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Preparation of *N*-arylpiperazines and other *N*-aryl compounds from aryl bromides as scaffolds of bioactive compounds

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Abstract—Aryl bromides are coupled with *N*-compounds to give the corresponding arylamines in the presence of a palladium catalyst, a suitable ligand, and a weak base. The catalysts perform well for a large number of different starting material combinations at 100–150 °C with drops of toluene or without solvent, and with low catalyst levels (0.12 mol % Pd). The low catalyst amount makes the process environment friendly.

In the course of our work aimed at obtaining new compounds with biological activity, we required an easy source of *N*-aryl derivatives to serve as precursors. *N*-arylpiperazines, *N*-arylindoles, *N*-arylpyrroles, and substituted anilines are important compounds, particularly in pharmaceutical research and also as intermediates of synthesis. The *N*-arylpiperazine subunit is embedded in several pharmacologically interesting targets such as compounds related to the serotonine ligands,[1] calcium blockers,[2] antipsychotic drugs,[3] antihypertensive,[4] and acetylcholinesterase inhibitory activity.[5] For these reasons significant efforts have gone into the development of efficient methods for their preparation.

In the last decade, several research groups such as Buchwald et al.[6–10] and Hartwig et al.[11–14] reported the palladium-catalyzed coupling of aryl halides with several amino-derivatives. This important reaction opens a new way for synthesizing several pharmaceutical molecules that are otherwise difficult to prepare.

This direct N-arylation is an alternative to classical S_NAr reactions for the preparation of arylamines. Compared to analogous C–C bond-forming such as Suzuki, Stille, and Heck coupling reactions, the cross-coupling methodology to form C–N bonds is more limited.

Recent reports from several research groups on the palladium-catalyzed cross coupling of aryl halides with *N*-derivatives have furnished interesting results but have revealed the need to find more general conditions or the optimization of each process is strongly recommended. Moreover, efficient conditions for the arylation of piperazines have not been reported up to now.

The synthesis of arylpiperazines by palladium-catalyzed amination reaction from unprotected piperazine has been previously reported.[15,16] The results clearly indicate that the piperazine arylation was successful only in low to moderate yields. Fort and co-workers[17] reported a nickel-catalyzed method for the synthesis of *N*,*N*′-diarylpiperazines from aryl chlorides and Zhao et al. described first the use of $Pd[P(o\text{-tolyl})_3]_2Cl_2$ catalyst for the arylation of piperazines.[16]

This work was initiated by searching efficient methods for the preparation of scaffolds for potential bioactive compounds, and intends to develop general reaction conditions for the palladium-catalyzed formation of these anilines. Herein we describe our results and details (Tables 1 and 2).

We have prepared arylamines from interesting substrates using $Pd[P(o\text{-tolyl})_3]_2Cl_2$ as catalyst, chelating ligand such as 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP) or triphenylphosphine (PPh_3), and cesium carbonate base without solvent or few drops of toluene were added when the starting material were solid compounds. The reagents can be weighed and manipulated in contact with air facilitating the industrial use. This is a fast and clean reaction and the results showed that it is possible to replace the expensive BINAP by PPh_3 more readily available than other classic used ligands. This is a modified Buchwald–Hartwig amination of aryl bromides using different substrates and

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Keywords: *N*-Arylpiperazines; *N*-Arylindoles; Substituted anilines; Palladium catalyst; N-Arylation; Aryl halides.

