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Synthesis of Enantioenriched Tertiary Boronic Esters from Secondary Allylic Carbamates. Application to the Synthesis of C30 Botryococcene

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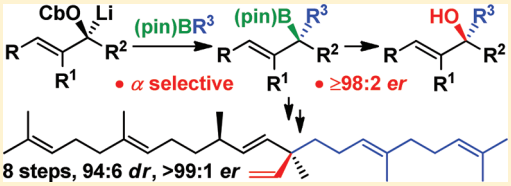
Supporting Information

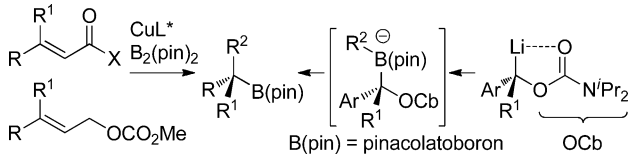
ABSTRACT: Enantioenriched secondary allylic carbamates have been deprotonated with *s*BuLi and reacted with boronic esters. In contrast to other electrophiles, high α-selectivity was observed and the boronate complexes were formed with almost complete retention of stereochemistry. The boronate complexes underwent a stereospecific 1,2-migration leading to tertiary allylic boronic esters with high *er* (>98:2). The scope of the reaction has been explored and found to embrace a broad range of both allylic carbamates and boronic esters. The methodology has been applied to an eight-step, stereoselective synthesis of each of the diastereoisomers of C30 botryococcene.



INTRODUCTION

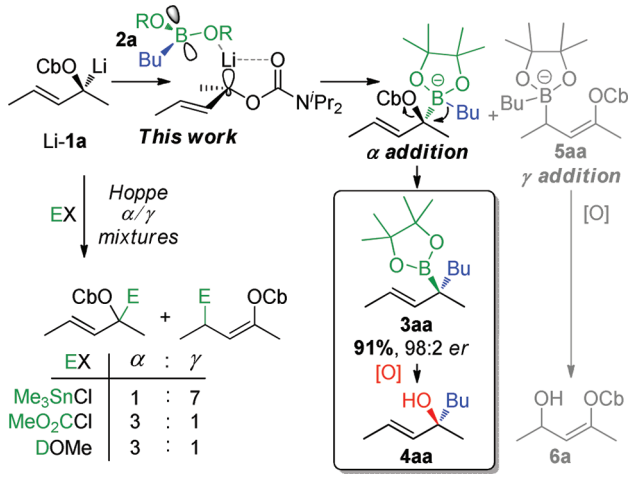
Enantioenriched tertiary boronic esters are useful synthetic intermediates in the creation of compounds bearing fully substituted carbon atoms, e.g. tertiary alcohols, C-tertiary amines, and quaternary centers.[1] They have been prepared in good to high enantioselectivity[2] by β-borylation of Michael acceptors[3] and allylic carbonates[4] (Scheme 1). Alternatively, we reported the lithiation−borylation of benzylic carbamates, a method capable of delivering tertiary boronic ester with >99:1 *er* (Scheme 1).[5]

Scheme 1. Enantioselective Routes to Tertiary Boronic Esters



However, while such methodology shows broad substrate scope in terms of both the boronic ester (primary/secondary alkyl, aryl, heteroaryl) and the carbamate, it is nevertheless limited to benzylic carbamates. The aryl group is essential as it acidifies the benzylic position, thereby enabling deprotonation; carbamates derived from secondary dialkyl alcohols are not sufficiently acidic and so cannot be employed.[6] In order to extend this useful methodology to all-alkyl substrates, we considered the possibility of employing secondary allylic carbamates, e.g. **1a**, as Hoppe had shown that they could be readily deprotonated and trapped by electrophiles (Scheme 2).[7] However, the regioselectivity of trapping was a major concern, as Hoppe had found that mixtures of α and γ products were invariably formed with most electrophiles [e.g., Me_3SnCl,[7a] methyl chloroformate,[7b] MeOD (see Supporting Information)]. Reactions with aldehydes are different and generally lead to γ-addition products through a Zimmerman−Traxler transition state structure.[8] Despite this unpromising precedent, we pursued our studies and now report that lithiated secondary allylic carbamates react with boronic esters with uniquely high α-selectivity and with very high retention of stereochemistry (Scheme 2).

