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α-Sulfanyl Benzoates as Precursors to Li and Mg Carbenoids for the Stereoselective Iterative Homologation of Boronic Esters

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Supporting Information

ABSTRACT: The stereoselective reagent-controlled homologation of boronic esters is one of a small number of iterable synthetic transformations that if automated could form the basis of a veritable molecule-making machine. Recently, α-stannyl trisopropylbenzoates and α-sulfanyl chlorides have emerged as useful building blocks for the iterative homologation of boronic esters. However, α-stannyl benzoates need to be prepared using stoichiometric amounts of the (+)- or (−)-enantiomer of the scarcely available and expensive diamine sparteine; also, these building blocks, together with the byproducts that are generated during homologation, are perceived as being toxic. On the other hand, α-sulfanyl chlorides are difficult to prepare with high levels of enantipurity and are prone to undergo deleterious acid–base side-reactions under the reaction conditions for homologation, leading to low stereoselectivity. Here, we show that the use of a hybrid of these two building blocks, namely, α-sulfanyl trisopropylbenzoates, largely overcomes the above drawbacks. Through either the sulfination of α-magnesiated benzoates with either enantiomer of Andersen’s readily available menthol-derived sulfate or the α-alkylation of enantiopure S-chiral α-sulfanyl benzoates, we have prepared a range of highly enantiopure mono- and disubstituted α-sulfanyl benzoates, some bearing sensitive functional groups. Barbier-type reaction conditions have been developed that allow these building blocks to be converted into lithium (t-BuLi) and magnesium (t-PrMgCl–LiCl) carbenoids in the presence of boronic esters, thus allowing efficient and highly stereospecific homologation. The use of magnesium carbenoids allows carbon chains to be grown with the incorporation of sensitive functional groups, such as alkyl/aryl halides, azides, and esters. The use of lithium carbenoids, which are less sensitive to steric hindrance, allows sterically encumbered carbon–carbon bonds to be forged. We have also shown that these building blocks can be used consecutively in three- and four-step iterative homologation processes, without intervening column chromatography, to give contiguously substituted carbon chains with very high levels of enantio- and diastereoselectivity.

1. INTRODUCTION

The development of stereoselective carbon–carbon bond-forming reactions that are insensitive to both the configuration of existing stereogenic centers and the presence of distal functional groups holds great promise as the driver that will usher in an era of molecule-making machines.1 Transformations that allow molecules to be grown one-, two-, or three carbon atoms at a time, in an iterative fashion, are especially attractive owing to their suitability for automation.2 The reagent-controlled stereoselective homologation of boronic esters, a transformation that employs chiral nonracemic carbenoid precursors as building blocks, is one such reaction (Figure 1A). Inspired by the work of Matteson,3 Hoppe,4 Beak,5 and Hoffmann,6 our research group (Figure 1B)7 and the research group of Blakemore (Figure 1C)8 have developed a series of building blocks and methods that has ripened this transformation for automation. An ideal process has emerged and satisfies the following conditions: (1) Ready access to a wide range of highly enantiomerically pure (>99:1) bench-stable carbenoid building blocks exists; the carbenoid carbon atom should bear (a) a group that can be rapidly and stereospecifically transformed into a reactive metal group, (b) a suitable leaving group, and (c) an arrangement of substituents (or protected forms thereof) that can be translated into one displayed by the desired product. (2) The process has the ability to stereospecifically metatate (Li or Mg) the carbenoid under reaction conditions that maintain high chemical and configurational stability. (3) In the presence of a boronic ester, which should be the limiting reactant, the metal carbenoid can undergo irreversible stereospecific metal–boron exchange to form a boronate complex in quantitative yield. (4) The boronate complex undergoes invertive 1,2-metalate rearrangement with high stereochemical fidelity, but only at higher

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temperatures in a regime where excess metal-stabilized carbenoid is no longer chemically stable, thus avoiding overhomologation. (5) The process has the ability to rapidly and efficiently isolate the homologated boronic ester for further transformations (including homologation), or byproducts are suitably benign to allow further homologations to be carried out in one pot.

