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Lithiation–Borylation Methodology and Its Application in Synthesis

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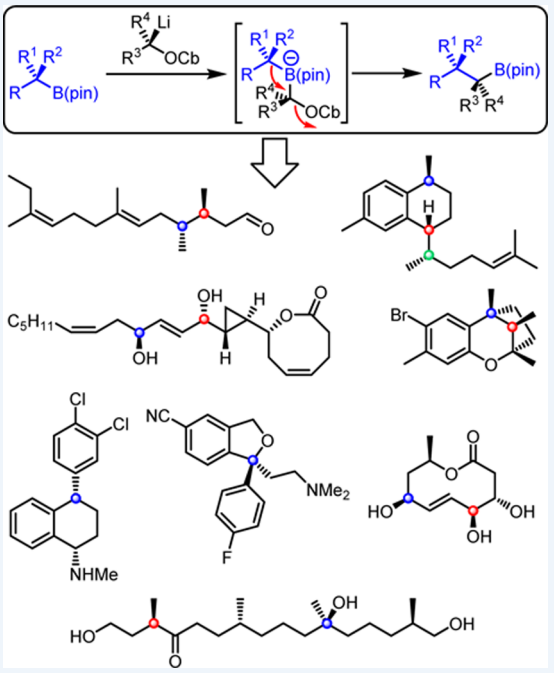
CONSPECTUS: Developing new methods that enable the synthesis of new and complex molecules with complete control of their 3-D shape is central to the advancement of synthetic chemistry with applications spanning from medicine to materials. Our approach consists of the iterative combination of small building blocks through the use of boron chemistry to essentially "grow" molecules. This approach, which we term assembly-line synthesis (ALS), resembles the way that nature assembles natural products (e.g., the polyketide synthase machinery) and has the advantage that many structural variations can be easily introduced and the products can be evaluated in structural or biological contexts.

Chiral boronic esters have been recognized as valuable building blocks due to their unique chemical properties. They are both chemically and configurationally stable, and they can be prepared with very high levels of enantioselectivity. Additionally they undergo a broad array of transformations that lead to the stereocontrolled formation of C–C and C–X (X = heteroatom) bonds. This versatility makes boronic acids ideal building blocks for iterative molecular assembly.

A powerful reaction platform for chemical diversification using chiral boronic esters is their homologation using lithium carbenoids via 1,2-metalate rearrangement. In the 1980s, Matteson described the use of boronic esters bearing a chiral diol in a two-step homologation process with dichloromethyl lithium and Grignard reagents (substrate-controlled approach). We have focused on reagent control and have found that Hoppe's chiral lithiated carbamates can be used as carbenoid equivalents in conjunction with achiral boronic esters. This reagent-controlled process offers many advantages due to the easy access of both the chiral lithiated carbamates and stable boronic esters. The carbamates can be derived from primary or secondary alcohols, and a broad range of functionalized boronic esters and boranes can be employed. Multiple homologations can be carried out in a one-pot sequence thereby streamlining the process to a single operation. This methodology has enabled the synthesis of many molecules containing multiple contiguous stereogenic centers with exquisite 3-D control. In this Account, we trace our own studies to establish the lithiation–borylation methodology and describe selected synthetic applications.



1. INTRODUCTION

Organoboranes and boronic esters are very useful synthetic intermediates because they can be converted into a broad range of functional groups, often with complete stereospecificity. These transformations are usually initiated by nucleophilic addition to the electrophilic boron atom followed by 1,2-migration.[1,2] 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.[3] Indeed, the hydroboration of alkenes using (−)-diisopinocampheylborane by H. C. Brown in 1961 provided the first nonenzymatic asymmetric synthesis that resulted in truly practical levels of enantioselection.[4,5] In the early 1980s, Matteson reported a complementary route to chiral boronic esters.[1,6,7] 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). This substrate-controlled approach relies on a two-step sequence consisting of (i) addition of dichloromethyl lithium ($LiCHCl_2$) to the boronic ester to give a chiral α-alkyl organoboron followed by (ii) addition of an achiral Grignard reagent (or other nucleophile) to deliver the homologation product (Scheme 1A). In fact, the discoveries by Matteson that very high levels of diastereoselectivity could be achieved in homologation opened up a whole new field in organoboron chemistry.[1,8] While extremely powerful in controlling the stereochemical outcome of the homologation process, its versatility and conciseness is somewhat limited. In particular, because the stereochemical outcome is dictated by the stereochemistry of the chiral diol

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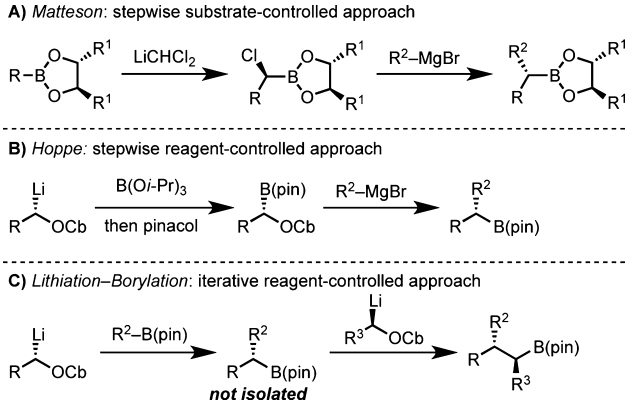
Scheme 1



embedded in the boronic ester, exchange of the chiral diol is required in order to obtain a different stereoisomer, a manipulation that occasionally can be troublesome due to difficulties associated with their hydrolysis.[9]

An alternative, complementary approach uses a chiral reagent to construct a related chiral ate complex, which subsequently evolves into the chiral boronic ester following 1,2-metalate rearrangement (reagent control; Scheme 1). This requires a reagent that behaves as a chiral carbanion and possesses a leaving group at the same carbon atom. We recognized that Hoppe's lithiated carbamates contained all the features required for stereocontrolled homologation of boronic esters. Indeed, Hoppe had shown that the individual steps in our proposed homologation sequence were viable: (i) chiral lithiated carbamates could be generated easily and trapped with B(O*i*-Pr)$_3$ (and they were subsequently converted into the stable pinacol boronic esters), and (ii) subsequent addition of a Grignard reagent gave boronate complexes, which underwent a stereospecific 1,2-metalate rearrangement to give boronic esters with excellent stereocontrol (Scheme 1B).

