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Enantiospecific sp^2-sp^3 coupling of secondary & tertiary boronic esters.

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The cross coupling of boronic acids and related derivatives with sp^2 electrophiles (the Suzuki-Miyaura reaction) is one of the most powerful C–C bond formation reactions in synthesis, with applications that span pharmaceuticals, agrochemicals, and high tech materials. Despite the breadth of its utility, the scope of this Nobel prize-winning reaction is rather limited when applied to aliphatic boronic esters. Primary organoboron reagents work well, but apart from a few specific and isolated examples, secondary and tertiary boronic esters do not. Through a non-transition-metal-mediated, alternative strategy we have discovered that enantioenriched, secondary and tertiary boronic esters can be coupled to electron rich aromatics with essentially complete enantiospecificity. As the enantioenriched boronic esters are easily accessible, this reaction should find considerable application, particularly in the pharmaceutical industry where there is growing awareness of the importance of, and greater clinical success in creating biomolecules with 3-D architectures.

The Suzuki-Miyaura cross-coupling reaction is one of the most widely used reactions in synthesis.[1,2] Indeed, it is the most widely used reaction in the preparation of drug candidates and is also commonly used in the synthesis of agrochemicals and conducting materials. The impact of this single reaction across many areas of society has been immense. However, whilst extraordinarily useful for sp^2-sp^2 coupling, this reaction actually shows rather limited scope particularly in relation to the nature of the aliphatic boron reagents that can be employed. Primary organoboron reagents work well, but apart from a few specific and isolated examples, (chiral) secondary[3-11] and tertiary boronic esters do not, limiting the application of this reaction to flat molecules.[12] This is because of unwanted side reactions which begin to compete with the much slower transmetallation and reductive elimination steps associated with the more hindered organometallic intermediates.[13,14] Such inherent problems have demanded alternative strategies,[15] the most successful being Fu's Ni-catalyzed enantioselective cross

couplings of either chiral (racemic) alkyl halides with achiral organometallic reagents[16-18] or achiral alkyl halides with chiral (racemic) organometallic reagents,[19] the stereospecific cross-coupling of chiral secondary organostannanes.[20-22] and the stereospecific cross-coupling of chiral secondary benzylethers.[23,24]

Our alternative strategy has centred on utilizing the readily accessible, stereo-defined, secondary boronic esters. We reasoned that addition of an electron rich aryl lithium reagent (e.g. 2-lithiofuran) to the boronic ester would give an intermediate boronate complex **I** which, upon reaction with a suitable electrophile, would generate cation **II** (Figure 1a, Path A). The cation was expected to trigger a 1,2-migration, and, following elimination, would give the aryl-coupled product stereospecifically. Whilst related reactions of electron rich aromatics with achiral boranes had been reported over 40 years ago (e.g. Figure 1b),[25-34] this chemistry did not develop further. Presumably, the combined difficulties associated with handling air sensitive boranes, creating stereodefined boranes and in particular, issues of which group would migrate in non-symmetrical boranes, thwarted its development. The intermediate boronate complex **I** could also react with electrophiles at the sp^3 carbon[35-38] (Path B) and so conditions/reagents would need to be carefully tuned in order to promote the desired reaction (Path A). In this paper we describe our success in promoting this pathway and thus achieving a practical, stereospecific coupling of secondary and tertiary boronic esters with electron rich aromatics.
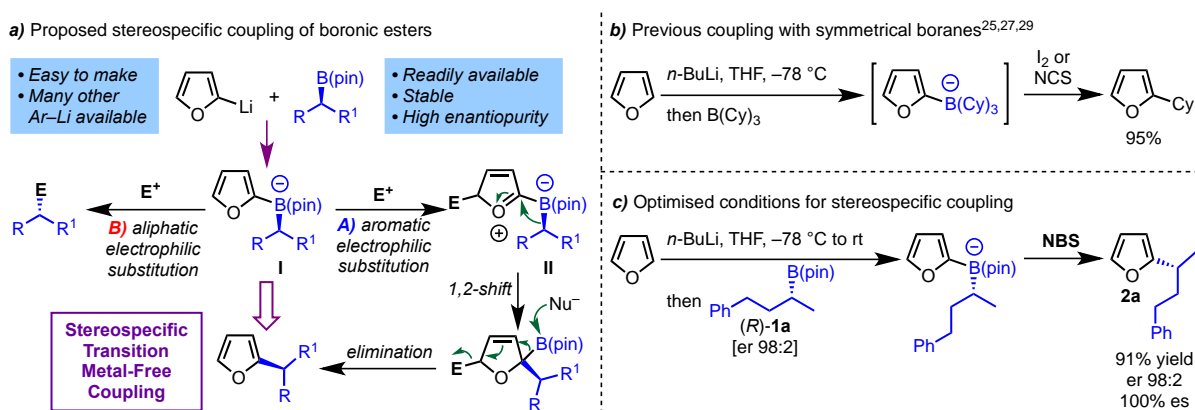

Figure 1. Proposed method for stereospecific coupling of boronic esters with an illustration of previous literature and key results. **a,** Proposed pathway for the stereospecific, transition-metal-free coupling of chiral secondary boronic esters with 2-lithiofuran. **b**, Previous coupling with symmetrical

boranes.[25,27,29] This reaction is believed to follow the mechanism shown in Figure 1a. **c,** Optimised conditions discovered for stereospecific coupling. Abbreviations: pin= pinacolato; E= electrophile; Cy= cylcohexyl; NCS= N-chlorosuccinamide.

