

Homologation and Alkylation of Boronic Esters and Boranes by 1,2-Metallate Rearrangement of Boron Ate Complexes

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ABSTRACT: Organoboranes and boronic esters readily undergo nucleophilic addition, and if the nucleophile also bears an α -leaving group, 1,2-metallate rearrangement of the ate complex results. Through such a process a carbon chain can be extended, usually with high stereocontrol and this is the focus of this review. A chiral boronic ester (substrate control) can be used for stereocontrolled homologations with (dichloromethyl)lithium in the presence of $ZnCl_2$. Subsequent alkylation by an organometallic reagent also occurs with high levels of stereocontrol. Chiral lithiated carbanions (reagent control) can also be used for the reaction sequence with achiral boronic esters and boranes. Aryl-stabilized sulfur ylide derived chiral carbanions can be homologated with a range of boranes including vinyl boranes in good yield and high diastereo- and enantioselectivity. Lithiated alkyl chlorides react with boronic esters, again with high stereocontrol, but both sets of reactions are limited in scope. Chiral lithiated carbamates show the greatest substrate scope and react with both boronic esters and boranes with excellent enantioselectivity. Furthermore, iterative homologation with chiral lithiated carbamates allows carbon chains to be “grown” with control over relative and absolute stereochemistry. The factors responsible for stereocontrol are discussed. © 2009 The Japan Chemical Journal Forum and Wiley Periodicals, Inc. Chem Rec 9: 24–39; 2009; Published online in Wiley InterScience (www.interscience.wiley.com) DOI 10.1002/tcr.20168

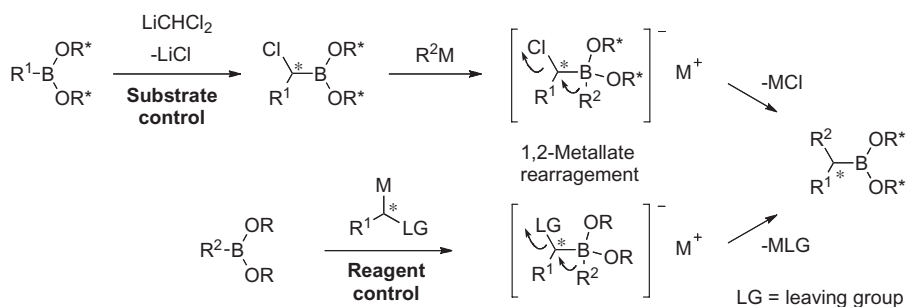
Key words: homologation; boronic ester; 1,2-metallate rearrangement; lithiated carbamates; sulfur ylides; chiral carbanions

Introduction

Organoboranes and boronic esters are very useful synthetic intermediates as they can be converted into a broad range of functional groups, often with complete stereospecificity.¹ These transformations are usually initiated by nucleophilic addition to the electrophilic boron atom followed by 1,2-migration. Among all the metals and semimetals, boron seems to possess a unique ability to orchestrate these processes cleanly and with high stereochemical fidelity. Another attractive feature is that chiral boron reagents are easily accessible in high enantiopurity. Indeed, the hydroboration of alkenes using (–)-diisopinocam-

phylborane by H. C. Brown in 1961 provided the first non-enzymatic asymmetric synthesis that resulted in truly practical levels of enantioselection.² In the early 1980s Matteson reported a complementary route to chiral boronic esters.³ In fact, the discoveries by Matteson that very high diastereoselectivities could be achieved in: (i) reactions of (dichloromethyl)lithium with boronic esters, and (ii) reactions of Grignard reagents

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Scheme 1. Complementary routes to homochiral organoboranes involving 1,2-metallate rearrangement.

with (α -haloalkyl)boronic esters opened up a whole new field in organoboron chemistry.⁴

In Matteson's approach, a chiral auxiliary is embedded in the diol moiety of the boronic ester and subsequent transformations are controlled by its architecture (substrate control; Scheme 1). An alternative approach uses a chiral reagent to construct a related chiral ate complex that subsequently evolves into the chiral boronic ester following 1,2-metallate rearrangement (reagent control; Scheme 1). These two approaches are discussed in this review.

Homologation–Alkylation of Chiral Boronic Esters: Substrate Control

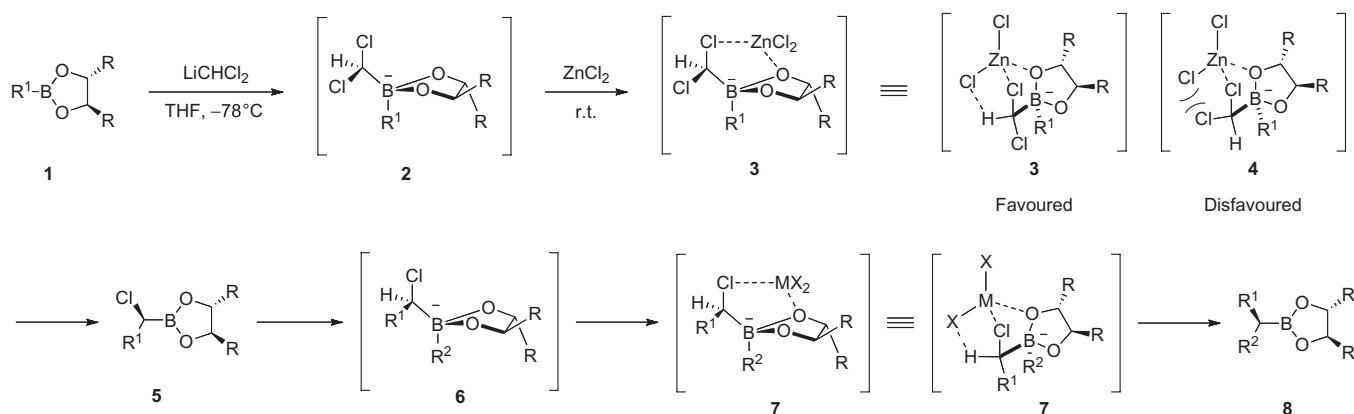
Reaction of an enantiopure boronic ester **1** with (dichloromethyl)lithium forms (dichloromethyl)borate complex **2**. In the presence of zinc chloride, borate **2** rearranges via transition structure (TS) **3** leading to a single α -chloroboronic ester **5** with a high diastereomeric purity, often >99:1 dr (Scheme 2). It has been proposed that in the preferred TS **3** zinc chloride promotes and directs the



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Scheme 2. Matteson homologation-alkylation sequence.

migration of R^1 by complexation to the less hindered oxygen atom of the boronic ester while simultaneously assisting the departure of a chloride ion.^{3c} It is also believed that this TS is further stabilized by an interaction between the chloride of zinc

chloride (which becomes more nucleophilic in the TS) and the C-H bond (which becomes more electrophilic in the TS as the chloride leaves).⁵ No such interaction can occur in the migration of the other diastereotopic chloride that is consequently



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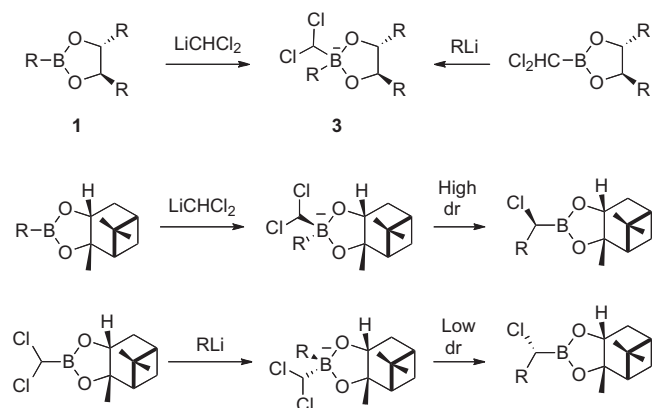
► Varinder K. Aggarwal was born in Kalianpur in North India in 1961 and emigrated to the United Kingdom in 1963. He received his B.A. (1983) and Ph.D. (1986) from Cambridge University, the latter under the guidance of Dr Stuart Warren. He was subsequently awarded a Harkness fellowship to carry out postdoctoral work with Professor Gilbert Stork at Columbia University, NY (1986–1988). He returned to a lectureship at Bath University and in 1991 moved to Sheffield University, where in 1997 he was promoted to Professor of Organic Chemistry. In 2000, he moved to the University of Bristol to take up the Chair of Synthetic Chemistry. He is the recipient of the AstraZeneca Award, Pfizer Award, GlaxoWellcome Award, Novartis Lectureship, RSC Hickinbottom Fellowship, Nuffield Fellowship, RSC Corday Morgan Medal and the Leibigs Lectureship, Liebig's Lectureship (Germany), 1999/2000 (inaugural), RSC Green Chemistry Award 2004, Zeneca Senior Academic Award 2004, RSC Reaction Mechanism Award 2004, Royal Society Wolfson Merit Award 2006, RSC/GDCh-Alexander Todd-Hans Krebs Lectureship 2007, RSC Tilden Lecturer awarded 2007, and an EPSRC Senior Research Fellowship 2007. ■

disfavored (TS 4). Indeed, Midland has calculated that there is a 12.6 kcal mol⁻¹ difference between the two TSs.⁶

Reaction of the α -haloboronic ester with a Grignard or organolithium reagent gives intermediate borate **6** that is analogous to intermediate borate **2**. However, in this case the reaction is stereospecific as the migrating group has to align anti-periplanar to the leaving group (TS 7, Scheme 2). Nevertheless, it is rather fortuitous that with this particular diastereoisomer the features required for the smooth 1,2-metallate rearrangement (chelation of the metal to the less hindered oxygen, binding of the leaving group to the metal and the stabilizing interaction between the halide and the C-H bond) are all still present. However, this is not always the case (see further discussion).