Kocienski[10] and our group[11] showed that this process could be streamlined in a single operation by direct addition of a pinacol boronic ester (or a borane) to the lithiated carbamate (Scheme 1C).[8] In related work, Blakemore showed that chiral α-chloroalkyllithium reagents can also be employed in stereocontrolled homologation of boronic esters, but these reagents are less stable and more difficult to prepare.[12,13] In addition to developing the methodology, we have demonstrated the power of the lithiation–borylation reaction in the synthesis of complex molecules containing multiple stereogenic centers and exemplified its use in iterative homologations.

This Account describes the development of our new method for the stereospecific homologation of chiral boronic esters via lithiation–borylation and its application to the total synthesis of complex natural products.

2. LITHIATION–BORYLATION PROCESS: BASIC PRINCIPLES

The general mechanism of a prototypical lithiation–borylation process consists of three main steps: (i) formation of a chiral lithium carbenoid by α-lithiation of a carbamate (OCb) or a hindered benzoate (OTIB), (ii) electrophilic trapping by addition of an organoboron reagent to form a chiral "boronate" complex, which after (iii) 1,2-metalate rearrangement evolves into the homologate organoboron ready for further transformations (Scheme 2). For this process to be synthetically useful several key factors need to be simultaneously fulfilled.

2.1. Lithiation (Step I)

The chiral lithium carbenoid needs to be accessed in high yield and selectivity. Three main approaches are normally used: (i) chiral ligand-assisted asymmetric deprotonation of primary carbamates or benzoates, (ii) stereospecific deprotonation of enantioenriched secondary carbamates or benzoates, and (iii) stereospecific tin–lithium exchange of enantioenriched α-Sn carbamates or benzoates. Once the chiral organolithium has been generated, it needs to be both chemically and configurationally stable under the reaction conditions to avoid detrimental decomposition and racemization.

2.2. Electrophilic Trapping (Step II)

Treatment of organolithiums with organoboron reagents results in direct electrophilic trapping giving boronate complexes. This process needs to be (i) fully stereospecific, either retentive (S_E2ret) or invertive (S_E2inv), and (ii) extremely fast compared with the following 1,2-shift (*vide infra*). In general, the electrophilic trapping of chiral organolithiums with organoborons occurs with retention of configuration, but invertive pathways have been observed in the case of reactions of organolithiums derived from secondary benzylic carbamates and boranes (*vide infra*).

Scheme 2

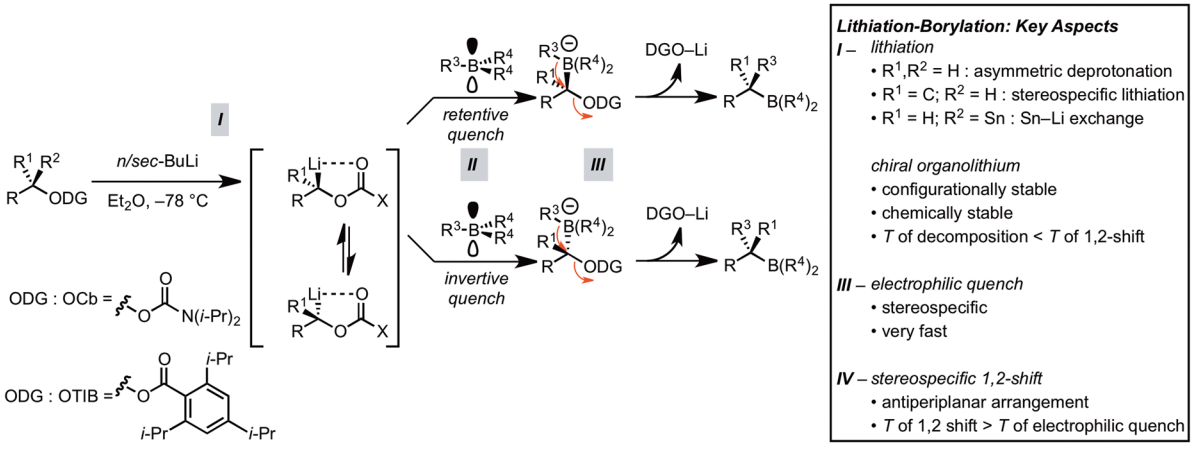


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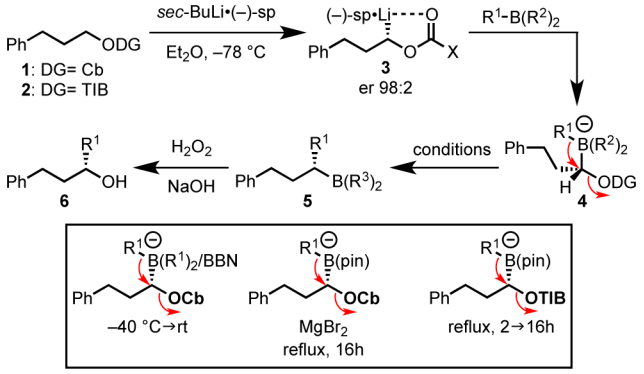
Table 1



entry	ODG	R^1	$B(R^2)_2$	T (°C), time (h)	Lewis acid	yield (%)	er
1	OCB	Et	BEt_2	−40 → rt		91	98:2
2	OCb	*i*-Pr	BBN	−40 → rt		81	98:2
3	OCb	Ph	BBN	−40 → rt		85	88:12
4	OCb	Ph	BBN	−40 → rt	$MgBr_2$	94	97:3
5	OCb	Ph	B(pin)	reflux, 16	$MgBr_2$	90	98:2
6	OCb	Et	B(pin)	reflux, 16		75	97:3
7	OCb	Me	B(pin)	reflux, 16	$MgBr_2$	50	95:5
8	OTIB	Me	B(pin)	reflux, 2		76	96:4
9	OCb	$(CH_2)_2CN$	B(pin)	reflux, 16	$MgBr_2$	0	
10	OTIB	$(CH_2)_2CN$	B(pin)	reflux, 2		46	97:3

2.3. 1,2-Metallate Rearrangement (Step III)

The stereospecific 1,2-metalate rearrangement requires an *anti*-periplanar arrangement of the migrating group on boron and the carbamate or benzoate leaving group and needs to proceed at temperatures higher than the borylation step to avoid undesired over-homologations.

