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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

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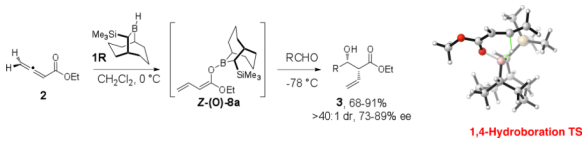
Abstract



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, Soderquist's borane) has been developed. Density functional theory calculations suggest that the allene hydroboration involves the 1,4-reduction of 2 with the chiral borane 1R, leading directly to dienolborinate *Z*-(O)-8a.

Syn-β-hydroxy-α-vinyl carboxylic esters **3** and the corresponding 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 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

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Supporting Information Available. Experimental procedures and tabulated spectroscopic data for new compounds. Full reference 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.

(DFT) calculations indicate that **Z-(O)-8a** is generated by a kinetically controlled 1,4-hydroboration reaction pathway.

We have previously reported studies of enantioselective allylboration reactions of reagents generated by hydroboration of 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 these 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**. In the event, however, this reaction sequence provided *syn*-β-hydroxy-α-vinyl ester **3a** as a single diastereoisomer (dr >40:1) in 81% e.e. and in 77% isolated yield. (Relative and absolute stereochemical assignments are provided in the Supporting Information). ^{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 chair-like 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 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 M or 0.5 M (entries 6,7).

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% 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 $(^l\text{Ipc})_2$BH as the hydroborating agent[16] resulted in an approximate 1:1 mixture of **3a** and ***anti*-3a** (80% ee), with benzaldehyde as the aldol partner (entry 1). Alternatively, use of 9-BBN as the hydroborating agent 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 products generated in the hydroboration of allene **2** with $(^l\text{Ipc})_2$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 $(^l\text{Ipc})_2$BH is used as the hydroborating agent (entry 1), since intermediate 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**.

We have used M06-2X/6-31G(d,p)[17] density functional theory (DFT)[18] to examine the hydroboration reaction and 1,3-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 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 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 a 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 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 require >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**. 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 $(^l\text{Ipc})_2\text{BH}$ (see Fig. 3 and SI) did not change over time, suggesting that this is the equilibrium mixture. Second, treatment of ethyl but-3-enoate (**10**) with $(^l\text{Ipc})_2\text{BCl}$ and Et_3N 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_3N 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 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 the Soderquist borane **1R** provides direct, 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). Density functional theory calculations and NMR evidence support the proposed 1,4-hydroboration pathway. To the best of our knowledge, this work also constitutes the first application of the Soderquist borane in enantioselective aldol reactions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References

1. (a) Evans DA, Dow RL, Shih TL, Takacs JM, Zahler R. J. Am. Chem. Soc. 1990; 112:5290.(b) McGarvey GJ, Mathys JA, Wilson KJ. J. Org. Chem. 1996; 61:5704.(c) Roush WR, Coffey DS, Madar DJ. J. Am. Chem. Soc. 1997; 119:11331.(d) Roush WR, Bannister TD, Wendt MD, Jablonowski JA, Scheidt KA. J. Org. Chem. 2002; 67:4275. [PubMed: 12054963] (e) Perez M, del Pozo C, Reyes F, Rodriguez A, Francesch A, Echavarren AM, Cuevas C. Angew. Chem. Int. Ed. 2004; 43:1724.(f) Fleming KN, Taylor RE. Angew. Chem. Int. Ed. 2004; 43:1728.(g) Packard GK, Hu Y, Vescovi A, Rychnovsky SD. Angew. Chem. Int. Ed. 2004; 43:2822.(h) Smith AB III, Lee D. J. Am. Chem. Soc. 2007; 129:10957. [PubMed: 17691787] (i) Hamel C, Prusov EV, Gertsch J, Schweizer WB, Altmann K-H. Angew. Chem. Int. Ed. 2008; 47:10081.(j) Dunetz JR, Julian LD, Newcom JS, Roush WR. J. Am. Chem. Soc. 2008; 130:16407. [PubMed: 18980317] (k) Pereira CL, Chen Y-H, McDonald FE. J. Am. Chem. Soc. 2009; 131:6066. [PubMed: 19354245]