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Table 1. Palladium-catalyzed formation of tertiary amines

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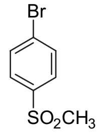
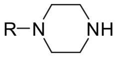
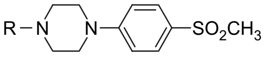
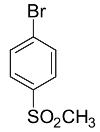
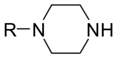
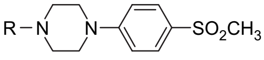
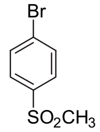
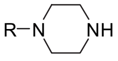
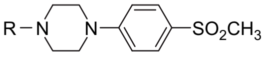
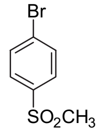
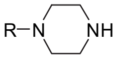
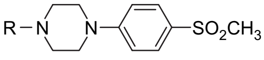
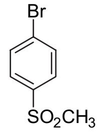
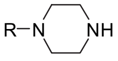
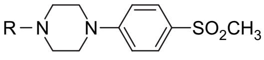
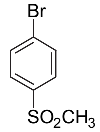
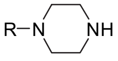
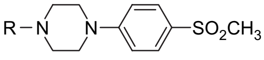
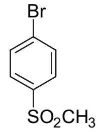
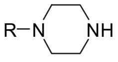
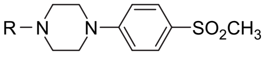
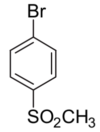
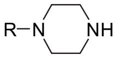
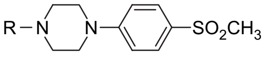
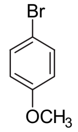
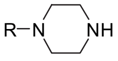
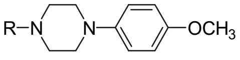
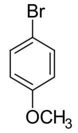
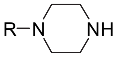
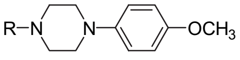
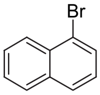
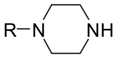
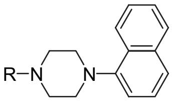
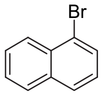
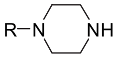
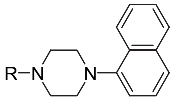
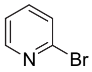
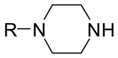
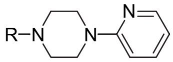
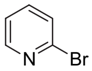
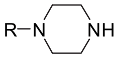
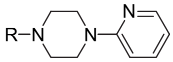
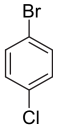
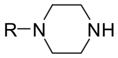
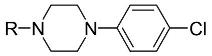
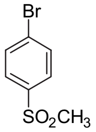
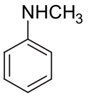
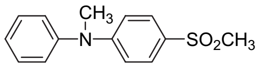
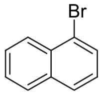
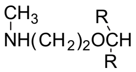
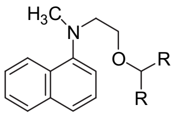
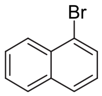
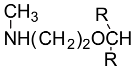
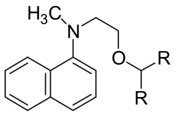
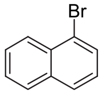
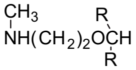
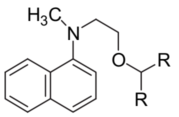
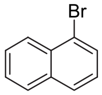
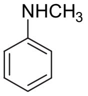
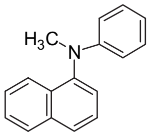
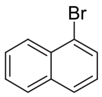
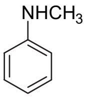
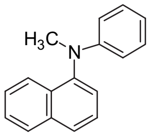
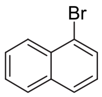
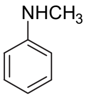
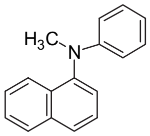
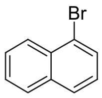
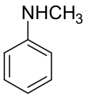
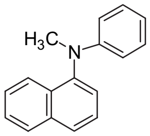
1		 R=4-fluorophenyl	 R=4-fluorophenyl	92 (75)	$Pd[P(o\text{-tolyl})_3]_2Cl_2$/BINAP (±)/$Cs_2CO_3$
2		 R=4-fluorophenyl	 R=4-fluorophenyl	91	$Pd[P(o\text{-tolyl})_3]_2Cl_2$/BINAP (+)/$Cs_2CO_3$
3		 R=4-fluorophenyl	 R=4-fluorophenyl	88	$Pd[P(o\text{-tolyl})_3]_2Cl_2/PPh_3/Cs_2CO_3$
4		 R=4-fluorophenyl	 R=4-fluorophenyl	0	$Pd[P(o\text{-tolyl})_3]_2Cl_2/Cs_2CO_3$ without ligand
5		 R=4-fluorophenyl	 R=4-fluorophenyl	23	$Pd(OAc)_2$/BINAP (+)/Cs_2CO_3
6		 R=4-fluorophenyl	 R=4-fluorophenyl	81 (78)	$Pd[P(o\text{-tolyl})_3]_2Cl_2$/BINAP (±)/KO*t*-Bu
7		 R=4-fluorophenyl	 R=4-fluorophenyl	55	Cu/K_2CO_3
8		 R=4-fluorophenyl	 R=4-fluorophenyl	0	BINAP (+)/Cs_2CO_3 without catalyst
9		 R=4-fluorophenyl	 R=4-fluorophenyl	43 (47)	$Pd[P(o\text{-tolyl})_3]_2Cl_2$/BINAP (±)/$Cs_2CO_3$
10		 R=4-fluorophenyl	 R=4-fluorophenyl	32	$Pd[P(o\text{-tolyl})_3]_2Cl_2/PPh_3/Cs_2CO_3$
11		 R=4-fluorophenyl	 R=4-fluorophenyl	81 (68)	$Pd[P(o\text{-tolyl})_3]_2Cl_2$/BINAP (+)/$Cs_2CO_3$

