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Base-Catalyzed Hydroamination of Aromatic Olefins- An Efficient Route to 1-Aryl-4-(arylethyl)piperazines[1)]

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Abstract: An efficient synthesis of pharmaceutically interesting 1-aryl-4-(arylethyl)-piperazines by base-catalyzed hydroamination is presented. Starting from substituted aryl olefins and various *N*-arylpiperazines, the desired products **3** - **12** were obtained in one step under mild conditions in the presence of a catalytic amount of *n*-butyllithium in yields up to 99 %.

Keywords: Anti-Markovnikov amination, base-catalyzed hydroamination, 1-aryl-4-(arylethyl)piperazines

Introduction

New methods for producing amines selectively in a catalytic manner from easily available feedstocks are of fundamental importance in organic chemistry. So far most of the explored laboratory methods make use of the *N*-alkylation of ammonia, primary amines or secondary amines using alkylating agents.[2)] In general, more than one equivalent of salt is produced as by-product. On the other hand reductive aminations using aldehydes as starting materials are employed for the synthesis of amines. Unfortunately, the required aldehydes have to be synthesized prior to the amination. A very attractive alternative one step amination process constitutes the hydroamination of ubiquitous available olefins. Due to the advantages of this reaction such as atom-efficiency and economics of starting materials a general hydroamination reaction is still one of the major goals for catalysis.[3)] Although transition metal catalysts[4)], and traditional acids[5)] as well as bases[6)] have been used as catalysts for the hydroamination of double bonds, so far no efficient general methodology has been discovered. While developing new ways to industrially important fine chemicals and pharmaceuticals we became interested recently in the development of amination reactions of aromatic olefins.[7)]

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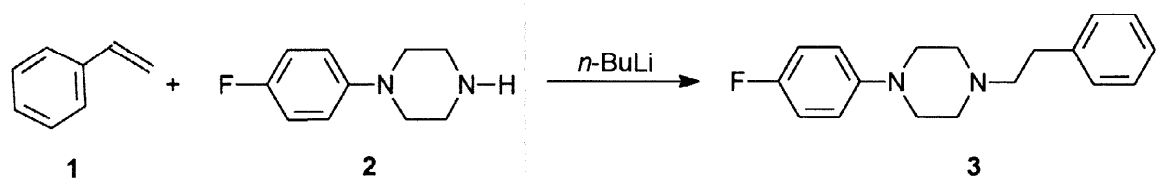
Surprisingly, there are few reports in the literature about base-catalyzed aminations of substituted styrenes.[6a, g, i, j] Up to now only unfunctionalized amines such as *n*-propylamine, *n*-butylamine, cyclohexylamine, diethylamine, and di-*n*-butylamine have been treated with styrene at elevated temperatures in the presence of metallic sodium, sodium naphthalene or lithium amides. It was obvious to us that the synthetic potential of this reaction has never been fully exploited. In this paper we describe for the first time the use of 1-arylpiperazines in base-catalyzed hydroamination reactions. With as little as 2.5 mol% of *n*-butyllithium as pre-catalyst quantitative conversion (99 % yield) was obtained.

Results and Discussion

1-Aryl-4-(arylethyl)piperazines contain the pharmaceutically important lead structure $ArCH_2CH_2N$- which is of major importance in medicinal chemistry.[8] 1-Aryl-4-(arylethyl)piperazines themselves have been the subject of more than 100 publications and patents since 1990.[9] In general, this class of compounds is synthesized by the reaction of *N*-arylpiperazines with substituted *β*-bromoethylbenzenes.[10] Another way to generate the „*N*-ethylpiperazine unit" starts from substituted anilines, which were treated with *N,N*-bis-(*β*-chloroethyl)-aminobenzenes. Both routes give the desired products in about 50 - 70 % yield. Moreover, the described syntheses start with halogenated substrates, thus a considerable amount of salt by-products is produced. To the best of our knowledge this class of important active agents has never been synthesized using a base-catalyzed hydroamination protocol.

