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A short and efficient synthesis of *N*-aryl- and *N*-heteroaryl-*N*′-(arylalkyl)piperazines

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Abstract—A new synthesis of *N*-aryl- and *N*-heteroaryl-*N*′-(arylalkyl)piperazines using palladium-catalyzed amination of aryl bromides and heteroaryl chlorides with mono *N*-benzyl- or *N*-(arylethyl)piperazines is reported. Most coupling processes proceed in high yield and good selectivity using either diadamantyl-*n*-butylphosphine (**1**), 2-(dicyclohexylphosphino)-2′-(*N*,*N*-dimethylamino)biphenyl (**2**), or 2-(di-*tert*-butylphosphino)biphenyl (**3**) as ligand. Applying an automated parallel synthesizer the preparation of a small library of potentially bioactive compounds is easily achieved.

The synthesis of new biologically active molecules is an important part in the development of better and innovative drugs. Clearly, current drug development is dominated by the use of stoichiometric organic transformations, however, a catalytic route to a desired active compound is often shorter in reaction steps giving the product in a faster and more economic manner and might be easier scaled up compared to a longer traditional route. Although in recent years catalytic reactions, especially palladium-catalyzed coupling reactions,[1] have become more and more used by medicinal chemists, still catalysis is somewhat underrated given the possibilities for unusual modifications of a desired lead structure.

Some time ago we started a program for the synthesis of potentially active amphetamine analogues using base-catalyzed hydroamination reactions.[2] More recently, we envisioned the serotonin (5-HT)-receptor subtype 2A as an interesting target, for which *N*-(arylalkyl)-*N*′-heteroarylpiperazines as shown in Figure 1 are known to be strong ligands.[3] Here, we describe for the first time the synthesis of this class of compounds by palladium-catalyzed amination[4] of different aryl and heteroaryl halides with piperazine derivatives. The obtained products are of interest for the treatment of different diseases such as psychosis, schizophrenia, depression, neural disorders, memory disorders, Parkinson's disease, amyotrophic lateral sclerosis, Alzheimer's disease, Huntington's disease, eating disorders, for example, nervous bulimia and anorexia, and premenstrual syndromes and for positive influencing compulsive behaviors (obsessive–compulsive disorder, OCD).[5]

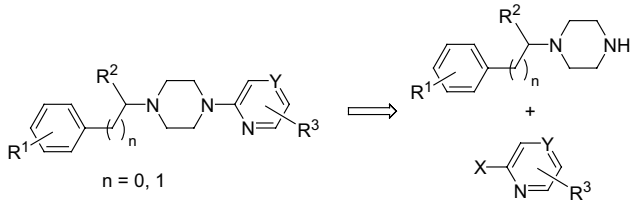

Figure 1. *N*-(Arylalkyl)-*N*′-heteroarylpiperazines.

Due to the broad pharmacological interest in piperazine derivatives, palladium-[6] and nickel-catalyzed[7] coupling reactions of piperazines with aryl halides have found widespread interest in the past.[8] In order to prepare the potential pharmaceuticals in a faster and more efficient way we envisioned to perform the synthesis of the desired compounds in an automated organic synthesizer. Thus, initially we studied the reaction of bromobenzene and *N*-benzylpiperazine as a model system

Keywords: Aminations; Piperazine; Palladium.
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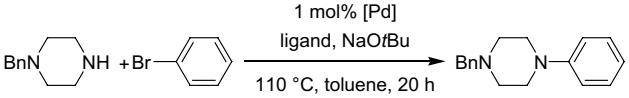
Table 1. Pd-catalyzed amination of bromobenzene with *N*-benzylpiperazine[9]



Entry	[Pd]	Ligand	Conversion [%][a]	Yield [%][b]
1	$Pd(OAc)_2$	**1**	100	91
2	$Pd_2(dba)_3$	**1**	100	93
3	$Pd(OAc)_2$	**2**	100	91
4	$Pd_2(dba)_3$	**2**	100	96
5	$Pd(OAc)_2$	**2**	12	0[c]
6	$Pd_2(dba)_3$	**2**	9	2[c]
7	$Pd(OAc)_2$	**3**	100	93
8	$Pd_2(dba)_3$	**3**	71	57
9	$Pd(OAc)_2$	**4**	20	10
10	$Pd_2(dba)_3$	**4**	28	13
11	$Pd(OAc)_2$	**4**	11	1[c]
12	$Pd_2(dba)_3$	**4**	11	1[c]
13	$Pd(OAc)_2$	PCy_3	16	1
14	$Pd_2(dba)_3$	PCy_3	7	2
15	$Pd(OAc)_2$	PCy_3	11	1[c]
16	$Pd_2(dba)_3$	PCy_3	9	1[c]

[a] With respect to PhBr.
[b] GC yield.
[c] Cs_2CO_3 instead of NaO*t*Bu.

using a Vantage parallel synthesizer.[9] Selected results from these screening experiments are shown in Table 1.