(*continued*)

Table 1. (*continued*)

Entry	Ar-X	R_1R_2NH	Product	Yield (%)[a]	Conditions
12		 R=4-fluorophenyl	 R=4-fluorophenyl	78	Pd[P(*o*-tolyl)$_3$]$_2$Cl$_2$/PPh$_3$/Cs$_2$CO$_3$
13		 R=4-fluorophenyl	 R=4-fluorophenyl	41	Pd[P(*o*-tolyl)$_3$]$_2$Cl$_2$/BINAP (±)/Cs$_2$CO$_3$
14		 R=4-fluorophenyl	 R=4-fluorophenyl	45 (48)	Pd[P(*o*-tolyl)$_3$]$_2$Cl$_2$/PPh$_3$/Cs$_2$CO$_3$
15		 R=4-fluorophenyl	 R=4-fluorophenyl	79	Pd[P(*o*-tolyl)$_3$]$_2$Cl$_2$/BINAP (±)/Cs$_2$CO$_3$
16				90	Pd[P(*o*-tolyl)$_3$]$_2$Cl$_2$/BINAP (+)/Cs$_2$CO$_3$
17		 $\overset{CH_3}{NH}(CH_2)_2O\underset{R}{\overset{R}{CH}}$ R=4-fluorophenyl	 R=4-fluorophenyl	85 (87)	Pd[P(*o*-tolyl)$_3$]$_2$Cl$_2$/BINAP (±)/Cs$_2$CO$_3$
18		 $\overset{CH_3}{NH}(CH_2)_2O\underset{R}{\overset{R}{CH}}$ R=4-fluorophenyl	 R=4-fluorophenyl	87	Pd[P(*o*-tolyl)$_3$]$_2$Cl$_2$/BINAP (+)/Cs$_2$CO$_3$
19		 $\overset{CH_3}{NH}(CH_2)_2O\underset{R}{\overset{R}{CH}}$ R=4-fluorophenyl		86	Pd[P(*o*-tolyl)$_3$]$_2$Cl$_2$/PPh$_3$/Cs$_2$CO$_3$
20				78 (69)	Pd[P(*o*-tolyl)$_3$]$_2$Cl$_2$/BINAP (±)/Cs$_2$CO$_3$
21				79	Pd[P(*o*-tolyl)$_3$]$_2$Cl$_2$/BINAP (+)/Cs$_2$CO$_3$
22				76	Pd[P(*o*-tolyl)$_3$]$_2$Cl$_2$/PPh$_3$/Cs$_2$CO$_3$
23				5	Pd(OAc)$_2$/BINAP (+)/Cs$_2$CO$_3$

