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Total Regio- and Diastereocontrol in the Aldol Reactions of Dienolborinates

P. Veeraraghavan Ramachandran,* Daniel Nicponski, and Bomi Kim

Herbert C. Brown Center for Borane Research, Department of Chemistry,
Purdue University, 560 Oval Drive, West Lafayette, Indiana 47907-2084, United States

chandran@purdue.edu

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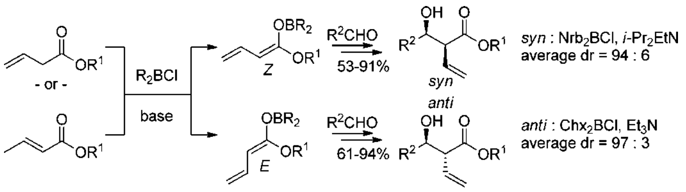
ABSTRACT



It is reported that appropriate dienolborinates can provide access to both diastereomers of 2-(hydroxymethyl)but-3-enoates through exclusive α-regiocontrol in a non-vinylogous pathway. Contrary to previous reports in which dialkylchloroboranes failed to enolize propanoates, acidity-enhanced but-3-enoates readily undergo enolization, offering unprecedented control over the formation of these valuable synthons. The first example of an aldol reaction in the presence of a phosphine–borane adduct is also reported.

The α-selective aldol reactions of vinylogous ester enolates provide access to the highly functionalized and synthetically versatile 2-(hydroxymethyl)but-3-enoate synthons. The latter have found use in a variety of synthetic endeavors[1] and in the production of pharmacologically active functionalities such as lactams and lactones.[2] The stereo- and regiocontrolled production of these compounds has been challenging, and only a limited number of methodologies have been developed for the production of these compounds, including elimination,[3] reductive allylic displacement,[4] Barbier-type reactions of allylic halides,[5] and aldol-style[6] reactions of esters and oxazolidine-derived imides.[6b,7] These methods usually suffer from a variety of setbacks, most especially with regard to α vs γ regio- and *syn* vs *anti* diastereoselectivity; controlling both of these variables simultaneously remains difficult. Vinylogous Mukaiyama enolates exemplify this issue: they not only react with carbonyl electrophiles under both neutral and Lewis acidic conditions to furnish crotonate derivatives but also undergo α-alkylation with little diastereocontrol when activated by an anionic species.[6f−i] While other metal cations are reported to proceed through a non-vinylogous pathway, they also provide poor diastereocontrol. Surprisingly, there remains no report detailing the production of these aldol products with simultaneous control of both the regio- and diastereoselectivities. We believed that the correct choice of reaction conditions in the application of boron-based aldol

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(1) For examples, see: (a) Hansen, F. G.; Bundgaard, E.; Madsen, R. *J. Org. Chem.* **2005**, *70*, 10139. (b) Forbes, J. E.; Saicic, R. N.; Zard, S. Z. *Tetrahedron* **1999**, *55*, 3791. (c) Markó, I. E.; Chesney, A. *Synlett* **1992**, 275. (d) Saicic, R. N.; Zard, S. Z. *Chem. Commun.* **1996**, 1631.

(2) (a) Shirai, F.; Nakai, T. *Chem. Lett.* **1989**, 445. (b) Mead, K. T.; Park, M. *Tetrahedron Lett.* **1995**, *36*, 1205. (c) Brown, H. C.; Kulkarni, S. V.; Racherla, U. S. *J. Org. Chem.* **1994**, *59*, 365.

(3) Kamimura, A.; Mitsudera, H. *Tetrahedron Lett.* **2001**, *42*, 7457.

(4) (a) Wallner, O. A.; Szabó, K. J. *J. Org. Chem.* **2003**, *68*, 2934. (b) Wallner, O. A.; Szabó, K. J. *Org. Lett.* **2004**, *6*, 1829. (c) Sebelius, S.; Szabó, K. J. *Eur. J. Org. Chem.* **2005**, 2539.

