

# Boronate linker for 'traceless' solid-phase synthesis

Christelle Pourbaix,<sup>a</sup> François Carreaux,<sup>\*a</sup> Bertrand Carboni,<sup>\*a</sup> and Hervé Deleuze<sup>b</sup>

<sup>a</sup> Synthèse et Electrosynthèse organiques, UMR 6510 CNRS, Université de Rennes 1, Campus de Beaulieu, 35042 Rennes Cedex, France. E-mail: francois.carreaux@univ-rennes1.fr

<sup>b</sup> Laboratoire de Chimie Organique et Organométallique, UMR 5802 CNRS, Université de Bordeaux 1, 351, Cours de la libération, 33405 Talence, France

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The development of a new boron-based strategy for 'traceless' solid-phase synthesis of aromatic compounds is reported. A resin capture process can precede the cleavage step.

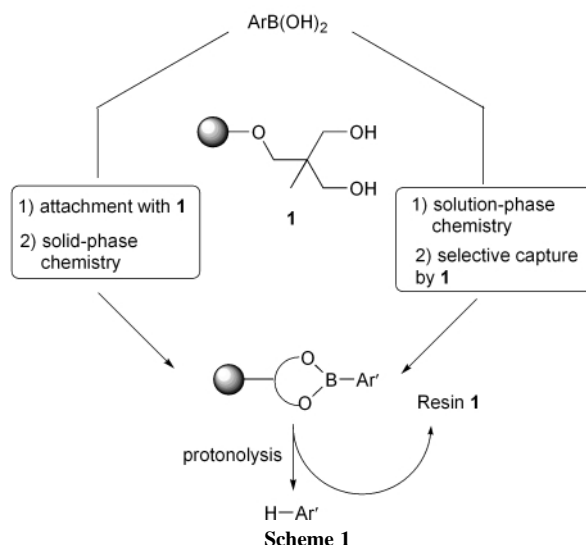
The combinatorial library approach is increasingly used for the discovery and development of new drugs, catalysts and materials.<sup>1</sup> Most of the organic chemical libraries reported to date have been constructed using solid-phase methods. A key aspect of these strategies is the linkage element, which acts as a tether to the polymeric support material. Typically, linkage to the polymeric support is based on a protecting group. However, after cleavage from the support, the presence of the functional group previously used for the attachment may have a negative effect on the biological or chemical properties of the target compounds. To overcome this disadvantage, alternative approaches were developed where linkage through a functional group can be excised efficiently, when desired, leaving behind no trace or 'memory' of the solid-phase synthesis (formation of a new C–H or C–C bond).

Only a few 'traceless' linkers have been reported so far for the synthesis of aromatic compounds, none of which are general.<sup>2</sup> As part of a program to develop new solid-phase synthetic methodologies, we became interested in exploring the use of polymer-supported arylboronates. We have prepared recently a macroporous support **1** which was found to be efficient in immobilizing a wide variety of arylboronic acids under mild and neutral conditions.<sup>3,4</sup> Since protonolysis of arylboranes is a well-documented reaction,<sup>5</sup> we planned to use the boronate functionality as a new traceless linker for the solid-phase synthesis of aromatic compounds. Furthermore, since the polymer **1** is extremely selective in its reactions with boronic acids, the boronate linker can be used in another strategy where the synthesis is initiated in solution and the material is subsequently captured by solid support before performing 'traceless' cleavage. In each approach, the cleavage step is associated with the regeneration of the resin **1** (Scheme 1).

In order to find an efficient procedure for the traceless cleavage of supported arylboronates, preliminary experiments have been performed on the resin-bound *m*-nitrophenylboronic acid (Table 1). Protodeboronation of arylboranes usually occurs under drastic hydrolytic conditions, catalysed by conc NaOH<sup>6</sup> or conc HCl.<sup>7</sup> Due to the incompatibility of these procedures with various acid or base sensitive functional groups, transition metal salts have attracted our attention as mild protonolysing reagents.<sup>8</sup> After some unsuccessful experiments, it was found that nitrobenzene can be obtained using an aqueous solution of Ag(NH<sub>3</sub>)<sub>2</sub>NO<sub>2</sub> in EtOH at rt (entry 1)<sup>9</sup> and that the use of THF instead of EtOH significantly improved the yield (entry 2). The optimized conditions required 10 equiv. of 0.5 M aq. Ag(NH<sub>3</sub>)<sub>2</sub>NO<sub>3</sub> in THF at 75–80 °C for 8 h (yield 75%, purity > 95%) (entry 4). The use of a gel-type glycerol-PS resin<sup>10</sup> led to < 50% of deboronation under the same conditions, clearly underlining the benefit of macroporous resin **1**. This cleavage was further examined with different aryl ring systems and the liberated products were isolated in moderate to good yields (entries 5–7).

