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Enantio- and Diastereoselective Synthesis of *syn*-β-Hydroxy-α-vinyl Carboxylic Esters via Reductive Aldol Reactions of Ethyl Allenecarboxylate with 10-TMS-9-Borabicyclo[3.3.2]decane and DFT Analysis of the Hydroboration Pathway

Jeremy Kister,[†] Daniel H. Ess,[‡] and William R. Roush*,[†]

Department of Chemistry, Scripps Florida, Jupiter, Florida 33458, United States, and Department of Chemistry and Biochemistry, Brigham Young University, Provo, Utah 84602, United States

roush@scripps.edu

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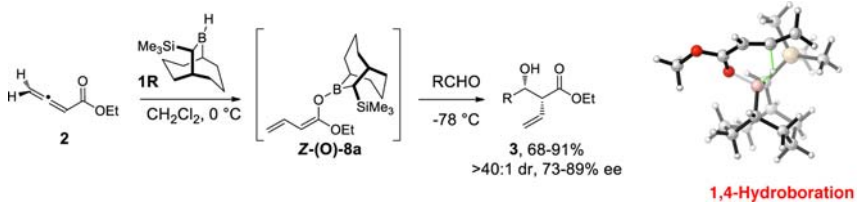
ABSTRACT



An enantio- and diastereoselective synthesis of *syn*-β-hydroxy-α-vinyl carboxylate esters 3 via the reductive aldol reaction of ethyl allenecarboxylate (2) with 10-trimethylsilyl-9-borabicyclo[3.3.2]decane (1R) has been developed. Density functional theory calculations suggest that the allene hydroboration involves the 1,4-reduction of 2 with the 1R, leading directly to dienolborinate *Z*-(O)-8a.

syn-β-Hydroxy-α-vinyl carboxylic esters **3** and imides **5** (Figure 1) are versatile intermediates widely used in organic synthesis.[1,2] Racemic **3** can be obtained with varying degrees of diastereoselectivity by allylation of aldehydes with γ-(alkoxycarbonyl)-substituted allyl metal reagents (e.g., indium,[3] tin,[4] zinc[5] and boron[6] reagents). Another approach to racemic **3** involves aldol[7,8] or Reformatsky[9] reactions of aldehydes with ester derived dienolates.

Given the widespread use of this structural unit in organic synthesis,[1,2] it is surprising that *direct* enantioselective methods for the synthesis of the *syn* or *anti* diastereoisomers of β-hydroxy-α-vinyl carboxylic esters **3** have not been reported. Both enantiomers of *syn*-β-hydroxy-α-vinyl

[†] Scripps Florida.
[‡] Brigham Young University.

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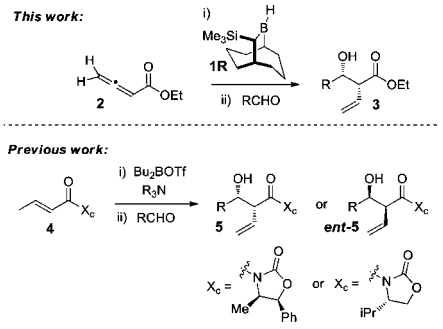

Figure 1. Approaches to the enantioselective synthesis of *syn*-α-vinyl-*β*-hydroxy esters **3** and imides **5**.

imides **5** can be obtained by using enantioselective aldol reactions of chiral crotonate imides (Figure 1). Evans' chiral *N*-acyl oxazolidinones[10] are widely applied for this purpose,[1] but other methods include use of Oppolzer's chiral sultam[11] and Crimmins' chiral oxazolidinethione reagents.[12] Here we report the development of an enantio- and diastereoselective synthesis of *syn*-*β*-hydroxy-α-vinyl carboxylate esters **3** via aldol reactions of aldehydes with (*Z*)-dienolborinate ***Z*-(O)-8a** that is generated in situ from the hydroboration of allenyl ester **2** with 10-trimethylsilyl-9-borabycyclo[3.3.2]decane (**1R**, also known as 10-TMS-9-BBD-H, and as the Soderquist borane).[13,14] Density functional theory (DFT) calculations indicate that ***Z*-(O)-8a** is generated by a kinetically controlled 1,4-hydroboration reaction pathway.

