Synthetic and Mechanistic Investigations of the Aldehyde Addition Reactions of Tartrate Ester Modified Allylboronates

by

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B. S., College of Charleston, S. C.
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ABSTRACT

A review of the reactions of allylic organometallic reagents and aldehydes is presented in Chapter 1. Emphasis is placed on the diastereoselectivity of reactions involving chiral reagents and chiral aldehydes in the context of Single and Double Asymmetric Synthesis. The utility of the allylic boronate reagents in this context is also discussed . The strengths and limitations of several groups of reagents for the control of acyclic stereochemistry are highlighted.

Our contributions to this area involving the highly selective tartrate ester-modified allylboronate reagent (**154**) are described in Chapter 2. Studies were carried out to determine the scope of the reagent as well as to establish the factors that influence the stereoselectivity in their reactions with achiral aldehydes. The stereoselectivity was found to be substrate dependent. Aliphatic aldehydes gave optimum selectivity (*ca.* 85% e. e.) when the allylboration reactions were performed in toluene at –78 °C in the presence of 4Å molecular sieves. In contrast, aromatic and α,β-unsaturated aldehydes gave lower selectivity (60% e. e.) under identical reaction conditions. However, the selectivity of the aromatic cases could be improved (72% e. e.) by performing the reaction in THF. The stereoselectivity of α-, β-, and γ-alkoxy substituted aldehydes also proceeded with lower selectivity (65%–75% e. e.), the selectivity being dependent on the proximity of the alkoxy substituent to the aldehydic center. The stereoselectivity was found to increase in the order: α-alkoxy < β-alkoxy < γ-alkoxy.

The asymmetric induction in these reactions appears to originate from a novel stereoelectronic effect involving *n*/*n* repulsive interactions between the aldehydic oxygen atom and an ester carbonyl in the disfavored transition state (**C**).

Finally, based on the transition state model proposed above, investigations were carried out toward the development of chiral auxiliaries with improved enantioselectivity. These studies are described in Chapter 3. Modification of the previously-reported cyclic tartramide auxiliary (**2**) led to auxiliary (**26**) with improved solubility and reactivity characteristics while retaining the high enantioselectivity (92% e. e.) of (**2**). Attempts to develop a reagent based on cyclic tartrate auxiliary (**43**) proved problematic, and difficulties were encountered in the attempted formation of the reagent (**32**). Solution ^{1}H NMR data coupled with computer NMR simulation and MMX calculations suggest that the formation of (**32**) is disfavored by the preference of (**43**) to exist as a doubly hydrogen-bonded diaxial conformer (**46**) in solvents (e. g. CH_2Cl_2, $CHCl_3$) which cannot effectively disrupt the hydrogen bonds. In contrast, solvents such as THF and DMSO favor the diequatorial conformer (**47**).

Thesis Supervisor: Dr. William R. Roush

Title: Professor of Chemistry

To Jeff and my Parents

Biographical Note

The author was born April 25, 1962 on the island of Penang, Malaysia. In 1980, he completed the Cambridge O-Level Examinations after attending the MARA Junior Science College. He accepted an Undergraduate Scholarship from MARA and attended the College of Charleston, South Carolina where he received the degree of Bachelor of Science (*summa cum laude*) in May 1984. He then moved to Boston to pursue graduate studies in Chemistry at M. I. T., working with Professor William R. Roush. In 1987, he moved with Professor Roush to Indiana University, Bloomington to complete his graduate work. Upon receipt of his doctorate he will begin postdoctoral studies in the laboratories of Professor Lanny S. Liebeskind at Emory University in Atlanta, Georgia.

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First and foremost, I would like to express my sincere appreciation and thanks to Professor Roush for his patience and guidance during my stay with his group. His enthusiasm and dedication to science has provided a stimulating environment in which to learn and grow.

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I am also thankful to Professor J. Gajewski for all his help with the MMX calculations and the PCPMR simulation software. Thanks also to Dr. John Huffmann and the staff at the Indiana University Molecular Structure Center who provided the X-ray analyses.

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I would like to express special thanks and appreciation to my parents and Jeff for their support and help in countless ways during my college and graduate career. Their love, encouragement, and advice have helped me keep everything in perspective and on a steady course over the years, especially through the difficult times. I am ever in their debt.

Abbreviations

Ac	acetyl
Ac_2O	acetic anhydride
BINAL-H	binaphthol aluminum hydride
Bzl	benzyl
c-C_6H_{11}	cyclohexyl
calcd.	calculated
CI	chemical ionization
conc.	concentration
d. e.	diastereomeric excess
DET	diethyl tartrate
DHP	dihydropyran
DIBAL-H	diisobutylaluminum hydride
DIPT	diisopropyl tartrate
DMAP	4-dimethylaminopyridine
DMF	*N,N*-dimethylformamide
DMS	dimethylsulfide
DMSO	dimethylsulfoxide
e. e.	enantiomeric excess
EI	electron impact
equiv.	equivalents
Et_2O	ethyl ether
EtOAc	ethyl acetate
EtOH	ethanol
GC	gas chromatography
HRMS	high resolution mass spectrometry
IR	infra-red spectroscopy
LAH	lithium aluminum hydride
LRMS	low resolution mass spectrometry
MTPA-Cl	α-methoxy-α-(trifluoromethyl)phenylacetyl chloride
MTPAA	α-methoxy-α-(trifluoromethyl)phenylacetic acid
Ni-4-pin	nickel (II) bis(heptafluorobutyryl-(1R,2S)-pinan-4-oate)
Ni-R-cam	nickel (II) bis(3-heptafluorobutyryl-(1R)-camphorate)
NMR	nuclear magnetic resonance

obsvd.	observed
PCC	pyridinium chlorochromate
Ph	phenyl
PMA	phosphomolybdic acid
PPTS	pyridinium para-toluenesulfonate
PTLC	preparative thin layer chromatography
pTsOH	para-toluenesulfonic acid
pyr	pyridine
Red-Al	sodium bis(2-methoxyethoxy)aluminum hydride
TBDMS	tert-butyldimethylsilyl
TBDPS	tert-butyldiphenylsilyl
THF	tetrahydrofuran
THP	tetrahydropyran
TLC	thin layer chromatography
t_R	retention time
UV	ultraviolet

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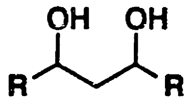
CHAPTER 1

Classification and Reactions of Allylorganometallic Reagents

1.1 Introduction

The common occurrence of substructures (**1**)–(**3**) in numerous natural products of propionate, acetate, and glycolate biosynthetic origin has resulted in considerable attention and effort being concentrated toward the development of efficient synthetic methodology which can be applied to the construction of such fragments in a highly stereoselective manner.[1–3]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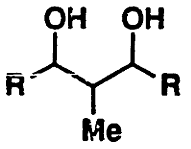
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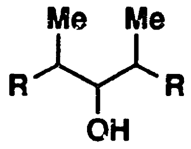
(3)

Techniques which allow for the formation of C—C bonds with the creation of two new chiral centers are of particular interest. One method which has proven very useful is the aldol condensation, especially since powerful chiral enolates have been developed which are capable of taking advantage of the principle of double asymmetric synthesis in controlling the stereochemical outcome of reactions with chiral aldehydes.[4, 5]

Methodology that is complementary to the aldol reaction for acyclic stereocontrol is found in the reactions of allylmetal reagents with carbonyl compounds.[6] Allylmetal reagents

---

[1] General Reviews: (a) Bartlett, P. A. *Tetrahedron* **1980**, *36*, 3. (b) McGarvey, G. J.; Kimura, M.; Oh, T.; Williams, J. M. *J. Carbohydr. Chem.* **1984**, *3*, 125.

[2] For reviews of synthetic efforts in the macrolide antibiotic area: (a) Paterson, I.; Mansuri, M. M. *Tetrahedron* **1986**, *41*, 3569. (b) Masamune, S.; McCarthy, P. A. in *Macrolide Antibiotics*, S. Omura, Ed.; Academic Press: New York, 1984, p. 127.

[3] Hoffmann, R. W. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 489.

[4] For reviews of the aldol reaction: (a) Heathcock, C. H. In "Asymmetric Synthesis;" Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, p. 111. (b) Evans, D. A.; Nelson, J. V.; Taber, T. R. *Topics Stereochem.* **1982**, *13*, 1. (c) Mukaiyama, T. *Org. React.* **1982**, *28*, 203.

[5] For a review of double asymmetric synthesis: Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1.

[6] For reviews of the reactions of allylmetal compounds with aldehydes and imines, see: (a) Yamamoto, Y. *Acc. Chem. Res.* **1987**, *20*, 243. (b) Hoffmann, R. W. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 555. (c) Yamamoto, Y.; Maruyama, K. *Heterocycles* **1982**, *18*, 357. (d) Courtois, G.; Miginic, L. *J. Organomet. Chem.* **1974**, *69*, 1.

are numerous, many affording high stereochemical control in their reactions with carbonyl compounds and imines. The attractiveness of employing these reagents in synthesis is further enhanced by the ease of preparation of many substituted and highly-functionalized allylorganometallic species, and by the ability to store many such reagents (e.g., reagents based on B, Si, Sn) until needed. Furthermore, the homoallylic alcohol reaction products are readily transformed into other desirable synthetic intermediates via appropriate manipulations of the double bond.

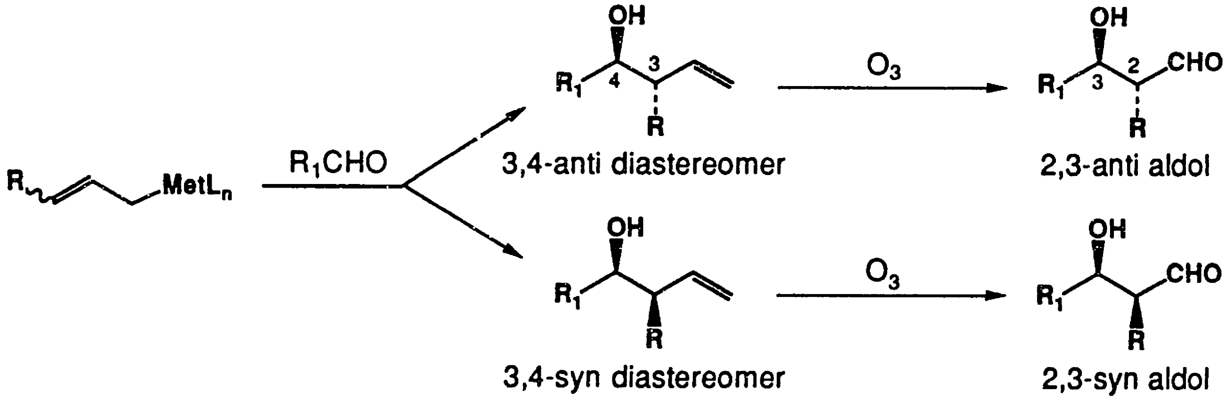

Figure 1

As indicated in Figure 1, the reaction between a crotylorganometallic species and an achiral aldehyde yields a product(s) in which two new chiral centers are formed at C(3) and C(4). The major concern here, that is, the issue of *simple diastereoselectivity*, is that the pair of stereocenters be generated in a highly stereoselective manner, ideally leading specifically to one of the two possible diastereomeric products. The syn/anti nomenclature system proposed by Masamune is used to describe them and will be used throughout this thesis for the sake of clarity.[7] If the reaction sequence in Figure 1 is carried out with a chiral aldehyde, an added degree of complexity is introduced since the stereochemistry of the new stereocenters relative to the pre-existing ones in the aldehyde must be taken into account. That is, four possible diastereomeric products may be produced (Figure 2). This is a problem of *relative diastereoselectivity*, and is also of concern in reactions involving allylmetal reagents with chiral C=X functional groups.

---

[7] Masamune, S.; Ali, S. A.; Snitman, D. L.; Garvey, D. S. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 557. The "threo" and "erythro" nomenclature that has found widespread application in the literature is ambiguous and should be avoided (see ref. 4a).

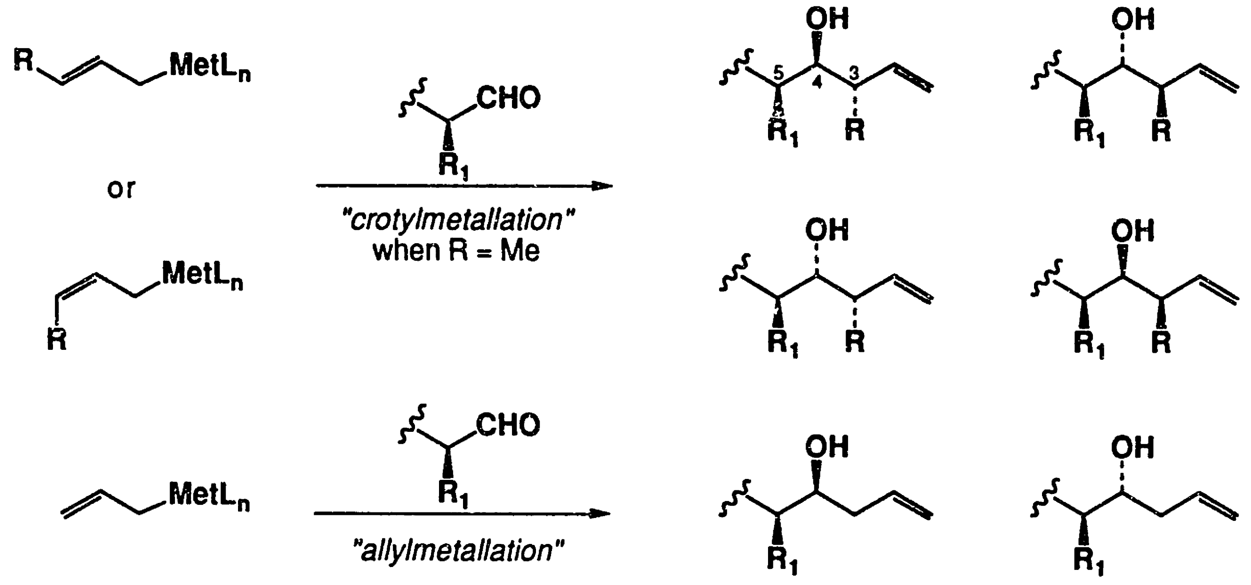

Figure 2

Ultimately, it is desirable to use a reagent, or a family of reagents, that enables each of the four possible crotyl addition products (or either of the two allyl transfer products) to be produced selectively. It is with this goal in mind that much research has been channelled toward the development of a group of highly stereoselective allyl- and crotylorganometallic reagents. While the problem of simple diastereoselectivity has been addressed, and solved, by many of the crotylorganometallic reagents that are currently known, the question of aldehyde diastereofacial selectivity (relative diastereoselectivity) has proven to be much more of a challenge. Even though specific cases are known that provide for excellent selectivity, these are currently the exceptional cases. The bulk of the reported achiral allyl- and crotylmetal reagents react with chiral aldehydes with poor to moderate diastereofacial selection. However, the powerful technique of double asymmetric synthesis furnishes a means to achieve synthetically acceptable levels of selectivity in the problem defined in Figure 2, to the extent that highly enantioselective allylmetal and crotylmetal reagents are available.

This chapter provides a brief overview of the various classes of allylorganometallic reagents and their reactions with C=O electrophiles, and serves as background material for the studies described in the main body of this thesis.

1.2 Classification of Crotyl- and Allylorganometallic Reagents

The reactions of carbonyl compounds and imines with allylmetal and crotylmetal reagents derived from a variety of metals including aluminum, antimony, bismuth, boron, cadmium, chromium, cerium, copper, indium, lithium, magnesium, manganese, molybdenum, potassium, silicon, tin, titanium, zinc, and zirconium, among others, have been investigated.[6] Before 1978, the main interest was in controlling the regioselectivity (S_E2 vs. S_E2') in the coupling reactions between these organometallic reagents with electrophiles.[6a] But the desire to control the stereochemistry of the C—C bond forming process was stimulated by the potential for applications in synthesis,[8] and in 1978 a report appeared from Heathcock that highly selective anti additions to aldehydes had been achieved by using the (E)-crotylchromium (II) reagent first developed by Hiyama.[9] This was followed a year later by reports from Hoffmann regarding the stereoselective crotylboration reactions of aldehydes and (Z)-crotylboronates that provided syn homoallylic alcohol products.[10]

Crotylorganometallic reagents have now been classified into three categories based on mechanistic and stereochemical considerations:[11]

---

[8] (a) An early study on the stereochemistry of the thermal reactions of crotylstannanes and aldehydes was reported in 1972: Servens, C.; Pereyre, M. *J. Organomet. Chem.* **1972**, *35*, C20. (b) Results of early stereochemical studies with crotylmagnesium, -cadmium and -zinc are summarized in ref. 6d.

[9] (a) Buse, C. T.; Heathcock, C. H. *Tetrahedron Lett.* **1978**, 1685. (b) Hiyama, T.; Kimura, K.; Nozaki, H. *Tetrahedron Lett.* **1981**, *22*, 1037. (c) Hiyama, T.; Okude, Y.; Kimura, K.; Nozaki, H. *Bull. Chem. Soc., Jpn.* **1982**, *55*, 561. (d) Okude, Y.; Hirano, S.; Hiyama, T.; Nozaki, H. *J. Am. Chem. Soc.* **1977**, *99*, 3179.

[10] (a) Hoffmann, R. W.; Zeiss, H. J. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 306. (b) Hoffmann, R. W.; Zeiss, H. J. *J. Org. Chem.* **1981**, *46*, 1309.

Type 1: The syn/anti ratio of the products reflects the (Z)/(E) ratio of the allylic moiety of the reagent. These organometallic entities presumably react with aldehydes via chair-like transition states such that the stereochemical information present in the reagent is transmitted to an anti (from (E)-olefin precursors) or a syn (from (Z)-olefin precursors) relationship about the new C—C bond in the product. Reagents exhibiting these characteristics include those that incorporate boron, aluminum, silicon, and tin (thermal reactions).

Type 2: Syn selective products are generated regardless of the geometry of the allyl unit of the reagent. These reagents undergo *Lewis acid-* catalyzed carbonyl additions and include reagents based on tin, silicon, and titanium.[12–14]

Type 3: Reagents that undergo anti selective reactions independent of the geometry of the allyl unit or its precursors.[9b, c, 15–17] Type 3 crotylmetal reagents are normally generated *in situ* and presumably equilibrate to the more stable and/or more reactive (E)-isomer which then reacts via a cyclic transition state to give the anti adduct. Reagents that fall into this category include those that are derived from titanium, chromium, and zirconium.[15–17]

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[11] Denmark, S. E.; Eber, E. J. *Helv. Chim. Acta* **1983**, *66*, 1655.

[12] (a) Yamamoto, Y.; Yatagai, H.;.Naruta, Y; Maruyama, K. *J. Am. Chem. Soc.* **1980**, *102*, 7107. (b) Yamamoto,Y.; Yatagai, H.; Ishihara, Y.; Maeda, N.; Maruyama, K. *Tetrahedron* **1984**, *40*, 2239. (c) Keck, G. E.; Abbott, D. E.; Boden, E. P.; Enholm, E. J. *Tetrahedron Lett.* **1984**, *25*, 3927. (d) Koreeda, M.; Tanaka, Y. *Chem. Lett.* **1982**, 1299.

[13] Hayashi, T.; Kabeta, K.; Hamachi, I.; Kumada, M. *Tetrahedron Lett.* **1983**, *24*, 2865.

[14] (a) For the syn-selective, Lewis acid catalyzed addition of an (E)-crotyltitanium reagent to aldehydes: Reetz, M. T.; Sauerwald, M. *J. Org. Chem.* **1984**, *49*, 2292. (b) For the reversal of diastereoselectivity in the BF_3 promoted additions of other crotylorganometallic reagents (Met = Cu, Cd, Hg, Tl, Ti, Zr, and V): Yamamoto, Y.; Maruyama, K. *J. Organomet. Chem.* **1985**, *284*, C45.

[15] (a) Sato, F.; Iida, K.; Iijima, S.; Moriya, H.; Sato, M. *J. Chem. Soc. Chem. Commun.* **1981**, 1140. (b) Seebach, D.; Widler, L. *Helv. Chim. Acta* **1982**, *65*, 1972. (c) Widler, L.; Seebach, D. *Helv. Chim. Acta* **1982**, *65*, 1085. (d) Seebach, D.; Weidmann, B. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 31. (e) Reetz, M. T. *Topics Current Chem.* **1982**, *106*, 1.

[16] (a) Mashima, K.; Yasuda, H.; Asami, T.; Nakamura, A. *Chem. Lett.* **1983**, 219. (b) Yamamoto, Y.; Maruyama, K. *Tetrahedron Lett.* **1981**, *27*, 2895.

[17] (a) Sato, F.; Iijima, S.; Sato, M. *Tetrahedron Lett.* **1981**, *22*, 243. (b) Lehmkuhl, H.; Gustero, S. *Liebigs Ann. Chem.* **1980**, 1371. (c) Martin, H. A.; Jellinek, F. *J. Organomet. Chem.* **1967**, *8*, 115; *Idem.* **1968**, *12*, 149.

1.2.1 Configurational Stability of Crotylorganometallic Reagents

The main difference between Type 1 and Type 2 or Type 3 crotylorganometallics is the configurational stability of the olefin functionality (Type 1), or lack thereof (Type 2 and Type 3), under the conditions of the reactions with C=O electrophiles. Since the syn/anti ratio of products from Type 1 reagents reflect the ratio of the (Z)/(E) olefin isomers respectively, the stereochemical integrity of the olefinic fragment prior to reaction becomes a crucial factor in deciding the efficiency of the reagent. It follows then that the reagents should be accessible by highly stereoselective synthetic routes, and they should, preferably, be stable to storage. The lack of configurational stability of Type 3 and Type 2 reagents, however, means that high stereochemical control need not be exercised over the construction of an allylic halide or other organometallic precursor. Thus, for example, many Type 3 crotyltitanium and zirconium reagents are prepared from crotyllithium or crotylmagnesium bromide, which exist as mixtures of rapidly equilibrating (E)- and (Z)-isomers,[18] since the (Z)-crotyltitanium or -zirconium species that are produced equilibrates rapidly to the (E)-isomer which is either highly favored at equilibrium or is the more reactive of the two.[15, 17] Crotyllithium or crotylmagnesium bromide, however, cannot be used in the preparation of Type 1 crotylorganometallics since mixtures of (E)- and (Z)-isomers will be produced. One route to configurationally defined Type 1 crotylorganometallics involves the (E)- and (Z)-crotylpotassiums which can be generated with high isomeric purity and are configurationally stable in the absence of traces of O_2.[18a, 19]

Allylmetal compounds can exist in either the *monohapto* (η^1)- or *trihapto* (η^3)-forms. Crotylmetal compounds that exist in the *monohapto* form, including those classified as Type 1 reagents, are generally sensitive to metallotropic rearrangements (sequential 1,3-shifts) which affect (E) to (Z) isomerization via the intermediacy of the methallylmetal isomer (Figure 3). *Trihapto*, or π-bound, allylmetal reagents can exist in either of two forms: the extended or (E)-isomer and the U-shaped or (Z)-isomer. These η^3 reagents can also isomerize if a pathway for interconversion with the η^1-methallyl intermediate is energetically accessible.

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[18] (a) Schlosser, M.; Hartmann, J. *J. Am. Chem. Soc.* **1976**, *98*, 4674. (b) Hutchison, D. A.; Beck, K. R.; Benkeser, R. A.; Grutzner, J. B. *Ibid.* **1973**, *95*, 7075. (c) West, P.; Purmort, J. I.; McKinley, S. V. *Ibid.* **1968**, *90*, 797. (d) Whitesides, G. M.; Norlander, J. E.; Roberts, J. D. *Ibid.* **1962**, *84*, 2010.

[19] (a) Schlosser, M. *Angew. Chem., Int. Ed. Engl.* **1974**, *13*, 701. (b) Stahle, M.; Hartmann, J.; Schlosser, M. *Helv. Chim. Acta* **1977**, *60*, 1730. (c) Fujita, K.; Schlosser, M. *Helv. Chim. Acta* **1982**, *65*, 1258. (d) Schlosser, M.; Fujita, K. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 309.

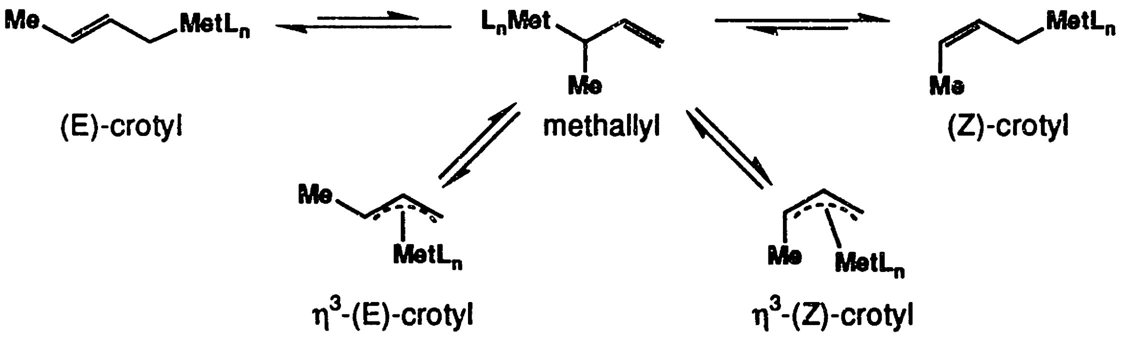

Figure 3

Allylboron compounds have been the most widely studied of the Type 1 allylorganometallics.[6b] Of these, the dialkylcrotylboranes isomerize most readily and often require handling at temperatures below –78 °C for isomerization to be suppressed.[20] Thus, it is probably more appropriate to view such compounds (e.g., crotyl-9-BBN) as Type 3 crotylorganometallics. The boratropic isomerization of dialkylcrotylboranes, however, is sensitive to steric factors. For example, the (E)- and (Z)-crotyl(diisopinocampheyl)boranes undergo highly stereoselective additions to aldehydes at –78° C.[21] Nevertheless, these reagents are too labile to be prepared and stored for subsequent use.[21c] The boratropic shift may also be suppressed by replacing the alkyl ligands on boron with electron-donating alkoxy or amino groups that stabilize the electrophilic boron atom by resonance. Replacement of one alkyl ligand of an allyldialkylborane with an alkoxy group stabilizes the reagent at temperatures up to –20 °C, but using an amino ligand suppresses the boratropic rearrangement at temperatures up to 150 °C.[22] Replacement of both alkyl ligands with alkoxy group gives allylboronic acid esters that can be handled at room temperature without isomerization; many have been distilled and their isomeric purity determined by capillary GC analysis.[23] These heteroatom stabilized allylboron reagents, however, readily isomerize in the presence of Lewis acids.[10b, 24]

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[20] (a) Mikhailov, B. M. *Organomet. Chem. Rev.* **1972,** *A8,* 1. (b) Kramer, G. W.; Brown, H. C. *J. Organomet. Chem.* **1977,** *132,* 9. (c) Yamaguchi, M.; Mukaiyama, T. *Chem. Lett.* **1980,** 993.

[21] (a) Brown, H. C.; Jadhav, P. K.; Bhat, K. S. *J. Am. Chem. Soc.* **1985,** *107,* 2564. (b) Brown, H. C.; Bhat, K. S. *Ibid.* **1986,** *108,* 293. (c) For an indication of the configurational instability of the related [(Z)-γ-alkoxyallyl]diisopinocampheylboranes: Brown, H. C.; Jadhav, P. K.; Bhat, K. S. *Ibid.* **1988,** *110,* 1535.

Type 1 crotylmetal reagents based on silicon and tin have also proven useful synthetically. Crotyltrimethylsilane is reported to be configurationally stable at elevated temperatures,[25] but only Type 2 carbonyl addition reactions (Lewis acid catalyzed) have been reported for this compound. Type 1 reactivity has been demonstrated for pentacoordinate crotylsilicates, and available stereochemical evidence suggests that these reagents are configurationally stable.[26] The crotyltrialkylstannanes, on the other hand, undergo carbonyl additions either thermally (Type 1)[8a] or in the presence of Lewis acid catalysts (Type 2 reactivity).[12] These compounds readily isomerize in the presence of Lewis acids,[12c, 27] and there are also indications that they may spontaneously isomerize (uncatalyzed) at temperatures below 100 °C.[28] Configurational instability, however, has not been demonstrated under the conditions of thermal additions to aldehydes.[8] Crotylstannanes such as (crotyl)SnX_3 and (crotyl)SnR_nX_{3-n} are more reactive than the trialkylcrotylstannanes,[29] and are probably highly prone towards isomerization owing to the Lewis acidity of the tin atom.[27, 30]

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[22] (a) Midland, M. M.; Preston, S. B. *J. Org. Chem.* **1980**, *45*, 747. (b) Hancock, K. G.; Kramer, J. D. *J. Am. Chem. Soc.* **1973**, *95*, 6463.

[23] Roush, W. R.; Adam, M. A.; Walts, A. E.; Harris, D. J. *J. Am. Chem. Soc.* **1986**, *108*, 3422.

[24] (a) Blais, J.; L'Honore, A.; Soulie, J.; Cadiot, P. *J. Organomet. Chem.* **1974**, *78*, 323. (b) Hancock, K. G.; Kramer, J. D. *Ibid.* **1974**, *64*, C29.

[25] (a) Slutsky, J.; Kwart, H. *J. Am. Chem. Soc.* **1973**, *95*, 8678. (b) Chan, T. H.; Fleming, I. *Synthesis* **1979**, 761.

[26] (a) Kira, M.; Kobayashi, M.; Sakurai, H. *Tetrahedron Lett.* **1987**, *28*, 4081. (b) Kira, M.; Sato, K.; Sakurai, H. *J. Am. Chem. Soc.*, **1988**, *110*, 4599. (c) Hosomi, A.; Kohra, S.; Tominaga, Y. *J. Chem. Soc., Chem. Commun.* **1987**, 1517. (d) Kira, M.; Hino, T.; Sakurai, H. *Tetrahedron Lett.*, 1989, **30**, 1099.

[27] Gambaro, A.; Marton, D.; Tagliavini, G. *J. Organomet. Chem.* **1981**, *210*, 57.

[28] (a) Verdone, J. A.; Mangravite, J. A.; Scarpa, N. M.; Kuvila, H. G. *J. Am. Chem. Soc.* **1975**, *97*, 843. (b) Yatagai, H.; Yamamoto, Y.; Maruyama, K. *Ibid.* **1980**, *102*, 4548.

[29] Gambaro, A.; Peruzzo, V.; Plazzogna, G.; Tagliavini, G. *J. Organomet. Chem.* **1980**, *197*, 45.

Configurational lability is desirable in Type 3 reagents, in as much as one geometric isomer is more reactive and/or highly favored at equilibrium. *Monohapto*-crotylchromium, titanium and zirconium compounds apparently satisfy these requirements,[9, 15, 16] while *trihapto*-crotyltitanium reagents such as dicyclopentadienylcrotyltitanium appear to be configurationally stable.[17] *Trihapto*-cyclopentadienylcrotylmolybdenum complexes also appear to be stable.[31]

Many other crotylorganometallics that would be classified as Type 3 reagents based on their configurational instability, including crotylcadmium, lithium, magnesium, and zinc, however, are not generally useful for diastereoselective synthetic conversions since mixtures of syn and anti homoallyl alcohols are obtained in reactions with achiral aldehydes.[6d] The equilibrium between the (E)- and (Z)-crotyl isomers is not highly biased in these cases,[19] consequently the poor diastereoselectivity suggests that the two isomers have comparable reactivity towards carbonyl electrophiles. Synthetically useful results have been obtained with reagents containing these metals only in cases where the crotylmetal compound is sterically biased or contains chelating substituents such that one geometric isomer is substantially favored at equilibrium.[32]

1.2.2 Transition States for the Reactions of Crotylorganometallic Reagents with C=O Electrophiles

Another factor that influences the diastereoselectivity of the C—C bond forming process concerns the selectivity for reaction through a single transition state. Clearly, if two or more diastereomeric transition states are accessible the reaction diastereoselectivity will suffer.

Possible transition states for the reactions of Type 1 and 3 crotylorganometallics with aldehydes are depicted in Figure 4. Most of the available stereochemical evidence suggests that

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[30] (a) Gambaro, A.; Marton, D.; Peruzzo, V.; Tagliavini, G. *J. Organomet. Chem.* **1982**, *226*, 149. (b) Auge, J.; David, S. *Tetrahedron Lett.* **1983**, *214*, 4009.

[31] (a) Faller, J. W.; John, J. A.; Mazzieri, M. R. *Tetrahedron Lett.*, submitted. (b) Faller, J. W.; Linebarrier, D. L. *J. Am. Chem. Soc.*, submitted.

[32] (a) Fang, J. -M.; Hong, B. -C. *J. Org. Chem.* **1987**, *52*, 3162. (b) Fang, J. -M.; Hong, B. -C.; Liao, L. -F. *Ibid.* **1987**, *52*, 855. (c) Auvray, P.; Knochel, P.; Normant, J. F. *Tetrahedron Lett.* **1986**, *27*, 5091.

these reactions proceed preferentially through transition state (7) in which the metal is coordinated to the carbonyl oxygen syn to the smallest carbonyl substituent, H. This necessitates that R of RCHO adopt an equatorial position if the transition state is chair-like, an arrangement that is structurally similar to the Zimmerman-Traxler model commonly invoked for many aldol reactions.[4a] Transition states (8) and (9), however, may potentially intervene and are frequently cited to rationalize the production of minor diastereomers (12).

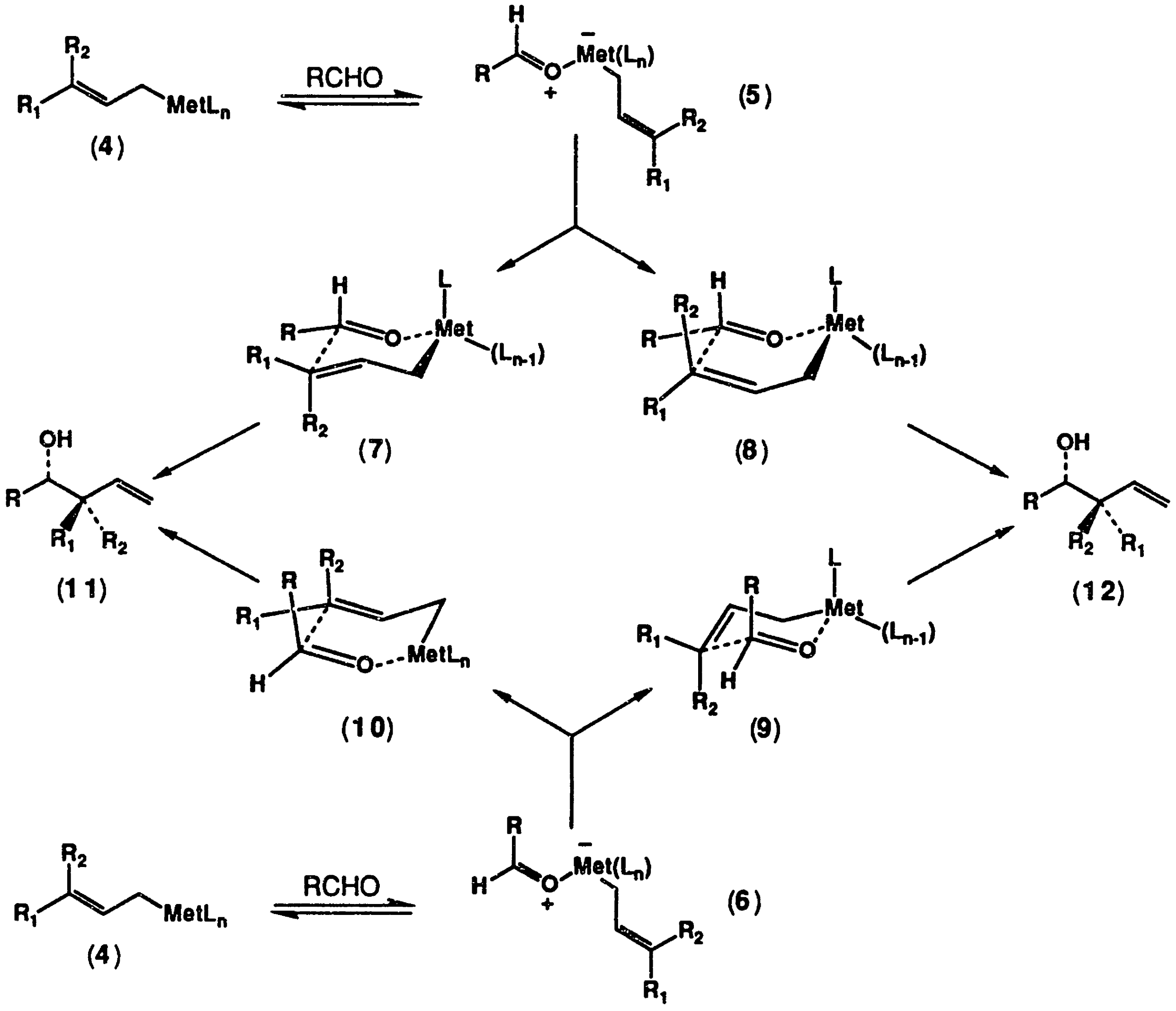

Figure 4

These reactions are probably initiated by the coordination of the carbonyl group with the Lewis acidic metal center (see structures (**5**) and (**6**)). Complex (**5**) should be highly favored as suggested by solution and X-ray structural investigations of Lewis acid aldehyde complexes.[33] It is productive then to view the conversion of complex (**5**) (or (**6**)) to products as a [3,3]-sigmatropic rearrangement of a 2-oxa-3-metalla-1,5-diene system. It would be expected then that chair-like transition state (**7**) would be favored over boat-like (**8**) for the same reasons that acyclic Claisen and other [3,3]-sigmatropic rearrangements are usually highly chair selective.[34] The alternative chair-like transition state (**9**) is usually viewed as unfavorable owing to the interactions of the axial R of RCHO with the axial metal ligand.

