DOI: 10.1002/ejoc.201500030

Efficient and Versatile Buchwald–Hartwig Amination of (Hetero)aryl Chlorides Using the Pd–PEPPSI-IPr$^{(NMe2)2}$ Precatalyst in the Presence of Carbonate Base

Yin Zhang,[a,b] Vincent César,*[a,b] and Guy Lavigne*[a,b]

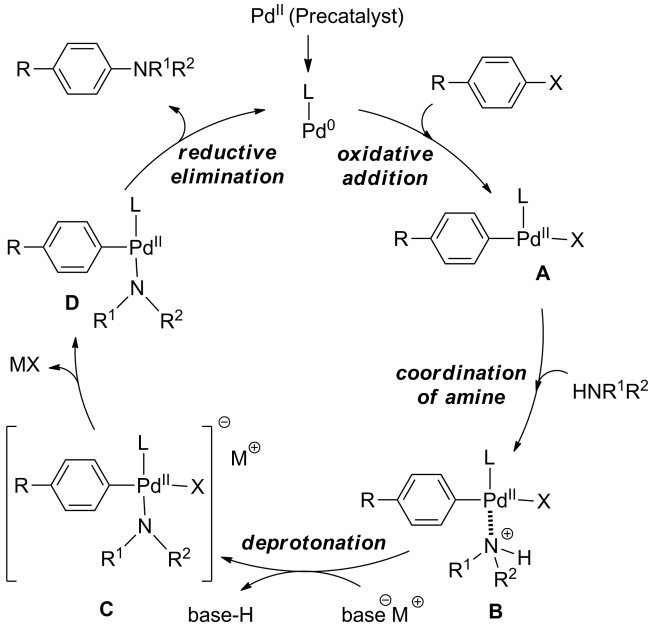
Keywords: Homogeneous catalysis / Amination / Nitrogen heterocycles / Carbene ligands / Palladium

The precatalyst Pd–PEPPSI-IPr$^{(NMe2)2}$, in which the IPr ligand was modified by attachment of two dimethylamino groups on to the 4- and 5-positions of the imidazolyl heterocycle, was found to show high catalytic efficiency in the Buchwald–Hartwig amination under mild conditions using Cs_2CO_3 as a weak base, using a low catalyst loading of 1 mol-%. The protocol is applicable to aryl chlorides bearing base-sensitive substituents, as exemplified by the coupling of 4-chloroacetophenone with aniline. It can also be used with an unprecedentedly wide range of amines, including strongly basic secondary alkylamines, primary arylamines, and primary alkylamines.

Introduction

Arylamines are frequently encountered in natural and pharmaceutical products,[1] as well as in materials with useful physical properties.[2] The Pd-catalysed Buchwald–Hartwig amination (BHA) of aryl halides has become the most valuable method for the formation of C(sp^2)–N bonds in contemporary organic synthesis, and it still receives much interest from academic and industrial research groups.[3–5]

The development of customized ligands, and a better understanding of the mechanism and the special requirements of the BHA, have resulted in this reaction becoming more widely used.[6] A simplified catalytic cycle implying a monodentate ligand is shown in Scheme 1. The active Pd^0 species is generated in situ from a ligand-stabilized Pd^{II} precatalyst. Initially, the aryl halide (or pseudo-halide) undergoes oxidative addition to the Pd^0 centre to give unsaturated Pd^{II} intermediate **A**. In a second step, coordination of the amine HNR^1R^2 generates tetracoordinated Pd^{II} adduct **B**. Thirdly, deprotonation of **B** with a base M^+B^- gives anionic amido complex **C**, which then loses MX to give tricoordinate complex **D**. Finally, reductive elimination from **D** produces the target amine $ArNR^1R^2$, with concomitant regeneration of the initial Pd^0 species.



Scheme 1. Simplified catalytic cycle for the palladium-catalysed Buchwald–Hartwig amination in the case of a monodentate supporting ligand L.

Historically, development of the BHA reaction has mainly focussed on the two redox steps, i.e., the oxidative addition and the reductive elimination. It has been shown that the rate of the oxidative addition is enhanced by an electron-rich metal centre, and that a sterically hindered ancillary ligand facilitates the reductive elimination. Such findings have led to the advent of several powerful, bulky, electron-rich phosphane ligands, such as BrettPhos, RuPhos, XPhos,[4a,4c,7] JosiPhos,[4b,8] CM-Phos,[9] or MorDalPhos.[10] In parallel, *N*-heterocyclic carbenes (NHCs),[11]

[a] CNRS, LCC (Laboratoire de Chimie de Coordination), 205 route de Narbonne, BP 44099, 31077 Toulouse Cedex 4, France
E-mail: vincent.cesar@lcc-toulouse.fr, guy.lavigne@lcc-toulouse.fr
http://www.lcc-toulouse.fr/lcc/spip.php?article24
[b] Université de Toulouse, UPS, INPT, 31077 Toulouse Cedex 4, France

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201500030.

which are stronger electron-donor ligands, and are even more sterically hindered than phosphanes, have appeared as complementary supporting ligands in Pd-catalysed cross-coupling reactions,[12] and in particular in the Buchwald–Hartwig amination.[13–15] As a result of these intense research efforts, the most advanced ligand archetypes now allow the use of (hetero)aryl chlorides, which are challenging substrates but are cheaper and more abundant than their bromide analogues, and they can be used with various "non-activated" reaction partners.[16]

Despite its popularity and widespread use, the BHA reaction usually requires aggressive alkoxide bases such as *tert*-butoxide for an efficient deprotonation of the Pd-coordinated ammonium species in intermediate **D**. These strongly basic reaction conditions still severely restrict the applicability of the methodology, as they are incompatible with base-sensitive functional groups, such as ketones, esters, or nitro groups. To circumvent this problem, the use of milder bases, and in particular of carbonate bases, has been proposed, but reported examples are quite scarce, and mainly concern phosphine-based catalysts.[7a,8a,9,17] The most impressive breakthrough in this direction was recently achieved by Organ and coworkers, with their Palladium PEPPSI-type precatalysts (PEPPSI = pyridine-enhanced precatalyst preparation stabilization and initiation). Indeed, the archetypal complex Pd–PEPPSI-IPr (**1**) (Figure 1) was shown to catalyse the amination of certain electron-deficient heteroaryl chlorides with secondary amines in the presence of Cs_2CO_3 as the base.[13f] Later, Organ disclosed a second generation precatalyst, Pd–PEPPSI-IPent ($\mathbf{2^H}$), in which the incorporation of 2,6-di(3-pentyl)phenyl groups as nitrogen substituents in place of the 2,6-diisopropylphenyl groups was intended to impart bulkiness and flexibility to the NHC ligand.[18,19] In BHA, the bulkier precatalyst $\mathbf{2^H}$ was shown to greatly outperform precatalyst **1** in the amination of secondary amines and anilines with a great variety of aryl chlorides.[6b,6c] Finally, even the coupling of weakly nucleophilic anilines with electron-rich aryl chlorides, which represents the most challenging combination of coupling partners, was recently and efficiently achieved by substituting the heterocyclic backbone of IPent with two chloride atoms to give precatalyst $\mathbf{2^{Cl}}$.[13a] Most importantly, on the basis of additional experiments, Organ and coworkers deduced that the observed enhancement of catalyst's performance is independent of the electronic nature of the backbone substituents, and is the result of steric rather than electronic effects.[20]

Following our interest in the functionalization of the skeleton of NHCs,[21] we recently reported that precatalysts **3** and **4**, obtained by formal substitution of the imidazolyl ring of the IPr ligand by one and two dimethylamino groups, respectively, show sequential enhanced catalytic efficiencies relative to **1** in the BHA.[22] Using KO*t*Bu as the base, complex **4** was found to be particularly efficient for the coupling of various amines and aryl chlorides at room temperature using 2 mol-% of catalyst, and to be remarkably stable, allowing a decrease of the catalyst loading to as little as 50 ppm for a range of challenging substrates (at 80 °C). Based on these experimental observations, the incremental increases in catalytic efficiency of **3** and **4** was rationalized in terms of i) an increase in the electron-donating abilities of the carbenes $IPr^{(NMe2)}$ and $IPr^{(NMe2)2}$, and ii) a slight increase of their steric bulk, which appears to be already maximized in complex **3**. Keeping in mind Organ's conclusions, we were thus prompted to study the catalytic efficiency of our precatalysts **3** and **4** in the BHA reaction with a mild base, and we report our results in this paper.