We have reported studies of enantioselective allylboration reactions of reagents generated by hydroboration of

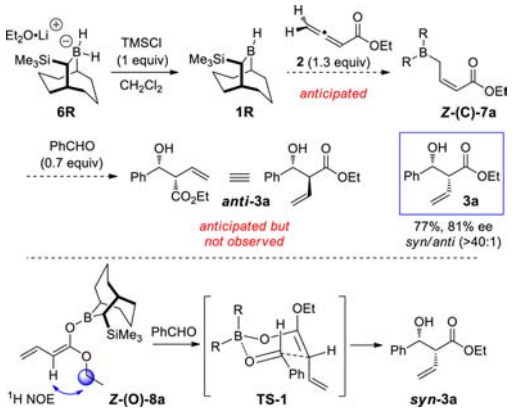

Figure 2. Anticipated versus observed outcome of hydroboration of allenoate **2** with borane **1R** and subsequent reaction with benzaldehyde.

monosubstituted allenes with the Soderquist borane **1**,[15] and were interested in extending these efforts to the hydroboration of allenecarboxylic ester **2** (Figure 2). Based on previous results,[15] we were hopeful that the hydroboration reaction of **2** would occur on the terminal allene double bond opposite to the ester moiety, leading directly to (*Z*)-*γ*-(ethoxycarbonyl)allylborane ***Z*-(C)-7a**. Further, it was anticipated that the reaction of allylborane ***Z*-(C)-7a** with aldehydes such as benzaldehyde would result in an enantioselective synthesis of *anti*-**3a**. However, this reaction sequence provided *syn*-*β*-hydroxy-α-vinyl ester **3a** as a single diastereoisomer (dr >40:1) in 81% ee and in 77% isolated yield. (See Supporting Information (SI) for stereochemical assignments). ^{1}H NMR analysis of the intermediate formed in the hydroboration step revealed the presence of a single (*Z*)-dienolborinate, ***Z*-(O)-8a**, and not the expected allylborane ***Z*-(C)-7a** (Figure 2). Based on this insight, the formation of *syn*-*β*-hydroxy-α-vinyl carboxylic ester **3a** can be rationalized by an aldol reaction of ***Z*-(O)-8a** with benzaldehyde via the chairlike transition state **TS-1**.

The optimization of several reaction variables is summarized in Table 1. The use of Et_2O or toluene instead of CH_2Cl_2 as a reaction solvent was detrimental to both the yield of **3a** and overall reaction enantioselectivity (entries 1−3). Increasing the reaction concentration and the reaction time led to an increased yield of **3a**, with essentially identical results being obtained if the reactions were performed at 0.25 or 0.5 M (entries 4, 5). However, when the less reactive cyclohexanecarboxaldehyde was used, **3b** was obtained in 64% and 80% yield when the reaction was performed at 0.25 or 0.5 M (entries 6,7).

The results of reductive aldol reactions of **2** with several representative aromatic, aliphatic, α,*β*-unsaturated, and heteroaromatic aldehydes are presented in Scheme 1. These reactions provided **3a**−**g** with >40:1 d.r. in 68−91%

