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ortho-Directing Chromium Arene Complexes as Efficient Media–tors for Enantiospecific sp^2-sp^3 Cross-Coupling Reactions

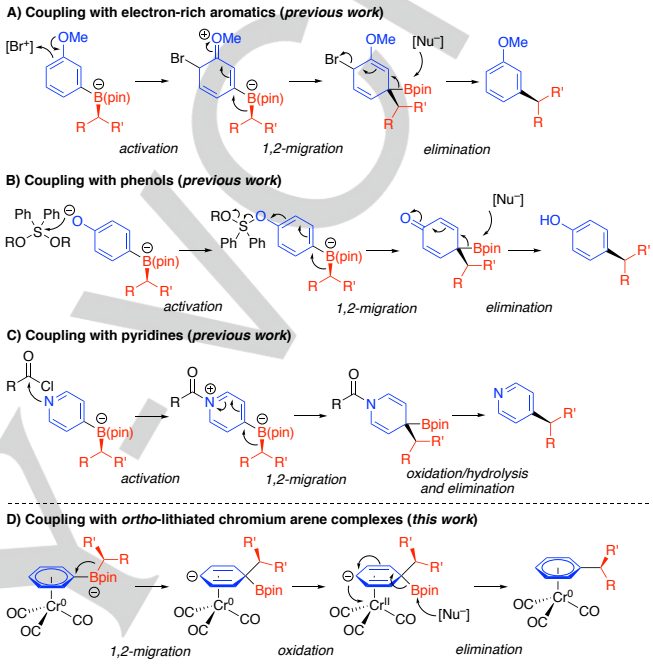
Raphael Bigler and Varinder K. Aggarwal*

Abstract: A new strategy for the coupling of a broad scope of electronically diverse aromatics to boronic esters is reported. The coupling sequence, which relies on the directed *ortho*-lithiation of chromium arene complexes followed by boronate formation and oxidation, occurs with complete *ortho*-selectivity and enantiospecificity to give the coupling products in excellent yields and with high functional group tolerance. An intermediate chromium arene boronate complex was characterized by X-ray, NMR and IR to elucidate the reaction mechanism.

While the coupling of aromatic building blocks *via* the Suzuki-Miyaura cross-coupling is well established in organic and medicinal chemistry, the enantiospecific coupling of secondary and tertiary alkyl boronic esters to aromatics through transition metal catalyzed processes is considerably more challenging.[1] Even though substantial progress has been made over the last two decades, most processes are not generally applicable with erosion of enantiomeric purity often observed.[2,3]

As an alternative to these palladium catalyzed processes, we[4] and Ready[5] have recently reported a series of transition metal-free, stereospecific couplings of chiral alkyl boronic esters with aryl lithium reagents (Scheme 1a-1c). These processes rely on four basic steps: (i) boronate formation, (ii) activation of the aromatic group, (iii) stereospecific 1,2-migration of the alkyl group, and (iv) elimination and rearomatization. Suitable activators were found for aromatics with electron-donating groups in the *meta*-positions and electron rich heterocycles (Scheme 1a),[4a,4b] phenols (Scheme 1b),[4f] and pyridines (Scheme 1c)[4c,5a].

However, aromatics without particular functional groups to react with an activating agent could not undergo such couplings (e.g. the simplest phenyl group). We reasoned that such couplings could be achieved if step (ii) in these transformations occurred spontaneously upon formation of the boronate complex. This could be realized if the aromatic possessed a strong electron sink. We therefore considered the possibility of using chromium arene complexes of the type [Cr(CO)$_3$(arene)], which are easily prepared[6] and known to react readily with organometallic reagents.[7] We queried whether they were sufficiently electron withdrawing to trigger the 1,2-migration without external activation (Scheme 1d). Subsequent oxidation of the resulting cyclohexadienyl anion to the corresponding cation and elimination of the boronic ester moiety would give the



Scheme 1. Enantiospecific sp^2-sp^3 coupling of electron-rich aromatics (A), phenols (B) or pyridines (C) and (D) proposed coupling work.

chromium arene complex. Further oxidation would lead to removal of the Cr(CO)$_3$ fragment to give the decomplexed coupled product. An additional attractive feature of chromium arene complexes is that they significantly acidify Ar–*H* bonds,[8a] facilitating lithiation including *ortho*-lithiation,[7b,8] thereby enabling the possibility for *ortho*-selective cross-coupling. In this paper we report our success in achieving this coupling reaction, although it ultimately differed mechanistically from the planned pathway.

