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THE ASYMMETRIC ALLYLBORATION REACTION: DEPENDENCE OF RATE AND ENANTIOSELECTIVITY ON THE CHIRAL AUXILIARY

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Abstract: *The rate and enantioselectivity of the asymmetric allylboration reaction depends on the diol auxiliary.*

The asymmetric allylboration reaction has proven to be an extremely useful method for the diastereo- and enantioselective synthesis of homoallylic alcohols and other optically active acyclic systems.[2,3] During the course of our studies we have examined a range of C_2 symmetric diols auxiliaries (Table I). With the exception of *N,N'*-dibenzyl-*N,N'*-ethylene tartramide, an auxiliary designed based on mechanistic considerations,[2f] the commercially available tartrate esters have proven to be the most selective of all other diols yet examined. Equally unexpected, however, was the observation that the tartrate ester derived reagents are also significantly more reactive than all other compounds in this series. This Letter serves to amplify these observations.

Allylboronates **12-22** were prepared by treating diols **1-11** with triallylborane (1.0-1.1 equiv.) in CH_2Cl_2.[2a,f] The resulting allylboronates were dissolved in the appropriate reaction solvent, treated with 4Å molecular sieves (typically 25 mg/mL), cooled to the indicated reaction temperature, and then treated with 1.0 equiv. of $C_6H_{11}CHO$.[4] The reactions were quenched by adding an excess of $NaBH_4$ in EtOH (precooled to the reaction temperature),[5] and the ratio of $C_6H_{11}CH_2OH$ to homoallyl alcohol **23**, determined by capillary GC, was used to calculate the % conversion. The absolute configuration and enantiomeric purity of **23** was determined by chiral capillary GC analysis of the derived methyl ether.[6]

The great range of enantioselectivity as well as the range in reactivity of these reagents is striking. The relative reactivity of these allylboronates (in toluene) is **12** >>**20** > **19** ≈ **15** > **13** > **14** > **22** > **18** > **16** ≈ **21** > **17**. It should be noted that these experiments were performed under relatively dilute conditions (typically ≤0.1 M) to facilitate direct comparison with the tartrate allylboronate **12** that is extraordinarily reactive: *the reaction of* ***12*** *and* $C_6H_{11}CHO$ *at 0.05 M in toluene is >95% complete after 15 min*! By way of comparison, the reaction of pinacol allylboronate **21** (0.1 M, -78°C) is only 4% complete after 72 h, while the reaction of the ethandiol ester **22** (0.1 M, -78°C) is 15% complete after 15 h. The reactions of **16** and **21** display clean, second order kinetics, and so for preparative purposes one simply performs these reactions at higher concentrations and/or at higher temperatures to achieve acceptable rates of conversion.[7]

The rates of these reactions are moderately solvent dependent, with rates generally decreasing along the following series: $CHCl_3$ > CH_2Cl_2 > toluene > THF (at a given temperature). The major influence on reactivity, however, is clearly the structure of the diol unit. Two factors appear to be involved. First, there is a steric effect that decreases reactivity, as evidenced by the following trend: **22** (ethandiol ester) > **16** (butandiol ester) ≈ **21** (pinacol ester) > **17** (diisopropylethandiol ester).[8] This may well be the result of steric deacceleration of complexation of the aldehyde to the boron atom. Interestingly, the almost identical reactivity of the pinacol (**21**) and butandiol esters (**16**) suggests that it is a pseudoaxial alkyl group that is responsible

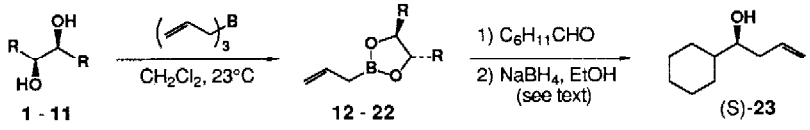
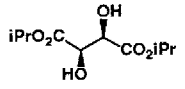
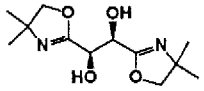
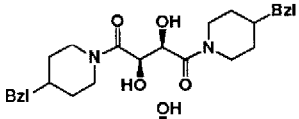
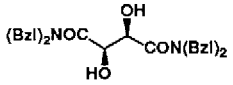
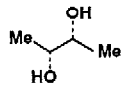
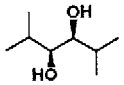
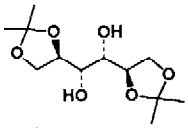
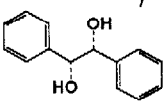
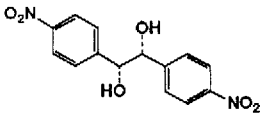


Table I. C_2 Symmetric Diol Auxiliaries for the Allylboration Reaction[a]

