIPr)Pd(cinnamyl)Cl (**8**), that can perform room-temperature *N*-aryl amination in minutes using aryl chlorides. Thus, the reaction of 2,6-diisopropylaniline and

(45) Navarro, O.; Oonishi, Y.; Kelly, R. A., III; Stevens, E. D.; Briel, O.; Nolan, S. P. *J. Organomet. Chem.* **2004**, *689*, 3722−3727.

(46) Stauffer, S. R.; Lee, S.; Stambuli, J. P.; Hauck, S. I.; Hartwig, J. F. *Org. Lett.* **2000**, *2*, 1423−1426.

Table 9. *N*-Aryl Amination Using Aryl Bromides[a]



Entry	Amine	Ar-Br	Product	Time (min)	Yield[b] (%)
1				1	96
2				30	94
3				60	88
4				5	90
5				5	83
6				20	93
7				40	98
8				30	88
9				60	94
10				1	99
11				15	97
12				90	96
13				75	87

[a] Reaction conditions: aryl bromide (1 mmol), amine (1.1 mmol), (SIPr)Pd(cin)Cl (**8**) (1 mol %), KO^{t}Bu (1.1 mmol), DME (1 mL). [b] Isolated yields, average of two runs.

2-chloro-*m*-xylene, which could not be completed even after 20 h by (IPr)Pd(allyl)Cl, reached completion after only 6 h when (IPr)Pd(cinnamyl)Cl was used. More strikingly, (SIPr)Pd(cinnamyl)Cl performed this reaction 4 times faster.

Room-Temperature Buchwald−Hartwig Amination Reactions of Aryl Bromides. A wide range of aryl bromides were tested under the reaction conditions previously described, these results are presented in Table 9. Secondary cyclic amines reacted in astonishingly short reaction times. (SIPr)Pd(cinnamyl)Cl, in conjugation with KO^{t}Bu, produced, in less than 20 min, *ortho*-substituted (entry 1), electron-poor (entry 4), and electron-rich anilines (entry 6) at room temperature. Even less reactive aryl bromides such as di-*ortho*-substituted mesitylbromide or sterically hindered and unactivated 2-bromoanisole were coupled at room temperature within 1 h in high yields (entries 2 and 3). It is worth noting that, for reactions completed in less than 15 min, we observed a strong exotherm immediately after the addition of the aryl bromide. We attribute this feature to the exothermicity of the coupling reaction associated with the generation of the catalytically active species.

The same trend was observed when 4-biphenyl bromide and piperidine were coupled to yield, in only 5 min, *N*-(4-biphenylyl)piperidine (entry 5). The construction of such a framework is appealing from a synthetic point of view as the diphenylamino group is of great interest for the elaboration of conjugated donor−acceptor polymers.[47] Dibutylamine, as expected, was found to be less reactive than piperidine, but still yielded almost quantitatively, in less than an hour, dialkylanilines even with unactivated aryl bromides (entries 7−9). The reaction between benzylamine and 2-bromo-*m*-xylene required only one minute to reach completion (entry 10). More interestingly, when this reaction was carried out with an equimolar amount of amine and bromide, a simple extraction followed by a filtration through Celite afforded a pure coupling product without the need of purification by column chromatography.

Finally, primary and secondary anilines were efficiently arylated (entries 11−13). Gratifyingly, sterically encumbered tri- and tetra-*ortho*-diarylamines were produced in high yields.

Room-Temperature Buchwald−Hartwig Amination Reactions of Aryl Chlorides. Next, we carried out coupling reactions of a wide array of aryl chlorides and amines. Remarkably, no loss of activity was observed when we carried out reactions at room temperature. As shown in Table 10, all reactions reached completion almost as fast as when aryl bromides were used.

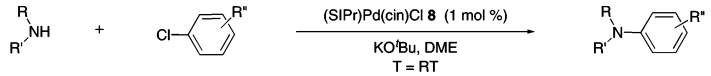
Secondary cyclic amines were easily coupled with activated (entry 4), neutral (entries 1−3), and unactivated chlorides (entries 5 and 6). As in the reactions with aryl bromides, a strong exotherm was observed after the addition of the chloride for every reaction completed within 15 min. Again, the exothermicity of the reaction is a testimony to an extremely efficient catalytic species.

