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Effect of Water on the Palladium-Catalyzed Amidation of Aryl Bromides

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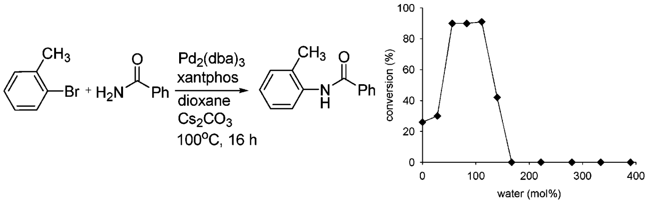
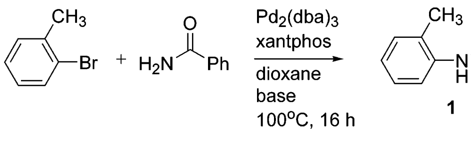


The presence of water was found to have a significant impact on the conversion of some Hartwig–Buchwald reactions between amides with arylbromides. Seven amidation reactions were studied in a series of experiments containing 0–400 mol % water. When cesium carbonate is used as the base both in dioxane and toluene, water can have a beneficial effect. The experiments have also shown that for some reactions, anhydrous conditions are unnecessary and sometimes can hinder the reaction.

The use of the Hartwig–Buchwald reaction as a palladium-catalyzed N–C coupling between amines/amides and aryl halides is becoming increasingly attractive.[1] These reactions have been studied extensively with the scope of the substrates being broadened and the reaction conditions being optimized. Palladium-catalyzed transformations are very important in both academic research and industrial applications; however, the system under investigation often needs fine-tuning. Therefore, under the reaction conditions of the Hartwig–Buchwald amination/amidations, the choice of base, ligand, and Pd source often needs to be optimized. Typically, these reactions are carried out in oxygen- and moisture-free environments, with inert atmospheres and dry solvents and reagents being employed.[2–4] However, during the course of our studies using these reactions, it has come to our attention that some conditions for these coupling reactions benefit from the addition of water to the reaction mixture. This has been previously noted in the palladium-catalyzed amination of aryl chlorides, bromides,[5a] and sulfonates[5b] in the presence of water. Buchwald and co-workers noted that copper-catalyzed coupling of aryl iodides with primary amides using cesium carbonate as the base in THF could also benefit from the addition of water.[6a] Yin et al. found that N-arylation of 2-aminothiazoles and analogues benefits in some cases from the addition of 1 equiv of water.[6b] We report here that cesium carbonate, when used for Pd-catalyzed N-arylations of amides, also benefits from the addition of water and that other bases may not require anhydrous conditions.

Initially, as part of our investigations we wished to employ the Hartwig–Buchwald cross-coupling to couple amides to aryl compounds, and we found that coupling between benzamide and 2-bromotoluene with Cs_2CO_3 and xantphos in dioxane (eq 1)[2] gave the best result when water was added to the reaction mixture. Therefore, it was decided to study the relation between the water content in the reaction mixture and the progress of the reaction. All reactions reported here are carried out using a 1:1:1.5 molar ratio of arylbromide:amide:base. Typically, a series of 8–11 reactions with water contents from 0 to 400 mol % were performed. The reaction progress was followed by GC-MS analysis of the crude product, and product conversion was obtained from these data. In Figure 1, the plots of the product conversion against the volume of water added are shown, measured as mol % aryl halide substrate.



