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Nickel-catalysed selective *N*-arylation or *N*,*N*′-diarylation of secondary diamines

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Abstract—The selective synthesis of *N*-aryl or *N*,*N*′-diaryl piperazines and trimethylene(bis)piperidines from the corresponding diamines and aryl chlorides using a catalyst combination of Ni(0) associated to 2,2′-bipyridine is described. The Ni/2,2′-bipyridine catalyst is also effective for the sequential arylation of piperazine. The preparation of novel and unsymmetrical 1,4-diaryl piperazines is reported. © 2002 Elsevier Science Ltd. All rights reserved.

1. Introduction

N-arylated and *N*,*N*′-diarylated piperazines are building blocks or intermediates widely used in the drug discovery process. Unsymmetrically substituted piperazines are present in several investigational and established biologically active compounds such as ligands of serotonin (5-HT) receptors,[1] antifungals,[2] antivirals,[3] antibacterials[4] or cholesterol ester transfer protein inhibitors.[5] Examples include the neurotransmitter TFMPP, the cardiotonic agent Vesnarinone and the antifungal Itraconazole (Chart 1).

During the last decade, numerous procedures have been reported for the preparation of these compounds including S_NAr reactions in liquid phase[6] or on solid support,[7] S_NAr reactions on tricarbonyl chromium complexes,[8] displacement of a chlorine atom in arene–iron complexes,[9] reaction of aniline derivatives with bis(2-bromoethyl) *N*-substituted amines on basic alumina.[10]

By contrast, palladium-catalysed aminations of aryl halides, extensively studied during recent years,[11] have only scarcely been used with piperazine itself due to the competitive bis-arylation reaction. A proper choice of catalyst seemed to be crucial for the success of the coupling. Zhao reported first the use of the $PdCl_2[P(o\text{-tolyl})_3]_2$ catalyst for the direct monoarylation of piperazine.[12] Koie disclosed a superior catalyst system which involved the $Pd/P(t\text{-Bu})_3$ combination for the coupling of aryl bromides with piperazine.[13] The Pd/BINAP catalyst system was also successfully employed for the amination of 1,2,3-trihalogeno substituted benzenes, bromotriazolones and benzimidazoles.[14] While all these 'one-pot' methods are noteworthy, they require an excess of piperazine (up to 6 equiv. relative to the aryl halide) to obtain 1-arylpiper-

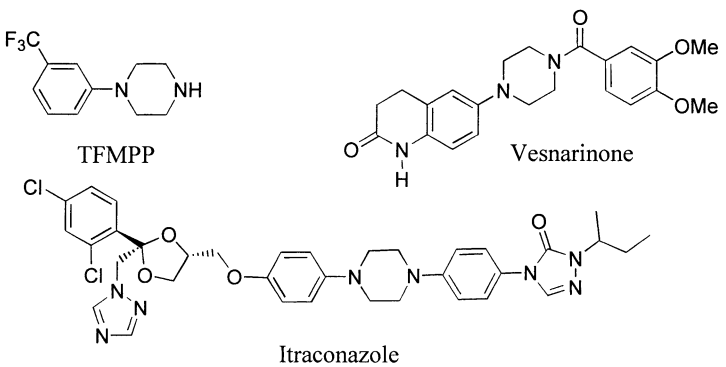

Chart 1.

Keywords: *N*-arylation; *N*,*N*′-diarylation; secondary diamines; nickel catalysis.

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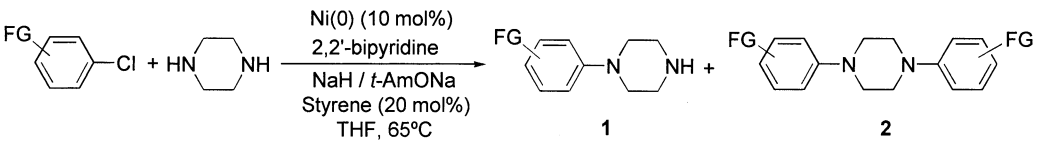
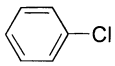
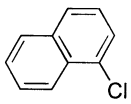
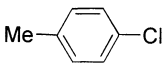
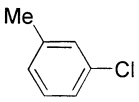
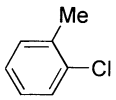
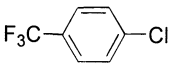
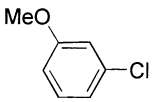
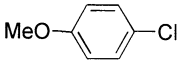
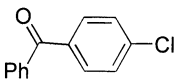
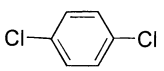
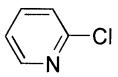


Scheme 1.

azines with good selectivity and yields. This excess can also be a drawback if expensive piperazines derivatives have to be coupled. Only Gala reported very recently the synthesis of 1-arylpiperazines using almost equimolar amounts of aryl bromides and piperazine in the presence of the Pd/BINAP catalyst.[15] Alternatively, the preparation of 1-arylpiperazines in a multistep protocol starting from Boc-protected piperazine had also been described and afforded disappointing results.[16]

Nickel-catalysed amination reactions have received less attention. Buchwald first reported the use of $Ni(cod)_2$ (cod=cyclooctadiene) associated with 1,1′-bis(diphenylphosphino)ferrocene (dppf) or 1,10-phenanthroline for the synthesis of arylamines.[17] A heterogeneous Ni(0)/C catalyst liganded with dppf was also recently developed by Lipshutz.[18] For our part, we have reported the use of a catalyst combination of in situ generated colloidal Ni(0) associated with 2,2′-bipyridine or *N*-heterocyclic carbenes

Table 1. Nickel-catalysed synthesis of 1-arylpiperazines **1** from aryl chlorides

Entry	Aryl chloride	Reaction conditions A[a]			Reaction conditions B[b]		
		Reaction time (h)[c]	Yield of **1** (%)[d]	Yield of **2** (%)[d]	Reaction time (h)[c]	Yield of **1** (%)[d]	Yield of **2** (%)[d]
a		8.5	61	16	6	86	8
b		8	65	23	5	87	7
c		9.5	56	15	6.5	81	8
d		9	57	15	6	82	9
e		12	29	2	8	42	0
f		8	62	10	6	87	4
g		9.5	52	11	6	87	5
h		12	23	1	8	41	0
i		9	84	3	5	90	0
j		9.5	58	28	7	85	6
k		8	63	12	7	78	4

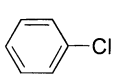
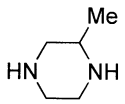
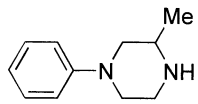
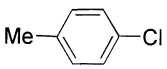
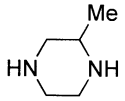
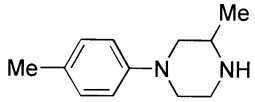
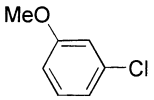
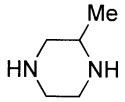
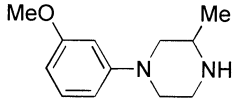
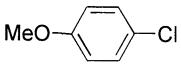
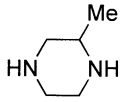
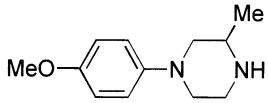
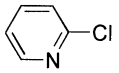
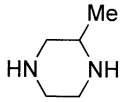
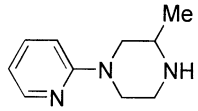
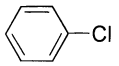
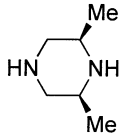
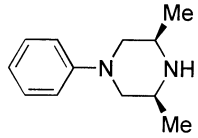
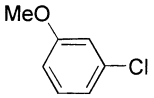
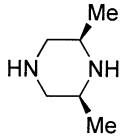
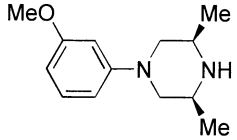
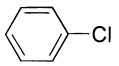
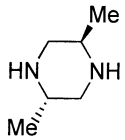
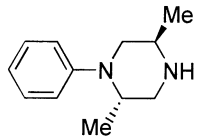
[a] Reactions were carried out with 25 mmol aryl chloride, 27.5 mmol piperazine, 2.5 mmol $Ni(OAc)_2$, 7.5 mmol bipyridine, 5 mmol *t*-AmOH, 30 mmol NaH and 5 mmol styrene in 40 ml THF.

