Nickel-mediated amination chemistry. Part 1: Efficient aminations of (het)aryl 1,3-di and 1,3,5-trichlorides

Christophe Desmarets, Raphaël Schneider and Yves Fort *

Synthèse Organique et Réactivité, UMR CNRS-UHP 7565, Université Henri Poincaré, Nancy I, Faculté des Sciences, BP 239, 54506 Vandoeuvre les Nancy Cedex, France

Abstract

The first Ni-catalysed synthesis of di- and triamino substituted benzenes and diamino substituted pyridines from the corresponding aryl chlorides and amines is described. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: nickel; arylamination; aryl dichlorides; aryl trichlorides.

Oligomeric and polymeric arylamines such as poly(aryleneamine)s or *m*- or *p*-polyaniline are important polymers which possess magnetic and conductive properties.[1] The current methods for the preparation of these compounds are based on high temperature copper-mediated Ullmann coupling of aryl iodides with amines[2] or palladium-catalysed multiple coupling of amines with polybromobenzenes.[3] Witulski and co-workers described the synthesis of di-, tri- and tetrasubstituted morpholinobenzenes using a palladium catalyst and bidentate ligands (BINAP, dppf).[4] Beletskaya and Guilard reported also very recently aminations of aryl dibromides with secondary amines using Pd(dba)$_2$ and P(*o*-tolyl)$_3$.[5] Among all recent arylamination reports,[6] our group has described a Ni-catalysed cross-coupling of secondary amines and piperazines with the readily available aryl chlorides.[7] The efficiency of our system is due to the use of styrene as additive to trap evolved hydrogen and thus inhibit side hydrogenolysis of the carbon–chlorine bond. It then appeared of interest to extend this Ni-catalysed carbon–nitrogen bond forming reaction to the synthesis of polyaminobenzenes, and herein, we report our initial results.

Secondary cyclic and acyclic amines were first reacted with *o*-, *m*- and *p*-dichlorobenzenes using our 2,2′-bipyridine liganded nickel catalyst (Scheme 1). The obtained results are summarised in Table 1 (entries a–g).

In an exploration of reactions parameters, the amount of amine was varied and we found that the use of 2 equivalents of amine per chlorine atom allowed a rapid conversion of the starting materials. Catalyst loadings of 10 and 20 mol% Ni per chlorine functionality were used, respectively, with cyclic and acyclic amines.

* Corresponding author. E-mail: yves.fort@sor.uhp-nancy.fr (Y. Fort)

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Scheme 1.

Ni(0)
2,2'-bipyridine

NaH / t-AmONa
THF , reflux

X = CH, N

1   2
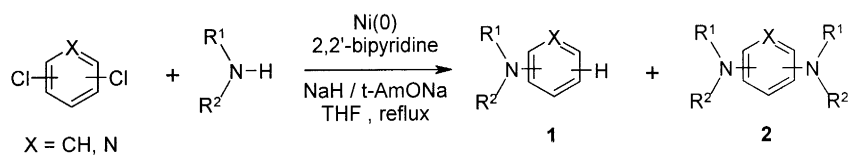
Table 1
2,2'-Bipyridine liganded Ni-catalysed amination of (het)aryl dichlorides with secondary amines[a]

Entry	Aryl Dichloride	Amine	Reaction Time (h)[b]	Isolated Yield of 1 (%)[c]	Isolated Yield of 2 (%)[c]
a	Cl—C$_6$H$_4$—Cl (3-chloro)	piperidine (NH)	1.5	4	78
b	"	morpholine (O...NH)	1.0	4	85
c	"	HN...NCOOEt	1.0	8	77
d	Cl—C$_6$H$_4$—Cl (1,4)	piperidine (NH)	8.0	63	25
e	1,2-dichlorobenzene	piperidine (NH)	5.0	16	25
f	Cl—pyridine—Cl (2,6)	piperidine (NH)	1.5	12	69
g	"	HN...NCOOEt	1.0	8	76
h	"	morpholine (O...NH)	1.5	13	73
i	"	n-Pr$_2$NH	3.0	21	49
j	"	Me–NH–CH$_2$–CH(OMe)$_2$	2.0	13	75
k	Cl—pyridine—Cl (3,5)	morpholine (O...NH)	2.0	4	81
l	"	HN...NCOOEt	1.5	4	82
m	"	Me–NH–CH$_2$–CH(OMe)$_2$	2.5	6	75