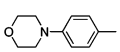
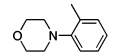
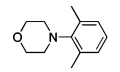
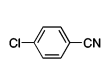
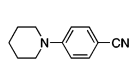
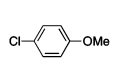
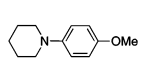
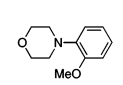
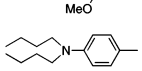
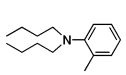
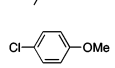
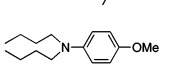
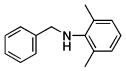
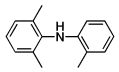
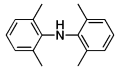
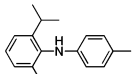
We then examined the reactivity of the less reactive, sterically hindered dibutylamine. It reacted smoothly with 2-chlorotoluene and the deactivated 4-chloroanisole in high yield (entries 7 and 9). More interestingly, we produced a dialkyl-*o*-arylamine in 90% isolated yield (entry 8). To the best of our knowledge, this is the first example of a coupling involving an acyclic dialkylamine and an *ortho*-substituted aryl chloride; moreover, it was achieved at room temperature and in a short reaction time.

Primary amines and anilines are other families of substrates that are compatible with our catalytic system, yielding within 1 h alkylarylamines and diarylamines (entries 10−15). We were particularly interested in the very sterically hindered 2,6-diisopropylaniline. 2- And 4-chlorotoluene could be coupled in high yields. Remarkably, even the di-*ortho*-substituted 2-chloro-*m*-xylene reacted in less than 2 h to yield 97% of the diarylamine. A short survey of the literature revealed that much harsher reaction conditions and the use of a bromide[48] or a nonaflate[49] were previously required to produce this compound. These last results finally highlight a general trend of the present catalytic system, its high compatibility for assembly of hindered compounds. This has allowed us to produce, always in high yields, tri- or tetra-*ortho*-substituted diarylamines even from less reactive aryl chlorides.

(47) Leung, M.-K.; Chou, M.-Y.; Su, Y. O.; Chiang, C. L.; Chen, H.-L.; Yang, C. F.; Yang, C.-C.; Lin, C.-C.; Chen, H.-T. *Org. Lett.* **2003**, *5*, 839−842.
(48) Sadighi, J. P.; Harris, M. C.; Buchwald, S. L. *Tetrahedron Lett.* **1998**, *39*, 5327−5330.
(49) Anderson, K. W.; Méndez-Pérez, M.; Priego, J.; Buchwald, S. L. *J. Org. Chem.* **2003**, *68*, 9563−9573.

Table 10. *N*-Aryl Amination Using Aryl Chlorides[a]



Entry	Amine	Ar-Cl	Product	Time (min)	Yield[b] (%)
1				2	95
2				2	92
3				20	93
4				5	96
5				40	95
6				60	92
7				90	87
8				75	90
9				120	95
10				40	90
11				30	90
12				40	86
13				150	87
14				120	93
15				90	97

[a] Reaction conditions: aryl chloride (1 mmol); amine (1.1 mmol); (SIPr)Pd(cin)Cl (**8**) (1 mol %); KO^{t}Bu (1.1 mmol); DME (1 mL). [b] Isolated yields, average of two runs.

Room-Temperature Buchwald−Hartwig Amination Reactions of Naphthyl and Anthryl Halides. In our continuing search for substrates of synthetic interest, we realized the increasing potential of naphthyl- and anthrylamines in materials chemistry and biochemistry. Well-known as hole transport materials[50] or photoactive chromophores,[51] they have been used lately as ligands in dendrimers to produce luminescent organometallic complexes.[52] Their applications in medicinal chemistry are multiple, ranging from spacer to improve drug delivery[53] to pharmacophore in a number of inhibitors.[54]

Despite their importance, the synthetic routes to produce naphthyl- or anthrylamines that have been explored to date involve, in general, the use of bromonaphthalene and amines (Scheme 3, path A) or naphthylamine and aryl bromides/iodides (Scheme 3, path B). The higher cost of bromonaphthalene compared to chloronaphthalene[55] does not favor approach A.