2. (a) Hudlicky T, Frazier JO, Seoane G, Tiedje M, Seoane A, Kwart LD, Beal C. J. Am. Chem. Soc. 1986; 108:3755.(b) Black CW, Giroux A, Greidanus G. Tetrahedron Lett. 1996; 37:4471.(c) Galatsis P, Millan SD, Ferguson G. J. Org. Chem. 1997; 62:5048.(d) Schneider C, Rehfeuter M. Chem. Eur. J. 1999; 5:2850.(e) Sumida, S-i; Ohga, M.; Mitani, J.; Nokami, J. J. Am. Chem. Soc. 2000; 122:1310.(f) Taylor RE, Englhardt CF, Schmitt MJ, Yuan H. J. Am. Chem. Soc. 2001; 123:2964.(g) Engelhardt FC, Schmitt MJ, Taylor RE. Org. Lett. 2001; 3:2209. [PubMed: 11440581] (h) Loh T-P, Hu Q-Y, Ma L-T. Org. Lett. 2002; 4:2389. [PubMed: 12098254] (i) Nguyen G, Perlmutter P, Rose ML, Vounatsos F. Org. Lett. 2004; 6:893. [PubMed: 15012058] (j) Weise CF, Immel S, Richter F, Schneider C. Eur. J. Org. Chem. 2012:1520.

3. (a) Isaac MB, Chan T-H. Tetraheron Lett. 1995; 36:8957.(b) Paquette LA, Rothhaar RR. J. Org. Chem. 1999; 64:217. [PubMed: 11674106] (c) Tan K-T, Chng S-S, Cheng H-S, Loh T-P. J. Am. Chem. Soc. 2003; 125:2958. [PubMed: 12617663] (d) Alam J, Keller TH, Loh T-P. Chem. Commun. 2011; 47:9066.

4. (a) Wallner OA, Szabo KJ. Org. Lett. 2002; 4:1563. [PubMed: 11975629] (b) Wang Z, Zha Z, Zhou C. Org. Lett. 2002; 4:1683. [PubMed: 12000273] (c) Wallner OA, Szabo KJ. J. Org. Chem. 2003; 68:2934. [PubMed: 12662072] (d) Wallner OA, Szabo KJ. Org. Lett. 2004; 6:1829. [PubMed: 15151425]

5. Gosmini C, Rollin Y, Perichon J, Wakselman C, Tordeux M, Marival L. Tetrahedron. 1997; 53:6027.

6. (a) Sebelius S, Wallner OA, Szabo KJ. Org. Lett. 2003; 5:3065. [PubMed: 12916982] (b) Sebelius S, Szabo KJ. Eur. J. Org. Chem. 2005:2539.

7. (a) Hertler WR, Reddy GS, Sogah DY. J. Org. Chem. 1988; 53:3532.(b) Kisanga PB, Verkade JG. J. Org. Chem. 2002; 67:426. [PubMed: 11798313] (c) Bellassoued M, Grugier J, Lensen N, Catherine A. J. Org. Chem. 2002; 67:5611. [PubMed: 12153258] (d) Otaka A, Yukimasa A, Watanabe J, Sasaki Y, Oishi S, Tamamura H, Fujii N. Chem. Commun. 2003:1834.(e) Bazan-Tejeda B, Bluet G, Broussal G, Campagne J-M. Chem. Eur. J. 2006; 12:8358. [PubMed: 16933344]

8. Ramachandran PV, Nicponski D, Kim B. Org. Lett. 2013; 15:1398. [PubMed: 23465070]

9. (a) Nelsen SF, Teasley MF, Kapp DL, Wilson MR. J. Org. Chem. 1984; 49:1845.(b) Hudlicky T, Natchus MG, Kwart LD, Colwell BL. J. Org. Chem. 1985; 50:4300.(c) Orsini F, Leccioli C. Tetrahedron: Asymmetry. 1997; 8:4011.

10. Evans DA, Sjogren EB, Bartroli J, Dow RL. Tetrahedron Lett. 1986; 27:4957.

11. (a) Tomooka K, Nagasawa A, Wei S-Y, Nakai T. Tetrahedron Lett. 1996; 37:8899.(b) Ciampini M, Perlmutter P, Watson K. Tetrahedron: Asymmetry. 2007; 18:243.

