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Enantiospecific sp^2–sp^3 coupling of secondary and 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 secondary and tertiary boronic esters do not (apart from a few specific and isolated examples). Through an alternative strategy, which does not involve using transition metals, 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 three-dimensional architectures.

The Suzuki–Miyaura cross-coupling reaction is one of the most widely used reactions in synthesis[1,2]. Indeed, it is the reaction used most widely 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, although 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, which limits the application of this reaction to flat molecules[12]. This limitation is because of unwanted side reactions that 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 and co-workers' Ni-catalysed enantioselective cross-couplings of chiral (racemic) alkyl halides with achiral organometallic reagents[16–18] and of 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 benzyl ethers[23,24].

Our alternative strategy centred on utilizing the readily accessible, stereodefined secondary boronic esters. We reasoned that the addition of an electron-rich aryl lithium reagent (for example, 2-lithiofuran) to the boronic ester would give an intermediate boronate complex **I** that, on reaction with a suitable electrophile, would generate cation **II** (Fig. 1a, Path A). The cation was expected to trigger a 1,2-migration and, after elimination, would give the aryl-coupled product stereospecifically. Although related reactions of electron-rich aromatics with achiral boranes were reported over 40 years ago (for example, Fig. 1b)[25–34], this chemistry was not developed further. Presumably, the combined difficulties associated with handling air-sensitive boranes, creating stereodefined boranes and, in particular, issues as to 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] (Fig. 1a, Path B) and so conditions/reagents would need to be tuned carefully to promote the desired reaction

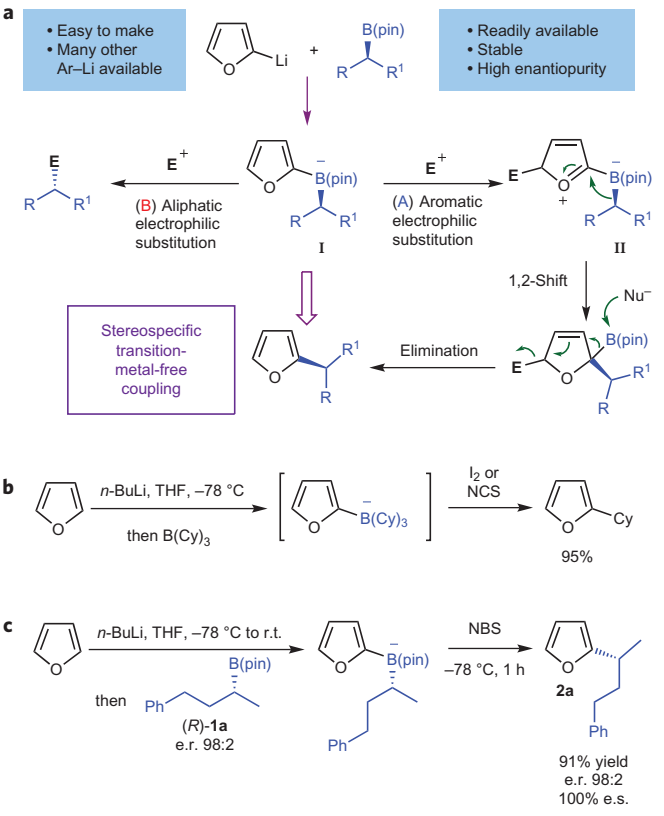

Figure 1 | Proposed method for stereospecific coupling of boronic esters with an illustration of previous literature and key results. a, Proposed pathway for the stereospecific, transition-metal-free coupling of chiral secondary boronic esters with 2-lithiofuran. **b**, Previous coupling with symmetrical boranes[25,27,29]. This reaction is believed to follow the mechanism shown in **a**. **c**, Optimized conditions discovered for stereospecific coupling. Cy, cyclohexyl; E, electrophile; e.r., enantiomeric ratio; NBS, *N*-bromosuccinimide; NCS, *N*-chlorosuccinimide; Nu, nucleophile; pin, pinacolato; r.t., room temperature.

