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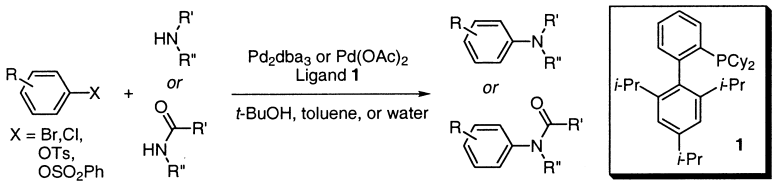
J. Am. Chem. Soc., **2003**, 125 (22), 6653-6655• DOI: 10.1021/ja035483w • Publication Date (Web): 07 May 2003



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Published on Web 05/07/2003

Expanding Pd-Catalyzed C−N Bond-Forming Processes: The First Amidation of Aryl Sulfonates, Aqueous Amination, and Complementarity with Cu-Catalyzed Reactions

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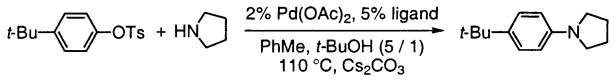
Despite significant improvements in palladium-catalyzed processes for the formation of C−N bonds,[1] many common functional groups have been incompatible with the normal reaction protocols. In some cases the use of weaker bases is beneficial.[2] However, reactions under these conditions are invariably slower or require higher levels of catalyst. Alternatively, the use of $LiN(TMS)_2$ as base sometimes allows for an increase in substrate scope.[3] A few years ago we reported a new class of biaryl monophosphine ligands that were highly active in several cross-coupling reactions.[4] Our continuing studies in this area have led to the discovery of a structural derivative of these ligands that produces a catalyst system with both a greater degree of activity and of stability than those that use our previous ligands. The study of this system has led us to try reactions and substrate combinations that have been recalcitrant in the application of previous catalysts. Herein, we disclose our results.

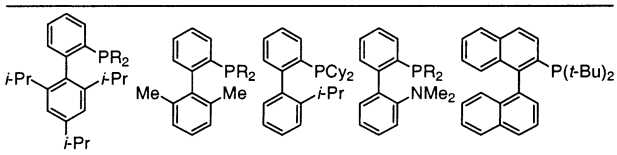
Our work began with the intention of developing general reaction conditions for the palladium-catalyzed amination of aryl tosylates and benzene sulfonates for which, to our knowledge, only two examples of the palladium-catalyzed amination of aryl tosylates have been reported.[5] We began by examining the reaction shown in Table 1. While we had previously noted a significant influence of the size of the dialkylphosphino group on the rate and efficacy of reactions using these ligands, we found an interesting and unexpected interplay between the nature of the phosphino group and that of the 2 and 6 substituents on the bottom ring. For example, ligand **3**, with the smallest PR_2 group is ineffective, whereas **2**, with the largest PR_2 group, is only moderately active. The best compromise is seen in **1**. Likewise, **1** is far superior to **4** as the ortho methyl groups either do not provide enough steric bulk or are more prone to cyclometalation. Ligand **1**, an air-stable crystalline compound available in one step from simple materials in 70−80% yield,[6] is a general ligand for the amination of arenesulfonates. While tosylates were often good substrates, the use of benzenesulfonates typically provided higher yields or shorter reaction times. As can be seen in Table 2, the process can be used with primary and secondary (both cyclic and acyclic) aliphatic amines, anilines, diarylamines, indole, benzophenone imine (an ammonia equivalent), and benzophenone hydrazone, a precursor to indoles.[7]

Encouraged by our findings, we sought to ascertain if previously unattainable processes could be accomplished using **1**. For example, we have been able to, for the first time, couple amides and carbamates with tosylates (Table 3);[8] the coupling of pyrrolidinone, primary amides, *N*-methyl formamide, and *N*-Boc amide proceeded with good-to-excellent yield. It was necessary in these cases to add a catalytic quantity of phenyl boronic acid to ensure complete conversion of the Pd(II) precatalyst to Pd(0). The best results were obtained using K_2CO_3 as base in *t*-BuOH;[9] other solvents (toluene, dioxane) provided much slower reaction rates.[10] We note that a number of other ligands were screened to determine their efficacy in supporting a catalytic system for this transformation, including $(t\text{-Bu})_3P$, 1,1′-bis-di-*tert*-butylferrocene, and the two ligands that have been found to effect the amination of tosylates;[5a,b] the most efficient of these provided only a 4% yield of the desired product.