12. Crimmins MT, Tabet EA. J. Org. Chem. 2001; 66:4012. [PubMed: 11375027]
13. (a) Gonzalez AZ, Román JG, Gonzalez E, Martinez J, Medina JR, Matos K, Soderquist JA. J. Am. Chem. Soc. 2008; 130:9218. [PubMed: 18582063] (b) Soderquist JA, Matos K, Burgos CH, Lai C, Vaquer J, Medina JR, Huang SD. ACS Symposium Series. 2001; 783:176.
14. Shibasaki has reported a catalytic enantioselective reductive aldol reaction of allenic esters with aromatic ketones: Zhao D, Oisaki K, Kanai M, Shibasaki M. J. Am. Chem. Soc. 2006; 128:14440. [PubMed: 17090010]
15. (a) Kister J, DeBaillie AC, Lira R, Roush WR. J. Am. Chem. Soc. 2009; 131:14174. [PubMed: 19775159] (b) Kister J, Nuhant P, Lira R, Sorg A, Roush WR. Org. Lett. 2011; 13:1868. [PubMed: 21375316] (c) Nuhant P, Kister J, Lira R, Sorg A, Roush WR. Tetrahedron. 2011; 67:6497. [PubMed: 21857752]
16. For recent studies of reductive aldol reactions using $(Ipc)_2BH$: Nuhant P, Allais C, Roush WR. Angew. Chem. Int. Ed. 2013; 52:8703. and references therein. Allais C, Nuhant P, Roush WR. Org. Lett. 2013; 15:3922. [PubMed: 23885946]
17. (a) Zhao Y, Truhlar DG. Theor. Chem. Acc. 2008; 120:215.(b) Zhao Y, Truhlar DG. Acc. Chem. Res. 2008; 41:157. [PubMed: 18186612]
18. (a) All calculations were carried out in *Gaussian 09*. Frisch MJ, et al. Gaussian 09. 2009Wallingford, CTGaussian, Inc.revision A.02 (c) Free energies in are reported for 298 K and relative to separated reactants. Methyl allenecarboxylate was used as a model for ethyl ester **3** in all calculations.
19. Boldrini GP, Bortolotti M, Mancini F, Tagliavini E, Trombini C, Umani-Ronchi A. J. Org. Chem. 1991; 56:5820.
20. Evans DA, Fu GC. J. Org. Chem. 1990; 55:5678.
21. Citations of other methods for reductive aldol reactions are provided in ref. 16
22. Ess DH, Kister J, Chen M, Roush WR. Org. Lett. 2009; 11:5538. [PubMed: 19899749]
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. [PubMed: 23559155]
24. Ganesan K, Brown HC. J. Org. Chem. 1994; 59:2336.