In 2014, we reported on α-stannyl ethyl benzoate 3 (Figure 1B) as a bench-stable carbenoid precursor for the iterative homologation of contiguously methyl-substituted hydrocarbon chains. This precursor, which could be obtained in very high levels of enantiopurity (>99.9:0.01) through recrystallization, allowed assembly line synthesis to be performed with exceptionally high levels of efficiency, where any diastereomer of a 10-carbon-long chain (e.g., 4, Figure 1B) could be grown one carbon atom at a time in high yield as a single enantiomer, without intervening column chromatography. However, despite the utility, a number of unfavorable attributes continue to concern us: (a) both enantiomers of sparteine are required but the (−)-enantiomer has become more difficult to access than the (+)-enantiomer; (b) only the methyl-substituted precursors are crystalline, thus making it difficult to obtain other derivatives in highly enantioenriched form; (c) toxic Me₃SnCl is required for their synthesis, and the precursors themselves (and byproducts produced during consumption) are perceived to be toxic, thus hampering uptake by the scientific community.

In the early stages of the development of our assembly line protocol, we were drawn to the α-chloro sulfoxides (e.g., anti-6, Figure 1C) employed by Blakemore,8 owing to the favorable attributes conferred by the sulfinyl moiety with respect to toxicity and that the more benign organomagnesium reagents could be used for their transformation into carbenoids. Moving away from chloride as the leaving group, thus hoping to avoid the side-reactions prevalent in Blakemore’s homologation protocol, we spent considerable effort investigating α-sulfinyl benzoates (Figure 1E).11 We found that their conversion into lithium or magnesium carbenoids through sulfoxide−metal exchange in single homologations of simple boronic esters led to the one-carbon-extended boronic esters in good yields and stereospecificity, as was later independently confirmed in a single example reported by O’Brien (Figure 1D).12 However, their use as the sole carbenoid precursor in sequential one-pot homologations gave levels of efficiency that paled in comparison to that of the α-stannyl derivatives. Recently, with the aim of preparing more elaborately substituted hydrocarbon chains and a changing viewpoint that a molecule-making machine need not make sole use of one part of the carbenoid, we decided to revisit the α-sulfinyl benzoates. Herein, we disclose much improved methods for their synthesis and reveal significant value in their use in assembly line iterative homologation of boronic esters.

2. RESULTS AND DISCUSSION

2.1. Synthesis of α-Sulfinyl Benzoates by Sulfinylation. Initially we focused on the preparation of α-sulfinyl benzoates by employing conditions reported for the corresponding carbamates. O’Brien discovered that treatment of racemic lithiated carbamate 8 with enantiomerically pure Andersen’s menthol-derived sulinate 9 gave a mixture of the syn and anti α-sulfinyl carbamates 10, but with only moderate levels of enantioselectivity (Figure 2A).12 The erosion of
forms of a range of enantiopure α-sulfinyl benzoates bearing substituents of varying steric demand (14b–e) and presenting useful functional handles, alkene 14f and ketal 14g (Figure 2B). The relative and absolute configuration of α-sulfinyl benzoates was determined by comparing chiral HPLC traces of products obtained from the sulfinylation of magnesiated benzoates by using (a) a racemic magnesiated benzoate/racemic sulfinylation reagent (mixture of all four stereoisomeric products); (b) a racemic magnesiated benzoate/enantiopure sulfinylation reagent (mixture of two isomers, epimeric at the carbon center); (c) an enantioenriched magnesiated benzoate/racemic sulfinylation reagent (mixture of two isomers, epimeric at the sulfur center; see the Supporting Information).

Through retentive sulfoxide–lithium exchange, the syn and anti diastereomers depicted in Figure 2 are precursors to the S- and R-configured lithium carbenoids, respectively. However, should the anti diastereomer be unavailable owing to difficulties in obtaining it in pure form, the R-configured lithium carbenoid could alternatively be formed through sulfoxide–lithium exchange of the enantiomer of the syn-diastereomer, which can be accessed using the other enantiomer of Andersen’s menthol-based sulfinate, the enantiomeric reagents being commercially available with equal readiness. Additionally, we investigated a number of epimerization experiments under both commercial and thermodynamic control and found that the Knochel–Hauser base (TMPPMgCLiCl)14 together with indene as a proton source could affect kinetic epimerization of a 1:1 mixture of syn- and anti-14b to give a mixture enriched with the syn-isomer (dr 86:14; see the Supporting Information).