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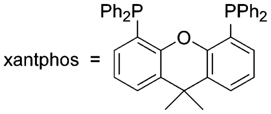

It was observed that the reaction in eq 1 was significantly affected by the volume of water present. There was a dramatic increase in the conversion with the addition of water. In fact, unless at least 50 mol % water was added, the reaction proceeded with low conversion of less than 30%, but in the presence of slightly higher amounts of water the product conversion increased dramatically

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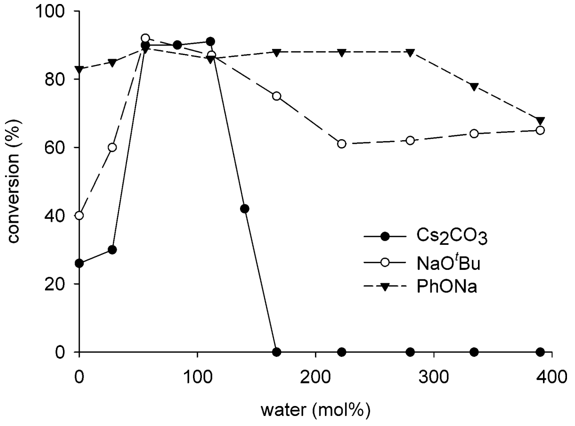


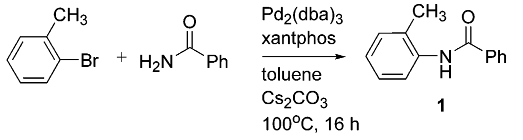
FIGURE 1. Effect of the addition of water measured in mol % on the reaction in eq 1 in the presence of Cs_2CO_3, *t*-BuONa, and PhONa as the base. Reaction time was 16 h.

to 90%. For reactions containing 150 mol % water or more the conversion decreased to 0%.

In other reactions, however, this strong dependence on water had not been observed. Since water might influence the solubility of the base in dioxane, we decided to study the same reaction in the presence of various bases (eq 1). Some other commonly used bases for this type of amidation reactions are sodium *t*-butoxide and sodium phenoxide.[2-4] When sodium *t*-butoxide was employed as the base, the addition of up to 150 mol % water led to a significant increase in the conversion compared to the dry reaction. The dramatic decrease in conversion observed for the reaction using Cs_2CO_3 at >150 mol % water was not observed when sodium *t*-butoxide was used. When sodium phenoxide was used as the base, no significant change in product conversion was seen with the addition of water. Hence, the effect of water on the conversion of the reaction between benzamide and 2-bromotoluene is highly dependent on the choice of base, and Cs_2CO_3 appears to cause the strongest water dependence in these reactions.

For the following reactions, we studied the effect of solvent and substrate on the water dependence of the amidation reactions. The results of reactions given in eqs 2−5, performed at different water contents, are shown in Figure 2. When the solvent of the reaction between benzamide and 2-bromotoluene in the presence of Cs_2CO_3 is changed from dioxane (eq 1) to toluene (eq 2), the strong influence of water on the conversion was maintained, albeit shifted, as a much greater volume of water of approximately 250 mol % was needed for the optimal conversion to be reached. To further test the impact of water content on conversion, three typical amidation reactions that had been reported previously by others were selected for water dependency studies (eqs 3−5).

To test the impact of changing the substrates while maintaining Cs_2CO_3 as the base and dioxane as the solvent, the reactions of 2-bromoanisole with acetamide[2] (eq 3) and 4-*tert*-butylbromobenzene with benzamide[2] (eq 4) were preformed in series with increasing water content (Figure 2). When water was present in 50 mol %, it promoted the reaction in eq 3 significantly compared to the dry reaction. The reaction in eq 4 proceeded with very high conversions for the nine reactions performed at



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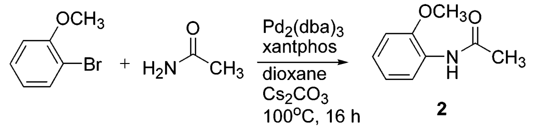

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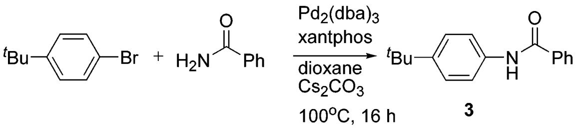

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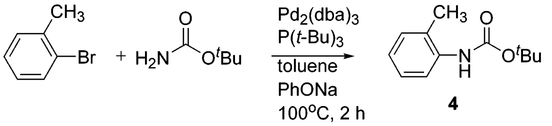