3. LITHIATION–BORYLATION WITH PRIMARY CARBAMATES AND BENZOATES

In 2007, we reported that lithiated carbamates react directly with boranes and boronic esters, furnishing homologated organoborons in high yields and excellent enantioselectivity.[11] As shown in Table 1, treatment of carbamate **1** with (−)-sparteine [(−)-sp][14] and *sec*-BuLi furnished the chemically and configurationally stable organolithium **3** in excellent enantioselectivity. Immediate electrophilic trapping with various organoborons (symmetrical and unsymmetrical boranes as well as pinacol boronic esters) gave the required boron-ate complexes **4** with retention of configuration. Following 1,2-metallate rearrangement, the homologation products **5** were produced and oxidized *in situ*. In all cases, the desired secondary alcohols **6** were formed in high yields and excellent enantioselectivity, showing that the criteria laid out above were fulfilled with lithiated carbamates. In the course of our initial investigations, we learned much about the factors that control the key 1,2-shift. In general, homologations with boranes were considerably faster than boronic esters with the 1,2-shift process starting to occur at −40 °C (entries 1−4, Table 1). In the case of boronic esters, high temperatures (refluxing Et_2O, 16 h) were required to effect the 1,2-shift (entries 5, 6).[15] Phenyl was found to be a slow migrating group and required the Lewis acid $MgBr_2$ to promote the desired 1,2-shift (entry 5). In addition, when particularly slow migrating groups [e.g., Me, $(CH_2)_2CN$] were employed, the process could be accelerated by using hindered benzoates (e.g., TIB ester **2**) instead of carbamates. In this case, their improved leaving group ability allowed the boron-ate complex to rearrange in a few hours under reflux without the need for a Lewis acid additive (entries 8 and 10).[16]

Having developed the methodology, we sought to apply it in synthesis. Figure 1 shows the diverse array of natural products that we have successfully targeted using the homologation of boronic esters with lithiated primary carbamates.[17−22]

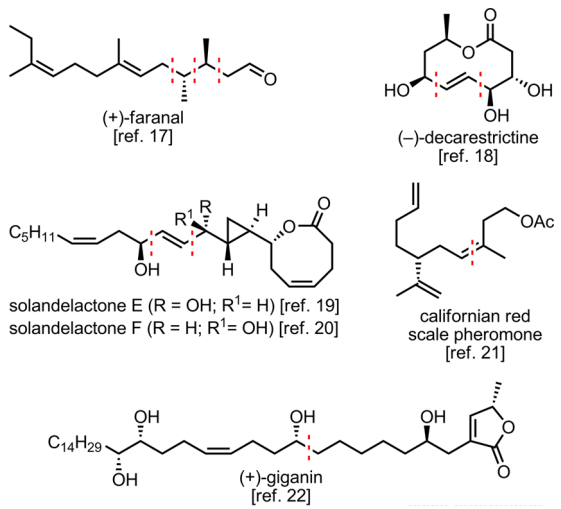


Figure 1.

The total synthesis of (+)-faranal (**7**) is representative.[17] This insect pheromone was selected because of its carbon chain containing adjacent methyl groups, a challenging motif present in a number of natural products.[23] By means of consecutive lithiation−borylation processes, (+)-faranal, **7**, was prepared in an enantio- and diastereospecific fashion in just two steps from the advanced vinyl iodide **8** and six overall steps from propyne (Scheme 3). A one-pot quadruple homologation of **8** was