We began our study by reacting Li[Cr(CO)$_3$(C$_6$H$_5$)] (1.25 equiv, generated by lithiation of [Cr(CO)$_3$(C$_6$H$_6$)] (**1a**) with *n*-BuLi) with boronic ester *rac*-**2a** in THF to give the corresponding boronate. After 4 h at –78 °C, I$_2$ (10 equiv) was added and the solution was warmed to rt overnight. To our delight, the decomplexed cross-coupled product *rac*-**3aa** was isolated in 21% yield. The major fraction contained a mixture of boron-incorporated products, indicating inefficient elimination of the boronic ester moiety in step (iv). By adding I$_2$ as a suspension in MeOH, the yield of *rac*-**3aa** dramatically increased to 83% and the only observed side product was the S_N2 iodination product 4-(4-methoxyphenyl)butan-2-yl iodide in 6% yield.[9] The formation of this side product was reduced to 3% by changing form MeOH to *n*-PrOH, and *rac*-**3aa** was obtained in 90% isolated yield. Importantly, when enantioenriched **2a** (er = 96:4) was used, **3aa** was obtained with identical enantiomeric excess indicating that the reaction occurs with perfect enantiospecificity (Table 1).

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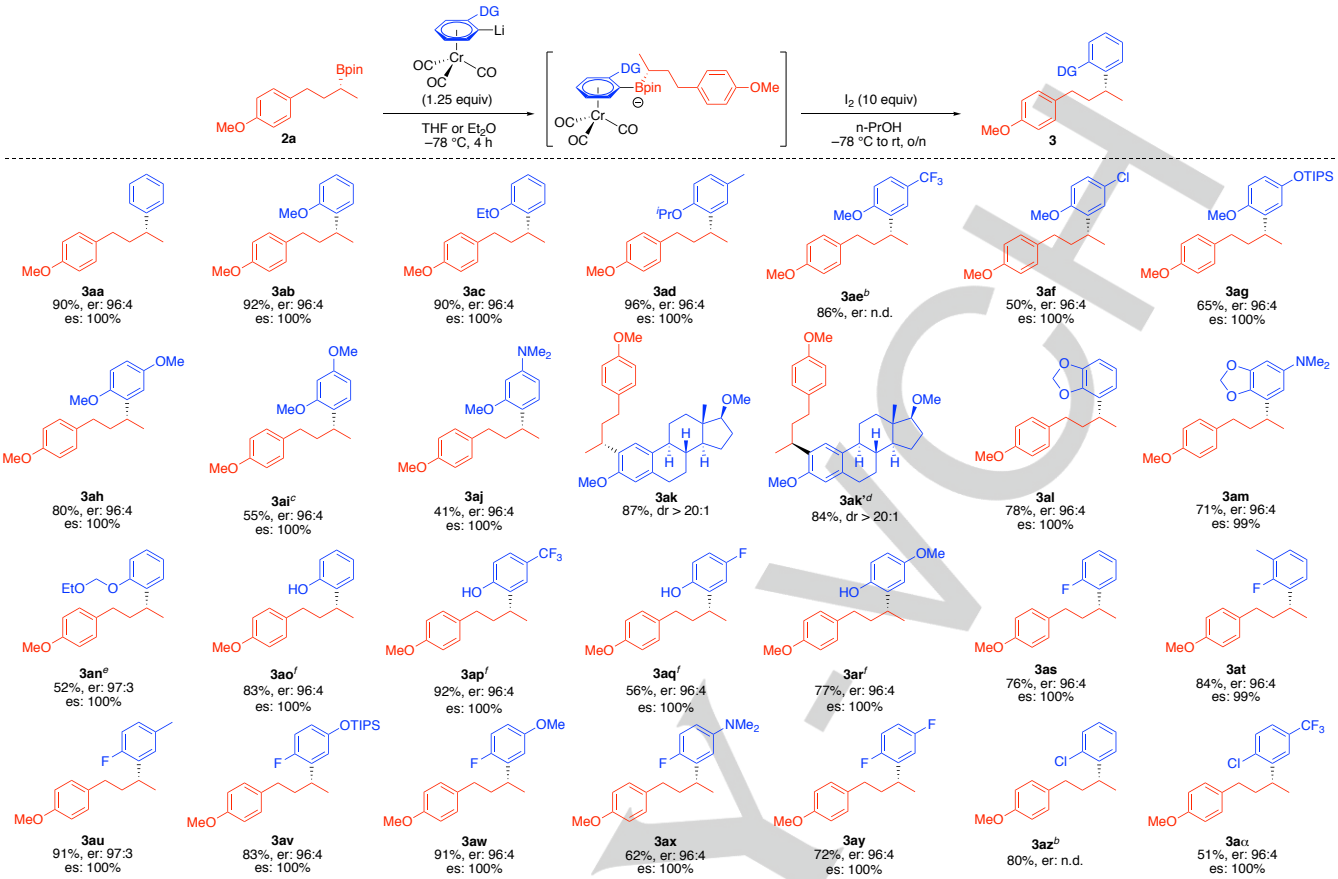
Table 1. Substrate scope of chromium arene complexes **1** for enantiospecific sp^2-sp^3 coupling to access *ortho*-cross-coupled aromatics.[a]



