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Enantioselective Synthesis of 1,5-*anti*- and 1,5-*syn*-Diols Using a Highly Diastereoselective One-Pot Double Allylboration Reaction Sequence

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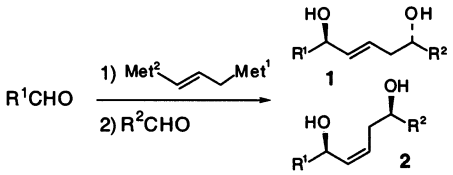
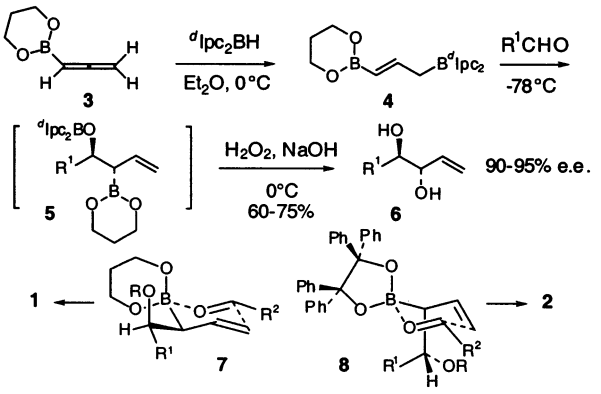
In connection with an ongoing problem in natural products synthesis, we were interested in developing a method for the diastereo- and enantioselective synthesis of 1,5-*anti*- and 1,5-*syn*-diols **1** and **2** via the reactions of two different aldehydes, R^1CHO and R^2CHO, with a chiral, 1,3-bifunctionalized allylmetal reagent.[1−3] This represents a fundamentally interesting problem in organic synthesis, for which practical solutions do not currently exist. While

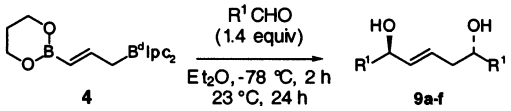


several groups have described diastereoselective syntheses of 1,5-diols and 1,5-amino alcohols via the reactions of aldehydes with structurally complex chiral allylstannane,[4,5] allylsilane,[6] and allyltitanium reagents,[7] no examples currently exist of the type of stereocontrolled, one-pot three-component coupling that we envisaged. We were intrigued by Brown's report that (*E*)-γ-(1,3,2-dioxaborinanyl)allyl]diisopinocampheylborane (**4**), generated by hydroboration of 2-allenyl-(1,3,2)-dioxaborinane (**3**) with diisopinocampheylborane [$(Ipc)_2BH$], reacts with aldehydes at −78 °C to give 1,2-*anti*-diols **6** with excellent enantioselectivity via the intermediacy of β-alkoxyallylboronate **5**.[8] We recognized that if intermediate **5**, or surrogates with different diol units on boron, could be induced to combine with a second aldehyde with control over the equatorial or axial nature of the substituent α to boron in the second allylboration transition state (cf., transition state **7** versus **8**),[9] then stereoselective access to **1** or **2** would be achieved.



This plan was probed by allowing the boryl-substituted allylborane **4** to react with a series of achiral aldehydes (Table 1). These reactions, performed by adding the aldehydes at −78 °C to a solution of the in situ generated reagent **4** and then allowing the reaction mixture to stir at ambient temperature for 24 h, provided the 1,5-*anti*-diols **9a**−**f** with ≥20:1 diastereoselectivity and 84−95% ee (Table 1). The 1,5-anti stereochemistry of diols **9a**−**f** was assigned by hydrogenation of the double bonds, thereby producing the optically active, C_2 symmetric saturated diols. The absolute stereochemistry of **9a**−**f** was assigned by using the Mosher method.[10] Thus, the allylboration of **5** proceeds with excellent selectivity by way of transition state **7**. Optimization studies (see Supporting Information) indicated that the chemical efficiency of this process is limited by the efficiency of the hydroboration of **3** and that effective yield of the allylborating agent **4** is in the range of 40−50% (based on **3**). In addition, use of 1.4 equiv of the aldehyde (based on **3**) is required to consume the intermediate α-substituted allylboronate **5** in the second allylboration step, thereby avoiding production of diol **6** after oxidative reaction workup.

