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New Efficient Nickel(0) Catalysed Amination of Aryl Chlorides

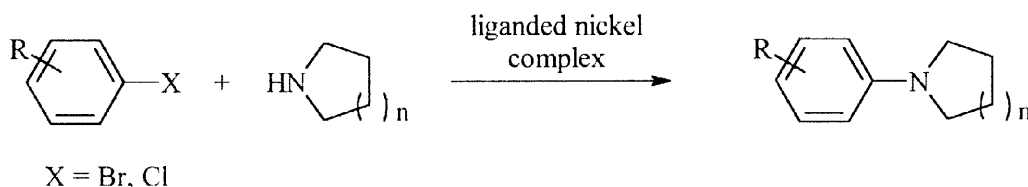
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Abstract: It is shown that a liganded Ni(0) complex reagent, prepared in THF from NaH, *t*.AmOH, Ni(OAc)₂ and 2,2'-bipyridine, efficiently catalyses amination of aryl chlorides under mild conditions.
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Aromatic amines play a central role in many areas of organic chemistry such as polymers, medicine and photography. In recent years, a number of efficient Pd(0) catalysed protocols for conversion of aryl halides to corresponding arylamines have been reported by both Hartwig's¹ and by Buchwald's groups.² More recently, Wolfe and Buchwald have described the first nickel-catalysed amination of aryl chlorides.³ In spite of this no mechanistic information was given and the reaction sequence may be similar to that proposed for Pd catalysed amination^{1b,2c} or may proceed through a classical Ni(0) induced coupling mechanism as proposed by Kochi.⁴ Thus, a Ni containing reagent known to be efficient in carbon-carbon bond forming reactions must be of some interest in the synthesis of arylamines. This prompted us to investigate the ability of our *in situ* generated and stable liganded metal complexes of Ni(0)^{5,6} to induce carbon-nitrogen bond formation (Scheme 1) and herein we report our initial results.



Scheme 1

We first performed the coupling of bromo- or chlorobenzene with amines using a stoichiometric amount of liganded Ni(0) complex. During this exploratory study, we found that PhBr reacts efficiently in THF at 63 °C with piperidine or pyrrolidine in the presence of NaH-*t*.AmONa-Ni(0)-bpy (2/2/1/2) reagent to afford phenylamines in good yields (Runs 1 and 2, Table 1). The main side-product of the reaction is biphenyl resulting from homocoupling of PhBr, although small amounts of benzene, obtained by reduction, were produced. It must be underlined that these side-products as well as 2,2'-bipyridine are readily separated from phenylamines after an aqueous workup and a flash chromatography on silica gel. As the experimental protocol

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is concerned, we have found that amine must be added during preparation of the reagent (Method A) rather than just before the substrate (Method B) (Runs 1 and 3).

Table 1. Synthesis of N-Phenylamines from Phenyl Halides Induced by Liganded Ni (0) Reagent.^a

Run	PhX (Equiv.)	Amine (Equiv.)	Reagent (constituents ratio)	Method ^b	Time ^c (h.)	Yield ^d (%)
1	PhBr (1)	Piperidine (1)	NaH- <i>t</i> .AmONa -Ni(0)-bpy (2/2/1/2)	A	1	78 (73)
2	PhBr (1)	Pyrrolidine (1)	NaH- <i>t</i> .AmONa -Ni(0)-bpy (2/2/1/2)	A	1	83
3	PhBr (1)	Piperidine (1)	NaH- <i>t</i> .AmONa -Ni(0)-bpy (2/2/1/2)	B	3.5	54
4	PhBr (1)	Piperidine (1)	NaH- <i>t</i> .AmONa (1/2)	-	18	5
5	PhBr (1)	Piperidine (1)	NaH- <i>t</i> .AmONa (3/2)	-	18	19
6	PhBr (1)	Piperidine (1)	NaH- <i>t</i> .AmONa-Ni(0) (2/2/1)	A	18	2
7	PhBr (1)	Piperidine (1)	NaH- <i>t</i> .AmONa -Ni(0)-bpy (1/2/1/2)	A	7	53
8	PhBr (1)	Piperidine (1)	NaH- <i>t</i> .AmONa -Ni(0)-bpy (3/2/1/2)	A	1	65
9	PhBr (1)	Piperidine (1)	NaH- <i>t</i> .AmONa -Ni(0)-bpy (3/2/1/2)	B	0.5	41
10	PhBr (1)	Piperidine (1)	NaH- <i>t</i> .AmONa -Ni(0)-PPh ₃ (1/2/1/4)	A	18	9
11	PhBr (1)	Piperidine (1)	NaH- <i>t</i> .AmONa -Ni(0)-Phen (1/2/1/2)	A	18	3
12	PhCl (1)	Piperidine (1)	NaH- <i>t</i> .AmONa -Ni(0)-bpy (2/2/1/2)	A	4.5	97 (87)
13	PhCl (1)	Pyrrolidine (1)	NaH- <i>t</i> .AmONa -Ni(0)-bpy (2/2/1/2)	A	2.5	98 (91)
14	PhCl (1)	Piperidine (1)	NaH- <i>t</i> .AmONa -Ni(0)-bpy (2/2/1/2)	B	3.5	80