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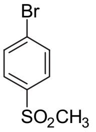
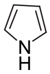
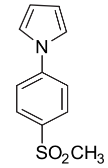
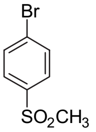
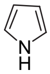
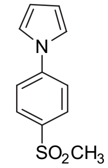
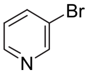
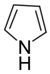
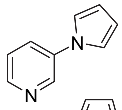
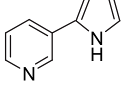
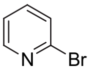
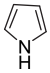
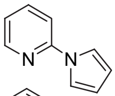
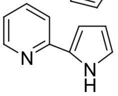
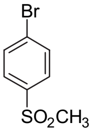
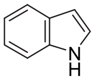
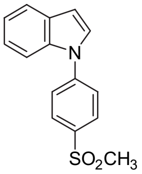
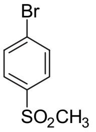
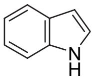
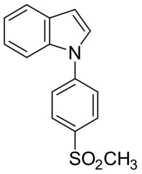
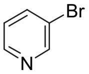
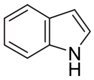
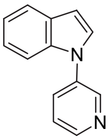
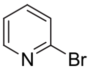
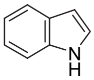
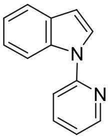
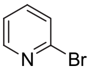
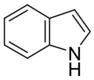
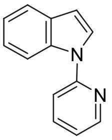
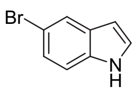
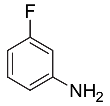
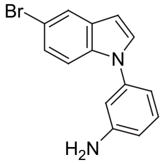
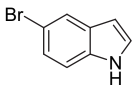
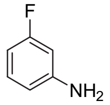
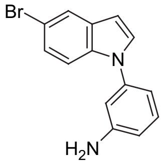
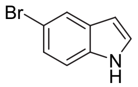
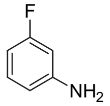
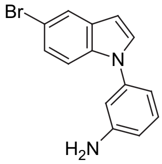
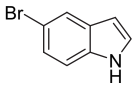
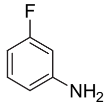
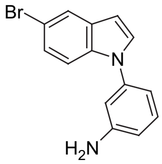
[a] Yields reported correspond to analytically pure isolated compounds (average of two or three runs). All the reactions were conducted at 120 °C for 2 h except for entries 7 (120 h) and 8 (24 h). Compounds of entries 1, 6, 9, 11, 14, 17, and 20 have been prepared on a 1-g scale and the yields are indicated in brackets.

Table 2. Palladium-catalyzed N-arylation of pyrrole and indole

Entry	Ar-X	R_1R_2NH	Product	Yield (%)	Conditions
1				75 (69)	Pd[P(*o*-tolyl)$_3$]$_2$Cl$_2$/BINAP (+)/Cs$_2$CO$_3$
2				72	Pd[P(*o*-tolyl)$_3$]$_2$Cl$_2$/PPh$_3$/Cs$_2$CO$_3$
3			 	21[a] 46[a]	Pd[P(*o*-tolyl)$_3$]$_2$Cl$_2$/BINAP (+)/Cs$_2$CO$_3$
4			 	72 18	Pd[P(*o*-tolyl)$_3$]$_2$Cl$_2$/BINAP (+)/Cs$_2$CO$_3$
5				87 (82)	Pd[P(*o*-tolyl)$_3$]$_2$Cl$_2$/BINAP (+)/Cs$_2$CO$_3$
6				90	Pd[P(*o*-tolyl)$_3$]$_2$Cl$_2$/PPh$_3$/Cs$_2$CO$_3$
7				48	Pd[P(*o*-tolyl)$_3$]$_2$Cl$_2$/BINAP (+)/Cs$_2$CO$_3$
8				86 (81)	Pd[P(*o*-tolyl)$_3$]$_2$Cl$_2$/BINAP (+)/Cs$_2$CO$_3$
9				88	Pd[P(*o*-tolyl)$_3$]$_2$Cl$_2$/PPh$_3$/Cs$_2$CO$_3$

