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Enantiospecific Synthesis of *ortho*-Substituted Benzylic Boronic Esters by a 1,2-Metalate Rearrangement/1,3-Borotropic Shift Sequence

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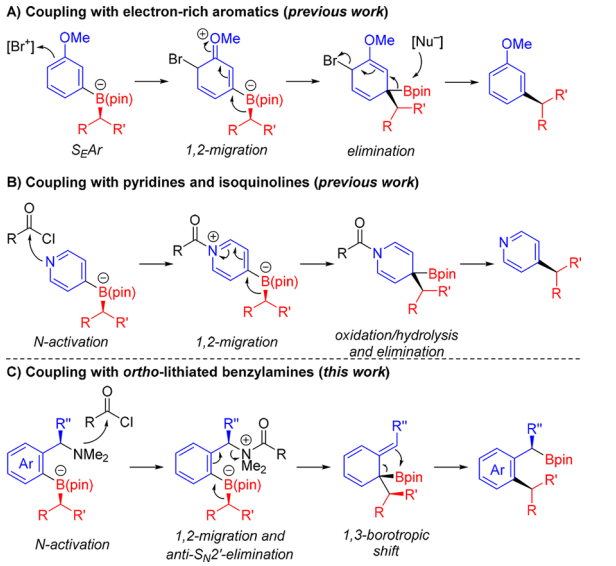
Supporting Information

ABSTRACT: Coupling reactions between benzylamines and boronic esters have been investigated. *ortho*-Lithiated benzylamines react with boronic esters and a *N*-activator to afford *ortho*-substituted benzylic boronic esters with formal 1,1′-benzylidene insertion into the C−B bond. The reaction occurs by a S_N2' elimination and 1,2-metalate rearrangement of the *N*-activated boronate complex to afford a dearomatized intermediate, which undergoes a Lewis-acid catalyzed 1,3-borotropic shift to afford the boronic ester products in high yield and with excellent enantiospecificity. The use of enantioenriched α-substituted benzylamines gave the corresponding secondary boronic esters with high ee.

The enantiospecific coupling of secondary and tertiary boronic esters to aromatics through transition-metal catalyzed processes is challenging.[1] Although some progress has been made enabling certain secondary boronic esters to be employed, the reactions are not generally applicable.[2,3] We recently reported an alternative transition metal-free and stereospecific sp^2-sp^3 coupling of chiral secondary and tertiary boronic esters with electron-rich aryl lithium reagents that showed considerable scope (Scheme 1a).[4] In related work, we[5] (and Ready[6]) showed that pyridines could also be coupled with complete stereospecificity to a similar range of boronic esters (Scheme 1b). These processes involve four basic steps: (i) boronate formation, (ii) activation, (iii) 1,2-migration, and (iv) elimination/rearomatization. We reasoned that this methodology would be significantly enhanced if the boron moiety could be retained in the product because of its broad versatility.[7] Inspired by the coupling reactions with pyridines, we considered a related transformation with *ortho*-lithiated benzylamines (Scheme 1c).[8] We considered that *N*-activation of the corresponding boronate complex would trigger the 1,2-migration/*anti*-S_N2' elimination of the carbamate to give a dearomatized intermediate, which should undergo a *suprafacial* 1,3-borotropic shift.[9] This would lead to the desired aromatic product in which the boron moiety is retained. Although the 1,3-borotropic shift of allylic boronic acid pinacol esters is exceedingly slow,[10] we reasoned that the driving force of aromatization would facilitate this rearrangement. In this communication, we describe the realization of this transformation to give a variety of *ortho*-substituted benzylic boronic esters in high yield and with excellent enantiospecificity.

Scheme 1. Enantiospecific sp^2-sp^3 Couplings of Boronic Esters with Electron-Rich Aromatic (A) or Pyridines (B) and Proposed Work



We began our study by reacting (2-((dimethylamino)-methyl)phenyl)lithium (**Li−1a**) with CyBpin (**2a**) to give the corresponding boronate complex and screened a broad range of *N*-activators (see SI for details). Among the electrophiles tested, $ClCO_2CMe_2CCl_3$ (Me_2Troc−Cl) was highly selective giving the dearomatized intermediate over borinic ester side products, rapidly, even at low temperature. However, despite having the driving force of rearomatization, the subsequent 1,3-borotropic shift was very slow even at elevated temperature, and considerable protodeboronation occurred. DFT calculations showed that rearomatization lowered the barrier for the 1,3-borotropic shift from 37 to 25 kcal/mol (see SI for details). We therefore investigated the use of Lewis acids to promote the 1,3-borotropic shift by coordinating to oxygen, hence reducing the p_O-p_B π-donation.[11] The dramatic effect π-donation of the ligand to boron has on the rate of the 1,3-borotropic shift is shown by the fact that allyl boranes[12] undergo 1,3-borotropic shifts much faster than pinacol boronic esters (−78 °C vs >120 °C),[10] whereas diamino boranes[13] require very high temper-