Results and Discussion

We began our studies with the addition of 2-lithiofuran to boronic ester (*R*)-**1a**, (prepared by our lithiation-borylation methodology)[39] and explored a range of electrophiles (see SI). Of the electrophiles tested, NBS was found to be optimum, reacting rapidly at low temperature, and furnishing the product with complete stereospecificity (100% es) (Figure 1c).

A range of enantioenriched secondary[39] and tertiary boronic esters[40-42] were then prepared by lithiation-borylation methodology or by hydroboration (Figure 2, see SI for details) and subsequently tested under these optimized reaction conditions (Table 1).

Lithiation-borylation

Secondary: $R^2 = H$

1a [er 98:2] : $R^1 = PhCH_2CH_2$ $R^3 = Me$
1b [er 96:4] : $R^1 = Me$ $R^3 = CH_2CH_2\text{-}p\text{-OMe-Ph}$
1c [er 97:3] : $R^1 = PhCH_2CH_2$ $R^3 = i\text{-Pr}$
1d [er 96:4] : $R^1 = CH_2CH_2CO_2t\text{-Bu}$ $R^3 = PhCH_2CH_2$
1e [er 93:7] : $R^1 = Ph$ $R^3 = Me$

1f   **1g**   **1h** [er 95:5]

1i: R = H
1j: R = TBS

Tertiary:

1k [er 99:1] : $R^1 = PhCH_2CH_2$ $R^2 = Me$ $R^3 = Et$
1l [er 99:1] : $R^1 = Ph$ $R^2 = Me$ $R^3 = Et$
1m [er 99:1] : $R^1 = Ph$ $R^2 = Me$ $R^3 = i\text{-Bu}$
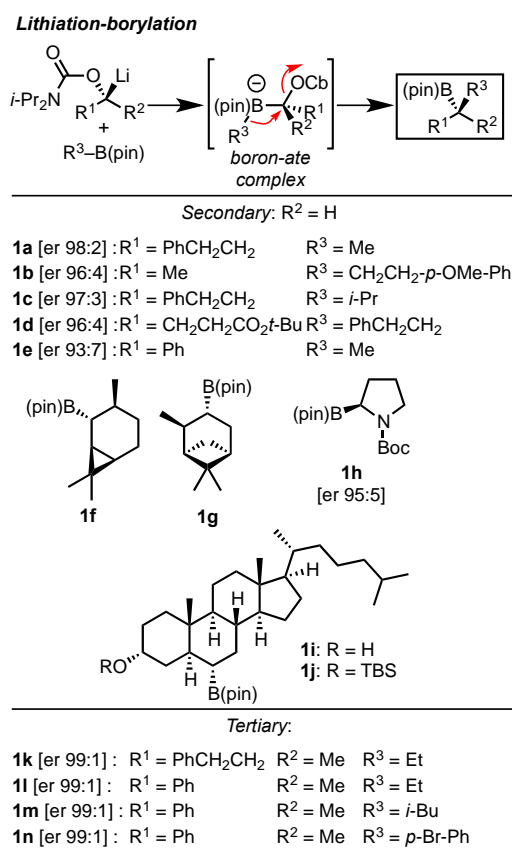**1n** [er 99:1] : $R^1 = Ph$ $R^2 = Me$ $R^3 = p\text{-Br-Ph}$

Figure 2. Range of secondary and tertiary boronic esters tested in this study. Whilst most were prepared by lithiation-borylation reactions of carbamates as described in the scheme, some were prepared by hydroboration (**1f**, **1g**, **1i**, **1j**) and some by deprotonation and borylation (**1h**). Abbreviations: er = enantiomeric ratio; Boc = *tert*-butoxycarbonyl; TBS = *tert*-butyl dimethylsilyl.

In general, secondary dialkyl and secondary benzylic substituted boronic esters **1a**,**c**-**e** reacted well giving the products **2a**,**c–e** with complete enantiospecificity (Table 1). This initial screening showed that the process tolerated increased steric hindrance on the boronic ester (**1c**) and was compatible with ester functionalities (**1d**). The utility of this chemistry was further evaluated in the stereospecific arylation of terpene-based secondary boronic esters **1f** and **1g** [derived from (+)-carene and (+)-pinene respectively]. In both cases the desired products **2f** and **2g** were obtained in high yields and complete diastereospecificity. (*R*)-2-Borylpyrrolidine[43] **1h** was also effectively coupled with 2-lithiofuran in good yield and complete enantiospecificity, extending the range of functional groups compatible with the new protocol (**2h**). Direct hydroboration of β-cholesterol[44] (see SI) gave cyclic boronic ester **1i** that underwent the desired arylation process without the need for protection of the hydroxyl group (**2i**).

The carene coupling reaction (Table 1, **2f**) has been carried out on gram scale and with all steps conducted at 0 °C, in similarly high yield and complete diastereospecificity. The larger scale, higher temperature, and transition-metal-free conditions demonstrate the potential of the methodology to industrial application.