In general 1 mol % of a palladium precursor was applied in the presence of 2 mol % of the corresponding ligand. Among the five different phosphine ligands tested diadamantyl-*n*-butylphosphine (**1**) (cata*CX*ium® A),[10] 2-(dicyclohexylphosphino)-2′-(*N*,*N*-dimethylamino) biphenyl (**2**),[11] and 2-(di-*tert*-butylphosphino)biphenyl (**3**) (Fig. 2) were found to perform best with NaO*t*Bu as base and toluene as solvent at 110 °C.

Next, we applied the optimized conditions using $Pd(OAc)_2$ in the presence of ligands **1** and **2**, respectively, for the synthesis of eight different *N*-benzyl-*N*′-heteroarylpiperazines on a preparative scale (3 mmol) in a parallel manner (Table 2). To the best of our knowledge no palladium-catalyzed reactions with heteroaryl chlorides have been described so far. Here, different chloropyridines, 2-chloroquinoline, and 2-chloro-1,4-pyrazine gave the aminated products in moderate to good isolated yields. As expected the amination of 2,5-dichloropyridine proceeded with high selectivity at the 2-position with only 9% of the other regioisomer. It is noteworthy that the obtained products constitute interesting piperazinyl building blocks, which might be

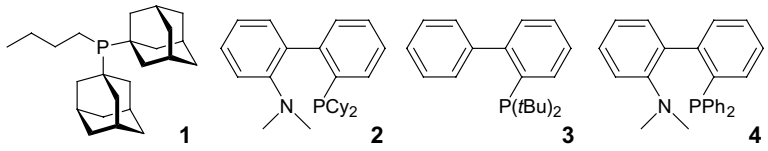
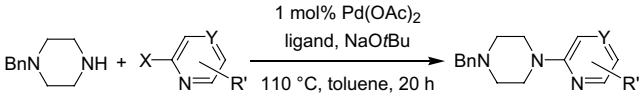


Figure 2. Ligands for the Pd-catalyzed amination of bromobenzene with *N*-benzylpiperazine.

Table 2. Pd-catalyzed amination of heteroaryl chlorides with *N*-benzylpiperazine[a]



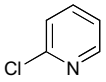
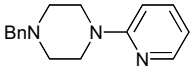
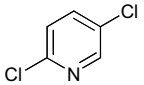
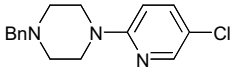
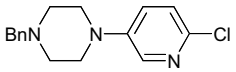
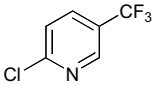
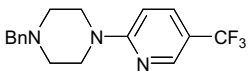
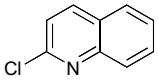
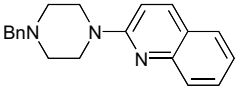
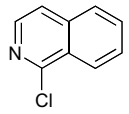
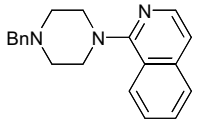
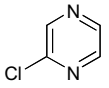
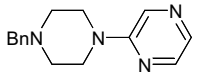
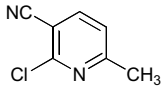
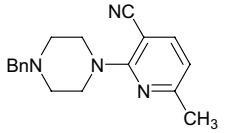
Entry	Substrate	Ligand	Product	Yield [%][b]
1		**1**		82
2		**2**		76
				9
3		**1**		58
4		**1**		85

Table 2 (*continued*)

Entry	Substrate	Ligand	Product	Yield [%][b]
5		**1**		13
6		**1**		72
7[c]		**1**		67

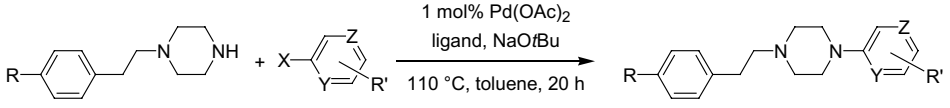
[a] Reaction conditions: *N*-Benzylpiperazine (3.0 mmol), heteroaryl chloride (3.5 mmol), NaO*t*Bu (4.0 mmol), $Pd(OAc)_2$ (0.03 mmol, 1 mol%), ligand (0.06 mmol, 2 mol%), toluene (anhydrous, 15 mL), 110 °C, 20 h in a 12 well Ares reactor.
[b] Isolated yield.
[c] Cs_2CO_3 (4.0 mmol) instead of NaO*t*Bu.

