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Solvent Free Amination Reactions of Aryl Bromides at Room Temperature Catalyzed by a (π-Allyl)palladium Complex Bearing a Diphosphinidenecyclobutene Ligand

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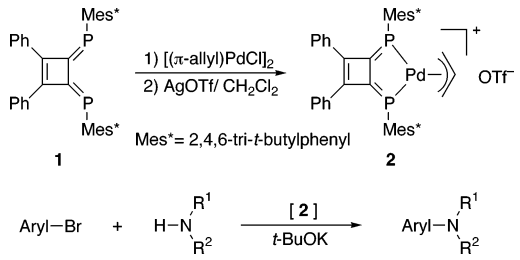
Abstract: An air- and moisture-stable (π-allyl)palladium complex bearing a unique diphosphinidenecyclobutene ligand effectively catalyzes amination reactions of aryl bromides with amines, where the reactions proceed under mild conditions without solvent, with 2 mol % of catalyst and 1 equiv of *t*-BuOK at room temperature. Under these conditions the amination products were obtained in good to excellent isolated yields.

Aromatic amines are important compounds found throughout the pharmaceutical, dye, agricultural, and polymer industries. Uses for aromatic amines can range from conducting polymers in material science to ligands for asymmetric homogeneous catalyst chemistry. It therefore follows that catalytic aromatic carbon−nitrogen bond forming reactions that are practical, relatively inexpensive, and feasible over a broad range of substrates would be valued in organic synthesis.[1] In recent years a number of reports have appeared on amination reactions; however, only a few methods are known at room temperature. For some examples of room temperature aminations, see ref 2.

We have been interested in developing sterically protected and multiple-bonded organophosphorus compounds.[3] Utilizing the 2,4,6-tri-*tert*-butylphenyl group (abbreviated to Mes*) as a protecting group,[4] we and others have been successful in the isolation and characterization of diphosphinidenecyclobutenes (DPCB),[5] containing low-coordinated phosphorus atom(s). DPCBs are phosphorus analogues of diimines and form stable chelate rings with transition metal species and those complexes are fairly stable toward air in solution as well as in solids. The DPCB derivatives with sp^2-hybridized phosphorus atoms have a marked propensity to engage in metal-to-phosphorus π back-bonding, comparable to that of the carbonyl ligand.[6] We have been interested in the coordination chemistry of DPCB and have characterized the complexes with the group 6 as well as the group 8−10 transition metals.[7] Indeed we found several organic reactions catalyzed by DPCB−Pd complexes[8,9] or DPCB−Pt complexes,[8,10] through the high coordination ability of the ligand owing to σ-donation/ π-back-donation interactions and the strong π-acceptor properties owing to the low-lying LUMO (π^*).

SCHEME 1



Herein we report that a (π-allyl)(dpcb)palladium complex **2**,[9b,c] prepared from DPCB **1** and [(π-allyl)PdCl]$_2$ followed by treatment with silver triflate, catalyzes amination reactions of aryl bromides with amines without solvent (Scheme 1). Those reactions proceed under mild conditions, with 2 mol % of catalyst **2** at room temperature.

For optimization studies we initially screened catalyst and base as shown in Table 1. The amination of bromobenzene with aniline in the presence of 1 equiv of *t*-BuOK/2 mol % of **2** at room temperature without solvent gave the best results (entry 1). As shown in entries 2 and 3, reactions conducted without catalyst or base did not occur, and reactions with 1 or 0.5 mol % of catalyst occurred to give products only in low yields (entries 4 and 5). The reaction conducted with 2 equiv of *t*-BuOK (entry 6) gave the product in slightly lower yield

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(1) For reviews see: (a) Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805. (b) Hartwig, J. F. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2046. (c) Muci, A. R. *Top. Curr. Chem.* **2002**, *219*, 131. (d) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176. (e) Hartwig, J. F. In *Modern Arene Chemistry*: *Concepts, Synthesis, and Applications*; Astruc, D., Ed.; Wiley Canada: Ontario, Canada, 2002; p 107.

(2) (a) Roy, A. H.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, *125*, 8704. (b) Zim, D.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 2413. (c) Wolfe, J. P.; Tomori, H.; Sadighi, J. P.; Yin, J.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1158. (d) Wolfe, J. P.; Buchwald, S. L. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 2413. (e) Hartwig, J. F.; Kawatsura, M.; Hauck, S. I.; Shaughnessy, K. H.; Alcazar-Roman, L. M. *J. Org. Chem.* **1999**, *64*, 5575.

