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

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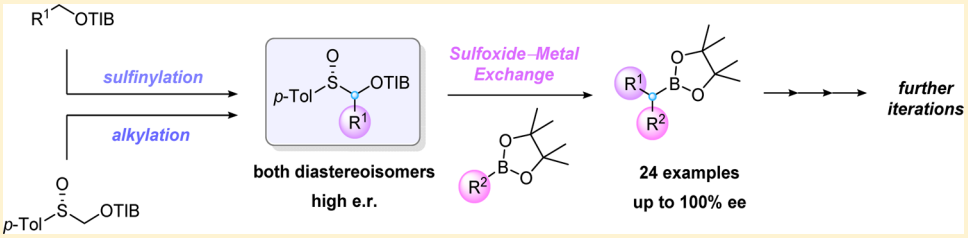
Supporting Information



ABSTRACT: The stereoselective reagent-controlled homologation of boronic esters is one of a small number of iteratable synthetic transformations that if automated could form the basis of a veritable molecule-making machine. Recently, α-stannyl triisopropylbenzoates and α-sulfinyl 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-sulfinyl chlorides are difficult to prepare with high levels of enantiopurity and are prone to undergo deleterious acid–base side-reactions under the reaction conditions for homologation, leading to low stereospecificity. Here, we show that the use of a hybrid of these two building blocks, namely, α-sulfinyl triisopropylbenzoates, largely overcomes the above drawbacks. Through either the sulfinylation of α-magnesiated benzoates with either enantiomer of Andersen's readily available menthol-derived sulfinate or the α-alkylation of enantiopure *S*-chiral α-sulfinyl benzoates, we have prepared a range of highly enantiopure mono- and disubstituted α-sulfinyl 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 (*i*-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 metalate (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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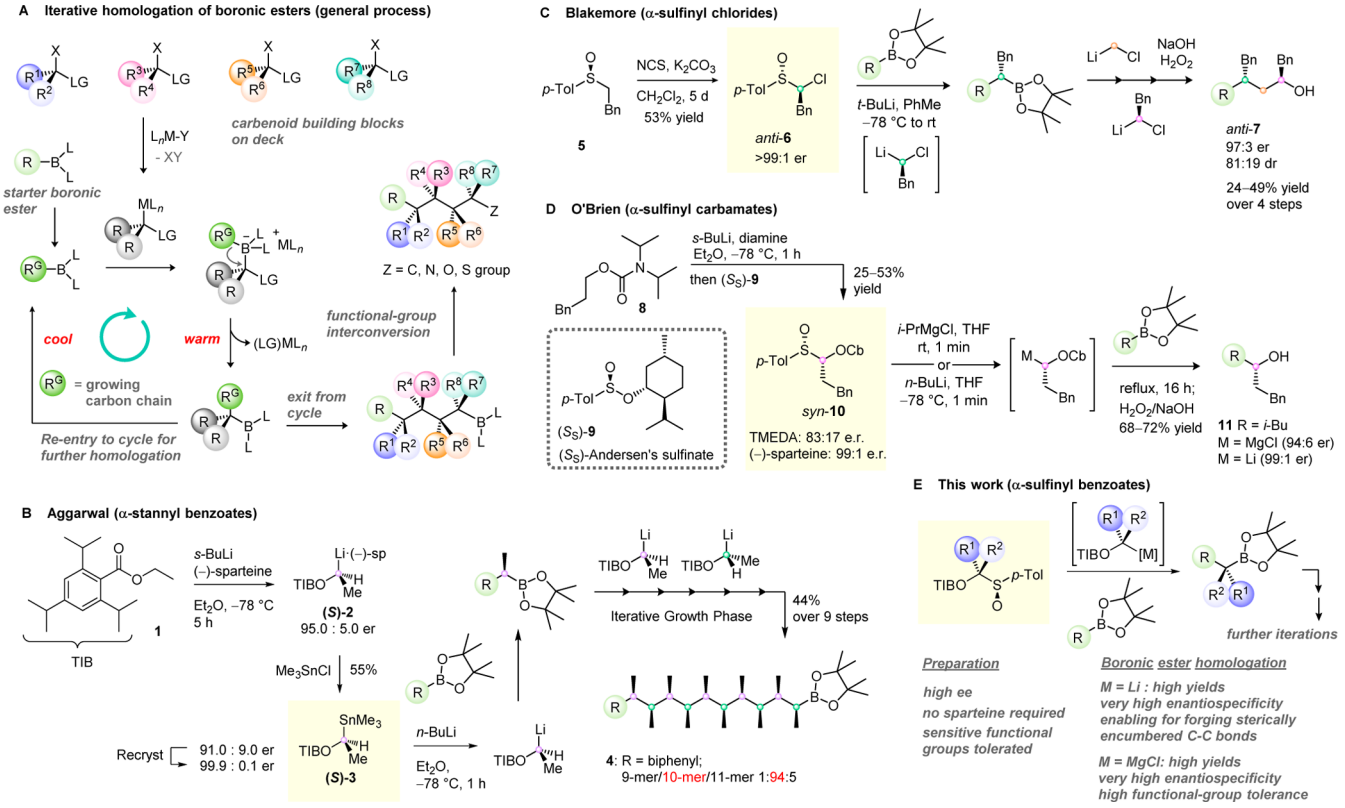

