Opening of Tartrate Acetals Using Dialkylboron Bromide: Evidence for Stereoselectivity Downstream from Ring Fission

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Abstract: Johnson-type acetals derived from dimethyl tartrate give, after opening with Me$_2$BBr and cuprate displacement, secondary alcohols with high diastereoselectivity (>30:1). The mechanism proposed for the induction of diastereoselectivity is downstream from the ring fission. It implies a direct participation of the Lewis acid as a source of nucleophile and the stereospecific transformation of the resulting bromo acetal through an invertive and temperature-dependent process. The acetals are prepared by reaction of the desired aldehyde with dimethyl tartrate. Removal of the auxiliary is accomplished through SmI$_2$ reduction or by an addition−elimination protocol using methoxide.

The induction of stereogenic centers on acyclic molecules is a topic of great research interest. The concept of using acetals as chiral templates to achieve such an objective originated from the seminal work of W. S. Johnson[1] and was later extended and enriched by the contributions of many other scientists.[2−6] The opening of acetals is now a commonly used approach in the synthesis of new molecules. A variety of reaction conditions involving different types of acetals, Lewis acids, and nucleophiles have been considered. To date, three mechanisms have

Scheme 1

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(1) (a) Johnson, W. S.; Harbert, C. A.; Stipanovic, R. D. *J. Am. Chem. Soc.* **1968**, *90*, 5279−5280. (b) Johnson, W. S.; Harber, B. E.; Ratcliffe, B. E.; Stipanovic, R. D. *J. Am. Chem. Soc.* **1976**, *98*, 6188−6193. (c) Bartlett, P. A.; Johnson, W. S.; Elliot, J. D. *J. Am. Chem. Soc.* **1983**, *105*, 2088−2089. (d) Johnson, W. S.; Kevson, A. B.; Elliott, J. D. *Tetrahedron Lett.* **1988**, 3757−3760.
(2) See, for example: (a) Denmark, S. E.; Wilson, T. M.; Almstead, N. G. *J. Am. Chem. Soc.* **1989**, *111*, 9258−9260. (b) Alexakis, A.; Mangeney, P. *Tetrahedron: Asymmetry* **1990**, *1*, 477−511.
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(4) (a) Denmark, S. E.; Almstead, N. G. *J. Am. Chem. Soc.* **1991**, *113*, 8089−8110. (b) Denmark, S. E.; Almstead, N. G. *J. Org. Chem.* **1991**, *56*, 6458−6467. (c) Denmark, S. E.; Almstead, N. G. *J. Org. Chem.* **1991**, *56*, 6485−6487.
(5) Bull, S. D.; Correia, L. M. A. R. B.; Davies, S. G. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2231−2233.
(6) (a) Sammakia, T.; Smith, R. S. *J. Org. Chem.* **1992**, *57*, 2997−3000. (b) Sammakia, T.; Smith, R. S. *J. Am. Chem. Soc.* **1992**, *114*, 10998−10999. (c) Sammakia, T.; Smith, R. S. *J. Am. Chem. Soc.* **1994**, *116*, 7915−7916.
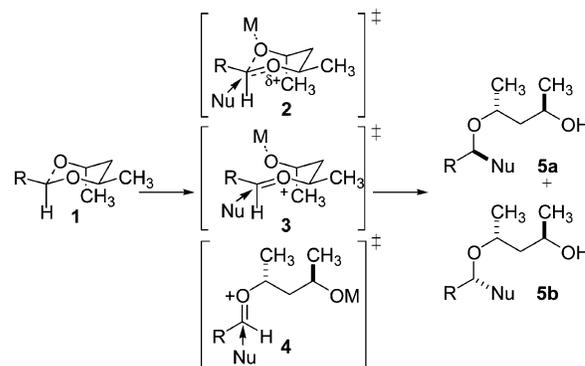
been envisaged for this process. The first mechanism proposed was an S$_N$2 process proceeding through a direct displacement of the acetal/Lewis acid complex. In this mechanism, the Lewis acid complexed selectively to the oxygen attached to the carbon bearing the axial substituent (**2**, Scheme 1).[1,2] Heathcock, Bartlett, and Yamamoto,[3] and then later Denmark[4] and Davies,[5] provided experimental evidence that an S$_N$1 oxocarbenium ion mechanism may be implicated in most instances. It was suggested that a cyclic tight ion pair such as **3** might be present in the transition state. In structure **3**, the presence of tight ion pairs produces facial selectivity during the approach of the nucleophile. The third mechanism proposed involved a solvated oxocarbenium ion such as **4** in a transition state leading to the major product **5a**, although the sense of diastereoselectivity in this case was more difficult to explain.[4]

Scheme 2
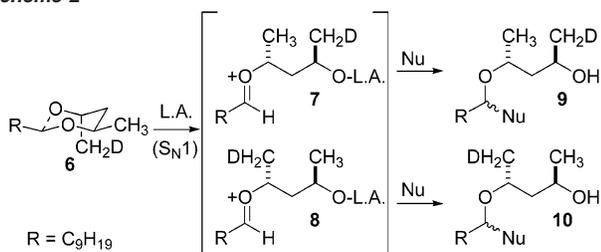
Results offered by Sammakia[6] indicated that selective complexation did not take place between the Lewis acid and the oxygen atoms of the acetal.[7] Using a labeled compound, Sammakia clearly showed that there was a similar distribution of **9** and **10** in the products, a result inconsistent with selective complexation (Scheme 2). Since either of the carbon−oxygen bonds may be cleaved in the opening of an acetal, it could be concluded that equilibration occurs between the oxocarbenium intermediates formed during the reaction.

Our studies have shown that secondary alcohols can be obtained with high selectivity when tartrate acetals are opened using dimethylboron bromide (Me₂BBr) and a mixed organo cuprate, Me₂Cu(CN)Li₂ (eq 1).[8]

$$(1)$$
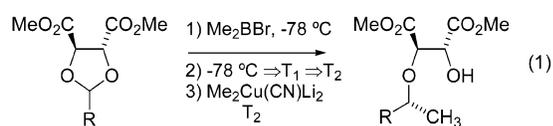
However, good selectivity was realized only when a particular set of experimental conditions was respected, suggesting that an unusual mechanism was operative in the reaction. The present study on the opening of tartrate acetals will show that the origin of diastereoselectivity is downstream from the opening of the acetal. This involves nucleophilic displacement of the bromide originating from the Me₂BBr to form intermediate bromo ethers that equilibrate under thermodynamic control before reacting with organo cuprates in a stereospecific and temperature-dependent manner. We believe that competing S$_N$1 and S$_N$2 mechanisms are involved in the cuprate displacement. These findings will be elaborated in the following pages.

Results and Discussion.

Addition of Me₂BBr to acetal **11** at −78 °C followed by the introduction of Me₂Cu(CN)Li₂[8,9] gave a 1:1 mixture of diastereomers (Table 1, entry 1). Modest selectivity for product **12a** was achieved only when, after the addition of Me₂BBr (at −78 °C), the reaction mixture was warmed to room temperature for 1 h and then recooled to −78 °C for the addition of cuprate (entry 2). Increasing the temperature at which the cuprate was added resulted in an increase in selectivity, the highest ratios being noted at −30 °C (entries 3 and 4). Above −30 °C, diastereoselection decreased (entries 5 and 6).

