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Rapid Room Temperature Buchwald–Hartwig and Suzuki–Miyaura Couplings of Heteroaromatic Compounds Employing Low Catalyst Loadings

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Abstract: The use of second-generation [(NHC)Pd(R-allyl)Cl] complexes for Suzuki–Miyaura and Buchwald–Hartwig cross-coupling reactions involving heteroaromatic halides at room temperature is reported. The first examples of room temperature Suzuki–Miyaura cross-coupling of deactivated aryl chlorides with alkenyl boronic acids are also disclosed. Terminal substitution at the allyl moiety of the palladium complex facilitates its activation at room temperature leading to very active catalytic species enabling the present catalytic transformations to be performed rapidly using very mild reaction conditions. Catalyst loadings can be as low as 10 ppm for the Buchwald–Hartwig aryl amination and 50 ppm for the Suzuki–Miyaura reaction.

Keywords: Buchwald–Hartwig reaction · carbenes · cross-coupling · palladium · Suzuki–Miyaura reaction

Introduction

Heteroaromatic compounds represent a recurring architectural motif found in various areas of chemistry, ranging from pharmaceutically active compounds[1,2] to polymers.[3] Although the Suzuki–Miyaura[4] and Buchwald–Hartwig[5] reactions arguably are among the most powerful and widely used methods to assemble C–C or C–N bonds, heterocyclic compounds are usually not easily coupled in these important reactions. These bond-making processes are achieved by coupling an organic halide or pseudohalide with an organoboron reagent or an amine, respectively, in the presence of a transition-metal catalyst.[6] It is well known that the ancillary ligands on the metal center play a major role in dictating the efficiency of a catalytic system.[5] Bulky, electron-rich phosphines such as P(*o*-tolyl)$_3$ and P(*t*Bu)$_3$ are by far the most utilized phosphorus-based ligands capable of stabilizing the active Pd^0 species presumably responsible for activity in these important bond-forming reactions.[7] The N-heterocyclic carbenes[8] (NHC) represent an alternative class of ligands becoming increasingly popular to achieve these couplings.[9]

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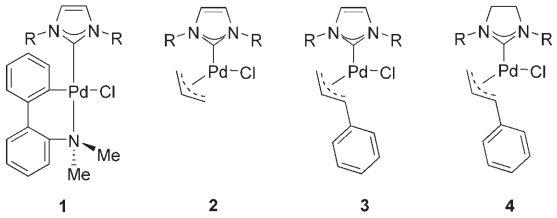
Results and Discussion

Aryl chlorides are very attractive halides due to their low cost and wide diversity and availability. Historically, their use in cross-coupling reactions has been somewhat limited due to their poor reactivity, attributed to the strength of the C–Cl bond.[10] Despite their importance, the coupling reactions of most heteroaromatic chlorides remain a challenge,[11] especially at low temperatures and/or low catalyst loadings. Although the poisoning effect of sulfur in some palladium-catalyzed reactions is well known, it should also be mentioned that such undesired effects have also been observed with nitrogen containing substrates.[12]

Our group recently reported a general system involving the use of palladacycle **1** for the room temperature Suzuki–Miyaura cross-coupling of aryl chlorides in technical grade isopropanol.[13] The system even allowed for the coupling of sterically hindered unactivated aryl chlorides with sterically hindered boronic acids under these mild conditions. Di- and tri-*ortho*-substituted biaryls were isolated in high yields using this simple protocol. In addition, the coupling of a series of heteroaromatic (S- and N-containing) halides could be carried out under these conditions in short reaction times and high yields.[14] The only drawbacks associated with the use of **1** are the harsh conditions required for the synthesis of the complex and the associated low synthetic yield (63%).[15] Furthermore, slow addition of the aryl chloride was required when performing the coupling to avoid the undesired competing dehalogenation of the aryl halide. To further explore and hopefully capitalize on ancillary ligand ef-

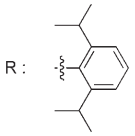
fects, the activation of complexes with the general formula [(NHC)Pd(allyl)Cl] was recently examined {in Scheme 1, [(IPr)Pd(allyl)Cl] (**2**) (IPr = (*N*,*N*′-bis(2,6-diisopropylphenyl)imidazol)-2-ylidene)}. This was studied in order to determine how the architecture could be fine-tuned and lead to an increase in the rate of activation of these catalyst precursors at room temperature.