It is difficult to assess the relative importance of transition states (**7**)–(**10**) in the reactions of Type 3 crotylorganometallics since their configurational instability provides an alternative set of pathways for generation of the minor diastereomer (**12**). This question can be addressed more easily with configurationally stable Type 1 reagents as long as the isomeric purity of the reagent is known. In a recent detailed study of the stereochemistry of the reactions of tartrate crotylboronates (**13**) and (**14**) with achiral aldehydes, for example, it has been shown that in most cases the (E)-crotyl reagent (**13**) of 98% isomeric purity provides the 3,4-anti diastereomer (**11**) (R_1 = Me, R_2 = H) with ≥98% diastereoselectivity, while with ≥98% pure (Z)-crotyl reagent (**14**) the 3,4-syn diastereomer (**11**) (R_1 = H, R_2 = Me) is usually obtained with at least 97% selectivity.[35] These reactions thus are highly selective for transition state (**7**), providing evidence that (**8**)–(**10**) must be highly disfavored.[36]

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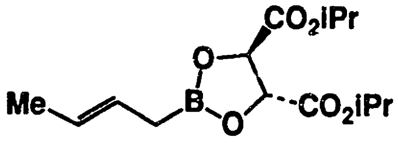
[33] (a) Reetz, M. T.; Hüllmann, M.; Massa, W.; Berger, S.; Rademacher, P.; Heymanns, P. *J. Am. Chem. Soc.* **1986**, *108*, 2405. (b) Denmark, S. E.; Henke, B. R.; Weber, E. *Ibid.* **1987**, *109*, 2512. (c) Childs, R. F.; Mulholland, D. L.; Nixon, A. *Can. J. Chem.* **1982**, *60*, 801.

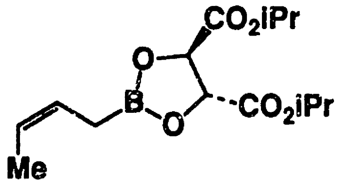
[34] For a recent review of the aliphatic Claisen rearrangement: Ziegler, F. E. *Chem. Rev.* **1988**, *88*, 1423.

[35] (a) Roush, W. R.; Ando, K.; Powers, D. B.; Halterman, R. L.; Palkowitz, A. D. *J. Am. Chem. Soc.*, submitted for publication. (b) Roush, W. R.; Ando, K.; Powers, D. B.; Halterman, R. L.; Palkowitz, A. D. *Tetrahedron Lett.* **1988**, *29*, 5579.

[36] Additional insight into the competition between the various cyclic transition states was provided by a recent study of the reactions between crotylboronates and oxime silyl ethers derived from benzaldehyde: Hoffmann, R. W.; Endesfelder, A. *Liebigs Ann. Chem.* **1987**, 215.



(R,R)-(13)



(R,R)-(14)

In contrast to the Type 1 and Type 3 allylmetal reagents, Type 2 allylorganometallics are believed to undergo Lewis acid-catalyzed addition to C=O species via open, acyclic transition states. Indeed, Yamamoto, in his investigations of the reactions of crotylstannanes with aldehydes in the presence of a Lewis acid catalyst, proposed antiperiplanar orientations (**20**) and (**21**) of the reactive components to account for the observed syn-selective diastereoselection in the resulting products.[12a] However, subsequent studies by Denmark on the intramolecular addition of allylsilane and allylstannane to an aldehyde have suggested that transition states which involve a synclinal arrangement [(**22**) and (**23**)] may play a greater role than previously suspected and that the adoption of a synclinal orientation may be the result of a stereoelectronic preference, the origin of which is as yet unclear.[11, 37]

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[37] (a) Denmark, S. W.; Weber, E. J. *J. Am. Chem. Soc.* **1984**, *106*, 7970. (b) Seebach, D.; Golínski, J. *Helv. Chim. Acta* **1981**, *5*, 1413.

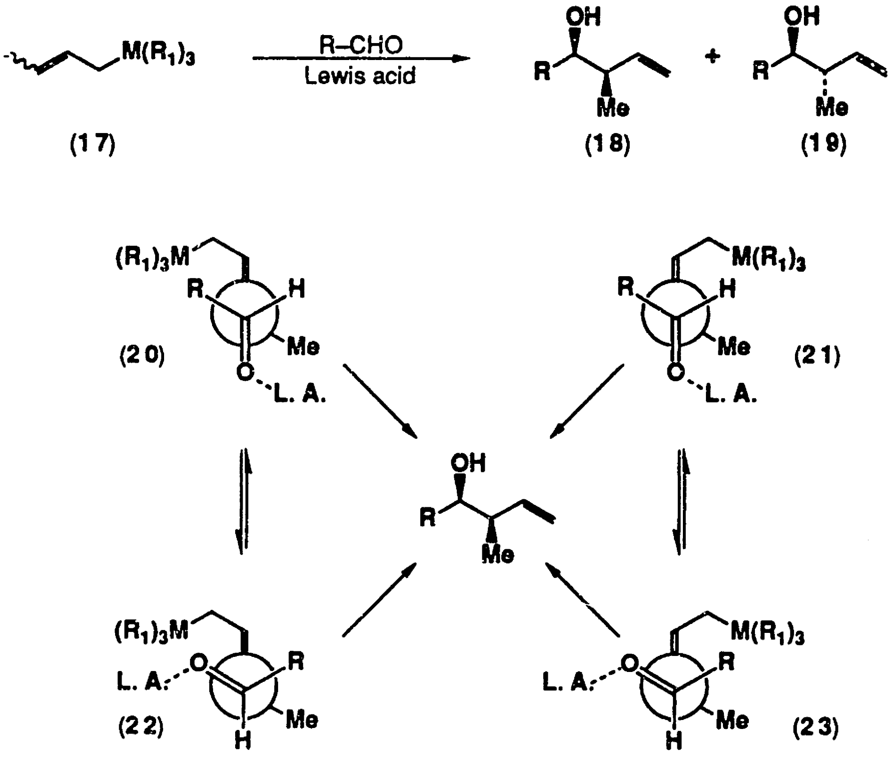

Figure 5

In addition, as a result of the potential lability of Type 2 reagents under the conditions of Lewis acid catalysis, other mechanistic pathways may become available as a consequence of *in situ* transmetallation reactions between the allylmetal and the catalyst to form new allyl-organometallic species which can then compete in the carbonyl additions via alternate routes (e.g., as Type 3 reagents). In some cases, this process can become dominant to the extent that complete reversal of the stereochemical outcome is observed.[12c, 38]

1.3 Reactions of Crotylorganometallic Reagents with Achiral Aldehydes

1.3.1 Type 1 Reagents

Reagents based on Aluminum. Even though many studies have been carried out on the reactions of heteroatom-substituted allylaluminum reagents (**(25)**, **(27)**–**(29)**), the parent crotylaluminum reagent **(24)** or its (E)-crotyl isomer have not been thoroughly

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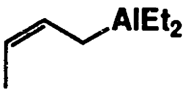
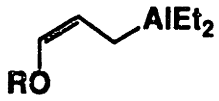
[38] Green, J. R.; Majewski, M.; Alo, B. I.; Snieckus, V. *Tetrahedron Lett.* **1986**, 535.

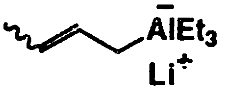
explored.[39] In general, reagents (**24**)–(**28**) have been prepared via the reactions of an alkali crotylmetal reagent and an appropriate alkylaluminum species at low temperatures (≤ –78 °C).[39–46] Excellent levels of stereocontrol have been realized with most of these reagents, and Type 1 diastereoselection is clearly evident in the data for the reactions of (**29a**) and (**29b**) (Figure 6).[43]



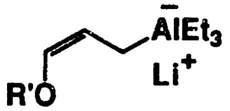
(24)



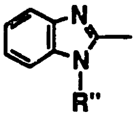
(25a) R = Me
(25b) R = CMe$_2$OMe



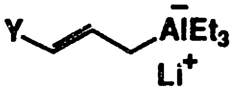
(26)



(27a), R' =



(27b), R' = Me$_2$CH-
(27c), R' = MeOCH$_2$O-



(28a) Y = S(*i*-Pr)
(28b) Y = SePh
(28c) Y = SiMe$_3$

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[39] Still, W. C.; Collum, D. B.; McDonald, J. H., III, *J. Am. Chem. Soc.* **1980**, *102*, 2118.

[40] (a) Keck, G. E.; Abbott, D. E. *Tetrahedron Lett.* **1984**, *25*, 1883. (b) Suzuki, K.; Katayama, E.; Tomooka, K.; Matsumoto, T.; Tsuchichashi, G. *Tetrahedron Lett.* **1985**, *26*, 3707. (c) Nakajima, N.; Hamada, T.; Tanaka, T.; Oikawa, Y.; Yonemitsu, O. *J. Am. Chem. Soc.* **1986**, *108*, 4645.

[41] Koreeda, M.; Tanaka, Y. *J. Chem. Soc., Chem. Commun.* **1982**, 845.

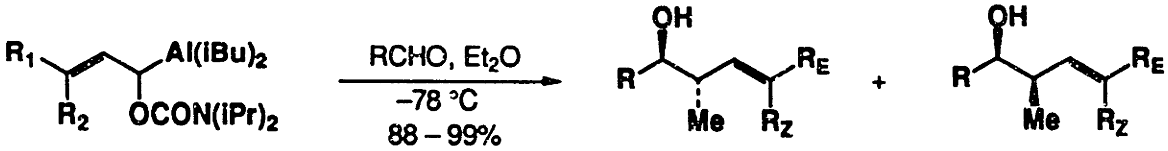
[42] (a) Hoppe, D.; Lichtenberg, F. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 372. (b) Hoppe, D.; Lichtenberg, F. *Ibid.* **1984**, *23*, 239.

[43] (a) Yamaguchi, M.; Mukaiyama, T. *Chem. Lett.* **1982**, 237. (b) Yamamoto, Y.; Yatagai, H.; Saito, Y.; Maruyama, K. *J. Org. Chem.* **1984**, *49*, 1096.

[44] (a) Yamamoto, Y.; Yatagai, H.; K. Maruyama, *J. Chem. Soc., Chem. Commun.* **1980**, 1072. (b) Yamamoto, Y.; Yatagai, H.; Maruyama, K. *J. Am. Chem. Soc.* **1981**, *103*, 1969.

[45] Yamamoto, Y.; Saito, Y.; Maruyama, K. *J. Chem. Soc., Chem. Commun.* **1982**, 1326.

[46] (a) Hanko, R.; Hoppe, D. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 372. (b) For a review: Hoppe, D. *Ibid.* **1984**, *23*, 932.



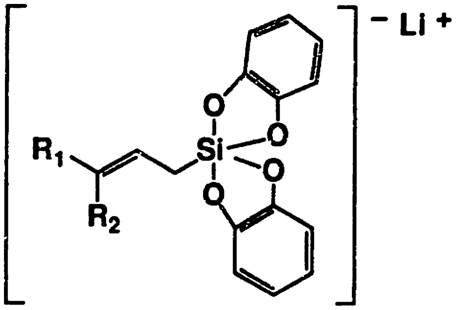
(29a) R_1 = Me, R_2 = H
(29b) R_1 = H, R_2 = Me

(30) R_E = OCON(iPr)$_2$, R_Z = H (32)
(31) R_E = H, R_Z = OCON(iPr)$_2$ (33)

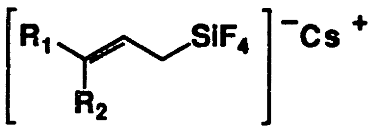
Reagent	RCHO	(30) : (31) : (32) : (33)	anti : syn
(29a)	PhCHO	77 6 16 < 1	83 : 17
(29a)	MeCHO	78 13 8 < 1	91 : 9
(29a)	i-PrCHO	90 4 5 < 1	94 : 6
(29a)	Me_3CCHO	87 10 2 < 1	97 : 3
(29b)	PhCHO	8 2 87 3	10 : 90
(29b)	MeCHO	8 7 79 6	15 : 85
(29b)	i-PrCHO	7 7 80 6	14 : 86

Figure 6

Reagents based on Silicon. Stereoselective reactions between crotylsilicates (34)–(35) and aldehydes have been reported (Figure 7).^{26} These reactions occur readily at room temperature in the absence of a Lewis acid catalyst, and Type 1 diastereoselectivity is quite apparent in the data.



(34a) R_1 = Me, R_2 = H
(34b) R_1 = H, R_2 = Me

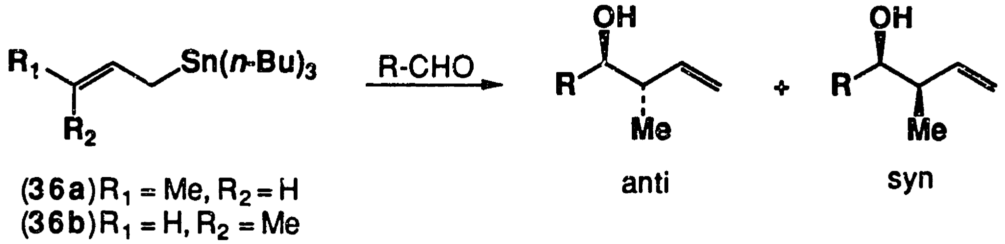


(35a) R_1 = Me, R_2 = H
(35b) R_1 = H, R_2 = Me

RCHO	Reagent	Isomeric Purity	% Yield	Product	anti : syn	Ref.
PhCHO	(34a)	88 : 12	82	(36)	88 : 12	[26b]
PhCHO	(34b)	21 : 79	91	(36)	22 : 78	[26b]
PhCHO	(35a)	99 : 1	92	(36)	99 : 1	[26a]
PhCHO	(35b)	1 : 9	96	(36)	1 : 99	[26a]
Et_2CHCHO	(35a)	99 : 1	96	(37)	99 : 1	[26a]
Et_2CHCHO	(35b)	1 : 99	89	(37)	2 : 98	[26a]

Figure 7

Reagents based on Tin. Type 1 reactions of aldehydes and trialkylcrotylstannanes have been found to proceed under thermal conditions (20–200 °C) as well as under high pressure (10 kbar). The thermal reaction of these reagents was initially carried out with isomerically impure crotyltributylstannanes (**38**) (Figure 8).[8a] Subsequent experiments of the reaction between chloral and isomerically pure (Z)-crotyltributylstannane (**36b**) determined that this reaction proceeds with high selectivity for syn-(**38**).[28b]



R-CHO	Reagent	Isomeric Purity	Temp.(°C)	Product	anti:syn
CCl_3CHO	**(36a)**	90 : 10	20°	**(38)**	90 : 10
CCl_3CHO	**(36a)**	65 : 35	20°	**(38)**	67 : 33
CCl_3CHO	**(36b)**	0 : 100	25°	**(38)**	1 : 99
PhCHO	**(36a)**	92 : 8	200°	**(36)**	87 : 13
PhCHO	**(36a)**	60 : 40	200°	**(36)**	62 : 38

Figure 8

Yamamoto has observed that the reactions of aldehydes less active than chloral occur at 23 °C under hyperbaric (10 kbar) conditions.[47] In contrast to the reactions with chloral, the selectivity of the reactions between (**38a**) and aryl aldehydes is lower, only 65–80% in favor of the anti diastereomer.

Excellent anti selectivity results from the thermal reactions of the readily-accessible alkoxy-substituted stannane (**39**) with a range of aromatic and aliphatic aldehydes,[48] as illustrated in Figure 9 by the reaction with benzaldehyde. However, subsequent reports have indicated that reactions of (**39**) with α,β-unsaturated aldehydes are problematic.[49]

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[47] Yamamoto, Y.; Maruyama, K.; Matsumoto, K. *J. Chem. Soc., Chem. Commun.* **1983**, 489.

[48] J. Pratt, A.; Thomas, E. J. *J. Chem. Soc., Chem. Commun.* **1982**, 1115.

[49] Marshall, J. A.; DeHoff, B. S.; Crooks, S. L. *Tetrahedron Lett.* **1987**, *28*, 527.

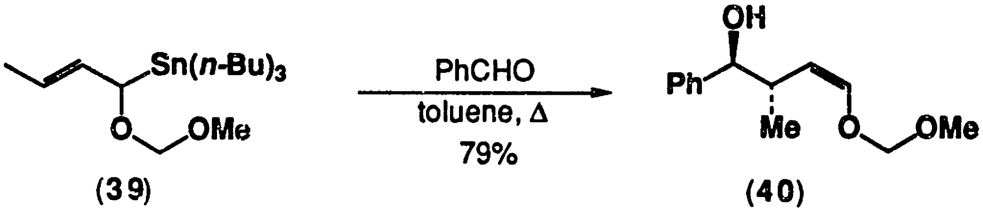


Figure 9

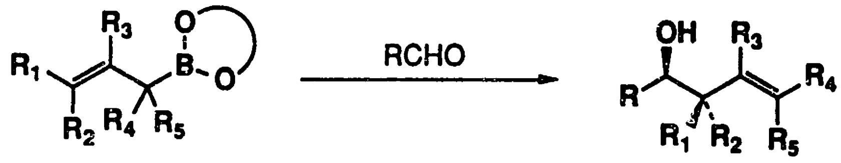
The thermal reactivity of the crotylstannane reagents is highly dependent on the substituents on tin. Although the reactions of (crotyl)SnX_3 and (crotyl)(butyl)$_nSnX_{3-n}$ with aldehydes have been reported, no cases have been found to exhibit high stereoselectivity.[29] Crotylstannanes of the general structure (crotyl)SnX_nY_{3-n} have also been synthesized via a number of methods,[50] but the observed diastereoselectivity of these reagents does not exceed 75 : 25, possibly resulting from the configurational instability of the reagents. Unfortunately, in these cases no diastereoselectivity exceeding 75 : 25 has been observed, and it is probable that this is caused by configurational instability of the reagents.[30b, 51] In spite of this, it is noteworthy that cinnamyl halides display very high anti selectivity (98%) in reactions with aldehydes, using $SnCl_2$-Al[51a] and Sn-Al[51b] as the reducing metal systems, in contrast to the disappointing results obtained with the crotyl systems.[30b, 51c]

Reagents based on Boron. Allylboron reagents are among the most extensively investigated and utilized of the Type 1 organometallics. The intense interest in these reagents is a consequence of not only the configurational stability of the allylic boronates which offers highly predictive transfer of stereoselectivity in their reactions with aldehydes but also the structural diversity that is available via convenient, efficient syntheses of this class of compounds. Thus, the reactions of a variety of allylboron reagents with achiral aldehydes proceed with a high degree of stereochemical control, the (E)/(Z) ratio in the olefinic fragment being efficiently reflected in the anti/syn ratio of the products (Figure 10).

---

[50] (a) From allylic halides, see: Mukayama, T.; Harada, T.; Shoda, S. *Chem. Lett.* **1980**, 1507. (b) From allylic acetates, see: Masuyama, Y.; Hayashi, R.; Otake, K.; Kurusu, Y. *J. Chem. Soc., Chem. Commun.* **1988**, 44. (c) From allylic carbonates, see: Masuyama, Y.; Otake, K.; Kurusu, Y. *Tetrahedron Lett.* **1988**, *29*, 3563. (d) From allylic alcohols, see: Masuyama, Y.; Takahara, J. P.; Kurusu, Y. *J. Am. Chem. Soc.* **1988**, *110*, 4437. (e) From allylic phosphates, see: Matsubara, S.; Wakamatsu, K.; Morizawa, Y.; Tsuboniwa, N.; Oshima, K.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 1196.

[51] (a) Uneyami, K.; Nanbu, H.; Torii, S. *Tetrahedron Lett.* **1986**, *27*, 2395. (b) Coxon, J. M.; van Eyk, S. J.; Steel, P. J. *Ibid.* **1985**, *26*, 6121. (c) Nokami, J.; Otera, J.; Sudo, T.; Okawara, R. *Organometallics* **1983**, *2*, 191.



(41)

Entry	R_1	R_2	R_3	R_4	R_5	(Z) : (E)	RCHO	Product	syn : anti	Ref.
a	Me	H	H	H	H	95 : 5	PhCHO	(36)	96 : 4	52a
b	H	Me	H	H	H	7 : 93	PhCHO	(36)	6 : 94	52a
c	OMe	H	H	H	H	95 : 5	PhCHO	(42)	95 : 5	52b
d	H	OMe	H	H	H	11 : 89	PhCHO	(42)	5 : 95	52b
e	H	SEt	H	H	H	25 : 75	EtCHO	(43)	23 : 77	52c
f	H	CH_2OTHP	H	H	H	7 : 93	$CH_3(CH_2)_4CHO$	(44)	7 : 93	52d
g	Me	H	Me	H	H	91 : 9	$CH_3(CH_2)_4CHO$	(45)	90 : 10	52d
h	Me	H	H	Me	Me	95 : 5	$CH_3(CH_2)_4CHO$	(45)	97 : 3	52a

Figure 10

1.3.2 Type 2 Reagents

Reagents based on Silicon. Substituted allylsilanes undergo addition reactions with aldehydes at –78 °C in the presence of Lewis acids to give predominantly syn products, characteristic of Type 2 reagents. However, the degree of syn selectivity varies with the geometry of the olefinic group, (E)-reagents resulting in greater selectivity than the corresponding (Z)-analogs (Figure 11).[13] The lower level of selectivity could be due to a more hindered synclinal transition state (**23**) in the case of the (Z)-isomer compared to an equivalent transition state for the (E)-isomer (**22**) thus enabling anti-selective transition states (not shown) to compete more effectively.

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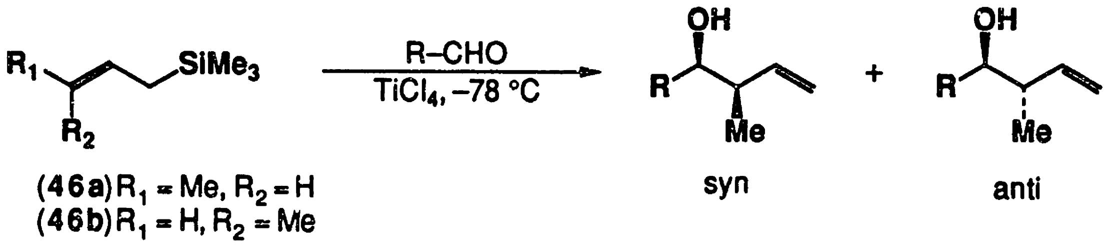
[52] (a) Hoffmann, R. W.; Zeiss, H. -J. *J. Org. Chem.* **1981**, *46*, 1309. (b) Hoffmann, R. W.; Kemper, B. *Tetrahedron Lett.* **1981**, *22*, 5263. (c) Hoffmann, R. W.; Kemper, B. *Ibid.* **1980**, *21*, 4883. (d) Wuts, P. G. M.; Thompson, P. A.; Callen, G. R. *J. Org. Chem.* **1983**, *48*, 5398


R₁
SiMe₃
R₂
(46a)R₁ = Me, R₂ = H
(46b)R₁ = H, R₂ = Me
R-CHO
TiCl₄, -78 °C
OH
R
Me
syn
+
OH
R
Me
anti

Reagent	Isomeric Purity (E) : (Z)	R-CHO	Product	syn : anti
(39a)	99 : 1	t-BuCHO	(47)	> 99 : < 1
(39a)	99 : 1	iPrCHO	(48)	97 : 3
(39a)	99 : 1	EtCHO	(49)	95 : 5
(39b)	3 : 97	t-BuCHO	(47)	65 : 35
(39b)	3 : 97	iPrCHO	(48)	64 : 36
(39b)	3 : 97	EtCHO	(49)	69 : 31

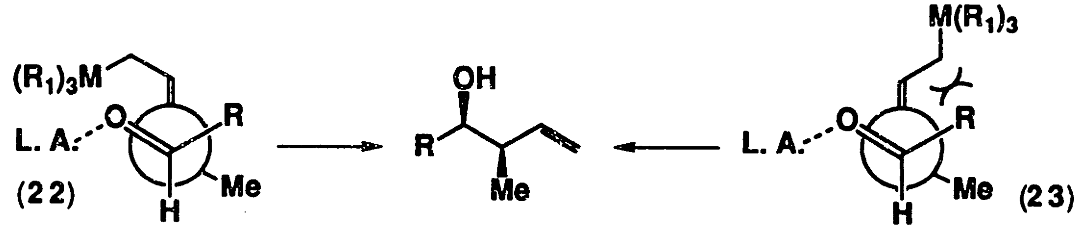

(R₁)₃M
L. A.
O
R
H
Me
(22)
OH
R
Me
M(R₁)₃
L. A.
O
R
H
Me
(23)

Figure 11

The carbonyl addition reactions of γ-carboxamidopropenyltrimethylsilanes (**50**) in the presence of $TiCl_4$ have likewise been studied. The results from these investigations indicated a preference for the formation of the anti homoallylic alcohol isomer . It has been postulated that the use of $TiCl_4$ as the catalyst results in a chair-like transition state (**51**) (Figure 12) in the course of the reaction, accounting for the reversal of the syn selectivity normally observed for Type 2 reagents.[38]

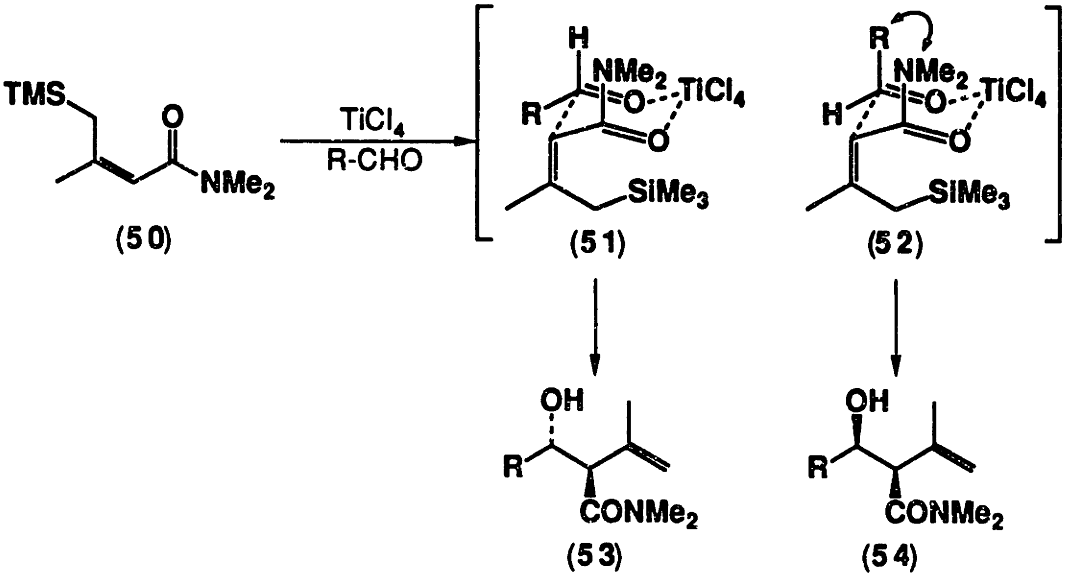

TMS
O
NMe2
(50)
TiCl4
R-CHO
H
NMe2
O
TiCl4
R
O
SiMe3
(51)
R
NMe2
O
TiCl4
H
O
SiMe3
(52)
OH
R
CONMe2
(53)
OH
R
CONMe2
(54)

Figure 12

Reagents based on Tin. In contrast to the crotylsilanes, crotylstannanes exhibit high syn selectivity (98–99%) in their reactions with aldehydes regardless of which geometrical isomer is involved (Figure 13).[12a]

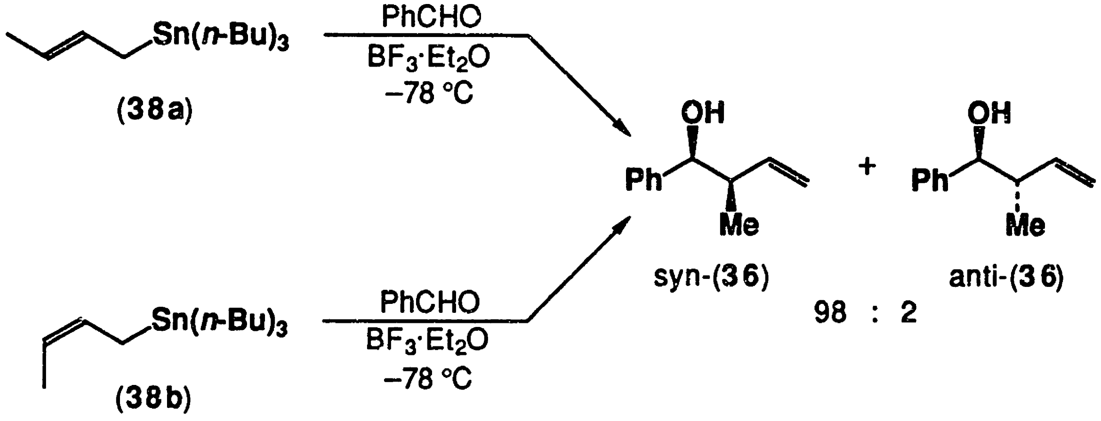

Sn(n-Bu)3
(38a)
PhCHO
BF3·Et2O
−78 °C
Sn(n-Bu)3
(38b)
PhCHO
BF3·Et2O
−78 °C
OH
Ph
Me
syn-(36)
+
OH
Ph
Me
anti-(36)
98 : 2

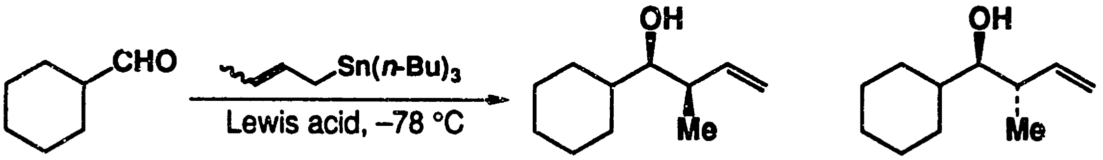
Figure 13

The selectivity of the crotylstannanes is, however, dependent on a number of other factors. Firstly, there appears to be a dependence on the nature of the substituents on tin, and a change of the ligands on the metal from methyl or n-butyl to phenyl causes the selectivity to drop from 98 : 2 to 83 : 17.[12d] Secondly, the stereochemical outcome of the reactions is influenced by the Lewis acid used, the ratio of the stannane to the Lewis acid, and the order in which the components of the reaction are mixed. The reaction between cyclohexanecarboxaldehyde (**55**) and crotyltributylstannane[12c] in Figure 14 serves to illustrate this. The shift in stereoselectivity is particularly pronounced in the case when $TiCl_4$ was used as the Lewis acid catalyst; the syn/anti ratio of 93 : 7 obtained when the reaction was performed with 1 equivalent of each component and the aldehyde and $TiCl_4$ were pre-mixed was effectively reversed to 5 : 95 when the Lewis acid and the stannane (2 equivalents each with respect to aldehyde) were pre-mixed before the introduction of the aldehyde. This rather spectacular reversal resulting from the pre-mixing of the crotylstannane and the Lewis acid probably results from the *in situ* formation of a transmetallated crotyltitanium species which then reacts with aldehyde as a Type 3 reagent via a chair-like cyclic transition state. In addition, the choice of Lewis acid also determines whether other side products (**57**) and (**58**) will be formed (in varying amounts) during the reaction.[53] These by-products are apparently another consequence of the *in situ* transmetallation reactions between Lewis acid and the crotylstannane[54] leading to new allylorganometallic species that in turn can act as a competitor in the addition reactions to aldehydes.

---

[53] In the case when $SnCl_4$ was utilized as the catalyst (order of addition = N; Figure 14), for instance, the ratio of the products obtained syn-(**56**) : anti-(**56**) : (**57**) : (**58**) was found to be 22.8 : 26.0 : 36.4 : 14.8 respectively.

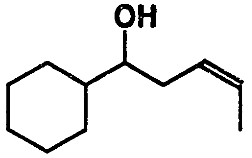
[54] For studies of *in situ* transmetallation reactions between allylic stannanes and Lewis acids, see: Denmark, S. E.; Wilson, T.; Willson, T. M. *J. Am. Chem. Soc.* **1988**, *110*, 984 and references cited therein.



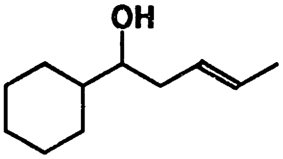
(55) syn-(56) anti-(56)

Equiv. of Reagent	Lewis Acid (equiv.)	Order of Addition*	syn : anti
1.0	$BF_3 \cdot Et_2O$ (1.05)	N	90 : 10
2.1	$BF_3 \cdot Et_2O$ (1.05)	N	96 : 4
2.1	$BF_3 \cdot Et_2O$ (1.05)	I	96 : 4
1.0	$MgBr_2$ (1.0)	N	58 : 42
1.0	ZnI_2 (1.0)	N	52 : 48
0.8	$SnCl_4$ (1.3)	N	48 : 52
0.8	$SnCl_4$ (1.3)	I	23 : 77
1.05	$TiCl_4$ (1.05)	N	93 : 7
2.0	$TiCl_4$ (2.1)	I	5 : 95

*N : Crotylstannane was added to a pre-mixed solution of Lewis acid and aldehyde.
I : Aldehyde was added to a pre-mixed solution of Lewis acid and crotylstannane.



(57)



(58)

Figure 14

Thirdly, the stereochemical preference has been found to vary to some extent with the nature of the substituent at the γ-position of the allylstannane component; a deviation from the usual syn selectivity has been observed in the aldehyde addition reactions of (E)-cinnamyltrialkylstannanes in the presence of $BF_3 \cdot Et_2O$.[12d]

Studies of the reactions of heteroatom-substituted allylstannanes have also been performed, both with reagents substituted at the α- and at the γ-position of the olefinic chain. These reactions have been found to be very syn selective.[55] Other substituted allylstannanes that have been investigated are γ-carboxylpropenyltrialkylstannanes. These reagents exhibited excellent syn selectivity in many of their addition reactions to aliphatic and aromatic aldehydes.[56]

---

[55] (a) Yamamoto, Y.; Saito, Y.; Maruyama, K. *J. Organomet. Chem.* **1985**, *292*, 311. (b) Quintard, J. -P.; Elissondo, B.; Pereyre, M. *J. Org. Chem.* **1983**, *48*, 1559.