2.2. Homologation of Boronic Esters with α-Sulfinyl Benzoates. With a selection of enantiopure α-sulfinyl benzoates 14a–g in hand, we tested their effectiveness as precursors to metal carbenoids, through sulfoxide–metal exchange, for the homologation of boronic esters. Optimization of the sulfoxide–metal exchange/borylation sequence was carried out using enantioenriched α-sulfinyl benzoate anti-14b and boronic ester 15. Because Blakemore and co-workers showed that the use of Li carbenoids, which were generated from α-chloro sulfoxides, gave significantly improved results in the homologation of boronic esters compared to the corresponding Mg carbenoids,36 we initially investigated the use of organolithium reagents to trigger the exchange (Figure 3). Treatment of a solution of anti-14b in tetrahydrofuran (THF) at −78 °C with n-BuLi, allowing the resulting mixture

Figure 2. Synthesis of α-sulfinyl carbamates (A) and benzoates (B) through the sulfinylation of α-lithiated and -magnesiated precursors with Andersen’s menthol-derived sulfinate. Diarylurea were not separable by column chromatography, and yields were determined based on 1H NMR analysis. A portion of the mixture was purified by reverse-phase HPLC to obtain analytically pure syn and anti-14d.

stereospecificity was surprising because it was well documented that organometals react with these sulfinyl reagents with high-fidelity inversion of configuration at the sulfur atom.13 The origin of the offending minor enantiomer for each diastereomer was attributed to the degenerate sulfinyl-transfer reaction of enantiomeric lithium carbamate and early formed α-sulfinyl carbamate product, effectively leading to products derived from a double-inversion pathway. O’Brien overcame this problem by generating the lithiated carbamate in enantioenriched form (using chiral nonracemic sparteine or 1,2-diaminocyclohexane derivative 12), thus allowing one diastereomer to be isolated with high levels of stereoselectivity. We confirmed that this enantioeroding side-reaction was also operating in the sulfinylation of benzoate 13, the chromatographically separable anti and syn α-sulfinyl products 14a being isolated in 87:13 and 88:12 er, respectively. Interestingly, increasing the number of equivalents of sulfinate 9 did not lead to a significant increase in er value of product, going against what would be predicted by the participation of competing sulfinylating species. We were hesitant about adopting O’Brien’s solution to the problem, as it would make us reliant on having ready access to sparteine or diamine 12. We wondered whether the nuclophilicity of the α-magnesiated benzoate would be sufficiently tempered to allow only sulfinyl transfer with Andersen’s reagent 9 and not the degenerate sulfinyl transfer with product. We were pleased to discover that upon transmetalation of the initially formed lithiated benzoate to the magnesiated benzoate (addition of MgBr2·OEt2) and then treatment with sulfinate 9, the syn and anti diastereomers 14a were isolated with near-perfect levels of enantiopurity. These highly enabling reaction conditions subsequently allowed the preparation of both diastereomeric
to evolve for only 1 min before addition of the boronic ester, and warming the ternary mixture to room temperature\textsuperscript{12} did not lead to the desired homologation reaction. Presumably, the initially generated lithium carbenoid is unstable in the presence of the relatively acidic alkyl–aryl sulfoxide byproduct; in contrast, the same carbenoid generated through tin–lithium exchange of the corresponding α-stannyl benzoate is stable for hours at −78 °C.\textsuperscript{7d} Using Barbier-type conditions—the addition of n-BuLi to a solution of anti-14b and boronic ester 15 in THF at −78 °C—delivered the one-carbon-homologated boronic ester 16 in 54% yield. Here, the sulfoxide–lithium exchange is sufficiently faster than reaction of n-BuLi with the boronic ester; also, the reaction of the lithium carbenoid with the boronic ester, thus forming the desired boronate complex, is faster than apparent side-reactions of the carbenoid. The use of t-BuLi under the same conditions gave the boronic ester 16 in slightly higher yield (59% yield), presumably owing to the absence of α-hydrogen atoms in the alkyl–aryl sulfoxide byproduct. Further exploration of reaction conditions revealed that the use of solvents other than THF (Et\textsubscript{2}O, TBME, CPME, PhMe) resulted in low conversion of the boronic ester starting material. Using α−BuLi (2.0 equiv) and anti-14b (1.05 equiv), with the boronic ester starting material 15 being the limiting species, proved to be optimal; these reaction conditions resulted in complete conversion of 15 (16/15 > 99:1, as determined by GCMS analysis) and isolation of the homologated boronic ester 16 in good yield and enantiopurity (78% yield, 99:1 er; Figure 3, entry 8). The extra equivalent of t-BuLi is needed as a sacrificial base to neutralize deleterious internal proton sources, specifically, the ortho-positioned sp\textsuperscript{2} C–H bonds in the alkyl–aryl sulfoxide byproduct (MeOD trapping experiments confirmed the operation of this process; see the Supporting Information)\textsuperscript{15} and adventitious H\textsubscript{2}O;\textsuperscript{16} the low yield of isolated byproduct might also point to t-BuLi-mediated fragmentation of the byproduct to the sulfenic acid and isobutene.

