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The application of organic bases in microwave-promoted Suzuki coupling reactions in water

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Abstract—Traditionally, mineral bases are used in Suzuki coupling protocols. The use of DBU or DABCO as alternative bases for the reaction is reported and the application discussed.

The Suzuki reaction (palladium-catalyzed cross-coupling of aryl halides with boronic acids) is one of the most versatile and utilized reactions for the selective construction of carbon–carbon bonds, in particular for the formation of biaryls.[1] As the biaryl motif is found in a range of pharmaceuticals, herbicides, and natural products, as well as in conducting polymers and liquid crystalline materials, development of improved conditions for the Suzuki reaction has received much recent attention. Indeed, in the last 10 years, there have been over 1000 publications on the area of aryl–aryl bond formation. We have studied the Suzuki reaction extensively and found that it is possible to perform couplings of aryl bromides in neat water using low concentration of 'ligandless' palladium as a catalyst.[2,3] Key to the success of the reaction is microwave heating and the use of water as solvent.[4,5] As well as being energy efficient, microwaves can also enhance the rate of reactions, and in many cases improve product yields. Water proves to be an excellent solvent for microwave-promoted synthesis.[6] Using a sealed vessel it is possible to heat water to well above its boiling point. Water also offers practical advantages over organic solvents.

Scale-up of microwave-promoted reactions has been an issue of considerable interest over the last few years. Although chemists are discovering that microwave chemistry has the advantage of greatly reducing reaction times and improving product yields when run on small scales, translation of methodologies to larger scale apparatus can be problematic. There are two possible scale-up options: the first is to use a continuous flow microwave cell,[7] a technology found to be successful for a number of different reactions[8–10] including Suzuki couplings.[11–14] The other option is to use a batch-type process. This could either involve using one large vessel or parallel batch reactors. For a microwave operating at the typical frequency of 2.45 GHz, microwave penetration is generally in the order of centimeter, depending on the dielectric properties of the reaction medium. This therefore limits the size of a large batch reactor. Success has been found using one large batch reactor,[15–17] and also using the parallel approach.[18,19] In our attempts to scale up our Suzuki coupling chemistry, we have focused our attention thus far on a microwave system that combines the advantages of a batch reactor with those of a continuous flow reactor.[20,21] It is a single-mode apparatus with one 80 mL vessel in the microwave cavity. The reaction mixture is passed into and out of the vessel by use of a peristaltic pump, which functions, as well as reaction's conditions are controlled through a computer. This gives a high degree of automation to the process. The reaction mixture can be introduced into the microwave vessel from two separate feed lines. After the reaction is complete, the reaction vessel can be vented to release excess pressure, and then the contents of the reactor can be pumped into a collection vessel. Since only one reaction vessel is used, the time taken to cool the reaction mixture down to room temperature at the end of the run is significantly shorter than that reported for the parallel batch reactors using multimode apparatus. If necessary, the reactor can then be cleaned with solvent before the next run.

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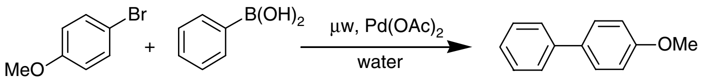
When performing Suzuki reactions in water using either a flow-through set-up or the hybrid stop-flow apparatus, the solubility of the organic reagents can be problematic. This can be alleviated by using a 1:1 ethanol/water mixture as the solvent. However, this in turn leads to solubility issues pertaining to the mineral base used in the reaction. To overcome this problem, we were keen to determine whether liquid organic bases could be used in aqueous-phase Suzuki reactions thus giving us a wholly homogeneous reaction mixture. Our results are presented here.

