

Report

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J. Comb. Chem., **2000**, 2 (3), 228-231 • DOI: 10.1021/cc990082r • Publication Date (Web): 31 March 2000

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Resin-to-Resin Suzuki Coupling of Solid Supported Arylboronic Acids

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Received December 10, 1999

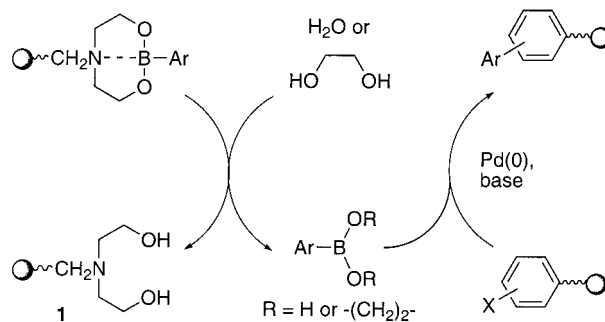
The concept of resin-to-resin transfer reactions (RRTR), also called two-resin systems, constitutes a significant simplification of solid-phase organic synthesis (SPOS) which can be extremely valuable as a time saving strategy in combinatorial chemistry.¹ RRTR systems allow for the convergent solid-phase synthesis and eventual coupling of fragments for which a linear SPOS strategy would involve incompatible reaction conditions. There are currently no RRTR systems available for carbon–carbon bond formation. Herein, we present a successful strategy for resin-to-resin Suzuki coupling reactions via phase transfer of solid supported arylboronic acids under both aqueous and anhydrous conditions.^{2,3} We demonstrate the potential of these methods with the convergent solid-phase synthesis of unsymmetrically functionalized biphenyl compounds.

Recently, we reported on the first solid support for the immobilization of boronic acids.⁴ Through forming stable, resin-bound boronic esters, the *N,N*-diethanolaminomethyl polystyrene support (DEAM-PS, **1**, in Scheme 1) can be employed to efficiently immobilize and transform functionalized arylboronic acids using amide coupling, acylation, and reductive amination methods. Despite their widespread use as building blocks in the Suzuki cross-coupling reaction,⁵ there remains a shortage of commercially available arylboronic acids.⁶ The use of DEAM-PS resin facilitates the synthesis of new arylboronic acids that could, in turn, provide novel biphenyl units such as those represented in several biologically active molecules.⁷

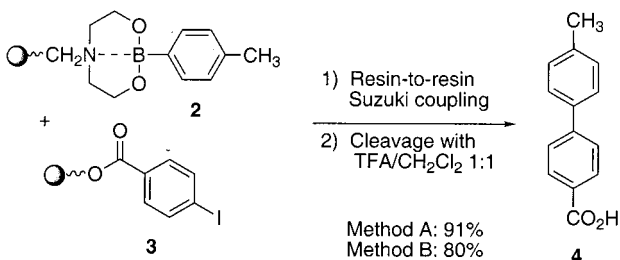
In RRTR, transfer of one resin-bound substrate to solution phase is necessary in order to effect its coupling to the other resin-bound substrate. A neutral chemical agent, or chaperone, is required to promote this event under conditions compatible with the desired reaction.⁸ The DEAM-PS boronate adducts can be cleaved under mild conditions such as prolonged exposure to water or alcohols. We have first optimized aqueous conditions for Suzuki cross-coupling in which water or a hydroxylic cosolvent acts as phase transfer agent. As shown conceptually in Scheme 1, hydrolysis or transesterification on the DEAM-PS boronate linkage is expected to liberate the free boronic acid (or ester) which will be transferred in situ to a haloarene resin under palladium(0) catalysis and added base.