A number of significant observations have been made by Matteson^{4c} over the course of his investigations that are summarized in the following.

1. Boronate complexes do not rearrange at low temperature (e.g., -78°C). This prevents multiple insertions of (dihalomethyl)lithium as any excess reagent decomposes before the homologated boronic ester has been formed.
2. The electrophilic nature of the boron atom results in an efficient ate-complex formation. This inhibits side reactions such as β -elimination.
3. As well as zinc, lithium cation has been shown to accelerate the rate of 1,2-metallate rearrangement but with lower stereoselectivity. This might be because zinc chloride can sequester free chloride, thus inhibiting the slow epimerization of the product by free chloride.
4. Boronic esters bearing β -halides, or other weakly basic functions, are not stable with respect to elimination of the halide and the boronic ester group.
5. C₂-symmetric boronic esters, for example, **1**, are generally more stereoselective than boronic esters derived from pinanediol as they lead to the same diastereomeric ate complex when starting from the α -(dichloromethyl)boronic ester and reacting with an organometallic reagent as when starting from the corresponding boronic ester and reacting with (dichloromethyl)lithium (Scheme 3). In contrast, pinanediol boronic esters give different diastereomeric ate complexes that show very different levels of stereocontrol in the subsequent migration. In order to achieve good diastereoselectivity the migrating group must be present on the pinanediol boronic ester before the addition of (dichloromethyl)lithium. In contrast, poor levels of stereocontrol are observed when pinanediol (dichloromethyl)boronate is reacted with an organometallic species.⁷
6. Alkoxy groups (OBn, OPMB, OCPH₃) and nitrides are well tolerated at both α - and β -positions in sequential homologations. Halide, carbonyl, thioether, and cyano substituents



Scheme 3. Effect of order of addition of reagents to different boronic esters.

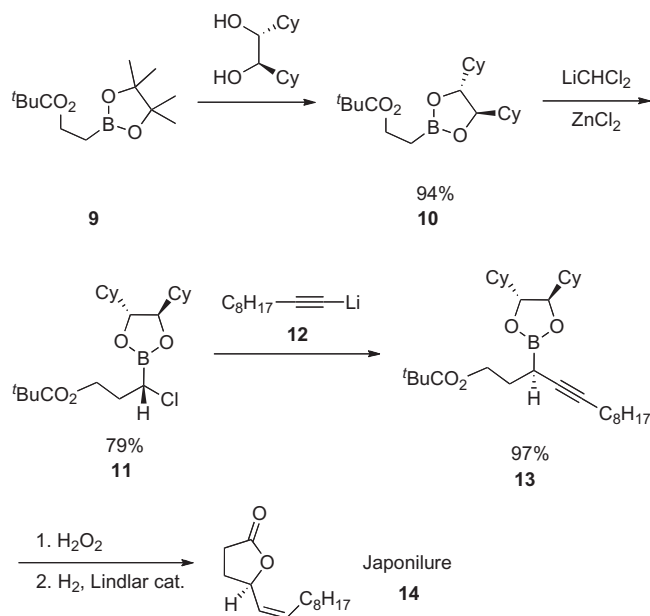
are compatible, but there must be at least two carbons between the functional group and the boron centre otherwise β -elimination results.

7. Suitably protected α -amino boronic esters and α -azido boronic esters are tolerated under certain reaction conditions.
8. A wide range of nucleophiles, including RMgX, RLi, RO⁻, RS⁻, R₂N⁻, N₃⁻, and LiCH₂CN, have been shown to undergo stereospecific 1,2-metallate rearrangement.

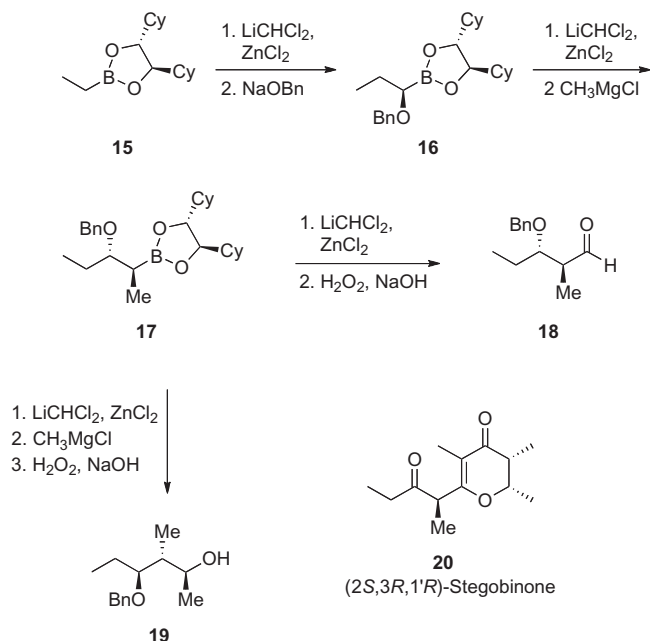
Applications of Matteson-Type Homologation-Alkylation in Synthesis

Matteson has elegantly demonstrated the potential of this homologation/alkylation methodology in the synthesis of numerous natural products. This is illustrated in the concise synthesis of japonilure **14**, a Japanese beetle pheromone.⁸ Reaction of boronic ester **10** with (dichloromethyl)lithium gave the (α -chloro)boronic ester **11** as a single diastereoisomer. Subsequent treatment with lithiated alkyne **12** gave, after 1,2-metallate rearrangement, boronic ester **13** that was readily converted to Japonilure **14** (Scheme 4).

Matteson further applied the homologation/alkylation methodology to the first total synthesis of the epimerically labile pheromone (2*S*,3*R*,1'*R*')-stegobinone **20** (Scheme 5).⁹ The two key synthetic components—aldehyde **18** and alcohol **19**—used in this synthesis were prepared from a common boronic ester **17**. Reaction of ethyl boronic ester **15** with (dichloromethyl)lithium followed by alkylation with sodium benzoxide gave the substituted boronic ester **16** that was converted into the common boronic ester **17** through a similar sequence. This was then subjected to a further (dichloromethyl)lithium homologation, and either oxidation to give aldehyde **18** or methyl magnesium chloride alkylation and oxidation to give alcohol **19**.

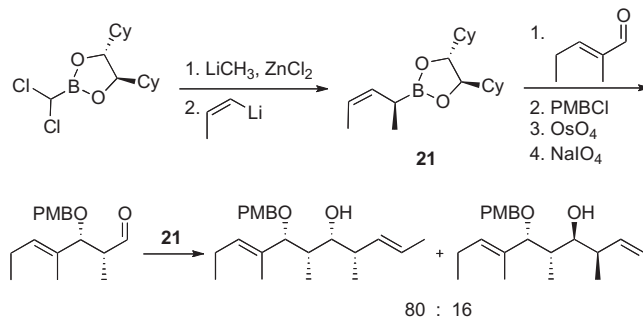


Scheme 4. Synthesis of Japonilure.

Scheme 5. Synthesis of the two key intermediates used in the first total synthesis of (2*S*,3*R*,1'*R*)-stegobinone.

Hoffmann has completed a number of natural product syntheses (e.g., erythronylide) using the Matteson-type homologation/alkylation methodology to prepare chiral allylic boronic ester **21**.¹⁰ Reaction of this boronic ester with chiral/achiral aldehydes usually proceeds with very high levels of stereocon-

trol. Even the mismatched case shown in Scheme 6 gave good levels of stereoselectivity.



Scheme 6. Synthesis and application of allyl boronates generated by Matteson homologation.

