Pd/P(*t*-Bu)$_3$-Catalyzed Synthesis of Aromatic Amines

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Pd/P(*t*-Bu)$_3$触媒を用いるアリールアミン合成法の開発

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The catalytic systems consisted of a palladium (II) compound ($Pd(OAc)_2$ or $Pd(dba)_2$) and tri(*t*-butyl)phosphine have been found to be highly effective and selective for the amination of aromatic halides. Using these catalysts, a variety of *N*-arylpiperazines and triarylamines are synthesized by the reaction of a wide range of aryl halides with piperazines and diarylamines. The bulky and electron-rich catalytic systems enable us to use fairly unreactive aryl chlorides as substrates. Coupled with the high turnover numbers up to 6,400, they provide an efficient practical method for the synthesis of aromatic tertiary amines.

1. Introduction

Transition metal-catalyzed reactions, particularly palladium-catalyzed, are becoming increasingly important for the synthesis of complex building blocks and basic industrial intermediates[1]. However, most of those reactions don't meet industrial requirements due to low turnover numbers, harsh reaction conditions and the use of harmful chemicals. If high catalytic activity is achieved under mild reaction conditions with environmentally safe chemicals, the method is to ease application to industrial production. Recently, palladium-catalyzed amination technology was reported by Buchwald and Hartwig, independently[2]. Although fairly large amount of catalyst was required, this technology provided a new synthetic method for arylamines. On the other hand, we developed a catalytic system consisting of palladium and P(*t*-Bu)$_3$, which were exceedingly more active and selective than any other system on amination. This our technology deserves a significant improvement in palladium-catalyzed chemistry and can provide a practical synthetic method of arylamines such as N-arylpiperazines and triarylamine[3].

2. Experimental

[1] General

Unless otherwise noted, starting materials were purchased from commercial suppliers and used without further purification. $Pd(OAc)_2$, $Pd_2(dba)_3$, and $P(t\text{-}Bu)_3$ were purchased from Wako chemicals, Strem chemicals, and Kanto chemicals, respectively. *o*-Xylene was degassed by N_2 bubbling. 50-200 mg/ml solution of $P(t\text{-}Bu)_3$ in *o*-xylene was prepared and used for reactions. *t*-BuONa was obtained from Tosoh Toyama plant. All reactions were conducted in N_2 atmosphere. GC analysis was performed with Shimazu GC-9A using capillary column DB-1 (60m). Most reactions were monitored by GC. ^1H(400 MHz) and ^{13}C NMR spectra were measured in $CDCl_3$.

[2] General procedure for amination

$Pd(OAc)_2$(0.025 mol% to aryl halide) and $P(t\text{-}Bu)_3$(0.10 mol%) were added to the mixture of aryl halide (40 mmol), diarylamine (40 mmol) and *t*-BuONa (48 mmol) in *o*-xylene 60 ml in N_2 atmosphere. The resulting mixture was heated at 120℃ in oil bath. After the reaction mixture was cooled to room temperature, 60 ml of water was added and the organic layer was separated. After further extractive work-up, products were isolated by reprecipitation with MeOH/THF or column chromatography on Al_2O_3. Products were identified by GC-MASS and NMR spectra.

3. Results and Discussion

[1] Synthesis of N-arylpiperazines

N-Arylpiperazines are important pharmaceutical intermediates and much development work using them has been undertaken recently[4), 5)]. The conventional synthetic method for N-arylpiperazines consists of cyclization of a substituted aniline with bis(2-haloethyl)amine. However, the scope of this synthetic method is often limited due to low yields and the toxicity and poor availability of bis (2-haloethyl) amine[6)]. Although other methodologies such as nucleophilic substitution of lithium amide to alkoxybenzene[7)] and nucleophilic aromatic substitution of a (η^6-fluoroarene) tricarbonylchromium complexes[8)] were reported, the development of general and commercially feasible synthetic method of N-arylpiperazines was still required.

Based on palladium-catalyzed amination method, synthesis of N-arylpiperazines from an aryl halide with unprotected or protected piperazines in the presence of a $Pd/P(o\text{-tolyl})_3$ catalyst was reported[9)], although this catalytic system gave fairly large amount of dehalogenated arenes and bisarylated piperazine if one of its nitrogens is not protected, and required large amount of catalyst (3-4 mol % of Pd). In spite of these shortcomings, this new amination technology opens a new synthetic method for N-arylpiperazines as an alternative to the classical cyclization process.

(1) Comparison of phosphines

To solve problems in the palladium-catalyzed amination, we explored the possibility of using other phosphines as ligand of palladium. After investigation of phosphine species, the catalytic system consisting of palladium and $P(t\text{-}Bu)_3$ was found to be exceedingly active and selective (**Fig. 1**)

We first examined the reaction of *m*-bromoanisole with 6 equivalents of piperazine and 1.4 equivalents of *t*-BuONa in *o*-xylene at 120℃ in the presence of palladium compound and a variety of phosphines (**Table 1**). Palladium and