Figure 1. (A) Iterative homologation of boronic esters for the synthesis of stereochemically well-defined substituted carbon chains. (B) α-Stannyl benzoates for iterative homologation of boronic esters. (C) α-Sulfinyl chlorides for the iterative homologation of boronic esters. (D) α-Sulfinyl carbamates for the homologation of boronic esters. (E) This work: α-sulfinyl benzoates.

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.[7g] 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;[9] (b) only the methyl-substituted precursors are crystalline, thus making it difficult to obtain other derivatives in highly enantioenriched form; (c) toxic Me_3SnCl is required for their synthesis, and the precursors themselves (and byproducts produced during consumption) are perceived to be toxic,[10] 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 particular 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 sulfinate **9** gave a mixture of the *syn* and *anti* α-sulfinyl carbamates **10**, but with only moderate levels of enantiospecificity (Figure 2A).[12] The erosion of

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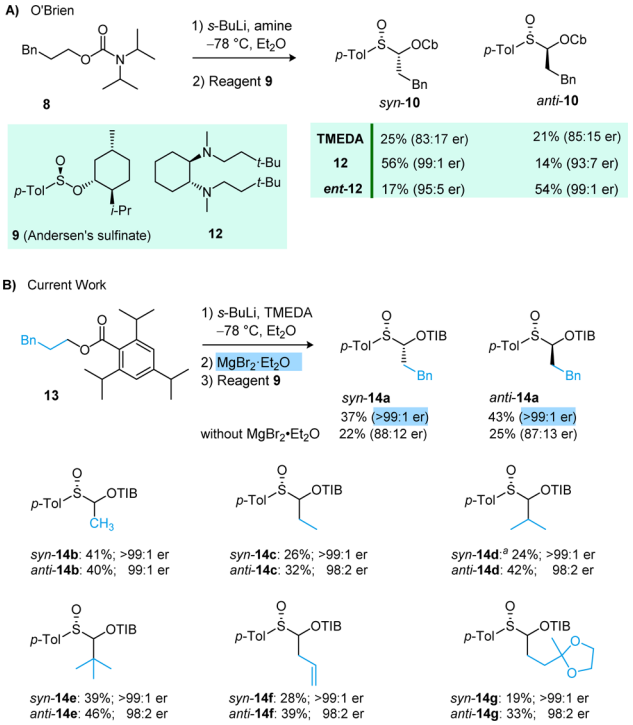
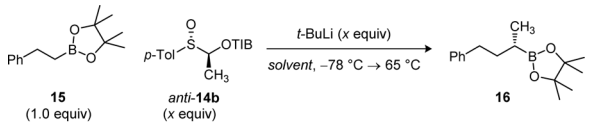