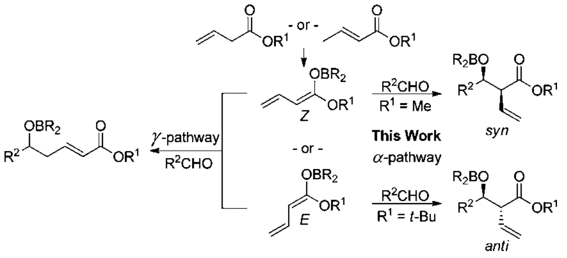
(5) For examples with: Barium: (a) Yamaguchi, A.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2009**, *131*, 10842. Bismuth: (b) Xu, X.; Zha, Z.; Miao, Q.; Wang, Z. *Synlett* **2004**, 1171. Cadmium: (c) Bo, L.; Fallis, A. G. *Tetrahedron Lett.* **1986**, *27*, 5193. Chromium: (d) Wessjohann, L.; Wild, H. *Synlett* **1997**, 731. Gallium: (e) Wang, Z.; Yuan, S.; Li, C.-J. *Tetrahedron Lett.* **2002**, *43*, 5097. Indium: (f) Kaur, P.; Singh, P.; Kumar, S. *Tetrahedron* **2005**, *61*, 8231. (g) Tan, K.-T.; Chng, S.-S.; Cheng, H.-S.; Loh, T.-P. *J. Am. Chem. Soc.* **2003**, *125*, 2958. Tin: (h) Houllemare, D.; Outurquin, F.; Paulmier, C. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1629. (i) Wang, Z.; Zha, Z.; Zhou, C. *Org. Lett.* **2002**, *4*, 1683.

(6) For examples with: Aluminum: (a) Maruoka, K.; Hashimoto, S.; Kitagawa, Y.; Yamamoto, H.; Nozaki, H. *J. Am. Chem. Soc.* **1977**, *99*, 7705. Boron (b) Evans, D. A.; Sjogren, E. B.; Bartroli, J.; Dow, R. J. *Tetrahedron Lett.* **1986**, *27*, 4957. (c) Davies, S. G.; Elend, D. L.; Jones, S.; Roberts, P. M.; Savory, E. D.; Smith, A. D.; Thomson, J. E. *Tetrahedron* **2009**, *65*, 7837. Lithium: (d) Tiecco, M.; Testaferri, L.; Santi, C. *Eur. J. Org. Chem.* **1999**, 797. (e) Galatsis, P.; Millan, S. D.; Nechala, P.; Ferguson, G. *J. Org. Chem.* **1994**, *59*, 6643. Potassium: See ref 6e. Silicon (f) Bazán-Tejeda, B.; Bluet, G.; Broustal, G.; Campagne, J.-M. *Chem.—Eur. J.* **2006**, *12*, 8358. (g) Hertler, W. R.; Reddy, G. S.; Sogah, D. Y. *J. Org. Chem.* **1988**, *53*, 3532. (h) Hassfeld, J.; Christmann, M.; Kalesse, M. *Org. Lett.* **2001**, *3*, 3561. (i) Simsek, S.; Horzella, M.; Kalesse, M. *Org. Lett.* **2007**, *9*, 5637. Zinc: See ref 6c. (j) Hudlicky, T.; Natchus, M. G.; Kwart, L. D.; Colwell, B. L. *J. Org. Chem.* **1985**, *50*, 4300.

(7) (a) Johnson, P. R.; White, J. D. *J. Org. Chem.* **1984**, *49*, 4424. (b) Kisanga, P. B.; Verkade, J. G. *J. Org. Chem.* **2002**, *67*, 426.

10.1021/ol400381q

Scheme 1. Three Possible Aldol Pathways for Dienolborinates



methodology could solve this long-standing synthetic problem. Specifically, we envisaged that the reaction of the boron enolates of either alkyl but-(2 or 3)-enoates with aldehydes could provide the desired adducts (Scheme 1). Our additional goal was to demonstrate that the enhanced allylic acidity could allow for enolization with chloroboranes, which, unlike bromoboranes[8] and boron triflates,[9] are considered incapable of enolizing simple esters.[10] However, we were hopeful, as we had recently shown that certain dialkylchloroboranes could affect the enolization–aldolization sequence of 3,3,3-trifluoropropionates.[11]

We first screened several classes of esters and boranes and found that some dialkylchloroboranes, such as dicyclohexylchloroborane (Chx$_2$BCl), and triflates affected the stereoselective enolization of but-(2 and 3)-enoates. The former reagent, which was first introduced for aldol reactions by Brown,[12] had previously been shown to be highly effective in enolizing aldehydes, ketones, and thioesters. We also found that certain triflates functioned, but their instability and cumbersome synthesis encouraged the use of the former.

