the mixture was shaken in a test tube. The ^1H NMR of the sample was run at different intervals of time. In the case of low temperature studies, a 0.1-g sample (2.69×10^{-4} mol) of bis(4-chlorophenyl)selenium dichloride (VI) was dissolved in about 1 mL of acetone-d_6, which had been previously cooled to −50 °C. An equimolar amount of antimony(V) chloride was then added. A portion of the contents was transferred to a NMR tube. The whole operation was performed in a glovebag filled with nitrogen gas, and the NMR tube was always kept in a mixture of isopropyl alcohol and liquid nitrogen at −50 °C. The NMR tube was sealed, and the ^1H NMR spectra were run at the required temperatures which varied from −30 °C to 50 °C.

Acknowledgment. We are grateful to the State of Michigan's Research Excellence Fund and Occidental Chemical Corporation for support of this work.

Asymmetric Synthesis Using Tartrate Ester Modified Allylboronates. 1. Factors Influencing Stereoselectivity

William R. Roush,*[1] Lee K. Hoong, Michelle A. J. Palmer, and Jae Chan Park

Department of Chemistry, Indiana University, Bloomington, Indiana 47405, and Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02138

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A detailed study of the factors that influence the enantio- and diastereoselectivity of the reactions of tartrate allylboronate **1** with chiral and achiral aldehydes is reported. The stereoselectivity of these reactions is sensitive to variables such as reaction temperature (best results invariably are obtained at −78 °C), solvent (toluene is best for aliphatic aldehydes; THF is preferred for aromatic aldehydes), and moisture (use of molecular sieves is recommended to maintain an anhydrous reaction environment), but not on the structure of the tartrate ester. Tartrate allylboronate **1** has been found to be exceptionally reactive compared to other, previously studied allylboronates, and even the reactions of very hindered substrates (e.g., pivalaldehyde) are complete within several hours at −78 °C. An improved method for synthesis of **1** is described that involves the reaction of allylmagnesium bromide with $(iPrO)_3B$ followed by aqueous hydrolysis and esterification with DIPT. Yields of **1** are considerably higher (65–76%) by using this new procedure, and the crude reagent so prepared may be used directly in allylboration experiments. A simple method for standardizing solutions of **1** is described. Finally, the absolute stereochemistry of five homoallylic alcohols (**5a–e**) were assigned by correlation with epoxy alcohols prepared via the Sharpless asymmetric epoxidation. The results of these correlations are in complete agreement with the stereochemical picture presented in our 1985 publication.

The reactions of allyl- and crotylmetal reagents with chiral carbonyl compounds are of considerable interest in the context of acyclic diastereoselective synthesis.[2,3] Studies from several laboratories have shown that allyl- and crotylboron reagents are particularly attractive as enolate surrogates for the aldol-like construction of the 1,3-dimethyl-2-hydroxy and 1,3-diol units that occur with high frequency in macrolide, ansamycin, and other natural products of propiogenic/acetogenic biosynthetic origin.[3-7] Like the aldol reaction, however, double asymmetric synthesis using chiral reagents is often necessary to achieve synthetically useful levels of aldehyde diastereofacial selectivity.[3,8,9] The chiral allylboron reagents developed by Hoffmann[4] and Brown[5] are noteworthy in this respect, as are the highly enantioselective allylmetal reagents recently introduced by Masamune, Reetz, Hoppe, Riediker, and Corey, among others.[6]

We have contributed the diisopropyl tartrate modified allyl- and crotylboronates **1–3** to this rapidly evolving field.[7] These readily accessible and synthetically convenient reagents exhibit good to excellent enantioselectivity with achiral aliphatic aldehydes and, more importantly, function

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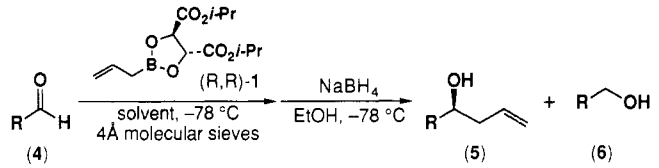
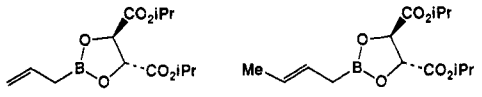
Table I. The Effect of 4-Å Molecular Sieves on Enantioselectivity[a]

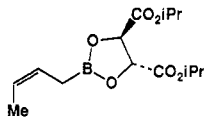


entry	RCHO	solvent	product	% yield	enantioselectivity (% ee) 4-Å sieves[b,c]	enantioselectivity (% ee) no sieves[d]
1	$C_6H_{11}CHO$ (**4a**)	toluene	(*S*)-**5a**	97	87 (87)	82
2	C_6H_5CHO (**4b**)	THF	(*S*)-**5b**	78	72	61
3	$C_{10}H_{19}CHO$ (**4c**)	toluene	(*R*)-**5c**	86	86 (79)	69
4	Me_3CCHO (**4d**)	toluene	(*S*)-**5d**	56	86 (82)	78

[a] All reactions were performed by adding neat RCHO to a −78 °C solution of distilled (*R,R*)-**1**; the initial concentration of the limiting reagent was 0.05 M. All reactions were quenched with $NaBH_4$ in EtOH prior to workup. [b] 4-Å sieves, typically 25–50 mg/mL, were used. [c] % ee's for **5a**, **5b**, and **5d** were determined by the chiral capillary GC method (ref 17), while the % ee of **5c** was determined by ^1H NMR analysis of the (*R*)-MTPA ester. The values in parentheses are % ee's determined by the Mosher ester analysis using the less enantiomerically pure (*S*)-MTPA reagent. [d] Determined by ^1H NMR analysis of the (*S*)-MTPA ester.

as highly diastereoselective chiral acetate and propionate enolate equivalents in reactions with chiral aldehydes.[7] Several applications of this methodology in the synthesis of complex targets have appeared.[7d,10]





We noted in our 1985 publication that best results for reactions with achiral aldehydes were obtained by using distilled **1** in toluene at −78 °C in the presence of 4-Å molecular sieves.[7a] Several results were presented that suggested that stereoselectivity was solvent and temperature dependent, but no clear diastereoselectivity pattern was apparent in the data that we reported for reactions with chiral aldehydes such as D-glyceraldehyde acetonide.[7a] This prompted us to undertake, and to report herein, a detailed study of the factors that influence stereoselectivity in order to define the optimum experimental conditions. Factors that were examined include the effect of 4-Å molecular sieves, reaction temperature, solvent, and the tartrate ester alkyl group on the reaction enantio- and diastereoselectivity. As a result of these efforts, several of the recommendations in our initial account have been modified, and previously published examples have been improved in several instances.

Results and Discussion

Enantiomeric Excess Determinations. At the outset of these investigations all % ee determinations were performed by NMR analysis (either ^1H or ^{19}F) of α-methoxy-α-(trifluoromethyl)phenylacetate (MTPA, or Mosher's ester) derivatives.[11,12] Because both enantiomers of α-methoxy-α-(trifluoromethyl)phenylacetic acid (MTPAA) were commercially available at equal cost and were presumed to be enantiomerically pure,[13] we arbitrarily selected (*S*)-(−)-MTPAA for use in our initial studies.[7a] Subsequent experimentation, however, revealed that the (*S*)-(−)-acid was only 94% ee,[14] causing us to suspect that our published data[7a] might be incorrect. This method also proved to be inconvenient for careful optimization studies that generated large numbers of samples owing to the dependence on the availability of high-field ^1H and ^{19}F NMR time.