Scheme 2. Reactions of Lithiated Allylic Carbamates



RESULTS AND DISCUSSION

As a starting point for our studies, we chose carbamate **1a** bearing Me groups at both α and γ positions in order to determine the inherent regioselectivity of the system,

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unencumbered by steric bias. The carbamate was conveniently prepared on a large scale by enzymatic resolution[9] of the allylic alcohol[10] followed by carbamoylation. Lithiation of **1a** with *s*BuLi in the presence of TMEDA in Et_2O for 15 min at −78 °C followed by addition of *n*BuB(pin) (**2a**), with subsequent warming to ambient temperature, led to the tertiary boronic ester **3aa** in 91% yield[11] or to alcohol **4aa** after direct oxidation in 75% yield and 98:2 *er* (Table 1, entry 1). None of the γ-addition products **5aa**/**6a** were detected.[12]

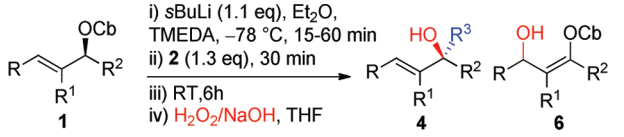
Reaction of Li-**1a** with triethyl borane was also explored but led to a complex mixture of products, perhaps arising from α- and γ-addition products and with variable levels of stereocontrol. In addition, the allyl boranes derived from α-addition would be prone to 1,3-borotropic shifts. As a result of these observations we focused on reactions with boronic esters.

The lithiation−borylation reaction was extended to a diverse range of boronic esters including primary alkyl (entry 2), secondary alkyl (entry 3), allyl (entry 4), phenyl (entry 5), and vinyl (entry 6), leading to the tertiary alcohols in very high *er* in all cases. In the cases of the allyl and Ph boronic esters, a small amount of the γ-addition product was observed (<10%).[13] Using the hindered secondary alkyl boronic ester we observed slight erosion in *er* under standard conditions (95:5 *er* observed). In previous work with benzylic carbamates we also found that a similar erosion in *er* was observed with hindered boronic esters,[5b] which was ascribed to reversibility in formation of the boronate complex followed by subsequent racemization of the configurationally unstable lithiated carbamate at elevated temperature (>−70 °C)[14] and readdition. In such cases, reversibility was minimized and racemization was arrested by the addition of $MgBr_2$/MeOH. Application of these conditions to the hindered secondary alkyl boronic ester restored the very high levels of *er* observed with other substrates (entry 3).[15]

The unusually high regioselectivity observed in the borylation reaction was investigated by varying the steric hindrance at both the α- and γ-positions. As expected, changing the methyl substituent for *i*Pr at the γ-position (**1b**) reinforced the high regioselectivity for borylation at the α-position (entries 6, 7). However, as we increased the steric demand at the α-position, γ-addition products began to be observed. While the ethyl substituted carbamate **1c** behaved in the same way as the methyl substituted carbamate (entry 8), when the steric bulk of the α-substituent was increased to *i*Bu (**1d**) {resulting in a substantial difference between the two ends [*i*Bu (R^2) vs Me (R)]} a more equal distribution of products was obtained (entry 9). Alkyl substitution at the β-position was tolerated and again led to high regio- and stereoselectivity in the lithiation−borylation reaction (entry 10), although best results were obtained using the $MgBr_2$/MeOH additive. The related cyclohexenyl lithiated carbamate **1f** gave a lower *er* due to its lower configurational stability.[16] The *Z*-allylic carbamate **1g** gave mostly the γ-addition product (with a high *er*) together with *E*-allylic alcohol **4ab**.[17] As reported by Hoppe, and as observed by us, γ,γ-disubstituted allyl carbamate **1h** could not be deprotonated cleanly.[7c]

We believe that the origins of both the high α-regioselectivity and high enantioselectivity (with retention) are intimately related. Precoordination of the oxygen of the boronic ester to the metal of the lithiated carbamate will deliver the boron reagent on the same side and at the same site as the metal (Scheme 2).

Table 1. Scope and Limitations of Lithiation−Borylation−Oxidation of Secondary Allylic Carbamates