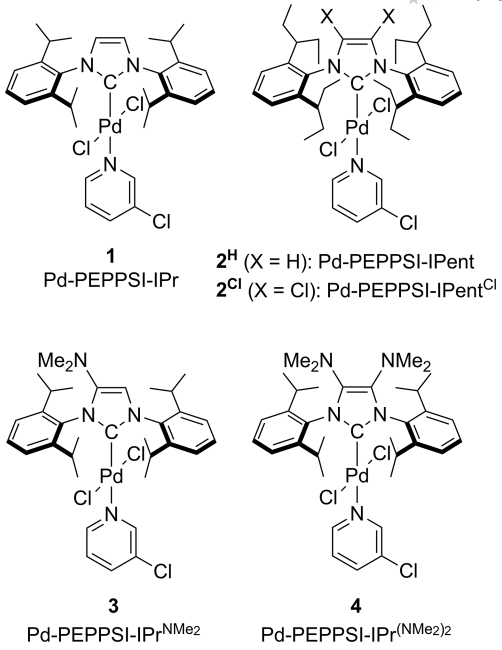


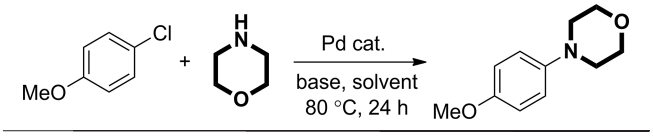
Figure 1. Palladium PEPPSI-type complexes considered in this study (PEPPSI = pyridine-enhanced precatalyst preparation stabilization and initiation).

Results and Discussion

In a first comparative evaluation of the precatalysts, the experimental conditions required to perform the Buchwald–Hartwig amination in the presence of a mild base like cesium carbonate were taken from the earlier recent report by Organ, using the reaction between 4-chloroanisole and morpholine as a standard model (Table 1). In a first catalytic test based on 4 mol-% of Organ's precatalyst Pd–PEPPSI-IPr (**1**) (Table 1, entry 1), we were able to reproduce his previously reported result corresponding to 15% conversion after 24 h.[13f] Under the same conditions, our precatalyst **3** (bearing one amino group on the heterocyclic backbone) (Table 1, entry 2) led to an improved conversion of 75%, whereas 100% conversion was reached with precatalyst **4** within an unoptimized time of 24 h (Table 1, entry 3). This result compares well with the 94% isolated yield obtained by Organ's group with catalyst $\mathbf{2^H}$ under the same conditions.[13f] Gratifyingly, it was even possible to reduce the loading of **4** down to 1 mol-% (Table 1, entry 5). The lower limit of the catalyst's efficiency was reached with

0.5 mol-% of **4** (Table 1, entry 6), when a slight erosion of the conversion to 80% was observed. Finally, 3 equiv. of Cs_2CO_3 were found to be necessary for complete conversion, since decreasing to 1.5 equiv. led to an 80% conversion of 4-chloroanisole after 24 h (Table 1, entry 10).

Table 1. Optimization of the Pd-catalysed amination reaction using complexes **3** and **4** vs. **1** in the presence of carbonate bases.[a]

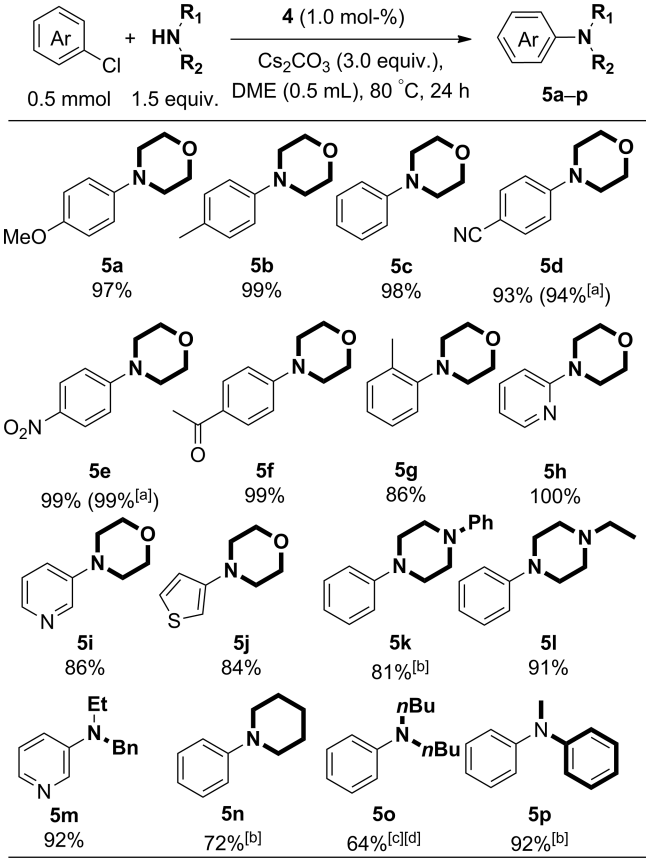


Entry	Pd cat. (mol-%)	Solvent	Base	Conv. [%][b]
1	**1** (4)	DME	Cs_2CO_3	15
2	**3** (4)	DME	Cs_2CO_3	75
3	**4** (4)	DME	Cs_2CO_3	100
4	**4** (2)	DME	Cs_2CO_3	100
5	**4** (1)	DME	Cs_2CO_3	100
6	**4** (0.5)	DME	Cs_2CO_3	80
7	**4** (1)	dioxane	Cs_2CO_3	92
8	**4** (1)	toluene	Cs_2CO_3	90
9	**4** (1)	DME	K_2CO_3	45
10	**4** (1)	DME	Cs_2CO_3	80[c]

[a] Reaction conditions: 4-chloroanisole (0.5 mmol), amine (0.75 mmol), base (1.5 mmol), solvent (0.5 mL), 80 °C. [b] Conversion rates were determined by GC based on 4-chloroanisole with dodecane as internal standard. [c] 1.5 equiv. of Cs_2CO_3 (0.75 mmol) was used.

Consistent with our previous report,[22] these experimental observations provided convincing evidence that decoration of the heterocyclic skeleton with two dimethylamino groups imparts high stability to the catalyst, whose lifetime then becomes much longer than that of the original unmodified complex Pd–PEPPSI-IPr (**1**). Further experiments focussing exclusively on the activity of **4**, indicated that DME (1,2-dimethoxyethane) is a better solvent than dioxane or toluene, and that Cs^+ is a much better counter-cation for the base than K^+ (Table 1, entries 7–10). Such a preference may be due either to the bigger size of Cs^+, which would more efficiently stabilize the large anionic complex at the intermediate stage, or to the higher solubility of its salts in the selected organic solvent.

The optimized conditions described above were subsequently used as standard conditions in further attempts to extend the application of **4** to a variety of (hetero)aryl chlorides and secondary aliphatic amines as reaction partners (Scheme 2). We found that aryl chlorides bearing either electron-donating (OMe or Me) or electron-withdrawing substituents (CN, NO_2, or Ac) in the *para* position could be coupled with morpholine to give the desired products (i.e., **5a**–**5f**) in excellent yields. In the most favourable cases of aryl chlorides bearing electron-withdrawing substituents, even a drastic reduction of the catalyst loading down to 0.2 mol-% did not affect the high yields of the resulting coupling products (i.e., **5d** and **5e**). This indicates that further optimization of the reaction time might be possible in such favourable cases. A good tolerance of steric hindrance in the aryl chloride component was noted in the coupling of 2-chlorotoluene with morpholine, which proceeded cleanly to give **5g**. The system was also found to be very efficient for the amination of heteroaryl chlorides such as 2-chloropyridine and 3-chloropyridine, which gave high yields of **5h** and **5i**, respectively. Impressively, even 3-chlorothiophene, which is considered to be quite a challenging coupling partner,[3b] was also successfully coupled with morpholine to give **5j** in 84% yield.



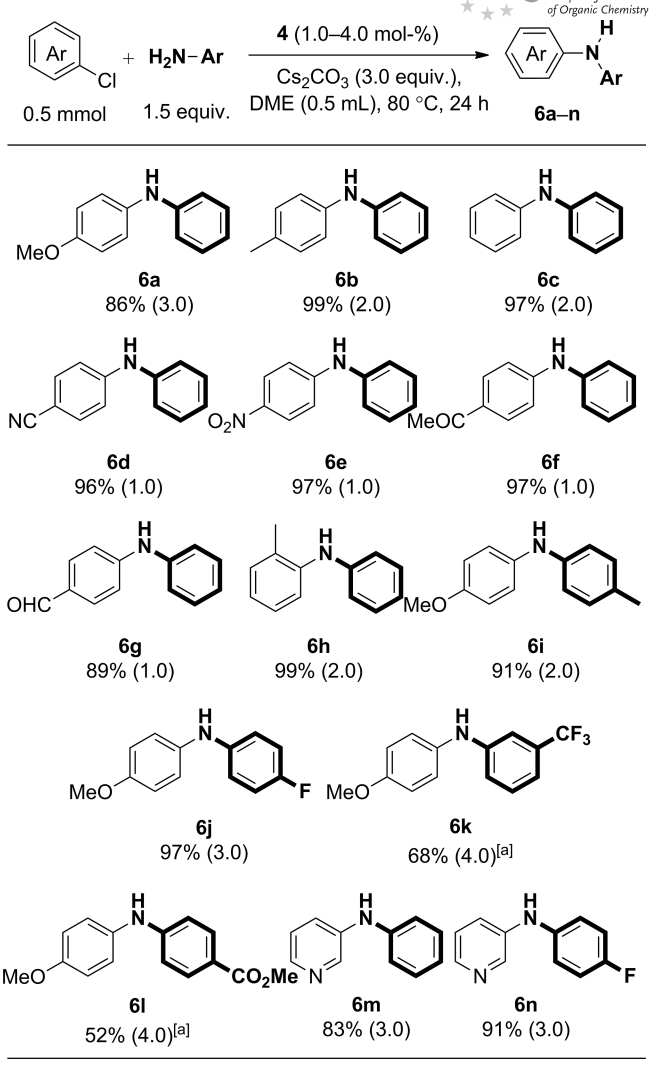
Scheme 2. Scope of the Buchwald–Hartwig amination with secondary amines catalysed by **4**, yields refer to the average of isolated yields of two runs after column chromatography. Reaction conditions: ArCl (0.5 mmol), amine (0.75 mmol), **4** (1.0 mol-%), Cs_2CO_3 (1.5 mmol), DME (0.5 mL), 80 °C, 24 h. [a] 0.2 mol-% of **4**. [b] 2.0 mol-% of **4**. [c] 4.0 mol-% of **4**. [d] 100 °C in dioxane.