These factors, among others,[15] prompted us to explore chiral capillary GC methods for the direct analytical resolution of the product homoallylic alcohols.[16] We investigated direct enantiomer resolution using the chiral nickel(II) bis(3-heptafluorobutyryl-(1*R*)-camphorate) (Ni-R-cam) and nickel(II) bis(heptafluorobutyryl-(1*R*,2*S*)-pinan-4-oate) (Ni-4-pin) capillary columns developed by Schurig,[16] but found that only the enantiomers of **5d** deriving from pivalaldehyde separated on these columns. All other homoallylic alcohols gave long retention times and broad, poorly resolved bands apparently due to overly strong complexation with the metal. These problems were solved, however, by using the methyl ether derivatives.[17]

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(11) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

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(13) The 1984–85 Aldrich Chemical catalog listed optical rotations of $[\alpha]^{20}_D \pm 72°$ for each of the enantiomeric Mosher's acids. More recent catalogs list $[\alpha]^{20}_D -70°$, corresponding to 94% ee, for the *S*-(−) enantiomer, and $[\alpha]^{20}_D +72°$, >98% ee, for the *R*-(+) enantiomer. The current catalog now also lists a more expensive and presumably purer (*S*)-(−)-MTPAA with an $[\alpha]^{18}_D$ of −72°.

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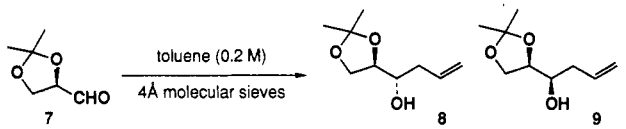
Table II. Influence of Temperature of the Enantioselectivity of the Reactions of (*S,S*)-1 and Cyclohexanecarboxaldehyde[a]

reactn temp, °C	enantioselectivity,[b] % ee	$\Delta\Delta G^{\ddagger}$, kcal/mol
25	50	0.65
0	57	0.70
-25	70	0.85
-50	82	1.02
-78	87	1.03

[a] All reactions were performed by adding neat RCHO to a solution of distilled (*S,S*)-1 in toluene (0.05 M) at the indicated temperatures in the presence of 4-Å sieves. All reactions were quenched with $NaBH_4$ in EtOH prior to workup. [b] Determined by the chiral capillary GC analysis of the derived methyl ethers (ref 17). (*R*)-**5a** is the major product of these reactions.

Scheme I



Temperature	Diastereoselectivity (8 : 9) with (R,R)-1	with (S,S)-1
25°C	93 : 7	36 : 64
0°C	94 : 6	30 : 70
-23°C	96 : 4	23 : 77
-78°C	98 : 2	7 : 93

This technique, described in detail elsewhere,[17] thus became a workhorse analytical method for the optimization studies described herein. It must be noted, however, that due to the temperature limits of the Ni-R-cam and Ni-4-pin chiral capillary columns, only relatively low molecular weight homoallylic methyl ethers can be resolved. The practical limit appears to be around the C_{14} alcohols. Enantiomeric excess determinations of less volatile or higher molecular weight homoallylic alcohols (e.g., **5c**, **5e**) were performed by using the Mosher ester technique (^1H or ^{19}F NMR, or capillary GC analysis of diastereomeric (*R*)-MTPA esters).

The Effect of 4-Å Molecular Sieves. We noted in our initial publication that enantioselectivity was improved when the asymmetric allylborations of **1** were preformed in the presence of 4-Å molecular sieves.[7a] Table I summarizes several experiments with achiral aldehydes that emphasize this point. The data in entries 3 and 4 for reactions of decanal and pivalaldehyde also illustrate the importance of analytical methods for the determination of % ee's. The % ee's previously reported for these reactions (79% and 82% ee, respectively, determined by the (*S*)-MTPA ester method)[7a] are lower than the actual values (86% ee).

We believe that the molecular sieves maximize enantioselectivity by maintaining an anhydrous reaction environment. This prevents adventitious hydrolysis of the moisture-sensitive chiral reagent to allylboronic acid which can function as a competitive, but achiral allyl transfer agent. Control experiments established that allylboronic acid readily reacts with aldehydes at -78 °C. Although we have found it possible to obtain excellent stereoselectivity in the absence of molecular sieves when **1**, the aldehyde, and the reaction solvent are each carefully purified immediately before use and all transfers are performed via syringe under an inert atmosphere, the reproducibility is not as good as when molecular sieves are included. *The use of molecular sieves allows for consistently high selectivities to be obtained, particularly when crude 1 is employed (vide infra).*

The Dependence of Stereoselectivity on Reaction Temperature. The temperature dependence of the asymmetric allylboration of cyclohexanecarboxaldehyde is summarized in Table II, while the effect of temperature on double asymmetric reactions with D-glyceraldehyde acetonide (**7**) appears in Scheme I. These data show that reaction selectivity is maximized by working at low temperatures, and that $\Delta\Delta G^{\ddagger}$ is also temperature dependent (Table II). We have interpreted the temperature dependence of $\Delta\Delta G^{\ddagger}$ in terms of conformational heterogeneity of the tartrate auxillary in the competing transition states.[18] Although the reaction of D-glyceraldehyde acetonide and (*R,R*)-1 (the "matched" case) is only moderately temperature sensitive, the mismatched case using (*S,S*)-1 is significantly so. Consequently, it is advisable that all asymmetric allylborations be performed at low temperature so as to maximize enantio- or diastereoselectivity.

Table III. Concentration Dependence of the Reaction of (*S,S*)-1 and D-Glyceraldehyde Acetonide (7)[a]

concentration of 1, M	diastereoselectivity (8:9)
0.1	6:94
0.2	7:93
1.0	11:89

[a] Allylborations were performed by adding neat **7** to a solution of distilled (*S,S*)-1 in toluene containing 4-Å sieves.

Table IV. Solvent Dependence of Enantioselectivity with Achiral Aldehydes[a]

RCHO	reagent	product	% ee toluene	Et_2O	THF	CH_2Cl_2
$C_6H_{11}CHO$ (**4a**)	(*S,S*)-1	(*R*)-**5a**	87	82	78	59
benzaldehyde (**4b**)	(*S,S*)-1	(*R*)-**5b**	60	59	72	59
(*E*)-decenal (**4e**)	(*S,S*)-1	(*R*)-**5e**	60	46	60	-

[a] All reactions were performed at -78 °C as described in Table I.

An intriguing observation made in our studies of the asymmetric allylboration of glyceraldehyde acetonide **7** is that the stereoselectivity proved to be dependent with an inverse relationship to the reaction concentration, at least when neat aldehyde was added to solutions of **1** at -78 °C (Table III). For this reason, most of our initial studies were performed at reaction concentrations of 0.05–0.2 M. We attribute this surprising effect to the high reactivity of **1** and the exothermicity of these reactions (vide infra). The net effect of the reaction exothermicity and "hot spots" resulting from the addition of neat, ambient temperature RCHO is that much of the reaction occurs at an *effective temperature* greater than -78 °C. This hypothesis is supported by our finding that the reaction stereoselectivity appears to be concentration independent when a solution of RCHO is added dropwise to a -78 °C solution of **1**. For cases where high stereoselectivity is difficult to achieve, we now recommend that a precooled solution of aldehyde be added slowly to a -78 °C solution of **1**.

The Dependence of Stereoselectivity on Reaction Solvent. Best results with aliphatic aldehydes (e.g., cyclohexanecarboxaldehyde, pivalaldehyde, decanal) were obtained when the reactions were performed in toluene (ca. 86–87% ee, Table I). Selectivity dropped slightly in ethereal solvents, enantioselectivity being a little higher in Et_2O than in THF, while significant decreases in enantioselectivity occurred in CH_2Cl_2 (Table IV). In contrast, α,β-unsaturated aldehydes (e.g., (*E*)-decenal, **4e**) exhibited comparable enantioselectivities in toluene and THF, but at a significantly lower level (60% ee) than observed with saturated aliphatic aldehydes. Lower levels of enantioselectivity were also realized with aromatic aldehydes. For

(18) Roush, W. R.; Banfi, L. *J. Am. Chem. Soc.* **1988**, *110*, 3979.

