Palladium-Catalyzed Aromatic Aminations with in Situ Generated Aminostannanes

Anil S. Guram and Stephen L. Buchwald*

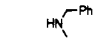
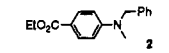
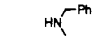
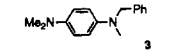
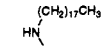
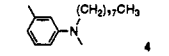
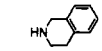
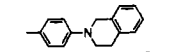
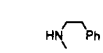
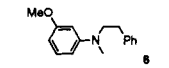
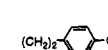
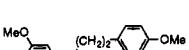
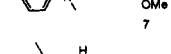
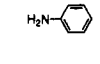
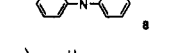
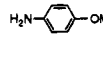
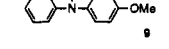
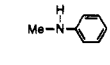
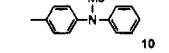
Department of Chemistry
Massachusetts Institute of Technology
Cambridge, Massachusetts 02139

Received May 23, 1994

The arylamine moiety is a structural component in a variety of synthetic and naturally occurring biologically active compounds. Many synthetic methods for the construction of an aryl–nitrogen bond have been reported, but in general these methods suffer from severe reaction conditions and/or are applicable only for activated substrates.[1] Research efforts in our laboratory directed toward the synthesis of arylamine-containing biologically active compounds[2] necessitated the exploration of newer methods. We were attracted to the critical although inconclusive report by Migita and co-workers describing the preparation of (*N*,*N*-diethylamino)benzenes from the $PdCl_2(P(o\text{-tolyl})_3)_2$-catalyzed reactions of aryl bromides and (*N*,*N*-diethylamino)tributyltin.[3-5] The lack of demonstrated applicability of this route in the general synthesis of arylamines was particularly surprising, but could be attributed in part to the high reactivity/instability[6] of the aminostannanes which hinder their efficient isolation and further manipulations.[7] Herein we describe our initial findings on a transamination/Pd-catalysis protocol which provides a fairly general and attractive route to arylamines.

The $PdCl_2(P(o\text{-tolyl})_3)_2$-catalyzed reaction of 3-bromoanisole with (*N*,*N*-diethylamino)tributyltin (toluene, ~105 °C, ~4 h) afforded 3-(*N*,*N*-diethylamino)anisole (**1**) (83% isolated yield).[8,9] Preliminary studies of catalyst and reaction conditions indicate that the $P(o\text{-tolyl})_3$ ligand and higher temperatures are desirable.[10]

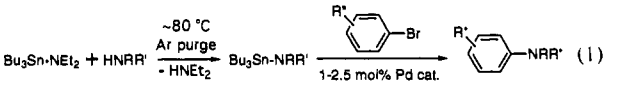
Table 1. Pd-Catalyzed Aromatic Aminations with in Situ Generated Aminostannanes

R* =	Amine	Work-up[a]	Aryl Amine	Yield(%)[b]
p-CO_2Et		B	 **2**	88
p-NMe_2		A	 **3**	81
m-Me		B	 **4**	79
p-Me		A	 **5**	55
m-OMe		A	 **6**	79
m-OMe		A	 **7**	84
m-Me		B	 **8**	66
m-Me		B	 **9**	64
p-Me		B	 **10**	73
p-CO_2Et		B	 **11**	83

[a] Workup A: The product was extracted with 4 N HCl, followed by neutralization of the aqueous fraction with 4 N NaOH and extraction with Et_2O. Workup B: The organics were washed with aqueous KF solution to remove the organostannane as an insoluble *n*-Bu_3SnF polymer. Details are provided in the supplementary material. [b] Yields reported correspond to analytically pure, isolated compounds.

Related $PdCl_2L_2$ catalysts (L_2 = $(PPh_3)_2$; DPPF; $Ph_2P(CH_2)_3PPh_2$) containing ligands other than $P(o\text{-tolyl})_3$ are not effective, affording only trace amounts of the desired arylamine.