We were keen to determine whether our method could be extended to the much more challenging coupling of enantioenriched tertiary boronic esters to make quaternary stereogenic centres; a process that is highly desirable but not achievable by current methods. We therefore tested enantioenriched, benzylic[40,41] and non-benzylic[42] tertiary boronic esters **1k–n** in our process (Table 2) and found that the desired products **2k–n** were obtained in good yields and complete stereospecificity, demonstrating the power of the new methodology. As these boronic esters were readily prepared in essentially

enantiopure form, the furyl-coupled products were also obtained in similarly enantiopure form as well.

Table 1. Scope of the secondary and tertiary boronic esters tested in the coupling reaction with furan.
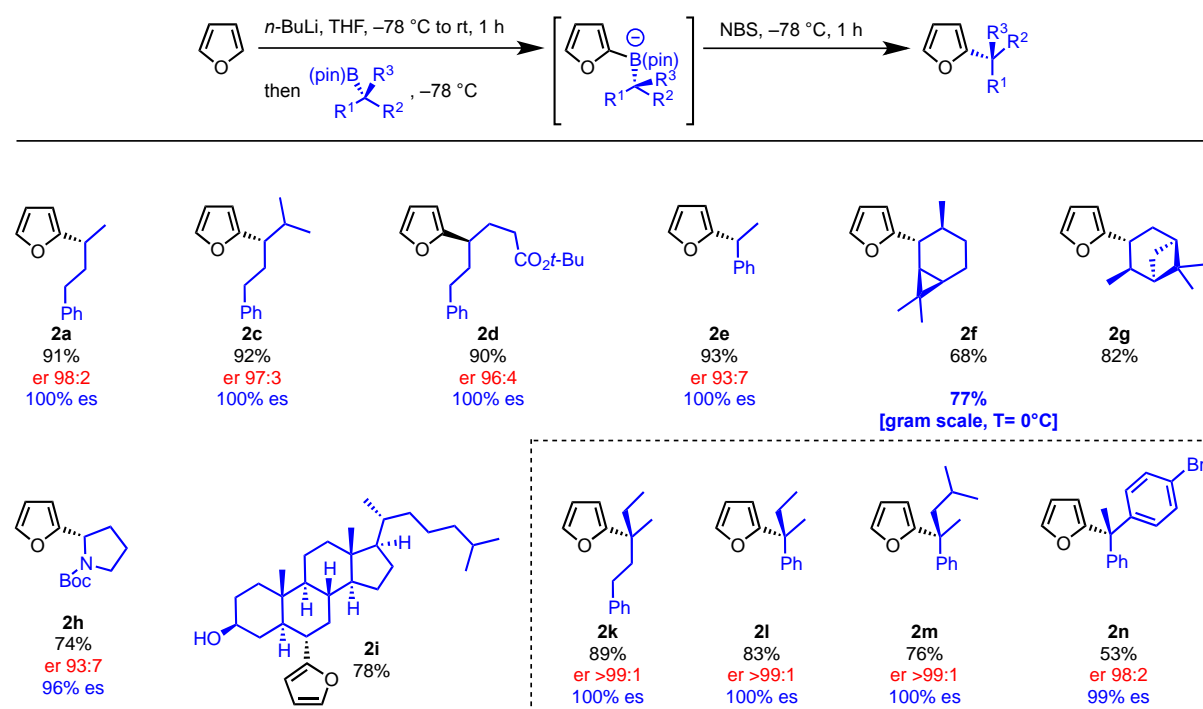

The scope of the aromatic component was also investigated with secondary and tertiary boronic esters (Table 2). In addition to the 2-substituted furan, the 3-substituted furan **3d** worked just as well. The reaction was also extended to other electron rich heteroaromatics. Thiophene, benzofuran and *N*-methyl indole all led to the coupled products **4a**, **5d** and **6a** in high yield and complete enantiospecificity, although in the case of *N*-Me indole, NIS was found to be superior to NBS as the latter reagent caused bromination of the indole ring.

We also found that the coupling could be applied to a broad range of electron rich benzene derivatives, although further modification of the reaction conditions was required. Under standard conditions (in THF), the coupling between the highly electron rich aromatic 3,5-dimethoxyphenyllithium and the secondary boronic ester **1a** resulted in an 87:13 mixture of the arylated product **7a** and bromide **12** (resulting from S_E2inv reaction) (Figure 3-I). However, in MeOH the arylated product **7a** was formed exclusively. 3-Dimethylaminophenyllithium behaved similarly,

although as with other highly electron rich aromatics, NIS was found to be superior to NBS. The dimethylamino group is an especially useful handle as it can be readily replaced by H[45] or used in subsequent Ni-catalyzed cross-coupling.[46] The use of MeOH in place of THF proved even more critical in the case of the weakly electron rich aromatics including 3-methoxyphenyllithium, 1-naphthyllithium and 3,5-dimethylphenyllithium, where we observed a complete switch from C(sp3)-bromination to the desired arylation (Figure 3). In all cases coupled products were obtained in high yield and complete enantiospecificity (Table 2, **7a**–**10a**, **11b**). The two representative enantioenriched, benzylic and non-benzylic tertiary boronic esters **1k** and **1l** were also tested with several representative aryl lithiums that span a range of aromatics: 3,5-dimethoxyphenyllithium, 3,5-dimethylphenyllithium and 1-lithionapthalene. Under optimised conditions, the tertiary boronic esters coupled in good-high yield and complete enantiospecificity in all cases (Table 2, **7k**, **7l**, **11k**, **10k**).

