Suzuki-Miyaura cross-coupling reactions using a small amount of dioxane

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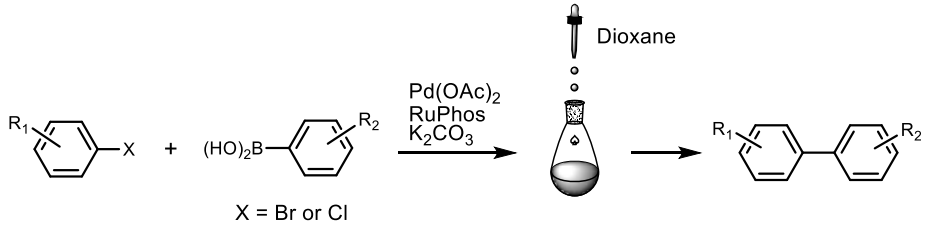
Suzuki-Miyaura cross-coupling are useful reactions in the synthesis of pharmaceuticals and other products. On the other hand, solvent-free reactions are environmentally friendly synthetic methods, but when the substrates are solids, the reactions hardly proceed. In such cases, the method by the addition of a small amount of solvents is known. We found that Suzuki-Miyaura cross-coupling reactions were largely accelerated by the addition of a small amount of the solvent.

First, the reactions of solid bromides with boronic acids were studied under nitrogen. The highest yields of biaryls were obtained when $Pd(OAc)_2$, RuPhos, K_2CO_3, and dioxane were used. The reactions were largely accelerated by the addition of a small amount of dioxane, whereas the reaction hardly proceeded under solvent-free conditions. Under normal conditions, in the presence of a large amount of dioxane, the yields were considerably lower. The reactions of liquid bromides also proceeded under solvent-free conditions, but stirring was difficult because of the high viscosity of the reaction mixture. On the other hand, biaryls were formed in good yields under our conditions. The products were obtained in good yields for various bromides and chlorides. Biaryls were obtained in high yields for base-sensitive esters.

Interestingly, the reactions of aryl chlorides were faster than those of bromides. The reaction of 4-$MeOC_6H_4Cl$ completed within 1 h at room temperature using 1 mol% $Pd(OAc)_2$ under our conditions. On the other hand, it required 21 h using 1.5 mol% $Pd(OAc)_2$ under Buchwald's conditions.[1)]

Thus, various aryl bromides and chlorides reacted with boronic acids at room temperature in the presence of a small amount of dioxane to give the corresponding biarys in good yields. 0.2-1.0 mol% of $Pd(OAc)_2$ was sufficient for the reactions of most of aryl chlorides. This procedure is especially useful for the reactions of aryl chlorides.



1) J. P. Wolfe and S. L. Buchwald, *Angew. Chem. Int. Ed.* **38** (1999) 2413-2416.