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Solid-phase Suzuki cross-coupling reactions using a phosphine ligand based on a phospha-adamantane framework

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Abstract—The use of a catalyst system based on $Pd_2dba_3{\cdot}CHCl_3$ and 1,3,5,7-tetramethyl-2,4,8-trioxa-6-phenyl-6-phospha-adamantane allows for Suzuki coupling aryl halides with an array of boronic acids on a solid-phase platform. The reactions can be carried out at room temperature with low palladium loadings in high yields.

Reactions involving organopalladium cross-coupling have become indispensable methods for carbon–carbon bond formation.[1] For example, the Suzuki–Miyaura reaction[2] (the Pd-mediated coupling of an aryl or alkenyl halide with an organoboron reagent) has been widely employed in organic syntheses and its use well documented in the chemical literature. Recently, the scope of applicability of palladium-catalyzed cross-coupling chemistry has been expanded as a result of the development of synthetic protocols employing sterically demanding, electron-rich phosphine ligands.[3] Utilization of catalytic systems incorporating these bulky phosphines has facilitated couplings involving even the least reactive coupling partners in the Suzuki,[4] Stille,[5] Sonogashira,[6] aryl amination[7] and ketone arylation[8] reactions. For example, our work involving the development of new phosphine ligands based on a phospha-adamantane framework has allowed for effective Suzuki cross-coupling of a variety of aryl halides and boronic acids under mild conditions.[9]

Solid-phase synthetic methodologies, meanwhile, have become well established in the drug discovery process allowing for the preparation of arrays of compounds and combinatorial libraries for the discovery and optimization of biologically active substances. An immense variety of synthetic transformations can now be achieved on polymer support and, not surprisingly, a number of examples exist describing the utilization of the Suzuki reaction on a solid-phase platform.[10] A range of systems has been prepared using the reaction as a key step.[11] Many of these cases, however, describe reactions employing PPh_3 as the ligand and often require elevated temperatures to achieve coupling of the less-reactive coupling partners. In addition, large amounts of Pd catalyst (as much as 10–20 mol% in some cases) are required to achieve reasonable yields. The present paper describes a general Suzuki reaction methodology for solid phase that permits the coupling of aryl halides with an array of boronic acids at room temperature with low palladium loadings by taking advantage of a catalyst system incorporating 1,3,5,7-tetramethyl-2,4,8-trioxa-6-phenyl-6-phospha-adamantane (PA-Ph, Fig. 1) as a ligand.[12]

p-Iodo-, *p*-bromo or *p*-chloro-benzoic acid was linked to commercially available tritylchloride–polystyrene resin

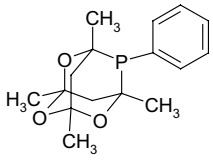

Figure 1.

Keywords: Solid-phase synthesis; Suzuki reaction; Organopalladium chemistry.

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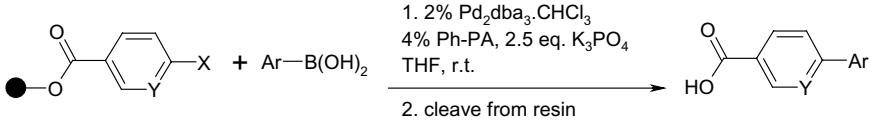
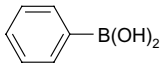
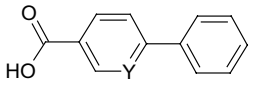
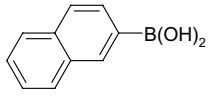
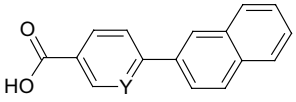
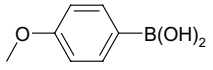
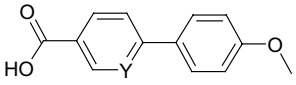
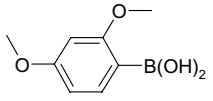
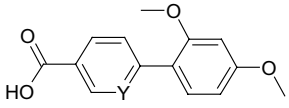
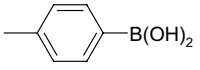
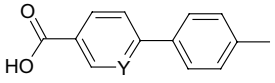
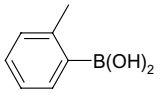
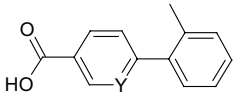
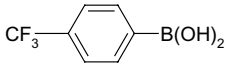
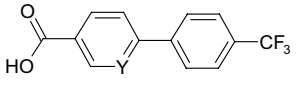
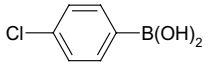
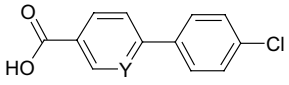
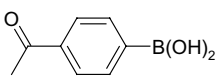
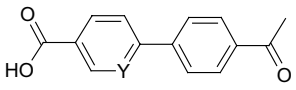
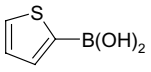
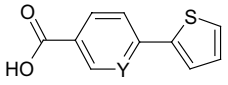
to provide the solid-supported aryl halides required.[13] The loading was determined to be roughly 1.00 mmol/g based on weight change. Given the established rates of oxidation addition of the aryl halides to palladium, attention was first directed to the Suzuki couplings involving the aryl bromide resin as this represented the intermediate case with respect to coupling difficulty. Initial screening revealed that $Pd_2dba_3{\cdot}CHCl_3$ was the best palladium source for the reaction and that optimum conditions were achieved when using metal to phosphaadamantane ligand in a 1:1 ratio. While the reactions proceed using various bases (CsF, $CsCO_3$, KF) or solvents (toluene, toluene/THF mixtures), the best results were obtained using potassium phosphate as the base and THF as the solvent. Furthermore, in the absence of the PA-Ph ligand, couplings involving the aryl bromide resin and phenyl boronic acid resulted in very low yields (generally less than 5%).