Neither the nature of the R₁ group on the acetals (Table 2, entries 1−4) nor the size of the nucleophile (entries 1, 5−7)

(7) Sammakia observed high selectivity when Lewis acid was added slowly and when milder Lewis acids were used.
(8) Guindon, Y.; Simoneau, B.; Yoakim, C.; Gorys, V.; Lemieux, R.; Ogilvie, W. *Tetrahedron Lett.* **1991**, 5453−5456.
(9) (a) Lipshutz, B. H. *Synthesis* **1987**, 325. (b) Lipshutz, B. H.; Wilhelm, R. S.; Kozlowski, J. A. *Tetrahedron* **1984**, *40*, 5005. (c) Lipshutz, B. H.; Moretti, R.; Crow, R. *Organic Synthesis* **1990**, *69*, 80.

Table 1. Reaction of Tartrate Acetal **11** with Me₂BBr and Me₂Cu(CN)Li₂ at Various Temperatures

| entry	T_1 (°C)	T_2 (°C)	ratio^a (**12a**:**12b**)	yield^b (%)
1	−78	−78	1:1	34
2	25	−78	8:1	52
3	25	−40	14:1	77
4	25	−30	22:1	76
5	25	−20	15:1	64
6	25	0	6:1	38

^{a} Determined by capillary GC. ^{b} Isolated yield.

Table 2. Reaction of Various Tartrate Acetals with Various Cuprates and Dialkylboron Bromides

entry	acetal	R₁	R₂	products A:B	ratio^a (A: B)	yield^b
1	**11**	nC₉H₁₉	CH₃	**12a**:**12b**	34:1	80
2	**13**	cC₆H₁₁	CH₃	**14a**:**14b**	17:1	83
3	**15**	(CH₃)₂CH	CH₃	**16a**:**16b**	12:1	82
4	**17**	nC₆H₁₃	CH₃	**18a**:**18b**	18:1	77
5	**11**	nC₉H₁₉	Bu	**19a**:**19b**	>20:1	67
6	**11**	nC₉H₁₉	Ph	**20a**:**20b**	14:1	45
7	**11**	nC₉H₁₉	CH₂CH^c	**21a**:**21b**	26:1	62
8	**13**	cC₆H₁₁	PhS^d	**22a**:**22b**	6:1	68

^{a} Determined by GC. ^{b} Combined isolated yield. ^{c} Cuprate added at −50 °C. ^{d} PhSH replaced R₂Cu(CN)Li₂ as a nucleophile.

Scheme 3: Removal of Tartrate Auxiliary^a
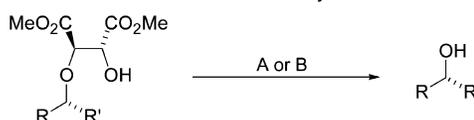
^{a} **Method A:** (i) 1.3 equiv of CH₃SO₂Cl, 2.0 equiv of Et₃N, 0 °C, 30 min; (ii) 10.0 equiv of DBU, CH₂Cl₂, 0 °C, 30 min; (iii) 5.0 equiv of NaOMe, 65 °C, 30 min. **Method B:** 5.0 equiv of SmI₂, 10.0 equiv of MeOH, 6.0 equiv of HMPA, THF, 25 °C, 2 h.

had much impact on the diastereoselectivity obtained. A survey of various reagents was conducted to find the optimal conditions for carbon−carbon bond formation. Almost no selectivity was observed with Me₂CuLi, Me₃CuLi₂,[10] Me₃Cu₂Li,[11] or Me₅Cu₃-Li₂.[10] Attempts to use Grignard-derived cuprates met with failure as did the use of MeCuCNLi. Only Me₂Cu(CN)Li₂[9] offered an excellent ratio for carbon−carbon bond formation. The use of thiophenol as a nucleophile (Table 2, entry 8) gave hemithioacetal products with a modest 6:1 diastereoselectivity.[12]

Auxiliary removal was accomplished using one of two possible methods (Scheme 3). The first approach involved the

(10) (a) Still, W. C.; MacDonald, T. L. *Tetrahedron Lett.* **1976**, *31*, 2659. (b) Ashby, E. C.; Noding, S. A. *J. Org. Chem.* **1979**, *44*, 4371. (c) Ashby, E. C.; Lin, J. J. *J. Org. Chem.* **1977**, *42*, 2805.
(11) Ashby, E. C.; Lin, J. J.; Watkins, J. J. *J. Org. Chem.* **1977**, *42*, 1099.
(12) Crystallographic analysis of the minor isomer (**22b**) indicated that the thiol addition had occurred with the same facial selectivity as was the case for the cuprate addition (see Supporting Information).

Table 3. Ratio of Bromo Ethers Observed at Various Temperatures
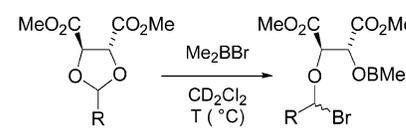
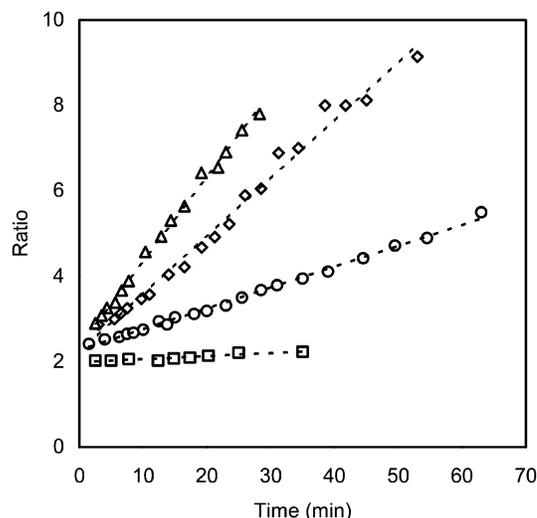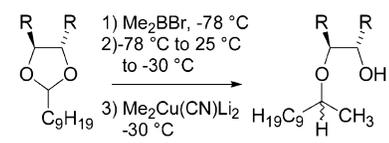| entry	acetal	R	T (°C)	ratio[a]
1	**13**	cC_6H_{11}	−78	1.2:1
2	**13**	cC_6H_{11}	20	8:1
3	**11**	nC_9H_{19}	20	5.3:1
4	**23**	CH_3	20	6.5:1
5	**15**	$(CH_3)_2CH$	20	7:1
6	**13**	cC_6H_{11}	−78 to −30	1.5:1
7	**13**	cC_6H_{11}	20 to −30	8:1

[a] Determined by NMR.