1.3.3 Type 3 Reagents

Reagents based on Chromium. Crotylchromium reagents are among the most selective and most widely applied of the Type 3 crotylorganometallics.[9] Allylchromiums are typically generated by the reduction of an allylic halide using $CrCl_2$ in THF; the diastereoselectivity decreases in other solvents such as DMF.[9b, c] Commercially available $CrCl_2$ is often used, but several cases have been reported where selectivity is substantially better when $CrCl_2$ is generated via the $LiAlH_4$ reduction of $CrCl_3$. Other methods of generating $CrCl_2$ *in situ* lead to crotylchromium reagents that show diminished stereoselectivity.[57] Allylchromium reagents containing vinyl or allylic halides,[9c, 58a] vinyl sulfones,[32c] and even carboalkoxy[58b] or cyano[58c] substituents have been prepared from suitable allyl halide precursors, while γ-alkoxyallylchromiums have been generated by the reduction of acrolein acetals with $CrCl_2$ in the presence of Me_3SiI (Figure 15).[58d] Stereoconvergence has been demonstrated in several instances, indicating that the isomeric purity and geometry of the allylchromium precursor is not a factor that influences diastereoselectivity.[9b, c, 58b]

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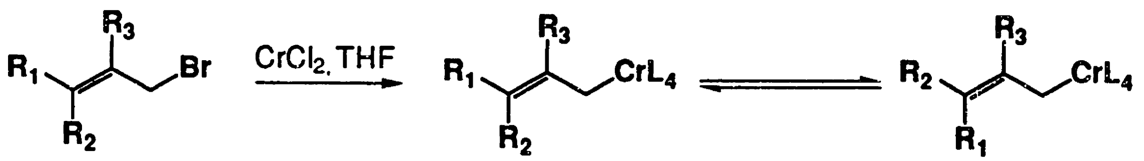
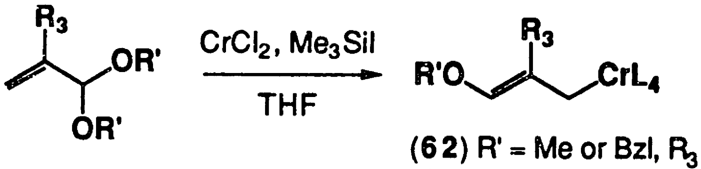
[56] (a) Yamamoto, Y.; Hatsuya, S.; Yamada, J. -I. *J. Chem. Soc., Chem. Commun.* **1987**, 561.

[57] Wuts, P. G. M. ; Callen. G. R. *Synth. Commun.* **1986**, *16*, 1833.

[58] (a) Augé, J. *Tetrahedron Lett.* **1988**, *29*, 6107. (b) Okuda, Y.; Nakatsukasa, S.; Oshima, K.; Nozaki, H. *Chem. Lett.* **1985**, 481. (c) Drewes, S. E.; Hoole, R. F. A. *Synth. Commun.* **1985**, *15*, 1067. (d) Takai, K.; Nitta, K.; Utimoto, K. *Tetrahedron Lett.* **1988**, *29*, 5263.



(59) $R_1 = Me, R_2 = R_3 = H$
(60) $R_1 = Me$ or Bu, $R_2 = H, R_3 = SO_2Ph$
(61) $R_1 = Me, Bu$ or Ph, $R_2 = H, R_3 = CO_2Me$



(62) $R' = Me$ or Bzl, $R_3 = H$
(63) $R' = Bzl, R_3 = Me$

Figure 15

The reaction of aldehydes and substituted allylchromiums **(59)**, **(62)** and **(63)** are generally highly selective for the anti product diastereomer (87–100%).[9b, c, 58d] The one exception are the reactions with pivaldehyde that provide the syn diastereomer with modest selectivity (~66%). This result has been attributed to the involvement of a boat transition state ((**13**), Figure 7),[9c] although the same product could also be produced via a chair-like transition state ((**12**), $R_1 = H$, $R_2 = Me$) if the (Z)-crotylchromium intermediate is more reactive than the (E)-isomer.[59] Boat-like transition states with internal coordination of Cr(II) by the (Z)-γ-alkoxy substituent have been postulated to rationalize the anti diastereoselectivity of the reactions of (**62**),[58c] although here again the stereochemistry is consistent with a chair-like transition state (**12**) and an (E)-geometry for (**62**).

In contrast to these results, syn diastereoselectivity is observed in the reactions of (**60**) and (**61**) with aldehydes,[32c, 58a, b] leaving little doubt that it is the (Z)-allylchromium species that is involved, presumably as a result of a destabilizing interaction between the C(2) and bulky C(3) substituents in the (E)-isomer (Figure 16).

---

[59] We favor the latter interpretation, since tartrate (Z)-crotylboronate (**14**) is more reactive than the (E)-crotyl isomer (**13**) towards pivaldehyde—the only documented case of a (Z)-crotylmetal reagent exhibiting greater reactivity than the (E)-isomer. (See ref. 35a.)

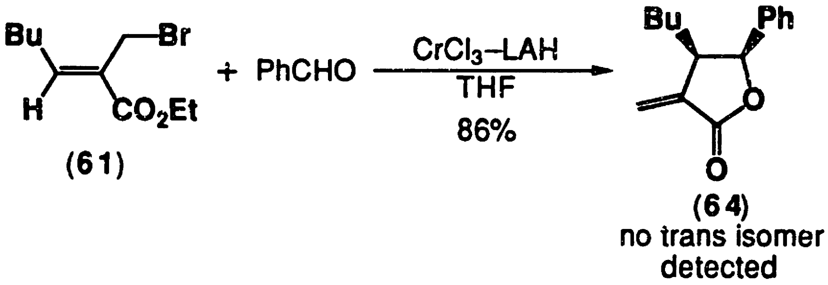


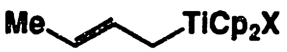
Figure 16

Reagents based on Titanium. *Monohapto*-crotyltitanium reagents (**65**)–(**67**), prepared by treatment of Cp_2TiX_2, $(RO)_3TiCl$, or $(Et_2N)_2TiCl$ with crotylmagnesium halides, react with aldehydes to give the anti diastereomer preferentially.[15] Greatest stereoselectivity in reactions with aldehydes has been achieved by using (**65a**). Reagent (**66a**) with R = Ph is more selective (anti : syn = 96 : 4) than other alkoxy- or amino substituted titanium derivatives, including (**66b**) and (**67**). Ate complexes (**68**) have also been studied,[15e] but seem to have no particular advantage relative to (**65**)–(**67**).[60] The reactions of a number of γ-heteroatom-substituted allyltitanium reagents have also been described.[44b, 61]

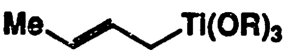
---

[60] For reactions of crotyltitanium ate complexes and ketones, see: (a) Reetz, M. T.; Westermann, J.; Steinbach, R.; Wenderoth, B.; Peter, R.; Ostarek, R.; Maus, S. *Chem. Ber.* **1985**, *118*, 1421. (b) Reetz, M. T.; Wenderoth, B. *Tetrahedron Lett.* **1982**, *23*, 5259.

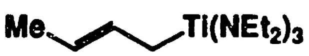
[61] (a) Ikeda, Y.; Ukai, J.; Ikeda , N.; Yamamoto, H. *Tetrahedron* **1987**, *43*, 723. (b) Ikeda, Y.; Ukai, J.; Ikeda , N.; Yamamoto, H. *Tetrahedron* **1987**, *43*, 731. (c) Widler, L.; Weber, T.; Seebach, D. *Chem. Ber.* **1985**, *118*, 1329. (d) Furuta, K.; Ikeda, Y.; Meguriya, N.; Ikeda, N.; Yamamoto, H. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 2781.



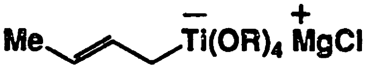
(65a) X = Br
(65b) X = Cl



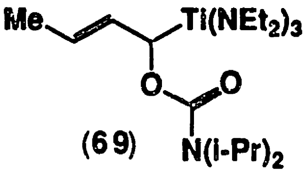
(66a) R = Ph
(66b) R = i-Pr



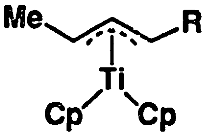
(67)



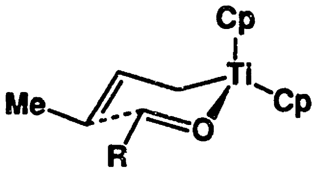
(68a) R = i-Pr
(68b) R = Ph



(69)



(70) R = H, SiMe$_3$, OPh, SPh



(71)

α-Substituted crotyltitanium reagent (**69**) displays exceptional levels of diastereoselectivity, and is much more selective than the corresponding lithium or aluminum derivatives.[42b,43]

The reactions of *trihapto*-crotyltitanium reagents (**70**) and aldehydes have been studied by Sato and coworkers.[17a,62] These reactions proceed in good yield and with high anti diastereoselectivity. For example, the reactions of (**70**), R = H, with propionaldehyde and benzaldehyde provide 93–95% of the anti homoallyl alcohol.[17a] The stereochemical course is consistent with the reaction proceeding by way of the usual chair-like transition state (**71**).

Reagents based on Zirconium. Crotylzirconiums (**72**)–(**75**) have been generated *in situ* by the addition of one, two and three equivalents of crotyllithium or crotylmagnesium chloride to Cp$_2$ZrCl$_2$ in THF, and show a preference for the anti homoallyl alcohol in reactions with aldehydes (87–95% yield) (Figure 17).[16]

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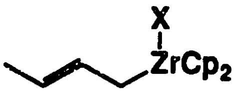
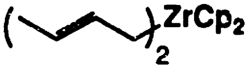
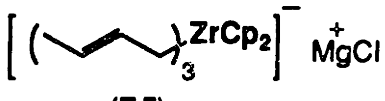
[62] (a) Sato, F.; Suzuki, Y.; Sato, M. *Tetrahedron Lett.* **1982**, *23*, 4589. (b) Sato, F.; Uchiyama, H.; Iida, K.; Kobayashi, Y.; Sato, M. *J. Chem. Soc., Chem. Commun.* **1983**, 921. (c) Kobayashi, Y.; Umeyama, K.; Sato, F. *Ibid.* **1984**, 621.



(72) X = Cl
(73) X = OC_5H_{11}



(74)



(75)

Reagent	Temp (°C)	Diastereoselectivity anti : syn PhCHO	MeCHO	EtCHO	iPrCHO
(72)	−78	86 : 14	73 : 27	86 : 14	88 : 12
(74)	30	—	78 : 22	79 : 21	72 : 28
	0	—	80 : 20	81 : 19	77 : 23
	−78	85 : 15	88 : 12	89 : 11	82 : 18
	−110	—	91 : 9	92 : 8	86 : 14
(75)	−78	—	58 : 42	66 : 34	55 : 45
(73)	−78	—	90 : 10	90 : 10	89 : 11

Figure 17

Variable temperature NMR experiments involving (74)[16a], (72) and (75) indicate that the reaction diastereoselectivity closely parallels the isomeric composition of these crotylzirconium species in solution. Crotylzirconium species of the general structure (crotyl)Zr$(OR)_3$, prepared by the addition of crotylmagnesium chloride and Zr$(OR)_4$, have also been studied, but in general are less diastereoselective than (72)–(75) or the comparable crotyltitanium complexes (69).[16a] The most selective of the alkoxy-substituted zirconium reagents is (73).

1.4 Reactions of Crotylorganometallic Reagents with Chiral Aldehydes.

The stereochemistry of the reactions of chiral carbonyl compounds with nucleophiles has been a topic of considerable theoretical and synthetic interest since the pioneering study by Cram appeared in 1952.[63] The available predictive models focus entirely on the conformational and stereoelectronic demands of the chiral carbonyl substrate, the implicit assumption being that the relative stabilities of the competing transition states are determined only by stereoelectronics and the minimization of nonbonded interactions between the substituents on the chiral center and the nucleophile. These models totally ignore the possibility, however, that the geometric requirements of the nucleophile may also have an effect on reaction diastereoselectivity. Considerable evidence is now available, particularly in the reactions of Type 1 (Z)-crotylboronates and Z(O)-metal enolates, that the stereochemistry of the nucleophile is indeed an important issue that must be considered when assessing reaction diastereoselectivity.

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[63] Transition state models for diastereoselective carbonyl additions: (a) Cram, D. J.; Elhafez, F. A. Abd *J. Am. Chem. Soc.* **1952**, *74*, 5828. (b) Cram, D. J.; Kopecky, K. T. *Ibid.* **1959**, *81*, 2748 (chelate model). (c) Cornforth, J. W. ; Cornforth, R. H.; Mathew, K. K. *J. Chem. Soc.* **1959**, 112. (d) Karabatsos, G. J. *J. Am. Chem. Soc.* **1967**, *89*, 1367. (e) Cherest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, 2199. (f) Ahn, N. T.; Eisenstein, O. *Nouv. J. Chim.*, 1977, **1**, 61. (g) Wu, Y. -D.; Houk, K. N. *J. Am. Chem. Soc.* **1987**, *109*, 908.

1.4.1 Type 1 and Type 3 Reagents.

The vast majority of the reactions of Type 1 and Type 3 allylmetal reagents with chiral C=O electrophiles proceed via the usual cyclic transition state models (Figure 4). Close examination of these models can usually account for the observed relative diastereoselection .

Consider the reactions of pinacol allylic boronates **(76)**, **(77)** and **(78)** with a chiral aldehyde, RCH(Me)CHO (Figure 18). In the case of reagents **(76)** and **(77)**, the four diastereomeric products **(79)**-**(82)** arise via the indicated transition states **(83)**-**(86)**. According either to the Cram rule or the Felkin-Ahn paradigm, the 3,4-anti-4,5-syn diastereomer **(79)** should be favored over anti,anti-**(80)** in the reactions of the (E)-crotyl isomer **(76)**, a result that is in fact observed experimentally.[64,65] The same reasoning leads to the prediction that syn,syn diastereomer **(81)** should be the major product of the reactions of (Z)-crotylboronate **(77)**. In this case, however, it is the 3,4-syn-4,5-anti diastereomer **(82)** that is produced preferentially.[64, 65] The reason that the reactions of (Z)-crotylboronates fail to follow the Felkin-Ahn paradigm is probably that transition state **(85a)** is destabilized by the indicated 1,5-interaction between methyl groups. Although **(81)** can also arise via **(85b)** in which the 1,5-Me-Me interaction of **(85a)** interaction is relieved, this transition state still suffers from a relatively large nonbonded interaction between Me and R. Transition state **(86)**, on the other hand,

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[64] (a) Hoffmann, R. W.; Weidmann, U. *Chem. Ber.* **1985**, *118*, 3966. (b) Hoffmann, R. W.; Zeiβ, H. -J.; Ladner, W.; Tabche, S. *Ibid.* **1982**, *115*, 2357.

[65] Roush, W. R.; Palkowitz, A. D.; Palmer, M. A. J. *J. Org. Chem.* **1987**, *52*, 316.

allows for fewer interactions between the crotyl unit and the substituents at C(2) of the chiral aldehyde substrate and consequently is favored even though it corresponds to an "anti-Felkin" arrangement. Similar "anti-Felkin" diastereoselectivity has been observed in reactions of various Z(O)-boron and lithium enolates with α-methyl chiral aldehydes, undoubtedly for similar reasons.[4a,5,66] An analogous set of transition states (**89**)–(**90**) may be invoked for the reactions involving pinacol allylboronate (**78**). However, in this case, the 1,5-non-bonded interactions are not as severe since the terminal hydrogen substituent of the allyl unit is less sterically demanding. As a result, the energies of the competing transition states should be closer to each other, and this is manifested in the lower selectivities observed with this reagent.

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[66] (a) Masamune, S., in "*Organic Synthesis, Today and Tomorrow*," Trost, B. M., and Hutchinson, C. R., Eds., Pergamon Press, Oxford, 1981. (b) Evans, D. A.; Bartroli, J. *Tetrahedron Lett.* **1982**, *23*, 807.

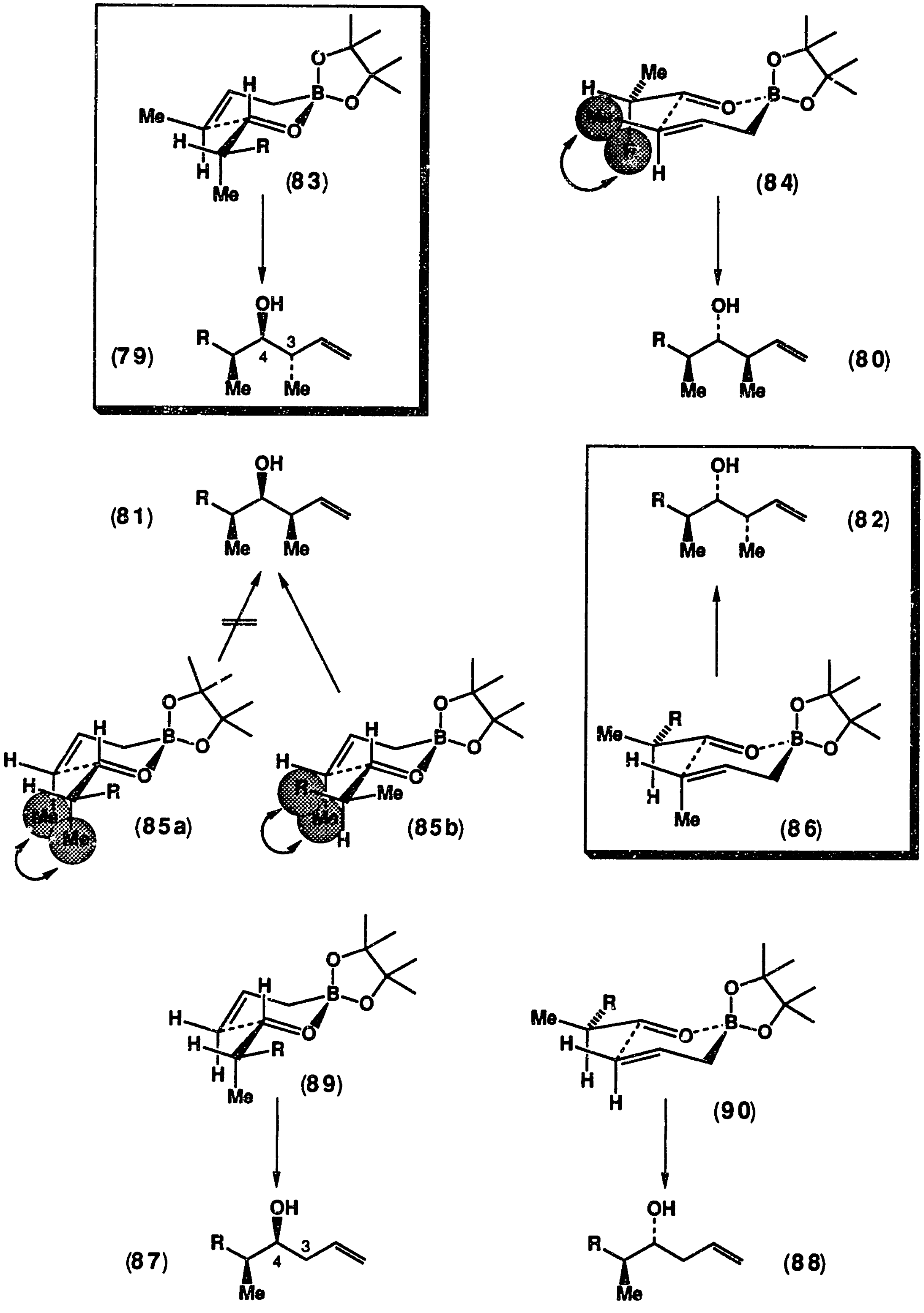
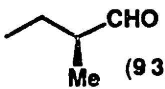
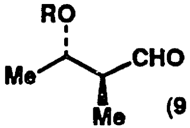
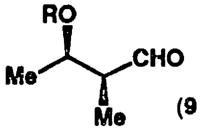

(83)
(79)
(84)
(80)
(81)
(82)
(85a)
(85b)
(86)
(89)
(90)
(87)
(88)
OH
R
Me
H
O
B
3
4

Figure 18

It is to be expected that the extent of relative diastereoselection will depend on the difference in size of the R substituent relative to Me (or H). The examples summarized in Figure 19 are generally supportive of this argument, particularly the reactions of (**76**) with aldehydes (**94**) and (**95**) that are much more selective than with the structurally less complex aldehyde (**93**).[64]

Reagent	 (93)	 (94)	 (95)[a]
pinacol (E)-crotylboronate (**76**)[b]	83 : 17	95 : 5 (R = TBDMS)	98 : 2 (R = TBDMS)
		89 : 11 (R = MOM)	94 : 6 (R = MOM)
pinacol allylboronate (**78**)	62 : 38	49 : 51 (R = TBDMS)	79 : 21 (R = TBDMS)
		61 : 39 (R = MOM)	79 : 21 (R = MOM)
pinacol (Z)-crotylboronate (**77**)[c]	30 : 70	9 : 91 (R = TBDMS)	40 : 60 (R = TBDMS)
		22 : 78 (R = MOM)	41 : 59 (R = MOM)

[a] The enantiomeric aldehyde was actually used (ref. 97a).

[b] 4,5-Syn diastereomer (**79**) is the major product.

[c] 4,5-Anti diastereomer (**82**) is the major product.

Figure 19. Relative Diastereoselection in the Reactions of Allylboronates and α-Methyl Chiral Aldehydes: Ratio of 4,5-Syn to 4,5-Anti Products.[64]

The data cited for reactions of pinacol allylboronate (**78**) and (Z)-crotylboronate (**77**), however, also show that diastereoselectivity depends on the stereochemistry at C(3) of (**94**) and (**95**). This can be rationalized by inspecting transition states (**96**) and (**97**) (Figure 20) that correspond to (**85b**) of Figure 18.

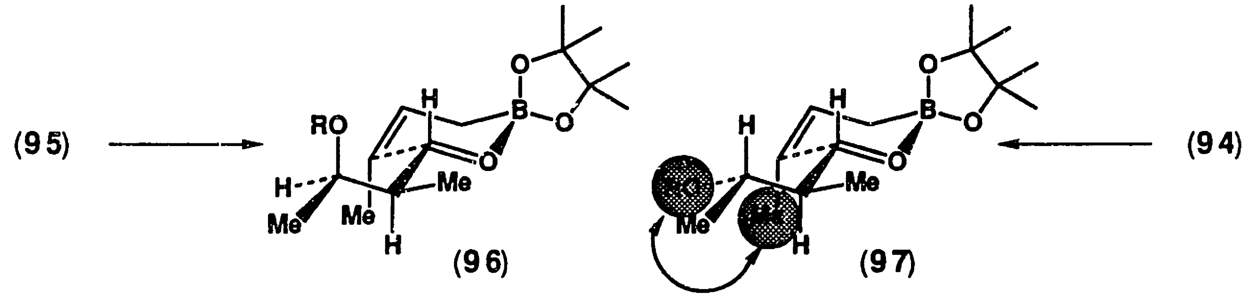


Figure 20.

Aldehyde (**95**) can easily adopt the conformation indicated in (**96**) that minimizes the interactions between C(3) and the crotyl unit. These interactions are only slightly greater than the methyl/methyl interactions in the favored transition state (**86**). With aldehyde (**94**), however, the interactions between the C(3) substituents and the crotyl unit are envisaged to be much more serious due to the conformation indicated in (**97**). The "R" substituent of (**94**) thus behaves as a more sterically demanding unit than in (**95**), and consequently the diastereoselectivity of the reaction of (**94**) is greater.

A more complete picture of relative diastereoselection in the reactions of allylboronates and chiral aldehydes is given in Figure 21; structures of the products in the glyceraldehyde acetonide (**101**) series are given in Figure 22.[25, 67–69]

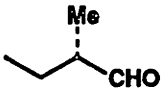
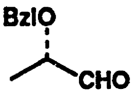
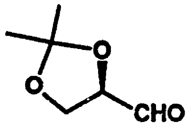
Reagent	 (**93**)	 (**100**)	 (**101**)
pinacol (E)-crotylboronate (**76**)	17 : 83[64]	—	55 : 45[25]
pinacol (E)-γ-methoxyallylboronate (**98**)	—	40 : 60	—
pinacol allylboronate (**78**)	38 : 62[64]	65 : 35[67a] (55 : 45)	80 : 20[25, 68]
pinacol (Z)-crotylboronate (**77**)	70 : 30[64]	—	97 : 3[25]
pinacol (Z)-γ-methoxyallylboronate (**99**)	—	82 : 18[67a] (90 : 10)[67b]	>95 : 5[25, 69]

Figure 21. Relative Diastereoselection in the Reactions of Substituted Allylboronates and Chiral Aldehydes: Ratios of 4,5-Anti to 4,5-Syn Products

---

[67] (a) Hoffmann, R. W.; Metternich, R.; Lanz, J. W. *Liebigs Ann. Chem.* **1987**, 881. (b) Wuts, P. G. M.; Bigelow, S. S. *J. Org. Chem.* **1983**, *48*, 3489.

[68] Hoffmann, R. W.; Endesfelder, A.; Zeiss, H. -J. *Carbohydr. Res.* **1983**, *123*, 320.

[69] For additional examples of the reactions of α,β-dialkoxyaldehydes with (Z)-γ-alkoxyallylboronates: (a) Roush, W. R.; Harris, D. J.; Lesur, B. M. *Tetrahedron Lett.* **1983**, *24*, 2227. (b) Roush, W. R.; Michaelides, M. R. *Ibid* **1986**, *27*, 3353. (c) Roush, W. R.; Michaelides, M. R.; Tai, D. F.; Chong, W. K. M. *J. Am. Chem. Soc.* **1987**, *109*, 7575.

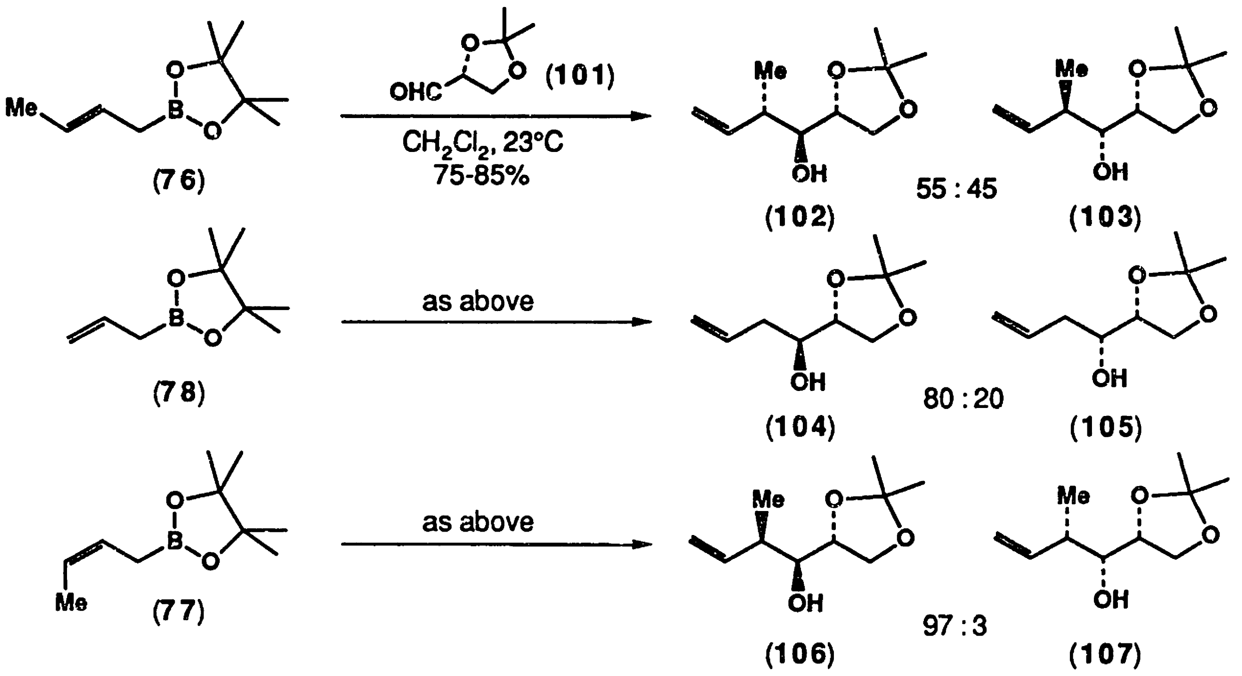


Figure 22

The data for **(100)** and **(101)** reconfirm the conclusion of Figure 19 that diastereoselectivity is dependent on the geometry and substitution pattern of the allylboronate. In addition, however, the data in Figure 21 also show that diastereoselectivity depends strikingly on the aldehyde, with greater selectivity for the 4,5-anti diastereomer being realized as one moves across any row of the Table. This is strongly suggestive of an electronic effect, particularly since it is believed, for example, that the reactions of (Z)-γ-substituted allylboronates **(77)** and **(99)** proceed preferentially via the same transition states: **(86)** for α-methyl chiral aldehydes and **(103)** for the α-oxygenated aldehydes.[25,67a] Transition state **(108)** corresponds to the Cornforth model and the increased diastereoselection in the reactions of **(77)** and **(99)** with oxygenated aldehydes vs. the reactions of **(77)** with aldehydes like **(93)** has been attributed to the electronic stabilization of **(108)** relative to competitive diastereomeric arrangements.[25] The usually invoked Felkin-Ahn arrangement **(109)** is probably not involved in the reactions of (Z)-allylboronates (**(77)**, **(99)**) owing to serious steric interactions between R of the allylboronate and the alkyl substituent at C(2) of the chiral aldehyde substrate.

Electronic effects are also clearly operational in the reactions of allylboronate **(78)** since the diastereofacial preference switches upon moving from an α-methyl chiral aldehyde (**93**) to an oxygenated aldehyde such as (**100**) or (**101**). The identity of the major transition state(s) is less clear with (**78**), however, since at least two reasonable possibilities exist in every case (those resembling (**84**) or (**85**) in reactions with α-methyl chiral aldehydes and (**108**) or (**109**) with oxygenated aldehydes).

Electronic arguments have been presented to rationalize the poor diastereoselectivity of the reactions of (**76**) and (**101**).[25] It was argued that even though transition state (**110**) (Figure 23) has more serious nonbonded interactions than (**111**) (which corresponds to (**83**), the major pathway in the reactions with α-methyl chiral aldehydes (Figure 18)), the electronic effect (Cornforth activation) is sufficient to lower the energy of (**110**) so that it is slightly more accessible than (**111**). This result probably represents a special case, however, since the C(2)-oxygen atom of (**101**) is not very sterically demanding in (**110**) owing to the acetonide unit that minimizes interactions of the C(2) alkoxy group with the crotyl unit. Indeed, the reaction of differentially protected α,β-dialkoxyaldehyde (**112**) and (E)-crotylboronate (**76**) provided (**113**) (Figure 24) with very high diastereoselectivity via a transition state corresponding to (**111**).[70] Thus, increased steric interactions are sufficient to destabilize (**110**) relative to (**111**).

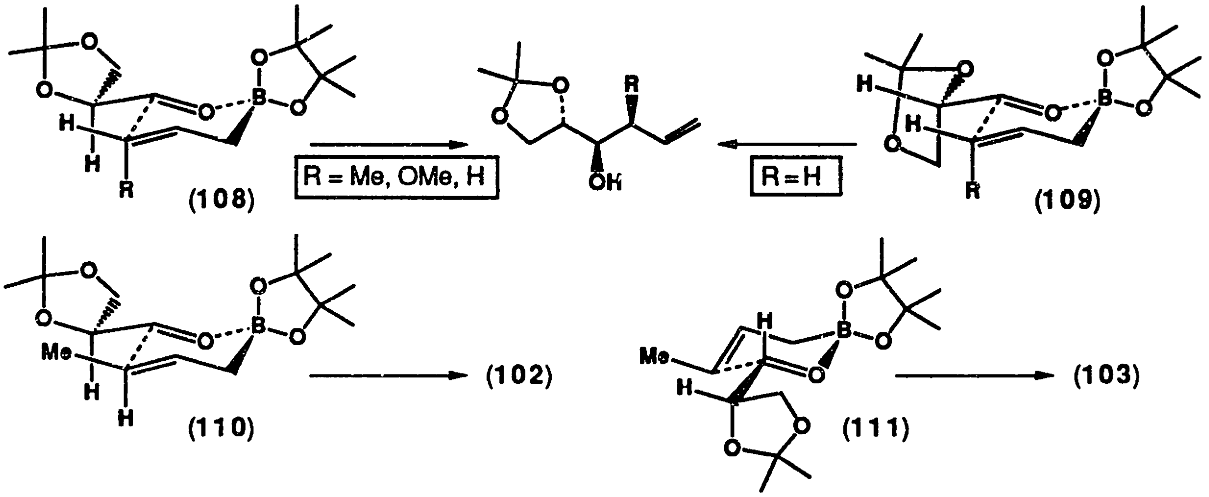


Figure 23

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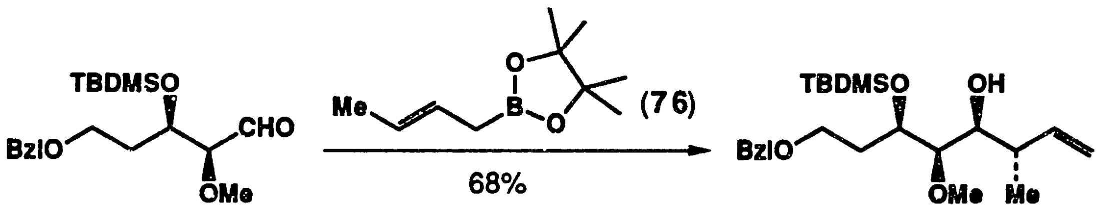
[70] Wuts, P. G. M.; Bigelow, S. S. *J. Org. Chem.* **1988**, *53*, 5023.



(112) (113) >99 : 1 selectivity

Figure 24

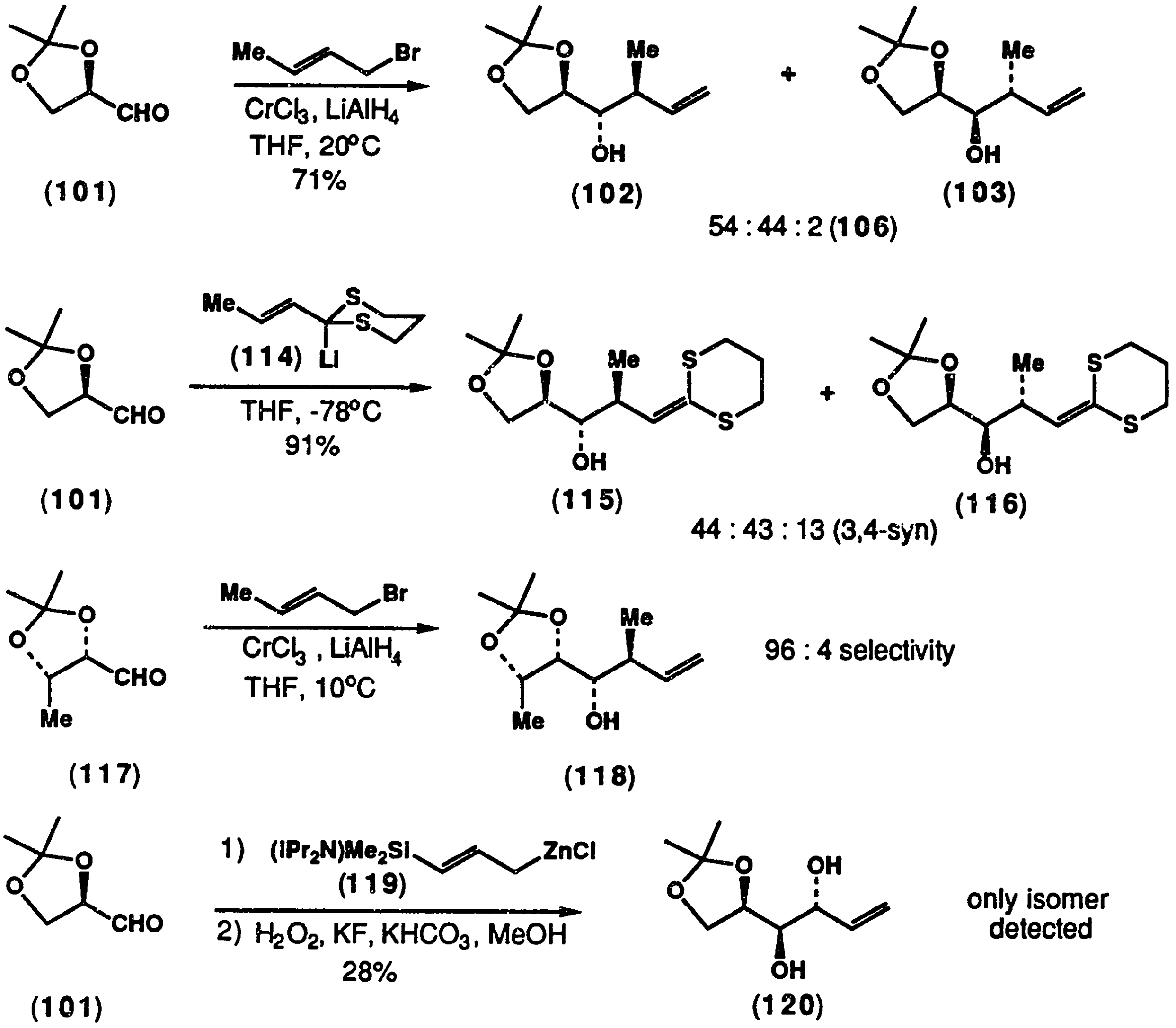
The aldehyde diastereofacial selectivity realized in the reactions of many other Type 1 and 3 crotylmetal reagents closely parallels the results summarized above for the crotylboronates. For example, the reactions of glyceraldehyde acetonide (**101**) either with the crotylchromium reagent[71] or with allyllithium (**114**)[34a] provide mixtures of diastereomers strikingly similar to those realized in the reaction of (**101**) and (E)-crotylboronate (**76**) (Figure 25). Steric effects certainly have an effect on diastereoselectivity, as evidenced by the reaction of (**117**) and crotylchromium (**59**) that provides (**118**) with excellent stereoselectivity,[72] and the reaction of (**151**) and substituted allylzinc reagent (**127**) that probably provides (**168**) and not the 3,4-syn-4,5-anti diastereomer as was originally assigned.[73]

---

[71] Mulzer, J.; deLasalle, P.; Freißler, A. *Liebigs Ann. Chem.* **1986**, 1152.