After confirming that both esters provided identical dr (Scheme 1), we chose to focus on the use of but-3-enoates, which are readily accessible from crotonic acid. Reports of boron enolates of esters have revealed a trend in which the smaller methyl esters provide *Z*-enolates[13] (*syn*-aldol products) and that larger groups such as *tert*-butyl provide *E*-enolates (*anti*-products), a trend similar to that seen with ketones.[12] We anticipated a similar effect in this case and, after initially screening the methyl (**1**), ethyl (**2**), isopropyl (**3**), benzyl (**4**), and *tert*-butyl (**5**) but-3-enoate esters, felt great satisfaction when we reaffirmed this trend: the initial reaction of **1** with benzaldehyde **6** provided methyl 2-(hydroxy(phenyl)methyl)-but-3-enoate in an approximately 1:1 dr with Chx$_2$BCl and triethylamine (Et$_3$N). The same conditions with **5** provided **7** in an initial ratio of 24:76. In these and all further reactions performed in this study, exclusive α-alkylation took place. We attribute this excellent regioselectivity to a kinetic pathway involving a six-membered chelative intermediate.[14]

The initial success in obtaining both diastereoisomers prompted the development and optimization of protocols for the selective formation of either one. A systematic screening of reaction conditions—choice of amine, solvent, boron ligand and leaving group, concentration, time, and temperature—was performed using **6** as the electrophile. The full optimization studies, which will be detailed at a later date, improved the *syn*- and *anti*-selectivity for the methyl and *tert*-butyl ester enolates to excellent levels in both cases. Unlike the case of methyl phenylacetate, wherein unusual solvent and temperature effects were demonstrated to exist,[15] no unexpected effects were noted. Ultimately, it was discovered that Et$_3$N, in combination with Chx$_2$BCl, provided the *anti*-*tert*-butyl isomers in excellent selectivities and yields, whereas the use of di(bicyclo[2.2.1]heptan-2-yl)-chloroborane (Nrb$_2$BCl) and ethyl-*N*,*N*-diisopropylamine (DIPEA) furnished the *syn*-methyl isomers in excellent selectivities but with slightly decreased yields. Deleteriously, it was discovered that the *syn*/*anti* ratio of these compounds could be readily degraded when the conditions were not carefully controlled, especially during the workup stage involving methanolic hydrogen peroxide oxidation. This is possibly due to the inherent instability of these compounds.[6b,j]

While it is perhaps not surprising that Chx$_2$BCl promoted *anti*-selectity, *the syn-selective aldolization seen with Nrb$_2$BCl is entirely unprecedented.* We recently showed that Nrb$_2$BOTf[16] was more *anti*-selective than Chx$_2$BOTf in enolizing trifluoropropionates.[17] Knowing this, we were astounded by the selectivity reversal, especially considering the fact that dialkylchloroboranes are usually considered *E*-selective enolization reagents.[18]

Careful studies of ketone substrates by Brown showed that larger boron ligands favor the formation of *anti*-aldol products. The large sterics of the cyclohexyl ligands, when combined with the bulkiness of the *tert*-butyl ester, are likely the source of *anti*-selectivity in these reactions. As the steric comparison between norbornane and cyclohexane is unclear at this time, the former's effects are obscure. One possibile explanation is that the methyl ester is mimicking the selectivity expected for hexan-3-one. This is an important consideration, as smaller ketones (such as pentan-3-one) were shown by Brown to give high *Z*-selectivity during enolization with all screened dialkylchloroboranes. Although unlikely, the possibility that the reaction furnishes the observed *syn*-stereochemistry[19] by way of either a closed boat or an open transition state cannot be ruled out. At this time, the exact

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(8) Corey, E. J.; Kim, S. S. *J. Am. Chem. Soc.* **1990**, *112*, 4976.

(9) Abiko, A. *Acc. Chem. Res.* **2004**, *37*, 387.

(10) (a) Brown, H. C.; Dhar, R. K.; Ganesan, K.; Singaram, B. *J. Org. Chem.* **1992**, *57*, 499. (b) Evans, D. A.; Nelson, J. V.; Vogel, E.; Taber, T. R. *J. Am. Chem. Soc.* **1981**, *103*, 3099.

(11) Ramachandran, P. V.; Gagare, P. D.; Parthasarathy, G. *Tetrahedron Lett.* **2011**, *52*, 6055.

(12) Brown, H. C.; Dhar, R. K.; Bakshi, R. K.; Pandiarajan, P. K.; Singaram, B. *J. Am. Chem. Soc.* **1989**, *111*, 3441.

(13) Evans, D. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, Ch. 1.

(14) Paterson, I.; Wallace, D. J.; Velázquez, S. M. *Tetrahedron Lett.* **1994**, *35*, 9083.