Table V. Solvent Dependence of Double Asymmetric Reactions with D-Glyceraldehyde Acetonide (7)[a]

solvent	dielectric constant	temp, °C	diastereoselectivity (8:9) with (*R*,*R*)-1	diastereoselectivity (8:9) with (*S*,*S*)-1
toluene	2.4	−78	98:2	7:93
CH_3CN	37.5	−30	–	28:72
CCl_4	2.2	−23	–	29:71
THF	7.5	−78	–	30:70
CH_2Cl_2	9.1	−78	96:4	39:61
Et_2O	4.3	−78	–	36:64
$CHCl_3$	4.8	−63	–	75:25

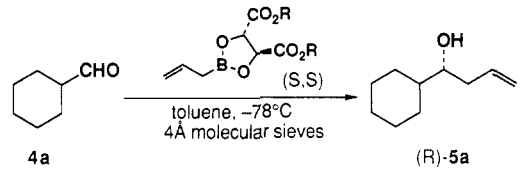
[a] All reactions were performed as described in Table I. Ratios of 8:9 were determined by capillary GC analysis as previously described (ref 7a).

example, the reaction of benzaldehyde (**4b**) in toluene at −78 °C provided **5b** in only 60% ee, but selectivity was somewhat improved in THF (72% ee). Similar levels of enantioselection (70–72% ee) are also realized with various para-substituted benzaldehydes (para-substituent = OMe, Me, Br, NO_2). The factors responsible for the low enantioselectivity with α,β-unsaturated and aromatic aldehydes is unclear at present, and studies directed toward the enhancement of enantioselectivity in these problematic cases have yielded some promising results.[19]

A detailed examination of the dependence of solvent on the diastereoselectivity of double asymmetric reactions with D-glyceraldehyde acetonide (**7**) has also been performed (Table V). These results show that the mismatched combination with (*S*,*S*)-**1** is particularly sensitive to solvent. There is no obvious relationship between reaction diastereoselectivity and solvent structure or dielectric constant, however, and it is striking that selectivity is again best in toluene. In fact, the vast majority of substrates, both chiral and achiral, that we have studied have given best results with **1**–**3** when the reactions are performed in toluene.[7] The only major exceptions to this generalization are the aromatic aldehydes that display highest enantioselectivity in THF (Table IV). Consequently, we regard toluene to be the solvent of choice for these reactions, and turn to other solvents (THF, Et_2O) only if poor results are obtained from initial exploratory experiments.

Effect of Tartrate Ester. The final variable that we probed was the effect of the tartrate ester group on enantioselectivity (Table VI). These results clearly demonstrate that the ester residue does not have a significant influence on reaction enantioselectivity, since all of the esters examined have given identical results within experimental error. We have also studied the matched and mismatched double asymmetric reactions of glyceraldehyde acetonide with the diethyl tartrate derived allylboronate **10**, and here also results were indistinguishable within experimental error to the optimized values presented in Scheme I for reactions with DIPT derived **1**. Assuming that the ester adopts an s-trans conformation in the reaction transition state, one would not expect the structure of the ester to influence reaction enantio- or diastereoselectivity, since the ester "R" group is positioned far from the site of developing asymmetry. This is in contrast to the asymmetric allenylborations reported by

Table VI. Dependence of Enantioselectivity on the Tartrate Ester[a]

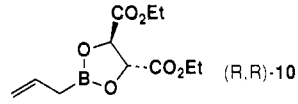


4a (R)-5a

R	% ee
i-Pr	86
Et	86
Me	84
cyclododecyl	86
2,4-dimethyl-3-pentyl	86

[a] All reactions were performed as described in Table III, with the exception that the reagents prepared from dimethyl tartrate, dicyclododecyl tartrate and bis(2,4-dimethyl-3-pentyl) tartrate were generated by treatment with triallylborane as described in ref 7a and were used without being purified by distillation.

Yamamoto, who has shown that enantioselectivity increases as the steric bulk of the tartrate ester alkyl group increases.[20] This reinforces our previous conclusion that the asymmetric allyl- and allenylborations have different mechanisms of asymmetric induction.[7a]



(R,R)-10

Given that the tartrate ester does not influence reaction stereoselectivity, the choice of tartrate to use in the synthesis of the chiral allylboronate is arbitrary, and we have routinely employed DIPT for these purposes. On several occasions, however, we have found it desirable to use DET-derived allylboronates (e.g., **10**) in order to take advantage of the different chromatographic properties of DET compared to DIPT in the purification of sensitive reaction products that do not withstand the hydrolytic workup described in the Experimental Section.

A final point concerns nomenclature. In our initial publication we referred to the allylboronates by their optical rotations.[7a] Thus, the reagent prepared from L-(+)-DIPT had a negative rotation and was therefore identified as (−)-**1**. This system is inherently confusing owing to the reversal of sign of the reagent compared to the tartrate precursor, and so we now identify the allylboronates by the absolute configuration of the tartrate residue. Since the absolute configuration of L-(+)-DIPT, the so-called "natural" tartrate ester, is *R*,*R*, the derived allylboronate is (*R*,*R*)-**1**.

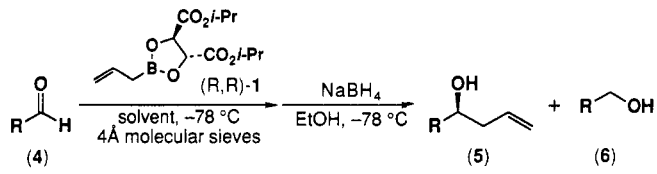
Qualitative Reaction Rates. The reactions of aldehydes and various substituted allylboronates had been extensively studied by Hoffmann prior to the initiation of our efforts in this area.[9a,21] The available data suggested, and indeed our experience with the pinacol allyl and crotylboronates confirmed,[9b] that the pinacol esters react sluggishly with aldehydes even at room temperature. We initially presumed, therefore, that **1** would also exhibit low reactivity with aldehydes especially at low temperatures. We quickly discovered, however, that the reactions of **1** were significantly faster than had been anticipated. Indeed, the reactions of **1** and achiral aldehydes at −78 °C proved to be so fast that it was difficult to obtain data

(19) We have observed that the asymmetric allylboration of benzaldehyde–$Cr(CO)_3$ complex in toluene provides (*S*)-**5b** (from (*R*,*R*)-**1**) in 84% ee, while the asymmetric allylboration of the $Co_2(CO)_6$ complex of 2-decynal (toluene, −78 °C) proceeds in a remarkable 92% ee (2-decynal itself reacts with only 70% ee under these conditions). The reactions of these substrates with the chiral (*E*)-crotylboronate are even more selective (92% and 96% ee, respectively): Roush, W. R.; Park, J. C. *J. Org. Chem.* **1990**, *55*, 1143.

(20) (a) Haruta, R.; Ishiguro, M.; Ikeda, N.; Yamamoto, H. *J. Am. Chem. Soc.* **1982**, *104*, 7667. (b) Ikeda, I.; Isao, A.; Yamamoto, H. *J. Am. Chem. Soc.* **1986**, *108*, 483.

(21) Hoffmann, R. W.; Zeiss, H.-J. *J. Org. Chem.* **1981**, *46*, 1309.

Table VII. Qualitative Rate Profiles of the Reactions of Tartrate Allylboronate 1 and Achiral Aldehydes[a]



RCHO (4)	concn [RCHO], M	solvent	quench,[b] min	convn[c] (5:6)
$C_6H_{11}CHO$ (4a)	0.05	toluene	5	92:8
			10	94:6
			25	99:1
4a	0.05	THF	30	32:68
			90	66:33
C_6H_5CHO (4b)	0.05	THF	5	63:37
			10	78:22
			30	94:6
$C_{10}H_{19}CHO$ (4c)	0.05	toluene	5	50:50
			10	80:20
			30	100:0
Me_3CCHO (4d)	0.05	toluene	5	9:91
			10	24:76
			30	50:50

[a] Reactions were preformed by adding neat RCHO to a −78 °C solution of 1 (1.2–1.5 equiv). The initial concentration of RCHO was 0.05 M. [b] Reactions were quenched with excess $NaBH_4$ in EtOH and then were worked up by the hydrolytic procedure described in the Experimental Section. [c] The ratio of 5 to 6 was determined by capillary GC analysis.

points at less than 50% conversion, even when the reactions were performed at 0.05 M (Table VII)! These prodigious rates precluded the removal of aliquots from the reaction mixture for quenching and then product analysis, so a series of "identical" reaction mixtures were run side by side and terminated individually by the addition of an excess of precooled (−78 °C) $NaBH_4$ in EtOH to reduce any unreacted aldehyde. The data in Table VII were generated in this way.

