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An improved synthesis of *N*-aryl and *N*-heteroaryl substituted homopiperazines—from conventional thermal conditions to scaling-up using microwave heating

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ABSTRACT

An efficient Pd(0)-catalyzed Buchwald–Hartwig protocol for the facile preparation of *N*-aryl and *N*-heteroaryl substituted homopiperazines is described. The syntheses proceeded with aryl- and heteroaryl halides in high yields using X-Phos as best ligand. The C–N coupling products were prepared both under conventional as well as microwave heating conditions and examples for microwave-assisted upscaling are included in this study.

1. Introduction

The piperazine scaffold has been classified as a privileged structure and especially *N*-arylpiperazines are frequently described in different therapeutic areas, e.g., as dopamine D_4 ligands.[1] In fact, pharmaceutical companies have mainly developed *N*-arylated piperazines during the past few years, but not much attention has been devoted to the corresponding homopiperazines in the literature.

Nucleophilic substitution reactions are described for the synthesis of electron-deficient *N*-aryl and *N*-heteroaryl substituted piperazine and homopiperazine derivatives.[2] Novel routes have been devised that rely on palladium or copper catalysis. Whereas, Nielsen et al.[3] described the Pd(0)-catalyzed coupling of *N*-protected piperazine and homopiperazine with substituted 3-bromo- and 3-chloropyridines, Beller et al.[4] published the synthesis of *N*-aryl- and *N*-heteroaryl-piperazines using the Buchwald–Hartwig amination. An Ullmann-type methodology has been reported by Buchwald et al., describing a method for the copper-catalyzed coupling of alkylamines and aryl halides.[5] To the best of our knowledge, a systematic investigation on N-arylation of homopiperazines by means of palladium chemistry is still missing.

2. Results and discussion

Since our research group is dedicated to the synthesis of *N*-aryl and *N*-heteroaryl substituted homopiperazines as building blocks for potential new pharmacological entities, we planned to broaden the synthetic scope of this methodology without any limitations concerning the substituent pattern. We planned to focus our study on the synthesis of such target entities via conventional as well as microwave-assisted Buchwald–Hartwig aminations of heteroaryl and aryl halides.

Additionally, we were interested to develop a protocol that can be used for parallel synthetic applications using simple experimental conditions, thus avoiding absolute dry and oxygen-free reaction conditions for which a glove-box would be required.

2.1. Comparison of conventional and microwave heating

Here, we describe the synthesis of *N*-aryl and *N*-heteroaryl substituted homopiperazines by palladium catalyzed Buchwald–Hartwig amination[6] of different aryl and heteroaryl halides according to the following general scheme (Scheme 1).

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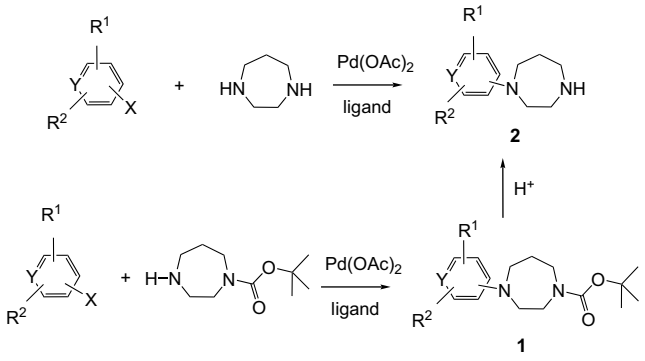
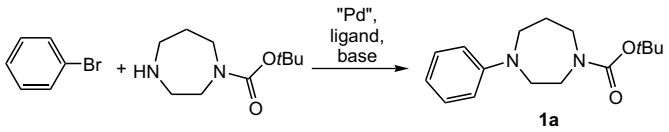


Scheme 1. Buchwald–Hartwig approach.

As the Pd-catalyzed coupling of homopiperazine with aryl halides would directly result in the desired product (see also Scheme 2), we initially attempted the coupling of homopiperazine with bromobenzene. However, yields ranged only between 45 and 50%. Similar results were reported by Zhao et al. for piperazines.[7] Thus, we pursued an alternative approach by using 4-Boc-homopiperazine and aryl/heteroaryl halides as coupling partners, yielding in the Boc-protected amination products. Subsequent removal of the Boc-group would lead to the target *N*-aryl/heteroaryl-homopiperazines.



Scheme 2. Buchwald–Hartwig amination of Boc-protected homopiperazine with bromobenzene (refer also to Tables 1 and 2).

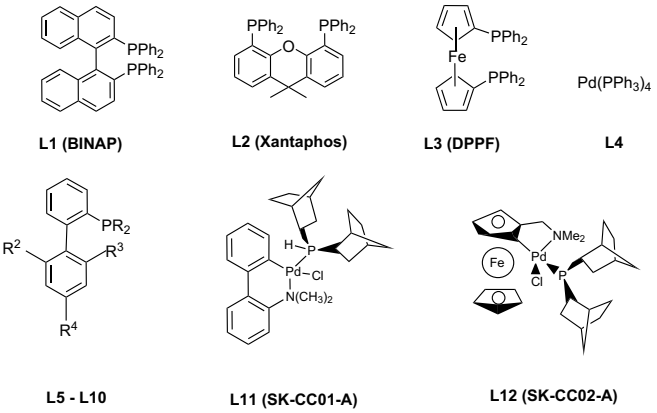
At first we had to optimize the reaction conditions for the synthesis of *N*-aryl and *N*-heteroaryl substituted homopiperazines by using different ligands, bases and solvents at different temperatures. Initially, we had to identify the ideal phosphine ligand for the condensation of 4-Boc-homopiperazine with bromobenzene. Buchwald[8] and co-workers thoroughly described the Pd-catalyzed amination of a variety of heteroaryl halides by utilizing bulky, electron-rich biaryl phosphine ligands. Based on this publication we selected 12 different ligands/catalysts as summarized in Figure 1.

Thus, in a typical experiment bromobenzene was subjected to the Pd(0)-catalyzed amination in the presence of one of 12 different phosphine ligands using Cs_2CO_3 as base in toluene/*t*-BuOH (5:1) at 120 °C for 18 h in sealed vials (Scheme 2). The results of this ligand screening are summarized in Table 1.