Preliminary studies on the base-catalyzed hydroamination to generate 1-aryl-4-(arylethyl)piperazines were performed using the reaction of styrene **(1)** and 1-(4-fluorophenyl)piperazine **(2)** (Scheme 1).[9] As shown in Table 1 (entry 1) the reaction proceeded smoothly in the presence of a catalytic amount of *n*-butyllithium (10 mol%) in THF as solvent to give the hydroamination product **3** in 99 % yield! In agreement with literature data[6] the *anti*-Markovnikov product was obtained as the major regioisomer (selectivity > 99 %). The reaction was initiated by adding the appropriate amount of *n*-butyllithium in *n*-hexane at –78 °C to the reaction mixture. After warming up to room temperature the mixture was allowed to react for several hours at 120 °C before quenching with water. The amount of the pre-catalyst could be



1 2 3

Scheme 1: Base-Catalyzed Hydroamination of Styrene **(1)** with 1-(4-Fluorophenyl)piperazine **(2)**

reduced up to 2.5 mol% (Table 1, entry 3) without significant change of the yield. In the

presence of smaller amounts of *n*-butyllithium, e.g. 1 mol%, the yield diminished to 62 % (Table 1, entry 4), which is explained both by a hydrolysis of *n*-BuLi with traces of water and a rapid deactivation of the resulting lithium piperazide at higher temperatures.

A brief variation of solvents shows that THF and dimethoxyethane are the most suited media. In order to get more information about the influence of the solvent on the hydroamination reaction, concentration vs. time diagrams for the model reaction in three different solvents (THF, toluene, *n*-hexane) were compared. In each case, the maximum yield of the hydroamination product **3** was already reached after 15 - 20 minutes. After that time the reaction stops and no further increase of **3** is observed. Regarding the rate of the reaction, THF is superior to *n*-hexane which is superior to toluene. Thus, the higher yield of **3** in THF compared to *n*-hexane and toluene is not due to a better stabilization of the *in situ* generated lithium amide species, but rather to the higher reactivity of the resulting lithium piperazide species. Less basic catalyst precursors such as potassium *tert*-butoxide or lithium *tert*-butoxide do not show any catalytic activity for this type of hydroamination reaction.

Table 1: Base-Catalyzed Hydroamination of Styrene (1) with 1-(4-Fluorophenyl)piperazine (2)

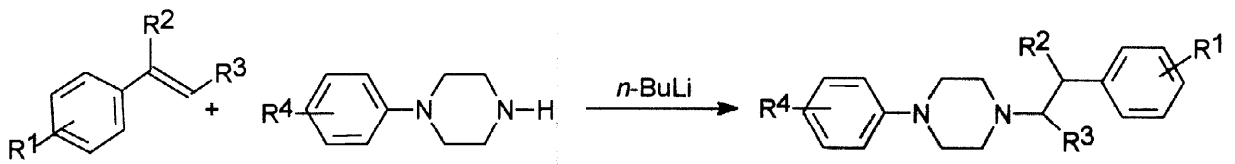
Entry	Solvent	Catalyst	Catalyst (mol%)	Temperature (°C)	Yield[a] (%)
1	THF	*n*-BuLi	10	90	99
2	THF	*n*-BuLi	5	90	99
3	THF	*n*-BuLi	2.5	90	99
4	THF	*n*-BuLi	1	90	62
5	dme[b]	*n*-BuLi	10	85	88
6	*n*-hexane	*n*-BuLi	5	90	66
7	toluene	*n*-BuLi	5	120	43
8	THF	KO^{t}Bu	10	90	-
9	THF	LiO^{t}Bu	10	90	-

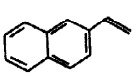
Reaction conditions: 2.22 mmol 1-(4-fluorophenyl)piperazine, 2.22 mmol styrene and corresponding amounts of catalyst were refluxed for 1 h in 4 ml of solvent. [a] Determined by GC with hexadecane as internal standard; [b] Dimethoxyethane.

In order to show that this convenient procedure is applicable to variations of the pharmaceutical lead structure, we tested a series of substituted styrenes and functionalized 1-arylpiperazines under our optimized reaction conditions. A summary of the catalytic reactions is given in Table 2. Styrene (entry 1) and also substituted styrenes bearing electron withdrawing or neutral substituents (Table 2, entries 4, 5) reacted in excellent yields (> 95 %). However, *p*-methoxystyrene and 2-vinylnaphthaline gave slightly lower yields (77 % and 84 %, respectively), probably due to the polymerization of the corresponding styrenes. Interestingly, α-methylstyrene

and β-methylstyrene (Table 2, entries 9-10) were hydroaminated by *N*-phenylpiperazine in 71 % and 86 % yield, respectively. Again, the slightly lower yield for these substituted styrenes is likely due to polymerization side-reactions. Different substituents on the aromatic ring of arylpiperazines such as F, CF_3, OMe (Table 2, entries 5-8) are tolerated without any problems, thus the desired products were obtained in 89 - 99 % yield.