In further catalytic experiments, whose results are displayed in the lower part of Scheme 2, we investigated the coupling of aryl chlorides such as chlorobenzene with a series of amines more basic than morpholine (pK_a = 8.36), for which the deprotonation step is more difficult. Gratifyingly, *N*-phenylpiperazine (pK_a = 8.8) could be introduced as a coupling partner to give **5k** in a satisfactory 81% yield. It was also still possible to activate piperidine, a strongly basic amine (pK_a = 11.22), but in that case, it was necessary to increase the amount of precatalyst to 2.0 mol-% to obtain **5n** in 72% yield. The catalytic system also proved efficient for the introduction of acyclic dialkylamines as coupling partners (see the production of **5m** and **5o**). Dibut-

ylamine, a highly challenging partner with both a high basicity and steric congestion, was successfully activated for the first time by a Pd–NHC catalyst under slightly modified standard conditions using a higher catalyst loading and higher temperature to produce **5o** in a reasonable 64% yield. Finally, to our delight, *N*-methylaniline, regarded as a much less nucleophilic amine, could be activated to produce **5p** in an impressive 92% yield. Taken together, these representative results establish the high efficiency of precatalyst **4**, whose performance can be seen to match and even sometimes surpass those of IPent derivative $\mathbf{2^H}$.

In a previous mechanistic investigation by Organ on the catalysts Pd–PEPPSI-IPr and Pd–PEPPSI-IPent,[6b,6c] it was proposed that the pK_a of the palladium(II)–ammonium species of type **B** (see Scheme 1) generated upon coordination of the amine might not only depend on the basicity of the amine, but that it might also be influenced by the donor properties of its coupling partner, namely, the aryl group in the adjacent position in the metal's coordination sphere. In order to corroborate such a hypothesis in the case of our modified precatalyst, two sets of parallel catalytic runs were conducted with two aryl chlorides showing different donor properties, namely, 4-chlorotoluene and 4-chloroanisole. In each experiment, 1 equiv. of the aryl halide together with a mixture of 1.5 equiv. of morpholine and 1.5 equiv. of piperidine was subjected to the reaction conditions. The first experiment, carried out with 4-chlorotoluene, gave a 2:1 ratio of *N*-(toluen-4-yl)morpholine and *N*-(toluen-4-yl)piperidine, whereas the second experiment (with 4-chloroanisole) gave a 3:1 ratio of *N*-(4-methoxyphenyl)morpholine and *N*-(4-methoxyphenyl)piperidine (see Supporting Information for details). These results are consistent with the hypothesis that variations in the electron-donating properties of the aryl group derived from the aryl chloride may influence the rate of deprotonation of the ammonium species, which is considered to be being rate determining in this case.[6c,23]

Based on the optimized results described above, we went on to examine the scope of complex **4** in a series of even more challenging amination reactions using anilines as substrates, which show much lower nucleophilicities than alkylamines (Scheme 3). The coupling reactions between aryl chlorides (irrespective of whether they had electron-rich or electron-poor substituents) and various anilines proceeded smoothly to give the mono-arylamination products in excellent yields. Nevertheless, in the most difficult cases of aryl chlorides bearing an electron-donating substituent such as methoxy or methyl in the *para* position, it was necessary to increase the catalyst loading to 3.0 mol-% or 2.0 mol-% in order to achieve an almost quantitative production of the corresponding amines (i.e., **6a** and **6b**, respectively). The *ortho*-methyl-substituted aryl chloride still gave an excellent yield of the coupling product (i.e., **6h**). Significantly, aryl chlorides bearing sensitive *para* substituents, such as cyanide or acetyl, were tolerated under these standard conditions, and, using a low catalyst loading of 1.0 mol-%, it was even possible to achieve a coupling reaction between unprotected 4-chlorobenzaldehyde and aniline to produce **6g** in 89% yield.

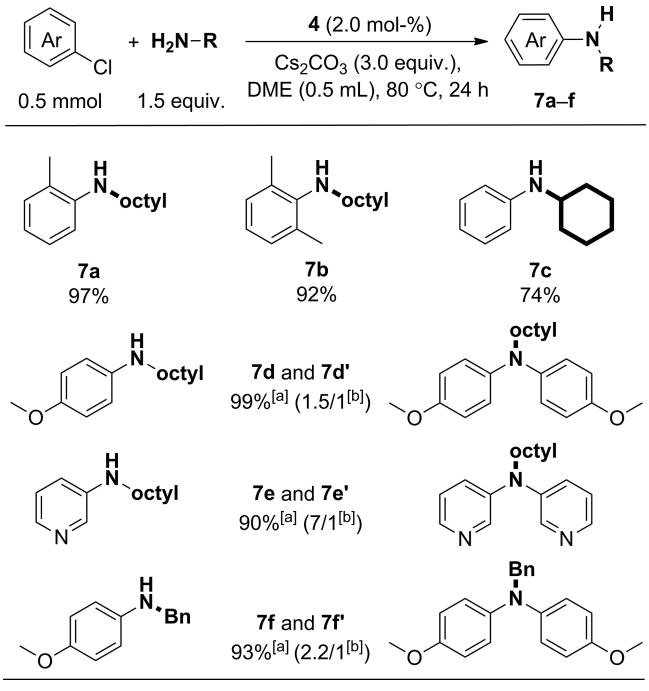


Scheme 3. Scope of the Buchwald–Hartwig amination with aniline derivatives catalysed by **4**, yields refer to the average of isolated yields of two runs after column chromatography. Reaction conditions: ArCl (0.5 mmol), aniline (0.75 mmol), **4** (1.0–4.0 mol-%, specified in parentheses), Cs_2CO_3 (1.5 mmol), DME (0.5 mL), 80 °C, 24 h. [a] 100 °C in dioxane.

Next, we turned our attention to the coupling of electron-rich aryl chlorides with electron-poor anilines, which has previously been identified as one of the most challenging combinations in BHA. We were pleased to observe that 4-chloroanisole could be efficiently coupled with 4-fluoroaniline and 3-(trifluoromethyl)aniline in the presence of precatalyst **4** (3.0 mol-% and 4.0 mol-%, respectively) to produce **6j** in 97% yield, and **6k** in 68% yield (the latter reaction required a higher temperature). A test reaction using an aniline bearing an ester in the *para* position also gave a positive result, but required 4.0 mol-% of precatalyst **4** and a higher temperature of 100 °C to produce **6l** in an acceptable 52% yield. In parallel, 3-chloropyridine, a heteroaryl chloride, was tested in combination with aniline and *para*-fluoroaniline, and this led to the formation of **6m** and **6n**, respectively, in excellent yields. By comparing these results with those reported by Organ for the same cou-

plings,[6c,13a] the following qualitative ranking of the supporting NHCs in the Pd–PEPPSI complexes could be drawn: IPr << IPent ≈ $IPr^{(NMe2)2}$ < $IPent^{Cl}$. This led to the conclusion that starting from the classical IPr ligand, decorating the carbenic heterocycle is a viable and complementary alternative to the strategy of varying the nitrogen-aryl substituents to optimize the catalyst efficiency in BHA.

Finally, we considered the case of primary alkylamines, which often tend to undergo competitive β-hydride elimination from the corresponding amido–Pd complexes.[24] This undesirable side-reaction (ending with the reduction of aryl halides into arenes) is avoided by using sterically demanding ligands. With this in mind, we were pleased to observe that our precatalyst was highly active for the transformation of primary alkylamines (Scheme 4). For example, with 2 mol-% of **4**, the reaction of 2-chlorotoluene or 2,6-dimethylchlorobenzene and octylamine gave 97 and 92% yields of the desired products (i.e., **7a** and **7b**, respectively). Under the same conditions, *N*-(cyclohexyl)aniline (**7c**) was obtained in a slightly reduced, but still satisfactory yield of 74%. Reactions of 4-chloroanisole and 3-chloropyridine with octylamine also proceeded to completion, but appeared to be less selective, and led to the formation of both mono- and bis-arylated products. Finally benzylamine was also tested, and was found to give two products. The ratio of the mono- to bis-arylated products was found to depend on the nature of both the aryl chloride and the amine.



