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Ate Complexes of Secondary Boronic Esters as Chiral Organometallic-Type Nucleophiles for Asymmetric Synthesis

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Supporting Information

ABSTRACT: The addition of an aryllithium reagent to a secondary boronic ester leads to an intermediate boron-ate complex that behaves as a chiral nucleophile, reacting with a broad range of electrophiles with inversion of stereochemistry. Depending on the electrophile, the C−B bond can be converted into C−I, C−Br, C−Cl, C−N, C−O, and C−C, all with very high levels of stereocontrol. This discovery now adds a new, readily available, configurationally stable, chiral organometallic-type reagent to the arsenal of methods for use in asymmetric organic synthesis.

The field of organic synthesis usually involves the union of nucleophiles with electrophiles.[1] However, while the development of complex chiral electrophiles has progressed significantly, the parallel development of chiral nucleophiles and in particular chiral organometallic reagents (without α-heteroatoms) has been considerably slower. Hoffmann[2] showed that chiral Grignard reagents could be obtained using the sulfoxide−Mg exchange reaction of halosulfoxides. Knochel[3] developed a method for converting organoboranes or catechol boronic esters into configurationally stable organozinc reagents. In both cases, the preparation of the organometallic was either somewhat limited in scope or rather cumbersome to perform in practice. More recently, Knochel has shown that configurationally labile organozinc reagents can be employed in highly diastereoselective synthesis.[4] In this paper, we report the discovery that secondary boronic esters can be converted into reactive nucleophiles by the addition of an aryllithium reagent and that the resulting boron-ate complexes react with a broad range of electrophiles with inversion of stereochemistry.

The limited progress in the development of enantioenriched chiral organometallics stems from the need to satisfy three fundamental requirements *simultaneously*: (i) ease of synthesis, (ii) configurational stability, and (iii) reactivity. The creation of chiral organometallics is especially challenging because these requirements are usually mutually exclusive. We believed that the choice of metal was critical, and elected boron since the first two requirements were easily met with chiral secondary boronic esters.[5] However, reactivity was a major issue, as boronic esters are stable, isolable compounds that are unreactive toward electrophiles. We reasoned that the corresponding boron-ate complexes should be more reactive. Indeed, some limited success had been reported in the reactions of benzyl trifluoroborate salts[6] and sp/sp^2 trifluoroborate salts[7] with specific electrophiles, but their scope was rather limited. In addition, secondary alkyl boranes have been halogenated with predominantly inversion

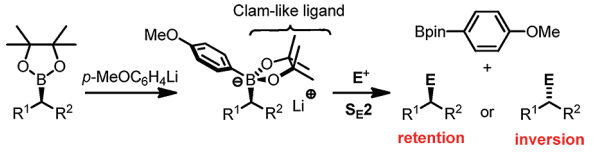
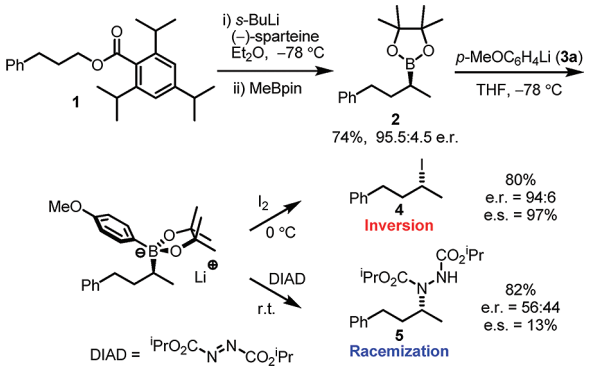


Figure 1. Formation of a reactive boron-ate complex and its potential reaction with electrophiles.

Scheme 1. Initial Investigations of the Reactivity of Boron-Ate Complexes



of configuration after activation with an alcoholic base.[8] In our design strategy, we chose to form a boron-ate complex directly from a boronic ester, initially with an electron-rich aryllithium, not only to provide further enhancement of its nucleophilicity but also to help stabilize the aryl boronic ester byproduct (Figure 1). In order to preserve the boron-ate complex, we needed a diol with a clamlike tendency to remain on boron and not dissociate, so we selected a simple pinacol (pin) ester.