As a working model, the transfer of DEAM-PS resin-bound *p*-tolueneboronic acid (**2**, Scheme 2) to Wang resin-bound *p*-iodobenzoic acid (**3**)³¹ was attempted with different

Scheme 1



Scheme 2^a



^a Method A: DEAM-PS-boronic ester (4 equiv), iodoarene resin (1 equiv), Na₂CO₃ (5 equiv, 2 M/H₂O), 20% Pd(PPh₃)₄, toluene/MeOH 3:1, 85 °C, 24 h. Method B: DEAM-PS-boronic ester (4 equiv), iodoarene resin (1 equiv), 20% Pd₂(dba)₃, DMF/Et₃N/(HOCH₂)₂ 8:1:1, 105 °C, 24 h.

Table 1. Suzuki RRTR of **2** and **3** under Aqueous Conditions^a

entry	solvent	base ^b	equiv of 2	temp (°C)	time (h)	conversion (%) ^c
1	PhMe/EtOH 3:1	Na ₂ CO ₃	4	85	20	100
2	PhMe/EtOH 3:1	K ₂ CO ₃	4	85	20	100
3	PhMe/EtOH 3:1	Na ₂ CO ₃	3	85	16	70
4	DME/H ₂ O 9:1	Na ₂ CO ₃	4	85	20	60
5	DMF/H ₂ O 9:1	Na ₂ CO ₃	3	85	20	35

^a Typical trials were carried out with 40 mg of **3** (0.55 mmol/g) and the according amount of **2** in 2 mL of degassed solvent and 10–20% Pd(PPh₃)₄ as catalyst. ^b An additional equivalent relative to **2** was employed (from a 2 M aqueous solution). ^c Measured by ¹H NMR integration on crude reaction products.

stoichiometries under various solvent, base, and temperature conditions. The resulting resin mixture was then treated with 1:1 trifluoroacetic acid/dichloromethane to liberate the biphenyl product **4** and, if any, unreacted *p*-iodobenzoic acid.⁹ The conversion results are summarized in Table 1. With 10–20% Pd(0) catalyst loading and either sodium or potassium carbonate as base, the original Suzuki conditions^{5b} using toluene/ethanol (3:1) as solvent gave the highest conversions (entries 1–2). By comparing entries 1 and 3, it is clear that 4 equiv of the resin-bound boronic acid are required to reach full conversion within 20 h at 85 °C. Using the optimal conditions of entry 1, designated method A, a larger scale reaction (~0.1 mmol) afforded a 91% yield of essentially pure **4** (Scheme 2).

To widen the scope of this RRTR process to the use of water sensitive substrates, we have also optimized anhydrous

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Table 2. Suzuki RRTR of **2** and **3** under Anhydrous Conditions^a

entry	solvent	base	transfer agent	temp (°C)	time (h)	conversion (%) ^d
1	DMF	Et ₃ N ^b	(HOCH ₂) ₂ ^b	105	20	100
2	DMF	Et ₃ N ^c	(HOCH ₂) ₂ ^c	105	20	100
3	DMF	Et ₃ N ^b	(HOCH ₂) ₂ ^b	85	20	100
4	DMF	Et ₃ N ^c	(HOCH ₂) ₂ ^c	85	20	85
5	DMF	N(CH ₂ CH ₂ OH) ₃ ^b		105	20	40
6	PhMe	N(CH ₂ CH ₂ OH) ₃ ^b		105	20	45
7	dioxane	NH(CH ₂ CH ₂ OH) ₂ ^b		85	20	25

^a Typical trial same as in Table 1 except for the constant use of 4 equiv of **2** (107 mg, 0.82 mmol/g). ^b A large excess is used, ca. 10% v/v. ^c 20 equiv. ^d Measured by ¹H NMR integration on crude reaction products.