Initial experiments to generalize this reaction to include other higher aminostannane derivatives via in situ generation of aminostannanes by the conventional reaction of lithium amides with *n*-Bu_3SnCl (in ether) were not successful, presumably due to deactivation of the active reagents by either the LiCl salt or residual BuLi or ether solvent. Indeed, the reaction of 3-bromoanisole with (*N*,*N*-diethylamino)tributyltin in the presence of LiCl (~1 equiv) (toluene, ~105 °C, ~4 h) is not efficient (~20% conversion by GC). These difficulties were overcome by in situ generation of aminostannanes from the reaction of an aminostannane derived from a volatile amine with a higher boiling amine (in toluene), concomitantly with removal of the volatile amine.[11] This efficient transamination reaction coupled with Pd catalysis provides a general access to a variety of arylamines (eq 1 and Table 1).



(1)

A typical experimental procedure involved in situ generation of the aminostannanes from the transamination reaction (toluene, ~80 °C, argon purge) of (*N*,*N*-diethylamino)tributyltin (~1.37

(1) (a) March, J. *Advanced Organic Chemistry*, 4th ed.; Wiley: New York, 1992. For recent reports on nucleophilic aromatic substitution reactions of N-nucleophiles with activated aromatic substrates, see: (b) Hattori, T.; Sakamoto, J.; Hayashizaka, N.; Miyano, S. *Synthesis* **1994**, 199. (c) Semmelhack, M. F.; Rhee, H. *Tetrahedron Lett.* **1993**, *34*, 1395. (d) Abd-El-Aziz, A. S.; Lee, C. C.; Piorko, A.; Sutherland, R. G. *J. Organomet. Chem.* **1988**, *348*, 95. For synthesis of arylamines via Cu-mediated Ullmann condensation, see: (e) Paine, A. J. *J. Am. Chem. Soc.* **1987**, *109*, 1496 and references therein.

(2) Tidwell, J. H.; Buchwald, S. L. *J. Org. Chem.* **1992**, *57*, 6380.

(3) Kosugi, M.; Kameyama, M.; Migita, T. *Chem. Lett.* **1983**, 927.

(4) Related research was recently described while this work was in progress: Hartwig, J. F.; Patt, J.; Paul, F.; Driver, M. S. *Abstracts of Papers*, 207th National Meeting of the American Chemical Society, San Diego, CA; American Chemical Society: Washington, DC, 1994; INOR 235.

(5) Related intramolecular aromatic aminations using stoichiometric amounts of $Pd(PPh_3)_4$ have been described: Boger, D. L.; Duff, S. R.; Panek, J. S.; Yasuda, M. *J. Org. Chem.* **1985**, *50*, 5782.

(6) Leading references: (a) Jones, K.; Lappert, M. F. *Organomet. Chem. Rev.* **1966**, *1*, 67 and references therein. (b) Chandra, G.; George, T. A.; Lappert, M. F. *J. Chem. Soc. C* **1969**, 2565 and references therein.

(7) In contrast, thiostannanes are very robust and have been more generally employed in related Pd-catalyzed reactions; see: (a) Dickens, M. J.; Gilday, J. P.; Mowlem, T. J.; Widdowson, D. A. *Tetrahedron* **1991**, *47*, 8621. (b) Kosugi, M.; Ogata, T.; Terada, M.; Sano, H.; Migita, T. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 3657.

(8) A byproduct (anisole, <5% by GC) resulting from reduction of the starting aryl bromide was also formed. Reduction may occur from β-hydride elimination followed by reductive elimination of the intermediate $Pd(NEt_2)(m\text{-}C_6H_4OMe)L_n$ species (see ref 15). Alternatively, β-hydride and reductive elimination of a $Pd(n\text{-}Bu)(m\text{-}C_6H_4OMe)L_n$ species, generated via *n*-Bu transfer from *n*-Bu_3SnX (X = Br, NEt_2) to the $Pd(Br)(m\text{-}C_6H_4OMe)L_n$ species, is also possible. Such *n*-Bu ligand transfer reactions from *n*-Bu_3SnCl are precendented (see: Pri-Bar, I.; Stille, J. K. *J. Org. Chem.* **1982**, *47*, 1215) and are anticipated to be relatively more facile in *n*-Bu_3SnNEt_2. Studies to elucidate the reduction mechanism are currently underway.