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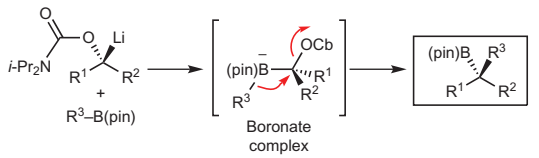
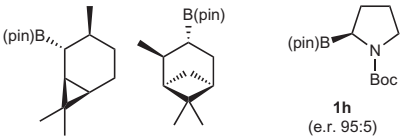
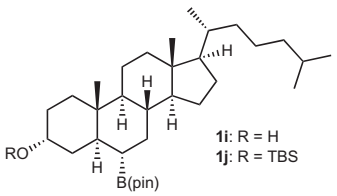


Secondary, R^2 = H

1a (e.r. 98:2) : R^1 = $PhCH_2CH_2$ R^3 = Me
1b (e.r. 96:4) : R^1 = Me R^3 = CH_2CH_2-*p*-OMe-Ph
1c (e.r. 97:3) : R^1 = $PhCH_2CH_2$ R^3 = *i*-Pr
1d (e.r. 96:4) : R^1 = $CH_2CH_2CO_2$-*t*-Bu R^3 = $PhCH_2CH_2$
1e (e.r. 93:7) : R^1 = Ph R^3 = Me



1f **1g** **1h** (e.r. 95:5)



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

Tertiary

1k (e.r. 99:1) : R^1 = $PhCH_2CH_2$ R^2 = Me R^3 = Et
1l (e.r. 99:1) : R^1 = Ph R^2 = Me R^3 = Et
1m (e.r. 99:1) : R^1 = Ph R^2 = Me R^3 = *i*-Bu
1n (e.r. 99:1) : R^1 = Ph R^2 = Me R^3 = *p*-Br-Ph

Figure 2 | Range of secondary and tertiary boronic esters tested in this study. Although most of the boronic esters were prepared by lithiation–borylation reactions of carbamates, as described in the scheme, some were prepared by hydroboration (**1f**, **1g**, **1i** and **1j**) and one by deprotonation and borylation (**1h**). Boc, *tert*-butoxycarbonyl; TBS, *tert*-butyldimethylsilyl.

(Fig. 1a, 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.

Results

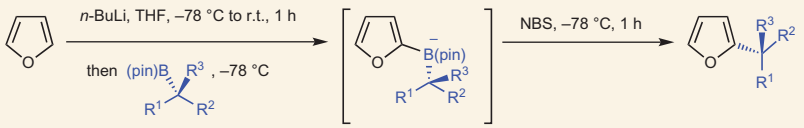
We began our studies with the addition of 2-lithiofuran to boronic ester (*R*)-**1a** (prepared by our lithiation–borylation methodology[39]) and explored a range of electrophiles (see the Supplementary Information). Of the electrophiles tested, *N*-bromosuccinimide (NBS) was found to be the optimum; it reacted rapidly at low temperature and furnished the product with complete stereospecificity (100% enantiospecificity (e.s.)) (Fig. 1c).

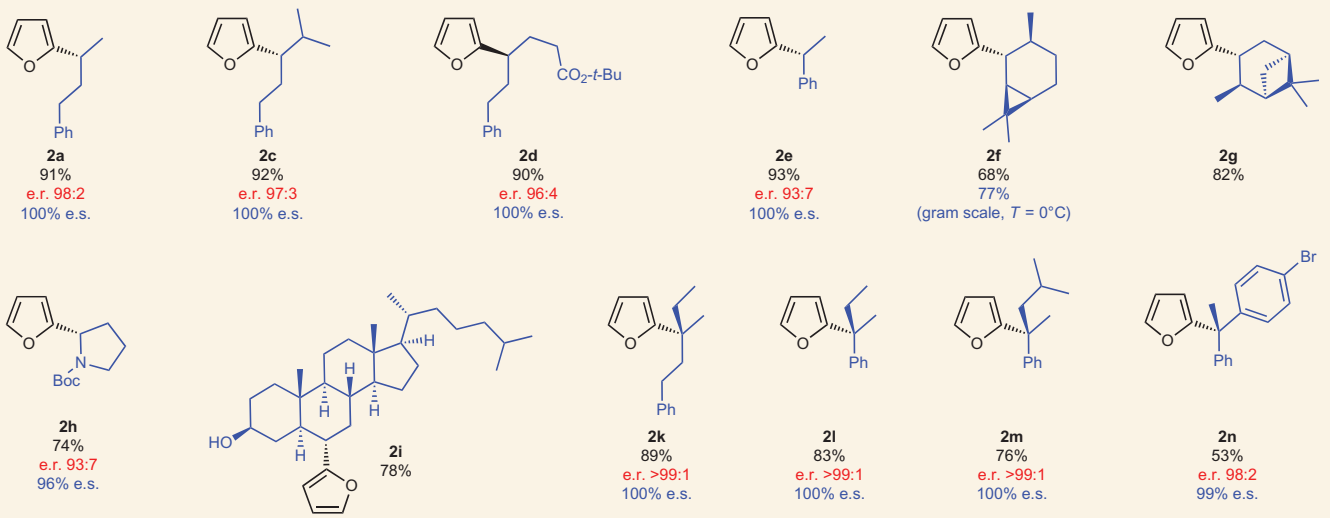
A range of enantioenriched secondary[39] and tertiary boronic esters[40–42] was then prepared by the lithiation–borylation methodology or by hydroboration (Fig. 2; see the Supplementary Information for details) and subsequently tested under these optimized reaction conditions (Table 1).

