A biaryl cross-coupling strategy for functionalisation of benzocrown ethers†

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Preparation of (di)benzocrown-substituted aryl-zinc or -boron reagents and their palladium-catalysed cross-coupling with functionalised aryl halides is described for convenient synthesis of novel crown ether systems.

The uses of crown ethers in supramolecular chemistry have evolved from metal cation complexation[1] through transporters for cations[2,3] and chiral recognition,[4] to sensors,[5] and as components of complex supramolecular assemblies[6–8] and prototypical molecular machines.[9,10] Despite the significant effort focused on the synthesis of functionalised crown ethers and bis-crown ether systems, there is still a need for new, high-yielding routes to functionalised derivatives of these useful compounds.

Palladium-catalysed Negishi cross-coupling between organozinc reagents and organohalides[11,12] has become an important method for the preparation of functionalised biphenyls[13] following the ready availability of functionalised arylzinc reagents, directly from arylhalides by insertion of zinc[14–20] or *via* transmetalation from aryl-lithium[21] or arylmagnesium[13] species'. Whilst halogen–lithium exchange requires low temperature reaction conditions under which most benzocrowns display poor solubility,[22] halogen–magnesium exchange occurs at higher temperatures. Attempted Grignard preparation of benzocrown-functionalised aryl magnesium reagents, using magnesium metal, has been demonstrated to result in cleavage of the crown ether ring by radical or carbanion species'.[23] Consequently, these potentially very powerful reagents have not, until now, been readily available for use in the synthesis of novel crown ethers.

Herein we report that benzocrown-substituted aryl magnesium reagents of type **2** are conveniently prepared by iodine–magnesium exchange from 4-iodobenzocrowns and participate in efficient transmetalation to either zinc or boron, followed by synthetically useful palladium-catalysed biaryl cross-couplings.

Iterative treatment of 4-iodobenzo-18-crown-6 ether **1** (n_1 = 2)[24–26] with *tert*-butyl lithium in THF at −78 °C, ZnBr$_2$ and a solution of **3** (n_2 = 2)/Pd(PPh$_3$)$_4$ (5 mol%) resulted in a low yield of biphenyl **4a** due to the sparing solubility of **1** at low temperature and consequent incomplete iodine–lithium exchange (Table 1, Entry 1).

Table 1 Synthesis of bis-crown ethers **4**

Entry	Product	n_1	n_2	Yield [%]^a
1	**4a**	2	2	21^b
2	**4a**	2	2	40^c
3	**4a**	2	2	79^d
4	**4b**	1	1	92
5	**4c**	2	1	76

^{a} Yields refer to isolated analytically pure material, purified by column chromatography. ^{b} From treatment of **1** with i) *tert*-BuLi (1.05 equiv.) at −78 °C; ii) ZnBr$_2$ (1.05 equiv.) −78 °C to −50 °C; iii) **3** (n_2 = 2), Pd(PPh$_3$)$_4$ (5 mol%), −50 °C to rt. ^{c} From treatment of **1** with i) *i*-PrMgCl (1.05 equiv.) at 0 °C; ii) **3** (n_2 = 2), Pd(PPh$_3$)$_4$ (5 mol%) at 0 °C. ^{d} With 0.5 equiv. ZnBr$_2$ **4a** was isolated in 46% yield.

Highly efficient iodine–magnesium exchange was conveniently achieved upon treatment of **1** (n_1 = 1 or 2) with *i*-propyl magnesium chloride at 0 °C, furnishing **2** (n_1 = 1 or 2) quantitatively as judged by ^{1}H NMR of the protonated material. Direct cross-coupling of arylmagnesium reagent **2** (n_1 = 2) with **3** (n_2 = 2) catalysed by Pd(PPh$_3$)$_4$ was incomplete and **4a** isolated in moderate yield (Table 1, Entry 2); gratifyingly magnesium–zinc transmetalation of **2** facilitated efficient Neghishi cross-coupling of the corresponding arylzinc reagent with 4-iodobenzocrowns **3**, furnishing biphenyl-linked bis-crowns **4a–c** in good yield (Scheme 1 and Table 1, Entries 3–5). This one-pot preparation has the key advantage that introduction of a group with different binding selectivity is possible in the final step and permits synthesis of useful, unsymmetrical products. The procedure may therefore be applied also to the synthesis of 4-(hetero)aryl functionalised benzocrowns and preparation of 4-[3-thiophene]benzo-18-crown-6 ether (**5**) was illustrative.