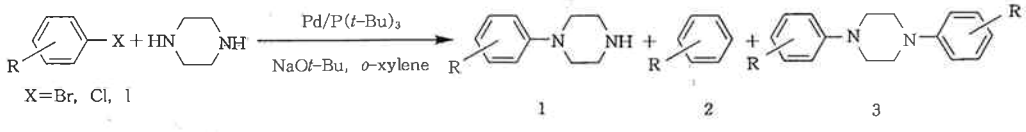


Fig. 1 Synthesis of N-arylpiperazines catalyzed by $P(t\text{-}Bu)_3$-ligated palladium complex.

phosphine were added into the reaction mixture, respectively, without mixing them prior to addition. As reported previously[9a], the catalyst derived from $Pd_2(dba)_3$ and P(*o*-tolyl)$_3$ gave the desired N-arylpiperazine (1) in moderate yield accompanied by anisole in 37% yield as a by-product (2) of debromination reaction (entry 1). Another sterically larger ligand, P(mesityl)$_3$, showed higher selectivity to the N-arylpiperazine, although its activity was low (entry 2). The electron-deficient $P(C_6F_5)_3$ was less selective (entry 3). Thus, these results implied that contribution of bulkiness of ligand to the selectivity was greater than that of electronics of ligand. In the investigation of aliphatic phosphines, less bulky P(*n*-Bu)$_3$ gave the poor selectivity, as expected (entry 4). The use of PCy_3 (Cy=cyclohexyl) led to the formation of anisole as the major product of the reaction, unexpectedly (entry 5). The mixture of $Pd_2(dba)_3$ and bulky P(*t*-Bu)$_3$ displayed excellent selectivity up to 96% of the desired coupling product (entry 6). While the poor selectivity of PCy_3 compared to P(*n*-Bu)$_3$ is a puzzle, fortunately we could find that P(*t*-Bu)$_3$ was a great ligand. Moreover, this catalytic system consisting of palladium and P(*t*-Bu)$_3$ showed similar good activity even if a much lower amount of palladium was employed (0.01～0.02 mol%, entries 7 and 8). BINAP, which is widely used for amination[2], showed insufficient activity and selectivity under the small amount of catalyst (entry 9). Although catalysis using P(*t*-Bu)$_3$ as ligand of transition metals might often have been reported, we believe this is the first example that P(*t*-Bu)$_3$ is much superior to other phosphines with respect to both catalytic activity and selectivity. Consequently, the turnover numbers (TON) as high as 6400 (mol product/mol palladium) were achieved. We assume that both the strong basicity and the steric bulkiness of P(*t*-Bu)$_3$ may contribute to the high activity and selectivity enhancing the rate of the reductive elimination from the aryl(amido)palladium complex to form N-arylpiperazines.

(2) Coupling reactions using Pd/P(t-Bu)$_3$ catalytic system

In order to examine the scope of the Pd/P(*t*-Bu)$_3$ catalytic system, the coupling reactions of various substituted aryl halides with piperazine was studied (**Tables 2** and **3**). As shown in **Table 2**, most of N-arylpiperazines

Table 1 Comparison of phosphines on reaction of *m*-bromoanisole with piperazine[a]

Entry	Rin PR_3	Cat.[b] [mol%]	Conv.[c] [mol%]	Sel. [mol%]	
				1	2[d]
1	*o*-tolyl	0.5(A)	100	61	37
2	mesityl	0.1(A)	14	81	12
3	C_6F_5	0.5(A)	100	42	44
4	*n*-Bu	0.5(A)	34	40	37
5	Cy	0.5(A)	100	15	78
6	*t*-Bu	0.5(A)	100	96	< 1
7	*t*-Bu	0.02(B)	100	94	2
8	*t*-Bu	0.01(B)	73	88	4
9	BINAP	0.02(B)	59	90	8

[a] Reaction conditions: solvent; *o*-xylene, Piperazine/NaO*t*-Bu/Arylbromide=6/1.4/1 (mole ratio), Temp; 120℃ (3～4hr), Conversion and selectivity were determined by GC analysis using biphenyl as internal standard.

[b] A:$Pd(dba)_2/PR_3$(P/Pd=4), B:$Pd(OAc)_2/PR_3$(P/Pd=4)

[c] Conversion of aryl bromide.

[d] The product number refers to that in **Fig. 1**.

could be prepared from not only the aryl iodide (entry 19) but the aryl bromides with electron-withdrawing (entries 15, 21) and electron-donating substituents (entries 11, 13-14) at *meta*- or *para*-position in generally excellent yields. On the other hand, reaction of aryl halides with coordinating substituents such as F and OMe at *ortho*-position gave moderate to low yields probably due to the intramolecular coordination of *ortho*-substituent to arylpalladium complex (entries 10,12). The reaction of phenyl chloride, which is so unreactive that it is usually difficult to be transformed to the corresponding arylpiperazine, gave the N-arylpiperazine in 83% conversion and 94% selectivity (entry 20). The influence of the ratio of piperazine to aryl halides on the selectivity was also examined (entry 17). When the ratio was lowered to two, the formation of undesired N,N'-diarylpiperazine (3) increased. Nevertheless, the amount of 3 was still small and the yield of N-arylpiperazine (1) was not significantly affected.