Scheme 3. Different Approaches to *N*-Naphthylamines

Approach B, using naphthylamine (which is another expensive substrate), is then more appealing for producing arylnaphthylamines; however, this route excludes the possibility of producing dialkylnaphthylamines. To overcome these difficulties, we thought of using our catalytic system in the coupling of inexpensive chloronaphthalene and amines (Scheme 3, path C). The results, all obtained at room temperature, are presented in Table 11.

We first attempted to react 1-chloronaphthalene with two cyclic secondary amines, morpholine and piperidine. We pleasantly observed that both reactions reached completion after only 5 min (entries 1 and 2). We noticed similar reaction times between 2-bromonaphthalene and piperidine (entry 6). Encouraged by these promising results, we carried out the coupling of the sterically hindered dibutylamine and dibenzylamine with

(50) (a) Thomas, K. R. J.; Lin, J. T.; Tao, Y.-T.; Ko, C.-W. *J. Am. Chem. Soc.* **2001**, *123*, 9404−9411. (b) Thelakkat, M. *Macromol. Mater. Eng.* **2002**, *287*, 442−461. (c) Lin, B. C.; Cheng, C. P.; Lao, Z. P. M. *J. Phys. Chem. A* **2003**, *107*, 5241−5251. (d) Nomura, M.; Shibasaki, Y.; Ueda, M.; Tugita, K.; Ichikawa, M.; Taniguchi, Y. *Macromolecules* **2004**, *37*, 1204−1210.

(51) (a) Fabbrizzi, L.; Licchelli, M.; Pallavicini, P.; Perotti, A.; Taglietti, A.; Sacchi, D. *Chem. Eur. J.* **1996**, *2*, 75−82. (b) Kubo, K.; Yamamoto, E.; Sakurai, T. *Heterocycles* **1998**, *48*, 1477−1483. (c) Costamagna, J.; Ferraudi, G.; Villagran, M.; Wolcan, E. *J. Chem. Soc., Dalton Trans.* **2000**, 2631−2637. (d) Bernardt, P. V.; Moore, E. G.; Riley, M. J. *Inorg Chem.* **2001**, *40*, 5799−5805.

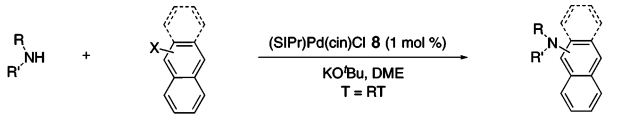
(52) Saudan, C.; Balzani, V.; Gorka, M.; Lee, S.-K.; Maestri, M.; Vicinelli, V.; Vögtle, F. *J. Am. Chem. Soc.* **2003**, *125*, 4424−4425.

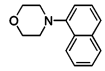
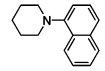
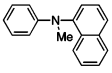
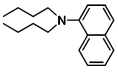
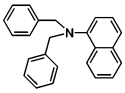
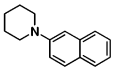
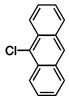
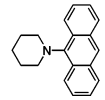
(53) de Groot, F. M. H.; et al. *J. Org. Chem.* **2001**, *66*, 8815−8830 (see Supporting Information for the complete reference).

(54) Bressi, J. C.; et al. *J. Med. Chem.* **2001**, *44*, 2080−2093 (see Supporting Information for the complete reference). (b) Honma, T.; et al. *J. Med. Chem.* **2001**, *44*, 4615−4627 (see Supporting Information for the complete reference). (c) Regan, J.; et al. *J. Med. Chem.* **2003**, *46*, 4676−4686 (see Supporting Information for the complete reference).

(55) According to the Acros catalog 2004−2005, 1-chloronaphthalene and 1-bromonaphthalene, when purchased by 100 mL quantities, cost respectively $28.9/mol and $57.6/mol.

Table 11. Room-Temperature *N*-Aryl Amination of Naphthyl and Anthryl Chlorides[a]



Entry	Amine	Ar-X	Product	Time (min)	Yield[b] (%)
1				5	91
2				5	87
3				120	89
4				60	95
5				30	74
6				5	92
7				60	95

[a] Reaction conditions: aryl chloride (1 mmol), amine (1.1 mmol), (SIPr)Pd(cin)Cl **8** (1 mol %), KO^{t}Bu (1.1 mmol), DME (1 mL). [b] Isolated yields, average of two runs.