We wished also to demonstrate practical usefulness of arylmagnesium reagent **2**. Importantly, **2** (n_1 = 2) displays good solubility in THF at −78 °C. Solubility of **2** (n_1 = 1) is reduced due to presumed competing intermolecular co-ordination of magnesium by the crown ether;[23,27] however transmetalation to boron upon treatment of **2** (n_1 = 1 or 2) with trimethyl borate at −78 °C furnishes stable, isolable arylboronic acids **6a/b**, both in reasonable yield following acid hydrolysis of the intermediate boronic acid methyl esters. Subsequent Suzuki coupling[28] of **6a/b** with 4-iodobenzocrowns **3** (n_2 = 1 or 2) led once more to biphenyl linked bis-crowns **4a/c** in high yield (Scheme 2).

Dibenzo-24-crown-8 ether (DB24C8) is an important motif in supramolecular templating[6] and construction of the bis-DB24C8 moiety constitutes a useful application of the described biphenyl cross-couplings. A bis-ethyleneoxy derivative of catechol was prepared[29] and tosylation of the diol[30] then carried out to furnish

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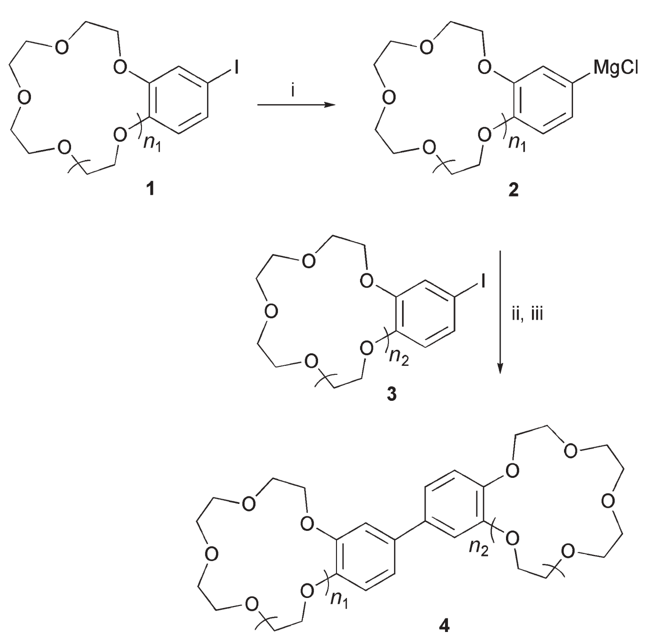
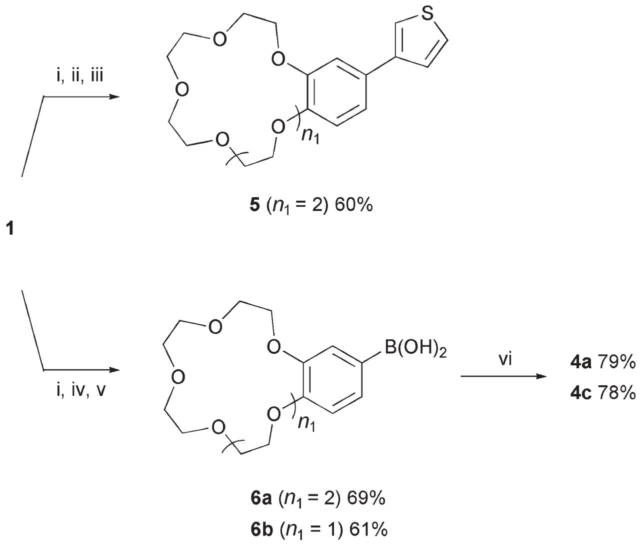
† Electronic supplementary information (ESI) available: representative experimental methods and spectroscopic characterisation of compounds **4a–c**, **5**, **6a–b** and **10**. See DOI: 10.1039/b709861h



