Palladium-Catalyzed Amination of Aryl Bromides with Hindered *N*-Alkyl-Substituted Anilines Using a Palladium(I) Tri-*tert*-butylphosphine Bromide Dimer

Mahavir Prashad,* Xiao Yin Mak,[1] Yugang Liu, and Oljan Repič

Process Research and Development, Chemical and Analytical Development, Novartis Institute for Biomedical Research, One Health Plaza, East Hanover, New Jersey 07936

mahavir.prashad@pharma.novartis.com

Abstract: An efficient palladium-catalyzed amination of aromatic bromides with hindered *N*-alkyl-substituted anilines is described, either using the combination of $Pd(OAc)_2$ and $P(t\text{-}Bu)_3$ or a palladium(I) tri-*tert*-butylphosphine bromide dimer, $[Pd(\mu\text{-}Br)(t\text{-}Bu_3P)]_2$, a new, commercially available, and easily handled catalyst.

We required a practical method for the preparation of hindered *N*-alkyl-substituted diarylamines, such as *N*-cyclohexyldiphenylamine and *N*-isopropyldiphenylamine. Their synthesis by a high-temperature and high-pressure reductive alkylation of diphenylamine with cyclohexanone and acetone, respectively, had previously been reported in the patent literature to give poor yields.[2] We envisioned that the most straightforward route to this class of compounds would be a palladium-catalyzed amination, pioneered by Buchwald[3−5] and Hartwig,[6−9] of aromatic halides with *N*-cyclohexylaniline or *N*-isopropylaniline. The palladium-catalyzed amination of aromatic halides with hindered *N*-alkyl-substituted anilines was reported[10] by Buchwald et al. using xantphos or 2-(diphenylphosphino)-2′-(*N*,*N*-dimethylamino)biphenyl as ligands. In this paper, we describe an efficient synthesis of hindered *N*-alkyl-substituted diarylamines by an amination of aromatic bromides with hindered *N*-alkyl-substituted anilines utilizing either a combination of $Pd(OAc)_2$ and $P(t\text{-}Bu)_3$ or the new, commercially available, air-stable, and easily handled solid palladium(I) tri-*tert*-butylphosphine bromide dimer, $[Pd(\mu\text{-}Br)(t\text{-}Bu_3P)]_2$, as the catalyst.[11] We had previously demonstrated the practical utility of the palladium-catalyzed amination reactions on a multikilogram scale.[12,13]

SCHEME 1

TABLE 1. Effect of Ligands and Temperature on the Amination of Bromobenzene (2a) with *N*-Cyclohexylaniline (1a)[a]

entry	mol % $Pd(OAc)_2$	ligand (mol %)	temp (°C)	% conversion[b]				isolated yield of 3a (%)
				1 h	3 h	6 h	21 h	
1	0.5	binap (0.5)	110	30	40.1	41		27
2	1.0	binap (2.0)	110	17.7	19.3			14
3	0.5	xantphos (0.5)	110	7.9	9.5	11	13.7	11
4	0.5	DPEphos (0.5)	110	0.8	1.2		2.3	not isolated
5	0.5	$P(t\text{-}Bu)_3$ (0.5)	110	100				86
6	0.1	$P(t\text{-}Bu)_3$ (0.3)	110	41.3	64.8	76.1	88.5	70
7	0.1	$P(t\text{-}Bu)_3$ (1.0)	110	100				87
8	1.0	$P(t\text{-}Bu)_3$ (1.0)	25	0		0		0
9	1.0	$P(t\text{-}Bu)_3$ (1.0)	70				66	not isolated
10	$[Pd(\mu\text{-}Br)(t\text{-}Bu_3P)]_2$ (0.25)		110	100				93

[a] Conditions: *N*-cyclohexylaniline (11.4 mmol), **2a** (13.7 mmol), sodium *tert*-butoxide (17.1 mmol), and toluene (20.0 mL). [b] Monitored by GC using an HP-5 column (30 m × 0.32 mm).

The palladium-catalyzed amination of bromobenzene (**2a**) with *N*-cyclohexylaniline (**1a**) to *N*-cyclohexyldiphenylamine (**3a**) was selected as the representative example to develop suitable reaction conditions (Scheme 1). The results with different commercially available ligands are summarized in Table 1. Amination of **2a** with **1a** in the presence of palladium acetate (0.5 mol %), 2,2′-bis-(diphenylphosphino)-1,1′-binaphthyl[14] (binap; 0.5 mol %), and sodium *tert*-butoxide in refluxing toluene afforded only a 27% yield (entry 1) of the desired **3a**. An increase in the amounts of the catalyst and the ligand did not improve the yield (entry 2). Almost no reaction was observed using DPEphos[15] as the ligand (entry 4). Xantphos,[16] which was reported as an effective ligand for such an amination,[10] afforded only an 11% yield (entry 3) of **3a**. In all cases, the reaction was monitored by GC, and the poor yield was due to the poor conversion. We next investigated $P(t\text{-}Bu)_3$, which has been reported[17−19] as a very effective ligand in the amination of aromatic halides

(1) Undergraduate Summer Intern (2002) from the University of Rochester, Rochester, NY.