(9) Analogous reactions of (*N*,*N*-diethylamino)tributyltin with aryl iodides were less efficient (6–38% variable yields of the desired arylamine) and primarily afforded the reduced product. However, satisfactory yields (>60% isolated) of the desired arylamine were obtained in the presence of ammonium salts. Thus, the reaction of (*N*,*N*-diethylamino)tributyltin with *p*-iodotoluene in the presence of *N*-benzyltriethylammonium chloride (toluene, 100 °C) afforded 3-(*N*,*N*-diethylamino)toluene (63% isolated yield, unoptimized).

(10) The reaction takes ca. 12 h to reach completion at 80 °C (82% isolated yield of **1**). The catalyst system $Pd(dba)_2/2P(o\text{-tolyl})_3$ is equally effective (81% isolated yield of **1**).

0002-7863/94/1516-7901$04.50/0

equiv) with primary and secondary amines (~1.45 equiv), followed by reaction with aryl bromides (1.0 equiv) at 105–110 °C in the presence of 1–2.5 mol % of $PdCl_2(P(o\text{-tolyl})_3)_2$.[12] The reactions were monitored by GC/TLC for the complete conversion of the starting aryl bromide, and the analytically pure arylamines were isolated in good yields by column chromatography on silica gel following either an extractive acidic or aqueous KF workup.

As illustrated in Table 1, the Pd-catalyzed aromatic aminations are fairly general for a variety of in situ generated aminostannanes. Aminostannanes derived from both aliphatic and aromatic amines including aniline undergo Pd-catalyzed reactions with aryl bromides substituted with either electron-withdrawing or electron-donating substituents to afford the desired arylamines in good yields. In general, aryl bromides substituted with a para electron-donating substituent reacted more slowly than those with a para electron-withdrawing substituent (~18 h for 4-bromo-*N*,*N*-dimethylaniline vs. ~1–2 h for ethyl 4-bromobenzoate). Slower reaction was also observed in the case of an aminostannane derived from aniline (~30–40 h). However, *p*-methoxyaniline (*p*-anisidine) and *N*-methylaniline reacted significantly faster (~12 and ~8 h, respectively). To date, aminostannanes derived from *n*-hexylamine and *N*-methylcyclooctylamine were found to be unreactive under similar conditions.[13]

The Pd-catalyzed aromatic amination most likely proceeds via initial aminostannane-induced reduction of Pd(II) complex to a Pd(0) species, followed by an oxidative addition, transmetalation, and reductive elimination sequence typical of Pd catalysis.[4,14] Experimental results indicate that, in general, transmetalation to form the Pd–N bond[15] is influenced by both the steric and electronic properties of the amine. Larger aminostannanes derived from *n*-hexylamine (aminodistannane is formed in this case)[11] and *N*-methylcyclooctylamine are unreactive presumably because the increased steric interactions with $P(o\text{-tolyl})_3$ ligands on palladium preclude transmetalation. This is consistent with the relatively higher reactivity (~1.8 times faster) exhibited by (*N*,*N*-dimethylamino)tributyltin compared to its homolog (*N*,*N*-diethylamino)tributyltin in the reaction with 3-bromoanisole at 80 °C.[16] The lower reactivity of aminostannane derived from aniline can be ascribed to its decreased nucleophilicity.

In summary, we have demonstrated that a range of aminostannanes, generated in situ via a simple transamination reaction, undergo Pd-catalyzed reactions with aryl bromides substituted with either electron-withdrawing or electron-donating substituents. Overall, the transamination/Pd-catalysis sequence provides a fairly general and attractive approach to arylamines. Efforts to clarify the reaction mechanism, modify the reaction conditions, broaden the scope, and develop synthetic applications of these and related reactions are currently in progress.

