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Stereodivergent Hydroboration of Allenes

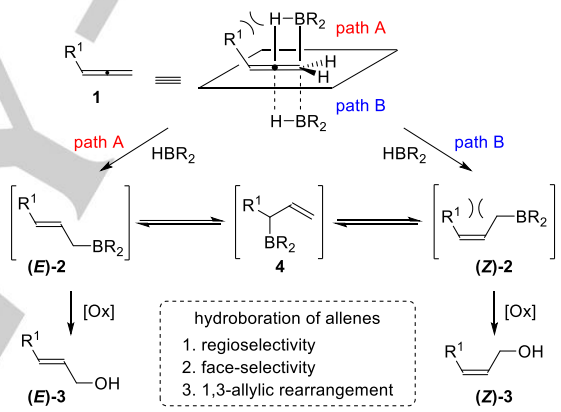
Yoshiyuki Nagashima, Keiji Sasaki, Takahiro Suto, Takaaki Sato* and Noritaka Chida*[a]

Abstract: Full details of the stereodivergent hydroboration of allenes are reported. While hydroboration of an allene with 9-BBN provided a thermodynamically stable (*E*)-allylic alcohol after oxidative work-up, the reaction of an identical allene with $HB(Sia)_2$ formed a (*Z*)-allylic alcohol as the kinetic product. The developed conditions allowed for the synthesis of trisubstituted olefins in a highly stereoselective fashion, which is known to be challenging. The method was also applied to the stereodivergent synthesis of structural motifs such as skipped dienes and allylbenzenes, which are often embedded in biologically active natural products.

Introduction

Allene is a unique functional group containing two contiguous carbon-carbon double bonds.[1] Recent studies on allene have made this unique functional group an attractive intermediate in the synthesis of complex molecules due to its easy accessibility and distinct reactivities derived from the two orthogonal π-bonds. However, reactions of allenes require precise control of the selectivities compared with the reactions of the corresponding alkenyl and alkynyl groups. For example, the hydroboration/oxidation of allene **1** to give allylic alcohol **3** must achieve three selectivities including the regioselectivity for two double bonds. (Scheme 1).[2] The face-selectivity is another challenge due to the two orthogonal double bonds. While hydroboration of **1** from the same face as the R^1 group would provide (*E*)-allylic borane **2** (path A), hydroboration from the less hindered side opposite to the R^1 group would give (*Z*)-allylic borane **2** as the kinetically favored intermediate (path B). Furthermore, (*Z*)-allylic borane **2** is known to undergo two 1,3-allylic rearrangements via **4** under equilibrium conditions, leading to the formation of thermodynamically stable **(*E*)-2**.[2,3] Although the simultaneous control of the three selectivities (regio-, stereo-, and kinetic vs thermodynamic) is highly challenging, the reaction has the potential to become a useful stereodivergent method to give both allylic alcohols **(*E*)-3** and **(*Z*)-3** from the identical allene **1**.

In 1979, Brown and co-workers reported the pioneering hydroboration of allene **1** with 9-BBN that resulted in the formation of thermodynamically stable allylic borane **(*E*)-2**, which was subsequently used as an allylating reagent with acetone.[2d] The Roush group disclosed that the proper choice of substituents on boron (10-TMS-9-borabicyclo[3,3,2]decane) could efficiently inhibit the isomerization of kinetically formed **(*Z*)-2**, which was also used in the enantioselective stereodivergent allylation of aldehydes.[2j-l] Very recently, the Huang/Hong group reported a stereodivergent allylation via hydroboration of allenes in the synthesis of functionalized tetrahydropyrans.[2r] Soon after their report, our research group independently disclosed a stereodivergent hydroboration/oxidation of allenes and its application to a unified total synthesis of the madangamine alkaloids.[4] In this paper, we report the full details of systematic studies on stereodivergent hydroboration/oxidation of allenes to give allylic alcohols. The developed method was then applied to the synthesis of skipped dienes and allylbenzenes embedded in a variety of biologically active natural products.



