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Nickel-catalysed synthesis of 3-chloroanilines and chloro aminopyridines via cross-coupling reactions of aryl and heteroaryl dichlorides with amines

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Abstract—Selective monoamination of aryl and heteroaryl dichlorides has been carried out using a catalyst combination of Ni(0) associated to 2,2′-bipyridine. The synthesis of novel 3-chloroanilines and chloro aminopyridines in good to excellent yields is allowed using an excess of amine, 10 or 20 mol% catalyst and short reaction times.

Oligoanilines have interesting electronic and magnetic properties.[1] They generate some of the most stable radical cations and are readily oxidised to the aminium state. Several methods for the construction of these arylamines are known, e.g. the high temperature copper-mediated Ullmann coupling of aryl iodides with amines[2] or the palladium-catalysed multiple coupling of amines with polybromobenzenes.[3] However, to our knowledge, both approaches have not been applied to the synthesis of unsymmetrical systems. Recently, we have described the preparation of di- and triaminobenzenes from aryl and heteroaryl di- and trichlorides by a catalyst combination of in situ generated colloidal Ni(0) and 2,2′-bipyridine.[4,5] In our search dealing with the construction of regiodefined oligoanilines from unsymmetrical 1,3-diaminobenzenes, we needed a convenient access to 3-halogenoaminobenzenes. Although palladium-catalysed carbon–nitrogen bond-forming reactions are valuable synthetic methods and have found wide applications in organic synthesis,[6] the preparation of 3-halogenoaminobenzenes has received little attention and was restricted to a few examples affording the desired products in modest yields. For instance, 3-bromophenylsulfoximine has been isolated in 51% yield by Bolm. However, this result is restricted to the Pd-catalysed arylation of sulfoximines.[7] We wish to describe now a novel synthesis of 3-chloroanilines and chloro aminopyridines from (het)aryl-1,3-dichlorides via a nickel-catalysed amination reaction.

In our precedent report dealing with polyaminations of aryl di- and trichlorides,[4] the intermediate chloroanilines could be isolated as side-products, even after extended reaction time at 65°C in THF. Interestingly, the presence of these intermediates was not observed under palladium catalysis. Indeed, Witulsky and Watanabe reported that during amination of aryl dibromides, only monoaminated products could be isolated as by-products.[8,9] Moreover, the work of Beletskaya and Guilard indicated that, using the $Pd(dba)_2/P(o\text{-tolyl})_3$ catalyst, the bromoamino intermediate was more reactive towards amines than the starting dibromobenzene since it did not accumulate.[10] Then we thought that a convenient method for the selective monoamination of aryl dichlorides could be developed and we first compared the reactivity of aryl dichlorides **1** and 3-chloroaminoarenes **2** towards *N*-methylpiperazine in the presence of the Ni(0)/2,2′-bipyridine catalyst under standard reaction conditions[4] (Scheme 1).

Under nickel catalysis, we evidenced a great difference of reactivity between starting materials. Indeed, a GC monitoring of the reaction indicated that **1** was much more rapidly consumed than **2**. Compounds **1a** and **1b**

Keywords: catalysis; nickel; amination; chloroanilines; chloro aminopyridines.

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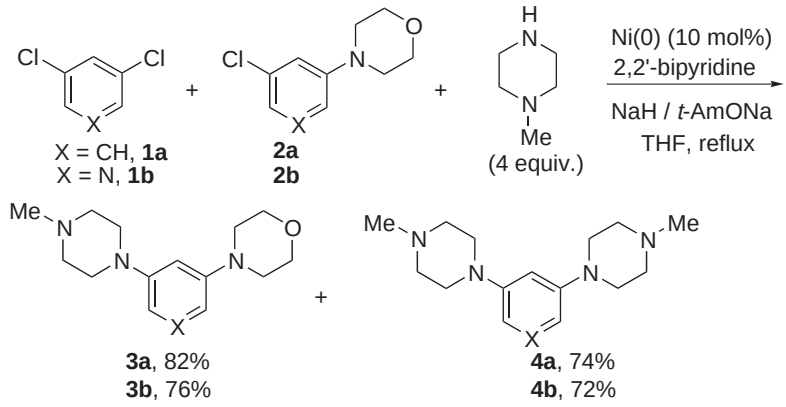
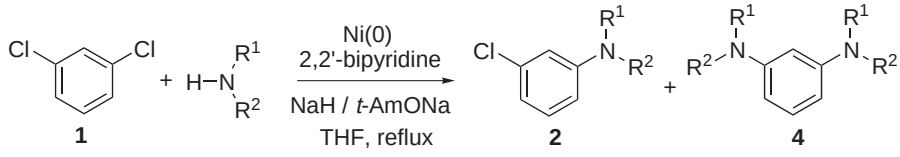