The highest yield was achieved by using X-Phos (**L8**). All other ligands gave moderate to good yields and the bidentate ligand Xantaphos (**L2**) and DPPF (**L3**) were observed to be highly ineffective.

In the next phase of this study, the use of other bases was investigated such as Et_3N, K_2CO_3, K_3PO_4, KO-*t*-Bu and NaO-*t*-Bu. With K_2CO_3 and K_3PO_4 as bases the yields are only moderate (50% and 58% isolated yields, respectively) and with KO-*t*-Bu and Cs_2CO_3 the product was obtained in 70% and 77% isolated yield, respectively. Product formation was not observed with triethylamine whereas NaO-*t*-Bu was identified as best base (99% yield and shorter reaction time).

Furthermore, we compared different solvent systems (see Table 2). Toluene and 1,4-dioxane are often employed as solvents for aryl aminations, while the mixture composed of toluene/*t*-BuOH has served for the amination of aryl sulfonates.[9] We recently published the use of DMF as an excellent solvent for the efficient preparation of 3-benzylaminoestrone from oestrone-triflate.[10] Therefore, we also tested our model reaction in DMF.



L	R	R^2	R^3	R^4	remarks
L5	C_6H_{11}	$N(CH_3)_2$	H	H	DavePhos
L6	C_6H_{11}	OCH_3	OCH_3	H	S-Phos
L7	C_6H_{11}	$OCH(CH_3)_2$	$OCH(CH_3)_2$	H	RuPhos
L8	C_6H_{11}	$CH(CH_3)_2$	$CH(CH_3)_2$	$CH(CH_3)_2$	X-Phos
L9	$C(CH_3)_3$	H	H	H	JohnPhos
L10	C_6H_5	$N(CH_3)_2$	H	H	PhDavePhos

Figure 1. Phosphine ligands and catalysts selected.

Table 1
Ligand effect on palladium catalyzed amination reactions (refer also to Scheme 2)[a]

Ligand	L1	L2	L3	L4	L5	L6
Yield (%)	75[c]	0	18[c]	37[b,d]	76[c]	22[b]
Ligand	L7	L8	L9	L10	L11	L12
Yield (%)	61[c]	95[c] 77[b]	49[c]	45[c]	58[c]	73[c]

[a] Reagents and conditions: 4-Boc-homopiperazine (1 equiv), bromobenzene (1.1 equiv), $Pd(OAc)_2$ (5 mol %), ligand (5 mol %), Cs_2CO_3 (1 equiv), toluene/*t*-BuOH (5:1), 120 °C, 18 h.
[b] Isolated yield.
[c] LC/MS yield.
[d] In the absence of $Pd(OAc)_2$.

Table 2
Solvent effect on palladium catalyzed amination reactions (see also Scheme 2 for general description)[a]

Solvent	Temp (°C)	Yield[b] (%)
DMF	120	40
NMP	120	63
1,4-Dioxane	120	43
DMA	120	36
Toluene/*t*-BuOH (5:1)	120	99

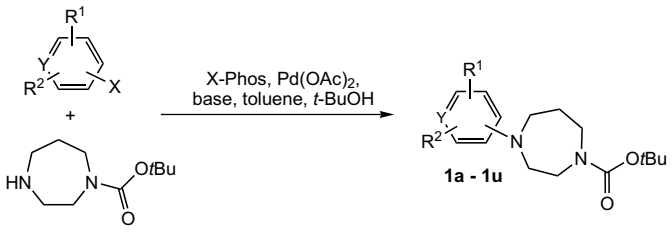
[a] Reagents and conditions: 4-Boc-homopiperazine (1 equiv), bromobenzene (1.1 equiv), $Pd(OAc)_2$ (5 mol %), X-Phos (5 mol %), NaO-*t*-Bu, 10 h.
[b] Isolated yield.

As summarized in Table 2, only the combination of toluene/*tert*-butyl alcohol (5:1) was found to result in good yields for the given amination.

Encouraged by these findings, we next started to investigate the scope of the Pd(0)-catalyzed Buchwald–Hartwig reaction for the preparation of *N*-aryl and *N*-heteroaryl substituted Boc-homopiperazines under conventional conditions and under microwave heating conditions in order to reduce reaction times. It is well documented that microwave assistance can lead to enormous rate enhancement compared to conventional heating.[11] Besides a better reproducibility, higher yields and less side reactions have often

been observed. Reports on microwave-assisted Pd-catalyzed aryl aminations have also appeared in the literature.[12]

So we carried out different reactions with different substituted aryl halides under microwave conditions[13] and compared the results with the reactions carried out under conventional thermal conditions (Scheme 3). In case of conventional heating in addition we compared NaO-*t*-Bu and Cs_2CO_3. Results are summarized in Table 3.



Scheme 3. Buchwald–Hartwig amination of Boc-protected homopiperazine with aryl- and heteroaryl halides (X=Hal, Y=CH, N; refer also to Tables 3 and 4).

Table 3
Synthesis of aryl substituted 4-Boc-homopiperazines (X=Br, Y=CH; refer also to Scheme 3)[12,a]