[a] Reactions were carried out with 0.30 mmol of boronic ester, 1.25 equiv of lithiated chromium arene complex, and 10.0 equiv of I_2. Yields recorded are those of isolated material. [b] No separation achieved by HPLC. [c] Reaction warmed to rt after addition of boronic ester. [d] *ent*-**2a** was used. [e] K_2HPO_4 added with I_2 in MeOH. [f] Ethoxymethyl acetal employed and no base used during oxidation.

When the $[Cr(CO)_3(anisole)]$ (**1b**) was employed under identical conditions, **3ab** was obtained in excellent yield and as a single regioisomer. Perfect *ortho*-selectivity was also observed for products **3ac** and **3ad** containing ethoxy and isopropoxy directing groups, respectively. A series of functional groups (i.e. alkyl (**3ad**), CF_3 (**3ae**), Cl (**3af**), OTIPS (**3g**), OMe (**3h**), and NMe_2 (**3j**)) were well tolerated and the sp^2-sp^3 cross-coupling occurred selectively *ortho* to the methoxy substituent.[6b,10] Interestingly, the 4-substituted product **3ai** was obtained as a single regioisomer in the case of the resorcinol derived chromium complex **1i**, indicating that the initially formed 2-lithiated arene is too hindered to form the boronate complex and rearranges to the 4-lithiated isomer, which is selectively trapped by **2a**.[11]

To highlight the synthetic utility of this method for late stage modification, the estradiol-derived chromium complex **1k** was selectively coupled in the 6-position with boronic esters **2a** and *ent*-**2a** to give the diastereomeric products **3ak** and **3ak'** in high yields and complete diastereoselectivity.[12] Furthermore, complexes **1l** and **1m** containing the benzodioxole motif, which is widely found in natural products and drugs, were selectively *mono*-lithiated and coupled to give products **3al** and **3am** in high yield and complete enantiospecificity.[13]

Besides ethers, acetal groups were also found to be effective directing group as exemplified by **3an**, which was obtained in 52% yield when KH_2PO_4 was added to quench HI formed during the reaction. In the absence of base, the free *ortho*-phenol **3ao** was isolated in 83% and with complete enantiospecificity. Again, functional groups were well tolerated as shown for products **3ap**–**3ar**. Even when other directing groups such as fluoro or methoxy were present, the *ortho*-phenols were obtained selectively.

As halogenated aromatics are important motifs in drugs and agrochemicals,[14] we next investigated the use of fluoro and chloro aromatics. To our delight, the reaction with fluorobenzene complex **1s** worked similarly well, and the desired product **3as** was obtained in 76% yield as a single regioisomer and with complete enantiospecificity. Again, functional groups such as methyl (**3t** and **3u**), OTIPS (**3av**), OMe (**3aw**), NMe_2 (**3ax**), and F (**3ay**) were well tolerated and the cross-coupling occurred selectively *ortho* to the fluoro substituent. Finally, the ability of chloride to act as a directing group was exemplified for the chlorinated chromium complexes **1z** and **1α**, which selectively afforded *ortho*-cross-coupled products **3az** and **3aα** in 80% and 51% isolated yield. Our results indicate that the order of *ortho*-directing ability decreases along the series: OCH_2OEt > F > OR > Cl > alkyl, CF_3, NMe_2, and OTIPS.[7b]

The scope of boronic esters was investigated next (Table 2). Boronic esters containing larger alkyl substituents such as ethyl (**2b**), isopropyl (**2c**) or cyclopropyl (**2d**) were well tolerated and the coupled products **3ba**–**3da** were isolated in 79–93% yield. An OTBS group was well tolerated when KH_2PO_4 was added with iodine as shown for **3ea**, which was obtained in 74% yield. Similarly to the OCH_2OEt group (*vide supra*), the OTBS group was cleaved in the absence of base and the free alcohol **3fa** was obtained in similar yield. Using KH_2PO_4 as additive, other functional groups such as acetal (**3ga**), ester (**3ha**), nitrile (**3ia**), azide (**3jb**), or olefin (**3kb**) were tolerated as well and the