This catalytic system can be applied to formation of N-naphthyl- and N-(heteroaryl) piperazines (entries 22-25). Pyridine was reported to deactivate palladium catalyst by forming the bis(pyridyl) complex. Although the employment of chelating bis(phosphines) such as BINAP could avoid this problem, the large amount of catalyst (4 mol% of Pd) was still necessary[10]. On the other hand, the mixture of $Pd(OAc)_2$ and the simple monodentate phosphine, $P(t\text{-}Bu)_3$, effectively catalyzed the amination of 3-bromopyridine to give the acceptable yield of N-(3-pyridyl)piperazine under the small amount of catalyst (entry 23). The highly

Table 2 Synthesis of various N-arylpiperazines with $Pd/P(t\text{-}Bu)_3$ catalyst[a]

Entry	Aryl halide R	Aryl halide X	Cat.[b] [mol%]	Conv.[c] [mol%]	Sel.[mol%] 1	Sel.[mol%] 2	Ratio[d] of 3 to 1[e]
10	*o*-OCH_3	Br	0.5(A)	100	63	35	2.9
11	*o*-CH_3	Br	0.5(A)	100	92	6	1.9
12	*o*-F	Br	0.5(A)	100	22	52	< 1
13	*m*-CH_3	Br	0.5(A)	100	92	2	2.0
14	*p*-OCH_3	Br	0.5(A)	100	84	5	2.4
15	*p*-F	Br	0.5(A)	100	91	6	2.1
16[f]	*p*-F	Br	0.25(B)	100	90	8	1.6
17[g]	*p*-F	Br	0.25(B)	100	90	5	5.3
18	H	Br	0.5(A)	100	89	2	2.4
19	*m*-OCH_3	I	0.5(A)	100	88	4	1.4
20	H	Cl	0.5(A)	88	94	2	2.0
21	*m*-CF_3	Br	0.1(B)	100	82	7	1.8

[a] Unless otherwise noted, reaction was conducted in the following conditions: solvent; *o*-xylene, Piperazine/NaO *t*-Bu/Arylbromide=6/1.4/1(mole ratio), Temp; 120℃ (3~4hr), Conversion and selectivity were determined by GC analysis using biphenyl as internal standard.

[b] A:$Pd(dba)_2/P(t\text{-}Bu)_3$ (P/Pd=4), B:$Pd(OAc)_2/P(t\text{-}Bu)_3$ (P/Pd=4)

[c] Conversion of aryl bromide.

[d] 100-fold

[e] The product number refers to that in **Fig. 1**.

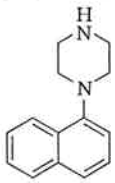
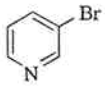
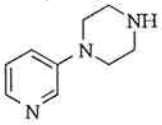
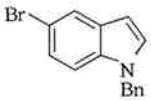
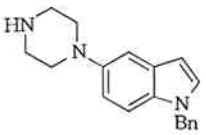
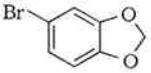
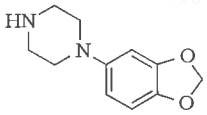
[f] Reaction was conducted at 105℃.

[g] 2 equivalents of piperazine to aryl bromide was used and reaction was conducted at 105℃.

electron-donating P(*t*-Bu)$_3$ may prevent the formation of the inactive bis(pyridyl)palladium complex.

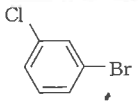
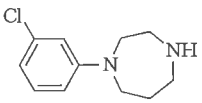
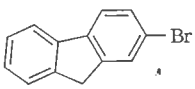
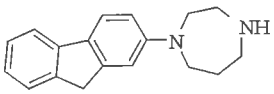
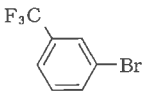
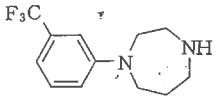
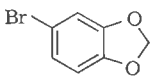
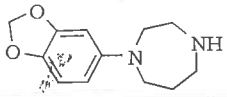
We also examined the amination of aryl bromides with homopiperazine. Synthesis of N-arylhomopiperazines by conventional aniline cyclization process is much more difficult than the corresponding six-membered ring formation.

Table 3 Synthesis of N-naphthyl- and N-(heteroaryl)piperazines[a]

Entry	Aryl halide	Cat.[b] [mol%]	Arylpiperazine	Yield [%][c]
22		0.1		84
23		0.1		76
24		0.1		89
25		0.025		85

[a]Reaction conditions : solvent ; *o*-xylene, Piperazine/NaO*t*-Bu/Arylbromide= 6/1.4/1(mole ratio), Temp ; 120℃ (3～4 hr).
[b]Pd(OAc)$_2$/P(*t*-Bu)$_3$(P/Pd=4) [c]Isolated yield.

Table 4 Synthesis of N-arylhomopiperazines[a]

Entry	Aryl halide	Cat.[mol%]	Arylhomopiperazine	Yield [%][b]
26		Pd(dba)$_2$[0.5]		92
27		Pd(OAc)$_2$[0.25]		98[c]
28		Pd(OAc)$_2$[0.35]		68
29		Pd(dba)$_2$[0.5]		87

[a]Reaction conditions : solvent ; *o*-xylene, Homopiperazine/NaO*t*-Bu/Arylbromide= 4/1.4/1 (mole ratio), Temp ; 120℃ (3hr), Pd/P(*t*-Bu)$_3$= 4 (mole ratio)
[b]GC yield. [c]Isolated yield.