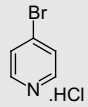
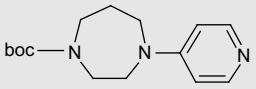
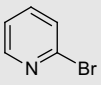
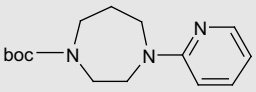
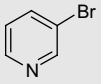
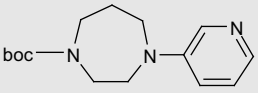
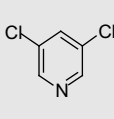
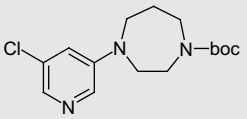
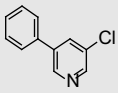
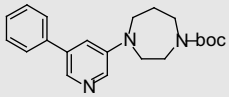
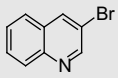
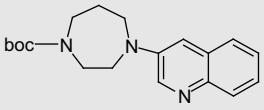
	R^1	R^2	Base[b]	Time (h)	Yield[c] (%)	MW 10 min, 160 °C	
						LC/MS[d]	Yield[c] (%)
1a	H	H	Cs	18	77		
			Na	8	99	99	95
1b	4-F	H	Cs	18	86		
			Na	10	88	95	83
1c	4-OCH_3	H	Cs	18	68		
			Na	10	98	100	74
1d[e]	3-OCH_3	H	Cs	18	59		
			Na	10	93		
1e	4-CH_3	H	Cs	18	66		
			Na	10	92	100	99
1f	4-CN	H	Cs	18	78		
			Na	10	93	91	64
1g	4-CF_3	H	Cs	18	74		
			Na	10	87	94	81
1h	4-Cl	3-CF_3	Cs	18	75		
			Na	10	95	96	90
1i[e]	3-Cl	H	Cs	18	43		
			Na	10	68		
1j	2-Cl	H	Cs	18	25		
			Na	10	26	99	48
1k	3-Cl	4-Cl	Cs				
			Na	10	70	100	75
1l	3-CH_3	H	Cs	18	80		
			Na	10	96	99	95
1m[e]	4-CHO	H	Cs	18	80		
			Na	10	85		
1n[e]	3,4-OCH_2CH_2O–		Na	18	72		
1o[e]	2-Naphthyl–		Na	10	87		

[a] Reagents and conditions: 4-Boc-homopiperazine (1 equiv), aryl bromide (1.2 equiv), $Pd(OAc)_2$ (5 mol%), X-Phos (5 mol%), NaO-*t*-Bu (1 equiv), toluene/*t*-BuOH (5:1), 120 °C, 10–18 h/microwave heating 160 °C for 10 min (reaction carried out in Emrys optimizer microwave device).
[b] Cs=Cs_2CO_3; Na=NaO-*t*-Bu.
[c] Isolated yield.
[d] Percentages are based on the product peak area by LC/MS (UV).
[e] Reactions of these substrates were carried out under conventional heating conditions only.

These data clearly demonstrate that it is possible to prepare the target *N*-aryl substituted 4-Boc-homopiperazines within 10 min under microwave conditions with comparable yields and purity, whereas conventional heating depending on the base used requires 10 to 18 h. All conventional reactions with NaO-*t*-Bu as base proceeded in shorter reaction time and resulted in higher yields.

After this substantial optimization we extended the product range by first applying the optimized conventional thermal conditions [i.e., 4-Boc-homopiperazine (1 equiv), aryl halide (1.2 equiv), NaO-*t*-Bu (1 equiv), 5 mol% of X-Phos and 5 mol% of $Pd(OAc)_2$ in toluene/*t*-BuOH (5:1) at 120 °C] for the synthesis of six different *N*-heteroaryl derivatives of 4-Boc-homopiperazines. Bromopyridines, chloropyridines and 3-bromoquinoline gave the corresponding amination products in moderate to good isolated yields (Table 4). In addition to the aminations carried out under conventional heating, we investigated the microwave supported Buchwald–Hartwig reaction of selected examples for comparison reasons. The electron-deficient heteroaryl halides required prolonged reaction times between 10 and 20 min. Furthermore, we changed the solvent system to benzotrifluoride/*t*-BuOH (5:1).

Table 4
Synthesis of heteroaryl substituted 4-Boc-homopiperazines (X=Hal, Y=N; refer also to Scheme 3)[a]

Product	Substrate	Product	Thermal heating[b]		MW[d]
			Time (h)	Yield[c] (%)	Yield[c] (%)
1p			16	85	
1q			16	53	59
1r			16	70	68
1s			18	92	48
1t			18	58	
1u			16	74	73

[a] Reagents and conditions: 4-Boc-homopiperazine (1 equiv), heteroaryl halide (1.1 equiv), $Pd(OAc)_2$ (5 mol%), ligand (5 mol%), NaO-*t*-Bu (1 equiv), toluene/*t*-BuOH (5:1), 120 °C, 10–18 h/microwave heating: benzotrifluoride/*t*-BuOH (5:1), 160 °C for 20 min.
[b] All reactions were performed in parallel using a carousel from Radley Ltd.
[c] Isolated yield.
[d] Reaction carried out in Emrys optimizer microwave device.

Summarizing these first results using X-Phos as best ligand, we have developed convenient protocols for the efficient preparation of *N*-aryl and *N*-heteroaryl substituted *N*-Boc-homopiperazines starting from *N*-Boc-homopiperazines and aryl halides or heteroaryl halides. The C–N coupling products were prepared in good to excellent yields both under conventional as well as microwave heating conditions.

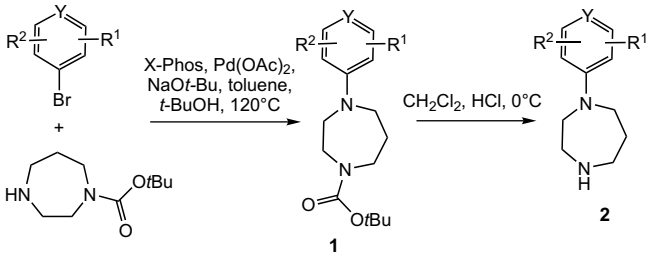
2.2. Upscaling Buchwald–Hartwig amination

Finally, scale-up of the palladium-catalyzed aminations was envisaged using conventional as well as microwave heating. With

respect to conventional heating recently Federsel et al. published pilot plant data about optimization and scale-up of Pd-catalyzed Buchwald–Hartwig chemistry as key step in the synthesis of a 5-HT receptor antagonist.[14]

We first applied the optimized conditions for conventional heating [4-Boc-homopiperazine (1 equiv), aryl or heteroaryl halide (1.1 equiv), NaO-*t*-Bu (1 equiv), X-Phos (5 mol %), $Pd(OAc)_2$ (5 mol %) in toluene/*t*-BuOH (5:1) at 120 °C; 10–18 h in a sealed vial] for the synthesis of eight different 1-aryl/heteroaryl-4-Boc-homopiperazines. These substituted 4-Boc-homopiperazine derivatives were prepared in 10–20 g scale. Subsequently, removal of the Boc-protection was accomplished in CH_2Cl_2/HCl or MeOH/HCl at 0 °C within 3–4 h to afford the corresponding aryl/heteroaryl substituted homopiperazines in good yields (Table 5).

