

An easily available *N*-heterocyclic carbene–palladium(II) catalyst for Buchwald–Hartwig amination of aryl chlorides

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Abstract An easily available *N*-heterocyclic carbene–palladium(II) complex was found to be an efficient catalyst for the Buchwald–Hartwig amination of aryl chlorides. Both secondary and primary amines were tolerated under the same reaction conditions. Under the optimal conditions, all reactions proceeded successfully to give the desired products in good to high yields within hours.

Introduction

The palladium-catalyzed amination of aryl halides (Buchwald–Hartwig amination) is one of the most important and frequently used methods for the formation of C–N bonds and has found widespread applications in organic synthesis [1–12].¹ Many catalyst systems have been explored in order to extend the scope of the reaction to more substrates, under milder conditions and with lower catalyst loadings. Most published examples concern the use of phosphine

palladium complexes as catalysts, providing the corresponding aminated products in good yields [13–20]. Recently, *N*-heterocyclic carbene (NHC)–palladium complexes [21–27], which have generally higher stabilities toward heat, air and moisture than analogous phosphine palladium complexes, have shown good catalytic activity in the amination of aryl halides. In addition, due to the strong σ -donating ability and sterically demanding character of NHCs, a few NHC–palladium complexes are even very efficient catalysts for the amination of less reactive but more economically attractive aryl chlorides. For example, Wu et al. [28] have developed an air- and moisture-stable carbene–palladacycle complex and found it to be an efficient catalyst for the Buchwald–Hartwig amination of a range of aryl chlorides with amines. The Pd–PEPPSI–NHC complexes [29–33] acting as highly effective pre-catalysts can perform the amination of aryl chlorides under mild conditions. Tu et al. have explored the application of acenaphthoimidazolyliidene [34] and benzimidazolyliidene [35]. NHC–palladium complexes for the amination of aryl chlorides, and the reaction was found to tolerate a wide range of substrates at low catalyst loadings. Meanwhile, [Pd(NHC)(acac)Cl] complexes [36] readily catalyzed the Buchwald–Hartwig coupling reaction of aryl chlorides with various anilines in excellent yields. The catalytic activities of functionalizable alkoxy-tethered *N*-heterocyclic carbene–palladium complexes were evaluated for more challenging Buchwald–Hartwig aminations [37]. Additionally, a variety of other *N*-heterocyclic carbene–palladium complexes have been developed for this purpose, including *N*-heterocyclic carbene–palladium(II) 4,5-dihydrooxazole complexes [NHC–Pd(II)–Ox] [38], and dinuclear NHC–palladium complexes containing imidazolidin-2-ylidene

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¹ For early references on amination reactions see Negishi [9].

derivatives as supporting ligands and diphosphine ligands as linkers [39]. During preparation of this manuscript, Lu et al. [40] have reported a new type of *N*-heterocyclic carbene–PdCl₂–(iso)quinoline complex, which proved to be an efficient catalyst for C–N coupling of primary and secondary amines with aryl chlorides at low catalyst loadings. Although these species have been found to be particularly useful as catalysts in the Buchwald–Hartwig amination of aryl chlorides, the development of easily prepared, highly reactive, and stable NHC–Pd(II) complexes still constitutes a challenging endeavor in current organometallic chemistry. Very recently, we reported the first synthesis of *N*-heterocyclic carbene–palladium(II) complexes **1–4** with benzoxazole or benzothiazole coligands (Scheme 1) [41]. The potential of these complexes in the catalytic Suzuki–Miyaura coupling of aryl chlorides and benzyl chlorides with arylboronic acids was evaluated. Under the optimal reaction conditions, the expected biaryl products were obtained in high yields of up to 99 %. Encouraged by these results, we have extended our investigations of the catalytic potential of these complexes. Herein, we report their application in the Buchwald–Hartwig amination of aryl chlorides with amines.