Scheme 4. Scope of the Buchwald–Hartwig amination with primary amine derivatives catalysed by precatalyst **4**, yields refer to the average of isolated yields of two runs after column chromatography. Reaction conditions: ArCl (0.5 mmol), amine (0.75 mmol), **4** (2.0 mol-%), Cs_2CO_3 (1.5 mmol), DME (0.5 mL), 80 °C, 24 h. [a] The yield was based on the aryl chloride. [b] Ratio between mono- and bis-arylation product.

Conclusions

In conclusion, the experimental results disclosed here reveal that the backbone-decorated precatalyst Pd–PEPPSI-$IPr^{(NMe2)2}$ **4** shows high activity for the coupling between various aryl chlorides and a broad range of amines, including secondary amines, primary alkylamines, and primary arylamines, in the presence of Cs_2CO_3 as a relatively weak base. In particular, the performance of **4** in terms of activity, low catalyst loading, and substrate scope, was found to be greatly superior to that of the unmodified precatalyst Pd–PEPPSI-IPr (**1**), and even slightly better than that of Organ's highly efficient second generation complex Pd–PEPPSI-IPent when challenging alkylamines were used as the coupling partners. The already spectacular results reported by Organ with the IPent derivative were principally ascribed to an increase in steric bulk, but the equally good results reported here with our complex **4** can be attributed to a synergy of steric and electronic effects. Both of these complexes are very close to the optimum level of efficiency and practical utility for the Buchwald–Hartwig amination. Further structural variations of the decorating groups of N-heterocyclic carbenes are under current investigation in our laboratory, where we are also examining their potential application to a wider range of transition-metal-catalysed reactions.

Experimental Section

Materials and Methods: All reactions were carried out under an inert atmosphere of dry nitrogen using standard vacuum line and Schlenk tube techniques. Glassware was dried at 120 °C in an oven for at least 3 h. DME and 1,4-dioxane were distilled from sodium/benzophenone, toluene was distilled from sodium, and [D]chloroform were dried with CaH_2 and subsequently distilled. DMF was degassed by bubbling N_2 for 15 min, and was stored over activated 4 Å molecular sieves. NMR spectra were recorded with Bruker AV300 or AV400 spectrometers. Chemical shifts are reported in ppm (δ) relative to tetramethylsilane (^1H and ^{13}C), and the residual peak of the deuterated solvent was used as an internal standard.[25] Pd–PEPPSI-IPr (**1**),[26] Pd–PEPPSI-IPr^{NMe2} (**3**),[22] and Pd–PEPPSI-$IPr^{(NMe2)2}$ (**4**),[22] were synthesized according to literature procedures. All other reagents were commercially available, and were used as received, except for the liquid amines, which were distilled before use. Cs_2CO_3 was purchased from Alfa Aesar. GC analysis was carried out with a Shimadzu GC-2014 chromatograph equipped with a 30 m capillary column (Supelco, SLB-5ms, fused-silica capillary column, 30 m × 0.32 mm × 0.25 μm film thickness), using helium as the vector gas. The following GC conditions were used: Initial temperature 40 °C for 1 min; then temperature increase at a rate of 30 °C min^{-1} until 250 °C; then 250 °C for 2 min; linear velocity of carrier gas, 30 cm s^{-1}.

General Procedure for the Optimization of the Pd-Catalysed Amination with Carbonate Base: Base (1.5 mmol, 3.0 equiv.) and palladium catalyst were put into a Schlenk tube under air. The tube was then sealed with a septum, and purged with nitrogen (3×). 4-Chloroanisole (55 μL, 0.5 mmol, 1.0 equiv.), morpholine (69 μL, 0.75 mmol, 1.5 equiv.), and solvent (0.5 mL) were then added by syringe at room temperature. The mixture was stirred for about 1 min at room temperature, and was then transferred to a preheated

oil bath (80 °C). The reaction was allowed to proceed for 24 h, unless otherwise specified. The reaction mixture was diluted with ethyl acetate (10 mL), and dodecane (112 μL, 0.5 mmol) was added as internal standard. Conversions were measured by passing an aliquot of the solution through a plug of silica gel using EtOAc as eluent, and monitoring the relative areas of the peaks compared to that of dodecane in the GC chromatogram.

Competitive Amination Experiments of 4-Chlorotoluene with Morpholine and Piperidine: Cesium carbonate (488 mg, 1.5 mmol, 3.0 equiv.) and complex **4** (3.9 mg, 0.005 mmol, 1.0 mol-%) were put into a Schlenk tube under air. The tube was then sealed with a septum, and purged with nitrogen (3 ×). 4-Chlorotoluene (59 μL, 0.5 mmol, 1.0 equiv.), morpholine (69 μL, 0.75 mmol, 1.5 equiv.), piperidine (59 μL, 0.75 mmol, 1.5 equiv.), and DME (0.5 mL) were then added by syringe at room temperature. The mixture was stirred for about 1 min at room temperature, and was then transferred to a preheated oil bath (80 °C). The reaction was allowed to proceed for 24 h. The ratio between the two products was determined from the NMR spectrum of the crude mixture.

Competitive Amination Experiments of 4-Chloroanisole with Morpholine and Piperidine: Cesium carbonate (488 mg, 1.5 mmol, 3.0 equiv.) and precatalyst **4** (3.9 mg, 0.005 mmol, 1.0 mol-%) were put into a Schlenk tube under air. The tube was then sealed with a septum, and purged with nitrogen (3 ×). 4-Chlorotoluene (61 μL, 0.5 mmol, 1.0 equiv.), morpholine (69 μL, 0.75 mmol, 1.5 equiv.), piperidine (68 μL, 0.75 mmol, 1.5 equiv.), and DME (0.5 mL) were then added by syringe at room temperature. The mixture was stirred for about 1 min at room temperature, and was then transferred to a preheated oil bath (80 °C). The reaction was allowed to proceed for 24 h. The ratio between the two products was determined from the NMR spectrum of the crude mixture.

General Procedure for the Palladium-Catalysed Buchwald–Hartwig Amination with Cesium Carbonate: Cesium carbonate (488 mg, 1.5 mmol, 3.0 equiv.) and precatalyst **4** (1–4 mol-%) were put into a Schlenk tube under air. The tube was then sealed with a septum and purged with nitrogen, through three vacuum/nitrogen cycles. The aryl halide (0.5 mmol), the amine (0.75 mmol, 1.5 equiv.), and DME (0.5 mL) were then added by syringe at room temperature. In cases where the aryl halide or the amine was solid at room temperature, it was introduced into the tube before purging with nitrogen. The mixture was stirred for about 1 min at room temperature, and was then transferred to a preheated oil bath at 80 °C. The reaction was allowed to proceed for 24 h. The reaction mixture was diluted with ethyl acetate (10 mL), then it was filtered through a small plug of silica gel, which was washed with ethyl acetate. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel flash chromatography.

4-(4-Methoxylphenyl)morpholine (5a): After flash chromatography on silica gel (pentane/Et_2O, 4:1), compound **5a** (94.0 mg, 97%) was obtained as a white solid. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.94–6.82 (m, 4 H), 3.90–3.82 (m, 4 H), 3.77 (s, 3 H), 3.09–3.02 (m, 4 H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ = 154.1, 145.7, 117.9, 114.6, 67.2, 55.7, 50.9 ppm.

4-(4-Methylphenyl)morpholine (5b): After flash chromatography on silica gel (pentane/Et_2O, 4:1), compound **5b** (88.0 mg, 99%) was obtained as a white solid. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.10 (d, J = 8.7 Hz, 2 H), 6.85 (d, J = 8.4 Hz, 2 H), 3.96–3.77 (m, 4 H), 3.20–3.03 (m, 4 H), 2.29 (s, 3 H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ = 149.3, 129.8, 129.7, 116.2, 67.1, 50.1, 20.5 ppm.

4-Phenylmorpholine (5c): After flash chromatography on silica gel (pentane/Et_2O, 10:1), compound **5c** (79.9 mg, 98%) was obtained as a white solid. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.32–7.27 (m, 2 H), 7.00–6.82 (m, 3 H), 3.91–3.83 (m, 4 H), 3.20–3.13 (m, 4 H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ = 151.4, 129.3, 120.2, 115.9, 67.1, 49.6 ppm.

4-Morpholinobenzonitrile (5d): After flash chromatography on silica gel (pentane/Et_2O, 3:2), compound **5d** (87.4 mg, 93%) was obtained as a yellow solid. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.52–7.48 (m, 2 H), 6.87–6.83 (m, 2 H), 3.86–3.82 (m, 4 H), 3.28–3.25 (m, 4 H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ = 153.6, 133.6, 120.0, 114.1, 101.0, 66.5, 47.4 ppm.

