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Nickel-catalysed sequential amination of aryl- and heteroaryl di- and trichlorides

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Abstract—Unsymmetrical 1,3-diaminobenzenes and diaminopyridines were efficiently prepared by reaction of 3-chloroanilines and chloroaminopyridines with amines via a nickel-catalysed amination. The Ni/2,2′-bipyridine catalyst is also effective for the sequential amination of aryl trichlorides. After a first selective monoamination of 1,3,5-trichlorobenzene, the obtained 3,5-dichloroanilines were subsequently transformed into novel and unsymmetrical 1,3,5-triaminobenzenes. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

Arylamines are common structural elements found in many biologically active substrates[1] as well as in materials possessing electronic and magnetic properties.[2] They are also used as key building blocks in the synthesis of heterocyclic compounds,[3] pharmaceuticals or pesticides[4] and in asymmetric catalysis.[5] For these reasons, there is still a search for methods allowing an efficient preparation of the less accessible derivatives and for the synthesis of novel arylamines.

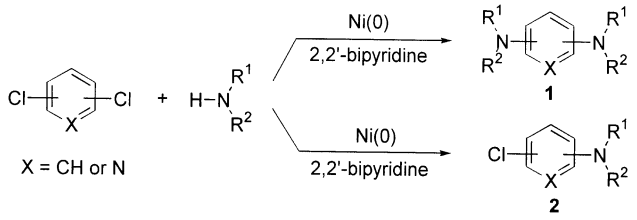
Recently developed palladium- or copper-catalysed aminations of aryl halides and arylboronic acids have emerged as powerful synthetic methods for the preparation of substituted arylamines.[6–8] Although polyamination products have been obtained in good yields by reacting aryl polybromides with amines under palladium catalysis,[9] sequential amination of aryl dihalides has received little attention and was limited to *ortho* derivatives. In 1996, Buchwald et al. reported first the use of the $Pd_2(dba)_3$-BINAP catalyst to couple 2-bromo-*N*,*N*-dimethylaniline with aniline.[10] Diver et al. described also the stepwise synthesis of unsymmetrical substituted 1,2-diaminobenzenes from *ortho* dibromobenzene using the same catalyst or $Pd_2(dba)_3$ associated to an electron-rich mixed P,N ligand.[11] Another approach to diaminobenzenes which invoke a nucleophilic substitution followed by a palladium-catalysed amination reaction has also been reported very recently by Brown et al.[12] In our effort toward the construction of new aminoanilines with potent ferromagnetic or conductive properties, we hoped to develop a general protocol for the efficient synthesis of 1,3-di- and 1,3,5-triaminobenzenes via nickel-catalysed amination chemistry.

Indeed, as part of our continuing studies on arylamination reactions,[13] we recently developed the synthesis of symmetrical di- and triaminobenzenes **1** from aryl and heteroaryl di- and trichlorides using a colloidal Ni(0), in situ generated by reduction of $Ni(OAc)_2$ with *t*-AmONa activated sodium hydride, associated to 2,2′-bipyridine as the ligand.[14] More recently, we established a novel method for the catalytic monoamination of aryl 1,3-dichlorides using a slightly modified nickel catalyst (Scheme 1).[15]

Herein, we report on the extension of this monoamination method first, to nickel-catalysed synthesis of novel unsymmetrical 1,3-diaminobenzenes and diaminopyridines and second, to sequential amination of 1,3,5-trichlorobenzene.

2. Results and discussion

The nickel-catalysed cross-coupling reactions of chloroaminoarenes **2**[15] with secondary amines were first examined (Scheme 2).



Scheme 1.

Keywords: nickel-catalysed amination; aryl trichlorides; diaminobenzenes; diamino-pyridines; triamino-pyridines.

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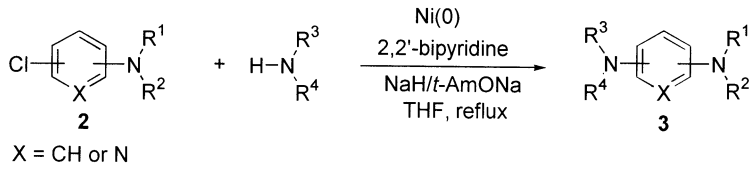
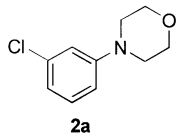
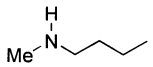
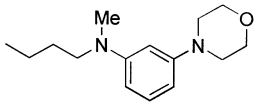
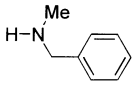
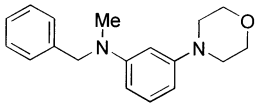
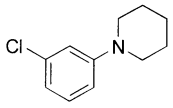
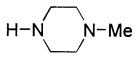
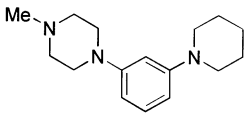
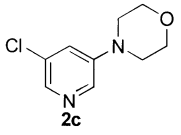
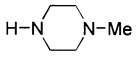
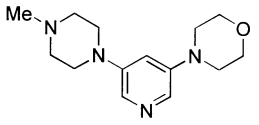
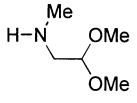
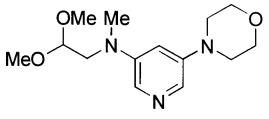
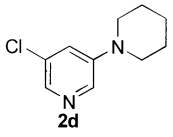
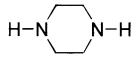
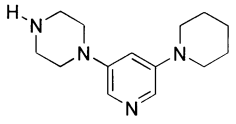
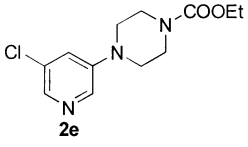
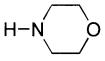
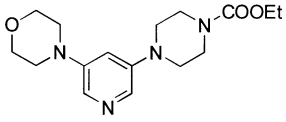
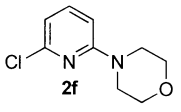
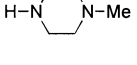
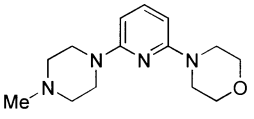
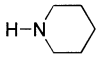
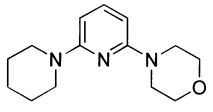