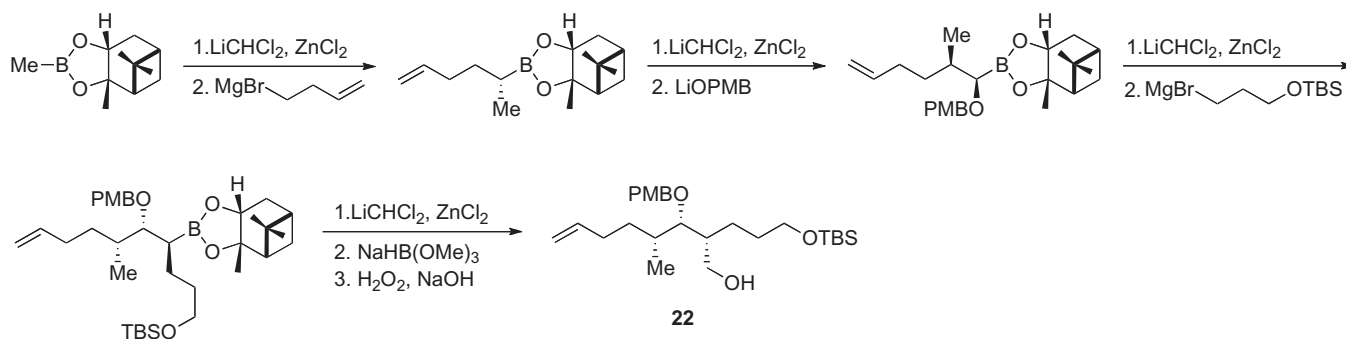
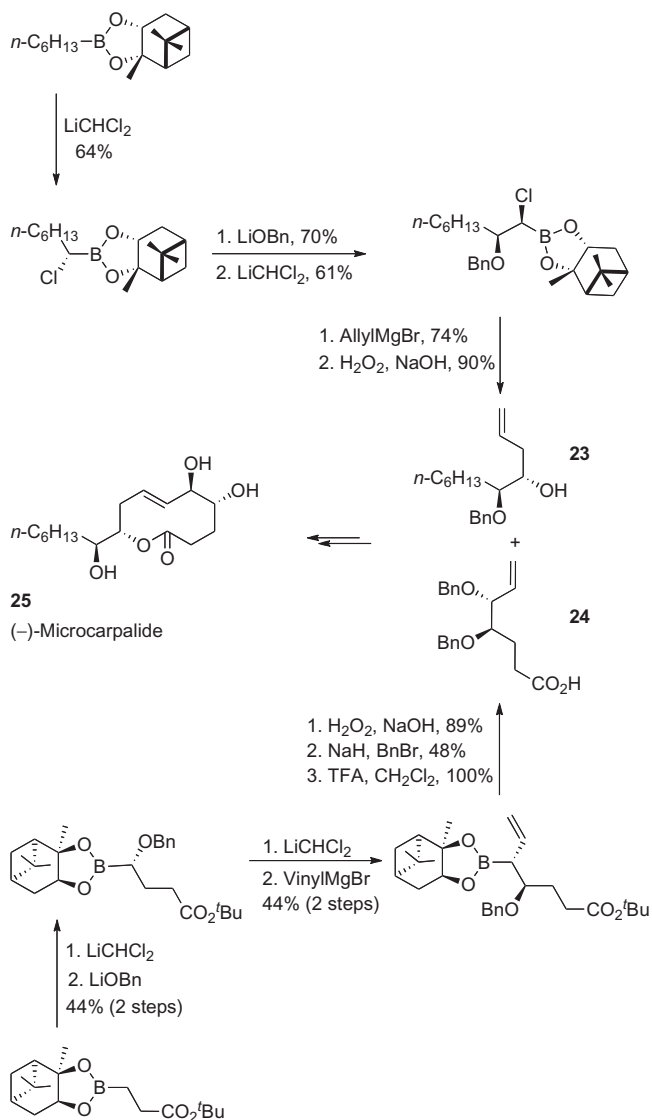
Armstrong has shown that the high levels of stereoselectivity observed for the homologation/alkylation reaction of pinanediol-derived boronic esters can be used to great effect in the synthesis of the C₁₀–C₂₁ fragment of tautomycin, a serine/threonine phosphatase inhibitor.¹¹ Four sequential Matteson-type homologation/alkylation sequences were used to prepare alcohol **22** with excellent stereocontrol over the three contiguous stereocentres (Scheme 7).

Davoli et al. used multiple Matteson-type homologation–alkylation reactions in the synthesis of (–)-microcarpalide **25**.¹² Using two boronic esters derived from the opposite enantiomers of pinanediol, successive (dichloromethyl)lithium homologations and 1,2-metallate rearrangements of both carbon and oxygen nucleophiles were used for the synthesis of intermediates **23** and **24** with excellent diastereoselectivity (Scheme 8).

Different diastereoisomers of a compound can usually be prepared by simply altering the order of addition of the component reagents as demonstrated in the synthesis of the pheromone **33** of the elm bark tree beetle *Scolytus multistriatus* and an epimer **29**. They were synthesized via diastereomeric intermediates **27** and **31** (Scheme 9).¹³ It should be noted that obtaining the different alcohol stereochemistries at C-3 in **29** and **33** required the (*R,R*) and (*S,S*) boronic ester diol stereochemistries, respectively. However, to obtain the (*S*)-stereochemistry at C-4 in both **27** and **31** required both a different addition sequence of nucleophiles and different enantiomeric chiral diols.

Limitations of the Matteson-type Homologation–Alkylation

Although a powerful transformation, Matteson's homologation–alkylation sequence suffers from a number of

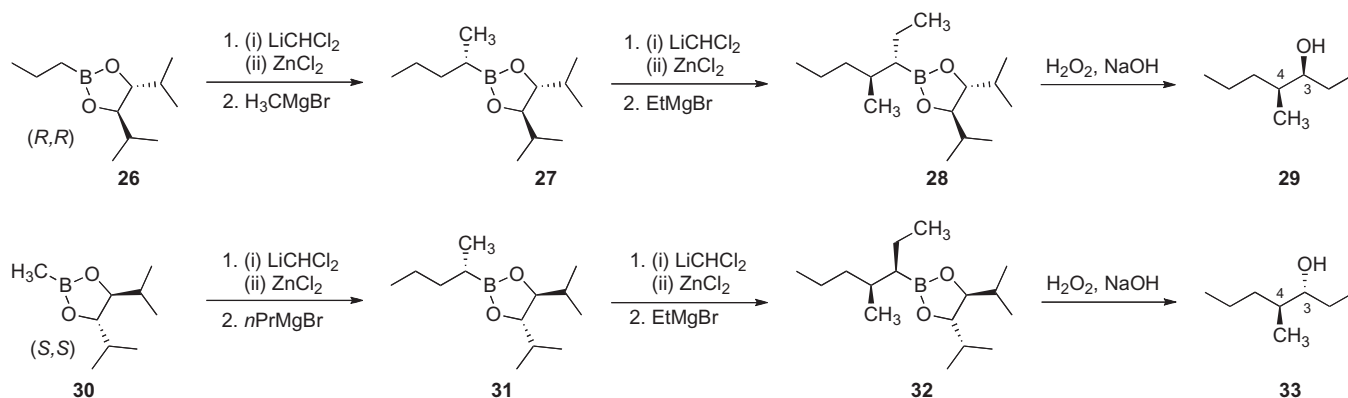
Scheme 7. Synthesis of the C₁₀–C₂₁ fragment of tautomycin.

Scheme 8. Synthesis of (-)-microcarpalide.

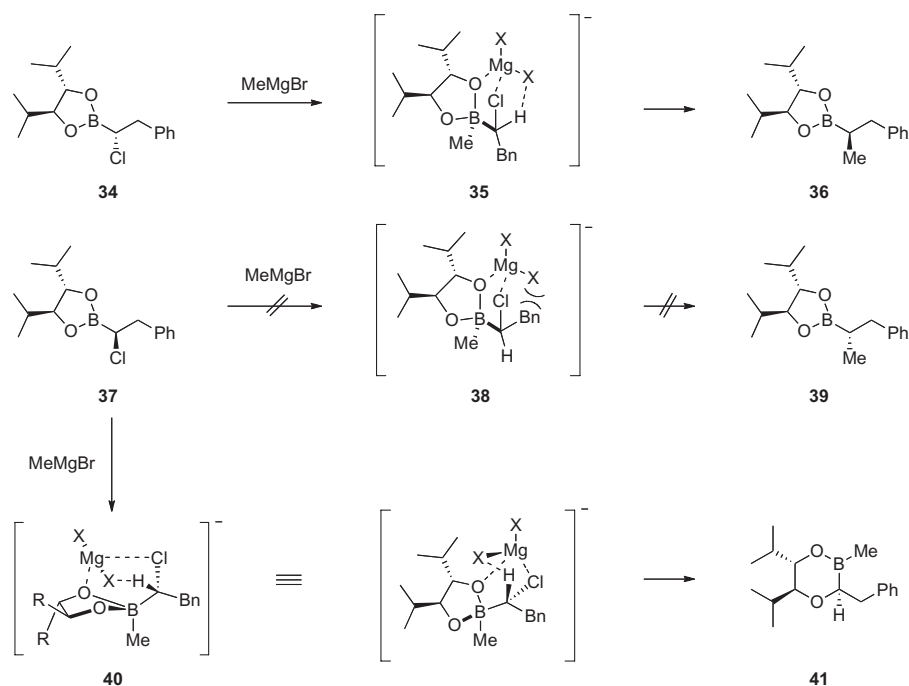
minor drawbacks. Occasionally, diastereomeric ate complexes do not behave in the same way. For example, although ate complex **34** uneventfully evolved to the homologated boronic ester **36**, its diastereoisomer **37** did not. In this case, instead of the standard *C*-migration, contra-thermodynamic *O*-migration occurred to give boronic ester **41** (Scheme 10).¹³ Evidently, the TS required for *C*-migration **38**, which suffers from both a loss of the stabilizing interaction between the halide and C–H bond, and steric clash between the benzyl group and the magnesium halide substituent, must be strongly disfavored. In contrast, TS **40** maintains all the features found in TS **35** (magnesium positioned on the less hindered oxygen atom of the diol, magnesium-activated halide displacement, and halide–CH interaction) but now has the oxygen antiperiplanar to the departing chloride and so this group migrates instead.

