Room-temperature activation of aryl chlorides in Suzuki–Miyaura coupling using a $[Pd(\mu\text{-}Cl)Cl(NHC)]_2$ complex (NHC = *N*-heterocyclic carbene)†

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A straightforwardly synthesised complex, $[Pd(\mu\text{-}Cl)Cl(NHC)]_2$ (NHC = bis(2,6-diisopropylphenyl)imidazol-2-ylidene, IPr), has been employed to mediate Suzuki–Miyaura reactions involving aryl chlorides at very low catalyst loadings and at room temperature.

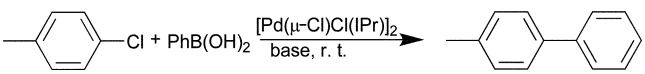
The Suzuki–Miyaura reaction has become a classic in modern molecular assembly protocols.[1] It is used to synthesise specialty polymers,[2] agrochemical[3] and pharmaceutical compounds.[4] The successful development of catalysts enabling the Suzuki–Miyaura reaction with aryl chlorides[5] started in 1998 when Littke and Fu first reported the use of P^tBu_3 to facilitate the Pd-mediated activation of the strong C–Cl aryl halide bond.[6]

A different class of ligands, the *N*-heterocyclic carbenes (NHC), can also enable this transformation. One of us,[7] and others,[8] have contributed to this area with the development of well-defined mono-NHC palladium complexes. Amongst them, the air- and moisture-stable complex $[Pd(\mu\text{-}Cl)Cl(IPr)]_2$ **1** (IPr = bis(2,6-diisopropylphenyl)imidazol-2-ylidene) has been reported as an efficient pre-catalyst for the Buchwald–Hartwig reaction even under aerobic conditions.[9] It seemed thus of great interest to assess the catalytic performance of **1** in the powerful C–C bond-forming reaction that is the Suzuki–Miyaura coupling. Herein, we report that this transformation can be achieved under mild reaction conditions at low catalyst loading.‡

As shown in Table 1, the study begins with an optimisation of the operating conditions on a model reaction involving 4-chlorotoluene and phenylboronic acid. The first solvent/base mixture tested was 1,4-dioxane/Cs_2CO_3 as it has proven to be efficient for *in situ* generated Pd–NHC catalysts and for Pd–P^tBu_3 systems. However, with the well-defined system **1**, only a small amount of coupling product was observed (Table 1, entry 1). We then moved to alkoxide bases that are known to facilitate the Suzuki–Miyaura reaction promoted by well-defined NHC systems. Here again, no coupling product was observed when 1,4-dioxane was used as the solvent (Table 1, entry 2). It was recently reported that alcoholic solvents could be quite beneficial in the Suzuki–Miyaura reaction with [PdCl(allyl)(NHC)] pre-catalysts.[10] The transformation of the Pd(II) complex into the "active" Pd(0) species is key and the selection of the solvent/base couple is crucial in generating the active species. Indeed, when moving to isopropanol as solvent and KO^tBu as base, the desired biphenyl product was obtained in 80% yield using 1 mol% of **1** (Table 1, entry 3). Screening of other alcohols (methanol, ethanol) was performed (Table 1, entries 4 and 5) and ethanol provided a yield of 87%, which is especially interesting in view of economic and environmental issues.

In order to test the limits of this system, the catalyst concentration was decreased by one order of magnitude. Here again, an excellent result was obtained in ethanol and 87% of 4-methylbiphenyl was formed in the presence of 0.1 mol% of **1** after 4 h at r.t. (Table 1, entry 6). With the inexpensive NaOMe,[11] the catalyst also performed well but more slowly. Indeed, after 4 h only 68% of biaryl was formed (Table 1,

Table 1 Optimisation (aerobic and anaerobic conditions)[a]



Entry	Cat. loading (mol%)	Solvent	Base	*t*/h	Conv.[b] (%)
1	1	1,4-Dioxane	Cs_2CO_3	1	4
2	1	1,4-Dioxane	KO^tBu	1	0
3	1	^{i}PrOH	KO^tBu	1	80
4	1	MeOH	KO^tBu	1	60
5	1	EtOH	KO^tBu	1	87
6	0.1	EtOH	KO^tBu	4	87
7	0.1	EtOH	NaOMe	4	68
8	0.1	EtOH	NaOH	4	0
9	0.1	EtOH	Cs_2CO_3	4	6
10	0.1	EtOH	K_2CO_3	4	66
11	0.1	EtOH	K_3PO_4	4	67
12	**0.1**	**EtOH**	**NaOMe**[c]	**4**	**96**
13	0.1	EtOH	KO^tBu[c]	4	95
14	1[d]	EtOH	NaOMe[c]	0.5	82
15	1[d]	EtOH	K_2CO_3[c]	0.5	55
16	1[d]	EtOH	K_3PO_4[c]	0.5	38
17	1[d]	EtOH	CsF[c]	0.5	57
18	1[d]	EtOH	NaOMe[ce]	0.5	91
19	**0.1**[d]	**EtOH**	**NaOMe**[ce]	**6**	**69**
20	1	EtOH	NaOMe[ce]	0.5	99
21	1[d]	EtOH	KO^tBu[ce]	0.5	6
22	1[d]	EtOH	KO^tBu[ce]	2	92
23	1	EtOH	KO^tBu[ce]	0.5	92