In general, secondary dialkyl- and secondary benzylic-substituted boronic esters **1a** and **1c**–**1e** reacted well to give the products **2a** and **2c**–**2e** 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 evaluated further 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 with complete diastereospecificity. (*R*)-2-borylpyrrolidine[43] (**1h**) also coupled effectively with 2-lithiofuran in good yield and complete enantiospecificity, which extended the range of functional groups compatible with the new protocol (**2h**). Direct hydroboration of β-cholesterol[44] (see the Supplementary Information) gave the cyclic boronic ester **1i**, which underwent the desired arylation process (**2i**) without the need for protection of the hydroxyl group.

The carene-coupling reaction (Table 1, **2f**) was carried out on a gram scale and with all the 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.

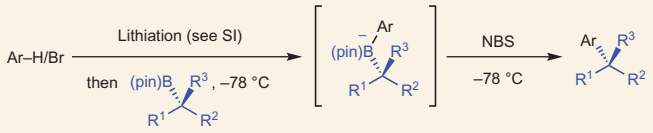
Table 1 | Scope of the secondary and tertiary boronic esters tested in the coupling reaction with furan.

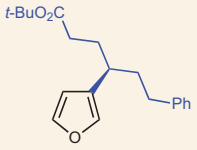




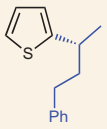
2a 91% e.r. 98:2 100% e.s.
2c 92% e.r. 97:3 100% e.s.
2d 90% e.r. 96:4 100% e.s.
2e 93% e.r. 93:7 100% e.s.
2f 68% 77% (gram scale, *T* = 0°C)
2g 82%
2h 74% e.r. 93:7 96% e.s.
2i 78%
2k 89% e.r. >99:1 100% e.s.
2l 83% e.r. >99:1 100% e.s.
2m 76% e.r. >99:1 100% e.s.
2n 53% e.r. 98:2 99% e.s.

Table 2 | Stereospecific coupling of electron-rich aromatics with secondary and tertiary boronic esters.

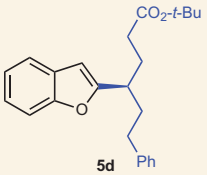




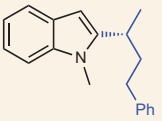
3d
85%
e.r. 96:4
100% e.s.



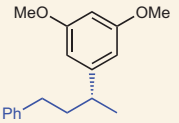
4a
92%
e.r. 98:2
100% e.s.



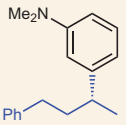
5d
66%
e.r. 96:4
100% e.s.



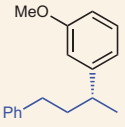
6a*
86%
e.r. 98:2
100% e.s.



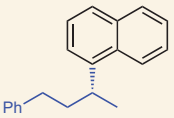
7a†
83%
e.r. 98:2
100% e.s.



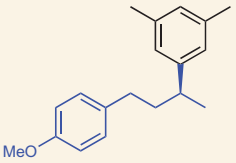
8a*
65%
e.r. 98:2
100% e.s.