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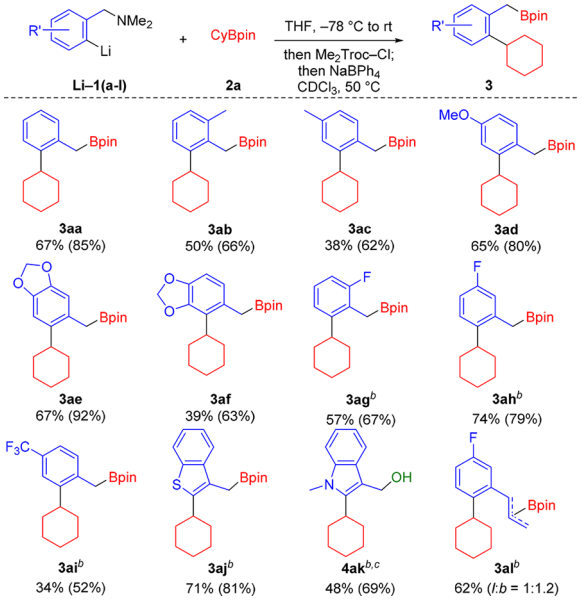
atures (>200 °C).[12] Unfortunately, most of the Lewis acids tested led to decomposition of the dearomatized intermediate (see SI for details). Interestingly, the addition of 12-crown-4 prevented the 1,3-borotropic shift, indicating that the LiCl generated during the reaction was catalyzing the rearrangement. To increase its potency, we performed an *in situ* salt metathesis with $NaBPh_4$ and a solvent exchange to noncoordinating chloroform to give "naked" $LiBPh_4$,[14] which then efficiently catalyzed the reaction affording the benzylic boronate product **3aa** in 85% NMR and 67% isolated yield.

Following this protocol, a series of *ortho*-lithiated benzylamines **Li−1** (generated either by Br/Li exchange or directed lithiation, see SI for details) was tested with CyBpin (**2a**) to assess the scope of the aromatic component that can be employed in this transformation (Scheme 2). A broad range of

Scheme 2. Scope of Lithiated Benzylamines[a]



[a]Reactions were carried out with 0.50 mmol of boronic ester, 1.05 equiv of Ar−Li, 1.10 equiv of Me_2Troc−Cl and 1.00 equiv of $NaBPh_4$. Yields recorded are those of isolated material (NMR yields in brackets). [b]1,3-Borotropic shift conducted at 65 °C. [c]Product isolated after oxidation with sodium perborate (see SI for details).

electron-rich (**3ab−3af**) and electron-poor (**3ag−3ai**) aromatics can be used in this coupling reaction, as well as heteroaromatic compounds exemplified by **3aj** and **4ak**. Finally, an allylic amine was also tested to afford allylic boronic ester **3al** (*l*:*b* = 1:1.2). Products **3aa−3al** were obtained in 52−92% NMR yield, with slightly lower isolated yields due to the moderate stability of primary benzylic boronic esters on silica gel. Furthermore, the reaction was readily scalable, and **3aa** was obtained in 64% isolated yield on a 10 mmol scale employing a catalytic amount of $NaBPh_4$ (10 mol %).

The scope of the boronic ester was also explored (Scheme 3) and included primary, secondary, aryl, and alkenyl boronic esters (**3aa−3ga**). Furthermore, the tertiary boronic ester AdBpin (**2e**) and even B_2pin_2 (**2h**) afforded the corresponding products in 64% and 44% isolated yield, respectively. Essentially perfect enantiospecificity was observed for enantio- and diastereo-enriched boronic esters (**2i−2v**) to afford the corresponding products **3ia−3va** in high enantiomeric purity (er = 95:5 to 99:1, dr >20:1). Importantly, a broad range of functional groups were well tolerated, highlighting synthetic utility of this dearomatizing 1,2-metalate rearrangement/rearomatizing 1,3-borotropic shift process.