(2) Malz, R. E.; Greenfield, H.; Wheeler, E. L. Eur. Patent 0014998, 1980; *Chem. Abstr.* **1981**, *94*, 121069.

(3) Muci, A. R.; Buchwald, S. L. *Top. Curr. Chem.* **2002**, *219*, 131−209.

(4) Yang, B. H.; Buchwald, S. L. *J. Organomet. Chem.* **1999**, *576*, 125−146.

(5) Wolfe, J. P.; Wagaw, S.; Marcoux, J. F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805−818.

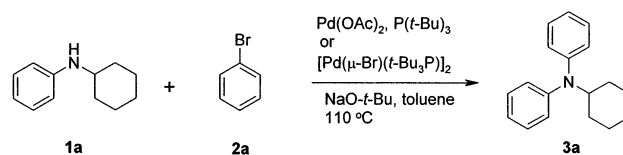(6) Hartwig, J. F. *Pure Appl. Chem.* **1999**, *71*, 1417−1423.

(7) Hartwig, J. F. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2046−2067.

(8) Hartwig, J. F. *Acc. Chem. Res.* **1998**, *31*, 852−860.

(9) Hartwig, J. F. *Synlett* **1997**, 327−340.

(10) Harris, M. C.; Geis, O.; Buchwald, S. L. *J. Org. Chem.* **1999**, *64*, 6019−6022.

(11) $[Pd(\mu\text{-}Br)(t\text{-}Bu_3P)]_2$ is available from Johnson Matthey, 2001 Nolte Drive, West Deptford, NJ 08066.

(12) Prashad, M.; Hu, B.; Har, D.; Repič, O.; Blacklock, T. J.; Acemoglu, M. *Adv. Synth. Catal.* **2001**, *343*, 461−472.

(13) Prashad, M.; Hu, B.; Lu, Y.; Draper, R.; Har, D.; Repič, O.; Blacklock, T. J. *J. Org. Chem.* **2000**, *65*, 2612−2614.

(14) Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1144−1157.

(15) Sadighi, J. P.; Harris, M. C.; Buchwald, S. L. *Tetrahedron Lett.* **1998**, *39*, 5327−5330.

(16) Yin, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 6043−6048.

TABLE 2. Amination with Hindered Anilines[a]

[a] All the compounds gave satisfactory spectral data. [b] 2.0 equiv of aromatic halide and 2.0 equiv of base were used. (A) With Pd(OAc)$_2$ and P(t-Bu)$_3$ and (B) with a palladium(I) tri-*tert*-butylphosphoine bromide dimer.

with various amines and anilines but not with hindered *N*-alkyl-substituted anilines such as **1a**. The amination of **2a** with **1a** was complete in 1 h using P(t-Bu)$_3$ (0.5 mol %) and palladium acetate (0.5 mol %) in refluxing toluene (entry 5), affording **3a** in an 86% yield. A decrease in the amount of the palladium catalyst to 0.1 mol % and an increase in the palladium-to-ligand ratio to 1:3 led to a slower reaction (entry 6). However, with 0.1 mol % palladium acetate using a 1:10 palladium-to-ligand ratio, the reaction was complete in 1 h, affording **3a** in an 87% yield (entry 7). The amination of aromatic bromides with *N*-methylaniline and diphenylamine has been reported at room temperature using palladium acetate and P(t-Bu)$_3$.[18] However, in our case with **1a**, no reaction was observed at room temperature (entry 8), further confirming the steric demands of the cyclohexyl group in **1a**. Only a 66% conversion was observed when the reaction was carried out at 70 °C for 21 h (entry 9).

We selected the P(t-Bu)$_3$ (0.5 mol %) and palladium acetate (0.5 mol %) catalytic system (entry 5) in refluxing toluene to study the amination of various aromatic bromides (**2a**−**d**) with several hindered *N*-alkyl-substituted anilines (**1a**−**c**). The results are listed in Table 2. In all cases the yields were excellent, except with the aromatic bromide containing an *o*-methyl substituent

(**2d**). While **6a** was obtained in moderate yield (52%) from the amination of **2d** with **1a**, the reaction of **2d** with **1b** and **1c** afforded **6b** and **6c** in poor yield, even with 2.0 equiv of **2d** and 2.0 equiv of base.