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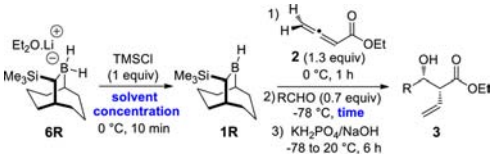
Table 1. Optimization of the Reaction Conditions for the Synthesis of *syn*-β-Hydroxy-α-vinyl Carboxylate Esters **3**



entry	RCHO	product[a]	solvent	% yield[b]	% ee[c]
1	PhCHO	**3a**	CH_2Cl_2[d,e]	77	82
2	PhCHO	**3a**	Et_2O[d,e]	36	72
3	PhCHO	**3a**	toluene[d,e]	47	71
4	PhCHO	**3a**	CH_2Cl_2[f,g]	83	82
5	PhCHO	**3a**	CH_2Cl_2[h,g]	86	82
6	$C_6H_{11}CHO$	**3b**	CH_2Cl_2[f,g]	64	83
7	$C_6H_{11}CHO$	**3b**	CH_2Cl_2[h,g]	80	83

[a] A single diastereoisomer (dr >40:1) was obtained in each entry (^{1}H NMR analysis). [b] Yield of product isolated chromatographically. [c] Determined by Mosher ester analysis. [d] Reaction concentration 0.17 M. [e] 12 h aldol reaction time. [f] Reaction concentration 0.25 M. [g] 36 h aldol reaction time. [h] Reaction concentration 0.5 M.

yields, and with very good to excellent enantioselectivity (73−89% ee). Either enantiomer of the *syn*-β-hydroxy-α-vinyl carboxylic esters, **3** and ***ent*-3**, can be obtained by using the appropriate enantiomer of borane **1R** or **1S**.[13]

Another variable that significantly impacts the reaction diastereoselectivity is the borane reagent used in the hydroboration step (Table 2). For example, use of (^{l}Ipc)$_2$BH as the hydroborating agent[16] resulted in an ~1:1 mixture of **3a** and ***anti*-3a** (80% ee), with benzaldehyde as the aldol partner (entry 1). Alternatively, use of 9-BBN lead to ***anti*-3a** exclusively in 90% yield (entry 2). While we have not explored the full scope of the latter reaction, it is conceivable that this process could be developed into a general, highly diastereoselective synthesis of racemic *anti*-β-hydroxy-α-vinyl carboxylic esters.[2,8]

^{1}H NMR analysis of the hydroboration of allene **2** with (^{l}Ipc)$_2$BH (toluene-d_8, 0 °C) revealed that a 2.3:0.05:1 mixture of ***Z*-(O)-8b**, ***E*-(O)-8b**, and ***Z*-(C)-7b** was formed. In contrast, ***Z*-(C)-7c** was formed exclusively when 9-BBN was used as the hydroborating agent (THF-d_8, 0 °C) (Figure 3). The exclusive formation of the *anti*-β-hydroxy-α-vinyl carboxylic ester ***anti*-3a** from the hydroboration of **2** with 9-BBN (entry 2) is easily understood since intermediate ***Z*-(C)-7c** (Figure 3) would be expected to undergo allylboration reactions to give ***anti*-3a** with high selectivity. Alternatively, a mixture of **3a** and ***anti*-3a** is produced when (^{l}Ipc)$_2$BH is used as the hydroborating agent (entry 1), since allylborane ***Z*-(C)-7b** should react with benzaldehyde to give ***anti*-3a** with high selectivity, while the dienolate ***Z*-(O)-8b** would be expected to undergo a syn-selective aldol reaction, leading to syn aldol **3**.

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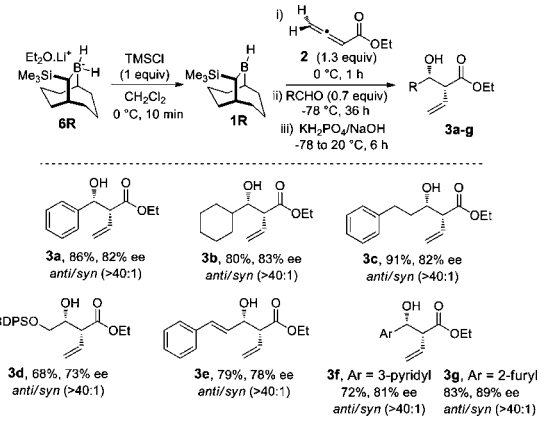
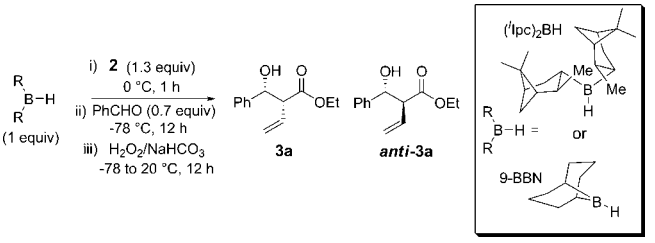
Scheme 1. Diastereo- and Enantioselective Synthesis of *syn*-β-Hydroxy-α-vinyl Carboxylate Esters **3a**−**g**