formation of an enol ether by mesylation and elimination followed by exposure to NaOMe in MeOH at reflux to give the secondary alcohols in good yield. The second and more convenient approach consisted of exposing the tartrate auxiliary to SmI_2 in the presence of HMPA using methanol or ethylene glycol as the hydrogen source.[13] In all cases, the configuration of the major alcohol isomer was *R* when L-tartrate was used, indicating that the reaction proceeded with consistent facial selectivity.[14]

Mechanistic considerations. In proposing a mechanistic rational for the various levels of selectivity obtained, we had to account for three significant observations: (1) good selectivity was achieved only when the reaction mixture was warmed briefly following the addition of Me_2BBr and before cuprate addition, (2) overall ratios were optimal when the cuprate was added at −30 °C, (3) the best nucleophiles tested were the Lipshutz-type cuprates[9,15] and thiolates. The fact that acetals are normally cleaved by Me_2BBr at −78 °C[16] and that good selectivity could be achieved only when the reaction was warmed at an early stage, implied that the diastereoselectivity observed was dependent upon events occurring after ring fission. To explore this conclusion further, we considered the role of acyclic bromo acetal derivatives in the reaction as well as their selective displacement by cuprates.

Acyclic Bromo Acetal Derivatives and Thermodynamic Control. NMR experiments indicated that the acetals reacted rapidly with Me_2BBr to give the corresponding bromo ethers (borate esters) in an equal ratio at −78 °C (Table 3, entry 1). Upon warming to room temperature, the bromo ethers equilibrated rapidly to give ratios of between 5:1 and 8:1 (entries 2−5). Warming the solution from −78 to −30 °C preserved the ratio obtained at −78 °C (entry 6). Cooling the solution from room temperature to −30 °C preserved the bromo ether distribution obtained at room temperature (entry 7).

From these results, two important observations could be made. First, achieving a diastereomeric excess of one of the bromo

(13) Kusuda, K.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett*. **1989**, *30*, 2945. For a review, see: Soderquist, J. A. *Aldrichimica Acta* **1991**, *24*, 15.

(14) The absolute configuration of the final products was assigned by correlation to literature values of specific rotation or by the preparation of Mosher esters and comparison of the resulting NMR spectra with those of authentic samples prepared from commercially available chiral alcohols (Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem*. **1969**, *34*, 2543−2549). The corresponding D-tartrate acetals produced secondary alcohols with *S* configurations.

(15) For complete results, see Supporting Information.

(16) (a) Guindon, Y.; Yoakim, C.; Morton, H. E. *J. Org. Chem*. **1984**, *49*, 3912−3920. (b) Guindon, Y.; Anderson, P. C.; Yoakim, C.; Girard, Y.; Berthiaume, S.; Morton, H. E. *Pure Appl. Chem*. **1988**, *60*, 1705−1714.

Figure 1. Plot showing change in ratio of bromo ethers derived from **15** and Me_2BBr as a function of time at various temperatures. Curves generated at −35 °C (□), −25 °C (○), −20 °C (◇), and −15 °C (△) are shown.

Table 4. Effect of Tartrate Functional Groups on the Ratio of Products Obtained

entry	acetal	R	products	ratio[a]	yield[b]
1	**11**	CO_2Me	**12a:12b**	34:1[c]	80
2	**24**	$CO_2{}^iPr$	**25a:25b**	25:1[c]	74
3	**26**	$CONMe_2$	**27a:27b**	27:1[c]	24
4	**28**	CH_2OMe	**29a:29b**	2:1	17
5	**30**	Me	**31a:31b**	1:1	42

[a] Ratio determined by NMR. [b] Total combined yield. [c] Ratio determined by GC.

ethers, following equilibration, was critical for obtaining a highly diastereoselective ratio of final products. Second, the ratio of final products was greater than the ratio of bromo acetals noted (cf. Tables 2 and 3).

The rate at which the acyclic bromo acetal derivatives equilibrated was found to be highly temperature-dependent. Figure 1 illustrates, for the opening of acetal **15** using Me_2BBr, the change in ratio of bromo ethers as a function of time at various temperatures.[17] At −35 °C, no equilibration was observed. As the temperature was increased to −20 °C and then to −15 °C, a slow equilibration was observed. At 0 °C, an 8:1 ratio was achieved after only 20 min, whereas at 20 °C, equilibrium was reached almost instantaneously.

The different structural features of the tartrate moiety were then considered. As seen in Table 4, the presence of esters or simple amides gave diastereoselective reactions (entries 1−3), while replacing the esters with methoxymethylenes or methyl groups led to a complete loss of diastereoselection (entries 4 and 5).

The cyclic and acyclic acetals used in the next part of our study were chosen for their capacity to produce comparable bromo acetal derivatives. As seen in Table 5, cyclic acetal **23**

(17) Me_2BBr was added to acetal **15** in CD_2Cl_2 at −78 °C, and the samples were monitored by NMR at various probe temperatures.

Table 5. Bromo Ether Ratios and Final Product Ratios of Acyclic Acetals Derived from Tartrates

| entry	acetal (**A**)	ratio (**B**)	products (**C**)	ratio (**C**)
1	**23**	6.5:1	**32a**:**32b**	15:1
2	**33**	9:1	**34a**:**34b**	7:1
3	**35**	*a*	**36a**:**36b**	1.2:1
4	**37**	*a*	**38a**:**38b**	1.1:1
5	**39**	9:1	**40a**:**40b**	7:1
6	**41**	4:1	**42a**:**42b**	1.6:1
7	**43**	4:1	**44a**:**44b**	1.6:1
8	**45**	4:1	**46a**:**46b**	1.6:1

a Ratio could not be determined.
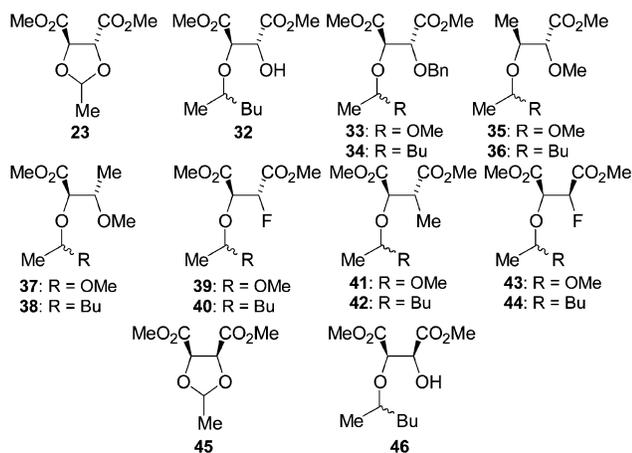
and acyclic acetal **33** gave similar ratios of bromo ether derivatives (**B**) (entries 1 and 2). Both substrates gave selective reactions, but acetal **33** did not show the magnification of ratio (vide supra) normally observed for cyclic tartrate acetals (entries 1 and 2, cf. ratios **B** and **C**).[18] This result suggested that the borate ester moiety formed during the opening of cyclic acetal **23** with Me₂BBr played a role in the magnification of the ratio seen for the cuprate addition.