One of the drawbacks with P(t-Bu)$_3$ is the handling of this air-sensitive and pyrophoric reagent on a large scale. We now report that this problem can be circumvented by using 0.25 mol % (0.5 mol % Pd) of the new, commercially available,[11] and easily handled solid [Pd(μ-Br)-(t-Bu$_3$P)]$_2$ catalyst. Amination of **2a** with **1a** in the presence of 0.25 mol % of [Pd(μ-Br)(t-Bu$_3$P)]$_2$ afforded **3a** in a 93% yield (Table 1, entry 10). Excellent yields were also obtained from the amination of aromatic bromides **2a**−**c** with anilines **1a**−**c** (Table 2) and were comparable to or better than those of the Pd(OAc)$_2$/P(t-Bu)$_3$ combination. In fact, the palladium(I) tri-*tert*-butylphosphine bromide dimer catalyst gave higher yields of **6a**−**c** (60, 51, and 61%, respectively) from the amination of **2d** with **1a**−**c**, compared to the Pd(OAc)$_2$/P(t-Bu)$_3$ combination (52, 25, and 12%, respectively).

In summary, an efficient palladium-catalyzed amination of aromatic bromides with hindered *N*-alkyl-substituted anilines is described, using either the combination of Pd(OAc)$_2$ and P(t-Bu)$_3$ or [Pd(μ-Br)(t-Bu$_3$P)]$_2$, a new, commercially available, and easily handled catalyst.

Experimantal Section

General Procedure for the Amination Using a Combination of Pd(OAc)$_2$ and P(t-Bu)$_3$. A dry three-necked flask, equipped with a magnetic stirring bar, septum, and condenser with an argon inlet−outlet was charged with palladium acetate (12.8 mg, 0.057 mmol), sodium *tert*-butoxide (1.64 g, 17.1 mmol), a hindered aniline (**1a**−**c**, 11.4 mmol), and aryl bromide (13.7 mmol). The flask was flushed with argon, and dry, deaerated toluene (20 mL) was added. The mixture was stirred at room temperature for 15 min, and P(t-Bu)$_3$ (11.5 mg, 0.057 mmol) was added as a solution in toluene (11.5 mg) using a syringe. The syringe was washed with toluene (1 mL), and the wash was added to the reaction mixture. The reaction mixture was heated to 108−110 °C and stirred with gentle reflux for the specified time (Tables 1 and 2). The reaction mixture was cooled to room temperature, and water (10 mL) was added. The organic layer was separated, washed with water (5 mL), and concentrated. The crude material was purified by silica gel chromatography. All of the compounds gave satisfactory spectroscopic data.

General Procedure for the Amination Using a Palladium(I) Tri-*tert*-butylphosphine Bromide Dimer. A dry three-necked flask, equipped with a magnetic stirring bar, septum, and condenser with an argon inlet−outlet was charged with [Pd(μ-Br)(t-Bu$_3$P)]$_2$[11] (22 mg, 0.0285 mmol), sodium *tert*-butoxide (1.64 g, 17.1 mmol), a hindered aniline (**1a**−**c**, 11.4 mmol), and aryl bromide (13.7 mmol). Dry, deaerated toluene (20 mL) was added. The mixture was stirred at room temperature for 15 min. The reaction mixture was heated to 108−110 °C and stirred with gentle reflux for the specified time (Tables 1 and 2). The reaction mixture was cooled to room temperature, and water (10 mL) was added. The organic layer was separated, washed with water (5 mL), and concentrated. The crude material was purified by silica gel chromatography.

Supporting Information Available: ^{1}H and ^{13}C NMR and MS for compounds **3c**, **4a**−**c**, **5a**−**c**, and **6a**−**c**. This material is available free of charge via the Internet at http://pubs.acs.org.

(17) Yamamoto, T.; Nishiyama, M.; Koie, Y. *Tetrahedron Lett.* **1998**, *39*, 2367−2370.

(18) Hartwig, J. F.; Kawatsura, M.; Hauck, S. I.; Shaughnessy, K. H.; Alcazar-Roman, L. M. *J. Org. Chem.* **1999**, *64*, 5575−5580.

(19) Lee, M.; Jorgensen, J.; Hartwig, J. F. *Org. Lett.* **2001**, *3*, 2729−2732.

JO020609D