1-chloronaphthalene (entries 4 and 5). Both reactions produced in high yields the corresponding *N*-naphthylamine, but surprisingly, they proceeded faster than the one involving *N*-methylaniline (entry 3), supposedly an easier coupling partner. Finally, the *N*-(9-anthryl)piperidine was produced in high yields and, interestingly, isolated without purification by column chromatography on silica gel. Taking advantage of the low solubility of the product in alkanes, a simple pentane wash followed by a filtration was sufficient to isolate the anthrylamine.

Buchwald−Hartwig Amination Reactions of Aryl Halides at Low Catalyst Loadings. The very rapid reactions observed for a wide array of substrates naturally led us to examine the effect of reducing the catalyst loading. The present catalytic system allowed for the use of as low as 10 ppm of catalyst if the temperature was raised to 80 °C (Table 12). It is noteworthy that, unlike what we observed in the Suzuki−Miyaura reaction, the unsubstituted allyl complex **3b** is not as efficient as the new complex **8** at elevated temperature and with extremely low catalyst loadings.

The reaction between morpholine and the sterically hindered bromomesitylene (entry 1) can be conducted at room temperature with only 0.1 mol % catalyst reaching completion in a few hours. Moreover, with 10 ppm catalyst the reaction reached completion at 80 °C after 30 h, providing a turnover number (TON) of 97 000, the highest observed to date for this type of substrate. The same trend was observed with a primary amine (entry 2) that could be coupled with as low as 10 ppm of **8**, providing a TON of 88 000. Interestingly, even strongly deactivated aryl chlorides (entries 4 and 5) reacted with dibutylamine to yield in reasonable reaction times the corresponding arylamine with as low as 0.01 mol % catalyst. The extremely bulky 2,6-diisopropylaniline, reacted with a di-*ortho*-substituted aryl chloride in only 10 h with 100 ppm of catalyst at 80 °C.

Conclusion

In summary, we have shown how simple modifications to the ancillary ligands surrounding palladium allow for dramatic changes in catalytic performance.[56] We have synthesized, in a very straightforward manner, a family of new air- and moisture-stable Pd(II) precatalysts derived from the (NHC)Pd(allyl)Cl where the allyl moiety is substituted. As shown by X-ray studies, substitution at the terminal position of the allyl moiety increases the dissymmetry of the allyl scaffold bound to the palladium. This induces a more facile activation step, from Pd(II) to Pd(0), for the new complexes. The ease of activation is then translated into a high catalytic activity even at room temperature. Therefore, (IPr)Pd(cinnamyl)Cl (**7**) permits the coupling of a wide range of aryl bromides, triflates, and chlorides with boronic acids at room temperature at extremely low catalyst loadings (0.05 mol %). When the reaction temperature is increased, catalyst loadings as low as 50 ppm can be used for Suzuki−Miyaura reactions with aryl chlorides. Furthermore, (SIPr)Pd(cinnamyl)Cl (**8**) can perform the Buchwald−Hartwig coupling reaction of a wide range of amines with aryl chlorides at room temperature in minutes (only one minute for some substrates). When the reaction temperature was raised to 80 °C, this system could be effective with as low as 10 ppm of catalyst, providing the highest turnover numbers to date. As added advantages, complexes **5**−**8** are air- and moisture-stable and can be prepared in multigram quantities in high yields. Studies aimed at exploring the activity of these latter-generation palladium precatalysts in related cross-coupling reactions are currently ongoing in our laboratories.