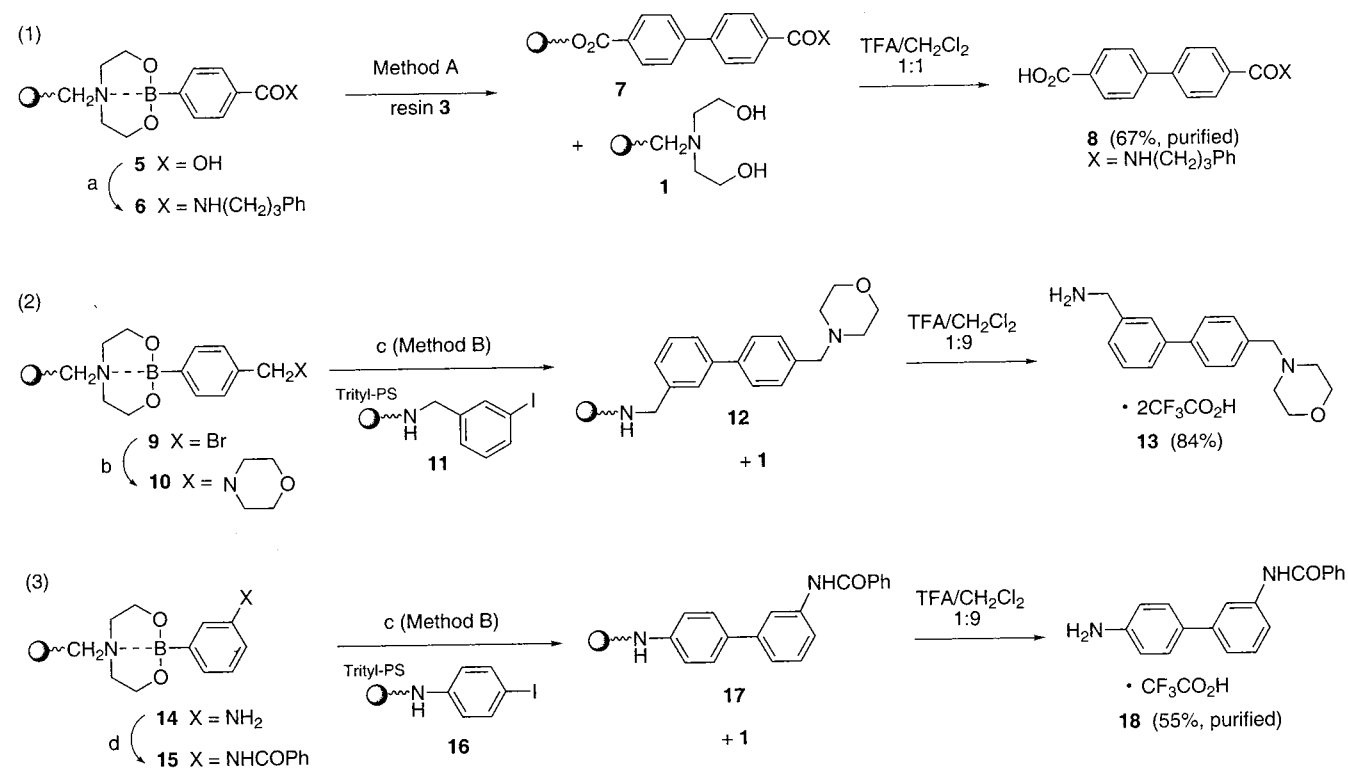
conditions employing a tertiary amine as base (Table 2).^{3h} Knowing the propensity of diethanolamine and triethanolamine to transesterify boronic esters,¹⁰ we examined their use as phase transfer agents that could also function as required base. However, as shown from entries 5–7, they were surprisingly ineffective.¹¹ The use of ethylene glycol as transfer agent (Scheme 1) with triethylamine as base in DMF was found to be superior (entries 1–4). When triethylamine and ethylene glycol (1:1) were used in large excess, full conversion was achieved at 85 °C for 20 h (entry 3). Furthermore, substitution of Pd(PPh₃)₄ for Pd₂(dba)₃ led to crude reaction products of apparently higher purity. We chose to adopt the latter conditions as optimal method B, with a temperature of 105 °C to ensure completion of more demanding substrates. On a larger scale, method B afforded a 80% yield of **4** (Scheme 2).