[b] Reactions were carried out with 25 mmol aryl chloride, 50.0 mmol piperazine, 2.5 mmol $Ni(OAc)_2$, 7.5 mmol 2,2′-bipyridine, 5 mmol *t*-AmOH, 30 mmol NaH and 5 mmol styrene in 40 ml THF.

[c] Determined by GC analysis.

[d] Products were isolated by chromatography on silica gel. Yields are based on the aryl chloride. All yields reported are isolated yields of compounds estimated to be >97% pure by NMR and GC analysis. All compounds were characterised by NMR (^1H, ^{13}C), IR, MS or combustion analysis.

Table 2. Nickel-catalysed synthesis of substituted 1-arylpiperazines **3** from aryl chlorides

Entry	Aryl chloride	Amine	Product **3**	Reaction time (h)[a]	Yield (%)[b]
a				9	66
b				10	53
c				9	65
d				13	34
e				8.5	54
f				9	69
g				9.5	70
h				12	26

Reactions were performed on 20 mmol aryl chloride and 22 mmol amine.

[a] Determined by GC analysis.

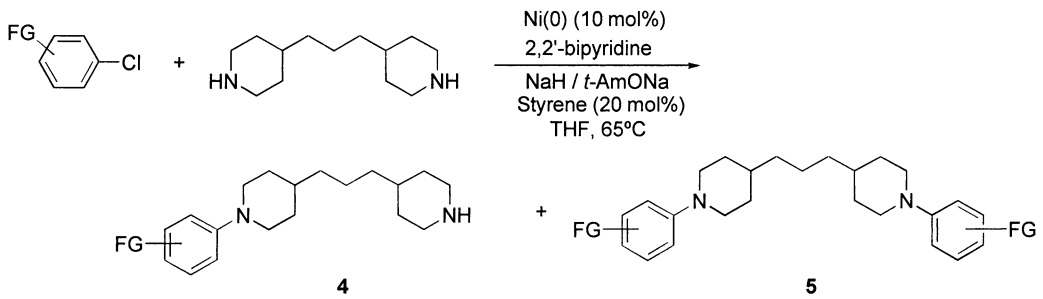
[b] Products were isolated by chromatography on silica gel. Yields are based on the aryl chloride. All yields reported are isolated yields of compounds estimated to be >97% pure by NMR and GC analysis. All compounds were characterised by NMR (^{1}H, ^{13}C), IR, MS or combustion analysis.

which provided efficient routes to substituted anilines.[19,20] In addition, the Ni/2,2′-bipyridine catalyst has also been shown to be effective for polyamination or selective monoamination of aryl di- and trichlorides.[21] Since the coupling of secondary amines with aryl chlorides was efficient with this new catalyst system, we sought to develop a simple, general and efficient method for the synthesis of arylpiperazines, thereby expanding the substrate scope of the nickel-catalysed amination methodology. A preliminary account of these nickel-catalysed arylation reactions has appeared.[22] Herein, we disclose the results of a detailed study of the use of Ni/2,2′-bipyridine catalyst in *N*- or *N*,*N*′-diarylation reactions of secondary cyclic amines.

2. Results and discussion

In order to investigate the conditions for the nickel-catalysed synthesis of 1-arylpiperazines (Scheme 1), the reaction of chlorobenzene with piperazine was initially studied.

A quick survey of reaction conditions revealed that a good yield (61%) of 1-phenylpiperazine **1a** could be obtained by heating the aryl chloride and the diamine (1.1 equiv.) with Ni(0) (10 mol%), the 2,2′-bipyridine ligand (20 mol%) and *t*-AmONa activated sodium hydride at 65°C in THF. Several details are worthy of comments. No reaction occurred in the absence of catalyst. 2,2′-Bipyridine was found to be the most effective ligand. The Ni/phenanthroline or Ni/triphenylphosphine complexes did not show any catalytic activity under classical reaction conditions. THF or dioxane were comparable as the solvent whereas reaction in toluene resulted in low conversion of the arylated product **1a**. As previously reported with simple secondary amines,[19,21] the efficiency of our system was markedly increased by adding a catalytic amount of styrene, simultaneously to the aryl chloride in the reaction medium, to trap hydrogen evolved and thus inhibit hydrogenolysis of the carbon–chlorine



Scheme 2.

bond. Finally, in contrast with most palladium-catalysed arylation reactions of piperazine, the reaction proceeded with equimolar ratios of the coupling substrates and resulted in the selective formation of **1a** accompanied by 16% of 1,4-diphenylpiperazine (Table 1, entry a, reaction conditions A).

Table 1 describes the results of coupling of piperazine with structurally and electronically diverse aryl and heteroaryl chlorides. Using the conditions described above (10 mol% Ni and 1.1 equiv. piperazine relative to the aryl chloride), the Ni-catalysed couplings provided a general route to the corresponding 1-arylpiperazines. The only side products observed were the 1,4-diarylpiperazine **2** and the arene resulting from reduction of the starting aryl chloride.

The amination reaction was found to be sensitive to an *ortho*-substitution of the aryl chloride. 2-Chlorotoluene reacted with piperazine in 29% yield (entry e) while 4- and 3-chlorotoluene reacted with the amine to give the desired arylpiperazines **1c** and **1d** in 56 and 57% yield, respectively (entries c and d). Electron-poor aryl chlorides gave the corresponding arylpiperazines **1** in good yields (entries f, g, i and k) whereas lower yields were obtained with electron-rich aryl chlorides (entry h). It must also be underlined that yields of bis-arylation products increased with electron-poor aryl chlorides due to their higher reactivity.

The selectivity of the coupling was markedly improved by increasing the initial amount of piperazine (Table 1, reaction conditions B). The use of 2 equiv. of piperazine was found to be more efficient at minimising, although not eliminating, the formation of 1,4-diarylpiperazines **2**. Yields of **1** were similar to those obtained in palladium-catalysed amination reactions using a larger excess (4–6 equiv.) of piperazine.[12–14] However, reaction conditions A (1.1 equiv. of piperazine) should allow easy access to 1-arylpiperazines especially when the starting materials are of high cost (see below).

Given our success in the arylation of piperazine itself, we turned our attention to substituted piperazines. Using 1.1 equiv. of 2-methylpiperazine and 10 mol% of the Ni/2,2′-bipyridine catalyst, satisfactory yields were obtained for the synthesis of arylpiperazines **3** (Table 2). The couplings occurred at the less-hindered nitrogen atom of the starting diamine and neither the other possible regioisomer nor the 1,4-diarylpiperazine were detected in the crude reaction mixture. The substrate scope was similar to that for reactions performed with piperazine. Good results were obtained with electron-neutral or electron-poor aryl chlorides (entries a–c and e) while an electron-rich substrate like 4-chloroanisole (entry d) afforded the desired arylpiperazine **3d** in a modest 34% yield.

Not surprisingly, couplings performed with *cis*-2,6-dimethylpiperazine gave the anticipated *cis*-1-aryl-3,5-dimethylpiperazines **3f** and **3g** in good yields (entries f and g) while reaction performed with *trans*-2,5-dimethylpiperazine in which both nitrogen atoms are hindered afforded only 26% of the arylpiperazine **3h**. In the latter case, attempts to increase the reaction yield by extending the reaction time or by heating at higher temperatures were not effective. Interestingly, whereas palladium-catalysed couplings performed with *trans*-3,5-dimethylpiperazine gave a mixture of *trans*- and *cis*-arylated-2,5-dimethylpiperazine in a 5/1 ratio,[12] such an isomerisation caused by a β-hydride elimination has not been observed under nickel-catalysis.