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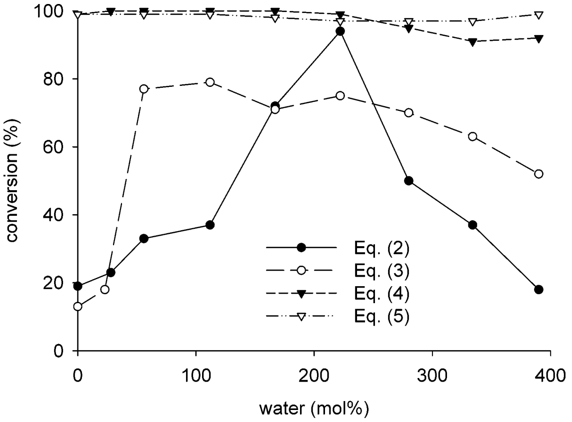

FIGURE 2. Effect of the addition of water measured in mol % on reactions in eqs 2−5. Reaction times for reactions in eqs 2−4 were 16 h, and the reaction time was 2 h for the reaction in eq 5.

different water contents, and the reaction was practically insensitive to water. In the last reaction series, the coupling between *N*-*t*-butylcarbamate and 2-bromotoluene with sodium phenoxide and tris(*t*-butyl)phosphine in toluene was tested (eq 5).[3] The reaction proceeded in high yields in all entries, and this reaction was unaffected by the addition of up to 400 mol % water. Several of the reactions show that a relatively large volume of water can be present in the system (certainly up to 4-fold molar excess). No detrimental effect to the catalyst or hydrolysis was noted to have occurred within the catalytic cycle when sodium *t*-butoxide or sodium phenoxide were employed as the base and for more activated substrates when cesium carbonate was used.

Focusing on the most water-sensitive reaction in eq 1, using Cs_2CO_3 as the base we decided to test if alcohols could be added to the reaction mixture and promote the reaction in the same way as water. Methanol, ethanol, and 2-propanol were added to the reactions at concentrations of 50 mol % with respect to aryl halide, as this proved to be the optimum level for water. However, the conversions were between 25 and 38% for the reactions

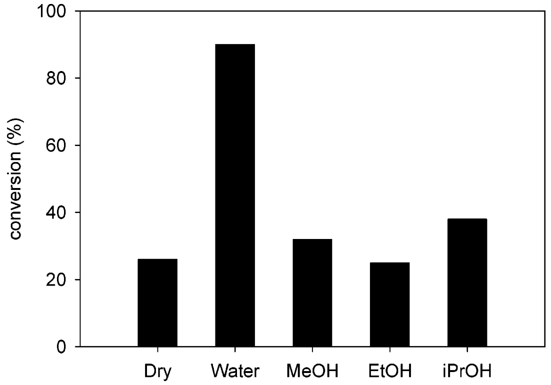

FIGURE 3. Effect of adding 50 mol % alcohols to the reaction in eq 1. Reaction conditions: benzamide, 2-bromotoluene, Cs_2CO_3, xantphos, dioxane, 100 °C, 16 h; H_2O or alcohol was added at 50 mol % with respect to aryl halide.

performed in the presence of alcohols, which is approximately the same when the reaction is carried out in anhydrous conditions, compared to 90% when water was present (Figure 3).

We believe the impact of water on the palladium-catalyzed amidation reactions may in part be a result of the solubility of the base. Different reaction mechanisms have been proposed,[1,7] and in all cases it is essential within the catalytic cycle that an amide proton is removed, either before or after interaction with the palladium catalyst. The vast majority of solvents used for these reactions are aprotic, such as toluene and dioxane, which poorly solubilize the essential base. Sodium *t*-butoxide and sodium phenoxide dissolve in dioxane and toluene more readily than cesium carbonate. Therefore, cesium carbonate, which is a weak base, will disassociate to a greater extent when water is added to the reaction mixture. The reaction in eq 2, carried out in toluene, supports this supposition, as cesium carbonate is less soluble in toluene and, therefore, a greater volume of water is needed to reach the same conversion rate as in dioxane. Therefore, it appears that the water acts as an agent to enable the anionic base to go into solution, thereby maximizing its efficiency in the catalytic cycle. However, as observed for the reaction in eq 4, the relation between water content and conversion is determined not only by the choice of base and solvent but also by the structure of the substrates. This study indicates that for more reactive amide or alkylbromide substrates, the water dependence is reduced.