During the course of our work we had reason to examine the Pd-catalyzed coupling reactions using 3-aminobenzamide as a nucleophile. This was despite the fact that amine substrates containing primary amides had not, to our knowledge, been

Table 1. Ligand Effects in Amination of an Aryl Tosylate





1, R = Cy
2, R = *t*-Bu
3, R = Et

4, R = Cy
5, R = *t*-Bu

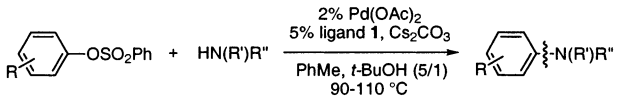
6

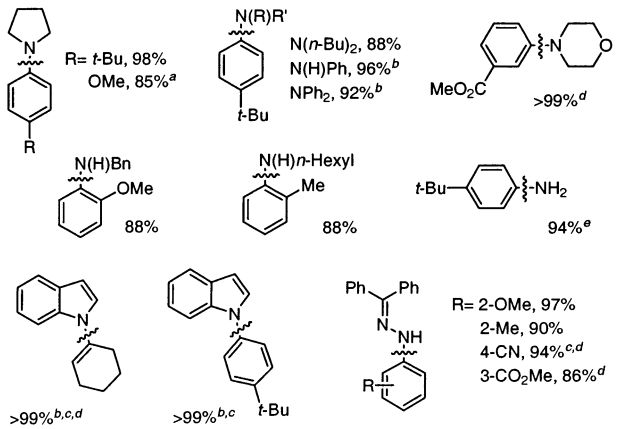
7, R = Cy
8, R = *t*-Bu

9

Ligand:	1	2	3	4	5	6	7	8	9
Conversion:	91%	41%	0%	12%	15%	15%	7%	32%	33%
Yield (GC):	84%	38%	0%	8%	12%	15%	6%	30%	30%

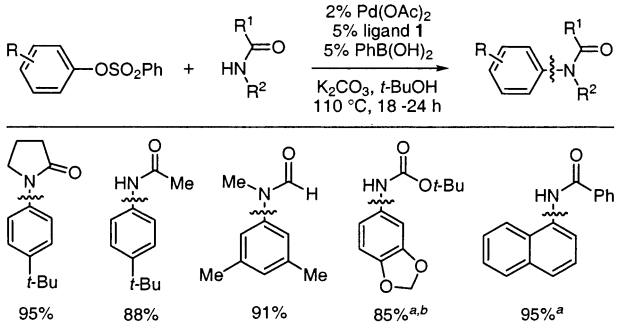
Table 2. Pd-Catalyzed Amination of Aryl Benzenesulfonates





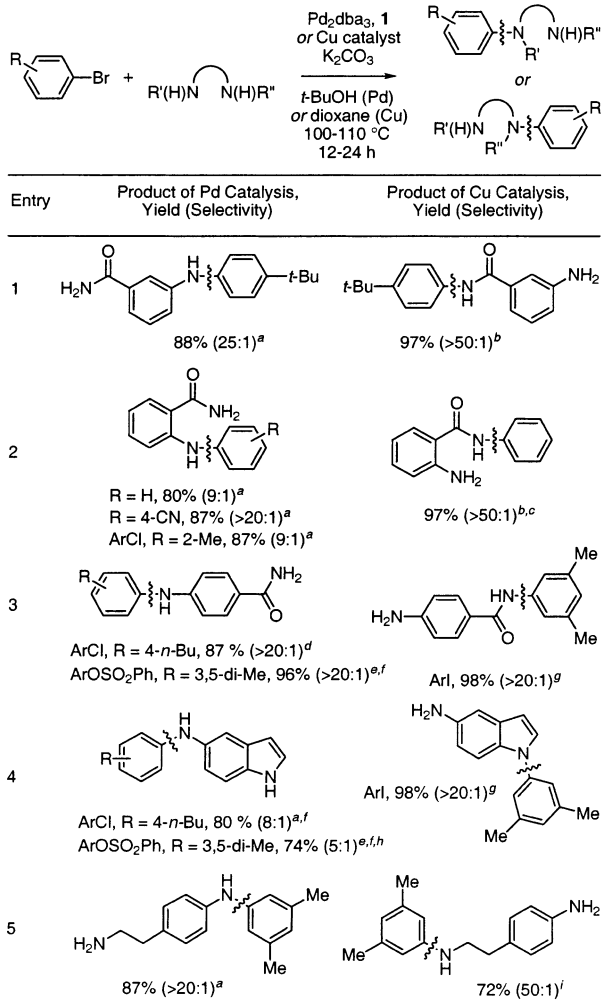
[a] With 8 mol % of **1**. [b] With 5 mol % $PhB(OH)_2$. [c] Using K_3PO_4 as base. [d] From aryl tosylate. [e] From coupling with benzophenone imine using 1 mol % Pd_2dba_3 in *t*-BuOH, followed by hydrolysis of the resulting imine.