Table 2: Base-Catalyzed Hydroamination of *N*-Arylpiperazines to Aryl Olefins



Entry	R^1 / Aryl olefin	R^2 / R^3	R^4	Product	Yield[a] (%)
1	H	H / H	*p*-F	**3**	99
2	*p*-OCH_3	H / H	*p*-F	**4**	77
3		H / H	*p*-F	**5**	84
4	*p*-Cl	H / H	*p*-F	**6**	98
5	*m*-CH_3	H / H	H	**7**	97
6	H	H / H	*m*-CH_3	**8**	99
7	H	H / H	*m*-CF_3	**9**	89
8	H	H / H	*o*-OCH_3	**10**	95
9[b]	H	H / -CH_3	H	**11**	71
10[b]	H	-CH_3 / H	H	**12**	86

Reaction conditions: 2.22 mmol *N*-arylpiperazine, 2.22 mmol aryl olefin and 5 mol% *n*-BuLi were heated for 17 h in 4 ml THF. The reaction was performed at 120 °C in a pressure tube purchased by Aldrich. [a] Determined by GC with hexadecane as internal standard; [b] The reaction was performed at 90 °C.

Conclusion

In conclusion, we realized for the first time the base-catalyzed hydroamination of aryl olefins with *N*-arylpiperazines. Various substituents are tolerated and the corresponding products were obtained in excellent yields. The here reported method shows several important advantages compared to former procedures for the synthesis of 1-aryl-4-(arylethyl)piperazines. The most impressive fact is that the reaction proceeds with 100 % atom-efficiency and no salt by-products are produced. Furthermore, the catalyst precursor is less expensive than traditional transition

metal catalysts. In addition, the reactions are easy to perform and were completed in less than 30 minutes. Clearly, this method offers not only an access to pharmaceutically important 1-aryl-(4-arylethyl)piperazines, but will be also a useful way to synthesize other interesting substituted β-arylethylamines.

Experimental

Chemicals were obtained from Aldrich, Fluka and Merck KgA and used without further purification. All operations were carried out under argon atmosphere. Solvents were dried according to standard procedures. NMR spectra (^1H, ^{13}C) were recorded with a 400 MHz Bruker AM 400 instrument. ^1H and ^{13}C NMR chemical shift were referenced to tetramethylsilane (0 ppm) and $CDCl_3$ (77.0 ppm), respectively. Coupling constants are reported in Herzt. GC-MS spectra were measured with a Hewlett Packard gas chromatograph GC 5890 A equipped with a mass-selective detector MS 5970 B. Elemental analyses were performed out by the Microanalytical Laboratory at the TU München. Quantitative analyses were performed with a Hewlett Packard 6890 instument using a HP-5 capillary column in conjunction with a flame ionization detector (GC/FID). Column chromatography was carried out using silica gel 60 (0.063-0.2 mm Fluka). The hydroamination reactions were performed in Aldrich ACE pressure tubes (30 ml).

General procedure

In a pressure tube (30 ml) 2.22 mmol *N*-arylpiperazine and 50 µl hexadecane were dissolved in 4 ml THF. The solution was cooled to -78 °C and 5 mol% *n*-BuLi (1.6 M *n*-BuLi solution in *n*-hexane) was added under an argon atmosphere. The resulting yellow or orange solution was stirred for 30 min and allowed to warm to room temperature. Then 2.22 mmol olefin was added and the reaction mixture was heated to 120 °C for 20 h. After cooling to room temperature, the solution was quenched with 2 ml water, whereby a decolorization of the solution was observed. For isolation of the products, the mixture was acidified with 5 ml of 1 M HCl, then 5 ml dichloromethane were added. The resulting aqueous phase was collected and the organic phase was extracted three times with 5 ml of 1 M HCl. The combined aqueous phases were neutralized with solid Na_2CO_3 and were extracted five times with 5 ml dichloromethane. The organic phases were washed with water and dried over $MgSO_4$. After removal of the solvent in vacuo the products were isolated by column chromatography.