We also investigated the use of readily available enantioenriched α-substituted benzylamines (Scheme 4). Following the standard procedure, reaction of **2a** with *ortho*-lithiated benzylamine **Li−1m** yielded the corresponding secondary boronic ester **3am** with 94:6 er and formal retention of configuration, indicating a high preference for the *anti*-S_N2' elimination pathway. Similarly, the reaction with **2d** afforded **3dm** with 96:4 er, whereas primary boronic esters **2b** and **2c** gave slightly reduced enantiospecificity (89:11 and 91:9 er, respectively). Importantly, the combination of enantioenriched boronic esters with either enantiomer of the *ortho*-lithiated α-methylbenzylamine afforded the corresponding, diastereomeric products **3im−3tn** with excellent diastereomeric ratios, indicating that the reaction does not suffer from significant matched/mismatched effects.

To determine the origin of both the sense and the level of stereospecificity, we performed further experimental and computational investigation. For the transformation of secondary boronic ester **2i** (95:5 er) with the *R* enantiomer of the *ortho*-lithiated benzyl amine **Li−1m** (99:1 er) to give boronic ester product **3im**, NMR analysis of the dearomatized intermediate showed a dr of 92:8, suggesting that the acylation-triggered 1,2-metalate rearrangement/fragmentation proceeded with 94% stereospecificity (Scheme 5), similar to that of secondary boronic esters **2a** and **2d**. Upon 1,3-borotropic shift, which was initiated through salt metathesis/solvent exchange, the benzylic boronic ester product was isolated in similar levels of diastereoselectivity,[15] pointing toward a highly stereospecific 1,3-borotropic shift, as expected.

DFT calculations (B3LYP/6-31G*) revealed that the less-than-perfect level of stereospecificity of the acylation-triggered 1,2-metalate rearrangement/fragmentation step was locked in at the acylation event (see SI for details). Specifically, both the *syn* and *anti* conformers of a zwitterionic *N*-acylated amino boronate of the type under investigation undergo C−N bond cleavage with a very low-barrier (<2 kcal/mol), significantly more facile than interconversion of the conformers through bond rotation (>17 kcal/mol; Figure 1). As expected, for all low-energy conformers, the benzylic hydrogen atom lies approximately in the plane of the aromatic ring pointing toward the boronate moiety. The resulting zwitterionic boronate carbenium species then undergoes a similarly facile 1,2-metalate rearrangement (~1.4 kcal/mol). A low-energy transition state for a more concerted 1,2-metalate rearrangement/fragmentation for either the *syn* or the *anti* conformer could not be identified, presumably owing to steric hindrance. These results show that both *syn* and *anti* conformers of the putative intermediate cannot interconvert and lead to stereoisomeric products with equal facility. Therefore, the higher levels of enantiospecificity for the transformation of secondary boronic esters (>90%) relative to that of primary boronic esters (~80%; see Scheme 4) has its origins in the former engendering a more selective *N*-acylation of the *anti* conformer of the amino boronate intermediate relative to the corresponding *syn* conformer. The surprisingly precarious origin of stereospecificity, as suggested by computation, was borne out experimentally where simply replacing the dimethyl amino group with a diethyl amino group for the transformation of CyBpin led to a switch in the sense of stereospecificity (94:6 versus 25:75 er; see SI for details).