Table 5
Scale-up synthesis of aryl/heteroaryl substituted homopiperazines



Entry	Y	R^1	R^2	**1** Yield (%)	**2** Yield (%)
1	C	H	H	**1a**: 99	**2a**: 100
2	C	4-F	H	**1b**: 88	**2b**: 90
3	C	4-CH_3	H	**1e:** 92	**2e:** 93
4	C	4-CN	H	**1f:** 93	**2f:** 100
5	C	4-CF_3	H	**1g**: 87	**2g**: 100
6	C	4-Cl	3-CF_3	**1h**: 95	**2h**: 85
7	C	3-CH_3	H	**1l:** 96	**2l:** 100
8	4-N	H	H	**1p**: 85	**2p**: 100

For the scale-up of microwave reactions, different microwave reactors are available and several studies have compared their performance.[15] These studies confirmed that microwave supported reactions can be scaled up starting from monomode reactors with small vials to large-scale multimode reactors with larger vials. In order to achieve a larger volume, whilst keeping

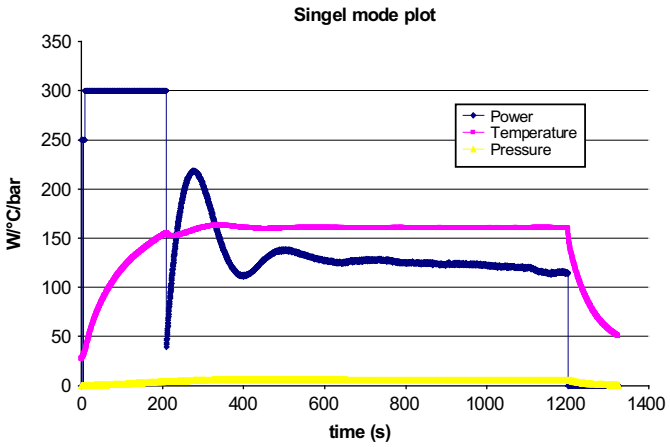


Figure 2. Microwave heating profile for single-mode irradiation (*x* axis=time [s] and *y* axis=temperature [°C], pressure [bar], power [W]); 5 ml sample volume.[13]

the pressure in any individual vessel within acceptable limits, our approach is based on the use of multiple small vessels in parallel (Anton Paar Synthos 3000, 15 rotor 16MF100, 50 ml each). This parallel batch processing technique not only circumvents the issue of penetration depth but also allows carrying out different chemical reactions simultaneously in a single irradiation experiment.

As heating rates are reduced when processing larger volumes compared to small volumes, in our case of a Pd-catalyzed Buchwald–Hartwig chemistry the reaction time needed to be increased to 40 min. Furthermore, to increase the absorption rate of microwave energy we had to change the solvent system from toluene/*t*-BuOH (5:1) to benzotrifluoride/*t*-BuOH (5:1).

As illustration, temperature and power profiles for a typical Buchwald–Hartwig reaction in the microwave field (in sealed vessel) are depicted below (Fig. 2: monomode; Fig. 3: multimode). Whereas in case of single-mode irradiation it takes about 200 s to reach the reaction temperature of 160 °C, in case of the multimode system this time is prolonged to about 600 s.

The rotor 16MF100 offers simultaneous processing of up to 16 different reactions. In our case we selected eight examples from Tables 3 and 4 for scale-up. Each derivative was produced two times. For the scale-up the individual reactions were performed

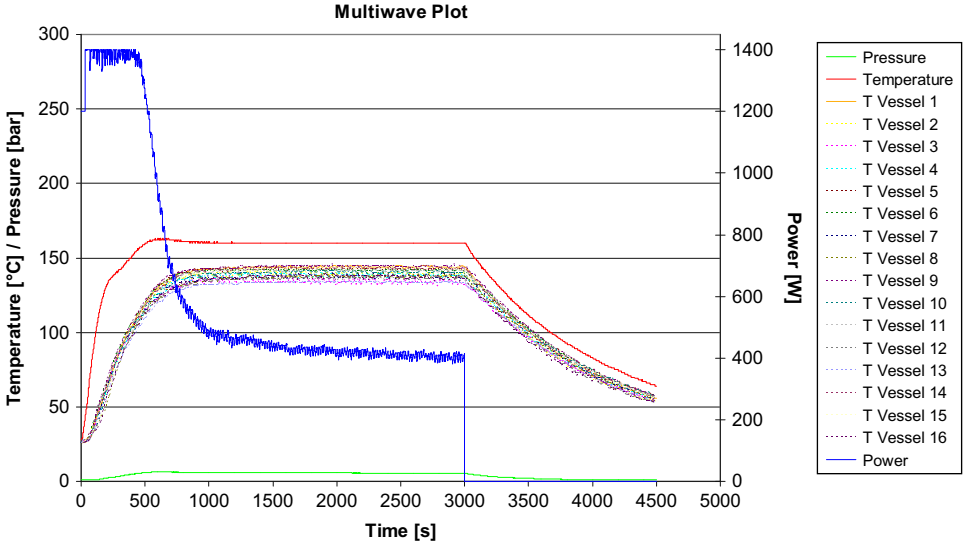


Figure 3. Microwave heating profile for multimode irradiation (x axis=time [s] and y axis=temperature [°C], pressure [bar], power [W]); rotor 16MF50; 16×50 ml sample volume.[16]

with 5 g of Boc-homopiperazine each. The results are summarized in Table 6.