Traditionally, the Suzuki reaction is performed using a mineral base such as an alkali-metal carbonate. Over the last year there have been a number of reports of the use of amines as ligands in conjunction with simple palladium salts such as $Pd(OAc)_2$ in Suzuki reactions, but these still require the use of an additional mineral base.[22] To probe these reported conditions more thoroughly, and to also solve our problem of solubility, we screened three simple amines as bases for the Suzuki coupling of 4-bromoanisole and phenylboronic acid in the *absence* of an additional mineral base (Table 1). Working on a 1 mmol scale, using a 1:1 water/ethanol mixture as solvent and 0.4 mol % $Pd(OAc)_2$ as catalyst precursor, we screened DBU, DABCO, and 1,1,3,3-tetramethylguanidine (TMG), running the reactions for 10 min at 150 °C using microwave heating. Both DBU and TMG worked well as bases for the reaction (Table 1, entries 1 and 2) but DABCO gave a significantly lower yield (Table 1, entry 3). Working with DBU, a screen of base concentration showed that a 1:1 ratio of base to aryl halide was optimal, and that a considerable decrease in yield was obtained if less base was used (Table 1, entries 4 and 5). A screen of reaction temperature showed that below 100 °C, little product was obtained (Table 1, entries 6–8) and above 150 °C product yields dropped (Table 1, entry 9), this being attributed to competitive decomposition of starting materials. Reduction of the palladium loading below 0.4 mol % resulted in a significant decrease in product yield; hence our ultra-low catalyst loading methodology was not amenable to the change from mineral to organic base. When screening other solvents in the coupling protocol, good results were only acquired when aqueous media were utilized (Table 1, entries 10–12). Expectantly, we also found that lower yield of product was obtained when using conventional heating compared to microwave heating (Table 1, entry 13). Thus, our optimal conditions were 1 equiv aryl halide, 1 equiv phenylboronic acid, 1 equiv DBU, 1:1 water/ethanol as solvent, 0.4 mol % $Pd(OAc)_2$, heating to 150 °C and holding at this temperature for 10 min using microwave heating.

With our optimal conditions in hand, we decided to explore the substrate scope of the reaction by performing the couplings of a range of aryl halides with phenylboronic acid. Our results are shown in Table 1.[23] Good yields were obtained with most of the substrates screened. However, the use of sterically hindered aryl halides was not satisfactory as low yields were acquired (Table 2, entries 8 and 9). In the case of 4-bromophenol, significant decomposition was observed, which showed some level of functional group intolerance when DBU was used as a base in the reaction.[24] Aryl bromide and iodide substrates gave comparable product yields while the corresponding chlorides gave appreciably lower yields.

Having shown the applicability of the amine base methodology to small scale couplings, we next performed the reaction using the hybrid stop-flow apparatus, working on a 20 mmol scale per batch. Using the same reaction conditions, we were able to scale up the reaction as

Table 1. Study of reaction parameters for the microwave-promoted Suzuki coupling of 4-bromoanisole and phenylboronic acid in water using $Pd(OAc)_2$[a]



Entry	Reaction conditions[b,c]	Yield (%)
1	0.4 mol % $Pd(OAc)_2$, 1 mmol DBU, H_2O/EtOH, 150 °C	99
2	0.4 mol % $Pd(OAc)_2$, **1 mmol TMG**, H_2O/EtOH, 150 °C	97
3	0.4 mol % $Pd(OAc)_2$, **1 mmol DABCO**, H_2O/EtOH, 150 °C	59
4	0.4 mol % $Pd(OAc)_2$, **0.5 mmol DBU**, H_2O/EtOH, 150 °C	45
5	0.4 mol % $Pd(OAc)_2$, **0.1 mmol DBU**, H_2O/EtOH, 150 °C	13
6	0.4 mol % $Pd(OAc)_2$, 1 mmol DBU, H_2O/EtOH, **50 °C**	1
7	0.4 mol % $Pd(OAc)_2$, 1 mmol DBU, H_2O/EtOH, **80 °C**	20
8	0.4 mol % $Pd(OAc)_2$, 1 mmol DBU, H_2O/EtOH, **100 °C**	74
9	0.4 mol % $Pd(OAc)_2$, 1 mmol DBU, H_2O/EtOH, **180 °C**	56
10	0.4 mol % $Pd(OAc)_2$, 1 mmol DBU, **acetone**, 150 °C	0
11	0.4 mol % $Pd(OAc)_2$, 1 mmol DBU, **DMF**, 150 °C	0
12	0.4 mol % $Pd(OAc)_2$, 1 mmol DBU, **EtOAc**, 150 °C	0
13[d]	0.4 mol % $Pd(OAc)_2$, 1 mmol DBU, H_2O/EtOH, 150 °C **conventional heating**	79