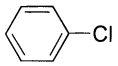
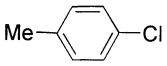
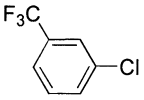
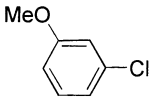
Encouraged by these promising results on selective *N*-monoarylation of piperazine using the Ni/2,2′-bipyridine catalyst, we wished to expand the method to other diamines like trimethylene(bis)piperidine used in the preparation of poly(aryleneamine)s by palladium-catalysed coupling with aryl dibromides (Scheme 2).[23]

The couplings were first carried out using the classical conditions for the arylation of piperazine (1.1 equiv. of the diamine relative to the aryl chloride, 10 mol% of the Ni/2,2′-bipyridine catalyst, THF, 65°C). Results are summarised in Table 3 (reaction conditions A). In all cases, the selectivity mono/bis arylation was disappointing and mixtures of *N*-mono and *N*,*N*′-bis-arylated trimethylene(bis)piperidines **4** and **5** were obtained. For example, the amination of chlorobenzene gave after work up and purification a mixture of **4a** and **5a** in 51 and 32% isolated yields, respectively (Table 3, entry a, reaction conditions A). Using 3-chloroanisole (entry d), the selectivity was even inverted and **5d** was the major product of the coupling.

This problem has been solved to some degree by increasing the initial amount of trimethylene(bis)piperidine to 2 equiv. (reaction conditions B, Table 3). Under these conditions, improved **4/5** product ratios were obtained. For example, the isolated yield of **4b** was 79% with 2 equiv. of diamine while this substrate was produced in a modest 48% yield using 1.1 equiv. of trimethylene(bis)piperidine (entry b).

The scope of the above arylation method was further

Table 3. Nickel-catalysed synthesis of *N*-aryl trimethylene(bis)piperidine **4** from aryl chlorides

Entry	Aryl chloride	Reaction conditions A[a]			Reaction conditions B[b]		
		Reaction time (h)[c]	Isolated yield of **4** (%)[d]	Isolated yield of **5** (%)[d]	Reaction time (h)[c]	Isolated yield of **4** (%)[d]	Isolated yield of **5** (%)[d]
a		12	51	32	9	81	8
b		14	48	29	11	79	5
c		10	43	34	8	74	6
d		11	36	42	9	78	8

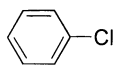
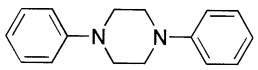
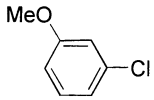
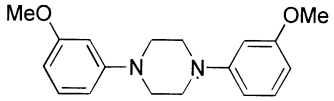
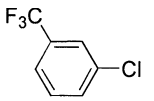
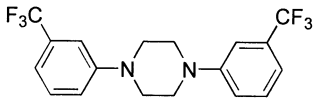
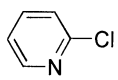
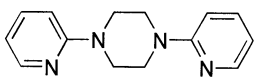
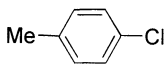
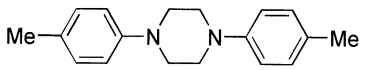
[a] Reactions were carried out with 25 mmol aryl chloride, 27.5 mmol trimethylene(bis)piperidine, 2.5 mmol $Ni(OAc)_2$, 7.5 mmol 2,2′-bipyridine, 5 mmol *t*-AmOH, 30 mmol NaH and 5 mmol styrene in 40 ml THF.
[b] Reactions were carried out with 25 mmol aryl chloride, 50.0 mmol trimethylene(bis)piperidine, 2.5 mmol $Ni(OAc)_2$, 7.5 mmol 2,2′-bipyridine, 5 mmol *t*-AmOH, 30 mmol NaH and 5 mmol styrene in 40 ml THF.
[c] Determined by GC analysis.
[d] Products were isolated by chromatography on silica gel. Yields are based on the aryl chloride. All yields reported are isolated yields of compounds estimated to be >97% pure by NMR and GC analysis. All compounds were characterised by NMR (^1H, ^{13}C), IR, MS or combustion analysis.

expanded by the use of the Ni/2,2′-bipyridine catalyst in bis-arylation reactions of piperazine and trimethylene(bis)-piperidine.

GC monitoring of the reaction mixture indicated in all cases that the initial coupling was more facile than the second one. Conversion into the desired products may be effected by extending the reaction time or by the use of an excess aryl chloride (4 equiv.). Under these conditions, symmetrically *N*,*N*′-biaryl substituted diamines **2** and **5** were obtained in good yields (Tables 4 and 5). Note that compounds **1** (or **4**) and biaryls resulting from the homocoupling of the starting aryl chloride were obtained as by-products in less than 5 and 10% isolated yields, respectively. Except 2-chloropyridine (entry d, Table 4), aryl chlorides bearing electron-withdrawing substituents were more reactive in bis-arylation reactions and gave higher yields of **2** and **5**. The reaction of 2-chloropyridine is typically slower than reactions using simple aromatic derivatives. A possible explanation is that the pyridinic substrate may compete with the 2,2′-bipyridine ligand for coordination to nickel, thereby inhibiting the coupling reaction.

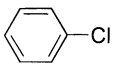
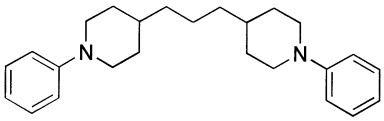
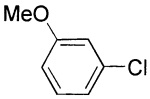
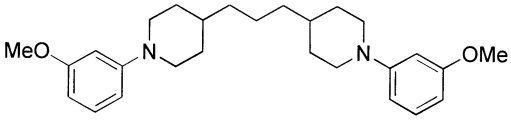
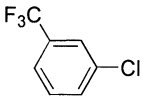
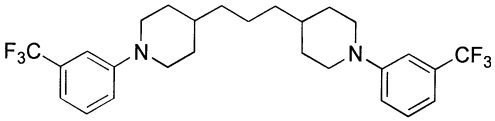
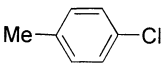
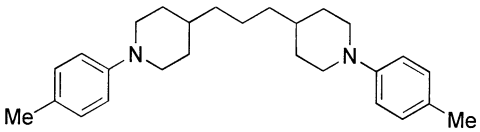
To further probe the application of our methodology, the sequential functionalisation of piperazine with two different aryl chlorides was examined. Initially, we attempted to

Table 4. Nickel-catalysed synthesis of 1,4-diarylpiperazines **2**

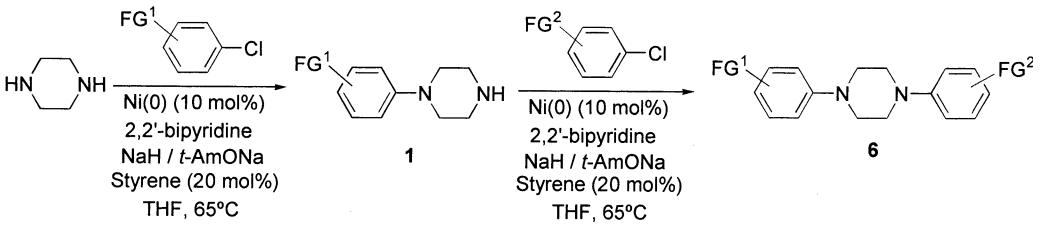
Entry	Aryl chloride	Product **2**	Reaction time (h)[a]	Yield (%)[b]
a			8	78
b			7	79
c			7	82
d			12	69
e			12	76

Reactions were performed on 20 mmol piperazine and 80 mmol aryl chloride.
[a] Determined by GC analysis.
[b] Products were isolated by chromatography on silica gel. Yields are based on piperazine. All yields reported are isolated yields of compounds estimated to be >97% pure by NMR and GC analysis. All compounds were characterised by NMR (^1H, ^{13}C), IR, MS or combustion analysis.