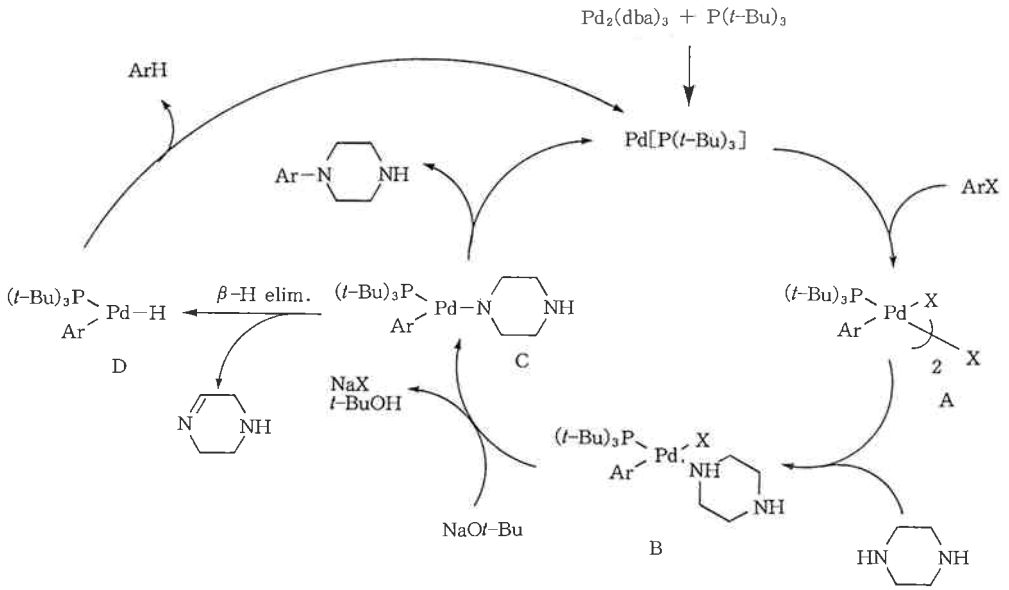


Fig. 2 Proposed mechanism of amination catalyzed by P(*t*-Bu)$_3$-ligated palladium complex.

However, reactions can be carried out by just replacing starting piperazine to homopiperazine in this amination technology. The results are shown in **Table 4**. P(*t*-Bu)$_3$-ligated palladium complex showed high catalytic activity in this reaction and high yields were obtained in most cases. Similarly reaction of aryl halides with piperazines bearing methyl substituent(s) on the carbon atom(s) can be carried out using the same protocol.

We suppose the mechanism of the amination reaction with the Pd/P(*t*-Bu)$_3$ catalyst is similar to that with Pd/P(*o*-tolyl)$_3$ proposed by Buchwald [11] (**Fig. 2**); initial oxidative addition of the aryl halide to a palladium (0) monophosphine species to form the arylpalladium (II) halide dimer (A), which reacts with amine to form the corresponding arylpalladium amine monomer (B), followed by deprotonation by *t*-BuONa and reductive elimination to form the corresponding arylamine and regenerate the catalytically active palladium (0) mono(phosphine)species. If the β-H elimination of the palladiumamide complex (C) occurs, the dehalogenated arene is formed *via* palladiumhydrido species (D). The high selectivity (the ratio of desired coupling product and dehalogenated arene) of Pd/P(*t*-Bu)$_3$ catalyst is to be attributed to bulkiness and high basicity of P(*t*-Bu)$_3$. The outstanding catalytic activity may be explained by much steadier bond between tertiary aliphatic carbon and phosphorus of P(*t*-Bu)$_3$ than that of aromatic phosphines, which undergo P-C bond cleavage in the catalytic cycle. Incorporation of aryl group from PAr$_3$ in products is often observed[12].

(3) Scope of the Pd/P(*t*-Bu)$_3$ catalyzed reaction

The reaction works very well with combination of many kinds of aryl halides and piperazines. The reaction also has a number of features that make it attractive for industrial use. First of all, high catalytic activity and selectivity were attained as noted above. Use of a small amount of catalyst is an obvious abvantage, both in cost and in ease of purification. Formation of undesired by-products of not only dehalogenated arenes of starting aryl halides but N,N'-bis(arylated) piperazines was highly suppressed. Interestingly, the formation of N,N'-bis(arylated) piperazines also depended on phosphine. For example, the ratio (100-fold) of N,N'-bis(arylated) piperazine (3) to N-mono (arylated) piperazine (1) was 1.6 using P(*t*-Bu)$_3$, whereas they were 4.6 and 3.2 using P(*o*-tolyl)$_3$ and BINAP, respectively, under the same

reaction conditions of 3-bromoanisole to 6 equivalents of piperazine in the presence of 0.5 mol% of Pd/phosphine. Sterically bulky P(*t*-Bu)$_3$ clearly suppresses the second arylation of the desired N-arylpiperazines. As shown in **Table 2** the amount of piperazine can be decreased to 2 equivalents. Therefore, the feature of the catalyst may allow to use unprotected piperazine circumventing tedious protection and deprotection process. Aryl chlorides are attractive substrates with respect to the price, availability and formation of naturally occurring NaCl, whereas they are fairly unreactive toward oxidative addition to an aromatic phosphine-ligated Pd (0) complex. Our electron-rich catalytic system, however, allows the use of the aryl chlorides. For example *p*-chloroanisole, which is an electron- rich aryl chloride, reacted with piperazine to give 99% conversion of *p*-chloroanisole and 94% selectivity of N-arylpiperazine. The selectivities of anisole and bis(arylated) piperazine were 4.6% and 1.4%, respectively (**Fig. 3**).