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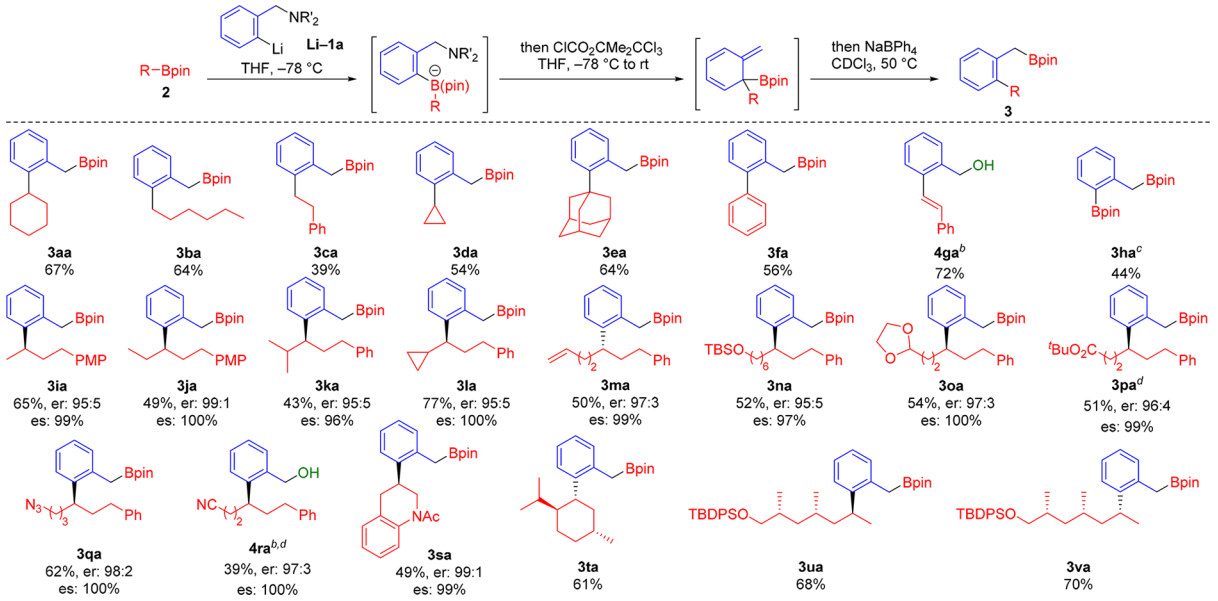
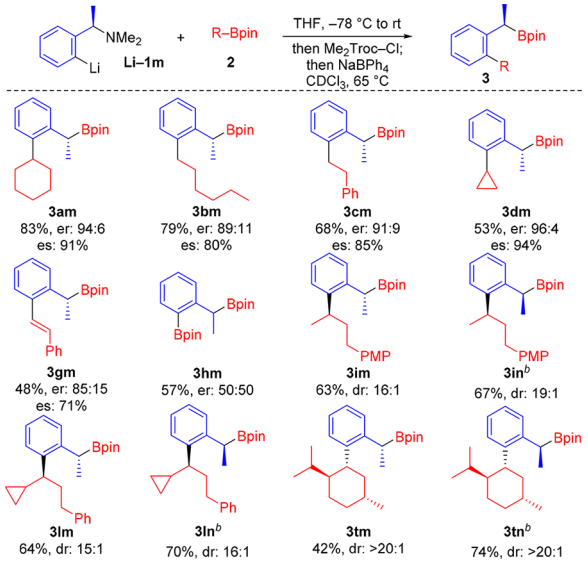
Scheme 3. Stereospecific Coupling of *ortho*-Lithiated *N,N*-Dialkyl Benzylamine with Boronic Esters[a]



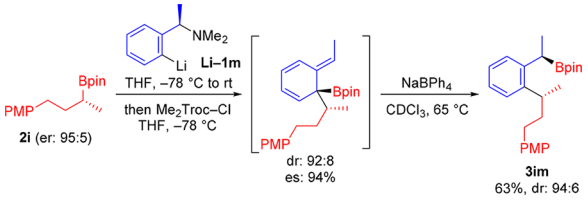
[a]Reactions were carried out with 0.50 mmol of boronic ester, 1.05 equiv of Ar–Li, 1.10 equiv of Me_2Troc–Cl, and 1.00 equiv of $NaBPh_4$. Yields recorded are those of isolated material; er determined by HPLC analysis. [b]Product isolated after oxidation (see SI for details). [c]1,3-Borotropic shift conducted at rt. [d]Boronate complex formed at −100 °C.

Scheme 4. *ortho*-Lithiated α-Methylbenzylamines[a]



[a]Reactions were carried out with 0.50 mmol of boronic ester, 1.05 equiv of Ar–Li, 1.10 equiv of Me_2Troc–Cl, and 1.00 equiv of $NaBPh_4$. Yields recorded are those of isolated material; es determined by HPLC analysis; dr determined by ^{1}H NMR analysis of purified product. [b]Enantiomeric (*S*)-(2-(1-(dimethylamino)ethyl)phenyl)lithium **Li–1n** was used instead.