Scheme 1. Hydroboration/oxidation of allenes.

Results and Discussion

The hydroboration of allenes was first evaluated using commercially available 1-cyclohexylallene **1a** with a variety of borane reagents (Table 1). A solution of allene **1a** in THF was treated with 9-BBN at room temperature for 30 min, and then quenched with H_2O_2 in aqueous NaOH to give allylic alcohols **(*E*)-3a** and **(*Z*)-3a** in 86% combined yield (Table 1, Entry 1). The reaction showed (*E*)-selectivity under thermodynamic control via 1,3-allylic rearrangement (*E*/*Z* = 13.3:1). The same reaction for a longer time (24 h) provided allylic alcohols **3a** in a lower combined yield but with the identical *E*/*Z*-selectivity (Table 1, Entry 2). The hydroboration with Cy_2BH (dicyclohexylborane) at 0 °C for 5 min showed a lower (*E*)-selectivity than that with 9-BBN (Table 1, Entry 3). Interestingly, the reaction for 24 h led to a slightly higher (*E*)-selectivity (Table 1, Entries 3 and 4, *E*/*Z* = 5.4:1 vs 8.5:1).[5] These results indicated that while the allylic boranes derived from 9-BBN quickly reached equilibrium, the allylic boranes derived from Cy_2BH underwent a slower equilibrium reaction. The hydroboration with $(Thx)BH_2$

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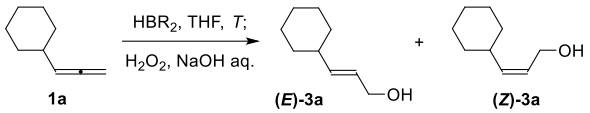
(thexylborane) for 5 min provided allylic alcohol **3a** with *E*/*Z* = 3.8:1 ratio (Table 1, Entry 5). In contrast, the reaction for 24 h did not provide the product, probably because of the second hydroboration (Table 1, Entry 6). Gratifyingly, hydroboration of allene **1a** with sterically bulky $HB(Sia)_2$ (disiamylborane) at 0 °C for 5 min showed (*Z*)-selectivity (*E*/*Z* = 1:4.3) in 89% combined yield (Table 1, Entry 7). The reaction time and the temperature were critical to keep the high (*Z*)-selectivity. A longer reaction time for 24 h at 0 °C resulted in a lower (*Z*)-selectivity probably due to the partial 1,3-allylic rearrangement (Table 1, Entry 8). The stereoselectivity was switched to the opposite (*E*)-preference by the reaction for 24 h at room temperature (Table 1, Entry 9, *E*/*Z* = 4.5:1).[6] Thus, we developed stereodivergent conditions to give both stereoisomers of allylic alcohols **3a** from the identical allene **1a** by simply changing the borane reagents.

Table 1. Optimization of hydroboration of allene **1a**[a]



Entry	HBR_2	*T* (°C)	Reaction time	Combined yields (%)[b]	*E*:*Z*
1	9-BBN	RT	30 min	86	13.3:1
2	9-BBN	RT	24 h	53	12.9:1
3	Cy_2BH	0	5 min	60	5.4:1
4	Cy_2BH	0	24 h	72	8.5:1
5	$(Thx)BH_2$	0	5 min	72	3.8:1
6	$(Thx)BH_2$	0	24 h	trace	-
7	$HB(Sia)_2$	0	5 min	89	1:4.3
8	$HB(Sia)_2$	0	24 h	62	1:1.9
9	$HB(Sia)_2$	RT	24 h	65	4.5:1

[a] Reaction conditions: **1a** (150 μmol), HBR_2 (1.5 equiv), THF (0.1 M), 0 °C, 5 min; then H_2O_2 (30% aq, 1 mL), NaOH aq. (3 M, 1 mL), 0 °C, 1 h. [b] Yields of isolated products after purification by column chromatography are given.

