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A New Approach to the Solid-Phase Suzuki Coupling Reaction.

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Abstract: Treatment of polymer-bound aryl halides with pinacol ester of diboron under palladium (0) catalysis gave the corresponding polymer-bound boronates. The Suzuki coupling reaction was then carried out using a variety of aryl halides. Cleavage from the solid support delivered the expected products in usually good yields and high purity.

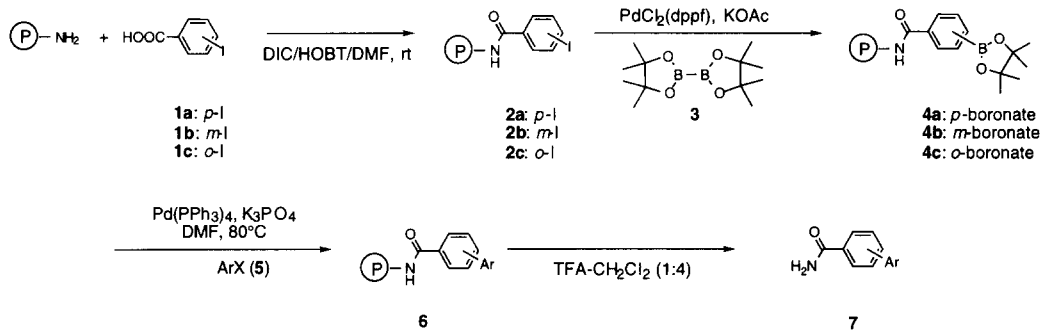
The past few years have witnessed a major development of the field of solid-phase chemistry. The needs and prospects to obtain large libraries of compounds for lead generation have induced most pharmaceutical companies to become involved in this new approach. Thus combinatorial chemistry and parallel synthesis have become two additional tools at the disposal of the medicinal chemist.[1] In that context it is not surprising that the palladium-mediated chemistry has attracted the attention of many research groups. In particular the Suzuki, Stille and Heck reactions have been adapted to solid-phase, due to their power to achieve high-yielding carbon-carbon bond formation and the mild conditions they require to attain completion.[1,2] The Suzuki coupling reaction has been the subject of several reports to date, all of which based on the reaction between a polymer-bound aryl halide and a free (i.e. in solution) boronic acid, typically in excess.[3]. However one of the limitations of conducting the reaction in such a way is represented by the rather limited number of commercially available boronic acids. We describe in this note a route to circumvent this difficulty by transforming *in situ* a polymer-bound aryl halide into the corresponding tetramethylethylene glycol boronate, and using the latter to carry out the Suzuki coupling reaction with another aryl halide.

Biaryl compounds were chosen to carry out the synthetic studies due to their interest as bioactive molecules. Numerous important natural products displaying both antitumor and antiviral activity, as well as unatural products possessing angiotensin II antagonistic or tubulin binding properties, and estrogenic activity, for example, incorporate this structural motif.[4]

Early on we looked for a way to conduct the *reversed* Suzuki reaction, thus reacting a polymer-bound aryl boronate or boronic acid and a free aryl halide. A similar approach has been successfully used by Ellman in the context of the Stille reaction; however the tin derivative had to be prepared using organometallic solution chemistry before attaching it to the resin.[5,6] We envisioned that developing milder conditions for solid-phase boronate synthesis which could then be applied to a whole set of reaction vessels would greatly widen the scope of the Suzuki coupling reaction in the context of generating libraries of compounds. In addition, such an approach would indeed eliminate the need of separately preparing the boronic acids (when required), and would instead allow the use of the much more widely available bromo or iodoaryl compounds. A quick search into a commercial database indicated the availablity of more than five thousands of these haloderivatives *versus* two hundreds, often much more expensive, boronic acids and esters.[7]

Efforts to prepare the boronic acid on solid-phase using classical methodology was met with little success.[8] On the other hand, application of Miyaura's conditions[9] (pinacol ester of diboron **3** (2 eq),

$PdCl_2$(dppf) (0.03 eq), KOAc (3 eq)) in DMF at 80°C for 20 hrs to a model polymer-bound *p*-iodobenzamide **2a**[10] led to a solid-phase boronate **4a** (Scheme).[11] A search for the optimal Suzuki coupling conditions was then undertaken by varying the reaction parameters (i.e. catalyst, base, solvent, temperature and heating time). This led to the identification of the $Pd(PPh_3)_4$ (0.02 eq)/K_3PO_4 (5 eq)/DMF system at 80°C as the most efficient system.[12] Application of those reaction conditions to **4a** and iodobenzene cleanly produced *p*-phenyl benzamide after cleavage with trifluoroacetic acid.



