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Synthesis of N-Arylpiperazines from Aryl Halides and Piperazine under a Palladium Tri-tert-butylphosphine Catalyst

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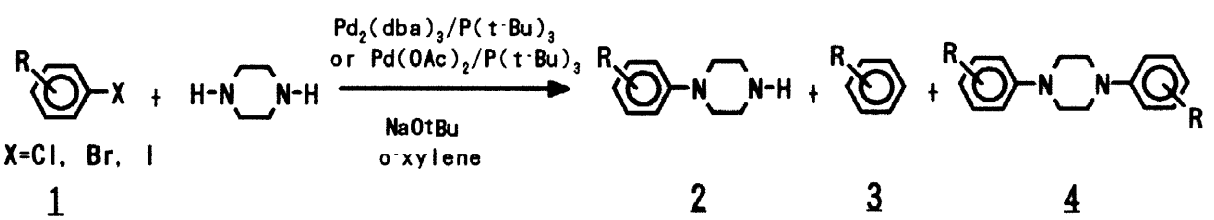
Abstract : A Pd/P(*t*-Bu)$_3$ catalyst system has revealed very high activity and selectivity for the amination of N-(hetero)aryl halides with unprotected piperazine. A wide variety of N-(hetero)arylpiperazines could be prepared using this catalyst. Turnover numbers up to 6400mol/mol have been obtained. © 1998 Elsevier Science Ltd. All rights reserved.

N-Arylpiperazines are important intermediates for pharmaceuticals such as antidepressants and others.[1] During the past few years, pharmaceuticals with the N-arylpiperazine moiety have been developed.[2]

Current synthetic methods of N-arylpiperazines involve cyclization[3] of a substituted aniline with bis(2-haloethyl)amine. However, this synthetic method is rather limited due to the toxicity of bis(2-haloethyl)amine and poor availability of substituted arylamines, especially heteroarylamines. Other methods have been proposed such as 1)cyclization from an aniline and bis(2-haloethyl)amine in the presence of Al_2O_3 support[4], 2)nucleophilic substitution of lithium-amide to alkoxybenzene derivatives[5], 3)nucleophilic aromatic substitution of a fluoroarene-tricarbonylchromium complex[6].

Recently, Buchwald and Hartwig[7] have developed unique palladium-catalyzed amination reactions of aryl halides with amines employing Pd catalysts bearing P(*o*-tolyl)$_3$ or chelating ligands. Based on their protocols, synthesis of N-arylpiperazines from an aryl halide and piperazine with a Pd-P(*o*-tolyl)$_3$ catalyst also has been reported[8].

This palladium-catalyzed procedure also could be improved, since the protocols produce a certain amount of arenes(**3**) as by-products, and require a fairly large amount of catalyst. Here, we report outstanding activities and selectivities of a Pd/P(*t*-Bu)$_3$ catalyst for the synthesis of N-aryl- and N-heteroarylpiperazines(**2**) from aryl halides(**1**) and unprotected piperazine.



We first investigated the phosphine effects on the palladium-catalyzed amination of m-bromoanisole

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with piperazine in *o*-xylene at 120℃(Table 1). As reported previously, the catalyst generated from $Pd_2(dba)_3$ and bulky P(*o*-tolyl)$_3$ gave the desired N-arylpiperazine in moderate yield along with anisole in 37% yield as a product of debromination reaction(entry 7).

Table 1. Influence of ligand on the reactivity of m-bromoanisole to 3-methoxyphenyl-piperazine

Entry	Ligand PR_3	Cat.[a] /mol%	Conv. /mol%	Sel. /mol% 2	3
1	n-Bu	0.5 (A)	34	40	37
2	Cy	0.5 (A)	100	15	78
3	*t*-Bu	0.5 (A)	100	96	< 1
4	*t*-Bu	0.02 (B)	100	94	2
5	*t*-Bu	0.01 (B)	73	88	4
6	C_6F_5	0.5	100	42	44
7	o-tolyl	0.5	100	61	37
8	mesityl	0.1	14	81	12

Condition solvent : *o*-xylene
Piperazine/NaO^{t}Bu/Arylbromide=6/1.38/1
[a] Catalyst A: $Pd_2(dba)_3/PR_3$(P/Pd=4)
B: $Pd(OAc)_2/PR_3$(P/Pd=4)
Temp : 120℃(3~4hr)
GC yields were calculated using biphenyl as internal standard.