[72] Fronza, G.; Fuganti, C.; Grasselli, P.; Pedrocchi-Fantoni, G.; Zirotti, C. *Chem. Lett.* **1984**, 335.

[73] Tamao, K.; Nakajo, E.; Ito, Y. *J. Org. Chem.* **1987**, *52*, 957.



Me
Br
CrCl3, LiAlH4
THF, 20°C
71%
(101)
(102)
(103)
54 : 44 : 2 (106)
(114) Li
THF, -78°C
91%
(101)
(115)
(116)
44 : 43 : 13 (3,4-syn)
CrCl3, LiAlH4
THF, 10°C
(117)
(118)
96 : 4 selectivity
1) (iPr2N)Me2Si ZnCl
(119)
2) H2O2, KF, KHCO3, MeOH
28%
(101)
(120)
only isomer detected

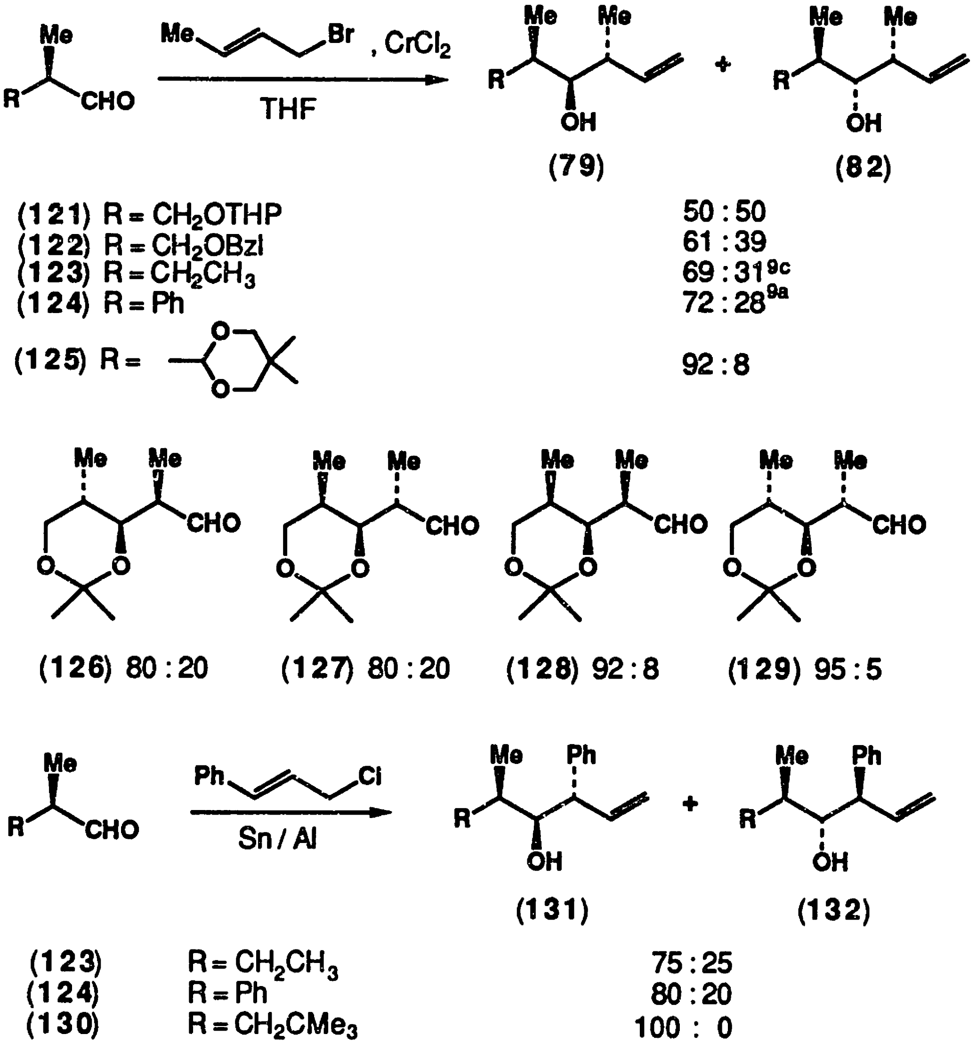
Figure 25

Reactions of the crotylchromium reagent (**59**) and α-methyl chiral aldehydes are summarized in Figure 30.[9a,c, 74] The results with (**121**)-(**125**) demonstrate that diastereoselectivity via a transition state analogous to (**83**) increases as the steric demands of R increase, while the data for (**126**)-(**129**) indicate that diastereoselectivity in these more stereochemically complicated cases depends subtly on the stereochemistry of the centers at C(3) and C(4) rela-

---

[74] (a) Lewis, M. D.; Kishi, Y. *Tetrahedron Lett.* **1982**, *23*, 2343. (b) Nagaoka, H.; Kishi, Y. *Tetrahedron* **1981**, *37*, 3873. (c) Suzuki, K.; Katayama, E.; Tomooka, K.; Matsumoto, T.; Tsuchihashi, G. *Tetrahedron Lett.* **1985**, *26*, 3707. (d) For reactions of O-protected lactaldehydes with $RCH=CHCH_2CrL_n$ that show that diastereofacial selectivity also increases with the size of R: Mulzer, J.; Schulze, T.; Strecker, A.; Denzer, W. *J. Org. Chem.* **1988**, *53*, 4098.

tive to C(2). This effect undoubtedly is related to the conformational preferences of the C(2)-C(3) bond, which influences the nonbonded interactions involving the bulky R unit in the disfavored transition state (**84**).[74a] Interestingly, the reaction of (E)-crotylboronate (**76**) with (**122**) provides (**79**) and (**82**) in a ratio of 68 : 32,[65] while the reaction of (**124**) and (crotyl)ZrCp$_2$Cl (**72**) provides (**79**) and (**82**) in the ratio of 73 : 27,[18b,75] diastereoselectivities very similar to those obtained with the crotylchromium reagent (**59**). The reactions of aldehyde (**130**) and the cinnamyl tin reagent also proceed via a transition state analogous to (**83**), again with diastereoselectivity increasing as the steric requirements of R increase.[51b, 74b]



Me
R
CHO
Me
Br
, CrCl$_2$
THF
Me
Me
R
OH
+
Me
Me
R
OH
(79)
(82)
(121) R = CH$_2$OTHP 50 : 50
(122) R = CH$_2$OBzl 61 : 39
(123) R = CH$_2$CH$_3$ 69 : 31[9c]
(124) R = Ph 72 : 28[9a]
(125) R = 92 : 8
O
O
Me
Me
CHO
O
O
(126) 80 : 20
(127) 80 : 20
(128) 92 : 8
(129) 95 : 5
Me
R
CHO
Ph
Cl
Sn / Al
Me
Ph
R
OH
+
Me
Ph
R
OH
(131)
(132)
(123) R = CH$_2$CH$_3$ 75 : 25
(124) R = Ph 80 : 20
(130) R = CH$_2$CMe$_3$ 100 : 0

Figure 26

---

[75] Yamamoto, Y.; Komatsu, T.; Maruyama, K. *J. Organomet. Chem.* **1985**, *285*, 31.

Numerous reactions of chiral aldehydes and allylmetal reagents have been reported. Some of the more highly selective examples are summarized in Figure 27. The stereochemistry of the reaction of (133)[74b] and the allyliodide/$SnCl_2$ reagent are typical of reactions of α-methyl chiral aldehydes; the 4,5-syn diastereomer predominates, but usually not with the level of stereoselection seen in this example.[64, 65, 75] The general agreement of the results with the different allylmetal reagents, especially those involving allylboronate (78), suggests that chelated transition states are not involved, as is often assumed by many investigators.[76]

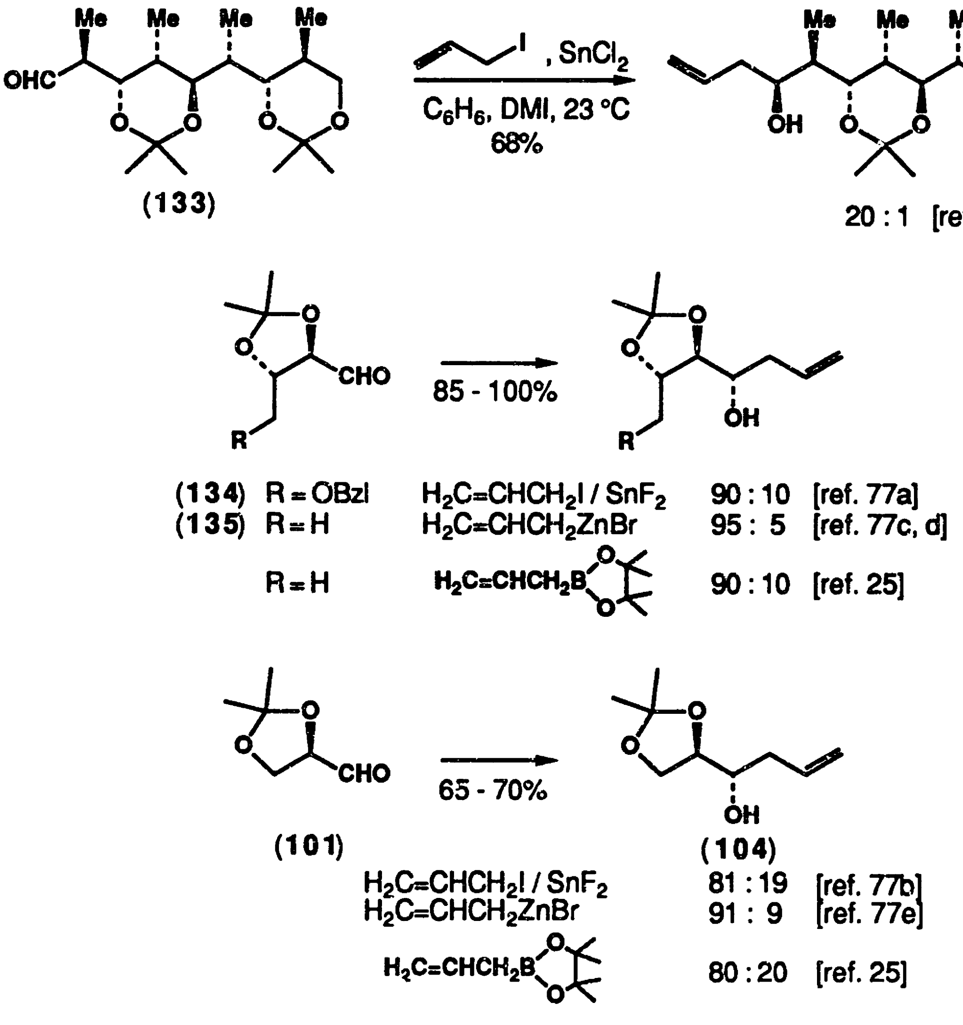

Me Me Me Me
OHC
O O O O
(133)
, SnCl2
C6H6, DMI, 23 °C
68%
Me Me Me Me
OH O O O O
20 : 1 [ref. 74b]
O O CHO
R
85 - 100%
O O
R OH
(134) R = OBzl H2C=CHCH2I / SnF2 90 : 10 [ref. 77a]
(135) R = H H2C=CHCH2ZnBr 95 : 5 [ref. 77c, d]
R = H H2C=CHCH2B(O)(O) 90 : 10 [ref. 25]
O O CHO
65 - 70%
O O
OH
(101)
(104)
H2C=CHCH2I / SnF2 81 : 19 [ref. 77b]
H2C=CHCH2ZnBr 91 : 9 [ref. 77e]
H2C=CHCH2B(O)(O) 80 : 20 [ref. 25]

Figure 27

---

[76] (a) Mulzer, J.; Angermann, A. *Tetrahedron Lett.* **1983**, *24*, 2843. (b) Jurczak, J.; Pikul, S.; Bauer, T. *Tetrahedron* **1986**, *42*, 447.

[77] (a) Mukiayama, T.; Yamada, T.; Suzuki, K. *Chem. Lett.* **1983**, 5. (b) Harada, T.; Mukiayama, T. *Ibid.* **1981**, 1109. (c) Fronza, G.; Fuganti, C.; Grasselli, P.; Pedrocchi-Fantoni, G.; Zirotti, C. *Tetrahedron Lett.*

1.4.2 Type 2 Reagents.

The Lewis-acid catalyzed reactions of the Type 2 allylmetal reagents with chiral aldehydes are generally most selective in cases that involve α- or β-alkoxy-substituted substrates. The presence of a proximal oxygen-containing substituent allows the aldehyde to exist as a chelate via interaction with the Lewis acid. As a result of the increased conformational rigidity, the chelated substrate usually exhibits a high facial preference for attack by the nucleophile.

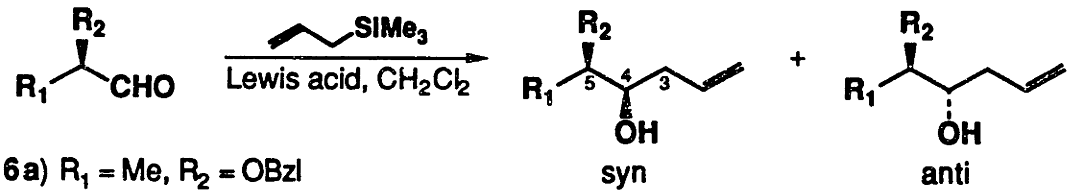
This effect has been observed in the Lewis-acid catalyzed reactions of allylsilanes and alkoxy-substituted aldehydes (Figure 28). Excellent 4,5-syn selectivity is observed in reactions with α- or β-alkoxyaldehydes using Lewis acids (e.g., $SnCl_4$) that can form a chelate with the neighboring alkoxy substituent (entries 1, 3, 5).[78, 79] Attempts to reverse the observed stereochemical bias, via the use of a Lewis acid ($BF_3 \cdot Et_2O$) which is unable to form a chelate, have not been as successful (entries 2, 4, 6). Reaction with chiral aldehydes lacking alkoxy substituents (e.g., (**136d**)) resulted in only marginal preference for the 4,5-syn adduct via the usual Felkin-Ahn transition state.[80]

1982, *23*, 4143. (d) Fujisawa, T.; Kojima, E.; Itoh, T.; Sato, T. *Ibid.* **1985**, *26*, 6089. (e) Mulzer, J.; Angermann, A. *Tetrahedron Lett.* **1983**, *24*, 2843.

[78] (a) Kiyooka, S. I.; Heathcock, C. H. *Tetrahedron Lett.* **1983**, *24*, 4765. (b) Heathcock, C. H.; Kiyooka, S. I.; Blumenkopf, T. A. *J. Org. Chem.* **1984**, *49*, 4214.

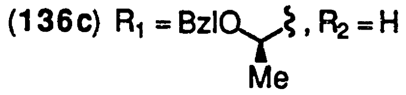
[79] Reetz, M. T.; Kesseler, K.; Jung, A. *Tetrahedron Lett.* **1984**, *25*, 729.

[80] Reactions of allylsilanes with chiral acetals have also been reported: Kiyooka, S. I.; Sasaoka, H.; Fujiyama, R.; Heathcock, C. H. *Tetrahedron Lett.* **1984**, *25*, 5331.



(**136a**) $R_1 = Me, R_2 = OBzl$

(**136b**) $R_1 = BzlOCH_2, R_2 = Me$



(**136c**) $R_1 = BzlOCH(Me)$, $R_2 = H$

(**136d**) $R_1 = Ph, R_2 = Me$

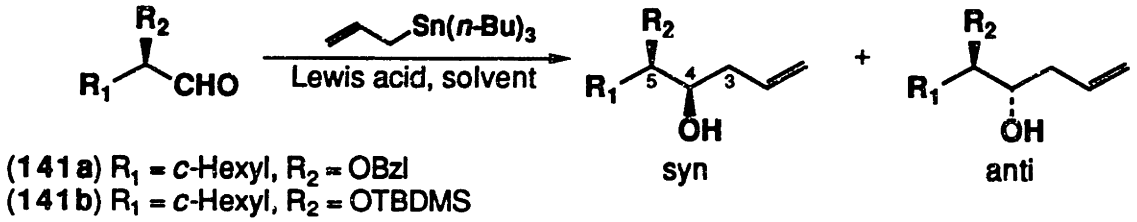
Entry	RCHO	Lewis acid	Product	(68) : (69)
1	(**136a**)	$SnCl_4$	(**137**)	97 : 3
2	(**136a**)	$BF_3 \cdot Et_2O$	(**137**)	40 : 60
3	(**136b**)	$SnCl_4$	(**138**)	92 : 8
4	(**136b**)	$BF_3 \cdot Et_2O$	—	no product
5	(**136c**)	$SnCl_4$	(**139**)	90 : 10
6	(**136c**)	$BF_3 \cdot Et_2O$	—	no product
7	(**136d**)	$SnCl_4$	(**140**)	69 : 31
8	(**136d**)	$BF_3 \cdot Et_2O$	(**140**)	67 : 33
9	(**136d**)	$TiCl_4$	(**140**)	62 : 38

Figure 28

Investigations of the Lewis acid-catalyzed reactions of allyl- and crotylstannanes with chiral alkoxy aldehydes have shown that the diastereofacial selectivity is strongly influenced by the choice of Lewis acid catalyst (e.g., entries 1 and 2; Figure 29, and entries 1 and 3; Figure 30), reaction solvent (Entries 1 and 3; Figure 29), and the alkoxy protecting group (Entries 1 and 4; Figure 29).[12c, 40a, 81] While these studies show outstanding relative (4,5-syn) diastereoselectivity in chelation-controlled addition reactions (entries 3, 4, 5, 7; Figure 30), the 3,4-syn selectivity (simple diastereoselection) about the newly-formed C—C bond was found to be *ca.* 90%, leaving room for improvement.

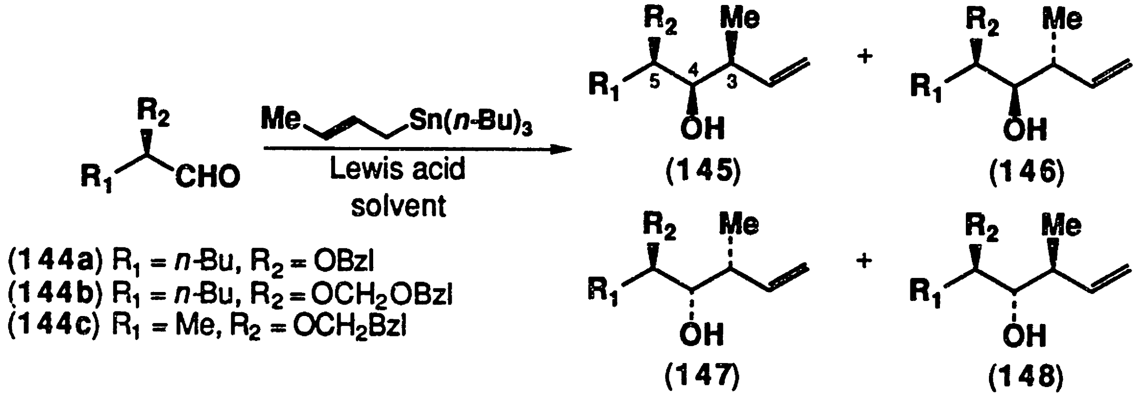
---

[81] (a) Keck, G. E.; Boden, E. P. *Tetrahedron Lett.* **1984**, *25*, 265. (b) Keck, G. E.; Boden, E. P. *Ibid.* **1984**, *25*, 1879.


R2
R1
CHO
Sn(n-Bu)3
Lewis acid, solvent
R2
R1
5
4
3
OH
syn
+
R2
R1
OH
anti
(141a) R1 = c-Hexyl, R2 = OBzl
(141b) R1 = c-Hexyl, R2 = OTBDMS

Entry	RCHO	Lewis acid	Solvent	Product	syn : anti
1	(141a)	$MgBr_2$ or $TiCl_4$	CH_2Cl_2	(142)	99.6 : 0.4
2	(141a)	$BF_3 \cdot Et_2O$	CH_2Cl_2	(142)	39 : 61
3	(141a)	$MgBr_2$	THF	(142)	20 : 80
4	(141b)	$MgBr_2$	CH_2Cl_2	(143)	21 : 79
5	(141b)	$BF_3 \cdot Et_2O$	CH_2Cl_2	(143)	5 : 95

Figure 29


R2
R1
CHO
Me
Sn(n-Bu)3
Lewis acid
solvent
(144a) R1 = n-Bu, R2 = OBzl
(144b) R1 = n-Bu, R2 = OCH2OBzl
(144c) R1 = Me, R2 = OCH2Bzl
R2
Me
R1
5
4
3
OH
(145)
+
R2
Me
R1
OH
(146)
R2
Me
R1
OH
(147)
+
R2
Me
R1
OH
(148)

Entry	RCHO	Lewis acid	(145) : (146) : (147) : (148)	4,5- syn : anti	3,4- syn : anti
1	(141a)	$BF_3 \cdot Et_2O$	66 : 1.1 : 26.2 : 6.7	67 : 33	98 : 8
2	(141a)	ZnI_2	48.6 : 49.4 : 0.9 : 1.1	98 : 2	50 : 50
3	(141a)	$TiCl_4$	63.3 : 36.7 : – : –	>99.5 : <0.5	63 : 34
4	(141a)	$MgBr_2$	92.5 : 7.5 : – : –	>99.5 : <0.5	92 : 8
5	(144a)	$MgBr_2$	90.8 : 9.2 : – : –	>99.5 : <0.5	91 : 9
6	(144a)	$BF_3 \cdot Et_2O$	39.1 : 4.2 : 45 : 11.7	43 : 57	84 : 16
7	(144b)	$MgBr_2$	91 : 9 : – : –	>99.5 : <0.5	91 : 9
8	(144c)	$MgBr_2$	89.2 : 9.9 : 0.6 : 0.3	99 : 1	90 : 10

Figure 30

1.5 Asymmetric Synthesis: Reactions of Chiral Allylorganometallics and Aldehydes.

In the preceding sections of this chapter, we have briefly reviewed the general trends in stereochemical selectivity of the numerous allylorganometallic reagents. It is apparent, specifically in the reactions with chiral aldehydes, that achiral organometallic reagents offer only limited diastereofacial control in the stereochemical outcome which is overwhelmingly influenced by and is subject to the whims of the facial bias inherent in the aldehyde (substrate-control). It is because of this that attempts have been made to develop chiral allylmetal reagents which, as a result of their chirality, possess a facial preference of their own that can ideally control the relative diastereoselectivity *regardless of the facial bias of the substrate* (reagent-control). A majority of these chiral organometallic reagents fall into two distinct groups:

1. Reagents with conventional, readily-introduced chiral auxiliaries.
2. Reagents in which the center of chirality is an integral structural component.

1.5.1 Chiral Allylorganometallics with Conventional Auxiliaries.

The synthetic utility of this group of chiral reagents depends on a number of factors. First, the incorporation of the chiral auxiliary should be easily achieved, ideally in a one-step procedure (e.g., via ligand exchange) without affecting the stereochemical integrity of the olefinic fragment of the reagent. Second, the auxiliary should be readily available in enantiomerically pure form, and should be cost effective if it is commercially available. Third, it is preferable that the auxiliary can be recovered easily, enantiomerically intact, so that it can be recycled for subsequent use.

The most highly enantioselective Type 1 and Type 3 allylmetal reagents that fall into this category are listed in Figure 31. Reagents **(149a)**–**(149c)** developed by Hoffmann are of historical significance since they were the first chiral allylmetal compounds to be studied, and were also among the first chiral reagents of any sort shown to be capable of increasing the stereoselectivity of moderately diastereoselective reactions of chiral aldehydes (i.e., matched double asymmetric synthesis).[75b, 82] Allyl reagent **(149a)** gives 86% e.e. in the reaction with acetaldehyde at –90°C, but for most other aldehydes the selectivity is in the range of 36% e.e.

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[82] (a) Hoffmann, R. W.; Zeiss, H. -J. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 218. (b) Herold, T.; Schrott, U.; Hoffmann, R. W.; Schnelle, G.; Ladner, W.; Steinbach, K. *Chem. Ber.* **1981**, *114*, 359. (c) Hoffmann, R. W.; Herold, T. *Ibid.* **1981**, *114*, 375. (d) R. W. Hoffmann,; W. Helbig, *Ibid.* **1981**, *114*, 2802.

(PhCHO) to 72% e.e. (C_3H_7CHO) for reactions at –40 °C. The allylborane (**150**) recently described by Reetz is substantially improved and gives 88–96% e.e. with a range of aldehydes at –78 °C.[83] The corresponding crotyl reagent, however, has not yet been described.

The allyldiisopinocampheylboranes (**151a**)–(**151d**) developed by Brown give consistently excellent results (83–96% e.e.) in reactions with aldehydes.[21c, 84] The analogous allylboranes prepared from (+)-3-carene show even greater levels of enantioselectivity, but the considerably greater expense of 3-carene renders these reagents less attractive as reagents for synthetic applications. The same comment applies to the crotyl-*trans*-2-5-dimethylborolanes (**152a**) and (**152b**) owing to the difficult synthesis of the *B*-methoxy-2,5-dimethylborolane precursor.[85a] Nevertheless, (**152a**) and (**152b**) are among the most highly enantioselective crotylmetal reagents yet described: in five of the six examples reported the enantioselectivity is 93–97% e.e. (simple diastereoselectivity is 93–96%). Allylborane (**153**) has recently been reported to be an exceptionally enantioselective allyl transfer reagent (92–97% e.e.)[85b]

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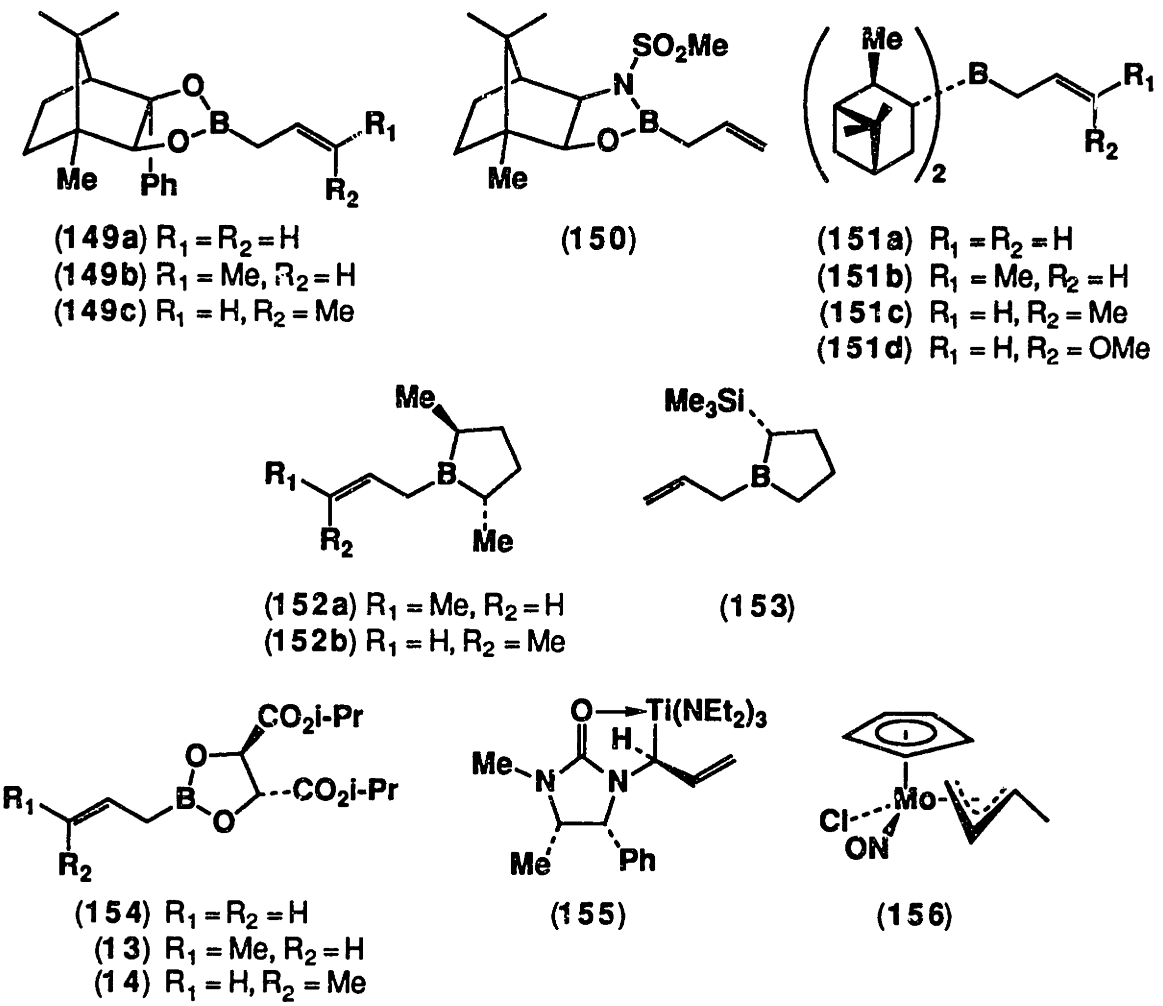
[83] Reetz, M. T.; Zierke, T. *Chem. and Ind. (London)* **1988**, 663.

[84] (a) Jadhav, P. K.; Bhat, K. S.; Perumal, P. T.; Brown, H. C. *J. Org. Chem.* **1986**, *51*, 432. (b) Brown, H. C.; Bhat, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 5919.

[85] (a) Garcia, J.; Kim, B. -M.; Masamune, S. *J. Org. Chem.* **1987**, *52*, 4831. (b) Short, R. P.; Masamune, S. *J. Am. Chem. Soc.* **1989**, *111*, 1892.



(149a) $R_1 = R_2 = H$
(149b) $R_1 = Me, R_2 = H$
(149c) $R_1 = H, R_2 = Me$

(150)

(151a) $R_1 = R_2 = H$
(151b) $R_1 = Me, R_2 = H$
(151c) $R_1 = H, R_2 = Me$
(151d) $R_1 = H, R_2 = OMe$

(152a) $R_1 = Me, R_2 = H$
(152b) $R_1 = H, R_2 = Me$

(153)

(154) $R_1 = R_2 = H$
(13) $R_1 = Me, R_2 = H$
(14) $R_1 = H, R_2 = Me$

(155)

(156)

Figure 31

The tartrate ester modified allylboronates **(154)**, **(13)** and **(14)** are attractive alternatives to the allylB(Ipc)$_2$ reagents owing to their ease of preparation and stability to storage.[35, 86] In the best cases the tartrate allylboronates are about as enantioselective as Brown's allylboranes (82–88% e.e. with unhindered aliphatic aldehydes), but with hindered aliphatic, aromatic, α,β-unsaturated and most α- and β-alkoxyaldehydes the enantioselectivity falls to a level of 55–75% e.e. Enantioselectivity is highly dependent on reaction solvent, with best results being obtained in toluene for all substrates except aromatic ones for which the % e.e. is highest in THF (See Chapter 2).

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[86] (a) Roush, W. R.; Walts, A. E.; Hoong, L. K. *J. Am. Chem. Soc.* **1985**, *107*, 8186. (b) For details concerning optimized experimental conditions, see Chapter 2 of this manuscript: Roush, W. R.; Hoong, L. K.; Palmer, M. A. J. manuscript in preparation.

Allyltitanium reagent **(155)** undergoes highly diastereoselective reactions with aldehydes (88–92% d.e.).[87] It is interesting that **(155)** possesses a stereocenter at C(1) of the allyl unit, but, unlike the other C(1) chiral reagents discussed in the following section, this center is introduced in a very simple manner by the metallation of the corresponding allylurea. The η^3-crotylmolybdenum reagent **(156)** undergoes a highly enantio- and diastereoselective reaction with benzaldehyde (> 98% e.e.; 96 : 4 anti : syn), but the full scope of this methodology has not yet been reported.[31]

1.5.2 Chiral Allylorganometallics with Stereocenters at C(1) or C(4).

Allylorganometallics with stereocenters at either C(1) or C(4) of the allyl/crotyl unit have been described. For such compounds to be useful in single or double asymmetric reactions it is necessary that they be accessible with a high degree of enantiomeric purity. Such reagents are frequently less convenient to synthesize than those with conventional auxiliaries, but the trade off is that the reactions with aldehydes often occur with nearly 100% asymmetric induction. Chiral, non-racemic reagents that fall into this category are shown in Figure 32.[88] Of these, **(158)**[89] and **(161)**[90a] provide homoallyl alcohols with the lowest enantiomeric purity, **(158)** owing to the method of synthesis and **(161)** presumably due to racemization, and examples of their reactions will not be discussed in text. The interesting, easily prepared chiral crotyllithium reagent **(162)**, however, undergoes transmetallation with $Ti(OiPr)_4$ at –70 °C to give a reagent that reacts with aldehydes with reasonable levels of enantioselectivity (80–84% e.e.)[90b]

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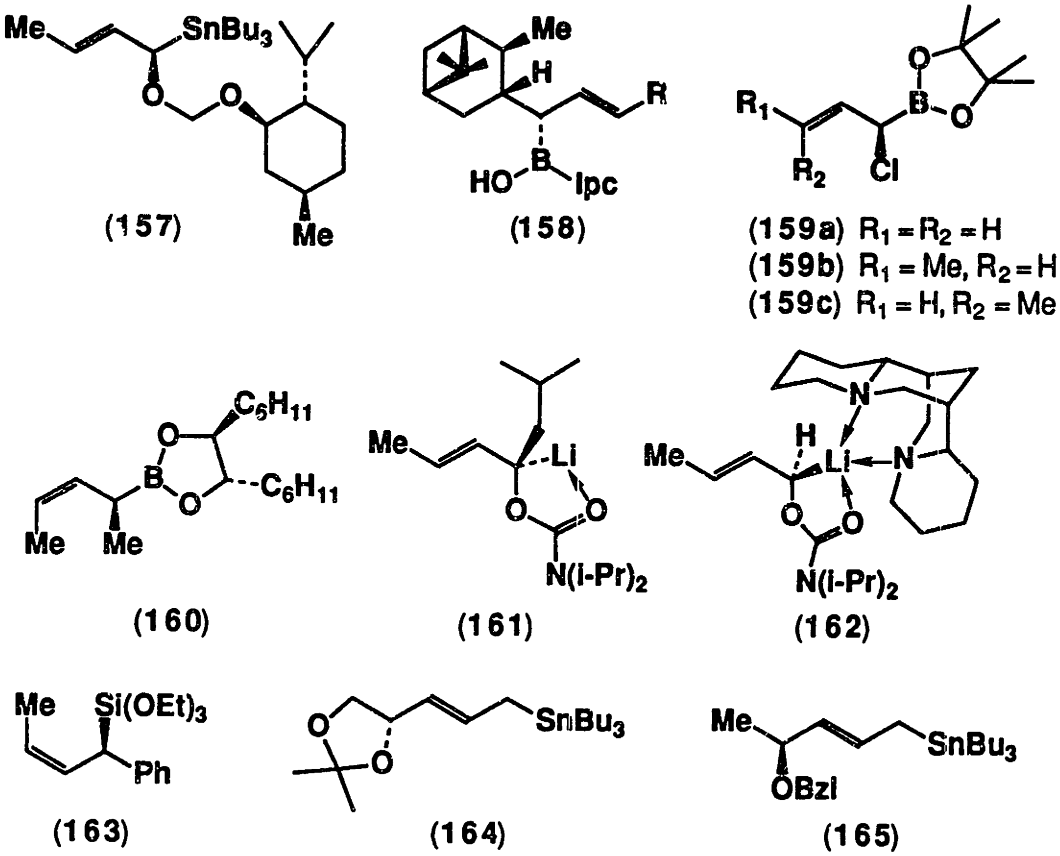
[87] Roder, H.; Helmchen, G.; Peters, E. -M.; Peters, K.; von Schnering, H. -G. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 898.