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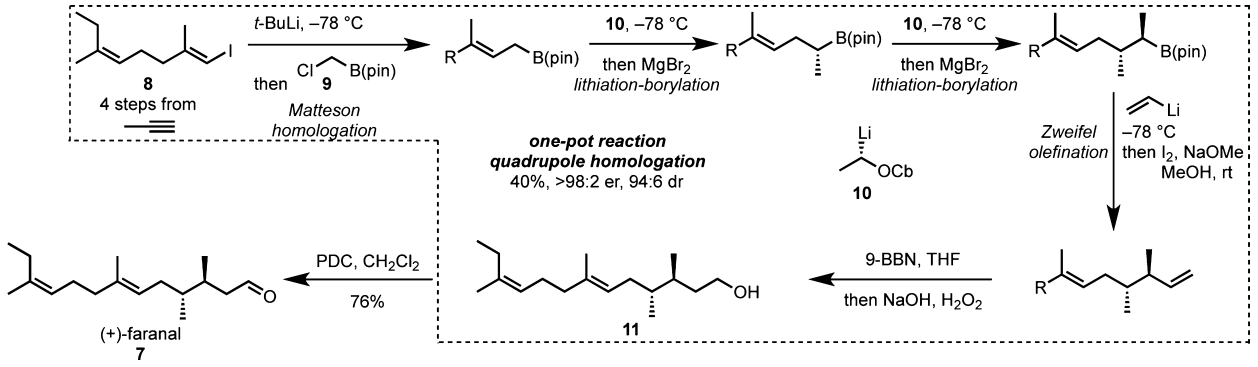
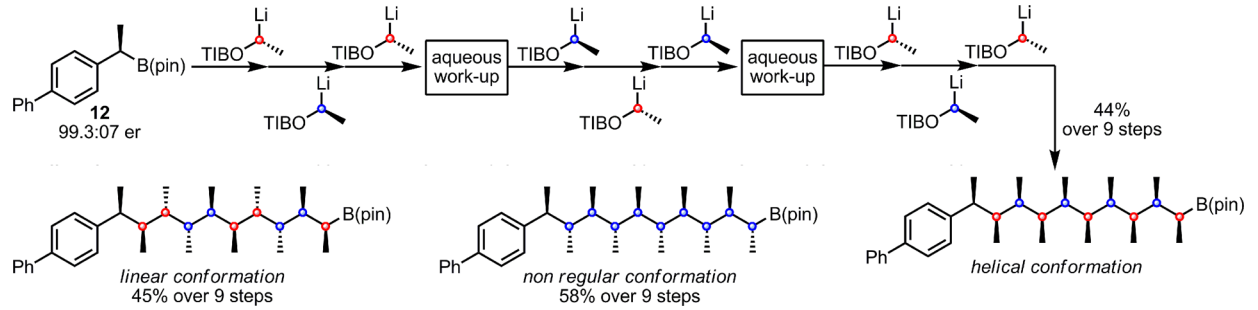
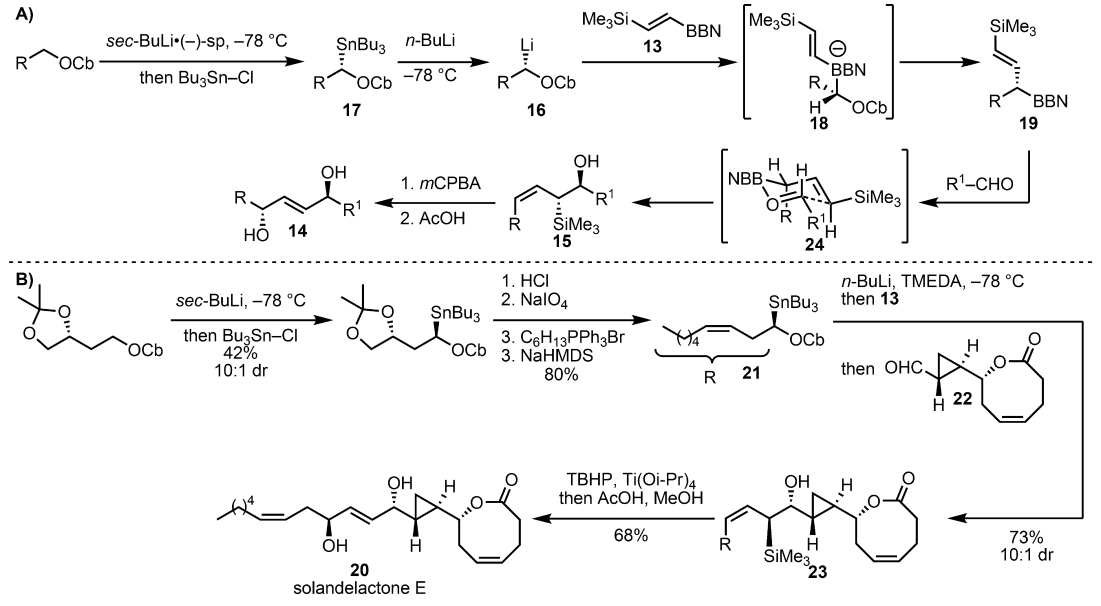
Scheme 3



Scheme 4



Scheme 5



developed to set the two contiguous stereocenters. This remarkable process consisted of (i) a Matteson homologation with choromethyl boronic ester **9**, (ii) two consecutive lithiation–borylations with **10**, and (iii) a Zweifel olefination[24]–hydroboration sequence, which gave **11** in 40% yield and excellent er and dr.

The limit to the number of iterative homologations that can be conducted without intermediate purification has been explored, but the limit has not yet been found. Starting from the benzylic boronic ester **12**, nine iterative homologations were carried out leading to a carbon chain bearing 10 contiguous methyl substituents with full stereocontrol (all *syn*). This is the longest array of contiguous alkyl substituents along a carbon chain reported to date. Different stereoisomers were targeted and prepared with equal ease demonstrating that no matched and mismatched effects intervened. It was found that the alternating *syn*–*anti* isomer adopted a linear conformation, the all *syn* isomer adopted a helical conformation, but the all *anti* isomer did not adopt a particular low energy conformation (Scheme 4).[25]

Lithiation–borylation can be used to not only create new C–C bonds but also simultaneously reveal new reactive functional groups such as allyl boranes and silanes.[18] Specifically, it was envisaged that a direct lithiation–borylation with a β-silicon-

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vinyl-organoboron reagent like **13** would enable the stereocontrolled synthesis of 2-ene-*anti*-1,4-diols **14** via chiral *β*-hydroxy allylsilanes **15** (Scheme 5A). Gratifyingly, this plan worked out exceedingly well. In this case, the chiral lithium carbenoid **16** was generated by diamine-free Sn−Li exchange from stannane **17** to enhance the stereoselectivity of the electrophilic quench. The intermediate boron-ate complex **18** rearranged rapidly delivering the allyl borane **19**, which was reacted *in situ* with an aldehyde. This sequence formed the *anti*-*Z*-*β*-hydroxy allylsilane **15**, which, following hydroxyl-directed epoxidation and elimination/ring-opening, provided the required 2-ene-*anti*-1,4-diol **14** in excellent yield and complete stereocontrol.

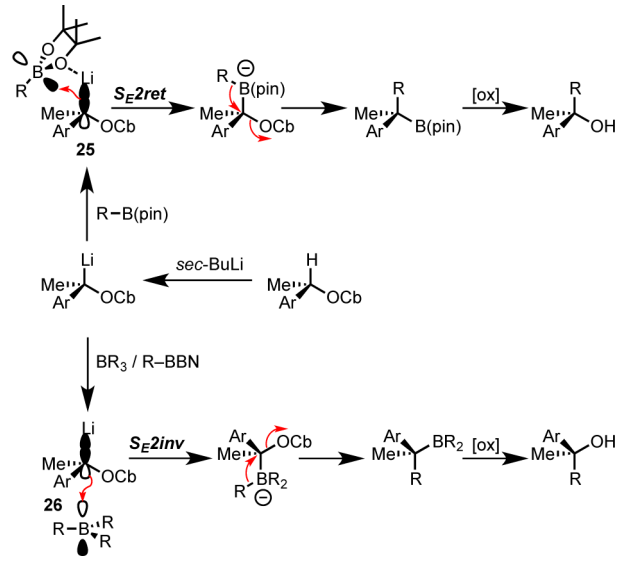
This methodology was exploited in a short total synthesis of the marine oxylipin solandelactone E (**20**).[19] As shown in Scheme 5B, Sn−Li exchange on chiral stannane **21** (prepared in five steps) and a subsequent lithiation−borylation−allylboration sequence by *in situ* addition of borane **13** and aldehyde **22** (prepared in 10 steps) delivered **23** in high yield and dr. It should be noted that use of the Sn−Li exchange reaction avoided competing *β*-lithiation and subsequent elimination of the homoallylic carbamate that was observed during deprotonation with *sec*-BuLi. Because **21** had an er of 10:1, the final diastereoselectivity shows that the entire sequence occurred with complete stereoselectivity in the lithiation−borylation step and complete control of stereochemistry in the allylboration step. Chemoselective epoxidation of the allylsilane and acid-catalyzed rearrangement gave solandelactone E in 13 steps (LLS).