Although it is often possible to obtain opposite stereoisomers simply by changing the order of addition of reagents (see Scheme 9), occasionally this is not possible and a three-step sequence to invert (by exchange) the boronic ester diol stereochemistry is required. In the synthesis of mono-protected diol **48**, an epimer of the diol used in the total synthesis of stegobinone (see Scheme 5), the (*R,R*)-diol **44** is required to “control” the stereochemistry of the ether stereogenic centre of **45** and the (*S,S*)-diol *ent*-**44** is needed for the subsequent homologation and methylation of boronic ester **46** (Scheme 11).¹⁴ Therefore, iterative homologation sequences may sometimes require additional steps to change the stereochemistry of the diol of the boronic ester prior to homologation.

Although highly successful for the synthesis of secondary alcohols,^{46h} 1,2-metallate rearrangement of boron-ate complexes have had limited success for the synthesis of tertiary alcohols as variable levels of selectivity were obtained and even the sense of asymmetric induction was unpredictable.¹⁵



Scheme 9. Variation in the sequence of reagent addition in a Matteson-type homologation-alkylation to give different diastereoisomers of the product.



Scheme 10. Example of different outcome from reaction of diastereomeric (α -chloro)boronic esters with Grignard reagents.

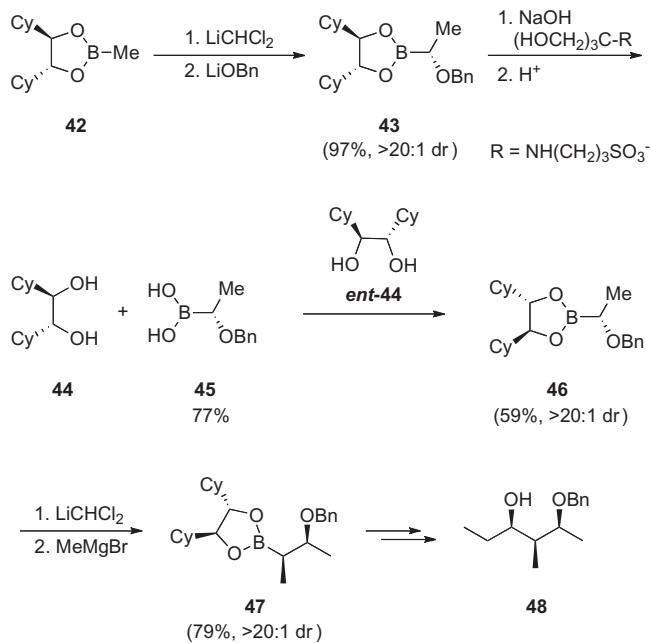
Homologation-Alkylation of Boronic Esters and Boranes using Chiral Carbanions: Reagent Control

In the previous section we discussed the use of boronic esters derived from chiral diols and their subsequent homologation with achiral organometallic reagents. In that section, newly formed stereogenic centers were controlled by the diol architecture (substrate control). The following section describes the reactions between chiral carbanions bearing potential leaving

groups with achiral boronic esters (reagent control). In this case, chirality is embedded in the reagent and so is complementary to the Matteson approach described earlier.

Chiral Carbanions Derived from Sulfur Ylides

Ylides represent a class of carbanions with leaving groups attached directly to the carbanion. In reactions of boranes with different ylides (sulfur-, nitrogen-, and phosphorus ylides),



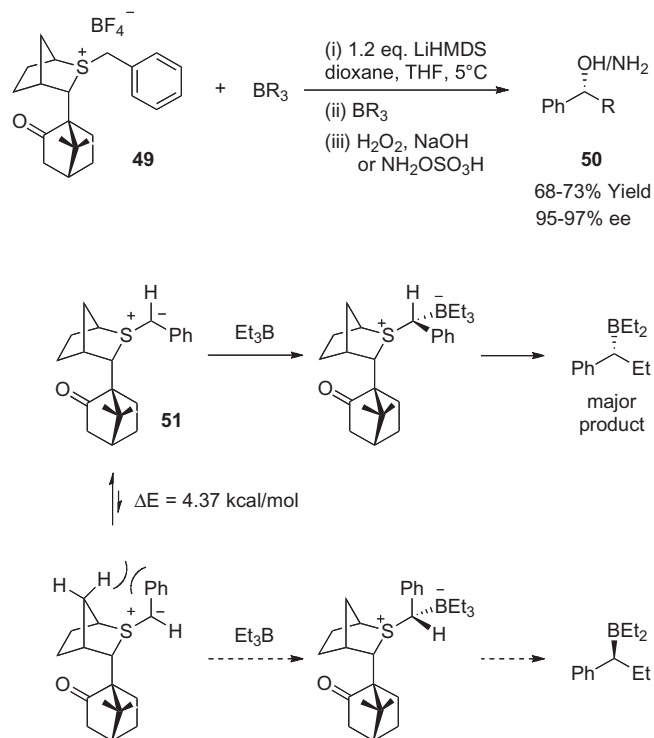
Scheme 11. Stereocontrol through change of boronic ester stereochemistry.

sulfur ylides were found to behave optimally as they possessed the best balance of stability and leaving group ability.¹⁶ Furthermore, such reactions could be easily rendered asymmetric using chiral sulfonium salts such as **49** that had been previously developed for asymmetric epoxidation, aziridination, and cyclopropanation reactions.¹⁷ Thus, reaction of an aryl-stabilized sulfur ylide, generated *in situ* by deprotonation of sulfonium salt **49**, with triaryl, or trialkyl boranes gave the homologated boranes that were oxidized to the corresponding alcohols and amines **50** in high yield and high ee.¹⁸ The major enantiomer is formed from the favored conformation of the ylide **51** reacting on the less hindered face (Scheme 12).

The synthesis of the enantioenriched alcohol **52** and amine **54**, intermediates in the synthesis of the anti-inflammatory agents nebenodine **53** and cetirizine **55**, respectively, demonstrated the potential of this methodology (Scheme 13).¹⁷

However, reactions with 9-BBN derivatives **57** gave mixed results (Table 1).¹⁹ Whereas aryl, alkenyl, and secondary alkyl borane derivatives resulted in exclusive migration of the desired boron substituent, hexynyl and cyclopropyl groups resulted in exclusive migration of the boracycle and primary alkyl groups gave mixtures of both. The main factors responsible for the outcome of the reaction are the conformations of the different intermediate ate complexes and the barriers to interconversion between them (Scheme 14).

The reactions of alkenyl 9-BBN derivatives with sulfur ylides provided a unique asymmetric route to α,γ -substituted

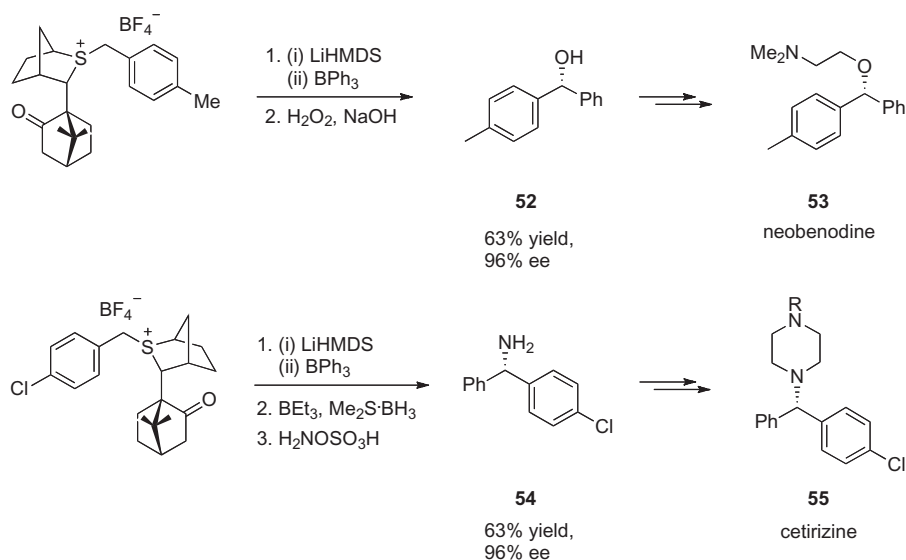


Scheme 12. Reactions of chiral sulfur ylides with organoboranes.

allylic boranes—compounds that had not been prepared previously due to their high lability (Scheme 15).²⁰ Reaction of the ylide derived from sulfonium salt **56** with vinylboranes at -100°C followed by the addition of benzaldehyde at the same temperature, and subsequent warming to room temperature gave the homoallylic alcohol **61** in 96% yield as a single anti-diastereoisomer with a high *Z* selectivity (Procedure A, Scheme 15). Using this protocol, the aldehyde trapped the allylic borane as it was formed, thus not allowing time for isomerization to occur. The high lability of these allylic boranes has also been exploited. If the intermediate allylic borane **60** was allowed to warm to 0°C , isomerization occurred to give the thermodynamically more stable allylic borane **62** that could be trapped with benzaldehyde at -78°C to give the isomeric alcohol **63** in high yield and with similarly high diastereoselectivity (Procedure B, Scheme 15).

