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Nickel-Catalysed Couplings of Aryl Chlorides with Secondary Amines and Piperazines

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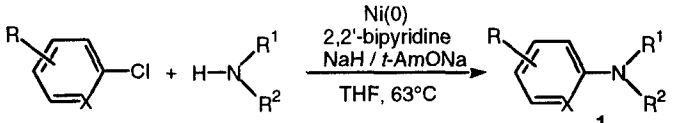
Abstract: The reaction of aryl chlorides with secondary amines or piperazines in the presence of an *in situ* generated liganded nickel catalyst gives arylamines in good yields. Our process provides a mild, convenient and cheap method of arylamination starting from readily available substrates. © 1999 Elsevier Science Ltd. All rights reserved.

INTRODUCTION

Aromatic amines are important substructures in natural products and organic materials.[1] Among amines, arylpiperazines are of particular interest for the synthesis of biologically active substances since this moiety is commonly found as a key structural element in many compounds possessing broad therapeutic activities.[2] In recent years, extensive research has been devoted to the transition-metal catalysed carbon-nitrogen couplings. Buchwald's and Hartwig's groups and others have independently developed a great number of palladium catalyst and ligands which are efficient for the cross-coupling of amines and aryl halides or sulfonates.[3] A particular effort has been directed toward the coupling of aryl chlorides with amines in the presence of electron-rich phosphine ligands.[3c,n,l,k,t] Buchwald also reported the synthesis of aniline derivatives by a nickel-catalysed arylamination of aryl chlorides using $Ni(COD)_2$ and 1,1'-bis(diphenylphosphino)ferrocene (dppf) or 1,10-phenanthroline.[4]

For our part, we have recently reported that secondary cyclic amines could be coupled with aryl chlorides in good to excellent yields using a non pyrophoric 2,2'-bipyridine liganded nickel catalyst (Scheme 1).[5]



Scheme 1

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As part of our current research interest, we needed to develop a rapid, cheap and large scale synthetic route to unsymmetrical and functionalised aryl piperazines. We describe herein the improvements of our protocol for the use of 2,2'-bipyridine liganded Ni catalyst which allows, under mild conditions, the synthesis of arylamines and arylpiperazines in good yields and excellent chemical purity from readily available aryl chlorides.

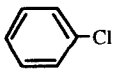
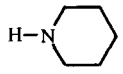
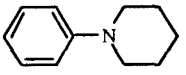
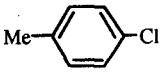
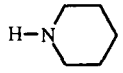
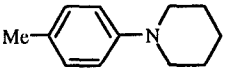
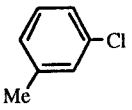
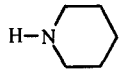
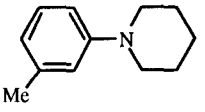
RESULTS AND DISCUSSION

A systematic study of the reaction conditions indicated us that: i) Much better yields were obtained when the Ni reagent was prepared in the presence of the amine. ii) Only 1.1 equivalent of cyclic amine (relative to aryl chloride) was necessary to ensure a complete and efficient reaction. iii) 2,2'-bipyridine was the best ligand of our Ni species. $Ni(PPh_3)_4$ or $Ni(1,10\text{-phenanthroline})_2$ were not effective and afforded only trace amounts of the desired arylamines. Note that 2,2'-bipyridine is easily recovered from arylamination products by chromatography. iv) side hydrogenolysis of the C-Cl bond could be strongly attenuated by the addition of styrene in the reaction medium.[5] v) The nickel reagent could be used at 10 mol% if the catalytic cycle was ensured by using an excess of sodium hydride (8 equivalents relative to Ni). In these conditions, it must be underlined that, in contrast with our previous works dealing with homocouplings,[6] this excess of sodium hydride did not favour side reduction of the starting aryl chloride during the catalytic arylaminations.

It then appeared that Ni-catalysed reactions of aryl or heteroaryl chlorides with secondary cyclic amines (in the ratio 1 equiv. / 1.1 equiv.) provided a general route to the corresponding arylamines **1** in good yields (Table 1). The only side products obtained in a few cases were the homocoupled biaryl and the arene resulting from reduction of the starting aryl chloride. Electron-poor aryl chlorides gave the amination products in good yields (entries k and l) while lower yields were obtained with electron-rich aryl chlorides (entries e and j). As reported in palladium-catalysed reactions,[3] aryl chlorides bearing electron withdrawing groups are more reactive since oxidative addition on Ni during the catalytic cycle is easier. Aminations are not sensitive to the steric hindrance of the starting aryl chloride. 2-Chlorotoluene reacted either with piperidine or pyrrolidine (entries d and i) to give the corresponding aromatic amines in good yields (respectively 75 and 78 % for the reactions performed with 10 mol% Ni).

Arylaminations using acyclic secondary amines were next examined under the same experimental conditions. Only poor yields (less than 25 % after 24 hours reaction time) were obtained when reacting di-*n*-propyl amine and chlorobenzene using 20 or 10 mol% of Ni. Attempts to increase yields by changing THF to DME, dioxane or toluene were all unsuccessful. As it can be seen from entry a, Table 2, good yields of *N*-phenyl-*N*,*N*-dipropylamine **2a** could be obtained using 2 equivalents of amine. Surprisingly, increasing amounts of di-*n*-propylamine to 3 or 4 equivalents reduced reaction yields (respectively 63 or 20 %). These results may be attributed to the chelating properties of the starting amine towards the nickel catalyst.

Table 1. Ni-catalysed synthesis of arylamines **1** from aryl chlorides and cyclic amines.[a]