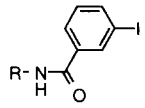
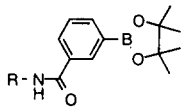
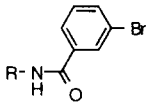
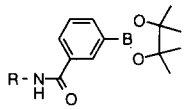
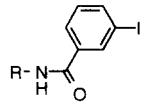
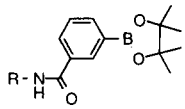
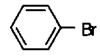
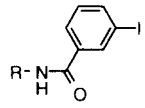
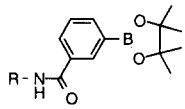
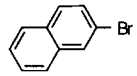
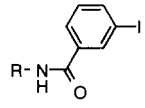
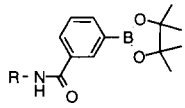
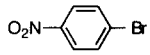
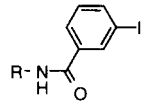
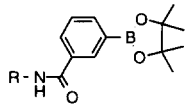
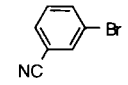
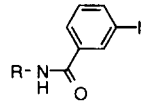
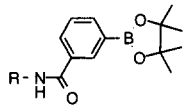
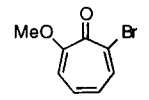
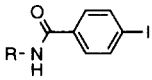
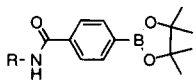
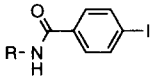
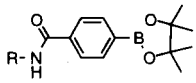
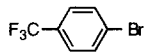
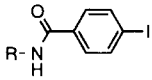
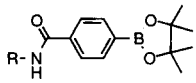
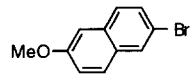
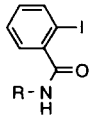
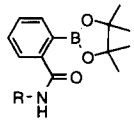
SCHEME

The generality of the reaction was next demonstrated by tethering *ortho*, *meta* and *para* iodobenzoic acids as well as *meta* bromobenzoic acid (**1a** to **1d**) to the resin and transforming these into the corresponding polymer-bound boronates **4**. The transformation of the polymer-bound *p*-iodobenzoic acid (**2a**), *m*-iodobenzoic acid (**2b**) and *m*-bromobenzoic acid (**2d**) went smoothly using the hereabove mentioned conditions. The reaction was found to be slower in the case of *o*-iodobenzoic acid (**2c**), and required longer reaction times for completion.[13] The subsequent Suzuki coupling reaction was then conducted using the conditions described in the previous paragraph, and with aryl iodides and bromides incorporating a variety of functional groups. The table shows that the strategy is widely applicable to the preparation of diversely functionalized biaryl derivatives **7**. Isolated yields are in most cases good to excellent. The lower yields observed in the case of products **7c** and **7h** (72 and 66%, respectively) are due to technical problems such as poor solubility of the compounds in most solvents[14], and, as in the case of compound **7i**, the sensitivity of the palladium-mediated reactions to steric factors.[13,15] The crude compounds from cleavage were usually subjected to a rapid chromatography (silica gel) to remove any palladium contaminant and were analyzed by ^{1}H-NMR spectroscopy, mass spectrometry and RP-HPLC. All compounds were found to possess a purity >98%.

A typical procedure is as follows: The pinacol ester of diboron **3** (102 mg, 0.4 mmol), potassium acetate (66 mg, 0.6 mmol) and $PdCl_2$(dppf) (1.6 mg, 0.018 mmol) were added sequentially to a degassed suspension of polymer **2b** (200 mg, 0.2 mmol) in anhyrous DMF (20 mL).[10] The resultant mixture was heated at 80°C under argon for 16 hours, cooled down to room temperature and filtered. The resin was washed with DMF (6x3 mL) and CH_2Cl_2 (6x3 mL), dried under vacuum and suspended in anhydrous DMF (10 mL). 3-Cyanophenyl bromide (182 mg, 1 mmol), $Pd[P(C_6H_5)_3]_4$ (4.6 mg, 0,004 mmol) and a 2M aquous solution of K_3PO_4 (0.5 mL) were then added. The mixture was heated at 80°C under argon for 20 hours and cooled to room temperature. The resin was filtered and washed with DMF (6x3 mL) and CH_2Cl_2 (6x3 mL). Cleavage of the compound was carried out in a 1/4 mixture of trifluoroacetic acid and methylene chloride (10 mL, 10 minutes). This was repeated twice and the resin was then filtered and sequentially washed with CH_2Cl_2 (6x3 mL) and MeOH (6x3 mL). Evaporation of the filtrate gave the crude product **7d** as a creamy solid. Chromatography on silica gel using ethyl acetate/cyclohexane (1:1) furnished **7d** as a colorless solid (40 mg, 90% yield).