Figure 2. Synthesis of α-sulfinyl carbamates (A) and benzoates (B) through the sulfinylation of α-lithiated and -magnesiated precursors with Andersen's menthol-derived sulfinate. [a]Diastereomers were not separable by column chromatography, and yields were determined based on ^{1}H NMR analysis. A portion 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 sulfinate 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 lithiated 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 nucleophilicity 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 $MgBr_2{\cdot}OEt_2$) 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 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 kinetic and thermodynamic control and found that the Knochel–Hauser base (TMPMgCl·LiCl)[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,[8g] 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



Entry	Equiv *anti*-14b	Equiv *t*-BuLi	Solvent	16:15
1	1.5	1.4	THF	92:8
2	1.5	1.4	Et_2O	20:80
3	1.5	1.4	TBME	58:42
4	1.5	1.4	CPME	28:72
5	1.5	1.4	PhMe	55:45
6	1.5	2.0	THF	96:4
7	1.2	2.0	THF	97:3
8	1.05	2.0	THF	>99:1

Figure 3. Optimization of reaction conditions for the homologation of boronic esters by using lithium carbenoids derived from α-sulfinyl benzoates. Reactions performed on a 0.1 mmol scale; conversion measured by GCMS of the crude reaction mixture; TBME = *tert*-butyl methyl ether; CPME = cyclopentyl methyl ether.

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to evolve for only 1 min before addition of the boronic ester, and warming the ternary mixture to room temperature[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.[7g] 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_2O, TBME, CPME, PhMe) resulted in low conversion of the boronic ester starting material. Using *t*-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^2 C−H bonds in the alkyl−aryl sulfoxide byproduct (MeOD-trapping experiments confirmed the operation of this process; see the Supporting Information)[15] and adventitious H_2O;[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.[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-metalate 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.[7g] Interestingly, the use of the turbo Grignard reagent, *i*-PrMgCl·LiCl,[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

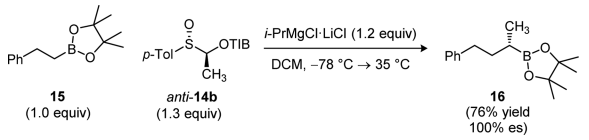

Figure 4. Optimal reaction conditions for the homologation of boronic esters by using magnesium carbenoids derived from α-sulfinyl benzoates.