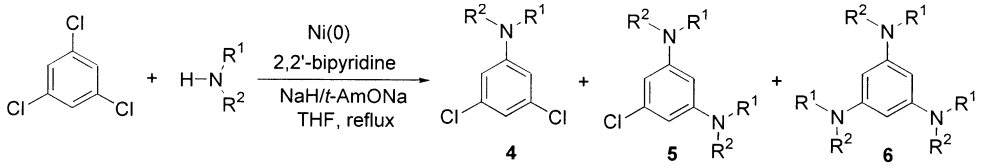
Scheme 2.

As shown in Table 1, a variety of amines are suitable coupling partners and compounds **3** could be prepared in good to excellent yields using the Ni/2,2′-bipyridine catalyst. For example, 1-(3-chlorophenyl)piperidine **2b** could be converted to product **3c** in 75% yield using 10 mol% Ni (entry c). The reaction of acyclic amines with compounds **2** was slow using 10 mol% catalyst (entries a, b and e). The desired products were obtained in good yields when 20 mol% of the

Table 1. Nickel-catalysed synthesis of unsymmetrical 1,3-diaminobenzenes and diaminopyridines

Entry	Starting material **2**	Amine	Reaction time (h)[a]	Product **3**	Isolated yield (%)[b]
a	 **2a**		3.0		52
b	**2a**		0.75		68
c	 **2b**		0.5		75
d	 **2c**		1.0		74
e	**2c**		1.0		69
f	 **2d**		4.0		68
g	 **2e**		1.0		86
h	 **2f**		0.5		79
i	**2f**		0.5		69

Catalyst loadings of 10 and 20 mol% Ni were used respectively with cyclic and acyclic amines. All reactions were performed using 20 mmol starting material.
[a] Determined by GC analysis.
[b] Isolated yield after silica gel chromatography.

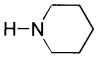
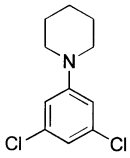
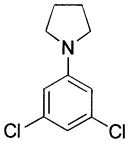
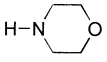
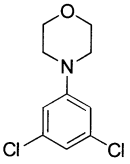
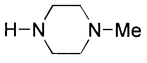
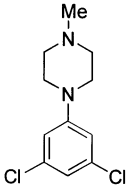
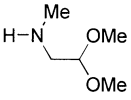
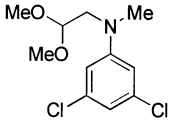


Scheme 3.

nickel catalyst was employed. In all cases, the starting material **2** was completely consumed and the main side-product observed was an aminoarene arising from reduction. In addition, we have also noted that variations of the molar ratio of amine/**2** exerted a notable effect on the outcome of the transformation. For example, the highest yield of **3a** (52%, entry a) was obtained in an experiment with a 2:1 ratio and 3 hours reaction time. Using only 1.1 equiv. methylbutylamine, a large proportion of 3,3′-bis(morpholino)biphenyl (27%), arising from homocoupling of 1-(3-chlorophenyl)morpholine **2a** with our 2,2′-bipyridine liganded Ni(0) catalyst, was formed after 4 h. All aminations were therefore performed using an excess amine (2 equiv.) to minimise the formation of such biaryls. As can be seen from Table 1, this methodology was successfully extended to 5-(or 6) chloro-3-(or 2) aminopyridines and enabled us to prepare an array of products with various nitrogen substituents on the aromatic ring (entries d–i).The substrate scope of our Ni reagent was also expanded to arylpiperazine, an important class of pharmaceutical compounds. Coupling of 3-chloro-5-piperidinopyridine **2d** with piperazine yielded 68% of the desired compound **3f** and the formation of undesired double coupling products was not observed.

The scope of our method was further expanded to the selective monoamination of 1,3,5-trichlorobenzene. However a

Table 2. Nickel-catalysed synthesis of 3,5-dichloroanilines **4** from 1,3,5-trichlorobenzene

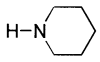
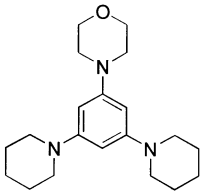
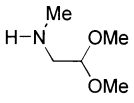
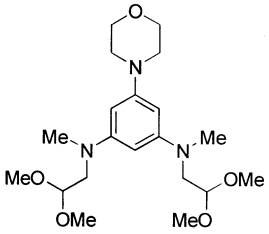
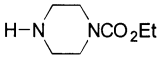
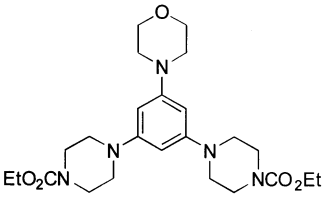
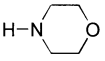
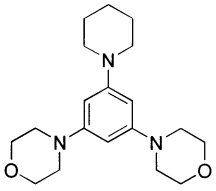
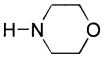
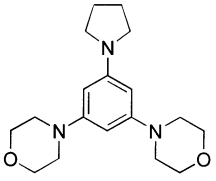
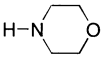
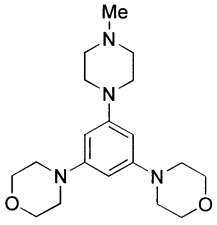
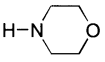
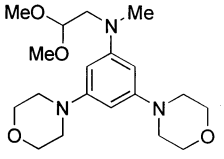
Entry	Amine	Ni (mol%)	Reaction time (h)[a]	Product **4**	Isolated yield (%)[b]
a		10	0.5		49
b		10	0.25		50
c		20	0.5		52
d		10	0.5		46
e		20	3		51

