



Nickel-catalysed amination of aryl chlorides using a dihydroimidazoline carbene ligand

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Abstract—A new arylation protocol has been developed using a catalyst combination prepared from Ni(acac)₂ associated to a sterically hindered dihydroimidazoline carbene ligand. A high efficiency was attained using, in most cases, only 2 mol% Ni/carbene clusters. © 2001 Elsevier Science Ltd. All rights reserved.

The synthesis of aromatic amines has attracted considerable attention since these compounds are found in biologically active products as well as in materials with useful electronic and mechanical properties.¹ Palladium-catalysed carbon–nitrogen bond-forming reactions has been the area of intensive research in recent literature. These studies have shown that the supporting ligands on the metal centre play a crucial role in dictating the efficiency of the catalytic system.² Recently, bulky *N*-heterocyclic carbenes have attracted considerable attention as ligands in carbon–carbon³ and carbon–nitrogen⁴ coupling reactions. These reports have demonstrated that such strong electron donating ligands can be incorporated into palladium catalysts and that an excess of ligand is not required to prevent aggregation of the metal.

Alternatively, nickel-catalysed amination reactions have received less attention. Buchwald reported first the use of Ni(COD)₂ associated to 1,1'-bis(diphenylphosphino)ferrocene (dppf) or 1,10-phenanthroline for the synthesis of arylamines.⁵ Bolm extended this *N*-arylation method for the coupling of sulfoximines with aryl tosylates using Ni(COD)₂ liganded with BINAP.⁶ An heterogeneous Ni/C catalyst liganded with dppf was also recently developed by Lipshutz.⁷

For our part, we have reported the use of a catalyst combination of in situ generated colloidal Ni(0) associa-

ted to 2,2'-bipyridine which provided an efficient route to substituted anilines.⁸ In addition to its utility in catalytic amination reactions of aryl chlorides substrates, the Ni/2,2'-bipyridine has also shown to be effective for a wide variety of carbon–nitrogen bond-forming processes including *N*-monoarylation of piperazine⁹ and polyamination or selective monoamination of aryl di- and trichlorides.¹⁰ Although a good catalytic activity and the synthesis of elaborated aryl amines were attained, ligand effect in nickel-catalysed arylation reactions is still of interest. We therefore, wondered if such reactions could be performed and improved using carbene ligands.

Herein, we wish to report our initial results on the synthesis of aromatic amines from aryl- or heteroaryl chlorides and secondary amines based on a Ni(0)/dihydroimidazoline carbene catalysed cross-coupling reactions. To select the most effective ligand, a number of 1,3-diaryl substituted imidazolium and dihydroimidazolium salts were used in a model reaction (Table 1).

1,3-Bis(2,4,6-trimethyl)substituted imidazolium salts **1** and **2** afforded the desired arylamine in poor yields (entries a–c). The sterically hindered 1,3-bis(2,6-diisopropylphenyl) imidazol-2-ylidenes, in situ generated from the corresponding imidazolium chlorides **3** and **4b**, were found to be the most effective carbene precursors leading to *N*-phenylmorpholine in a 99% isolated yield (Table 1, entries d and f). The results obtained with unsaturated and saturated imidazolium chlorides **3** and **4b** indicate clearly that their higher performances are due to their steric hindrance. The counter-ion associated to the dihydroimidazolium salt was however

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Table 1. Effect of the ligand precursors on the nickel-catalysed coupling of chlorobenzene with morpholine^a

Entry	Ligand precursor		Time ^b (h)	Yield ^c (%)
a		1a , X = BF ₄	15	Traces
b		1b , X = Cl	15	12
c		2	15	17
d		3	3	99
e		4a , X = BF ₄	15	37
f		4b , X = Cl	3	99

^a All reactions were performed using 10 mmol chlorobenzene and 15 mmol morpholine.

^b Determined by GC analysis

^c Yields refer to isolated yields (average of two runs) of compounds estimated to be >95% pure as determined by ¹H and ¹³C NMR and GC analysis.

found to have a profound effect on the outcome of the reaction. The use of the tetrafluoroborate salt of the protonated carbene resulted in a low yield of phenylmorpholine (entry e) probably due to the in situ formation of sodium borohydride arising from the reaction of the fluoroborate with sodium hydride used to regenerate active nickel species. Carbenes generated from **3** and **4b** are equally efficient in nickel-catalysed amination reactions and couplings were conducted using **4b** as precursor.

Ni(acac)₂ was found to be the best nickel source. Ni(OAc)₂ can also be used (85% yield after 3 h reaction time) while the reaction of chlorobenzene with morpholine using NiCl₂ proceeded in only 50% yield. We have also determined that a 4/1 ratio of carbene to Ni gave the best catalyst combination. Lowering (1/1, 1/2 or 1/3) or increasing (5/1) this ratio resulted in a decrease of the reaction rate (8–10 h) and poorer yields of the amination products were obtained.