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

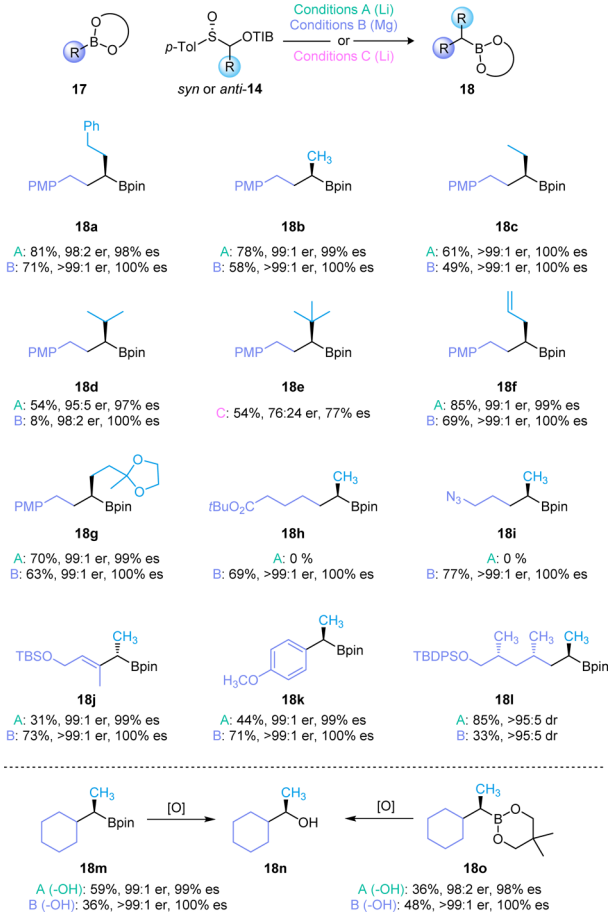

Figure 5. Homologation of boronic esters with lithium or magnesium carbenoids derived from α-sulfinyl benzoates, as prepared through the sulfinylation of α-magnesiated benzoates. Conditions A: **14** (1.05 equiv), **17**, and *t*-BuLi (2.0 equiv) in THF. Conditions B: **14** (1.3 equiv), **17**, and *i*-PrMgCl·LiCl (1.2 equiv) in DCM. Conditions C: addition of **14** (1.3 equiv) to *t*-BuLi (2.0 equiv) and PMDTA (*N*,*N*,*N*′,*N*″,*N*″-pentamethyldiethylenetriamine. 2.0 equiv); then adding **17**. Reactions performed on a 0.2 mmol scale. Yields are based on isolated product. The er values were determined by chiral HPLC analysis of the corresponding alcohols.

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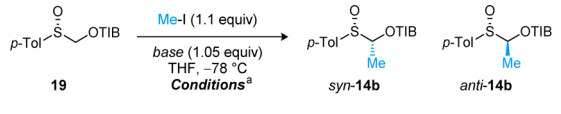
equiv; *i*-PrMgCl·LiCl, 1.2 equiv; Barbier-type conditions). In general, the use of α-sulfinyl benzoates bearing nonbranched substituents (**14a**−**c**, **14f**, **14g**) gave good yields of the homologated boronic ester with excellent levels of enantiospecificity for both sets of reaction conditions (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,[8f,g] 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 effect 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.[8b] For Blakemore, this side-reaction could be partially suppressed by using the deuterium isotopomer 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 (protodesulfinylation 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 Et_2O 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,[7d,h,j] 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.[19] 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



Entry	Base	Conditions	*syn*-14b:*anti*-14b	% Yield *syn*-14b	% Yield *anti*-14b
1	LiHMDS	in situ	31:69	16	33
2	LiHMDS	ex situ	12:88	20	63
3	KHMDS	in situ	83:17	48	19
4	NaHMDS	in situ	80:20	52	23
5[b]	NaHMDS	in situ	43:57	43[c]	56[c]

Figure 6. Optimization of reaction conditions for the methylation of α-sulfinyl benzoate **19**. [a]Reactions performed on a 0.1 mmol scale. In situ: sulfoxide and MeI premixed prior to the addition of the base; ex situ: sulfoxide treated with the base at −78 °C; then, after 10 min, MeI is added. dr values determined by ^1H NMR analysis of the crude reaction mixture. [b]Reaction performed on a 7.7 mmol scale. [c]Yields of isolated product.

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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

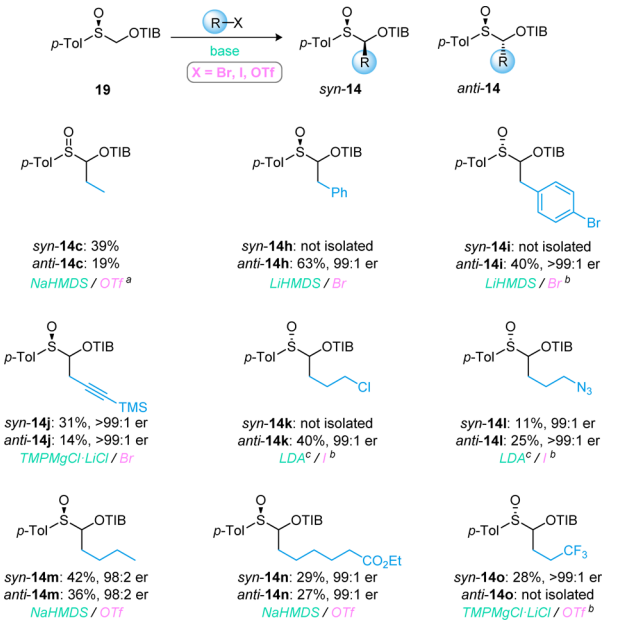

Figure 7. Optimal reaction conditions for the alkylation of α-sulfinyl benzoate **19** with a range of electrophiles. [a]Prepared from (±)-**19**. [b]Prepared from *ent*-**19**. [c]In the presence of HMPA.