Scheme 1.

were completely converted after, respectively, 15 and 20 min. It also appeared that both reactions are competitive since conversions of **2a** and **2b** were, respectively, 57 and 53% after 30 min. Finally, chloroaminoarenes were totally converted into diaminobenzenes **3** and **4** after 1.75 h reaction time.

These results encouraged us to study the selective introduction of one amine group on aryl dichlorides. The success of this methodology was, however, hinged upon proper selection of reaction conditions. In a preliminary study, monoaminations were first examined using 1,3-dichlorobenzene **1a** and piperidine (Table 1). When classical reaction conditions of polyaminations were applied (2 equiv. of amine per C-Cl unit and 10 mol% of Ni(0)/2,2′-bipyridine catalyst in THF at 65°C),[4] the desired 1-(3-chlorophenyl)piperidine **2c** was obtained in 44% yield after 30 min and the selectivity **2c**/**4c** was poor (entry 1). Increasing the amount of catalyst to 20 mol% did not afford a better result (entry 2), while decreasing the amount of sodium hydride in the reaction medium gave **2c** in lower yields and larger amounts of dehalogenated starting material. The reaction rate tended to slow greatly near the reaction completion and lowering the reaction temperature resulted in incomplete conversion. Finally, the rate and the yield were improved by increasing the amount of piperidine (3 equiv.), adding a slight excess of sodium hydride (2 mmol) and decreasing the reaction time to 15 min (entry 3). Next, the efficiency of this protocol depends on the nature of the starting amine. Using the conditions determined with piperidine, 1-(3-chlorophenyl)-morpholine **2a** was obtained in only 41% yield (entry 6). The use of 20 mol% Ni afforded product **2a** in 85% yield (entry 7). We also studied the influence of the catalyst amount during selective monoamination of 1,3-dichlorobenzene varying the nature of the amine (Table 2). The use of 10 mol% Ni was effective for the synthesis of 3-chloroanilines from cyclic amines like pyrrolidine, piperidine and *N*-methylpiperazine (entries 1, 3 and 4), while reactions using morpholine and secondary acyclic amines (entries 2, 5 and 6) required 20 mol% Ni to achieve completion. In all cases, the starting material was completely consumed and the

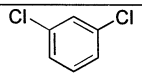
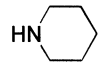
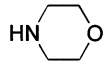
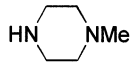
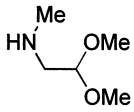
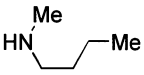
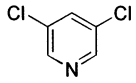
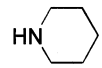
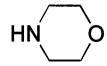
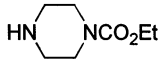
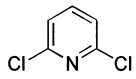
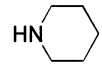
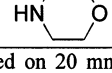
Table 1. Optimisation of amine equivalents, catalyst loading and reaction time in nickel-catalysed monoamination of 1,3-dichlorobenzene[a]



Entry	Amine	Amine (equiv.)	Ni (mol%)	Reaction time (min.)[b]	Selectivity **2**/**4** (%)[b]	Product	Yield (%)[c]
1	Piperidine	2	10	30	50/50	**2c**	44
2	–	2	20	30	58/42	–	51
3	–	3	10	15	75/25	–	68
4	–	3	20	10	67/23	–	60
5	–	4	10	10	73/27	–	66
6	Morpholine	3	10	60	50/50	**2a**	41
7	–	3	20	15	90/10	–	85

[a] Reactions were performed on 20 mmol of 1,3-dichlorobenzene; see Ref. 11 for further details.
[b] Determined by GC analysis.
[c] Isolated yields are average of at least two runs.