To the best of our knowledge, these are the first examples of polymer-bound boronates in the context of solid phase synthesis. By eliminating the need for starting boronic acids, these results are likely to have an impact on automated preparation of compounds incorporating a biaryl motif, and on the diversity of the libraries thereby generated.

Table. Sequential transformation of haloamides 2 into polymer-bound boronates 4 and biaryl derivatives 7.

Starting haloamide **2** [a]	Boronate **4** [a]	Heating time (hrs; **2** to **4**)	Yield (%)[b]	**5**	Heating time (hrs; **4** to **6**)	Product	Yield (%)[c]
		20	95		2.5	**7a**	95
		20	92		2.5	**7a**	82
		20	92		20	**7a**	80
		20	93		20	**7b**	82
		20	92		20	**7c**	72
		20	95		20	**7d**	90
		20	95		20	**7e**	95
		20	94		2.5	**7f**	92
		20	94		20	**7g**	87
		20	94		20	**7h**	66
		20 40	50[d] 71[d]		2.5 20	**7i** **7i**	26[e] 48[e]

[a]: R=Rink amide; [b]: see note 11; [c]: isolated yields are based on incorporation of halobenzoic acid on the resin[10,16,17]; [d]: by 600 MHz ^{1}H NMR spectroscopy[13]; [e]: starting from boronate **4c** pure at 71%.

References and Notes.

¶ Now Synthelabo Biomoléculaire, same address; fax number: (33) 388.45.90.70.

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6. A somewhat different strategy using polymer-supported tin reagent has also been developed; see: Kuhn H.; Neumann, W. P. *Synlett* **1994**, 123-124.
7. Of these, forty are available at a reasonable cost, while about 170 additional boronates can be ordered from service companies at a price of 500-800 USD a batch (typically 1 to 5 g).
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10. Fmoc-Rink amide resin (Novabiochem, 0.45 mmol/g) was deprotected (50% piperidine in DMF) and coupled with the required iodobenzoic acid (DIC (4 eq)/HOBT (4 eq)) in DMF (negative to Kaiser ninhydrin test). Incorporation of the acid on the resin was verified by cleavage from the polymer; 96(± 2)% of the theoretical amount of iodobenzoic acid was consistently recovered.
11. Formation of the boronate was verified by cleavage from the resin (1:4 mixture of trifluoroacetic acid/methylene chloride (3x5 minutes)); the desired free pinacol boronate was obtained with a purity of 92-95% (^{1}H-NMR spectroscopy) and no iodobenzoic acid could be detected by HPLC.
12. For example, potassium or cesium carbonate were found to be equally effective, while triethylamine promoted a much lower conversion (20-25%) of boronate **3** into the bisaryl derivative. In addition, longer reaction time with potassium phosphate resulted in lower isolated yields.
13. The lower reaction rate is probably due to steric hindrance generated by the *ortho* substitution (see reference 14). We found that about 50% of polymer-bound *o*-iodobenzoate remained unconsumed after 20 hours of heating, while 48 hours of heating led to a 71% consumption of the iodo derivative. Similarly, The Suzuki reaction was much slower than with boronates **4a** and **4b**.
14. For example, cleavage of compound **7h** from the resin afforded the desired product with a purity of 91(±1)% (estimated by 600 MHz ^{1}H-NMR spectroscopy; one unidentified by-product), but with a mass recovery of 74%.
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16. All compounds described in the paper had analytical data in accordance with the structures.
17. Melting points (°C, uncorrected) for compounds **7a**-**7i**: **7a**: 160-161; **7b**: 199-200; **7c**: 182-183; **7d**; 147-148; **7e**: 175-176; **7f**: 228-229 (lit.[18a] 226-228); **7g**: 250-251; **7h**: 274-275 (dec); **7i**: 173-175 (lit.[18b] 177).
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