1-(4-Fluorophenyl)-4-(2-phenyl-1-ethyl)piperazine (3). According to the general procedure 1-(4-fluorophenyl)piperazine (2.22 mmol; 0.40 g) and styrene (2.22 mmol; 0.23 g) reacted in the presence of 5 mol % *n*-BuLi solution (0.111 mmol; 70 µl). The residue was purified by chromatography (*n*-hexane/ethyl acetate = 1:3) to afford **3** as light-brown solid. - Yield: 99 %

(GC); 76 % (isolated). - ^{1}H NMR ($CDCl_3$, 25°C, δ = ppm): 2.55-3.30 (m, 12 H, aliphatic), 6.80-6.95 (m, 4 H, aromatic *N*-phenylpiperazine), 7.10-7.25 (m, 5 H, aromatic phenyl). ^{13}C NMR ($CDCl_3$, 25°C, δ = ppm): 34.0, 50.6, 53.6, 60.8, 115.8-116.0 (d, $^2J_{CF}$ = 22), 118.2-118.3 (d, $^3J_{CF}$ = 8), 126.5, 128.8, 129.1, 140.5, 148.3, 156.4-158.8 (d, $^1J_{CF}$ = 239). GC-MS: m/e = 284 [M^+], 207 [M^+ - phenyl], 193 [M^+ - CH_2-phenyl], 150, 122, 70. *Anal.* Calcd. for $C_{18}H_{21}FN_2$: C, 76.03; H, 7.44; N, 9.85. Found: C, 75.50; H, 7.75; N, 10.02.

1-(4-Fluorophenyl)-4-[2-(4-methoxyphenyl)-1-ethyl]piperazine (4). According to the general procedure 1-(4-fluorophenyl)piperazine (2.22 mmol; 0.40 g) and *para*-methoxystyrene (2.22 mmol; 0.30 g; 0.30 ml) reacted in the presence of 5 mol % *n*-BuLi solution (0.111 mmol; 70 µl). The residue was purified by chromatography (ethyl acetate) to afford **4** as light-yellow solid. - Yield: 77 % (GC); 66 % (isolated). - ^{1}H NMR ($CDCl_3$, 25°C, δ = ppm): 2.55-2.80 (m, 8 H, aliphatic), 3.07-3.16 (m, 4 H, aliphatic), 3.72 (s, 3 H, OMe), 6.75-6.80 (d, 2 H, *J* = 8.5, aromatic), 6.80-6.95 (m, 4 H, aromatic), 7.06-7.12 (d, 2 H, *J* = 8.5, aromatic). ^{13}C NMR ($CDCl_3$, 25°C, δ = ppm): 34.1, 50.5, 53.6, 55.7, 61.1, 114.3, 115.8-116.0 (d, $^2J_{CF}$ = 22), 118.2-118.3 (d, $^3J_{CF}$ = 8), 125.3, 130.0, 156.4-158.4 (d, $^1J_{CF}$ = 199). GC-MS: m/e = 314 [M^+], 193 [M^+ - CH_2-phenyl-OCH_3], 150, 122, 95 [phenyl-F^+]. *Anal.* Calcd. for $C_{19}H_{23}FN_2O$: C, 72.58; H, 7.37; N, 8.91. Found: C, 72.30; H, 7.37; N, 8.95.