^{1}H NMR experiments were performed to elucidate the mechanistic details of the hydroboration (Figure 1). Upon treatment of allene **1a** with 9-BBN (2.0 equiv) in d_8-THF at room temperature, two newly generated intermediates were observed (spectra A-C). The major compound contained a doublet-triplet-doublet peak at δ 5.65 (*J* = 15.1, 7.8, 1.1 Hz, H2) and a doublet-doublet-triplet peak at δ 5.16 (*J* = 15.1, 6.9, 1.4 Hz, H3), which indicated the formation of (*E*)-allylic borane **5a**. On the other hand, the minor compound corresponded to (*Z*)-allylic borane **5a** containing a doublet-triplet-doublet peak at δ 5.54 (*J* = 11.0, 8.0, 0.9 Hz, H2) and a doublet-doublet-triplet peak at δ 5.03 (*J* = 11.0, 9.2, 1.8 Hz, H3). Comparison between spectra B and C showed that the starting material **1a** still remained after 10 min, but the *E*/*Z* ratio of the generated allylic boranes **5a** was identical to the ratio after 1 h. These results revealed that the

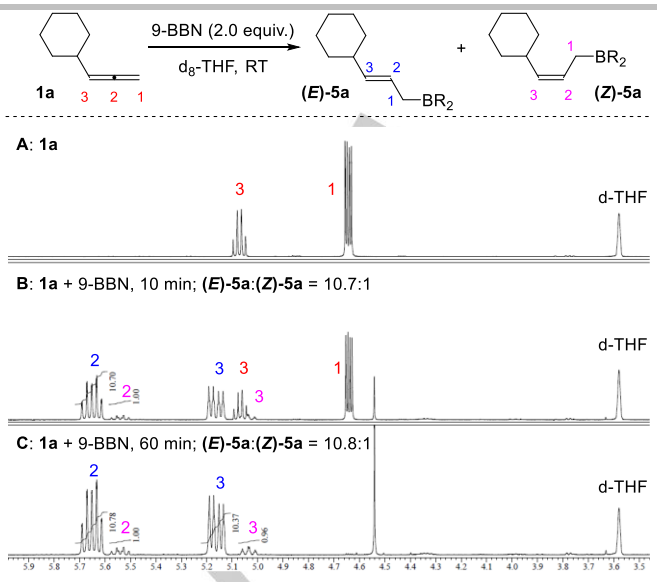


Figure 1. ^{1}H NMR spectra (400 MHz) in the hydroboration of allene **1a** with 9-BBN in d_8-THF. (A) allene **1a** in d_8-THF; (B) allene **1a**, 9-BBN (2.0 equiv) in d_8-THF, RT, 10 min; (C) allene **1a**, 9-BBN (2.0 equiv) in d_8-THF, RT, 60 min.