4-(4-Nitrophenyl)morpholine (5e): After flash chromatography on silica gel (pentane/Et_2O, 4:1), compound **5e** (103.0 mg, 99%) was obtained as an orange solid. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.12 (dd, J = 9.2, 3.7 Hz, 2 H), 6.82 (d, J = 9.3 Hz, 2 H), 3.94–3.76 (m, 4 H), 3.42–3.26 (m, 4 H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ = 155.1, 139.1, 126.0, 112.7, 66.5, 47.2 ppm.

4-(4-Acetylphenyl)morpholine (5f): After flash chromatography on silica gel (hexane/EtOAc, 1:1), compound **5f** (102.0 mg, 99%) was obtained as an orange solid. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.93–7.83 (m, 2 H), 6.90–6.80 (m, 2 H), 3.92–3.77 (m, 4 H), 3.38–3.16 (m, 4 H), 2.52 (s, 3 H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ = 196.7, 154.3, 130.5, 128.3, 113.4, 66.7, 47.7, 26.3 ppm.

4-(2-Methylphenyl)morpholine (5g): After flash chromatography on silica gel (hexane/EtOAc, 10:1), compound **5g** (76 mg, 86%) was obtained as a colourless oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.21 (t, J = 7.2 Hz, 2 H), 7.09–6.98 (m, 2 H), 3.88 (t, J = 4.5 Hz, 4 H), 2.94 (t, J = 4.6 Hz, 4 H), 2.35 (s, 3 H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ = 151.4, 132.7, 131.3, 126.7, 123.5, 119.0, 67.6, 52.4, 18.0 ppm.

4-(Pyridin-2-yl)morpholine (5h): After flash chromatography on silica gel (pentane/Et_2O, 2:1), compound **5h** was obtained (81.9 mg, 100%) as a colourless oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.16 (ddd, J = 5.0, 2.0, 0.9 Hz, 1 H), 7.45 (ddd, J = 8.5, 7.2, 2.0 Hz, 1 H), 6.64–6.54 (m, 2 H), 3.82–3.71 (m, 4 H), 3.49–3.40 (m, 4 H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ = 159.6, 148.0, 137.5, 113.8, 106.9, 66.8, 45.6 ppm.

4-(Pyridin-3-yl)morpholine (5i): After flash chromatography on silica gel (EtOAc), compound **5i** (70.2 mg, 86%) was obtained as a yellow oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.34–8.19 (m, 1 H), 8.19–7.98 (m, 1 H), 7.0–7.07 (m, 2 H), 3.94–3.67 (m, 4 H), 3.24–3.04 (m, 4 H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ = 147.0, 141.2, 141.2, 138.4, 123.6, 122.2, 66.8, 48.7 ppm.

4-(Thiophen-3-yl)morpholine (5j): After flash chromatography on silica gel (pentane/EtOAc, 3:1), compound **5j** (71.2 mg, 84%) was obtained as a yellow solid. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.25 (dd, J = 5.2, 3.1 Hz, 1 H), 6.86 (dd, J = 5.2, 1.5 Hz, 1 H), 6.21 (dd, J = 2.9, 1.5 Hz, 1 H), 3.91–3.72 (m, 4 H), 3.18–2.96 (m, 4 H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ = 152.5, 125.7, 119.7, 100.6, 66.8, 50.9 ppm.

1,4-Diphenylpiperazine (5k): After flash chromatography on silica gel (pentane/Et_2O, 95:5), compound **5k** (95.9 mg, 81%) was obtained as shiny white crystals. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.28 (m, 4 H), 7.05–6.98 (m, 4 H), 6.96–6.87 (m, 2 H), 3.37 (d, J = 1.4 Hz, 8 H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ = 151.4, 129.3, 120.2, 116.5, 49.6 ppm.

1-Ethyl-4-phenylpiperazine (5l): After flash chromatography on silica gel (CH_2Cl_2/MeOH, 90:10), compound **5l** (86.4 mg, 91%) was obtained as an orange oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.31–7.20 (m, 2 H), 6.98–6.91 (m, 2 H), 6.90–6.81 (m, 1 H), 3.23 (t, J = 5.0 Hz, 4 H), 2.63 (t, J = 5.2 Hz, 4 H), 2.49 (q, J = 7.2 Hz, 2 H),

1.14 (t, J = 7.2 Hz, 3 H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ = 151.4, 129.2, 119.8, 116.2, 53.0, 52.5, 49.2, 12.1 ppm.

***N*-Benzyl-*N*-ethylpyridin-3-amine (5m):** After flash chromatography on silica gel (EtOAc/pentane, 3:7), compound **5m** (97.5 mg, 92%) was obtained as a yellow oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.14 (d, J = 3.1 Hz, 1 H), 7.92 (dd, J = 4.7, 1.3 Hz, 1 H), 7.37–7.15 (m, 5 H), 7.05 (dd, J = 8.5, 4.5 Hz, 1 H), 6.97–6.84 (m, 1 H), 4.51 (s, 2 H), 3.50 (q, J = 7.1 Hz, 2 H), 1.22 (t, J = 7.1 Hz, 3 H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ = 144.4, 138.1, 137.2, 134.5, 128.9, 127.2, 126.5, 123.8, 118.9, 53.8, 45.3, 12.1 ppm.

1-Phenylpiperidine (5n): After flash chromatography on silica gel (pentane/Et_2O, 95:5), compound **5n** (57.4 mg, 71%) was obtained as a colourless oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.33–7.21 (m, 2 H), 6.97 (d, J = 7.9 Hz, 2 H), 6.85 (t, J = 7.3 Hz, 1 H), 3.18 (t, J = 5.4 Hz, 4 H), 1.80–1.70 (m, 4 H), 1.65–1.56 (m, 2 H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ = 152.4, 129.1, 119.3, 116.6, 50.8, 26.0, 24.5 ppm.

***N*,*N*-Dibutylaniline (5o):** After flash chromatography on silica gel (hexane/EtOAc, 20:1), compound **5o** (65.8 mg, 64%) was obtained as a colourless oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.25–7.18 (m, 2 H), 6.73–6.57 (m, 3 H), 3.32–3.23 (m, 4 H), 1.66–1.52 (m, 4 H), 1.44–1.31 (m, 4 H), 1.02–0.94 (m, 6 H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ = 148.3, 129.3, 115.2, 111.8, 50.9, 29.6, 20.5, 14.2 ppm.

***N*-Methyl-*N*-phenylamine (5p):** After flash chromatography on silica gel (hexane/EtOAc, 99:1), compound **5p** (84.5 mg, 92%) was obtained as a colourless oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.34 (t, J = 7.5 Hz, 4 H), 7.09 (d, J = 7.7 Hz, 4 H), 7.02 (t, J = 7.3 Hz, 2 H), 3.38 (s, 3 H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ = 149.1, 129.3, 121.4, 120.6, 40.3 ppm.

***N*-Phenyl-4-methoxyaniline (6a):** After flash chromatography on silica gel (pentane/Et_2O, 95:5), compound **6a** (86.1 mg, 86%) was obtained as a beige solid. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.32–7.20 (m, 2 H), 7.17–7.06 (m, 2 H), 7.00–6.83 (m, 5 H), 5.52 (br. s, 1 H), 3.84 (s, 3 H) ppm. $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ = 155.4, 145.3, 135.8, 129.4, 122.3, 119.7, 115.8, 114.8, 55.7 ppm.

***N*-Phenyl-4-methylaniline (6b):** After flash chromatography on silica gel (hexane/EtOAc, 97:3), compound **6b** (91.4 mg, 99%) was obtained as a white solid. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.33–7.26 (m, 2 H), 7.15 (d, J = 8.1 Hz, 2 H), 7.09–7.03 (m, 4 H), 6.94 (tt, J = 7.8, 1.0 Hz, 1 H), 5.63 (br. s, 1 H), 2.37 (s, 3 H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ = 144.1, 140.4, 131.0, 130.0, 129.4, 120.5, 119.1, 117.0, 20.8 ppm.

Diphenylamine (6c): After flash chromatography on silica gel (pentane/EtOAc, 95:5), compound **6c** (80.0 mg, 95%) was obtained as a white solid. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.31 (t, J = 7.9 Hz, 4 H), 7.11 (d, J = 8.4 Hz, 4 H), 6.98 (t, J = 7.3 Hz, 2 H), 5.73 (br. s, 1 H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ = 143.2, 129.5, 121.1, 117.9 ppm.

4-(Phenylamino)benzonitrile (6d): After flash chromatography on silica gel (hexane/EtOAc, 4:1), compound **6d** (93.4 mg, 96%) was obtained as a beige solid. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.50 (d, J = 8.6 Hz, 2 H), 7.43–7.32 (m, 2 H), 7.23–7.17 (m, 2 H), 7.17–7.10 (m, 1 H), 7.04–6.94 (m, 2 H), 6.13 (br. s, 1 H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ = 148.1, 140.1, 133.9, 129.8, 124.1, 121.4, 120.0, 115.0, 101.6 ppm.