P(*t*-Bu)$_3$ can be prepared from phosphorus trichloride and 3 equivalents of *t*-BuLi in benzene [13]. We found that a crude solution obtained in the above reaction in xylene instead of benzene could be used as a source of P(*t*-Bu)$_3$ in amination reaction giving comparable results to the reaction using purified P(*t*-Bu)$_3$ by distillation.

[2] Synthesis of triarylamines

Recently, extensive research has been directed at the development of new triarylamines as hole-transport materials for organic electroluminescent (EL) display devices[14]. The conventional method to synthesize triarylamines is Ullmann coupling of aryl iodides with diarylamines in the presence of nearly stoichiometric amount of copper[15]. Unfortunately, Ullmann reactions require high temperatures such as 200℃ and toxic polar solvents, and generally give low to moderate yields accompanied by large amount of copper wastes that restrict application on an industrial scale. Therefore our efforts have been focused on the development of facile and general synthetic method of triarylamines with palladium catalysts.

(1) Coupling reactions using Pd/P(*t*-Bu)$_3$ catalytic system

Investigation on effect of phosphine ligands in the reaction of bromobenzene with 3-methyldiphenylamine revealed that the use of P(*t*-Bu)$_3$ was essential for obtaining an exceptionally high catalytic activity compared with other phoshines[16].

We also examined amination reactions of polybrominated aromatic compounds in the presence of Pd(OAc)$_2$ and P(*t*-Bu)$_3$ since many triarylamines developed for hole-transport materials have at least two triarylamine moieties (**Table 5**). 1,4-Dibromobenzene and 1,3,5-tribromobenzene gave the corresponding desired products in high isolated yields (entries 30 and 31). The reaction gave complete conversion of aryl polybromides as well as no formation of side products by gas chromatography. Triarylamines were usually isolated by recrystallization. On the other hand, 1,2-dibromobenzene did not give any products and was recovered after the reaction (entry 32). The reason is thought to be that the intramolecular coordination of another vicinal bromine to the arylpalladium bromide complex resulted in prevention of the coordination of diarylamine. Amination reactions of 4,4'-

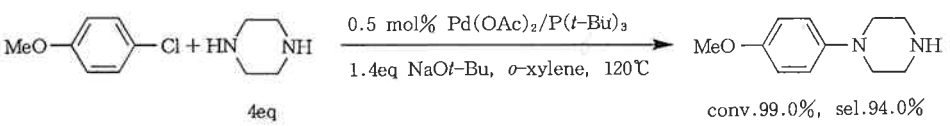


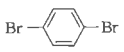
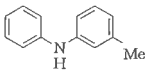
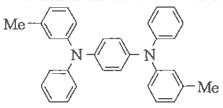
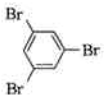
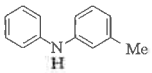
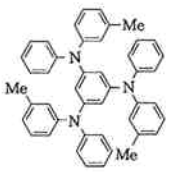
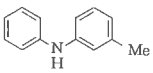
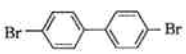
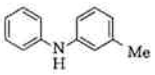
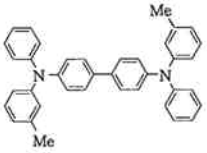
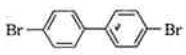
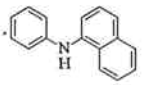
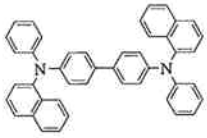
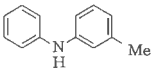
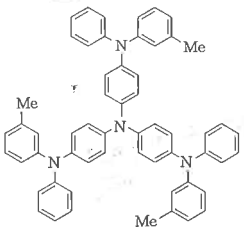
Fig. 3 Synthesis of N-arylpiperazine starting from aryl chloride.

dibromobiphenyl and tris(4-bromophenyl) amine gave the targeted diamines and a tetraamine, respectively, in excellent isolated yields over 90% (entries 33-35). The product (MTDATA) in entry 35 is known to show good performance in organic EL devices[14c].

This amination technology allows to use aniline derivatives, which are attractive due to its low prices and the possibility of synthesis of unsymmetrical triarylamines. Indeed, nitrogen of aniline was substituted stepwise by aryl group giving intermediate diarylamine selectively and then finally furnishing complex triarylamines[16]. Therefore this method is also excellent for diarylamine synthesis. This feature of the catalytic system was utilized for synthesis of one of actual charge-transporting materials with fluorenyl group in one-pot as depicted in **Fig. 4**. While this kind of fluorenyl-containing amines were produced by a tedious copper-mediated manner[17], our palladium-catalysed method can afford easy access to those unsymmetrical triarylamines.