Reactions were performed on 20 mmol 1,3,5-trichlorobenzene.

[a] Determined by GC analysis.

[b] Yields refer to isolated yields (average of two runs) of compounds estimated to be >95% pure as determined by ^{1}H, ^{13}C NMR, GC and HRMS analysis.

Table 3. Amination of 3,5-dichloroanilines **4**

Entry	Starting material	Amine	Ni (mol%)	Reaction time (h)[a]	Product **7**	Yield (%)[b]
a	**4c**		10	2		73
b	**4c**		20	3		75
c	**4c**		10	2		55
d	**4a**		10	2		60
e	**4b**		10	1.5		76
f	**4d**		10	1.5		71
g	**4e**		10	2		76

Reactions were performed using 20 mmol **4** and 60 mmol amine in THF at 65°C.

[a] Determined by GC analysis.

[b] Yields refer to isolated yields (average of two runs) of compounds estimated to be >95% pure as determined by ^{1}H, ^{13}C NMR, GC and HRMS analysis.

further problem in the synthesis of 3,5-dichloroaminobenzenes **4** was the formation of di- and triaminated products **5** and **6** (Scheme 3).

As an exploratory study, we examined the monoamination of 1,3,5-trichlorobenzene using piperidine as a model amine under the conditions defined for aryl dichlorides,[15] namely using 3 equiv. of amine and 10 mol% Ni during a short reaction time. The reaction was monitored by GC and stopped promptly when the starting material was consumed. Under these conditions, we found that, besides the desired 1-(3,5-dichlorophenyl)piperidine **4a** (49%), substantial amounts of diaminated **5** (6%) and triaminated **6** (21%) by-products were also isolated. Because of the strong electron-withdrawing properties of the *m*-amino group introduced, π-deficient compounds **4** and especially **5** underwent easily a new and competitive Ni-catalysed amination reaction. Unfortunately, no significant improvement of the yield of **4a** was observed by decreasing the amount of sodium hydride or amine in the catalyst. Lowering the reaction temperature or using 5 mol% Ni resulted in a decrease of the reaction rate and hydrodehalogenation products were also observed.

Results of the nickel-catalysed monoaminations of 1,3,5-trichlorobenzene are summarised in Table 2. As previously observed with our Ni catalyst,[15] the structure of the amine was found to have a profound effect on the reaction time and yield. The use of 10 mol% Ni was effective for the synthesis of 3,5-dichloroanilines **4** from cyclic amines like piperidine, pyrrolidine, and *N*-methylpiperazine (entries a, b and d). Aryl aminations involving the less reactive amines, morpholine and *N*-methylaminoacetaldehyde dimethyl acetal (entries c and e), required 20 mol% Ni for the first coupling. Finally, the 2,2′-bipyridine liganded Ni catalyst provided acceptable yields of the desired products **4** and cross-couplings of these 3,5-dichloro aminobenzenes with diverse selection of amines were studied. Table 3 provides the results of the double amination of substrates **4** using the optimised conditions for the second coupling, which consisted of 2 equiv. amine per carbon–chlorine function and 10 or 20 mol% of the Ni catalyst respectively for cyclic and acyclic amines. Under these conditions, our synthetic method allowed the preparation of a variety of novel and elaborated triaminobenzenes **7**, obtained in good yields ranging from 55 to 80%.

3. Conclusion

In summary, we have demonstrated that the catalytic system consisting of Ni(0) associated to 2,2′-bipyridine allowed the sequential coupling of aryl- and heteroaryl di- and trichlorides with amines. The synthesis of novel aryl and heteroaryl di- and triamines has thus been achieved in good yields by combination of two nickel-catalysed amination reactions.

4. Experimental

4.1. General comments

All experiments were carried out under a nitrogen atmosphere. THF was distilled from benzophenone-sodium adduct and stored over sodium wire. *tert*-Amyl alcohol was distilled from sodium. Crushed $Ni(OAc)_2$. $4H_2O$ (Fluka) was dried under vacuum (20 mm Hg) at 110°C for 12 h. Sodium hydride (65% in mineral oil, Fluka) was used after two washings with THF under nitrogen. 2,2′-Bipyridine was recrystallised in hexane before use. All reagents were purchased from commercial sources and were used without purification. Melting points were taken on a Tottoli apparatus and were uncorrected. GC analysis were conducted on a Shimadzu GC-8A instrument equipped with a flame-ionisation detector and using an Alltech EC5 column (30 m×0.32 mm×2.65 μm). Flash chromatography was performed using Kieselgel 60 (230–400 mesh, Merck). NMR spectra were recorded with Brucker AM 400 (^{1}H at 400 MHz, ^{13}C at 100 MHz) or AC 250 (^{1}H at 250 MHz, ^{13}C at 62.5 MHz). Chemical shifts are expressed in δ (ppm) values with tetramethylsilane (TMS) as internal reference. IR spectra were recorded on a Perkin–Elmer 841 spectrometer. Yields refer to isolated yields of compounds estimated to be up to 95% pure as determined by ^{1}H NMR and up to 98% pure as determined by capillary GC. HRMS and combustion analysis were performed by the Service central d'analyses du CNRS (Vernaison, France).