Entry	Aryl halide	Amine	Product **1**	Reaction conditions[b]	Reaction time[c] (h)	Yield[d] (%)
a				A	4	85
				B	8	84
b				A	4	81
				B	9	82
c				A	4	77
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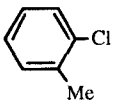
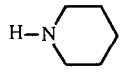
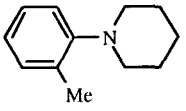
d				A	3.5	78
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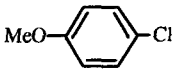
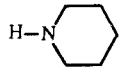
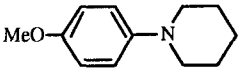
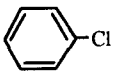
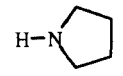
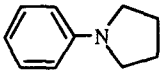
e				B	12	51
f				A	3.5	85
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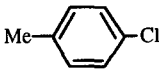
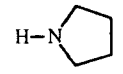
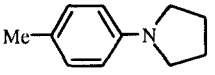
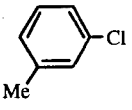
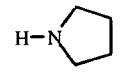
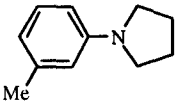
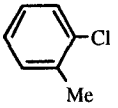
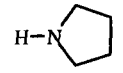
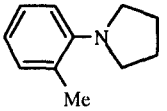
g				A	3.5	82
h				A	3	82
i				A	4	84
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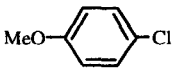
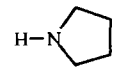
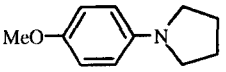
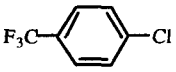
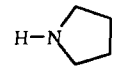
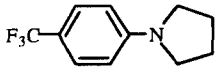
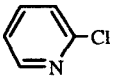
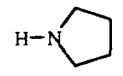
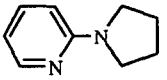
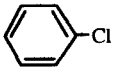
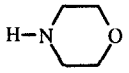
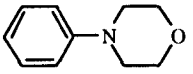
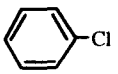
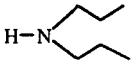
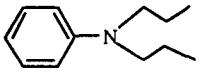
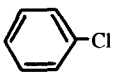
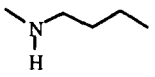
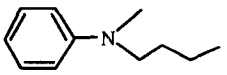
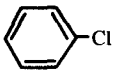
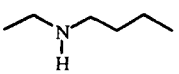
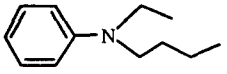
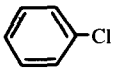
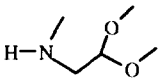
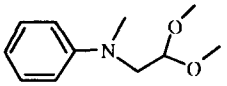
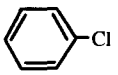
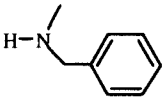
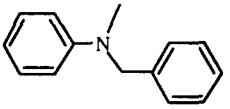
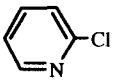
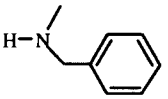
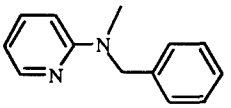
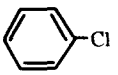
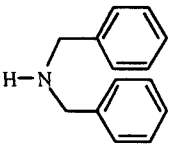
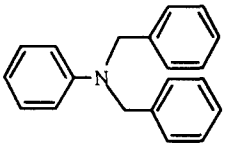
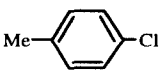
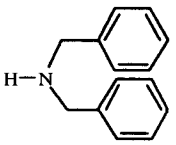
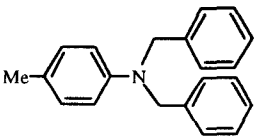
j				A	7	37
k				A	2.5	87
l				A	4	70
m				A	6	65
				B	9	59

[a] All reactions were performed on a 25 mmoles scale of aryl chloride. [b] Reaction conditions A : 20 mol % Ni. Reaction conditions B : 10 mol % Ni. [c] Determined by GC analysis. [d] Yield of the isolated product.

We then prepared several aniline derivatives from aryl chlorides by using 2 equivalents of acyclic secondary amines and 20 mol% of liganded nickel reagent (Table 2).

Table 2. Ni-catalysed synthesis of arylamines **2** from aryl chlorides and secondary acyclic amines.[a]

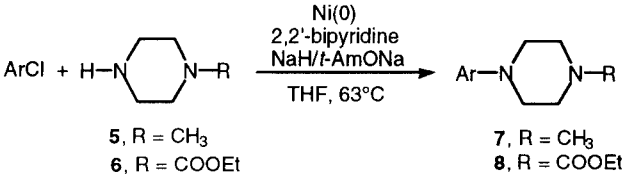
Entry	Aryl halide	Amine	Product **2**	Reaction conditions[b]	Reaction time[c] (h)	Yield[d] (%)
a				A	10	68
				B	13	23
b				A	9	63
c				A	12	7
d				A	8	73
e				A	9	71
f				A	9	70
g				A	10	58
h				A	10	57

[a] All reactions were performed on a 25 mmoles scale of aryl chloride. [b] Reaction conditions A employ 20 mol % Ni. Reaction conditions B employ 10 mol % Ni. [c] Determined by GC analysis. [d] Yield of the isolated product.

It is worthy to note that products obtained with *N*-methylbenzylamine and *N,N*-dibenzylamine may serve as synthetic equivalents of primary amine and ammonia in arylamination reactions. Cleavage of the benzylic group of compounds **2e** and **2g** by hydrogenolysis over Pd/C in acidic medium[7] provided respectively *N*-methyl- phenylamine **3** and phenylamine **4** in 91 and 71 % yield.

With all these results in hand, we studied the couplings of aryl chlorides with 1-substituted piperazines. (Scheme 2). Arylaminations results obtained with 1-methylpiperazine under 10 mol% Ni-catalysis (reaction

conditions B) are summarised in Table 3 in which we have reported the results obtained using 20 mol% catalyst (reaction conditions A) for the less efficient reactions.



5, R = CH_3
6, R = COOEt

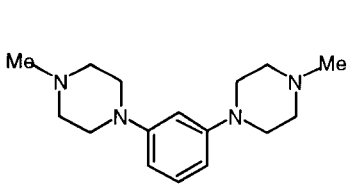
7, R = CH_3
8, R = COOEt

Scheme 2

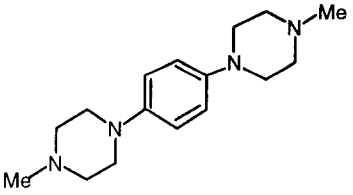
As expected, yields depend on the steric and electronic properties of the starting aryl chloride. Aryl chlorides bearing electron-withdrawing substituents underwent the amination reaction most efficiently. The difference in reactivity between *m*- and *p*-chloroanisole is particularly significative (entries g and h). The electron-donating effect of the *p*-methoxy group caused a dramatic decrease of the arylamination yield to 19 % while the withdrawing effect of the *m*-methoxy group enhanced it to 80 %.

Surprisingly, the yield of the reaction between *p*-chlorobenzonitrile and 1-methylpiperazine is only 35 % when 10 mol% Ni were used (entry i). Increasing amounts of catalyst to 20 mol% gave product **7i** in 77 % yield. We thought that this behaviour must be due to an inhibition of the Ni catalyst by a competitive coordination with the nitrile function. To confirm this hypothesis, chlorobenzene was reacted with **5** in the presence of benzonitrile (1 equivalent). 1-Methyl-4-phenylpiperazine **7a** was then obtained in only 8 % yield while benzonitrile was recovered.

In contrast to the results obtained with methoxy substituted compounds, 1,3-dichlorobenzene gave lower yields of amination than the 1,4-derivative (entries j and k). In fact, 1-(3-Chlorophenyl)-4-methylpiperazine **7k** initially formed underwent a second competitive Ni catalysed reaction with 1-methylpiperazine to give the bis-adduct, 1-methyl-4-(3-(4-methylpiperazino) phenyl) piperazine **9a**, in 28 % yield.