(3) (a) *Multiple Bonds and Low Coordination in Phosphorus Chemistry*; Regitz, M., Scherer, O. J., Eds.; Georg Thieme Verlag: Stuttgart, Germany, 1990. (b) Dillon, K. B.; Mathey, F.; Nixon, J. F. *Phosphorus*: *Carbon Copy*; Wiley: Chichester, UK, 1998.

(4) Yoshifuji, M.; Shima, I.; Inamoto, N.; Hirotsu, K.; Higuchi, T. *J. Am. Chem. Soc.* **1981**, *103*, 4587; **1982**, *104*, 6167.

(5) (a) Appel, R.; Winkhaus, V.; Knoch, F. *Chem. Ber.* **1987**, *120*, 243. (b) Märkl, G.; Kreitmeier, P.; Nöth, H.; Polborn, K. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 927. (c) Yoshifuji, M.; Toyota, K.; Murayama, M.; Yoshimura, H.; Okamoto, A.; Hirotsu, K.; Nagase, S. *Chem. Lett.* **1990**, 2195.

(6) For reviews, see: (a) Le Floch, P.; Mathey, F. *Coord. Chem. Rev.* **1998**, *179/180*, 771. (b) Mathey, F. *Acc. Chem. Res.* **1992**, *25*, 90. (c) Yoshifuji, M. *J. Chem. Soc., Dalton Trans.* **1998**, 3343.

(7) (a) Yoshifuji, M. *J. Synth. Org. Chem. Jpn.* **2003**, *61*, 1116. (b) Ozawa, F.; Kawagishi, S.; Ishiyama, T.; Yoshifuji, M. *Organometallics* **2004**, *23*, 1325.

(8) Ikeda, S.; Ohhata, F.; Miyoshi, M.; Tanaka, R.; Minami, T.; Ozawa, F.; Yoshifuji, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 4512.

(9) (a) Toyota, K.; Masaki, K.; Abe, T.; Yoshifuji, M. *Chem. Lett.* **1995**, 221. (b) Minami, T.; Okamoto, H.; Ikeda, S.; Tanaka, R.; Ozawa, F.; Yoshifuji, M. *Angew. Chem., Int. Ed.* **2001**, *40*, 4501. (c) Ozawa, F.; Okamoto, H.; Kawagishi, S.; Yamamoto, S.; Minami, T.; Yoshifuji, M. *J. Am. Chem. Soc.* **2002**, *124*, 10968.

(10) Ozawa, F.; Yamamoto, S.; Kawagishi, S.; Hiraoka, M.; Ikeda, S.; Minami, T.; Ito, S.; Yoshifuji, M. *Chem. Lett.* **2001**, 972.

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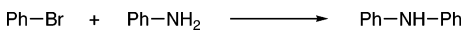
TABLE 1. Selection of Catalyst and Base for Amination Reaction[a]



entry	catalyst [mol %]	base[b] [equiv]	solvent	*T*, °C	yield,[c] %
1	**2** [2]	K [1.00]		rt	98
2		K [1.00]		rt	NR
3	**2** [2]			rt	NR
4	**2** [1]	K [1.00]		rt	45
5	**2** [0.5]	K [1.00]		rt	24
6	**2** [2]	K [2.00]		rt	81
7	**2** [2]	K [0.50]		rt	70
8	**2** [2]	K [0.25]		rt	70
9	**2** [2]	Cs [1.00]		rt	33
10	*e*	K [1.00]		100	4[d]
11	*e*	K [1.00]	*g*	100	53[d]
12	*f*	K [1.00]	*g*	100	50[d]

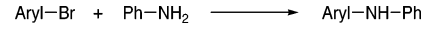
[a] Bromobenzene (1 equiv), aniline (1 equiv), 12 h. [b] K = *t*-BuOK and Cs = Cs_2CO_3; [c] Isolated yields. [d] No reaction at room temperature. [e] The catalyst was prepared in situ from 2 mol % of **1** and 2 mol % of $(MeCN)_2PdCl_2$. [f] The catalyst was prepared in situ from 2 mol % of **1** and 2 mol % of $Pd(OAc)_2$. [g] Toluene (2 mL) was used as solvent.

than that with 1 equiv of *t*-BuOK. The use of 0.50 and 0.25 equiv of *t*-BuOK (entries 7 and 8) afforded the corresponding product in 70% yield. Although in some cases milder bases such as Cs salts have been reported to be effective in catalytic amination reactions on aromatic rings,[11] cesium carbonate did not give good results (entry 9), indicating that a strong base is required in these amination reactions. Catalysts generated in situ from DPCB and bis(acetonitrile)dichloropalladium (entries 10 and 11) or palladium acetate (entry 12) gave the corresponding products only in low yields at 100 °C with the use of toluene as solvent. In no reaction did we observe arenes as side products, which would result from β-hydride elimination from an amido intermediate.[12]

After exploring a wide array of conditions we determined that the amination of bromobenzene with aniline in the presence of 1 equiv of *t*-BuOK and 2 mol % of **2** at room temperature without solvent gave the best results (entry 1, Table 2 as well as Table 1).