Scheme 1. Complexes **1**–**4**.

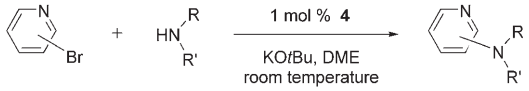
These complexes and this framework were selected since their synthesis is very straightforward and proceed in high yields, even in multigram preparations.[16] By decreasing the stability of the η^3 bond by control of electronic and steric effects, we reasoned that terminal substitution (alkyl or aryl) at the allyl moiety would facilitate the activation of the complexes at room temperature[16a,17] leading to the postulated active catalytic species, [(NHC)Pd^0]. To test our hypothesis, we prepared a series of complexes with general formula [(NHC)Pd(R-allyl)Cl], and examined their reaction profiles for the Suzuki–Miyaura and the Buchwald–Hartwig reactions with aryl chlorides. These trials provided excellent results.[18] Herein, we report on the use of two of those substituted-allyl palladium complexes, [(IPr)Pd(cinnamyl)Cl] (**3**) (cinnamyl = 3-phenylallyl) and [(SIPr)Pd(cinnamyl)Cl] (**4**) (SIPr = (*N*,*N*′-bis(2,6-diisopropylphenyl)-4,5-dihydroimidazol)-2-ylidene) for specific trials with heteroaromatic halides as substrates.

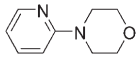
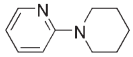
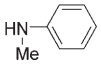
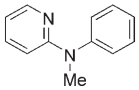
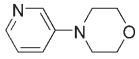
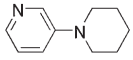
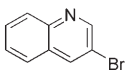
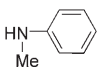
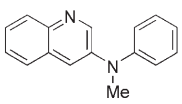
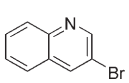
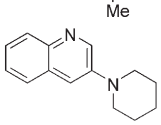
Buchwald–Hartwig reactions: As we[16a] and others[19] have reported the use of the SIPr carbene leading to a better catalyst performance than the IPr carbene in this reaction, we tested the activity of **4** in a series of reactions involving the coupling of N-containing heteroaromatic halides with primary and secondary amines at room temperature (Tables 1 and 2). 2-Bromo- and 2-chloropyridine were found to react very efficiently with a range of amines. Reactions with cyclic dialkylamines reached completion within five minutes (Tables 1 and 2, entries 1 and 2) and are quantitative; leading, in the case of entry 1 to a workup that simply required filtration through Celite without purification by column chromatography. As expected, the more sterically demanding dibutyl- and diallylamine required a longer reaction time to provide in almost quantitative yield the corresponding 2-pyridyl derivatives (Table 2, entries 3 and 4). It is noteworthy that this is the first example, to the best of our knowledge, of chloropyridines coupled with amines under such mild conditions and in such short reaction times.[20,11a] The same trend was observed with *N*-methylaniline which produced diaryl compounds within 15 minutes (Table 1, entry 3 and Table 2, entry 5). Surprisingly, coupling reactions with 3-chloro- and 3-bromopyridine, strongly unactivated compared with 2-pyridyl halides,[21] proceeded rapidly. This allowed for the formation of 3-pyridylamino compounds at room temperature in no more than 45 minutes.



More strikingly, when 3-bromopyridine was added to reaction mixtures containing morpholine or piperidine, an intense exotherm was observed and these reactions reached completion within five minutes (Table 1, entries 4 and 5). Encouraged by the reactivity of 3-halopyridines, we carried

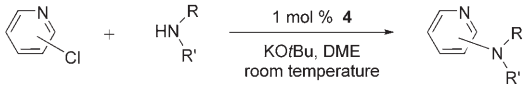
Table 1. Buchwald–Hartwig reactions with N-containing heteroaromatic bromides.

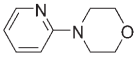
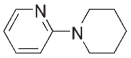
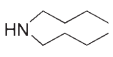
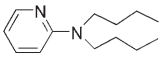
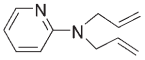
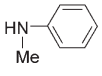
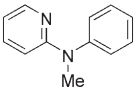
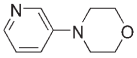
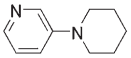


Entry	Bromide	Amine	Product	*t* [min]	Yield [%][a]
1				1	94
2				2	96
3				10	92
4				5	90
5				5	72
6				90	92
7				40	87

Reaction conditions: 1 mmol aryl bromide; 1.1 mmol amine; 1 mol% **4**; 1.1 mmol KO*t*Bu; 1 mL DME. [a] Isolated yields, average of two runs.