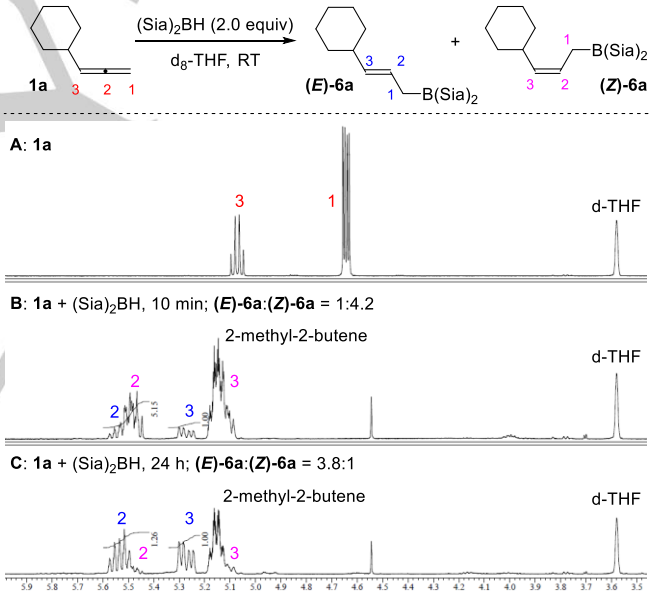
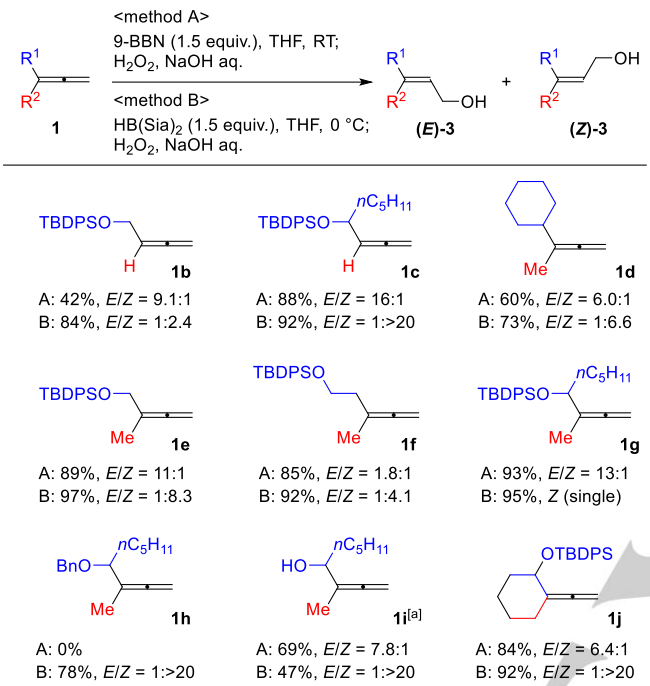


Figure 2. ^{1}H NMR spectra (400 MHz) in the hydroboration of allene **1a** with $HB(Sia)_2$ in d_8-THF. (A) allene **1a** in d_8-THF; (B) allene **1a**, $HB(Sia)_2$ (2.0 equiv) in d_8-THF, RT, 10 min; (C) allene **1a**, $HB(Sia)_2$ (2.0 equiv) in d_8-THF, RT, 24 h.

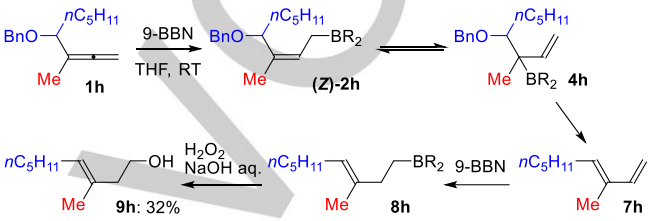
1,3-allylic rearrangement of (*Z*)-allylic borane **5a** was much faster than the hydroboration itself, and the rearrangement of two allylic boranes **5a** quickly reached equilibrium. A different mechanistic tendency was observed by ^{1}H NMR experiments with $HB(Sia)_2$, which was prepared with $BH_3{\cdot}SMe_2$ (2.0 equiv) and 2-methyl-2-butene (6 equiv) (Figure 2). After 10 min at room temperature, the ^{1}H NMR spectrum showed the complete consumption of allene **1a**, and the formation of two new intermediates (Spectra B, *E*/*Z* = 1:4.2). While the major intermediate was assigned as (*Z*)-allylic borane **6a** by the coupling constant of the double bond ($J_{2,3}$ = 10.7 Hz), the minor

isomer was identified as (*E*)-allylic borane **6a** by the resonances of (*E*)-olefin peaks ($J_{2,3}$ = 15.3 Hz). However, the ^{1}H NMR spectrum after 24 h indicated that (*E*)-allylic borane **6a** became the major isomer (Spectra C, *E*/*Z* = 3.8:1). These results suggested that the 1,3-allylic rearrangement took place even if sterically bulky $HB(Sia)_2$ was used, but the rate of the rearrangement was much slower than that with 9-BBN, allowing for the (*Z*)-selective hydroboration.



Scheme 2. Substrate scope in the hydroboration/oxidation of allenes. [a] 2.5 equivalents of 9-BBN and $HB(Sia)_2$ were used.