We believe the findings reported here will add to the studies that are being conducted to increase the efficacy of palladium-catalyzed N−C(aryl) coupling reactions. Previously, many studies have stressed the need for anhydrous conditions; however, this investigation has shown that this precaution is unnecessary and in some cases can actually hinder the reaction progress. In fact, we have shown that some systems are very tolerant to the addition of water, and in some cases, especially with the mild, versatile, and commonly used cesium carbonate base, it promotes the product yield and is sometimes essential for the reaction to proceed satisfactorily.

Experimental Section

Materials and Methods. $Pd_2(dba)_3$, xantphos, anhydrous NaO^tBu, and anhydrous Cs_2CO_3 were purchased from Aldrich and used without further purification. Tri-*tert*-butylphosphine was purchased from ABCR and stored under argon in a refrigerator. Toluene was distilled from CaH_2, and dioxane was distilled from Na/benzophenone. Both solvents were stored under an argon atmosphere over molecular sieves and contained 4 and 5 ppm of H_2O after distillation. The solid reagents were stored in a desiccator over P_2O_5. PhONa was prepared according to the procedure of Hartwig et al.[3] ^1H NMR spectra were recorded at 400 MHz. A Karl Fischer coulometer was used to check the water content of the reagents and solvents in order to ensure that no residual water was present. All manipulations were carried out in air, and the reactions were carried out in flame-dried Schlenk tubes in argon atmospheres and subjected to three freeze−thaw cycles to ensure complete removal of any oxygen from the system. The ligand and metal were used in a 3/1 ratio of xantphos:$Pd_2(dba)_3$ (1.5/1 L:Pd) and a 4:1 ratio of $(^tBu)_3P$:$Pd_2(dba)_3$ (2/1 L:Pd). All compounds have been previously reported and were identified by comparison with the literature ^1H NMR data (compounds **1**,[8] **2**,[8] **3**,[2,9] **4**[10]) and by GC-MS analysis.

General Procedure for Reactions in Equations 1−4. Amide (0.5 mmol), xantphos (0.017 g, 0.03 mmol, 6 mol %), $Pd_2(dba)_3$ (0.009 g, 0.01 mmol, 2 mol %), and base (0.75 mmol) were added to a flame-dried Schlenk tube under a positive pressure of argon. The tube was capped with a rubber septum, and dioxane (1 mmol, 0.5 M), 2-bromotoluene (0.06 mL, 0.5 mmol), and water (0−35 μL, 0−400 mol %) were added via syringe. The reaction mixture was cooled in liquid nitrogen, and three freeze−thaw cycles were performed. Then, the reaction mixture was heated at 100 °C for 16 h. The crude mixture was diluted with dichloromethane and filtered through a small plug of silica, which was washed with methanol. The crude sample was then filtered again, if necessary, and GC-MS analysis was carried out.

Reaction in Equation 5. *N-tert*-Butylcarbamate (59 mg, 0.5 mmol), $^tBu_3P$ (0.010 mg, 0.05 mmol), $Pd_2(dba)_3$ (0.0014 g, 0.013 mmol, 1.25 mol %), and PhONa (0.087 g, 0.75 mmol) were added to a flame-dried Schlenk tube under positive pressure of argon. The tube was capped with a rubber spectum, and toluene (2 mL, 1 M), 2-bromotoluene (0.06 mL, 0.5 mmol), and water (0−35 μL, 0−400 mol %) were added via syringe. The rest of the procedure was completed as above, except that the reaction mixture was heated at 100 °C for 2 h.

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