With the aim of identifying reaction conditions that are milder and more tolerant of sensitive functional groups, we also investigated the homologation of boronic ester 15 by using the in situ generated magnesium carbenoids, which are more chemically and configurationally stable than the corresponding lithium carbenoids.\textsuperscript{8g,12,17} Initial experiments revealed that using i-PrMgCl to trigger the putative sulfoxide–magnesium exchange of α-sulfinyl benzoate, anti-14b, at −78 °C, followed by addition of the boronic ester 15, gave an inseparable mixture of the desired one-carbon-homologated boronic product together with the two-carbon-homologated boronic ester. Presumably, the in situ formed magnesium carbenoid is stable at the temperature where the intermediate boronate undergoes 1,2-metallate rearrangement, thus allowing the desired one-carbon-homologated boronic ester to react with another equivalent of carbenoid; in contrast, lithium carbenoids decompose at ca. −40 °C to benign byproducts.\textsuperscript{8} Interestingly, the use of the turbo Grignard reagent, i-PrMgCl-LiCl,\textsuperscript{18} led to much improved results; the boronic ester starting material 15 was completely converted into the desired one-carbon-homologated boronic ester 16, with none of the higher homologues detected (76% yield, >99:1 er; Figure 4). The same result was obtained by using the more convenient Barbier-like conditions (addition of the turbo Grignard to a mixture of the α-sulfinyl benzoates and the boronic ester). Moreover we did not observe any differences in the reactivity of the syn and anti diastereomers of α-sulfinyl benzoate 14b for the homologation of boronic ester 15 under the optimal homologation conditions.

With optimal conditions for homologating with both lithium and magnesium carbenoid intermediates established (Figure 3, entry 8; Figure 4), we explored the substrate scope of the homologation reactions (Figure 5). Therefore, a range of boronic esters (17) were homologated with a range of substituted α-sulfinyl benzoates 14a–g as precursors to lithium carbenoids (conditions A: sulfinyl benzoate, 1.05 equiv; t-BuLi, 2.0 equiv; Barbier-type conditions) and as precursors to magnesium carbenoids (conditions B: sulfinyl benzoate, 1.3 equiv, and warming the ternary mixture to room temperature\textsuperscript{12} did not lead to the desired homologation reaction. Presumably, the initially generated lithium carbenoid is unstable in the presence of the relatively acidic alkyl–aryl sulfoxide byproduct; in contrast, the same carbenoid generated through tin–lithium exchange of the corresponding α-stannyl benzoate is stable for hours at −78 °C.\textsuperscript{7d} Using Barbier-type conditions—the addition of n-BuLi to a solution of anti-14b and boronic ester 15 in THF at −78 °C—delivered the one-carbon-homologated boronic ester 16 in 54% yield. Here, the sulfoxide–lithium exchange is sufficiently faster than reaction of n-BuLi with the boronic ester; also, the reaction of the lithium carbenoid with the boronic ester, thus forming the desired boronate complex, is faster than apparent side-reactions of the carbenoid. The use of t-BuLi under the same conditions gave the boronic ester 16 in slightly higher yield (59% yield), presumably owing to the absence of α-hydrogen atoms in the alkyl–aryl sulfoxide byproduct. Further exploration of reaction conditions revealed that the use of solvents other than THF (Et\textsubscript{2}O, TBME, CPME, PhMe) resulted in low conversion of the boronic ester starting material. Using α−BuLi (2.0 equiv) and anti-14b (1.05 equiv), with the boronic ester starting material 15 being the limiting species, proved to be optimal; these reaction conditions resulted in complete conversion of 15 (16/15 > 99:1, as determined by GCMS analysis) and isolation of the homologated boronic ester 16 in good yield and enantiopurity (78% yield, 99:1 er; Figure 3, entry 8). The extra equivalent of t-BuLi is needed as a sacrificial base to neutralize deleterious internal proton sources, specifically, the ortho-positioned sp\textsuperscript{2} C–H bonds in the alkyl–aryl sulfoxide byproduct (MeOD trapping experiments confirmed the operation of this process; see the Supporting Information)\textsuperscript{15} and adventitious H\textsubscript{2}O;\textsuperscript{16} the low yield of isolated byproduct might also point to t-BuLi-mediated fragmentation of the byproduct to the sulfenic acid and isobutene.