[a] *Reaction conditions*: ArCl (0.5 mmol), $ArB(OH)_2$ (0.525 mmol), base (0.55 mmol), solvent (1 mL). [b] Conversion to coupling product, based on ArCl, determined by GC. [c] Base 0.75 mmol. [d] Aerobic conditions. [e] ArCl = 0.6 mmol, $ArB(OH)_2$ = 0.5 mmol.

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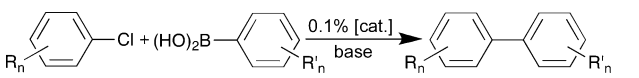
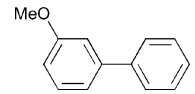
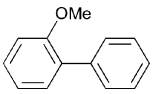
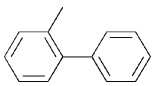
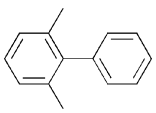
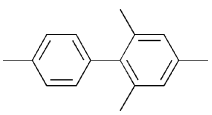
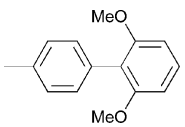
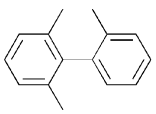
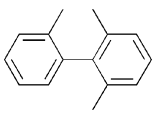
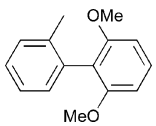
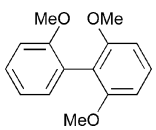
entry 7) whereas after 6 h the yield reached 83%. It is noteworthy that some inorganic bases allow for the formation of the coupling product under these conditions. This is of great importance as it shows that alkoxide-sensitive substrates could still be efficiently coupled using catalyst **1** (Table 1, entries 10 and 11). However, for the latter cases, longer reaction times did not lead to further conversion to product. Using an excess of alkoxide base, in ethanol, led to a slightly improved catalyst performance, as the coupling product was obtained in an almost quantitative yield within 4 h at r.t. (Table 1, entries 12 and 13). To our delight, with 1 mol% of **1**, the test reaction rapidly led to product at r.t. in air (Table 1, entries 14–18). This was also observed when inorganic bases were used. The optimum and most economical base, NaOMe, also permits the aerobic reaction to be performed with 0.1 mol% of **1** (Table 1, entry 19). As shown in entry 20, conducting the reaction under an argon atmosphere leads to a slight increase in activity when NaOMe is used. Indeed, almost complete conversion is obtained after 0.5 h compared to 91% under aerobic conditions (entry 18). In contrast, when carrying out such experiments in the presence of KO^{t}Bu, a deleterious effect of the presence of air is seen (see entries 21–23). This poor catalytic performance might be attributed to the known instability of KO^{t}Bu in air and moisture conditions.

The assessment of the efficiency of a catalytic system is its performance with challenging substrates. Some of these are listed in Table 2 and present sterically hindered C–C biaryl junctions. Only a few palladium systems are capable of performing these couplings.[12] The optimised reaction conditions (0.1 mol% of **1**, EtOH/NaOMe) were then employed to perform Suzuki–Miyaura reactions with the substrates listed in Table 2. Entries 2 and 3 clearly illustrate that the coupling is feasible with singly *ortho*-substituted coupling partners as the product is formed at room temperature in good isolated yields. A double substitution in *ortho* positions to the carbon atom to be coupled is also tolerated under these conditions (Table 2, entries 4 and 5). As shown in entry 6, the presence of OMe groups in *ortho* positions results in more sluggish reactions. This can be explained by the propensity of oxygen to act as a donor atom thus stabilising the Pd-centre. This slow kinetic profile can be overcome by heating the reaction mixture to 60 °C since the catalyst is thermally stable. Tri-*ortho*-substituted biaryls can also be generated at r.t. (Table 2, entries 7 and 8). Again, the presence of OMe groups led to slower reactions. The system can generate tri-*ortho* substituted biaryls containing two MeO groups (Table 2, entry 9) in good isolated yields while products bearing three *ortho*-MeO groups (Table 2, entry 10) proved difficult to obtain.

