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Application of the 'resin-capture–release' methodology to macrocyclisation *via* intramolecular Suzuki–Miyaura coupling

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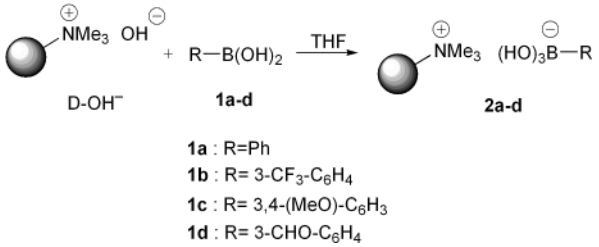
Aryl boronic acids can be trapped by an ammonium hydroxide-form Dowex® Ion Exchangers resin (D-OH$^-$) leading to polymer-ionically bound borates and cyclized, when properly designed, into macroheterocycles under Suzuki–Miyaura coupling conditions.

Biarylcyclopeptides are important targets[1] since such compounds are potentially promising therapeutic agents.[2] The solid phase synthesis of macrocyclic systems involving a transition metal catalysed C–C bond formation is a current challenge investigated with polymer-covalently bound precursors.[3] However, such synthetic strategies involving an aryl–aryl coupling at a final stage are scarse. To the best of our knowledge, only one example describing the synthesis of a β-turn mimic *via* a Suzuki–Miyaura ring-closing reaction has been reported.[4] These approaches generally required sophisticated multistep synthesis on the solid support prior the crucial C–C bond formation.

In this context, we thought that the application of the 'resin-capture–release' hybrid technique[5] to the generation of polymer supported borate species bearing a remote aryl halide moiety followed by a releasing cyclisation under Suzuki–Miyaura's conditions could bring an efficient and easy solution to the synthesis of biarylic macrocyles. In order to check this idea, we developed a simple resin-capture method to immobilize arylboronic acids species by reaction with macroporous ammonium hydroxide-form Dowex® Ion Exchangers resin (D-OH$^-$) as B^{IV}-arylborates. The simple addition of a dilute THF solution of boronic acids **1** onto D-OH$^-$ resin resulted in the quaternization of the boron atom, leading to the formation of the corresponding immobilized hydroxyborate adduct **2** (Scheme 1).

Loading of the resin was easily achieved and controlled with **1a–d** featuring various functionalities. In all cases, about 75% of the given theoretical capacity (*ca.* 1.6 mmol g^{-1} of dry resin) can be reached.[6] The strength of this ionic linkage was evaluated by submitting the phenylhydroxyborate resin **2a** (as a representative example) to continuous extraction with Soxhlet apparatus. With water as solvent, only 10% leaching of **1a** from **2a** was observed after 72 h while no leaching could be detected after 18 h using THF. Another interesting feature is that despite their total insolubility, resins **2** can be readily analysed by standard ^{11}B NMR spectroscopic methods as a heterogeneous suspension in classical solvents. The NMR spectra of such

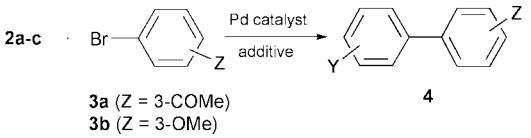


Scheme 1 Resin-capture of arylboronic acids.

Table 1 ^{11}B NMR chemical shifts for **1** and **2**

	δ^{11}B/ppm		
1a:	28.7 (THF–C_6D_6)	**2a**:	2.9 (D_2O)-$\nu_{1/2}$ = 339 Hz
1b:	28.5 (d_6-DMSO)	**2b**:	1.8 (D_2O)-$\nu_{1/2}$ = 225 Hz
1c:	28.8 (d_6-DMSO)	**2c**:	2.0 (D_2O)-$\nu_{1/2}$ = 345 Hz
1d:	29.3 (d_6-acetone)	**2d**:	2.0 (D_2O)-$\nu_{1/2}$ = 270 Hz

suspensions of resins **2** in D_2O for example are well-resolved ($\nu_{1/2}$ < 500 Hz) with ^{11}B chemical shifts observed in the expected region (typically δ ~2 ppm Table 1). Efficient Suzuki–Miyaura coupling reactions could be achieved with these immobilized arylhydroxyborates (Scheme 2). The reac-



Scheme 2 *Reagents and conditions*: loading of 0.8 mmol g^{-1}, D-Br$^-$ (1 eq.), cat. $Pd(OAc)_2$ (2 mol%), H_2O, rt, 17 h.

tions leading to **4** were performed in water[7] in the presence of two bromoarenes bearing respectively an activating electron-withdrawing group (**3a**; Z = 3-COMe) and an electron-donating-group (**3b**; Z = 3-OMe) selected for their different reactivity towards the rate-determining oxidative addition step in the catalytic cycle.[8] The results reported in Table 2 verify this trend. In the case of **2c** (entries 5 and 6), the expected protodeboronation side-reaction occurs at the expense of the formation of **4**.