Table 2. Stereospecific coupling of electron rich aromatics with secondary and tertiary boronic esters. [#] NIS was used instead of NBS; [*] the solvent was switched to MeOH before NBS addition; [+] NBS was added in MeOH.
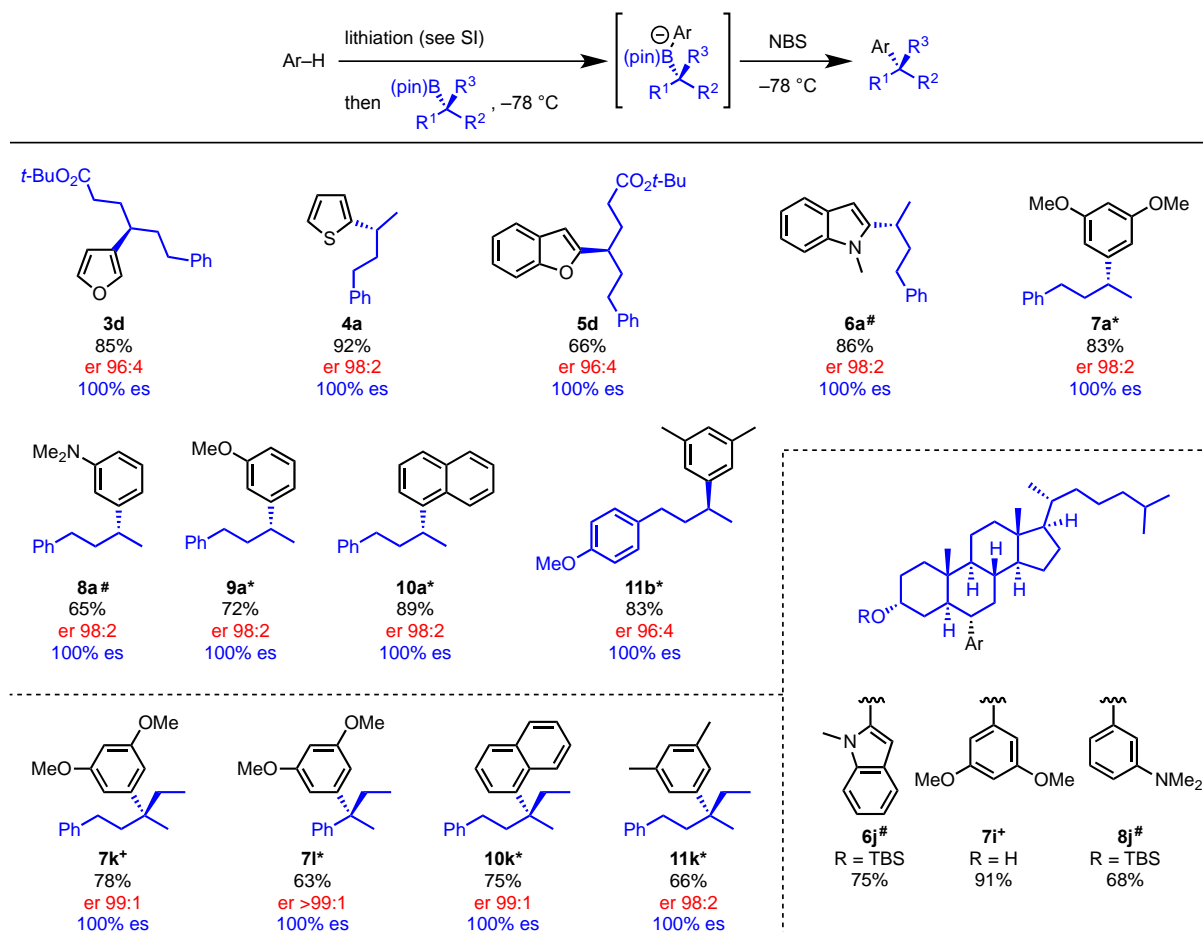
However, not all aromatics worked. They needed to be sufficiently electron rich (phenyllithium and 3-methylphenyllithium were unsuccessful) and have a donor substituent *meta* to the boronate complex (2- or 4-methoxyphenyllithium were not effective whereas 3-methoxyphenyllithium was [**9a**]) otherwise competing electrophilic attack at the sp[3] carbon centre occurred.[38] In the case of the least electron rich aromatic, 3-methylphenyllithium, a 28:72 mixture of products comprising of the desired coupled product and 2-bromo-4-phenylbutane **12** were obtained showing the lower limit of the aromatic group that can be employed. This aspect is discussed in the mechanism.

The development of methodology that enables the chemical modification of complex natural products is extremely challenging but can be highly rewarding as it can lead to molecules with improved

properties.[47] By introduction of boron to a natural product through the routine procedure of hydroboration and the methodology described herein, it is now possible to introduce a library of aromatic substituents at an olefinic site in a regio- and stereocontrolled manner, as illustrated with steroid **1j**. Thus, coupling of **1j**, with indole and several benzene derivatives gave cholesterol analogues **6j**, **7i** and **8j** with full control of regio- and stereochemistry.