[a] With cyclic amines, reactions were carried out with 20 mmol aryl dichloride, 80 mmol amine, 4 mmol Ni(OAc)$_2$, 12 mmol 2,2'-bipyridine, 8 mmol t-AmOH, 64 mmol NaH and 8 mmol styrene in 50 mL THF. With acyclic amines, 8 mmol Ni(OAc)$_2$, 16 mmol 2,2'-bipyridine, 16 mmol t-AmOH and 48 mmol NaH were used. [b] GC yields. [c] Isolated yields after chromatography on silica gel. All compounds were were fully characterised by NMR (^{1}H, ^{13}C), IR, MS or combustion analysis.

Dehalogenation product **3** and diaminobiaryl **4** (Scheme 2), formed by nickel-catalysed homocoupling of **1**, could only be detected by GC–MS. In these reactions, the only by-product which could be isolated was the chloroaminobenzene **1**.
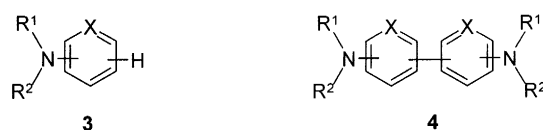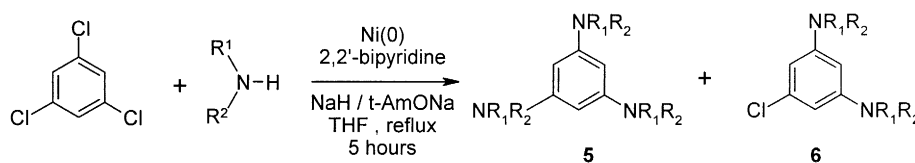

Scheme 2.

The amounts of **1** were found to be dependent on the steric and electronic properties of the starting aryl dichloride. The same reaction conditions applied to 1,4- and 1,2-dichlorobenzene conducted to different results. 1,4-Dichlorobenzene afforded mainly monoamination product **1** (entry d). According to our previous works obtained for Ni-catalysed amination of aryl chlorides,[7] these results may be explained by the strong electron-donating effect of the *para* amino group introduced in the first step of the reaction. For 1,2-dichlorobenzene, amination products were obtained in poor yields beside reduction products as a consequence of steric and electronic effects (entry e).

We then focused our attention on the amination of 2,6- and 3,5-dichloropyridines (Table 1, entries f–m). Ni-catalysed diaminations were successfully extended to the synthesis of 2,6- and 3,5-diaminopyridines. Cyclic amines afforded the desired products in good yields while the sterically hindered di-*n*-propylamine coupled less easily than *N*-methyl-2,2-dimethoxy-1-ethanamine (compare entries i and j). Since aminopyridines have been used as ligand[8] in organometallic chemistry and are key structural elements in many biologically active compounds,[9] the method described herein could provide a good alternative for their preparation.

Threefold couplings were next studied starting from 1,3,5-trichlorobenzene. The targeted triamines **5** were isolated in good yields (Table 2).[10] Major by-product was the intermediate chlorodiaminobenzene **6** while reductive dehalogenation products could only be detected by GC–MS.