The solutions obtained after filtration of the resin were evaporated to dryness, the residue was taken up in a mixture of EtOAc and H<sub>2</sub>O, and, after separation of the layers, the organic solvent was evaporated. In all cases, the remaining products were > 85% pure as determined by GC or NMR.<sup>11</sup>

Of particular interest to combinatorial chemistry is the use of resin **1** to immobilize functionalized boronic acid templates and carry out different solid-phase transformations. As an example, butan-1-ol was coupled to resin-bound *p*-carboxyphenylboronic acid **2**, to afford the corresponding ester **3** in 56% after cleavage. Similarly, resin-bound *m*-aminophenylboronic acid **4** was



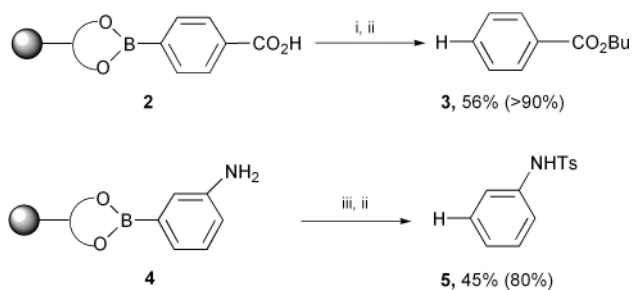
**Table 1** Protodeboronation of resin-bound arylboronic acids using an aqueous silver ammonium nitrate complex<sup>a</sup>

Entry	Ar	Conditions	Yield (%) <sup>b</sup>	Purity (%) <sup>c</sup>
1	3-NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub>	Ag(NH <sub>3</sub> ) <sub>2</sub> NO <sub>3</sub> (2 equiv.), EtOH–H <sub>2</sub> O (1:1), 48 h, rt	36	> 95
2	3-NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub>	Ag(NH <sub>3</sub> ) <sub>2</sub> NO <sub>3</sub> (2 equiv.), THF–H <sub>2</sub> O (1:1), 48 h, rt	60	> 95
3	3-NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub>	Ag(NH <sub>3</sub> ) <sub>2</sub> NO <sub>3</sub> (10 equiv.), THF–H <sub>2</sub> O (1:1), 48 h, rt	75	> 95
4	3-NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub>	Ag(NH <sub>3</sub> ) <sub>2</sub> NO <sub>3</sub> (10 equiv.), THF–H <sub>2</sub> O (1:1), reflux, 8 h	77	> 95
5	1-Naphthyl	Ag(NH <sub>3</sub> ) <sub>2</sub> NO <sub>3</sub> (10 equiv.), THF–H <sub>2</sub> O (1:1), reflux, 8 h	95	> 95
6	3,4-OCH <sub>2</sub> O-C <sub>6</sub> H <sub>4</sub>	Ag(NH <sub>3</sub> ) <sub>2</sub> NO <sub>3</sub> (10 equiv.), THF–H <sub>2</sub> O (1:1), reflux, 8 h	80	85
7	4-MeO-C <sub>6</sub> H <sub>4</sub>	Ag(NH <sub>3</sub> ) <sub>2</sub> NO <sub>3</sub> (10 equiv.), THF–H <sub>2</sub> O (1:1), reflux, 8 h	35	86

<sup>a</sup> Aqueous silver diamine nitrate (0.5 M) was prepared by titrating silver nitrate solution with sufficient ammonia to dissolve all precipitate (pH 7–8).

<sup>b</sup> Yields of isolated product (based upon loading of resin **1**, 1 mmol g<sup>-1</sup>).

<sup>c</sup> GC purity of the crude reaction mixture.



**Scheme 2** GC or NMR purities are given in brackets. *Reagents and conditions:* i,  $\text{SOCl}_2$  (15 equiv.), toluene, 70 °C, 12 h, then filtration and washing, then  $\text{BuOH}$  (10 equiv.), pyridine (15 equiv.), toluene, 25 °C, 24 h; ii,  $\text{Ag}(\text{NH}_3)_2\text{NO}_3$  (0.5 M in water, 10 equiv.), THF, reflux, 8 h; iii, 4-MePhSO<sub>2</sub>Cl (5 equiv.), EtN(Pri)<sub>2</sub> (10 equiv.),  $\text{CH}_2\text{Cl}_2$ , 25 °C, 12 h.

transformed into sulfonyl amide **5** upon treatment with *p*-methylphenylsulfonyl chloride (Scheme 2).

The exact mechanism of the silver ion catalyzed protodeboronation has not been clearly demonstrated, but the hypothesis of an arylmetal intermediate is strongly favoured.<sup>8</sup> Note that, after washing (water, THF and  $\text{Et}_2\text{O}$ ), the filtered slightly green resin can be reused for another attachment without requiring a regeneration step and with no apparent loss of activity.