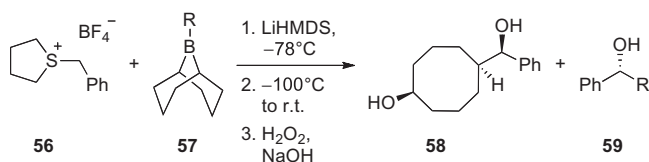
These mentioned processes were rendered asymmetric by the use of the enantiopure sulfonium salt **49**.²⁰ In all cases, essentially complete enantio- and diastereoselectivity was observed, with a very high *Z* selectivity (Table 2). The chiral sulfide was also re-isolated routinely in greater than 90% yield. With less electron-rich vinyl groups (entries 3–5), yields were lower due to competing migration of the boracycle.

Procedure B was also applied to the same range of vinyl boranes and chiral sulfonium salt **49** (Table 3). Again,

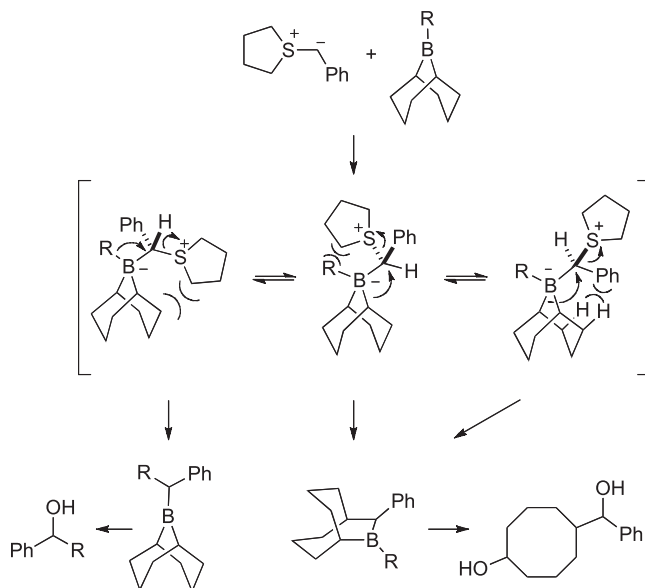


Scheme 13. Application of ylide methodology to the synthesis of pharmaceuticals containing diaryl methanols and diaryl methylamines.

Table 1. Outcome of the 1,2-metallate rearrangement at complexes resulting from the 9-BBN derivatives.



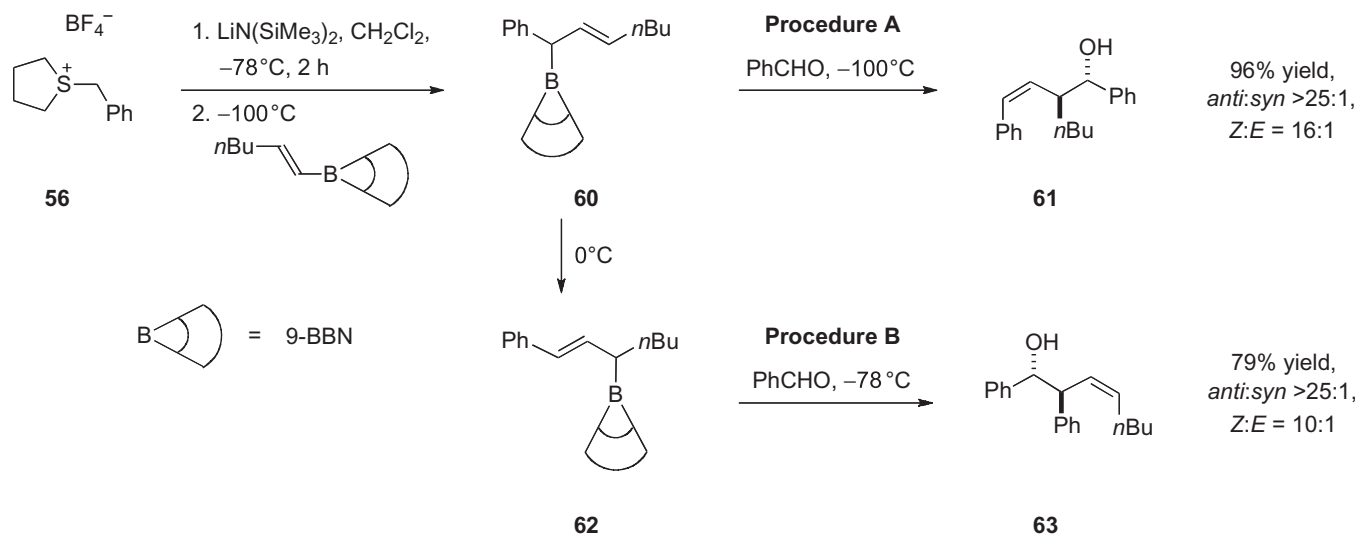
| Entry | R | Yield 58 | Yield 59 |
|-------|-------------|-----------------|-----------------|
| 1 | Hexyl | 56% | 41% |
| 2 | Allyl | 51% | 39% |
| 3 | Benzyl | 51% | 35% |
| 4 | i-Pr | Trace | 77% |
| 5 | Cyclopropyl | 89% | Trace |
| 6 | Ph | Trace | 94% |
| 7 | 1-Hexenyl | Trace | 21% |
| 8 | 1-Hexynyl | 92% | Trace |



Scheme 14. Origin of the selectivity in the migration of the boron substituent or boracycle in boronate complexes derived from sulfur ylides.

essentially complete enantio- and anti-diastereoselectivity was observed with a high *Z* selectivity. As procedures A and B share common borate intermediates, the competing migration of the boracycle previously observed with less electron-rich vinyl boranes led to lower yields again (Table 3, entries 3, 4). The observed complete selectivity in the allyl borane isomerization when following procedure B is consistent with a highly stereoselective, intramolecular 1,3-borotropic rearrangement process. The preferred isomer results from the minimization of $A^{1,3}$ strain²¹ in the conformations required for the borotropic rearrangement to occur.

This work was applied to the synthesis of (+)-iso-agatharesinol **66**.¹⁷ The key ylide addition, 1,2-metallate rearrangement, and trapping with the aldehyde occurred in 72% yield and with >99% ee giving (+)-iso-agatharesinol precursor (+)-**65** (Scheme 16). This allowed the unambiguous assignment of the relative and absolute stereochemistry of the natural product.



Scheme 15. Synthesis of isomeric homoallylic alcohols by lithiation-borylation reaction of sulfur ylides.

Table 2. Asymmetric synthesis of homoallylic alcohols.