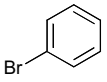
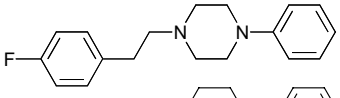
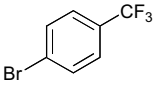
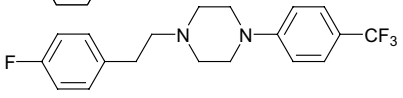
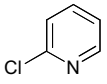
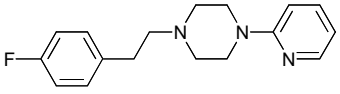
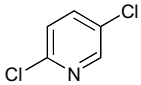
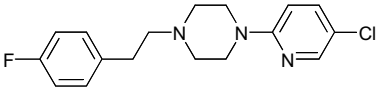
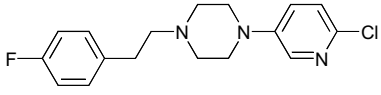
used for further C–N coupling processes after debenzylation.[12]

Finally, the palladium-catalyzed coupling reactions of two different *N*-(arylethyl)piperazines with eight different aryl or heteroaryl halides were performed. *N*-(Arylethyl)piperazines are easily accessible by base-catalyzed hydroamination of styrenes with *N*-benzylpiperazine and subsequent palladium-catalyzed debenzylation in >70% overall yield.[12] Due to the expected pharmacological properties in most cases *N*-[2-(4-fluorophenyl)ethyl]piperazine was allowed to react with selected aromatic or heteroaromatic halides under the same conditions as described above in an ACT Vantage reactor (Table 3). Most coupling products were obtained in sufficient to good yield. Isolation was easily achieved by column chromatography. Similar to the coupling with *N*-benzylpiperazine, 2-chloroisoquinoline proved to be the most difficult substrate and gave the desired product in only 36% yield. Apart from *N*-[2-(4-fluorophenyl)ethyl]piperazine also *N*-(2-phenylethyl)piperazine was arylated in good yield.

In summary, a facile synthesis of potential biologically active *N*-(arylalkyl)-*N*′-heteroarylpiperazines has been developed. The resulting compounds are of broad

Table 3. Pd-catalyzed arylation of *N*-(arylethyl)piperazines[a]



Entry	(Hetero)aryl halide	Product	Yield [%][b]
1			68
2			62
3			64
4			59
			8

(*continued on next page*)

Table 3 (*continued*)

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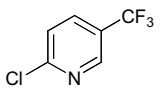
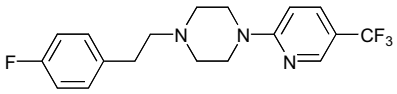
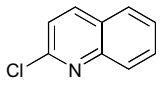
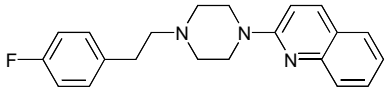
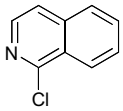
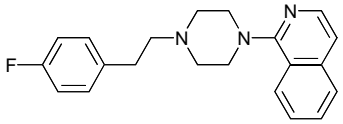
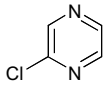
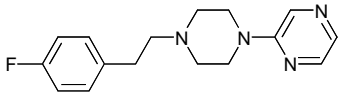
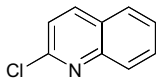
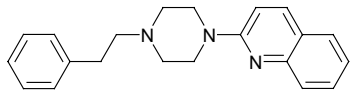
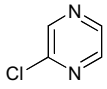
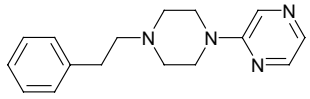
5			56
6			75
7			36
8			69
9			70
10			50

[a] Reaction conditions: *N*-(Arylethyl)piperazine (3.0 mmol), (hetero)aryl halide (3.5 mmol), NaO*t*Bu (4.0 mmol), $Pd(OAc)_2$ (0.03 mmol, 1 mol%), ligand **2** (0.06 mmol, 2 mol%), toluene (anhydrous, 15 mL), 110 °C, 20 h in a 12 well Ares reactor.
[b] Isolated yield.

interest as 5-HT_{2A} receptor antagonists. Despite the usage of sensitive ligands and base coupling reactions of heteroaryl chlorides and piperazine derivatives can be easily applied on an automated parallel synthesizer allowing an efficient preparation of libraries of biologically active compounds.

Acknowledgements

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References and notes

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9. General procedure: In a typical experiment (Table 1), NaO*t*Bu (1.5 mmol) was placed in each vessel of a 48 well Ares reaction block of the ACT Vantage prior setup and flushed with argon. Then, $Pd(OAc)_2$ (1 mol%), ligand (2 mol%), *N*-benzylpiperazine (1.5 mmol), (hetero)aryl halide (1.25 mmol), and hexadecane (100 μL; as internal standard for GC) were transferred subsequently from inert stock solutions (anhydrous toluene) and diluted with anhydrous toluene (total volume of toluene: 3 mL). The reactor was kept shaking with 350 rpm over 20 h at 110 °C. After cooling to rt and automatical filtration using a cleavage block, reaction mixtures were removed from reactor, analyzed by GC and/or chromatographed on silica using eluent mixtures of hexane/ethyl acetate in different ratios. The identity of the products was confirmed by GC–MS and NMR data.
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