9a

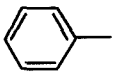
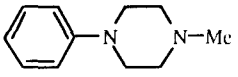
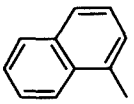
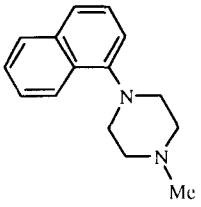
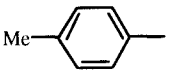
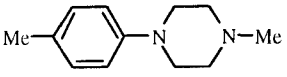
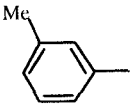
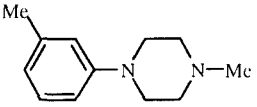
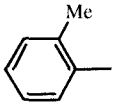
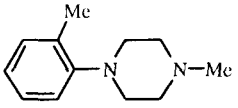
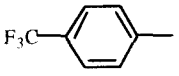
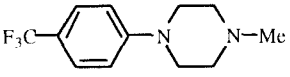
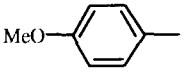
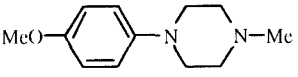
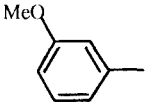
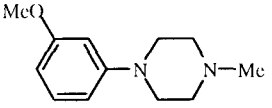
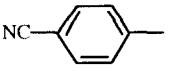
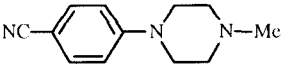
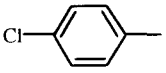
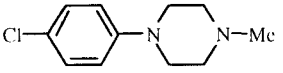
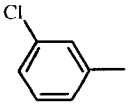
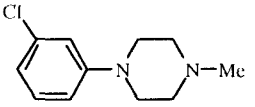
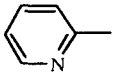
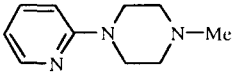


9b

Bis-adduct **9b** was obtained in less than 5% yield starting from 1,4-dichlorobenzene using either 20 or 10 mol% Ni. Finally, 2-chloropyridine was also coupled with 1-methylpiperazine to produce 1-methyl-4-(2-pyridyl)piperazine **7l** in 69 % isolated yield using 10 mol% Ni.

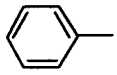
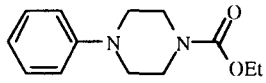
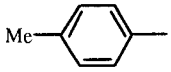
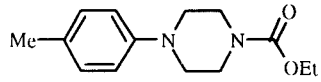
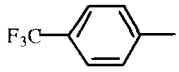
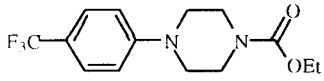
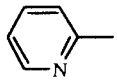
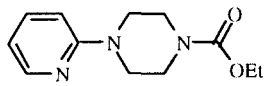
As illustrated in Table 4, our Ni-catalysed amination is not only limited to 1-methylpiperazine. Indeed, ethyl 1-piperazine carboxylate **6** reacts efficiently with arylchlorides in the presence of 10 mol% Ni in refluxing tetrahydrofuran to give compounds **8** in 69-74% yields.

Table 3. Ni-catalysed synthesis of 1-aryl-4-methylpiperazines **7**.[a]

Entry	Ar	Products **7**	Reaction Conditions[b]	Time[c] (h)	Yield[d] (%)
a			B	10	85
b			B	13	85
c			B	13	78
d			B	13	76
e			A B	9 14	41 35
f			B	9	80
g			A B	8 14	22 19
h			B	10	80
i			A B	7 15	77 35
j			A B	9 12	65 57
k			A B	10 13	36 35
l			A B	8 11	79 69

[a] All reactions were performed on a 25 mmoles scale of aryl chlorides. [b] Reaction conditions A : 20 mol% Ni. Reaction conditions B : 10 mol% Ni. [c] Determined by GC analysis. [d] Reported yields corresponded to analytically pure isolated compounds. All products gave satisfactory spectral and analytical data.

Table 4. Ni-catalysed synthesis of ethyl 4-aryl-1-piperazine carboxylates **8**.[a]

Entry	Ar	Products **8**	Time[b] (h)	Yield[c] (%)
a			10	74
b			11	70
c			9	78
d			8	69

[a] Reactions performed on a 25 mmoles scale of aryl chorides using 10 mol% Ni. [b] Determined by GC analysis. [c] Yields reported correspond to analytically pure, isolated compounds. All products gave satisfactory spectral and analytical data.

Products **8b** and **8d** were respectively reduced into arylpiperazines **10a** (Ar = *p*-$CH_3C_6H_4$, yield = 91 %) and **10b** (Ar = 2-pyridyl, yield = 84 %) possessing a free nitrogen atom by treatment with excess lithium aluminium hydride (4 equivalents) in tetrahydrofuran for 1 hour. Among all the reports made during the last decade for the preparation of 1-arylpiperazines (S_NAr reactions in liquid phase[8] or solid support,[9] S_NAr reactions on tricarbonyl chromium complexes,[10] displacement of a chlorine atom in arene-iron complexes,[11] reaction of aniline derivatives with bis(2-bromoethyl) *N*-substituted amines[12] or palladium-catalysed amination reactions[13]), the method described herein provides a mild alternative for the synthesis of these compounds.

CONCLUSION

We have shown that our 2,2'-bipyridine liganded Ni catalyst allows the coupling of aryl chlorides with secondary amines and piperazines in good yields. The reaction conditions are sufficiently mild to tolerate a variety of functional groups including ethers, nitriles, acetals or carbamates. The method described herein is a convenient, large scale (all reactions may be carried out on a 100 mmoles scale) and cheap procedure for the synthesis of arylamines starting from readily available substrates.

EXPERIMENTAL SECTION

All experiments were carried out under a nitrogen atmosphere. THF was distilled from benzophenone-sodium adduct and stored over sodium wire. *tert*-Amyl alcohol (Aldrich) was distilled from sodium. Crushed $Ni(OAc)_2.4\ H_2O$ (Fluka) was dried under vacuum (20 mm Hg) at 110°C for 12 hours. Sodium hydride (65 %

in mineral oil, Fluka) was used after three 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 x 0.32 mm x 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 (^{19}F at 235 MHz) spectrometers. 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 or capillary GC. Combustion analysis or HMRS were performed by the Service central d'analyses du CNRS (Vernaison, France).

General procedure for the 10 mol % Ni-catalysed arylaminations.

A solution of *t*-AmOH (0.44 g, 5 mmol) in THF (5 mL) was added to a suspension of NaH (1.19 g, 30 mmol) in THF (20 mL) and the mixture was heated to 63°C. The amine (27.5 mmol) in THF (5 mL) was added followed by dried $Ni(OAc)_2$ (0.44 g, 2.5 mmol) and 2,2'-bipyridine (1.17 g, 7.5 mmol) and the reflux was maintained for 2 h. To the dark suspension of 2,2'-bipyridine liganded Ni(0) thus obtained was added the aryl chloride (25 mmoles) and styrene (0.52 g, 5 mmol) in THF (5 mL) and the mixture was heated for the time indicated in the tables. After cooling to room temperature, hydrolysis with water (1 mL) and dilution with ether, the mixture was filtered, dried over $MgSO_4$ and concentrated. The crude material was purified by flash chromatography on silica gel.