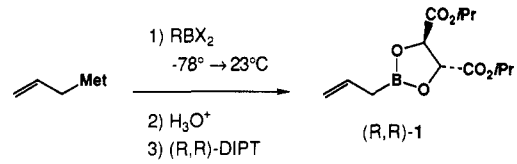
These data show that the reactions of 1 and achiral aldehydes are faster in toluene than in THF and that the relative reactivity of the four aldehydes studied is C_6H_5CHO > $C_6H_{11}CHO$ > $C_{10}H_{19}CHO$ > Me_3CCHO (solubility problems were encountered with $C_{10}H_{19}CHO$ which tended to freeze when added neat to −78 °C solutions of 1). By way of comparison, the reaction of pinacol allylboronate and $C_6H_{11}CHO$ under analogous conditions (0.1 M, toluene, −78 °C) proceeds to only 4% conversion after a 72 h period, while at −25 °C this reaction is only 42% complete after 20 h![22,23] We attribute the tremendous rate acceleration associated with the tartrate auxiliary to the inductive effect of the CO_2iPr groups that increase the Lewis acidity of the boron atom, thereby increasing the rate of complexation of the allylboronate and aldehyde. Evidence supporting this argument is presented elsewhere.[22]

Questions remained, however, that the $NaBH_4$–EtOH quench was a reliable method for the *rapid* reduction of unconsumed RCHO at −78 °C.[23] In order to verify that the data in Table I provide a reasonable, qualitative description of the reactivity of 1, a parallel series of experiments was performed by using DIBAL-H to quench the

(22) Roush, W. R.; Banfi, L.; Park, J. C.; Hoong, L. K. *Tetrahedron Lett.* **1989**, *30*, 6457.

(23) An independent study of the influence of solvent and diol unit on allylboronate reactivity have been performed by Professor H. C. Brown and his group (*J. Org. Chem.*, submitted). We thank Professor Brown for discussions of these and related topics.

Table VIII. Preparation of Tartrate Allylboronate 1[a]



entry	organometallic reagent	RBX_2	solvent	% yield[b]	% ee[c]
1	allylmagnesium bromide	$(iPrO)_3B$	Et_2O	65–76[d]	83–88 (86)
2	allylmagnesium bromide	$(MeO)_3B$	Et_2O	51[d]	85
3	allylmagnesium bromide	$(MeO)_3B$	Et_2O	30–44[e]	83–88 (86)
4	allylmagnesium bromide	$(MeO)_3B$	THF	36–39[e]	–
5	allylmagnesium bromide	$(MeO)_2BF$	Et_2O	35–46[d]	–
6	allyllithium	$(iPrO)_3B$	Et_2O	35–56[e]	–
7	allyllithium	$(MeO)_2BF$	Et_2O	17[d]	–
8	allylpotassium[f]	$(iPr_2O)_3B$	THF	47[d]	85
9	allylpotassium[f]	$(MeO)_2BF$	THF	27–43[d]	–

[a] All reactions were performed with equimolar amounts of the organometallic and RBX_2. [b] Yield of 1 determined by the titration procedure discussed in text. [c] % ee of reactions with cyclohexanecarboxaldehyde (4a) in toluene at −78 °C. The values in parentheses are the averages of repeated experiments with crude 1 prepared according to the specified methods. [d] The extracts containing allylboronic acid were immediately treated with DIPT and then dried over $MgSO_4$. [e] The extracts containing allylboronic acid were dried over $MgSO_4$, concentrated in vacuo, redissolved in Et_2O, and then treated with DIPT. [f] Allylpotassium was prepared by treatment of propene (2.5 equiv) with *n*-BuLi/KOtBu (1.0 equiv each) in THF at −50 °C for 3 h (see ref 25).

allylborations of $C_6H_{11}CHO$. *Essentially identical results (% conversions) were obtained for experiments in toluene and THF quenched with either DIBAL-H or $NaBH_4$ at −78 °C.* That the DIBAL-H reduction of $C_6H_{11}CHO$ is extremely rapid at −78 °C was verified by two control experiments. First, a 0.05 M solution of $C_6H_{11}CHO$ in toluene at −78 °C was treated with an excess of DIBAL-H and then quenched 1 min later with a large excess of MeOH to consume unreacted DIBAL-H. GC analysis of this mixture revealed that >98% of the aldehyde had been reduced. Second, a solution of DIBAL-H in toluene at −78 °C was treated with an excess of MeOH and then 1 min later was treated with the standard amount of $C_6H_{11}CHO$. Capillary GC analysis of this mixture revealed that only 1% of the aldehyde had been reduced. Thus, the reactions of tartrate allylboronate 1 and aldehydes are indeed extremely rapid at −78 °C.

Improved Preparation of Tartrate Allylboronate 1. Virtually all of the studies described in the preceding sections were performed by using 1 that had been purified by distillation.[7a] We observed over the course of these investigations, however, that the yield of distilled 1 varied from batch to batch owing to decomposition that was particularly problematic during large-scale distillations, especially when the bath temperature exceeded 100–110 °C for extended periods of time. We were delighted to discover, therefore, that crude, undistilled 1 gives excellent results in aldehyde allylborations as long as molecular sieves are also employed. This prompted us to reexamine and optimize the preparation of 1 for use directly in the aldehyde addition reactions, thereby avoiding the distillation step.

Since we wished to employ crude 1 in the allylboration process, it was necessary to devise a method of determining the amount of 1 present in any batch. This was easily accomplished by dissolving crude 1 in a known volume of toluene (or THF) and then treating an aliquot with a

known excess of cyclohexanecarboxaldehyde (**4a**) at 23 °C. This reaction ("titration") was quenched with $NaBH_4$ in EtOH, and then the ratio of cyclohexylmethanol (**6a**) to homoallyl alcohol **5a** was determined by capillary GC. The molarity of these solutions can be calculated from this ratio, as well as the yield of **1** if the total volume is known. The data that appear in Table VIII were generated in this way.

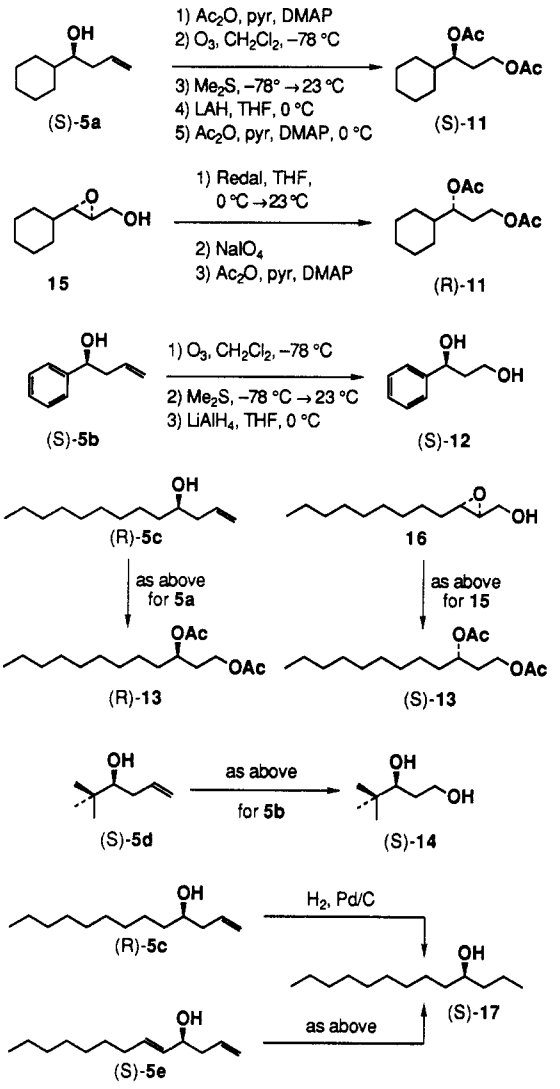
By using this titration procedure, we discovered that the effective yield of **1** prepared according to the original method (treatment of allylmagnesium bromide with $(MeO)_3B$ in Et_2O) was only 30–44% (based on allylmagnesium bromide), with some variation occurring from run to run (Table VIII, entry 3). Several modifications of this procedure were examined, and ultimately a superior method for the synthesis of **1** was developed.