Table 2. Buchwald–Hartwig Reactions with N-containing heteroaromatic chlorides.



Entry	Chloride	Amine	Product	t [min]	Yield [%][a]
1				2	89
2				5	98
3				15	94
4				60	92
5				15	92
6				15	86
7				45	82

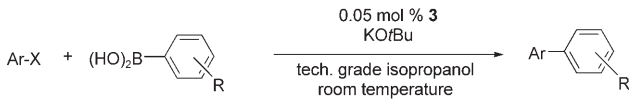
Reaction conditions: 1 mmol aryl chloride; 1.1 mmol amine; 1 mol % **4**; 1.1 mmol KO*t*Bu; 1 mL DME. [a] Isolated yields, average of two runs.

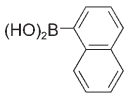
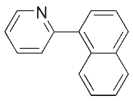
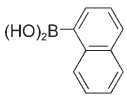
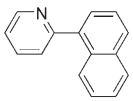
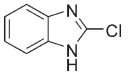
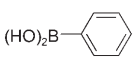
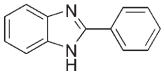
out reactions with 3-bromoquinoline. *N*-Methylaniline and piperidine yielded the corresponding 3-aminoquinolines (Table 1, entries 6 and 7). Considering the mild reaction conditions employed, this is a considerable advance since few reports on aryl amination involve haloquinolines.[22]

Suzuki–Miyaura reactions: In earlier work, we identified (IPr)-bearing palladium complexes as the most effective for Suzuki–Miyaura coupling reactions,[16,18] the following experiments were carried out using **3** as pre-catalyst. As for the Buchwald–Hartwig reaction, attempts to couple sulfur-containing heteroaromatic halides (2- or 3-bromo- or chlorothiophenes and 2-chlorobenzothiazole) with boronic acids at room temperature invariably failed but reactions carried out at 60 °C proceeded smoothly. The Suzuki–Miyaura coupling of chlorothiophenes at room temperature has been reported.[14,23] However, in the present system since the high thiophilicity of Pd^{II} may cause the heteroaromatic substrate to interact with the pre-catalyst and thereby inhibit activation, our results suggest that the formation of the [(NHC)Pd^0] species is not immediate under these conditions. Interestingly, unlike the Buchwald–Hartwig reaction, the position of the nitrogen in the ring has a major effect in the Suzuki–Miyaura coupling: the couplings of 3-bromopyridine, 3-chloropyridine and 3-bromoquinoline with boronic acids did not take place under these conditions, while 2-bromo- and 2-chloropyridine coupled smoothly in high yields (Table 3, entries 1, 2) using **3** in as low as 0.05 mol % (or 500 ppm). We have not found precedents in the literature for the room temperature Suzuki–Miyaura coupling of 2-chlorobenzimidazole (Table 3, entry 3) or 5-chloro-1,3-benzodioxole (Table 3, entry 4). 2-Substituted benzimidazoles are a ubiquitous moiety in heteroaromatic chemistry and can be found in applications ranging from anticancer drugs[24] to conducting polymers.[3] As an additional practical advantage, for all Suzuki–Miyaura couplings reported here, catalyst solutions where prepared with technical grade isopropanol (IPA) and injected in the sample vials through a septum cap. From a practical point of view, these conditions are very appealing, especially since it makes use of an inexpensive and environmentally friendly solvent (IPA) without the need for predrying or purification.

We then proceeded to examine whether this system could facilitate the coupling of heteroaromatic halides with alkenylboronic acids, another significant challenge (Table 4). Mild temperatures are often mandatory for the coupling of aryl bromides with vinylboronic acids, this to favor desired high *E*/*Z* selectivity. Buchwald and co-workers recently reported on a very efficient system to couple aryl bromides and a variety of alkenylboronic acids.[25]

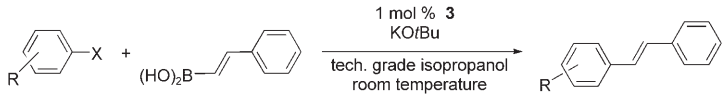
Table 3. Suzuki–Miyaura couplings of heteroaryl halides.