[88] Hayashi, T.; Matsumoto, Y.; Kiyoi, T.; Ito, Y. *Tetrahedron Lett.* **1988**, *29*, 5667.

[89] (a) Midland, M. M.; Preston, S. B. *J. Am. Chem. Soc.* **1982**, *104*, 2330. (b) For an α-chiral allyl(Ipc)$_2$borane prepared by the hydroboration of a diene that is highly enantioselective, see ref. 21a.

[90] (a) Hoppe, D.; Krämer, T. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 160. (b) Hoppe, D.; Zschage, O. *Ibid.* **1989**, *28*, 69.



(157) (158)

(159a) $R_1 = R_2 = H$
(159b) $R_1 = Me, R_2 = H$
(159c) $R_1 = H, R_2 = Me$

(160) (161) (162)

(163) (164) (165)

Figure 32

Thomas and coworkers have shown that the chiral crotylstannane (**157**) undergoes highly diastereoselective reactions with benzaldehyde, cinnamaldehyde and cyclohexanecarboxaldehyde (99% d. e.).[91] These reactions occur by way of a chair-like transition state (analogous to (**7**); Figure 4) with the α-alkoxy unit occupying an axial position so as to avoid nonbonded interactions with the butyl substituents on tin. Reagent (**157**) was prepared via the addition of Bu_3SnLi to crotonaldehyde and then resolved via the reaction with chloromethyl (-)-menthyl ether. The menthyl unit probably has little to do with the asymmetric induction in aldehyde reactions, since diastereoselection is identical to that obtained with the racemic reagent (**39**) (Figure 9). Consequently, recent reports that α,β-unsaturated acyl stannanes undergo highly enantioselective reductions with BINAL-H should provide an alternative preparative route to non-racemic crotylstannanes of this class.[92]

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[91] Jephcote, V. J.; Pratt, A. J.; Thomas, E. J. *J. Chem. Soc., Chem. Commun.* **1984**, 800.

[92] (a) Marshall, J. A.; Gung, W. Y. *Tetrahedron Lett.* **1988**, *29*, 1657. (b) Chan, P. C. -M.; Chong, J. M. *J.*

The α-chiral allyl and crotylboronates **(159)**–**(160)** have been developed and studied extensively by Hoffmann and his coworkers.[93] Reagents **(159a)** (92% e.e.) and **(160)** (>95% e.e.) are synthesized by using the Matteson α-haloalkylboronate alkylation procedure,[94] while **(159b)** (95–98% e.e.) is prepared via the hydroboration of 3-butyn-2-yl trimethylsilyl ether followed by an allylic rearrangement with $SOCl_2$.[95] (Z)-α-Chlorocrotylboronate **(159c)** has so far been studied only as the racemate.[93b] Allylboronate **(159a)**[96] and (E)-crotylboronate **(159b)** provide roughly 95 : 5 mixtures of **(166)** : **(167)** in reactions with aldehydes, with the enantiomeric purity of the major (Z)-chloro isomer closely paralleling the enantiomeric purity of the starting materials.[93a,b] (Z)-α-Methylcrotylboronate **(160)** also undergoes an exceptionally enantioselective reaction with benzaldehyde.[93c] α-Chloroallyl and -crotylboronates **(159a)** and **(159b)** react preferentially via transition state **(168)** with an axial orientation of the chloro substituent that is favored apparently for steric and/or stereoelectronic reasons (Figure 33).[97] With **(159c)** and **(160)**, however, the α-substituent prefers an equatorial position as indicated in **(169)** in order to avoid 1,3-interactions with the (Z)-Me group.

Org. Chem. **1988**, *53*, 5584.

[93] (a) Hoffmann, R. W.; Landmann, B. *Chem. Ber.* **1986**, *119*, 2013. (b) Hoffmann, R. W.; Dresely, S.; Lanz, J. W. *Ibid.* **1988**, *121*, 1501. (c) Ditrich, K.; Bube, T.; Stürmer, R.; Hoffmann, R. W. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 1028.

[94] Sadhu, K. M.; Matteson, D. S.; Hurst, G. D.; Kurosky, J. M. *Organometallics* **1984**, *3*, 804.

[95] Hoffmann, R. W.; Dresely, S. *Synthesis* **1988**, 103.

[96] The experiments summarized here were actually performed with the enantiomer of **(96a)**.

[97] (a) Hoffmann, R. W.; Weidmann, U. *J. Organomet. Chem.*, 1980, **195**, 137. (b) Hoffmann, R. W.; Landmann, B. *Chem. Ber.*, 1986, **119**, 1039.

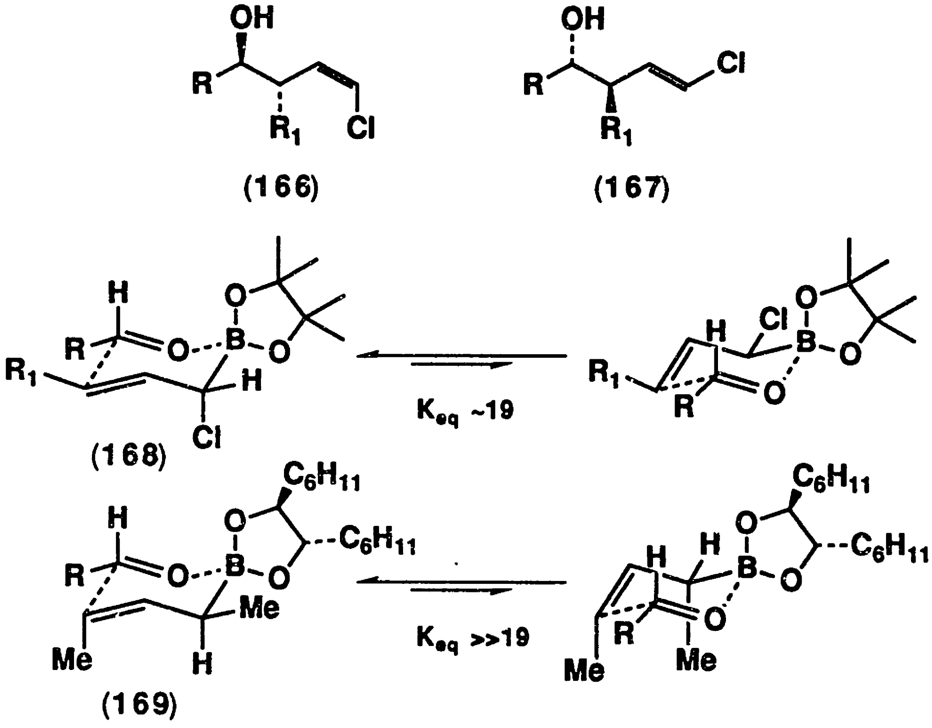

Figure 33

Finally, Thomas has reported that allylstannanes (**164**) and (**165**) possessing stereocenters at C(4) undergo moderately diastereoselective reactions with p-nitrobenzaldehyde.[98]

1.6 Double Asymmetric Synthesis: Reactions of Chiral C=O Electrophiles and Chiral Allylorganometallics.

We have seen in Section 1.4 that reactions of many allylorganometallics and chiral C=O electrophiles proceed with only modest levels of relative diastereoselection. Significant improvement in diastereoselectivity is possible, however, by using double asymmetric synthesis,[5] that is, by using the highly enantioselective allylmetal reagents described in Section 1.5 rather than the less diastereoface selective achiral allylmetal compounds discussed in Section 1.4. Two types of double asymmetric reactions are possible: those in which the intrinsic diastereofacial preferences of the C=O electrophile and the chiral allylmetal reagent are cooperative, each favoring the production of the same product diastereomer ("*matched double*

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[98] Mortlock, S. V.; Thomas, E. J. *Tetrahedron Lett.*, 1988, **29**, 2479.

asymmetric synthesis"), and those in which the intrinsic diastereofacial preferences of the two reactants are dissonant, each favoring different stereochemical outcomes ("*mismatched double asymmetric synthesis*"). If the chiral reagent has a larger diastereofacial preference than the chiral C=O electrophile, and as long as the transition state of the double asymmetric reaction is similar to that involved in single asymmetric induction experiments, the reagent will dominate the stereochemical course and the otherwise intrinsically disfavored product diastereomer will be formed preferentially. It is almost always more difficult to achieve high diastereoselection in mismatched than in matched double asymmetric reactions since the reagent is always fighting against the intrinsic diastereofacial preference of the C=O electrophile, and the larger that preference the more difficult the goal. Consequently, highly enantioselective reagents should be used, the more selective the better. On the other hand, high levels of diastereoselection are relatively easy to achieve in matched double asymmetric reactions since the intrinsic face selectivity of the substrate reinforces that of the reagent, and in many cases it has been possible to achieve synthetically useful levels of matched diastereoselection by using only moderately enantioselective reagents. Finally, it is worth reminding the reader that both components of double asymmetric reactions need to be *chiral and nonracemic* in order for the maximum diastereoselectivity to be realized.

The first examples of highly diastereoselective double asymmetric reactions involving chiral allylmetal reagents were obtained in reactions with D-glyceraldehyde acetonide (**101**) (Figure 34). Aldehyde (**101**) displays an 80 : 20 preference for (**104**) in reactions with the achiral pinacol allylboronate (**78**) (entry 4),[25, 68] and the selectivity for (**104**) improves to 96-98% with reagents (-)-(**149a**) and (R,R)-(**154**).[68, 86] With (R,R)-(**170**) the diastereoselectivity is 300 : 1, which is the highest selectivity yet documented for a reaction of a chiral allylmetal reagent.[99] Tartrate allylboronate (S,S)-(**154**) undergoes a highly diastereoselective mismatched double asymmetric reaction with D-(**101**), providing the 4,5-syn (threo) diastereomer (**105**) with 92% selectivity. Here again, diastereoselectivity for (**105**) increases to 98 : 2 by using the more enantioselective allylboronate (S,S)-(**170**). Matched double diastereoselectivity is also very good (94%) by using α-chloroallylboronate (R)-(**159a**), but mismatched diastereoselection using (S)-(**159a**), leading to (**173**), is considerably lower (77%) than that realized with tartrate allylboronate (S,S)-(**154**) (Figure 35).[93a]

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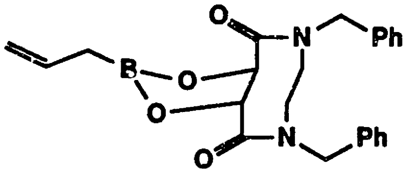
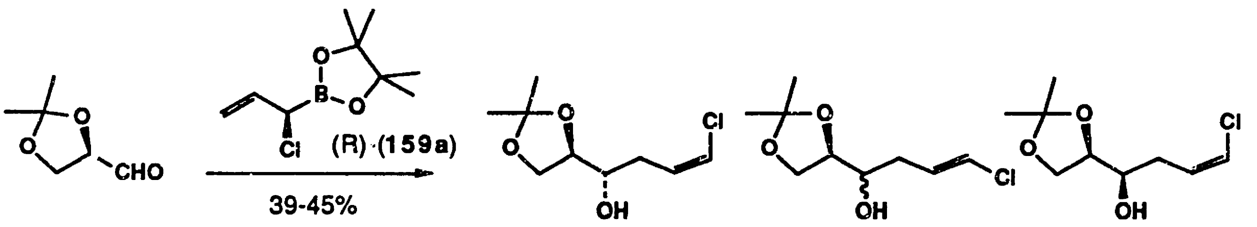
[99] Roush, W. R.; Banfi, L. *J. Am. Chem. Soc.*, 1988, **110**, 3979.

Reagents	Yield	(104) : (105)	Ref.
(R,R)-(154)	90%	98 : 2	86
(R,R)-(170)	81%	99.7 : 0.3	99
(-)-(149a)	87%	96 : 4	68
(78)	75%	80 : 20	25, 68
(S,S)-(154)	85%	8 : 92	86
(S,S)-(170)	84%	2 : 98	99



(R,R)-(170)

Figure 34. Reactions of D-Glyceraldehyde Acetonide (101) and Chiral Allylmetal Reagents



(171) (172) (173)

(R)-(159a)	94: 2: 4
(S)-(159a)	11 : 12 : 77

Figure 35

Excellent double diastereoselection has also been realized in the reactions of (**101**) and chiral crotylboron reagents (Figure 36). Interestingly, the best selectivity for diastereomers (**103**) and (**106**) are obtained by using the tartrate crotylboronates (S,S)-(**13**) and (R,R)-(**14**), respectively (entries 2, 3),[100, 101] while Masamune's 2,5-dimethylborolane reagents (R,R)-

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[100] Roush, W. R.; Halterman, R. L. *J. Am. Chem. Soc.*, 1986, **108**, 294.

[101] Roush, W. R.; Halterman, R. L. Unpublished research, 1985-86.

(**152a**) and (S,S)-(**152b**) provide the greatest selectivity for diastereomers (**102**) and (**107**) (entries 7,10).[85] Comparative data for the diastereoselectivity obtained with the achiral crotylboronates (**76**) and (**77**) appear in the last two entries of Figure 36.

Reagents	Yield	(152)	(153)	(156)	(157)	Ref.
(R,R)-(**13**)	87%	87	9	4	—	100
(S,S)-(**13**)	85%	2	96	2	—	100
(R,R)-(**14**)	84%	1	—	99	—	100
(S,S)-(**14**)	90%	7	2	76	15	100
(-)-(**149b**)	85%	72	28	—	—	68
(-)-(**149c**)	86%	—	—	>98	<2	68
(R,R)-(**152a**)	71%	96	3	1	—	85
(S,S)-(**152a**)	74%	12	86	—	2	85
(R,R)-(**152b**)	66%	4	2	92	2	85
(S,S)-(**152b**)	65%	—	2	16	82	85
(**76**)	75%	52	42	6	—	25
(**77**)	85%	5	1	91	5	25

Figure 36. Reactions of D-Glyceraldehyde Acetonide (101) and Chiral Crotylmetal Reagents.

Results of reactions of chiral α-methyl aldehydes and several chiral crotylboron reagents are summarized in Figure 37. It is apparent from these data that the Brown (Ipc)-$_2$B(crotyl) reagents (**151b**) and (**151c**) consistently give excellent results for the synthesis of each product diastereomer (Figure 37, entries 3–6, 11, 16, 20, and 24). This is true also for their reactions with chiral α- and β-alkoxy aldehydes (Figure 38).[102–104] The tartrate crotylboronates (**13**) and (**14**) also display excellent selectivity in the synthesis of crotyl diastereomers (**79**), (**80**) and (**81**) (Figure 37, entries 7, 10, 13, 17, 25, 28), but are much less selective for the synthesis of crotyl diastereomer (**82**), especially from β-alkoxy substituted aldehydes such as (**174**).[65] This trend is also paralleled in the corresponding allyl reagents, (**154**) giving lower selectivities (≥ 79%)[65] than (**159a**) (≥ 95% diastereoselectivity) in reactions with chiral α-methyl aldehydes as well as α- and β-alkoxy aldehydes (e.g., (**185**); Figure 38).[104]

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[102] (a) Brown, H. C.; Bhat, K. S.; Randad, R. S. *J. Org. Chem.*, 1987, **52**, 3701. (b) Brown, H. C.; Bhat, K. S.; Randad, R. S. manuscript submitted. We thank Professor Brown for a copy of this manuscript prior to publication. (c) Brown, H. C.; Bhat, K. S.; Randad, R. S. *J. Org. Chem.*, 1987, **52**, 319.

[103] (a) Schreiber, S. L.; Goulet, M. T. *J. Am. Chem. Soc.*, 1987, **109**, 8120. (b) For related studies, see: Nicolaou, K. C.; Ahn, K. H. *Tetrahedron Lett.*, 1989, **30**, 1217.

[104] Roush, W. R.; Palmer, M. A. J. Unpublished research, 1986.

Substantial improvements in selectivity have been realized by using the tartramide based allylboronate (**170**), however, and the results with this reagent (≥ 95% diastereoselectivity) compare very favorably with those obtained with (**151a**).[99] The data summarized in entries 9, 14 and 27 of Figure 37 (compare entries 8, 13, and 26) also indicate that stereoselectivity may be improved in the crotyl series by using tartramide crotylboronate (**176**).[105]

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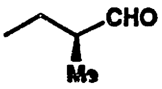
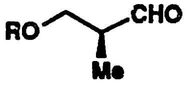
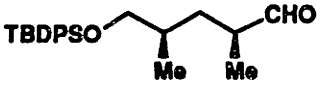
[105] Roush, W. R.; Ando, K. Unpublished research, 1987-88.



(93)



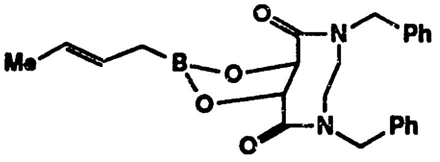
(174a), R = TBDMS
(174b), R = TBDPS
(174c), R = Bzl



(175)

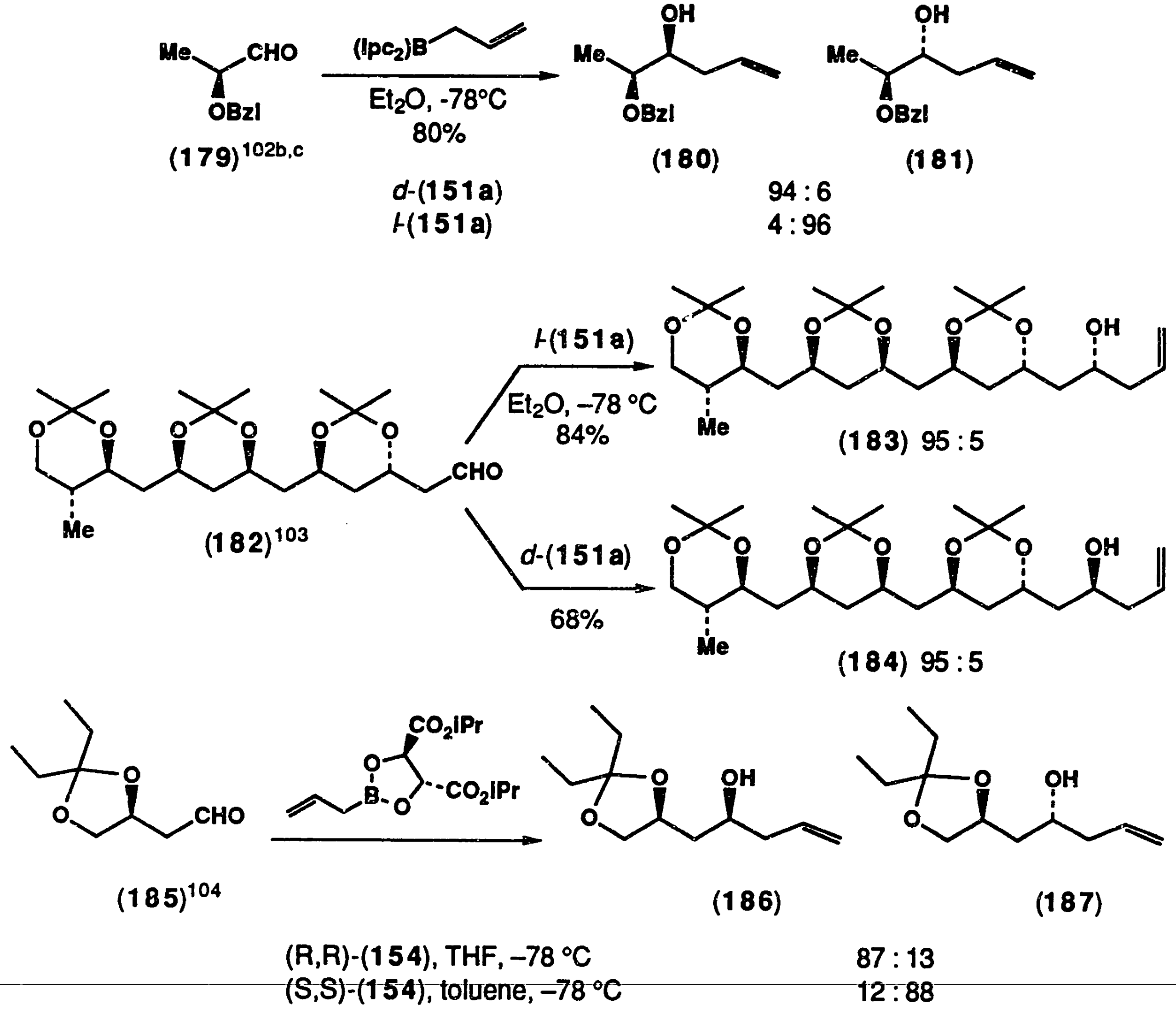
Entry	RCHO	Reagent[a]	Yield	Reaction Products[b,c] (79)	(80)	(81)	(82)	Ref.
1	(93)	(-)-(149b)	74%	92	8	—	—	64b
2	(93)	(-)-(149c)	99%	—	—	45	55	64b
3	(93)	*d*-(151b)	75%	96	4	—	—	102
4	(93)	*l*-(151b)	70%	5	95	—	—	102
5	(93)	*d*-(151c)	79%	—	—	96	4	102
6	(93)	*l*-(151c)	73%	—	—	18	82	102
7	(174a)	(R,R)-(13)	80%	97	3	—	—	65
8	(174b)	(R,R)-(13)	—	82	16	1	2	65
9	(174b)	(R,R)-(176)	26%	92	7	1	—	105
10	(174c)	(R,R)-(13)	—	93	5	1	1	65
11	(174c)	*d*-(151b)	—	98	2	—	—	102b
12	(174a)	(S,S)-(13)	—	16	81	3	—	65
13	(174b)	(S,S)-(13)	85%	10	90	—	—	65
14	(174b)	(S,S)-(176)	27%	4	96	—	—	105
15	(174c)	(S,S)-(13)	—	14	85	1	—	65
16	(174c)	*l*-(151b)	—	6	95	—	—	102b
17	(174a)	(S,S)-(14)	71%	—	4	95	1	65
18	(174b)	(S,S)-(14)	—	—	4	85	12	65
19	(174c)	(S,S)-(14)	—	—	3	88	9	65
20	(174c)	*l*-(151c)	—	—	—	95	5	102b
21	(174a)	(R,R)-(14)	—	12	2	45	41	65
22	(174b)	(R,R)-(14)	—	9	3	24	64	65
23	(174c)	(R,R)-(14)	—	8	2	45	45	65
24	(174c)	*d*-(151c)	—	—	—	8	92	102b
25	(175)	(R,R)-(13)	56%	>98	<2	—	—	105
26	(175)	(S,S)-(13)	55%	16	84	—	—	105
27	(175)	(S,S)-(176)	51%	12	88	—	—	105
28	(175)	(S,S)-(14)	63%	—	—	94	6	105
29	(175)	(R,R)-(14)	55%	6	—	16	78	105

(a) Reagents (-)-(**149b**) and (-)-(**149c**) are prepared from (1R,2S,3S,4S)-3-endo-phenylbornane-2-exo-3-exo-diol, while *d*-(**151b**) and *d*-(**151c**) are prepared from (+)-α-pinene, respectively. (b) Refer to Figure 18 for structures. (c) Additional minor diastereomers are produced in the reactions of (**151b**), (**151c**), (**149b**), and (**149c**), but only the amounts of the two most predominant products are cited in the original literature.



(R,R)-(**176**)

Figure 37. Reactions of Chiral α-Methyl Aldehydes and Chiral Crotylboron Reagents.



(179)[102b,c]
(Ipc2)B
Et2O, -78°C
80%
(180)
(181)
d-(151a)
l-(151a)
94 : 6
4 : 96
(182)[103]
l-(151a)
Et2O, –78 °C
84%
(183) 95 : 5
d-(151a)
68%
(184) 95 : 5
CO2iPr
(185)[104]
(186)
(187)
(R,R)-(154), THF, –78 °C
(S,S)-(154), toluene, –78 °C
87 : 13
12 : 88

Figure 38

It was noted at the beginning of this section that as the intrinsic diastereofacial selectivity of the chiral aldehyde increases, the ease of accomplishing highly diastereoselective matched double asymmetric reactions increases and, correspondingly, the difficulty of achieving success in the mismatched pair also increases. The intrinsically favored products of reactions of α-methyl chiral aldehydes and (E)- and (Z)-crotylmetal reagents are diastereomers (**79**) and (**81**), respectively (Figure 18 and Figure 19), and it is this pair of diastereomers that will always be easily prepared with very high diastereoselection by using matched double asymmetric reactions (Figure 37). Diastereomers (**80**) and (**82**), however, are the intrinsically disfavored set of products, and it is these that are the most difficult to access with synthetically useful levels of mismatched double diastereoselectivity especially as the intrinsic diastereofacial selectivity of the aldehyde increases. The examples presented in Figure 39 illustrate this point.[106] First, the mismatched double asymmetric reaction of **(188)** and (S,S)-**(13)** provides the 3,4-anti-4,5-anti diastereomer **(190)** (c.f., **(80)**) with only 73% selectivity. This is a substantial drop in stereoselectivity compared to the mismatched reaction of (S,S)-**(13)** and **(175)** that provides **(80)** with 84% selectivity (Figure 37, entry 26). Substrate **(191)** is even more problematic: diastereomer **(192)** predominates with >95 : 5 selectivity from the reaction with (R,R)-**(13)**, while **(193)** was the "expected" product based on the stereochemical preferences of (R,R)-**(13)**. Thus, the intrinsic diastereofacial selectivity of **(191)** totally overwhelmed that of (R,R)-**(13)** in this attempted mismatched double asymmetric reaction.

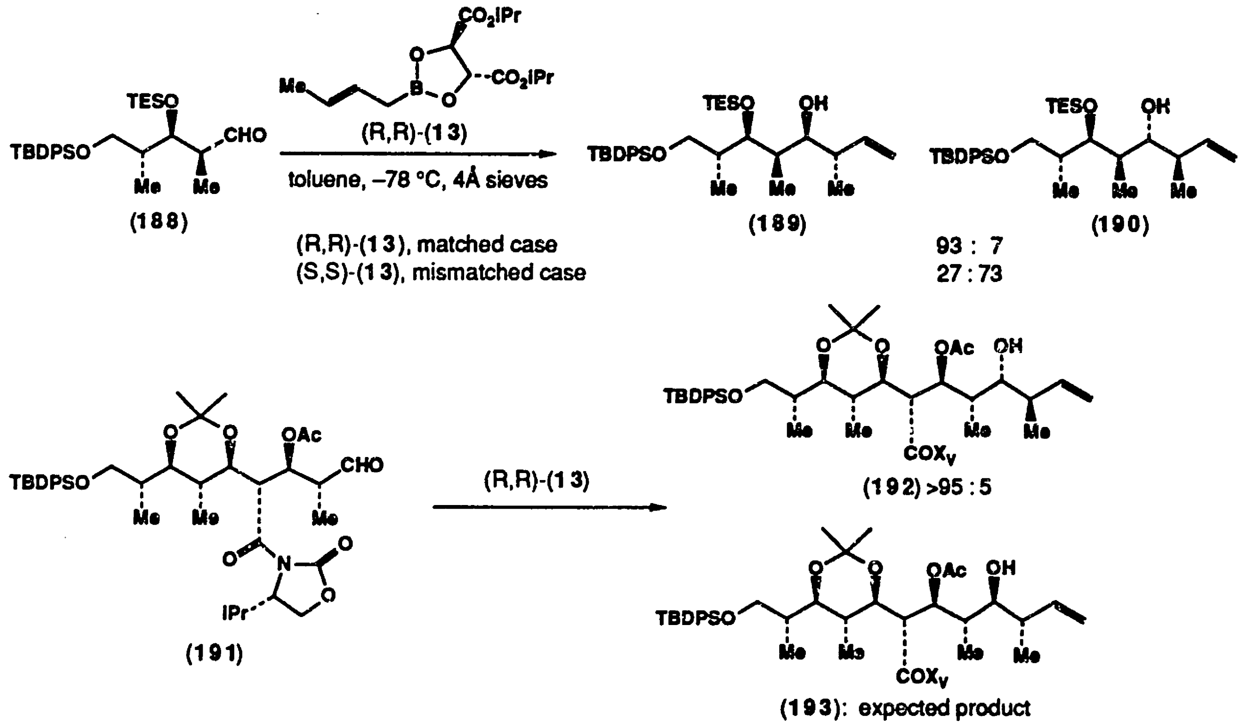

CO2iPr
CO2iPr
Me
B
O
TESO
TBDPSO
CHO
Me Me
(188)
(R,R)-(13)
toluene, –78 °C, 4Å sieves
(R,R)-(13), matched case
(S,S)-(13), mismatched case
TESO OH
TBDPSO
Me Me Me
(189)
93 : 7
27 : 73
(190)
OAc
CHO
N
iPr
(191)
(R,R)-(13)
OAc OH
COXv
(192) >95 : 5
(193): expected product

Figure 39

Of all the chiral allylmetal reagents reported to date, the one that is most effective in demanding cases of mismatched double diastereoselection is the α-methoxycrotylboronate

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[106] Roush, W. R.; Palkowitz, A. D. Unpublished research, 1986-88.

(**195**) developed by Hoffmann.[107] Two illustrative cases are presented in Figure 40. First, the reaction of (**194**) and (R)-(**195**) provides the 3,4-anti-4,5-anti diastereomer (**196**) with roughly 84% stereoselectivity. This is remarkable in view of the very high intrinsic diastereofacial selectivity (98 : 2) for the 3,4-anti-4,5-syn diastereomer exhibited by the structurally related aldehyde (**95**) (Figure 19). The second involves (**198**) that with (S)-(**195**) provides 3,4-anti-4,5-anti (**199**) with 73% stereoselection. By way of comparison, the α-chlorocrotylboronate (S)-(**159b**) is incapable of overriding the intrinsic diastereofacial preference of (**198**), giving 3,4-anti-4,5-syn diastereomer (E)-(**200**) with 92% selectivity (compare also (**191**), Figure 39).

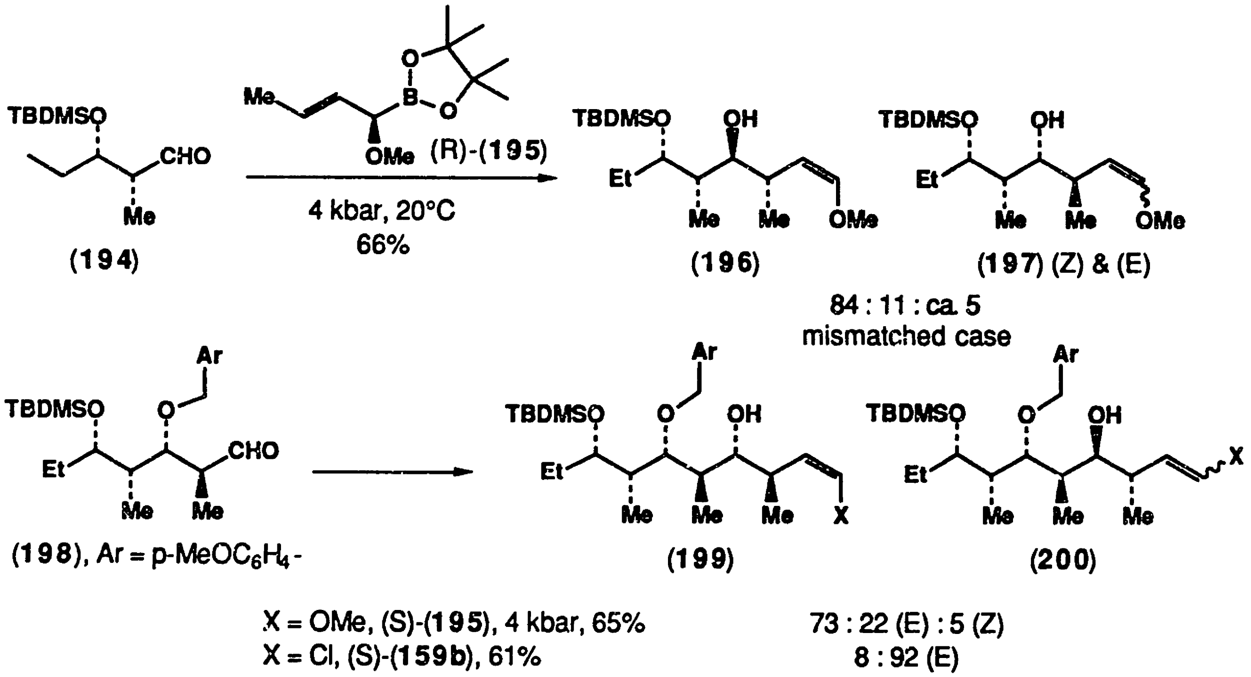
TBDMSO
CHO
Me
(194)
Me
B
O
O
OMe
(R)-(195)
4 kbar, 20°C
66%
TBDMSO
OH
Et
Me
Me
OMe
(196)
TBDMSO
OH
Et
Me
Me
OMe
(197) (Z) & (E)
84 : 11 : ca. 5
mismatched case
Ar
TBDMSO
O
Et
CHO
Me
Me
(198), Ar = p-MeOC6H4-
Ar
TBDMSO
O
OH
Et
Me
Me
Me
X
(199)
Ar
TBDMSO
O
OH
Et
Me
Me
Me
X
(200)
X = OMe, (S)-(195), 4 kbar, 65%
X = Cl, (S)-(159b), 61%
73 : 22 (E) : 5 (Z)
8 : 92 (E)

Figure 40.

1.7 Summary

Outstanding progress has been realized in the past decade concerning the stereochemistry of the reactions of allylmetal compounds with C=O compounds. A variety of reagents are now available that provide excellent stereochemical control in reactions with achiral aldehydes (simple diastereoselection), and a clear stereochemical picture has emerged, particularly involving the reactions with chiral aldehydes (relative diastereoselection). Even more extraordinary has been the development of highly enantioselective chiral allylmetal reagents capable of enhancing, or reversing, depending on the absolute configurations of the two reactants, the diastereofacial selectivity of the chiral $C=O$ moiety via the strategy of double asymmetric synthesis. Hence, the ambition of developing a family of organometallics capable of providing highly selective access to each of the products, depicted in Figure 2, has been attained. While there is yet some room for improvements, especially in terms of the discovery of reagents which are both economical and practical as well as highly enantioselective, the state of the art of allylorganometallic chemistry is now at an adequately high level that significant opportunities exist for its application to the highly stereocontrolled synthesis of complex, biologically-active molecules.

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[107] (a) Hoffmann, R. W.; Dresely, S. *Tetrahedron Lett.*, 1987, **28**, 5303. (b) Hoffmann, R. W.; Dresely, S.; Hildebrandt, B. *Chem. Ber.* 1988, **121**, 2225.