Experimental

General remarks

Solvents were dried by standard methods and freshly distilled prior to use if needed. All other chemicals were used as purchased. The *N*-heterocyclic carbene–palladium(II) complexes were synthesized according to our previous report [41]. Preparations of the complexes as well as all the catalytic reactions were carried out under a nitrogen atmosphere. NMR spectra were recorded on a Bruker DPX 400 instrument using TMS as an internal standard.

General procedure for the catalytic amination

A Schlenk flask was charged with the required aryl chloride (0.25 mmol), amine (0.30 mmol), *N*-heterocyclic carbene–palladium(II) complex (2 mol%), KO^tBu (1.3 equiv),

and toluene (0.5 mL). The mixture was stirred at 110 °C for 15 h under N₂. After cooling, the mixture was evaporated and the product was isolated by preparative TLC on silica gel plates. The purified products were identified by ¹H NMR spectra, and their analytical data are given in the Supporting Information.

Results and discussion

In order to test the catalytic activities of these *N*-heterocyclic carbene–palladium(II) complexes **1–4**, initial experiments were carried out using chlorobenzene (0.25 mmol) and morpholine (0.30 mmol) as the reactants, plus complex **1** (2.0 mol%) as the catalyst, in toluene (0.5 mL) at 110 °C, with the results shown in Table 1. The choice of base proved to have an important influence on the reaction (Table 1, entries 1–6) [42]. The reaction proceeded efficiently only when KO^tBu was used as base, giving the corresponding coupling product **5a** in 91 % yield in this case (Table 1, entry 1). When 3.0 mol% of complex **1** was tested, the yield was not enhanced further (Table 1, entry 7). However, by prolonging the reaction time to 15 h the product **5a** was obtained in a 99 % yield (Table 1, entry 8). Complex **3** also showed good catalytic activity (Table 1, entry 10), although slightly lower than that of complex **1**, indicating that bulkier NHC ligands make a more reactive catalyst. Interestingly, complexes **2** and **4** were much less efficient than **1** and **3** under identical conditions (entry 8 vs. entry 9; entry 10 vs. entry 11) which

Table 1 Optimization of reaction conditions for the coupling of chlorobenzene with morpholine catalyzed by the NHC–Pd(II) complexes

Entry	Cat.	Base	Yield (%) ^a
1	1	KO ^t Bu	91
2	1	K ₂ CO ₃	53
3	1	Cs ₂ CO ₃	37
4	1	NaOH	43
5	1	NaO ^t Bu	67
6	1	KOH	9
7 ^b	1	KO ^t Bu	92
8 ^c	1	KO ^t Bu	99
9 ^c	2	KO ^t Bu	47
10 ^c	3	KO ^t Bu	83
11 ^c	4	KO ^t Bu	37

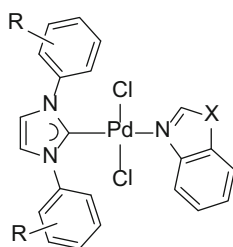
All reactions were carried out using chlorobenzene (0.25 mmol), morpholine (0.30 mmol), base (1.3 equiv), plus catalyst (2.0 mol%) in toluene (0.5 mL) at 110 °C for 12 h

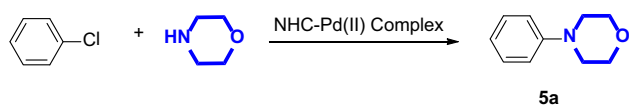
^a Isolated yields

^b Cat. (3.0 mol%)

^c Reaction time was 15 h

Scheme 1 *N*-Heterocyclic carbene–palladium(II) complexes. **1**: R = *o,o'*-Pr₂, X = O; **2**: R = *o,o'*-Pr₂, X = S; **3**: R = *o,p,o'*-Me₃, X = O; **4**: R = *o,p,o'*-Me₃, X = S





Scheme 2 The coupling of chlorobenzene with morpholine

might be ascribed to the different coordination abilities of benzoxazole and benzothiazole. It is worth mentioning that a related complex, (IPr)Pd(acac)Cl when used as a catalyst for these reaction at 50 °C in dimethyl ether gave similar yields after 30 min [43] (Scheme 2).