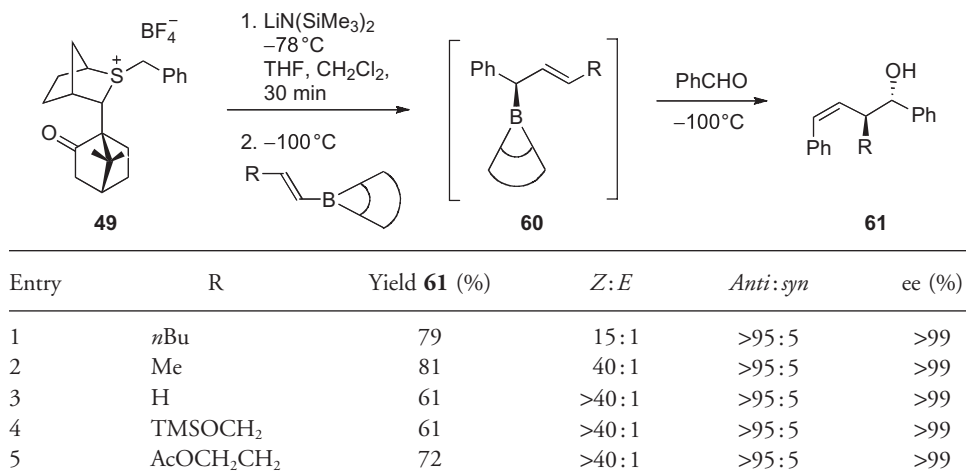
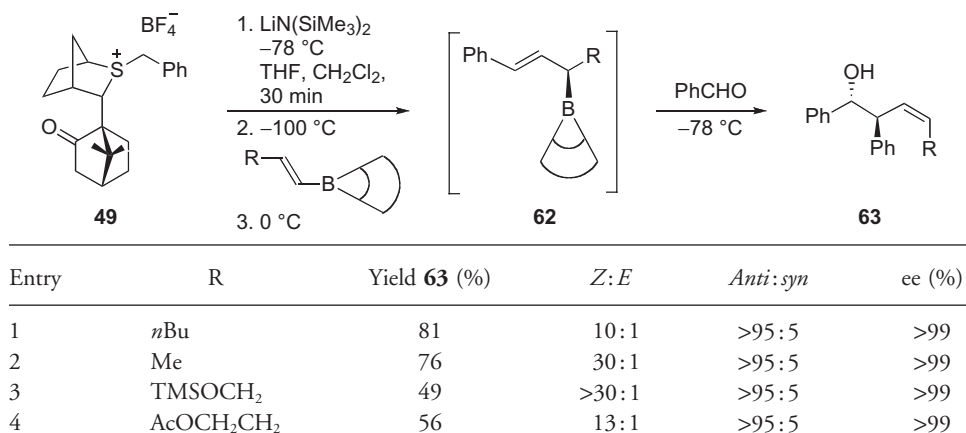
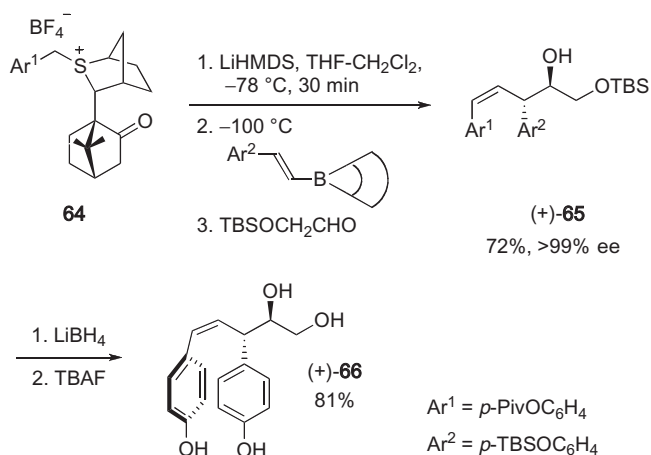


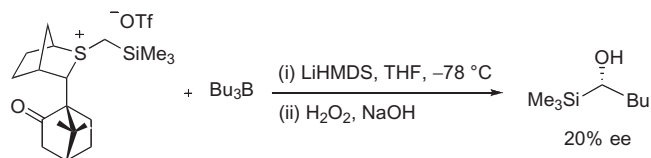
Table 3. Synthesis of homoallylic alcohols with 1,3-transposition of allylic borane.





Scheme 16. Synthesis of (+)-iso-agatharesinol.

The reactions of sulfur ylides with boranes are limited to aryl substituents: alkyl- and silyl-substituted ylides give low enantioselectivity. In the case of the latter ylides, it was found that ate complex formation was reversible and the migration step was now the selectivity-determining step (Scheme 17).²²



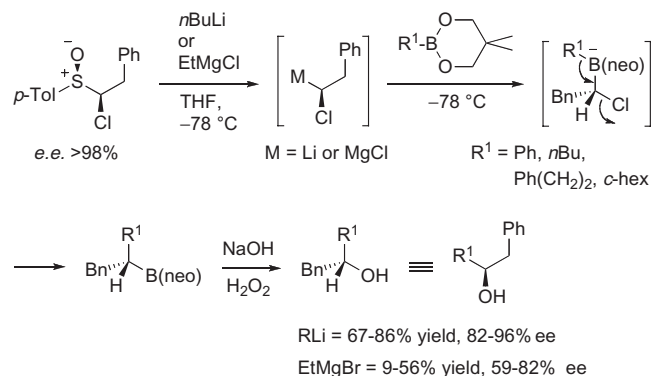
Scheme 17. Lithiation-borylation reaction of trimethylsilyl-stabilized sulfur ylides.

A significant limitation of the sulfur ylide reactions is that the outcome with nonsymmetrical boranes is highly dependent on the substituents on boron. A potential solution to this problem is to use boronic esters. Unfortunately, boronic esters do not react with sulfur ylides. They are much less electrophilic and the barrier to migration is considerably higher.^{19,23} With relatively stable anions like aryl-stabilized sulfur ylides, addition may occur but the high barrier to migration results in reversibility in the ate complex formation and ultimately decomposition of the ylide.¹⁹ To carry out reagent-controlled additions and subsequent 1,2-metallate rearrangements with boronic esters requires a less stable carbanion that possesses a good enough leaving group.

Chiral Carbanions of Lithiated Alkyl Chlorides

Blakemore et al. have developed the homologation of boronic esters using enantioenriched Hoffmann-type magnesium car-

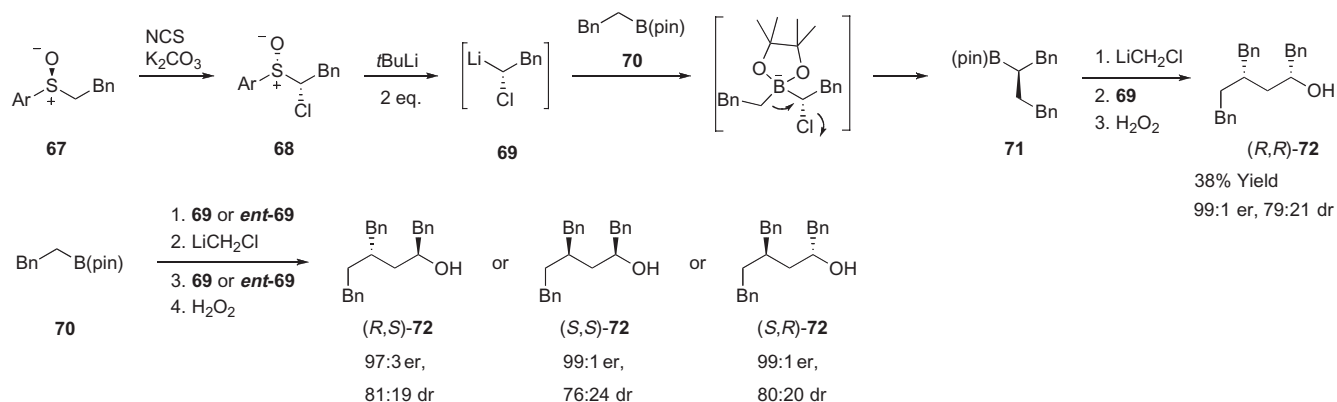
benoids.²⁴ However, in contrast to reaction with organomagnesium reagents they found that sulfoxide ligand exchange with alkyl lithium reagents gave a lithium carbenoid that underwent chain extension of catechol and neopentyl glycol boronic esters with considerably higher levels of stereochemical control (Scheme 18).²⁵



Scheme 18. Homologation of boronic esters with lithiated alkyl chlorides.

The process mentioned earlier showed good substrate scope in the range of boronic esters that could be employed (primary or secondary aliphatic; pinacol or neopentyl glycol) leading to secondary alcohols in 82–96% ee. The scope in terms of the chiral organometallic was more limited: although primary aliphatic substrates worked well (Bn, Et, *i*-Bu, BnCH₂), secondary (*i*-Pr, 0% yield) and methyl (23% yield, 60% ee) were less effective.²⁶

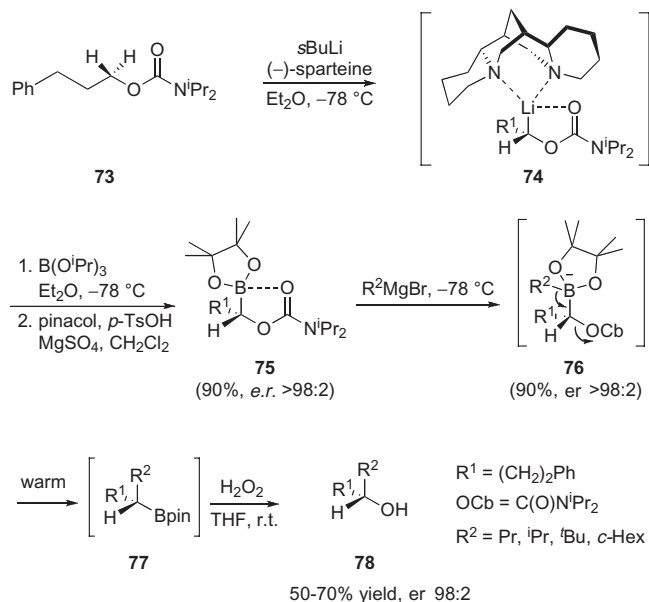
This work was extended to iterative stereospecific reagent-controlled homologations. Alkyl lithium-effected sulfoxide ligand exchange using *t*-BuLi in toluene of enantioenriched α -chloroalkyl sulfoxide **68**, prepared by chlorination of sulfoxide **67**, gave the enantioenriched lithiated carbanion **69** that was reacted with boronic ester **70** to give the homologated boronic ester **71**. One carbon chain extension followed by treatment with the organolithium **69** then gave alcohol **72**, after oxidation, as a 79:21 mixture of diastereoisomers in which the major isomer was formed with >99:1 er. This protocol was then used to prepare all four diastereoisomers of alcohol **72** from boronic ester **70** by sequential reaction with the required enantiomer of carbanion **69/ent-69**, (dichloromethyl)lithium, and carbanion **69/ent-69** followed by oxidative work-up (Scheme 19).²⁶ It should be noted that when enantiomerically enriched components are coupled together the enantiomeric ratio of the desired product is enhanced but at the expense of formation of diastereomeric by-products. This occurs through a statistical amplification process first reported by Horeau.²⁷



Scheme 19. Iterative boronic ester homologation with lithiated alkyl chlorides.