The most efficient method for the synthesis of **1** now involves the reaction of triisopropylborate and allylmagnesium bromide in Et_2O followed by an extractive workup and direct esterification with DIPT (entry 1).[24] Yields of crude reagent consistently in the 65–76% range, and occasionally even higher, have been obtained. Other organometallic reagents (e.g., allyllithium or allylpotassium,[25] entries 6–9) and other electrophilic boron reagents [$(MeO)_3B$ or $(MeO)_2BF$] gave considerably lower yields. Another important variable is the handling of the intermediate allylboronic acid that is unstable toward aerial oxidation. Consistently best results have been obtained when the extracts containing allylboronic acid are blanketed with argon and treated immediately with DIPT prior to drying with $MgSO_4$. Yields are 10–20% lower when the allylboronic acid containing extracts are dried and concentrated before exposure to DIPT (compare entries 2 and 3). Tartrate allylboronate **1** is considerably more stable than the boronic acid, and no special precautions are taken in its handling other than to blanket its solutions with argon during filtration, rotary evaporation, etc. (see the Experimental Section).

Crude allylboronate **1** so prepared is reasonably stable—when anhydrous—and has been stored in a −20 °C freezer under argon for 1–2 months with little noticeable deterioration. However, since reactions with the majority of aldehydes are most selective when performed in toluene (THF for aromatic substrates, vide supra), we have found it more convenient to store **1** as a solution in toluene (or THF) at −20 °C. This greatly facilitates transfer of known quantities for individual experiments, and the titration procedure described above provides a convenient means of restandardizing solutions that have been stored for extended periods of time.

The final column of Table VIII provides evidence that the enantioselectivity of crude **1** is virtually indistinguishable from that of the distilled reagent. The experiments summarized in entries 1 and 3 have been performed dozens of times, and the range of enantioselectivity determined through standard reactions with cyclohexanecarboxaldehyde is 83–88% ee. The most frequently encountered values are 86–87% ee, identical with the best obtained by using purified **1** under optimized conditions. Nevertheless, it is conceivable that substrates may be encountered for which best results will be obtained by using distilled rather than crude **1**. Thus, while we now routinely employ crude **1** in our synthetic studies, consumers of this technology should use distilled **1** whenever a substrate is encountered for which high stereoselectivity proves difficult to achieve. Reagent **1** prepared by this new procedure has been distilled on a 25-mmol scale without complication (see the Experimental Section).

Scheme II. Absolute Stereochemical Assignments for Homoallylic Alcohols 5a–e



Absolute Stereostructural Assignments. The absolute stereochemistry of homoallylic alcohols **5a**, **5b**, and **5d** were assigned originally by comparison of optical rotations with literature values.[26] These assignments, as well as those for **5c** and **5e** deriving from decanal and 2-decenal were verified by the correlation studies summarized in Scheme II. Thus, (*S*)-**5a**, (*S*)-**5b**, (*R*)-**5c**, and (*S*)-**5d**, each deriving from asymmetric allylborations using (*R*,*R*)-**1**, were converted to the corresponding 1,3-diols or diacetates (*S*)-**11**, (*S*)-**12**, (*R*)-**13**, and (*S*)-**14** by a standard ozonolytic sequence. 1,3-Diacetates **11** and **13** were correlated with authentic reference samples prepared by the Red-Al (Aldrich) reduction[27] of epoxy alcohols **15** and **16** prepared by the Sharpless asymmetric epoxidation using (*R*,*R*)-DIPT as the chiral auxiliary.[28,29] In both cases, the 1,3-

(24) For an earlier study on the optimization of boronic ester synthesis, see: Brown, H. C.; Cole, T. E. *Organometallics* **1983**, *2*, 1316.

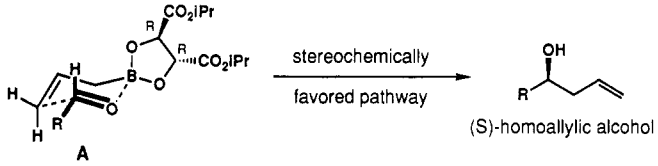
(25) Prepared by the general procedure of: Schlosser, M.; Fujita, K. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 309. Fujita, K.; Schlosser, M. *Helv. Chim. Acta* **1982**, *65*, 1258.

(26) (a) Brown, H. C.; Jadhav, P. K. *J. Am. Chem. Soc.* **1983**, *105*, 2092. (b) Bartlett, P. A.; Johnson, W. S.; Elliott, J. D. *Ibid.* **1983**, *105*, 2088.

(27) For the Red-Al reduction of 2,3-epoxy alcohols: (a) Ma, P.; Martin, V. S.; Masamune, S.; Sharpless, K. B.; Viti, S. M. *J. Org. Chem.* **1982**, *47*, 1378. (b) Minami, N.; Ko, S. S.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 1109. (c) Viti, S. M. *Tetrahedron Lett.* **1982**, *23*, 4541.

diacetates 11 and 13 deriving from the allylboration sequence proved to be enantiomeric to samples prepared via the Sharpless asymmetric epoxidation. Similarly, (*R,R*)-1 derived 1,3-diols (*S*)-12 and (*S*)-14 proved to be enantiomeric, by optical rotation comparison, to materials that Masamune and co-workers had already prepared by Redal reduction of (*R,R*)-DIPT derived Sharpless epoxy alcohols.[30] Finally, (*R,R*)-1 derived homoallylic alcohols (*R*)-**5c** and (*S*)-**5e** were correlated by hydrogenation of each to (*S*)-tridecan-4-ol ((*S*)-**17**).

The sense of asymmetric induction in each of these reactions is the same: *an (S)-alcohol is produced preferentially from the reactions of (R,R)-tartrate derived allylboronates, assuming that the "R" substituent of the aldehydic substrate, RCHO, takes priority over the allyl group that is transferred.* In fact, no exceptions to this generalization have yet been found in over 40 well-characterized cases where the tartrate auxiliary controls the stereochemical outcome of the allyl or crotyl transfer (in the case of crotylboronates 2 and 3).[7,10] The stereochemistry induced by the tartrate auxiliary, therefore, is defined by transition state paradigm A as previously deduced.[7a]



Concluding Remarks

We have shown that the tartrate allylboronate 1 is an easily prepared and reasonably enantioselective allyl transfer reagent. Reaction variables and structural features that influence enantio- or diastereoselectivity have been defined. While 1 remains one of the most synthetically accessible chiral allylmetal reagents reported to date, its enantioselectivity characteristics are somewhat lower than that of other chiral allylmetal reagents.[4-6] Additional studies directed toward the improvement of enantioselectivity especially with the problematic substrate classes are in progress and will be reported upon in due course.[18,19]

Experimental Section

General. ^{1}H NMR spectra were measured at 250, 300, and 500 MHz. ^{19}F NMR spectra were obtained at 376.3, 338.7, or 282.2 MHz and were referenced with external 4-bromobenzotrifluoride (δ −63.31 ppm in $CDCl_3$). Low- and high-resolution mass spectra were measured at 70 eV.

All reactions were conducted in oven-dried (125 °C) or flame-dried glassware under atmospheres of dry argon or nitrogen. All solvents were purified before use. Ether, THF, and toluene were distilled from sodium benzophenone ketyl. Methylene chloride was distilled from CaH_2.

Gas chromatographic analyses, including the determination of % ee's via the separation of diastereomeric MTPA esters, were carried out using a capillary gas chromatograph equipped with 50 m × 0.25 mm Bonded FSOT Carbowax 20M. Chiral capillary GC % ee determinations of methyl ethers were performed by using 25 m × 0.25 mm 10% nickel(II) bis(3-heptafluorobutyryl-(1*R*)-camphorate)/OV-1 [Ni-R-Cam] or 25 m × 0.25 mm 10% nickel(II) bis (heptafluorobutyryl-(1*R*,2*S*)-pinan-4-oate)/OV-1 [Ni-4-Pin] chiral capillary columns.[17]

Analytical thin-layer chromatography (TLC) was performed by using 2.5 cm × 10 cm plates coated with a 0.25-mm thickness of silica gel containing PF 254 indicator (Analtech). Preparative thin-layer chromatography (PTLC) was performed by using 20 cm × 20 cm plates coated with 0.25- or 0.5-mm thickness of silica gel containing PF254 indicator (Analtech). Flash chromatography was performed as described by Still,[31] by using Kieselgel 60 (230–400 mesh) or Kieselgel 60 (70–230 mesh). Unless otherwise noted, all compounds were purified by chromatography are sufficiently pure (> 95% by ^{1}H NMR analysis) for use directly in subsequent transformations.