General procedure for the 20 mol% Ni-catalysed arylaminations.

t-AmOH (0.88 g, 10 mmol), NaH (1.34 g, 35 mmol), $Ni(OAc)_2$ (0.89 g, 5 mmol), 2,2'-bipyridine (1.56 g, 10 mmol) and styrene (0.26 g, 2.5 mmol) were used for the arylamination of 25 mmol aryl chloride using the standard procedure described above.

*Synthesis of arylamines **1** from aryl chlorides and cyclic secondary amines.*

1-Phenylpiperidine[15] **(1a)** (Table 1): colorless liquid. 85% yield (method A) and 84% yield (method B). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.27-7.16 (m, 2 H), 6.97-6.86 (m, 2 H), 6.78 (dd, 1 H, $^3J = {}^3J' = 5.5$ Hz), 3.17-3.12 (m, 4 H), 1.77-1.62 (m, 4 H), 1.57-1.48 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 152.71, 129.45, 119.68, 117.02, 51.16, 26.33, 24.80.

1-(4-Methylphenyl)piperidine[15] **(1b)** (Table 1): colorless liquid. 81% yield (method A) and 82 % yield (method B). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.02 (d, 2 H, J = 8.6 Hz), 6.84 (d, 2 H, J = 8.6 Hz), 3.09-3.01 (m, 4 H), 2.24 (s, 3 H), 1.76-1.62 (m, 4 H), 1.56-1.47 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 150.70, 130.01, 129.34, 117.56, 51.88, 26.40, 24.77, 20.94.

1-(3-Methylphenyl)piperidine[16] **(1c)** (Table 1): colorless liquid. 77% yield (method A) and 82% yield (method B). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.10 (dd, 1 H, $^3J = {}^3J' = 8.6$ Hz), 6.77-6.68 (m, 2 H), 6.64-6.58 (m, 1 H), 3.13-3.05 (m, 4 H), 2.28 (s, 3 H), 1.72-1.61 (m, 4 H), 1.58-1.48 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 152.89, 139.02, 129.35, 120.69, 117.96, 114.25, 51.34, 26.48, 24.92, 20.05.

1-(2-Methylphenyl)piperidine[15] **(1d)** (Table 1): colorless liquid. 78% yield (method A) and 76% yield (method B). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.14-7.08 (m, 2 H), 7.00-6.90 (m, 2 H), 2.84-2.78 (m, 4 H), 2.28 (s, 3 H), 1.72-1.64 (m, 4 H), 1.58-1.51 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 153.38, 133.11, 131.38, 126.87, 123.07, 119.41, 53.83, 27.12, 24.93, 18.32.

1-(4-Methoxyphenyl)piperidine[15] **(1e)** (Table 1): white solid; m.p. 35°C (lit.,[15] m.p. 37°C). 51% yield (method B). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 6.89 (d, 2 H, J = 10.0 Hz), 6.81 (d, 2 H, J = 10.0 Hz), 3.73 (s, 3 H), 3.03-2.96 (m, 4 H), 1.75-1.65 (m, 4 H), 1.57-1.47 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 153.45, 146.76, 118.65, 114.15, 55.36, 52.20, 26.01, 24.07.

1-Phenylpyrrolidine[17] **(1f)** (Table 1): colorless liquid. 85% yield (method A) and 84% yield (method B). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.25-7.14 (m, 2 H), 6.68-6.59 (m, 1 H), 6.56-6.43 (m, 2 H), 3.32-3.12 (m, 4 H), 2.02-1.82 (m, 4 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 148.51, 129.52, 115.92, 112.20, 48.10, 26.04.

1-(4-Methylphenyl)pyrrolidine[18] **(1g)** (Table 1): colorless oil. 82% yield (method A). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.02 (d, 2 H, J = 8.6 Hz), 6.49 (d, 2 H, J = 8.6 Hz), 3.31-3.12 (m, 4 H), 2.24 (s, 3 H), 2.01-1.85 (m, 4 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 146.01, 129.48, 124.14, 111.72, 46.67, 25.36, 20.28.

1-(3-Methylphenyl)pyrrolidine[18] **(1h)** (Table 1): colorless liquid. 82% yield (method A). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.21-7.14 (m, 1 H), 6.74-6.64 (m, 2 H), 6.60-6.54 (m, 1 H), 3.21-3.09 (m, 4 H), 2.23 (s, 3 H), 1.92-1.83 (m, 4 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 148.93, 138.35, 127.61, 118.53, 115.46, 112.14, 47.44, 25.36, 21.81.

1-(2-Methylphenyl)pyrrolidine[18] **(1i)** (Table 1): colorless liquid. 84% yield (method A) and 78% yield (method B). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.12-7.07 (m, 2 H), 6.88-6.78 (m, 2 H), 3.19-3.12 (m, 4 H), 2.30 (s, 3 H), 1.93-1.86 (m, 4 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 149.32, 131.58, 128.62, 126.19, 120.17, 115.67, 50.92, 24.87, 20.51.

1-(4-Methoxyphenyl)pyrrolidine[18] **(1j)** (Table 1): pale yellow oil. 37% yield (method A). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 6.84 (d, 2 H, J = 8.6 Hz), 6.53 (d, 2 H, J = 8.6 Hz), 3.68 (s, 3 H), 3.32-3.13 (m, 4 H), 2.04-1.95 (m, 4 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 150.77, 143.68, 114.78, 112.52, 55.53, 47.63, 25.33.

1-[(4-Trifluoromethyl)phenyl]pyrrolidine (1k) (Table 1): white solid; m.p. 90°C. 87% yield (method A). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.43 (d, 2 H, J = 8.6 Hz), 6.54 (d, 2 H, J = 8.6 Hz), 3.39-3.24 (m, 4 H), 2.11-1.92 (m, 4 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 150.20; 127.22, 125.88 (q, J = 269 Hz), 116.85 (q, J = 32 Hz), 111.24, 48.09, 26.04. ^{19}F NMR (235 MHz) δ ppm: -61.78. IR (KBr) ν cm^{-1} 1385 (C-F). Anal. Calcd. for $C_{11}H_{12}F_3N$: C, 61.39; H, 5.62; F, 26.48, N, 6.51. Found: C, 61.42; H, 5.33; F, 26.85; N, 6.62.

2-Tetrahydro-1*H*-1-pyrrolylpyridine[19] **(1l)** (Table 1): colorless liquid. 70% yield (method A). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 8.14 (d, 1 H, J = 4.0 Hz), 7.36-7.34 (m, 1 H),6.48-6.45 (m, 1 H), 6.28-6.26 (m, 1 H), 3.45-3.34 (m, 4 H), 2.01-1.85 (m, 4 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 156.37, 148.41, 137.12, 124.05, 121.29, 46.86, 25.79.