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equiv; i-PrMgCl-LiCl, 1.2 equiv; Barbier-type conditions). In general, the use of α-sulfinyl benzoates bearing nonbranched substituents (14a–c, 14f, 14g) gave good yields of the homologated boronic esters with excellent levels of enantiospecificity for both sets of reaction conditions (Figure 5). The yields were always 10–20% higher when using lithium carbenoids. However, α-sulfinyl benzoates bearing branched substituents could provide serviceable quantities of the homologated boronic ester only when using the lithium carbenoids (14d). In agreement with the results of Blakemore,14e the insertion of magnesium carbenoids into the C–B bond of boronic esters is much more sensitive to steric hindrance than that of the corresponding lithium carbenoids, and thus magnesium carbenoids do not possess the level of reactivity required for inserting methine units bearing branched substituents. However, although Blakemore’s isopropyl-substituted α-chloro lithium carbenoid, the precursor of which could be prepared in only 70:30 er, did not affect the desired homologation to any detectable level,8f the corresponding benzoate, as described here, allowed the same homologation to be effected in 54% yield and with very high levels of enantiospecificity (95% es, Figure 5). The superior performance of the α-sulfinyl benzoates is due to the greater steric hindrance in the vicinity of the carbenoid carbon atom, a characteristic that increases the stability of the carbenoid precursor with respect to α-deprotonation.8d For Blakemore, this side-reaction could be partially suppressed by using the deuterium isopropyl ether of the carbenoids, thus taking advantage of a primary kinetic isotope effect.8b–d When using tert-butyl-substituted benzoate 14e, none of the desired homologated boronic ester was detected using either set of conditions; the isolation of the neopentyl benzoate (protodesulfination of the carbenoid precursor) suggests that internal quenching of the lithium carbenoid was the dominant process, formation of the desired boronate complex being too slow owing to steric hindrance.

However, moderate conversion of the starting boronic ester (18e/17a, 80:20) and moderate levels of enantiospecificity (77% es) were observed by using an inverse-addition protocol: addition of the carbenoid precursor to a Et2O solution of t-BuLi in the presence of the tridentate ligand N,N,N′,N″,N‴-pentamethyldiethylenetriamine (PMDTA), followed by addition of the boronic ester (Figure 5, conditions C). These results suggest that for sterically hindered α-sulfinyl benzoates, sulfoxide–lithium exchange is significantly slower than what is typically expected, where even in the presence of a large excess of organolithium reagent (inverse addition) internal quenching of the desired lithium carbenoid through an acid–base reaction with a carbenoid precursor is a competing process. The boronic ester component was also varied (products 18h–o). Boronic esters bearing either a tert-butyl ester group or an azido group could be homologated only with in situ formed magnesium carbenoids (products 18h and 18i); evidently, for lithium carbenoids, these functional groups react with the organolithium species faster than the formation of the requisite boronate complex. Again, the magnesium carbenoids were superior for the homologation of vinyl and aryl boronic esters (products 18j and 18k). However, lithium carbenoids were superior for the homologation of more sterically hindered pinacol boronic esters (products 18m and 18l). We wondered whether the use of a less sterically hindered diol ligand on the boron center, specifically a neopentylglycol boronic ester,30a could lead to improved yields for the homologation of sterically hindered organoborons with magnesium carbenoids. Indeed for the homologation of cyclohexyl neopentylglycol boronic ester with the magnesium carbenoid, product 18n, which was obtained through oxidation of the initially formed product 18o, was obtained in 10% higher yield (48%) compared to the process with the pinacol boronic ester (36%). Interestingly, for the corresponding homologations with lithium carbenoids, the neopentylglycol boronic ester gave significantly lower yields (59% versus 36%).

