Palladium-Catalyzed Formation of Carbon-Nitrogen Bonds. Reaction Intermediates and Catalyst Improvements in the Hetero Cross-Coupling of Aryl Halides and Tin Amides

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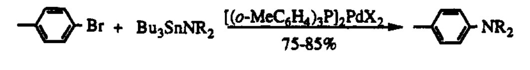
Methods to construct the carbon-nitrogen bond in aryl amines are limited, rely on high temperatures, mechanistically ill-defined copper mediated processes,[1,2] occur under the highly reducing conditions of $S_{RN}1$ reactions,[3] or provide nonregiospecific products by way of aryne intermediates.[4] Ten years ago, it was noted that palladium compounds can catalyze the regiospecific formation of aryl amines from aryl halides and the weakly nucleophilic tin amides.[5,6] This hetero cross-coupling is remarkable, considering its relationship to Stille carbon-carbon bond-forming cross-couplings[7,8] but the absence of known reductive eliminations reactions that form carbon-nitrogen bonds in amines. We report the identification and crystallographic characterization of several kinetically competent intermediates in the C-N hetero cross-coupling, isolation of a catalyst for room temperature formation of *N,N*-dialkylanilines, and mechanistic data that suggest C-N bond formation by reductive elimination.

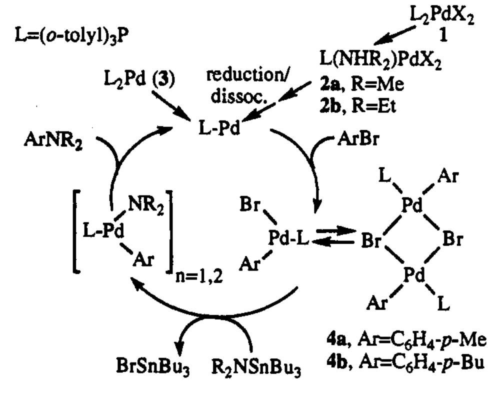
The palladium(II) compound $[(o\text{-MeC}_6H_4)_3P]_2PdX_2$ [X = Cl (**1**-Cl), Br (**1**-Br)] catalyzes the hetero cross-coupling of Bu_3SnNMe_2 and phenyl or *p*-alkylphenylbromides at 90-110 °C in arene solvents to form *N,N*-dimethylanilines in 75-85% yields (eq 1). We probed for both Pd(0) compounds on the catalytic cycle and intermediates between Pd(II) complex **1** and a Pd(0) species, since most palladium-catalyzed carbon-carbon bond-forming processes are believed to involve complexes in these two oxidation states. Scheme 1 shows a mechanism for the coupling chemistry that is consistent with our experimental results.



(1)

Addition of 2-10 equiv of Bu_3SnNR_2 (R = Me, Et) to **1-Cl** led to a toluene-soluble compound displaying ^{31}P NMR resonances at δ 24.6 (R = Me) or δ 24.1 (R = Et), along with free phosphine and a black precipitate that is insoluble in all common solvents, preventing full characterization.[9] The soluble species were identified as the mixed amine/phosphine complexes *trans*-$[(o\text{-MeC}_6H_4)_3P](NHR_2)PdCl_2$ [R = Me (**2a**); R-Et (**2b**)] and were formed in 50-60% yields (^{31}P NMR spectroscopy) under these conditions. Both compounds were generated and isolated in >90% yield by addition of the free amine to **1** at 80 °C, and the structure of **2b** was determined by X-ray diffraction analysis of a single crystal, confirming our assignment.[10] The amine N-H proton is most likely derived from β-hydrogen elimination of a transient palladium alkyl or amido intermediate followed by extrusion of HCl that creates free amine from tin amide.

Scheme 1



The toluene-soluble compounds **2a** and **2b** were shown to catalyze the cross-coupling at 60 °C in yields that were essentially identical to those observed with **1**.[11] Importantly, the black precipitate formed during reaction of **1** with the tin amide was isolated and shown to be inactive as a catalyst in this process. Moreover, palladium on carbon did not catalyze the hetero cross-coupling reaction, and elemental mercury had no effect on the rate or product selectivity during catalysis, strongly suggesting a homogeneous process.[12]

In order to test the ability of Pd(0) analogs of **1** and **2** to catalyze the coupling chemistry, we developed a reliable preparation of $[(o\text{-MeC}_6H_4)_3P]_2Pd$ (**3**).[13] Addition of 7 equiv of $(o\text{-MeC}_6H_4)_3P$ to $Pd(dba)_2$[14] (dba = dibenzylideneacetone) in benzene for 12 h, followed by filtration and addition of ether, led to crystallization of **3** (60-75%) in analytically pure form after several days. This complex displayed a $^{31}P\{^1H\}$ NMR signal at δ -6.7 and was identified crystallographically. An ORTEP drawing, along with selected distances and angles, is shown in Figure 1.