We have used M06-2X/6-31G(d,p)[17] density functional theory (DFT)[18] to examine the hydroboration reaction and isomerization pathways in order to rationalize the selective formation of intermediates ***Z*-(C)-7** or ***Z*-(O)-8** using 9-BBN or **1R**, respectively. For **1R**, the direct and stereospecific 1,4-hydroboration of allenyl ester **2** to give ***Z*-(O)-8a** is 2−4 kcal/mol lower in energy than potentially competitive 3,4-, and 5,4-hydroboration transition states (Scheme 2). This concerted 1,4-addition transition state is

Table 2. Influence of the Borane Reagent on Reaction Diastereoselectivity



entry	R_2BH	ratio **3a**/*anti*-**43**	solvent	% yield[a]
1	(^{l}Ipc)$_2$BH	1:1	toluene	51
2	9-BBN	1:>40[b]	THF	90

[a] Isolated yield of the mixture of **3** and *anti*-**3**. [b] Racemic *anti*-**3a** was the only product detected.

akin that proposed for the formation of boron (*Z*)-enolates via 1,4-hydroboration of α,β-unsaturated ketones with alkylboranes[19] or catecholborane.[20,21] The alternative

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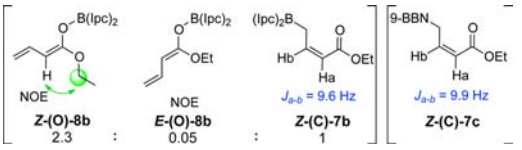

Figure 3. Intermediates formed in the hydroboration of allene **2** with (^{t}Ipc)$_2$BH (left) and 9-BBN (right).

3,4- and 5,4-hydroboration pathways also require either a single 1,5-boratropic shift or multiple 1,3-boratropic shifts in order to produce ***Z*-(O)-8a**. We have previously shown that the steric bulk of the 10-TMS group in products of hydroboration reactions of **1R** retards the 1,3-boratropic rearrangement transition state.[22] Here also, the 10-TMS group provides large kinetic stability to intermediate ***Z*-(O)-8a** with >20 kcal/mol free energy barriers for 1,3- and 1,5-rearrangement pathways. In addition, ***Z*-(O)-8a** is 8−10 kcal/mol more stable than ***Z*-(C)-7a** and ***E*-(C)-7a**.[23]

For the 9-BBN hydroboration sequence, 1,4-addition also provides the lowest energy hydroboration transition state. However, in this case there is a low free energy barrier (9 kcal/mol) for the 1,5-boratropic shift to directly convert ***Z*-(O)-8c** to ***Z*-(C)-7c**. To our knowledge, this is the first prediction of a 1,5-boratropic shift. Importantly, ***Z*-(C)-7c** is 5 kcal/mol more stable than **Z-(O)-8c** and 9 kcal/mol more stable than ***E*-(C)-7c** due to intramolecular coordination of boron by the ester carbonyl. In ***Z*-(C)-7a** this interaction is prevented due to the steric bulk of the 10-TMS group. The alternative route via two 1,3-boratropic shifts requires >6 kcal/mol higher free energy barriers than the direct 1,5-boratropic shift pathway.