2.3. Synthesis of α-Sulfinyl Benzoates by Alkylation. One of the potential advantages of using sulfoxides in place of stannanes for the homologation of boronic esters is the extremely rapid sulfoxide–metal exchange reaction in the presence of organometals; this transformation is typically so fast that trace amounts of water are trapped by the metal carbenoid rather than by the initially added organolithium reagent.15 This rapid exchange process means that the carbenoids can be generated in the presence of the boronic ester (Barbier-type conditions) and, if the ensuing trapping of the boronic ester with carbenoid to form the boronate is sufficiently rapid, that functional groups that would normally be reactive toward organometals would be left unscathed. However, the method described above for preparing α-sulfinyl benzoates (the sulfinylation of metal carbenoids) nullifies this particular utility because it is not amenable for preparing α-sulfinyl benzoates containing such sensitive functional groups. Therefore, we also decided to explore the synthesis of these precursors through the alkylation of α-sulfinyl benzoate 19, which can be deprotonated at the α-position by using relatively weak bases, such as lithium diisopropylamide (LDA). Enantiomerically pure α-sulfinyl benzoate 19 could be prepared using the sulfinylation of magnesiated methyl benzoate or through the S_N2 displacement reaction of known enantioenriched α-chloro sulfoxide.19b The alkylation of benzoate 19 proved to be highly dependent on the electrophile and required extensive optimization. For the methylation of benzoate 19 by using methyl iodide as the electrophile, the overall yield and diastereoselectivity were dependent on the base used, whether using in situ (Barbier-type conditions) or ex situ conditions (MeI added after deprotonation), and on scale (Figure 6). The use of lithium hexamethyldisilazane (LiHMDS) under in situ conditions gave substantial quantities of the dialkylated product; however, by using ex situ conditions, this undesired process could be suppressed to give a mixture of the syn and anti products (83% overall yield), favoring the latter (1:3). The use of NaHMDS

![Figure 6](image-url)
under in situ conditions on a moderately large scale (7.7 mmol) proved superior, allowing both diastereomers to be isolated in excellent overall yield and in roughly equal amounts. Unfortunately, the conditions optimized for MeI (NaHMDS under in situ conditions) were unsuitable for both less reactive more hindered electrophiles and highly reactive electrophiles, decomposition of the in situ formed carbanion or the desired product being apparent. Therefore, further optimization was necessary for preparing other classes of substituted α-sulfinyl benzoates (Figure 7). For example, the introduction of an ethyl substituent, using either EtBr or EtI in conjunction with a variety of bases, failed to give the desired product in useful levels of conversion. However, treatment of a solution of α-sulfinyl benzoate 19 and EtOTf (1.1 equiv) in THF at −78 °C with NaHMDS (1.05 equiv) gave the desired product in 58% yield as a separable mixture of syn and anti diastereomers (anti-14c/syn-14c, ca. 1:2). This protocol with highly reactive triflate electrophiles also proved suitable for introducing a butyl substituent (anti-14m/syn-14m, ca. 1:1; 78% yield) and an ester-terminated pentyl substituent (anti-14n/syn-14n, ca. 1:1; 56% yield). For semiactivated alkyl halides, we found that the use of LDA in the presence of hexamethylphosphoramide (HMPA) was necessary for the desired level of reactivity. Using the use of LDA in the presence of hexamethylphosphoramide (HMPA) was necessary for the desired level of reactivity. Using LiCl) carbenoids (Figure 8). In general, the use of the milder conditions, thus generating the more functional-group-tolerant magnesium carbenoids, was superior in most cases in terms of both yield and levels of enantioselectivity. Unsurprisingly, attempts at generating the lithium carbenoids for the α-sulfinyl benzoates bearing p-bromobenzyl, azidopropyl, trifluoropropyl, and ethyl ester-terminated pentyl substituents, were met with low yields or no detectable amounts of the desired homologated boronic ester. However, the in situ generation of magnesium carbenoids proved highly enabling, the desired products being isolated in moderate to good yields and with very high levels of enantioselectivity.

2.4. Homologation of Boronic Esters with Functional-Group-Rich α-Sulfinyl Benzoates. With a set of highly enantioenriched, more functional-group-rich α-sulfinyl benzoates in hand (Figure 7), we tested them as homologating reagents for our standard boronic ester, p-methoxyphenethyl pinacol boronic ester (17a), using the conditions established for generating lithium (t-BuLi) and magnesium (i-PrMgCl-LiCl) carbenoids (Figure 8). In general, the use of the milder conditions, thus generating the more functional-group-tolerant magnesium carbenoids, was superior in most cases in terms of both yield and levels of enantioselectivity. Unsurprisingly, attempts at generating the lithium carbenoids for the α-sulfinyl benzoates bearing p-bromobenzyl, azidopropyl, trifluoropropyl, and ethyl ester-terminated pentyl substituents, were met with low yields or no detectable amounts of the desired homologated boronic ester. However, the in situ generation of magnesium carbenoids proved highly enabling, the desired products being isolated in moderate to good yields and with very high levels of enantioselectivity.

