Buchwald–Hartwig Aminations of Aryl Chlorides: A Practical Protocol Based on Commercially Available Pd(0)-NHC Catalysts

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Received 15 October 2004

In fond memory of Martin Rentzsch

Abstract: Commercially available, air- and water-stable naphthoquinone imidazolin-2-ylidene-palladium(0) complexes were found to be highly active one-component catalysts for the amination of aryl halides. With these very robust catalysts, the expensive bases Cs_2CO_3 or NaO*t*-Bu traditionally used can be replaced by KOH. A convenient reaction protocol has been developed for the coupling of a wide range of aryl chlorides with primary or secondary amines.

Key words: carbene ligands, amination, palladium, aryl chlorides

Within a few years after its discovery, the Buchwald–Hartwig amination or aryl halides has become the method of choice for the synthesis of functionalized aryl amines.[1] Systematic studies have led to the development of highly active catalyst systems, some of them allowing even the room temperature conversion of deactivated aryl chlorides.[2,3] However, the reaction protocols usually involve air-sensitive, electron-rich ligands. Another common disadvantage of the existing methods is the use of expensive bases with a high molecular weight, i.e. Cs_2CO_3 or NaO*t*-Bu.

For applications in drug discovery and large-scale manufacture, a generally applicable process featuring an easy-to-handle one-component catalyst system in combination with an inexpensive base would be highly desirable. As catalysts, Pd(0) complexes with N-heterocyclic carbene (NHC) ligands[4] appeared to be the most promising, since they have displayed potent catalytic activity in Buchwald–Hartwig aminations,[5] and are particularly insensitive against oxygen. However, the generation of the

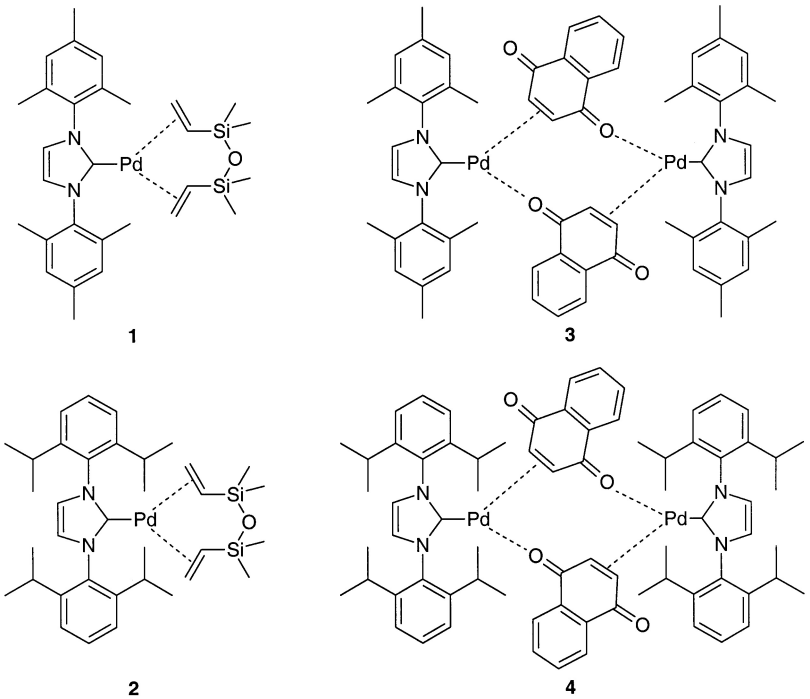


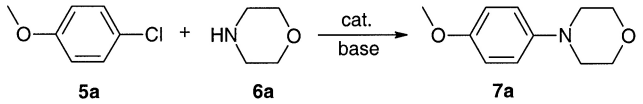
Figure 1 Preformed Pd(0)monocarbene complexes

SYNLETT 2005, No. 2, pp 0275–0278
Advanced online publication: 17.12.2004
DOI: 10.1055/s-2004-837205; Art ID: G41504ST

catalytically active species – presumably monoligated, coordinatively highly unsaturated Pd(0) complexes – from Pd(II)-NHC precursors was often found to be troublesome.[4]

In this respect, preformed Pd(0)-NHC complexes **1**–**4** should be advantageous, since the desired Pd(0) species are accessible simply by dissociation of a naphthoquinone or divinylsiloxane ligand (Figure 1). The complexes are easily accessible,[6] stable against air and water, and have recently become commercially available on a large scale. They have also been demonstrated to show high reactivity in Suzuki,[6] Heck,[6,7] Kumada[8] and telomerization reactions.[9]

In order to develop a convenient reaction protocol for Buchwald–Hartwig aminations based on these complexes, we chose the coupling of morpholine with *p*-chloroanisole, a particularly unreactive aryl halide, as the model reaction (Scheme 1).[10] The results of our screening experiments are summarized in Table 1.