4.2. Nickel-catalysed synthesis of diaminobenzenes and diaminopyridines 3

4.2.1. *N*-Butyl-*N*-methyl-3-morpholinoaniline 3a (Table 1). Typical procedure for aminations using 20 mol% Ni catalyst. To a suspension of degreased NaH (30 mmol) in THF (20 mL) were added methylbutylamine (40 mmol) and *t*-AmOH (8 mmol) in THF (10 mL) followed by 2,2′-bipyridine (8 mmol) and the mixture was heated at 65°C. Dried $Ni(OAc)_2$ (4 mmol) was then added and the mixture was further stirred at 65°C for 2 h. A solution of 1-(3-chlorophenyl)morpholine **2a** (20 mmol) and styrene (2 mmol) in THF (10 mL) was then added dropwise. The reaction was monitored by GC and after complete consumption of the starting material (3 hours), 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 $MgSO_4$ and evaporated. The residue was purified by silica gel column chromatography using *n*-hexane–AcOEt (70:30) as eluant to give **3a** as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.81–7.77 (m, 1H), 7.30–7.25 (m, 2H), 6.91–6.85 (m, 1H), 3.86–3.82 (m, 4H), 3.28–3.23 (m, 2H), 3.13 (t, J=5.20 Hz, 4H), 2.90 (s, 3H), 1.53–1.51 (m, 2H), 1.34–1.32 (m, 2H), 0.93 (t, J=7.60 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 156.02, 149.07, 136.80, 120.96, 115.58, 66.82, 52.54, 49.32, 38.54, 28.89, 20.27, 13.94. HREIMS Obsd. m/z=248.187 (M), $C_{15}H_{24}N_2O$ requires 248.1888.

4.2.2. *N*-Benzyl-*N*-methyl-3-morpholinoaniline 3b (Table 1). According to the typical procedure, **3b** was obtained as a pale yellow oil from the reaction of 1-(3-chlorophenyl)morpholine **2a** with methylbenzylamine using 20 mol% Ni. Purification was performed by silica gel column chromatography using *n*-hexane–AcOEt (70:30) as eluent. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.31–7.28 (m, 2H), 7.27–7.22 (m, 3H), 7.11 (dd, J=J'=8.40 Hz, 1H), 6.34–6.29 (m, 3H), 4.50 (s, 2H), 3.83–3.78 (m, 4H), 3.13–3.09 (m, 4H), 2.99 (s,

3H). ^{13}C NMR (100 MHz, $CDCl_3$): 152.48, 150.79, 139.10, 129.67, 128.48, 126.77, 105.16, 104.73, 100.38, 66.96, 56.75, 49.65, 38.54. HREIMS Obsd. m/z=282.1728 (M), $C_{18}H_{22}N_2O$ requires 282.1732.

4.2.3. 1-Methyl-4-(3-piperidinophenyl)piperazine 3c (Table 1). Typical procedure for aminations using 10 mol% Ni catalyst. *N*-methylpiperazine (40 mmol), *t*-AmOH (4 mmol), NaH (26 mmol), $Ni(OAc)_2$ (2 mmol), 2,2′-bipyridine (6 mmol) and styrene (2 mmol) were used for the amination of 1-(3-chlorophenyl)piperidine **2b** using the standard procedure described above. **3c** was obtained as a pale yellow oil after purification by silica gel column chromatography using AcOEt as eluent. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.14 (brs, 1H), 6.52 (d, J=4.00 Hz, 1H), 6.48–6.46 (m, 1H), 6.43 (d, J=4.00 Hz, 1H), 3.22–3.18 (m, 4H), 3.16–3.11 (m, 4H), 2.60–2.55 (m, 4H), 2.36 (s, 3H), 1.72–1.68 (m, 4H), 1.59–1.57 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 153.39, 152.22, 129.40, 108.92, 107.88, 105.28, 55.14, 51.00, 49.10, 46.02, 25.94, 24.35. HREIMS Obsd. m/z=259.2041 (M), $C_{16}H_{25}N_3$ requires 259.2048.

4.2.4. 4-[5-(4-Methylpiperazino)-3-pyridinyl]morpholine 3d (Table 1). According to the typical procedure, **3d** was obtained as a pale yellow oil from the reaction of 4-(5-chloro-3-pyridyl)morpholine **2c** with *N*-methylpiperazine using 10 mol% Ni. Purification was performed by silica gel column chromatography using AcOEt as eluent. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.86 (d, J=2.80 Hz, 1H), 7.80 (d, J'=2.80 Hz, 1H), 6.67 (dd, J=J'=2.80 Hz, 1H), 3.84 (t, J=6.80 Hz, 4H), 3.22 (t, J=6.40 Hz, 4H), 3.16 (t, J=6.40 Hz, 4H), 2.57 (t, J=6.40 Hz, 4H), 2.34 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 147.03, 129.97, 129.20, 108.96, 66.31, 54.47, 48.54, 48.15, 45.71. HREIMS obsd. m/z=262.179 (M), $C_{14}H_{22}N_4O$ requires 262.1793.