Another sterically large ligand, P(mesityl)$_3$, showed high selectivity to the N-arylpiperazine, although its activity was low(entry 8). The use of electron-rich P(Cy)$_3$ led to the formation of anisole as the major product of the reaction(entry 2). The mixture of $Pd_2(dba)_3$ and bulky P(*t*-butyl)$_3$ displayed excellent selectivity up to 96% of the desired coupling product according to GC analysis(entry 3). Interestingly, this catalyst system showed similar good activity even if a much lower concentration of palladium was used(0.01~0.02mol%, entry 4, 5). Consequently, turnover numbers(TON) as high as 6400(mol product/mol palladium) were achieved. We estimate that both the strong basicity and the moderate steric bulkiness of P(*t*-Bu)$_3$ may contribute to the high activity and selectivity through enhancing the rate of the reductive elimination from the aryl(amido)palladium intermediate complex to form N-arylpiperazines.

In order to examine the scope of the Pd/P(*t*-Bu)$_3$ catalyst system, we studied the coupling reaction of various substituted aryl halides with piperazine(Table 2 or 3).

As shown in Table 2, most of the N-arylpiperazines can be prepared[9] from not only the aryl iodide(entry 18), but also the aryl bromides with electron-withdrawing(entry 14, 20) or electron-donating groups(entry 10, 12, 13) at the meta or para- position, without a substituent(entry 17, 21) in excellent yields by using the catalyst.

In addition, the reaction of aryl chloride, in which it is thought it is difficult for the oxidative addition of the Pd catalyst to proceed, with piperazine gave the N-arylpiperazine in 83% conversion and 94% selectivity(entry 19).

However, aryl halides with a fluoro- and methoxy-group at the ortho-position provided the N-arylpiperazines in low yields(entry 9, 11).

We also examined the influence of the ratio of piperazine to **1** on the selectivity (entry 15, 16). When the ratio was lowered to two, N,N'-diarylpiperazine(**4**) was formed two-fold; on the other hand, **3** was 40% reduced. But the yield of **2** was not changed.

The catalyst system can be applied to the N-heteroarylpiperazines(entry 22, 23, 24) such as N-pyridinyl or N-indolyl-piperazine. Buchwald reported[10] that the amination reaction of bromopyridine with Pd/monodentate P(*o*-tolyl)$_3$ was unsuccessful. However, the mixture of $Pd(OAc)_2$ and P(*t*-Bu)$_3$

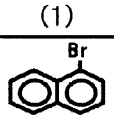
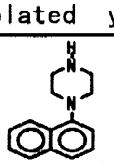
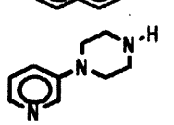
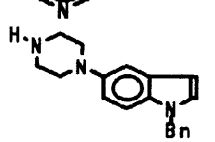
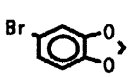
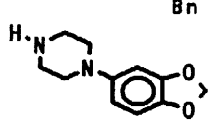
effectively catalyzed the amination of bromopyridine and bromoindole. Although the reason for the difference in susceptibility to pyridinyl bromides between Pd/P(*o*-tolyl)$_3$ and Pd/(*t*-Bu)$_3$ is not clear, the electron-donating P(*t*-Bu)$_3$ may prevent the formation of the inactive bis(pyridine)-Pd-complex.