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 these conditions, the chloropropyl- and azidopropyl-substituted α-sulfinyl benzoates, **14k** and **14l**, respectively, could be obtained in serviceable yields with very high levels of enantiopurity, the *anti* diastereomer being the major product. For more activated electrophiles, namely, benzyl bromides (benzyl bromide and *p*-bromobenzyl bromide), the use of LiHMDS under in situ conditions proved optimal; undesired dialkylation, which was observed for MeI as the electrophile under these conditions (Figure 6, entry 1), was not apparent. The benzyl- and *p*-bromobenzyl-substituted α-sulfinyl benzoates were isolated in good yield, 63% and 40%, respectively, the *anti* diastereomer being the major product in each case. The product bearing the substituent with the opposite configuration at the carbenoid carbon atom would be obtainable from *ent*-**19**, which would in turn be obtainable by using the alternative enantiomer of Andersen's sulfinate. The use of tetramethylsilane (TMS)-protected propargylic bromide as the electrophile proved challenging owing to a facile E2 elimination reaction of the desired product: the use of LiHMDS gave a mixture of the enynyl sulfoxide and starting material. We reasoned that the use of the Knochel–Hauser base, which would lead to the less reactive magnesiated carbanion, might engender more stable conditions for the desired product. Indeed, these reaction conditions allowed isolation of propargylic-substituted α-sulfinyl benzoate **14j** in moderate yield, this time favoring the *syn* product (*anti*-**14j**/*syn*-**14j**, 1:2). These conditions were also suitable for introducing a trifluoropropyl group, a transformation that was effected using the triflate electrophile. The diastereoselectivity of these alkylation reactions was difficult to predict, but with these sets of results in hand, some general trends can be noted: the use of lithium bases favors the *anti* diastereomer; the use of sodium bases shows low levels of diastereoselectivity; magnesium bases favor the *syn* diastereomer. Presumably both the ability of the counterion to activate or precomplex the incoming electrophile and its effect on the aggregation state of the carbanion and on the propensity of the product to undergo deprotonation under the reaction conditions contribute in varying degrees to dictate the diastereoselectivity.[20]

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 enantiospecificity. 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 enantiospecificity.

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-tertiary boronic 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 benzoate **14b** with LDA and benzyl bromide, the electrophile being present during addition of the base, gave disubstituted α-sulfinyl benzoate **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

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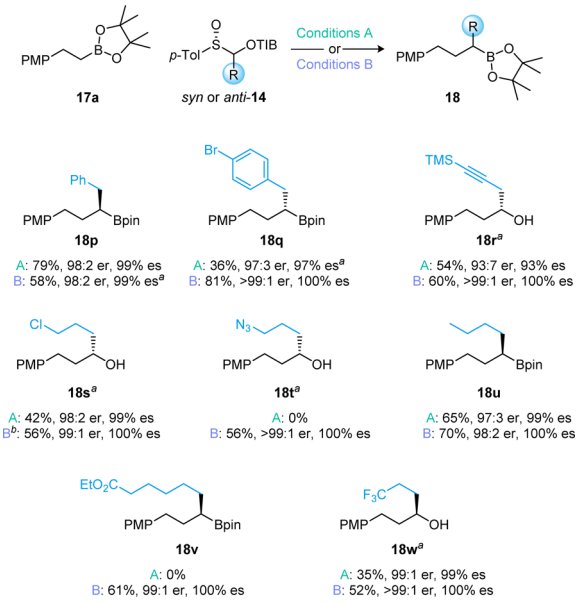
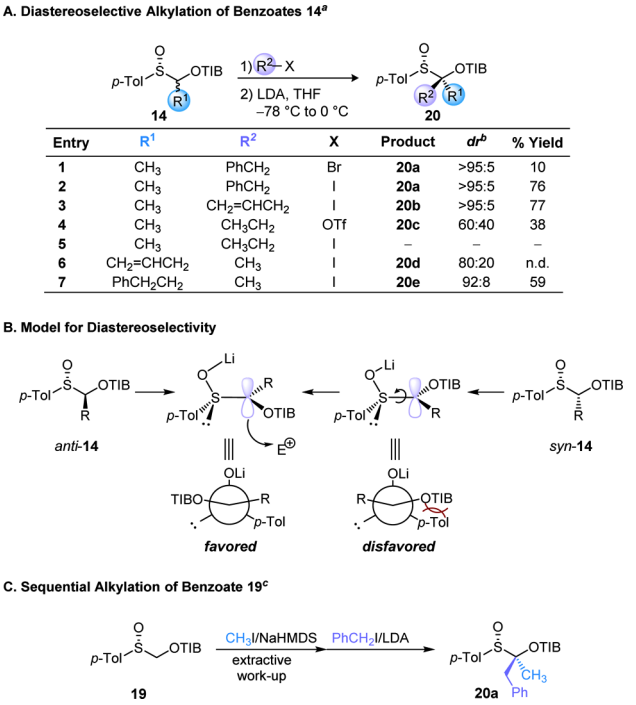