A representative chiral secondary boronic ester, **2**, was prepared by lithiation−borylation of primary 2,4,6-triisopropylbenzoate **1** (Scheme 1).[9] We were delighted to find that treatment of boronic ester **2** with *p*-MeOC$_6$H$_4$Li (**3a**) followed by I$_2$ gave the corresponding secondary alkyl iodide **4** in high yield and with almost complete inversion of stereochemistry (Scheme 1). The enantiospecificity (e.s.) of the reaction ([ee of product/ee of starting material] × 100%) was 97%.[10] Interestingly, the intermediate boron-ate complex bearing two different carbon substituents reacted exclusively with the secondary alkyl substituent in preference to the aryl substituent, a feature

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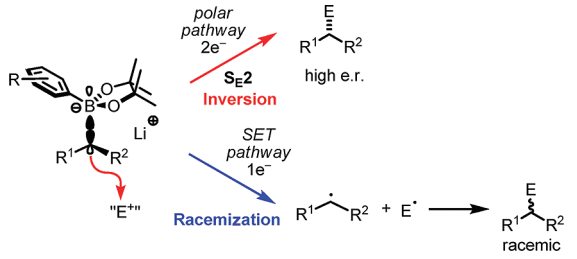
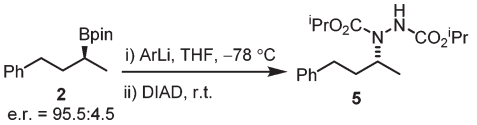


Figure 2. Possible reaction pathways of boron-ate complexes with electrophiles.

Table 1. Effect of Electron-Donating and -Withdrawing Substituents on the Enantioselectivity



entry	Ar	yield (%)	e.r.	e.s. (%)
1	4-MeOC$_6$H$_4$ (**3a**)	82	56:44	13
2	4-FC$_6$H$_4$	78	59:41	20
3	Ph	90	63:37	29
4	4-CF$_3$C$_6$H$_4$	85	70:30	44
5	3,5-(CF$_3$)$_2$C$_6$H$_3$ (**3b**)	74	80:20	66

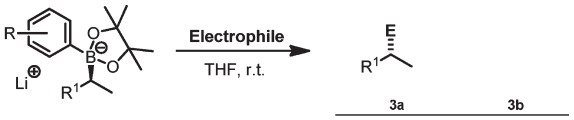
observed with all of the electrophiles explored. In contrast, in reactions of related boron-ate complexes with metal salts, exclusive transfer of the aryl group and not the secondary alkyl group to the electrophilic metal is consistently observed.[11]

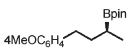
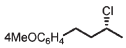
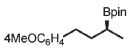
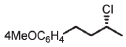
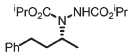
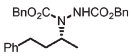
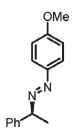
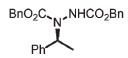
However, the high stereoselectivity observed with I_2 was not general for other electrophiles. For example, reaction with diisopropyl azodicarboxylate (DIAD) gave hydrazine **5** in high yield but in virtually racemic form (Scheme 1). We presumed that in this case, the reaction occurred predominantly through a single-electron transfer (SET) pathway (Figure 2),[2b,12] leading to the racemic product, whereas the reaction with I_2 occurred predominantly via a polar (two-electron) pathway, leading to the enantioenriched product. On this basis, we reasoned that the balance between the two pathways should be tunable through variation of the nature of the aryl group on boron. An electron-deficient aromatic group on boron should make the boron-ate complex less nucleophilic, but we expected the SET process to be slowed more than the polar process because removing an electron from the C−B bond of the boron-ate complex should be considerably harder.

A range of aryllithiums were therefore explored in the reaction with DIAD, and we indeed found that the e.s. steadily increased with increasing electron-withdrawing capacity of the aromatic ring, with the maximum stereoselectivity being observed with 3,5-(CF$_3$)$_2$C$_6$H$_3$Li (**3b**) (Table 1). Pentafluorophenyllithium was not effective in this process.

Reactions of several boron-ate complexes derived from both aryllithium reagents **3a** and **3b** were tested with a broad range of electrophiles (Table 2). *N*-iodosuccinimide (NIS) gave essentially complete enantiospecificity with both aryllithium reagents (entry 2), while *N*-bromosuccinimide (NBS) gave complete selectivity only with aryllithium **3b** (entry 3). For chlorination,

Table 2. Investigation into the Scope of Possible Electrophiles[a]



entry	boronic ester	electrophile	product	3a yield (%)	3a e.s. (%)	3b yield (%)	3b e.s. (%)
1[b]		I$_2$		84	97	---	---
2		NIS		80	100	85	99
3		NBS		50	90	85	100
4[c,d]		TCCA		60	66	80	92
5[d,e]		TCCA		---	---	83	100
6		DIAD		82	13	74	66
7[f]		DBAD		---	---	66	92
8[g]				---	---	64[h]	70
9				67	93	62	100
10				98	100	---	---
11				0	---	64	94
12[b]				0	---	44	100
13[e]		TCCA		52[i]	65	54[i]	96
14		DBAD		85	0	80	98