Table 5. Nickel-catalysed synthesis of *N*,*N*′-diaryl trimethylene(bis)piperidines **5**

Entry	Aryl chloride	Product **5**	Reaction time (h)[a]	Yield (%)[b]
a			12	73
b			10	78
c			10	75
d			15	71

Reactions were performed on 20 mmol trimethylene(bis)piperidine and 80 mmol aryl chloride.
[a] Determined by GC analysis.
[b] Products were isolated by chromatography on silica gel. Yields are based on trimethylene(bis)piperidine. All yields reported are isolated yields of compounds estimated to be >97% pure by NMR and GC analysis. All compounds were characterised by NMR (^{1}H, ^{13}C), IR, MS or combustion analysis.

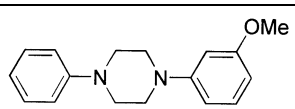
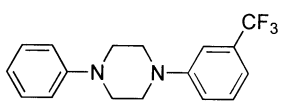
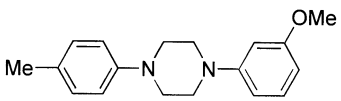


Scheme 3.

prepare unsymmetrical 1,4-diarylpiperazines by a one-pot method wherein the second aryl chloride was added after complete consumption of the first one. Unfortunately, both steps were sluggish. Apparently, the use of a larger amount of sodium hydride for both Ni(0)-catalysed aminations caused an increase of reduction products during the first coupling. In most cases, the homocoupling of the aryl chloride competed with the aryl amination reaction during the second step and unsymmetrical *N*,*N*′-diarylpiperazines **6** were obtained in poor yields, usually less than 20%.

We therefore developed a two-step procedure for the synthesis of **6** from piperazine and two different aryl chlorides (Scheme 3).

Table 6. Nickel-catalysed synthesis of unsymmetrical 1,4-diarylpiperazines **6**

Entry	FG^1	FG^2	Product **6**	Overall yield[a] (%)
a	H	*m*-OMe		71
b	H	*m*-CF_3		66
c	*p*-Me	*m*-OMe		73

Reactions were performed on 27.5 mmol piperazine. Each step was carried out with 25 mmol aryl chloride, 2.5 mmol $Ni(OAc)_2$, 7.5 mmol 2,2′-bipyridine, 5 mmol *t*-AmOH, 30 mmol NaH and 5 mmol styrene in 40 ml THF.
[a] Products were isolated by chromatography on silica gel. Yields are based on the aryl chloride. All yields reported are isolated yields of compounds estimated to be >97% pure by NMR and GC analysis. All compounds were characterised by NMR (^{1}H, ^{13}C), IR, MS or combustion analysis.

Reactions conditions A (Table 1) were employed for the first coupling. The catalyst and the ligand were removed from the reaction mixture by filtration through silica gel followed by concentration. The crude 1-arylpiperazine was used for the second step without further purification. Table 6 provides the results of these double arylation reactions of piperazine. Using this procedure, unsymmetrical 1,4-diarylpiperazines **6** were obtained in yields ranging from 66 to 73%.

3. Conclusion

In conclusion, we have developed nickel-catalysed methods for the selective *N*-mono- or *N*,*N*′-di-arylation of piperazine and trimethylene(bis)piperidine that proceed under mild conditions using readily available and easily handled reagents. A two step procedure for the synthesis of unsymmetrical *N*,*N*′-diarylpiperazines is also described.

These catalytic couplings display broad scope with respect to the steric and electronic properties of the substrate combinations and are compatible with many functional groups. These methods should therefore find wide applications in medicinal chemistry and drug discovery processes.

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 $Ni(OAc)_2{\cdot}4H_2O$ (Fluka) was dried under vacuum (20 mmHg) 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 from hexane before use. All reagents were purchased from commercial sources and were used without purification. Melting points were taken on a Tottoli apparatus and are 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 (^{19}F at 235 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 analyses were performed by the Service central d'analyses du CNRS (Vernaison, France).

4.2. Nickel-catalysed synthesis of 1-arylpiperazines 1

Representative procedure for reaction conditions A. To a suspension of degreased NaH (30 mmol) in THF (20 mL) were added piperazine (27.5 mmol) and *t*-AmOH (5 mmol) in THF (10 mL) followed by 2,2′-bipyridine (7.5 mmol) and the mixture was heated at 65°C. Dried $Ni(OAc)_2$ (2.5 mmol) was then added and the mixture was further stirred at 65°C for 2 h. To the dark suspension of 2,2′-bipyridine liganded Ni(0) thus obtained was added the aryl chloride (25 mmol) and styrene (5 mmol) in THF. The reaction was monitored by GC and after complete consumption of the starting aryl chloride (see Table 1), 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 MeOH–AcOEt as eluant.

Representative procedure for reaction conditions B. NaH (30 mmol), piperazine (50 mmol), *t*-AmOH (5 mmol), 2,2′-bipyridine (7.5 mmol), $Ni(OAc)_2$ (2.5 mmol) and styrene (5 mmol) were used for the amination of 25 mmol aryl chloride using the standard procedure described above.

4.2.1. 1-Phenylpiperazine[13] **1a** (Table 1)**.** Purification was performed by silica gel chromatography using MeOH–AcOEt (40/60) as eluant. The title compound was isolated as a light yellow oil. 61% yield (method A) and 86% yield (method B). IR (NaCl, cm^{-1}): ν_{NH} 3353. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.23 (t, J=7.6 Hz, 2H), 6.93–6.80 (m, 3H), 3.13–3.03 (m, 4H), 2.99–2.89 (m, 4H), 2.18 (NH). ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm: 152.20, 129.48, 120.09, 116.48, 50.71, 46.48.

4.2.2. 1-(1-Naphthyl)piperazine[13] **1b** (Table 1)**.** Purification was performed by silica gel chromatography using MeOH–AcOEt (40/60) as eluant. The title compound was isolated as a yellow oil. 65% yield (method A) and 87% yield (method B). IR (NaCl, cm^{-1}): ν_{NH} 3313. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 8.15 (d, J=7.6 Hz, 1H), 7.72 (d, J=7.6 Hz, 1H), 7.44–7.30 (m, 3H), 7.26 (dd, J=8.0, 7.6 Hz, 1H), 6.81 (d, J=8.0 Hz, 1H), 2.91–2.68 (m, 8H), 2.03 (NH). ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm: 148.73, 133.39, 127.48, 126.99, 124.54, 124.37, 123.86, 122.25, 121.90, 113.21, 52.83, 44.95.

4.2.3. 1-(4-Methylphenyl)piperazine[24] **1c** (Table 1)**.** Purification was performed by silica gel chromatography using MeOH–AcOEt (40/60) as eluant. The title compound was isolated as a yellow oil. 56% yield (method A) and 81% yield (method B). IR (NaCl, cm^{-1}): ν_{NH} 3402. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.04 (d, J=8.6 Hz, 2H), 6.84 (d, J=8.6 Hz, 2H), 3.20–3.12 (m, 4H), 2.61–2.53 (m, 4H), 2.32 (s, 3H), 2.26 (NH). ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm: 149.12, 129.26, 129.00, 116.18, 50.04, 45.31, 20.09.

4.2.4. 1-(3-Methylphenyl)piperazine[13] **1d** (Table 1)**.** Purification was performed by silica gel chromatography using MeOH–AcOEt (40/60) as eluant. The title compound was isolated as a light yellow solid. 57% yield (method A) and 82% yield (method B). Mp=101°C (lit. mp=101°C). IR (KBr, cm^{-1}): ν_{NH} 3383. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.10 (t, J=7.6 Hz, 1H), 6.76–6.60 (m, 3H), 3.08–2.98 (m, 4H), 2.93–2.84 (m, 4H), 2.27 (s, 3H), 1.78 (NH). ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm: 151.28, 137.86, 128.25, 119.87, 116.18, 112.56, 49.75, 45.53, 21.19.