With the stereodivergent conditions with 9-BBN [method A] and $HB(Sia)_2$ [method B] in hand, we then surveyed the substrate scope of the stereodivergent hydroboration (Scheme 2). When allenes **1** possess a branched substituent, both *E*- and *Z*-selective hydroborations showed higher diastereoselectivity (**1b** vs **1c**). The reactions of 1,1-disubstituted allenes under both conditions gave trisubstituted olefins with comparable or even higher stereoselectivities than the corresponding 1-substituted allenes (**1a** vs **1d**, **1b** vs **1e**, **1c** vs **1g**). It is noteworthy that the high level of stereocontrol for trisubstituted olefins is known to be challenging even in modern organic synthesis. However, our stereodivergent hydroboration can provide both (*E*)- and (*Z*)-trisubstituted olefins from an identical allene. The stereoselectivity depended highly on the steric bulkiness of the two substituents R^1 and R^2 of allenes **1**. While the hydroborations of **1f** with a less hindered substituent than **1e** showed lower stereoselectivities under both conditions, the reactions of **1g** bearing a bulky branched substituent resulted in higher stereoselectivities. When using 9-BBN, the reaction depended highly on the nature of the protecting groups on the allenyl alcohols. For example, while the reaction of TBDPS-protected allenyl alcohol **1g** with 9-BBN showed both a high yield and (*E*)-selectivity, Bn-protected allenyl alcohol **1h** did not provide allylic alcohol **(*E*)-3h** at all. As shown in Scheme 3, primary alcohol **9h** was obtained in 32% yield instead, probably through the β-elimination of **4h** and the subsequent hydroboration of diene **7h**. In contrast to 9-BBN, the hydroboration with $HB(Sia)_2$ was relatively independent of the nature of the protecting groups, leading to high (*Z*)-stereoselectivities (**1g** vs **1h**). Interestingly, free allenyl alcohol was tolerated with both (*E*)- and (*Z*)-selective hydroborations, although 2.5 equivalents of borane reagents were needed (**1i**). The exo allene of cyclohexane derivative **1j** underwent the stereoselective hydroborations under both conditions.

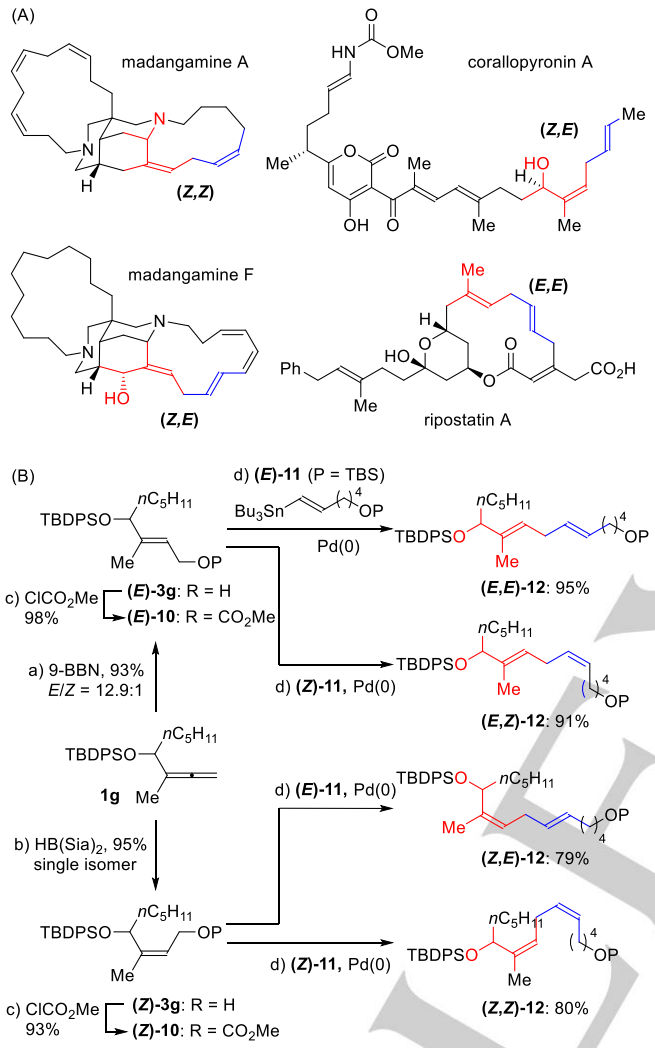


Scheme 3. Formation of primary alcohol **9h** via β-elimination.