Discussion

Our proposed mechanism of these reactions is presented in Figure 1 and 3. The addition of an aryl lithium to a chiral boronic ester generates a boronate complex. We have previously shown that these complexes are good nucleophiles, reacting with a range of electrophiles with inversion (S_E2inv, e.g. Figure 3, Path B).[38,48] In order to promote nucleophilic reaction of the boronate complex at the aromatic ring rather than the sp^3 centre (as required for an arylation process) we reasoned that more electron rich aromatics were required and initially selected furan. These boronate complexes reacted with NBS at the aromatic ring and, following 1,2 migration and elimination, gave the furyl-coupled product stereospecifically as illustrated in Figure 1.

In the case of differently substituted benzene derivatives, donor groups in the *meta* position relative to the boronate complex lead to bromination at the *para* position, which triggers the 1,2-migration and subsequent elimination (Fig 3-I). The boronate moiety is also a strong donating group[49] and evidently, the directing effects of both the boronate and the donor groups must reinforce each other in order to favour Path A over the competing Path B. When the donor substituent is in either the *ortho* or *para* position, Path A is retarded since now the two donor substituents do not reinforce each other, and Path B is enhanced leading to reaction *via* Path B (Figure 3-II).
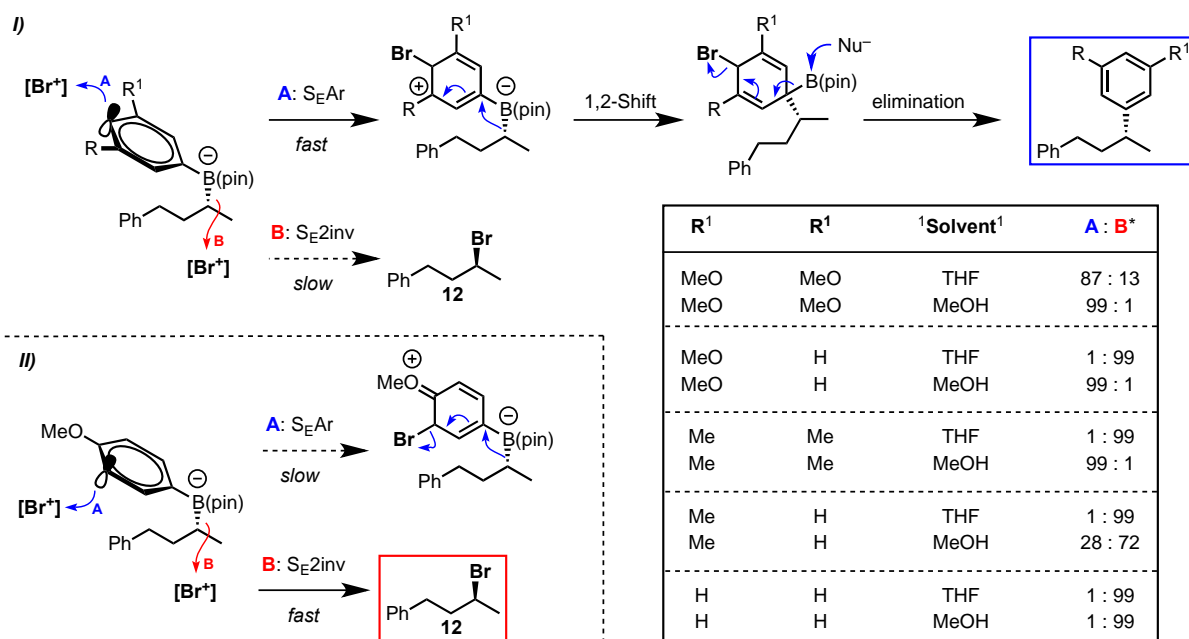
I)

A: S$_E$Ar *fast* → 1,2-Shift → *elimination* → product

B: S$_E$2inv *slow* → Ph⌒⌒Br **12**

II)

A: S$_E$Ar *slow*

B: S$_E$2inv *fast* → Ph⌒⌒Br **12**

R¹	R¹	Solvent	A : B*
MeO	MeO	THF	87 : 13
MeO	MeO	MeOH	99 : 1
MeO	H	THF	1 : 99
MeO	H	MeOH	99 : 1
Me	Me	THF	1 : 99
Me	Me	MeOH	99 : 1
Me	H	THF	1 : 99
Me	H	MeOH	28 : 72
H	H	THF	1 : 99
H	H	MeOH	1 : 99

Figure 3. Possible reaction pathways for reactions of aryl-boronate complexes with electrophiles, illustrated with [Br$^+$]. This highlights the major difference in reaction pathway according to the substitution of the aromatic ring: meta donor groups favour pathway A (**I**), whereas para donor groups favour pathway B (**II**). A further solvent effect was found in the cases of the meta donor groups in that pathway A was favoured in polar protic media (MeOH). *Ratio determined by GC-MS spectrometry and ^{1}H NMR spectroscopy analysis of the crude reaction mixture.

The dramatic effect of solvent on the success of the coupling reaction is especially striking in the case of weakly donating aromatic boronate complexes: in THF, S$_E$2inv dominated (Path B) but in MeOH, arylation dominated (Path A). This solvent effect is believed to be due to increased rates of S$_E$Ar processes (which have cationic intermediates) in more polar media.[50]

The dramatic effect of even weak donor substituents in the *meta* position on the success of the coupling reaction is also striking. With no donor groups (i.e. Ph; just H in the *meta* position), Path B dominated over Path A (>98:2), with just one Me group a 72:28 ratio of products derived from Paths B and A were obtained, but with two Me groups (*meta*-dimethyl) Path A dominated over Path B (99:1) (Figure 3).