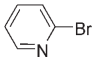
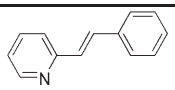
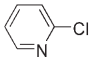
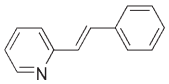
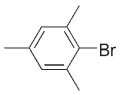
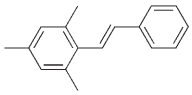
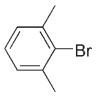
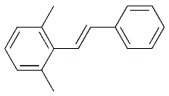
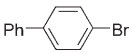
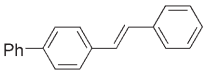
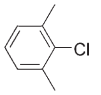
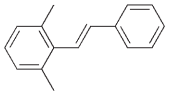
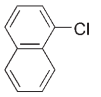
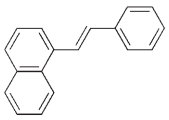


Entry	Ar-X	Boronic acid	Product	t [h]	Yield [%][a]
1				3.5	94
2				15	96
3				15	95

Reaction conditions: 1 mmol aryl halide; 1.05 mmol boronic acid; 0.05 mol % **3**; 1.1 mmol KO*t*Bu; 1 mL technical grade isopropanol. [a] Isolated yields, average of two runs.

Table 4. Suzuki–Miyaura couplings of *trans*-2-phenylvinylboronic acid.



Entry	Ar-X	Product	*t* [h]	Yield [%][a]
1			0.5	94
2			1	94
3			1.5	92
4			1	92
5			1	95
6			2	61
7			1	78[b]
7			1	94

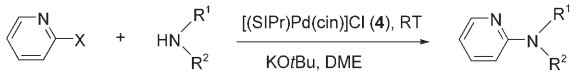
Reaction conditions: 1 mmol aryl halide; 1.05 mmol boronic acid; 1.0 mol % **3**; 1.1 mmol KO*t*Bu; 1 mL technical grade isopropanol. [a] Isolated yields. >99:1 *trans*:*cis* isomers. [b] 2 mol % catalyst loading.

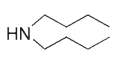
While substrates without *ortho*-substituents coupled at room temperature, electron-rich and *ortho*-substituted bromides required a reaction temperature of 40 °C. Higher temperatures were required to couple the analogous chlorides, leading to the undesired *E*/*Z* alkene isomerization. In the present NHC-based system, reactions proceeded smoothly at room temperature using 1 mol % of **3** in very short reaction times and high yields for the coupling of 2,4,6-trimethylphenyl bromide, 2,6-dimethylphenyl bromide, 4-bromobiphenyl and 2-bromopyridine. Longer reaction times were required for the coupling of analogous aryl chlorides, and the electron-rich, sterically demanding 2,6-dimethylphenyl chloride did not reach completion despite using a higher catalyst loading (2 mol %) and a longer reaction time. In all cases, *E*/*Z* alkene isomerization was negligible. To the best of our knowledge, these are the first examples of Suzuki–Miyaura cross coupling of unactivated aryl chlorides with an alkenylboronic acid performed in such yields and reasonable reaction times at room temperature.

Buchwald–Hartwig and Suzuki–Miyaura reactions at low catalyst loadings: Decreasing the amount of palladium necessary to catalyze a process is desirable not only because of cost, but also in order to facilitate metal removal once the reaction is complete. This is especially important in industrial settings where concerns of product purity, toxicity associated with residual metal and general environmental issues have significant health and economical consequences.[26] The very rapid reactions observed for a wide array of substrates naturally led us to examine the effect of reducing the catalyst loading.

For the Buchwald–Hartwig reaction, the use of **4** allowed for the use of as low as 10 parts per million (ppm) pre-catalyst if the temperature was raised to 80 °C. The reaction between morpholine and 2-bromopyridine (Table 5, entry 1) can be conducted at room temperature with a catalyst loading of only 0.1 mol %; the reaction reached completion in

Table 5. Buchwald–Hartwig reactions at room temperature and low catalyst loadings.



Entry	Aryl halide	Amine	Cat. loading [mol %]	*t*	Yield [%][a]
1			1	1 min	99
			0.1	2 min	93
			0.001	50 h	97
			0.001	12 h	91[b]
2			1	1 min	100
			0.1	5 min	93
			0.001	48 h	95
			0.001	20 h	94[b]
3			1	15 min	98
			0.1	1 h	99
			0.001	50 h	73
			0.001	40 h	93[b]

Reaction conditions: 1 mmol halopyridine; 1.1 mmol amine; 1.1 mmol KO*t*Bu; 1 mL DME. [a] GC yields (hexamethylbenzene as internal standard) average of two runs. [b] $T = 80$ °C.