(15) Ramachandran, P. V.; Chanda, P. B. *Org. Lett.* **2012**, *14*, 4346.

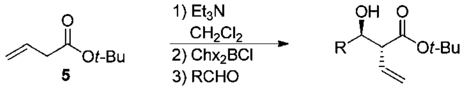
(16) Ramachandran, P. V.; Parthasarathy, G.; Gagare, P. D. *Org. Lett.* **2010**, *12*, 4474.

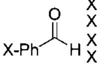
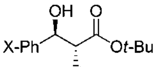
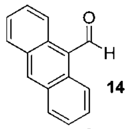
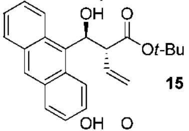
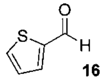
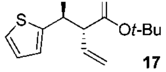
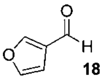
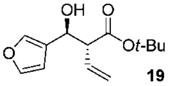
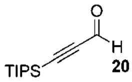
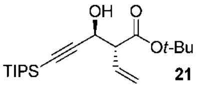
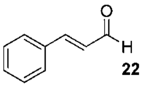
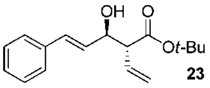
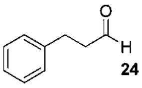
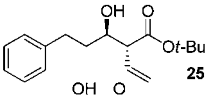
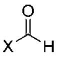
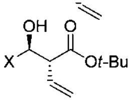
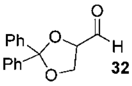
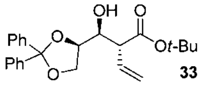
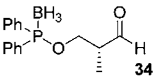
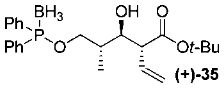
(17) It was initially thought (ref 10b) that R$_2$BOTf could not function as an enolization agent. This was disproved by Abiko et al. See ref 9.

(18) Brown, H. C.; Ganesan, K.; Dhar, R. K. *J. Org. Chem.* **1993**, *58*, 147.

(19) Li, Y.; Paddon-Row, M. N.; Houk, K. N. *J. Am. Chem. Soc.* **1988**, *110*, 3684.

Table 1. *Anti*-Selective Aldol Reactions of Aldehydes with **5**



entry	RCHO	product	yield (%)[a]	dr[b]
1 2 3 4	 X = H, **6** X = 4-NO_2, **8** X = 3-F, **10** X = 4-MeO, **12**	 **7** **9** **11** **13**	61 84 72 73	1:99[c] 1:99[c] 1:99[c] 4:96
5	 **14**	 **15**	90	1:99[c]
6	 **16**	 **17**	70	5:95
7	 **18**	 **19**	77	10:90
8	 **20**	 **21**	90	1:99[c]
9	 **22**	 **23**	81	1:99[c]
10	 **24**	 **25**	79	3:97
11 12 13	 X = *n*-C_8H_{17}, **26** X = Chx, **28** X = Me_3C, **30**	 **27** **29** **31**	85 88 71	1:99[c] 1:99[c] 1:99[c]
14	 **32**	 **33**	61	9:91
15	 **34**	 **(+)-35**	94	5:95

[a] Isolated yields are given for the purified major diastereomer. [b] ^{1}H NMR analysis was used to measure the dr. Values given are measured when ^{13}C satellite peaks were resolved, thus ensuring measurability to 1% in the ^{1}H NMR. [c] Ratio of 99:1 means only one detected diastereomer.

origin of the *syn*-selectivity remains unclear, but we can speculate that the thermodynamically favored *Z*-enolate must be preferentially formed under the given conditions.

The optimized conditions for the production of the *anti*-isomers (Table 1) were applied to a wide variety of structurally and functionally unique aldehydic electrophiles. They were chosen for their varying electronic and steric requirements and as a means to measure the incredible generality of this methodology.

The reaction of **6** furnished **7** with no detectable *syn*-isomer (Table 1, entry 1). Electron-deficient 4-nitro- (**8**) and 3-fluorobenzaldehydes (**10**) (entries 2–3) provided an improvement in the yields while still maintaining excellent dr. Even 4-methoxybenzaldehyde (**12**) was well-tolerated, providing **13** in very good yield and excellent dr (entry 4). 9-Anthraldehyde (**14**) provided **15** in excellent yield and without the loss of dr (entry 5).