Table 3. Amidation of Aryl Benzenesulfonates



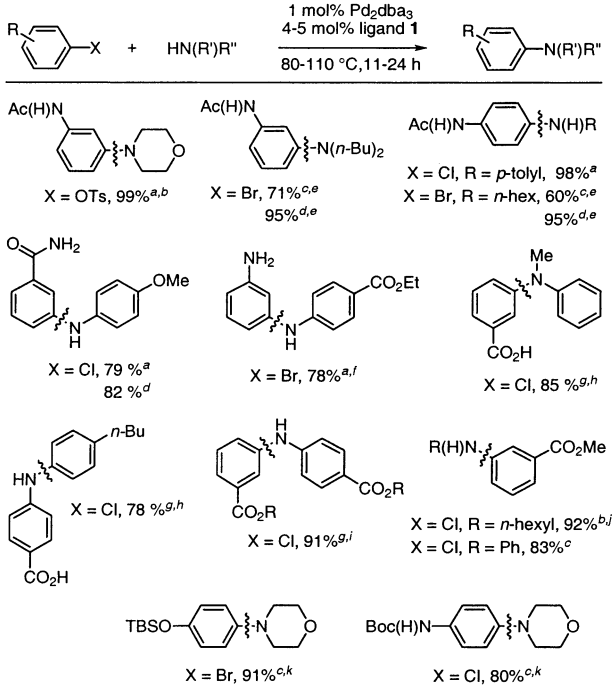
[a] From aryl tosylate. [b] With 8% of ligand **1**.

Table 4. Complementary C−N Couplings Using Pd and Cu Catalysts



[a] Using 1 mol % Pd_2dba_3, 5 mol % ligand **1**, and 2.5 equiv K_2CO_3 in *t*-BuOH. [b] Using 5 mol % CuI, 10 mol % *N*,*N*′-dimethylethylenediamine, 2 equiv K_2CO_3 in dioxane. [c] In toluene. [d] With 0.5 mol % Pd_2dba_3, 2 mol % ligand **1**, and 2 equiv K_2CO_3 in *t*-BuOH. [e] With 2 mol % $Pd(OAc)_2$, 5 mol % ligand **1**, and 2.5 equiv K_2CO_3 in *t*-BuOH. [f] For 3 h at 110 °C. [g] With 1 mol % CuI, 10 mol % *rac*-*trans*-1,2-cyclohexanediamine, and 2 equiv K_3PO_4 in dioxane. This example is taken from ref 12. [h] With 5 mol % $PhB(OH)_2$. [i] With 5 mol % CuI, 20 mol % *N*,*N*-diethylsalicylamide and 2 equiv K_3PO_4 in DMF. For the preparation of the same compound from aryl iodide using a slightly different catalyst system, see ref 13b.

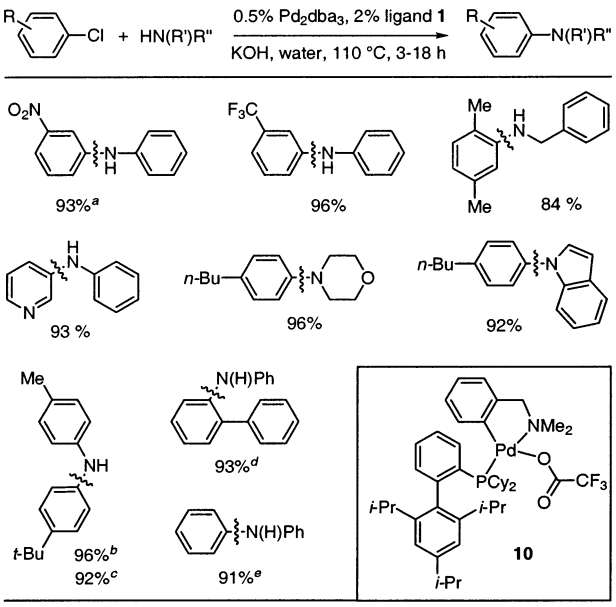
Table 5. Pd-Catalyzed Amination of Functionalized Aryl Halides



[a] K_2CO_3 as base in *t*-BuOH. [b] With 2 mol % $Pd(OAc)_2$. [c] NaO*t*-Bu as base in *t*-BuOH. [d] NaO*t*-Bu as base in toluene. [e] For 2 h at 90 °C. [f] With 8 mol % of ligand **2**. [g] KOH as base in *t*-BuOH. [h] For 3 h at 110 °C. [i] Starting materials with R = H were used; the product (R = Me) was isolated after treatment with TMSCl in MeOH at 0 °C to room temperature for 12 h. [j] Cs_2CO_3 as base in toluene. [k] For 30 min at 100 °C.