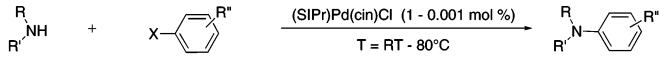
Experimental Section

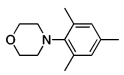
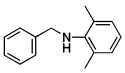
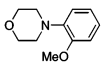
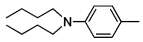
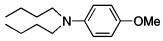
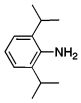
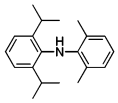
Synthesis of Pd(R-allyl)Cl Dimers.[57] **General Procedure.** A 250-mL double-necked round-bottom flask, equipped with a magnetic bar, was charged with 250 mL of distilled water in which argon was bubbled for 30 min. After this time, the flask was opened under argon flow; $PdCl_2$ (10 mmol, 1.77 g, 1 equiv) and KCl (20 mmol, 1.42 g, 2 equiv) were added in turn; and the flask was sealed with a rubber septum. The mixture was allowed to stir for 1 h, and an excess of the corresponding (R-allyl)Cl (30 mmol, 3 equiv) was then injected through the septum. The mixture was allowed to stir for 24 h. After this time, the reaction mixture was extracted with three portions of chloroform, and the organic layers were gathered, dried over $MgSO_4$, filtered, and reduced to yield the corresponding dimer. The identity and purity of the dimers were confirmed by comparison with data reported in the literature.

Synthesis of (NHC)Pd(R-allyl)Cl Complexes.[44] **General Procedure.** In a glovebox, a scintillation vial was charged with a stirring bar, 2.2 mmol of IPr or SIPr carbene, and 15 mL of dry THF. Once dissolved, 1 mmol of the corresponding palladium dimer was added and the mixture stirred at room temperature for 1.5 h. Outside of the glovebox, the solvent was evaporated in vacuo and the remaining solid

(56) Fairlamb and co-workers recently reported on a similar effect for η^2-dba complexes of Pd(0): Fairlamb, I. J. S.; Kapdi, A. R.; Lee, A. F. *Org. Lett.* **2004**, *6*, 4435−4438.
(57) Auburn, P. R.; Mackenzie, P. B.; Bosnich, B. *J. Am. Chem. Soc.* **1985**, *107*, 2033−2046.

Table 12. Buchwald−Hartwig Amination at Low Catalyst Loading



Entry	Amine	Ar-Br	Product	Cat. loading (mol %)	Time	Yield[b] (%)
1				1 0.1 0.001	30 min 5 h 30 h	98 92 97[c]
2				1 0.1 0.001	1 min 2 h 40 h	99 92 88[c]
3				1 0.1 0.01	1 h 12 h 10 h	97 85 99[c]
4				1 0.1 0.01	1.5 h 20 h 15 h	97 85 97[c]
5				1 0.1 0.01	2 h 20 h 12 h	100 85 96[c]
6				1 0.1 0.01	1.5 h 22 h 10 h	97 98 93[c]

[a] Reaction conditions: aryl halide (1 mmol), amine (1.1 mmol), (SIPr)Pd(cin)Cl (**8**) (1−0.001 mol %), KO^{t}Bu (1.1 mmol), DME (1 mL). [b] GC yields based on hexamethylbenzene as internal standard, average of two runs. [c] T = 80 °C.

triturated with pentane and collected by filtration on a sintered frit in air. The complex was then recrystallized from DCM/pentane.

(IPr)Pd(crotyl)Cl (5). The general procedure yielded 1.09 g (92%) of the complex. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.42 (t, J = 7.6 Hz, 2H), 7.25 (d, J = 1.6 Hz, 4H), 7.14 (s, 2H), 4.49 (dt, J = 6.8, 4.8 Hz, 1H), 3.46 (sextet, J = 6.4 Hz, 1H), 3.06 (q, J = 6.8 Hz, 2H), 2.89 (q, J = 6.8 Hz, 2H), 2.71 (d, J = 6.4 Hz, 1H), 1.41 (d, J = 8 Hz, 1H), 1.35 (d, J = 6.8 Hz, 12H), 1.15 (d, J = 6.8 Hz, 6H), 1.11 (d, J = 6.8 Hz, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 187.0, 146.3, 146.2, 136.24, 130.0, 124.2, 124.0, 113.3, 90.2, 44.9, 28.7, 26.5, 26.0, 23.1, 17.1. Anal. Calcd for $C_{31}H_{43}ClN_2Pd$ (MW 585.56): C, 63.59; H, 7.40; N, 4.78. Found: C, 63.42; H, 7.53; N, 4.63.