***N*-Phenyl-4-nitroaniline (6e):** After flash chromatography on silica gel (pentane/Et_2O, 7:3), compound **6e** (104.2 mg, 97%) was obtained as a yellow solid. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.15–8.06 (m, 2 H), 7.44–7.35 (m, 2 H), 7.24–7.12 (m, 3 H), 6.97–6.87 (m, 2 H), 6.30 (br. s, 1 H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ = 150.3, 139.9, 139.6, 129.9, 126.4, 124.8, 122.1, 113.8 ppm.

***N*-(4-Acetylphenyl)aniline (6f):** After flash chromatography on silica gel (hexane/EtOAc, 7:3), compound **6f** (99.7 mg, 94%) was obtained as a yellow solid. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.91–7.82 (m, 2 H), 7.39–7.30 (m, 2 H), 7.22–7.14 (m, 2 H), 7.13–7.04 (m, 1 H), 7.03–6.94 (m, 2 H), 2.53 (s, 3 H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ = 196.5, 148.5, 140.7, 130.7, 129.7, 129.2, 123.5, 120.8, 114.6, 26.3 ppm.

4-(Phenylamino)benzaldehyde (6g): After flash chromatography on silica gel (pentane/Et_2O, 8:1), compound **6g** (88.1 mg, 89%) was obtained as a yellow solid. ^1H NMR (400 MHz, $CDCl_3$): δ = 9.79 (s, 1 H), 7.81–7.68 (m, 2 H), 7.43–7.30 (m, 2 H), 7.23–7.18 (m, 2 H), 7.16–7.08 (m, 1 H), 7.06–6.99 (m, 2 H), 6.40 (br. s, 1 H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ = 190.5, 150.0, 140.2, 132.2, 129.7, 128.6, 124.0, 121.4, 114.6 ppm.

***N*-Phenyl-2-methylaniline (6h):** After flash chromatography on silica gel (hexane/EtOAc, 20:1), compound **6h** (91.0 mg, 99%) was obtained as a colourless oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.26 (m, 4 H), 7.22 (td, J = 7.8, 1.4 Hz, 1 H), 7.06–6.95 (m, 4 H), 5.43 (br. s, 1 H), 2.33 (s, 3 H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ = 144.1, 141.3, 131.0, 129.4, 128.4, 126.8, 122.1, 120.5, 118.9, 117.5, 18.0 ppm.

***N*-(4-Methylphenyl)-4-methoxyaniline (6i):** After flash chromatography on silica gel (hexane/EtOAc, 8:1), compound **6i** (97.4 mg, 91%) was obtained as a white solid. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.06–7.01 (m, 4 H), 6.88–6.83 (m, 4 H), 5.42 (br. s, 1 H), 3.80 (s, 3 H), 2.2 (s, 3 H) ppm. $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ = 154.9, 142.5, 136.7, 129.9, 129.5, 121.2, 116.7, 114.8, 55.7, 20.7 ppm.

***N*-(4-Methoxyphenyl)-4-fluoroaniline (6j):** After flash chromatography on silica gel (pentane/Et_2O, 9:1), compound **6j** was obtained as a grey solid: 105.5 mg (97% yield). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.05–6.98 (m, 2 H), 6.97–6.81 (m, 6 H), 5.39 (br. s, 1 H), 3.80 (s, 3 H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ = 157.3 (d, J = 238 Hz), 155.1, 141.2 (d, J = 2 Hz), 136.6, 121.3, 117.9 (d, J = 7 Hz), 115.9 (d, J = 22 Hz), 114.9, 55.7 ppm.

***N*-(4-Methoxyphenyl)-3-(trifluoromethyl)aniline (6k):** After flash chromatography on silica gel (pentane/Et_2O, 7:1), compound **6k** (90.3 mg, 68%) was obtained as a beige solid. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.28 (t, J = 8.2 Hz, 1 H), 7.14–7.06 (m, 3 H), 7.06–6.96 (m, 2 H), 6.95–6.85 (m, 2 H), 5.62 (br. s, 1 H), 3.82 (s, 3 H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ = 156.3, 146.1, 134.4, 131.8 (q, J = 32 Hz), 129.9, 124.3 (q, J = 273 Hz), 123.6, 118.0, 115.7 (q, J = 4 Hz), 115.0, 111.4 (q, J = 4 Hz), 55.7 ppm.

Methyl 4-(4-Methoxyphenylamino)benzoate (6l): After flash chromatography on silica gel (pentane/Et_2O, 7:1), compound **6l** (67.2 mg, 52%) was obtained as a beige solid. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.87 (d, J = 8.4 Hz, 2 H), 7.12 (d, J = 8.5 Hz, 2 H), 6.90 (d, J = 8.6 Hz, 2 H), 6.81 (d, J = 8.5 Hz, 2 H), 5.99 (s, 1 H), 3.85 (s, 3 H), 3.81 (s, 3 H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ = 167.2, 156.5, 150.0, 133.5, 131.6, 124.4, 119.9, 114.8, 113.3, 55.6, 51.7 ppm.

***N*-Phenylpyridin-3-amine (6m):** After flash chromatography on silica gel (hexane/EtOAc, 1:4), compound **6m** (70.6 mg, 83%) was obtained as a white solid. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.39 (s, 1 H), 8.16 (d, J = 3.9 Hz, 1 H), 7.41 (ddd, J = 8.2, 2.5, 1.2 Hz, 1 H), 7.30 (t, J = 7.9 Hz, 2 H), 7.17 (dd, J = 8.2, 4.7 Hz, 1 H), 7.08 (d, J = 7.6 Hz, 2 H), 6.99 (t, J = 7.4 Hz, 1 H), 5.89 (d, J = 14.3 Hz, 1 H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ = 142.1, 142.0, 140.3, 140.0, 129.7, 123.8, 123.5, 122.1, 118.4 ppm.

***N*-(4-Fluorophenyl)pyridin-3-amine (6n):** After flash chromatography on silica gel (EtOAc), compound **6n** (82.3 mg, 88%) was obtained as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.31 (d, J = 2.7 Hz, 1 H), 8.13 (d, J = 4.6 Hz, 1 H), 7.28 (ddd, J = 8.3, 2.8, 1.4 Hz, 1 H), 7.14 (dd, J = 8.3, 4.7 Hz, 1 H), 7.10–6.95 (m, 4 H), 5.81 (d, J = 38.2 Hz, 1 H) ppm. ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 158.7 (d, J = 242 Hz), 141.7 (d, J = 3 Hz), 140.7, 139.4, 123.9, 122.5, 121.4 (d, J = 8 Hz), 116.3 (d, J = 22 Hz) ppm.

***N*-Octyl-2-methylaniline (7a):** After flash chromatography on silica gel (hexane/EtOAc, 20:1), compound **7a** (106 mg, 97%) was obtained as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.23 (td, J = 7.6, 1.2 Hz, 1 H), 7.15 (d, J = 7.7 Hz, 1 H), 6.79–6.64 (m, 2 H), 3.52 (br. s, 1 H), 3.24 (t, J = 7.1 Hz, 2 H), 2.23 (s, 3 H), 1.76 (pent, J = 7.1 Hz, 2 H), 1.57–1.33 (m, 10 H), 1.06–0.95 (m, 3 H) ppm. ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 146.5, 130.1, 127.2, 121.7, 116.7, 109.7, 44.1, 32.0, 29.7, 29.6, 29.4, 27.4, 22.8, 17.5, 14.2 ppm.

***N*-Octyl-2,6-dimethylaniline (7b):** After flash chromatography on silica gel (pentane/EtOAc, 20:1), compound **7b** (109.6 mg, 94%) was obtained as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.00 (d, J = 7.4 Hz, 2 H), 6.81 (t, J = 7.4 Hz, 1 H), 3.07–2.90 (m, 3 H), 2.30 (s, 6 H), 1.64–1.52 (m, 2 H), 1.46–1.24 (m, 10 H), 0.95–0.84 (m, 3 H) ppm. ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 146.6, 129.2, 128.9, 121.6, 48.8, 32.0, 31.4, 29.7, 29.4, 27.3, 22.8, 18.7, 14.2 ppm.

***N*-Cyclohexylaniline (7c):** After flash chromatography on silica gel (hexane/EtOAc, 10:1), compound **7c** (64.5 mg, 74%) was obtained as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.23–7.13 (m, 2 H), 6.73–6.65 (m, 1 H), 6.65–6.55 (m, 2 H), 3.53 (br. s, 1 H), 3.35–3.22 (m, 1 H), 2.08 (d, J = 12.6 Hz, 2 H), 1.86–1.73 (m, 2 H), 1.74–1.61 (m, 1 H), 1.48–1.33 (m, 2 H), 1.32–1.10 (m, 3 H) ppm. ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 147.5, 129.4, 116.9, 113.2, 51.8, 33.6, 26.1, 25.2 ppm.