Our research group has been pursuing the utility of allenes as productive intermediates in the synthesis of complex natural products. For example, a skipped diene is an important structural motif widely distributed in biologically active natural products such as madangamines,[4,7] corallopyronin A[8] and ripostatin A[9] (Scheme 4A).[10] The skipped diene natural products consist of a variety of stereoisomers derived from two olefins of the skipped dienes. Another structural feature is that one of two olefins embedded in most of these natural products is a challenging trisubstituted olefin. Our stereodivergent hydroboration has the potential to provide quick access to all four possible stereoisomers of skipped dienes by combination with the well-known Migita-Kosugi-Stille coupling[11] (Scheme 4B). The sequence commenced with stereodivergent hydroboration of allene **1g** with 9-BBN and $HB(Sia)_2$, providing allylic alcohols **(*E*)-3g** and **(*Z*)-3g**, respectively. After transformation of allylic alcohol **(*E*)-3g** to methyl carbonate **(*E*)-10**, the Migita-Kosugi-Stille coupling of the resulting **(*E*)-10** with both vinyl stannanes **(*E*)-** and **(*Z*)-11** provided skipped dienes **(*E*,*E*)-** and **(*E*,*Z*)-12** in high yields. Allylic alcohol **(*Z*)-3g** was also converted to skipped dienes **(*Z*,*E*)-** and **(*Z*,*Z*)-12** with retention of the stereochemistry. It is noteworthy that the resulting geometry of **(*Z*,*E*)-12** corresponds to that of corallopyronin A. Thus, we demonstrated that the developed method would be useful for the synthesis of skipped diene natural products including challenging trisubstituted olefins with a high level of stereocontrol.

The method was then applied to construction of an allylbenzene motif embedded in biologically active natural products including cylindrol A[12] and lobatamide C[13] (Scheme 5A). These natural products also contain a trisubstituted olefin with either (*E*)- or (*Z*)-arrangements. Allylic carbamate **(*E*)-10**, which was prepared through *E*-selective hydroboration of allene **1g** with 9-BBN, was subjected to the Migita-Kosugi-Stille coupling with $PhSnBu_3$ in the presence of $Pd_2(dba)_3{\cdot}CHCl_3$ (5 mol%) and LiCl (Scheme 5B). Although slight scrambling of

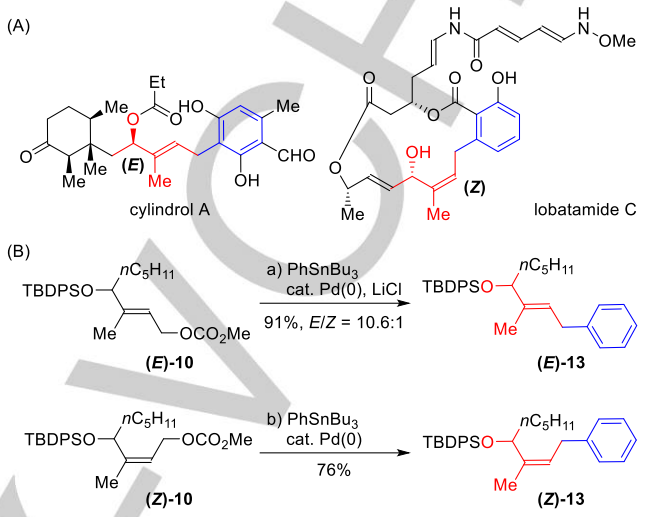
stereochemistry was observed, allylbenzene **(*E*)-13** was obtained in 91% yield (*E*/*Z* = 10.6:1). On the other hand, the cross-coupling of allylic carbonate **(*Z*)-10** proceeded in 76% yield with the retention of the stereochemistry in the absence of LiCl.[14] The resulting (*E*)- and (*Z*)-allylbenzenes **13** correspond to the substructures of cylindrol A and lobatamide C, respectively.