Our efforts in this area of research, the development and investigations of the scope of the tartrate-derived allylboronate reagents (e.g., **(13)**, **(14)**, and **(154)**), are described in detail in the following chapter.

CHAPTER 2

Investigations of the Reactions of Tartrate-derived Allylboronates

Factors Influencing Stereoselectivity

2.1 Introduction

The overview of the numerous allylorganometallic reagents in Chapter 1 served to highlight the broad potential for the use of these reagents in the context of practical organic synthesis, particularly for the control of acyclic stereochemistry . Allylboron compounds, in particular, offer significant advantages compared to other allylmetal species in view of their chemoselectivity, versatility, ease of preparation, and the high degree of predictability in the stereochemical outcomes of their reactions with carbonyl electrophiles. Indeed, these attributes have earned them a place in the research efforts of several groups worldwide.

While various chiral allylmetal reagents are now available that provide exceptional levels of diastereoselectivity in reactions with chiral aldehydes, by the mid 1980's the problem of relative diastereoselection involving chiral substrates had not yet been adequately addressed. This state of affairs prompted Roush,Walts, and Adam to initiate investigations toward the development of a chiral allylboron reagent that would provide a general solution to this challenging issue.[1] At the time these studies were begun, only two classes of chirally-modified allylic boron reagents had been reported—the bornanediol-derived allylboronates (**1**)[2] and the pinene-derived allylborane (**3**).[3a]

However, the bornanediol-derived allylboronates (**1**) described by Hoffmann proved only marginally selective in their addition reactions with chiral aldehydes or achiral aldehydes

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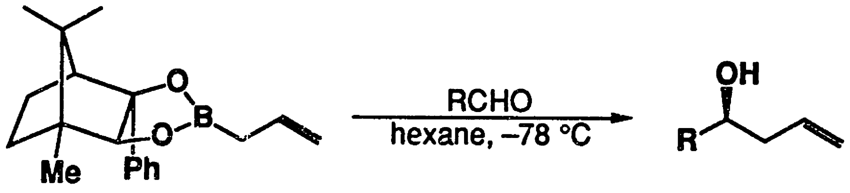
[1] (a) Roush, W. R.; Adam, M. A.; Harris, D. J. *J. Org. Chem.* **1985**, *50*, 2000. (b) Roush, W. R.; Adam, M. A.; Walts, A. E.; Harris, D. J. *J. Am. Chem. Soc.* **1986**, *108*, 3422. (c) Walts, A. E., Ph. D. Thesis, Massachusetts Institute of Technology, Cambridge, MA, 1985. (d) Adam, M. A., Ph. D. Thesis, Massachusetts Institute of Technology, Cambridge, MA, 1985. (e) Roush, W. R.; Walts, A. E.; Hoong, L. K. *J. Am. Chem. Soc.* **1985**, *107*, 8186.

[2] (a) Hoffmann, R. W.; Zeib, H. -J.; Ladner, W.; Tabche, S. *Ibid.* **1982**, *115*, 2357. (b) Hoffmann, R. W.; Endesfelder, A.; Zeiss, H. -J. *Carbohydr. Res.* **1983**, *123*, 320. (c) Herold, T.; Schrott, U.; Hoffmann, R. W.; Schnelle, G.; Ladner, W.; Steinbach, K. *Chem. Ber.* **1981**, *114*, 359. (d) Hoffmann, R. W.; Herold, T. *Ibid.* **1981**, *114*, 375.

[3] (a) Brown, H. C.; Jadhav, P. K. *J. Am. Chem. Soc.* **1983**, *105*, 2092. (b) Brown, H. C.; Jadhav, P. K.; Perumal, P. T. *Tetrahedron Lett.* **1984**, *25*, 5111. (c) Brown, H. C.; Jadhav, P. K. *Ibid.* **1984**, *25*, 1215. (d) Brown, H. C.; Jadhav, P. K. *J. Org. Chem.* **1984**, *49*, 4089. (e) Brown, H. C.; Jadhav, P. K.; Bhat, K. S. *J. Am. Chem. Soc.* **1985**, *107*, 2564.

(Figure 1).

In contrast, the chiral allylborane (3) developed by Brown displayed impressive levels of enantioselectivity in their reactions with achiral aldehydes (Figure 2).[3] However, at the time, it was felt that an extension of this particular methodology to the analogous crotyl reagents would prove problematic due to the well-known borotropic shift of allylic boranes, a process that results in (E) to (Z) isomerization[4] of the olefinic fragment.

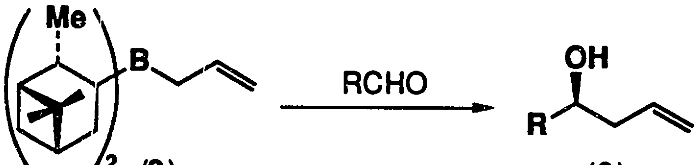


(1)

(2)

Entry	R	% e.e.
1	Ph	30%
2	*t*-Bu	45%
3	$(CH_3)_2CH$	70%
4	C_3H_7	72%
5	CH_3	86% (propane, –90 °C)

Figure 1



(3)

(2)

Entry	R	% e.e.
1	*t*-Bu	83%
2	C_3H_7	87%
3	CH_3	93%

Figure 2

Consequently, a strategy was formulated for the development of an allylboron reagent that would be configurationally stable as well as highly enantioselective. This strategy was based on a number of criteria:

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[4] (a) Kramer, G. W.; Brown, H. C. *J. Organomet. Chem.* **1977**, *132*, 9. (b) Yamaguchi, M.; Mukaiyama, T. *Chem. Lett.* **1980**, 993. (c) In later publications, Brown demonstrated the apparent lack of borotropic isomerization in substituted $(Ipc)_2B(allyl)$ reagents : See ref. 3e and Brown, H. C.; Bhat, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 293.

1. The chiral auxiliary should be symmetrical, preferably of C_2 symmetry, so as to reduce the degrees of freedom available to the reagent. This would simplify the predictive and analytical process with regard to the stereochemical outcome of the reactions.
2. The chiral auxiliary should be readily available, preferably in both antipodal forms and inexpensive.
3. The chiral auxiliary should be easily introduced and easily separated from the reaction products. Ideally, the auxiliary should be amenable to recovery and recycle.

With this strategy in hand, Walts proceeded to synthesize allylboronates, of the general structure (**4**) (Figure 3), which incorporated chiral diols (**6**)–(**12**) as auxiliaries.[1c]

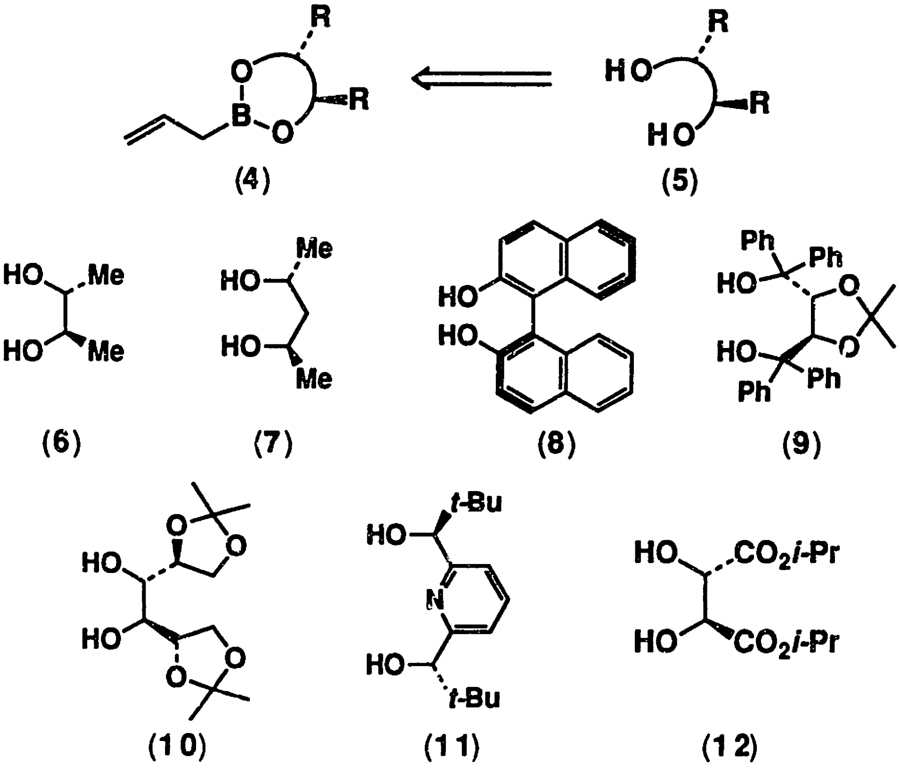
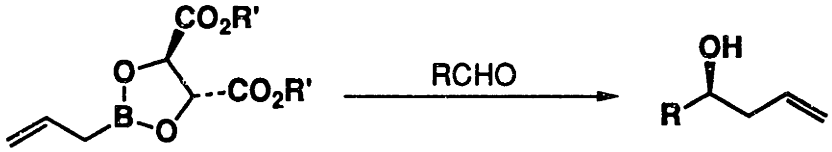


Figure 3

The screening process revealed that the only allylboronate that showed promising enantioselectivity were the the tartrate-derived reagent (**13**) (Figure 4). Initial studies of the reactions of the tartrate allylboronates with chiral aldehydes such as D-glyceraldehyde acetonide showed an improvement in stereoselectivity relative to the results obtained by using achiral pinacol-derived allylboronate.[1c]



(13) R' = *i*-Pr
(14) R' = adamantyl
(15) R' = Et

Entry	R	Aldehyde	Reagent	Reaction conditions	Product	% Yield	% e.e.
1	*c*-C_6H_{11}	(16)	(S,S)-**13**	toluene, –78 °C	(20)	70	82
2	Ph	(17)	(R,R)-**13**	toluene, –78 °C	(21)	66	61
3	Ph	(17)	(R,R)-**13**	CH_2Cl_2, –78 °C	(21)	55	54
4	Ph	(17)	(R,R)-**13**	CH_2Cl_2, 23 °C	(21)	61	30
5	Ph	(17)	(R,R)-**14**	CH_2Cl_2, –78 °C	(21)	—	60
6	*t*-Bu	(18)	(R,R)-**13**	toluene, –78 °C	(22)	—	78
7	C_9H_{19}	(19)	(R,R)-**13**	toluene, –78 °C	(23)	96	58
8	C_9H_{19}	(19)	(R,R)-**13**	CH_2Cl_2, –78 °C	(23)	98	26

Figure 4[1c]

Examination of the data from these investigations (e.g., Figure 4) indicated a marked dependence of the stereochemical outcome on the reaction solvent and temperature. It must be stressed that these early experiments were performed under un-optimized conditions, and it was at this point that we began our explorations into the factors that influenced the stereoselectivity in the reactions of these reagents. Our results are presented in the following section.

2.2 Investigations of the Factors Influencing Stereoselectivity in the Reactions of Tartrate-derived Allylboronates and Aldehydes.

Walt's encouraging initial results with the DIPT-derived allylboronates (Section 2.1) motivated us to undertake a detailed investigation into the parameters that affect the stereochemical course of these reactions. We decided to focus our efforts on the reactions involving achiral aldehydes with the ultimate goal of applying the insights gained from these investigations to the analogous crotylboronate systems that were concurrently being developed in our research group.[5] Of particular interest to us was the dependence of the stereoselectivity on the following factors:

1. The use of 4Å molecular sieves.
2. Reaction temperature.
3. Reaction solvent.
4. The structure of the tartrate ester alkyl group.

However, before proceeding with the systematic study of these factors, there were two potentially problematic issues that had to be resolved. One centered around the question of reaction rate and the verification that the reactions had indeed gone to completion at the designated reaction temperature. Since the selectivity of the reactions were known already to be dependent on reaction temperature, any reaction that occurred *as the reaction mixture was being warmed up during work-up* would lead to distortion of the actual ratios of enantiomeric homoallyl alcohol products. Our solution to this problem was to find some means of destroying one of the reaction components in the form of a rapid quench, thereby precluding the possibility of any further reaction during workup.

The second problem concerned the development of a rapid, efficient means of enantiomeric excess determination, since all of the studies we planned would necessarily depend heavily on such data.

2.2.1 Development and Verification of a Protocol for Terminating the Allylboration by Reducing Unconsumed Aldehyde; Qualitative Reaction Rates.

The least complicated method for terminating the allylboration involves the addition of a reducing reagent to the reaction mixture. We favored the use of ethanolic $NaBH_4$ for this purpose due to its convenience and ease of handling. Our initial quenching experiments were performed with cyclohexanecarboxaldehyde. The $NaBH_4$/EtOH solution was precooled to –78

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[5] Roush, W. R.; Halterman, R. L. *J. Am. Chem. Soc.* **1986**, *108*, 294.

°C before being transferred to the reaction mixture via cannula. To our delight we found that the allylboration reaction with cyclohexanecarboxaldehyde is extremely fast (92% complete after 5 min. in toluene at –78 °C), even at very low aldehyde concentrations (0.05 M). Subsequent experiments with various aldehydes confirmed that this was not an isolated phenomenon. In general, the low temperature (–78 °C) addition reactions of unhindered aldehydes proceed very rapidly (≥ 94% complete within 30 min.) (Figure 5). This is in stark contrast to the aldehyde addition reactions of other allylboronates that proceed at considerably slower pace at low temperatures.[6] The exceptional reactivity of the tartrate-modified allylboronates is presumably a result of the electron withdrawing carboalkoxy group that enhances the electrophilic character of the boron center. This allows for the reagent to function as a more efficient Lewis acid for coordinating with the aldehyde.

To ascertain that $NaBH_4$/EtOH was indeed an efficient scavenger for unreacted aldehyde at low temperature (–78 °C), a number of additional experiments were carried out. The allylboronate addition reactions with cyclohexanecarboxaldehyde were repeated using DIBAL-H as the quenching agent.[7] Essentially identical results were obtained when compared to $NaBH_4$. A similar set of experiments with THF as the reaction solvent again revealed very similar reaction profiles using both reducing agents (Figure 6). These experiments also indicated that the allylboration reactions are considerably more rapid in toluene than in THF.

The efficacy of DIBAL-H as a quenching agent at –78 °C was determined from two sets of control experiments. First, a series of identical solutions of cyclohexanecarboxaldehyde were set up at –78 °C, and each was quenched with excess DIBAL-H. Each experiment was then treated with MeOH after a certain amount of time had elapsed, and the ratio of RCHO to

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[6] Investigations in our laboratories on the reactions of various allylic boronates have shown that without the presence of electron-withdrawing substituents, the rates of these reactions slow down considerably. For instance, the reaction of 2,3-butanediol-modified allylboronate with cyclohexanecarboxaldehyde (toluene, 0.1 M, –25 °C) is 46% complete after 20 h. The reaction of ethylene glycol-derived allylboronate with cyclohexanecarboxaldehyde (toluene, 0.1 M, –78 °C) is 15% complete after 15 h: Roush, W. R.; Banfi, L.; Park, J. C.; Hoong, L. K. Submitted for publication.

[7] Similar experiments were also performed with $LiAlH_4$ as the reducing agent. The reaction profiles of these reactions are very similar to those seen with $NaBH_4$/EtOH and DIBAL-H.

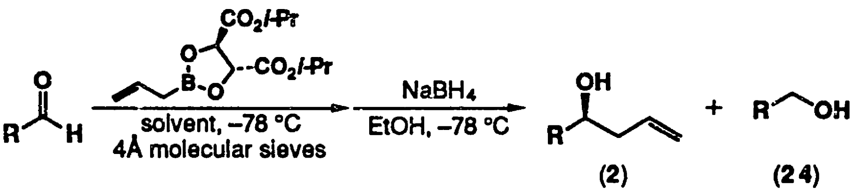
RCH_2OH was determined by GC:

Duration before the Addition of MeOH	% Aldehyde Reduced
1 min.	97%
5 min.	98%
30 min.	98%

Second, a set of experiments was run in which the order of addition was reversed, i.e., DIBAL-H was added to the reaction solvent at –78 °C followed by excess MeOH. Cyclohexanecarboxaldehyde was then added after a 1 or 5 minute waiting period:

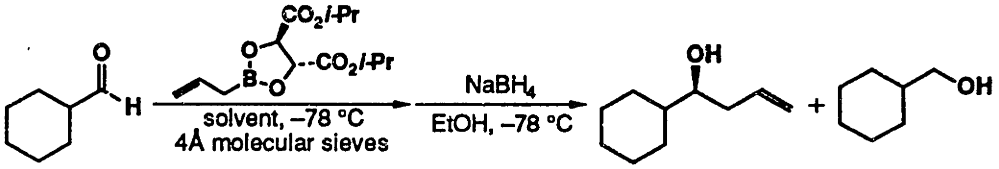
Duration before the Addition of Aldehyde	% Aldehyde Reduced
1 min.	1.7%
5 min.	1.0%

These control experiments prove conclusively that DIBAL-H rapidly reduces cyclohexanecarboxaldehyde at –78 °C. The similarity of the allylboration reaction profiles when either $NaBH_4$/EtOH or DIBAL-H was used as quenching agent (Figure 5) suggest that both these quenching agents are of comparable efficiency. With these experiments in hand, confident that $NaBH_4$/EtOH is a proficient scavenger for unreacted aldehyde, we were ready to proceed with our investigations of the factors that influence stereoselectivity in the allylboration reactions of the tartrate allylboronates.


CO$_2$i-Pr
CO$_2$i-Pr
solvent, –78 °C
4Å molecular sieves
NaBH$_4$
EtOH, –78 °C
OH
R
H
(2)
(24)

R	Conc.[aldehyde]	Solvent	Quench time [min.]	% Conversion[8a, b] (24) : (2)
Cyclohexyl	0.05 M	toluene	5	8 : 92
			10	6 : 94
			25	1 : 99
Phenyl	0.05 M	THF	5	37 : 63
			10	22 : 78
			30	6 : 94
t-Butyl	0.05 M	toluene	5	91 : 9
			10	76 : 24
			30	50 : 50
n-Nonyl	0.05 M	toluene	5	51 : 49
			10	20 : 80
			30	0 : 100

Figure 5.
Profiles of the Reactions of Aldehydes and Tartrate Allylboronate (13)


CO$_2$i-Pr
CO$_2$i-Pr
solvent, –78 °C
4Å molecular sieves
NaBH$_4$
EtOH, –78 °C
OH
OH
H

(16) (20) (25)

	Quench time [min.]	% Conversion (10)[8a, c] NaBH$_4$/EtOH	DIBAL-H
In Toluene:	10	94	98
	30	99	>99.5
	90	99	>99.5
In THF:	10	14	32
	30	32	38
	90	66	65

Figure 6.
Comparison of NaBH$_4$/EtOH and DIBAL-H as Quenching Agents for the Allylboration Reaction.

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[8] (a) The crude reaction mixture was worked up using the usual hydrolytic procedure (see Experimental Section). The Et$_2$O extracts were analyzed by capillary GC (50 m x 0.25 mm Bonded FSOT Carbowax 20 column; 100 °C for 4 min. then 10 °C/min. to a final temperature of 190 °C). (b) The % conversion was determined from the ratios of (2) and (24) obtained from the analyses. (c) The % conversion was determined from the ratios of (20) and (25) obtained from the analyses.

2.2.2 Analytical Methods for the Determination of Enantiomeric Excess

In our studies of the allylborations of achiral aldehydes, we originally determined the enantioselectivity by NMR analysis of MTPA ester derivatives of the homoallyl alcohols.[9] This method, however, proved to be inconvenient for careful optimization studies owing to the dependence on the availability of high-field ^1H and ^{19}F NMR time. Moreover, this procedure suffers from analytical imprecision due to possible kinetic fractionation during the esterification step[10] and the questionable enantiomeric purity of the commercial reagents. We have observed that several commercial batches (Aldrich) of (S)-(–)-α-methoxy-α-(trifluoromethyl)phenyl acetic acid ((S)-MTPAA) are only 94% e.e.[11] In comparison, the (R)-acid is > 98% e.e. This has caused incorrect % e.e. data to be reported in our initial publication regarding these allylborations.[1e] Consequently, the determination of enantioselectivity via this method in the studies described in this chapter have been carried out using the (R)-MTPAA reagent.

As a result of these problems, we sought an analytical method that did not require NMR or the analysis of diastereomeric derivatives. In conjunction with Dr. R. L. Halterman, we investigated the use of direct enantiomer resolution using the chiral nickel (II) bis(3-heptafluorobutyryl-(1R)-camphorate (Ni-R-cam) and nickel (II) bis(heptafluorobutyryl-(1R,2S)-pinan-4-oate (Ni-4-pin) derived capillary GC columns developed by Schurig.[12]

With the exception of (**22**), our initial attempts to separate the product homoallyl alcohols (**20**)–(**23**) directly on the Ni-R-cam column were unsuccessful. This was presumably a result of low volatility and overly strong complexation with the metal. To overcome both these problems, we examined the previously unreported method of separating methyl ethers.

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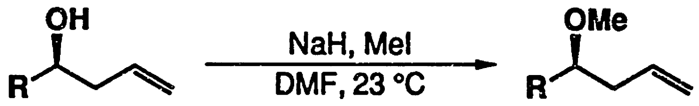
[9] Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

[10] For an example of kinetic resolution during the preparation of an MTPA ester derivative, see: Dutcher, J. S.; MacMillan, J. G.; Heathcock, C. H. *J. Org. Chem.* **1976**, *41*, 2663.

[11] Essenfeld, A. P., Ph. D. Thesis, Massachusetts Institute of Technology, Cambridge, MA, 1986.

[12] (a) Schurig, V. In "Asymmetric Synthesis," Morrison, J. D., Ed. Academic Press: New York, 1984, Vol. 1, p. 87. (b) Schurig, V. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 747. (c) Schurig, V.; Weber, R. *J. Chromatog.* **1984**, *289*, 321. (d) Schurig, V.; Wistuba, D. *Tetrahedron Lett.* **1984**, *25*, 5633.

Although this method required a derivatization, methylations are clean and rapid and are unlikely to give accidental stereoisomeric enrichment, as can be the case in the preparation of diastereomeric derivatives (Figure 7).



(20) R = cyclohexyl
(21) R = benzyl

(26) R = cyclohexyl
(27) R = benzyl

Figure 7.
Synthesis of Methyl Ether Derivatives of Homoallyl Alcohols

As hoped, the methyl ethers proved to be superior substrates in giving short retention times, sharp peaks and for most compounds, resolution by at least one column. In general, the Ni-4-pin column was markedly superior for aromatic substrates, while the Ni-R-cam column with its higher temperature limit proved more useful for the less volatile, higher molecular weight compounds (Figure 8).[13]

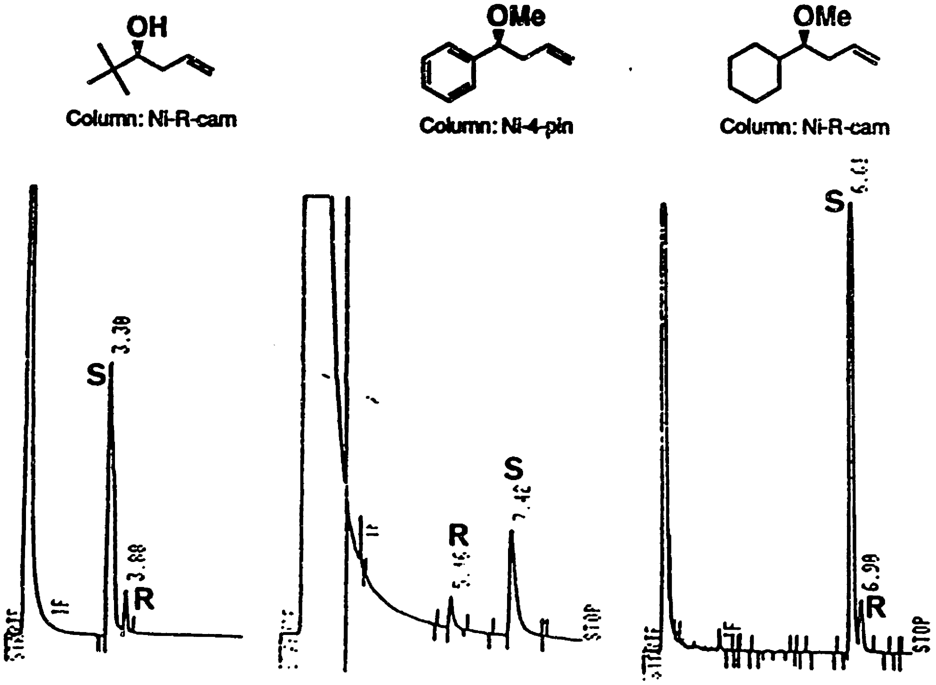


Figure 8.
Resolution of Enantiomeric Methyl Ethers by Chiral Capillary GC

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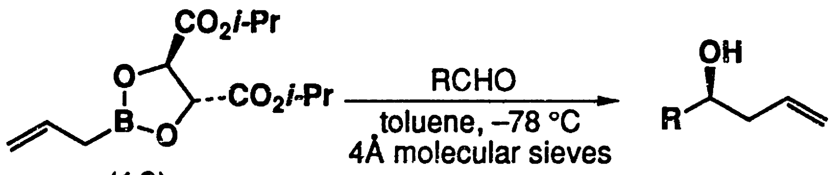
[13] Halterman, R. L.; Roush, W. R.; Hoong, L. K. *J. Org. Chem.* **1987**, *52*, 1152.

The upper limit to the usefulness of this method, dependent on substrate volatility and the temperature limits of the columns,[14] appears to be around the C_{14} alcohols. This method for the determination of % e.e. was utilized in most of the investigations described in the proceeding sections.

2.2.3 The Effect of 4Å Molecular Sieves.

The observation by a coworker[15] that the use of molecular sieves enhanced selectivities in the reactions of tartrate ester-modified crotylboronates prompted us to initiate an analogous study with the allyl system. Indeed, addition of 4Å molecular sieves to the reaction mixtures resulted in improved selectivities in the reactions of all the aldehydes that were investigated (Figure 9).



(13)

Entry	R	%Yield	Product	% e.e.[16]
1	Cyclohexyl	72	(20)	86 (82)
2	Phenyl	78	(21)	72 (61)[16d]
3	*t*-Butyl	52	(22)	85 (78)
4	*n*-Nonyl	86	(23)	84 (69)

Figure 9

The molecular sieves appear to maximize enantioselectivity by maintaining a rigorously anhydrous reaction environment. This prevents any adventitious hydrolysis of the reagent to achiral allylboronic acid which can function as a competitive, but achiral, allylating reagent.

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[14] The temperature limits of the Ni-R-cam and Ni-4-pin columns are 110 °C and 100 °C, respectively.

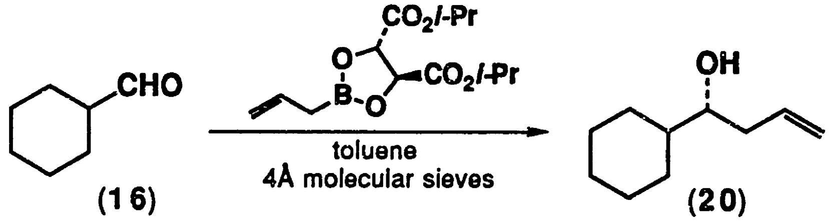
[15] The observation that addition of molecular sieves improves the enantioselectivity of these reactions was first made in our laboratory by Dr. R. L. Halterman.

[16] (a) The % e. e.'s were determined by chiral capillary GC analysis of the alcohol or corresponding methyl ether derivative on Ni-R-cam or Ni-4-pin column unless otherwise specified. (b) The % e. e. of (23) was determined by ^1H NMR analysis of the corresponding (R)-MTPA ester derivative. (c) The numbers in parenthesis are from reactions without 4Å molecular sieves, and the % e. e.'s from these reactions were obtained by ^1H NMR analysis of the corresponding (S)-MTPA ester derivatives. (d) The reaction was performed in THF.

Although it is still possible to obtain the maximum stereochemical induction in the absence of drying agent, especially when distilled reagents are employed, we have found that *the use of sieves allows for consistently high selectivities.* All of the studies subsequently described were performed with added molecular sieves.

2.2.4 The Dependence of Stereoselectivity on Reaction Temperature.

A systematic study on the temperature dependence of the stereoselectivity of the allylboron reagent (**13**) confirmed the observations made by Walts in the earlier studies . The experiments were carried out in toluene in the presence of 4Å molecular sieves and, as expected, the selectivity increased with decreasing reaction temperature (Figure 10).



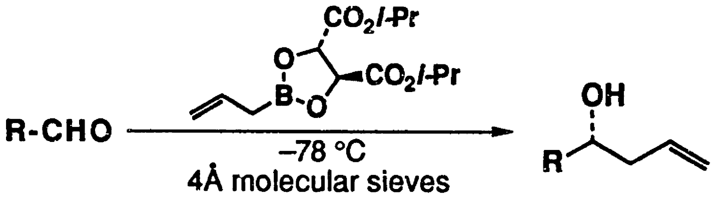
Reaction Temperature	Enantioselectivity[16a]
25 °C	50% e. e.
0 °C	57% e. e.
–25 °C	70% e. e.
–50 °C	82% e. e.
–78 °C	87% e. e.

Figure 10

The inverse dependence of stereoselectivity on reaction temperature was not unexpected, as it is a direct reflection of the temperature dependence of $\Delta\Delta G^{\ddagger}$, the difference in energy of the competing transition states. A lowering of the reaction temperature would be expected to lead to a greater difference in the transition state energies, especially if there is a significant contribution of $T\Delta\Delta S^{\ddagger}$ to $\Delta\Delta G^{\ddagger}$.

2.2.5 The Dependence of Stereoselectivity on Reaction Solvent.

An investigation of the effect of the reaction solvent on stereoselectivity revealed some interesting trends. First, saturated aliphatic aldehydes (cyclohexanecarboxaldehyde, 2,2-dimethylpropanal, and decanal) gave the best results (~85% e.e.) when the allylborations were performed in toluene (Figure 11). Selectivity dropped slightly in ethereal solvents, Et_2O being slightly better than THF, while significant decreases in enantioselectivity occurred in halogenated solvents. In contrast, α,β-unsaturated aldehydes like 2,3-(E)-decenal (**28**) exhibited comparable selectivities in toluene and THF (60% e.e), but these enantioselectivities were lower than the best cases observed with saturated substrates (e.g., cyclohexanecarboxaldehyde (**16**); 86% e.e. in toluene). Lower levels of enantioselectivity were also realized with aromatic aldehydes. For example the allylboration of benzaldehyde (**17**) in toluene gave (**21**) with only 60% e.e. However, unlike decenal, improvement (72% e.e.) in enantioselectivity occurred when the reaction was conducted in THF. There is no apparent correlation of reaction enantioselectivity and solvent dielectric constant (ε), and the reasons that aromatic and α,β-unsaturated aldehydes show a different solvent dependence than aliphatic aldehydes is unclear at present. Fortunately, studies of asymmetric allyl- and crotylborations of chiral aldehydes have generally displayed greatest selectivity in toluene, and so toluene is the recommended solvent for all double asymmetric reactions.



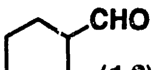
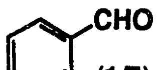
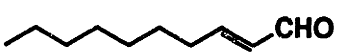
Solvent	 (16)	 (17)	 (28)	ε
Toluene	87% e.e.	60% e.e.	60% e.e.[17]	2.4
Et_2O	82%	59%	46%	4.3
THF	78%	72%	60%	7.4
CH_2Cl_2	59%	59%	—	8.9
Product:	(20)	(21)	(29)	

Figure 11[16a]

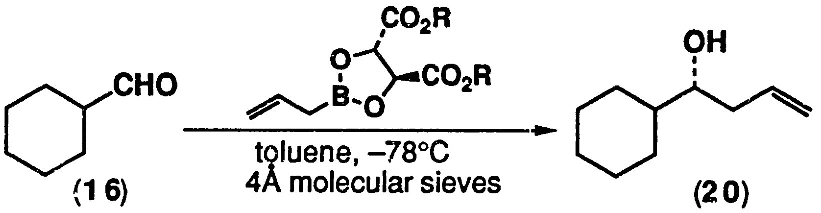
2.2.6 The Dependence of Stereoselectivity on the Tartrate Ester Alkyl Group.

We anticipated at the outset that enantioselectivity would not depend on the structure of the tartrate ester alkyl group, since the preferred s-trans conformation holds the alkyl group, R, far from the aldehyde in the allylboration transition state. Indeed, as shown in Figure 12, a series of tartrate esters have been examined as auxiliaries in these reactions, and our results show that they give identical results within experimental error. This is in contrast to the outcome reported with allenylboronate reagents, developed by Yamamoto, who has shown that enantioselectivity increases as the steric bulk of the tartrate ester alkyl group increases.[18] Thus, the tartrate allylboronates and the tartrate allenylboronates must have different mechanisms of asymmetric induction.

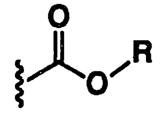
---

[17] The % e. e. of (29) was determined by ^{1}H NMR analysis of the corresponding (R)-MTPA ester derivative.

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



Reagent	R	% e.e.[16a]
(13)	*i*-Pr	86%
(15)	Et	86%
(30)	Me	84%
(31)	cyclododecyl	86%
(32)	2,4-dimethyl-3-pentyl	86%



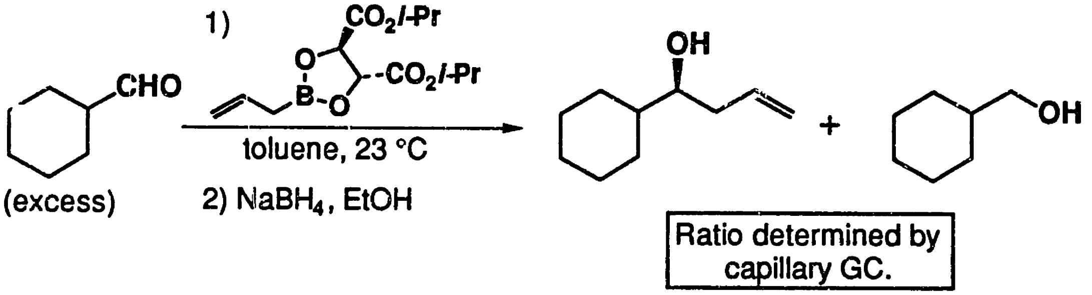
s-trans ester conformation

Figure 12

2.3 Optimized Preparation of Tartrate Allylboronate (13).

The asymmetric allylboration reactions studied originally by Walts were carried out using crude reagent which contained excess amounts of tartrate ester.[1c] There was some initial apprehension regarding the effect that reagent purity might have on stereoselection. It was with this concern in mind that most of the studies described in Sections 2.2.3–2.2.6 were performed with distilled reagent. Unfortunately, the purification of (**13**) by distillation was frequently accompanied by significant decomposition, resulting in low yields. The amount of decomposition varied from batch to batch of reagent, becoming particularly problematic when the bath temperature exceeded 100–110 °C. Later experiments utilizing crude reagents, however, indicated that enantioselectivities identical to those obtained with distilled reagents could be achieved when molecular sieves were employed.

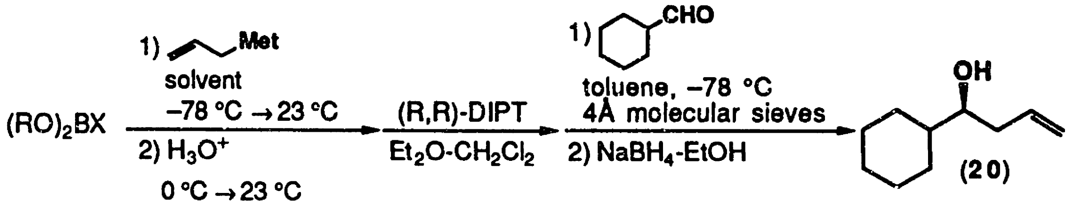
The originally recommended method for synthesizing (**13**) involved treatment of allylmagnesium bromide with $(MeO)_3B$ in Et_2O. The reaction mixture was hydrolyzed with aqueous HCl and then allylboronic acid was extracted into Et_2O-CH_2Cl_2. The extracts were dried over anhydrous $MgSO_4$, concentrated *in vacuo*, and then the allylboronic acid was esterified by treatment with DIPT in CH_2Cl_2 in the presence of a drying agent. Since we wished to employ crude **(13)** in the allylboration process, it was necessary to devise a method of determining the amount of reagent present in any batch. This was easily accomplished by dissolving the crude **(13)** in a known volume of toluene (or THF) and then titrating an aliquot with known excess of cyclohexanecarboxaldehyde at 23 °C. This reaction ("titration") was quenched with $NaBH_4$ in EtOH, and then the ratio of cyclohexanemethanol **(25)** to homoallyl alcohol **(20)** was determined by capillary GC (see Experimental Section). From this ratio, the molarity of these solutions and also the yield of **(13)**, if the total volume is known, can be calculated.