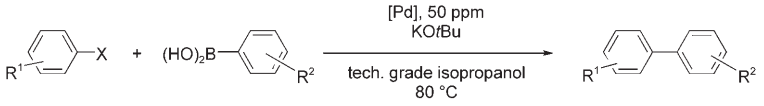
two minutes, corresponding to a turnover frequency (TOF) of 27900 h^{-1}. Moreover, with a 10 ppm catalyst loading the reaction reached completion at room temperature but required 50 h, providing a turnover number (TON) of 97000.[11a] Remarkably, the reaction time could be reduced by a factor of 4 if the temperature was raised to 80 °C.

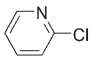
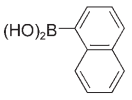
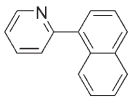
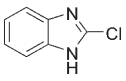
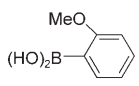
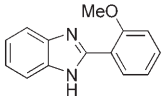
2-Chloropyridine also reacted very rapidly with morpholine with 0.1 mol % catalyst (TOF = 11160 h^{-1}). A TON of 95000 was obtain when 10 ppm catalyst used (Table 5, entry 2). This TON value is very similar to the one recently reported by Hartwig.[11a] Finally, we carried out the reaction between 2-chloropyridine and dibutylamine. Strikingly, even with a sterically demanding amine, high TON values were obtained at room temperature and at 80 °C (73000 and 93000, respectively). It is of note that a literature search revealed that this particular coupling was carried out with the corresponding bromide prior to the present study and required elevated temperatures (80 °C) and high catalyst loading (2–3 mol %).[27]

For the Suzuki–Miyaura reaction, when the temperature is increased to 80 °C, the catalyst loading can be reduced to 50 ppm with no loss of yield and proceeds in even shorter reaction times.

As expected, the use of the commercially available [(IPr)Pd(allyl)Cl] (**2**) at high temperature provides the same results as when **3** is used (Table 6, entry 1),[18,28] highlighting again the significant role of the higher terminal substitution at the allyl moiety in activating the catalyst at lower temperatures. This effect is in contrast to our observations for the Buchwald–Hartwig reaction where terminal allylic substitution has a profound influence on activation regardless of temperature.

Table 6. Suzuki–Miyaura reactions at low catalyst loading.



Entry	Ar-X	Boronic acid	Product	[Pd]	t [h]	Yield [%][a]
1				**3**	3	93
				2	3	92
2				**2**	3	91

Reaction conditions: 1 mmol aryl chloride; 1.05 mmol boronic acid; 1.1 mmol KO*t*Bu; 1 mL technical grade isopropanol. [a] Isolated yields, average of two runs.

Conclusion

In summary, we have demonstrated how simple modifications to the ancillary ligands surrounding palladium allow for dramatic changes in catalytic performance.[29] This effect is attributed to a facile activation step leading to the efficient generation of a catalytically active palladium(0) species in solution. We have presented examples of couplings of heteroaryl bromides and chlorides with boronic acids or amines at room temperature proceeding in extremely short reaction times. When the temperature is increased, catalyst loadings as low as 50 ppm of **2** or **3** can be used for the Suzuki–Miyaura reaction, and as low as 10 ppm of **4** for the Buchwald–Hartwig reaction. We have also reported the first examples of room temperature Suzuki–Miyaura coupling of unactivated aryl chlorides with alkenyl boronic acids. Additionally, complexes **2**–**4** are air- and moisture-stable and can be prepared on multigram scale in high yields. Complex **2** is commercially available and congeners will also shortly be offered.[30] Studies aimed at exploring the reaction chemistry of these latter generation palladium catalysts in related cross-coupling reactions are currently ongoing in our laboratories.

Experimental Section

General information: All aryl halides, amines and boronic acids were used as received (Aldrich, Acros). Technical grade isopropanol was used to carry out catalytic reactions (Mallinckrodt Chemicals). Potassium *tert*-butoxide (Acros) was stored under argon in an M. Braun glovebox. Complexes **2**–**4** were prepared according to the literature.[16b,18] Flash chromatography was performed on silica gel (230–400 mesh, Silicycle). ^{1}H and ^{13}C nuclear magnetic resonance spectra were recorded on a Varian-300 or Varian-400 MHz spectrometer at ambient temperature in $CDCl_3$, C_6D_6 or [D_6]DMSO (Cambridge Isotope Laboratories, Inc). Elemental analyses were performed at Robertson Microlit Laboratories, Inc., Madison, NJ.