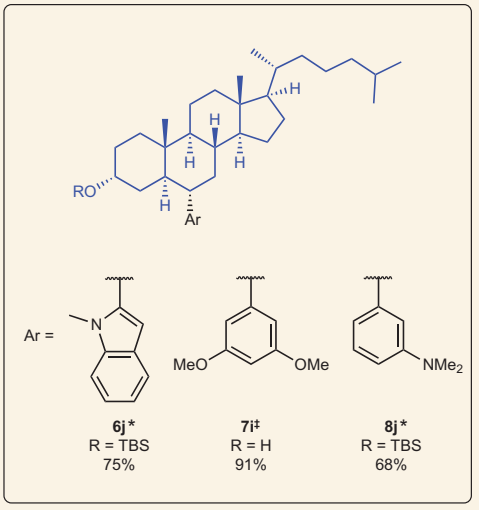
9a†
72%
e.r. 98:2
100% e.s.



10a†
89%
e.r. 98:2
100% e.s.



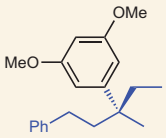
11b†
83%
e.r. 96:4
100% e.s.



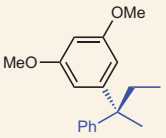
6j*
R = TBS
75%

7i‡
R = H
91%

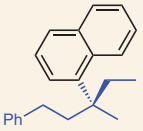
8j*
R = TBS
68%



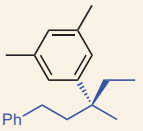
7k‡
78%
e.r. 99:1
100% e.s.



7l†
63%
e.r. >99:1
100% e.s.



10k†
75%
e.r. 99:1
100% e.s.



11k†
66%
e.r. 98:2
100% e.s.

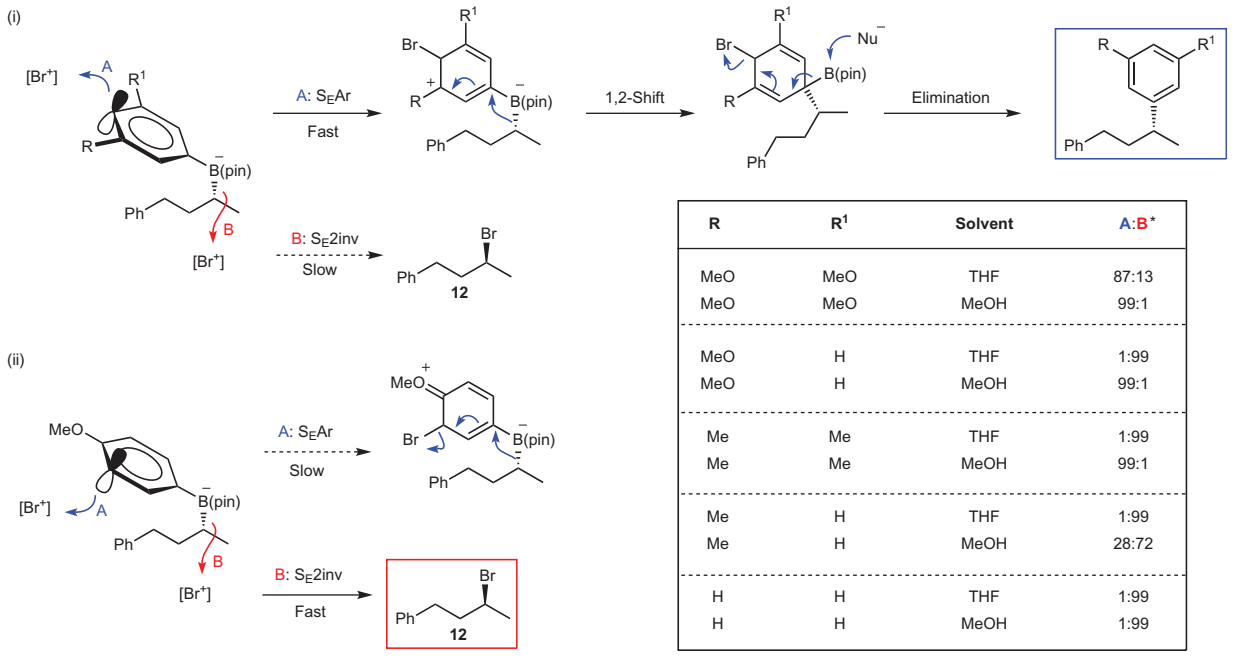
*NIS was used instead of NBS. †The solvent was switched to MeOH before NBS addition. ‡NBS was added in MeOH. SI, Supplementary Information.