Ratio determined by capillary GC.

Figure 13. Titration Sequence

By using this titration procedure, we discovered that the effective yield of **(13)** in the crude reagent prepared via Walt's procedure was only 30–44%, with some variation occurring from run to run (entry 3, Figure 14). This prompted us to re-examine and optimize the preparation of **(13)**. We varied both the electrophilic boron reagent and the allylmetal precursor in hope that a more efficient procedure could be developed. Results of this investigation are summarized in Figure 14.



Entry	Organometallic[19a] Reagent	$(\text{RO})_2\text{BX}$[19a]	Solvent	% Yield[19b]	%e.e.[19c]
1	Allylmagnesium bromide	$(i\text{-PrO})_3\text{B}$	Et_2O	65–76[19d]	83–88 (86)
2	Allylmagnesium bromide	$(\text{MeO})_3\text{B}$	Et_2O	51[19d]	85
3	Allylmagnesium bromide	$(\text{MeO})_3\text{B}$	Et_2O	30–44[19e]	83–88 (86)
4	Allylmagnesium bromide	$(\text{MeO})_3\text{B}$	THF	36–39[19e]	—
5	Allylmagnesium bromide	$(\text{MeO})_2\text{BF}$	Et_2O	35–46[19d]	—
6	Allyllithium	$(i\text{-PrO})_3\text{B}$	Et_2O	35–56[19e]	—
7	Allyllithium	$(\text{MeO})_2\text{BF}$	Et_2O	17[19d]	—
8	Allylpotassium[19f]	$(i\text{-PrO})_3\text{B}$	THF	47[19d]	—
9	Allylpotassium	$(\text{MeO})_2\text{BF}$	THF	27–43[19d]	—

Figure 14

The most significant modification involves the use of $(i\text{-PrO})_3\text{B}$ in place of $(\text{MeO})_3\text{B}$, and yields of up to 76% are now consistently obtained (entry 1). Use of the more electrophilic borane $(\text{MeO})_2\text{BF}$ gave lower yields than those obtained with $(\text{MeO})_3\text{B}$ (compare entries 2 and 5), especially in reactions involving allyllithium and allylpotassium (entries 7, 9).

Brown has previously noted that the yields of allylboronic esters are maximized by using $(i\text{-PrO})_3\text{B}$ as the electrophilic boron species.[20] Brown has argued that the ate complex (**33**) is comparatively stable under the reaction conditions, thereby preventing addition of a second organometallic to the electrophilic $\text{RB}(\text{O}i\text{-Pr})_2$ species that can arise only by loss of $\text{Li}(\text{O}i\text{-Pr})$ from ate complex (**33**).

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[19] (a) All reactions were performed with equimolar amounts of the organometallic and $(\text{RO})_2\text{BX}$ reagents. (b) Yield of (**13**) was determined by the titration procedure described in the Experimental section. (c) The % e. e.'s are from reactions of (**13**) with cyclohexanecarboxaldehyde (**16**) at –78 °C. The values in parentheses are the averages of repeated experiments. (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/KO*t*Bu (1.0 equiv. each) in T at –50 °C for 3h.

[20] Brown, H. C.; Cole, T. E. *Organometallics* **1983**, *2*, 1316.

$$\mathrm{R{-}Li} + (i\text{-}\mathrm{PrO})_3\mathrm{B} \longrightarrow \underset{\mathbf{(33)}}{\left[\mathrm{R{-}B(O}i\text{-}\mathrm{Pr})_3\right]^-}\ \mathrm{Li}^+ \not\longrightarrow \mathrm{RB(O}i\text{-}\mathrm{Pr})_2 + \mathrm{Li(O}i\text{-}\mathrm{Pr})$$

Figure 15

This has relevance to the synthesis of (**13**) since multiple additions of allylmetal units to the boron center may give rise to allylboron species (**34**)–(**39**) as shown in Figure 16. Each of the di-, tri- or tetraallylboron species will undergo hydrolysis to allylboronic acid (**40**) upon exposure to water,[21] and consequently the overall yield of (**13**) is inversely related to the amount of allylmagnesium bromide that is unproductively connected to (**34**)–(**39**).

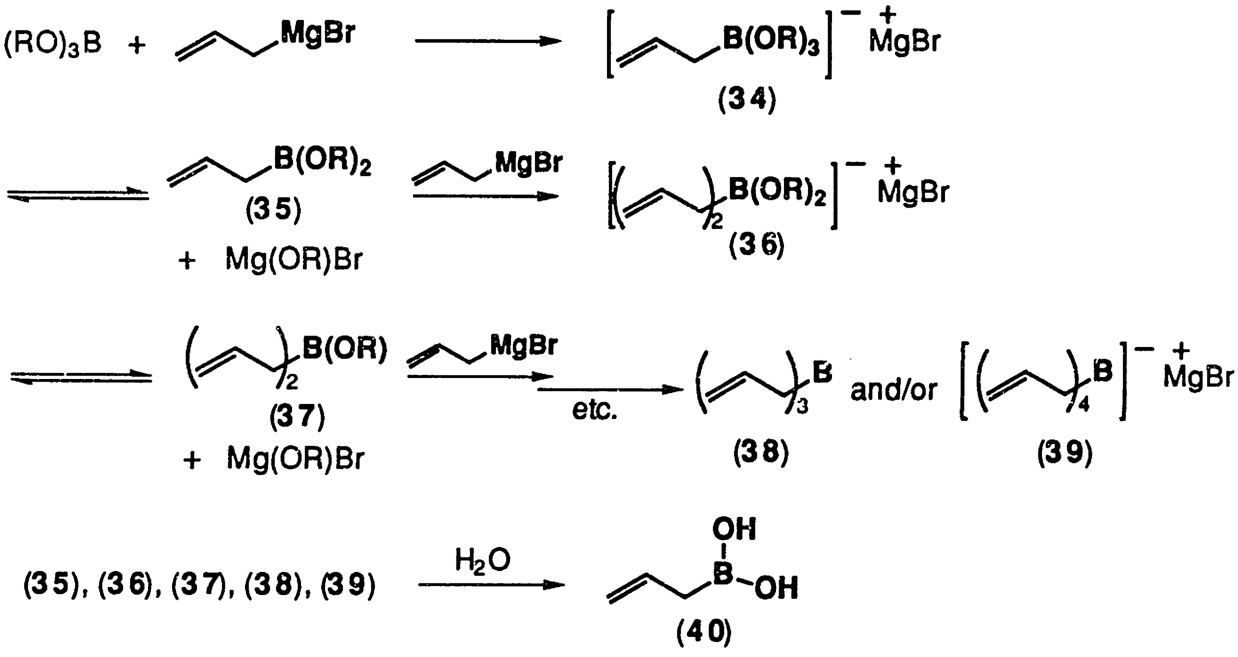

Figure 16

Another important variable is the handling of the intermediate allylboronic acid (**40**) which is unstable towards 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 boronic acid containing extracts are dried and concentrated prior to exposure to DIPT (compare entries 2 and 3;

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[21] Mikhailov, B. M. *Organomet. Chem Rev. A* **1972**, *8*, 1.

Figure 14). Tartrate allylboronate (**13**) is considerably more stable than the boronic acid (**40**), and no special precautions are taken in handling this material other than to keep its solutions under argon during filtration, rotary evaporation and subsequent manipulations (see Experimental Section).

Thus, entry 1 of Figure 14 defines the optimal procedure for the synthesis of the tartrate allylboronates. The crude allylboronate (**13**) so prepared is reasonably stable and its solutions have been stored at –20 °C under argon for up to 2 months with negligible deterioration. Although crude allylboronate (**13**) may also be stored neat, we find it more convenient to store it in standardized solution since this facilitates transfer of known quantities for individual experiments. The increased yields and the ability to store these reagents for extended periods enhance their attractiveness as a practical synthetic tool. These developments have been successfully extended to the development of an efficient method of synthesis of the tartrate crotylboronates.[26]

2.4 Absolute Stereochemical Assignments

The major products of the reactions of allylboronate (R,R)-(**13**) and cyclohexanecarboxaldehyde, benzaldehyde, pivaldehyde and decanal are (S)-(**20**), (S)-(**21**), (S)-(**22**), and (R)-(**23**), respectively. The absolute stereochemistry of these compounds was assigned as follows. Alcohols (S)-(**20**) and (R)-(**23**) were converted to 1,3-diacetates (S)-(**41**) and (R)-(**43**), respectively, as shown in Figure 18. These samples proved enantiomeric to reference samples prepared via the Red-Al reduction[22] of epoxyalcohols (**42**) and (**44**) that, in turn, were prepared by the Sharpless asymmetric epoxidation[23] [(R,R)-DIPT as auxiliary].[24] Similarly, homoallyl alcohols (S)-(**21**) and (S)-(**22**) ((R,R)-(**13**) derived) were converted to 1,3-diols (S)-(**45**) and (S)-(**46**), respectively, that proved to be enantiomeric to (R)-(**45**) and (R)-(**46**) that Masamune and coworkers had already synthesized by Red-Al reduction of the corresponding (R,R)-DIPT derived epoxyalcohols.[25]

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[22] For the Red-Al reduction of 2,3-epoxyalcohol, see: (a) Ma, P.; Martin, V. S.; Masamune, S.; Sharpless, K. B.; Viti, S. M. *J. Org. Chem.* **1982**, *47*, 1380. (b) Viti, S. M. *Tetrahedron Lett.* **1982**, *23*, 4541.

[23] (a) Sharpless, K. B.; Katsuki, T. *J. Am. Chem. Soc.* **1980**, *102*, 5974. (b) Hill, J. G.; Sharpless, K. B.; Exon, C. M.; Regenye, R. *Org. Syn.* **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..

[24] We thank Dr. R. L. Halterman for generously providing us with samples of epoxyalcohols (**102**) and (**104**) which were obtained in > 95% e.e. via the Sharpless asymmetric epoxidation.

The picture that has emerged from these, and numerous other absolute stereochemical correlations that have been performed in our group,[1e, 27, 26] is that an (S)-alcohol is produced preferentially from the reactions of allylboronates derived from (R,R)-tartrates, assuming that "R" of the aldehydic substrate takes priority over the allyl group that is transferred.

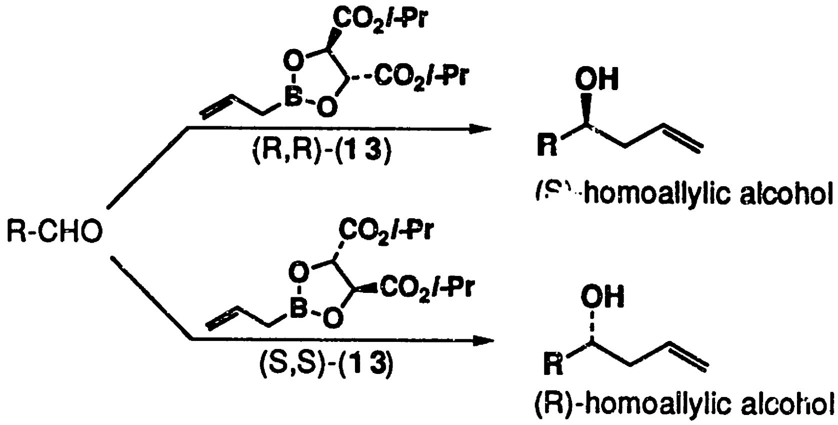

Figure 17

In fact, no exceptions to this generalization have been found in over forty well-characterized cases where the tartrate auxiliary controls the stereochemical outcome of the allyl/crotyl transfer process. This stereochemical pattern therefore is assumed for all other allylborations described in this chapter.

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[25] Masamune, S.; Sato, T.; Kim, B. M.; Wollmann, T. A. *J. Am. Chem. Soc.* **1986**, *108*, 8279. Data for the synthesis of (**105**) and (**106**) appear in the Supplementary Material Section of this paper.

[26] (a) Roush, W. R.; Palkowitz, A. D. *J. Am. Chem. Soc.* **1987**,*109*, 953. (b) Roush, W. R.; Palkowitz, A. D.; Palmer, M. A. J. *J. Org. Chem.* **1987**, *52*, 316..

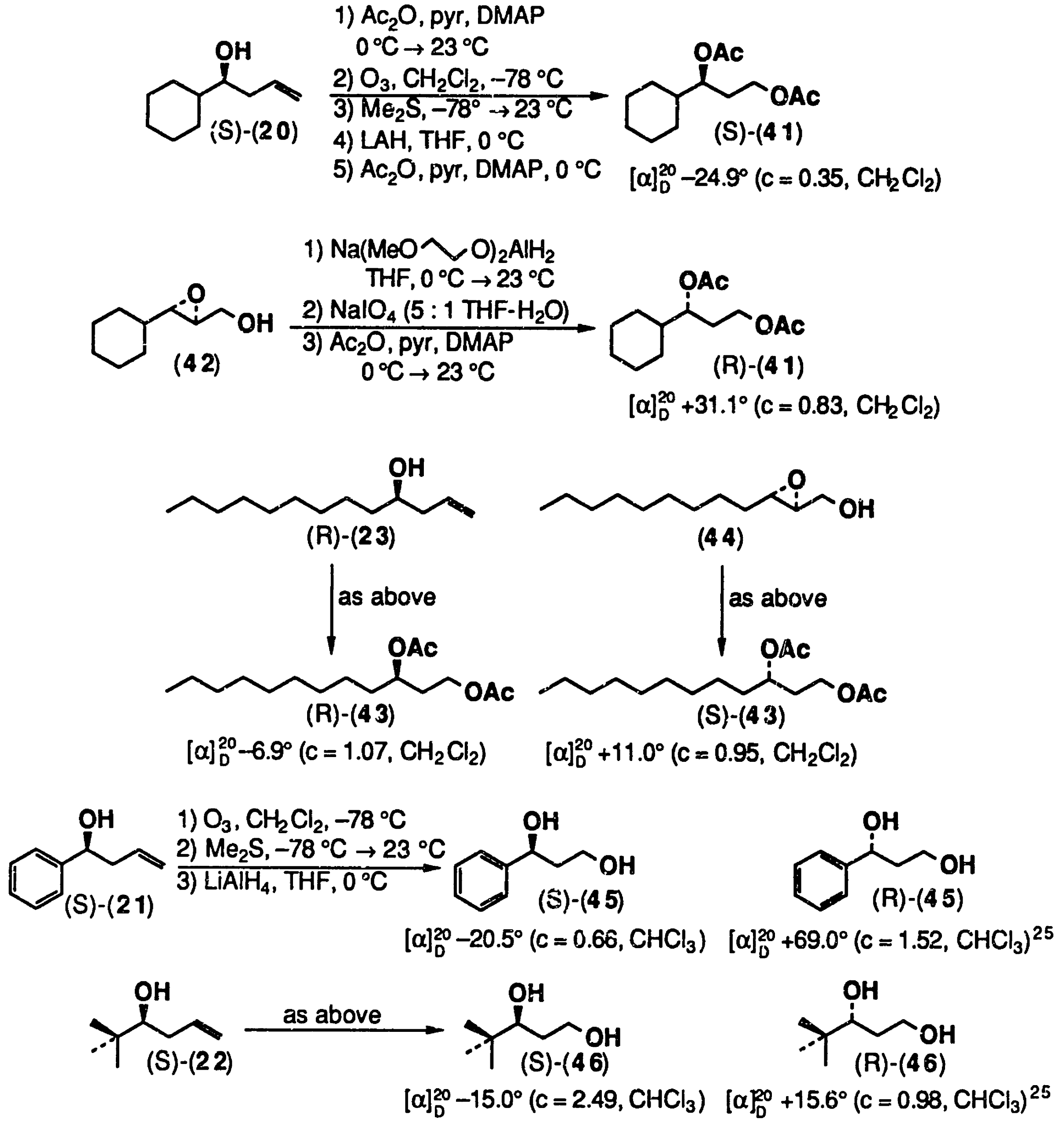
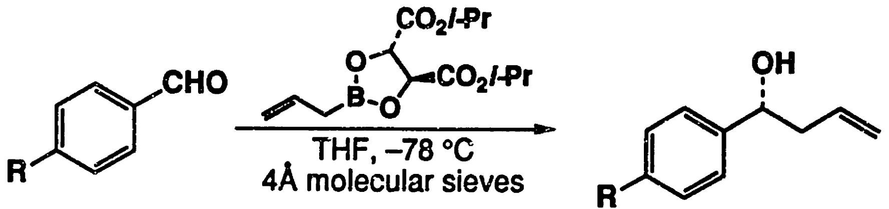

1) Ac2O, pyr, DMAP 0 °C → 23 °C
2) O3, CH2Cl2, –78 °C
3) Me2S, –78° → 23 °C
4) LAH, THF, 0 °C
5) Ac2O, pyr, DMAP, 0 °C
OH
(S)-(20)
OAc
OAc
(S)-(41)
[α]20D –24.9° (c = 0.35, CH2Cl2)
1) Na(MeO⁀O)2AlH2 THF, 0 °C → 23 °C
2) NaIO4 (5 : 1 THF-H2O)
3) Ac2O, pyr, DMAP 0 °C → 23 °C
O
OH
(42)
(R)-(41)
[α]20D +31.1° (c = 0.83, CH2Cl2)
(R)-(23)
(44)
as above
as above
(R)-(43)
[α]20D –6.9° (c = 1.07, CH2Cl2)
(S)-(43)
[α]20D +11.0° (c = 0.95, CH2Cl2)
1) O3, CH2Cl2, –78 °C
2) Me2S, –78 °C → 23 °C
3) LiAlH4, THF, 0 °C
(S)-(21)
(S)-(45)
[α]20D –20.5° (c = 0.66, CHCl3)
(R)-(45)
[α]20D +69.0° (c = 1.52, CHCl3)25
(S)-(22)
as above
(S)-(46)
[α]20D –15.0° (c = 2.49, CHCl3)
(R)-(46)
[α]20D +15.6° (c = 0.98, CHCl3)25

Figure 18.
Correlation of Absolute Stereochemistry of Homoallyl Alcohols.

2.5 Asymmetric Allylborations of Other Substrates.

With the conditions of the allylboration now fully optimized, we proceeded to study additional substrates in order to define the scope of of this process. We were particularly intrigued by the observations that benzaldehyde and decenal gave substantially lower enantioselectivity than saturated aliphatic aldehydes (e.g, cyclohexanecarboxaldehyde), and were curious if this effect was in some way related to the different electronic structure of the unsaturated aldehydes compared to their saturated counterparts. Consequently, the reactions of a number of *p*-substituted aromatic aldehydes were investigated (Figure 19).



(17) R = H
(47) R = Me
(48) R = MeO
(49) R = Br
(50) R = NO_2

(21) R = H
(51) R = Me
(52) R = MeO
(53) R = Br
(54) R = NO_2

Entry	RCHO	% Yield	% e.e.[27]
1	(17)	78	71% (70%)
2	(47)	70	70% (72%)
3	(48)	80	72%
4	(49)	82	72% (70%)
5	(50)	73	72%

Figure 19

The results of this study were most unexpected in that there was no observable dependence of % e.e. on the nature of the substituent on the aromatic ring.

Another class of substrates that we decided to examine was alkoxy-substituted aldehydes. Results of the asymmetric allyl- and crotylborations of chiral β-alkoxy-α-methylpropionaldehydes showed that diastereoselectivities were lower than expected based on the enantioselectivity realized with achiral aliphatic aldehydes. There was an apparent dependence of selectivity on the nature of the protecting group present in the alkoxy substituent.[26b]

Hence, we prepared the alkoxy substituted aldehydes (67)–(75), as outlined in Figure 20. These syntheses involve standard functional group manipulations and are fully described in the Experimental Section.

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[27] The % e. e.'s were determined by ^1H NMR analysis of the corresponding (R)-MTPA ester derivatives. Values in parenthesis were obtained from chiral capillary GC (Ni-4-pin) analysis of the corresponding methyl ethers.

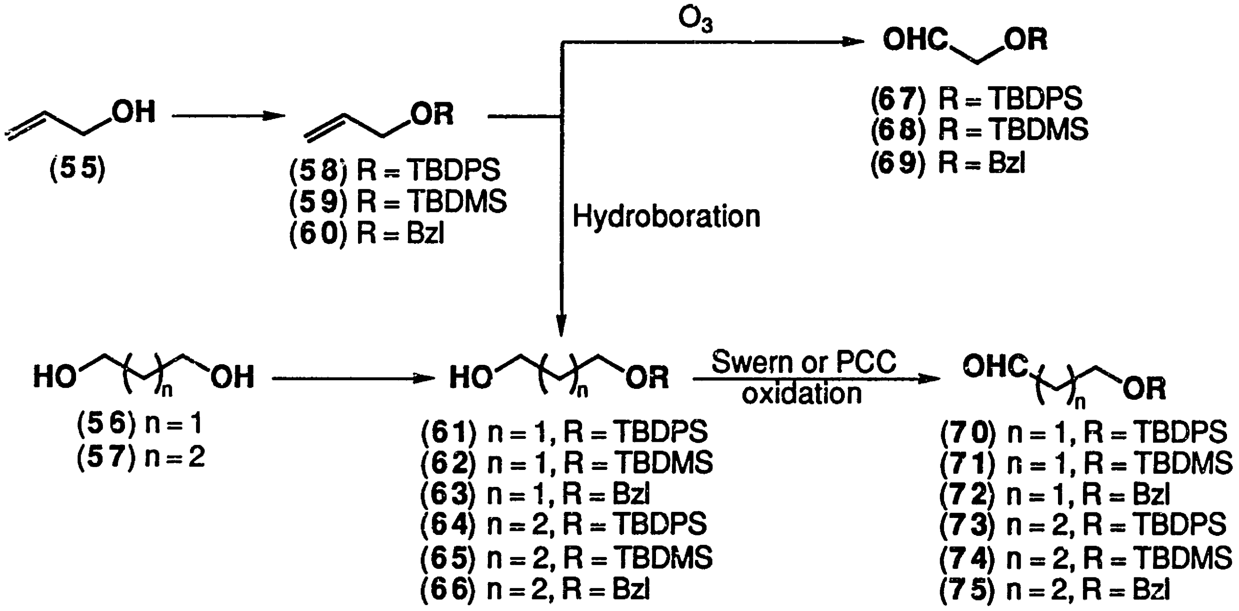
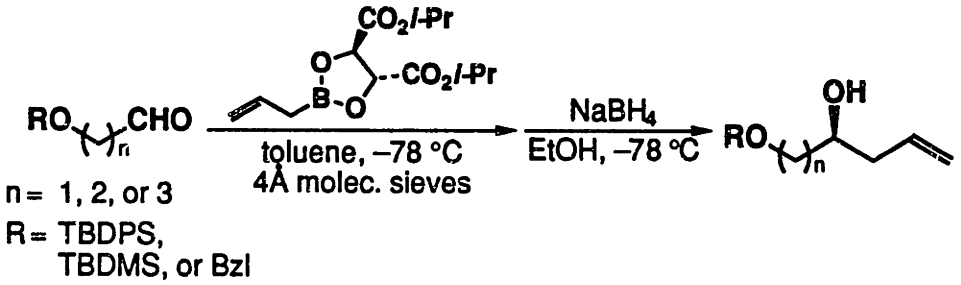

O3
OHC OR
(67) R = TBDPS
(68) R = TBDMS
(69) R = Bzl
OH
(55)
OR
(58) R = TBDPS
(59) R = TBDMS
(60) R = Bzl
Hydroboration
HO OH
n
(56) n = 1
(57) n = 2
HO OR
(61) n = 1, R = TBDPS
(62) n = 1, R = TBDMS
(63) n = 1, R = Bzl
(64) n = 2, R = TBDPS
(65) n = 2, R = TBDMS
(66) n = 2, R = Bzl
Swern or PCC
oxidation
OHC OR
(70) n = 1, R = TBDPS
(71) n = 1, R = TBDMS
(72) n = 1, R = Bzl
(73) n = 2, R = TBDPS
(74) n = 2, R = TBDMS
(75) n = 2, R = Bzl

Figure 20

The results of the asymmetric allylborations of **(67)**–**(75)** are summarized in Figure 21. Our results did not reveal a dependence on the protecting group on the alkoxy fragment, as was observed with the earlier chiral aldehyde substrates.^{26b} There was, however, an association between enantioselectivity and the proximity of the alkoxy group to the reaction center (Figure 21). Thus, the selectivity was found to increase as the alkoxy substituent was positioned further away from the aldehydic functionality (γ-alkoxy > β-alkoxy > α-alkoxy). Best results were obtained here, as with other aliphatic aldehydes, when the reactions were performed in toluene.

While it is not entirely clear why the alkoxy groups have a negative effect on stereoselectivity, we suspect that subtle electronic or inductive effects may be coming into play in the competing transition states. An attempt to rationalize these effects is presented in a subsequent section (see Section 2.6).



Entry	Aldehyde	n	R	Reaction Conditions	Product	% Yield	% e.e.[28]
1	**(67)**	1	TBDPS	toluene, –78 °C	**(76)**[29]	30	56
2	**(68)**		TBDMS	toluene, –78 °C	**(77)**	42	59
3	**(69)**		Bzl	toluene, –78 °C	**(78)**[29]	58	59
4	**(70)**	2	TBDPS	toluene, –78 °C	**(79)**[29]	98	63
5				THF, –78 °C			60
6	**(71)**		TBDMS	toluene, –78 °C	**(80)**	48	66
7				THF, –78 °C			64
8	**(72)**		Bzl	toluene, –78 °C	**(81)**[29]	44	66
9				THF, –78 °C			39
10	**(73)**	3	TBDPS	toluene, –78 °C	**(82)**	52	74
11	**(74)**		TBDMS	toluene, –78 °C	**(83)**	49	77
12	**(75)**		Bzl	toluene, –78 °C	**(84)**	39	78

Figure 21

2.6 The Origin of Asymmetric Induction: A Novel and Unprecedented Stereoelectronic Effect.

Any transition state model that seeks to explain the origin of the asymmetric induction of the tartrate allylboronate must be consistent with the observations described in the previous sections. The absence of a dependence on the bulkiness of the ester group rules out any conventional nonbonded steric interactions as the cause of the stereoselection. As already noted, the s-trans conformation of the ester precludes any significant interaction with the aldehydic R substituent, no matter what conformation is chosen about the —OCH—CO_2R single bond. In addition, all attempts to perform asymmetric allylborations using other C_2 symmetric diol auxiliaries, such as those listed in Figure 22, have resulted in considerably lower levels of enantioselectivity compared to the tartrate based system.[30]

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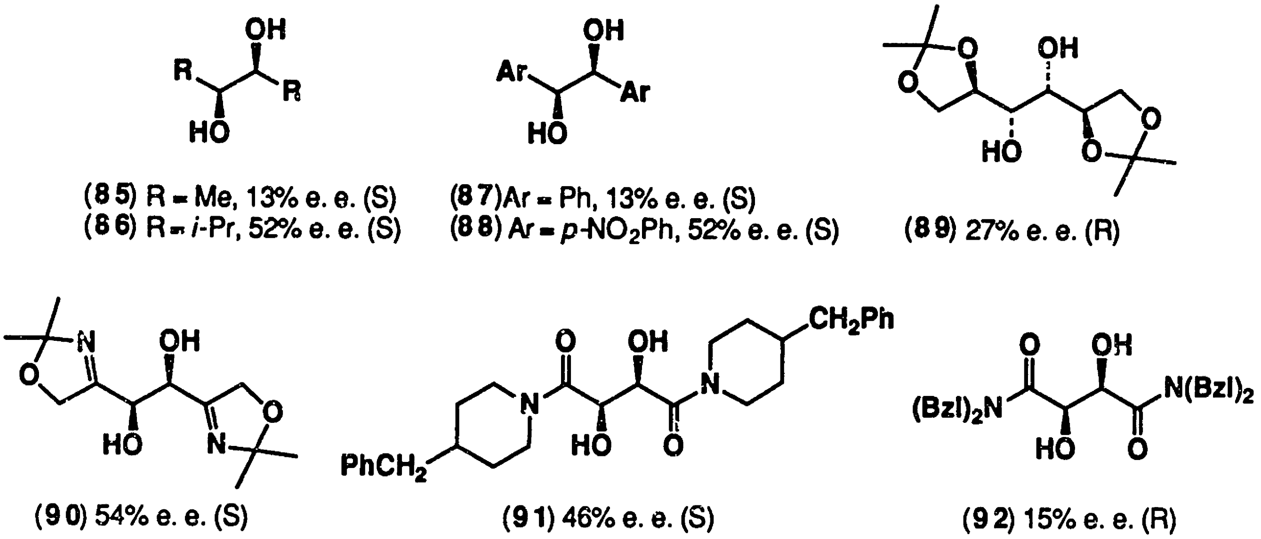
[28] The % e.e.'s were determined by ^{1}H or ^{19}F NMR analysis of the corresponding (R)-MTPA ester derivatives of **(76)**–**(84)**.

[29] The allylboration was performed with (S,S)-**(13)**.



(85) R = Me, 13% e. e. (S)
(86) R = *i*-Pr, 52% e. e. (S)

(87) Ar = Ph, 13% e. e. (S)
(88) Ar = *p*-NO_2Ph, 52% e. e. (S)

(89) 27% e. e. (R)

(90) 54% e. e. (S)

(91) 46% e. e. (S)

(92) 15% e. e. (R)

Figure 22.
C_2 Diols used in the Allylboration Reaction.

These data implicate a very special role for the tartrate carbonyl groups, and a transition state model that involves a previously undocumented stereoelectronic effect has been developed (Figure 23).

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[30] The % e. e.'s indicated in Figure 22 are maximum values obtained in reactions with cyclohexanecarboxaldehyde: Roush, W. R.; Banfi, L. Unpublished research results.

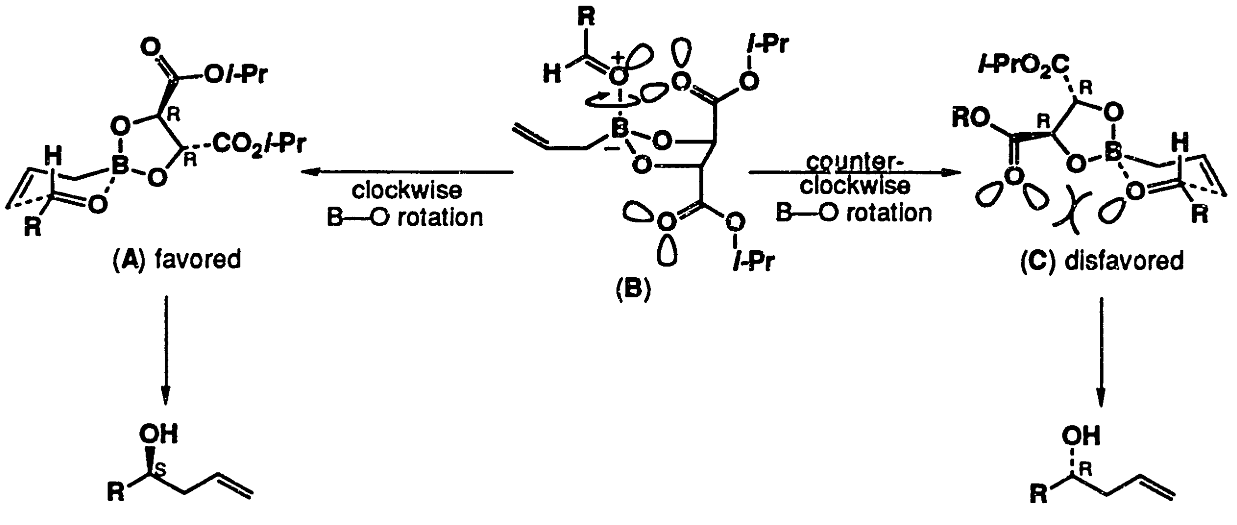

Figure 23

The well established stereochemistry of the asymmetric allylboration requires that transition state (A) is favored over (C). We have assumed that (A) is favored as a consequence of *n*/*n* electronic repulsive interactions between the aldehydic oxygen atom and the β-face ester group that destabilizes (C) relative to (A). These interactions are possible since an easily accessible and frequently favored conformation of α-heteroatom-substituted carbonyl systems is one in which the heteroatom and the carbonyl are syn-coplanar.[31] Toluene appears to be particularly effective among nonpolar solvents in stabilizing this conformation[32] and, interestingly, also happens to be the solvent in which the tartrate allylboronates generally display the greatest enantioselectivity.

For this mechanism to be correct, it is also necessary for the dioxaborolane to exist in conformation (B) with the two —CO_2*i*-Pr units pseudoaxial. In any other conformation about the C—CO_2*i*-Pr bond or in the dioxaborolane system, the ester and the aldehydic oxygen atoms are too far removed to interact. It should be noted further that reasonable transition states for C—C bond formation are inaccessible if the aldehyde is symmetrically disposed with respect to the dioxaborolane system. Clockwise rotation about the B—O bond as indicated in (**B**) moves the aldehyde nonbonding lone pair away from the proximate ester carbonyl and leads to the favored transition state (**A**). Rotation of the B—O bond in the reverse direction increases the *n*/*n* interactions and leads to disfavored transition state (**C**).

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[31] (a) Karabatsos, G. J.; Taller, R. A. *Top. Stereochem.* **1970**, *5*, 167 (b) Kroon, J. In "Molecular Structure and Biological Activity," Griffin, J. F., Duax, W. L., Eds.; Elsevier Biomedical: New York, 1982; p. 151. (c) Trost, B. M.; Belletire, J. L.; Godleski, S.; McDougal, P. G.; Balkovec, J. M.; Baldwin, J. J.; Christig, M. E.; Ponticello, G. S.; Varga, S. L.; Springer, J. P. *J. Org. Chem.* **1986**, *51*, 2370. (d) Siegel, C.; Thornton, E. R. *Tetrahedron Lett.* **1988**, *29*, 5225.

[32] (a) Karabatsos, G. J.; Fenoglio, D. J.; Lande, S. S. *J. Am. Chem. Soc.* **1969**, *91*, 3572. (b) Karabatsos, G. J.; Fenoglio, D. J. *Ibid.* **1969**, *91*, 3577.

These arguments imply that the aldehyde to boronate complexation step (a Lewis acid/Lewis base reaction) is the critical enantioselectivity-determining event, since conformation (**B**) most probably represents the ground state Lewis acid aldehyde complex. This conformation may be stabilized by a boron-centered anomeric effect ($n_O - \sigma^*$ interactions between the axial lone pairs of the ring oxygens and the B—O=CHR single bond).[33] The actual transition state for the allyl transfer probably occurs during a flipping motion of the dioxaborolane O—B—O unit that moves the allyl group toward a pseudoaxial position with development of two anti $n_O - \sigma^*_{B\text{–}C}$ interactions that facilitate cleavage of the B—C bond.

One further point is worthy of mention. While we have focused on lone pair/lone pair repulsive interactions that destabilize (**C**), it is conceivable that (**A**) is actually stabilized relative to (**C**) by a favorable charge-charge interaction between the ester carbonyl (δ^-) and the aldehydic carbonyl carbon (δ^+) owing to the proximity of these groups in (**A**). While it is not yet possible to resolve the relative contributions of these distinct stereoelectronic effects, it is clear that this proposal explains the experimental results only if the dioxaborolane and the C—CO_2*i*-Pr bonds exist in the conformations indicated in (**B**). Any conformational infidelity at either site would be expected to lead to diminished enantioselectivity.