[a] All of the boronic esters had e.r. > 95:5. See the Supporting Information for full details. [b] Electrophile was added at 0 °C. [c] Electrophile was added as a solution in acetonitrile. [d] Separation of the enantiomers of the chloro analogue of **2** was not possible, but the 4-MeO derivative was separable. [e] Electrophile was added as a solution in acetonitrile at −40 °C. [f] Electrophile was added as a solution in propionitrile with 12-crown-4. [g] Electrophile was added as a solution in propionitrile at −78 °C with 12-crown-4. [h] The intermediate TMP-protected alcohol was directly converted to the secondary alcohol. The reported yield is for the two steps. [i] Yield was calculated by ^{1}H NMR analysis using an internal standard because of product volatility.

we found that trichloroisocyanuric acid (TCCA) was superior to *N*-chlorosuccinimide (which was unreactive) and that once again higher selectivity was found with aryllithium **3b** than with aryllithium **3a** (entry 4).[13] Performing the reaction at −40 °C

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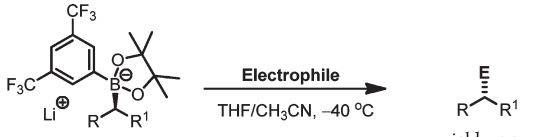
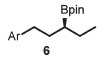
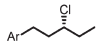
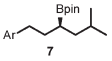
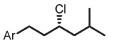
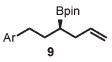
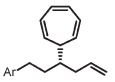
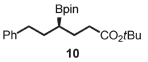
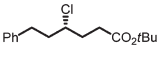
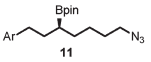
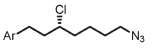
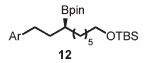
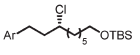
Table 3. Investigation into the Scope of Boronic Esters[a]



entry	boronic ester	electrophile	product	yield (%)	e.s. (%)
1		TCCA		91	100
2		TCCA		41	98
3		TCCA		79[b]	88
4[c]				59	73
5		TCCA		84	100
6		TCCA		61	98
7		TCCA		92	100

[a] All of the boronic esters had e.r. > 96:4. See the Supporting Information for full details. Ar = 4-$MeOC_6H_4$. [b] Yield was calculated by ^1H NMR analysis using an internal standard. The product was prone to decomposition on silica gel. [c] Electrophile was added at −40 °C with 12-crown-4 and then warmed to room temperature.

with aryllithium **3b** led to essentially complete enantiospecificity (entry 5). As indicated above, reaction with DIAD employing aryllithium **3b** led to high e.s. (entry 6), and through further optimization of the conditions[14] and switching to dibenzyl azodicarboxylate (DBAD), we obtained considerably higher selectivity (entry 7). This one-pot transformation of a secondary boronic ester into an amino functionality is a significant advance over current methods.[15]

The oxidation of a boronic ester to an alcohol with *retention* of configuration is the archetypal transformation of organoboron intermediates. With a suitable electrophilic oxidant, we expected that this fundamental transformation could be made to occur with *inversion* of stereochemistry using our novel protocol. After exploration of various oxidants and reaction optimization, we found that 2,2,6,6-tetramethylpiperidine-1-oxoammonium tetrafluoroborate[16] was an effective electrophilic oxidant, and following cleavage of the N−O bond, the secondary alcohol was obtained in 70% e.s. with predominantly *inversion* of stereochemistry (entry 8). Reaction with tropylium tetrafluoroborate was also successful and again furnished the adduct with essentially complete enantiospecificity (inversion) even with electron-rich aryllithium **3a** (entry 9).

Benzylic boronic esters were also explored. These were expected to be much more reactive but also considerably more prone to SET processes because of the increased stability of an intermediate benzylic radical. Indeed, while there are a few examples of benzylic organometallic reagents bearing neighboring chelating substituents to hold and lock the stereochemistry of the metal, racemization results without such groups.[17] In the event, the reaction with tropylium tetrafluoroborate gave the desired adduct *without any racemization* with both aryllithium reagents **3a** and **3b** (entry 10). Eschenmoser's salt and a diazonium salt were also suitable electrophiles, furnishing the corresponding amine and azo products with *complete enantiospecificity* (entries 11 and 12). The latter two electrophiles did not react with secondary dialkylboronic esters, demonstrating the increased reactivity of the benzylic substrate. The reaction with TCCA also occurred with essentially complete enantiospecificity (entry 13).