In conclusion, we have discovered a general method for coupling electron rich aromatic and heteroaromatic compounds with enantioenriched secondary and tertiary boronic esters for the first time. The reaction involves initial formation of a boronate complex followed by activation of the electron rich aromatic moiety by an electrophile (NBS), which triggers a stereospecific 1,2-migration and subsequent elimination/rearomatisation. The methodology, which uses simple, readily available reagents, no transition metals and user-friendly conditions, shows broad scope in both the boronic ester and the electron rich aromatic, and shows complete stereospecificity. Application to a number of more complex and functionalised boronic esters also highlights the broad utility of the new methodology.

Methods

Stereospecific synthesis of **2a** was performed as follows: A solution of furan (1.2 eq.) in THF (0.3M) was cooled to –78 °C and treated with *n*-BuLi (1.2 eq., 1.6 M in hexanes). The cooling bath was removed and the mixture was stirred at room temperature for 1 h. The mixture was cooled to –78 °C and **1a** (1 eq.) was added dropwise as a solution in THF (0.5M). The mixture was stirred at – 78 °C for 1 h at which point ^{11}B NMR spectroscopy showed complete formation of the 'ate' complex [^{11}B NMR (96 MHz, THF) $\delta_B \sim 8$ ppm]. A solution of NBS (1.2 eq.) in THF (0.3M) was added dropwise. After 5 min at –78 °C, $Na_2S_2O_3$ (aq. sat.) was added and the reaction mixture was allowed to warm to room temperature. The reaction mixture was diluted with Et_2O and water. The layers were separated and the aqueous layer was extracted with Et_2O. The combined organic layers were dried ($MgSO_4$), filtered and concentrated under vacuum. The crude material was adsorbed on silica and purified by flash column chromatography on silica gel eluting with *n*-hexane. For complete experimental details and characterisation of compounds, see Supplementary Information.

References

1   Suzuki, A. *Angew Chem Int Ed* **50**, 6722-6737 (2011).
2   Miyaura, N. & Suzuki, A. Palladium-catalyzed cross-coupling reactions of organoboron compounds. *Chem. Rev.* **95**, 2457-2483 (1995).
3   Molander, G. A. & Wisniewski, S. R. Stereospecific Cross-Coupling of Secondary Organotrifluoroborates: Potassium 1-(Benzyloxy)alkyltrifluoroborates. *J. Am. Chem. Soc.* **134**, 16856-16868 (2012).

4   Awano, T., Ohmura, T. & Suginome, M. Inversion or Retention? Effects of Acidic Additives on the Stereochemical Course in Enantiospecific Suzuki–Miyaura Coupling of α-(Acetylamino)benzylboronic Esters. *J. Am. Chem. Soc.* **133**, 20738-20741 (2011).

5   Ohmura, T., Awano, T. & Suginome, M. Stereospecific Suzuki−Miyaura Coupling of Chiral α-(Acylamino)benzylboronic Esters with Inversion of Configuration. *J. Am. Chem. Soc.* **132**, 13191-13193 (2010).

6   Sandrock, D. L., Jean-Gérard, L., Chen, C.-Y., Dreher, S. D. & Molander, G. A. Stereospecific Cross-Coupling of Secondary Alkyl β-Trifluoroboratoamides. *J. Am. Chem. Soc.* **132**, 17108-17110 (2010).

7   Imao, D., Glasspoole, B. W., Laberge, V. S. & Crudden, C. M. Cross Coupling Reactions of Chiral Secondary Organoboronic Esters With Retention of Configuration. *J. Am. Chem. Soc.* **131**, 5024-5025 (2009).

8   Lee, J. C. H., McDonald, R. & Hall, D. G. Enantioselective preparation and chemoselective cross-coupling of 1,1-diboron compounds. *Nat. Chem.* **3**, 894-899 (2011).

9   Zhou, S.-M., Deng, M.-Z., Xia, L.-J. & Tang, M.-H. Efficient Suzuki-Type Cross-Coupling of Enantiomerically Pure Cycloproprylboronic Acids. *Angew. Chem. Int. Ed.* **37**, 2845-2847 (1998).

10   Partridge, B. M., Chausset-Boissarie, L., Burns, M., Pulis, A. P. & Aggarwal, V. K. Enantioselective Synthesis and Cross-Coupling of Tertiary Propargylic Boronic Esters Using Lithiation-Borylation of Propargylic Carbamates. *Angew. Chem. Int. Ed.* **51**, 11795-11799 (2012).

11   Chausset-Boissarie, L., Ghozati, K., LaBine, E., Chen, J. L. Y. & Aggarwal, V. K. Enantiospecific, Regioselective Cross-Coupling Reactions of Secondary Allylic Boronic Esters. *Chem. Eur. J.* **19**, 17698-17701 (2013).

12   Lovering, F., Bikker, J. & Humblet, C. Escape from Flatland: Increasing Saturation as an Approach to Improving Clinical Success. *J. Med. Chem.* **52**, 6752-6756 (2009).

13   Dreher, S. D., Dormer, P. G., Sandrock, D. L. & Molander, G. A. Efficient Cross-Coupling of Secondary Alkyltrifluoroborates with Aryl Chlorides—Reaction Discovery Using Parallel Microscale Experimentation. *J. Am. Chem. Soc.* **130**, 9257-9259 (2008).