Control experiments were devised to confirm the role and efficiency of ethylene glycol as phase transfer agent under

anhydrous method B. Resin-to-resin cross-coupling of model substrates **2** and **3** in the absence of ethylene glycol gave largely incomplete transfer as shown by a lower than 50% conversion to product **4**.¹² This confirms the expected advantage of using the phase transfer agent. In fact, ethylene glycol transesterifies the resin-bound boronic acid within a time scale that minimizes any rate-lowering of the cross-coupling. When resin **2** was treated for 0.5 h in a 8:1:1 mixture of DMF/triethylamine/ethylene glycol at 105 °C, less than 10% of the boronic acid remained bound to the DEAM-PS support.

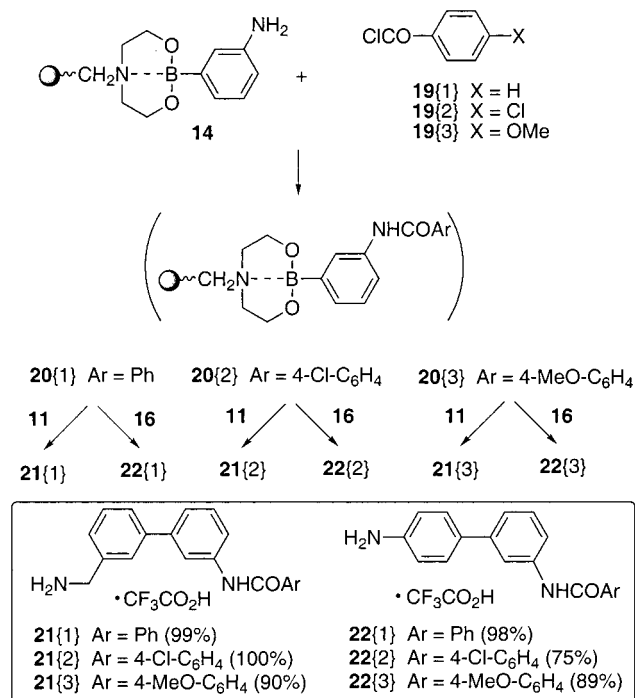
The usefulness of DEAM-PS to synthesize new aryl-boronic acids and the potential of the resin-to-resin Suzuki coupling strategy are clearly demonstrated by the convergent synthesis of unsymmetrically functionalized biphenyl compounds (Scheme 3, eqs 1–3). Amide derivative **6** was made¹³ from DEAM-PS-bound *p*-carboxybenzeneboronic acid (**5**) under standard carbodiimide methods.⁴ Following washing and drying operations, resin **6** was reacted with **3** using method A, affording 4,4'-biphenyl dicarboxylic acid monoamide **8** after cleavage from the resin mixture (**7**+**1**). This example makes a very significant case for using a convergent RRTR strategy in solid-phase synthesis. Indeed, as *p*-carboxybenzeneboronic acid is inept as a substrate in Suzuki reactions,¹⁴ a linear solid-phase strategy involving its coupling to **3** followed by amide formation would be impracticable.

The Suzuki RRTR strategy is also useful to afford monoalkylated biphenyl dibenzylamines (Scheme 3, eq 2). For example, DEAM-PS-bound *p*-(bromomethyl)benzeneboronic acid (**9**) was alkylated with morpholine to give **10**.¹³

Scheme 3^a

^a Methods A, B: see legend below Scheme 2. (a) Ph(CH₂)₃NH₂, DIC, HOBT, DMF, rt, 6 h. (b) Morpholine (10 equiv), DMF, rt, 17 h. (c) Modified method B using 6 equiv of **10** or **15**, and K₂CO₃ (8 equiv) in place of Et₃N, 115 °C, 60 h. (d) PhCOCl (10 equiv), (*i*-Pr)₂EtN (11 equiv), THF, rt, 8 h.