successfully arylated. To our surprise, the reaction of 3-aminobenzamide with 4-*tert*-butyl bromobenzene proceeded in excellent yield with nearly complete selectivity (25:1) for reaction at the aniline NH_2 group. Of importance is that this result is complementary to that seen using our Cu-catalyzed method[11] where exclusive C−N coupling on the amide NH_2 group is observed (Table 4, entry 1). This provides the ability to switch the chemoselectivity of the coupling reactions by changing the catalyst employed, something not previously possible with reactions of this type. As is shown in Table 4, there are many instances where the Cu- and Pd-catalyzed processes provide complementary products. For example, the switch between amido and aniline reactivity is seen for not only 3-aminobenzamide but for the para and even the ortho isomers as well. We previously have shown that the Cu-catalyzed coupling of 5-aminoindole with simple aryl bromides gives exclusively arylation on the indole nitrogen;[12] moderate-to-high selectivity is seen for arylation of the 5-amino group when the palladium catalyst is used. Finally, using our recently reported method, we have been able to selectively arylate either the aliphatic NH_2 group (Cu-catalyzed)[13] or the aniline NH_2 group (Pd-catalyzed) (Table 4, entry 5). The observed selectivity may result from higher affinity of Cu(I) toward amides and alkylamines. Alternatively, the lowest-energy transition state may provide the major product irrespective of the binding preferences in the ground state, according to the Curtin−Hammett principle. Thus, oxidative addition to Cu(I)−amide or Cu(I)−alkylamine complexes may have a lower transition-state energy compared to oxidative addition to Cu(I)−aniline complexes. The selectivity observed in the Pd-catalyzed reactions may originate from discrimination occurring in the Pd−N bond-formation step (binding of the nitrogen nucleophile to the aryl Pd(II) complex or the subsequent deprotonation of the metal-bound nucleophile).

Table 6. Pd-Catalyzed Amination in Water



[a] For 8 h at 100 °C. [b] With 2.5 mol % of ligand **1**. [c] With 2.5 mol % of *t*-$Bu_3PH^+BF_4^-$ as ligand. [d] From aryl nonaflate; for 16 h at 80 °C. [e] From aryl tosylate; with 1 mol % of **10** as catalyst.

A consistently problematic class of substrates has been secondary amides derived from haloanilines. We have now found that the use of ligand **1** allows the Pd-catalyzed coupling of a wide range of amines with meta and para amidohalobenzenes in good-to-excellent yield (Table 5). K_2CO_3 in *t*-BuOH is optimal for the arylation of anilines; however, many alkylamines require a stronger base, NaO*t*-Bu, in either *t*-BuOH or toluene. Another troublesome class of aryl halide substrates are those bearing a primary amide. We find that the addition of *p*-anisidine to 3-chlorobenzamide proceeds in good yield indicating, for the first time, that the chemistry is compatible with a halide substrate containing a primary amide. Substrates containing free carboxylic acid groups have, to date, failed to be transformed to coupling products by Pd-catalyzed amination. As can be seen, this now can be accomplished for aromatic carboxylic acids with the carboxylic acid group being either on the aryl halide, the aniline, or both. We believe, in this case, that the key is to have sufficient solubility of the carboxylic acid-containing substrates under the basic reaction conditions that are employed.

As the use of KOH in *t*-BuOH oftentimes gave superior results, we decided to examine the use of water as a "solvent" for aminations using no cosolvent.[14] The use of **1**/Pd_2dba_3 and KOH in water in many cases gives excellent results.[15] Table 6 demonstrates the amination of aryl chlorides containing nitro, trifluoromethyl, and pyridyl groups. Additionally, we have shown that indole can be arylated in high yield. Interestingly, we have also been able to aminate a hindered aryl nonaflate in good yield. Even an aryl tosylate could be arylated employing the aqueous conditions although in this case the palladacycle **10**, incorporating ligand **1**, had to be used instead of the combination of Pd_2dba_3 and **1**.[16]

In summary, we have developed the first general catalytic system for the amination of aryl sulfonates other than triflates or nonaflates, significantly expanded the substrate scope of Pd-catalyzed aromatic amination, and reported the first examples of the Pd-catalyzed amidation of arenesulfonates and the first aqueous amination protocols that do not necessitate the use of cosolvents. Further uses of **1** will be reported in due course.

Acknowledgment. We thank the National Institutes of Health (GM 45906) for supporting this work. We are grateful to Pfizer, Merck, Lundbeck, and Rhodia Pharmaceutical Solutions for additional unrestricted support. D.Z. thanks CNPq for a postdoctoral fellowship. L.J. was supported as a postdoctoral trainee of the National Cancer Institute (NCI Training Grant CI T32CA09112). We are also grateful to Mr. Joseph R. Martinelli for developing a procedure for the preparation of ligand **1**.

Supporting Information Available: Experimental procedures and characterization data for all unknown compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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JA035483W