Optimized Procedure for the Preparation of Diisopropyl 2-Allyl-1,3,2-dioxaborolane-4,5-dicarboxylate (Tartrate Allylboronate (1)). Solutions of triisopropyl borate (40 mmol) in 10 mL of dry Et_2O and allylmagnesium bromide in Et_2O (40.0 mmol, 0.87 M) were added dropwise simultaneously, but separately, to 10 mL of dry Et_2O at −78 °C. This mixture was stirred for 0.5 h at −78 °C, allowed to warm to room temperature, and stirred for 3 h. The slurry was recooled to 0 °C, and then 40 mmol of aqueous HCl (1 N solution saturated with NaCl) was added dropwise over a 15-min period. The mixture was warmed to room temperature, and stirring was continued for 10 min. The organic layer was separated and directly treated with 40 mmol of (*R,R*)-DIPT. The aqueous phase was extracted with 5:1 Et_2O–CH_2Cl_2 (3 × 50 mL). The combined organic layers were stirred over anhydrous $MgSO_4$ for 2.5 h and then filtered under Ar. The filtrate was concentrated in vacuo to give a clear, colorless, semiviscous liquid. Dry toluene was added to give 50.0 mL of a clear solution. A 1-mL aliquot of the solution of crude reagent was treated with 4-Å molecular sieves. After being stirred for 15 min at room temperature, a known excess of cyclohexanecarboxaldehyde was added. The reaction was quenched 15 min later with excess $NaBH_4$ in EtOH, stirred for 30 min, and then diluted with 1:1 Et_2O/1 M NaOH. The organic layer was separated, dried over anhydrous Na_2SO_4, and then analyzed by capillary GC (50 m × 0.25 mm Bonded FSOT Carbowax 20M; 100 °C/4 min → 10 °C/min → 190 °C) for cyclohexylmethanol (**6a**) (t_R 7.6 min) and 1-cyclohexylbut-3-en-1-ol (**5a**) (t_R 9.6 min).[32] The yield of this particular batch of crude reagent was found to be 86% (yields in the range of 65–75% are typical), and the concentration of the standardized solution was calculated to be 0.7 M. Reagent 1 prepared in this way has been distilled (bp 88–90 °C, 0.03 mmHg) efficiently on a 25-mmol scale without decomposition.

Enantioselective Allylborations of Aldehydes. The general procedure described in our initial publication was followed,[7a] with the exception that reaction times were typically 2–3 h. Analytical-scale reactions were terminated by adding an excess of $NaBH_4$ in EtOH (precooled to the reaction temperature), while most preparative-scale experiments were directly diluted with aqueous NaOH to hydrolyze the tartrate ester. This two-phase mixture was stirred for 1–3 h, and then the product homoallylic alcohols were isolated by a standard extraction sequence and were purified chromatographically. In cases where the product homoallylic alcohols are sensitive to and do not survive the alkaline hydrolysis step, the tartrate ester may be removed either by H_5IO_6 cleavage or by chromatography. Compounds **5a**,[26b] **5b**,[4b] **5d**,[4b] 8, and **9**[7a] are previously known.

(*S*)-1-Cyclohexylbut-3-en-1-ol (5a): $[\alpha]^{20}_D$ −8.7° (*c* = 0.54, absolute EtOH) [lit.[26b] $[\alpha]^{25}_D$ −7° (EtOH)] for 64% ee (*S*)-**5a**; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.90–5.73 (m, 1 H), 5.18–5.11 (m, 2 H), 3.37 (m, 1 H), 2.4–2.25 (m, 1 H), 2.2–2.05 (m, 1 H), 1.9–1.5 (series of m, 6 H), 1.45–0.9 (series of m, 6 H); IR (neat) 3410 (br), 3075, 2925, 2855, 1640, 1450, 1035, 984, 910 cm^{-1}.

(*S*)-1-Phenylbut-3-en-1-ol (5b): $[\alpha]^{20}_D$ −30.8° (*c* = 1.9, benzene) [lit.[4b] $[\alpha]^{20}_D$ −44.9° (*c* = 7.38, benzene)] for 96% ee (*S*)-**5b**; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.35–7.20 (m, 5 H), 5.8 (m, 1 H), 5.21–5.12 (m, 2 H), 4.74 (t, *J* = 6.6 Hz, 1 H), 2.60–2.40 (m, 2 H); IR (neat) 3380 (br), 3075, 3030, 2980, 2935, 2910, 1641, 1493, 1455,

(28) (a) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974. (b) Hill, J. G.; Sharpless, K. B.; Exon, C. M.; Regenye, R. *Org. Synth.* **1984**, *63*, 66. (c) Rossiter, B. E. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1985; Vol. 5, p 193. (d) Finn, M. G.; Sharpless, K. B. *Ibid.*, Vol. 5, p 247.

(29) We thank Dr. R. L. Halterman for providing us with >95% ee samples of epoxy alcohols **15** and **16**, each (*R,R*)-DIPT derived, for use in these correlation studies.

(30) Masamune, S.; Sato, T.; Kim, B. M.; Wollmann, T. A. *J. Am. Chem. Soc.* **1986**, *108*, 8279. Physical constants and other data pertaining to the synthesis of (*R*)-12 and (*R*)-14 appear in the Supplementary Material accompanying this paper.

(31) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

(32) This GC analysis was calibrated by using known mixtures of **5a** and **6a**, ranging from 10:90 to 90:10, respectively. The data reported in text (Table VIII) are uncorrected since the calibration studies revealed only slight deviation between the actual and observed values.

1198, 1043, 1000, 915, 870, 757, 700 cm^{-1}.

(*R*)-Tridec-1-en-4-ol (5c): $[\alpha]^{20}_D$ +5.3° (*c* = 1.2, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 5.89–5.73 (m, 1 H), 5.17–5.10 (m, 2 H), 3.61 (br m, 1 H), 2.35–2.23 (m, 1 H), 2.17–2.08 (m, 1 H), 1.54 (d, *J* = 3.9 Hz, 1 H), 1.50–1.35 (br m, 3 H), 1.35–1.20 (br m, 13 H), 0.86 (t, *J* = 6.1 Hz, 3 H); IR (neat) 3360 (br), 3080, 2935, 2860, 1645, 1465, 900 cm^{-1}; mass spectrum, *m/z* 157 (M^+ – 41). Anal. Calcd for $C_{13}H_{26}O$: C, 78.72; H, 13.21. Found: C, 78.86; H, 13.06.

(*S*)-2,2-Dimethylhex-5-en-3-ol (5d): $[\alpha]^{20}_D$ –3.8° (*c* = 1.5, benzene) [lit.[4b] $[\alpha]^{20}_D$ –9.8° (*c* = 11.9, benzene)] for 83% ee (*S*)-**5d**; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.74 (m, 1 H), 5.20–5.10 (m, 2 H), 3.26 (d, *J* = 11.1 Hz, 1 H), 2.40–2.33 (m, 1 H), 2.04–1.93 (m, 1 H), 1.59 (br s, 1 H, OH), 0.88 (s, 9 H); IR (neat) 3435 (br), 3075, 2985, 2909, 2870, 1640, 1480, 1433, 1395, 1364, 1293, 1210, 1070, 1007, 990, 910, 861, 770 cm^{-1}.