Figure 8. Homologation of boronic esters with lithium or magnesium carbenoids derived from α-sulfinyl benzoates, as prepared through the alkylation of α-sulfinyl benzoate **19** or *ent*-**19**. Conditions A: **14** (1.05 equiv) and *t*-BuLi (2.0 equiv) in THF. Conditions B: **14** (1.3 equiv) and *i*-PrMgCl·LiCl (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. [a]Boronic ester oxidized to the corresponding alcohol prior to isolation. [b]Magnesium carbenoid formed prior to the addition of the boronic ester. TIB = triisopropylbenzoate.



Entry	R^1	R^2	X	Product	dr[b]	% Yield
1	CH_3	$PhCH_2$	Br	**20a**	>95:5	10
2	CH_3	$PhCH_2$	I	**20a**	>95:5	76
3	CH_3	CH_2=$CHCH_2$	I	**20b**	>95:5	77
4	CH_3	CH_3CH_2	OTf	**20c**	60:40	38
5	CH_3	CH_3CH_2	I	–	–	–
6	CH_2=$CHCH_2$	CH_3	I	**20d**	80:20	n.d.
7	$PhCH_2CH_2$	CH_3	I	**20e**	92:8	59

Figure 9. (A) Synthesis of disubstituted α-sulfinyl benzoates through alkylation of monosubstituted derivatives. (B) Proposed model rationalizing diastereoselectivity. (C) Sequential alkylation of α-sulfinyl benzoate **19**. [a]Reaction conditions: benzoate **14** (1.0 equiv), R^2X (1.5 equiv), LDA (1.8 equiv), THF, −78 °C; then 0 °C. [b]Determined by ^1H NMR analysis. [c]Benzoate **19** (1.0 equiv), CH_3I (1.1 equiv), NaHMDS (1.1 equiv), −78 °C to rt; extractive workup; $PhCH_2I$ (1.5 equiv), LDA (1.8 equiv), THF, −78 °C then 0 °C.