With the optimized conditions in hand, a series of aryl chlorides were first used as reactants with morpholine to test the generality of the reaction. As shown in Scheme 3, most of the coupling reactions proceeded efficiently to give the corresponding aminated products **5a–m** in good to excellent yields. Both electron-donating and withdrawing substituents on the aryl chlorides were tolerated and yields of 71–99 % were obtained for **5a–i**. The position of the aryl substituted did not seem to affect the product yields. In particular, the reaction was quite feasible with sterically encumbered ortho-substituted aryl chlorides (**5d** and **5h**), while the very sterically hindered 2-chloro-*m*-xylene reacted with morpholine giving 71 % isolated yield (**5e**). Subsequently, when heteroaromatic aryl chlorides such as 2-chloropyridine and 3-chloropyridine were used as the substrates, high yields of the corresponding products were observed (**5j** and **5k**).

We next studied the reactions of 1-chloro-2-methylbenzene with piperidine or *N*-methylaniline. Unlike the corresponding reaction with morpholine, the yields of **5l**

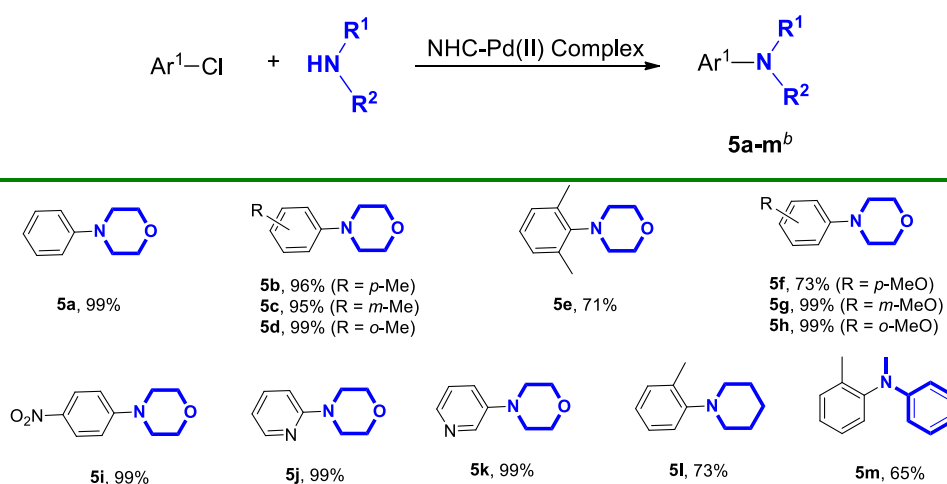
and **5m** were somewhat lower in these experiments (Scheme 3).

We then turned our attention to the reaction of aryl chlorides with primary amines, giving the results presented in Scheme 4. Each of these reactions gave the corresponding monoaminated products **6a–o** in moderate to good yields. In particular, the reaction of 1-chloro-2-methylbenzene with aniline proceeded in excellent yield (**6d**). This may be due to the ortho-substituent of the aryl chloride preventing formation of the triarylamine. The results showed that 1-chloro-2-methylbenzene could be arylated with electronically diverse primary amines. Highly sterically hindered amines such as 2,4,6-trimethylaniline and 2,6-diisopropylaniline were also tolerated, giving the corresponding aminated products **6k–l** in high yields. Electron-donating substituents in the phenyl ring of the primary amine showed some beneficial effect on the yields (**6h–m** vs. **6n–o**). Overall, the results indicated that complex **1** is an efficient catalyst for these reactions.