(IPr)Pd(prenyl)Cl (6). The general procedure yielded 1.13 g (95%) of the complex. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.47 (t, J = 8 Hz, 2H), 7.32 (d, J = 8 Hz, 4H), 7.20 (s, 2H), 4.42 (dd, J = 12.4, 7.2 Hz, 1H), 3.23 (q, J = 6.8 Hz, 2H), 2.85 (q, J = 6.8 Hz, 2H), 2.70 (dd, J = 7.2, 1.6 Hz, 1H), 1.58 (d, J = 8.4 Hz, 1H), 1.49 (s, 3H), 1.46 (d, J = 6.8 Hz, 6H), 1.36 (d, J = 6.8 Hz, 6H), 1.23 (d, J = 6.8 Hz, 6H), 1.11 (d, J = 6.8 Hz, 6H), 0.78 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 187.1, 146.4, 146.1, 136.4, 130.0, 124.1, 124.0, 123.8, 106.6, 105.7, 41.6, 28.8, 28.6, 26.8, 26.0, 23.7, 20.0. Anal. Calcd for $C_{32}H_{45}ClN_2Pd$ (MW 599.59): C, 64.10; H, 7.56; N, 4.67. Found: C, 64.36; H, 7.66; N, 4.34.

(IPr)Pd(cinnamyl)Cl (7). The general procedure yielded 1.10 g (85%) of the complex. ^{1}H NMR (C_6D_6, 400 MHz): δ 7.21−7.10 (m, 9H), 6.98 (d, J = 7.2 Hz, 2H), 6.64 (s, 2H), 5.07 (dd, J = 18.8, 6.8 Hz, 1H), 4.30 (d, J = 12.8 Hz, 1H), 3.31 (t, J = 6.4 Hz, 2H), 3.13 (t, J = 6.4 Hz, 2H), 3.02 (d, J = 6.4 Hz, 1H), 1.80 (d, J = 11.6, 1H), 1.46 (d, J = 6.4 Hz, 6H), 1.39 (d, J = 6.4 Hz, 6H), 1.03 (d, J = 4 Hz, 12H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 185.2, 146.2, 138.1, 136.1, 130.1, 128.4, 127.5, 126.8, 124.4, 124.0, 123.9, 109.0, 90.4, 28.8, 26.2, 23.1, 46.3. Anal. Calcd for $C_{36}H_{45}ClN_2Pd$ (MW 647.63): C, 66.76; H, 7.00; N, 4.33. Found: C, 67.03; H, 7.25; N, 4.03.

(SIPr)Pd(cinnamyl)Cl (8). The general procedure yielded 1.06 mg (82%) of the title complex. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.38 (t, J = 7.6 Hz, 2H), 7.25 (d, J = 8 Hz, 4H), 7.15−7.11 (m, 5H), 5.05 (dt, J = 12.4, 9.2, 1H), 4.34 (d, J = 13.2 Hz, 1H), 4.03 (s, 4H), 3.44 (broad s, 4H), 2.89 (broad s, 1H), 1.57 (broad s, 1H), 1.43 (d, J = 2.8 Hz, 12H), 1.27 (d, J = 6.8 Hz, 12H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 212.3, 147.3, 137.8, 136.6, 129.3, 128.5, 127.5, 126.9, 125.3, 124.5, 109.3, 91.9, 54.2, 46.2, 28.7, 26.8, 24.0. Anal. Calcd for $C_{36}H_{47}ClN_2$-Pd (MW 649.64): C, 66.56; H, 7.29; N, 4.31. Found: C, 66.27; H, 7.09; N, 4.13.

Suzuki−Miyaura Cross-Coupling Reactions. Preparation of the Precatalyst Solutions. In a glovebox, 0.01 mmol of complex (5.7 mg of **3a** or 6.5 mg of **7**) was added to a vial equipped with a magnetic bar and a screw cap fitted with a septum. Outside the glovebox, technical grade 2-propanol (4.0 mL) was injected into the vial through the septum and the mixture stirred at room temperature for 15 min prior to the injection of the required amount of substrates.

Suzuki−Miyaura Cross-Coupling Reactions. General Procedure. In a glovebox to a vial that closed with a screw cap fitted with a septum and that was equipped with a magnetic stir bar were added in turn potassium *tert*-butoxide (1.1 mmol, 124 mg), boronic acid (1.05 mmol), and aryl halide (if solid, otherwise vide infra). Outside the glovebox, the required amount of catalyst solution (catalyst loading 0.05 mol %, 200 μL, catalyst loading 0.005 mol %, 20 μL) was injected through the septum, followed by addition of technical grade 2-propanol (1 mL). The mixture was then stirred at room temperature unless otherwise indicated. After 15 min, the aryl halide (1 mmol) was injected (if liquid), and the reaction was monitored by gas chromatography. When the reaction reached completion, or no further conversion was observed by gas chromatography, water was added to the reaction mixture, the organic layer was extracted with *tert*-butylmethyl ether (MTBE), dried over magnesium sulfate, and the solvent was evaporated in vacuo. When necessary the product was purified by flash chromatography on silica gel.