(*R*)-Trideca-1,5-dien-4-ol (5e) (obtained from the reaction with (*S,S*)-(1) in THF): $[\alpha]^{20}_D$ +1.7°, $[\alpha]^{20}_{546}$ +2.7° (*c* = 0.52, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 5.86–5.72 (m, 1 H), 5.70–5.60 (m, 1 H), 5.51–5.44 (dd, *J* = 9.0 Hz, *J* = 15.0, 1 H), 5.16–5.10 (m, 2 H), 4.15–4.08 (br m, 1 H), 2.36–2.20 (m, 2 H), 2.02 (q, *J* = 7.20 Hz, 2 H), 1.56 (d, *J* = 4.5 Hz, 1 H), 1.38–1.26 (m, 10 H), 0.88 (t, *J* = 6.0 Hz, 3 H); IR (neat) 3440 (br), 3079, 2980, 2960, 2929, 2859, 1740, 1641, 1469, 1376, 1255 (br), 1105 (br), 995, 970, 911, 825, 721 cm^{-1}; high-resolution mass spectrum [CI] for $C_{13}H_{23}O$ (M^+ – 1) calcd 195.1749, found 195.1756; calcd for $C_{13}H_{23}$ (M^+ – 17) 179.1800, found 179.1797. Anal. Calcd for $C_{13}H_{24}O$: C, 79.53; H, 12.32. Found: C, 79.69; H, 12.23.

(*S*)-3-Cyclohexyl-1,3-diacetoxypropane (11). A solution of (*S*)-**5a** (70 mg, 0.46 mmol) in 1.0 mL of distilled pyridine was treated with 5.3 mmol of acetic anhydride in the presence of DMAP at 0 °C. After being stirred at 0 °C for 1 h, the mixture was allowed to warm to room temperature and stirred overnight. The mixture was concentrated in vacuo followed by repeated coevaporation with heptane to remove residual pyridine, Ac_2O, and acetic acid. The crude product so obtained was purified by PTLC (2 × 0.5 mm plates) using 3:1 hexane–Et_2O as eluant to give 45 mg (50% yield) of (*S*)-1-acetoxy-1-cyclohexylbut-3-ene as a clear, colorless liquid: $[\alpha]^{25}_D$ +15.7°, $[\alpha]^{25}_{546}$ +18.2° (*c* = 1.15, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 5.80-5.66 (m, 1 H), 5.08–5.01 (m, 2 H), 4.80–4.72 (m, 1 H), 2.39–2.19 (m, 2 H), 2.02 (s, 3 H), 1.76–1.41 (series of m, 6 H), 1.29–0.92 (series of m, 5 H); IR (neat) 3070, 2930, 2850, 1740, 1640, 1445, 1365, 1235, 1015, 910 cm^{-1}; high-resolution mass spectrum [CI] for $C_{12}H_{21}O_2$ (M^+ + 1) calcd 197.1541, found 197.1585; calcd for $C_{10}H_{17}$ (M^+ – 59) 137.1330, found 137.1325. Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.46; H, 10.43.

A –78 °C solution of 37 mg (0.19 mmol) of the above acetate in 10 mL of dry CH_2Cl_2 was treated with a stream of O_3 until the reaction mixture turned blue (4 min). The system was then flushed with O_2 to remove excess ozone. Me_2S (1 mL, 13.6 mmol) was added, and the mixture was allowed to warm to room temperature. Solvent was removed in vacuo, and the crude ozonide was dissolved in 10 mL of dry THF. The resulting mixture was cooled to 0 °C before 2.8 mmol of $LiAlH_4$ was added. After being stirred for 30 min, the reaction was quenched with 0.25 mL of H_2O followed by 0.75 mL of 1 N NaOH. The resulting white slurry was filtered through Celite, and the clear, colorless filtrate was dried over anhydrous Na_2SO_4. Filtration followed by concentration in vacuo gave 37 mg of crude material that was dissolved in 1 mL of pyridine. The solution was cooled to 0 °C and DMAP and 5.3 mmol of acetic anhydride were added. The mixture was stirred for 14 h, then was concentrated in vacuo and repeatedly coevaporated with heptane to remove pyridine, acetic acid, and excess Ac_2O. The resulting crude product was purified by PTLC (0.5-mm silica gel plate) using 3:1 hexane–Et_2O as eluant, providing 20 mg (47% overall yield) of the desired diacetate (*S*)-**11**: $[\alpha]^{20}_D$ –24.9° (*c* = 0.35, CH_2Cl_2); ^1H NMR ($CDCl_3$, 300 MHz) δ 4.86–4.79 (m, 1 H), 4.07–4.02 (m, 2 H), 2.02–0.82 (series of overlapping s and m, 19 H); IR (neat) 2920, 2850, 1740, 1450, 1365, 1230, 1040 cm^{-1}; high-resolution mass spectrum [CI] for $C_{13}H_{23}O_4$ (M^+ + 1) calcd 243.1596, found 243.1604. Anal. Calcd for $C_{13}H_{22}O_4$: C, 64.44; H, 9.15. Found: C, 64.50; H, 9.26.

Synthesis of (*R*)-11 via the Red-Al Reduction of Epoxy Alcohol 15.[27] A solution of 108 mg (0.53 mmol) of epoxy alcohol **15** [(*R,R*)-DIPT derived][28,29] in 6 mL of dry THF was cooled to 0 °C. The solution was treated with 1.36 mmol of Red-Al (3.4 M in toluene) and stirred for 2 h at 0 °C before being allowed to warm to room temperature. The mixture was stirred for another 2 h and then was treated with 5 mL of H_2O followed by 5 mL of Et_2O. The organic layer was separated and washed sequentially with 1 M HCl, saturated $NaHCO_3$, and saturated NaCl after which it was dried over anhydrous Na_2SO_4. The solution was filtered and concentrated in vacuo to give 108 mg of crude material that was dissolved in 6 mL of 5:1 THF–H_2O and treated with 1.42 mmol of $NaIO_4$. A white slurry formed after 5 min, and the mixture was stirred overnight. It was then treated with 1 g of anhydrous Na_2SO_4 followed by 5 mL of Et_2O and 3 mL of CH_2Cl_2. The resulting mixture was filtered through a pad of cotton and then concentrated to give 255 mg of crude product that was dissolved in 1.4 mL of pyridine. The solution was cooled to 0 °C, and 7.3 mmol of acetic anhydride was added along with a few crystals of DMAP. The mixture was allowed to warm to room temperature after 1 h. As the reaction was still incomplete after 1 h, an additional 5.3 mmol of acetic anhydride was added. One hour later, pyridine and acetic acid were removed azeotropically by coevaporation with heptane (4 × 4 mL). The crude material (0.27 g) was purified by PTLC (1.5 mm silica gel plate) using 3:1 hexane–Et_2O as eluant, giving 78 mg (51% overall yield) of (*R*)-**11** that was enantiomeric to the sample produced from homoallylic alcohol (*S*)-**5a**: $[\alpha]^{20}_D$ +31.1° (*c* = 0.83, CH_2Cl_2). The spectroscopic properties were otherwise identical with those reported above for (*S*)-**11**.

(*R*)-1,3-Diacetoxydodecane (13). Diacetate (*R*)-**13** was prepared in 47% yield starting from (*R*)-**5c** by using the procedure described for the synthesis of (*S*)-**11** from (*S*)-**5a**: $[\alpha]^{20}_D$ –6.9° (*c* = 1.1, CH_2Cl_2); ^1H NMR ($CDCl_3$, 300 MHz) δ 4.96 (m, 1 H), 4.07 (t, *J* = 6.7 Hz, 2 H), 2.04 (s, 6 H), 1.95–1.80 (m, 2 H), 1.60–1.16 (series of br m, 16 H), 0.88 (t, *J* = 6.8 Hz, 3 H); IR (neat) 2920, 2850, 1740, 1465, 1365, 1230, 1040 cm^{-1}; high-resolution mass spectrum [CI] for $C_{14}H_{27}O_2$ (M^+ – 59) calcd 227.2011, found 227.2007. Anal. calcd for $C_{16}H_{30}O_4$: C, 67.10; H, 10.56. Found: C, 67.36; H, 10.66.

Compound (*R*)-**13** prepared in this way was enantiomeric to a sample of (*S*)-**13** prepared (50% yield) via the Red-Al reduction of epoxy alcohol **16**:[29] $[\alpha]^{20}_D$ + 11.0° (*c* = 0.95, CH_2Cl_2).