4.2.5. 1-(2-Methylphenyl)piperazine[13] 1e (Table 1). Purification was performed by silica gel chromatography using MeOH–AcOEt (40/60) as eluant. The title compound was isolated as a yellow solid. 29% yield (method A) and 42% yield (method B). Mp=177°C (lit. mp=175°C). IR (KBr, cm^{-1}): ν_{NH} 3391. ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 7.15–7.09 (m, 2H), 7.04–6.96 (m, 2H), 3.15–3.07 (m, 4H), 2.85–2.66 (m, 4H), 2.35 (s, 3H), 2.21 (NH). ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm: 151.61, 132.86, 131.52, 127.21, 122.95, 119.57, 51.73, 46.35, 18.54.

4.2.6. 1-[4-(4-Trifluoromethyl)phenyl]piperazine[25] 1f (Table 1). Purification was performed by silica gel chromatography using MeOH–AcOEt (40/60) as eluant. The title compound was isolated as a white solid. 62% yield (method A) and 87% yield (method B). Mp=107°C (lit. mp=109°C). IR (KBr, cm^{-1}): ν_{NH} 3321. ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 7.49 (d, J=8.8 Hz, 2H), 6.93 (d, J=8.8 Hz, 2H), 3.27–3.20 (m, 4H), 3.07–2.98 (m, 4H), 1.84 (NH). ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm: 153.66, 126.28, 124.86 (q, J=269 Hz), 120.48 (q, J=32 Hz), 114.41, 49.02, 45.82. ^{19}F NMR (235 MHz, $CDCl_3$) δ ppm: −61.79.

4.2.7. 1-(3-Methoxyphenyl)piperazine[13] 1g (Table 1). Purification was performed by silica gel chromatography using MeOH–AcOEt (40/60) as eluant. The title compound was isolated as a yellow oil. 52% yield (method A) and 87% yield (method B). IR (NaCl, cm^{-1}): ν_{NH} 3323. ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 7.15 (t, J=8.4 Hz, 1H), 6.51 (dd, J=8.4, 1.6 Hz, 1H), 6.45 (dd, J=1.6 Hz, 1H), 6.40 (dd, J=8.4, 1.6 Hz, 1H), 3.75 (s, 3H), 3.14–3.08 (m, 4H), 3.02–2.95 (m, 4H), 2.18 (NH). ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm: 160.27, 152.90, 129.47, 108.58, 104.17, 102.17, 54.85, 49.94, 45.77.

4.2.8. 1-(4-Methoxyphenyl)piperazine[13] 1h (Table 1). Purification was performed by silica gel chromatography using MeOH–AcOEt (40/60) as eluant. The title compound was isolated as a brown solid. 52% yield (method A) and 87% yield (method B). Mp=167°C (lit. mp=168°C). IR (KBr, cm^{-1}): ν_{NH} 3323. ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 6.89 (d, J=8.8 Hz, 2H), 6.81 (d, J=8.8 Hz, 2H), 3.71 (s, 3H), 3.28–3.18 (m, 4H), 3.02 (NH). ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm: 152.07, 142.78, 116.49, 112.47, 53.42, 46.02, 41.64.

4.2.9. Phenyl(4-piperazinophenyl)methanone 1i (Table 1). Purification was performed by silica gel chromatography using MeOH–AcOEt (50/50) as eluant. The title compound was isolated as a yellow solid. 84% yield (method A) and 90% yield (method B). Mp=185°C. IR (KBr, cm^{-1}): ν_{NH} 3315, ν_{CO} 1633. ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 7.70–7.63 (m, 4H), 7.62–7.56 (m, 1H), 7.54–7.48 (m, 2H), 7.03–6.95 (m, 2H), 3.36–3.30 (m, 4H), 2.94–2.88 (m, 4H), 2.65 (NH). ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm: 193.91, 153.14, 137.83, 131.43, 130.60, 128.44, 127.20, 125.97, 112.40, 46.59, 44.17. HREIMS Obsd m/z=266.1423 (M), $C_{17}H_{18}N_2O$ requires 266.1419.

4.2.10. 1-(4-Chlorophenyl)piperazine[24] 1j (Table 1). Purification was performed by silica gel chromatography using MeOH–AcOEt (40/60) as eluant. The title compound was isolated as a white solid. 58% yield (method A) and 85% yield (method B). Mp=85°C (lit. mp=85°C). IR (KBr, cm^{-1}): ν_{NH} 3347. ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 7.19 (d, J=8.6 Hz, 2H), 6.81 (d, J=8.6 Hz, 2H), 3.21–2.91 (m, 8H), 2.84 (NH). ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm: 150.17, 128.86, 124.34, 117.12, 49.97, 45.66.

4.2.11. 1-(2-Pyridinyl)piperazine[26] 1k (Table 1). Purification was performed by silica gel chromatography using MeOH–AcOEt (45/55) as eluant. The title compound was isolated as a yellow oil. 63% yield (method A) and 78% yield (method B). IR (NaCl, cm^{-1}): ν_{NH} 3321. ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 8.17 (dd, J=4.75, 1.25 Hz, 1H), 745 (ddd, J=7.4, 1.25 Hz, 1H), 6.67–6.57 (m, 2H), 3.53–3.45 (m, 4H), 3.01–2.92 (m, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm: 159.44, 147.60, 137.11, 112.96, 106.74, 45.98, 45.57.

4.3. Nickel-catalysed synthesis of substituted 1-arylpiperazines 3

Compounds **3** were prepared according to the typical procedure A described for piperazine.

4.3.1. 3-Methyl-1-phenylpiperazine[27] 3a (Table 2). Purification was performed by silica gel chromatography using MeOH–AcOEt (40/60) as eluant. The title compound was isolated as a pale yellow oil. 66% yield. IR (NaCl, cm^{-1}): ν_{NH} 3387. ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 7.21 (dd, J=8.4, 7.6 Hz, 2H), 6.86 (d, J=8.4 Hz, 2H), 3.38–3.29 (m, 2H), 2.99 (ddd, J=11.6, 3.2, 2.8 Hz, 1H), 2.95–2.84 (m, 2H), 2.62 (ddd, J=11.6, 11.6, 3.2, 1H), 2.52 (NH), 2.29 (dd, J=11.6, 11.6, 1H), 1.06 (d, J=6.4 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm: 150.94, 128.50, 119.01, 115.54, 56.23, 49.93, 48.69, 45.21, 19.14.

4.3.2. 3-Methyl-1-(4-methylphenyl)piperazine[12] 3b (Table 2). Purification was performed by silica gel chromatography using MeOH–AcOEt (40/60) as eluant. The title compound was isolated as a pale yellow oil. 53% yield. IR (NaCl, cm^{-1}): ν_{NH} 3425. ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 7.06 (d, J=8.4 Hz, 2H), 6.83 (d, J=8.4 Hz, 2H), 3.47–3.38 (m, 2H), 3.10 (ddd, J=11.6, 3.2, 2.8 Hz, 1H), 3.05–2.95 (m, 2H), 2.66 (ddd, J=11.6, 11.6, 3.2 Hz, 1H), 2.42 (NH), 2.31 (dd, J=11.6, 11.6 Hz; 1H), 2.26 (s, 3H), 1.12 (d, J=6.4 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm: 149.22, 129.43, 129.03, 116.37, 57.26, 50.40, 49.69, 45.57, 20.23, 19.45.