Conclusion

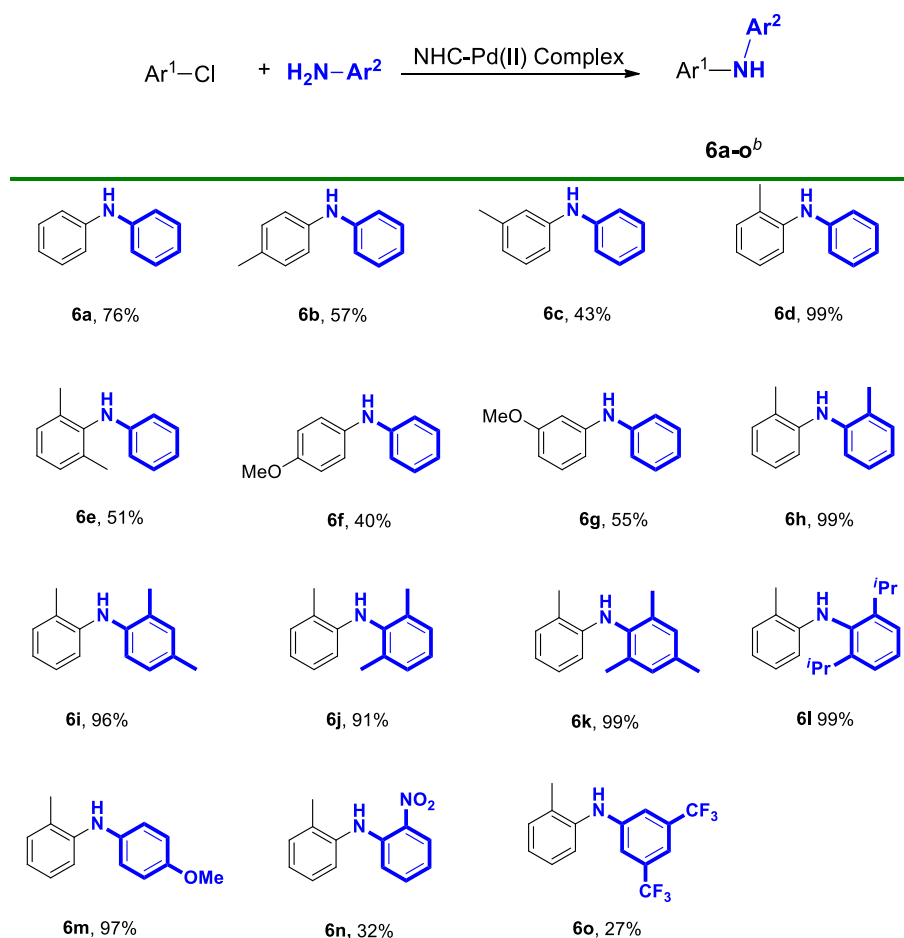
In summary, the easily available, well-defined *N*-heterocyclic carbene–palladium(II) complexes **1–4**, being derived from the corresponding imidazolium salts, palladium chloride and benzoxazole or benzothiazole, showed good catalytic activity in the Buchwald–Hartwig amination of aryl chlorides. In addition to secondary amines, a series of primary amines performed very well with aryl chlorides

Scheme 3 Substrate scope for the catalytic coupling of aryl chlorides with secondary amines using the NHC–Pd(II) complex **1** as the catalyst^a



^aAll reactions were carried out using aryl chlorides (0.25 mmol), secondary amines (0.30 mmol), KO^tBu (1.3 equiv), plus catalyst **1** (2.0 mol%) in toluene (0.5 mL) at 110 °C for 15 h. ^bIsolated yields.

Scheme 4 Substrate scope for the catalytic coupling of aryl chlorides with primary amines using the NHC–Pd(II) complex **1** as the catalyst^a



^aAll reactions were carried out using the aryl chloride (0.25 mmol), primary amine (0.30 mmol), KO^tBu (1.3 equiv), and complex **1** (2.0 mol%) in toluene (0.5 mL) at 110 °C for 15 h. ^bIsolated yields.

using the same catalytic system. Further exploration of these *N*-heterocyclic carbene–palladium(II) complexes and their catalytic applications in other reactions is in progress.

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