4. LITHIATION−BORYLATION WITH SECONDARY CARBAMATES AND BENZOATES

4.1. Secondary Benzylic Carbamates

Lithiated primary benzylic carbamates generated by kinetic deprotonation cannot be used in lithiation−borylation processes due to their configurational instability even at very low temperatures. However, Hoppe[26] showed that under thermodynamic control, bisoxazoline ligands are effective with this class of carbamate, and Crudden and Aggarwal found that the combination of this ligand with the more reactive neopentyl glycol boronic esters gives chiral benzylic boronic esters with high enantioselectivity.[27,28] In contrast, lithiated secondary benzylic carbamates are sufficiently configurationally stable at low temperature to enable their use in lithiation−borylation reactions.[29,30] However, in contrast to primary lithiated carbamates, which react with retention with both boranes and boronic esters, lithiated secondary benzylic carbamates react with retention with boron esters but inversion with boranes (Table 2).[31,32] The different stereochemical course of the reactions can be explained by means of the model proposed in Table 2. While boronic esters can complex the lithium atom of the metalated carbamate and be delivered on the same face as the metal (S_E2ret) (**25**), boranes cannot. In this case, borylation occurs on the face opposite to the metal where, in the case of benzylic substrates, there is significant electron density due to mesomeric stabilization (**26**). Furthermore, as a result of mesomeric stabilization the carbanion is more trigonal, opening up space opposite the metal, making this face less hindered. In the absence of mesomeric stabilization (non-benzylic carbamates), the anion is tetrahedral and so the face opposite the metal is hindered and reactions occur almost always with retention.[33] This process allows the synthesis of either

Table 2



entry	Ar	organoboron	yield (%)	er (*S*/*R*)
1	Ph	EtB(pin)	95	1:99
2	Ph	BEt_3	91	99:1
3	Ph	*i*-PrB(pin)	92	4:96 (<1:99)[a]
4	Ph	*i*-Pr-BBN	91	98:2
5	Ph	vinyl-B(pin)	75	2:98
6	Ph	allyl-B(pin)	95	1:99
7	Ph	*p*-MeO-Ph-B(pin)	92	98:2
8	Ph	*m*-CF_3-Ph-B(pin)	92	99:1
9	*p*-Cl-Ph	*i*-PrB(pin)	89	(<1:99)[a]
10	*o*-MeO-Ph	*i*-PrB(pin)	79	(<1:99)[a]

[a]$MgBr_2$/MeOH added after boronate complex formation.

enantiomer of chiral tertiary alcohols from the same secondary alcohol depending simply on the nature of the boron electrophile. The reaction shows broad scope in both the carbamate and boronic ester including heterocyclic boronic esters.[32]

The lithiation−borylation of secondary carbamates with especially hindered boronic esters or with carbamates bearing electron-withdrawing substituents on the aromatic ring are accompanied by considerable erosion in ee as a result of the intermediate boronate complex dissociating back to the starting lithiated carbamate, a species that is prone to racemization upon warming. The dissociation−racemization pathway can be essentially eliminated through the use of either $MgBr_2$/MeOH as an additive or of the less hindered neopentyl boronic esters in place of pinacol esters.[34]

Tertiary benzylic boronic esters and boranes are a very versatile class of reagents that can undergo a broad array of stereospecific transformations (Scheme 6). These processes include synthetically useful oxidation, amination,[35] protodeboronation,[36,37] arylation,[38] and more importantly a series of C-based homologations that give access to chiral quaternary centers.[39,23]

The synthetic utility and practicality of these procedures has been exemplified in the synthesis of a number of natural products and pharmaceutical compounds where the stereospecific functionalization of a tertiary boronic ester represented a key step in the synthetic sequence (Figure 2).[35,36,39−46]

The development of the stereospecific protodeboronation of tertiary boronic esters has been particularly rewarding because

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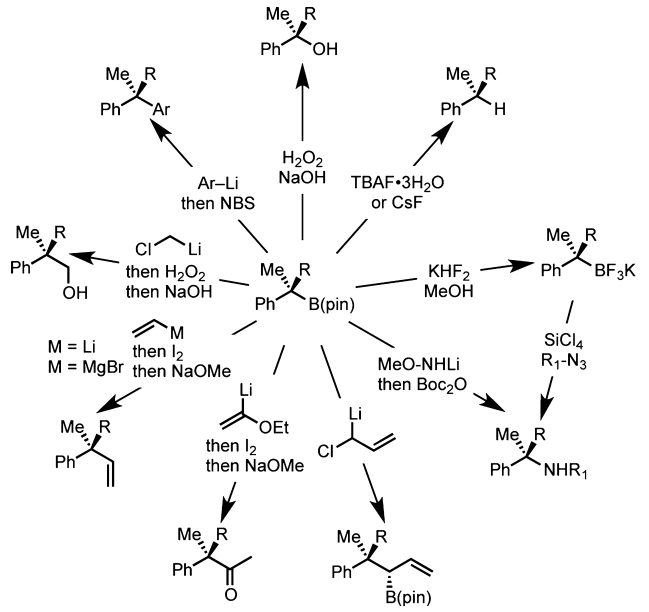
Scheme 6