Buchwald–Hartwig cross-coupling reactions

General procedure: In a glovebox, **4** (1 mol %, 6.5 mg), potassium *tert*-butoxide (1.1 mmol, 124 mg) and anhydrous 1,2-dimethoxyethane (DME) (1 mL) were added in turn to a vial equipped with a magnetic bar, and sealed with a screw cap fitted with a septum. Outside the drybox, 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 drybox through the septum.) The vial was then stirred on a stirring plate at room temperature unless otherwise indicated. The reaction was monitored by gas chromatography. When the reaction reached completion, or no further conversion could be observed, water was added to the reaction mixture, the organic layer was extracted with *tert*-butyl methyl 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*-(3-Pyridyl)piperidine** (Table 1, entry 5):[31] The general procedure yielded, after flash chromatography on silica gel (pentane/MTBE 80:20), the title compound (117 mg, 72 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.30 (s, 1H, H^{Ar}), 8.05 (d, J = 4.5 Hz, 1H, H^{Ar}), 7.19–7.10 (m, 2H, H^{Ar}), 3.18 (t, J = 5.1 Hz, 4H, CH_2-N), 1.75–1.67 (m, 4H, CH_2-CH_2-N), 1.63–1.57

(m, 2H, CH_2(CH_2)$_2$-N); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 147.9 (C, N-C^{Ar}), 140.2 (CH, C^{Ar}), 139.1 (CH, C^{Ar}), 123.5 (CH, C^{Ar}), 122.7 (CH, C^{Ar}), 50.0 (CH_2, CH$_2$-N), 25.7 (CH_2, CH$_2$-CH_2-N), 24.2 (CH_2, CH$_2$(CH_2)$_2$-N).

***N*-(3-Quinolinyl)piperidine** (Table 1, entry 7):[32] The general procedure yielded, after flash chromatography on silica gel (pentane/MTBE 70:30), the title compound (185 mg, 87%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.78 (d, J = 2.7 Hz, 1H, H^{Ar}), 7.97 (d, J = 7.8 Hz, 1H, H^{Ar}), 7.63 (d, J = 9.3 Hz, 1H, H^{Ar}), 7.49–7.38 (m, 2H, H^{Ar}), 7.28 (d, J = 2.7 Hz, 1H, H^{Ar}), 3.21 (t, J = 5.1 Hz, 4H, CH_2-N), 1.77–1.70 (m, 4H, CH_2-CH_2-N), 1.62–1.55 (m, 2H, CH_2(CH_2)$_2$-N); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 145.6 (CH, N-CH^{Ar}), 142.7 (C, C^{Ar}), 129.1 (C, C^{Ar}), 128.9 (CH, C^{Ar}), 127.8 (C, C^{Ar}), 126.8 (CH, C^{Ar}), 126.5 (CH, C^{Ar}), 126.0 (CH, C^{Ar}), 116.6 (CH, C^{Ar}), 50.6 (CH_2, CH$_2$-N), 25.7 (CH_2, CH$_2$-CH_2-N), 24.1 (CH_2, CH$_2$(CH_2)$_2$-N).

***N*,*N*-Diallyl-*N*-(2-pyridyl)amine** (Table 2, entry 4):[33] The general procedure yielded, after flash chromatography on silica gel (pentane/MTBE 90:10), the title compound (159 mg, 98%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.15 (d, J = 3.3 Hz, 1H, H^{Ar}), 7.43–7.37 (m, 1H, H^{Ar}), 6.55–6.51 (m, 1H, H^{Ar}), 6.47 (d, J = 8.7 Hz, 1H, H^{Ar}), 5.91–5.82 (m, 2H, -CH=CH_2), 5.17–5.12 (m, 4H, -CH=CH_2), 4.11 (d, J = 5.1 Hz, 4H, CH_2-N); ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.9 (C, N-C^{Ar}), 148.1 (CH, C^{Ar}), 137.3 (CH, CH=CH_2), 134.2 (CH, C^{Ar}), 116.2 (CH_2, -CH=CH_2), 115.1 (CH, C^{Ar}), 106.3 (CH, C^{Ar}), 50.3 (CH_2, CH$_2$-N).