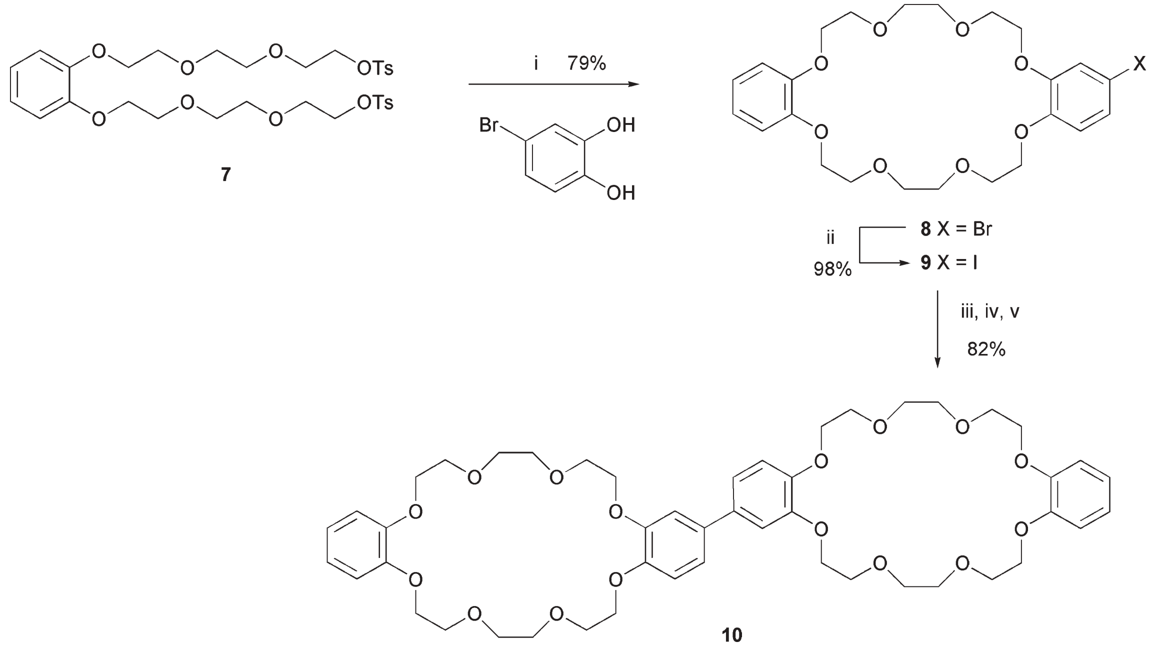
Scheme 1 *Reagents and conditions*: i) *i*-PrMgCl (1.05 equiv.), THF, 0 °C, 2 h; ii) $ZnBr_2$ (1.05 equiv.), 0 °C, 45 min; iii) **3** (1.0 equiv.), $Pd(PPh_3)_4$ (5 mol%), 0 °C to rt then rt overnight.



Scheme 2 *Reagents and conditions*: i) *i*-PrMgCl (1.05 equiv.), THF, 0 °C, 2 h; ii) $ZnBr_2$ (1.05 equiv.), 0 °C, 45 min; iii) 3-iodothiophene (1.0 equiv.), $Pd(PPh_3)_4$ (5 mol%), 0 °C to rt then rt overnight; iv) $B(OMe)_3$, −78 °C to r.t 16 h; v) HCl (aq.), rt; vi) **3** (n_2 = 1 or 2), $Pd(PPh_3)_4$, Na_2CO_3 (2 M), toluene/MeOH, 80 °C 16 h.

7. Coupling of **7** with 4-bromocatechol was templated with Cs^+ and 4-bromo-DB24C8 (**8**) was obtained in good yield (Scheme 3).[31] Halogen–metal exchange of **8** with *i*-propyl magnesium chloride or *i*-propyl magnesium chloride·LiCl at 0 °C[32] did not take place and although improved solubility of **8** (*cf.* **1**) at −78 °C enabled us to carry out bromine–lithium exchange of **8**, subsequent transmetalation to zinc was incomplete[33] and emphasises the requirement for magnesium–zinc transmetalation. However, 4-iodo-DB24C8 (**9**) underwent efficient iodine–magnesium exchange, transmetalation to zinc and palladium-catalysed coupling with a further equivalent of **9**. Bis-crown **10** was obtained in good yield.

We have demonstrated for the first time efficient iodine–magnesium exchange reaction of 4-iodobenzocrown ethers in THF under mild conditions and subsequent transmetalation to either zinc or boron. Complementary routes for biphenyl cross-coupling of the resulting arylzinc or arylboron reagents have been applied to the preparation of various functionalised benzocrowns. This route gives access to a plethora of new crown ether compounds with many potential uses in the supramolecular chemistry arena.



Scheme 3 *Reagents and conditions*: i) 4-bromobenzene-1,2-diol, $CsCO_3$, MeCN; ii) *n*-BuLi, −78 °C then I_2; iii) *i*-PrMgCl (1.05 equiv.), THF, 0 °C, 2 h; iv) $ZnBr_2$ (1.05 equiv.), 0 °C, 45 min; v) **9** (1.0 equiv.), $Pd(PPh_3)_4$ (5 mol%), 0 °C to rt then rt overnight.

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33 Preparation of **10** from **8** was made in 42% isolated yield: i) **8**, *n*-BuLi (1.0 equiv.), −78 °C, 40 min; ii) $ZnBr_2$ (1.05 equiv.), −78 °C to 0 °C; iii) **9** (1.0 equiv.), $Pd(PPh_3)_4$ (5 mol%), 0 °C to rt then rt overnight.