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Biaryl Synthesis via Suzuki Coupling on a Solid Support

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Abstract: Aryl boronic acids undergo a facile and efficient palladium catalyzed cross-coupling reaction with aryl bromides and iodides that are bound to a Merrifield resin. Simple transesterification releases the biaryl products from the solid support in excellent purity and yield.

The desire to attain molecular diversity, as it relates to the generation of lead compounds for medicinal chemistry, has increased greatly over the past several years.[1] The optimization of the solid phase synthesis of peptides, coupled with the evolution of combinatorial synthesis, has resulted in the preparation of peptide libraries containing millions of unique oligomers.[2] However, due to problems associated with their metabolic instability and poor oral bioavailability, these peptides are seldom realistic drug candidates. We have endeavoured to explore the possiblity that synthetically useful reactions that are typically carried out in solution can be extended and applied to the heterogeneous conditions encountered when one uses a substrate bound to a solid support. In this way, the potential for generating molecular diversity in a non-peptide environment would be greatly increased. Indeed, various reports in the last two years have described the successful preparation of ureas,[3] oligosaccharides,[4] benzodiazepines,[5,6] hydantoins,[6] γ-butyrolactones[7] and β-mercapto ketones[8] via polymer-supported synthesis. Very recently, catalytic asymmetric hydrogenations,[9] [3+2] cycloadditions[10] and Stille reactions[11] with polymer bound substrates have been described. Since the biaryl subunit is an important pharmacophore that is present in a variety of biologically active compounds,[12] we wished to determine whether the synthesis of this moiety would be amenable to such a solid phase synthesis strategy. In this communication, we report that the well-characterized Suzuki coupling reaction[13] of aryl boronic acids and aryl halides to form biaryls is readily accomplished using polymer bound aryl halides.

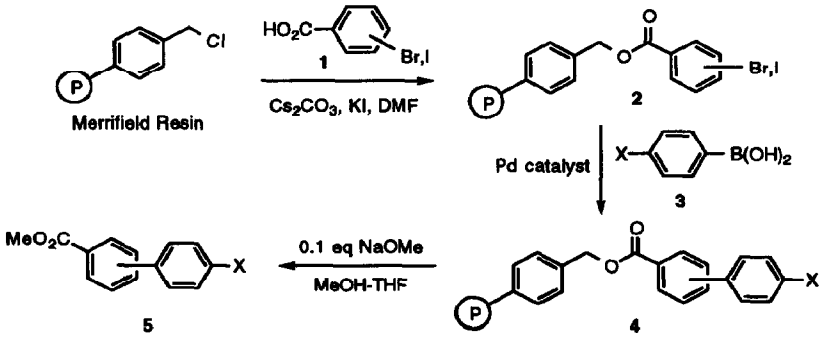
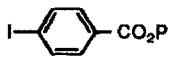
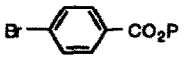
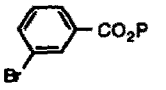
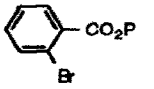
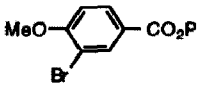
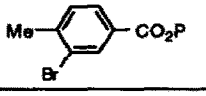


Table 1. Biaryl Synthesis via Suzuki Coupling of Aryl Boronic Acids to Polymer Bound Aryl Halides

Entry	Aryl Halide 2[a]	Boronic Acid 3[b]	Palladium Catalyst[c]	Biaryl Ester 5	Yield (%)[d]
1	 **2a**	**3a** X = OMe	$Pd(Ph_3P)_4$	**5a**	>95
2		**3a** X = OMe	$Pd(Ph_3P)_2Cl_2$	**5a**	>95
3		**3a** X = OMe	$Pd(Ph_3P)_2Br_2$	**5a**	>95
4		**3a** X = OMe	$PdBn(Ph_3P)_2Cl$	**5a**	>95
5		**3a** X = OMe	$Pd_2(C_3H_5)_2Cl_2/Ph_3P$	**5a**	>95
6		**3a** X = OMe	$Pd_2(C_3H_5)_2Cl_2$	**5a**	18 (82)
7	 **2b**	**3a** X = OMe	$Pd(Ph_3P)_4$	**5a**[e]	>95
8		**3b** X = H	$Pd(Ph_3P)_4$	**5b**	95
9		**3c** X = Me	$Pd(Ph_3P)_4$	**5c**[e]	95
10		**3d** X = NO_2	$Pd(Ph_3P)_4$	**5d**	95
11		**3e** X = F	$Pd(Ph_3P)_4$	**5e**	91
12	 **2c**	**3b** X = H	$Pd(Ph_3P)_4$	**5f**	90
13	 **2d**	**3b** X = H	$Pd(Ph_3P)_4$	**5g**[e]	>95
14	 **2e**	**3b** X = H	$Pd(Ph_3P)_4$	**5h**[e]	>95
15	 **2f**	**3b** X = H	$Pd(Ph_3P)_4$	**5i**[e]	>95

[a] P = Merrifield resin. [b] Boronic acids are commerically available. [c] 5 mol% catalyst. [d] Isolated yield (based upon loading of aryl halide onto resin) after cleavage. Unless stated in brackets, <1% starting aryl halide was observed by ^1H NMR and/or HPLC analysis. [e] 0.2 eq NaOMe used in cleavage.