Buchwald–Hartwig cross-coupling at low catalyst loading

Preparation of catalyst solutions: In a glovebox, in a scintillation vial, [(SIPr)Pd(cinnamyl)Cl] (**4**) (6.5 mg, 0.01 mmol) was dissolved in DME (10 mL), providing solution A. In another vial, DME (9 mL) was added to solution A (1 mL), providing solution B. A third vial containing solution B (1 mL) and DME (9 mL) provided solution C.

General procedure: In a glovebox, potassium *tert*-butoxide (1.1 mmol, 124 mg), hexamethylbenzene (1 mmol, 153 μL) and catalyst solution (1 mL solution A for 0.1 mol% of **4**, solution C for 0.001 mol% of **4**) were added in turn to a vial equipped with a magnetic bar, and sealed with a screw cap fitted with a septum. Outside the glovebox, the amine (1.1 mmol) and the aryl halide (1 mmol) were injected in turn through the septum. The reaction mixture was then stirred at room temperature unless otherwise indicated. The reaction was monitored by gas chromatography and the yields given using hexamethylbenzene as internal standard.

Suzuki–Miyaura cross-coupling reactions

Preparation of the catalyst solutions: In a glovebox, **3** (6.5 mg, 0.01 mmol) was added to a vial equipped with a magnetic bar, and closed with a screw cap with a septum. Outside the glovebox, technical grade isopropanol (1.0 mL) was injected into the vial and the mixture stirred on a stirring plate at room temperature for 15 min prior to the injection of the required amount in the reaction vials.

Suzuki–Miyaura cross-coupling of heteroaryl chlorides or bromides with boronic acids at room temperature

General procedure: In a glovebox, potassium *tert*-butoxide (1.1 mmol, 124 mg), boronic acid (1.05 mmol) and aryl halide (if solid, otherwise see below) were added in turn to a vial equipped with a magnetic bar, and closed with a screw cap with a septum. Outside the glovebox, the required amount of catalyst **3** solution (catalyst loading 0.05 mol%, 200 μL) was injected through the septum, followed by technical grade isopropanol to a final volume of 1 mL. The mixture was stirred on a stirring plate at room temperature for 15 min. Aryl halide (1 mmol) was then injected (if liquid) and the reaction was monitored by gas chromatography. When the reaction reached completion, or no further conversion could be observed, water was added to the reaction mixture, the organic layer was extracted with MTBE, dried over magnesium sulfate and the solvent was evaporated in vacuo. When necessary the product was purified by flash chromatography on silica gel using mixtures pentane/MTBE 95:5.

Suzuki–Miyaura cross-coupling of aryl and heteroaryl halides with *trans*-2-phenylvinylboronic acid at room temperature

General procedure: In a glovebox, **3** (6.5 mg), potassium *tert*-butoxide (1.1 mmol, 124 mg), boronic acid (1.05 mmol) were added in turn to a vial equipped with a magnetic bar, and closed with a screw cap with a septum. Outside the glovebox, technical grade isopropanol (1 mL) was injected through the septum and the mixture was stirred on a stirring plate at room temperature for 15 min. Aryl halide (1 mmol) was then injected and the reaction was monitored by gas chromatography. When the reaction reached completion, or no further conversion could be observed, water was added to the reaction mixture, the organic layer was extracted with diethyl ether, dried over magnesium sulfate and the solvent was evaporated in vacuo. When necessary the product was purified by flash chromatography on silica gel using mixtures hexanes/EtOAc 95:5.

Suzuki–Miyaura cross-coupling of heteroaryl chlorides with boronic acids at low catalyst loadings

General procedure: In a glovebox, potassium *tert*-butoxide (1.1 mmol, 124 mg), boronic acid (1.05 mmol) and aryl chloride (if solid, otherwise see below) were added in turn to a vial equipped with a magnetic bar, and closed with a screw cap with a septum. Outside the glovebox, the required amount of catalyst solution (catalyst loading 0.005 mol%, 20 μL) was injected through septum, followed by technical grade isopropanol (1 mL). The reaction mixture was placed in an oil bath at 80°C over a magnetic stirring plate. 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 could be observed, water was added to the reaction mixture, the organic layer was extracted with MTBE, dried over magnesium sulfate and the solvent was evaporated in vacuo. When necessary, the product was purified by flash chromatography on silica gel using mixtures pentane/MTBE 95:5.

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