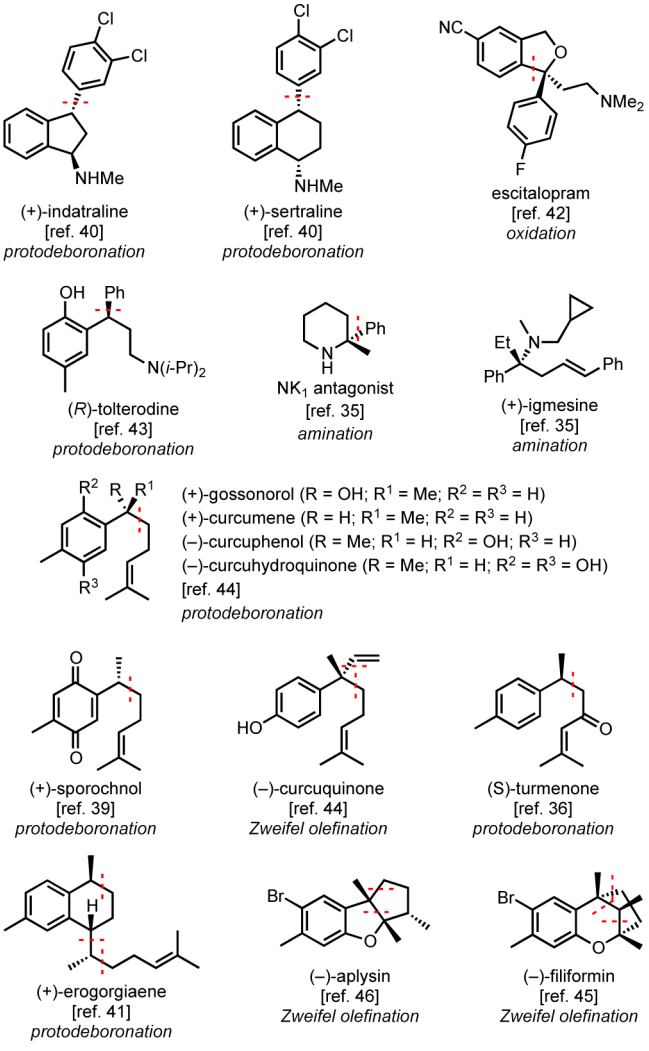
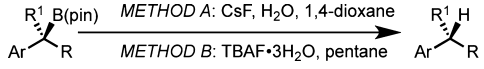


Figure 2.

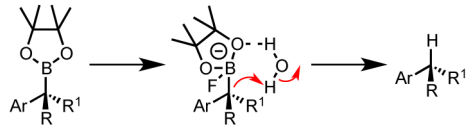
it provides ready access to synthetically useful but challenging diarylalkane motifs.[47] We found that tertiary benzylic boronic esters underwent highly stereocontrolled protodeboronation upon treatment in nonpolar solvents with TBAF·$3H_2O$ or CsF·xH_2O (in the case of dibenzylic substrates).[36] Following ate complex formation with [F^-] and due to hydrogen bonding between fluoride ions and water molecules, "front-side" proton delivery occurred delivering retentive protodeboronation (Table 3).

Table 3



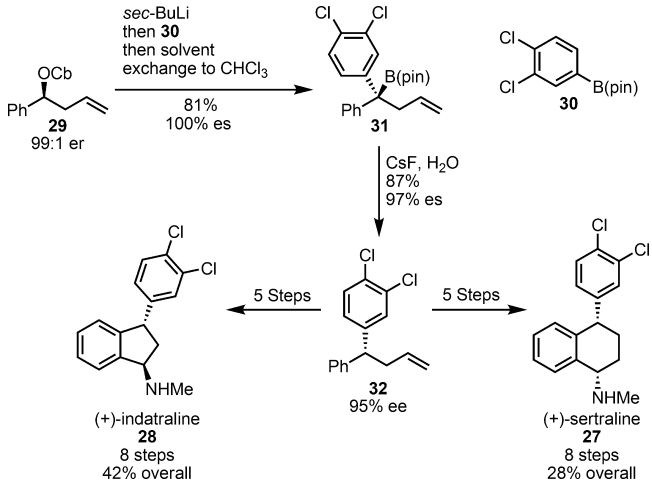
entry	Ar	R	R^1	yield (%)	er	es (%)
			Method A			
1	Ph	Me	*p*-Cl-Ph	82	97:3	98
2	*p*-MeO-Ph	Me	Ph	99	98:2	99
			Method B			
3	*p*-Cl-Ph	Me	Et	99	99:1	99
4	Ph	Et	allyl	79	>99:1	99

Proposed Mechanism



This methodology was applied to the synthesis of several natural products and pharmaceutical agents. (+)-Sertraline (**27**) and (+)-indatraline (**28**) were initially selected due to their relevance as pharmaceutical agents (Scheme 7).[40] Thus,

Scheme 7



lithiation–borylation of benzylic–homoallylic carbamate **29** with aryl boronic ester **30** gave the desired tertiary diarylboronic ester **31** in excellent yield and enantiospecificity. For this particular case involving the pendant alkene, the 1,2-metalate rearrangement was found to be very slow, but it could be accelerated by solvent exchange to a noncoordinating solvent, for example, $CHCl_3$ or toluene. This strategy has since been found to be useful in other cases where slow migrations were encountered. Stereospecific protodeboronation with CsF gave the highly enantioenriched *gem*-diarylcompound **32**, which was converted in five steps to (+)-sertraline and (+)-indatraline.

