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Solvent-free aryl amination catalysed by [Pd(NHC)] complexes[†]

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A highly effective solvent-free protocol for the Buchwald-Hartwig amination of unactivated aryl chlorides is described. The effect of various [Pd(NHC)] pre-catalyst systems on the reactivity has been studied. [Pd(IPr*)(cin)Cl] is reported as the complex of choice for the transformation.

Solvent-free reactions have attracted considerable attention for sustainable organic synthesis.¹ Despite the great interest in crosscoupling reactions,² solvent-free methods in this domain still remain rare and anecdotal. Some examples are nevertheless reported in the literature for the Suzuki-Miyaura,³ Sonogashira⁴ and Hiyama⁵ reactions. Taking the particular case of the Buchwald-Hartwig amination reaction,⁶ to the best of our knowledge, only three reports exist in the literature.⁷

In 2004, Yoshifuji and co-workers were the first to describe a solvent-free palladium-catalysed protocol^{7a} for the coupling of aryl bromides with a range of amines using a palladium (π -allyl) complex bearing a diphosphinidenecyclobutene ligand. In most cases, the coupling is described to take place at room temperature, however the reaction is limited to the use of aryl bromides. In 2011, Beccalli and co-workers reported the use of a Pd₂(dba)₃/IAPU system (IAPU = 2,8,9-triisobutyl-2,5,8,9-tetraaza-1-phosphabicyclo [3.3.3]undecane) to mediate the solvent-free arylation of indolines.^{7b} Unlike the previous report, the latter includes the reactivity of aryl chlorides. Nevertheless, the protocol is limited to the use of indolines as amines, and the products are obtained in moderate yields at high temperatures using thermal or microwave heating. Finally in 2012, Tardiff and Stradiotto reported the use of a [Pd(cinnamyl)]₂/Mor-DalPhos system to promote the coupling of aryl chlorides. The reaction works efficiently for a wide range of substrates. However, it requires a high temperature to proceed (110 °C) and the scope does not exhibit the reactivity of challenging electron-rich chlorides.^{7c} One of the common points between these different procedures is the use of a relatively bulky phosphine ligand. Previous investigations by Nolan and co-workers have shown that bulky yet flexible ligands such as IPr* (1,3-bis(2,6bis(diphenylmethyl)-4-methylphenyl)imidazol-2-ylidene)⁸ can lead to unique reactivities in catalysis.9 In the present contribution, a highly efficient solvent-free protocol for the Buchwald-Hartwig amination of unactivated aryl chlorides that uses the [Pd(IPr*)(cin)Cl] (1) pre-catalyst (cin = cinnamyl) is reported.

Results obtained during preliminary screening experiments highlighted the efficiency of [Pd(IPr*)(cin)Cl] to couple 2-chloro-1,3-dimethylbenzene and 2,6-dimethylaniline. Interestingly, at room temperature, the reaction leads to a complete conversion in 5 minutes under solvent-free conditions (Table 1, entry 1). On the other hand, this reaction carried out under similar conditions

Table 1 Optimisation of the solvent-free amination

	CI + H ₂ N	[Pd] (x mol Base, solve 25°C, 30 m	%) ent	
Entry	[Pd] (mol%)	Base ^b	Solvent	Conversion ^c
1^d	[Pd(IPr*)(cin)Cl] (1)	KO <i>t</i> Am	-	$>99\% (98\%)^e$
2^{f}	[Pd(IPr*)(cin)Cl] (1)	KOtAm	DME	0
3	$\left[Pd(IPr^{*})(cin)Cl \right] (0.5)$	KOtAm	-	59%
4	[Pd(IPr)(cin)Cl] (1)	KOtBu	-	11%
5	$\left[Pd(SIPr)(cin)Cl \right] (1)$	KOtBu	-	12%
6^d	$\left[Pd(IPr^{*Tol})(cin)Cl \right] (1)$	KOtAm	-	>99%
7	[Pd(IPr)(PEPPSI)] (1)	KOtBu	-	4%
8	[Pd(SIPr)(PEPPSI)] (1)	KOtBu	-	1%
9	[Pd(IPr*)(PEPPSI)] (1)	KOtBu	-	4%
10	[Pd(IPr*)(acac)Cl] (1)	LiHMDS	-	85%
11	[Pd(IPr)(acac)Cl] (1)	KO <i>t</i> Bu	-	12%

