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Hydroboration of Mono-Substituted Allenes: A General Synthetic Route to the Higher Crotylboranes and *anti*-3-Alkyl/Aryl-4-hydroxy-1-alkenes

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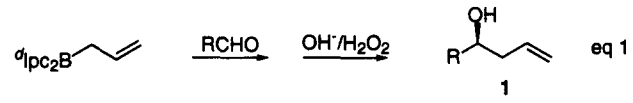
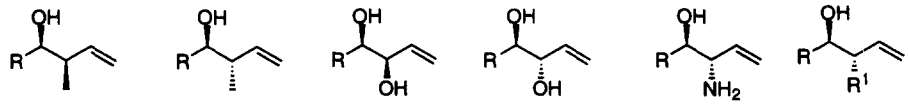
Abstract: Hydroboration of mono-substituted allenes with Chx_2BH at 0 °C leads to the corresponding (*E*)-substituted allylboranes, known as higher crotylboranes, exclusively. These higher crotylboranes react with aldehydes, and on oxidation, provide the corresponding *anti*-3-alkyl/aryl-4-hydroxy-1-alkenes in high diastereomeric excess. By changing the hydroborating reagent to $^{d}Ipc_2BH$, synthesis of the corresponding optically active *anti*-3-alkyl/aryl-4-hydroxy-1-alkenes is achieved in excellent diastereo- and good enantioselectivities.

Over the last decade, asymmetric allyl- and crotylborane reagents have received increasing attention for their ability to create carbon-carbon bonds in a stereodefined fashion.[2] Various terpene and tartrate based chiral allyl- and crotylborane reagents have been developed both by our group[3] and by other groups.[4] The applications of these reagents have been well documented in the literature.[5] The reagents developed so far can be used in the synthesis of chiral 4-hydroxy-1-alkenes (from allylboration, **1**),[3a] *syn*- and *anti*-3-methyl-4-hydroxy-1-alkenes (**2** and **3**, from crotylboration),[3b] *syn*- and *anti*-3,4-dihydroxy-1-alkenes (**4** and **5**)[3c,d] and *anti*-3-amino-4-hydroxy-1-alkenes (**6**).[4e]



eq 1

1

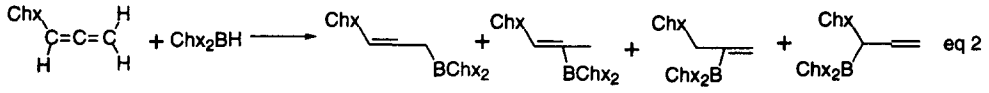


2 **3** **4** **5** **6** **7**

There are many natural products such as lipstatin and esterastin,[6] which contain the structural unit **7** (R = Hex-, Bu-) and these can be easily prepared from the γ-substituted allylboranes, the substituent being Hex- or Bu- (*i.e.*, any alkyl or aryl) group. There are few methods available in the literature[7] for the synthesis of such molecules. From our previous experience in this area, we thought that a simple hydroboration of mono-substituted allenes with a monohydroborating reagent, such as Chx_2BH, would give us γ-substituted allylboranes.[7] Depending on the stereochemistry of the resulting double bond, these substituted allylboranes, also known as higher crotylboranes, should react with aldehydes to give the corresponding *syn*- and *anti*-3-alkyl/aryl-4-hydroxy-1-alkenes from (*Z*)- and (*E*)-higher crotylboranes respectively.

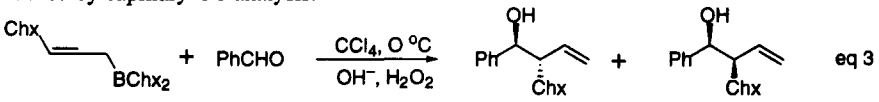
Herein we report a general procedure for the generation of (*E*)-higher crotylboranes, from the hydroboration of monosubstituted allenes, and their reactions with aldehydes to provide the *anti*-3-alkyl/aryl-4-hydroxy-1-alkenes in a single step. We have also extended this methodology to synthesize the corresponding optically active compounds by using a chiral hydroborating reagent, $^{d}Ipc_2BH$, in high diastereomeric- and enantiomeric purities.

The hydroboration of cyclohexylallene with Chx_2BH was studied in detail. This could give a mixture of the following four types of organoboranes (eq 2). The reaction is over in less than 15 min. at 0 °C, and the ^{11}B and ^{1}H NMR analysis of the reaction mixture indicated the product to be **9a** exclusively. Hydroboration in this case is highly selective with the *B*-atom attacking the least substituted carbon atom. We did not detect any other boron species in the reaction mixture.



8 **9a** **9b** **9c** **9d**

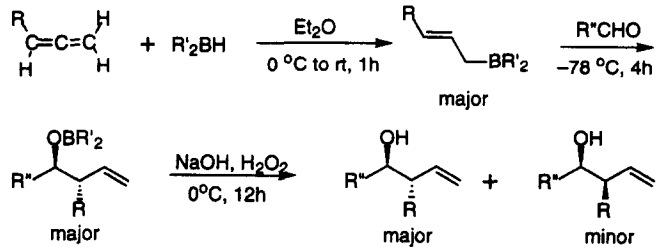
The stereochemistry of the resulting double bond in this substituted allylborane is trans (from the decoupling studies of the ^{1}H NMR spectrum)[9] and this is further confirmed by its reaction with aldehydes. It is well established that (*E*)-crotylboranes would react with aldehydes to give *anti*-3-methyl-4-hydroxy-1-alkenes, while (*Z*)-crotylboranes give the corresponding *syn*-3-methyl-4-hydroxy-1-alkenes, corresponding to reaction involving a cyclic transition state.[3b] It is very clear from the following reaction (eq 3) that **9a** reacts with benzaldehyde to give, on oxidation, *anti*-3-cyclohexyl-4-hydroxy-4-phenyl-1-butene (**10a**) in high diastereoselectivity (96:4). The relative stereochemistry of the product **10a** was established by comparing the ^{1}H NMR spectrum of the product with spectra reported in the literature.[6c] The ratio of the diastereomers was further confirmed by capillary GC analysis.