1-(4-Fluorophenyl)-4-[2-(2-naphthyl)-1-ethyl]piperazine (5). According to the general procedure 1-(4-fluorophenyl)piperazine (2.22 mmol; 0.40 g) and 2-vinylnaphthaline (2.22 mmol; 0.34 g) reacted in the presence of 5 mol % *n*-BuLi solution (0.111 mmol; 70 µl). The residue was purified by chromatography (*n*-hexane/ethyl acetate = 1:1) to afford **5** as light-yellow solid. - Yield: 84 % (GC); 67 % (isolated). - ^{1}H NMR ($CDCl_3$, 25°C, δ = ppm): 2.51-2.73 (m, 6 H, aliphatic), 2.92-3.01 (m, 2 H, aliphatic), 3.03-3.15 (m, 4 H, aliphatic), 6.79-6.93 (m, 4 H, aromatic *N*-phenylpiperazine), 7.27-7.32 (dd, 1 H, *J* = 8.0, *J* = 1.5, aromatic), 7.34-7.42 (m, 2 H, aromatic), 7.57-7.62 (s, 1 H, aromatic), 7.68-7.77 (m, 3 H, aromatic). ^{13}C NMR ($CDCl_3$, 25°C, δ = ppm): 34.1, 50.6, 53.6, 60.7, 115.8-116.0 (d, $^2J_{CF}$ = 22), 118.2-118.3 (d, $^3J_{CF}$ = 8), 125.7-128.4, 132.5, 134.0, 138.0, 148.3, 156.4-158.8 (d, $^1J_{CF}$ = 239). GC-MS: m/e = 334 [M^+], 193 [M^+ - CH_2-naphthyl], 150, 122, 95 [phenyl-F^+], 70. *Anal.* Calcd. for $C_{22}H_{23}FN_2$: C, 79.01; H, 6.93; N, 8.38. Found: C, 78.65; H, 7.12; N, 8.17.

1-(4-Fluorophenyl)-4-[2-(4-chlorophenyl)-1-ethyl]piperazine (6). According to the general procedure 1-(4-fluorophenyl)piperazine (2.22 mmol; 0.40 g) and 4-chlorostyrene (2.22 mmol; 0.31 g; 0.28 ml) reacted in the presence of 5 mol % *n*-BuLi solution (0.111 mmol; 70 µl). The residue was purified by chromatography (ethyl acetate) to afford **6** as light-yellow solid. - Yield: 98 % (GC); 81 % (isolated). - ^{1}H NMR ($CDCl_3$, 25°C, δ = ppm): 2.51-2.82 (m, 6 H, aliphatic), 3.09 (dd, 2 H, aliphatic), 3.12-3.29 (m, 4 H, aliphatic), 6.76-6.95 (m, 4 H, aromatic *N*-

arylpiperazine), 7.08 (d, 2 H, J = 8.5, aromatic), 7.17-7.23 (m, 2 H, aromatic). ^{13}C NMR ($CDCl_3$, 25°C, δ = ppm): 32.9, 50.2, 53.2, 60.1, 115.4-115.6 (d, $^2J_{CF}$ = 22), 117.8-117.9 (d, $^3J_{CF}$ = 8), 128.5, 130.0, 131.8, 138.7, 147.9, 156.0-158.4 (d, $^1J_{CF}$ = 238). GC-MS: m/e = 318 [M^+], 193 [M^+ - CH_2-Cl-phenyl], 178, 150, 122, 95, 70, 42, 28. *Anal.* Calcd. for $C_{18}H_{20}ClFN_2$: C, 67.81; H, 6.32; N, 8.79. Found: C, 67.57; H, 6.45; N, 8.97.

4-(2-Phenyl-1-ethyl)-1-(3-tolyl)piperazine (7). According to the general procedure 1-(3-methylphenyl)piperazine (2.22 mmol; 0.39 g) and styrene (2.22 mmol; 0.23 g; 0.25 ml) reacted in the presence of 5 mol % *n*-BuLi solution (0.111 mmol; 70 µl). The residue was purified by chromatography (ethyl acetate) to afford **7** as light-brown solid. - Yield: 99 % (GC); 76 % (isolated). - ^{1}H NMR ($CDCl_3$, 25°C, δ = ppm): 2.24 (s, 3 H, Me), 2.57-2.66 (m, 6 H, aliphatic), 2.76-2.83 (m, 2 H, aliphatic), 3.13-3.20 (m, 4 H, aliphatic), 6.60-6.71 (s and 2 d, 3 H, J = 8.0, aromatic *N*-phenylpiperazine), 7.06-7.10 (t, 1 H, J = 8.0, aromatic *N*-phenylpiperazine), 7.10-7.25 (m, 5 H, aromatic phenyl). ^{13}C NMR ($CDCl_3$, 25°C, δ = ppm): 22.2, 34.0, 49.6, 53.8, 60.9, 113.6, 117.3, 121.1, 126.5, 128.8, 129.1, 129.3, 139.2, 140.6, 151.7. GC-MS: m/e = 280 [M^+], 189 [M^+ - CH_2-phenyl], 146, 91 [phenyl-CH_3^+], 70. *Anal.* Calcd. for $C_{19}H_{24}N_2$: C, 81.38; H, 8.63; N, 9.99. Found: C, 81.16; H, 8.75; N, 9.70.