Triarylamines with high molecular weight are

Table 5 Synthesis of triarylamines from aryl polybromides with diarylamines[a]

Entry	Aryl polybromide	Diarylamine	Product	Yield[%][b]
30				80
31				77
32				NR[c]
33				91
34				92
35			 MTDATA	92

[a]Reaction conditions : solvent ; *o*-xylene, Diarylamine/NaO*t*-Bu/a Br in aryl bromide=1/1.2/1 (mole ratio), Temp ; 120℃ (3hr), $Pd(OAc)_2/P(t\text{-}Bu)_3$=1/4 (mole ratio), $Pd(OAc)_2$; 0.025 mol% a Br of aryl bromide.
[b]Isolated yields by reprecipitation from THF/MeOH.
[c]No reaction.

paid attention in an effort to improve heat resistance and durability. Therefore we pursued the coupling reaction of primary amines with dibromoarene compounds. The palladium-catalyzed polycondensation successfully occured in high yields (**Table 6**). Polyaniline has a electrical conductive property and was used as polymer condenser and positive electrode of second battery[18]. Treatment of *p*-bromoaniline with 0.25 mol% $Pd(dba)_2/P(t\text{-}Bu)_3$ gave a quantitative yield of polyaniline, which showed deep purple (**Fig. 5**).

Aryl chlorides are attractive substrates with respect to the price and availability, whereas they are fairly unreactive toward oxidative addition to an Pd(0) complex. One feature of this electron-rich catalytic system is to render the employment of aryl chlorides feasible. We focused on the synthesis of 4-formyltriphenylamine, which is an important building block as charge-transporting material. So far, it was prepared by formylation of triphenylamine using Vilsmeier reagent[19]. However, both a large amount of phosphorus waste and uneasy availability of triphenylamine diminish the applicability of the method for large scale processes. On the other hand, *p*-chlorobenzaldehyde is a cheap bulk chemical, whereas *p*-bromobenzaldehyde is fairly expensive. Therefore, we attempted to prepare 4-formyltriphenylamine examining reaction of *p*-chlorobenzaldehyde with diphenylamine. Unfortunately, direct amination of *p*-chlorobenzaldehyde failed because formyl group on aryl chloride could not be tolerated sufficiently under the reaction conditions using *t*-BuONa.

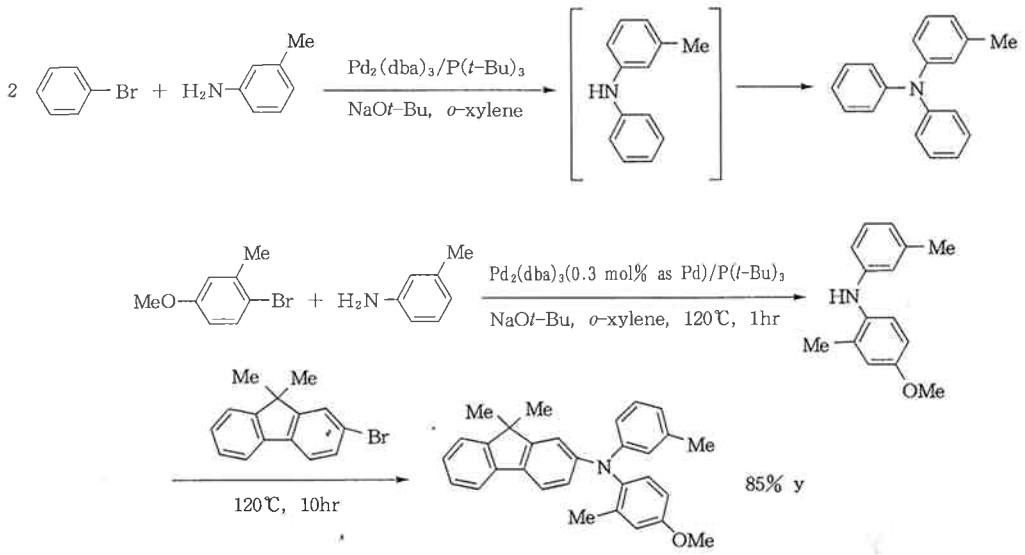


Fig. 4 Synthesis of triarylamines starting from aniline derivatives.

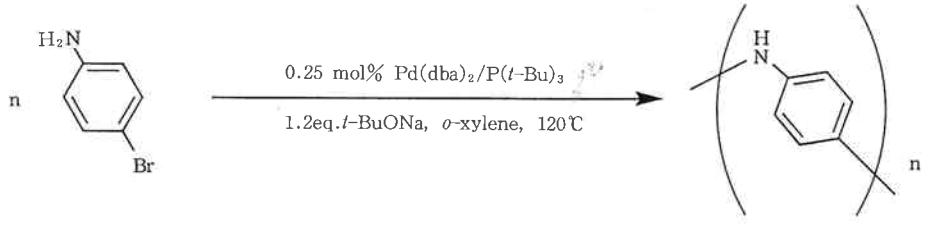
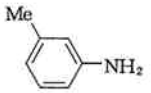
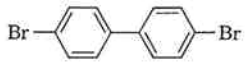
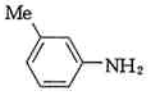
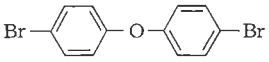
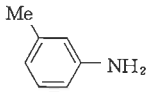
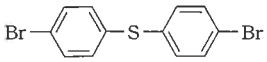
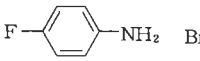
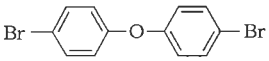
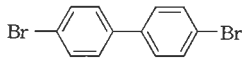


Fig. 5 Synthesis of polyaniline based on Pd-catalyzed polycondensation of 4-bromoaniline.