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 the enantioenriched benzylic[40,41] and non-benzylic[42] tertiary boronic esters **1k**–**1n** in our process (Table 2) and found that the desired products **2k**–**2n** were obtained in good yields and complete stereospecificity, which demonstrates the power of the new methodology. As these boronic esters were prepared readily in an essentially enantiopure form, the furyl-coupled products were also obtained in a similarly enantiopure form.

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**, respectively, in high yield and complete enantiospecificity, although in the case of *N*-methyl indole, *N*-iodosuccinimide (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 NBS attack at the sp^3 carbon) (Fig. 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 replaced readily by hydrogen[45] or used in subsequent Ni-catalysed 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, for which we observed a complete switch from C(sp^3)-bromination to the desired arylation (Fig. 3). In all cases, coupled products were obtained in high yield and complete enantiospecificity (Table 2, **7a**–**10a** and **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-lithionaphthalene. Under optimized conditions, the tertiary boronic esters coupled in good-to-high yield and complete enantiospecificity in all cases (Table 2, **7k**, **7l**, **10k** and **11k**).

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, otherwise competing electrophilic attack at the sp^3



R	R^1	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 the reactions of aryl–boronate complexes with electrophiles, illustrated with [Br$^+$]. This highlights the major difference in the reaction pathway according to the substitution of the aromatic ring: *meta* donor groups favour (i), whereas *para* donor groups favour (ii). A further solvent effect was found in the cases of the *meta* donor groups in that (i) was favoured in polar protic media (MeOH). *Ratio determined by gas chromatography mass spectrometry and ^{1}H NMR spectroscopy analysis of the crude reaction mixture. S_EAr, aromatic electrophilic substitution.

carbon centre occurred (2- and 4-methoxyphenyllithium were not effective, whereas 3-methoxyphenyllithium was (**9a**))[38]. In the case of the least electron-rich aromatic, 3-methylphenyllithium, a 28:72 mixture of products comprising the desired coupled product and 2-bromo-4-phenylbutane **12** was obtained, showing the lower limit of the aromatic group that can be employed (see Discussion for this aspect of the mechanism).

The development of a methodology that enables the chemical modification of complex natural products is extremely challenging, but it can be highly rewarding as it can lead to molecules with improved properties[47]. By the 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 the steroid **1j**. Thus, coupling of **1j** with indole and several benzene derivatives gave the cholesterol analogues **6j**, **7i** and **8j** (Table 2) with full control of the regio- and stereochemistry.

Discussion

Our proposed mechanism for these reactions is presented in Figs 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 and react with a range of electrophiles with inversion (S_E2inv, for example, Fig. 3, Path B)[38,48]. To promote nucleophilic reaction of the boronate complex at the aromatic ring rather than at the sp^3 centre (as required for an arylation process) we reasoned that aromatics that are more electron rich would be required; we 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 Fig. 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 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 because now the two donor substituents do not reinforce each other, and Path B is enhanced, which leads to reaction via Path B (Fig. 3, (ii)).

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_E2inv dominated (Path B), but in MeOH, arylation dominated (Path A). This solvent effect is believed to result from increased rates of electrophilic aromatic substitution 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 (that is 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) (Fig. 3).

In conclusion, we have discovered, for the first time, a general method for coupling electron-rich aromatic and heteroaromatic compounds with enantioenriched secondary and tertiary boronic esters. The reaction involves the 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/rearomatization. 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 functionalized 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 equiv.) in THF (0.3 M) was cooled to −78 °C and treated with *n*-BuLi (1.2 equiv.,

1.6 M in hexanes). The cooling bath was removed and the mixture was stirred at room temperature for one hour. The mixture was cooled to −78 °C and **1a** (1 equiv.) was added dropwise as a solution in THF (0.5 M). The mixture was stirred at −78 °C for one hour, at which point ^{11}B NMR spectroscopy showed complete formation of the 'ate' complex (^{11}B NMR (96 MHz, THF) $\delta_B \approx 8$ ppm). A solution of NBS (1.2 equiv.) in THF (0.3 M) was added dropwise. After one hour at −78 °C, $Na_2S_2O_3$ (aqueous, saturated) 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 the complete experimental details and the characterization of compounds, see the Supplementary Information.

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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 the mechanistic discussions.

Additional information

Supplementary information and chemical compound information are available in the online version of the paper. Reprints and permissions information is available online at www.nature.com/reprints. Correspondence and requests for materials should be addressed to V.K.A.

Competing financial interests

The authors declare no competing financial interests.