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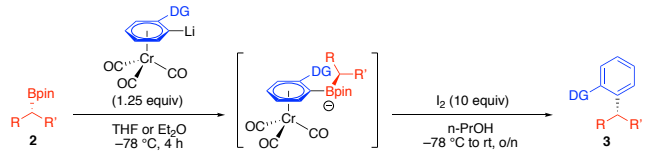
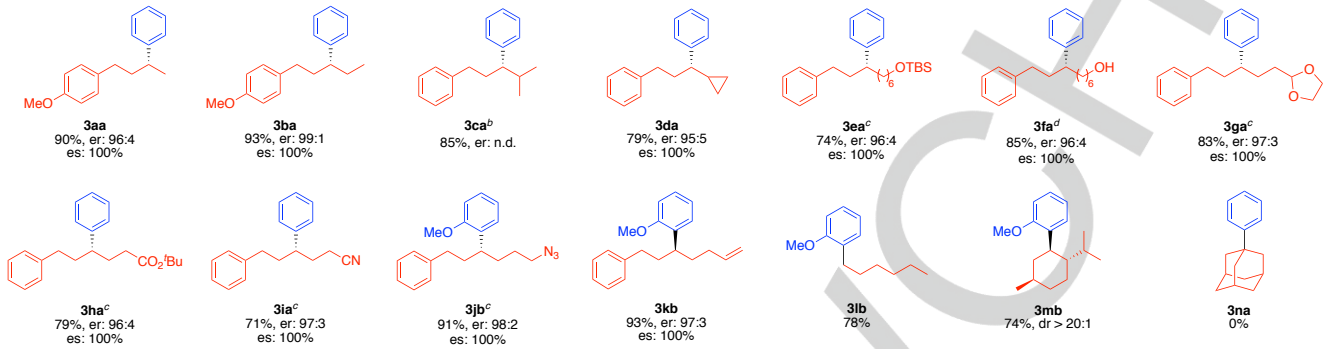
Table 2. Substrate scope of boronic esters **2** for enantiospecific sp^2-sp^3 coupling to access *ortho*-cross-coupled aromatics.[a]

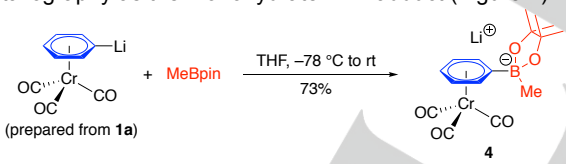




[a] Reactions were carried out with 0.30 mmol of boronic ester, 1.25 equiv of lithiated chromium arene complex, and 10.0 equiv of I_2. Yields recorded are those of isolated material. [b] No separation achieved by HPLC. [c] K_2HPO_4 added with I_2 in MeOH. [d] TBS ether employed and no base used during oxidation.

products were obtained in high yield and with perfect enantiospecificity. Finally, while the sterically demanding menthyl boronic ester **2m** was successfully coupled to afford **3mb** in 74% and >20:1 dr, the coupling was unsuccessful with tertiary boronic esters such as AdBpin (**2n**), possibly because of the increased steric bulk leading to inefficient boronate formation.

To shed light on the reaction mechanism of this new transformation, chromium benzene complex **1a** was treated with *n*-BuLi and MeBpin and the solution was stirred for 4 h at –78 °C in THF, at which point the ^{11}B NMR spectrum showed a singlet at 3.0 ppm characteristic of boronate complex **4** (Scheme 2). To our surprise, the ^{11}B NMR spectrum did not change upon stirring overnight at rt indicating that the chromium tricarbonyl group was not sufficiently electron-withdrawing for the 1,2-migration to occur. Complex **4** was isolated in 73% after trituration with Et_2O and the structure was unambiguously proven by X-ray crystallography as the monohydrate THF adduct (Figure 1).[15]



Scheme 2. Isolation of surprisingly stable chromium boronate complex **4**.

The crystal structure of **4** shows a planar arrangement of the six-membered ring with aromaticity clearly intact. The lithium counterion coordinates to an oxygen of the pinacol moiety, two solvent molecules (water and thf), as well as end-on to a CO ligand of the $Cr(CO)_3$ fragment. When this fragment is compared to the related complex $[Cr(CO)_3(C_6H_5CH(OEt)_2)]$,[16] the average C–O (carbon monoxide) bond length in **4** is slightly longer (1.160 Å vs. 1.152 Å) and the average Cr–C bond length is slightly shorter (1.828 Å vs. 1.840 Å). This indicates a stronger back-donation from the metal center, which can be attributed to greater electron donation from the electron rich aromatic ring. This is in agreement with IR spectroscopy, where the CO bands are at considerably lower frequency when compared to the parent chromium complex **1a** (1940 and 1825 cm^{-1} vs. 1982 and 1915 cm^{-1}),[17] indicating an electron-rich chromium center.