1-Phenyl-4-[2-(3-methylphenyl)-1-ethyl]piperazine (8). According to the general procedure phenylpiperazine (2.22 mmol; 0.36 g; 0.34 ml) and 3-methylstyrene (2.22 mmol; 0.26 g; 0.30 ml) reacted in the presence of 5 mol % *n*-BuLi solution (0.111 mmol; 70 µl). The residue was purified by chromatography (*n*-hexane/ethyl acetate = 1:3) to afford **8** as light-yellow solid. - Yield: 93 % (GC); 82 % (isolated). - ^{1}H NMR ($CDCl_3$, 25°C, δ = ppm): 2.52 (s, 3 H, Me), 2.82-2.95 (m, 6 H, aliphatic), 3.01 (m, 2 H, aliphatic), 3.48 (m, 4 H, aliphatic), 7.03-7.27 (m, 6 H, aromatic), 7.39 (t, 1 H, J = 7.0 aromatic), 7.48 (t, 2 H, J = 7.5, aromatic). ^{13}C NMR ($CDCl_3$, 25°C, δ = ppm): 21.4, 33.5, 49.2, 53.2, 60.6, 116.0, 119.7, 125.7, 126.8, 128.3, 129.1, 129.5, 138.0, 140.1, 151.3. GC-MS: m/e = 280 [M^+], 151, 137, 129. *Anal.* Calcd. for $C_{19}H_{24}N_2$: C, 81.38; H, 8.63; N, 9.99. Found: C, 81.01; H, 8.48; N, 9.84.

4-(2-Phenyl-1-ethyl)-1-(3-trifluoromethylphenyl)piperazine (9). According to the general procedure 1-(3-trifluoromethylphenyl)piperazine (2.22 mmol; 0.51 g) and styrene (2.22 mmol; 0.23 g; 0.25 ml) reacted in the presence of 5 mol % *n*-BuLi solution (0.111 mmol; 70 µl). The residue was purified by chromatography (*n*-hexane/ethyl acetate = 1:1) to afford **9** as yellow oil. - Yield: 89 % (GC); 70 % (isolated). ^{1}H NMR ($CDCl_3$, 25°C, δ = ppm): 2.62-2.78 (m, 6 H, aliphatic), 2.85-2.96 (m, 2 H, aliphatic), 3.26-3.38 (m, 4 H, aliphatic), 7.08-7.41 (m, 9 H, aromatic). ^{13}C NMR ($CDCl_3$, 25°C, δ = ppm): 34.1, 49.2, 53.6, 60.1, 112.6-112.7 (q, $^3J_{CF}$ = 4), 115.3-115.5 (q, $^3J_{CF}$ = 4), 119.1, 120.8-128.9 (q, $^1J_{CF}$ = 273), 126.7, 129.0, 129.2, 130.1, 131.4-132.6 (q, $^2J_{CF}$ = 19), 140.6, 151.9. GC-MS: m/e = 334 [M^+], 243 [M^+ - CH_2-phenyl], 200, 172,

145 [phenyl-CF_3^+], 105, 91, 70.

1-(2-Methoxyphenyl)-4-(2-phenyl-1-ethyl)piperazine (10). According to the general procedure 1-(2-methoxyphenyl)piperazine (2.22 mmol; 0.43 g) and styrene (2.22 mmol; 0.23 g; 0.25 ml) reacted in the presence of 5 mol % *n*-BuLi solution (0.111 mmol; 70 µl). The residue was purified by chromatography (*n*-hexane/ethyl acetate = 2:1) to afford **10** as yellow oil. Yield: 95 % (GC); 77 % (isolated). - ^{1}H NMR ($CDCl_3$, 25°C, δ = ppm): 2.62-2.89 (m, 6 H, aliphatic), 2.80-2.89 (m, 2 H, aliphatic), 3.07-3.19 (m, 4 H, aliphatic), 3.37 (s, 3 H, OMe), 6.83-7.03 (m, 4 H, aromatic *N*-arylpiperazine), 7.17-7.33 (m, 5 H, aromatic phenyl). ^{13}C NMR ($CDCl_3$, 25°C, δ = ppm): 34.0, 51.5, 53.8, 55.7, 61.0, 111.6, 118.6, 121.4, 123.3, 126.5, 128.8, 129.1, 140.7, 141.7, 152.7. GC-MS: m/e = 296 [M^+], 205 [M^+ - CH_2-phenyl], 190 [M^+ - CH_3-CH_2-phenyl], 162, 120, 105, 91, 70.