4.3.3. 1-(3-Methoxyphenyl)-3-methylpiperazine 3c (Table 2). Purification was performed by silica gel chromatography using MeOH–AcOEt (40/60) as eluant. The title compound was isolated as a yellow oil. 65% yield. IR (NaCl, cm^{-1}): ν_{NH} 3364. ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 7.14 (dd, J=8.4, 8.4 Hz, 1H), 6.51 (dd, J=8.4, 2.0 Hz, 1H), 6.45 (dd, J=2.0, 2.0 Hz, 1H), 6.40 (dd, J=8.4, 2.0 Hz, 1H), 3.74 (s, 3H), 3.48 (d, J=12.0 Hz, 2H), 3.09 (ddd, J=12.0, 3.2, 2.8 Hz, 1H), 3.03–2.92 (m, 2H), 2.74 (ddd, J=12.0, 12.0, 3.2 Hz, 1H), 2.48 (NH), 2.41 (dd, J=12.0, 12.0 Hz, 1H), 1.14 (d, J=6.4 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm: 160.13, 152.19, 129.36, 108.58, 104.19, 102.21, 55.82, 54.67, 50.07, 48.33, 44.84, 18.68. HREIMS Obsd m/z=206.1426 (M), $C_{12}H_{18}N_2O$ requires 206.1419.

4.3.4. 1-(4-Methoxyphenyl)-3-methylpiperazine 3d (Table 2). Purification was performed by silica gel chromatography using MeOH–AcOEt (40/60) as eluant. The title compound was isolated as a pale yellow oil. 34% yield. IR (NaCl, cm^{-1}): ν_{NH} 3431. ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 6.89 (d, J=9.2 Hz, 2H), 6.83 (d, J=9.2 Hz, 2H), 3.75 (s, 3H), 3.42–3.33 (m, 2H), 3.13–2.99 (m, 3H), 2.67 (ddd, J=11.6, 11.6, 3.2 Hz, 1H), 2.39 (NH), 2.33 (dd, J=11.6, 11.6 Hz, 1H), 1.13 (d, J=6.4 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm: 153.47, 145.53, 118.01, 114.05, 57.98, 55.12, 50.39, 50.35, 45.46, 19.22. HREIMS Obsd m/z=206.1424 (M), $C_{12}H_{18}N_2O$ requires 206.1419.

4.3.5. 3-Methyl-1-(2-pyridinyl)piperazine[27] 3e (Table 2). Purification was performed by silica gel chromatography using MeOH–AcOEt (45/55) as eluant. The title compound was isolated as a yellow oil. 54% yield. IR (NaCl, cm^{-1}): ν_{NH} 3356. ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 8.16 (dd, J=4.8, 2.0 Hz, 1H), 7.42 (ddd, J=8.4, 8.4, 2.0 Hz, 1H), 6.63–6.55 (m, 2H), 4.13 (d, J=11.6 Hz, 1H), 4.06 (d, J=11.6 Hz, 1H), 3.05 (ddd, J=11.6, 3.2, 3.2 Hz, 1H), 2.88–2.80 (m, 3H), 2.52 (NH), 2.45 (dd, J=11.6, 11.6 Hz, 1H), 1.11 (d, J=6.4 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm: 158.67, 147.10, 136.68, 112.53, 106.30, 51.56, 49.59, 44.72, 44.46, 18.78.

4.3.6. 3,5-Dimethyl-1-phenylpiperazine 3f (Table 2). Purification was performed by silica gel chromatography using MeOH–AcOEt (40/60) as eluant. The title compound was isolated as a pale yellow oil. 69% yield. IR (NaCl, cm^{-1}): ν_{NH} 3392. ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 7.25 (dd, J=7.6, 1.2 Hz, 2H), 6.92 (d, J=7.6 Hz, 2H), 6.84 (dd, J=7.6, 7.6 Hz, 1H), 3.51 (dd, J=11.6, 2.8 Hz, 2H), 3.04 (ddq, J=3.6, 2.8, 0.8 Hz, 2.28 (dd, J=11.6, 11.6 Hz, 2H), 1.99 (NH), 1.13 (d, J=6.4 Hz, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm: 151.15, 128.97, 119.45, 116.07, 56.11, 50.51, 19.60. HREIMS Obsd m/z=190.1475 (M), $C_{12}H_{18}N_2$ requires 190.1469.

4.3.7. 1-(3-Methoxyphenyl)-3,5-dimethylpiperazine 3g (Table 2). Purification was performed by silica gel chromatography using MeOH–AcOEt (40/60) as eluant. The title compound was isolated as a pale yellow oil. 70% yield. IR (NaCl, cm^{-1}): ν_{NH} 3385. ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 7.14 (dd, J=8.4, 8.0 Hz, 1H), 6.51 (dd, J=8.4, 2.0 Hz, 1H), 6.44 (dd, J=4.4, 2.0 Hz, 1H), 6.37 (dd, J=8.0, 2.0 Hz, 1H), 3.75 (s, 3H), 3.48 (dd, J=11.6, 2.8 Hz, 2H), 3.01 (ddq, J=3.6, 2.8, 0.8 Hz, 2H), 2.29 (dd, J=11.6, 11.6 Hz, 2H), 2.24 (NH), 1.11 (d, J=6.4 Hz, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm: 160.20, 152.23, 129.38, 108.54, 103.84, 102.13, 55.56, 54.73, 50.26, 19.22. HREIMS Obsd m/z=220.1580 (M), $C_{13}H_{20}N_2O$ requires 220.1575.

4.3.8. 2,5-Dimethyl-1-phenylpiperazine[28] 3h (Table 2). Purification was performed by silica gel chromatography using MeOH–AcOEt (40/60) as eluant. The title compound was isolated as a colourless oil. 26% yield. IR (NaCl, cm^{-1}): ν_{NH} 3388. ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 7.30 (dd, J=7.6, 7.6 Hz, 2H), 7.13–7.09 (m, 3H), 3.33–3.25 (m, 3H), 3.11 (dd, J=12.0, 3.2 Hz, 1H), 2.81 (dd, J=12.0, 12.0 Hz, 2H), 2.09 (NH), 1.28 (d, J=6.4 Hz, 3H), 0.92 (d, J=6.0 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm: 150.62, 128.84, 124.55, 60.50, 52.28, 51.51, 51.09, 17.44, 17.05.

4.4. Nickel-catalysed monoarylation of trimethylene(bis)piperidine

Compounds **4** were prepared according to the typical procedures A and B described for piperazine.

4.4.1. 1-Phenyl-4-[3-(4-piperidinyl)propyl]piperidine 4a (Table 3). Purification was performed by silica gel chromatography using MeOH–AcOEt (40/60) as eluant. The title compound was isolated as a white solid. 51% yield (method A) and 81% yield (method B). Mp=186°C. IR (KBr, cm^{-1}): ν_{NH} 3397. ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 7.24 (dd, J=8.4, 7.6 Hz, 2H), 6.93 (d, J=8.4 Hz, 2H), 6.81 (dd, J=7.6, 7.6 Hz, 1H), 3.65 (d, J=12.0 Hz, 2H), 3.46 (d, J=12.0 Hz, 2H), 2.84 (dd, J=12.0, 12.0 Hz, 2H), 2.66 (dd, J=12.0, 12.0 Hz, 2H), 1.86 (d, J=12.0 Hz, 2H), 1.76 (d, J=12.0 Hz, 2H), 1.66–1.56 (m, 2H), 1.49 (NH), 1.38–1.22 (m, 10H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm: 151.68, 128.80, 119.01, 116.29, 49.83, 43.97, 36.33, 35.76, 35.43, 33.96, 32.03, 28.67, 23.27. HREIMS Obsd m/z=286.2422 (M), $C_{19}H_{30}N_2$ requires 286.2408.