4.2.5. *N*-(2,2-Dimethoxyethyl)-*N*-methyl-5-morpholino-3-pyridinamine 3e (Table 1). According to the typical procedure, **3e** was obtained as a pale yellow oil from the reaction of 4-(5-chloro-3-pyridyl)morpholine **2c** with *N*-methylaminoacetaldehyde dimethyl acetal using 20 mol% Ni. Purification was performed by silica gel column chromatography using *n*-hexane–AcOEt (30/70) as eluent. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.73 (d, J=2.40 Hz, 1H), 7.71 (d, J'=2.70 Hz, 1H), 6.50 (dd, J=2.40 Hz, J'=2.70 Hz, 1H), 4.50 (t, J=5.20 Hz, 1H), 3.88–3.82 (m, 4H), 3.45–3.40 (m, 2H), 3.40 (s, 6H), 3.18–3.13 (m, 4H), 3.00 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 147.16, 145.26, 126.74, 126.62, 104.99, 102.96, 66.41, 54.74, 54.43, 48.68, 38.72. HREIMS Obsd. m/z=281.173 (M), $C_{14}H_{23}N_3O_3$ requires 281.1739.

4.2.6. 1-(5-Piperidino-3-pyridinyl)piperazine 3f (Table 1). According to the typical procedure, **3f** was obtained as a pale yellow oil from the reaction of 3-chloro-5-piperidinopyridine **2d** with piperazine using 10 mol% Ni. Purification was performed by silica gel column chromatography using AcOEt–MeOH (70/30) as eluent. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.84 (d, J=2.00 Hz, 1H), 7.79 (d, J'=2.40 Hz, 1H), 6.71 (dd, J=2.00 Hz, J'=2.40 Hz, 1H), 3.48 (s, 1H), 3.18–3.16 (m, 4H), 3.05–3.04 (m, 4H), 1.80–1.79 (m, 4H), 1.71–1.69 (m, 4H), 1.59–1.58 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 147.90, 146.08, 130.72, 129.80, 110.40, 50.23, 50.05, 45.96, 25.62, 24.10. HREIMS Obsd. m/z=246.1852 (M), $C_{14}H_{22}N_4$ requires 246.1844.

4.2.7. Ethyl 4-(5-morpholino-3-pyridinyl)tetrahydro-1(*2H*)-pyrazine carboxylate 3g (Table 1). According to the typical procedure, **3g** was obtained as a pale yellow oil from the reaction of ethyl 4-(5-chloro-3-pyridyl)-1-piperazine carboxylate **2e** with morpholine using 10 mol% Ni. Purification was performed by silica gel column chromatography using AcOEt as eluent. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.86 (2d, J=2.00 Hz, 2H), 6.67 (dd, J=2.00 Hz, 1H), 4.19 (q, J=7.20 Hz, 2H), 3.88–3.83 (m, 4H), 3.65–3.61 (m, 4H), 3.18–3.15 (m, 8H), 1.29 (t, J=7.20 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 155.18, 147.17, 146.69, 130.72, 130.28, 109.84, 66.48, 61.36, 48.81, 48.65, 48.38, 43.27, 14.49. IR (NaCl) ν cm^{-1} 1699 (C=O). HREIMS Obsd. m/z=320.1857 (M), $C_{16}H_{24}N_4O_3$ requires 320.1848.

4.2.8. 4-[6-(4-Methylpiperazino)-2-pyridinyl]morpholine 3h (Table 1). According to the typical procedure, **3h** was obtained as a pale yellow oil from the reaction of 3-(3-chloro-2-pyridyl)morpholine **2f** with *N*-methylpiperazine using 10 mol% Ni. Purification was performed by silica gel column chromatography using *n*-hexane–AcOEt (20/80) as eluent. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.35 (dd, J=J'=8.00 Hz, 1H), 6.04 (d, J=8.00 Hz, 1H), 5.98 (d, J'=8.00 Hz, 1H), 3.83–3.78 (m, 4H), 3.55–3.49 (m, 4H), 3.48–3.42 (m, 4H), 2.52–2.48 (m, 4H), 2.34 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 158.43, 158.31, 139.07, 96.35, 95.62, 66.80, 54.93, 49.21, 45.59, 45.06. HREIMS obsd. m/z=262.1797 (M), $C_{14}H_{22}N_4O$ requires 262.1793.

4.2.9. 4-(6-Piperidino-2-pyridinyl)morpholine 3i (Table 1). According to the typical procedure, **3i** was obtained as a pale yellow oil from the reaction of 3-(3-chloro-2-pyridyl)morpholine **2f** with piperidine using 10 mol% Ni. Purification was performed by silica gel column chromatography using *n*-hexane–AcOEt (50/50) as eluent. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.32 (dd, J=8.40 Hz, 1H), 6.04 (d, J=8.40 Hz, 1H), 5.92 (d, J=8.00 Hz, 1H), 3.82–3.78 (m, 4H), 3.46–3.42 (m, 8H), 1.62–1.60 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): 158.58, 158.52, 138.98, 96.53, 94.75, 68.88, 46.20, 45.68, 25.52, 24.82. HREIMS Obsd. m/z=247.1693 (M), $C_{14}H_{21}N_3O$ requires 247.1684.