Table 2. Synthesis of various N-arylpiperazines with Pd/P(*t*-Bu)$_3$ catalyst

Entry	Arylhalide (1) R	X	Cat.[b] /mol%	Conv. /mol%	Sel./mol% 2	3	Ratio[c] of 4 to 2
9	*o*-OCH_3	Br	0.5 (A)	100	63	35	3
10	*o*-CH_3	Br	0.5 (A)	100	92	6	2
11	*o*-F	Br	0.5 (A)	100	22	52	< 1
12	*m*-CH_3	Br	0.5 (A)	100	92	2	2
13	*p*-OCH_3	Br	0.5 (A)	100	84	5	2
14	*p*-F	Br	0.5 (A)	100	91	6	2
15[d]	*p*-F	Br	0.25 (B)	100	90	8	2
16[e]	*p*-F	Br	0.25 (B)	100	90	5	5
17	H	Br	0.5 (A)	100	89	2	2
18	*m*-OCH_3	I	0.5 (A)	100	88	4	1.4
19	H	Cl	0.5 (A)	88	94	2	2
20[a]	*m*-CF_3	Br	0.1 (B)	100	82	7	2

[a] Isolated yield. Others determined by GC using biphenyl as internal standard.
[b] Cat A ; $Pd_2(dba)_2$/P(*t*-Bu)$_3$ Cat B ; $Pd(OAc)_2$/P(*t*-Bu)$_3$
[c] The ratio of 4 to 2(=100) determined by GC analysis.
[d] Reaction was conducted at piperazine/(1)=6 and 105℃(3hr).
[e] Reaction was conducted at piperazine/(1)=2 and 105℃(3hr).

Table 3. Synthesis of N-heteroarylpiperazines

Entry	Arylhalide (1)	Cat. mol%	Arylpiperazine Isolated yield/mol%	Ratio[a] of 3 to 2	Ratio[b] of 4 to 2
21		0.1	 84	7	1
22		0.1	 76	3	1.3
23		0.1	 89	3	—[c]
24		0.025	 85	7	3

Isolated yield. [a] The ratio of 3 to 2(=100) determined by GC analysis.
[b] The ratio of 4 to 2(=100) determined by GC analysis. [c] Not detected by GC.
Cat ; $Pd(OAc)_2$/P(*t*-Bu)$_3$ NaO^{t}Bu/Piperaizine/Aryl bromide=1.36/6/1, Temp;120℃(3~4hr)

We consider the mechanism of an amination reaction with the Pd/P(*t*-Bu)$_3$ catalyst is similar to that with Pd/(P(*o*-tolyl)$_3$ reported by Buchwald and Hartwig[11] as follows; the generation of a palladium(Ⅱ) halide dimer on the heels of oxidative addition of aryl halide to Pd(0) species , followed by amine coordination to Pd(Ⅱ), and next dehydrobromination by NaO^{t}Bu, and finally the production of arylamines by reductive elimination or arenes as a side product by β-elimination, which we ascertained by NMR[12]

In summary, the Pd/P(*t*-Bu)$_3$ catalyst very effectively catalyzes the amination reaction of aryl halides and heteroaryl halides with piperazine to form the corresponding N-arylpiperazines.

This reaction, when it comes to regioselective or commercial production of arylamines, is very interesting. We are now following up on the ligand effect affecting the difference of activity or selectivity and to developing the application of the methodology to other reactions.

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9) **Typical procedure**

Pd(OAc)$_2$ and P(*t*-Bu)$_3$(P/Pd=4) was added to the suspension of aryl halide(42mmol), piperazine(256mmol) and NaO^{t}Bu(59mmol) in dry o-xylene in N_2 atmosphere.

The mixture was heated for 3～4hrs at 120℃. Subsequently, it was cooled to room temperature. H_2O was added to it, and the organic layer was separated.

Yield was determined by GC with internal method. Without the authentic sample, the yield of the desired compound was isolated by distillation or crystallization.

Pd/P(*t*-Bu)$_3$ catalyst can be prepared from Pd(OAc)$_2$/P(*t*-Bu)$_3$ and Pd$_2$(dba)$_3$/P(*t*-Bu)$_3$ *in situ* or before the reaction.

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