Table 6 Pd-catalyzed polycondensation of primary amines with aryl dibromides[a]

Entry	Amine	Aryl dibromide	Yield[%][b]	Mw[c]
36			quant	—[d]
37			73	19,600
38			93	—[d]
39			97	19,800
40	n-$C_6H_{17}NH_2$		98	9,700

[a]Reaction conditions : solvent ; *o*-xylene, Amine/NaO*t*-Bu/aryl dibromide= 1/2.4/1 (mole ratio), Temp ; 120℃, $Pd(dba)_2/P(t\text{-}Bu)_3$=1/4 (mole ratio), $Pd(dba)_2$; 0.25 mol% a Br of aryl bromide.
[b]Isolated yields.
[c]Determined by GPC in THF relative to polystyrene standard.
[d]GPC analysis was not done due to the less solubility in THF.

Nevertheless, the facile aldehyde protection method could avert the above problem as follows. Acetal formation of *p*-chlorobenzaldehyde with ethylene glycol readily took place in *o*-xylene in the presence of a small amount of *p*-TsOH (0.2 mol%). Amination reaction with diphenylamine with 0.1 mol% of $Pd(OAc)_2$ followed by deprotection by 10% H_2SO_4 then gave 4-formyltriphenylamine in 82% yield after recrystallization. The procedure could be conducted in one-pot in xylene solvent without isolation of intermediate acetal compounds (**Fig. 6**). We also found that the concentration of aryl halide in xylene greatly influenced the reaction rate especially in the case of employing aryl chlorides. Higher concentration of aryl chlorides made the reaction rate faster and the catalyst load smaller. Therefore a weight ratio more than 0.9 of *p*-chlorobenzaldehyde to xylene was used for synthesis of 4-formyltriphenylamine.

Although the oxidative addition of aryl chlorides to Pd(0) species readily takes place

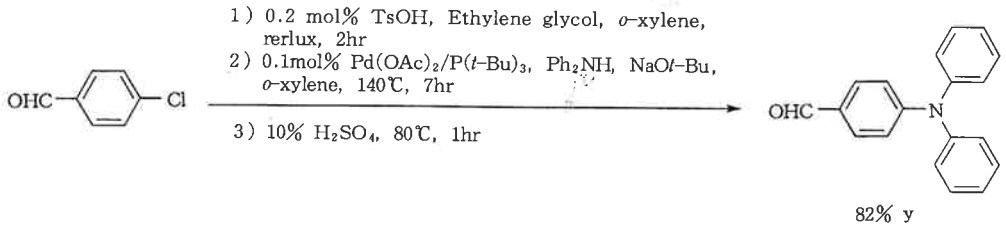


Fig. 6 One-pot synthesis of 4-formyltriphenylamine starting from 4-chlorobenzaldehyde.

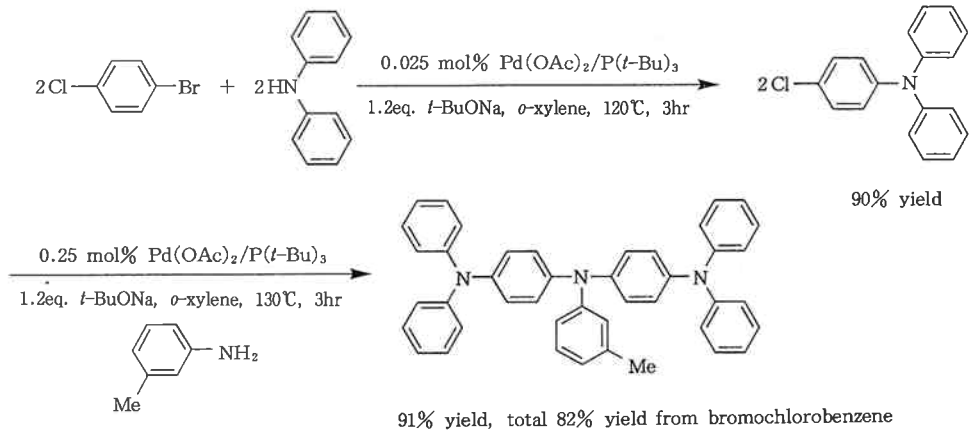
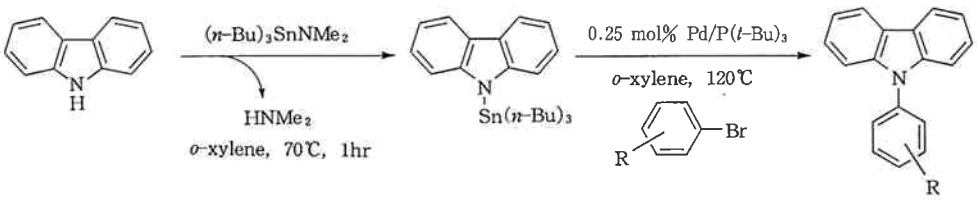


Fig. 7　Synthesis of triarylamine utilizing the difference of the reactivity between Ar–Br and Ar–Cl.