Furthermore, other interesting substrates, as they are ubiquitously encountered in the pharmaceutical industry, and also considered as "challenging", are the heteroaromatic halides. It seemed thus relevant to test **1** in a number of cross-couplings involving pyridines and thiophenes. The reactions carried out using 2- and 3-chloropyridines (2-Clpy, 3-Clpy), with non-optimised reaction times, led from good to excellent isolated yields at a low catalyst concentration (Table 3, entries 1–4). The coupling depicted in entry 1 proved difficult at r.t. (17% isolated yield after 20 h) but led to 69% after 20 h at 60 °C. In contrast, the coupling depicted in entry 2 proved facile as almost complete conversion is reached at r.t. after 20 h. This suggests that the catalytic cycle goes through an *o*-tolyl–Pd–aryl intermediate complex, which drives the reductive elimination of the product because of steric pressure

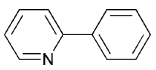
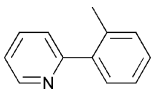
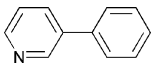
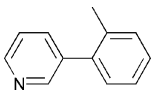
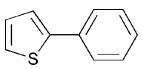
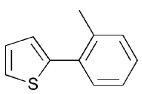
Table 2 Coupling of hindered substrates with arylboronic acids[a]



Entry	R_n	R'_n	Product	t/h	Yield[b] (%)
1	3-OMe	H		20	87
2	2-OMe	H		20	96
3	2-Me	H		24	86
4	2,6-Me	H		24	72
5	4-Me	2,4,6-Me		24	82
6	4-Me	2,4-(OMe)		24[c]	78
7	2,6-Me	2-Me		24	80
8	2-Me	2,6-Me		24	36
9	2-Me	2,6-(OMe)		20[c]	84
10	2-OMe	2,6-(OMe)		24[c]	29

[a] *Reaction conditions*: ArCl (0.5 mmol), $ArB(OH)_2$ (0.525 mmol), NaOMe (0.75 mmol), EtOH (1 mL), r.t., 0.1 mol% [Pd(μ-Cl)-Cl(IPr)]$_2$. [b] Isolated yields are the average of two runs. [c] Reaction performed at 60 °C.

Table 3 Coupling of heterocycles, 2-chloropyridine (2-Clpy), 3-chloropyridine (3-Clpy) and 2-chlorothiophene (2-ClC_4H_3S), with arylboronic acids[a]

Entry	Heterocycle	$ArB(OH)_2$	Product	Yield[b] (%)
1	2-Clpy	$PhB(OH)_2$		69[c]
2	2-Clpy	*o*-tolylB$(OH)_2$		99
3	3-Clpy	$PhB(OH)_2$		91[c]
4	3-Clpy	*o*-tolylB$(OH)_2$		70[c]
5	2-ClC_4H_3S	$PhB(OH)_2$		87
6	2-ClC_4H_3S	*o*-tolylB$(OH)_2$		79

[a] *Reaction conditions*: ArCl (0.5 mmol), $ArB(OH)_2$ (0.525 mmol), NaOMe (0.75 mmol), EtOH (1 mL), 20 h, r.t., 0.1 mol% $[Pd(\mu\text{-}Cl)Cl(IPr)]_2$. [b] Isolated. [c] Reaction performed at 60 °C.

brought about by the presence of the *ortho* methyl group. Entry 3 involves a fragment where the heteroatom is in a position *meta* with respect to the chloride. These have been historically more difficult to couple due to electronic effects.[13] Finally, entry 4 highlights the extent of this electronic deactivation that overrides the steric pressure-release caused by the *ortho* methyl substituent.

Thiophenes also represent an important class of compounds since they can be used in a Suzuki–Miyaura protocol to form conducting polymers.[14] The examples illustrated in Table 3 with 2-chlorothiophene (2-ClC_4H_3S) (entries 5 and 6) clearly show thiophenes to be tolerated and compatible with the present method as high yields of coupling products were obtained at r.t. with 0.1 mol% catalyst loading.

In conclusion, $[Pd(\mu\text{-}Cl)Cl(IPr)]_2$ **1**, is an excellent pre-catalyst for the Suzuki–Miyaura coupling involving challenging aryl chlorides at low catalyst loading and under mild and economical reaction conditions. Studies aimed at extending the scope of **1** to other types of cross-coupling and related reactions are currently ongoing in our laboratories.

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Notes and references

‡ Optimised protocol for Suzuki–Miyaura reactions: In a glovebox, a 4 mL screwcap-vial containing a magnetic stirring bar was charged with sodium methoxide (40.5 mg, 0.75 mmol), the boronic acid (0.525 mmol) and fitted with a septum. Outside the glovebox, the required amount of catalyst solution (catalyst loading 0.1 mol%) was injected through the septum, followed by addition of technical grade degassed ethanol (1 mL). The mixture was then stirred at room temperature unless otherwise indicated. After 15 min, the aryl halide (0.5 mmol) was injected, and the reaction was monitored by gas chromatography. When the reaction reached completion, or no further conversion was observed by gas chromatography, the solvent was removed under vacuum and the resulting solid was filtered on a pad of silica (using hexanes–ethyl acetate mixtures, depending on the polarity of the product). When necessary, the product was purified by flash chromatography on silica gel.

For reactions carried out under aerobic conditions, all solids were weighed in air. The solvents were dried over molecular sieves and all liquids were injected in vials opened to air.

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