Table 1. Syntheses of (*E*)-1,5-*anti*-Diols from a Single Aldehyde[a]



entry	R^1CHO	product[b]	%yield[c]	% ee[d]
1	$Ph(CH_2)_2CHO$	**9a**	38	91
2[e]	$Ph(CH_2)_2CHO$	*ent*-**9a**	42	92
3	$C_6H_{11}CHO$	**9b**	38	84
4	$(CH_3)_2CHCHO$	**9c**	34	82
5	$BnOCH_2CHO$	**9d**	42	92
6	PhCHO	**9e**	40	93
7[e]	PhCHO	*ent*-**9e**	42	95
8	$(CH_3)_3CCHO$	**9f**	34	92

[a] Reactions were performed by treating 1 equiv of **3** with Ipc_2BH (1 equiv) in Et_2O at 0 °C followed by the addition of 1.4 equiv of R^1CHO at −78 °C. The mixture was then allowed to stir at 23 °C for 24 h. The reactions were subjected to standard oxidative workup (NaOH, H_2O_2) before product isolation. [b] The diastereoselectivity in all cases was ≥20:1. [c] Yields are based on **3**. [d] Determined by the Mosher ester method. [e] *ent*-**4** was used in this experiment.

We next explored the use of two different aldehydes in the double allylboration reaction (Table 2). Optimal results were obtained when a −78 °C solution of **4**, prepared in situ by the hydroboration of allene **3**, was treated with 0.54 equiv of the first aldehyde (R^1-CHO). The mixture was stirred for 2 h at −78 °C, and then a full equivalent of the second aldehyde (R^2CHO) was added, and the mixture was allowed to warm to ambient temperature and stir for 24 h. This provided the 1,5-*anti*-diols **1a**−**e** with 20:1 diastereoselectivity, 89−95% ee, and in 65−87% yield based on R^1CHO as the limiting reagent. Small amounts (1−5%) of the 1,5-*anti*-diols **9** resulting from double allylboration of the second aldehyde (R^2-

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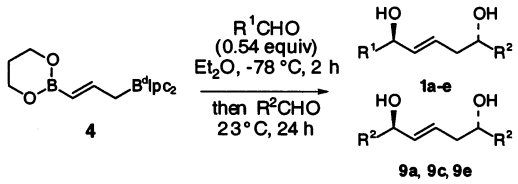
Table 2. Synthesis of (*E*)-1,5-*anti*-Diols from Two Aldehydes[a]



entry	R^1CHO	R^2CHO	product[b]	yield[c]	1:9[d]	% ee[e]
1	$(CH_3)_2CHCHO$	$Ph(CH_2)_2CHO$	**1a**	69	50:1	92
2	$Ph(CH_2)_2CHO$	PhCHO	**1b**	83	100:1	89
3	PhCHO	$Ph(CH_2)_2CHO$	**1c**	87	20:1	91
4	$C_6H_{11}CHO$	PhCHO	**1d**	74	100:1	96
5	PhCHO	$(CH_3)_3CCHO$	**1e**	65	50:1	95

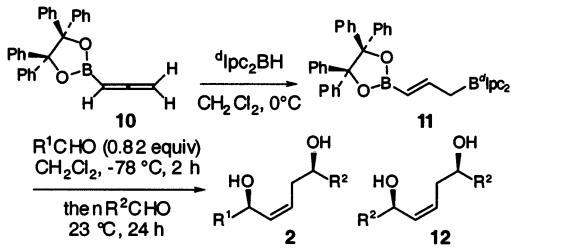
[a] Reagent **4** was prepared as described in Table 1. After the addition of R^1CHO (0.54 equiv) at −78 °C (2 h), 1 equiv of R^2CHO was added, and the mixture was then allowed to stir for 24 h at 23 °C. Reaction workup was performed as described in Table 1. [b] Diastereoselectivity in all cases was ≥20:1. [c] Yields are based on R^1CHO as the limiting reagent. [d] Product ratios determined by ^1H NMR analysis. [e] Determined by the Mosher ester method.

CHO) were also obtained. If smaller quantities of R^1CHO were used at the outset, greater amounts of 1,5-*anti*-diols **9** were obtained. Conversely, if greater amounts of R^1CHO were used, the products of double allylboration of the first aldehyde (R^1CHO) were produced. Thus, the relative rates of the two allylboration reactions are sufficiently different[11,12] that clean heterocoupling of two different aldehydes can be achieved, provided that the proper amount of R^1CHO relative to **4** is used.

On the basis of early studies published by Hoffmann,[9] we reasoned that if a bulky diol unit was incorporated in the starting allenylboronic ester, the second allylboration would proceed preferentially by way of transition state **8** with the substituent α to boron in an axial position, thereby providing stereoselective access to the 1,5-*syn*-diols **2** with an intervening (*Z*)-double bond. After screening several hindered diols, we determined that the tetraphenylethylene glycol ester in **10** and the derived allylborane **11** would nicely serve our purposes. Owing to the poor solubility of **10** in Et_2O, the hydroboration of **10** was performed in CH_2Cl_2 using 1.0 equiv of Ipc_2BH. The hydroboration of **10** is more efficient than that of **3**, as treatment of the in situ generated **11** with 2 equiv of $PhCH_2CH_2CHO$ provides the targeted (*Z*)-*syn*-1,5-diol **2a** in 72% yield, with an enantiomeric purity of 91% ee and diastereoselectivity of 14:1 (Table 3, entry 1). In addition, optimal conditions for the double allylboration of **11** using two different aldehydes were achieved by using 0.82 equiv of the first aldehyde (R^1CHO). Under these conditions, the ratio of the heterocoupled product **2** to the product **12** of homocoupling of the second aldehyde (R^2CHO) was 30:1. In all cases (entries 2−6, Table 3), the targeted 1,5-*syn*-diols **2** were obtained in 88−95% yield and 92−95% ee.