4-Phenylmorpholine[20] **(1m)** (Table 1): white solid; m.p. 54°C (lit.,[20] 52-53°C). 65% yield (method A) and 59% yield (method B). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.35-7.17 (m, 2 H), 6.96-6.77 (m, 3 H), 3.85-3.75 (m, 4 H), 3.15-3.05 (m, 4 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 151.76, 129.64, 120.46, 116.14, 67.38, 49.78.

*Synthesis of arylamines **2** from aryl chlorides and acyclic secondary amines.*

All arylaminations were conducted using 25 mmol of aryl chloride, 50 mmol of amine and 20 mol% Ni(0).

***N*-Phenyl-*N*,*N*-dipropylamine**[21] **(2a)** (Table 2): pale yellow oil. 68% yield (method A) and 23% yield (method B). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.22-7.11 (m, 2 H), 6.65-6.54 (m, 3 H), 3.18 (t, 4 H, J = 7.6 Hz), 1.63-1.49 (m, 4 H), 0.88 (t, 6 H, J = 7.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 148.10, 129.08, 115.07, 111.61, 52.79, 20.33, 11.36.

***N*-Butyl-*N*-methyl-*N*-phenylamine[22] (2b)** (Table 2): colorless liquid. 63% yield (method A). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.24-7.11 (m, 2 H), 6.75-6.54 (m, 3 H), 3.24 (t, 2 H, *J* = 7.6 Hz), 2.84 (s, 3 H), 1.62-1.43 (m, 2 H), 1.40-1.19 (m, 2 H), 0.91 (t, 3 H, *J* = 7.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 149.22, 128.97, 115.68, 111.95, 52.37, 38.06, 28.76, 20.26, 13.92.

***N*-(2,2-Dimethoxyethyl)-*N*-methyl-*N*-phenylamine (2d)** (Table 2): colorless liquid. 73% yield (method A). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.26-7.14 (m, 2 H), 6.76-6.64 (m, 3 H), 4.49 (t, 1 H, *J* = 5.2 Hz), 3.42 (d, 2 H, *J* = 5.2 Hz), 3.37 (s, 6 H), 2.96 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 149.09, 129.06, 116.21, 111.79, 103.14, 55.18, 54.42, 39.07. Anal. Calcd. for $C_{11}H_{17}NO_2$: C, 67.69; H, 8.71; N, 7.18. Found: C, 67.85; H, 8.55; N, 7.05.

***N*-Benzyl-*N*-methyl-*N*-phenylamine[20] (2e)** (Table 2): colorless liquid. 71% yield (method A). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.32-7.13 (m, 7H), 6.74-6.65 (m, 3H), 4.47 (s, 2H), 2.95 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 149.63, 138.93, 129.08, 128.46, 126.75, 126.62, 116.44, 112.24, 56.48, 38.37.

***N*-Benzyl-*N*-methyl-*N*-(2-pyridyl)amine[23] (2f)** (Table 2): pale yellow oil. 70% yield (method A). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 8.16 (bd, 1 H), 7.43-7.32 (m, 1 H), 7.29-7.13 (m, 5 H), 6.57-6.42 (m, 2 H), 4.76 (s, 2 H), 3.02 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 158.69, 147.78, 138.55, 137.10, 128.34, 126.82, 126.69, 111.63, 105.48, 52.97, 35.93.

***N,N*-Dibenzylphenylamine[24] (2g)** (Table 2): pale yellow solid; m.p. 66°C (lit.,[24] m.p. 65.8-67.2°C). 58 % yield (method A). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.33-7.09 (m, 12 H), 6.73-6.64 (m, 3 H), 4.60 (s, 4 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 149.08, 138.52, 129.16, 128.56, 126.80, 126.57, 116.65, 112.35, 54.08.

***N,N*-Dibenzyl-4-methylphenylamine[21] (2h)** (Table 2): yellow oil. 57 % yield (method A). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.31-7.14 (m, 10 H), 6.95 (d, 2 H, *J* = 8.0 Hz), 6.63 (d, 2 H, *J* = 8.0 Hz), 4.57 (s, 4 H), 2.20 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 146.98, 138.20, 129.69, 128.52, 126.73, 126.64, 125.73, 112.60, 54.30, 20.18.

*Synthesis of arylamines **3** and **4**.*

***N*-Methylphenylamine (3):** In an oven dried two necked 25 mL bottom flask fitted with a magnetic stirrer and rubber septa, 10 % Pd/C (0.21 g), MeOH (10 mL) and HCl 12 N (0.5 mL) were added. The apparatus was charged with H_2 and evacuated. After two purges, the apparatus was charged with H_2 and **2e** (4 mmol) in MeOH (3 mL) was added and stirring was continued for 15 min. The mixture was filtered through Celite and concentrated to give *N*-methylphenylamine **3a** in 91 % yield.

Phenylamine (4): Debenzylation of **2g** was performed in acetic acid at 80°C following the procedure described above. Phenylamine was obtained in 71 % yield.

Spectroscopic data are fully consistent with those of commercial samples.

*Synthesis of arylpiperazines **7** from aryl chlorides and 1-methylpiperazine **5**.*

1-Methyl-4-phenylpiperazine[8a] (7a) (Table 3): pale yellow oil. 85% yield (method A). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.35-7.22 (m, 2 H), 7.03-6.83 (m, 3 H), 3.35-3.13 (m, 4 H), 2.66-2.55 (m, 4 H), 2.38 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 151.09, 128.91, 119.46, 115.84, 54.95, 48.87, 45.97.

1-Methyl-4-(1-naphthyl)piperazine[8a] (7b) (Table 3): white solid; m.p. 54°C (lit.,[25] m.p. 54-55°C). 85% yield (method A). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 8.17 (d, 1 H, *J* = 8.0 Hz), 7.75 (d, 1 H, *J* = 8.0 Hz), 7.55-7.26 (m, 4 H), 7.09-6.97 (m, 1 H), 3.18-2.98 (m, 4 H), 2.74-2.52 (m, 4 H), 2.34 (s, 3 H). ^{13}C NMR (100 MHz,

$CDCl_3$) δ ppm: 149.35, 134.50, 128.64, 128.15, 125.62, 125.52, 125.03, 123.34, 123.22, 114.50, 55.37, 52.64, 45.93.

1-Methyl-4-(4-methylphenyl)piperazine[8a] **(7c)** (Table 3): white solid; m.p. 73°C (lit.,[26] m.p. 72-73°C). 78% yield (method A). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.05 (d, 2 H, J = 8.6 Hz), 6.82 (d, 2 H, J = 8.6 Hz), 3.17-3.10 (m, 4 H), 2.59-2.51 (m, 4 H), 2.32 (s, 3 H), 2.25 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 148.93, 129.40, 128.92, 116.19, 54.92, 49.36, 45.87, 20.23.