Heteroaromatic aldehydes thiophene-2- (**16**) and furan-3-carbaldehydes (**18**) gave moderate yields and very good selectivities (entries 6–7). 1,2-Addition was exclusively observed in the cases of α,β-unsaturated aldehydes (entries 8–9) such as silyl-protected prop-2-ynal (**20**) and cinnamaldehyde (**22**), providing excellent yields of only the *trans*-isomers. Switching to aliphatic aldehydes such as hydrocinnanaldehyde (**24**) still furnished the expected product **25** but in a slightly lower yield (entry 10). Other aliphatic aldehydes such as the straight-chained, branched, and hindered electrophiles nonanal (**26**), cyclohexanecarbaldehyde (**28**), and pivalaldehyde (**30**), respectively, provided the expected products in very high yields and as single diastereomers (entries 11–13). Benzophenone ketal-protected glyceraldehyde (**14**) also provided a high dr and good yield as a single (*anti*) diastereomer (**33**) about the C3–C4 bond (entry 14). (The origin of this selectivity is detailed below.) Most gratifyingly, the use of an enantiopure diphenylphosphinite–borane adduct (**34**) furnished the expected *anti*-product (**35**) as nearly a single stereoisomer and in near-quantitative yield. To the best of our knowledge, this represents the first known example of an aldol reaction in the presence of a phosphine–borane adduct. The chemistry of these P–B compounds is remarkable; they have been shown to survive a wide variety of reaction conditions and chemical manipulations, including chromatography.[20]

The study's success did not come without a cost. For example, capricious but small amounts of alcohol (reduced aldehyde) pervaded these reactions, as did relatively consistent levels of cyclohexylated aldehydes.[21] The latter problem was readily made nugatory by the use of an excess of aldehyde in the reaction mixtures (1.5 equiv). Additionally, the slow hydrolysis rate for the formed dialkylborinate products necessitated the use of a methanolic hydrogen peroxide workup. Despite their instability, the products tolerated this workup, excepting **17** and **41**, wherein small amounts of thiophene oxidation was observed[22] (Tables 1 and 2, entry 6).

The application of the *syn*-selective conditions to the same series of aldehydes was also performed (Table 2). Generally speaking, the reactions again proceeded in good yields and excellent selectivities. While in a few cases the yields (entries 9, 12, and 14) and selectivities (entries 6 and 14) of these *syn*-products were slightly better than their *anti*-counterparts, there was generally a slight decrease in both the yields and selectivities of the *syn*-products. The decreased yields obtained in the formation of these *syn*-isomers can be mostly attributed to what we observed to be a greater level of aldehyde reduction by Nrb_2BCl than Chx_2BCl.[23] This is attributable to a strict co-planarity of the

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[20] Brunel, J. M.; Faure, B.; Maffei, M. *Coord. Chem. Rev.* **1998**, *178–180*, 665.

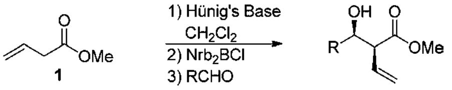
[21] Aggarwal, V. K.; Fang, G. Y.; Ginesta, X.; Howells, D. M.; Zaja, M. *Pure Appl. Chem.* **2006**, *78*, 215.

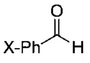
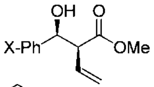
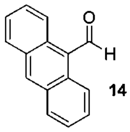
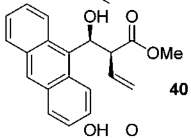
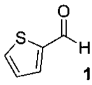
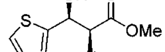
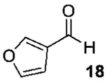
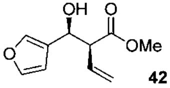
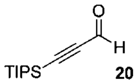
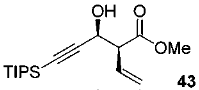
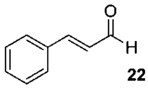
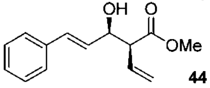
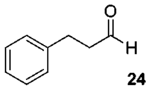
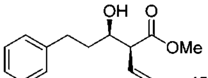
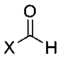
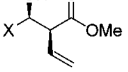
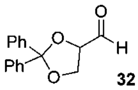
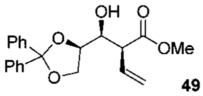
[22] Theimann, T.; Walton, D. J.; Brett, A. O.; Iniesta, J.; Marken, F.; Li, Y.-q. *ARKIVOC* **2009**, 96.

[23] Application of syn-selective conditions to **34** resulted in the 23% yield of **50** due to significant amounts of aldehyde reduction.