(*continued*)

Table 2. (*continued*)

Entry	Ar-X	R_1R_2NH	Product	Yield (%)	Conditions
10				0[b]	Pd[P(*o*-tolyl)$_3$]$_2$Cl$_2$/BINAP (+)/Cs$_2$CO$_3$
11				30[c]	Pd[P(*o*-tolyl)$_3$]$_2$Cl$_2$/BINAP (+)/Cs$_2$CO$_3$
12				65[d]	Pd[P(*o*-tolyl)$_3$]$_2$Cl$_2$/BINAP (+)/Cs$_2$CO$_3$
13				0[e]	BINAP (+)/Cs$_2$CO$_3$ without catalyst

Compounds of entries 1, 5, and 8 have been prepared on a 1-g scale and the yields are indicated in brackets.

Yields reported correspond to analytically pure isolated compounds (average of two or three runs). All the reactions were conducted at 120 °C for 2 h. Except the indicated cases.

[a] 4 h at 150 °C.

[b] 24 h at 130 °C.

[c] 6 h at 150 °C.

[d] 24 h at 150 °C.

[e] 24 h at 180 °C without catalyst.

optimized conditions, which allows the synthesis of precursors of bioactive compounds. Aryl bromides were chosen as starting compounds because they are readily available and more reactive than aryl chlorides and triflates.[18] Furthermore, the preparation of functionalized aryl iodides was more difficult.[19]

According to Buchwald and co-workers[8] and Ma and co-workers,[20] the acyclic secondary amines are usually problematic substrates for the coupling reactions, probably due to steric hindrance, high nucleophilicity, and basicity and also the possibility of β-elimination hydrogen can be considered. The preparation of hindered *N*,*N*-dialkylarylamines was successful in these conditions giving the corresponding disubstituted anilines (Table 1). Acyclic secondary amine substrates (Table 1, entry 18) gave a lower yield of coupled product than those obtained with cyclic secondary amines and electron poor aryl bromide (Table 1, entry 1), but better than cyclic secondary amines and electron rich aryl bromide (Table 1, entry 9). Electron poor aryl bromides containing a sulfone group afforded the expected products with excellent yields within 2 h (Table 1, entry 1). The reaction was shown to tolerate the naphthyl group with good yield of 76–87% (Table 1, entries 17–22). Another interesting observation was the regioselective reaction of 1-bromo-4-chlorobenzene with the substituted piperazine under the same reaction conditions (Table 1, entry 15). Changing the chelating ligand from BINAP to triphenylphosphine (PPh$_3$), which is less expensive, resulted in non-significant modification of yields (Table 1, compare entry 1 vs entry 3; entry 9 vs entry 10; entry 13 vs entry 14; entry 17 vs entry 19). In the same way, both racemic and non-racemic BINAP ((*R*)-(+)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl) gave similar results in all the tested transformations (Table 1, compare entry 1 vs entry 2; entry 17 vs entry 18; entry 20 vs entry 21). Moreover addition of a large excess of BINAP did not modify the yields under our experimental conditions and also was determined that the order of addition of reagents was not important. The experiments carried out from 1 g of substrate provide the desired compounds in acceptable yields using a minimal amount of catalyst (see Tables 1 and 2, the yields of 1-g scale reactions were indicated in brackets).