^a Reagents and conditions: (i) 2-chloro-1,3-dimethylbenzene (1 mmol), base (1.1 mmol), [Pd] (mol%), 25 $^{\circ}$ C, 5 min, (*ii*) 2,6-dimethylaniline (1.1 mmol), 25 $^{\circ}$ C, 30 min. ^{*b*} The optimal base was selected for each pre-catalyst according to previous reports. See the ESI[†] for more information about optimisation reactions.

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^c Conversion to coupling product based on the starting material determined by GC. ^d Conversion was complete in 5 minutes. ^e Isolated yield after chromatography on silica gel, average of two runs. ^f Performed in DME (1 M) at 25 °C for 24 h.

using 1,2-dimethoxyethane (DME) as a solvent does not lead to any conversion of the starting materials (Table 1, entry 2). To optimize the solvent-free reaction conditions, three different families of [Pd(NHC)] pre-catalysts (NHC = *N*-heterocyclic carbene) were tested: [Pd(NHC)(cin)Cl],^{9b,9c,10} [Pd(NHC)(acac)Cl]¹¹ and [Pd(NHC)(PEPPSI)]¹² where acac = acetylacetonato and PEPPSI = pyridine-enhanced pre-catalyst preparation, stabilization and initiation (Fig. 1). These are reported to be amongst the best for the Buchwald-Hartwig amination cross-coupling reaction. Three different bases were also screened: KOtBu and KOtAm (KOtAm = potassium *tert*-amylate), which are the most popular and efficient bases for arylamination, and LiHMDS (HMDS = hexamethyldisilazane) that has already shown high efficiency in this C-N bond forming reaction.^{11c,13} As observed in Table 1, and as it was postulated, the reaction is strongly influenced by the nature of the ligand. It is clear that bulky NHCs (IPr* and IPr*^{Tol}, IPr*^{Tol} = 1,3bis(2,6-bis(di-p-tolylmethyl)-4-methylphenyl)imidazol-2-ylidene)

promote the reaction most efficiently. On the other hand, IPr and SIPr (IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene; SIPr = 1,3-bis(2,6-diisopropylphenyl)-4,5-dihydroimidazol-2-ylidene) lead to poor conversions in each case, whatever the nature of the palladium complex (1–12%, Table 1, entries 4, 5, 7, 8 and 11). The leaving group on the palladium pre-catalyst also plays a crucial role. [Pd(NHC)(cin)Cl] and [Pd(NHC)(acac)Cl] derivatives promote the reaction efficiently. On the other hand, the [Pd(NHC)(PEPPSI)] family does not lead to any significant conversion of the starting materials, even when the bulky IPr* ligand (Table 1, entries 7–9) is the NHC. Finally, the best reaction conditions make use of [Pd(IPr*)(cin)Cl] (1 mol%), using KOtAm as the base. The desired product is then obtained in an excellent isolated yield (98%,