A more detailed investigation was carried out using a variety of acyclic precursors to determine the relative contribution of each of the chemical features of the tartrate. With acyclic compounds, we were able to selectively alter X, Y, and Z (Table 5) and thus study the relative contribution of these functionalities to diastereoselection. Each ester was systematically replaced with a methyl group (Table 5, entries 3 and 4). The results implied that both of the ester functions were required to obtain high stereoselection, as the deletion of either resulted in a 1:1 mixture of products. The presence of an electronegative substituent at the Z position also proved necessary (entries 2 and 5), since replacing the benzyl ether with a fluorine maintained selectivity while the use of a methyl group at this position gave a nonselective reaction (entry 6). The relative configuration of the tartrate acetal was also found to be important. Cis tartrate acetals such as **43** gave no diastereoselection (entry 7), as was the case with meso cyclic acetal **45** (entry 8).

(18) Hydrogenation of a 7:1 final product mixture of **34a**:**34b** with Pd(OH)₂ gave a 7:1 mixture of **32a**:**32b**, indicating that the same facial bias was maintained with the acyclic acetal system.
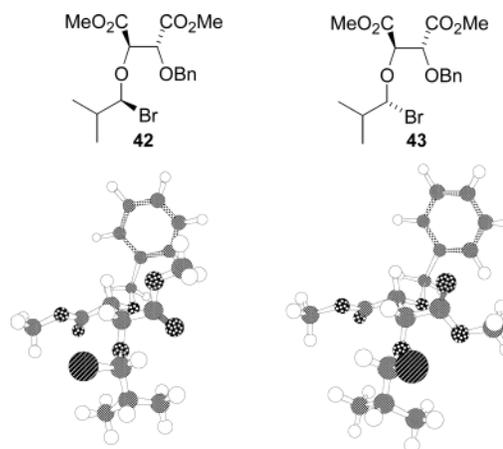

Figure 2. Low-energy conformations optimized for bromo ethers **47** and **48**.

The configuration of the thermodynamically preferred bromo acetal was subsequently considered. Our initial experience with such molecules had indicated that they were extremely temperature- and air-sensitive. Theoretical calculations had to be used to determine the thermodynamic stability of benzylated adducts **47** and **48**. A conformational search was carried out using Monte Carlo methods in MACROMODEL. The low-energy conformations thus obtained were optimized using the AM1 Hamiltonian in MOPAC, and the resulting optimized structures were used to estimate the Boltzmann energy (Figure 2). Isomer **47**, bearing an *S* configuration at the bromo ether carbon, was found to have a ΔH°_{f} of -26.5 kJ/mol, 10.3 kJ/mol lower than the ΔH°_{f} for **48**, indicating that the *S* bromo ether was the preferred configuration.

Closer inspection of these calculations provided insight into the reason for the *S* configuration preference. The tartrate portion of the molecules appeared to be extremely rigid, bearing conformations as shown in Figure 2. The tartrate torsional angles had relatively high barriers of rotation as indicated by MOPAC. There were two potential reasons for this: (1) the two esters tended to adopt an anti orientation to minimize electrostatic repulsions, and (2) the two electron-withdrawing groups tended to adopt a gauche relationship to take advantage of the gauche effect.[19] These two factors explained our previous results from the structural studies on cyclic and acyclic acetals (Tables 4 and 5). In entries 3 and 4 (Table 5), the removal of one ester resulted in no diastereoselection, indicating that both esters were required for the minimization of the dipole−dipole interaction. Unlike the methyl-substituted acetal, the fluorine-substituted acetal gave good diastereoselection (cf. entries 5 and 6, Table 5), results consistent with the need for electronegative groups at the Z position. Finally, altering the tartrate configuration (entries 7 and 8) eliminated the possibility of a stabilizing gauche effect and dipole opposition occurring simultaneously. In summary, a favorable combination of interactions between the X, Y, and Z components locked the tartrate into a rigid conformation. Any change to the harmony of the interactions would disrupt the rigidity of such derivatives (Table 5) translating into lower selectivity.

The energy of **48**, being significantly higher than that of **47**, arose from van der Waals and torsional components between

(19) Labelle, M.; Morton, H. E.; Guindon, Y.; Springer, J. P. *J. Am. Chem. Soc.* **1988**, *110*, 4533.
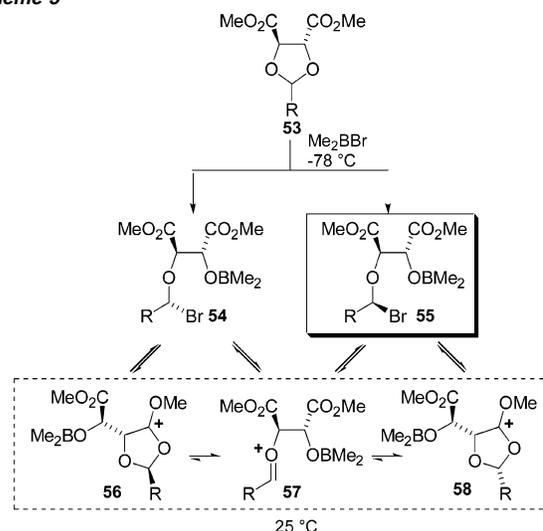
Scheme 4 [a]
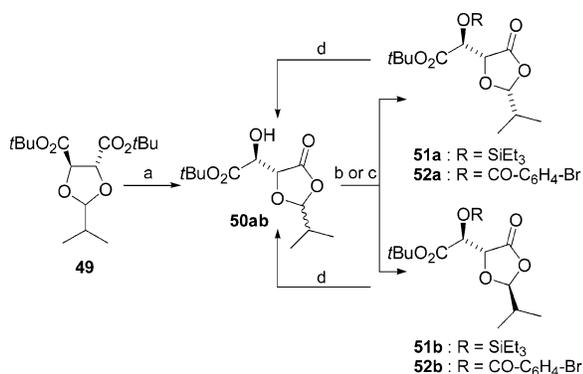
[a] **Reagents and conditions**: (a) 1.2 equiv of Me$_2$BBr, CH$_2$Cl$_2$, −78 °C and then allowed to warm to 25 °C, 15 min, 40%; (b) 1.5 equiv of Et$_3$SiCl, 2.0 equiv of imidazole, DMF, 25 °C, 2 h, 95%; (c) Br-C$_6$H$_4$-COCl, py; (d) HF·py, py, THF, 1 h, 100%.

the bromide and the nearest carbonyl group as indicated by MMX calculations. The distribution of bromo ethers **47** and **48** was therefore a result of the conformational bias of the tartrate and of the steric effects involving the bromide. These results were later confirmed by single-crystal X-ray diffraction analysis of the major isomer of the bromo ethers derived from the reaction of **13** with Ph$_2$BBr.[20] This study indicated that the major isomer took on the predicted *S* configuration at the bromo ether carbon. In addition, the solid-state conformation, being very similar to the low-energy conformation of **47**, further validated the calculations that had initially been used to arrive at **47**.