Additional experiments were performed to explore the origin of **7** and the proposed equilibria between **8** and **7** (Figure 4). First, ^{1}H NMR studies demonstrated that the 2.3:0.05:1 mixture of ***Z*-(O)-8b**, ***E*-(O)-8b**, and ***Z*-(C)-7b** generated by the hydroboration of **3** with (^{t}Ipc)$_2$BH (see Figure 3 and SI) did not change over time, suggesting that this is the equilibrium mixture. Second, treatment of ethyl but-3-enoate (**10**) with (^{t}Ipc)$_2$BCl and Et$_3$N in toluene-d_8, conditions known to generate ester enolborinates,[24] provided after 10 min a 2.7:0.7:1 mixture of ***Z*-(O)-8b**, ***E*-(O)-8b**, and ***Z*-(C)-7b** that over a ca. 2 h period isomerized to a 2.3:0.1:1 mixture that remained constant over a 12 h period. Finally, treatment of **10** with B-iodo-9-BBN and Et$_3$N in THF-d_6 provided ***Z*-(C)-7c** exclusively, with no change observed over a 1 h monitoring period. These data are consistent with our proposal that allylborane ***Z*-(C)-7** can arise by isomerization of dienolborinate **8** as suggested by the computational studies (Scheme 2). These observations

(21) Citations of other methods for reductive aldol reactions are provided in ref 16.

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(23) A 3,4-addition pathway has been proposed for the borylcupration of allenamides: Yuan, W.; Zhang, X.; Yu, Y.; Ma, S. *Chem.—Eur. J.* **2013**, *19*, 7193.

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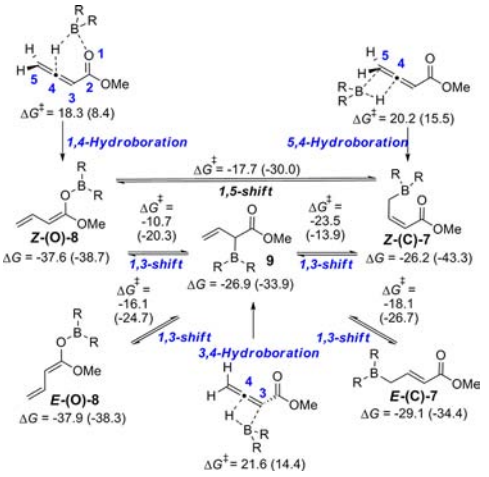
Scheme 2. M06-2X Free Energies (kcal/mol) for Hydroboration of Methyl Allenylcarboxylate with **1R** (series a) and 9-BBN (series b; data in parentheses are for 9-BBN)[18c]



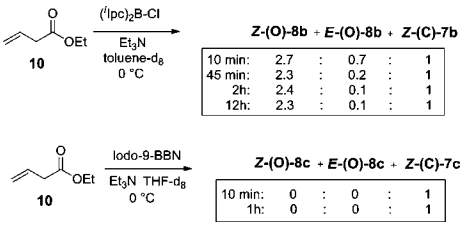


Figure 4. Studies concerning the origin of **7** and the proposed equilibration of **8** and **7**.

may also be relevant to understanding the 'unusual' stereochemical course of the 'aldol' reactions of ethyl but-3-enoate and di(bicyclo[2.2.1]heptan-2-yl)chloroborane recently reported by Ramachandran.[8]

In conclusion, hydroboration of allenecarboxylate **2** with borane **1R** provides stereoselective formation of (*Z*)-dienolborinate ***Z*-(O)-8a**, which upon treatment with aldehydes provides *syn* α-vinyl-β-hydroxy esters **3a**−**g** in 68−91% yields with excellent diastereoselectivities (dr >40:1) and with good to excellent enantioselectivity (73−89% ee). DFT calculations and NMR evidence support the proposed 1,4-hydroboration pathway.

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Supporting Information Available. Experimental procedures and tabulated spectroscopic data for new compounds. Full ref 18b and *xyz* coordinates for the calculations summarized in Scheme 2. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.