4.3. Synthesis of 3,5-dichloroanilines 4 from 1,3,5-trichlorobenzene

4.3.1. 1-(3,5-Dichlorophenyl)piperidine 4a (Table 2). Typical procedure for aminations using 10 mol% Ni catalyst. Piperidine (60 mmol), *t*-AmOH (4 mmol), NaH (26 mmol), $Ni(OAc)_2$ (2 mmol), 2,2′-bipyridine (6 mmol) and styrene (2 mmol) were used for the amination of 1,3,5-trichlorobenzene (20 mmol). **4a** was obtained as a pale yellow oil after purification by silica gel column chromatography using *n*-hexane–AcOEt (98/2) as eluent. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 6.72 (s, 3H), 3.16–3.14 (m, 4H), 1.67–1.62 (m, 4H), 1.60–1.58 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 135.26, 117.85, 113.79, 49.51, 25.36, 24.11. HREIMS obsd. m/z=229.042 (M), $C_{11}H_{13}Cl_2N$ requires 229.0424.

4.3.2. 1-(3,5-Dichlorophenyl)pyrrolidine 4b (Table 2). According to the typical procedure, **4b** was obtained as a pale yellow oil from the reaction of 1,3,5-trichlorobenzene with pyrrolidine using 10 mol% Ni. Purification was performed by silica gel column chromatography using *n*-hexane as eluent. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 6.57 (t, J=1.60 Hz, 1H), 6.33 (d, J=1.60 Hz, 2H), 3.19–3.16 (m, 4H), 1.98–1.95 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 148.92, 135.16, 114.74, 109.71, 47.51, 25.33. HREIMS obsd. m/z=215.0259 (M), $C_{10}H_{11}Cl_2N$ requires 215.0268.

4.3.3. 4-(3,5-Dichlorophenyl)morpholine 4c (Table 2). Typical procedure for aminations using 20 mol% Ni catalyst. Morpholine (60 mmol), *t*-AmOH (8 mmol), NaH (40 mmol), $Ni(OAc)_2$ (4 mmol), 2,2′-bipyridine (8 mmol) and styrene (2 mmol) were used for the amination of 1,3,5-trichlorobenzene (20 mmol). **4c** was obtained as a white solid after purification by silica gel column chromatography using *n*-hexane–AcOEt (95/5) as eluent. Mp 86°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 6.82 (t, J=1.60 Hz, 1H), 6.73 (d, J=1.60 Hz, 2H), 3.88–3.81 (m, 4H), 3.15–3.13 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 152.61, 135.45, 119.18, 113.48, 66.47, 48.32. HREIMS Obsd. m/z=231.022 (M), $C_{10}H_{11}Cl_2NO$ requires 231.0218.

4.3.4. 1-(3,5-Dichlorophenyl)-4-methylpiperazine 4d (Table 2). According to the typical procedure, **4d** was obtained as a pale yellow oil from the reaction of 1,3,5-trichlorobenzene with *N*-methylpiperazine using 10 mol% Ni. Purification was performed by silica gel column chromatography using AcOEt as eluent. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 6.78 (t, J=1.20 Hz, 1H), 6.73 (d, J=1.20 Hz, 2H), 3.21–3.19 (m, 4H), 2.55–2.36 (m, 4H), 2.34 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 45.99, 48.06, 54.63, 113.66, 118.67, 135.35, 152.51. HREIMS obsd. m/z=244.0521 (M), $C_{11}H_{14}Cl_2N_2$ requires 244.0534.

4.3.5. 3,5-Dichloro-*N*-(2,2-dimethoxyethyl)-*N*-methylaniline 4e (Table 2). According to the typical procedure, **4e** was obtained as a pale yellow oil from the reaction of 1,3,5-trichlorobenzene with *N*-methylaminoacetaldehyde dimethyl acetal using 20 mol% Ni. Purification was performed by silica gel column chromatography using *n*-hexane–AcOEt (98/2) as eluent. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 6.65 (t, J=1.60 Hz, 1H), 6.55 (d, J=1.60 Hz, 2H), 4.45 (t, J=5.20 Hz, 1H), 3.41–3.37 (m, 8H), 2.96 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 150.60, 135.42, 115.88, 110.06, 102.76, 54.91, 54.70, 39.31. HREIMS obsd. m/z=263.0435 (M), $C_{11}H_{15}Cl_2NO_2$ requires 263.0480.

4.4. Synthesis of triaminobenzenes 7 from 3,5-dichloroanilines 4

4.4.1. 4-(3,5-Diperidinophenyl)morpholine 7a (Table 3). According to the typical procedure, **7a** was obtained as a yellow solid from the reaction of **4c** with piperidine using 10 mol% Ni. Purification was performed by silica gel column chromatography using *n*-hexane–AcOEt (60/40) as eluent. Mp 137°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 6.15 (t, J=1.60 Hz, 1H), 6.07 (d, J=1.60 Hz, 2H), 3.83–3.81 (m, 4H), 3.19–3.16 (m, 4H), 3.13–3.16 (m, 8H), 1.72–1.67 (m, 8H), 1.57–1.54 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 154.02, 152.91, 98.39, 97.95, 67.02, 51.34, 49.89, 26.00, 24.36. HREIMS obsd m/z=329.2457 (M), $C_{20}H_{31}N_3O$ requires 329.2467.

4.4.2. N^1,N^3-bis(2,2-dimethoxyethyl)-N^1,N^3-dimethyl-5-morpholino-1,3-benzenediamine 7b (Table 3). According to the typical procedure, **7b** was obtained as a pale yellow oil from the reaction of **4c** with *N*-methylaminoacetaldehyde dimethyl acetal using 20 mol% Ni. Purification was performed by silica gel column chromatography using *n*-hexane–AcOEt (65/35) as eluent. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 5.76 (d, J=2.00 Hz, 2H), 5.73 (t, J=2.00 Hz, 1H), 4.52 (t, J=4.80 Hz, 2H), 3.85–3.83 (m, 4H), 3.43–3.38 (m, 16H), 3.16–3.14 (m, 4H), 2.03 (s, 6H), 1.58–1.55 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 153.34, 150.87, 103.49, 90.49, 89.92, 66.91, 60.12, 55.62, 54.36, 50.01, 39.28. HREIMS obsd. m/z=398.2647 (MH^+), $C_{20}H_{36}N_3O_4$ requires 398.2655.