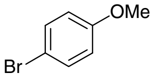
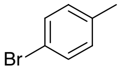
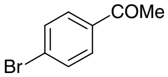
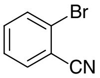
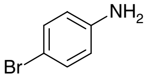
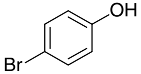
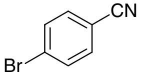
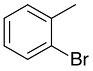
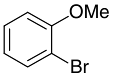
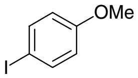
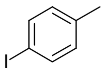
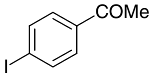
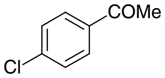
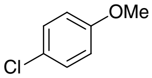
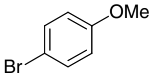
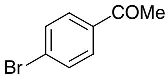
[a] 1 mmol of 4-bromoanisole, 1 mmol of $PhB(OH)_2$, 2 mL solvent. Microwave irradiation: initial power of 50 W, temperature ramped to that stated and held there for 10 min.

[b] Conditions changed from entry 1 are highlighted in bold.

[c] Using 1:1 ratio of water/ethanol in entries 1–9.

[d] Reaction mixture placed into a pre-heated oil-bath and held there for 13 min.

Table 2. Coupling of aryl halides with phenylboronic acid[a]

Entry	Aryl halide	Yield (%)
1		99
2		81
3		94
4		83
5		74
6		24
7		79
8		63
9		8
10		88
11		75
12		85
13		58
14		14
15		92
16		92

[a] Reactions were run in a sealed tube, using 1.0 mmol aryl halide, 1.0 mmol phenylboronic acid, 0.4 mol % $Pd(OAc)_2$, 1.0 mmol DBU, 1.0 mL ethanol, and 1.0 mL water. An initial microwave irradiation of 50 W was used, the temperature being ramped from rt to 150 °C where it was then held for 10 min.

equivalent results were obtained (Table 2, entries 15 and 16).

In summary, we have shown that mineral bases are not essential to the success of the $Pd(OAc)_2$ catalyzed Suzuki coupling of aryl halides and phenylboronic acid when using water as a solvent and 1 equiv of DBU or TMG as a base. As well as adding to the literature in an area of current interest, this new protocol is operationally simple for application to flow-through or stop-flow scale-up using microwave heating.

Acknowledgements

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23. *Typical procedure for the coupling of aryl halides with phenylboronic acid*: In a 10 mL glass tube was placed 4-bromoanisole (187 mg, 0.125 mL, 1.0 mmol), phenylboronic acid (122 mg, 1.0 mmol), DBU (152 mg, 0.149 mL, 1.0 mmol), and $Pd(OAc)_2$ (1 mg, 0.4 mol %). After adding water (1 mL) and ethanol (1 mL), the vessel was sealed with a septum and placed into the microwave cavity (CEM Discover). Initial microwave irradiation of 50 W was used, the temperature being ramped from rt to the desired temperature of 150 °C. Once this was reached, the reaction mixture was held at this temperature for 10 min. The reaction mixture was stirred continuously during the reaction. After allowing the mixture to cool to room temperature, the reaction vessel was opened and the contents poured into a separating funnel. Water (30 mL) and ethyl acetate (30 mL) were added, and the organic material extracted and removed. After further extraction of the aqueous layer with ethyl acetate, combining the organic washings, and drying them over $MgSO_4$, the ethyl acetate was removed in vacuo leaving the crude product. That product was then isolated and characterized by comparison of NMR data with that in the literature.
24. Interestingly, no reference is made to the reactivity of phenolic substrates in the literature reports of $Pd(OAc)_2$/amine catalyst systems used in conjunction with mineral bases.