4.4.2. 1-(4-Methylphenyl)-4-[3-(4-piperidinyl)propyl]-piperidine 4b (Table 3). Purification was performed by silica gel chromatography using MeOH–AcOEt (40/60) as eluant. The title compound was isolated as a pale yellow solid. 48% yield (method A) and 79% yield (method B). Mp=215°C. IR (KBr, cm^{-1}): ν_{NH} 3412. ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 7.04 (d, J=8.6 Hz, 2H), 6.89 (d, J=8.6 Hz, 2H), 3.58 (d, J=12.0 Hz, 2H), 3.48 (d, J=12.0 Hz, 2H), 2.79 (dd, J=12.0, 10.4 Hz, 2H), 2.64 (dd, J=12.0, 10.4 Hz, 2H), 1.82 (d, J=12.0 Hz, 2H), 1.74 (d, J=12.0 Hz, 2H), 1.63–1.48 (m, 3H), 1.40–1.28 (m, 10H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm: 151.12, 129.92, 129.53, 117.65, 49.42, 43.30, 37.02, 35.84, 35.70, 34.36, 31.65, 27.47, 22.84, 20.06. HREIMS Obsd m/z=300.2569 (M), $C_{20}H_{32}N_2$ requires 300.2565.

4.4.3. 4-[3-(4-Piperidinyl)propyl]1-[(3-trifluoromethyl)-phenyl]piperidine 4c (Table 3). Purification was performed by silica gel chromatography using MeOH–AcOEt (40/60) as eluant. The title compound was isolated as a pale yellow oil. 43% yield (method A) and 74% yield (method B). IR (NaCl, cm^{-1}): ν_{NH} 3405. ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 7.11 (dd, J=8.0, 8.0 Hz, 1H), 6.51 (dd, J=8.0, 2.0 Hz, 1H), 6.47–6.38 (m, 2H), 3.63 (d, J=12.4 Hz, 2H), 3.41 (d, J=12.4 Hz, 2H), 2.90 (dd, J=12.6, 12.4 Hz, 2H), 2.72 (dd, J=12.6, 12.4 Hz, 2H), 1.88–1.80 (m, 3H), 1.76 (d, J=12.0 Hz, 2H), 1.56–1.46 (m, 2H), 1.36–1.23 (m, 10H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm: 151.79, 131.63, 130.05, 124.63, 118.95, 115.13, 112.20, 49.18, 46.32, 36.86, 35.60, 35.48, 33.97, 32.28, 27.65, 24.03. ^{19}F NMR (235 MHz, $CDCl_3$) δ ppm: −57.65. Anal. Calcd for $C_{20}H_{29}N_2F_3$: C, 67.80, H, 8.19, N, 7.91, F, 16.10. Found: C, 67.65, H, 8.21, N, 7.84.

4.4.4. 1-(3-Methoxyphenyl)-4-[3-(4-piperidinyl)propyl]-piperidine 4d (Table 3). Purification was performed by silica gel chromatography using MeOH–AcOEt (40/60) as eluant. The title compound was isolated as a pink solid. 36%

yield (method A) and 78% yield (method B). Mp=265°C. IR (KBr, cm^{-1}): ν_{NH} 3395. ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 7.07 (dd, J=8.4, 8.4 Hz, 1H), 6.48 (dd, J=8.4, 2.0 Hz, 1H), 6.38 (dd, J=4.0, 2.0 Hz, 1H), 6.30 (dd, J=8.4, 2.0 Hz, 1H), 3.63 (d, J=12.4 Hz, 2H), 3.26 (d, J=12.4 Hz, 2H), 2.81 (dd, J=12.4, 12.4 Hz, 2H), 2.63 (dd, J=12.4, 12.4 Hz, 2H), 2.63 (dd, J=12.4, 12.4 Hz, 2H), 1.89 (NH), 1.84–1.73 (m, 4H), 1.41–1.38 (m, 2H), 1.32–1.18 (m, 10H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm: 158.52, 151.12, 127.74, 106.97, 101.90, 100.30, 53.08, 47.56, 41.87, 34.52, 34.18, 33.56, 31.79, 30.12, 26.95, 21.38. Anal. Calcd for $C_{20}H_{32}N_2O$: C, 75.95, H, 10.13, N, 8.86. Found: C, 75.80, H, 10.03, N, 8.60.

4.5. Nickel-catalysed synthesis of symmetrical 1,4-diarylpiperazines 2

Representative procedure. To a suspension of degreased NaH (32.5 mmol) in THF (20 mL) were added piperazine (12.5 mmol) and *t*-AmOH (5 mmol) in THF (10 mL) followed by 2,2′-bipyridine (7.5 mmol) and the mixture was heated at 65°C. Dried $Ni(OAc)_2$ (2.5 mmol) was then added and the mixture was further stirred at 65°C for 2 h. To the dark suspension of 2,2′-bipyridine liganded Ni(0) thus obtained was added the aryl chloride (50 mmol) and styrene (5 mmol) in THF. The reaction was monitored by GC and after complete consumption of the starting material, 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.

4.5.1. 1,4-Diphenylpiperazine[13] **2a** (Table 4)**.** Purification was performed by silica gel chromatography using hexane–AcOEt (4/96) as eluant. The title compound was isolated as a white solid. 78% yield. Mp=164°C (lit. mp=164°C). ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 7.29 (dd, J=8.4, 7.2 Hz, 4H), 6.98 (d, J=8.4 Hz, 4H), 6.89 (dd, J=7.2, 7.2 Hz, 2H), 3.33 (s, 8H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm: 151.67, 129.61, 120.48, 116.76, 49.85.

4.5.2. 1,4-Bis(3-methoxyphenyl)piperazine[12] **2b** (Table 4)**.** Purification was performed by silica gel chromatography using hexane–AcOEt (10/90) as eluant. The title compound was isolated as a white solid. 79% yield. Mp=141°C (lit. mp=142°C). ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 7.17 (dd, J=8.4, 8.4 Hz, 2H), 6.53 (dd, J=8.4, 2.0 Hz, 2H), 6.49 (dd, J=4.0, 2.0 Hz, 2H), 6.42 (dd, J=8.4, 2.0 Hz, 2H), 3.77 (s, 6H), 3.29 (s, 8H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm: 161.07, 153.05, 130.31, 109.51, 105.16, 103.19, 55.64, 49.67.

4.5.3. 1,4-Bis[(3-trifluoromethyl)phenyl)piperazine[13] **2c** (Table 4)**.** Purification was performed by silica gel chromatography using hexane–AcOEt (4/96) as eluant. The title compound was isolated as a pale yellow oil. 82% yield. ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 7.37 (dd, J=8.0, 8.0 Hz, 2H), 7.18–7.16 (m, 2H), 7.14–7.09 (m, 4H), 3.38 (s, 8H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm: 151.12, 131.21, 129.67, 124.27, 119.08, 116.39, 112.49, 48.73. ^{19}F NMR (235 MHz, $CDCl_3$) δ ppm: −63.02.

4.5.4. 1,4-Bis(2-pyridinyl)piperazine[26] **2d** (Table 4)**.** Purification was performed by silica gel chromatography using hexane–AcOEt (15/85) as eluant. The title compound was isolated as a white solid. 69% yield. Mp=121°C (lit. mp=121°C). ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 8.21 (dd, J=8.0, 2.0 Hz, 2H), 7.48 (ddd, J=8.0, 8.0, 2.0 Hz, 2H), 6.68–6.60 (m, 4H), 3.67 (s, 8H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm: 159.21, 147.82, 137.36, 113.31, 106.98, 44.74.

4.5.5. 1,4-Bis(4-methylphenyl)piperazine[29] **2b** (Table 4)**.** Purification was performed by silica gel chromatography using hexane–AcOEt (4/96) as eluant. The title compound was isolated as a white solid. 76% yield. Mp=127°C (lit. mp=128°C). ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 7.09 (d, J=8.0 Hz, 4H), 6.89 (d, J=8.0 Hz, 4H), 3.27 (s, 8H), 2.28 (s, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm: 149.14, 129.63, 129.49, 116.62, 49.96, 20.41.