With optimum conditions in hand,[14] the scope of the developed solid-phase Suzuki coupling was determined via the screening of a variety of boronic acids. The couplings involving the aryl bromide resin were found to proceed smoothly using 2% $Pd_2dba_3{\cdot}CHCl_3$ and 4% PA-Ph at room temperature over a period of 15 h. The benzoate was cleaved from the polymer support using 10% TFA in dichloromethane and provided the products shown in Table 1.[15] The purity of the cleaved biaryls was confirmed by HPLC and ^1H NMR. Percent conversion was then calculated by comparing the relative amounts of uncoupled benzoic acid with biaryl product. As seen in Table 1, a diverse array of boronic acids could be coupled to the resin using the described

Table 1.



Entry	Boronic acid	Biaryl product	% Conversions	
			Y = CH, X = Br	Y = N, X = Cl
1			96	91
2			92	90
3			100	89
4			100	93
5			91	96
6			42	83
7			91	56
8			84	78
9			58	62
10			76	68

protocol. Most interesting are those involving the deactivated systems such as entries **7**–**10** or sterically demanding substrates such as **4** and **6**. In all cases, the boronic acids were efficiently coupled in high yields. It is worth pointing out that while the reactions were allowed to take place over 15 h, in some cases coupling could be achieved in less time. For example, cleavage of entry **3** after 2 h afforded an 85% yield of the biaryl benzoate.

As previously described by Guiles et al.,[16] polymer bound *p*-iodobenzoic acid can be coupled in high yields at room temperature using 5–10 mol% of a suitable palladium catalyst (such as Pd_2dba_3) with no additional ligand. Repeating these reactions with our optimized conditions, we found that the addition PA-Ph resulted in no appreciable gain in either yield (quantitative with each boronic acid listed in Table 1) or the rate of Suzuki coupling. It should be noted, however, that the immobilized aryl iodide used in the both our study and that of Guiles represents an activated Suzuki coupling partner. While the addition of the PA-Ph ligand had a minor influence in this case, its effect is likely to be more pronounced in systems wherein the immobilized aryl iodide contains electron donating groups. Work to confirm this is ongoing in our laboratory.

Attempts to couple the analogous aryl chloride resin resulted in low yields even at elevated temperatures. When 6-chloronicotinic acid was used in place of *p*-chloro-benzoic acid, however, the resultant polystyrene resin readily underwent the Suzuki reaction at room temperature in the presence of 2% $Pd_2dba_3{\cdot}CHCl_3$ and 4% PA-Ph in excellent yields. The results appear in Table 1.

The Suzuki protocol described above is readily applicable to parallel synthesis, requiring less catalyst and facilitating couplings at lower temperatures than previously published procedures. Applications involving the palladium/PA-Ph catalyst system in other organopalladium cross-coupling reactions on a solid-phase platform are currently being developed.

Acknowledgements

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12. Available from Cytec Canada, PO Box 240, Niagara Falls, Ontario, Canada L2E 6T4.
13. General procedure for resin loading: Tritylchloride-polystyrene resin (2.00 g, 2.88 mmol, available from PepChem, Reutlingen, Germany, loading 1.44 mmol/g) was treated with the appropriate *p*-halobenzoic acid (1.5 equiv), diisopropylethyl amine (3 equiv, 1.48 mL) in dry CH_2Cl_2 (20 mL). Dry DMF (0.5 mL) was added to fully dissolve the starting material. Reactions were carried out at room temperature over 18 h. The resin was then washed successively with MeOH (20 mL), DMF (2×20 mL), MeOH (2×20 mL), CH_2Cl_2 (2×20 mL), and *tert*-butylmethyl ether (20 mL). The resin was dried over-night under high vacuum until a constant weight was obtained. Loadings were determined by weight increase.
14. General procedure for the Suzuki coupling: The resin loaded with the *p*-halobenzoic acid (0.19 mmol, based on a loading of 0.94 mmol/g), K_3PO_4 (100 mg, 0.47 mmol), boronic acid (0.75 mmol), phenyl-phospha-adamantane (2.2 mg, 0.004 mmol), and $Pd_2dba_3{\cdot}CHCl_3$ (3.9 mg, 0.002 mmol) were placed in the reaction vessel and flushed with argon for 10 min. Tetrahydrofuran (7 mL) and distilled water (150 μL) were added and reaction vessel agitated at room temperature for 15 h. The resin was then washed successively with MeOH (7 mL), DMF (7 mL), 7 mL of a quench solution (containing 50 mg of sodiumdiethylthiocarbamate, 50 mL of *N*-ethyldiisopropylamine and 10 mL of DMF), MeOH (7 mL) and CH_2Cl_2 (2×7 mL) before being dried under vacuum for 18 h at elevated temperature.
15. General procedure for the cleavage of the product from the resin: Cleavage of the product from the resin was achieved by treatment with the resin with a solution of freshly prepared 10% TFA in dry CH_2Cl_2 for 1.5 h at room temperature. The spent resin was filtered off and the solvent evaporated under reduced pressure. The pure products were obtained after heating under vacuum for 12 h to remove residual Hunig's base and DMF. Compound identity and purity was determined by ^1H NMR and HPLC.
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