Scheme 4



The latter was treated with trityl-PS-bound *m*-iodobenzylamine (**11**) under modified RRTR method B (K₂CO₃ as base), and after cleavage of the resin mixture, it afforded crude diamine **13** in 84% yield and high purity (>90% by HPLC). Again, with this example, a linear synthesis based on the cross-coupling of **11** with *p*-(bromomethyl)benzeneboronic acid would be hampered by incompatible reaction conditions. The basic conditions required in the Suzuki coupling could promote nucleophilic displacement on the benzylic bromide which, in addition, can react with palladium(0) by oxidative addition.¹⁵ As shown through the formation of **18**, monoacylated biphenyl dianilines can also be synthesized efficiently (Scheme 3, eq 3).¹⁶ In the above examples, cleavage and handling of the boronic acid prior to the Suzuki coupling were obviously eliminated, and there is no need for transferring the resin to a new reaction vessel after washing and drying operations.¹⁷ These advantages are very appealing toward combinatorial chemistry applications where libraries of new DEAM-PS-bound arylboronic acids could be made and combined with libraries of supported haloarenes. To demonstrate this, a small model library was made using a commercial, semiautomated parallel synthesizer (Scheme 4).¹⁸ Supported boronic acids **20**{1–3} were synthesized from **14** and acid chlorides **19**{1–3}, and after resin rinsing were immediately reacted with iodoarene resins **11** and **16** using the same conditions used for the synthesis of **18**. After on-line cleavage, all six biphenyl products **21**{1–3} and **22**{1–3} were obtained in good to excellent yields (75–100%) and high purity (>90% by NMR). Interestingly, reactions performed with the synthesizer were significantly more efficient and cleaner compared to the manual protocol using glass vessels. This was clearly shown by comparing spectra of reference library member **22**{1} with another sample made previously via manual synthesis (see **18** in Scheme 3).

In summary, we have developed the first resin-to-resin transfer reaction for the formation of carbon–carbon bonds. The Suzuki RRTR system described herein allows for the convergent solid-phase synthesis of unsymmetrically functionalized biphenyl compounds that would be difficult to access using a linear solid-phase strategy. Added with the potential of DEAM-PS resin to generate libraries of several new arylboronic acids as coupling partners, this simple and practical strategy is particularly promising toward high-throughput combinatorial library synthesis. We are currently looking to expand this concept to other types of reactions involving boronic acids.¹⁹

Acknowledgment. This work was funded by the Natural Sciences and Engineering Research Council (NSERC) of Canada and the University of Alberta. NSERC is acknowledged for a Postgraduate Scholarship (to M.G.) and a Summer Undergraduate Award (to C.D.B.).

Supporting Information Available. Experimental details for the preparation of all starting resins and resin-bound intermediates **6**, **10**, and **15** and for their cleavage to the corresponding boronic acids. Procedures for the synthesis of **4**, **8**, **13**, **18** and library members **21**{1–3} and **22**{1–3} including selected NMR, MS, and HPLC data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- (9) In all cases no boronic acid was recovered. It was therefore completely released from the resin to solution under the reaction and resin washing conditions used. Leftover DEAM-PS resin does not liberate any byproducts upon treatment with TFA.
- (10) For example, see: Tripathy, P. B.; Matteson, D. S. *Synthesis* **1990**, 200–206.
- (11) We suspect that transmetalation of the corresponding diethanolamine boronic esters with the PS-Ar-Pd-I intermediate is significantly slower than with the ethylene glycol esters.
- (12) Treatment of resin **2** alone in hot anhydrous DMF/Et₃N (9:1, 105 °C, 24 h) led to less than 25% leaching of the boronic acid.
- (13) The efficiency of this step was validated via cleavage of a resin sample (THF/AcOH/H₂O 90:5:5, 1 h) followed by characterization of the resulting boronic acid (see Supporting Information).
- (14) As reported in ref 3c. Our own attempt at coupling *p*-carboxybenzeneboronic acid with resin **3** has also failed.
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- (16) Acylation of **14** fails with aliphatic acid chlorides under these conditions.
- (17) In addition, solid-phase immobilization circumvents the tendency of free boronic acids to dehydrate by forming anhydrides which are difficult to characterize and weight accurately.
- (18) A Quest 210 instrument with solvent wash unit was employed (Argonaut Technologies). Cleavage was effected on-line, and crude products were obtained after evaporation of solvents. Yields and purity were estimated by comparison with an internal NMR standard.
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CC990082R