Scheme 4. (A) Representative natural products containing skipped dienes. (B) Application of 1,1-disubstituted allene **1g** to stereodivergent synthesis of skipped dienes **12**. Reagents and conditions: a) 9-BBN (1.5 equiv), THF (0.1 M), RT; H_2O_2, NaOH aq; b) $HB(Sia)_2$ (1.5 equiv), THF (0.1 M), 0 °C; H_2O_2, NaOH aq; c) $ClCO_2Me$ (1.5 equiv), py (1.5 equiv), CH_2Cl_2 (0.1 M), 0 °C; d) **9** (1.5 equiv), $Pd_2(dba)_3{\cdot}CHCl_3$ (5 mol%), LiCl (10 equiv), DMF (8 mM), RT.

Conclusions

We have developed a stereodivergent hydroboration of allenes, which can provide quick access to both (*E*)- and (*Z*)-allylic alcohols from an identical allene by simply changing borane reagents. While use of 9-BBN provided a thermodynamically stable (*E*)-allylic alcohol, the reaction of $HB(Sia)_2$ resulted in the formation of (*Z*)-allylic alcohol as the kinetic product. The synthetic utility was demonstrated when the stereodivergent method was applied to 1,1-disubstituted allenes, giving (*E*)- and (*Z*)-trisubstituted olefins. Combination of our hydroboration with the Migita-Kosugi-Stille coupling achieved a stereodivergent sequence, successfully giving all four possible stereoisomers of skipped dienes embedded in biologically active natural products. The method was also applicable to the stereodivergent synthesis of allylbenzene motifs.



Scheme 5. (A) Representative natural products containing the allyl benzene motif. (B) Stereodivergent synthesis of allylbenzenes **13** derived from 1,1-disubstituted allene **1g**. Reagents and conditions: a) $PhBu_3Sn$ (1.5 equiv), $Pd_2(dba)_3{\cdot}CHCl_3$ (5 mol%), LiCl (10 equiv), DMF (50 mM), RT. b) $PhBu_3Sn$ (1.5 equiv), $Pd_2(dba)_3{\cdot}CHCl_3$ (5 mol%), DMF (50 mM), RT.

Keywords: allene • hydroboration • natural product • skipped diene • stereoselectivity

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[5] The hydroboration of **1a** with Cy_2BH for prolonged reaction time (36 h) provided **3a** in 29% yield with *E*/*Z* = 9.8:1.

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[14] The Migita-Kosugi-Stille coupling of **(*Z*)-10** with $PhSnBu_3$ in the presence of LiCl caused partial isomerization of the stereochemistry, providing a mixture of two isomers **13** in 53% yield with *E*/*Z* = 1:5.5.

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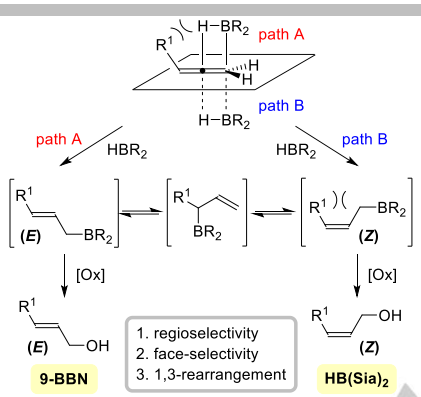
FULL PAPER

The full details of stereodivergent hydroboration of allenes were described. The hydroboration with 9-BBN provided thermodynamically stable *E*-allylic alcohols. On the other hand, the reaction with $HB(Sia)_2$ gave *Z*-allylic alcohols as a kinetic product. The method was then applied to stereodivergent synthesis of skipped dienes and allylbenzenes, which are embedded in biologically active natural products.



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