#	**1** (*er*)[a]	R	R^1	R^2	R^3	**4** / % (*er*)[b]	**6** / %[b]
1	**1a** (>99:1)	Me	H	Me	*n*Bu **2a**	**4aa**	75 (98:2)	[c]
2	**1a** (>99:1)	Me	H	Me	$(CH_2)_2Ph$ **2b**	**4ab**	92 (98:2)	[c]
3	**1a** (>99:1)	Me	H	Me	cHex **2c**	**4ac**	76[d,e] (99:1)	[c]
4	**1a** (>99:1)	Me	H	Me	allyl **2d**	**4ad**	77 (98:2)	7[f]
5	**1a** (>99:1)	Me	H	Me	Ph **2e**	**4ae**	84 (98:2)	7[g]
6	**1b** (>99:1)	*i*Pr	H	Me	vinyl **2f**	**4bf**	79[d,h,i] (98:2)	[c]
7	**1b** (>99:1)	*i*Pr	H	Me	Et **2g**	**4bg**	72 (98:2)	[c]
8	**1c** (>99:1)	Me	H	Et	$(CH_2)_2Ph$ **2b**	**4cb**	83[d,j] (99:1)	<5
9	**1d** (*rac*)	Me	H	*i*Bu	$(CH_2)_2Ph$ **2b**	**4db**	34	50
10	**1e** (98:2)	Me	Me	Me	$(CH_2)_2Ph$ **2b**	**4eb**	81[d,k] (94:6)	[c]
11	**1f** (>99:1)	-$(CH_2)_4$-		Me	$(CH_2)_2Ph$ **2b**	**4fb**	86[l] (72:28)	[c]
12	**1f** (>99:1)	-$(CH_2)_4$-		Me	$(CH_2)_2Ph$ **2b**	**4fb**	87[m] (58:42)	[c]
13	**1g** (>99:1)	*Z*-Me	H	Me	$(CH_2)_2Ph$ **2b**	**4ab**	19 (79:21)	54[n]
14	**1h**[o] (rac)	OCb			-	-	-	-

[a]Determined on parent allylic alcohol prior to carbamoylation. [b]Reactions performed on 1 mmol scale; isolated yield; *er* determined by chiral GC or HPLC. [c]None detected by ^1H NMR or GCMS of the crude reaction mixture. [d]1 M $MgBr_2$ in MeOH used. [e]Without $MgBr_2$/MeOH, gave 95:5 *er*. [f]76:24 *er*. [g]50:50 *er*. [h]Without $MgBr_2$/MeOH, gave 90:10 *er*. [i]2 h migration time to avoid 1,3-borotropic shift of **3bf**. [j]Without $MgBr_2$/MeOH, gave 96:4 *er*. [k]Without $MgBr_2$/MeOH, gave 89:11 *er*. [l]Lithiation time = 15 min. [m]Lithiation time = 60 min. [n]95:5 *er*. [o]30% lithiation/dueteration after 5 h, −78 °C, side products dominate. cHex = cyclohexyl.

Having developed the methodology we sought to apply it in the synthesis of C30 botryococcene, an unusual triterpenoid natural product from the microalgae *Botryococcus braunii*.[18] Botryococcene biosynthesis is thought to resemble that of squalene, originating from a common intermediate, presqualene diphosphate (PSPP).[19] Reductive rearrangement of the cyclopropane present in PSPP leads to either squalane or

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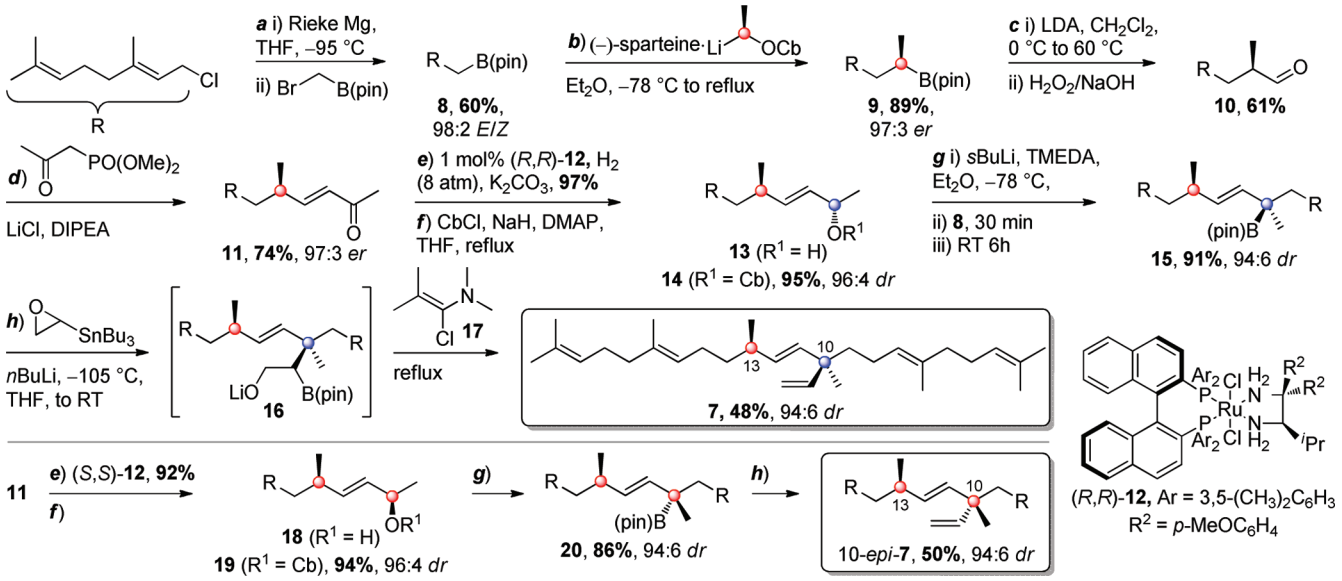
Scheme 3. Synthesis of Botryococcene and 10-*epi*-Botryococcene