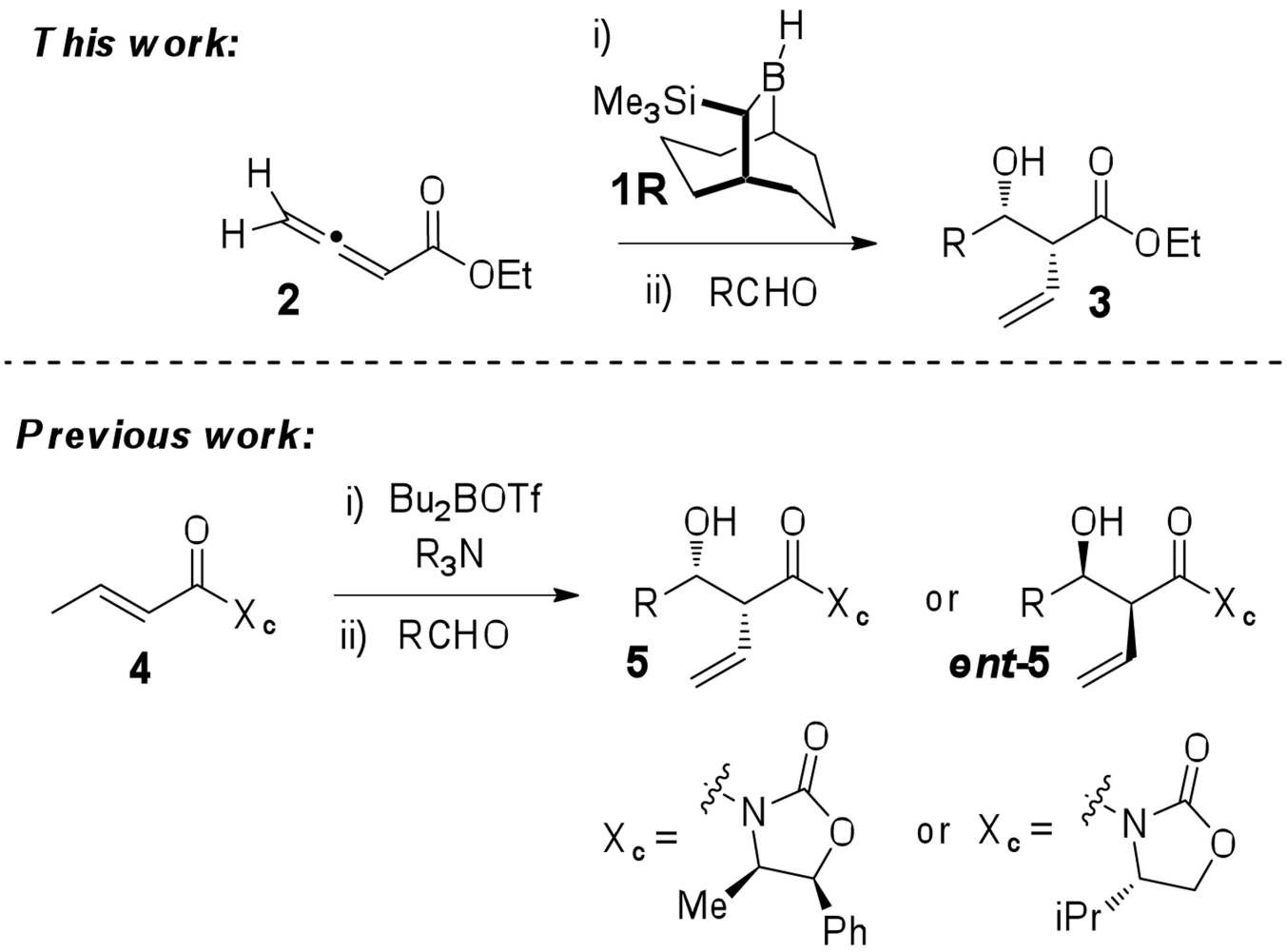


Figure 1.
Approaches to the enantioselective synthesis of *syn*-α-vinyl-β-hydroxy esters **3** and imides **5**.