That the reaction required both esters suggested that anchimeric participation may have been involved during the equilibration of the bromo ether derivatives. To investigate this, we prepared tartrate **49** containing two *tert*-butyl esters that could potentially trap any intermediate oxocarbenium species as lactones. When bis-*tert*-butyl ester **49** was treated with Me$_2$-BBr at −78 °C and then allowed to warm to room temperature, a 40% yield of lactones **50ab** was obtained as an inseparable mixture of isomers in a 2:1 ratio (Scheme 4). These compounds were converted to the corresponding triethylsilyl ethers **51a** and **51b**, which were readily separable by flash chromatography. Treatment of each product with HF·py led to the re-installment of isomers **50a** and **50b**. The relative configuration of the two adducts was determined by NOE measurements on the *p*-bromobenzoate derivatives **52a** and **52b**. These experiments established that there was a cis stereochemical relationship of dioxolane substituents for major product **50a**. A temperature profile was established to determine the rate of interconversion of the bromo ethers (vide supra). Exposure of **49** to Me$_2$BBr at −78 or −30 °C did not produce more than a trace of lactones, indicating that equilibration occurred only at higher temperatures and through the anchimeric participation of the esters.

Scheme 5 illustrates our rationale for the bromo acetal equilibrium. The opening of tartrate acetal **53** at −78 °C provided an equal amount of the two bromo esters **54** and **55**. The mixture of isomers was warmed to room temperature, and equilibrium was achieved via the intermediacy of either one of the two esters to form the five-membered ring oxoniums **56** and **58**. Bromo ether **55** was thermodynamically preferred over **54** as the latter was destabilized by steric interactions between

(20) Drouin, M.; Michel, A. G.; Guindon, Y.; Ogilvie, W. *Acta Crystallogr., Sect. C* **1993**, *C49*, 75.

Scheme 5

the bromide and the proximal ester, a consequence of the conformational locking of the tartrate moiety (Figure 2).

A few preliminary conclusions could be drawn at this point. First, the ring fission of the tartrate acetal was nonselective at −78 °C, suggesting that preferential complexation with one of the oxygen atoms of the acetal did not occur and that this step proceeded through an S$_N$1 mechanism. Second, enriching the *S* bromo ether proved essential for achieving a high diastereoselectivity of final products. Third, the level of diastereoselectivity for the final products, when cuprates were used as nucleophiles, was much higher than that of the bromo ethers. The increase in selectivity for the final products suggested that the cuprate displacement had an effect on the stereochemical outcome of the reaction.

Selective Displacement by Cuprates. Elucidation of the carbon−carbon bond-forming step involving the cuprate reagent began with an examination of the relationship between the ratio of the bromo ethers and the overall diastereoselectivity. A variety of bromo ether mixtures, of varying ratios, had to be accessed for this part of the study. This was accomplished by mixing different volumes of stock solutions containing different ratios of bromo acetals. The first solution, containing a 1:1 mixture of bromo ethers, was obtained by opening the acetal at −78 °C. The second stock solution, containing an 8:1 mixture of bromo ethers, was obtained by warming the previous 1:1 mixture to room temperature and then recooling the solution to −78 °C. Various amounts of each stock solution were mixed at −78 °C−since the rate of equilibration was negligible at this temperature−to arrive at the variety of bromo ether ratios needed to carry out a rigorous analysis. The resulting solutions were then warmed to −30 °C for the addition of the cuprate reagent. Figure 3 illustrates the results obtained. The first graph (Figure 3a) shows the mol % fraction of **16a** in relation to the mol % of **59a**, the major *S* isomer. This experiment indicated that a linear relationship existed between the ratio of the bromo ethers and the diastereoselectivity obtained for the carbon−carbon bond-forming reaction, the increase of **16a** being proportional to the increase of **59a**. Interestingly, an increase in yield proportional to the mole fraction of **59a** was also found, as shown in Figure 3b.

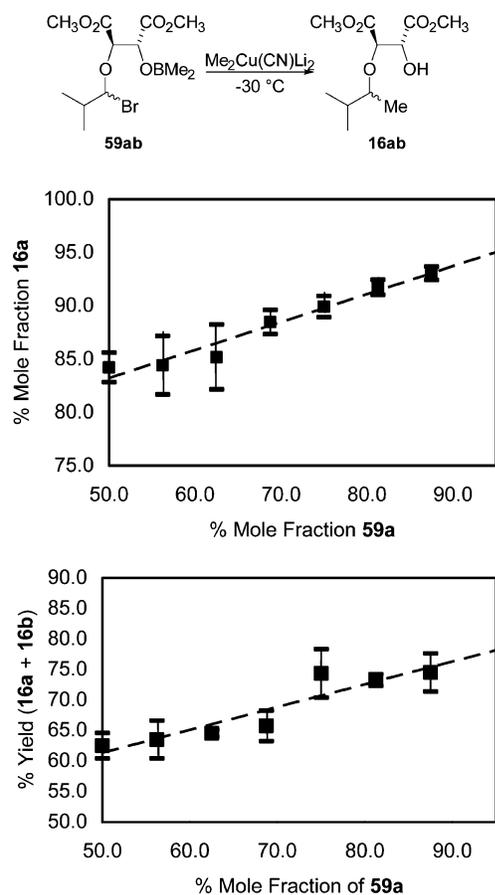These results, along with the fact that equilibration of the bromo ether derivatives was required for inducing diastereose-

Figure 3.

Table 6. Effect of Amount of Cuprate on Reaction Yield for the Conversion of **15** to **16**

entry	equivalents Me$_2$Cu(CN)Li$_2$	yield (%)
1	0.5	0
2	1.0	0
3	1.5	0
4	2.0	44
5	2.5	72
6	3.0	76

lectivity, were inconsistent with an S_N1 mechanism being operative in the cuprate displacement. An S_N1 mechanism would involve a common oxocarbenium intermediate for the two acyclic bromo ether acetals, and thus the final ratio of products would be independent of the intermediate ratio of bromo ethers.

An excess of cuprate also proved to be necessary for achieving high yield. This was illustrated by an experiment in which the number of equivalents of cuprate was varied. As shown in Table 6, significant quantities of product could only be obtained when at least 2 equiv of cuprate was used. This observation, together with the previous observation of ratio magnification only in the presence of borate esters (Table 5, entries 1 and 2), suggested the possibility that an intermediate had formed by interaction of the cuprate with the borate ester function.