2.5. Synthesis of Fully Substituted α-Sulfinyl Benzoates. We then turned our attention to investigating fully substituted α-sulfinyl benzoates for the homologation of boronic esters to give enantiopure α-tertiaryboronic esters. At the outset, it was unclear whether we would be able to prepare the reagents with high levels of diastereoselectivity, anticipating that diastereomeric mixtures would be difficult to separate. However, the alkylation of methyl-substituted α-sulfinyl benzene 14b with LDA and benzyl bromide, the electrophile being present during addition of the base, gave substituted α-sulfinyl benzene 20a with high levels of diastereoselectivity (>95:5) in favor of the diastereomer displaying the newly introduced substituent anti to the oxygen atom of the sulfinyl group, albeit with low yield (10%). The origin of the diastereoselectivity presumably arises from favored approach of the electrophile from the less-hindered re face of the carbanion center presented by the more thermodynamically stable conformer, that is, the one that places the large OTIB...
alkylation of the unsubstituted $\alpha$-sulfinyl benzoate, as prepared through the alkylation of $\alpha$-sulfinyl benzoate 19 or ent-19. Conditions A: 14 (1.05 equiv) and $t$-BuLi (2.0 equiv) in THF. Conditions B: 14 (1.3 equiv) and i-PrMgCl·LiCl (1.2 equiv) in DCM. Reactions performed on a 0.2 mmol scale. Yields are based on isolated product. The er values were determined through chiral HPLC analysis of the corresponding alcohols. 1Boronic ester oxidized to the corresponding alcohol prior to isolation. 2Magnesium carbene formed prior to the addition of the boronic ester. TIB = trisopropylbenzoate.

Figure 9. (A) Synthesis of disubstituted $\alpha$-sulfinyl benzoates through alkylation of monosubstituted derivatives. (B) Proposed model rationalizing diastereoselectivity. (C) Sequential alkylation of $\alpha$-sulfinyl benzoate 19. 2Reaction conditions: benzoate 14 (1.0 equiv), RX (1.5 equiv), LDA (1.8 equiv), THF, $-78^\circ$C; then 0°C. 3Determined by $^1$H NMR analysis. 4Benzoate 19 (1.0 equiv), CH$_3$I (1.1 equiv), NaHMDS (1.1 equiv), $-78^\circ$C to rt; extractive workup; PhCH$_2$I (1.5 equiv), LDA (1.8 equiv), THF, $-78^\circ$C then 0°C.

2.6. Synthesis of Enantioenriched Tertiary Boronic Esters. With diaireo- and enantiopure disubstituted $\alpha$-sulfinyl benzoates 20a and 20b in hand, we tested them as reagents for homologating our standard boronic esters in a single process without intervening chromatographic purification. Thus, treatment of $\alpha$-sulfinyl benzoate 19 with NaHMDS/MeI and the performance of an extractive workup, followed by treatment of a solution of the crude product with LDA/BnI, gave the desired product 20a in 64% yield with a very high level of diastereoselectivity (>95:5; Figure 9).

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homologation of boronic esters with tert-butyl-substituted α-sulfinyl benzoate 14e, steric hindrance also precluding the use of our standard conditions; in that case, the desired product (18e, Figure 5) was obtained in low yield and with poor levels of enantiospecificity. The low-fidelity transfer of chirality was ascribed to competing in situ deprotonation/reprotonation of the α-sulfinyl benzoate. The very high levels of enantiospecificity observed for homologating with disubstituted α-sulfinyl benzoates lends further credence to the operation of an enantioselective deprotonation/reprotonation process when employing stericly hindered monosubstituted α-sulfinyl benzoates.

2.7. Iterative Homologation of Boronic Esters Using α-Sulfinyl Benzoates. Having demonstrated that functional-group-rich α-sulfinyl benzoates can be used to homologate boronic esters, we wanted to investigate their use in iterative homologation processes. We targeted the contiguously substituted phenylpentanol 22, which would be obtained through three consecutive iterations of our homologation protocol on phenethyl pinacol boronic ester (15) by using allyl-substituted α-sulfinyl benzoate ent-14f (iterations 1 and 2) and methyl-substituted α-sulfinyl benzoate 14b (iteration 3); oxidation of the resulting C–B bond would give the alcohol.