Table 6
Microwave-assisted scale-up (refer also to Scheme 3; benzotrifluoride was used instead of toluene, X=Br, Y=CH)[a]

Compound **1**	R^1, R^2	Isolated amount[b] (g)	Yield[c] Synthos 3000 (%)	Yield[c] Biotage (%)
1a	H	12.6	91	95
1b	4-F	11.6	79	83
1c	4-OCH_3	9.3	61	74
1e	4-CH_3	10.4	72	99
1g	4-CF_3	16.2	94	81
1h	4-Cl, 3-CF_3	16.6	88	90
1l	3-CH_3	10.6	73	95
1u	3-Quinoline	15.4	94	73

[a] Reagents and conditions per vessel: 4-Boc-homopiperazine (5 g, 25 mmol), aryl or heteroaryl bromide (1.1 equiv), $Pd(OAc)_2$ (5 mol %), X-Phos (5 mol %), NaO-*t*-Bu (1.1 equiv), 50 ml of benzotrifluoride/*t*-BuOH (5:1), 160 °C for 40 min.
[b] Total isolated amount from two reactions of **5g**.
[c] Isolated yield.

Comparing the yields these data clearly demonstrate that microwave supported reactions can be scaled up starting from monomode reactors with small vials to large-scale multimode reactors with larger vials. Within one run eight different homopiperazine derivatives were synthesized separately in 10 g scale each.

Finally, we used the same conditions to synthesize compound **1h** 16 times in parallel [in total 80 g of 4-Boc-homopiperazine, 114 g of 4-bromo-1-chloro-2-trifluoromethyl-benzene, 800 ml of benzotrifluoride/*t*-BuOH (5:1), 40 min at 160 °C]. Each vessel was analyzed separately giving a very reproducible picture: ELSD (n=16) in all cases indicated a conversion rate of 100%, whereas UV detector analysis (n=16) showed a conversion rate between 91 and 100%. After work-up and purification, 147 g of **1h** was isolated (97% yield). Thus, within 1 day by principally repeating the set of experiments seven times, about 1 kg of these BOC-protected *N*-aryl or heteroaryl substituted homopiperazines become rapidly accessible.

3. Conclusions

In summary, we have developed a convenient protocol for the efficient preparation of *N*-aryl and *N*-heteroaryl substituted homopiperazines starting from Boc-homopiperazines and aryl halides or heteroaryl halides followed by routine deprotection under acidic conditions. In order to speed up the synthesis we switched from conventional heating to microwave irradiation using a monomode system for the preparation of small amounts as well as a multimode system for large-scale synthesis. Based on these results, one will be able to synthesize these Boc-protected *N*-aryl- or *N*-heteroaryl-substituted homopiperazines up to 1 kg within 1 day.

In order to compare different classes of ligands further investigations will include the use of well-defined NHC-containing palladium(II) precatalysts.[17]

4. Experimental

4.1. General

^{1}H NMR and ^{13}C NMR spectra were recorded with a Bruker Avance 500 spectrometer at 501 MHz (^{1}H NMR) and at 126 MHz (^{13}C NMR) in $CDCl_3$ using tetramethylsilane as the internal standard. Multiplicities are described using the following abbreviations: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet. Coupling constants (J) are quoted in hertz. High-resolution mass spectra were obtained with Waters Micromass Q-TOF Premier (ESI, positive ions, mass resolution >12,000). LC/MS spectra were obtained using Waters Micromass ZQ equipped with a C-18 column (50×2.1 mm; grain size: 1.7 μm) using electrospray ionization (ESI) mode. The solvents and all commercially available reagents were used as received. Reactions were monitored by TLC on silica gel 60 F_{254} (E. Merck, Darmstadt) and spots were detected by UV-absorption (254 nm). Some new compounds were isolated by preparative HPLC.

For most of the described compounds the corresponding analytical data are already known. Applying the copper-catalyzed coupling methodology[5] these *N*-aryl and *N*-heteroaryl substituted homopiperazines have been described in EP 1764367.[18]

4.2. Synthesis of Boc-protected derivatives (1)

4.2.1. Thermal conditions

4.2.1.1. General procedure for conventional heating. In an oven dried reaction tube, $Pd(OAc)_2$ (5 mol %), ligand X-Phos (5 mol %) and Cs_2CO_3 or NaO-*t*-Bu (0.5 mmol) were taken up in toluene/*t*-BuOH (20 ml, 5:1). The reaction mixture was purged with nitrogen and was capped with a rubber septum. After stirring for 1 min, 4-Boc-homopiperazine (0.1 g, 0.5 mmol), aryl or heteroaryl bromide (0.6 mmol) in toluene/*t*-BuOH (10 ml, 5:1) were added via a syringe. Then, the septum was replaced with a Teflon screw cap and the resulting mixture with stirring was heated at 120 °C in an oil bath for about 10–18 h. The reaction mixture was cooled to rt and filtered over Celite™ and rinsed well with ethyl acetate. The filtrate was subsequently evaporated under reduced pressure and the residue was purified by flash column chromatography on silica gel.

*4.2.1.2. 4-Phenyl-1,4-diazepane-1-carboxylic acid tert-butyl ester (**1a**)[18].* Yield (using NaO-*t*-Bu): 99%, 137 mg (0.49 mmol) of yellow thick mass; R_f=0.4 (EtOAc/Hexane, 2:8, v/v).

^{1}H NMR (501 MHz, DMSO-d_6) δ ppm 1.20 and 1.33 (s, 9H), 1.73–1.89 (m, 2H), 3.11–3.25 (m, 2H), 3.42–3.60 (m, 6H), 6.53–6.59 (m, 1H), 6.67–6.74 (m, 2H), 7.09–7.16 (m, 2H); ^{13}C NMR (126 MHz, DMSO-d_6) δ ppm 24.4, 24.8, 27.7, 27.9, 44.7, 44.8, 45.3, 45.4, 47.4, 48.2, 48.6, 49.1, 78.2, 78.3, 111.4, 111.5, 115.4, 129.0, 129.1, 146.9, 154.0, 154.3. HRMS calcd for $C_{16}H_{25}N_2O_2$ $[M+H]^+$: 277.1916; found: 277.1911.

*4.2.1.3. 4-(4-Fluorophenyl)-1,4-diazepane-1-carboxylic acid tert-butyl ester (**1b**)[18].* Yield (using NaO-*t*-Bu): 88%, 130 mg (0.44 mmol) of yellow thick mass; R_f=0.4 (EtOAc/Hexane, 3:7, v/v).