14   Kataoka, N., Shelby, Q., Stambuli, J. P. & Hartwig, J. F. Air Stable, Sterically Hindered Ferrocenyl Dialkylphosphines for Palladium-Catalyzed C−C, C−N, and C−O Bond-Forming Cross-Couplings. *J. Org. Chem.* **67**, 5553-5566 (2002).

15   Swift, E. C. & Jarvo, E. R. Asymmetric transition metal-catalyzed cross-coupling reactions for the construction of tertiary stereocenters. *Tetrahedron* **69**, 5799-5817 (2013).

16   Saito, B. & Fu, G. C. Enantioselective Alkyl−Alkyl Suzuki Cross-Couplings of Unactivated Homobenzylic Halides. *J. Am. Chem. Soc.* **130**, 6694-6695 (2008).

17   Zhou, J. & Fu, G. C. Cross-Couplings of Unactivated Secondary Alkyl Halides: Room-Temperature Nickel-Catalyzed Negishi Reactions of Alkyl Bromides and Iodides. *J. Am. Chem. Soc.* **125**, 14726-14727 (2003).

18   Son, S. & Fu, G. C. Nickel-Catalyzed Asymmetric Negishi Cross-Couplings of Secondary Allylic Chlorides with Alkylzincs. *J. Am. Chem. Soc.* **130**, 2756-2757 (2008).

19   Cordier, C. J., Lundgren, R. J. & Fu, G. C. Enantioconvergent Cross-Couplings of Racemic Alkylmetal Reagents with Unactivated Secondary Alkyl Electrophiles: Catalytic Asymmetric Negishi α-Alkylations of N-Boc-pyrrolidine. *J. Am. Chem. Soc.* **135**, 10946-10949 (2013).

20   Li, L., Wang, C.-Y., Huang, R. & Biscoe, M. R. Stereoretentive Pd-catalysed Stille cross-coupling reactions of secondary alkyl azastannatranes and aryl halides. *Nat. Chem.* **5**, 607-612 (2013).

21   Kalkofen, R. & Hoppe, D. First Example of an Enantiospecific sp3-sp2 Stille Coupling of a Chiral Allylstannane with Aryl Halides. *Synlett* **12**, 1959-1961 (2006).

22   Falk, J. R., Patel, P. K. & Bandyopadhyay, A. Stereospecific Cross-Coupling of alpha-(Thiocarbamoyl)organostannanes with Alkenyl, Aryl, and Heteroaryl Iodides. *J. Am. Chem. Soc.* **129**, 790-793 (2007).

23   Yonova, I. M. *et al.* Stereospecific Nickel-Catalyzed Cross-Coupling Reactions of Alkyl Grignard Reagents and Identification of Selective Anti-Breast-Cancer Agents. *Angew. Chem. Int. Ed.*, DOI: 10.1002/ange.201308666 (2014).

24   Zhou, Q., Srinivas, H. D., Dasgupta, S. & Watson, M. P. Nickel-Catalyzed Cross-Couplings of Benzylic Pivalates with Arylboroxines: Stereospecific Formation of Diarylalkanes and Triarylmethanes. *J. Am. Chem. Soc.* **135**, 3307-3310 (2013).

25   Levy, A. B. Aromatic substitution via organoboranes. Regiospecific formation of 2-alkylindoles. *J. Org. Chem.* **43**, 4684-4685 (1978).

26   Ishikura, M. & Kato, M. A synthetic use of the intramolecular alkyl migration process in indolylborates for intramolecular cyclization: a novel construction of carbazole derivatives *Tetrahedron* **58**, 9827-9838 (2002).

27   Akimoto, I. & Suzuki, A. Synthesis of 2-Alkylfurans via the Reaction of Iodine with the Ate-Complexes Obtained from 2-Furyllithium and Trialkylboranes. *Synthesis*, 146-148 (1979).

28   Pelter, A., Williamson, H. & Davies, G. M. Aryl coupling through borate complexes with ethanolamine. *Tetrahedron Lett.* **25**, 453-456 (1984).

29   Marinelli, E. R. & Levy, A. B. Aromatic substitution via organoboranes 2. Regiospecific alkylation of the furan and pyrrole nucleus. *Tetrahedron Lett.* **20**, 2313-2316 (1979).

30   Ishikura, M., Kato, M. & Ohnuki, N. A novel C–C bond formation reaction with 1-methoxymethylindolylborate. *Chem. Commun.*, 220-221 (2002).

31   Kagan, J. & Arora, S. K. The synthesis of alpha-thiophene oligomers via organoboranes *Tetrahedron Lett.* **24**, 4043-4046 (1983).

32   Davies, G. M., Davies, P. S., Paget, W. E. & Wardleworth, J. M. Borinic acids: novel intermediates in regiospecific synthesis of biaryls. *Tetrahedron Lett.* **17**, 795-798 (1976).

33   Labadie, S. S. & Teng, E. Indol-2-yltributylstannane: A Versatile Reagent for 2-Substituted Indoles. *J. Org. Chem.* **59**, 4250-4254 (1994).

34   Levy, A. B. Aromatic substitution via organoboranes 3. simultaneous regiospecific functionalization of the indole nucleus at the 2- and 3-positions. *Tetrahedron Lett.* **20**, 4021-4024 (1979).