No reaction occurred without addition of ligand BINAP or triphenylphosphine to Pd[P(*o*-tolyl)$_3$]$_2$Cl$_2$, substrate, and cesium carbonate (Table 1, entry 4). The results showed that P(*o*-tolyl)$_3$ present in the catalyst system was ineffective, even for the N-arylation of the activated substrates. The use of Pd(OAc)$_2$ as a precatalyst was found to be less efficient than Pd[P(*o*-tolyl)$_3$]$_2$Cl$_2$ in the tested substrates (Table 1, entries 5 and 23). When strongly basic KO*t*-Bu was used instead of Cs$_2$CO$_3$ the expected piperazine was obtained in a good yield (Table 1, entry 6).

On the other hand the Ullmann-type coupling using Cu/K$_2$CO$_3$ gave the desired product in 55% yield and starting aryl bromide remained unreacted after 120 h of reaction (Table 1, entry 7). In this study the Pd catalyst revealed superiority over the Cu system.

When $Pd_2(dba)_3$ was used as catalyst under conditions presented by Verkade and Urgaonkar the aryl bromide reacted very slowly and the reaction was not complete after 3 days.[21]

In the same way, the synthesis of *N*-arylpyrrole or indole has been achieved by using the same conditions. Hartwig et al. have reported previously the preparation of *N*-arylazoles using the combination of $Pd(dba)_2$ and dppf in the presence of NaO*t*-Bu or Cs_2CO_3.[11] The $Pd(dba)_2$ is a good catalyst but difficult the purification of products. More late the same authors have optimized the reaction conditions using $Pd(dba)_2$/P(*t*-Bu)$_3$.[22] When 5-bromoindole was treated with 3-fluoroaniline, both possessing two reactive positions, the arylation took place exclusively at the 1-position over the N-atom, giving the corresponding *N*-arylindole as a single isomeric product at temperature near to 150 °C (Table 2, entries 11 and 12), and the expected 5-(3-fluorophenylamino)indole was not detected under these conditions. In contrast, the reaction was unsuccessful at 130 °C after more than 24 h (Table 2, entry 10). Thus, this method allowed the synthesis of *N*-(3-aminophenyl)-5-bromoindole from 5-bromoindole and 3-fluoroaniline under severe reaction conditions (Table 2, entry 12). The 3-fluoroaniline was the choice thinking that the arylation will take place at the amine group. The displacement of fluoride (3-fluoroaniline) instead of bromine (5-bromoindole) is not clear; aryl fluorides have long been considered inert to Pd-catalyzed coupling reactions,[22] and only aryl fluorides with strong electron-withdrawing substituents give coupling reactions.[23] Only the high temperatures can explain this behavior. Attempts at the same temperature in the absence of Pd catalyst were unsuccessful (Table 2, entry 13), result that corroborate the radical mechanism of this reaction.

The pyridinylation of indole was also conducted in the same manner as described above using 3-bromopyridine and indole but the intended coupled product was obtained in low yield (Table 2, entry 7). Nevertheless, the 2-bromopyridine in the same conditions gives the *N*-arylpyrrole in excellent yield (Table 2, entry 8). It is interesting the reactivity of pyrrole with heteroaromatic substrates such as the 2- and 3-bromopyridine. In all cases, mixtures of two isomers were obtained. The reaction of 3-bromopyridine with pyrrole gave the *N*-arylpyrrole (21%) and the nornicotyrine (46%) (Table 2, entry 3). Whereas the treatment of pyrrole with 2-bromopyridine afforded the 2-(1-pyrrolyl) pyridine (72%) and the 2,2′-pyrrolylpyridine (18%) (Table 2, entry 4). The reaction of 2-bromopyridine with the pyrrole and indole rings proceeded with more yield and selectivity than the reaction of 3-bromopyridine. Our hypothesis is that the 2-bromopyridine facilitates the complexation with the catalyst system and N-arylation of the azole was preferable as expected (Table 2, entries 4 and 8). Recently, Doucet et al. reported the significant effect of the position and the nature of the halide on the heteroaromatic nuclei on catalyzed palladium reactions.[24]