(*S*)-1-Phenylpropane-1,3-diol (12). The ozonolysis was performed directly on (*S*)-**5b** by using the procedure described for the ozonolysis of (*S*)-1-acetoxy-1-cyclohexylbut-3-ene (see procedure for synthesis of (*S*)-**11**. The ozonolysis was carefully monitored by TLC to prevent over oxidation. Diol (*S*)-**12** so obtained was the enantiomer of (*S*)-**12** prepared by the Red-Al reduction of an (*R,R*)-DIPT-derived epoxy alcohol reported in the literature:[30] $[\alpha]^{20}_D$ –20.5° (*c* = 0.66, $CHCl_3$) [lit.[30] for (*R*)-**12** $[\alpha]^{20}_D$ +69.0° (*c* = 1.51, $CHCl_3$)]; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.41–7.29 (m, 5 H), 5.03–4.99 (m, 1 H), 3.92 (q, *J* = 5.1 Hz, 2 H), 2.73 (d, *J* = 3.3 Hz, 1 H, OH), 2.28 (t, *J* = 5.1 Hz, 1 H, OH), 2.09–1.98 (m, 2 H); IR ($CHCl_3$ solution) 3610 (sharp), 3600 (sharp), 3490 (br), 3010, 2930, 2850, 1450, 1050 cm^{-1}; high-resolution mass spectrum for $C_9H_{12}O_2$ calcd 152.0837, found 152.0841.

(*S*)-4,4-Dimethylpentane-1,3-diol (14). Diol (*S*)-**14** was similarly prepared from (*S*)-**5d** (90% yield) and was enantiomeric to the sample of (*R*)-**14** ((*R,R*)-DIPT derived) reported in the literature:[30] $[\alpha]^{20}_D$ –15.0° (*c* = 2.49, $CHCl_3$) [lit.[30] for (*R*)-**14** $[\alpha]^{20}_D$ +15.6° (*c* = 1.15, $CHCl_3$)]; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.89–3.84 (m, 2 H), 3.50 (br d, *J* = 10.2 Hz, 1 H), 2.62 (br s, 1 H, OH), 2.42 (br s, 1 H, OH), 1.80–1.57 (m, 2 H), 0.92 (s, 9 H); IR ($CHCl_3$) 3630 (sharp), 3450 (br), 2960, 2870, 1055 cm^{-1}.

(*S*)-4-Tridecanol (17). A solution of 100 mg (0.50 mmol) of (*R*)-**5c** (84% ee) in 2 mL of ethanol was hydrogenated over 20 mg of 5% Pd/C at atmospheric pressure. The progress of the reaction was monitored by TLC. When complete, the mixture was filtered through Celite, concentrated in vacuo, and chromatographed on a short flash silica gel column to give 84 mg (84%) of (*S*)-**17**. The same procedure was employed for the hydrogenation of (*S*)-**5e**. Data for **17**: ^1H NMR ($CDCl_3$, 300 MHz) δ 3.60 (br m, 1 H), 1.10–1.60 (m, 21 H), 1.00–0.80 (m, 6 H); IR (neat) 3530–3100 (br, –OH), 2958, 2923, 2853, 1453 cm^{-1}; mass spectrum (CI, CH_2Cl_2), *m/z* 199 (M^+ – H), 183 (M^+ – OH). Anal. Calcd for $C_{13}H_{28}O$: C, 77.93; H, 14.08. Found: C, 78.15; H, 14.31.

The optical rotations of these samples of **17** were very low and could not be measured accurately. Therefore, the absolute configurations of (*S*)-**17** deriving from (*R*)-**5c** and (*S*)-**5e** were de-

termined by the Mosher ester technique (500 MHz). Critical ^1H NMR resonances used in this determination are as follows. Partial data for the (*R*)-MTPA derivative of (*S*)-17: δ 3.57 (q, J = 1.2 Hz, 3 H, OMe), 0.92 (t, J = 7.4 Hz, 3 H, CH_3), and 0.88 (t, J = 7.1 Hz, 3 H, CH_3); partial data for the (*S*)-MTPA derivative of (*S*)-17: δ 3.56 (q, J =1.2 Hz, 3 H, OMe), 0.88 (t, J = 7.1 Hz, 3 H, CH_3), and 0.85 (t, J = 7.4 Hz, 3 H, CH_3). By this method it was determined that the absolute configurations of 17 deriving from (*R*)-**5c** and (*S*)-**5e** are the same (*S*).

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Asymmetric Synthesis Using Tartrate Ester Modified Allylboronates. 2. Single and Double Asymmetric Reactions with Alkoxy-Substituted Aldehydes

William R. Roush,*[1] Lee K. Hoong, Michelle A. J. Palmer, Julie A. Straub, and Alan D. Palkowitz

Department of Chemistry, Indiana University, Bloomington, Indiana 47405, and Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

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The reactions of tartrate allylboronates **1a** and **1b** with a series of chiral and achiral alkoxy-substituted aldehydes are described. It is shown that conformationally unrestricted α- and β-alkoxy aldehyde substituents have a significant, negative impact on the stereoselectivity of the asymmetric allylborations. For example, α-alkoxy aldehydes **25–27** and β-alkoxy aldehydes **28–30** undergo asymmetric allylborations with **1** in only 56–59% and 63–66% ee, respectively, while the reactions of **1** and aliphatic aldehydes such as decanal or cyclohexanecarboxaldehyde proceed in 86–87% ee under the same conditions. Evidence of reduced stereoselection is also apparent in the double diastereoselectivity data reported in Table I and Scheme I for the asymmetric allylborations of chiral β-alkoxy aldehydes **16** and **19** and chiral α-alkoxy aldehyde **22**. In contrast, chiral aldehydes containing alkoxy groups that are conformationally constrained by incorporation in rings, as in glyceraldehyde acetonide **4**, 4-deoxythreose ketal **7**, and α,β-epoxy aldehydes **10** and **13**, are excellent allylboration substrates, with diastereoselection in the cases of **4** and **7** being significantly greater than that obtained with simpler achiral substrates. A model that rationalizes this "alkoxy effect" is presented. Specifically, it is inferred that the observed trends in stereoselection are not steric in origin, but rather that unfavorable lone pair/lone pair interactions occur between the tartrate ester carbonyl and alkoxy substituents particularly of conformationally unconstrained aldehyde substrates (e.g., **16**, **19**, **22**, **25–30**) that results in diminished reaction stereoselection (see transition structures **58** and **61**). For substrates with conformationally constrained alkoxy substituents, e.g., **4** and **7**, favorable lone pair/dipole interactions between the tartrate ester carbonyl and the backside of the β-alkoxy C–O bond leads to increased stabilization of the favored transition state (see transition structures **59** and **60**) and hence to increased reaction diastereoselection. A simple method for the analysis of the *average diastereofacial selectivity* of a chiral reagent in a pair of double asymmetric reactions is also presented. This analysis, which is independent of the intrinsic diastereofacial bias of the chiral aldehyde, enables one to make direct comparisons of the relative diastereoselectivities of a range of chiral substrates with a given chiral reagent (or vice versa). In this way, double diastereoselectivity data are easily analyzed to determine if the chiral reagent/chiral substrate pair is "well behaved" compared to typical achiral substrate reference systems, thereby providing insight into the structural features that influence reaction stereoselectivity.

The reactions of allyl- and crotylmetal reagents with chiral carbonyl compounds are of considerable interest in the context of acyclic diastereoselective synthesis.[2] Many reagents are now available that permit high levels of simple diastereoselection (that is, the stereochemistry associated with the C–C bond formation) to be achieved in reactions with aldehydes. Like the aldol reaction, however, double asymmetric synthesis using chiral allylmetal reagents is often necessary to achieve synthetically useful levels of diastereofacial selectivity in reactions with chiral aldehydes.[2-4]

In previous papers we have shown that the tartrate allyl- and crotylboronates **1–3** are a family of readily accessible and synthetically convenient allylmetal reagents that exhibit good to excellent enantioselectivity and excellent simple diastereoselectivity in reactions with achiral aldehydes.[5] We have also shown that they function as highly diastereofacially selective chiral acetate and pro-

(1) Current address: Indiana University.

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