^{1}H NMR (501 MHz, DMSO-d_6) δ ppm 1.20 and 1.32 (s, 9H), 1.70–1.88 (m, 2H), 3.12–3.26 (m, 2H), 3.40–3.61 (m, 6H), 6.64–6.74 (m, 2H), 6.96 (t, J=8.7 Hz, 2H); ^{13}C NMR (126 MHz, DMSO-d_6) δ ppm 24.3, 24.7, 27.7, 27.9, 44.4, 44.7, 45.0, 45.4, 48.0, 48.7, 48.8, 49.3, 78.2, 78.3, 112.4, 115.3 (d, J=22.0 Hz), 115.4 (d, J=22.0 Hz), 143.7, 154.0 (d, J=232.0 Hz), 154.0, 154.3. HRMS calcd for $C_{16}H_{24}N_2O_2F$ $[M+H]^+$: 295.1822; found: 295.1817.

4.2.2. Microwave heating (Emrys™ Optimizer)

4.2.2.1. General procedure for the microwave palladium catalyzed amination of aryl bromides. In a pressure vial (10 ml) $Pd(OAc)_2$ (5 mol %), ligand (5 mol %) and NaO-*t*-Bu (53 mg, 0.55 mmol) were taken up in 1 ml of toluene/*t*-BuOH (5:1), flushed with nitrogen, stirred for a minute and capped with a rubber septum. Then, through a syringe 4-Boc-homopiperazine (0.1 g, 0.5 mmol) and aryl/heteroaryl halide (0.55 mmol) were added in 4 ml of toluene/*t*-BuOH (5:1). The septum was replaced with a sealed cap and the reaction tube was heated to 160 °C under microwave irradiating conditions. The total heating time of all reactions was between 8 and 10 min. After the reaction vials were cooled to rt, the mixture was filtered over Celite™ and rinsed well with ethyl acetate. The filtrate was subsequently evaporated under reduced pressure and the residue purified by flash chromatography on silica gel.

*4.2.2.2. 4-(4-Methoxyphenyl)-1,4-diazepane-1-carboxylic acid tert-butyl ester (**1c**)*[18]. Yield: 74%, 113 mg (0.25 mmol) of yellow coloured thick mass; R_f=0.3 (EtOAc/Hexane, 3:7, v/v). ^{1}H NMR (501 MHz, DMSO-d_6) δ ppm 1.22 and 1.34 (s, 9H), 1.70–1.90 (m, 2H), 3.08–3.25 (m, 2H), 3.38–3.54 (m, 6H), 3.64 (s, 3H), 6.60–6.69 (m, 2H), 6.71–6.81 (m, 2H); ^{13}C NMR (126 MHz, DMSO-d_6) δ ppm 24.6, 25.1, 27.7, 27.9, 44.8, 44.9, 45.4, 47.9, 48.6, 49.1, 49.6, 55.2, 55.3, 78.2, 78.3, 112.7, 112.7, 114.8, 141.4, 150.3, 154.0, 154.3. HRMS calcd for $C_{17}H_{25}N_2O_3$ $[M+H]^+$: 307.2022; found: 307.2018.

*4.2.2.3. 4-(4-Methylphenyl)-1,4-diazepane-1-carboxylic acid tert-butyl ester (**1e**)*[18]. Yield: 99%, 143 mg (0.49 mmol) of yellow coloured thick mass; R_f=0.4 (EtOAc/Hexane, 3:7, v/v). ^{1}H NMR (501 MHz, DMSO-d_6) δ ppm 1.22 and 1.34 (s, 9H), 1.70–1.90 (m, 2H), 2.15 (s, 3H), 3.07–3.24 (m, 2H), 3.39–3.57 (m, 6H), 6.57–6.65 (m, 2H), 6.91–6.98 (m, 2H); ^{13}C NMR (126 MHz, DMSO-d_6) δ ppm 19.8, 24.4, 24.9, 27.7, 27.9, 44.8, 44.9, 45.4, 47.5, 48.2, 48.8, 49.3, 78.2, 78.3, 111.5, 111.6, 123.7, 123.8, 129.5, 129.6, 144.7, 144.8, 154.0, 154.3. HRMS calcd for $C_{17}H_{27}N_2O_2$ $[M+H]^+$: 291.2073; found: 291.2072.

4.2.3. Upscaling using conventional heating

4.2.3.1. General procedure. In a steel bomb, 4-Boc-homopiperazine (15 g, 75 mmol), Pd(OAc)2 (5 mol %), ligand X-Phos (5 mol %) and NaO-*t*-Bu (7.2 g, 75 mmol) were taken up in toluene/*t*-BuOH (250 ml, 5:1). The reaction mixture was purged with nitrogen and after stirring for 5 min, aryl bromide (0.15 mol) in toluene/*t*-BuOH (50 ml, 5:1) was added. Then, the resulting mixture was purged with nitrogen, sealed and heated at 120 °C with stirring in an oil bath for about 10–18 h. The reaction mixture was cooled to rt and filtered over Celite™ and rinsed well with ethyl acetate. The filtrate was subsequently evaporated under reduced pressure and the residue was purified by flash column chromatography on silica gel.

*4.2.3.2. 4-Phenyl-1,4-diazepane-1-carboxylic acid tert-butyl ester (**1a**)*[18]. Yield: 99%, 20.5 g (74 mmol) of yellow coloured sticky mass; R_f=0.4 (EtOAc/Hexane, 2:8, v/v).

*4.2.3.3. 4-(4-Fluorophenyl)-1,4-diazepane-1-carboxylic acid tert-butyl ester (**1b**)*[18]. Yield: 88%, 19.4 g (66 mmol) of buff coloured solid, mp 95–98 °C; R_f=0.4 (EtOAc/Hexane, 3:7, v/v).

*4.2.3.4. 4-(4-Methylphenyl)-1,4-diazepane-1-carboxylic acid tert-butyl ester (**1e**)*[18]. Yield: 92%, 19.5 g (69 mmol) of yellow coloured thick mass; R_f=0.4 (EtOAc/Hexane, 3:7, v/v).