The substitution of the two different positions of the pyrrole by the reaction of the pyrrole with the bromopyridine is dependent on the position of the bromine atom over the pyridine nucleus (Table 2, entries 3 and 4). So, it is know that the 2-position of bromopyridines is most susceptible to do oxidative addition to palladium than the 3-position. Moreover, due to pyrrole electronic distribution, it might be involved in two different arylation mechanisms, as suggested by the ab initio computational data included in Supplementary material. Pyrrole and indole react readily with electron poor aryl bromide and give *N*-arylpyrrole (Table 2, entry 1) and *N*-arylindole (Table 2, entry 5) in good yield.

The N-arylation of pyrrole and indole can be obtained at 100 °C, but a significant amount of starting material remained unreacted after a long reaction time at this temperature. Considering these results, the process was optimized at a higher temperature (130–150 °C). In general, this coupling reaction was found to be temperature dependent, higher reaction temperatures increases the yield, but by raising the temperature to 180 °C, the ratio of side products was increased.

In summary, we report new conditions for the palladium-catalyzed amination of aryl bromides, which do not require the use of solvent or few drops of toluene (exceptional cases), and need low catalyst amounts. The direct N-arylation of substituted piperazines was an interesting aspect of this strategy. This developed methodology was efficient on a 1-g scale for coupling aryl and aliphatic amines. This protocol will be applied to the preparation of more complex and interesting nitrogen containing compounds and these studies will be reported in due course.

Amination of aryl halides (Tables 1 and 2). General procedure. A flask was charged with aryl halide (1.0 mmol), amine (1.2 mmol), cesium carbonate (1.0 mmol), Pd[P(*o*-tolyl)$_3$]$_2$Cl$_2$ (0.12 mol % Pd), and BINAP (0.0075 mmol) under argon without addition of solvent (just drops of toluene was added only in exceptional cases when both starting compounds were solids). The flask was hermetically closed and the mixture was heated at 100–130 °C (after the substrate and all reagents have been added without any period of incubation) with stirring until the starting material has been completely consumed as analyzed by TLC. The mixture was then allowed to cool to room temperature and the crude product was directly purified further by flash chromatography on silica gel, eluting with mixtures of hexane/ethyl acetate. All the commercially available reagents used were purchased from Aldrich Chemical Co. and were used without previous purification. The catalyst was acquired from Strem (Chemicals for Research). Yields reported correspond to analytically pure isolated compounds.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.07.011