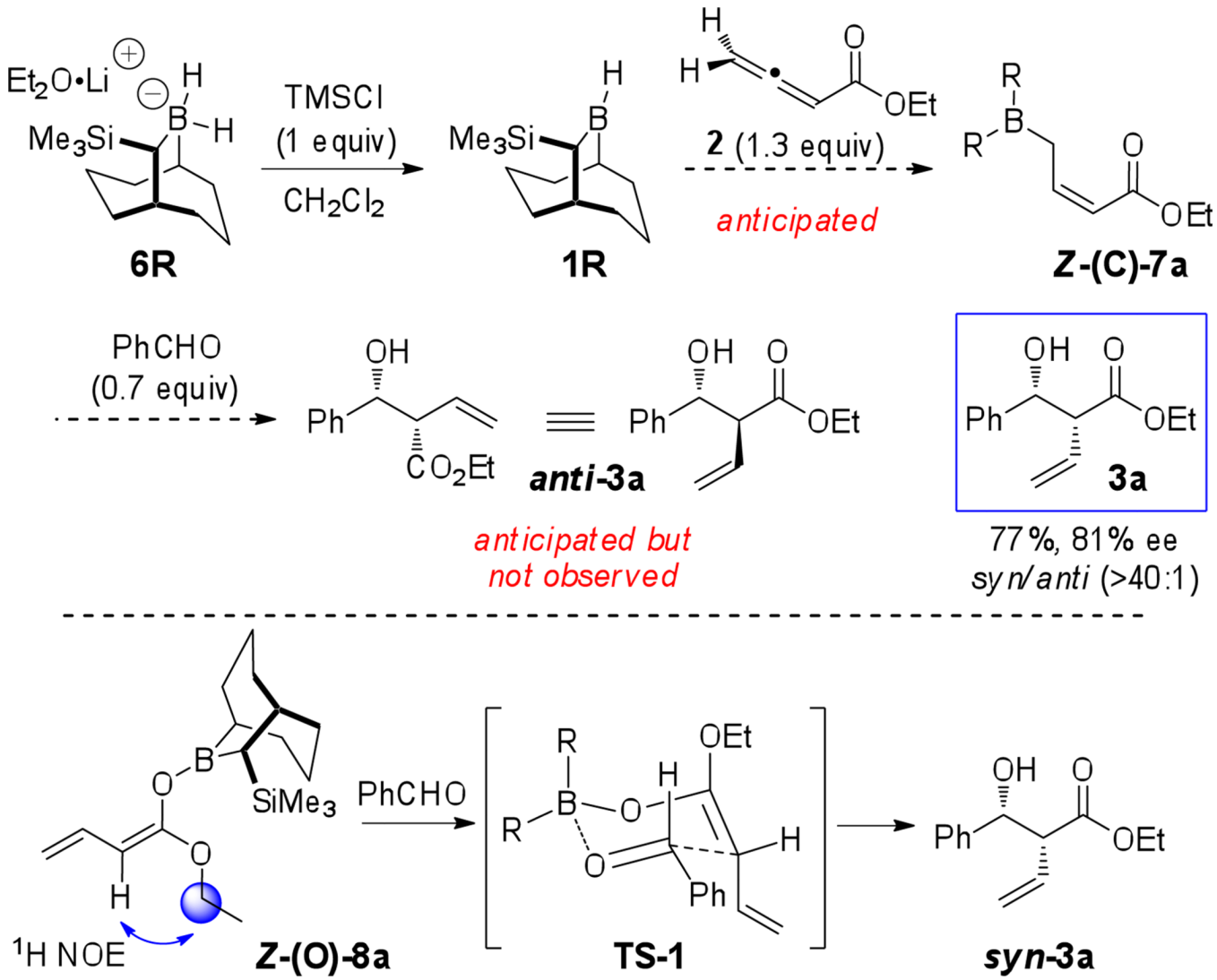


Figure 2.
Anticipated versus observed outcome of hydroboration of allenoate **2** with borane **1R** and subsequent reaction with benzaldehyde.

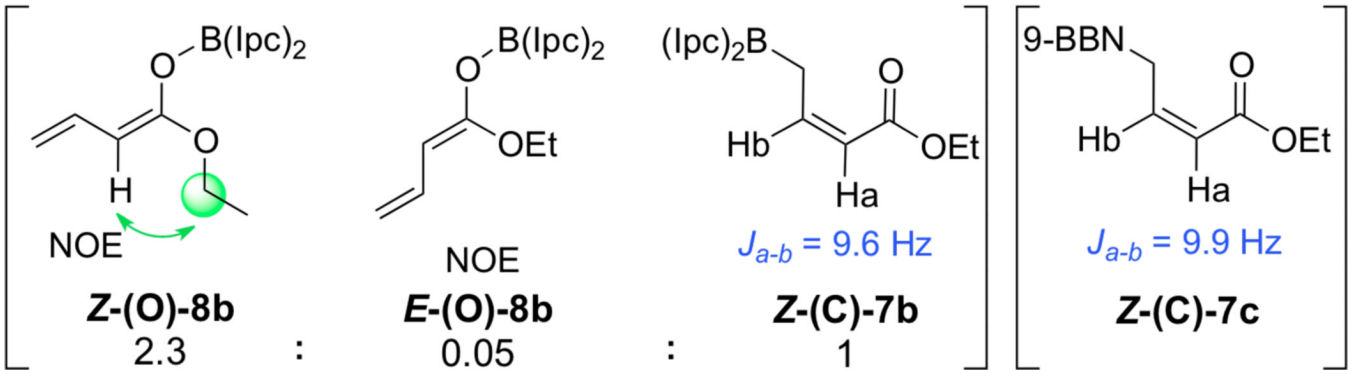


Figure 3.
Intermediates formed in the hydroboration of allene **2** with (^{l}Ipc)$_2$BH (left) and 9-BBN (right).