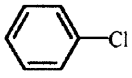
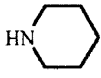
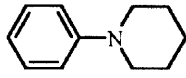
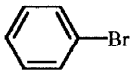
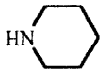
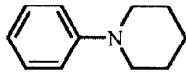
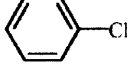
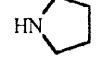
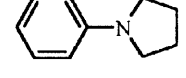
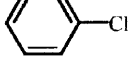
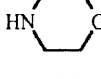
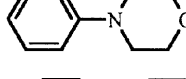
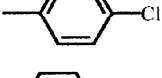
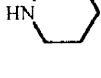
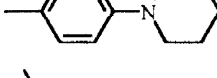
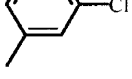
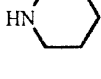
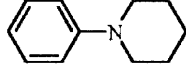
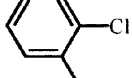
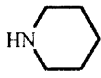
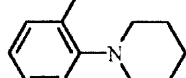
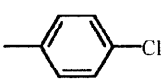
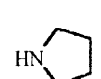
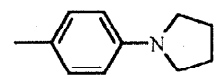
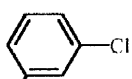
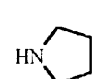
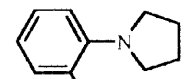
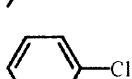
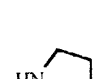
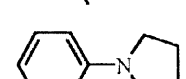
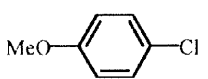
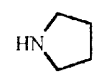
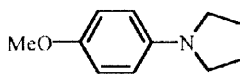
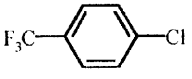
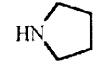
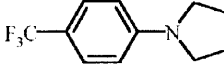
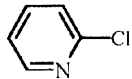
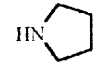
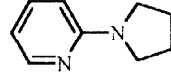
a) Reaction performed on a 10 mmoles scale of ArX in THF at 63°C. b) In method A, amine is added during the preparation of the reagent; in method B, amine is dropwise added to the reagent just before the substrate. c) Time of completion or after which no evolution was observed in GC analysis. d) GC yields; in parentheses, isolated yields.

We have subsequently verified that in the absence of Ni(0) species and/or 2,2'-bipyridine, only low yields were obtained (Runs 4 to 6). We have also found that the amounts of side-products are dependent on the constituent ratio in the reagent. Indeed, a larger excess of NaH in the reagent led to an increase in the benzene formation while a decrease of NaH content favoured the homocoupling reaction, both leading to lower yields (Runs 7 to 9). Finally other ligands examined (PPh₃, 1,10-phenanthroline (Phen)) gave low conversion and poor product/reduced substrate ratios for the coupling reaction (Runs 10 and 11). With chlorobenzene (Runs 12 to 14), no by-product was formed and yields in phenylamines reached 98 % using method A. These results are consistent with those obtained in classical coupling reactions induced by our systems as far as the reactivity of aromatic halides is concerned.^{6a}

These first results encouraged us to perform aromatic amination under catalytic conditions. After some experimentation, we found that a 20 % catalytic amount of Ni(0) and the use of a small excess of amine allowed the fast and complete conversion of aromatic halides. Unfortunately, yields never reached up 30 % with PhBr or 55 % with PhCl. The main side product formed in these reactions is benzene resulting from the reduction-hydrogenation of the substrate. This may be due to the formation of hydrogen in the regeneration of

the active Ni(0) species by NaH during the catalytic cycle. We thus decided to perform reactions in the presence of a variable amount of a very easily hydrogenated compound. After some experimentation, we chose styrene and we determined that an amount of 0.5 equivalent was sufficient to prevent hydrogenation of phenyl chloride and to obtain a Ni(0) catalysed reaction. The GC yield then reached 91 % in 4 h (85 % isolated, Run 1, Table 2). This benefit was also observed with PhBr to a smaller extent (Run 2).