The expected increase in the radical (SET) pathway and therefore erosion of the e.s. did not materialize with these benzylic substrates; in fact, the exact opposite was observed. We presume that the π system of the aromatic ring must enhance the polar ($2e^-$) pathway to a greater extent than the radical ($1e^-$) pathway.

The most dramatic effect of the nature of aryllithium reagent **3** on the enantiospecificity of the reaction was observed in the amination of the benzylic boronic ester using DBAD (entry 14): with electron-rich *p*-$MeOC_6H_4Li$ (**3a**), racemic hydrazine was obtained, whereas with electron-deficient 3,5-$(CF_3)_2C_6H_3Li$ (**3b**), the hydrazine was formed with 98% e.s.

In order to determine the scope of this chemistry, we briefly explored reactions of more hindered and more functionalized boronic esters, predominantly with TCCA (Table 3).[13] We were pleased to see that not only the ethyl analogue **6** but also the considerably more hindered isobutyl analogue **7** could be used, furnishing the corresponding chloride with high e.s. (entries 1 and 2). Chlorination of the similarly hindered benzylic boronic ester **8** also occurred with good enantiospecificity (entry 3). While chlorination using TCCA was not compatible with the pendant alkene on boronic ester **9**, alkylation with tropylium tetrafluoroborate occurred uneventfully to furnish the desired adduct with good selectivity (entry 4). Esters are common functional groups in organic synthesis, so it was important to find out whether aryllithium **3b** would show sufficient chemoselectivity and react with the hindered pinacol boronic ester rather than a carboxylic ester.[18] Chlorination of boronic ester **10** was therefore tested, and the product was obtained in high yield with complete enantiospecificity (entry 5), thus indicating a very high level of chemoselectivity. Finally, we have shown that boronic esters bearing an azide (**11**, entry 6) or a silylether (**12**, entry 7) are also tolerated, thus demonstrating the relatively broad functional group compatibility of this chemistry.

The reactions of chiral organometallic reagents (Grignard reagents, organolithiums, organozincs) with electrophiles usually occur with retention of configuration.[2c,19] In contrast, it was reported that Stille-type cross-coupling of benzylic stannanes[20] and halosilanes[21] occurs with inversion. Sporadic examples of Suzuki-type cross-coupling of secondary boronic esters have also been reported. Crudden[22] reported reactions of benzylic boronic esters that occurred with retention of configuration, and Suginome[23] extended this protocol to include α-(acylamino)benzylic boronic esters. More recently, Molander reported the coupling of β-amido secondary alkyl trifluoroborates.[24] In the latter two cases, the reactions occurred with inversion of stereochemistry. The closest examples to the current work involve the halogenation of boron-ate complexes derived from chiral boranes which occurred with inversion.[8] The S_E2 reactions that we have described also occur with inversion, presumably because of the steric hindrance of the boron-ate complex (Figure 2); its bulk prevents the electrophile from approaching from the same side as boron, so the reactions occur with inversion. The fact that the S_E2 reactions must occur with

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inversion also accounts for the observed chemoselective reaction of the alkyl over the aryl substituent; the aryl substituent cannot invert.

In conclusion, we have discovered a surprisingly simple approach for the creation of a new class of enantioenriched, chiral organometallics that *simultaneously* satisfies the three fundamental requirements of ease of synthesis, configurational stability, and reactivity: the addition of an aryllithium to a secondary pinacol boronic ester. The subsequent boron-ate complex that is generated behaves like a new class of organometallic reagents that react with a broad range of electrophiles, all with inversion of configuration. Depending on the nature of the electrophile, some of the reactions are complicated by competing SET processes, which result in a diminution of the enantiospecificity. This is often a dominant feature of many conventional chiral organometallic reagents but one that was only occasionally observed with the boron-ate complexes. Furthermore, and unlike other organometallic reagents, we have the capacity to tune the reactivity of the boron-ate complex by varying the aryl group to minimize competing SET processes, thereby leading to an enhancement in the enantiospecificity.

■ ASSOCIATED CONTENT

Supporting Information. Details of mechanistic studies demonstrating the competing radical pathway in the amination process, experimental procedures, and analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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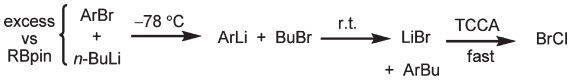

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