Chiral Carbanions of Lithiated Carbamates

An alternative to lithiated chlorides are the more stable lithiated carbamates. Hoppe et al. have shown that borate ester **75**, derived from the corresponding carbamate **73** by asymmetric lithiation and borylation, reacted with Grignard reagents to give, after oxidation, secondary alcohols **78** in good yield and high ee.²⁸ This showed that the carbamate group was a good enough leaving group in the 1,2-metallate rearrangement of boronic ester ate complexes **76**, although it was probably facilitated by the magnesium bromide present in the reaction (Scheme 20).



Scheme 20. Hoppe-type alkylation of boronic esters by carbamate lithiation/borylation and subsequent nucleophile triggered 1,2-metallate rearrangement.

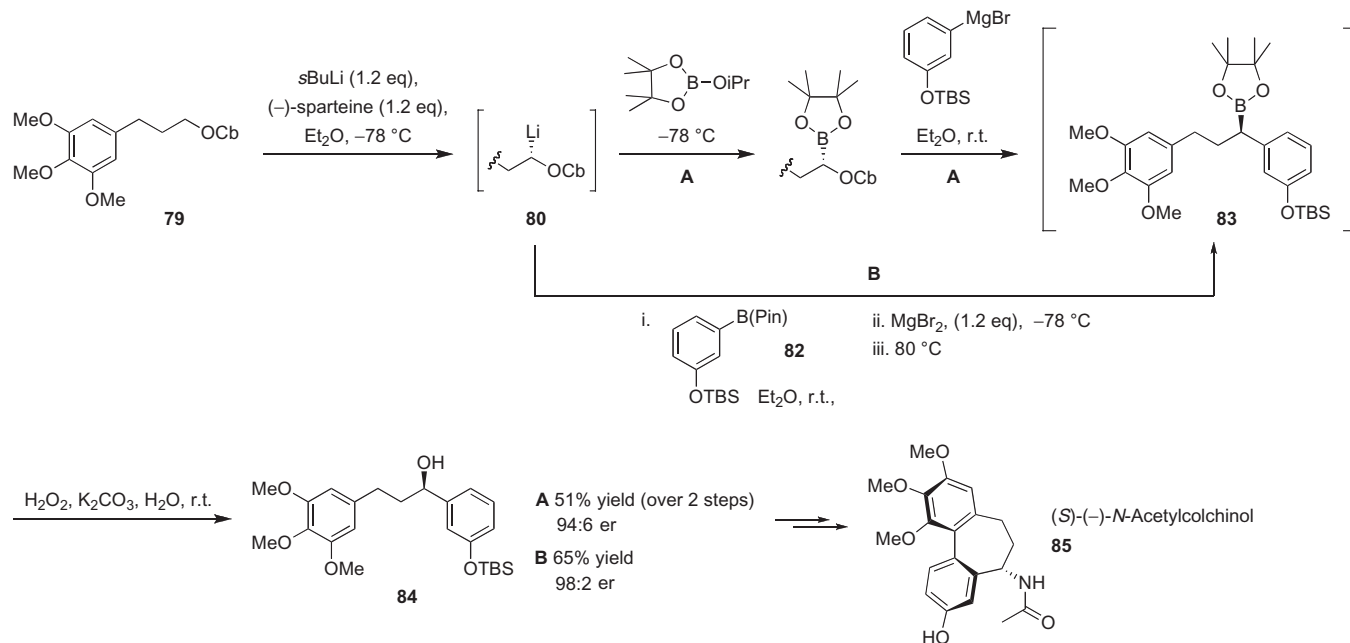
This type of reaction was recently applied by Kocienski in the synthesis of (*S*)-(-)-*N*-acetylcolchicol **85** (Scheme 21).²⁹ Along with the stepwise reaction (Scheme 21, path A), Kocienski also showed that a chiral lithiated carbamate could react directly with *B*-aryl-pinacol boronic ester **82** (Scheme 21, path B). However, to achieve rearrangement required exchange of solvent, addition of magnesium bromide, and heating to 80°C. Notably, this direct reaction of boronic ester **82** with lithiated carbamate **80** gave alcohol **84** in higher yield and excellent enantiomeric ratio.

Direct reaction of Lithiated Carbamates with Boronic Esters and Boranes

Aggarwal et al. have shown that the direct reaction of lithiated carbamates with boranes and boronic esters shows considerable scope and therefore potential for synthesis (Table 4). In all cases high enantioselectivities were observed (er 95:5–98:2).^{30,31}

A number of points worthy of note:

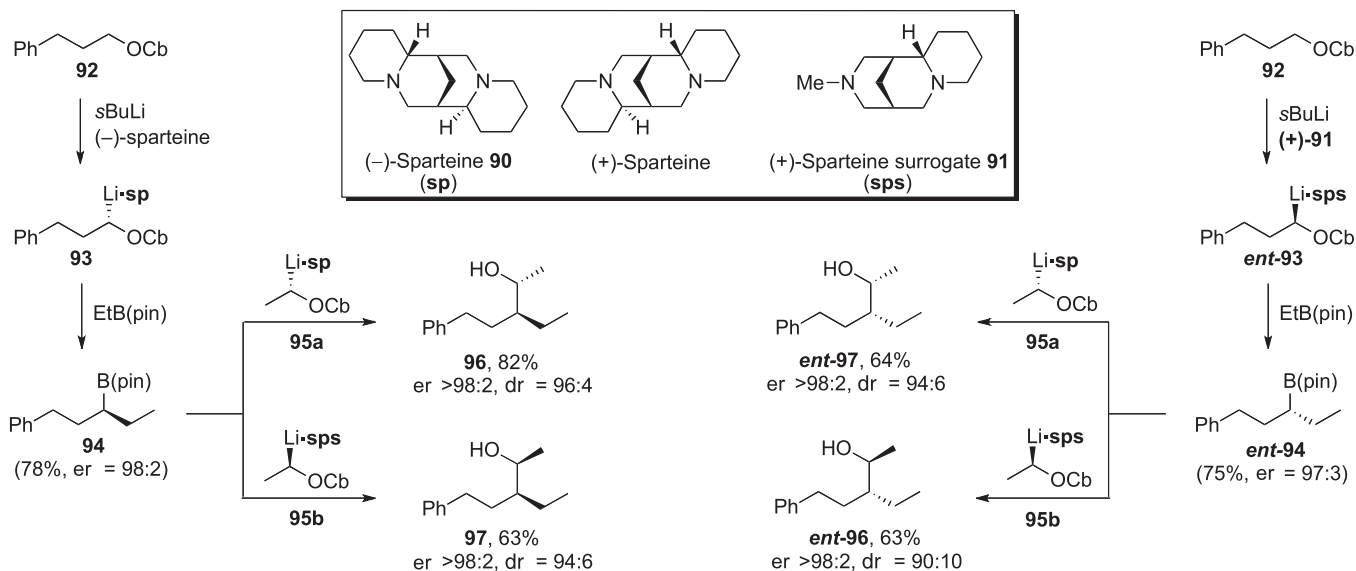
1. In contrast to the reactions of sulfur ylides with 9-BBN derivatives, reaction with lithiated carbamates resulted in clean migration of the boron substituent rather than the boracycle in all cases. This is highly unusual³² and has only previously been observed with halide leaving groups, suggesting that the carbamate should also be considered as a small substituent in these types of reaction.
2. In the case of *B*-Ph-9-BBN, higher er was obtained in the presence of magnesium bromide (entries 4 vs. 5, Table 4), whereas in other cases involving aliphatic groups magnesium bromide was not found to be necessary. It is believed that magnesium bromide sequesters the diamine ligand preventing it from binding to the borane. Binding of the diamine to benzylic boranes results in an erosion in er.



Scheme 21. Synthesis of (S)-(-)-N-acetylcolchicol.