Scheme 1 Pd-catalyzed amination of *p*-chloroanisole with morpholine

Using NaO*t*-Bu as base, no conversion was observed with $Pd(OAc)_2$, $Pd(dba)_2$ and $Pd(dba)_2/PPh_3$ (Table 1, entries 1–3), while state-of-the-art catalyst systems with the electron rich, sterically hindered phosphines 2-(di-*tert*-butylphosphino)biphenyl [*o*-biph-P(*t*-Bu)$_2$] and 2-(dicyclohexylphosphino)-biphenyl (*o*-biph-PCy$_2$) showed the expected high reactivities (entries 4, 5). Under these conditions, the preformed Pd(0)-NHC complexes **1** and **3** bearing mesitylene substituents gave unsatisfactory yields. In contrast, near quantitative yields were obtained with the sterically crowded 2,6-diisopropyl containing complexes **2** and **4** (entries 6–9). For this model reaction, the performance of the naphthoquinone-1,3-bis(2,6-diisopropylphenyl)imidazole-2-ylidene-palladium(0) (**4**) fully matches that of the above-mentioned high-tech systems (entries 5, 9).

To further improve the reaction protocol, we investigated if with catalyst **4**, standard, inexpensive bases could replace sodium *tert*-butoxide. For this particular test reaction with a strongly basic amine, carbonate and phosphate bases were ineffective (entries 10–12). In contrast, simple alkali hydroxides gave excellent results (entries 13, 14).[11] Near quantitative yields were obtained with standard grade potassium hydroxide, especially when used in excess (see entry 15). Surprisingly, the natural water content of this base (>15%) did not impede the reaction.

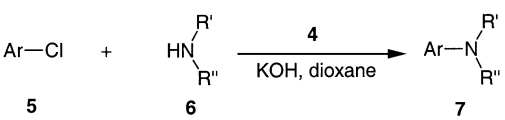
Among the solvents tested, dioxane and NMP were the most effective, while in non-polar solvents such as toluene, only modest yields were obtained (entries 14, 18–20). For the comparatively unreactive substrate **5a**, quantitative turnover was achieved at 100 °C within 16 hours, but even at lower temperatures, good yields were obtained (entries 14, 16–17).

Table 1 Optimization of the Reaction Conditions[a]

Entry	Catalyst	Solvent	Base	Yield (%)
1	$PdOAc_2$	Dioxane	NaO*t*-Bu	0
2	$Pd(dba)_2$	Dioxane	NaO*t*-Bu	0
3	$Pd(dba)_2$/ PPh_3	Dioxane	NaO*t*-Bu	0
4	$Pd(dba)_2$/ *o*-biph-P(*t*-Bu)$_2$	Dioxane	NaO*t*-Bu	47
5	$Pd(dba)_2$/ *o*-biph-PCy$_2$	Dioxane	NaO*t*-Bu	96
6	**1**	Dioxane	NaO*t*-Bu	<10
7	**2**	Dioxane	NaO*t*-Bu	95
8	**3**	Dioxane	NaO*t*-Bu	<10
9	**4**	Dioxane	NaO*t*-Bu	96
10	**4**	Dioxane	Na_2CO_3	0
11	**4**	Dioxane	Cs_2CO_3	0
12	**4**	Dioxane	K_3PO_4	0
13	**4**	Dioxane	NaOH	42
14	**4**	Dioxane	KOH	96
15[b]	**4**	Dioxane	KOH	60
16[c]	**4**	Dioxane	KOH	72
17[d]	**4**	Dioxane	KOH	66
18	**4**	Toluene	KOH	20
19	**4**	NMP	KOH	81
20	**4**	Diglyme	KOH	76