The requisite benzoic acid **1** was tethered to a commercially available Merrifield resin[14] (3 eq Cs_2CO_3, 0.5 eq KI, 1.5 eq acid per Cl residue, DMF, 80°C, O/N), providing polymer **2**. A variety of resins were produced in this manner with substrate loading of approximately 1 meq/g in each case. We initially investigated the effect of the palladium catalyst on the cross-coupling reaction of halide **2a** and boronic acid **3a** utilizing standard Suzuki reaction conditions[13] (3-5 mol% catalyst, DME, 2M aq Na_2CO_3, reflux overnight) (Table 1, entries 1-6). Cleavage of the product from the resin was readily achieved by transesterification (0.1-0.2 eq NaOMe, MeOH-THF (1:4), reflux overnight), providing the biaryl ester **5a**. All of the catalysts that we tested (with the exception of $Pd_2(allyl)_2Cl_2$ in the absence of phosphine (entry 6)) appeared to be equally effective in the cross-coupling reaction. In each case, **5a** of >90% purity was obtained in >95% yield and there was no methyl 4-iodobenzoate (<1%) observed upon ^1H NMR and HPLC analysis of the crude filtrate. For all of the subsequent reactions, $Pd(Ph_3P)_4$ was employed as the catalyst.

Since aryl bromides are typically more readily available than the corresponding aryl iodides, but are also less reactive with respect to cross coupling,[13] we felt that it was an appropriate test of the method to use aryl bromides in our subsequent studies. We investigated the scope of the Suzuki reaction in terms of the substrate composition by varying both the polymer bound aryl bromide and the boronic acid (Table 1, entries 7-15).

As can be seen from the Table, the Suzuki reaction for the preparation of biaryl esters **5** via this strategy is widely applicable, both in terms of aryl halide and boronic acid coupling partners. Suitable aryl bromides include those that are ortho-, meta-, para- and poly-substituted, while a wide range of substituted (from electron deficient to electron rich) aryl boronic acids are viable substrates. The biaryl ester products **5** are obtained in high yield without significant contamination from byproducts or starting halide. Moreover, the procedure is carried out on readily available and inexpensive Merrifield resin. With these results in hand, studies directed toward building a combinatorial library that incorporate the biphenyl moiety are now possible.

A typical procedure (entry 8) for the cross-coupling is as follows: To a degassed suspension of the resin **2b** (500 mg; loading 1.0 meq/g resin) in DME (4 mL) was added $Pd(Ph_3P)_4$ (29 mg, 0.05 eq). After stirring for 5 min., phenyl boronic acid (**3b**; 122 mg, 2 eq) and 2M Na_2CO_3 (0.63 mL, 2.5 eq) were added and the mixture was refluxed overnight under an argon atmosphere. The mixture was cooled to room temperature, diluted with 25% NH_4OAc (10 mL), stirred for 5 min., and filtered on a fritted reservoir. The resin was washed successively with DME:H_2O (1:1, 5 mL), H_2O (10 mL), 0.2N HCl (10 mL), H_2O (10 mL), DME (10 mL), EtOAc (10 mL), EtOAc:MeOH (1:1, 10 mL) and MeOH (10 mL) and then dried under high vacuum. The product was cleaved from the resin by refluxing a mixture of polymer **4b** (490 mg) in MeOH-THF (1:4, 5 mL) in the presence of NaOMe (0.05 mL of a 1.0M solution in MeOH, 0.1 eq) overnight. The resin was removed by filtration and was washed with MeOH:THF (1:1, 10 mL), THF (10 mL) and MeOH (10 mL). The filtrate and washings were concentrated to provide the biaryl ester **5b** as a white solid (100 mg) in 95% yield (based on loading of the aryl halide to the resin). Analysis of the product by ^1H NMR and HPLC (see Figure 1) indicated that the product had a purity >90% and was contaminated by <1% starting material.

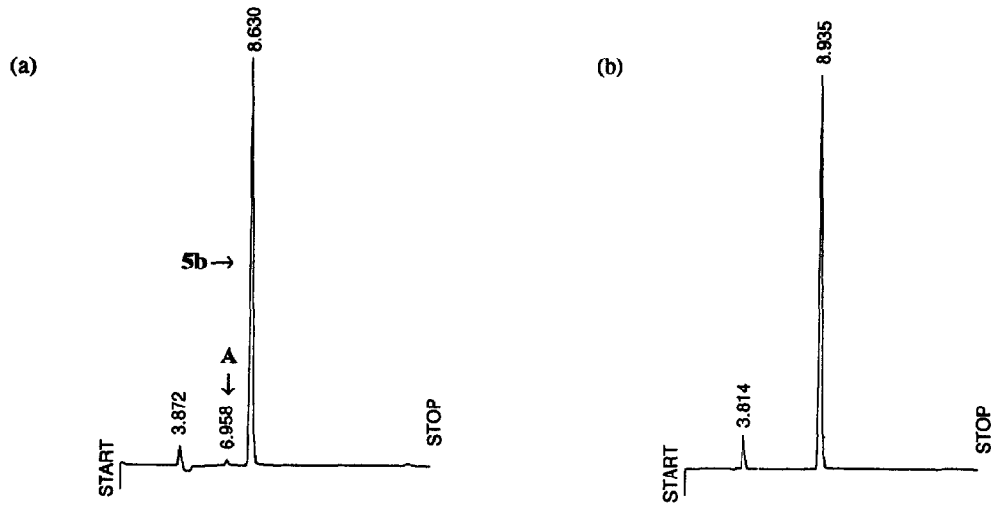


Figure 1. HPLC traces of: (a) a mixture of authentic methyl 4-bromobenzoate **A** (1 mol %) and authentic **5b**; (b) crude filtrate upon cleavage of **5b** from resin (from entry 8).

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14. Merrifield resin purchased from Bio-Rad Laboratories, Inc. as Bio-Beads S-X1 Beads (Catalog # 152-2150), copolymer of chloromethylpolystyrene cross-linked with 1% divinyl benzene, 200-400 mesh, 1.2 mmol of Cl/g resin.

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