We then examined various substrates as listed in Table 2 under the optimized conditions. Not only aromatic amines but also alkylamines gave the corresponding products with bromobenzene in moderate to good yields (entries 2−6). An electron-donating substitutent on the aniline ring gave an excellent result (entry 7). Substitution effects on the bromobenzene did not show any disadvantage to the reaction with aniline (entries 9−10), except for *p*-methoxybromobenzene (entry 8) either at room temperature or at an elevated temperature. 4-*tert*-Butylbromobenzene and 1-bromo-3,5-dimethylbenzene reacted with aniline at room temperature to form the corresponding *N*-aryl products in 78−97% yield (entries 11 and 12). In the case of entry 13, *p*-dibromobenzene, 2 mL of toluene was used to facilitate stirring to give a 71% yield of monosubstitution product. In the case of entry 14, the use of 2 equiv of aniline provided for sufficient stirring without the use of toluene, giving only monosubstituted product.

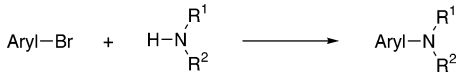
TABLE 2. Amination Reactions at Room Temperature without Solvent Catalyzed by (π-Allyl)(dpcb)palladium Complex[a]



entry	aryl bromide	amine	yield,[b] %
1	PhBr	$PhNH_2$	98
2	PhBr	$Ph(CH_2)_2NH_2$	82
3	PhBr	*p*-$MeC_6H_4CH_2NH_2$	80
4	PhBr	α-$NaphCH_2NH_2$	69
5	PhBr	$PhCHMeNH_2$	60
6	PhBr	$CH_3(CH_2)_{15}NH_2$	62
7	PhBr	*p*-$MeOC_6H_4NH_2$	99
8	*p*-$MeOC_6H_4Br$	$PhNH_2$	63 [65[c]]
9	*p*-$EtOC(O)C_6H_4Br$	$PhNH_2$	95
10	*o*-$MeOC_6H_4Br$	$PhNH_2$	97
11	*p*-*t*-BuC_6H_4Br	$PhNH_2$	97
12	*m*,*m*′-$Me_2C_6H_3Br$	$PhNH_2$	78
13	*p*-$C_6H_4Br_2$	$PhNH_2$	71[d]
14	*p*-$C_6H_4Br_2$	$PhNH_2$[e]	71

[a] Aryl bromide (1 mmol), amine (1 equiv), *t*-BuOK (1 equiv), **2** (2 mol %), at room temperature, 12 h. [b] Isolated yields. [c] Yield at 100 °C. [d] Toluene (2 mL) was added. [e] Amine (2 equiv) was used.

TABLE 3. Amination Reactions without Solvent Catalyzed by (π-Allyl)(dpcb)palladium Complex[a]



entry	aryl halide	amine	*T*, °C	yield,[b] %
1	PhBr	$PhNH_2$	100	84[c]
2	PhBr	PhNHMe	100	70[d]
3	PhBr	$Ph_2C{=}NH$	rt	76 [81[e]]
4	PhBr	morpholine	rt	55 [58[e]]
5	PhBr	piperidine	rt	70 [73[e]]
6	*p*-*t*-BuC_6H_4Br	piperidine	rt	64 [74[e]]
7	PhBr	THIQ[f]	100	51

[a] Aryl halide (1 equiv), amine (1 equiv), *t*-BuOK (1 equiv), **2** (2 mol %), 12 h. [b] Isolated yields. [c] Aryl halide (2 equiv). [d] No reaction at room temperature. [e] Yields at 100 °C. [f] Tetrahydroisoquinoline.

Table 3 shows the effect of temperature on the reaction. Even when 2 equiv of bromobenzene was used and heated with aniline for 12 h at 100 °C, diphenylamine was obtained in 84% yield (entry 1), indicating monosubstitution is predominant in these catalytic reactions. *N*-Methylaniline reacted with bromobenzene to form the corresponding tertiary amine in 70% yield at 100 °C, but no reaction was observed at room temperature (entry 2). Benzophenone imine, which contains an sp^2 nitrogen atom, formed the corresponding amination product in good yield (entry 3).