4.4.3. Ethyl 4-{3-[4-(ethoxycarbonyl)piperazino]-5-morpholinophenyl}tetrahydro-1(*2H*)-pyrazine carboxylate 7c (Table 3). According to the typical procedure, **7c** was obtained as a pale yellow oil from the reaction of **4c** with ethyl tetrahydro-1(*2H*)-pyrazine carboxylate using 10 mol% Ni. Purification was performed by silica gel column chromatography using *n*-hexane–AcOEt (20/80) as eluent. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 6.08 (s, 3H), 4.13 (q, J=7.60 Hz, 4H), 3.85–3.83 (m, 4H), 3.63–3.60 (m, 8H), 3.21–3.18 (m, 4H), 3.14–3.11 (m, 8H), 1.26 (t, J=7.60 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 155.32, 153.08, 152.45, 98.95, 98.29, 66.82, 61.32, 60.23, 49.86, 49.59, 43.59, 14.55. IR (NaCl) ν cm^{-1} 1699 (C=O). HREIMS obsd. m/z=475.2786 (M), $C_{24}H_{37}N_5O_5$ requires 475.2794.

4.4.4. 4-(3-Morpholino-5-piperidinophenyl)morpholine 7d (Table 3). According to the typical procedure, **7d** was obtained as a pale yellow oil from the reaction of **4a** with morpholine using 10 mol% Ni. Purification was performed by silica gel column chromatography using *n*-hexane–AcOEt (70/30) as eluent. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 6.11 (d, J=2.00 Hz, 2H), 6.03 (t, J=2.00 Hz, 1H), 3.86–3.81 (m, 8H), 3.19–3.16 (m, 4H), 3.13–3.10 (m, 8H), 1.73–1.68 (m, 4H), 1.58–1.55 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 152.80, 152.16, 98.08, 96.62, 66.77, 51.05, 49.83, 25.79, 24.17. HREIMS obsd. m/z=331.2263 (M), $C_{19}H_{29}N_3O_2$ requires 331.2259.

4.4.5. 4-[3-Morpholino-5-(1-pyrrolidinyl)phenyl]morpholine 7e (Table 3). According to the typical procedure, **7e** was obtained as a pale yellow oil from the reaction of **4b** with morpholine using 10 mol% Ni. Purification was performed by silica gel column chromatography using *n*-hexane–AcOEt (65/35) as eluent. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 5.89 (t, J=2.00 Hz, 1H), 5.73 (d, J=2.00 Hz, 2H), 3.87–3.83 (m, 8H), 3.28–3.25 (m, 4H), 3.15–3.13 (m, 8H), 2.00–1.96 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 153.30, 149.36, 93.41, 93.13, 67.01, 50.11, 47.64, 25.35. HREIMS obsd. m/z=317.211 (M), $C_{18}H_{27}N_3O_2$ requires 317.2103.

4.4.6. 4-[3-(4-Methylpiperazino)-5-morpholinophenyl]-morpholine 7f (Table 3). According to the typical procedure, **7f** was obtained as a thick oil from the reaction of **4d** with morpholine using 10 mol% Ni. Purification was performed by silica gel column chromatography using AcOEt–MeOH (95/5) as eluent. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 6.08 (d, J=2.00 Hz, 2H), 6.06 (t, J=2.00 Hz, 1H), 3.88–3.83 (m, 8H), 3.23–3.19 (m, 4H), 3.15–3.12 (m, 8H), 2.70–2.68 (m, 4H), 2.40 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 153.06, 152.79, 97.86, 97.32, 66.87, 54.50, 49.88, 48.87, 45.21. HREIMS obsd. m/z=346.2371 (M), $C_{19}H_{30}N_4O_2$ requires 346.2368.

4.4.7. *N*-(2,2-Dimethoxyethyl)-*N*-methyl-3,5-dimorpholinoaniline 7g (Table 3). According to the typical procedure, **7g** was obtained as a thick oil from the reaction of **4e** with morpholine using 10 mol% Ni. Purification was performed by silica gel column chromatography using *n*-hexane–AcOEt (60/40) as eluent. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 5.93 (t, J=1.60 Hz, 1H), 5.91 (d, J=1.60 Hz, 2H), 4.51 (t, J=5.20 Hz, 1H), 3.86–3.84 (m, 8H), 3.43–3.39 (m, 8H), 3.16–3.14 (m, 8H), 2.05 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 153.32, 150.92, 103.47, 94.16, 93.66, 67.02, 60.34, 55.74, 54.57, 50.04, 39.46. HREIMS obsd. m/z=365.233 (M), $C_{19}H_{31}N_3O_4$ requires 365.2314.