References and notes

1. (a) Evrad, D. A.; Zhou, D.; Stack, G. P.; Venkatesan, A. M.; Failli, A. A.; Croce, S. C. Application: US 2004142926; CAN 141:123658; (b) Leopoldo, M.; Berardi, F.; Colabuto, N. A.; Contino, M.; Lascivita, E.; Perrone, R.; Tortorella, V. *J. Pharm. Pharmacol.* **2004**, *56*, 247–255; (c) López-Rodríguez, M. L.; Benhamu, B.; Morcillo, M. J.; Tejada, I.; Avila, D.; Marco, I.; Schiapparelli, L.; Frechilla, D.; Del Rio, J. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3177–3180; (d) López-Rodríguez, M. L.; Ayala, D.; Benhamu, B.; Morcillo, M. J.; Viso, A. *Curr. Med. Chem.* **2002**, *9*, 443–469.
2. Annoura, H.; Usesugi, M.; Fukunaga, A.; Tamura, S. Application: WO 96-JP469 19960228; CAN 125:275912.
3. González-Gómez, J. C.; Santana, L.; Uriarte, E.; Brea, J.; Villason, M.; Loza, M. I.; De Luca, M.; Rivas, M. E.; Montenegro, G. Y.; Fontenia, J. A. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 175–178.
4. Klioze, S. S.; Allen, R. C.; Wilker, J. C.; Woodward, D. L. *J. Med. Chem.* **1980**, *23*, 677–679.
5. Cappelli, A.; Gallelli, A.; Manini, M.; Anzini, M.; Mennuni, L.; Makovec, F.; Menziani, M. C.; Alcaro, S.; Ortuso, F.; Vomero, S. *J. Med. Chem.* **2005**, *48*, 3567–3575.
6. Wolfe, J. P.; Wagaw, S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 7215–7216.
7. Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **1997**, *62*, 1264–1267.
8. Wolfe, J. P.; Rennels, R. A.; Buchwald, S. L. *Tetrahedron* **1996**, *52*, 7525–7546.
9. Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1144–1157.
10. Wolfe, J. P.; Buchwald, S. L. *Tetrahedron Lett.* **1997**, *38*, 6359–6362.
11. Mann, G.; Hartwig, J. F.; Driver, M. S.; Fernández-Rivas, C. *J. Am. Chem. Soc.* **1998**, *120*, 827–828.
12. Hartwig, J. F. *Synlett* **1996**, 329–340.
13. Driver, M. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **1996**, *118*, 7217–7218.
14. (a) Hartwig, J. F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2046–2067; (b) Shekhar, S.; Ryberg, R.; Hartwig, J. F.; Mathew, J. S.; Blackmond, D. G.; Strieter, E. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2006**, *128*, 3584–3591.
15. (a) Torisawa, Y.; Nishi, T.; Minimikawa, J.-I. *Bioorg. Med. Chem.* **2002**, *10*, 4023–4027; (b) Hepperle, M.; Eckert, J.; Gala, D.; Shen, L.; Evans, C. A.; Goodman, A. *Tetrahedron Lett.* **2002**, *43*, 3359–3363; (c) Bueno, A. B.; Flynn, C. J.; Gilmore, J.; Marcos, A.; Montero, C.; Porter, W.; Willians, A. C. *Tetrahedron Lett.* **2005**, *46*, 7769–7771.
16. (a) Zhao, S.-H.; Miller, A. K.; Berger, J.; Flippin, L. A. *Tetrahedron Lett.* **1996**, *37*, 4463–4466; (b) Nishiyama, M.; Yamamoto, T.; Koie, Y. *Tetrahedron Lett.* **1998**, *39*, 617–620.
17. (a) Brenner, E.; Schneider, R.; Fort, Y. *Tetrahedron* **2002**, *58*, 6913–6924; (b) Brenner, E.; Schneider, R.; Fort, Y. *Tetrahedron* **1999**, *55*, 12829–12842.
18. Harrak, Y.; Romero, M.; Constans, P.; Pujol, M. D. *Lett. Org. Chem.* **2006**, *3*, 29–34.
19. (a) Merkushev, E. B. *Synthesis* **1988**, 923–927; (b) Barluenga, J.; González, J. M.; García-Martín, M. A.; Campos, P. J.; Asensio, G. *J. Org. Chem.* **1993**, *58*, 2058–2061.
20. Zhang, H.; Cai, Q.; Ma, D. *J. Org. Chem.* **2005**, *70*, 5164–5173.
21. Urgaonkar, S.; Verkade, J. G. *J. Org. Chem.* **2004**, *69*, 9135–9142.
22. Hartwig, J. F.; Kawatsura, M.; Hauck, S. I.; Sahughnessy, K. H.; Alcazar-Roman, L. M. *J. Org. Chem.* **1999**, *64*, 5575–5580.
23. Young, M. K.; Shu, Y. *J. Am. Chem. Soc.* **2003**, *125*, 1696–1697.
24. Feuerstein, M.; Doucet, H.; Santelli, M. *Tetrahedron Lett.* **2005**, *46*, 1717–1720.