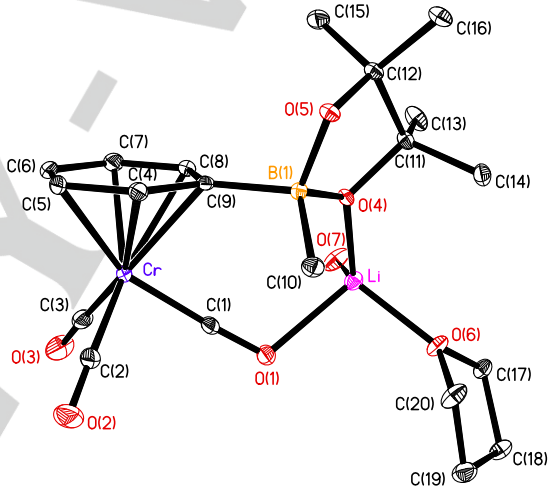
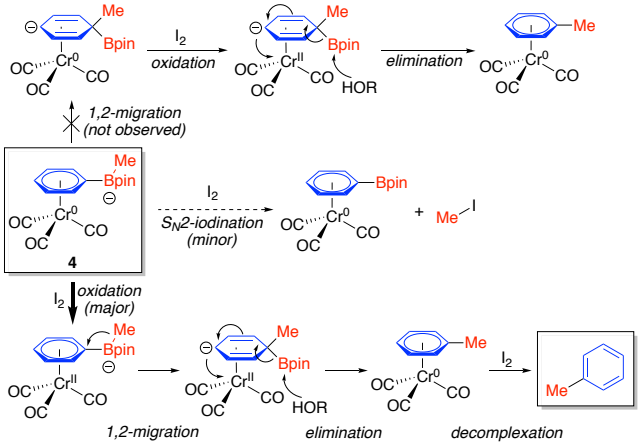


Figure 1. X-ray structure of **4** (ellipsoids are set at 30% probability (hydrogen atoms and a THF molecule omitted for clarity). Selected bond lengths [Å]: Cr–C1 1.810(2), C1–O1 1.166(3), Cr–C2 1.837(2), C2–O2 1.159(3), Cr–C3 1.837(3), C3–O3 1.156(3).

To explain the observed reactivity we propose the mechanism outlined in Scheme 3. Two reaction pathways are feasible when boronate **4** is treated with I_2. In the minor pathway, it reacts as an organometallic-type nucleophile at the sp^3 carbon to give the S_N2 iodination product (*vide supra*).[9] In the major pathway however, oxidation occurs at the electron-rich chromium center. This would render the $Cr(CO)_3$ motif more electron-withdrawing, triggering the 1,2-migration leading to the cyclohexadienyl complex. In the presence of alcoholic solvent, the boronic ester is eliminated (with formation of H^+) to give the cross-coupled chromium arene complex. Finally, the arene is decomplexed in the presence of excess iodine.

In conclusion, we have developed a new sp^2-sp^3 cross-coupling reaction, which relies on the use of easily accessible, electronically diverse chromium arene complexes, which act as traceless mediators to give the desired products in high yield, excellent *ortho*-selectivity and complete enantiospecificity. Based of the X-ray structure of boronate **4**, a mechanism based



Scheme 3. Proposed mechanism for chromium arene-mediated coupling.

on selective oxidation of Cr(0) followed by 1,2-migration and elimination is proposed. Although there has been a recent surge in stereoselective cross-coupling strategies,[2–5] most of the products presented here are inaccessible by such methods. Thus, the current method is a valuable addition to the ever-growing arsenal of cross-coupling reactions.

Acknowledgements

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Keywords: boronic esters • chromium complexes • aromatics • arylation • cross-coupling

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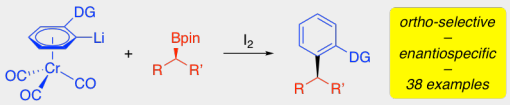

The sp^2-sp^3 coupling of chromium arene complexes with boronic esters is reported. After *ortho*-selective lithiation of the aromatic and boronate formation, oxidation at the electron-rich chromium center with I_2 triggers the 1,2-migration and Bpin elimination to directly afford the decomplexed *ortho*-coupled products in high yield and with complete enantiospecificity.

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