*4.2.3.5. 4-(4-Cyanophenyl)-1,4-diazepane-1-carboxylic acid tert-butyl ester (**1f**)*[18]. Yield: 93%, 21 g (70 mmol) of pale yellow solid; R_f=0.3 (EtOAc/Hexane, 3:7, v/v).

*4.2.3.6. 4-(4-Trifluoromethylphenyl)-1,4-diazepane-1-carboxylic acid tert-butyl ester (**1g**)*[18]. Yield: 87%, 22.4 g (65 mmol) of yellow coloured thick mass; R_f=0.4 (EtOAc/Hexane, 2:8, v/v). ^{1}H NMR (501 MHz, DMSO-d_6) δ ppm 1.15 and 1.29 (s, 9H), 1.70–1.87 (m, 2H), 3.15–3.29 (m, 2H), 3.46–3.59 (m, 4H), 3.60–3.70 (m, 2H), 6.79–6.89 (m, 2H), 7.36–7.48 (m, 2H); ^{13}C NMR (126 MHz, DMSO-d_6) δ ppm 23.8, 24.2, 27.5, 27.8, 43.9, 44.7, 45.5, 47.9, 48.5, 48.7, 48.9, 78.3, 78.4, 111.1, 111.2, 115.2 (q, J=32.0 Hz), 125.2 (q, J=272.0 Hz), 126.2, 149.7, 153.9, 154.2. HRMS calcd for $C_{17}H_{24}N_2O_2F_3$ $[M+H]^+$: 345.1790; found: 345.1788.

*4.2.3.7. 1-(3-Trifluoromethyl-4-chlorophenyl)-1,4-diazepane-1-carboxylic acid tert-butyl ester (**1h**).* Yield: 95%, 26.9 g (71 mmol) of pale light solid, mp 108–110 °C; R_f=0.3 (EtOAc/Hexane, 2:8, v/v). ^{1}H NMR (501 MHz, DMSO-d_6) δ ppm 1.14 and 1.29 (s, 9H), 1.69–1.82 (m, 2H), 3.19–3.30 (m, 2H), 3.47–3.58 (m, 4H), 3.60–3.72 (m, 2H), 6.94–7.02 (m, 2H), 7.33–7.41 (m, 1H); ^{13}C NMR (126 MHz, DMSO-d_6) δ ppm 23.5, 23.9, 27.4, 27.7, 43.4, 44.1, 44.6, 45.5, 48.3, 48.4, 48.6, 49.0, 78.2, 78.3, 109.8, 115.4, 116.3, 116.5, 123.1 (q, J=272.0 Hz), 126.9 (q, J=33.0 Hz), 127.0 (q, J=32.0 Hz), 131.9, 146.0, 153.9, 154.1. HRMS calcd for $C_{17}H_{23}N_2O_2F_3Cl$ $[M+H]^+$: 379.1400; found: 379.1404.

*4.2.3.8. 4-(3-Methylphenyl)-1,4-diazepane-1-carboxylic acid tert-butyl ester (**1l**)*[18]. Yield: 96%, 20.8 g (72 mmol) of yellow coloured thick mass; R_f=0.4 (EtOAc/Hexane, 2:8, v/v). ^{1}H NMR (501 MHz, DMSO-d_6) δ ppm 1.21 and 1.26 (s, 9H), 1.71–1.88 (m, 2H), 2.21 (s, 3H), 3.11–3.24 (m, 2H), 3.41–3.59 (m, 6H), 6.37–6.41 (m, 1H), 6.47–6.55 (m, 2H), 6.97–7.04 (m, 1H); ^{13}C NMR (126 MHz, DMSO-d_6) δ ppm 21.5, 24.4, 24.9, 27.7, 27.9, 44.8, 45.4, 45.5, 47.4, 48.2, 48.6, 49.2, 78.2, 78.3, 108.7, 112.0, 112.1, 116.3, 116.4, 128.9, 129.0, 137.9, 138.1, 147.0, 154.0, 154.3. HRMS calcd for $C_{17}H_{27}N_2O_2$ $[M+H]^+$: 291.2073; found: 291.2074.

*4.2.3.9. 4-(4-Pyridyllphenyl)-1,4-diazepane-1-carboxylic acid tert-butyl ester (**1p**)*[18]. Yield: 85%, 17.5 g (63.75 mmol) of light brown solid, mp 78–80 °C; R_f=0.4 (DCM/MeOH/NH_3, 90:10:01, v/v).

4.2.4. Upscaling using microwave heating (Synthos 3000)

4.2.4.1. General procedure for the palladium catalyzed amination. Each liner (100 ml) containing 50 ml of benzotriflouride/*t*-BuOH (5:1) was filled with 5 g of 4-Boc-homopiperazine (25 mmol) and 27.5 mmol of the aryl halide (1.1 equiv), $Pd(OAc)_2$ (5 mol %), X-Phos (5 mol %) and NaO-*t*-Bu (2.64 g, 27.5 mmol). The stirred reaction mixture was heated in total for 50 min at 160 °C (10 min for heating up to 160 °C, further 40 min at constant temperature of 160 °C). After the reaction vials were cooled to rt, the mixture was filtered over Celite™. The organic phase was dried with sodium sulfate and concentrated under reduced pressure. The outcome of the reaction was monitored by LC/MS-analysis and the residue purified by flash chromatography on silica gel (ethyl acetate/cyclohexane (1:9)).

*4.2.4.2. 4-(4-Trifluoromethylphenyl)-1,4-diazepane-1-carboxylic acid tert-butyl ester (**1g**)*[18]. Yield: 94%, 8.1 g (23.5 mmol) of yellow coloured thick mass; R_f=0.4 (EtOAc/Hexane, 2:8, v/v).

*4.2.4.3. 4-(3-Trifluoromethyl-4-chlorophenyl)-1,4-diazepane-1-carboxylic acid tert-butyl ester (**1h**).* Yield: 88%, 8.3 g (22 mmol) of yellow coloured thick mass; R_f=0.4 (EtOAc/Hexane, 2:8, v/v).