group *gauche* to the small substituent (the lone pair) of the vicinal sulfur center (Figure 9).[21] Additionally, *re* face attack of this conformer would proceed through a pathway where the dihedral angle that defines the relative position of the existing substituent (the R group) and the vicinally related *p*-Tol group will increase as the reacting center transforms from sp^2 to sp^3; *si* face attack would involve this dihedral angle getting smaller, thus causing increased strain. The lower diastereoselectivity for alkylation of the unsubstituted α-sulfinyl benzoate **19** (Figures 6 and 7) could be explained by the absence of this strain in the corresponding *si* face attack; in some cases, poor stereocontrol may be due to deprotonation of the highly acidic α-proton. The yield could be increased to 77% by using the more reactive iodide, the diastereoselectivity remaining high. The use of either diastereomer of starting material **14b** in pure form (or mixtures of *syn* and *anti* diastereomers) gave the same diastereomer of product, supportive of there being a common intermediate with a highly trigonal carbanion center.[22] The use of allyl iodide as the electrophile gave the desired product **20b** in equally high yield and level of diastereoselectivity. However, the introduction of an ethyl substituent, a transformation that could only be effected by using EtOTf as the electrophile, gave the desired dialkylated α-sulfinyl benzoate **20c** with low levels of diastereoselectivity (60:40), the constituents being inseparable. The origin of the low diastereoselectivity might be due to the small size of the electrophile and that the triflyl moiety presents oxygen atoms that, through coordination to the lithium ion, could guide the electrophile to the *si* face of the major conformer.[20] The order of incorporation of substituents was important for obtaining high yields and levels of diastereoselectivity. The methylation of allyl- and phenethyl-substituted α-sulfinyl benzoates, thus employing the smaller and less reactive MeI as the second electrophile, gave the corresponding products, **20d** and **20e**, respectively, in lower yield and, crucially, with lower levels of diastereoselectivity (80:20 and 92:8); the constituents were inseparable by column chromatography. Disubstituted α-sulfinyl benzoate could also be prepared from methylene derivative **19** in a single process without intervening chromatographic purification. Thus, treatment of α-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).

2.6. Synthesis of Enantioenriched Tertiary Boronic Esters. With diastereo- and enantiopure disubstituted α-sulfinyl benzoates **20a** and **20b** in hand, we tested them as reagents for homologating our standard boronic esters to give α-tertiary boronic esters. The use of our standard conditions for the in situ generation of lithium and magnesium carbenoids did not lead to detectable levels of desired product. Clearly, sulfoxide−metal exchange for these sterically hindered disubstituted α-sulfinyl benzoates is too slow, thus allowing boronic ester to be unproductively consumed by the organolithium or organomagnesium reagent. However, generation of the lithium carbenoids through an inverse-addition protocol, that is, addition of the disubstituted α-sulfinyl benzoate to a solution of *t*-BuLi in Et_2O in the presence of PMDTA at −78 °C, followed by addition of the boronic ester, gave the desired products **21a** and **21b** in good yield and with very high levels of enantiospecificity (Figure 10). It is instructive at this point to hark back to when the same protocol was used for the

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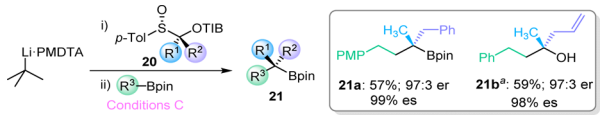
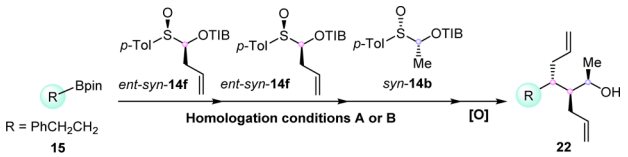


Figure 10. Homologation of boronic esters with disubstituted α-sulfinyl benzoates. Conditions C: addition of benzoate **20** (1.3 equiv) to a solution of *t*-BuLi (2.0−2.3 equiv) and PMDTA (2.0−2.3 equiv) in Et_2O, then boronic ester (1.0 equiv). [a]The boronic ester was oxidized to the corresponding alcohol prior to isolation.

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 enantioeroding deprotonation/reprotonation process when employing sterically 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



Entry	Conditions	1st P:SM	2nd P:SM	3rd P:SM	% Yield 22	dr
1	A	98:2	96:4	60:40	29	>95:5
2	B	99:1	26:74	–	–	–
3	A′	98:2	96:4	85:15	41	>95:5

Figure 11. Iterative homologation of boronic esters by using α-sulfinyl benzoates. Conditions A: boronic ester (1.00 equiv), sulfoxide (1.05 equiv), and *t*-BuLi (2.0 equiv) in THF (Barbier conditions). Conditions B: boronic ester (1.00 equiv), sulfoxide (1.3 equiv), and *i*-PrMgCl·LiCl (1.2 equiv) in DCM (Barbier conditions). Conditions A′: boronic ester (1.00 equiv), sulfoxide (1.5 equiv), and *t*-BuLi (3.0 equiv) in THF (Barbier conditions). The first two homologations were performed on a 1.00 mmol scale and the third on a 0.33 mmol scale. The oxidation step was performed using $NaBO_3{\cdot}4H_2O$. Reaction conversion measured by GCMS analysis of the crude mixtures. Yields reported are those of alcohol isolated by column chromatography (over the 4 steps). Diastereomeric ratios were determined by ^{13}C NMR analysis.