[24] Brown, H. C.; Ramachandran, P. V.; Chandrasekharan, J. *Organometallics* **1986**, *5*, 2138.

Table 2. *Syn*-Selective Aldol Reactions of Aldehydes with **1**



entry	RCHO	product		yield (%)[a]	dr[b]
1	 X = H, **6**		**36**	67	85:15
2	X = 4-NO$_2$, **8**		**37**	73	97:3
3	X = 3-F, **10**		**38**	69	86:14
4	X = 4-MeO, **12**		**39**	60	92:8
5	 **14**		**40**	84	99:1[c]
6	 **16**		**41**	56	97:3
7	 **18**		**42**	55	88:12
8	 **20**		**43**	75	99:1[c]
9	 **22**		**44**	82	99:1[c]
10	 **24**		**45**	67	96:4
11	 X = *n*-C$_8$H$_{17}$, **26**		**46**	73	94:6
12	X = Chx, **28**		**47**	91	93:7
13	X = Me$_3$C, **30**		**48**	53	99:1[c]
14	 **32**		**49**	87	99:1[c]

[a] Isolated yields are given for the purified major diastereomer. [b] ^{1}H NMR analysis was used to measure the dr. Values given are measured when ^{13}C satellite peaks were resolved, thus ensuring measurability to 1% in the ^{1}H NMR. [c] Ratio of 99:1 means only one detected diastereomer.

H−C−C−B bond linkage.[24] Likewise, a larger amount of nucleophilic 1,2-attack onto the aldehydes by the norbornyl nucleophile was obtained. This is to be expected based on the relatively high migratory aptitude of norbornanyl ligands.[21]

The reaction dr values were obtained by ^{1}H NMR analysis of the crude reaction mixtures. The relative stereochemistries were assigned from literature precedent (*J*-value differences for the α and *β* protons for the isomers,[25] along with a downfield chemical shift in both the vinylic protons of the *syn*-isomer[6e] and the backbone carbons in ^{13}C NMR[26]). For **35**, the absolute configuration of the carbinol was determined by Mosher analysis.[27]

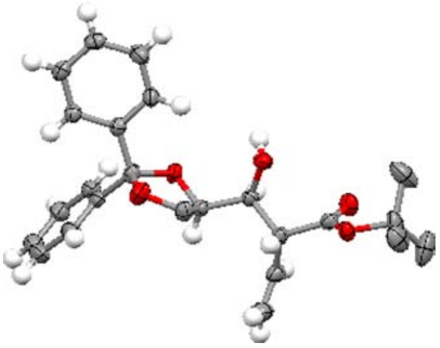


Figure 1. ORTEP rendering of **33**. White = H, gray = C, red = O. Some H atoms have been omitted for clarity. Ellipsoids are shown at the 50% probability level, with H radii fixed at 0.3 Å.

We sought concrete evidence of the stereochemistry of the C3−C4 linkage in the aldol product **33**. To this end, its crystals (recrystallization in pentanes/Et$_2$O at 0 °C for 48 h, mp 92.4−94.6 °C, uncorrected) were subjected to single-crystal X-ray analysis. The ORTEP diagram (Figure 1) clearly shows the *anti*,*anti*-relationship of **33**.[28]

We postulate that the observed C2−C3 *anti*-relationship of **33** is explained by the invocation of a transition state akin to those postulated by Paterson and co-workers,[14] wherein the vinyl and C3-alkyl groups adopt pseudoequatorial positions, whereas the C3−C4 *anti*-relationship is that predicted by the α-heteroatom-modified Felkin−Anh model of facial selectivity.

In conclusion, we have developed the first synthesis of both the *syn*- anti *anti*-isomers of 2-(hydroxymethyl)but-3-enoate synthons from dienolborinates. These reactions proceed in very high yields and selectivities. The application of these developed chemistries to a wide variety of aldehydes, including one containing a P−B adduct, demonstrated the generality of this chemistry. In so doing, the first use of Nrb$_2$BCl as a *syn*-selective enolization reagent has been demonstrated. This new route to these compounds is a significant improvement over existing ones and will likely find much synthetic use. Further work on this methodology is ongoing in our laboratory and will be reported in due course.

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Supporting Information Available. Experimental and full characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(28) Single-crystal X-ray analysis was performed in-house by Dr. Phil Fanwick. CCDC 908643 contains the supplementary crystallographic data for compound **33**. These data may be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

The authors declare no competing financial interest.