botryococcene. Unlike other eukaryotes, the algae *B. braunii* evolved separate squalene synthases for specialized triterpene oil production more than 500 million years ago. This organism is of considerable contemporary attention because (i) it is considered an ancient algal species which contributed to the existing oil and coal shale deposits found on Earth and (ii) the hydrocarbon oils are being considered as potential renewable petrochemicals and biofuels.[18b] Such fuels are in fact currently being tested by the US Navy.[20]

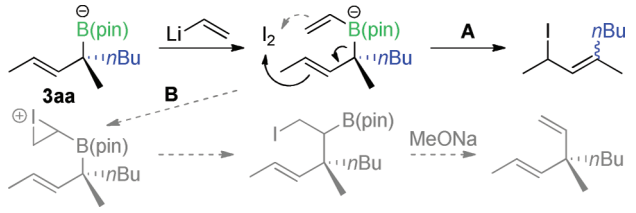
The synthesis of C30 botryococcene is especially challenging as it is devoid of functional group handles that might be used to assemble smaller building blocks, and because it contains distal tertiary alkyl and quaternary stereogenic centers (at C10 and C13). Only one asymmetric synthesis has been reported to date which was by Maxwell who was only able to synthesize a 1:1 mixture of diastereoisomers of **7** [without control of the difficult stereochemistry at C10 (quaternary center)]. His synthesis was completed in eight steps from (*S*)-3-hydroxy-2-methylpropionic acid methyl ester.[21] We believed that the triterpenoid could be assembled in short order and with greater precision of stereocontrol using our lithiation–borylation methodology.

Our synthesis began with the reaction of geranyl magnesium chloride[22] with bromomethylB(pin) which gave homogeranylB(pin) **8** (Scheme 3). In the first key step, asymmetric deprotonation of ethyl carbamate mediated by (–)-sparteine,[23] followed by addition of **8**, furnished secondary boronic ester **9** in 89% yield and 97:3 *er* (control of C13). Homologation with dichloromethyllithium,[24] followed by oxidative workup, led to aldehyde **10**, and subsequent Horner–Wadsworth–Emmons olefination gave enone **11**.

Asymmetric hydrogenation of **11** using Noyori's ruthenium-diphosphine catalyst **12**[10c] gave allylic alcohol **13** with 96:4 *dr* and >99:1 *er*. In the second key step, lithiation–borylation of carbamate **14** with homogeranylB(pin) **8** gave tertiary boronic ester **15** in 91% yield and 94:6 *dr* (control of C10), indicative of a highly stereoselective transformation.

All that remained was Zweifel olefination[25] of the tertiary boronic ester, a reaction that we had successfully reported with tertiary aryldialkyl and diarylalkyl boronic esters.[26] However addition of iodine to the intermediate ate complex formed from the addition of vinyl lithium to boronic ester **15** led to a complex mixture. Model studies on tertiary allylic boronic ester **3aa** revealed that the ate complex reacted in a fashion akin to an allylic metal species with iodine giving an allyl iodide (Scheme 4, pathway A) rather than as an electron rich alkene attached to

Scheme 4. Attempted Zweifel Olefination



boron (pathway B). We reasoned that a nucleophilic 2-carbon building block was required to add to the tertiary boronic ester which was already predisposed for 1,2-migration without further activation and so considered the use of lithiated oxirane. The reaction of lithiated substituted epoxides with boronic esters has been reported, and while 1,2-migration occurred easily,[27] elimination only occurred when an anion-stabilizing group was attached to the boronic ester.[28]

After some experimentation we were ultimately able to effect a novel olefination reaction. Lithiated oxirane was generated from the corresponding stannane[29] and trapped in situ with boronic ester **15**. The ate complex formed underwent a 1,2-migration to give β-alkoxy boronic ester **16**. Elimination was effected under mild conditions by addition of the Ghosez reagent **17**[30] and heating.[31] This gave C30 botryococcene in just eight steps from geranyl chloride in >99:1 *er* and 94:6 *dr*.