Table 2. Selective monoamination of aryl dichlorides[a]

Entry	Aryl Dichloride	Amine	Ni (mol%)	Reaction Time (h)[b]	Selectivity **2** / **4** [b]	Product	Yield of **2** (%)[c]
1			10	0.25	75/25	**2c**	68
2			20	0.25	90/10	**2a**	85
3			10	0.25	80/20	**2d**	60
4			10	0.5	73/27	**2e**	66
5			20	1.5	68/32	**2f**	67
6			20	1.5	75/25	**2g**	43
7			10	0.25	85/15	**2h**	69
8			20	0.5	85/15	**2b**	68
9			10	0.5	75/25	**2i**	57
10			10	0.25	75/25	**2j**	70
11			20	0.5	68/32	**2k**	58

[a] Reactions were performed on 20 mmol aryl dichloride; see [11] for further details. [b] Determined by GC analysis. [c] Isolated yields are average of at least two runs. All new compounds were characterised by ^{1}H/ ^{13}C NMR spectroscopy and elemental analysis or HRMS.

desired 3-chloroanilines **2** were readily isolated in good yields.[11] The main side products observed were the monoaminoarenes arising from partial reduction, although in some cases traces of 3,3′-diaminobiphenyls were produced by homocoupling of the intermediate chloroaminoarene.

As can be seen from Table 2, this methodology was successfully extended to 3,5- and 2,6-dichloropyridines and enabled us to prepare an array of products with various nitrogen substituents on the aromatic ring (entries 7–11). At the present time, we assume that the reaction proceeds at first by coordination of the amine towards Ni(0). The subsequent oxidative addition of the aryl halide was probably followed by C–N bond formation by reductive elimination. However, the dependence of nickel loading on the nature of the amine suggests that reaction of the catalyst with amine is the rate limiting step of the process or that catalyst lifetime depends strongly on the used amine.

In summary, we have demonstrated that chloro amino-(het)arenes are efficiently prepared by a selective monoamination of aryl dichlorides using a Ni(0)/2,2′-bipyridine catalyst system. The ready accessibility of our catalyst associated with its low cost allows the synthesis of these materials to be efficiently carried out on a multigram scale. This catalytic process displays broad scope and efforts to design new aminoanilines with potent ferromagnetic or conductive properties are currently underway in our laboratories.

References

1. (a) Inada, H.; Yonemoto, Y.; Wakimoto, T.; Imai, K.; Shirota, Y. Mol. *Cryst. Liq. Cryst.* **1996**, *280*, 331. (b) Liu, S.; Jiang, X.; Ma, H.; Liu, M.-S.; Jen, A. K.-Y. *Macromolecules* **2000**, *33*, 3514. (c) Yu, W.-L.; Pei, J.; Huang, W.; Heeger, A. J. *Chem. Commun.* **2000**, 681.
2. (a) Ito, A.; Ota, K.; Tanaka, K.; Yamabe, T.; Yoshizawa, K. *Macromolecules* **1995**, *28*, 5618. (b) Goodbrand, H. B.; Hu, N.-X. *J. Org. Chem.* **1999**, *64*, 670.
3. (a) Kanbara, T.; Honma, A.; Hasegawa, K. *Chem. Lett.* **1996**, 1135. (b) Louie, J.; Hartwig, J. P. *J. Am. Chem. Soc.* **1997**, *119*, 11695. (c) Kanbara, T.; Izumi, K.; Nakadami, Y.; Narise, T.; Hasegawa, K. *Chem. Lett.* **1997**, 1185. (d) Louie, J.; Hartwig, J. F. *Macromolecules* **1998**, *31*, 6737. (e) Kanbara, T.; Imayasu, T.; Hasegawa, K. *Chem. Lett.* **1998**, 709. (f) Yamamoto, T.; Nishiyama, M.; Koie, Y. *Tetrahedron Lett.* **1998**, *39*, 2367. (g) Singer, R. A.; Sadighi, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 213. (h) Goodson, F. E.; Hartwig, J. F. *Macromolecules* **1998**, *31*, 1700. (i) Spetseris, N.; Ward,