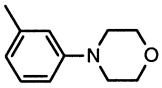
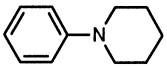
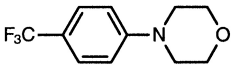
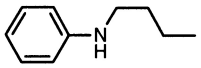
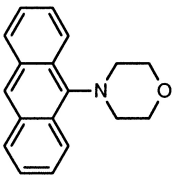
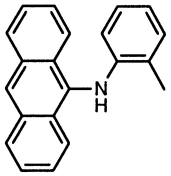
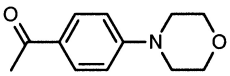
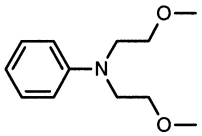
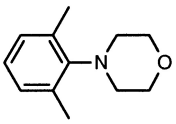
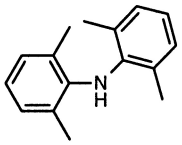
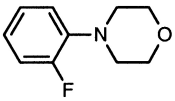
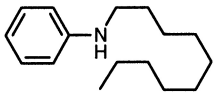
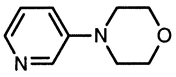
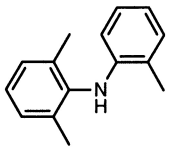
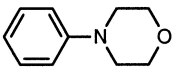
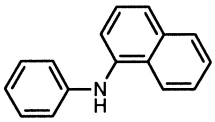
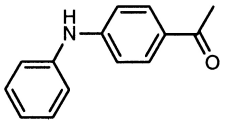
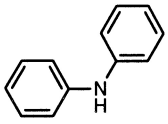
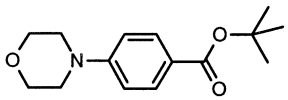
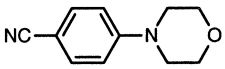
[a] *Conditions*: 1.00 mmol *p*-chloroanisole, 1.50 mmol morpholine, 1 mol% Pd source, 2 mol% ligand, 3.00 mmol base, 16 h, 100 °C, GC yields using *n*-tetradecane as internal standard.
[b] 1.30 mmol base.
[c] At 80 °C.
[d] At 60 °C.

Having established a practical reaction protocol, we went on to investigate the scope of the transformation using different aryl chlorides **5a**–**h** in combination with various amines **6a**–**j** (Scheme 2). Selected results are summarized in Table 2.



Scheme 2 Scope of the transformation using catalyst **4**

Table 2 Scope of the Reaction[a]

Entry	Compound	Yield (%)	Entry	Compound	Yield (%)
1		83	11		89
2		95	12		75[c]
3		95	13		79
4		27 (48)[b]	14		67
5		47	15		85
6		62	16		47[c]
7		81	17		90
8		93 (83)[d]	18		73
9		25	19		88
10		55[b]	20		88[b]

[a] *Conditions*: 1.00 mmol aryl chloride, 1.50 mmol amine, 0.50 mol% **4**, 3.00 mmol KOH, 4 mL dioxane, 100 °C, 16 h, isolated yields.
[b] With NaO*t*-Bu as base.
[c] <10% Bisarylated product.
[d] 30.0 mmol aryl chloride, 40.0 mmol amine, 0.05 mol% **4**, 75.0 mmol KOH, 40 mL dioxane.

Catalyst **4** shows high activity for both electron rich and electron poor aryl and heteroaryl chlorides, and even sterically hindered derivatives are converted in excellent yields. The high efficiency of the catalyst system is demonstrated by the formation of the sterically crowded bis-(2,6-dimethylphenyl)amine (entry 15). Several functional groups are tolerated (entries 2, 4, 9, 14). However, with KOH as the base, enolizable ketones give only modest yields (entries 4, 9), and hydrolytically unstable molecules are not suitable. For such substrates, the use of anhydrous bases such as NaO*t*-Bu led to much higher yields (entries 4, 10, 20).

The protocol is equally suitable for primary and secondary aromatic and aliphatic amines. By-products from β-hydride elimination, often an issue with aliphatic amines and

standard catalysts, were observed only in traces, and likewise, only small quantities of the biarylated amine were detected. In an attempt to reduce the catalyst loading, the reaction of chlorobenzene and morpholine (**6b**) was performed on a larger scale. *N*-Phenylmorpholine could be isolated in 83% yield using only 0.05 mol% of **4** (entry 8).

In summary, we have demonstrated that one-component palladium(0)-NHC complexes are a highly effective alternative for the Buchwald–Hartwig amination of aryl chlorides, with key advantages in the commercial availability of the preformed complexes, their stability towards oxygen and water, the low catalyst loading and the use of a simple and cheap base. Thus, important drawbacks of this elegant transformation have been overcome and its practical usefulness especially for combinatorial chemistry and industrial applications is greatly enhanced.

Synthesis of *N*-Phenylmorpholine:
A 20 mL round-bottom flask was charged successively with naphthoquinone-1,3-bis(2,6-diisopropylphenyl)imidazole-2-ylidene-palladium(0) (**1**, 6.50 mg, 5.0 μmol), finely powdered KOH (168 mg, 3.0 mmol), dry dioxane (4 mL), *p*-chloroanisole (125 μL, 1.0 mmol) and morpholine (115 μL, 1.3 mmol). The mixture was purged with argon for 3 min and heated to 100 °C. After complete conversion (usually 16 h) the mixture was cooled, filtered over silica gel and the volatile components were removed in vacuo. The residue was purified by column chromatography (SiO_2, hexane–EtOAc 80:20) yielding *N*-phenylmorpholine (153 mg, 0.93 mmol, 93%) as a white solid. The spectroscopic data were identical to those reported in literature.

Acknowledgment

We thank M. Eckardt for experimental assistance. LJG thanks Prof. Dr. M. T. Reetz for constant support and encouragement.

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