Further analysis of the cuprate displacement was conducted to determine the reactive species responsible for the increase in diastereoselectivity in this step of the process. ^{11}B NMR investigations shed light on the interaction between the dialkylborates and the higher-order cuprates. In the control experiment,

Scheme 6
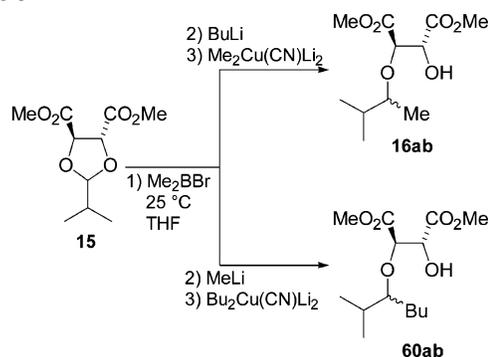
Et$_2$BOMe was used as a model for the tartrate-derived borate ester. This compound displayed a broad resonance in THF at 54.4 ppm[21,22] and a small resonance at 31.9 ppm (attributable to small amounts of EtB(OMe)(OEt)).[22] When 2.0 equiv of Me$_2$-Cu(CN)Li$_2$ were added, the signals at 54.4 and 31.9 ppm were no longer observed, but three new resonances at 7.7, 0.1, and −17.9 ppm appeared. These new resonances were assigned to Li[MeEt$_2$BOMe], Li[Et$_2$B(OMe)$_2$], and Li[Me$_2$Et$_2$B], respectively.[23] The latter two species had originated from a disproportionation of an initially formed -ate complex, this being the Li[MeEt$_2$BOMe].[24] To verify this result, the experiment was repeated using another alkylating agent. Et$_2$BOMe and 2 equivalents of MeLi gave similar results with signals at 7.9, 0.3, and −17.6 ppm, confirming that the formation of an -ate complex had indeed taken place.

This model study was then extended to the borate ester derived from tartrate **15**, for which a resonance at 54.8 ppm was observed. ^{11}B NMR showed that this resonance was replaced by resonances at 8.5 and −23 ppm when a slight excess of Me$_2$Cu(CN)Li$_2$ was added. The fact that a resonance near 0 ppm did not appear on the spectra suggested that disproportionation did not occur for the tartrate-derived borates.[25] These observations suggested that the first equivalent of Me$_2$Cu(CN)-Li$_2$ was consumed as a source of MeLi for the formation of a boron -ate complex from the borate ester function.

We had to question whether a significant amount of the final products achieved for **15** had been the result of intramolecular delivery of an alkyl group from the -ate complex to the bromo acetal. To elucidate the alkyl delivery, a crossover experiment was performed using MeLi and a butyl cuprate reagent (Scheme 6). The required bromo ethers were prepared using standard conditions. The bromo ether mixture was cooled to −30 °C and 1 equiv of MeLi was added followed immediately by the addition of 2.0 equiv of Bu$_2$Cu(CN)Li$_2$. After workup, the only product observed was **60ab**, which resulted from the introduction of a butyl group. Similarly, only methylated adduct **16ab** was isolated when BuLi was added followed by Me$_2$Cu(CN)-

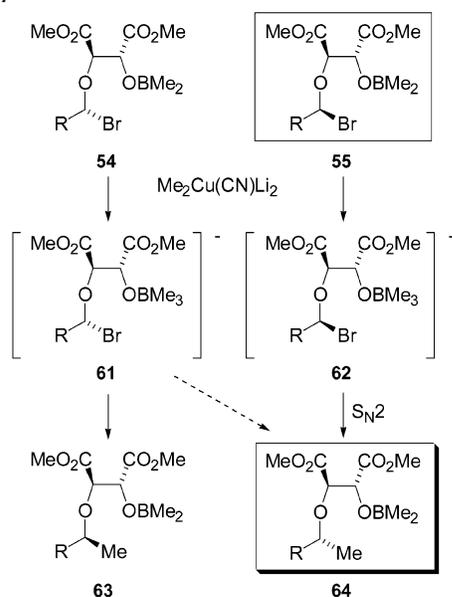(21) BF$_3$·OEt$_2$ (1.0 M in CD$_2$Cl$_2$) was used as an external reference.
(22) Reported for Et$_2$BOMe (neat): 53.6. Reported for EtB(OMe)$_2$ (neat): 31.5. (a) Nöth, H.; Vahrenkamp, H. *Chem. Ber.* **1966**, *99*, 1049−1067. (b) Dahlhoff, W. V.; Köster, R. *Liebigs Ann. Chem.* **1975**, 1625−1636.
(23) Reported for Li[BMe$_4$] (Et$_2$O): −20.2 to −21.1. Reported for Li[BEt$_4$] (Et$_2$O): −17.5. Reported for K[Me$_2$BOMe] (MeOH): −1.0. Nöth, H.; Wrackmeyer, B. *Nuclear Magnetic Resonance Spectroscopy of Boron Compounds*; Springer-Verlag: New York, 1978.
(24) (a) Brown, H. C.; Cole, T. E. *Organometallics* **1983**, *2*, 1316−1319. (b) Brown, H. C.; Cole, T. E.; Srebnik, M. *Organometallics* **1985**, *4*, 1788−1792.
(25) The resonance at −23 ppm could be attributed to the slight excess of Me$_2$-BBr used to open the acetal.

Scheme 7

Table 7. Selective Labeling of Bromo Ether Diastereoisomer

entry	T_H (°C)	T_D (°C)	initial ratio (D:H)	final ratio (D:H)
1	−78	25	1:1	1.3:1
2	−78	25	3:1	4:1
3	−78	25	1:5	1:4.3
4	25	−78	1:1	1:1.7
5	25	−78	3:1	1.8:1
6	25	−78	1:5	1:8.6

Li$_2$. This experiment showed that the formation of the -ate complex was irreversible under the reaction conditions and that an intermolecular alkyl delivery did in fact occur.

The mechanistic hypothesis for the cuprate displacement is shown in Scheme 7. Two -ate complexes, **61** and **62**, were generated from bromo ethers **54** and **55**, respectively, following the addition of cuprate at low temperatures. Given that the cuprate additions performed at −78 °C led to a major product with an inverse configuration from that of the major bromo ether, and that the bromo ether ratio and final product ratios were identical, it could be suggested that an S$_N$2-like process (an S$_N$1 process involving an intimate ion pair) takes place for both -ate complexes at −78 °C. However, magnification of the final product ratio at −30 °C suggested that the two -ate complexes, **61** and **62**, reacted differently with the cuprate at this temperature, meaning that two different pathways were involved (**61** → products; **62** → products). The fact that both the increase of the ratio of final products (Figure 3a) and the increase in yield (Figure 3b) were proportional to the amount of major bromo ether **55** suggested that the cuprate displacement of *S* isomer **62** was highly selective and thus S$_N$2-like. To explain the increase in diastereoselectivity (i.e. magnification of final product ratio), we proposed that the displacement of the *R* isomer **61** was less efficient in terms of both selectivity and total conversion to final products. It follows that, at −30 °C, **61** may react through an S$_N$1 process involving an oxocarbenium intermediate. Further support of this may be drawn from our previous calculations, which showed that **61** was higher in energy than **62**, as a result of steric constraints, suggesting that the ionization of **61** may have been favored relative to the ionization of **62**.

The validity of these hypotheses seemed apparent. Indeed, if both diastereoisomers reacted in the same way in a stereoselective process, how could the final ratios be higher than the starting ratios? To verify that the two -ate complexes, **61** and **62**, reacted differently, we used solutions containing different ratios of labeled (D) and nonlabeled (H) bromo ethers for our study of the cuprate displacement. The analysis of the final D:H

product ratio could then be rationalized by the reactivity of the -ate complexes.