Buchwald−Hartwig Cross-Coupling Reactions. General Procedure. In a glovebox, to a vial that closed with a screw cap fitted with a septum and that was equipped with a magnetic stir bar were added in turn (SIPr)Pd(cinnamyl)Cl (1 mol %, 6.5 mg), potassium *tert*-butoxide (1.1 mmol, 124 mg), and anhydrous DME (1 mL). Outside the glovebox, the amine (1.1 mmol) and the aryl halide (1 mmol) were injected in turn through the septum. If one of the two starting materials was a solid, it was added to the vial inside the glovebox, and DME and the second starting material were added outside the glovebox under argon. The reaction mixture was then stirred at room temperature unless otherwise indicated. When the reaction reached completion, or no further conversion was observed by gas chromatography, water was added to the reaction mixture, the organic layer was extracted with *tert*-butylmethyl ether (MTBE), dried over magnesium sulfate, and the solvent was evaporated in vacuo. When necessary the product was purified by flash chromatography on silica gel. The reported yields are the average of at least two runs.

***N*-(4-Biphenylyl)piperidine**[58] **(Table 9, entry 5).** The general procedure yielded, after flash chromatography on silica gel (pentane/

(58) This compound had already been reported, but our spectroscopic data were not in accordance with the literature. Louie, J.; Driver, M. S.; Hamann, B. C.; Hartwig, J. F. *J. Org. Chem.* **1997**, *62*, 1268−1273.

DCM, 90/10), 197 mg (83%) of the title compound. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.55 (d, J = 7.2 Hz, 2H, H^{Ar}), 7.48 (d, J = 8.4 Hz, 2H, H^{Ar}), 7.40−7.35 (m, 2H, H^{Ar}), 7.25 (t, J = 7.2 Hz, 1H, H^{Ar}), 6.98 (d, J = 8.4 Hz, 2H, H^{Ar}), 3.19 (t, J = 4.8 Hz, 4H, CH_2−N), 1.74−1.67 (m, 4H, CH_2−CH_2−N), 1.61−1.56 (m, 2H, CH_2(CH_2)$_2$−N). ^{13}C NMR (75 MHz, $CDCl_3$): δ 151.6 (C, N−C^{Ar}), 141.2 (C, C^{Ar}), 131.8 (C, C^{Ar}), 128.8 (CH, C^{Ar}), 127.8 (CH, C^{Ar}), 126.6 (CH, C^{Ar}), 126.4 (CH, C^{Ar}), 116.6 (CH, C^{Ar}), 50.6 (CH_2, CH_2−N), 26.0 (CH_2, CH_2−CH_2−N), 24.5 (CH_2, CH_2(CH_2)$_2$−N). Anal. Calcd for $C_{17}H_{19}N$ (MW 237.34): C, 86.03; H, 8.07; N, 5.90. Found: C, 86.28; H, 7.78; N, 5.87.

***N*-(2,6-Diisopropylphenyl)-2′,6′-dimethylaniline**[59] **(Table 9, entry 13 and Table 10, entry 15). A.** The general procedure with the aryl bromide yielded, after flash chromatography on silica gel (pentane/DCM, 80/20), 245 mg (87%) of the title compound.

B. The general procedure with the aryl chloride yielded, after flash chromatography on silica gel (pentane/DCM, 80/20), 273 mg (97%) of the title compound. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.13−7.09 (m, 3H, H^{Ar}), 6.91 (d, J = 7.5 Hz, 2H, H^{Ar}), 6.69 (t, J = 7.5 Hz, 1H, H^{Ar}), 3.15 (septet, J = 6.6 Hz, 2H, CH(CH_3)$_2$), 1.97 (s, 6H, C^{Ar}−CH_3), 1.11 (d, J = 6.6 Hz, 12H, CH(CH_3)$_2$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 144.3 (C, C^{Ar}), 143.3 (C, C^{Ar}), 139.0 (C, C^{Ar}), 129.7 (CH, C^{Ar}), 125.8 (C, C^{Ar}), 125.0 (CH, C^{Ar}), 123.4 (CH, C^{Ar}), 119.8 (CH, C^{Ar}), 28.2 (CH, CH(CH_3)$_2$), 23.7 (CH_3, CH(CH_3)$_2$), 19.5 (CH_3, C^{Ar}−CH_3).