1-Methyl-4-(3-methylphenyl)piperazine[8a] **(7d)** (Table 3): pale yellow oil. 76% yield (method A). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.17-7.08 (m, 1 H), 6.76-6.60 (m, 3 H), 3.21-3.14 (m, 4 H), 2.58-2.51 (m, 4 H), 2.32 (s, 3 H), 2.29 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 151.12, 138.46, 128.72, 120.35, 116.63, 112.96, 54.97, 48.91, 45.93, 21.57.

1-Methyl-4-(2-methylphenyl)piperazine[13d] **(7e)** (Table 3): colorless oil. 35% yield (method A) and 41% yield (method B). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.19-7.09 (m, 2 H), 7.06-6.89 (m, 2 H), 2.97-2.88 (m, 4 H), 2.62-2.52 (m, 4 H), 2.34 (s, 3 H), 2.28 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 151.25, 132.34, 130.84, 126.37, 122.95, 118.52, 55.40, 51.42, 45.93, 17.68.

1-Methyl-4-[4-(trifluoromethyl)phenyl]piperazine (7f) (Table 3): white solid; m.p. 91°C. 80% yield (method A). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.47 (d, 2 H, J = 8.8 Hz), 6.91 (d, 2 H, J = 8.8 Hz), 3.32-3.25 (m, 4 H), 2.59-2.51 (m, 4 H), 2.34 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 153.20, 126.31, 124.82 (q, J = 292 Hz), 120.3 (q, J = 32 Hz), 114.41, 54.73, 47.83, 46.04. ^{19}F NMR (235 MHz) δ ppm: -61.85. IR (KBr) ν cm^{-1} 1333 (C-F). HREIMS Obsd. m/z = 245.1267 $(MH)^+$, $C_{12}H_{16}F_3N_2$ requires m/z = 245.1265.

1-(4-Methoxyphenyl)-4-methylpiperazine[8a] **(7g)** (Table 3): white solid; m.p. 66°C (lit.,[27] m.p. 67-70°C). 19% yield (method A) and 22% yield (method B). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 6.90 (d, 2 H, J = 8.8 Hz), 6.83 (d, 2 H, J = 8.8 Hz), 3.75 (s, 3 H), 3.15-3.06 (m, 4 H), 2.62-2.53 (m, 4 H), 2.34 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 153.55, 145.56, 118.03, 114.30, 55.42, 55.14, 50.44, 46.01.

1-(3-Methoxyphenyl)-4-methylpiperazine[8a] **(7h)** (Table 3): pale yellow oil. 80% yield (method A). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.14 (dd, 1 H, ^3J = $^3J'$ = 8.0 Hz), 6.57-6.35 (m, 3 H), 3.74 (s, 3 H), 3.23-3.17 (m, 4 H), 2.62-2.48 (m, 4 H), 2.31 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 160.27, 152.34, 129.45, 108.49, 104.03, 102.13, 54.77, 48.65, 45.84.

4-(4-Methylpiperazino)benzonitrile[13d] **(7i)** (Table 3): white solid; m.p. 110°C (lit.,[28] m.p. 112.5-113.5°C). 35% yield (method A) and 77% yield (method B). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.46 (d, 2 H, J = 8.8 Hz), 6.84 (d, 2 H, J = 8.8 Hz), 3.37-3.27 (m, 4 H), 2.58-2.48 (m, 4 H), 2.32 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 152.94, 133.00, 119.68, 113.76, 99.53, 54.18, 46.61, 45.70; IR (KBr) ν cm^{-1} 2205 (CN).

1-(4-Chlorophenyl)-4-methylpiperazine (7j) (Table 3): white solid; m.p. 78°C. 57% yield (method A) and 65% yield (method B). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.19 (d, 2 H, J = 8.8 Hz), 6.83 (d, 2 H, J = 8.8 Hz), 3.20-3.13 (m, 4 H), 2.60-2.52 (m, 4 H), 2.34 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 149.70, 128.92, 124.18, 116.98, 54.79, 48.87, 45.95. Anal. Calcd for $C_{11}H_{15}ClN_2$: C, 62.70; H, 7.18; Cl, 16.83; N, 13.30. Found: C, 62.7; H, 7.3; Cl, 16.5; N, 13.2. Spectral data for **9b**: yellow solid; m.p. 164°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 6.89 (s, 4 H), 3.21-3.14 (m, 8 H), 2.75-2.65 (m, 8H), 2.42 (s, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 145.10, 117.81, 54.89, 49.56, 45.37.

1-(3-Chlorophenyl)-4-methylpiperazine[29] **(7k)** (Table 3): colorless oil. 35% yield (method A) and 36% (method B). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.12 (dd, 1 H, ^3J = $^3J'$ = 8.0 Hz), 6.89-6.70 (m, 3 H), 3.22-3.13 (m, 4 H), 2.57-2.49 (m, 4 H), 2.31 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 152.08, 134.69, 129.81,

118.96, 115.46, 113.62, 54.68, 48.33, 45.89. Spectral data for **9a**: yellow solid; decomposition 220°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.14 (dd, 1 H, $^3J = {}^3J' = 8.2$ Hz), 6.53-6.44 (m, 3 H), 3.26-3.17 (m, 8H), 2.64-2.55 (m, 8H), 2.36 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 152.23, 129.50, 108.23, 104.64, 55.07, 49.22, 45.98.

1-Methyl-4-(2-pyridyl)piperazine[28a] **(7l)** (Table 3): pale yellow oil. 69% yield (method A) and 79% yield (method B). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 8.17 (dd, 1 H, $^3J = 5.0$ Hz, $^4J = 1.2$ Hz), 7.51-7.36 (m, 1 H), 6.68-6.53 (m, 2 H), 3.60-3.50 (m, 4 H), 2.55-2.46 (m, 4 H), 2.31 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 159.00, 147.48, 136.98, 112.85, 106.62, 54.39, 45.71, 44.63.

*Synthesis of arylpiperazines **8** from aryl chlorides and 1-piperazine carboxylate **6**.*

Ethyl-4-phenyl-1-piperazine carboxylate[30] **(8a)** (Table 4): white solid; m.p. 61°C (lit.,[28] m.p. 61.5 °C). 74% yield (method B). ^{1}H NMR (250 MHz, $CDCl_3$) δ ppm: 7.34-7.21 (m, 2 H), 6.98-6.84 (m, 3 H), 4.17 (q, 2 H, $J = 7.3$ Hz), 3.67-3.58 (m, 4 H), 3.20-3.10 (m, 4 H), 1.28 (t, 3 H, $J = 7.3$ Hz). ^{13}C NMR (60 MHz, $CDCl_3$) δ ppm: 155.07, 150.86, 128.81, 119.97, 116.32, 61.06, 49.01, 43.29, 14.37. IR (KBr) ν cm^{-1} 1711 (C=O).