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,[3] $LiCH_2Cl$), 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,[3] $LiCH_2Cl$, which, owing to its instability, can sometimes preclude high yields in homologation reactions. In a test

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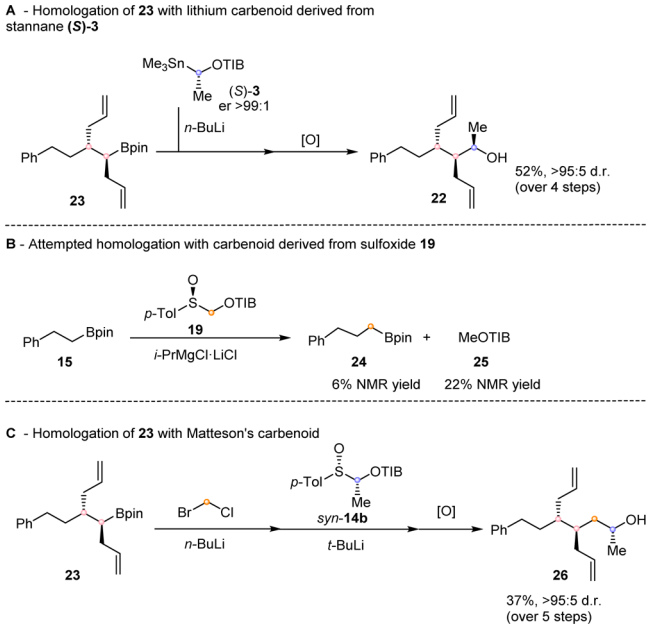

Figure 12. (A) Iterative homologation by using a combination of α-sulfinyl benzoates and α-stannyl benzoates. (B) Investigation of α-sulfinyl benzoate **19** as an alternative reagent for Matteson-type homologation. (C) Iterative homologation by using α-sulfinyl benzoates with an intervening Matteson insertion of a methylene group. Conditions for **22**: (*S*)-**3** (1.35 equiv) and *n*-BuLi (1.30 equiv) in Et_2O; then boronic ester **23** (1.00 equiv). Conditions for **24**: sulfoxide (2.00 equiv), boronic ester **15** (1.00 equiv), and *i*-PrMgCl·LiCl (2.00 equiv) in DCM (Barbier conditions). Conditions for **26**: boronic ester **23** (1.00 equiv), bromochloromethane (3.00 equiv), and *n*-BuLi (2.50 equiv) in Et_2O; *syn*-**14b** (1.10 equiv) and *t*-BuLi (2.00 equiv) in THF (Barbier conditions). The oxidation step was performed using $NaBO_3{\cdot}4H_2O$ (10 equiv) in THF/H_2O (3:2). Diastereomeric ratios were determined by ^{13}C NMR analysis.

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 protodesulfinylated 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 carbenoid 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 alkylation reactions employing mild bases and because they are precursors to magnesium carbenoids, which react with boronic esters in the presence of electrophilic functional groups. Because α-sulfinyl benzoates can be prepared in very high levels of enantiopurity and are more resistant to acid–base side-reactions, owing to increased steric hindrance around the carbenoid carbon atom, they outperform α-sulfinyl chlorides in iterative homologation processes. Furthermore, the emergence of this class of carbenoid precursor is timely because they can now be prepared without employing sparteine, or other nonracemic chiral diamines, which are currently difficult to source commercially.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.7b05457.

Full experimental data (PDF)

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Notes

The authors declare no competing financial interest.

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