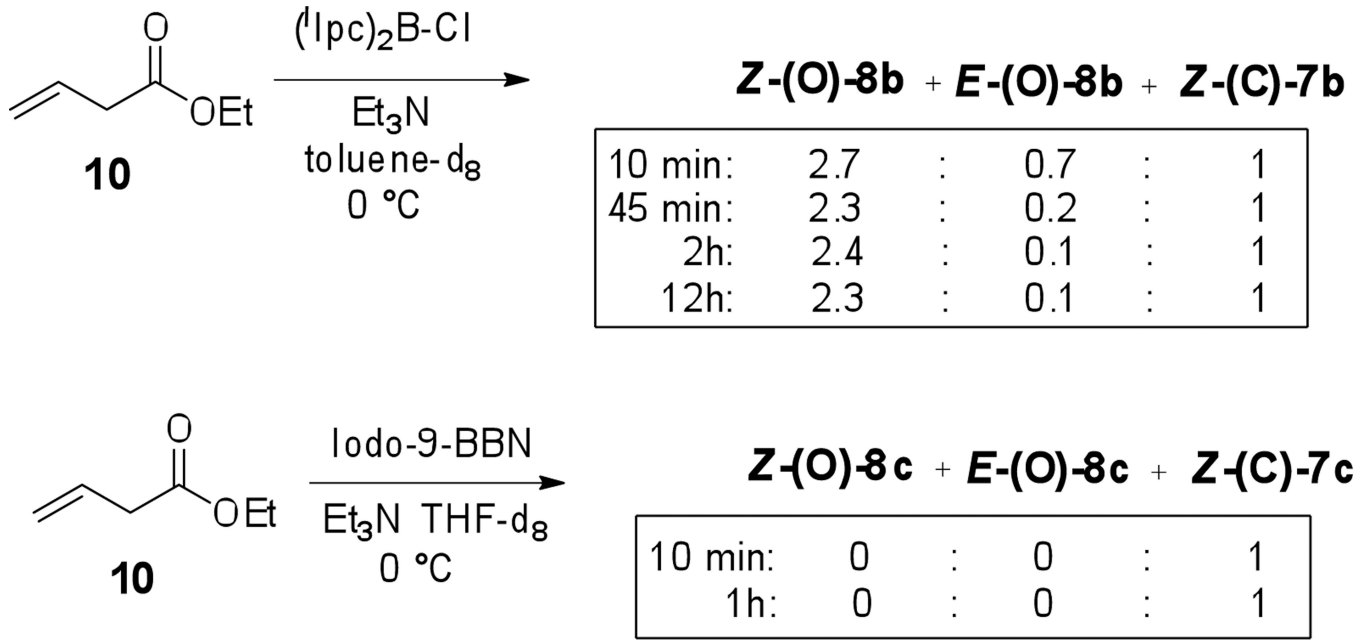
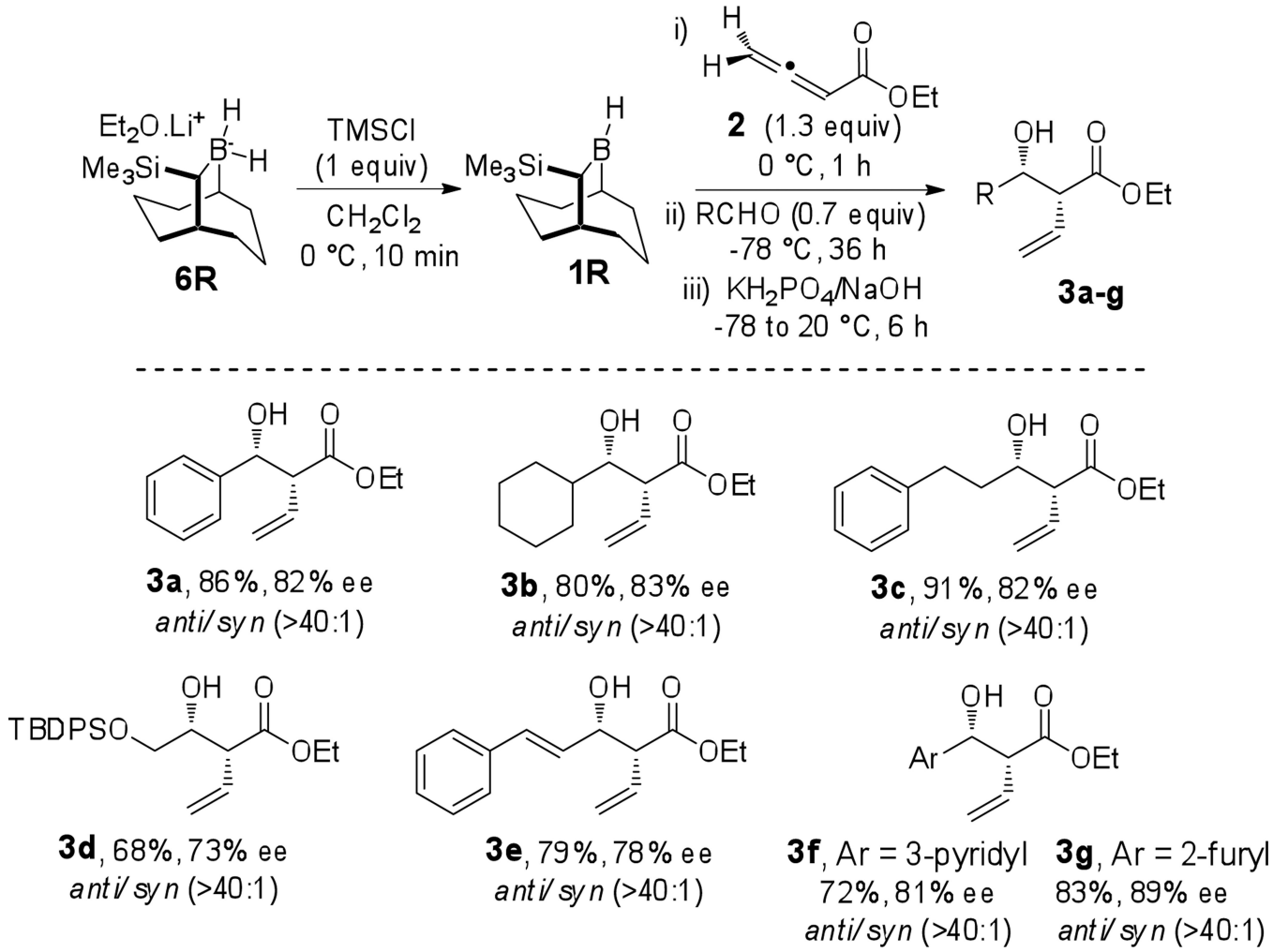