The power of the methodology is further illustrated by the synthesis of 10-*epi*-C30 botryococcene bearing the opposite configuration at the difficult quaternary center. Simply using the enantiomeric catalyst in the reduction of enone **11** and subsequent carbamoylation gave the allylic carbamate **19** with the same *er* and *dr*, indicative of a high level of reagent control without interference from the substrate. The remaining steps were completed as before. The two diastereoisomers of C30

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botryococcene had very similar ^{1}H NMR spectra, but distinct signals were evident in their ^{13}C NMR spectra. It is interesting to note that all but one of the C−C bond forming steps were mediated by a 1,2-metelate rearrangement of a boron ate complex.

CONCLUSION

In this paper we have described efficient methodology that furnishes tertiary allylic boronic esters with high yields and excellent enantioselectivity from readily available secondary allylic alcohols. Unlike other electrophiles, the reaction of lithiated-allylic carbamates with boronic esters is highly α-selective. The tertiary allylic boronic esters provide access to tertiary allylic alcohols[32] and thus all-alkyl substituted quaternary stereocenters with predictably high enantiopurity. This method is particularly useful as it does not rely upon a steric bias between the substituents at the stereogenic carbon. The methodology has been exemplified in a short highly stereoselective synthesis of C30 botryococcene which includes a new reaction for the vinylation of boronic esters. The broad range of functional groups that the boron atom can be potentially converted into, and the breadth of well established chemistry for manipulation of the double bond (from the allylic carbamate), adds considerably to this new asymmetric methodology.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and analytical data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(11) Tertiary pinacol boronic esters isolated in this paper (and in ref 5, as well as primary and secondary pinacol boronic ester reagents used here) are stable at room temperature, stored under air in a closed container for over 12 months.

(12) The γ-addition product **5** cannot be easily isolated, and so the reaction mixture was oxidized. The γ-addition product **6** is stable to basic conditions, and so the ratios observed after oxidation reflect the ratios of the initial addition.

(13) The *er* of the minor product **6a** from the reactions with **2d** (Table 1, entry 4, R^3 = allyl) and **2e** (entry 5, R^3 = Ph) was 76:24 and 50:50 respectively. The cause of the low enantioselectivity observed is open to speculation and could be due to one or both of the following factors: (i) the inherent facial selectivity during the addition of the electrophile to the lithiated species (*syn*-S_E' vs *anti*-S_E'); (ii) whether the oxidation proceeds through a polar or radical pathway. In the case of R^3 = Ph, homolytic cleavage of the C−B bond in **5** will produce two stabilized radicals, resulting in racemization of the γ-stereocenter. For radical oxidation of boronic esters, see: Cadot, C.; Dalko, P. I.; Cossy, J. *J. Org. Chem.* **2002**, *67*, 7193.

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(15) See Supporting Information for yields and *er* of all reactions without $MgBr_2$/MeOH.

(16) Deprotonation of **1f** over 15 and 60 min, followed by trapping with boronic ester **2b**, gave **4fb** with 72:28 and 58:42 *er* respectively indicating that the lithiated carbamate was configurationally unstable at this temperature. The reasons for this are unclear but could be related to cyclohex-2-enyl carbamate that Hoppe has studied: Becker, J.; Fröhlich, R.; Salorinne, K.; Hoppe, D. *Eur. J. Org. Chem.* **2007**, 3337. Hoppe used the more hindered and rigid diamines [(−)-sparteine and *rac-trans*-1,2-bis(dimethylamino)cyclohexane (TMCDA)] to impart improved configurational stability and facial selectivity during the stannylation of lithiated cyclohex-2-enyl carbamate. The use of TMCDA instead of TMEDA with carbamate **1f**, with a 15 min

lithiation time, gave 59:41 *er* in the product tertiary alcohol. This seems to indicate that facial selectivity is also a problem in this case.

(17) Both *E* and *Z* allyl carbamates **1a** and **1g** gave the same major enantiomer and double bond isomer tertiary alcohol **4ab** upon lithiation−borylation. This was surprising, as Hoppe had found that stannylation of the same lithiated carbamates led to enantiomeric stannanes: Zschage, O.; Schwark, J.-R.; Krämer, T.; Hoppe, D. *Tetrahedron* **1992**, *48*, 8377.

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