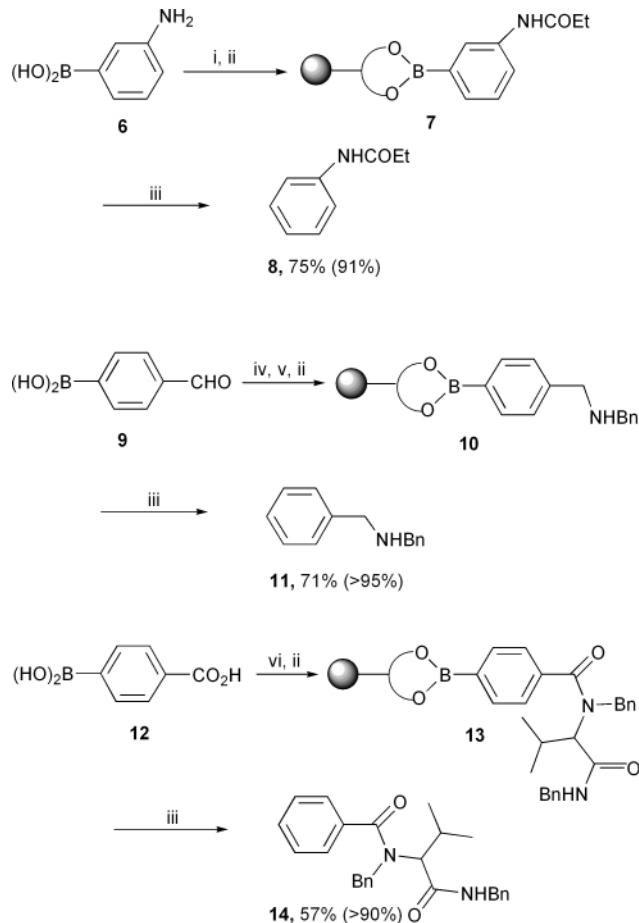
The resin capture strategy is very promising for library generation since it combines the flexibility of solution synthesis with the purity of solid-phase products. In this regard, resin **1** could be very useful in capturing only organoboron products from complex reaction mixtures and, subsequently, to perform 'traceless' cleavage. For example, some transformations in the solution-phase of functionalized boronic acids have been realized using an excess of various reagents. *m*-Aminophenylboronic acid **6** was transformed into anilide by treatment with benzoyl chloride and *p*-formylphenylboronic acid **9** was subjected to a reductive amination with benzylamine. The crude products of these reactions were combined with resin **1** at reflux in THF to afford **7** and **10**. The desired products **8** and **11** were obtained in excellent purities and yields after cleavage. As another significant demonstration of the interest of such an approach, an UGI four-component condensation<sup>12</sup> was carried out with **12**, benzylamine, benzylisocyanide and isobutyraldehyde in MeOH at 60 °C for 12 h. After evaporation of the solvent, the crude product was treated with **1** to selectively afford **13**. After cleavage, the  $\alpha$ -(acylamino) amide **14** was obtained in 57% yield and with a high purity (>90%), as shown in Scheme 3. To the best of our knowledge, this constitutes the first example of resin capture which releases product with formation of a carbon–hydrogen bond in place of the resin attachment.

In conclusion, we have developed a new 'traceless' linker technology for solid-phase chemistry. The conditions of cleavage are compatible with the presence of functional groups such as amines, amides, esters, ethers and sulfonamides.<sup>13</sup> The boronate linker system is distinct from the existing alternatives by its ability to regenerate the polymer, and its use in a resin capture process. Other reactions of polymer-supported boronates in the formation of a new carbon–carbon bond instead of the initial boron–carbon bond are currently in progress in our laboratory.

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## Notes and references

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**Scheme 3** In brackets are given the GC or NMR purities. *Reagents and conditions:* i, EtCOCl (7 equiv.), pyridine (7 equiv.),  $\text{CH}_2\text{Cl}_2$ , rt, 20 h; ii, resin **1** (1 equiv.), THF, reflux, 16 h; iii,  $\text{Ag}(\text{NH}_3)_2\text{NO}_3$  (0.5 M in water, 10 equiv.), THF, reflux, 8 h; iv, propanediol (1.2 equiv.),  $\text{Et}_2\text{O}$ , rt, 30 min; v,  $\text{PhCH}_2\text{NH}_2$  (4 equiv.),  $\text{NaBH}(\text{OAc})_3$  (4 equiv.),  $\text{CH}_2\text{Cl}_2$ –DMF (1 : 1), rt, 24 h; vi,  $\text{PhCH}_2\text{NH}_2$  (1.2 equiv.), Pr<sub>2</sub>CHO (1.2 equiv.),  $\text{PhCH}_2\text{NC}$  (1.2 equiv.), MeOH, 60 °C, 12 h.

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- 10 The glycerol-PS resin (Purchased from Novabiochem. Inc.) was coupled to *m*-nitrophenylboronic acid in THF, under the same conditions as with resin **1**.
- 11 A small amount of boronic acid can be detected in some cases, (5–10%). This by-product results from the hydrolysis of the boronate linker and is easily removed by treating the crude of the reaction after cleavage with the diol resin **1** under the immobilization conditions of boronic acids. The polymer **1** is then used as solid-supported scavenger of boronic acids.
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