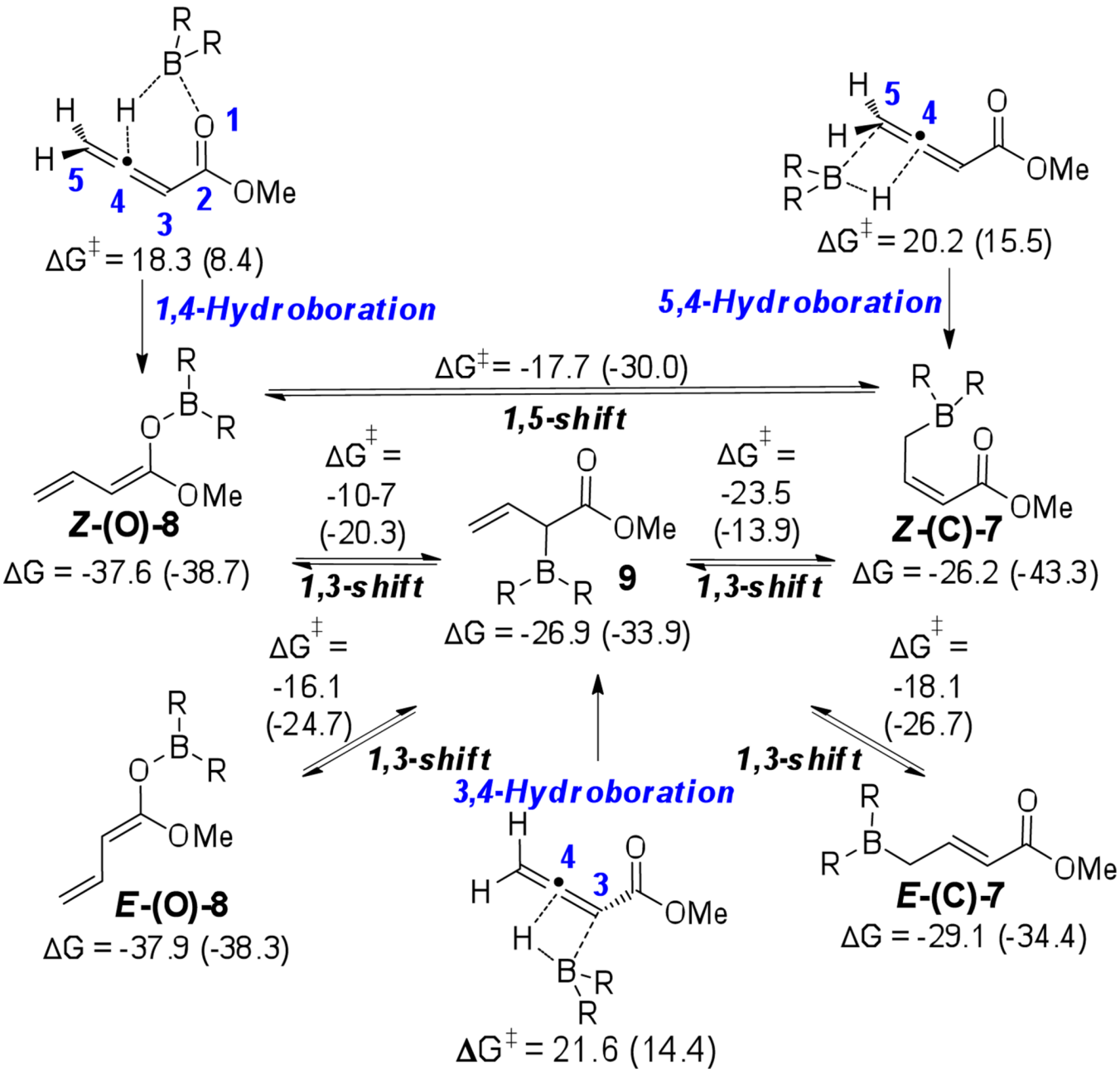