Diol	Reagent	Conditions	[Conc.][b]	Conv. (%)[c]	Enantioselectivity[d]
	(R,R)-**1**	(R,R)-**12**	toluene, -78°C, 15 min	0.05 M	>95%	87% e.e. (S) ←
			THF, -78°C, 90 min	0.05 M	70%	78% e.e. (S)
			CH_2Cl_2, -78°C	0.05 M	n.d.	59% e.e. (S)
	(R,R)-**2**	(R,R)-**13**	toluene, -78°C, 16 h	0.08 M	27%	21% e.e. (S)
			Et_2O, -78°C, 20 h	0.08 M	14%	32% e.e. (S)
			CH_2Cl_2, -78°C, 18 h	0.10 M	80%	53% e.e. (S) ←
	(R,R)-**3**	(R,R)-**14**	toluene, -78°C, 16 h	0.05 M	24%	27% e.e. (S)
			THF, -78°C, 16 h	0.05 M	8%	30% e.e. (S)
			CH_2Cl_2, -78°C, 18 h	0.05 M	40%	46% e.e. (S) ←
	(R,R)-**4**	(R,R)-**15**	toluene, -78°C, 16 h	0.06 M	50%	15% e.e. (R)
			CH_2Cl_2, -78°C, 16 h	0.06 M	67%	6 % e.e. (R)
	(R,R)-**5**	(R,R)-**16**	toluene, -25°C, 20 h	0.10 M	46%	1% e.e. (S)
			CH_2Cl_2, -25°C, 20 h	0.10 M	46%	4% e.e. (S)
			CH_2Cl_2, -78°C, 15 h	0.20 M	2%	13% e.e. (R)
			$CHCl_3$, -25°C, 19 h	0.15 M	80%	7% e.e. (S)
	(S,S)-**6**	(S,S)-**17**	toluene, -25°C, 40 h	0.06 M	18%	37% e.e. (S)
			THF, -25°C, 40 h	0.07 M	10%	29% e.e. (S)
			$CHCl_3$, -25°C, 40 h	0.07 M	30%	52% e.e. (S) ←
	(S,S)-**7**	(S,S)-**18**	toluene, -25°C, 40 h	0.08 M	75%	25% e.e. (R)
			THF, -25°C, 40 h	0.08 M	91%	23% e.e. (R)
			CH_2Cl_2, -25°C, 40 h	0.08 M	94%	27% e.e. (R)
			CH_2Cl_2, -78°C, 15 h	0.08 M	21%	30% e.e. (R)
	(R,R)-**8**	(R,R)-**19**	toluene, -78°C, 5 h	0.08 M	21%	11% e.e. (R)
			CH_2Cl_2, -78°C, 16 h	0.07 M	64%	6% e.e. (R)
			$CHCl_3$, -58°C, 21 h	0.08 M	85%	13 e.e. (S)
	(R,R)-**9**	(R,R)-**20**	toluene, -78°C, 15 h	0.05 M	82%	11% e.e. (R)
			CH_2Cl_2, -78°C, 18 h	0.05 M	95%	6% e.e. (S)
pinacol[e]	**10**	**21**	toluene, -78°C, 72 h	0.10 M	4%	--
			toluene, -25°C, 20 h	0.10 M	46%	--
ethylene glycol[e]	**11**	**22**	toluene, -78°C, 15 h	0.10 M	15%	--
			toluene, -25°C, 20 h	0.10 M	73%	--

(a) The data reported here are for reactions with cyclohexanecarboxaldehyde performed as described in text. (b) Concentration of $C_6H_{11}CHO$. (c) Calculated from the ratio of $C_6H_{11}CH_2OH$ and homoallyl alcohol **23**. All reactions were terminated with $NaBH_4$ in EtOH. (d) Determined by chiral capillary GC analysis of the derived methyl ethers (ref. 6). (e) The reactions were performed with distilled **21** and **22**.

for this effect. Second, working in the opposite direction is an inductive effect that presumably increases the Lewis acidity of the boron atom, thereby increasing the rate of complexation of the two reactants. The greater reactivity of **18** (mannitol diacetonide) compared to **17** (diisopropylethandiol), of p-nitrohydrobenzoin derivative **20** compared to the hydrobenzoin reagent **19**, and especially of the tartrate ester reagent **12** compared to tartramide and oxazoline derivatives **13-15**, are indicative of this effect.