Table 1, entry 1). It is noteworthy that 1 mol% of the pre-catalyst is necessary to reach complete conversion. Indeed, if the amount of palladium is reduced by half, the conversion is proportionately divided by nearly two (59%, Table 1, entry 3). It is important to state here that the reaction is initially carried out at room temperature.¹⁴ Nevertheless, during the course of the reaction, a strong self-generated exotherm is detected in the reaction medium. Notably, the formation of fumes can be observed in the vial. A probe placed inside the reaction vessel indicated an increase of temperature from 25 °C to approximately 80 °C in just a few seconds. The subsequent decrease of temperature was then as fast as the increase was, and the system stabilised at 25 °C after a few seconds. After this thermal event, reaction completion was reached. This phenomenon explains why the reaction occurs without solvents. In the presence of DME, the heat generated by the reaction is probably absorbed and dissipated by the solvent, thereby disfavouring the C-N bond formation. It should also be stated clearly here that there is a clear danger associated with such an exotherm if the reaction were to be carried out on a very large scale. The scope and limitations of the solvent-free amination process were next investigated. Results are reported in Table 2. Both arylbromides and chlorides are suitable substrates for the reaction. To the best of our knowledge, this is the first report of a palladium catalysed solvent-free amination of aryl chlorides without the addition of an external source of heat. Arylbromides displayed higher activities leading to the formation of the desired products in slightly shorter times (Table 2, entries 2, 4 and 7 vs. entries 1, 3 and 6). Primary amines were coupled very efficiently to neutral aryl halides, including sterically hindered congeners, in short reaction times (93-99%, Table 2, entries 1-9). In fact, the use of bulkier amines appears to correlate to faster reactions.¹⁵ This statement can notably be highlighted by the case of the simplest aniline. No conversion was observed after 10 min and a reaction time of 24 h was required to reach complete conversion and an excellent isolated yield (95%, Table 2, entry 10). Electron-rich chlorides were next involved in the coupling reaction. Excellent conversions were obtained at longer reaction times. After 24 h, the expected coupled products were consequently obtained in excellent isolated yields (94-98%, Table 2, entries 11 and 12). Using a non-aromatic primary amine does not appear to be a limitation of the system. However this specific example required an increase of the reaction time (93%, Table 2, entry 13). The reactivity of the secondary amines was next explored. N-Methylaniline and morpholine were shown to be superb coupling partners, yielding the desired products in excellent yields and reaction times ranging from 10 minutes to 24 h (83-97%, Table 2, entries 14-17). Noteworthy here is that in all these examples, the aryl chloride was a liquid, solubilising the palladium complex and KOtAm prior to the addition of the amine. Nevertheless, when the reaction required extended reaction times, the exotherm was not observed, the reaction mixture became solid after a few minutes and the coupling occurred mainly as a solid state reaction. To confirm that the reaction was possible using solid halides, the reactivity of 1-bromopentamethylbenzene was finally examined. After 24 h, a conversion of 73% was measured by



F	R ¹ X	+ HNR ² R ³	1 (1 mol%) KOtAm, 25°C, Time Solvent-free	NR ² R ³
Entry	y X	Time	Product	Yield ^b
$\frac{1^c}{2}$	Cl Br	5 min 3 min		98% 93%
3 ^c 4	Cl Br	5 min 5 min		96% 99%
5	Cl	5 min		99%
6 7	Cl Br	10 min 3 min		99% 94%
8	Cl	5 min		97%
9	Cl	5 min		93%
10 ^c	Cl	24 h		95%
11	Cl	24 h	OMe H	94%
12	Cl	24 h	MeO-N-N-	98%
13	Cl	24 h		93%
14	Cl	10 min		92%
15	Cl	24 h		97%
16 ^{<i>c</i>}	Cl	24 h	Meo	94%
17	Cl	24 h	OMe N O	83%

 Table 2 (Continued)



^a Reagents and conditions: (i) ArX (1 mmol), 1 (1 mol%), KOtAm (1.1 mmol), 25 °C, 5 min, (ii) amine (1.1 mmol), 25 °C, time. ^b Isolated yield after chromatography on silica gel, average of two runs.
^c Reaction performed in DME (1 M) at 25 °C for 24 h does not lead to any significant conversion of the starting materials.

gas chromatography and a good isolated yield was obtained (66%, Table 2, entry 18).

Conclusion

In summary, the reactivity of various [Pd(NHC)] complexes has been examined in the solvent-free Buchwald–Hartwig amination of aryl chlorides. The need for bulky ligands and easily activated systems was shown to be crucial and [Pd(IPr*)(cin)Cl] proved to be the best pre-catalyst to achieve this coupling. The reaction is carried out at room temperature but is enhanced in some cases by a strong self-generated exotherm. A range of secondary and tertiary amines has been efficiently prepared, in reaction times ranging from minutes to hours (18 examples, 66–99%).

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