Figure 4.
Studies concerning the origin of **7** and the proposed equilibration of **8** and **7**.



Scheme 1.
Diastereo- and enantioselective synthesis of *syn*-β-hydroxy-α-vinyl carboxylate esters **3a–g**

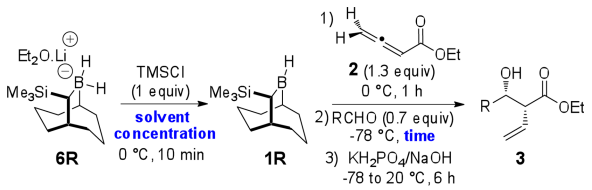


Scheme 2.

M06-2X free energies (kcal/mol) for hydroboration of methyl allenylcarboxylate with **1R** (series a) and 9-BBN (series b; data in parenthesis are for 9-BBN).[18c]

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.

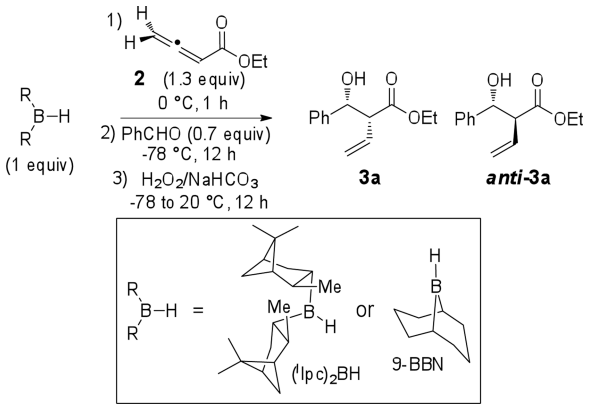
[f] Reaction concentration 0.25 M.

[g] 36 h aldol reaction time.

[h] Reaction concentration 0.5 M.

Table 2

Influence of the borane reagent on reaction d.s.



entry	R_2BH	ratio 3a/*anti*-43	solvent	% yield[a]
1	$(^{l}Ipc)_2BH$	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.