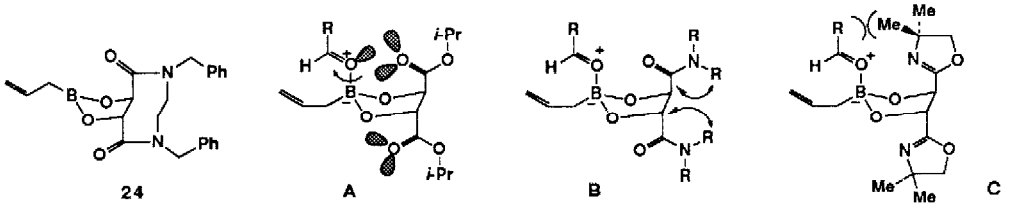
The relative reactivity of the allylboronates correlates reasonably well with the ^{11}B NMR chemical shift (Table 2). Comparison of the data for **21**, **16**, and **22** reveals that diol alkyl substituents tend to shield the boron atom, perhaps in a manner analogous to the well known γ-effect in ^{13}C NMR spectroscopy, while the data for **19**, **20**, and **12** compared to **16** are indicative of the inductive deshielding of the boron atom. That the ^{11}B chemical shift for the tartrate allylboronate **12** is not more deshielded relative to **19**-**20** may suggest that a small percentage of **12** exists in solution with the boron atom coordinated to an adjacent -CO_2iPr group, an effect that should significantly shield the boron atom.[9]

Table 2. ^{11}B NMR Chemical Shifts of Allylboronates[a]

Solvent	21	16	22	19	20	12
Et_2O	33.3	33.5	34.0	34.4	–	34.7
THF	32.8	–	33.3	–	–	–
$CDCl_3$	32.7	32.6	33.3	33.8	34.2	ca. 35 (br)

a ^{11}B chemical shifts are referenced to $BF_3{\cdot}Et_2O$ (d 0.00).

The enantioselectivity data summarized in Table 1 underscores the unique properties of tartrate esters as auxiliaries for these reactions.[10] While simple (but not necessarily obvious) steric effects may play some role as suggested by the results with the diisopropylethandiol and mannitol diacetonide reagents **17** and **18** (up to 52% e.e. with **17**), it is clear that other factors must also contribute to the excellent results realized with **12**. We have previously suggested a model that requires that the tartrate auxiliary adopt a conformation in the transition state with the esters diaxial with respect to the dioxaborolane system and the carbonyl groups syn coplanar with the adjacent C-O bonds (see **A**).[2a,f] The favored transition state is presumed to arise from **A** by a clockwise rotation about the axial B-O bond that moves the aldehyde nonbonding lone pair away from the proximate ester carbonyl; counterclockwise B-O rotation results in increased repulsive interactions between the nonbonding lone pairs on the two carbonyl groups. The model further predicts that any conformational heterogeneity in **A**, that is, transition state structures with other conformations within the dioxaborolane (e.g., diequatorial esters) or with other rotamers about the C-CO_2iPr linkage, will result in diminished enantioselectivity. Based on this model, allylboronate **24** containing a conformationally rigid tartramide auxiliary was synthesized and shown to be substantially more enantioselective than **12**.[2f]



The data reported here for reagents **13**, **14**, and **15** are supportive of this model. Examination of molecular models of aldehyde complexes of tartramides **14** and **15** reveal that the s-cis amide substituent

interacts with the rest of the tartrate backbone (see **B**). Thus, less enantioselective rotamers with the amide carbonyl eclipsing either the C-C bond and/or the tartrate C-H bond probably become competitive in this case. These rotamers are apparently more significant in the case of **15** with floppy N-benzyl groups since the enantioselectivity is substantially less than **14**, and the sense of asymmetric induction is also reversed. Similarly, examination of molecular models of aldehyde complexes of oxazoline **13** (see **C**) reveals that the aldehyde R group interacts with the endo methyl group when this system adopts a conformation resembling the favored ester conformation **A**, thus enabling less enantioselective transition states with other conformations about the C-C(=N) unit to be competitive here as well. These data, together with that previously reported for **24**,[2f] provide strong evidence in support of the conformations argued as necessary in the tartrate allylboronate aldehyde complex **A**.

In conclusion, the structural features required for high reactivity and high enantioselectivity in asymmetric allylboration reactions using diol auxiliaries have been defined. Opportunities clearly exist for application of the concept of ligand accelerated catalysis to the design of highly enantioselective, catalytic allylboronate reagents.[11,12]

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5. Similar results (% conversion) were obtained by using excess $NaBH_4$ in EtOH or DIBAL-H in hexane, to quench the allylborations. Control experiments established that the DIBAL reduction of $C_6H_{11}CHO$ (0.05 M) is complete within 2 min at -78°C.
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10. Details of the syntheses of auxiliaries (R,R)-**2**, (R,R)-**3**, (R,R)-**4**, and (R,R)-**9** will be provided elsewhere. Diol (S,S)-**6** was provided by Professor D. S. Matteson, to whom we are most grateful..
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12. Professor H. C. Brown has informed us his group has performed an analogous study on the influence of solvent and the diol unit on allylboronate reactivity (*J. Org. Chem.*, submitted).

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