Ethyl-4-(4-methylphenyl)-1-piperazine carboxylate (8b) (Table 4): white solid; m.p. 62°C. 70% yield (method B). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.08 (d, 2 H, $J = 8.6$ Hz), 6.84 (d, 2 H, $J = 8.6$ Hz), 4.17 (q, 2 H, $J = 7.3$ Hz), 3.67-3.59 (m, 4 H), 3.12-3.02 (m, 4 H), 2.27 (s, 3 H), 1.28 (t, 3 H, $J = 7.3$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 155.87, 149.50, 130.40, 130.11, 117.47, 61.82, 50.40, 40.08, 20.83, 15.09. IR (KBr) ν cm^{-1} 1690 (C=O). HREIMS Obsd. m/z = 248.1518 (M)$^+$, $C_{14}H_{20}N_2O_2$ requires m/z = 248.1524.

Ethyl-4-[4-(trifluoromethyl)phenyl)-1-piperazine carboxylate (8c) (Table 4): white solid; m.p. 69-70°C. 78% yield (method B). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.47 (d, 2 H, $J = 8.6$ Hz), 6.90 (d, 2 H, $J = 8.6$ Hz), 4.16 (q, 2 H, $J = 7.3$ Hz), 3.66-3.58 (m, 4 H), 3.27-3.18 (m, 4 H), 1.27 (t, 3 H, $J = 7.3$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 155.29, 153.02, 126.30, 120.69, 114.86, 61.44, 47.87, 43.13, 14.78. ^{19}F NMR (235 MHz) δ ppm: -61.77. IR (KBr) ν cm^{-1}: 1703 (C=O). HREIMS Obsd. m/z = 302.1255 (M)$^+$, $C_{14}H_{17}F_3N_2O_2$ requires m/z = 302.1241.

Ethyl-4-(2-pyridyl)-1-piperazine carboxylate[31] **(8d)** (Table 4): white solid; m.p. 66°C (lit.,[29] m.p. 66-67°C). 69% yield (method B). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 8.17 (d, 1 H, $J = 4.0$ Hz), 7.53-7.42 (m, 1 H), 6.69-6.57 (m, 2 H), 4.16 (q, 2 H, $J = 7.3$ Hz), 3.64-3.45 (m, 8 H), 1.27 (t, 3 H, $J = 7.3$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 155.29, 153.02, 126.61, 124.52 (q, $J = 269$ Hz), 122.82 (q, $J = 32$ Hz), 120.35, 61.43, 47.87, 43.13. IR (KBr) ν cm^{-1} 1686 (C=O).

*Synthesis of arylpiperazines **10**. Typical procedure.*

The arylpiperazine carboxylate (6.04 mmol) dissolved in THF (10 mL) was added dropwise to a suspension of $LiAlH_4$ (0.918 g, 24.2 mmol) in THF (20 ml) cooled to 0°C. After the addition was completed, the ice-bath was removed and the mixture was refluxed for 1h. After cooling to room temperature, the reaction was carefully quenched with water (10 mL) and the aryl piperazine **10** extracted with Et_2O (2 x 50 ml). The combined ethereal extracts were dried over $MgSO_4$ and the solvent removed under reduced pressure. The crude product was purified by column chromatography on silica gel (solvent: 50/50 AcOEt/MeOH).

1-(4-Methylphenyl)piperazine[32] **(10a).** Yellow oil. 90 % yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.04 (d, 2 H, $J = 8.6$ Hz), 6.84 (d, 2 H, $J = 8.6$ Hz), 3.20-3.12 (m, 4 H), 2.61-2.53 (m, 4 H), 2.34 (s, 3 H), 2.26 (NH). ^{13}C

NMR (100 MHz, $CDCl_3$) δ ppm: 149.13, 129.56, 129.12, 116.32, 55.10, 49.59, 20.34. IR (KBr) ν cm^{-1} 3402 (N-H).

1-(2-Pyridyl)piperazine[33] (10b). Yellow oil. 94 % yield. ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 8.22-8.15 (m, 1 H), 7. 50-7.41 (m, 1 H), 6.67-6.57 (m, 2 H), 3.53-3.45 (m, 4 H), 3.01-2.92 (m, 4 H), 2.33 (NH). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 159.44, 147.60, 137.11, 112.96, 106.74, 45.98, 45.57. IR (film) ν cm^{-1} 3321 (N-H).

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REFERENCES AND NOTES

1. (a) Negwer, M.; Organic Chemical Drugs and their Synonyms, 7th Ed., Akademie Verlag GmbH : Berlin 1994. (b) Loutfy, R.O.; Hsiao, C.K.; Kazmaier, P.M. *Photogr. Sci. Eng.* **1983**, *27*, 5. (c) D'Aprano, G.; Leclerc, M.; Zotti, G.; Schiavon, G. *Chem. Mater.* **1995**, *7*, 33.
2. (a) Catto, A.; Motta, G.; Tajana, A.; Cazzulani, P.; Nardi, D.; Leonardi, A. *J. Med. Chem.* **1987**, *30*, 13. (b) Gazit, A.; Osherov, N.; Posner, I.; Yaish, P.; Paradsu, E.; Gilon, C.; Levitsky, A. *J. Med. Chem.* **1991**, *34*, 1896. (c) Perez, M.; Fourrier, C.; Sigogneau, I.; Pauwels, P. J.; Palmier, C.; John, G. W.; Valentin, J. P.; Halazy, S. *J. Med. Chem.* **1995**, *38*, 3602. (d) Broekkamp, C. L. E.; Leysen, D.; Peeters, B. W. M. M.; Pinder, R.M. *J. Med. Chem.* **1995**, *38*, 4615.
3. (a) Hartwig, J.F. *Synlett* **1997**, 329 and references cited therein. (b) Beller, M.; Riermeier, T.H.; Reisinger, C.P.; Hermann, W.A. *Tetrahedron Lett.* **1997**, *38*, 2073. (c) Prabhakar Reddy, N.; Tanaka, M. *Tetrahedron Lett.* **1997**, *38*, 4807. (d) Wolfe, J.P.; Wagaw, S.; Marcoux, J.F.; Buchwald, S.L. *Acc. Chem. Res.* **1998**, *31*, 805. (e) Hartwig, J.F. *Acc. Chem. Res.* **1998**, *31*, 852. (f) Hartwig, J.F. *Angew. Chem. Int. Ed.* **1998**, *37*, 2046 and references cited therein. (g) Hartwig, J.F. *Angew. Chem. Int. Ed.* **1998**, *37*, 2090. (h) Singer, R.A.; Sadighi, J.P.; Buchwald, S.L. *J. Am. Chem. Soc.* **1998**, *120*, 213. (i) Mann, G.; Hartwig, J.F.; Driver, M.S.; Fernandez-Rivas, C. *J. Am. Chem. Soc.* **1998**, *120*, 827. (j) Hamann, B.C.; Hartwig, J.F. *J. Am. Chem. Soc.* **1998**, *120*, 7369. (k) Old, D.W.; Wolfe, J.P.; Buchwald, S.L. *J. Am. Chem. Soc.* **1998**, *120*, 9722. (l) Yamamoto, T.; Nishiyama, M.; Koie, Y. *Tetrahedron Lett.* **1998**, *39*, 2367. (m) Singer, R.A.; Buchwald, S.L. *Tetrahedron Lett.* **1999**, 40, 1095. (n) Bei, X.; Guram, A.S.; Turner, H.W.; Weinberg, W.H. *Tetrahedron Lett.* **1999**, *40*, 1237. (o) Shakespeare, W.C. *Tetrahedron Lett.* **1999**, *40*, 2035. (p) Wang, Z.; Skerlj, R.T.; Bridger, G.J. *Tetrahedron Lett.* **1999**, *40*, 3543. (q) Cabanal-Duvillard, I.; Mangeney, P. *Tetrahedron Lett.* **1999**, *40*, 3877. (r) Guari, Y.; Van Es, D.S.; Reek, J.N.H.; Kamer, P.C.J.; Van Leuwen, P.W.N.M. *Tetrahedron Lett.* **1999**, *40*, 3789. (s) Yang, B.H.; Buchwald, S.L. *J. Organomet. Chem.* **1999**, *576*, 125. (t) Hartwig, J.F.; Kawatsura, M.; Hauck, S.I.; Shaughnessy, K.H.; Alcazar-Roman, L.M. *J. Org. Chem.* **1999**, *64*, 5575.
4. Wolfe, J.P.; Buchwald, S.L. *J. Am. Chem. Soc.* **1997**, *119*, 6054.
5. Brenner, E.; Fort, Y. *Tetrahedron Lett.* **1998**, *37*, 2090.
6. (a) Lourak, M.; Vanderesse, R.; Fort, Y.; Caubère, P. *J. Org. Chem.* **1989**, *54*, 4840. (b) Lourak, M.; Vanderesse, R.; Fort, Y.; Caubère, P. *J. Org. Chem.* **1989**, *54*, 4844.
7. Velluz, L.; Amiard, G.; Heymès, R. *Bull. Soc. Chim. Fr.* **1954**, 1012.
8. (a) Ten Hoeve, W.; Kruse, C.G.; Luteyn, J.M.; Thiecke, J.R.G.; Wynberg, H. *J. Org. Chem.* **1993**, *58*, 5101. (b) Neuville, L.; Zhu, J. *Tetrahedron Lett.* **1997**, *38*, 4091.