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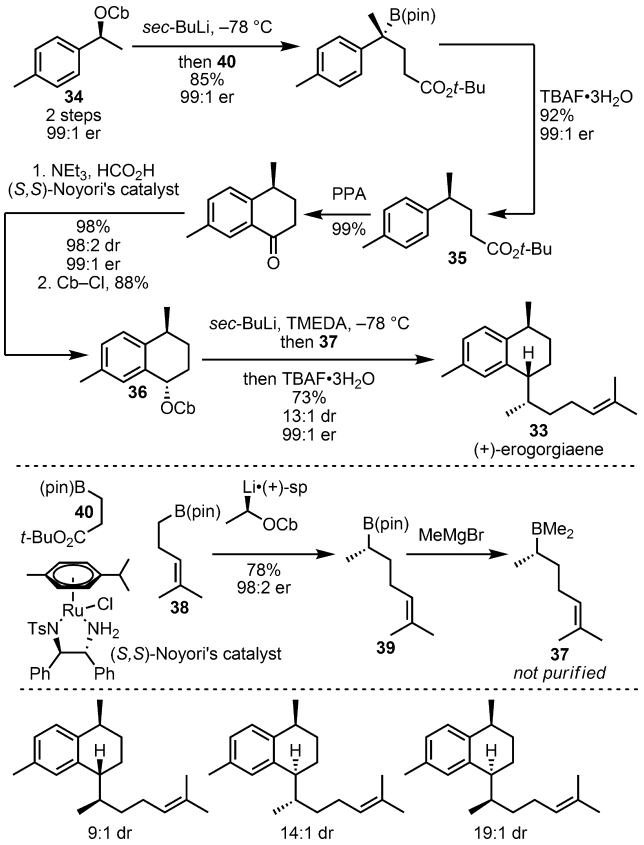
Two lithiation−borylation−protodeboronation sequences were employed in the total synthesis of the marine diterpene (+)-erogorgiaene (**33**) (Scheme 8).[41] We selected this bioactive metabolite in light of the synthetic challenge posed by the lack of functional groups proximal to the branching chiral centers. Enantiopure benzylic carbamate **34** (obtained in two steps) was subjected to a lithiation−borylation−protodeboronation sequence (with TBAF) to give ester **35** in excellent yield and high enantioselectivity.[48,49] Further elaboration of this intermediate via Friedel−Crafts acylation followed by Noyori reduction and carbamoylation gave the *anti*-tetralol **36**. Unfortunately, lithiation−borylation of **36** with pinacol boronic esters was not possible and resulted in a 1:1 mixture of diastereomers. In contrast to acyclic- and indanol-derived carbamates, tetralol-derived carbamates gave low enantioselectivity in lithiation−borylation with boronic esters.[31] However, engaging the lithiated carbamate in a lithiation−borylation process with the unhindered and more reactive dimethyl borane **37** (prepared by a lithiation−borylation−Grignard addition sequence on **38**) gave the desired homologated borane that underwent *in situ* protodeboronation yielding (+)-erogorgiaene in 13:1 dr and 44% overall yield. By changing the nature of the chiral ligand in the preparation of **39** [from (+)-sp to (−)-sp] or the chiral catalyst in the Noyori reduction used to set the carbamate stereocenter in **36**, each of the remaining diastereoisomers were prepared in similarly high yields and selectivity.

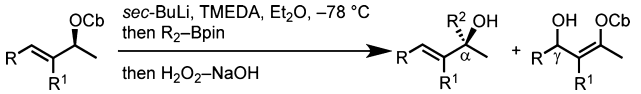
Scheme 8



4.2. Secondary Allylic Carbamates

Like primary benzylic carbamates, lithiated primary allylic carbamates are not configurationally stable, while secondary allylic carbamates are and can therefore be exploited in lithiation−borylation processes. However, these species usually react with electrophiles giving mixtures of α- and γ-addition products.[50−52] In contrast, we found that boronic esters uniquely react with lithiated secondary allylic carbamates with high α-selectivity (Table 4).[53] The high selectivity has been rationalized on the basis of an initial coordination between the pinacol O atoms and the lithium ion, which delivers the boron reagent at the same site as the metal (α-selectivity) and on the same face (S_E2ret).

Table 4



entry	R	R^1	R^2	yield (%)	er	α/γ
1	Me	H	*n*-Bu	75	98:2	>20:1
2	Me	H	Ph	84	98:2	92:8
3	Me	Me	$(CH_2)_2Ph$	81	94:6	>20:1

We have used this methodology in the synthesis of the natural products C30 botryoccocene[53] and the universal mating hormone α-1 (**41**) (Figure 3).[54]

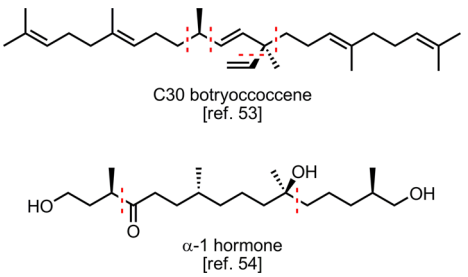


Figure 3.

The latter complex target **41** has been assembled from fragment **42**, which we prepared in four steps from citronellal (Scheme 9). This substrate contains two carbamate functionalities but was chemoselectively deprotonated at the more acidic allylic position and used in lithiation−borylation methodology with the allylic boronic ester **43** (prepared in six steps from the Roche ester). Following oxidation, hydrogenation, and protection, the tertiary alcohol was afforded in good yield. At this stage, we performed a late-stage lithiation−borylation−oxidation sequence on the primary carbamate with boronic ester **44** (made in four steps) to give secondary alcohol **45**. Oxidation and deprotection afforded α-1 hormone **41** in 21% overall yield and 96:4 dr.[54]

4.3. Secondary Alkyl Benzoates

Secondary carbamates are a very versatile class of substrates in lithiation−borylation methodology. However, a major limitation is that their use is restricted to substrates that have an aryl/allyl group that acidifies the benzylic/allylic position enabling deprotonation. Without such groups, it had been reported that deprotonation cannot occur.[55] Nevertheless, by exploring alternative solvents and additives, we have successfully identified conditions for the deprotonation of secondary TIB esters lacking groups that acidify the adjacent proton (Scheme 10).[56] Following addition of neopentyl boronic esters, the desired 1,2-metalate rearrangement gave the homologated boronic esters, which were oxidized (Scheme 10A) or