9a **10a** 96 **10b** 4

We selected the following four allenes, 1,2-heptadiene, 1,2-nonadiene, 1-cyclohexyl-1,2-propadiene and 1-phenyl-1,2-propadiene, as a representative set, and studied their hydroborations, followed by aldehyde additions. The two hydroborating reagents selected for study were, an achiral monohydroborating reagent, dicyclohexylborane, and a chiral monohydroborating reagent,[10] ^{d}diisopinocampheylborane[11] (Scheme 1).

Scheme 1



The results from these experiments are given in Table 1. Among all the allenes studied, phenylallene gave excellent diastereoselectivities with both hydroborating reagents (>99 anti, entries 7-10).[12] In the case of the aliphatic allenes, 1,2-heptadiene and 1,2-nonadiene, the corresponding products exhibited reasonable diastereoselectivities (87-90 *anti*, entries 1-4). The secondary allene studied here is cyclohexylallene and this gave a very high diastereoselectivity (96:4, *anti:syn*, entry 5) with Chx_2BH. When the hydroborating reagent was changed to a bulkier Ipc_2BH, the diastereoselectivity of the reaction decreased (80:20, *anti:syn*, entry 6). The enantioselectivities observed in all the cases are modest (74-78% ee), when compared to the results with other allyl- and crotylborane reagents derived from the α-pinene chiral auxiliary.

Table 1. Synthesis of *anti*-3-alkyl/aryl-4-hydroxy-1-alkenes.[a]

entry	$RCH=C=CH_2$ R=	R'_2BH R'=	R"CHO R"=	Yield[b]	anti:syn[c]	ee (conf)[d,e]
1	*n*-C_4H_9	Chx	Ph	81	87:13	–
2	*n*-C_4H_9	[d]Ipc	Ph	78	88:12	78 (3S,4R)[f]
3	*n*-C_6H_{13}	Chx	Ph	82	88:12	–
4	*n*-C_6H_{13}	[d]Ipc	Ph	81	90:10	74 (3S,4R)[f]
5	Chx	Chx	Ph	77	96: 4	–
6	Chx	[d]Ipc	Ph	80	80:20	80 (3S,4R)[f]
7	Ph	Chx	Ph	90	>99:0	–
8	Ph	[d]Ipc	Ph	84	>99:0	84 (3S,4R)[g]
9	Ph	Chx	Me	82	>99:0	–
10	Ph	[d]Ipc	Me	75	>99:0	80 (3S,4R)[g]

[a] All new compounds exhibited satisfactory ^1H, ^{13}C NMR and elemental analysis. [b] Isolated yield. [c] The ratio of anti : syn was determined from capillary GC analysis and from ^1H NMR spectrum.[7b,c] [d]The ee given here is of the major diastereomer (*anti*). [e] Predicted by analogy with those obtained in the reactions of [d]*B*-allyldiisopinocampheylborane.[3a-d] [f]By ^1H NMR analysis of the corresponding Mosher ester. [g]By capillary GC analysis of the corresponding MCF derivative.

A typical procedure for the synthesis of alcohol **10** is as follows (entry 9): To a stirred suspension of Chx_2BH (1.77g, 10.0 mmol)[10] in diethyl ether (10.0 mL) at 0 °C was added phenylallene (1.16g, 10.0 mmol)[13], dropwise. After stirring for 10 min, the solid Chx_2BH dissolves completely, indicating the completion of hydroboration. The reaction was further stirred for 1h at room temperature. It was then cooled to –78 °C and a solution of benzaldehyde (1.0 mL, 10.0 mmol) in ether (5.0 mL), cooled to –78 °C, was added to it slowly via a double ended needle. After 4h, it was allowed to come to room temperature and subjected to oxidation by the addition of 3M NaOH (5.0 mL, 15.0 mmol) and 30% aqueous H_2O_2 (5.0 mL, 44.1 mmol). The reaction mixture was stirred for 12h and the organic layer was separated and washed with water (2 X 20 mL), dried over $MgSO_4$, and concentrated. Flash column chromatography over silica gel with hexane : ethyl acetate (98 : 2) as eluent gave the pure alcohol, *anti*-3-phenyl-4-hydroxy-1-pentene (1.2 g, 75% yield). ^1H NMR ($CDCl_3$): δ 7.3 (m, 5H), 6.15

(dt, 1H), 5.25 (s, 1H) (ɔ.12, d, 1H for *syn* isomer), 5.2 (d, 1H) (5.11, d, 1H for *syn* isomer), 3.9 (m, 1H), 3.2 (dt, 1H), 1.9 (br, 1H, D_2O washable), 1.1 (d, 3H) (1.23, d, 3H for *syn* isomer).

In conclusion, we have developed a general, highly efficient method for the generation of [*E*]-higher crotylboranes, by the hydroboration of the corresponding allenes, and have synthesized representative *anti*-3-alkyl/aryl-4-hydroxy-1-alkenes in good diastereo- and enantioselectivity. This methodology should be especially valuable for the synthesis of natural products with structures **7**.

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