The level of selectivity reported here for the double allylboration reactions of reagents **4** and **11** is unprecedented. Although Hoffmann has previously reported that methallylboronates could be induced to react with the α-methyl substituent either in an equatorial or an axial position in the six-centered, chairlike allylboration transition state by changing the boronate ester, the level of selectivity achieved was only ca. 3:1 at best.[9] The exquisite control over the 1,5-diol relationships in **1** and **2** is a consequence of the pericyclic nature of the second allylboration step, in which the C−B stereochemistry

Table 3. Synthesis of (*Z*)-1,5-*syn*-Diols from Two Aldehydes[a]



entry	R^1CHO	R^2CHO	product[b,c]	yield[d]	% ee[e]
1[f]	$Ph(CH_2)_2CHO$	$Ph(CH_2)_2CHO$	**2a**	72	91
2	$(CH_3)_2CHCHO$	PhCHO	**2b**	88	92
3	PhCHO	$Ph(CH_2)_2CHO$	**2c**	95	95
4	$Ph(CH_2)_2CHO$	$(CH_3)_2CHCHO$	**2d**	92	94
5	$(CH_3)_2CHCHO$	$Ph(CH_2)_2CHO$	**2e**	95	95
6	$Ph(CH_2)_2CHO$	$C_6H_{11}CHO$	**2f**	91	94

[a] Reagent **11** was prepared in situ by hydroboration of **10** (1 equiv) with 1.0 equiv of Ipc_2BH in CH_2Cl_2 at 0 °C. R^1CHO (0.82 equiv) was added at −78 °C (2 h), followed by 1.7 equiv of R^2CHO. The mixture was then allowed to stir at 23 °C for 24 h. All reactions were then worked up as described in Table 1. [b] Diastereoselectivity in all cases was ≥14:1, and the ratio of **2** to **12** was ≥30:1 in all cases. [c] Product ratios determined by ^1H NMR analysis. [d] Yields are based on R^1CHO as the limiting reagent. [e] Determined by the Mosher ester method. [f] Reaction was performed by adding 2 equiv of $PhCH_2CH_2CHO$ to the reaction mixture at −78 °C, and then allowing the mixture to stir at ambient temperature for 24 h.

in **5** (or in the analogous substituted methallylboronate deriving from **11**) is transmitted to a new C−O stereocenter via transition states **7** and **8**. Thus, keys to the success of this method are the excellent stereocontrol in the allylboration step leading to **5**,[8] the stereospecificity of the subsequent allylboration reaction of **5** and the corresponding intermediate derived from **11**, and the ability of the diol auxiliary to induce equatorial or axial placement of the α-boryl substituent in transition states **7** and **8**.

Applications of this method in the synthesis of natural products will be reported in due course.

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Supporting Information Available: Experimental procedures, optimization studies, stereochemical assignments, and tabulated spectroscopic data for all new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Roush, W. R. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 2, p 1.
(2) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207.
(3) Chemler, S. R.; Roush, W. R. In *Modern Carbonyl Chemistry*; Otera, J., Ed.; Wiley-VCH: Weinheim, 2000; p 403.
(4) Taylor, N. H.; Thomas, E. J. *Tetrahedron* **1999**, *55*, 8757.
(5) Thomas, E. J. In *Stereocontrolled Organic Synthesis*; Trost, B. M., Ed.; Blackwell Scientific Publications: Oxford, 1994; p 235.
(6) Panek, J. S.; Yang, M. *J. Org. Chem.* **1991**, *56*, 5755.
(7) Xin, T.; Okamoto, S.; Sato, F. *Tetrahedron Lett.* **1998**, *39*, 6927.
(8) Brown, H. C.; Narla, G. *J. Org. Chem.* **1995**, *60*, 4686.
(9) Hoffmann, R. W.; Weidmann, U. *J. Organomet. Chem.* **1980**, *195*, 137.
(10) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092.
(11) Roush, W. R.; Banfi, L.; Park, J. C.; Hoong, L. K. *Tetrahedron Lett.* **1989**, *30*, 6457.
(12) Brown, H. C.; Racherla, U. S.; Pellechia, P. J. *J. Org. Chem.* **1990**, *55*, 1868.

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