Entry	Palladium[a]	Azole [eq][b]	Aryl bromide	Time [hr]	Yield [%][c]
41	$Pd(OAc)_2$	Carbazole/1.0	Bromobenzene	3	96
42	$Pd(OAc)_2$	Carbazole/3.0	Tris(4-bromophenyl)amine	24	81
43	$Pd(dba)_2$	Phenoxazine/3.0	Tris(4-bromophenyl)amine	3	97
44	$Pd(dba)_2$	Indole/2.0	4,4'-Dibromobiphenyl	3	74

[a]0.25 mol% a Br of aryl bromide.
[b]Equivalent(s) to aryl bromide.
[c]Isolated yields by reprecipitation from THF/MeOH.

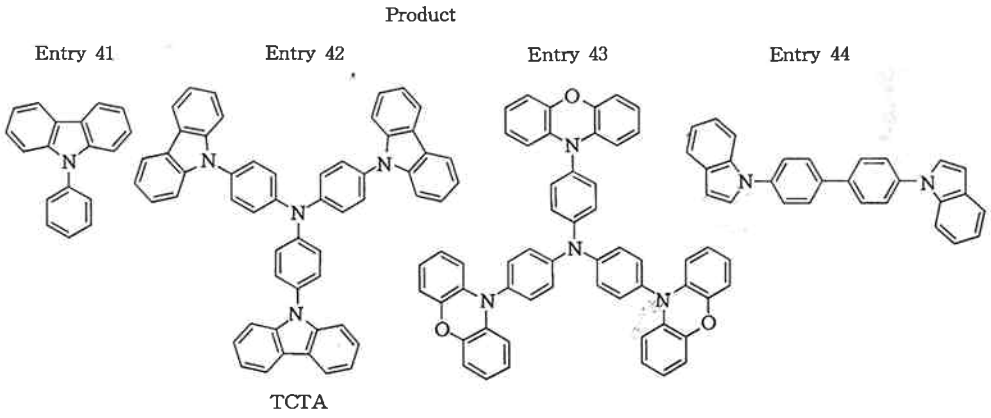
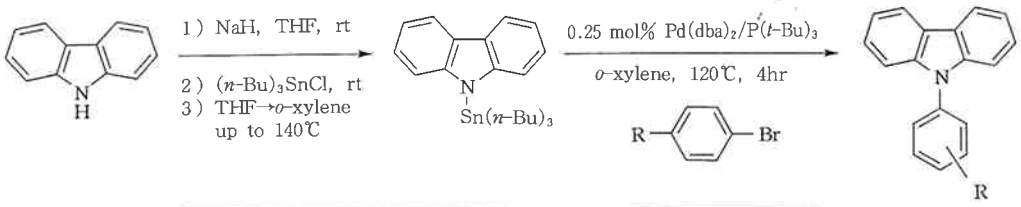
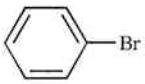
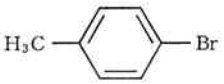
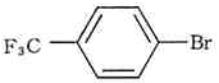


Fig. 8　N-Arylation of azoles with tributyltin amides.



Entry	Aryl bromide	Yield [%][a]
45		96
46		81
47		74

[a]Isolated yields by column chromatography

Fig. 9 N-Arylation of carbazole with tributyltin chloride.

in this electron-rich catalytic system, the reactivity of aryl bromides is much faster. Therefore, the difference of the reactivity can make the scope of this technology wider. For example, the triarylamine bearing phenylenediamine structure was selectively synthesized from easily available *p*-bromochlorobenzene in 82% yield as depicted in Fig. 7. Since this triarylamine was prepared in 32% yield by Ullmann coupling[20], the Pd-catalyzed method can provide a significant synthetic improvement of these class of compounds.

(2) N-Arylazole synthesis

N-Arylcarbazoles, such as TCTA, were also developed for hole-transport materials for organic EL[14d] and N-arylindoles are important as medicinally relevant compounds[21]. The general synthetic method of N-Arylazole compounds is the copper-mediated Ullmann coupling. However, the new efficient route was greatly demanded because of generally low yields of the conventional method. Therefore our catalytic system consisting of palladium and P(*t*-Bu)$_3$ was applied for N-arylazole synthesis by N-arylation of azole compounds. While the role of *t*-BuONa is crucial for this palladium-catalysed amination, the strong base was not good at all as to N-arylazole synthesis. Acidic azoles react with *t*-BuONa to form the corresponding sodium salts, which are assumed to deactivate the catalyst. On the other hand, a clean reaction took place when tin amide was used (Fig. 8). Azoles reacted with tributyltin amide in *o*-xylene giving the (N-tributylstannyl) azoles and dimethylamine, whose evolution was ceased in an hour at 70℃. Although reaction using zero valent palladium compound (Pd(dba)$_2$) took place much faster than Pd(OAc)$_2$ (entries 41 and 42), employment of more easily available Pd(OAc)$_2$ gave TCTA in high yield (entry 42). Phenoxazine and indole also could couple with aryl bromides (entries 43 and 44). Moreover tributyltin chloride also worked very well in this catalytic system (Fig. 9). Reaction of carbazolyl sodium, prepared from carbazole and sodium hydride, with tributyltin chloride was conducted in THF at room temperature. After THF was substituted by