As depicted in Table 7, treatment of deuterated cyclic acetal **65** with Me$_2$BBr gave, after equilibration at room temperature (T_D = 25), an 8:1 ratio favoring the *S* isomer. This stock solution was mixed at −78 °C, a temperature where no equilibration had previously been detected (vide supra), with different volumes of a stock solution containing nondeuterated -ate complexes in a 1:1 ratio (obtained after opening of **15** at T_H = −78 °C). The resulting solutions were allowed to react with cuprates at −30 °C. Increases in the amount of labeled relative to unlabeled products were noted, suggesting that the nonlabeled -ate complexes had decomposed (entries 1 and 2, respectively). Other permutations were realized to confirm the observation. As seen in entry 3, decomposition of nonlabeled -ate complexes was also observed when a 1:5 ratio of bromo ethers (D:H) was used for the cuprate displacement. From these results, and assuming that the deuterated and nondeuterated isomers would react in the same way given their similar structures, we suggest that a decomposition of the nonlabeled *R* -ate complex was responsible for the increase in ratio of the label D over the label H.

Three additional experiments were performed to take into account any potential isotopic effects. A stock solution of *S*:*R* nonlabeled bromo ethers in an 8:1 ratio (T_H = 25) was mixed at −78 °C with different volumes of a stock solution (obtained after the opening of **65** at T_D = −78 °C) containing deuterated bromo ethers in a 1:1 ratio. The resulting solutions were allowed to react with cuprates at −30 °C. As seen in entries 4−6, an increase in ratio of H over D was consistently observed, suggesting that the deuterated -ate complexes had decomposed. The arguments given above for the previous series of experiments could also apply here. Once again, the *R* isomer, this time deuterated, seemed to react with lower conversion. The percentage of decomposition was higher for this series, indicating that an isotopic effect perhaps took place. Overall, the results obtained support the fact that selective conversion at −30 °C was less efficient with the *R* -ate complex than with the *S* isomer.

Figure 3 could now be analyzed in greater detail. As noted before, a linear relationship existed between the ratio of bromo

Table 8. Mathematical Reconstructions of Figure 3
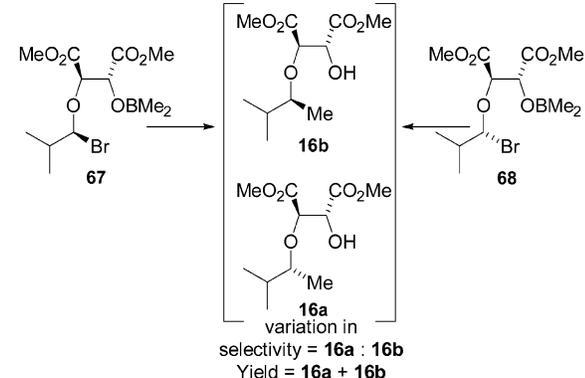
entry	temp	bromo ether	minimum selectivity (a:b)	maximum selectivity (a:b)	minimun yield (a + b)	maximum yield (a + b)
1	−30	**67**	93:7	98:2	77	83
2	−30	**68**	35:65	94:6	34	51
3	−78	**67**	87:13	100: 0	25	33
4	−78	**68**	20:80	0:100	30	45

ethers **59a**:**59b** and the ratio and yield of the final products. We had hypothesized that the two -ate complexes reacted through two separate chemical reactions: (1) the high-yielding and stereospecific displacement of the *S* bromo ether **59a** into **16a**, and (2) the low-yielding and unselective displacement of the *R* isomer **59b** into both **16a** and **16b**. We felt that our hypothesis could be further supported through a mathematical reconstruction of the experimental findings in Figure 3.

The scheme presented in Table 8 gives an empirical description of all the reactions that were performed using the intermediates derived from **15**. Both bromo ethers **67** and **68**, upon reaction with $Me_2Cu(CN)Li_2$, give final products **16a** and **16b**. A computer program was devised to process all of the possible values that could be achieved for **67** and **68** in terms of yield and selectivity. The resulting data was plotted on a curve using standard linear regression. The program then verified each curve and returned sets of parameters that reproduced the experimentally derived results.[26] Different sets of results that were consistent with our experimental observations were generated by the program, and several trends became apparent.

The bromo ether **67**, in simulations at −30 °C, appeared to be a very good substrate for the cuprate displacement, giving overall combined yields of **16a** and **16b** in the range of 77−83%. Furthermore, this isomer showed good selectivity for **16a** (Table 8, entry 1). The mathematical reconstruction that presented the closest match to the original experimental results indicated **67** was converted to **16a** by inversion of configuration (an S_N2-like process) with a minimum selectivity of 93:7 (**16a**: **16b**) and a minimum yield of 77% (**16a** + **16b**).

Conversely, intermediate **68** at −30 °C appeared to be a poor candidate for the cuprate displacement, giving low overall yields of **16a** and **16b** and moderate selectivity for **16a** (entry 2). The mathematical reconstructions for **68** are summarized in entry 2 and show that this isomer was displaced in an unselective S_N1

process with a range in selectivity from 35:65 to 94:6, surprisingly in favor of **16a**, and a maximum yield of 51% (**16a** + **16b**).[27]

Results of a similar experiment and simulation, in which the cuprate was added at −78 °C, are presented in entries 3 and 4. At this temperature, both intermediates were displaced selectively, although in low yield, with an inversion of configuration. Taken together, the data obtained from these calculations offered support that an S_N2-like mechanism was operative for **67** and **68** at −78 °C. This result supported the hypothesis that when the cuprate displacement took place at −30 °C, the behavior of the minor (*R*) isomer was responsible for the increase in diastereoselectivity.

Conclusions

The opening of acetals derived from tartaric esters using Me_2-BBr as the Lewis acid and $Me_2Cu(CN)Li_2$ as the alkylating agent is a valuable method for the synthesis of chiral secondary alcohols. Good selectivity was realized only when a particular set of experimental conditions was respected, following the opening of the acetal, suggesting that the mechanism of this reaction was different from those published previously for Johnson-type acetal substitutions. The diastereoselectivity originated from equilibration of bromo ether derivatives formed during the opening of the tartrate acetals with Me_2BBr. With L-tartrate as the chiral auxiliary, the most favorable isomer takes on the *S* configuration at the bromo ether carbon, a result supported by calculations and confirmed by X-ray diffraction analysis. The preference observed for the *S* isomer was dictated by the minimization of the ester dipole and by the gauche effect between the two oxygen atoms, both interactions being responsible for the conformational locking of the tartrate moiety.