Table 2. Synthesis of N-Arylamines from Aryl Halides catalysed by Liganded Ni (0) Reagent.^a

Run	PhX	Amine	Time (h.)	Product	Yield (%) ^b
1			4		85
2			3.5		39
3			3.5		85
4			6		65
5			4.25		81
6			4		77
7			3.5		78
8			3.5		82
9			3		82
10			4		84
11			7		37
12			2.5		87
13			4.25		70 ^c

a) Reaction performed on a 50 mmole scale with ArX/amine/ styrene/NaH/*t*-AmONa/Ni(0)/bpy = 5/5.5/0.5/3/2/1/2 ratio (Ref. 7).

b) Isolated yields after flash chromatography. c) See Ref. 7.

As illustrated in Table 2, the Ni-catalysed aromatic amination provides an efficient route to aryl amines. This constitutes the first effective catalytic use of our liganded Ni(0) complexes. The reactions are generally complete in 3 to 4 hours and side reduction or coupling never exceed 20 %. *Ortho*, *meta* or *para* substitution is tolerated (Runs 5 to 12). Aryl chlorides with an electron-withdrawing substituent also react efficiently (Run 12) while the presence of an electron-donating substituent leads to a decrease in the coupling reaction with a higher side reduction (Run 11). Finally, heteroaromatic amination is obtained in good yield. Further studies are in progress on the scope and limitations as well as the mechanistic pathway.

References and notes

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6. Liganded complexes of Ni(0) (also noted NiCRA-L) have been previously found efficient in the homo- and cross-coupling reaction of aryl and heteroaryl halides: a) Lourak, M.; Vanderesse, R.; Fort, Y.; Caubère, P. *J. Org. Chem.*, **1989**, *54*, 4840-4844. b) Lourak, M.; Vanderesse, R.; Fort, Y.; Caubère, P. *J. Org. Chem.*, **1989**, *54*, 4844-4848. c) Fort, Y.; Becker, S.; Caubère, P. *Tetrahedron.*, **1994**, *50*, 11893-11902.
7. *Typical experiment:* A solution of piperidine (55 mmol) in 10mL of dry THF was added to a mixture of *t*-AmONa (20 mmol) and NaH (50 mmol) (obtained from *t*-AmOH (20 mmol) and degreased NaH (70 mmol)) in 20 mL of dry THF at 63°C. After 0.5 h, dry Ni(OAc)₂ (10 mmol) and 2,2'-bipyridine (20 mmol) were added through a solid funnel. After 1 hour, the black reagent formed was ready for use. A solution of chlorobenzene (50 mmol) and styrene (5 mmol) in 10 mL of THF was then dropwise added over a period of 15 mn. The reaction was monitored by GC analyses (Alltech Econo-Cap EC-5 column (30 m x 0.32 mm ID x 0.25 mm at 150 °C,)) and GC-MS (CI, CH₄) analyses (HP1 (15 m x 0.32 mm ID x 0.25 µm, 120 to 200°C at 5°C/mn,)) using dodecane as internal standard. After completion, the excess of hydride was carefully destroyed by dropwise addition of water at 25 °C until hydrogen evolution ceased. Products were extracted by ether and separated by flash chromatography.
All compounds have been previously described, with the exception of N-*p*-trifluoromethyl phenylpyrrolidine, for which the following additional spectral data are reported: m.p. 90°C (Tottoli). ¹H NMR (CDCl₃, 400 MHz) δ: 2.03 (m,4H), 3.32 (4H), 6.54 (d, 2H) and 7.43 ppm (d, 2H). ¹³C NMR (CDCl₃, 400 MHz) δ: 25.84, 47.88, 111.24, 116.88, 126.32, 127.22 and 150.20 ppm. CIMS (CH₄) m/z: 216 (M+H)⁺ (48%), 215 (51%), 196 (100%). Elemental anal.: Calc. for C₁₁H₁₂NF₃: C, 60.67; H, 5.45; N, 6.44. Found: C, 61.29; H, 5.62; N, 6.51. Product was obtained as a white solid which rapidly turn to violin under air exposure.