Table 2
2,2′-Bipyridine liganded Ni-catalysed amination of 1,3,5-trichlorobenzene with secondary amines[a]

Entry	Amine	Reaction Time (h)[b]	Isolated Yield of **5** (%)[c]	Isolated Yield of **6** (%)[c]
a	⟨ ⟩NH	2.5	71	14
b	HN⟨ ⟩NMe	3.0	60	7
c	HN⟨ ⟩NCOOEt	2.0	75	7

[a] Reactions were carried out with 25 mmol 1,3,5-trichlorobenzene, 100 mmol amine, 7.5 mmol Ni(OAc)₂, 22.5 mmol 2,2′-bipyridine, 15 mmol *t*-AmOH, 90 mmol NaH and 3.75 mmol styrene in 50 mL THF. [b] Determined by GC analysis. [c] Isolated yields after chromatography on silica gel. All compounds were estimated to be > 97% pure by NMR and GC analysis. All compounds were characterised by NMR (^{1}H, ^{13}C), IR, MS or combustion analysis.

Concerning the experimental procedure,[10] a slow addition of the starting aryl di- or trichloride (over a period of 30 min for 20 mmoles) is crucial to the success of the arylamination process in order to minimise the formation of **4**. It is also noteworthy that aryl polychlorides possess a considerably enhanced activity compared to arylchlorides.[7] Indeed, aryl dichlorides and trichlorides were immediately consumed (<5 min) leading to mixtures of products **1** and **2** (**5** and **6**, respectively). Reactions involving an electron poor aryl group were clearly faster than reactions involving an electron rich aryl group. All the reactions starting from *meta* substituted dichlorides were completed in less than 3 h.

This enhanced reactivity prompted us to perform control experiments in order to demonstrate that the reaction process is actually Ni-catalysed. Non-catalysed reactions between aryl dichloride (20 mmol) and morpholine (80 mmol) were conducted in the presence of NaH (50 mmol) and *t*-AmONa (8 mmol) in refluxing THF for 24 h. Dichlorobenzenes and 3,5-dichloropyridine afforded less than 10% of **1** by an aryne type mechanism. On the other hand, in the absence of Ni catalyst, 2,6-dichloropyridine yielded a mixture of compounds **1**, **2** and **3** in, respectively, 35, 45 and 18% yield by a S_NAr mechanism.

In summary, 2,2′-bipyridine liganded nickel catalysed amination of aryl di- and trichlorides under mild conditions. The efficiency of our protocol associated to the low cost of all reagents allowed the large scale synthesis of new di- and triaminobenzenes. We are currently exploring the different aspects of this methodology in order to extend its scope to the synthesis of aminated dendrimers potentially displaying redox properties.

Acknowledgements

References

1. (a) Louie, J.; Hartwig, J. F. *J. Am. Chem. Soc.* **1997**, *119*, 11695. (b) Goodson, F. E.; Hartwig, J. F. *Macromolecules* **1998**, *31*, 1700. (c) Spetseris, N.; Ward, R. E.; Meyer, T. Y. *Macromolecules* **1998**, *31*, 3158. (d) Louie, J.; Hartwig, J. F. *Macromolecules* **1998**, *31*, 6737. (e) Kanbara, T.; Oshima, M.; Imayasu, T.; Hasegawa, K. *Macromolecules* **1998**, *31*, 8725. (f) Goodson, F. E.; Hauck, S. I.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 7527. (g) Ito, A.; Ono, Y.; Tanaka, K. *J. Org. Chem.* **1999**, *64*, 8236.

2. (a) Tsuji, K.; Sasaki, S.; Yoshifuji, M. *Tetrahedron Lett.* **1999**, *40*, 3203. (b) Goodbrand, H. B.; Hu, N.-X. *J. Org. Chem.* **1999**, *64*, 670.

3. (a) Goodson, F. E.; Hauck, S. I.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 7527 and references cited therein. (b) Yamamoto, T.; Nishiyama, M.; Koie, Y. *Tetrahedron Lett.* **1998**, *39*, 2367. (c) Kanbara, T.; Izumi, K.; Nakadani, Y.; Narise, T.; Hasegawa, K. *Chem. Lett.* **1997**, 1185. (d) Kanbara, T.; Honma, A.; Hasegawa, K. *Chem. Lett.* **1996**, 1135. For palladium catalysed diaminations, see also: (e) Rossen, K.; Pye, P. J.; Maliakal, A.; Volante, R. P. *J. Org. Chem.* **1997**, *62*, 6462. (f) Wagaw, S.; Buchwald, S. L. *J. Org. Chem.* **1996**, *61*, 7240.