R. E.; Meyer, T. Y. *Macromolecules* **1998**, *31*, 3158. (j) Kanbara, T.; Oshima, M.; Imayasu, T.; Hasegawa, K. *Macromolecules* **1998**, *31*, 8725. (k) Ito, A.; Taniguchi, A.; Yamabe, T.; Tanaka, K. *Org. Lett*. **1999**, **1**, 741. (l) Goodson, F. E.; Hauck, S. I.; Hartwig, J. F. *J. Am. Chem. Soc*. **1999**, *121*, 7527. (m) Ito, A. Ono, Y.; Tanaka, K. *J. Org. Chem*. **1999**, *64*, 8236. (n) Selby, T. D.; Blockdock, S. C. *Org. Lett*. **1999**, *1*, 2053. (o) Hauck, S. I.; Lakshmi, K. V.; Hartwig, J. F. *Org. Lett*. **1999**, *1*, 2057. (p) Ito, A.; Ono, Y.; Tanaka, K. *Angew. Chem. Int. Ed*. **2000**, *39*, 1072.

4. Desmarets, C.; Schneider, R.; Fort, Y. *Tetrahedron Lett*. **2000**, *41*, 2875.
5. (a) Brenner, E.; Fort, Y. *Tetrahedron Lett*. **1998**, *39*, 5359. (b) Brenner, E.; Schneider, R.; Fort, Y. *Tetrahedron* **1999**, *55*, 12829. (c) Brenner, E.; Schneider, R.; Fort, Y. *Tetrahedron Lett*. **2000**, *41*, 2881.
6. (a) Hartwig, J. F. *Synlett* **1997**, 329. (b) Hartwig, J. F. *Acc. Chem. Res*. **1998**, *31*, 852. (c) Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res*. **1998**, *31*, 805. (d) Yang, B. H.; Buchwald, S. L. *J. Organomet. Chem*. **1999**, *546*, 125. (e) Belfield, A. J.; Brown, G. R.; Foubister, A. J. *Tetrahedron* **1999**, *55*, 11399.
7. Bolm, C.; Hildebrand, J. P. *J. Org. Chem*. **2000**, *65*, 169.
8. (a) Witulsky, B.; Senft, S.; Thum, A. *Synlett* **1998**, 504. (b) Witulsky, B. *Synlett* **1999**, 1223.
9. Watanabe, M.; Yamamoto, T.; Nishiyama, M. *Chem. Commun*. **2000**, 133.
10. Beletskaya, I. P.; Bessmertnykh, A. G.; Guilard, R. *Tetrahedron Lett*. **1999**, *40*, 6393.
11. **Typical procedure**. 1-(3-Chlorophenyl)piperidine **2c** (Table 2, entry 1). To a suspension of degreased NaH (26 mmol) in THF (20 mL) were added piperidine (60 mmol) and *t*-AmOH (4 mmol) in THF (10 mL) followed by 2,2′-bipyridine (6 mmol) and the mixture was heated at 65°C. Dried $Ni(OAc)_2$ (2 mmol) was then added and the mixture was further stirred at 65°C for 2 h. A solution of 1,3-dichlorobenzene (20 mmol) and styrene (1 mmol) in THF (10 mL) was then added. The reaction was monitored by GC and after complete consumption of the aryl dichloride, the mixture was cooled to room temperature. Water (1 mL) and dichloromethane (50 mL) were added sequentially and the reaction mixture was filtered, dried over magnesium sulfate and concentrated in vacuo. The crude material was purified by flash chromatography on silica gel using 2% ethyl acetate/hexane as eluant to afford **2c** (68%) as a pale yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): 7.10 (dd, $^3J = {}^3J' = 8.0$ Hz, 2H); 6.85 (dd, $^4J = {}^4J' = 2.0$ Hz, 1H); 6.76–6.72 (m, 1H); 3.15–3.10 (m, 4H); 1.68–1.64 (m, 4H); 1.55–1.53 (m, 2H). ^{13}C NMR ($CDCl_3$, 400 MHz): 153.0; 134.7; 129.8; 118.4; 115.8; 114.13; 49.96; 25.72; 24.20. Anal. calcd for $C_{11}H_{14}NCl$: C, 67.51; H, 7.21; N, 7.16; Cl, 18.12. Found: C, 67.47; H, 7.33; N, 7.02. MS: m/z 194 (M^+), 154, 140, 112, 77.