Scheme 5. Mechanistic Analysis with Boronic Ester 2i



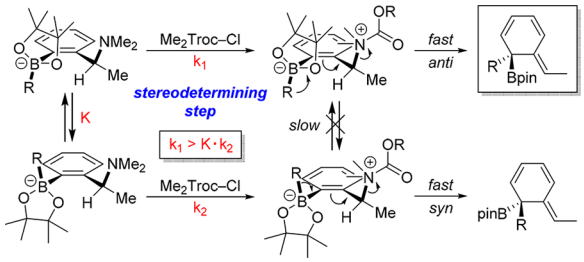


Figure 1. Reaction profile of the acylation-triggered 1,2-metalate rearrangement/fragmentation step.

However, not all of the boronic esters tested worked. Notable exceptions included benzylic and tertiary boronic esters (with the exception of AdBpin (**2e**, *vide supra*)). In both cases, the 1,2-metalate rearrangement occurred, but the dearomatized intermediate did not undergo the 1,3-borotropic shift. In the former case, the intermediate underwent a Cope rearrangement to yield arylboronic ester **3wa′** instead (Scheme 6a). In the latter case, a *retro*-ene reaction intervened affording the *ortho*-tolylboronic ester **3xa′** (Scheme 6b). This reaction does not occur for AdBpin (**2ea**, Scheme 3), as an *anti*-Bredt product would arise. Finally, dearomatized intermediates generated from *para*-lithiated benzylamines did not undergo a double 1,3-borotropic shift sequence (Scheme 6c). Instead, a non-stereoselective von Auwers-type reaction[16] afforded arylboronic ester **3uo′** with formal inverse 1,4′-benzylidene insertion.

The synthetic utility of the dearomatized intermediate is not restricted to the 1,3-borotropic-shift process (Scheme 7). For example, allylboration of benzaldehyde or ethyl glyoxalate afforded the corresponding alcohols **5** and **6** with excellent diastereo- and enantiocontrol (dr > 20:1, er = 95:5 and 91:9, respectively).[17] Similarly to benzylic boronic esters (Scheme 6a), the intermediate prepared from allylBpin underwent an enantiospecific Cope rearrangement to give **7** with 97:3 er. That the Cope rearrangement is significantly more facile than

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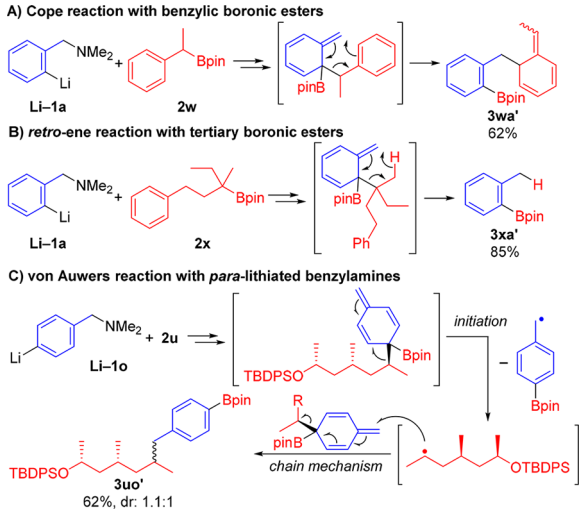
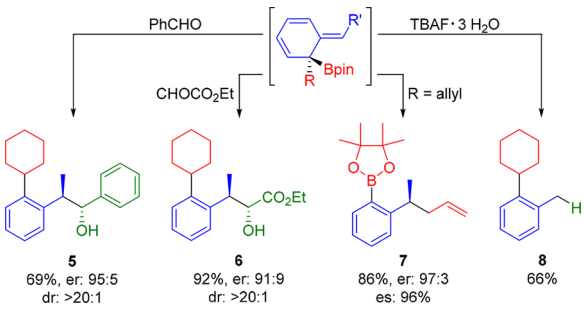
Scheme 6. Unsuccessful Substrates



Scheme 7. Synthetic Utility of Intermediate



the 1,3 borotropic shift was confirmed through computation (see SI for details). Finally, treatment of the intermediate with TBAF trihydrate[18] selectively yielded protodeboronation product **8**, an example in which the benzylic amine acted as a traceless directing group.

In conclusion, a new strategy for the stereospecific synthesis of *ortho*-substituted benzylic boronic esters has been developed. The method relies on a 1,2-metalate rearrangement/*anti*-S_N2' reaction followed by a suprafacial 1,3-borotropic shift giving rise to sp^2–sp^3 cross-coupled products in high enantiopurity in which the boronic ester moiety is retained for further transformations.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.7b05880.

Detailed experimental procedures and characterization of all products (PDF)

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Notes

The authors declare no competing financial interest.

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