Compound **3** catalyzed the coupling chemistry of dialkyltin amides in yields that were comparable to those of the Pd(II) compounds **1a** and **1b**. Moreover, measurements of the catalytic activity of **2** and **3** under identical conditions clearly indicated that reactions were faster with the Pd(0) species, making **3** kinetically competent to be an intermediate and the preferred catalyst. In fact, the coupling of Bu_3SnNMe_2 with *p*-MeC_6H_4Br with 2 mol % palladium in toluene provided *ca.* 10 turnovers in 18 h *at room temperature*.

Compound **3** was inert to the tin amide reagents but reacted rapidly with aryl bromides in arene solvents to provide solutions displaying a single broad ^{31}P resonance at δ 28.1 and a sharp resonance corresponding to an equivalent of free phosphine. Addition of ether to the reaction solution led to analytically pure single crystals (87%, **4a**; 80-90%, **4b**) of the dimeric **4a** and **4b**, $\{[(o\text{-MeC}_6H_4)_3P]Pd(Ar)(Br)\}_2$. An ORTEP diagram is provided in Figure 1. The NMR spectra of **4a** and **4b** displayed broad lines and were not straightforward at low temperature. However, at 90 °C, a simple spectrum was obtained and conclusively showed a 1:1 ratio of phosphine ligand and palladium-bound aryl group. The ^{31}P NMR spectra of **4a** and **4b** showed no measurable concentration dependence, and a solution molecular weight

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(9) Combustion analysis indicated the presence of one tri-*o*-tolylphopshine per palladium in this material.

(10) A partial data set was obtained, but the structure refined to R = 4.0, R_w = 3.7. Crystal parameters for Mo Kα irradiation: $C_{25}H_{32}NPCl_2Pd$, $P2_1/n$, a = 9.827(6), b = 17.69(1), and c = 14.65(1) Å, α = 90°, β = 98.06(6)°, γ = 90°, V = 2522(6) Å^3.

(11) Although the rates for catalysis with **2a**, and **2b** were faster than those for that with **1**, this may be attributed to the much greater solubility of **2a** and **2b**.

(12) Anton, D. R.; Crabtree, R. H. *Organometallics* **1983**, *2*, 855-859.

(13) We found the preparation in the following patent to provide mixtures of L_2Pd and L_2PdCl_2 and in low yields. Enomoto, S.; Wada, H., Nishida, S.; Mukaida, Y.; Yanaka, M.; Takita, H. Jpn. Kokai Tokkyo Koho JP 53144552, 1978, 7 pp.

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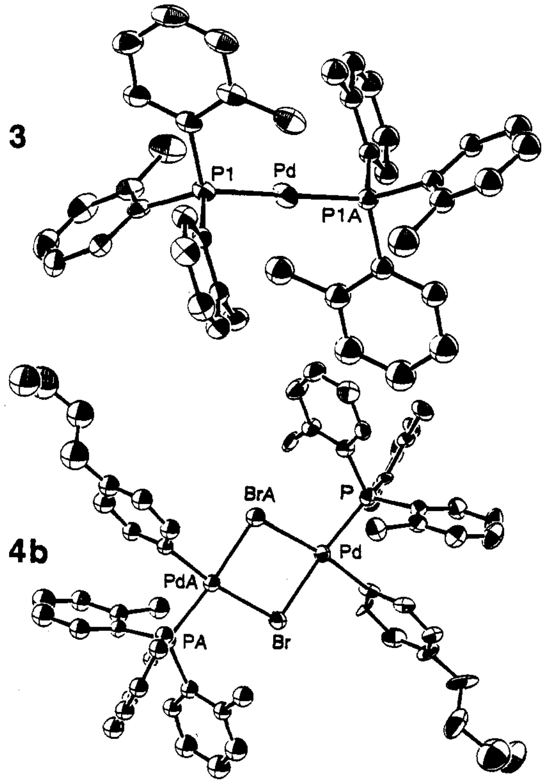