Table 2 Releasing Suzuki–Miyaura cross-coupling reaction

Entry	**2**	**3**	**4**[a]
1	**2a**	**3a**	86%
2	**2a**	**3b**	60%
3	**2b**	**3a**	75%
4	**2b**	**3b**	61%
5	**2c**	**3a**	38%(65%)[b]
6	**2c**	**3b**	22%

[a] Isolated yield respect to **3**. [b] Reaction carried out at 56 °C

We then developed an original route to build up precursors **5** (Scheme 3) containing both the arylboronic and bromoaryl moieties necessary to perform the macrocyclisation reaction using an expedient multicomponent one pot synthesis.[9] Compounds **5** were obtained in good yields by mixing 3-propanalbenzeneboronic acid, morpholine and the selected isocyanoacetamide[10] in MeOH. As described (*vide supra*), **5** was efficiently anchored and in addition purified as **6** at an optimized loading of *ca.* 0.15 mmol g^{-1} of dry resin. In the absence of added base, by mixing **6** (1 eq.) with quaternary

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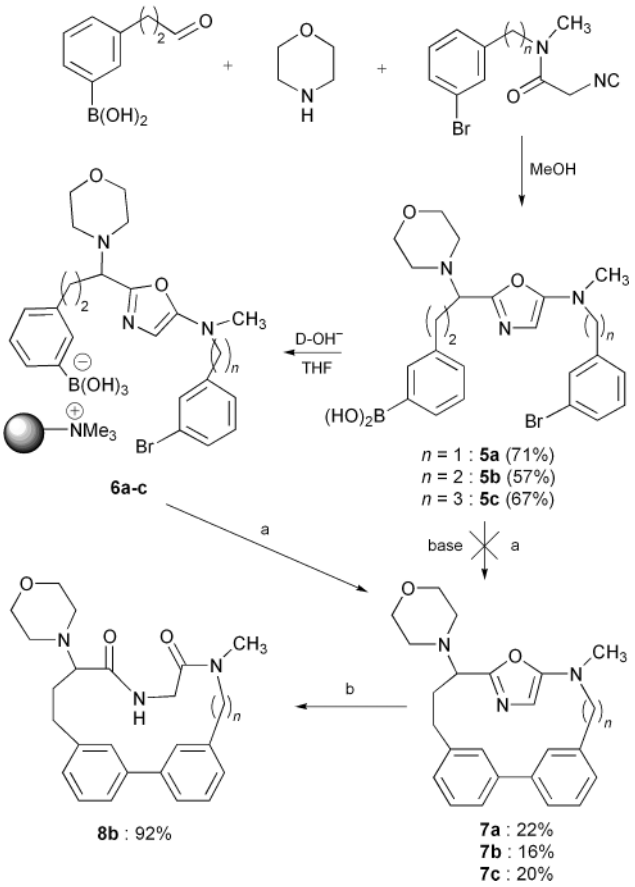

Scheme 3: *Reagents and conditions*: (a) D-Br$^-$ (1 eq.), cat. $Pd(OAc)_2$ (5 mol%), TPPDS (20 mol%), THF–H_2O (4:1), 40 °C, 40 h; (b) TFA (120 eq.), H_2O (30 eq.), rt, 2 h.

ammonium bromide-form Dowex® Ion Exchangers resin (D-Br$^-$), $Pd(OAc)_2$ (5 mol%) and triphenylphosphine disulfonic acid disodium salt (TPPDS, 20 mol%) in a THF–H_2O mixture at 40 °C, fourteen- to sixteen-membered macrocycles **7** were released and successfully isolated pure after a simple filtration–extraction sequence followed by a filtration through a pad of silica gel in 16–22% yield. For comparison, when compounds **5** were submitted to identical conditions in THF solution, macroheterocycles **7** were not obtained (Scheme 2).

HRMS and collected NMR data are in agreement with the proposed structures which have been confirmed by an X-ray diffraction study performed on **7b**[11] Under acidic conditions the oxazole **7b** could be ring-expanded into the corresponding biarylcyclopeptide **8b**[11] in 92% yield, thus opening the way to a general and efficient synthesis of this class of macroheterocycles.

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6 The loading is determined by differential weighing between the quantity of **1** initially introduced and recovered after several washings of the resin.

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11 Selected physical data: **7b** mp (Et_2O) 176 °C, ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.91 (s, oxazolic-CH); ^{13}C NMR (50.33 MHz, $CDCl_3$) δ 98.8 (oxazolic-*C*H), 123.7, 124.1, 127.2, 127.3, 127.8, 128.5, 128.9, 130.4 (8 × aryl-*C*H), 138.8, 140.8, 141.5, 141.7 (4 × aryl-C_{IV}), 151.4, 156.6 (2 × oxazolic-C_{IV}), HRMS [M$^{+\cdot}$] calcd. for $C_{25}H_{28}N_3O_2$: *m*/*z* 403.2260. Found: 403.2275. **8b** ^{13}C NMR (50.33 MHz, $CDCl_3$) δ 41.5 (NH-CH_2-CO), 70.2 (N-*C*H-CO), 139.0, 140.7, 141.1, 142.4 (4 × aryl-C_{IV}), 168.3 (NH-CH_2-*C*O), 172.0 (NH-*C*O), HRMS [M$^{+\cdot}$] calcd. for $C_{25}H_{31}N_3O_3$: *m*/*z* 421.2365. Found: 421.2380.