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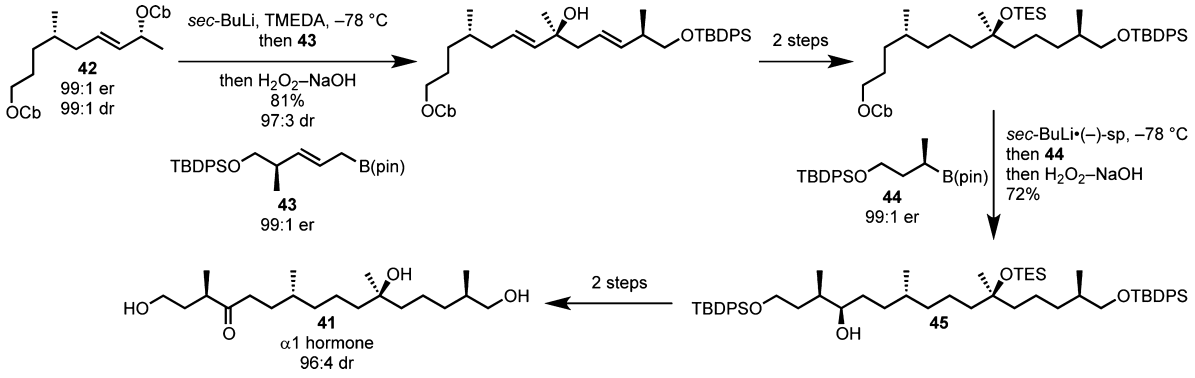
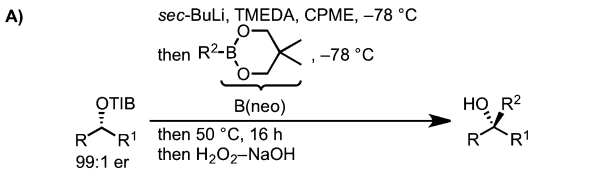
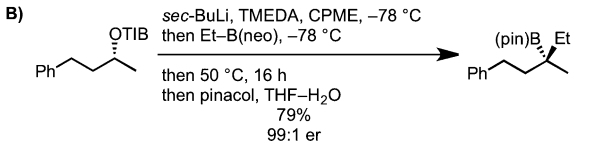
Scheme 9



Scheme 10



entry	R	R^1	R^2	yield (%)	er
1	$Ph(CH_2)_2$	Me	Et	80	99:1
2	$Ph(CH_2)_2$	Me	$(CH_2)_2CO_2t$-Bu	69	98:2
3	$Ph(CH_2)_2$	Me		73	99:1
4	$THPO(CH_2)_3$	Me	Et	72	99:1
5	$Ph(CH_2)_2$	Et	allyl	40	99:1



transesterified *in situ* with pinacol (to aid their purification and stability) in high yield and es (Scheme 10B). The direct use of pinacol boronic esters was also possible but slightly decreased levels of es (~95%) were observed.

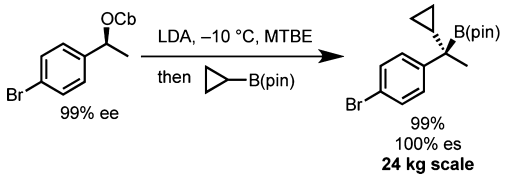
5. CONCLUSIONS AND OUTLOOK

The reagent-controlled asymmetric homologation of boronic esters is a powerful method for the stereocontrolled synthesis of substituted carbon chains. The reagents with the greatest scope are Hoppe's lithiated carbamates: a broad range of primary alkyl carbamates can react with a range of alkyl and aryl boranes and boronic esters. Since the 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 substituents of specific stereochemistry. They therefore offer the greatest versatility and flexibility in the homologation of boranes and boronic esters in particular. The methodology has been extended to include primary benzylic carbamates where the enantioenriched lithiated carbamate is generated under thermodynamic control.

Secondary allylic, benzylic, and dialkyl carbamates/TIB esters can also be employed in lithiation–borylation. The secondary alcohols are easily obtained in high enantiopurity and undergo stereospecific lithiation and stereoselective borylation leading to tertiary boronic esters (or boranes) with very high er.

This methodology has been applied effectively at various stages in the synthesis of a number of natural products and pharmaceuticals. Its use at the start of a total synthesis requires large scale applications. Indeed, and rather impressively, the lithiation–borylation reaction of secondary benzylic carbamates has recently been scaled up to 24 kg by Fandrick et al. at Boehringer-Ingelheim (Scheme 11).[57]

Scheme 11



In terms of functional group compatibility, the carbamate cannot contain functional groups that could react with *sec*-BuLi, although the faster Sn–Li exchange enables a broader range of carbamates to be employed, and the boronic ester component must not have functional groups that are more electrophilic than the pinacol boronic ester. Potential leaving groups β to the boronic ester should be avoided; otherwise at the boronate complex stage, elimination competes with 1,2-migration. Providing these limitations are satisfied, this methodology can be applied with confidence.

Indeed the methodology has been applied extensively in the synthesis of acyclic molecules with high stereocontrol. It would be interesting to see whether this methodology could also be applied to cyclic substrates since they too are very common in nature.

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Notes

The authors declare no competing financial interest.

Biographies

Daniele Leonori was born in Italy in 1982. He studied Medicinal Chemistry at the Università degli Studi di Perugia (Italy) and completed his Ph.D. studies in 2010 at the University of Sheffield working under the supervision of Prof. Iain Coldham. He carried out postdoctoral studies with Prof. Magnus Rueping at the RWTH-Aachen University (2010–2011) and with Prof. Peter H. Seeberger at the Max-Planck Institute of Colloids and Interfaces (2011–2012). He was

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Varinder K. Aggarwal studied chemistry at Cambridge University and received his Ph.D. in 1986 under the guidance of Dr. Stuart Warren. After postdoctoral studies (1986−1988) under Prof. Gilbert Stork, Columbia University, he returned to the U.K. as a Lecturer at Bath University. In 1991, he moved to Sheffield University, where he was promoted to Professor in in 1997. In 2000, he moved to Bristol University where he holds the Chair in Synthetic Chemistry. He has received numerous awards including RSC Hickinbottom Fellowship (1997), RSC Corday Morgan Prize (1999), Novartis Lecturship (1999/2000), Liebigs Lecturship (Germany), (1999/2000) (inaugural), RSC Green Chemistry Award (2003), RSC Reaction Mechanism Award (2004), RSC/GDCh-Alexander Todd-Hans Krebs Lectureship (2007) (inaugural), RSC Tilden Lecturer (2007), RSC Stereochemistry Award (2009), GSK, AZ & Pfizer prize for Process Research (2009), Elected Fellow of the Royal Society (2012), and RSC Perkin Award (2013). His current research interests center on the development of new catalytic processes for asymmetric synthesis.

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