1-Phenyl-4-(1-methyl-2-phenylethyl)piperazine (11). According to the general procedure phenylpiperazine (2.22 mmol; 0.36 g; 0.34 ml) and *β*-trans-methylstyrene (2.22 mmol; 0.26 g; 0.29 ml) reacted in the presence of 5 mol % *n*-BuLi solution (0.111 mmol; 70 µl). The residue was purified by chromatography (*n*-hexane/ethyl acetate = 1:3) to afford **11** as yellow solid. - Yield: 71 % (GC); 61 % (isolated). - ^{1}H NMR ($CDCl_3$, 25°C, δ = ppm): 0.97 (d, 3 H, *J* = 6.5, Me), 2.42 (dd, 1 H, *J* = 12.5, *J* = 9.0, aliphatic), 2.76 (m, 4 H, aliphatic), 2.84 (m, 1 H, aliphatic), 3.00 (dd, 1 H, *J* = 13.0, *J* = 4.0, aliphatic), 3.19 (m, 4 H, aliphatic), 6.82 (t, 1 H, *J* = 7.0, aromatic *N*-arylpiperazine), 6.91 (d, 2 H, *J* = 8.0, aromatic *N*-arylpiperazine), 7.11-7.27 (m, 7 H, aromatic). ^{13}C NMR ($CDCl_3$, 25°C, δ = ppm): 14.4, 39.4, 48.5, 49.6, 61.3, 116.1, 119.6, 125.8, 128.2, 129.1, 129.3, 140.5, 151.5. GC-MS: m/e = 280 [M^+], 189 [M^+ - CH_2-phenyl], 174 [M^+ - CH_2-phenyl, -CH_3], 160, 132, 120, 91, 56, 28. *Anal.* Calcd. for $C_{19}H_{24}N_2$: C, 81.38; H, 8.63; N, 9.99. Found: C, 81.57; H, 8.76; N, 9.75.

1-Phenyl-4-(2-phenylpropyl)piperazine (12). According to the general procedure phenylpiperazine (2.22 mmol; 0.36 g; 0.34 ml) and *α*-methylstyrene (2.22 mmol; 0.26 g; 0.29 ml) reacted in the presence of 5 mol % *n*-BuLi solution (0.111 mmol; 70 µl). The residue was purified by chromatography (*n*-hexane/ethyl acetate = 1:3) to afford **12** as light-yellow solid. - Yield: 86 % (GC); 70 % (isolated). - ^{1}H NMR ($CDCl_3$, 25°C, δ = ppm): 1.33 (d, 3 H, *J* = 7.0, Me), 2.53-2.72 (m, 6 H, aliphatic), 3.03 (sextett, 1 H, *J* = 7.0, -CH-), 3.15-3.25 (m, 4 H, aliphatic), 6.86 (t, 1 H, *J* = 7.0, aromatic *N*-arylpiperazine), 6.93 (d, 2 H, *J* = 8.0, aromatic *N*-arylpiperazine), 7.20-7.35 (m, 7 H, aromatic). ^{13}C NMR ($CDCl_3$, 25°C, δ = ppm): 20.0, 37.4, 49.1, 53.5, 66.1, 115.0, 119.5, 126.1, 127.2, 128.3, 129.0, 146.1, 151.4. GC-MS: m/e = 280 [M^+], 175 [M^+ - CH_3-CH-phenyl], 160 [M^+ - CH_3-CH-phenyl, -CH_3], 132, 104, 70, 56, 28. *Anal.* Calcd. for $C_{19}H_{24}N_2$: C, 81.38; H, 8.63; N, 9.99. Found: C, 81.37; H, 8.65; N, 9.82.

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