Acknowledgment. This work was supported by the National Science Foundation (CHE-9000482) and the National Institutes of Health (GM34917). A.S.G. is a Postdoctoral Trainee supported by NIH Cancer Training Grant CI T32CA09112. We also thank Professor John F. Hartwig for discussions of related results prior to publication.

Note Added in Proof: A related communication by Hartwig and co-workers has recently appeared.[17]

Supplementary Material Available: Details of experimental procedures and spectroscopic and analytical data for compounds **1–11** (7 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(11) This transamination reaction was originally reported by Jones and Lappert. Secondary amines and primary aromatic amines (e.g., aniline and derivatives) form aminostannanes, whereas primary aliphatic amines form aminodistannanes; see: Jones, K.; Lappert, M. F. *J. Chem. Soc.* **1965**, 1944.

(12) (*N*,*N*-Dimethylamino)tributyltin can also be used in the transamination reaction. Detailed experimental procedures and complete characterization data are provided in the supplementary material. Typical reaction procedure, **3-(*N*-(3,4-dimethoxyphenethyl)-*N*-methylamino)anisole (7)**: A solution of 3,4-dimethoxy-*N*-methylphenethylamine (349 mg, 1.79 mmol) and (*N*,*N*-diethylamino)tributyltin (600 mg, 1.66 mmol) in toluene (2 mL) was heated at 85 °C under argon purge for 1 h. 3-Bromoanisole (221 mg, 1.12 mmol), $PdCl_2(P(o\text{-tolyl})_3)_2$ (10 mg, 0.02 mmol), and toluene (8 mL) were added and the reaction mixture heated under argon at ~105 °C overnight. The reaction mixture was cooled, diluted with Et_2O (20 mL), and extracted with 4 N HCl solution (2 × 10 mL) (workup A). The aqueous fraction was cooled to 0 °C, made alkaline with 4 N NaOH solution (25–30 mL), and extracted with Et_2O (2 × 15 mL). The organic fraction was dried with $MgSO_4$, concentrated in vacuo, and subjected to column chromatography on silica gel using hexane–EtOAc (10:1, 4:1) to afford compound **7** as a light pink oil (301 mg, 84%). ^1H NMR (300 MHz, $CDCl_3$): δ 7.16 (t, *J* = 8 Hz, 1H, ArH), 6.82–6.70 (m, 3H, ArH), 6.36 (d, *J* = 8 Hz, ArH), 6.30 (obs, 1H, ArH), 6.27 (br s, 1H, ArH), 3.86 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 3.54 (t, *J* = 8 Hz, NCH_2), 2.86 (s, 3H, NCH_3), 2.80 (t, *J* = 8 Hz, CH_2Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ 160.8, 150.2, 148.9, 147.4, 132.4, 129.9, 120.6, 112.1, 111.1, 105.3, 100.8, 98.7, 55.9, 55.8, 55.1, 54.8, 38.6, 32.6. Anal. Calcd for $C_{18}H_{23}NO_3$: C, 71.73; H, 7.69. Found: C, 71.88; H, 7.56.

(13) The aryl bromide reactant also remained mostly unreacted in these reactions.

(14) For a general review on transition metal catalyzed coupling reactions, see: Tamao, K. *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press, Inc., New York, 1991; Vol. 3, p 435.

(15) Complexes containing a Pd–N bond are rare and presumably decompose via β-hydride elimination: (a) Murahashi, S.-I.; Yoshimura, N.; Tsumiyama, T.; Kojima, T. *J. Am. Chem. Soc.* **1983**, *105*, 5002. (b) Bryndza, H. E.; Tam, W. *Chem. Rev.* **1988**, *88*, 1163.

(16) A 1.0:1.0:0.7 mixture of (*N*,*N*-dimethylamino)tributyltin, (*N*,*N*-diethylamino)tributyltin, and 3-bromoanisole, respectively, was heated at 80 °C and monitored by GC.

(17) Paul, F.; PaH, J.; Hartwig, J. F. *J. Am. Chem. Soc.* **1994**, *116*, 5969.