*4.2.4.4. 4-(3-Methylphenyl)-1,4-diazepane-1-carboxylic acid tert-butyl ester (**1l**)*[18]. Yield: 73%, 5.3 g (18 mmol) of yellow coloured thick mass; R_f=0.4 (EtOAc/Hexane, 2:8, v/v).

*4.2.4.5. 4-(3-Quinolylphenyl)-1,4-diazepane-1-carboxylic acid tert-butyl ester (**1u**).* Yield: 94%, 7.7 g (23.5 mmol) of yellow coloured thick mass; R_f=0.4 (EtOAc/Hexane, 2:8, v/v). ^{1}H NMR (501 MHz, DMSO-d_6) δ ppm 1.02 and 1.24 (s, 9H), 1.80–1.94 (m, 2H), 3.20–3.32 (m, 2H), 3.54–3.64 (m, 2H), 3.64–3.69 (m, 2H), 3.71–3.81 (m, 2H), 7.32–7.37 (m, 2H), 7.38–7.43 (m, 1H), 7.67–7.71 (m, 1H), 7.76–7.82 (m, 1H), 8.66–8.74 (m, 1H); ^{13}C NMR (126 MHz, DMSO-d_6) δ ppm 24.0, 24.6, 27.4, 27.8, 44.2, 44.7, 45.4, 48.0, 48.4, 48.6, 48.8, 78.2, 78.3, 111.0, 111.1, 124.2, 125.9, 126.4, 128.2, 129.2, 140.3, 140.5, 140.6, 153.9, 154.2. HRMS calcd for $C_{19}H_{26}N_3O_2$ $[M+H]^+$: 328.2025; found: 328.2020.

4.3. Synthesis of *N*-aryl and *N*-heteroaryl substituted homopiperazines (2)

4.3.1. General procedure for removal of the Boc-group

Aryl substituted 4-Boc-homopiperazine (60 mmol) was dissolved in methanol, cooled to 5–10 °C and HCl gas was passed until saturation for 3–4 h. The methanol solution was concentrated under reduced pressure to collect the deprotected *N*-aryl/heteroaryl

substituted homopiperazine hydrochloride salt, which was further purified by crystallization.

*4.3.1.1. 1-Phenyl-1,4-diazepane (**2a**)[18]·1HCl.* Yield: 100%, 12.7 g (60 mmol) of brown coloured thick mass; R_f=0.4 (DCM/MeOH/NH_3, 85:15:01, v/v).

*4.3.1.2. 1-(4-Fluorophenyl)-1,4-diazepane (**2b**)[18]·1HCl.* Yield: 90%, 12.7 g (54 mmol) of buff coloured solid, mp: 212–215 °C; R_f=0.3 (DCM/MeOH/NH_3, 90:10:01, v/v).

*4.3.1.3. 1-(4-Methylphenyl)-1,4-diazepane (**2e**)[18]·1 HCl.* Yield: 93%, 12.6 g (55.8 mmol) of buff coloured solid, mp 212–215 °C; R_f=0.4 (DCM/MeOH/NH_3, 90:10:01, v/v). ^{1}H NMR (501 MHz, DMSO-d_6) δ ppm 2.12–2.19 (m, 2H), 2.21 (s, 3H), 3.06–3.17 (m, 2H), 3.22–3.35 (m, 2H), 3.48–3.60 (m, 2H), 3.71–3.82 (m, 2H), 6.82–6.99 (m, 2H), 7.03–7.13 (m, 2H), 9.47 (br s, 2H); ^{13}C NMR (126 MHz, DMSO-d_6) δ ppm 19.9, 23.7, 44.2, 44.3, 47.0, 48.7, 113.9, 130.5, 129.8, 144.8. HRMS calcd for $C_{12}H_{19}N_2$ $[M+H]^+$: 191.1548; found: 191.1544.

*4.3.1.4. 1-(4-Cyanophenyl)-1,4-diazepane (**2f**)[18]·1HCl.* Yield: 100%, 14.25 g (60 mmol) of coloured mass; R_f=0.3 (DCM/MeOH/NH_3, 90:10:01, v/v). ^{1}H NMR (501 MHz, DMSO-d_6) δ ppm 2.08–2.14 (m, 2H), 3.06–3.11 (m, 2H), 3.17–3.22 (m, 2H), 3.57–3.61 (m, 2H), 3.80–3.83 (m, 2H), 6.87–6.91 (m, 2H), 7.55–7.59 (m, 2H), 9.47 (br s, 2H); ^{13}C NMR (126 MHz, DMSO-d_6) δ ppm 24.0, 44.5, 44.6, 44.9, 46.5, 96.7, 111.8, 120.1, 133.4, 150.9. HRMS calcd for $C_{12}H_{16}N_3$ $[M+H]^+$: 202.1344; found: 202.1340.

*4.3.1.5. 1-(4-Trifluoromethylphenyl)-1,4-diazepane (**2g**)[18].* Yield: 100%, 16.8 g (60 mmol) of brown coloured thick mass; R_f=0.4 (DCM/MeOH/NH_3, 85:15:01, v/v).

*4.3.1.6. 1-(3-Trifluoromethyl-4-chlorophenyl)-1,4-diazepane (**2h**)·1HCl.* Yield: 85%, 16 g (51 mmol) of buff coloured solid, mp 212–215 °C; R_f=0.3 (DCM/MeOH/NH_3, 90:10:01, v/v).

*4.3.1.7. 1-(3-Methylphenyl)-1,4-diazepane (**2l**)[18]·1HCl.* Yield: 100%, 13.59 g (60 mmol) of reddish brown coloured thick mass; R_f=0.4(DCM/MeOH/NH_3, 85:15:01, v/v).

*4.3.1.8. 1-(4-Pyridyl)-1,4-diazepane (**2p**)[18]·1HCl.* Yield: 100%, 12.81 g (60 mmol) of reddish coloured thick mass; R_f=0.4 (DCM/MeOH/NH_3, 90:10:01, v/v).

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