***N*-Octyl-4-methoxy-aniline (7d):** After flash chromatography on silica gel (hexane/EtOAc, 20:1), compound **7d** (51.6 mg, 44%) was obtained as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.82–6.76 (m, 2 H), 6.62–6.55 (m, 2 H), 3.75 (s, 3 H), 3.12 (br. s, 1 H), 3.06 (t, J = 7.1 Hz, 2 H), 1.61 (pent, J = 7.0 Hz, 2 H), 1.44–1.23 (m, 10 H), 0.90 (t, J = 6.7 Hz, 3 H) ppm. ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 152.1, 143.0, 115.0, 114.1, 56.0, 45.2, 32.0, 29.8, 29.6, 29.4, 27.4, 22.8, 14.2 ppm.

***N*,*N*-Bis(4-methoxyphenyl)octylamine (7d′):** After flash chromatography on silica gel (hexane/EtOAc, 20:1), compound **7d′** (48.6 mg, 57%) was obtained as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.92–6.86 (m, 4 H), 6.86–6.80 (m, 4 H), 3.79 (s, 6 H), 3.60–3.52 (m, 2 H), 1.62 (pent, J = 7.6 Hz, 2 H), 1.35–1.23 (m, 10 H), 0.89 (t, J = 6.6 Hz, 3 H) ppm. ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 154.3, 142.7, 122.2, 114.7, 55.7, 53.0, 32.0, 29.6, 29.5, 27.7, 27.3, 22.8, 14.2 ppm.

***N*-Octyl-pyridin-3-amine (7e):** After flash chromatography on silica gel (EtOAc), compound **7e** (72 mg, 70%) was obtained as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.01 (d, J = 2.8 Hz, 1 H), 7.93 (dd, J = 4.7, 1.2 Hz, 1 H), 7.10–7.01 (m, 1 H), 6.84 (ddd, J = 8.3, 2.9, 1.4 Hz, 1 H), 3.66 (br. s, 1 H), 3.10 (t, J = 7.0 Hz, 2 H), 1.62 (pent, J = 7.1 Hz, 2 H), 1.44–1.22 (m, 10 H), 0.93–0.82 (m, 3 H) ppm. ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 144.5, 138.6, 136.2, 123.8, 118.4, 43.7, 31.9, 29.6, 29.5, 29.4, 27.2, 22.8, 14.2 ppm.

***N*,*N*-Bis(pyridin-3-yl)octylamine (7e′):** After flash chromatography on silica gel (EtOAc), compound **7e′** (14 mg, 20%) was obtained as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.35 (d, J = 2.4 Hz, 2 H), 8.23 (d, J = 3.8 Hz, 2 H), 7.30–7.25 (m, 2 H), 7.19 (dd, J = 8.3, 4.6 Hz, 2 H), 3.70 (t, J = 7.7 Hz, 2 H), 1.66 (pent, J = 7.6 Hz, 2 H), 1.33–1.21 (m, 10 H), 0.86 (t, J = 6.9 Hz, 3 H) ppm. ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 143.6, 143.1, 127.7, 124.0, 52.4, 31.9, 29.5, 29.4, 27.4, 27.1, 22.7, 14.2 ppm.

***N*-Benzyl-4-methoxyaniline (7f):** After flash chromatography on silica gel (hexane/EtOAc, 20:1), compound **7f** (52.4 mg, 49%) was obtained as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.27 (m, 4 H), 7.31–7.27 (m, 1 H), 6.82–6.78 (m, 2 H), 6.64–6.60 (m, 2 H), 4.30 (s, 2 H), 3.79 (br. s, 1 H), 3.76 (s, 3 H) ppm. ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 152.3, 142.6, 139.8, 128.7, 127.7, 127.3, 115.0, 114.2, 55.9, 49.4 ppm.

***N*,*N*-Bis(4-methoxyphenyl)benzylamine (7f′):** After flash chromatography on silica gel (hexane/EtOAc, 20:1), compound **7f′** (35.1 mg, 44%) was obtained as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.27 (m, 4 H), 7.22 (t, J = 7.1 Hz, 1 H), 7.00–6.91 (m, 4 H), 6.84–6.75 (m, 4 H), 4.89 (s, 2 H), 3.77 (s, 6 H) ppm. ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ = 154.4, 142.6, 139.7, 128.6, 126.8, 126.8, 121.9, 114.7, 57.2, 55.7 ppm.

Supporting Information (see footnote on the first page of this article): ^{1}H and ^{13}C NMR spectra of products **5a**–**5p**, **6a**–**6n**, **7a**–**7f**, and **7d′**–**7f′**.

Acknowledgments

The authors thank the Centre National de la Recherche Scientifique (CNRS) for financial support, and the Chinese Scholarship Council (CSC) for a Ph. D. grant to Y. Z.

[1] a) D. A. Horton, G. T. Bourne, M. L. Smythe, *Chem. Rev.* **2003**, *103*, 893–930; b) J. Magano, J. R. Dunetz, *Chem. Rev.* **2011**, *111*, 2177–2250.

[2] For selected references and reviews, see: a) J. J. Armao, M. Maaloum, T. Ellis, G. Fuks, M. Rawiso, E. Moulin, N. Giuseppone, *J. Am. Chem. Soc.* **2014**, *136*, 11382–11388; b) A. Iwan, D. Sek, *Prog. Polym. Sci.* **2011**, *36*, 1277–1325; c) Z. J. Ning, H. Tian, *Chem. Commun.* **2009**, 5483–5495; d) R. Lygaitis, V. Getautis, J. V. Grazulevicius, *Chem. Soc. Rev.* **2008**, *37*, 770–788.

[3] For book chapters, see: a) J. F. Hartwig, in: *Modern Amination Methods* (Ed.: A. Ricci), Wiley-VCH, Weinheim, Germany, **2000**, p. 195; b) J. F. Hartwig, in: *Handbook of Organopalladium Chemistry for Organic Synthesis* (Ed.: E.-i. Negishi), Wiley, New York, **2002**, p. 1051; c) L. Jiang, S. L. Buchwald, in: *Metal-Catalyzed Cross-Coupling Reactions* (Eds.: A. de Meijere, F. Diederich), Wiley-VCH, Weinheim, Germany, **2004**, p. 699.

[4] For recent selected reviews, see: a) D. S. Surry, S. L. Buchwald, *Chem. Sci.* **2011**, *2*, 27–50; b) J. F. Hartwig, *Acc. Chem. Res.* **2008**, *41*, 1534–1544; c) D. S. Surry, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2008**, *47*, 6338–6361; *Angew. Chem.* **2008**, *120*, 6438–6461.

[5] a) C. Torborg, M. Beller, *Adv. Synth. Catal.* **2009**, *351*, 3027–3043; b) S. L. Buchwald, C. Mauger, G. Mignani, U. Scholz, *Adv. Synth. Catal.* **2006**, *348*, 23–39; c) B. Schlummer, U. Scholz, *Adv. Synth. Catal.* **2004**, *346*, 1599–1626.

[6] For recent experimental and theoretical contributions, see: a) Y. Sunesson, E. Limé, S. O. N. Lill, R. E. Meadows, P.-O. Norrby, *J. Org. Chem.* **2014**, *79*, 11961–11969; b) K. H. Hoi, S. Çalimsiz, R. D. J. Froese, A. C. Hopkinson, M. G. Organ, *Chem. Eur. J.* **2012**, *18*, 145–151; c) K. H. Hoi, S. Çalimsiz, R. D. J. Froese, A. C. Hopkinson, M. G. Organ, *Chem. Eur. J.* **2011**, *17*, 3086–3090; d) C. L. McMullin, R. Bastian, M. Besora, G. A. Orpen, J. N. Harvey, N. Fey, *J. Mol. Catal. A* **2010**, *324*, 48–55; e) T. E. Barder, M. R. Biscoe, S. L. Buchwald, *Or-*

ganometallics **2007**, *26*, 2183–2192; f) T. E. Barder, S. L. Buchwald, *J. Am. Chem. Soc.* **2007**, *129*, 12003–12010; g) S. Shekhar, J. F. Hartwig, *Organometallics* **2007**, *26*, 340–351.

[7] a) D. Maiti, B. P. Fors, J. L. Henderson, Y. Nakamura, S. L. Buchwald, *Chem. Sci.* **2011**, *2*, 57–68; b) B. P. Fors, D. A. Watson, M. R. Biscoe, S. L. Buchwald, *J. Am. Chem. Soc.* **2008**, *130*, 13552–13554; c) M. R. Biscoe, B. P. Fors, S. L. Buchwald, *J. Am. Chem. Soc.* **2008**, *130*, 6686–6687; d) X. Huang, K. W. Anderson, D. Zim, L. Jiang, A. Klapars, S. L. Buchwald, *J. Am. Chem. Soc.* **2003**, *125*, 6653–6655.