9. (a) Dankwardt, S.M.; Newman, S.R.; Krstenansky, J.L. *Tetrahedron Lett.* **1995**, *36*, 4923. (b) Pan, P. C.; Sun, C.M. *Tetrahedron Lett.* **1998**, *39*, 9505.
10. Perez, M.; Potier, P.; Halazy, S. *Tetrahedron Lett.* **1996**, *37*, 8487.
11. (a) Pearson, A.J.; Gelormini, A.M.; Fox, M.A.; Watkins, D. *J. Org. Chem.* **1996**, *61*, 1297. (b) Pearson, A.J.; Gelormini, A.M. *Tetrahedron Lett.* **1997**, *38*, 5123.
12. Mishani, E.; Dence, C.S.; McCarthy, T.T.; Welch, M.J. *Tetrahedron Lett.* **1996**, *37*, 319.
13. (a) Guram, A.S.; Rennels, R.A.; Buchwald, S.L. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1348. (b) Zhao, S.H.; Miller, A.K.; Berger, J.; Flippin, L.A. *Tetrahedron Lett.* **1996**, *37*, 4463. (c) Wolfe, J.P.; Wagaw, S.; Buchwald, S.L. *J. Am. Chem. Soc.* **1996**, *118*, 7215. (d) Kamikawa, K.; Sugimoto, S.; Uemura, M. *J. Org. Chem.* **1998**, *63*, 8407. (e) Witulsky, B.; Senft, S.; Thum, A. *Synlett* **1998**, 504. (f) Kerrigan, F.; Martin, C.; Thomas, G.H. *Tetrahedron Lett.* **1998**, *39*, 2219.
14. Percec, V.; Bae, J.Y.; Zhao, M.; Hill, D.H. *J. Org. Chem.* **1995**, *60*, 176.
15. Verardo, G.; Giumanini, A.G.; Favret, G.; Strazzolini, D. *Synthesis* **1991**, 447.
16. Tsuji, Y.; Huk, K.T.; Ohsugi, Y.; Watanabe, Y. *J. Org. Chem.* **1985**, *50*, 1365.
17. Bhaskar Kanth, J.V.; Periasamy, M. *J. Org. Chem.* **1993**, *58*, 3156.
18. Shim, S.C.; Huh, K.T.; Park, W.H. *Tetrahedron* **1986**, *42*, 259.
19. Venuti, M.C.; Ort, O. *Synthesis* **1988**, 985.
20. Kang, S.K.; Lee, H.W.; Choi, W.K.; Hong, R.K.; Kim, J.S. *Synthetic Commun.* **1996**, *26*, 4219.
21. Watanabe, Y.; Tsuji, Y.; Ige, H.; Ohsugi, Y.; Ohta, T. *J. Org. Chem.* **1984**, *49*, 3359.
22. Shono, T.; Matsumura, Y.; Inoue, K.; Ohmizu, H.; Kashimura, S. *J. Am. Chem. Soc.* **1982**, *104*, 5753.
23. Wagaw, S.; Buchwald, S.L. *J. Org. Chem.* **1996**, *61*, 7240.
24. Kawakami, T.; Sugimoto, T.; Shibata, I.; Baba, A.; Matsuda, H.; Sonoda, N. *J. Org. Chem.* **1995**, *60*, 2677.
25. Cervena, I.; Dlabac, A.; Nemec, J.; Protiva, M. *Collect. Czech. Chem. Commun.* **1975**, *40*, 1612.
26. Nagarajan, K.; Venkateswarlu, A. *Tetrahedron Lett.* **1967**, 293.
27. Chapman, D.R.; Bauer, L.; Waller, D.P.; Zaneveld, L.J.D. *J. Heterocyclic Chem.* **1990**, *27*, 2063.
28. Sharpe, C.J.; Shadbolt, R.S.; Brown, G.R.; Ashford, A.; Ross, J.W. *J. Med. Chem.* **1971**, *14*, 836.
29. Ames, D.E. *J. Chem. Soc.* **1960**, 3163.
30. Stewart, H.W.; Turner, R.J.; Denton, J.J.; Kushner, S.; Brancone, L.M.; Mc Ewen, W.L.; Hewitt, R.I.; Subbarow, Y. *J. Org. Chem.* **1948**, 134.
31. Howard, K.L.; Stewart, H.W.; Conroy, E.A.; Denton, J.J. *J. Org. Chem.* **1953**, 1484.
32. Pollard, C.B.; Wicker, T.H. *J. Am. Chem. Soc.* **1954**, *76*, 1853.
33. Hamlin, K.E.; Weston, A.W.; Fischer, F.E.; Michaels, R.J. *J. Am. Chem. Soc.* **1949**, *71*, 2734.