We investigated a three-pot process (a filtration through a silica pad between each iteration) by using the in situ generation of both lithium and magnesium carbenoids (Figure 11). In accordance with the results above, analysis of the crude reaction mixtures obtained from the first homologation showed excellent levels of conversion for both sets of conditions. However, with increased steric hindrance around the boron center, and thus lower rates for the formation of the intermediate boronate complex, the conditions deviated markedly in levels of efficiency for the second iteration: although the use of lithium carbenoids gives very high levels of conversion (98%; Figure 11, entry 1), the use of magnesium carbenoids, which are more sensitive to steric hindrance, showed low levels of conversion (26%; Figure 11, entry 2). The low levels of conversion were countered by the detection of significant amounts of protodesulfinylated starting material.

The sequence using the magnesium carbenoids was aborted at this stage. The third iteration of the lithium-carbenoid homologation process was carried out using methyl-substituted α-sulfinyl benzoate 14b; however, only moderate levels of conversion were observed (60%, Figure 11, entry 1), thus marking the territory where steric hindrance begins to impact on the efficiency of homologation using lithium carbenoids. The target alcohol was isolated in 29% yield, based on a four-step process from phenethyl pinacol boronic ester (15), thus representing an average of 65% yield per iteration. At this point, we decided to reoptimize the lithium-carbenoid conditions for our target molecule. Ultimately, we found that when the third iteration was carried out using 1.5 equiv of α-sulfinyl benzoate 14b and 3.0 equiv of t-BuLi, the level of conversion of the boronic ester for the problematic third iteration could be increased from 65% to 85%; the target alcohol 22 was then isolated in 41% overall yield (based on 4 steps; average of 75% yield per iteration; Figure 11, entry 3).

As an alternative, we considered using the methyl-substituted α-stannyl benzoate 3 as the carbenoid precursor for the third iteration. Upon generation of the lithium carbenoid ex situ (benzoate 3, 1.35 equiv; n-BuLi, 1.30 equiv), followed by addition of the vicinal diallyl-substituted boronic ester 23, the level of conversion for that step was increased to 99% and the overall yield for the process, based on isolated alcohol 22, was increased to 52% (average of 80% yield per iteration; Figure 12A). The very high levels of conversion observed for the use of the α-stannyl benzoate highlights once again the relevance of the acidity of monosubstituted α-sulfinyl benzoates in the efficiency of forming sterically hindered boronate complexes: when boronate complex formation is slow for a Barbier-type process involving dropwise addition of t-BuLi, the lithium carbenoid is competitively consumed in an acid–base reaction with its precursor α-sulfinyl benzoate.

To investigate further the effect of steric hindrance on iterative homologation of boronic esters, we decided to prepare alcohol 26, which would involve a similar protocol to what is described above, except that a Matteson homologation is incorporated between the above second and third iterations. Owing to the alleviation of steric hindrance through the insertion of the extra methylene group (effected by the in situ generation of Matteson’s reagent, LiCH2Cl), the final iteration, where methyl-substituted α-sulfinyl benzoate 14b is used as the precursor to the corresponding lithium carbenoid, proceeds with high levels of conversion of the intermediate boronic ester (desired secondary boronic ester/underhomologated primary boronic ester; 91:9). Ultimately, target alcohol 26 was isolated in 37% yield, based on a five-step process from boronic ester 15, thus representing an average of 82% yield per iteration (Figure 12C). During this investigation, we considered using the magnesium carbenoid derived from the unsubstituted α-sulfinyl benzoate 19 as an alternative to the Matteson reagent, LiCH2Cl, which, owing to its instability, can sometimes preclude high yields in homologation reactions. In a test
reaction, upon addition of i-PrMgCl-LiCl to a mixture of benzoate 19 and boronic ester 15, the desired homologation product could be detected in only 6% yield. The major species detected was the protodesulfinylation product 25, thus pointing toward a highly competitive acid–base side-reaction.

3. CONCLUSION

The above results show that the use of α-sulfinyl benzoates in iterative homologation processes closely approaches the level of efficiency observed for that of α-stannyl benzoates. Crucially, this class of carbeneoid precursor is highly enabling for the growing of carbon chains bearing sensitive functional groups. This unique capability arises from the ability to prepare substituted α-sulfinyl benzoates by using alkylthiation reactions employing mild bases and because they are precursors to magnesium carbeneoids, which react with boronic esters in the presence of electrophilic functional groups. Because α-sulfinyl benzoates can be prepared in very high levels of enantio purity and are more resistant to acid–base side-reactions, owing to increased steric hindrance around the carbene carbon atom, they outperform α-sulfinyl chlorides in iterative homologation processes. Furthermore, the emergence of this class of carbeneoid precursor is timely because they can now be prepared without employing sparteine, or other nonracemic chiral diamines, which are currently difficult to source commercially.
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