Table 4. Direct reaction of boronic ester with enantioenriched lithiated carbamates.

| Entry | R ¹ | R ² | (R ³) ₂ | Lewis acid | Yield 89 (%) | er |
|-------|--|----------------|--------------------------------|-------------------|---------------------|-------|
| 1 | Ph(CH ₂) ₂ | Et | Et ₂ | — | 91 | 98:2 |
| 2 | | <i>n</i> Hex | 9BBN | — | 90 | 98:2 |
| 3 | | <i>i</i> Pr | 9BBN | — | 81 | 98:2 |
| 4 | | Ph | 9BBN | — | 85 | 88:12 |
| 5 | | Ph | 9BBN | MgBr ₂ | 94 | 97:3 |
| 6 | | Et | Pinacol | MgBr ₂ | 90 | 98:2 |
| 7 | Me ₂ C=CH(CH ₂) ₂ | Et | Et ₂ | — | 90 | 97:3 |
| 8 | | Ph | 9BBN | MgBr ₂ | 71 | 95:5 |
| 9 | | Et | Pinacol | MgBr ₂ | 75 | 97:3 |
| 10 | | Ph | Pinacol | MgBr ₂ | 73 | 98:2 |
| 11 | TBSO(CH ₂) ₂ C(Me) ₂ | Et | Et ₂ | — | 67 | 95:5 |
| 12 | CH ₂ | Ph | 9BBN | MgBr ₂ | 65 | 97:3 |
| 13 | | Ph | Pinacol | MgBr ₂ | 64 | 98:2 |
| 14 | <i>i</i> Pr | Ph | 9BBN | MgBr ₂ | 68 | 96:4 |
| 15 | | Ph | Pinacol | MgBr ₂ | 70 | 98:2 |
| 16 | Me | Ph | Pinacol | MgBr ₂ | 70 | 97:3 |



Scheme 22. Synthesis of all four stereoisomers of alcohols **96** and **97**.

- 1,2-Metallate rearrangement of ate complexes is much slower in the case of boronic esters compared to boranes and required magnesium bromide in diethyl ether at reflux in the former case whereas the ate complexes derived from boranes began to rearrange at -40°C without further additives.
- A broad range of alkyl carbamates including methyl, primary, and branched secondary alkyl chains can be employed together with a broad range of aryl and alkyl boranes and boronic esters. The methodology therefore shows considerable substrate scope.
- Reactions of lithiated carbamates with both the boranes and boronic esters occurred with retention of configuration (**74**→**87**, Table 4). This is probably because the non-stabilized anion is sp^3 hybridized and as such there is little electron density opposite the metal.

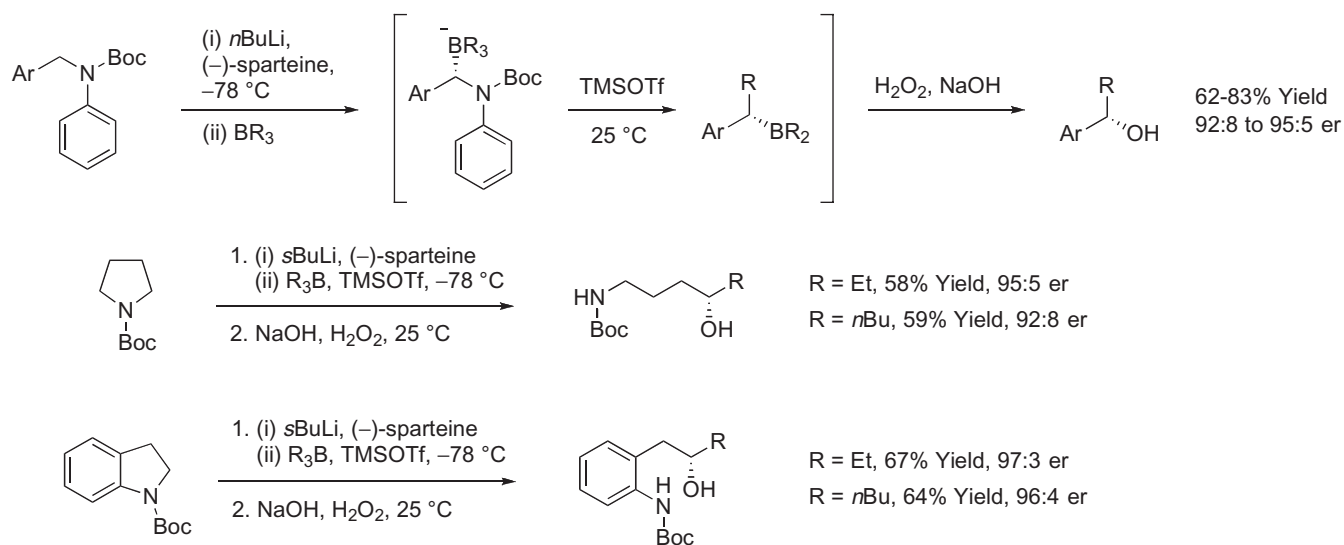
Extension of this methodology to iterative homologations was demonstrated by the synthesis of all four stereoisomers of alcohols **96/97** (Scheme 22). Lithiation of carbamate **92** in the presence of $(-)$ -sparteine and trapping with EtB(pinacol) gave boronic ester **94** in 78% yield and 98:2 er. Reaction of boronic ester **94** with lithiated carbamate **95a** gave, after oxidative work-up, alcohol **96** as a 96:4 mixture of diastereoisomers and with an enantiomeric ratio of $>98:2$ for the major diastereomer. The diastereomeric alcohol **97** was prepared by reaction of boronic ester **94** with the enantiomer of lithiated carbamate **95b**, prepared using O'Brien's sparteine surrogate $(+)$ -**91**^{33,34} in place of $(-)$ -sparteine **90**, in similarly high diastereo- (94:6 dr) and enantioselectivities (er $>98:2$; Scheme 22). The absence of matched/mismatched pairs indicates that

the chiral lithiated carbamate is effectively blind to the stereochemistry of the chiral boronic ester. Thus, the outcome of the reaction is completely controlled by the chiral reagent and is not influenced by the inherent chirality of the substrate. The enantiomeric pair to alcohols **96** and **97** were obtained with similar diastereo- and enantioselectivities using the same protocol but from the enantiomer of boronic ester **ent-94**, which was obtained using O'Brien's sparteine surrogate $(+)$ -**91** in the first homologation (Scheme 22). As was the case in the iterative homologations of Blakemore et al. (Scheme 19),²⁶ statistical enhancement of enantiomeric excess²⁷ further increases the enantiopurity of alcohols **96** and **97**.

The asymmetric lithiation-borylation and 1,2-metallate rearrangement has also been applied to *N*-linked benzylic and cyclic carbamates (Scheme 23).⁵⁵ However, the poorer leaving-group ability of the *N*-linked carbamate limited the scope of the methodology to boranes and even then a strong Lewis acid (TMSOTf) was required to trigger the 1,2-metallate rearrangement.

Conclusions and Future Outlook

The asymmetric homologation of boronic esters is a powerful method for the stereocontrolled synthesis of substituted carbon chains. It can be conducted using either substrate or reagent control. In the substrate-controlled process the key step involves the addition of (dichloromethyl)lithium to a chiral diol-derived boronic ester and subsequent 1,2-metallate rearrangement. This rearrangement is highly diastereoselective when conducted in the presence of zinc chloride. The (α -chloro)boronic



Scheme 23. Secondary alcohol synthesis by lithiation–borylation of benzylic *N*-linked carbamates.

ester that is formed is subsequently reacted with a Grignard reagent, or other nucleophile, to give a secondary alkyl boronic ester stereospecifically. The reactions show considerable scope and have been applied in synthesis. It is especially suited to the synthesis of α -amido boronic esters, a class of protease inhibitors now used on the clinic, where it has been utilized on considerable scale.³⁶ Considering the practicality of the process it is somewhat surprising that the methodology has not been employed more widely. It is not clear whether this is because of reports that occasionally the intermediate ate complex undergoes *O*-migration instead of *C*-migration or because specific stereoisomers could only be made through a rather difficult and lengthy exchange of diol ligands.

In the reagent-controlled processes, chiral sulfur ylides have been found to react with boranes giving homologated products with high ee but reactions are limited to aryl-stabilized ylides. A further limitation is that sulfur ylides only react with boranes. Nevertheless, reactions with alkenyl 9-BBN derivatives provide a unique entry to α,γ -substituted allylic boranes that are important intermediates in stereoselective synthesis. α -Chloroalkyllithiums are considerably more reactive and less stable than sulfur ylides and consequently react with boronic esters. They can be used iteratively but suffer from somewhat limited scope in the nature of the alkyl group that can be used (not methyl or β -branched). The reagents with the greatest scope are Hoppe's lithiated carbamates: a broad range of alkyl carbamates can react with a range of alkyl and aryl boranes and boronic esters. As chiral carbanions are derived from simple primary alcohols, access to these chiral reagents is especially facile. Furthermore, they can be used iteratively thus allowing carbon chains to be grown interspersed with substitu-

ents of specific stereochemistry. They therefore offer the greatest versatility and flexibility in the homologation of boranes and boronic esters.

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