***N*,*N*-Dibutyl-*N*-(1-naphthyl)-amine (Table 11, entry 4).** The general procedure yielded, after flash chromatography on silica gel (pentane/DCM, 95/5), 243 mg (95%) of the title compound. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.31 (d, J = 9.0 Hz, 1H, H^{Ar}), 7.76 (d, J = 9.0 Hz, 1H, H^{Ar}), 7.50 (d, J = 10.8 Hz, 1H, H^{Ar}), 7.46−7.33 (m, 3H, H^{Ar}), 7.13 (d, J = 7.5 Hz, 1H, H^{Ar}), 3.10 (t, J = 7.2 Hz, 4H, N−CH_2), 1.51−1.42 (m, 4H, N−CH_2−CH_2), 1.33−1.20 (m, 4H, N−(CH_2)$_2$−CH_2), 0.83 (t, J = 7.5 Hz, 6H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 148.9 (C, N−C^{Ar}), 135.2 (C, C^{Ar}), 131.5 (C, C^{Ar}), 128.3 (CH, C^{Ar}), 125.8 (CH, C^{Ar}), 125.7 (CH, C^{Ar}), 125.2 (CH, C^{Ar}), 124.5 (CH, C^{Ar}), 123.4 (CH, C^{Ar}), 118.2 (CH, C^{Ar}), 54.3 (CH_2, N−CH_2), 29.6 (CH_2, N−CH_2−CH_2), 20.8 (CH_2, N−(CH_2)$_2$−CH_2), 14.2 (CH_3, CH_3). Anal. Calcd for $C_{18}H_{25}N$ (MW 255.40): C, 84.65; H, 9.87; N, 5.48. Found: C, 84.63; H, 9.83; N, 5.20.

***N*-(2-Naphthyl)piperidine**[60] **(Table 11, entry 6).** The general procedure yielded, after flash chromatography on silica gel (pentane/DCM, 80/20), 192 mg (92%) of the title compound. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69−7.65 (m, 3H, H^{Ar}), 7.39−7.35 (m, 1H, H^{Ar}), 7.28−7.23 (m, 2H, H^{Ar}), 7.11 (s, 1H, H^{Ar}), 3.23 (t, J = 4.8 Hz, 4H, CH_2−N), 1.77−1.71 (m, 4H, CH_2−CH_2−N), 1.62−1.58 (m, 2H, CH_2(CH_2)$_{2-}$N). ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.3 (C, N−C^{Ar}), 134.9 (C, C^{Ar}), 128.7 (CH, C^{Ar}), 128.5 (C, C^{Ar}), 127.6 (CH, C^{Ar}), 126.9 (CH, C^{Ar}), 126.3 (CH, C^{Ar}), 123.3 (CH, C^{Ar}), 120.4 (CH, C^{Ar}), 110.5 (CH, C^{Ar}), 51.2 (CH_2, CH_{2-}N), 26.1 (CH_2, $CH_{2-}CH_{2-}$N), 24.6 (CH_2, CH_2(CH_2)$_2$−N).

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Supporting Information Available: Experimental procedures and crystallographic information files (CIFs) for **5**−**8**. This material is available free of charge via the Internet at http://pubs.acs.org. CCDC-27868-279871 contains the supplementary crystallographic data for this paper. These data can be downloaded free of charge via www.ccdc.cam.ac.uk/conts/retrieving.hmtl (or obtained from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB21EZ, UK; fax (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

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(59) For complementary characterization of this compound, see ref 53.

(60) For complementary characterization of this compound, see: Carmack, M.; Behforouz, M.; Berchtold, G. A.; Berkowitz, S. M.; Wiesler, D.; Barone, R. J. *Heterocycl. Chem.* **1989**, *26*, 1305−1318.