Initial introduction of $Me_2Cu(CN)Li_2$ resulted in the formation of -ate complexes through a trans-metalation process that was apparently faster than the displacement of the bromine. When cuprate displacement was realized at −78 °C, the *S* and *R* bromo ethers (the -ate complexes) reacted through S_N2-like mechanisms. At −30 °C, the two isomers behaved differently with $Me_2Cu(CN)Li_2$. The major *S* bromo ether reacted in a highly selective manner and with high yield through an invertive S_N2-like mechanism. By contrast, the minor *R* isomer, for which oxocarbenium formation seemed to be favored in conjunction with an increase in temperature, reacted inefficiently through an S_N1 mechanism, resulting in *overall* increased selectivity during the cuprate displacement. This conclusion is supported both by the experimental data that was obtained and by the mathematical reconstruction that was subsequently performed.

These results illustrate the importance of considering the role of a potentially competing nucleophile as well as the source and fate of minor products, aspects often overlooked in investigations of selectivity and mechanistic elucidations.

Experimental Section[28]

General Procedure for the Preparation of Tartrate Acetals. To a mixture of aldehyde (10.0 mmol) and trimethylorthoformate (10.0 mmol) at 0 °C was added *p*-toluenesulfonic acid (0.5 mmol) in one

(26) We used the largest experiment error to construct a "window" within which calculated curves were accepted.

(27) This type of enhancement, where selectivity is generated on two or more levels, has been more rigorously described. Buschmann, H.; Scharf, H.-D.; Hoffmann, N.; Esser, P. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 477−515. See also: Ward, D. E.; Liu, Y.; Rhee, C. K. *Synlett* **1993**, 561−563.

(28) General experimental comments, physical properties, and analytical data are given in Supporting Information.

portion. After stirring for 1 h the mixture was diluted with benzene (60 mL), dimethyl tartrate was added (11.0 mmol), and the mixture refluxed overnight using a Soxlith packed with molecular sieves to remove methanol. The solution was then cooled to room temperature and diluted with ether. Washing with saturated NaHCO₃ and brine was followed by drying over MgSO₄ and flash chromatography to afford the desired acetals.

General Procedure for the Preparation of Mixed Acetals. **Method A.** To a cold (−78 °C) solution of acetaldehyde dimethyl acetal (1 equiv) in CH₂Cl₂ was added a solution of Me₂BBr in CH₂Cl₂ (1.2 equiv, ca. 1.5 M) and the resulting solution stirred at −78 °C for 10 min. Et(ⁱPr)₂N (2.5 equiv) was then added followed by a solution of the appropriate alcohol (1 equiv). After 1 h at −78 °C, the solution was poured into saturated NaHCO₃ and extracted with EtOAc. The organic phase was washed with brine, dried (MgSO₄), and concentrated in vacuo. Flash chromatography gave the desired products. **Method B.** A solution of methylvinyl ether was prepared by sparging methylvinyl ether into a cold (0 °C) solution of triethanolamine (ca. 40 mg) in CH₂-Cl₂ (20 mL). Typically 1−3 g was collected. A portion of this solution (1.3 equiv) was added to a solution of tartrate alcohol in CH₂Cl₂ (0.1 M) at 0 °C. Camphorsulfonic acid (0.02 equiv) was then added and stirring continued until TLC indicated that the reaction was complete (30 min). The mixture was then diluted with ether and washed with saturated NaHCO₃ and brine and dried (MgSO₄). Flash chromatography afforded the desired acetal.

General Procedure for Me₂BBr-Promoted Opening of Tartrate Acetals by Higher-Order Cuprates. A solution of Me₂BBr (ca. 1.5 M, 1.25 equiv) in CH₂Cl₂ was added dropwise to a cold (−78 °C) solution of acetal in CH₂Cl₂ (0.1 M). The resulting mixture was stirred at room temperature for 1 h before being cooled to −30 °C and stirred at this temperature for 15 min. A solution of Me₂Cu(CN)Li₂ (3 equiv) in THF (0.25 M) was then introduced via cannula (5 min addition) and the resulting solution stirred at −30 °C for 1 h before being quenched with MeOH (10 equiv). The mixture was then poured into an aqueous solution of NH₄Cl:NH₄OH (4:1), diluted with EtOAc, and stirred at room temperature for 15 min. Brine was added, the phases were separated, and the aqueous layer was extracted with EtOAc. The combined organic extracts were washed with brine, dried (MgSO₄), and concentrated in vacuo. The crude material was purified by flash chromatography. Diastereomeric ratios were determined by capillary gas chromatography.

General Procedure for Me₂BBr-Promoted Opening of Tartrate Acetals Using Thiophenol. A solution of Me₂BBr (ca.1.5 M, 1.25 equiv) in CH₂Cl₂ was added dropwise to a cold (−78 °C) solution of acetal in CH₂Cl₂ (0.1 M). The resulting solution was stirred at ambient temperature for 1 h before being cooled to −78 °C and stirred at that temperature for 15 min. Et(ⁱPr)₂N (4 equiv) or Et₃N (4 equiv) was then added dropwise followed immediately by a solution of PhSH in CH₂-Cl₂ (1.0 M). It was imperative that the PhSH solution be injected as rapidly as possible. After stirring for 1 h at −78 °C, the solution was poured into a solution of NaHCO₃ in water and stirred 15 min. Extraction with EtOAc was followed by washing with brine and drying over MgSO₄. Flash chromatography afforded the pure products.

General Procedures for the Removal of Tartrate Auxiliary. Method A. To a solution of substrate (0.5 mmol) and Et₃N (3 equiv) in CH₂Cl₂ (0.1 M) was added methanesulfonyl chloride (1.5 eq). After the mixture stirred for 30 min, DBU was added (10 equiv), and the solution was stirred at 0 °C until TLC indicated that the reaction was complete (30 min). The solution was then diluted with ether, washed with water, 10% HCl, saturated NaHCO₃, and brine, dried (MgSO₄), and concentrated in vacuo. The residue was then taken up in methanol (2 mL), NaOMe was added (1 mL of a 25% solution in MeOH), and the resulting solution refluxed 30 min. Brine was added (20 mL) after cooling to room temperature, and the solution was extracted with EtOAc (5 ×). Drying (MgSO₄) and concentrating were followed by flash chromatography to afford the pure alcohols. **Method B.** To a mixture of substrate (ca. 0.5 mmol), alcohol (MeOH or ethylene glycol, 10 equiv), and HMPA (6.0 equiv) was added 0.1 M SmI₂²⁹ in THF.³⁰ When TLC indicated that the reaction was complete (0.5−6 h), the septum was removed, and the mixture was stirred to destroy excess SmI₂ (blue solution becomes yellow). The mixture was then diluted with ether and washed with 10% HCl, 10% Na₂S₂O₃, saturated NaHCO₃, and brine, and dried (MgSO₄). Flash chromatography afforded the pure alcohols.

Supporting Information Available: Experimental procedures and characterizations for all new compounds, X-ray crystallographic structure for **22b** as well as ¹H or ¹³C NMR spectra for those compounds without elemental analysis, and ¹H NMR spectra for the Mosher ester derived from secondary alcohols (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

(29) Evans, D. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1990**, *112*, 6447−6449.
(30) All reagents were degassed by sparging with dry nitrogen. Commercially available (Aldrich) SmI₂ gave satisfactory results only if the solution was very fresh.