35   Brown, H. C., De Lue, N. R., Kabalka, G. W. & Hedgecock, H. C. J. Consistent inversion in the base-induced reaction of iodine with organoboranes. A convenient procedure for the synthesis of optically active iodides. *J. Am. Chem. Soc.* **98**, 1290-1291 (1976).

36   Kabalka, G. W. & Gooch, E. E. I. A mild and convenient procedure for conversion of alkenes into alkyl iodides via reaction of iodine monochloride with organoboranes. *J. Org. Chem.* **45**, 3578-3580 (1980).

37   Brown, H. C. & Lane, C. F. Base-induced bromination of tri-exo-norbornylborane: an electrophilic substitution with predominant inversion of configuration. *J. Chem. Soc. D: Chem. Commun.*, 521-522 (1971).

38   Larouche-Gauthier, R., Elford, T. G. & Aggarwal, V. K. Ate Complexes of Secondary Boronic Esters as Chiral Organometallic-Type Nucleophiles for Asymmetric Synthesis. *J. Am. Chem. Soc.* **133**, 16794-16797 (2011).

39   Stymiest, J. L., Dutheuil, D., Mohmood, E. & Aggarwal, V. K. Lithiated Carbamates: Chiral Carbenoids for Iterative Homologation of Boranes and Boronic Esters. *Angew. Chem. Int. Ed.* **46**, 7491-7494 (2007).

40   Stymiest, J. L., Bagutski, V., French, R. M. & Aggarwal, V. K. Enantiodivergent conversion of chiral secondary alcohols into tertiary alcohols. *Nature* **456**, 778-782 (2008).

41   Bagutski, V., French, R. M. & Aggarwal, V. K. Full Chirality Transfer in the Conversion of Secondary Alcohols into Tertiary Boronic Esters and Alcohols Using Lithiation–Borylation Reactions. *Angew. Chem. Int. Ed.* **49**, 5142-5145 (2010).

42   Pulis, A. P., Blair, D. J., Torres, E. & Aggarwal, V. K. Synthesis of Enantioenriched Tertiary Boronic Esters by the Lithiation/Borylation of Secondary Alkyl Benzoates. *J. Am. Chem. Soc.* **135**, 16054-16057 (2013).

43   Batsanov, A. S., Grosjean, C., Schultz, T. & Whiting, A. A (–)-Sparteine-Directed Highly Enantioselective Synthesis of Boroproline. Solid- and Solution-State Structure and Properties. *J. Org. Chem.* **72**, 6276-6279 (2007).

44   Villa, G., Povie, G. & Renaud, P. Radical Chain Reduction of Alkylboron Compounds with Catechols. *J. Am. Chem. Soc.* **133**, 5913-5920 (2011).

45   Paras, N., Simmons, B. & MacMillan, D. W. C. A process for the rapid removal of dialkylamino-substituents from aromatic rings. Application to the expedient synthesis of (R)-tolterodine. *Tetrahedron* **65**, 3232-3238 (2009).

46   Blakey, S. B. & MacMillan, D. W. C. The First Suzuki Cross-Coupling of Aryltrimethylammonium Ions. *J. Am. Chem. Soc.* **125**, 6046-6047 (2003).

47   Koehn, F. E. & Carter, G. T. The evolving role of natural products in drug discovery. *Nature Reviews* **4**, 206-220 (2005).

48   Mohiti, M., Rampalakos, C., Feeney, K., Leonori, D. & Aggarwal, V. K. Asymmetric addition of chiral boron-ate complexes to cyclic iminium ions. *Chem. Sci.* **5**, 602-607 (2013).

49   Berionni, G., Maji, B., Knochel, P. & Mayr, H. Nucleophilicity parameters for designing transition metal-free C–C bond forming reactions of organoboron compounds. *Chem. Sci.* **3**, 878-882 (2012).

50   Reichardt, C. & Welton, T. e. *Solvents and Solvent Effects in Organic Chemistry, Fourth Edition.* (John Wiley & Sons, 2010).

Supplementary Information is linked to the online version of the article at www.nature.com/nature.

Author Contributions D. L. and V. K. A. designed the project and wrote the manuscript. A. B. and M. O. contributed intellectually and practically to the laboratory experiments, S. E. performed preliminary computational studies and was involved in mechanistic discussions.

Graphical Abstract
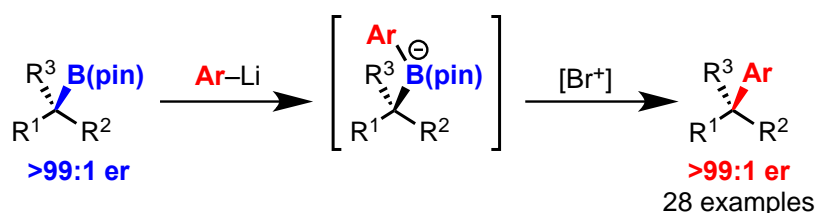
• *stereospecific coupling* • *gram scale* • *quaternary centers*

Table of contents summary:

A general and broad ranging, stereospecific coupling of secondary and tertiary boronic esters with

electron rich aromatics is reported. The reaction involves initial formation of a boronate complex

followed by activation of the electron rich aromatic moiety by an electrophile, which triggers a stereospecific 1,2-migration and subsequent elimination/rearomatization.