4.6. Nickel-catalysed synthesis of *N*,*N*′-diaryl trimethylene(bis)piperidines 5

Compounds **5** were prepared according to the typical procedure described for *N*,*N*′-diaryl piperazine **2**.

4.6.1. 1-Phenyl-4-[3-(1-phenyl-4-piperidinyl)propyl]-piperidine 5a (Table 5)**.** Purification was performed by silica gel chromatography using hexane–AcOEt (4/96) as eluant. The title compound was isolated as a white solid. 73% yield. Mp=105°C. ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 7.22 (dd, J=8.4, 7.6 Hz, 4H), 6.92 (d, J=8.4 Hz, 4H), 6.81 (dd, J=7.6, 7.6 Hz, 2H), 3.65 (d, J=12.0 Hz, 4H), 2.65 (dd, J=12.0, 12.0 Hz, 4H), 1.77 (d, J=12.0 Hz, 4H), 1.40–1.22 (m, 12H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm: 151.88, 128.93, 119.10, 116.41, 50.01, 36.71, 35.64, 32.25, 23.74. Anal. Calcd for $C_{25}H_{34}N_2$: C, 82.82, H, 9.45, N, 7.73. Found: C, 82.59, H, 9.23, N, 7.61.

4.6.2. 3-(4-{3-[3-Methoxyphenyl)-4-piperidinyl]propyl}-piperidino)phenylmethyl ether 5b (Table 5)**.** Purification was performed by silica gel chromatography using hexane–AcOEt (4/96) as eluant. The title compound was isolated as a white solid. 78% yield. Mp=103°C. ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 7.13 (dd, J=8.4, 8.0 Hz, 2H), 6.54 (dd, J=8.4, 2.0 Hz, 2H), 6.47 (dd, J=4.4, 2.4 Hz, 2H), 6.36 (dd, J=8.0, 2.0 Hz, 2H), 3.76 (s, 6H), 3.65 (d, J=12.4 Hz, 4H), 2.66 (dd, J=12.4, 12.0 Hz, 4H), 1.75 (d, J=12.0 Hz, 4H), 1.32–1.22 (m, 12H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm: 160.41, 153.16, 129.52, 109.17, 103.76, 102.64, 54.99, 49.84, 36.66, 35.64, 32.13, 23.67. Anal. Calcd for $C_{27}H_{38}N_2O_2$: C, 76.74, H, 9.06, N, 6.63, O, 7.57. Found: C, 76.67, H, 8.87, N, 6.44.

4.6.3. 1-[3-(Trifluoromethyl)phenyl]-4-(3-{1-[(trifluoromethyl)phenyl]-4-piperidinyl}propyl) piperidine 5c (Table 5)**.** Purification was performed by silica gel chromatography using hexane–AcOEt (4/96) as eluant. The title compound was isolated as a white solid. 75% yield. Mp=87°C. ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 7.31 (dd, J=8.0, 8.0 Hz, 2H), 7.14–7.10 (m, 2H), 7.09–7.01 (m, 4H), 3.70 (d, J=12.4 Hz, 4H), 2.74 (dd, J=12.4, 12.0 Hz, 4H), 1.80 (d, J=12.0 Hz, 4H), 1.45–1.24 (m, 12H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm: 151.87, 131.50, 129.40, 124.42, 119.06, 115.17, 112.40, 49.51, 36.66, 35.60, 32.04. ^{19}F NMR (235 MHz, $CDCl_3$) δ ppm: −63.11. Anal. Calcd for

$C_{27}H_{32}N_2F_6$: C, 65.05, H, 6.47, N, 5.62, F, 22.86. Found: C, 64.96, H, 6.36, N, 5.54.

4.6.4. 1-(4-Methylphenyl)-4-{3-[1-(4-methylphenyl)-4-piperidinyl]propyl}piperidine 5d (Table 5)**.** Purification was performed by silica gel chromatography using hexane–AcOEt (4/96) as eluant. The title compound was isolated as a white solid. 71% yield. Mp=99°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.04 (d, J=8.6 Hz, 4H), 6.85 (d, J=8.6 Hz, 4H), 3.57 (d, J=11.6 Hz, 4H), 2.61 (dd, J=11.6, 11.6 Hz, 4H), 2.25 (s, 6H), 1.77 (d, J=11.6 Hz, 4H), 1.39–1.26 (m, 12H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm: 149.85, 129.45, 128.64, 116.84, 50.67, 36.72, 35.58, 32.31, 23.76, 20.37. Anal. Calcd for $C_{27}H_{38}N_2$: C, 83.02, H, 9.81, N, 7.17. Found: C, 82.85, H, 9.71, N, 7.12.

4.7. Nickel-catalysed synthesis of unsymmetrical 1,4-diarylpiperazines 6

Compounds **6** were prepared using general reaction conditions A for each N-arylation step.

4.7.1. 1-(3-Methoxyphenyl)-4-phenylpiperazine[30] **6a** (Table 6)**.** Purification was performed by silica gel chromatography using hexane–AcOEt (4/96) as eluant. The title compound was isolated as a yellow solid. 71% overall yield. Mp=118–119°C (lit. mp=118°C). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.26 (dd, J=7.6, 7.6 Hz, 2H), 7.17 (dd, J=8.4, 8.4 Hz, 1H), 6.94 (d, J=8.0 Hz, 2H), 6.86 (dd, J=7.6, 7.6 Hz, 1H), 6.57 (dd, J=8.4, 1.6 Hz, 1H), 6.50 (dd, J=2.4, 2.0 Hz, 1H), 6.43 (dd, J=8.4, 1.6 Hz, 1H), 3.76 (s, 3H), 3.32–3.36 (m, 8H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm: 152.45, 151.05, 129.72, 129.03, 119.89, 116.16, 108.91, 104.54, 102.61, 55.02, 49.15, 49.11.

4.7.2. 1-Phenyl-4-[(4-trifluoromethyl)phenyl]piperazine 6b (Table 6)**.** Purification was performed by silica gel chromatography using hexane–AcOEt (4/96) as eluant. The title compound was isolated as a white solid. 66% overall yield. Mp=162°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.45 (d, J=8.8 Hz, 2H), 7.29 (dd, J=7.6, 7.6 Hz, 2H), 6.97 (d, J=8.8 Hz, 2H), 6.92–6.85 (m, 3H), 3.33–3.27 (m, 8H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm: 153.16, 151.67, 129.61, 126.45, 124.91, 120.48, 120.27, 116.76, 114.53, 49.35, 49.30. ^{19}F NMR (235 MHz, $CDCl_3$) δ ppm: −61.85. HREIMS Obsd m/z=306.1350 (M), $C_{17}H_{17}N_2F_3$ requires 306.1343.

4.7.3. 1-(3-Methoxyphenyl)-4-(4-methylphenyl)piperazine 6c (Table 6)**.** Purification was performed by silica gel chromatography using hexane–AcOEt (4/96) as eluant. The title compound was isolated as a yellow oil. 73% overall yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.18 (dd, J=8.4, 8.4 Hz, 1H), 7.10 (d, J=8.0 Hz, 2H), 6.92 (d, J=8.0 Hz, 2H), 6.56 (dd, J=8.4, 2.0 Hz, 1H), 6.50 (dd, J=2.4, 2.0 Hz, 1H), 6.42 (dd, J=8.4, 2.0 Hz, 1H), 3.75 (s, 3H), 3.29–3.27 (m, 4H), 3.27–3.25 (m, 4H), 2.29 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm: 161.21, 153.32, 149.18, 130.42, 129.72, 116.82, 109.63, 105.23, 103.44, 55.62, 49.86, 49.51, 20.27. HREIMS Obsd m/z=282.1739 (M), $C_{18}H_{22}N_2O$ requires 282.1732.

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