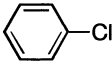
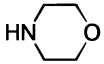
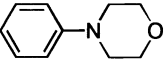
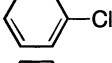

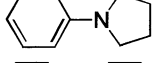
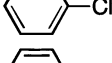
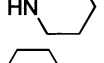
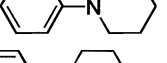
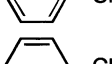
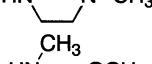
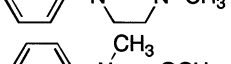
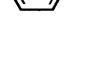
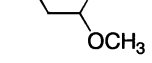
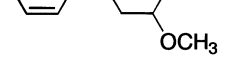
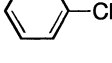
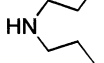
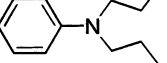
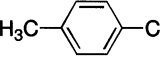
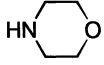
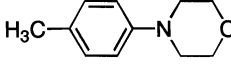
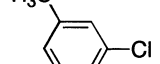
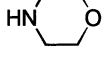
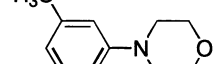
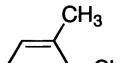
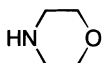
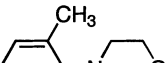
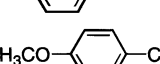
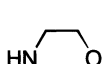
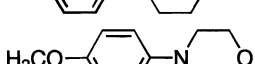


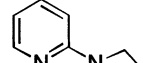


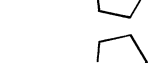
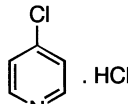

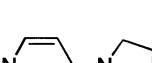
The role of the in situ generated *t*-BuONa (0.4 equiv. relative to ArCl) is two fold: it initially activates sodium hydride used to reduce Ni(acac)₂ into Ni(0) and deprotonates the dihydroimidazolium chloride to form the carbene ligand which coordinates to the metal. The use of non-activated sodium hydride as reductant and base was not effective in these reactions and resulted in slow

catalyst formation associated to poor yields (less than 10%) of the desired arylamine. It was finally observed that the use of 1.5 equiv. amine relative to the aryl chloride was the best compromise. Decreasing the amount of amine to 1.2 equiv. afforded the arylamine in similar yields but reaction times were increased.

In comparison to our previously described Ni/2,2'-bipyridine clusters which were composed of hcp nanometric particles,¹¹ transmission electron microscopy (TEM) of the Ni/carbene clusters obtained revealed an homogeneous distribution of uniformly sized (less than 0.5 nm), amorphous and subnanometrical Ni particles. Such a dispersion has a strong effect on the catalytic activity as evidenced by the amount of nickel necessary for the coupling (generally 2 mol%) and by the short reaction times.

Using the optimal conditions, the Ni-catalysed reactions of aryl or heteroaryl chlorides with secondary amines provided a general route to the corresponding arylamines **3** (Table 2).¹² The only side product observed was the arene resulting from reduction of the starting aryl chloride. This observation led us to think that Ni/carbene clusters might have a potential interest in dehalogenation reaction. Electron-poor aryl chlorides gave the amination products in excellent yields (entries k, l and m) while lower yields were obtained

Table 2. Amination of aryl chlorides using the Ni/carbene catalyst^a

Entry	ArCl	Amine	Product	Time ^b (h)	Yield ^c (%)
a				3	99
b				3	96
c				15	47
d				3	98
e				8	74
f				10	66
g				2.5	87
h				2	94
i				3	79
j				10	75
k				2	95
l				2.5	91
m				2.5	90 ^d

^a Typical reaction conditions for cyclic amines : aryl chloride (10 mmol), amine (15 mmol), Ni(acac)₂ (0.2 mmol), carbene (0.8 mmol), *t*-BuOH (1.2 mmol) and NaH (12.2 mmol). Typical reaction conditions for acyclic amines : aryl chloride (10 mmol), amine (15 mmol), Ni(acac)₂ (0.5 mmol), carbene (1 mmol), *t*-BuOH (2 mmol) and NaH (13.5 mmol).

^b Determined by GC analysis.

^c Yields refer to isolated yields (average of two runs) of compounds estimated to be >95% pure as determined by ¹H and ¹³C NMR and GC analysis.

^d 22.2 mmol NaH were employed.

with electron-rich aryl chlorides (entry j). Surprisingly, while morpholine and pyrrolidine were efficiently coupled with chlorobenzene in high yields (entries a and b), the reaction with piperidine gave a large amount of reduced side product and *N*-phenylpiperidine **3c** was obtained in a poor 47% yield. Note that such a limitation was previously observed with the Pd/BINAP catalyst and is, for the moment, difficult to explain.^{2f}

Ni/carbene-catalysed aminations were only slightly sensitive to the steric hindrance of the aryl chloride. 2-

Chlorotoluene reacted with morpholine to give the corresponding aromatic amine in 79% yield (entry i). The Ni/carbene catalyst is also effective for the arylation of secondary acyclic amines (entries e and f). However, reaction rates were slower and a catalyst loading of 5 mol% Ni was necessary to achieve completion.

In conclusion, our work constitutes the first example of carbon–nitrogen couplings mediated by a nickel–dihydroimidazolidine carbene catalyst. The synthesis of aryl-

amines from readily available aryl chlorides was thus allowed in good to excellent yield depending on the substitution pattern of the aryl fragment. Future work will include efforts to circumvent the use of sodium hydride to regenerate active Ni species and will be reported in due course.

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- Representative procedure for N-phenylmorpholine (3a):** In a Schlenk tube containing degreased NaH (12.2 mmol) in THF (3 mL) were added Ni(acac)₂ (0.2 mmol) and the dihydroimidazolium chloride **2b** (0.8 mmol) and the mixture was heated at 65°C. A solution of morpholine (15 mmol) and *t*-BuOH (1.2 mmol) in THF (3 mL) was then added dropwise and the mixture was further stirred at 65°C for 1 h. A solution of chlorobenzene (10 mmol) in THF (3 mL) was then added and the reaction was monitored by GC. After complete consumption of the aryl chloride, the mixture was cooled to room temperature and adsorbed onto silica gel. The crude reaction mixture was purified by silica gel column chromatography using *n*-hexane–AcOEt (90:10) as eluant to give **3a** as a pale yellow solid. All products in Table 2 have been previously characterised.