Arylmorpholine and arylpiperidine are an important class of medicinal compounds and have been prepared by using palladium-catalyzed amination with aryl chloride,[13] aryl bromides,[14] and iodides.[15] By using the (π-

(11) Wolfe, J. P.; Buchwald, S. L. *Tetrahedron Lett.* **1997**, *38*, 6359.
(12) (a) Paul, F.; Patt, J.; Hartwig, J. F. *J. Am. Chem. Soc.* **1994**, *116*, 5969. (b) Paul, F.; Patt, J.; Hartwig, J. F. *Organometallics* **1995**, *14*, 3030. (c) Hartwig, J. F.; Paul, F. *J. Am. Chem. Soc.* **1995**, *117*, 5373. (d) Driver, M. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **1995**, *117*, 4708.

(13) (a) Beller, M.; Riemeier, T. H.; Reisinger, C.-P.; Herrmann, W. A. *Tetrahedron Lett.* **1997**, *38*, 2073. (b) Stauffer, S. R.; Lee, S.; Stambuli, J. P.; Hauck, S. I.; Hartwig, J. F. *Org. Lett.* **2000**, *2*, 1423. (c) Reddy, N. P.; Tanaka, M. *Tetrahedron Lett.* **1997**, *38*, 4807.

allyl)(dpcb)palladium system, aryl bromides couple with piperidine or morpholine to form the corresponding *N*-aryl product in good yields, at room temperature as well as at 100 °C. No significant temperature effect was found on the yields (entries 4 and 5). The reaction of 4-*tert*-butylbromobenzene with piperidine at room temperature afforded only the desired product in 64% yield and in 74% at 100 °C (entry 6), with no cleavage observed for 4-*tert*-butylbromobenzene.[15b] Tetrahydroisoquinoline reacted with bromobenzene to afford the corresponding *N*-phenyl product in an acceptable yield (entry 7).

Although we have discovered that the DPCB−Pd complex exhibits unique reactivity for amination reactions, we observed some limitations. No reaction was observed at room temperature or at 100 °C with cyclohexylamine, urea, pivaloyl amide or *p*-nitroaniline, and bromobenzene.

It seems likely a catalytic cycle for this amination reaction involves a palladium(0) intermedate[16] ligated with DPCB (see Supporting Information for a proposed catalytic cycle). The formation of (dpcb)Pd(0) has already been proposed in the reaction of **2** with amine.[9b,17]

In summary, we have demonstrated that a (π-allyl)-palladium complex **2** bearing the unique DPCB ligand effectively catalyzes amination reactions of aryl bromides and amines, where the reactions proceed under mild conditions without solvent, with 2 mol % of catalyst **2** at room temperature. It should be noted here that these catalytic reactions can be carried out without a drybox. Under these conditions the amination products were obtained in good to excellent isolated yields.

Experimental Section

Materials and Methods. See the Supporting Information.

General Procedure for the Amination Reactions of Aryl Bromides. All reactions were performed without a drybox, and **2** and *t*-BuOK were weighed in air. An oven-dried Pyrex screw tube was charged with *t*-BuOK (1 mmol) and **2** (2 mol %). The tube was evacuated and filled with argon. To the mixture were added aryl bromide (1 mmol) and amine (1 mmol) at room temperature (the solution turned black). The viscous reaction mixture was stirred vigorously at room temperature for 12 h. After all starting material had been consumed, as judged by TLC, the reaction mixture was diluted with ethyl acetate. After water was added, the mixture was stirred vigorously to dissolve the precipitates, then extracted with ethyl acetate 3 times. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated in vacuo. Silica gel column chromatography (hexane−EtOAc) of the crude material provided pure amination products.

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Supporting Information Available: Spectral data for amination products, copies of ^{1}H NMR spectra for amination products, and proposed catalytic cycle for the amination reaction. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) (a) Urgaonkar, S.; Xu, J.-H.; Verkade, J. G. *J. Org. Chem.* **2003**, *68*, 8416. (b) Wolfe, J. P.; Wagaw, S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 7215.

(15) (a) Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **1996**, *61*, 1133. (b) Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **1997**, *62*, 6066.

(16) (a) Singh, U. K.; Strieter, E. R.; Blackmond, D. G.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 14104. (b) Alcazar-Roman, L. M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 12905. (c) Guari, Y.; van Strijdonck, G. P. F.; Boele, M. D. K.; Reek, J. N. H.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *Chem. Eur. J.* **2001**, *7*, 475.

(17) Ozawa, F.; Ishiyama, T.; Yamamoto, S.; Kawagishi, S.; Murakami, H.; Yoshifuji, M. *Organometallics* **2004**, *23*, 1698.