4. Witulski, B.; Senft, S.; Thum, A. *Synlett* **1998**, 504.

5. Beletskaya, I. P.; Bessmertnykh, A. G.; Guilard, R. *Tetrahedron Lett.* **1999**, *40*, 6393.

6. (a) Hartwig, J. F. *Angew. Chem.*, *Int. Ed.* **1998**, *37*, 2046 and references cited therein. (b) Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805 and references cited therein. (c) Hartwig, J. F. *Acc. Chem. Res.* **1998**, *31*, 852 and references cited therein. (d) Yang, B. H.; Buchwald, S. L. *J. Organomet. Chem.* **1999**, *576*, 125 and references cited therein. (e) Belfield, A. J.; Brown, G. R.; Foubister, A. J. *Tetrahedron* **1999**, *55*, 11399 and references cited therein. (f) Hartwig, J. F.; Kawatsura, M.; Hauck, S. I.; Shaughnessy, K. H.; Alcazar-Roman, L. M. *J. Org. Chem.* **1999**, *64*, 5575. (g) Harris, M. C.; Geis, O.; Buchwald, S. L. *J. Org. Chem.* **1999**, *64*, 6019.

7. (a) Brenner, E.; Schneider, R.; Fort, Y. *Tetrahedron* **1999**, *55*, 12829. (b) Brenner, E.; Fort, Y. *Tetrahedron Lett.* **1998**, *39*, 5359.

8. (a) Kempe, R.; Arndt, P. *Inorg. Chem.* **1996**, *35*, 2644. (b) Nagao, N.; Mukaida, M.; Tachiyashiki, S.; Mizumachi, K. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 1802.

9. Lechat, P.; Tesleff, S.; Bowman, W. C. *Aminopyridines and Similarly Acting Drugs*; Pergamon Press: Oxford, NY, 1982.

10. Representative procedure: Ethyl 4-{3,5-di[4-(ethoxycarbonyl)piperazino]phenyl}-1-piperazine carboxylate (**5c**): A solution of *t*-AmOH (15 mmol) in THF (5 mL) was added to a suspension of NaH (90 mmol) in THF (30 mL) and the mixture was heated to 63°C. Ethyl 1-piperazine carboxylate (100 mmol) was added followed by dried Ni(OAc)$_2$ (7.5 mmol) and 2,2′-bipyridine and the reflux was maintained for 2 h. To the dark suspension of 2,2′-liganded Ni(0) thus obtained was added 1,3,5-trichlorobenzene (25 mmol) and styrene (3.75 mmol) in THF (5 mL) and the mixture was heated for 6 h. After cooling to room temperature, hydrolysis with water (1 mL) and dilution with CH$_2$Cl$_2$, the mixture was filtered, dried over MgSO$_4$ and concentrated. The crude material was purified by chromatography on silica gel. ^{1}H NMR (CDCl$_3$, 400 MHz): 6.09 (s, 3H); 4.16 (q, J=6.8 Hz, 6H); 3.65–3.57 (m, 12H); 3.15–3.09 (m, 12H); 1.27 (t, J=6.8 Hz, 9H). ^{13}C NMR (CDCl$_3$, 100 MHz): 155.34, 155.07, 99.19, 61.36, 49.81, 43.59, 14.58. IR (ν, cm^{-1}): 1696 (C=O). Anal. calcd for C$_{27}$H$_{42}$N$_6$O$_6$: C, 59.32; H, 7.74; N, 15.37; O, 17.56. Found: C, 59.32; H, 7.76; N, 15.18.