Figure 1. ORTEP drawings of 3 and **4b**. Both molecules lie on an inversion center. Selected distances and angles for compound **3**: Pd-P 2.276(1) Å, P–Pd–P 180.00°. Selected distances for compound **4b**: Pd–Br 2.527(2), 2.582(2), Pd–P 2.288(3), Pd–C22 2.02 (1) Å, Br–Pd–Br 84.04(5), Pd–Br–Pd 95.96(5)°.

analysis in benzene provided molecular weights corresponding to the dimeric form. Compounds **4a** and **4b** appeared to be the only species present during ^{31}P NMR spectroscopic investigation of catalytic reaction solutions and would therefore be the resting state of the catalyst, although broad resonances due to the fluxionality of these compounds leads to poor resolution.

Reaction of **3** with identical excess concentrations of aryl bromide was retarded by the addition of increasing amounts of $(o\text{-}MeC_6H_4)_3P$ to the reaction solution, although quantitative rate studies have not been performed. Several potential explanations for phosphine inhibition exist, but a mechanism involving initial, reversible dissociation of phosphine is favored, since $[(o\text{-}MeC_6H_4)_3P]_3Pd$ is never observed. Thus, the monophosphine rather than the bisphosphine complex **3** is the likely palladium(0) intermediate participating directly in the catalytic cycle. Catalysis that occurs through the reduction product of **2** would generate the same intermediate.

Compound **4** reacted with tin and lithium amides at room temperature, and when these reactions were conducted in the presence of $(o\text{-}MeC_6H_4)_3P$, the only phosphine-containing palladium product was **3**. Under conditions that would mock the reaction of **4** during catalysis (*ca.* 10 μM palladium, 20–50 equiv of Bu_3SnNMe_2, and 1 equiv of phosphine), the yield of *N,N*-dimethyl-substituted aniline was >90%. Only traces of Ar-Bu coupled products were observed, demonstrating that transfer of the amide group to **4a** or **4b** occurs almost exclusively. This transmetalation of dialkylamide appears to be the rate-determining step of the catalysis, as is transfer of a hydrocarbyl group during carbon–carbon bond-forming cross-couplings with tin reagents.[8]

Importantly, formation of **4a** or **4b** is not reversible under the conditions of reaction with tin amides, and thus catalysis by a pathway separate from one involving **4a** or **4b** is unlikely. Compound **4a** does not undergo exchange with $p\text{-}BuC_6H_4Br$ after several days at room temperature. Moreover, aryl bromide is not generated in the presence of tin amide. Addition of Bu_3SnNMe_2 to **4a** in the presence of 1–2 equiv of $p\text{-}BuC_6H_4Br$ or to **4b** in the presence of 1–2 equiv of $p\text{-}MeC_6H_4Br$ was analyzed after 15 min at room temperature. Formation of both $p\text{-}BuC_6H_4NMe_2$ and $p\text{-}MeC_6H_4NMe_2$ was observed, one by reaction of tin amide with **4a** or **4b** constituting the first turnover and one by subsequent turnovers involving the Pd(0) product. Most significantly, the pool of unreacted aryl bromides consisted of only added $p\text{-}BuC_6H_4Br$ in the reaction with **4a** and of only added $p\text{-}MeC_6H_4Br$ in the reaction with **4b**. Thus, our data strongly suggest that **4a** and **4b** or their corresponding monomers react with tin amide and are directly involved in the catalysis. Transmetalation of the amide and reductive elimination of arylamine is therefore the most likely pathway to arylamine from these Pd(II) species. Addition of lithium dimethylamide immediately formed the coupled product in yields of 60–70%, consistent with this mechanism, although this result does not rule out the less likely direct addition to the electron-rich σ-bound aryl group.

We are presently conducting kinetic experiments to determine the intermediacy of monomeric or dimeric complexes, synthetic studies to generate potential palladium amido intermediates, and investigations of alternative main-group amide sources. We are concurrently comparing the scope and rates of catalysis with **3** relative to that with **1** in hetero cross-couplings and are investigating the synthetic potential of this process.

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Supplementary Material Available: Spectroscopic and analytical data for compounds **1–4**, including tables of positional and thermal parameters, along with complete tables of intramolecular distances and angles and experimental details for compounds **3** and **4** (24 pages); listing of observed and calculated structure factors (26 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.