References

1. (a) Negwer, M. *Organic Chemical Drugs and their Synonyms*; 7th ed.; Akademie Verlag GmbH: Berlin, 1994. (b) Lechat, P.; Tesleff, S.; Bowman, W. C. *Aminopyridines and Similarly Acting Drugs*; Pergamon: Oxford, 1982.
2. (a) Stejskal, J.; Krantoshvil, P.; Jenkins, A. *Polymer* **1996**, *37*, 367–369. (b) Liu, S.; Jiang, X.; Ma, H.; Liu, M.-S.; Jen, A. J.-Y. *Macromolecules* **2000**, *33*, 3514–3517. (c) Yu, W.-L.; Pei, J.; Huang, W.; Heeger, A. J. *Chem. Commun.* **2000**, 681–682. (d) Adronov, A.; Frechet, J. M. J. *Chem. Commun.* **2000**, 1701–1710 and references therein. (e) Han, C.-C.; Hong, S.-P.; Yang, K.-F.; Bai, M.-Y.; Lu, C.-H.; Huang, C.-S. *Macromolecules* **2001**, *34*, 587–591.
3. (a) Wagaw, S.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 10251–10263. (b) Iwaki, T.; Yasuhara, A.; Sakamoto, T. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1505–1510. (c) Edmonson, S. D.; Mastracchio, A.; Parmee, E. R. *Org. Lett.* **2000**, *2*, 1109–1112.
4. (a) Rouden, J.; Bernard, A.; Lasne, M.-C. *Tetrahedron Lett.* **1999**, *40*, 8109–8112. (b) Mederski, W. W. K. R.; Lefort, M.; Germann, M.; Kux, D. *Tetrahedron* **1999**, *55*, 12757–12770. (c) Wang, X.-J.; Tan, J.; Zhang, L. *Org. Lett.* **2000**, *2*, 3107–3109. (d) Bonala, R. R.; Shishkina, I. G.; Johnson, F. *Tetrahedron Lett.* **2000**, *41*, 7281–7284.
5. Asami, M.; Sato, S.; Watanabe, H. *Chem. Lett.* **2000**, 990–991.
6. For reviews on palladium-catalysed aminations, see: (a) Hartwig, J. F. *Synlett* **1997**, 329–340. (b) Hartwig, J. F. *Acc. Chem. Res.* **1998**, *31*, 852–860. (c) Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805–818. (d) Yang, B. H.; Buchwald, S. L. *J. Organomet. Chem.* **1999**, *546*, 125–146. (e) Belfield, A. J.; Brown, G. R.; Foubister, A. *J. Tetrahedron* **1999**, *55*, 11399–11428.
7. (a) For recent reports on palladium-catalysed aminations, see: (a) Huang, J.; Grasa, G.; Nolan, S. P. *Org. Lett.* **1999**, *1*, 1307–1309. (b) Harris, M. C.; Geis, O.; Buchwald, S. L. *J. Org. Chem.* **1999**, *64*, 6019–6022. (c) Bolm, C.; Hildebrand, J. P. *J. Org. Chem.* **2000**, *65*, 169–175. (d) Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1144–1157. (e) Wolfe, J. P.; Tomori, H.; Sadighi, J. P.; Yin, J.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1158–1174. (f) Yin, J.; Buchwald, S. L. *Org. Lett.* **2000**, *2*, 1101–1104. (g) Stauffer, S. R.; Lee, S.; Stambuli, J. P.; Hauck, S. I.; Hartwig, J. F. *Org. Lett.* **2000**, *2*, 1423–1426. (h) Harris, M. C.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 5327–5333. (i) Zhang, X.-X.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 8027–8031. (j) Li, G. Y. *Angew. Chem. Int. Ed.* **2001**, *40*, 1513–1516. (k) Ali, M. H.; Buchwald, S. L. *J. Org. Chem.* **2001**, *66*, 2560–2565.
8. For recent reports on copper-catalysed aminations, see: (a) Collman, J. P.; Zhong, M. *Org. Lett.* **2000**, *2*, 1233–1236. (b) Elliot, G. I.; Konopelski, J. P. *Org. Lett.* **2000**, *2*, 3055–3057. (c) Lam, P. Y. S.; Deudon, S.; Hauptman, E.; Clark, C. G. *Tetrahedron Lett.* **2001**, *42*, 2427–2429. (d) Song, J. J.; Yee, N. K. *Tetrahedron Lett.* **2001**, *42*, 2937–2940.
9. (a) Witulsky, B.; Senft, S.; Thum, A. *Synlett* **1998**, 504–506. (b) Witulsky, B. *Synlett* **1999**, 1223–1226. (c) Beletskaya, I. P.; Bessmertnykh, A. G.; Guilard, R. *Tetrahedron Lett.* **1999**, *40*, 6393–6397. (d) Watanabe, M.; Yamamoto, T.; Nishiyama, M. *Chem. Commun.* **2000**, 133–134.
10. Wolfe, J. P.; Wagaw, S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 7215–7216.
11. Rivas, F. M.; Riaz, U.; Diver, S. T. *Tetrahedron: Asymmetry* **2000**, *11*, 1703–1707.
12. Brown, G. R.; Foubister, A. J.; Roberts, C. A.; Wells, S. L.; Wood, R. *Tetrahedron Lett.* **2001**, *42*, 3917–3919.
13. (a) Brenner, E.; Fort, Y. *Tetrahedron Lett.* **1998**, *39*, 5359–5362. (b) Brenner, E.; Schneider, R.; Fort, Y. *Tetrahedron* **1999**, *55*, 12829–12842. (c) Brenner, E.; Schneider, R.; Fort, Y. *Tetrahedron Lett.* **2000**, *41*, 2881–2884.
14. Desmarets, C.; Schneider, R.; Fort, Y. *Tetrahedron Lett.* **2000**, *41*, 2875–2879.
15. Desmarets, C.; Schneider, R.; Fort, Y. *Tetrahedron Lett.* **2001**, *42*, 247–250.