[8] a) T. Ogata, J. F. Hartwig, *J. Am. Chem. Soc.* **2008**, *130*, 13848–13849; b) Q. Shen, T. Ogata, J. F. Hartwig, *J. Am. Chem. Soc.* **2008**, *130*, 6586–6596; c) Q. Shen, S. Shekhar, J. P. Stambuli, J. F. Hartwig, *Angew. Chem. Int. Ed.* **2005**, *44*, 1371–1375; *Angew. Chem.* **2005**, *117*, 1395–1399.

[9] C. M. So, Z. Zhou, C. P. Lau, F. Y. Kwong, *Angew. Chem. Int. Ed.* **2008**, *47*, 6402–6406; *Angew. Chem.* **2008**, *120*, 6502–6506.

[10] a) P. G. Alsabeh, R. J. Lundgren, R. McDonald, C. C. C. Johansson Seechurn, T. J. Colacot, M. Stradiotto, *Chem. Eur. J.* **2013**, *19*, 2131–2141; b) R. J. Lundgren, B. D. Peters, P. G. Alsabeh, M. Stradiotto, *Angew. Chem. Int. Ed.* **2010**, *49*, 4071–4074; *Angew. Chem.* **2010**, *122*, 4165–4168; c) R. J. Lundgren, M. Stradiotto, *Angew. Chem. Int. Ed.* **2010**, *49*, 8686–8690; *Angew. Chem.* **2010**, *122*, 8868–8872.

[11] For recent general reviews, see: a) M. N. Hopkinson, C. Richter, M. Schedler, F. Glorius, *Nature* **2014**, *510*, 485–496; b) D. J. Nelson, S. P. Nolan, *Chem. Soc. Rev.* **2013**, *42*, 6723–6753; c) L. Benhamou, E. Chardon, G. Lavigne, S. Bellemin-Laponnaz, V. César, *Chem. Rev.* **2011**, *111*, 2705–2733; d) M. Melaimi, M. Soleilhavoup, G. Bertrand, *Angew. Chem. Int. Ed.* **2010**, *49*, 8810–8849; *Angew. Chem.* **2010**, *122*, 8992–9032.

[12] For Pd–NHC complexes in cross-coupling reactions, see: a) C. Valente, S. Çalimsiz, K. H. Hoi, D. Mallik, M. Sayah, M. G. Organ, *Angew. Chem. Int. Ed.* **2012**, *51*, 3314–3332; *Angew. Chem.* **2012**, *124*, 3370–3388; b) N. Marion, S. P. Nolan, *Acc. Chem. Res.* **2008**, *41*, 1440–1449.

[13] For selected contributions from the Organ's group, see: a) M. Pompeo, J. L. Farmer, R. D. J. Froese, M. G. Organ, *Angew. Chem. Int. Ed.* **2014**, *53*, 3223–3226; *Angew. Chem.* **2014**, *126*, 3287–3290; b) C. Valente, M. Pompeo, M. Sayah, M. G. Organ, *Org. Process Res. Dev.* **2014**, *18*, 180–190; c) K. H. Hoi, J. A. Coggan, M. G. Organ, *Chem. Eur. J.* **2013**, *19*, 843–845; d) K. H. Hoi, M. G. Organ, *Chem. Eur. J.* **2012**, *18*, 804–807; e) see ref.[6b,6c]; f) M. G. Organ, M. Abdel-Hadi, S. Avola, I. Dubovyk, N. Hadei, E. A. B. Kantchev, C. J. O'Brien, M. Sayah, C. Valente, *Chem. Eur. J.* **2008**, *14*, 2443–2452.

[14] For selected contributions from the Nolan's group, see: a) G. Bastug, S. P. Nolan, *Organometallics* **2014**, *33*, 1253–1258; b) G. Le Duc, S. Meiries, S. P. Nolan, *Organometallics* **2013**, *32*, 7547–7551; c) S. Meiries, G. Le Duc, A. Chartoire, A. Collado, K. Speck, K. S. A. Arachchige, A. M. Z. Slawin, S. P. Nolan, *Chem. Eur. J.* **2013**, *19*, 17358–17368; d) S. Meiries, K. Speck, D. B. Cordes, A. M. Z. Slawin, S. P. Nolan, *Organometallics* **2013**, *32*, 330–339; e) S. Meiries, A. Chartoire, A. M. Z. Slawin, S. P. Nolan, *Organometallics* **2012**, *31*, 3402–3409; f) A. Chartoire, X. Frogneux, A. Boreux, A. M. Z. Slawin, S. P. Nolan, *Organometallics* **2012**, *31*, 6947–6951; g) N. Marion, O. Navarro, J. Mei, E. D. Stevens, N. M. Scott, S. P. Nolan, *J. Am. Chem. Soc.* **2006**, *128*, 4101–4111.

[15] For selected recent contributions from other groups, see: a) J. L. Krinsky, A. Martínez, C. Godard, S. Castillón, C. Claver, *Adv. Synth. Catal.* **2014**, *356*, 460–474; b) C. A. Wheaton, J.-P. J. Bow, M. Stradiotto, *Organometallics* **2013**, *32*, 6148–6161; c) T. Tu, W. Fang, J. Jiang, *Chem. Commun.* **2011**, *47*, 12358–12360.

[16] For selected recent reviews on Pd-catalysed amination with aryl chlorides and sulfonates, see: a) A. F. Littke, G. C. Fu, *Angew. Chem. Int. Ed.* **2002**, *41*, 4176–4211; *Angew. Chem.* **2002**, *114*, 4350–4386; b) A. Zapf, M. Beller, *Chem. Commun.* **2005**, 431–440; c) C. M. So, F. Y. Kwong, *Chem. Soc. Rev.* **2011**, *40*, 4963–4972.

[17] a) B. P. Fors, S. L. Buchwald, *J. Am. Chem. Soc.* **2010**, *132*, 15914–15917; b) B. P. Fors, P. Krattiger, E. Strieter, S. L. Buchwald, *Org. Lett.* **2008**, *10*, 3505–3508.

[18] a) S. Çalimsiz, M. Sayah, D. Mallik, M. G. Organ, *Angew. Chem. Int. Ed.* **2010**, *49*, 2014–2017; *Angew. Chem.* **2010**, *122*, 2058–2061; b) M. G. Organ, S. Çalimsiz, M. Sayah, K. H. Hoi, A. J. Lough, *Angew. Chem. Int. Ed.* **2009**, *48*, 2383–2387; *Angew. Chem.* **2009**, *121*, 2419–2423.

[19] For the quantification of the stereoelectronics of IPent, see also: A. Collado, J. Balogh, S. Meiries, A. M. Z. Slawin, L. Falivene, L. Cavallo, S. P. Nolan, *Organometallics* **2013**, *32*, 3249–3252.

[20] A detailed examination of structural data indicates that the presence of an X substituent (necessarily bulkier than H) at the 4- and 5-positions of the imidazolyl ring tends to exert a slight steric pressure on the adjacent aryl groups of the NHC, thereby leading to a global increase of its steric bulk, substantiated by an enlargement of the buried volume. Such a steric effect may be observed irrespective of whether the X substituent is an electron-donating or an electron-withdrawing group.

[21] For selected references, see: a) V. César, S. Labat, K. Miqueu, J.-M. Sotiropoulos, R. Brousses, N. Lugan, G. Lavigne, *Chem. Eur. J.* **2013**, *19*, 17113; b) V. César, J. C. Tourneux, N. Vujkovic, R. Brousses, N. Lugan, G. Lavigne, *Chem. Commun.* **2012**, *48*, 2349; c) N. Vujkovic, V. César, N. Lugan, G. Lavigne, *Chem. Eur. J.* **2011**, *17*, 13151; d) V. César, N. Lugan, G. Lavigne, *Chem. Eur. J.* **2010**, *16*, 11432; e) L. Benhamou, V. César, H. Gornitzka, N. Lugan, G. Lavigne, *Chem. Commun.* **2009**, 4720; f) V. César, N. Lugan, G. Lavigne, *J. Am. Chem. Soc.* **2008**, *130*, 11286.

[22] Y. Zhang, V. César, G. Storch, N. Lugan, G. Lavigne, *Angew. Chem. Int. Ed.* **2014**, *53*, 6482–6486; *Angew. Chem.* **2014**, *126*, 6600–6604.

[23] C. Meyers, B. U. W. Maes, K. T. J. Loones, G. Bal, G. L. F. Lemière, R. A. Dommisse, *J. Org. Chem.* **2004**, *69*, 6010–6017.

[24] J. P. Wolfe, S. Wagaw, S. L. Buchwald, *J. Am. Chem. Soc.* **1996**, *118*, 7215–7216.

[25] G. R. Fulmer, A. J. M. Miller, N. H. Sherden, H. E. Gottlieb, A. Nudelman, B. M. Stoltz, J. E. Bercaw, K. I. Goldberg, *Organometallics* **2010**, *29*, 2176–2179.

[26] C. J. O'Brien, E. A. B. Kantchev, C. Valente, N. Hadei, G. A. Chass, A. Lough, A. C. Hopkinson, M. G. Organ, *Chem. Eur. J.* **2006**, *12*, 4743–4748.

Received: January 9, 2015
Published Online: February 9, 2015