Other evidence has appeared in support of this mechanistic hypothesis. First, we have performed an X-ray crystal structure analysis of dimethyl benzylidenetartrate, the ORTEP drawing of which appears in Figure 24.[34] While caution obviously must be exercised when extrapolating from solid state to solution structures, it is striking that the conformation of the benzylidenetartrate system—esters pseudoaxial and the carbonyl groups eclipsing the adjacent C—O bonds—is exactly that implicated in our transition state model. Examination of data from both X-ray analyses and solution NMR studies of benzylidene acetals of a number of tartrate derivatives reveal that there is good correlation between $J_{3,4}$ in solution and H_3–C–C–H_4 torsion angles measured from X-ray diffraction (Figure 25). The observed $J_{3,4}$ values increase in accordance with an increase in torsion angles (Entries 1, 6 and 8), suggesting that the conformations in solution parallel those in the solid state. In addition, members of each structurally related series show similar $J_{3,4}$ values. Hence, entries 1–5 exhibit very similar $J_{3,4}$ values (3.9–5.0 Hz) while entries 6–7 show identical J values.

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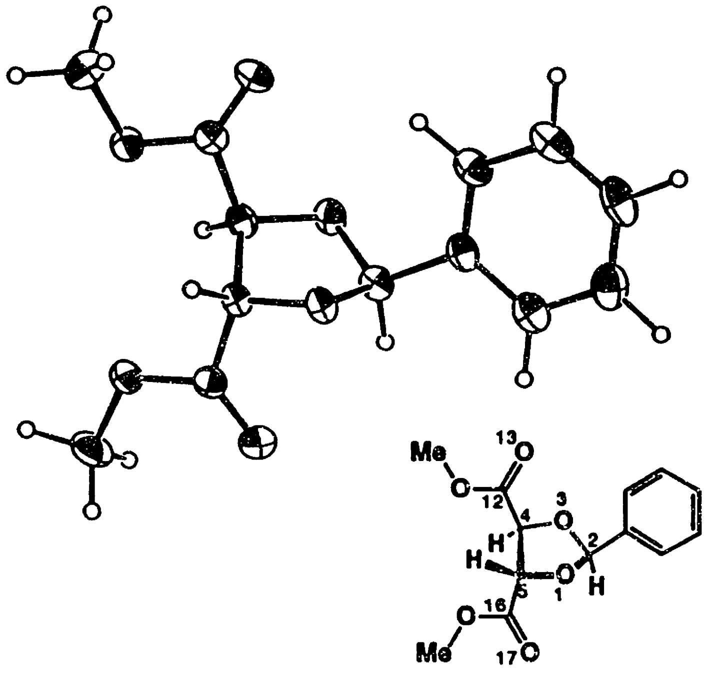
[33] For a previous example of a boron-centered anomeric effect, see: Shiner, C. S.; Garner, C.; Haltiwanger, R. C. *J. Am. Chem. Soc.* **1985**, *107*, 7167.

[34] (a) Crystal data for dimethyl benzylidenetartrate $C_{13}H_{14}O_6$: space group: $P2_12_12_1$; cell dimensions (at −144 °C): a = 8.463(2), b = 8.302(2), c = 17.771(5) Å; Z (molecules/cell): 4; volume: 1248.57 Å^3; calculated



O(1)–C(5)–C(16)–O(17)	–9.97°
O(3)–C(4)–C(12)–O(13)	–1.94°
C(12)–C(4)–C(5)–C(16)	143.08°
O(3)–C(4)–C(5)–C(16)	–96.57°
O(1)–C(5)–C(4)–C(12)	–96.64°
O(1)–C(5)–C(4)–O(3)	23.72°
H–C(4)–C(5)–H	–98.92°

Figure 24. ORTEP Drawing of Dimethyl Benzylidene Tartrate.

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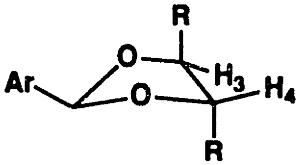
density: 1.416 g/cm^3; wavelength: 0.71069 Å; linear absorption coefficient: 1.058 cm^{-1}. The structure was solved using a combination of direct methods and Fourier techniques, and was refined to final residuals R(F) = 0.039 and R_w(F) = 0.389 for 4307 independent reflections (F > 3Σ(F)) of 2335 unique intensities collected in the range 6° ≤ 2q ≤ 55°. Details of the data collection and structure solution, atomic positional and thermal parameters, complete bond distance and bond angle data, and a listing of F_{obs} vs. F_{calc} may be obtained directly from the Indiana University Molecular Structure Center. Request report No. 89061. (b) X-ray crystallography was carried out by Dr. William E. Streib at the Indiana University Department of Chemistry Molecular Structure Center, Indiana University, Bloomington, IN 47405.



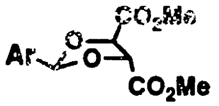
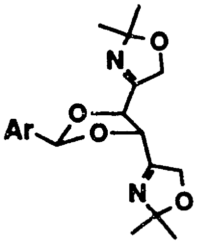
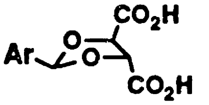
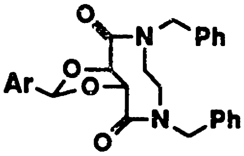
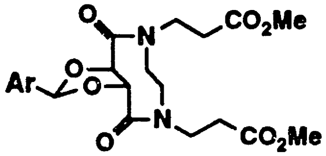
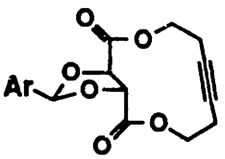
Entry	Benzylidene Acetal	Ar	H_3-C-C-H_4 Torsion Angle (X-ray)	$J_{3,4}$ (Solvent)
1		Ph	96°	3.9 Hz ($CDCl_3$)
2		(p-MeO)C_6H_4–	—	4.1 Hz ($CDCl_3$)
3		Ph	—	5.0 Hz ($CDCl_3$)
4		p-Tolyl	—	5.0 Hz ($CDCl_3$)
5		Ph	—	3.9 Hz (DMSO)
6		Ph	123°	6.2 Hz ($CDCl_3$)
7		Ph	—	6.2 Hz ($CDCl_3$)
8		Ph	150°	8.5 Hz ($CDCl_3$)

Figure 25.
Correlation between Solid State and Solution Conformations of Tartrate Derivatives

Second, based on this model, a coworker has developed the diol auxiliary (**93**) and shown that allylboronate (**94**) (Figure 26) is substantially more enantioselective than (**13**).[35] The conformation of the structurally rigid tartramide and dioxaborolane units in (**D**) mimic very closely those found in (**B**) for the parent tartrate allylboronate system. Further studies of related tartramide systems are described in Chapter 3 of this thesis.

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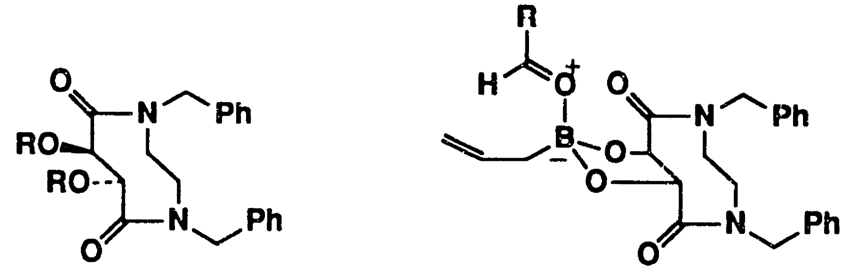
[35] Roush, W. R.; Banfi, L. *J. Am. Chem. Soc.* **1988**, *110*, 3979.

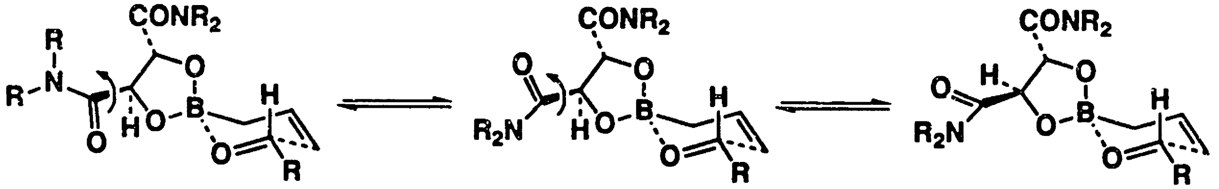


(R,R)-(**93**) R = H
(R,R)-(**94**) R = $BCH_2CH=CH_2$

(**D**)

Figure 26

The high conformational rigidity of the Banfi auxiliary in (**D**) is clearly critical to the high enantioselectivity realized, since acyclic tartramides such as (**91**) and (**92**) (Figure 22) are considerably less enantioselective.[30] In this case, the preferred "ester" rotamer (**C-1**) (Figure 27), in which the carbonyl eclipses the adjacent C—O bond, is destabilized by interactions between the s-cis amide R substituent and the tartrate C—C backbone, and rotamers (**C-2**) and/or (**C-3**) probably are much more competitive in the amide series, with detrimental results on enantioselectivity.



(**C-1**)
C = O syn to C—O

(**C-2**)
C = O syn to C—C

(**C-3**)
C = O syn to C—H

Figure 27

Similar considerations account for the decreased enantioselectivity of oxazoline derivative (**90**) (Figure 28). Examination of models reveals that the aldehyde R group interacts with the endo methyl of the oxazolidine when this system adopts a conformation resembling the favored ester conformation A. Thus the transition states with other conformations about the

C—C(=N) unit are probably competitive here as well.

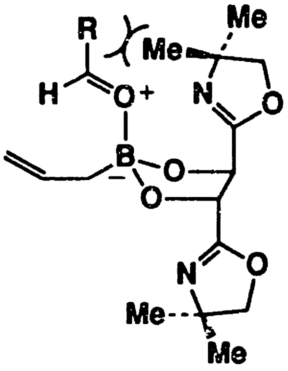
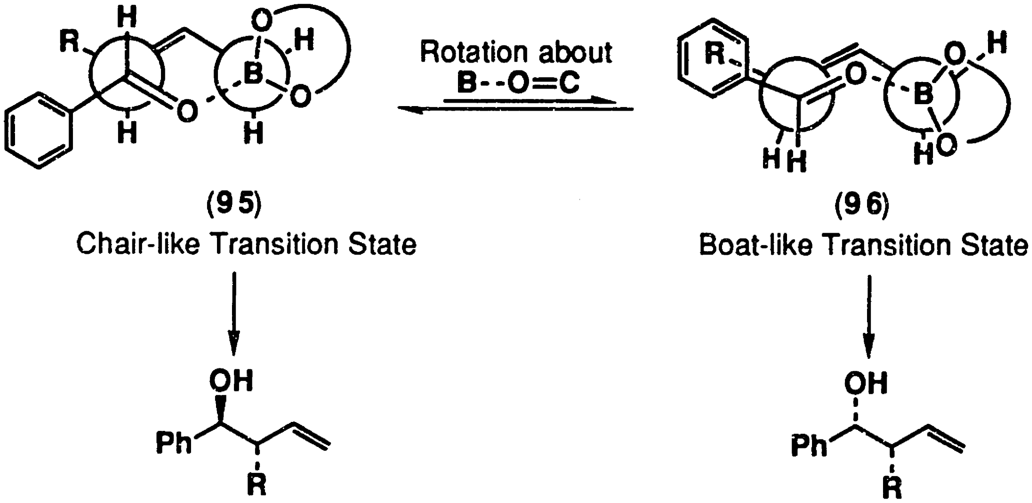


Figure 28

It is of interest to attempt to rationalize the lower enantioselectivities realized with aromatic, α,β-unsaturated, and alkoxy-substituted aldehydes in view of this model. At first glance, one might be tempted to rationalize the lower selectivities observed with the aromatic and α,β-unsaturated aldehydes by invoking the involvement of boat-like transition state (96) (Figure 29) since the "flatness" of the aryl and olefinic R groups conceivably could minimize eclipsing interactions with substituents at the terminal carbon of the allyl unit.



(95)
Chair-like Transition State

(96)
Boat-like Transition State

Figure 29

This could allow boat transition states to compete more efficiently, resulting in a deterioration of the diastereo- and enantiofacial bias that is usually observed with the saturated aliphatic aldehydes. However, the reaction of aromatic aldehydes with the analogous (E)-

crotylboronates proceed with very high (> 99%) 3,4-anti selectivity (simple diastereoselection) but still with poor enantioselectivity (55–65% e.e.),[36] suggesting that boat-like arrangements (**96**) are highly disfavored and are not significant contributors in these reactions. Hence, the minor enantiomer must arise via the competing, disfavored chair-like transition state (C). Whether a steric or electronic effect (or a combination of the two) is responsible for the reactions proceeding with increased contribution from (C) is not clear. The constant level of enantioselectivity with various *p*-substituted benzaldehydes (Section 2.2.7) rules out a simple electronic effect as the explanation.

Recent investigations by a coworker in our laboratories have shown that significant gains in enantioselectivity occur when the (benzaldehyde)chromiumtricarbonyl (**97**) is used (Figure 30).

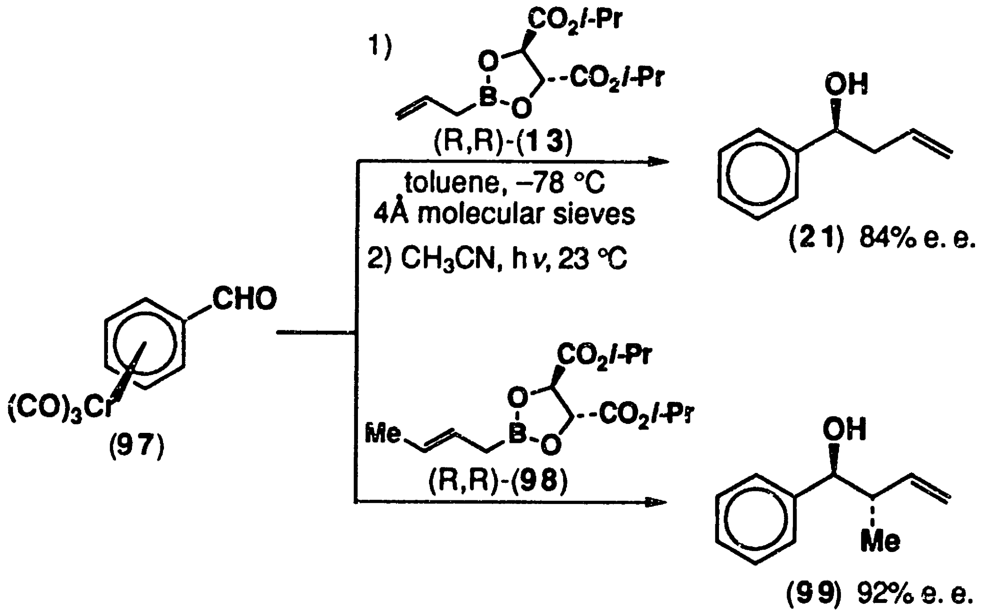


Figure 30

Reactions of (**97**) with allylboronate (**13**) (–78 °C, toluene, 4Å molecular sieves) gave the corresponding homoallylic alcohol in 84% e.e., comparable to those seen with cyclohexanecarboxaldehyde (**16**). The analogous reaction with (E)-crotylboronate (**98**) also resulted in substantially increased enantioselection. Although these experiments may eventually offer insights into the reactions of the aromatic aldehydes, there is currently insufficient data to determine if these enhanced selectivities are due to steric or electronic factors.[37]

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[36] (a) Roush, W. R.; Ando, K.; Powers, D. B.; Halterman, R. L.; Palkowitz, A. D. *Tetrahedron Lett.* **1988**, *29*, 5579. (b) Roush, W. R.; Ando, K.; Powers, D. B.; Halterman, R. L.; Palkowitz, A. D. *J. Am. Chem. Soc.*, submitted for publication.

Alkoxy-substituted aldehydes also react with lower enantioselectivity. However, in these cases, the erosion of the facial preference may also be due to subtle stereoelectronic effects. Clues which point to the involvement of these effects may be found in the reactions of α,β-dialkoxy aldehydes with the tartrate-modified allyl- and (E)-crotylboronates (**13**) and (**98**). The data from the studies of the reactions with D-glyceraldehyde (**102**) are summarized in Figure 31.[1c, 5]

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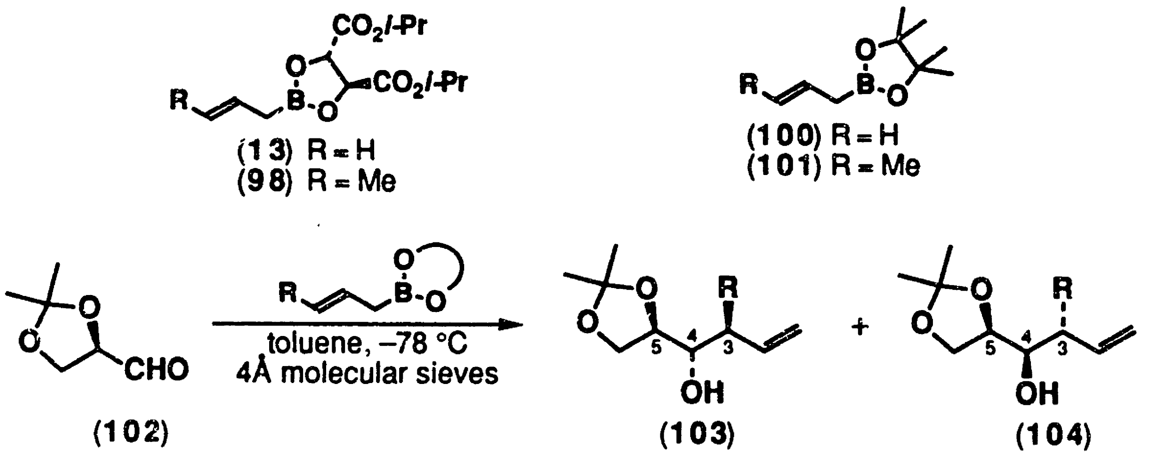
[37] Roush, W. R.; Park, J. C. Unpublished results.



(13) R = H
(98) R = Me

(100) R = H
(101) R = Me

(102)

(103)

(104)

Entry	Reagent	(103) : (104)	$\Delta G^{\ddagger}_{reaction}$ (kcal/mol)	$\Delta\Delta G^{\ddagger}_{reagent}$ (kcal/mol)
1	(R,R)-(13)	96 : 4	1.23^{M}	0.88
2	(100)	71 : 29	0.35	1.35
3	(S,S)-(13)	7 : 93	1.00^{MM}	
4	(R,R)-(98)	91 : 9	0.88^{M}	0.80
5	(101)	55 : 45	0.08	1.58
6	(S,S)-(98)	2 : 98	1.50^{MM}	

$$\Delta G^{\ddagger}_{matched} \approx \Delta\Delta G^{\ddagger}_{reagent} + \Delta\Delta G^{\ddagger}_{aldehyde}$$
$$\Delta G^{\ddagger}_{mismatched} \approx \Delta\Delta G^{\ddagger}_{reagent} - \Delta\Delta G^{\ddagger}_{aldehyde}$$

^{M}Matched double asymmetric induction.
^{MM}Mismatched double asymmetric induction.

Figure 31

Calculations of the relative transition state energies ($\Delta\Delta G^{\ddagger}$)[38] reveal that the mismatched double asymmetric reactions (Entries 3 and 6) give selectivities that are much higher than expected based on analogies to achiral aldehyde models. The $\Delta\Delta G^{\ddagger}_{reagent}$ value for the –78 °C reaction of (**13**) and an an achiral aldehyde like cyclohexanecarboxaldehyde (86% e.e.) is roughly 1.0 kcal mol^{-1}. Examination of Dreiding molecular models suggests that the relative orientations of the ester carbonyl group and the glyceraldehyde C(2) and C(3) oxygen substituents in the competing transition states may be contributing factors (Figure 32).

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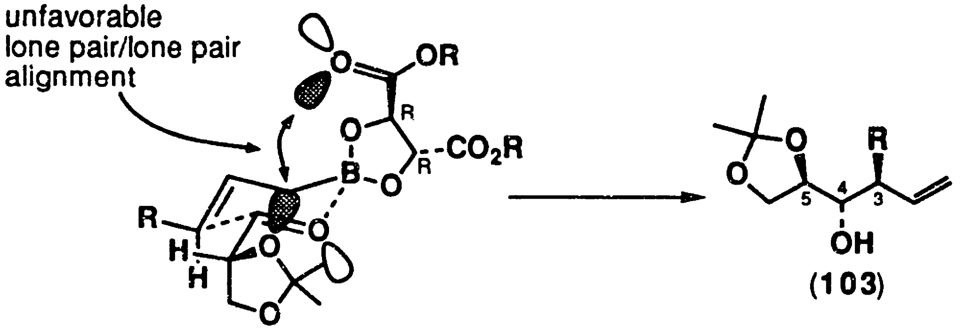
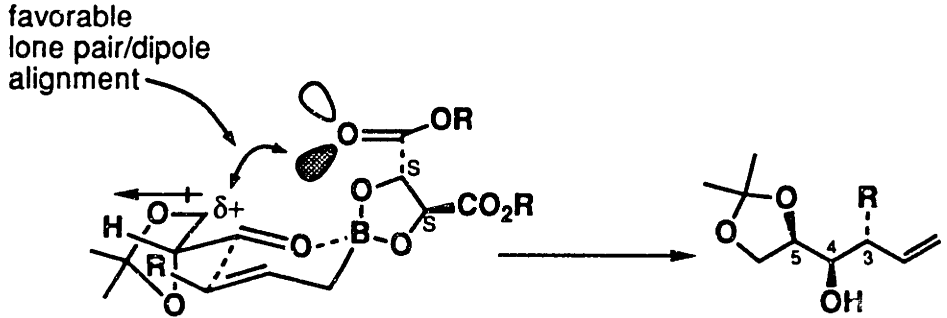
[38] For a discussion of $\Delta G^{\ddagger}$ and $\Delta\Delta G^{\ddagger}$ in the context of matched and mismatched cases of double asymmetric synthesis, see: Masamune, S.; Choy, W.; Peterson, J. S.; Sita, L. R. *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 1.



(103)

(105) Major pathway, matched pair



(106) Major pathway, mismatched pair

(104)

Figure 32

The chair-like transition states (**105**) and (**106**), corresponding to the predominant pathway in the matched and mismatched reaction pairs respectively, are shown in Figure 32. The conformations of the aldehyde in these transition states are those that have been previously assigned for the reactions with the pinacol allylboronates.[1a, b] In (**105**), the major pathway accessible to the matched pair of reactants, it is apparent that the "front side" tartrate ester carbonyl comes relatively close to the glyceraldehyde C(2) oxygen atom (a comparable interaction is absent in the disfavored transition state; not drawn). This presumably results in an unfavorable lone pair/lone pair interaction that detracts from this otherwise energetically favored arrangement. As a result, transition state (**A**) is no longer as highly favored compared to the disfavored arrangement (**C**) as it is in cases where the negative lone pair/lone pair interaction of (**105**) is absent; recall that $\Delta\Delta G^{\ddagger}_{reagent}$ for the matched pair is only *ca.* 0.8–0.9 kcal mol^{-1}, a value somewhat lower than $\Delta\Delta G^{\ddagger}_{reagent}$ for reactions with achiral aliphatic aldehydes.

In the mismatched double asymmetric reaction, however, the ester carbonyl comes closest to the back side of the glyceraldehyde C(3)—O bond in favored transition state (**106**). The possibility exists that (**106**) is then additionally stabilized by a lone pair/dipole arrangement that results from the proximity of these groups; transition state (**106**) is substantially more favorable ($\Delta\Delta G^{\ddagger}_{reagent} \approx 1.35$–$1.6$ kcal mol^{-1}) than observed in any reactions with achiral aldehydes.

Such an stereoelectronic effect, particularly that in (**105**), may be responsible for the drop in selectivity of the reactions of the tartrate allylboronate (**13**) and alkoxy aldehydes (**67**)–(**75**). Since the alkoxy groups in these aldehydes are not conformationally constrained as are the alkoxy groups of (**102**), the alkoxy substituents can possibly adopt conformations in the transition states similar to those in (**105**) such that interactions occur with the tartrate ester carbonyl. This would result in the overall lowering of the energy of the favored chair-like transition states (e.g., analogous to (**105**)) thereby enabling pathway leading to the minor product to be increasingly competitive.

If this analysis is correct, one expects this effect to drop off as the distance between the alkoxy substituent and the aldehydic center is increased. Indeed, our data indicate that the aldehydes with alkoxy substituents at the α- or β-carbons show the greatest drop in enantioselectivity while the γ-alkoxyaldehydes exhibit selectivities very close to the "normal" range. It should be pointed out, however, that the involvement of such electrostatic stabilization/destabilization is purely speculation. Conclusive evidence for the existence of such a stereoelectronic effect may be difficult to prove since these systems are highly flexible, with many degrees of freedom. Steric effects cannot be ruled out entirely.

One criterion in evaluating a proposed transition state model is that it should agree with experimental observations. A second is that the model should be testable. That is, the model should enable one to design or modify the reagent so as to improve the selectivity of the reaction. We found that this was indeed the case with the model we have proposed, especially since it allowed for the development of second-generation reagents (e.g., (**94**))[35] with improved stereoselectivity. Additional studies on the development of improved, second generation auxiliaries are described in Chapter 3.

Experimental Section

General. ^{1}H NMR spectra were measured in $CDCl_3$ at 250 MHz on a Bruker WM 250 instrument, at 300 and 400 MHz on Varian XL-300 and XL-400 instruments, at 360 MHz on a Nicolet 360 instrument, and at 500 MHz on a Bruker AM 500 instrument. Residual chloroform (δ 7.26 ppm) was used as internal reference. ^{13}C NMR spectra were recorded at 75.4 MHz on the XL-300 and were referenced with the δ 77.0 ppm resonance of $CDCl_3$. ^{19}F NMR spectra were obtained at 376.3 MHz, 338.7 MHz, or 282.2 MHz on the XL-400, Nicolet 360, or XL-300 instruments respectively and were referenced with external 4-bromobenzotrifluoride [Aldrich; δ –63.31 ppm in $CDCl_3$]. ^{11}B NMR were recorded at 115.8 MHz on a Nicolet 360 instrument and were referenced with external $BF_3{\cdot}Et_2O$ (δ 0.0 ppm). Infrared spectra were recorded on a Perkin-Elmer Model 1420 Infrared Spectrophotometer and were referenced by the 1601 cm^{-1} absorption of polystyrene. Optical rotations were measured on a Rudolph Autopol III Automatic Polarimeter using a 1 cm^3 quartz cell (10 cm path length). Mass spectra were measured at 70 eV on a Varian MAT 44 or a Finnegan MAT 8200 instrument. High-resolution mass spectra were measured at 70 eV on the Finnegan MAT 8200.

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 % e.e.'s via the separation of diastereomeric MTPA esters, were carried out using a Shimadzu GC-9A Gas Chromatograph equipped with 50 m x 0.25 mm Bonded FSOT Carbowax 20M. Chiral capillary GC % e.e. determinations of methyl ethers were performed on a Hewlett Packard 5890A Gas Chromatograph equipped with 25 m x 0.25 mm 10% nickel (II) bis(3-heptafluorobutyryl-(1R)-camphorate)/OV-1 [Ni-R-Cam] or 25 m x 0.25 mm 10% nickel (II) bis (heptafluorobutyryl-(1R, 2S)-pinan-4-oate)/OV-1 [Ni-4-Pin] chiral capillary columns.

Analytical thin-layer chromatography (TLC) was performed by using 2.5 cm x 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 x 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,[39] using Kieselgel 60 (230–400 mesh) or Kieselgel 60 (70–230 mesh). Compounds were visualized by charring with ethanolic vanillin/H_2SO_4, phosphomolybdic acid (PMA), ammonium molybdate/ceric sulfate (Ce-Mo) or by staining with iodine vapor. Unless otherwise noted, all compounds purified by chromatography are sufficiently pure (> 95% by ^{1}H NMR analysis) for use directly in subsequent transformations.

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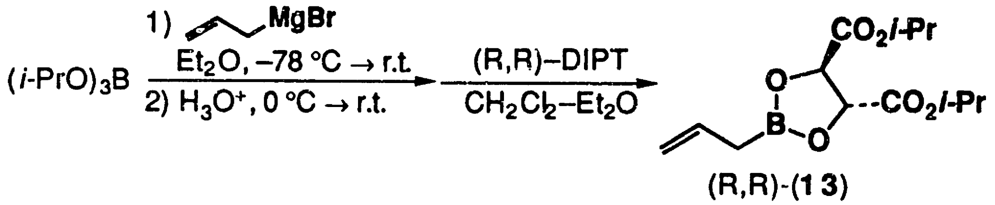
[39] Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.



Optimized Procedure for the Preparation of Diisopropyl 2-Allyl-1,3,2-dioxaborolane-4,5-dicarboxylate (Tartrate allylboronate (13)).

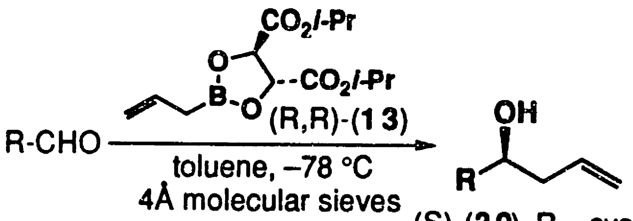
Procedure: Solutions of triisopropylborate (0.04 mol) in 10 mL of dry Et_2O and allylmagnesium bromide (0.87 M in Et_2O) were added simultaneously, but separately, dropwise to 10 mL of dry Et_2O at –78 °C. This mixture was stirred for 0.5 h at –78 °C, then was allowed to warm to room temperature and stirred for 3 h. The slurry was recooled to 0 °C, and then 0.04 mol of 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 0.04 mol of (R,R)-DIPT. The aqueous phase was extracted with 5 : 1 Et_2O-CH_2Cl_2 (3 x 50 mL). The combined organic layers were stirred over anhydrous $MgSO_4$ for 2.5 h, then filtered under Ar. The filtrate was concentrated *in vacuo* to give a clear, colorless, semi-viscous liquid. Dry toluene was added to give 50.0 mL of clear solution. A 1 mL aliquot of the solution of crude reagent was treated with 4Å molecular sieves. After stirring for 15 min at room temperature, a known excess of cyclohexanecarboxaldehyde (**16**) was added. The reaction was quenched 15 min later with $NaBH_4$-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 x 0.25 mm Bonded FSOT Carbowax 20M; 100 °C/4 min → 10 °C/min → 190 °C] for cyclohexanemethanol (**25**) [t_R 7.65 min] and 1-cyclohexylbut-3-en-1-ol (**20**)

[t_R 9.64 min]. The yield of this particular batch of crude reagent was found to be 86% and the concentration of the standardized solution was calculated to be 0.7 M. The yields of various batches of reagent prepared in this manner were typically found to vary in the range 65–75%.

Calibration Studies: Known amounts of cyclohexanemethanol (**25**) and 1-cyclohexylbut-3-en-1-ol (**20**) were combined in various molar ratios, and the resulting mixtures were analyzed by capillary GC [50 m x 0.25 mm Bonded FSOT Carbowax 20M; 100 °C/4 min → 10 °C/min → 190 °C].

Molar Ratio (25) : (20)	**GC Ratio** (25) : (20)	Δ% (20)
12 : 88	10 : 90	2
36 : 64	31 : 69	5
48 : 52	43 : 57	5
52 : 48	47 : 53	5
80 : 20	76 : 24	4
84 : 16	82 : 18	2
89 : 11	87 : 13	2

The results indicate that the error in the measured ratios do not exceed 5% of the actual values. Consequently, yields and concentrations of (**13**) determined in this way are not corrected.



(S)-(**20**) R = cyclohexyl
(S)-(**21**) R = phenyl
(S)-(**22**) R = *t*-butyl
(R)-(**23**) R = *n*-nonyl
(S)-(**29**) R = 1-(E)-nonenyl

General Procedure for the Enantioselective Allylboration of Achiral Aldehydes.

Procedure: To a dry 10 mL flask was charged with oven-dried, powdered 4Å molecular sieves (50 mg) was added 0.26 mmol of (R,R)-(**13**) in 1.0 mL of toluene. The stirred mixture was cooled to –78 °C, and 0.40 mmol (45 mg) of cyclohexanecarboxaldehyde (**16**) was added. After being stirred for 2 h, the reaction mixture was treated with excess $NaBH_4$/EtOH (precooled to –78 °C). The resulting mixture was stirred at –78 °C for 30 min before being added to 1 : 1 Et_2O-1 M NaOH. The layers were separated, and the aqueous phase was extracted with Et_2O (3 x 1.5 mL). The combined organic layers were dried over anhydrous Na_2SO_4 then filtered and concentrated *in vacuo*. The crude product was purified by PTLC (2 x 0.5 mm plates) using 2 : 1 hexane-Et_2O as eluant to give 39 mg (97% yield) of (S)-1-cyclohexylbut-3-en-1-ol (**20**). In cases that utilize valuable aldehydes, the procedure may be carried out using (**13**) in excess.

Data for (S)-1-Cyclohexylbut-3-en-1-ol (20): (Obtained in 97% yield) $[\alpha]^{20}_{D}$ –8.7° (c = 0.54, abs. EtOH); *^{1}H NMR* [$CDCl_3$, 250 MHz] δ 5.90–5.73 [m, 1H], 5.12 [d, J = 15.4 Hz, 1 H], 5.11 [d, J = 11.9 Hz, 1H], 3.37 [m, 1H], 2.4–2.25 [m, 1H], 2.2–2.15 [m, 1H], 1.9–1.5 [series of m, 7H], 1.45–0.9 [series of m, 7H]; *IR* (neat) 3410 (br), 3075, 2925, 2855, 1640, 1450, 1035, 984, 910 cm^{-1}; R_f 0.62 [1 : 1 hexane-ether; I_2, PMA/char]

The enantiomeric excess of (S)-(**20**) was determined (i) by integration of the H(2) signals from ^{1}H NMR (400 MHz) analysis of the corresponding (R)-MTPA ester derivative:[9] (R,S)-isomer δ 5.84–5.71 (m), (R,R)-isomer δ 5.68–5.58 (m). Alternatively, the enantiomeric excess may also be determined by capillary GC analysis of the (R)-MTPA ester derivative. The (R)-MTPA derivative of (S)-(**20**) is faster eluting (t_R 10.7 min) than its (R,R)-diastereomer (t_R 10.9 min; 200 °C isotherm). (ii) Analysis and resolution of the corresponding methyl ether derivative by chiral capillary GC.[13]

Data for (S)-1-Phenylbut-3-en-1-ol (21): (Obtained in 78% yield; the reaction was run in THF) $[\alpha]^{20}_{D}$ $-40.7°$ (c = 1.21, benzene); *^{1}H NMR* [$CDCl_3$, 250 MHz] δ 7.35–7.2 [m, 5H], 5.8 [m, 1H], 5.15 [br d, J = 17.5 Hz, 1H], 5.13 [br d, J = 9.2 Hz, 1H], 4.72 [t, J = 6.6 Hz, 1H], 2.60–2.40 [m, 2H]; *IR* (neat) 3380 (br), 3075, 3030, 2980, 2935, 2910, 1641, 1493, 1455, 1198, 1043, 1000, 915, 870, 757, 700 cm^{-1}; R_f 0.51 [2 : 1 hexane-ether; UV, PMA/char]

The enantiomeric excess of (S)-(**21**) was determined (i) by integration of the following signals from ^{1}H NMR (400 MHz) analysis of the corresponding (R)-MTPA ester derivative:[9] H(2) (R,S)-isomer δ 5.68–5.58 (m), (R,R)-isomer δ 5.81–5.68 (m); H(4) (R,S)-isomer δ 6.07–6.02 (m), (R,R)-isomer δ 6.00–5.95 (m). Alternatively, the enantiomeric excess may also be determined by capillary GC analysis of the (R)-MTPA ester derivative. The (R)-MTPA derivative of (S)-(**21**) is slower eluting (t_R 15.1 min) than its (R,R)-diastereomer (t_R 10.9 min; 200 °C isotherm). (ii) Analysis and resolution of the corresponding methyl ether derivative by chiral capillary GC.[13]

Data for (S)-2,2-Dimethylhex-5-en-3-ol (22): (Obtained in 56% yield) $[\alpha]^{20}_{D}$ −1.8° (c = 0.92, benzene) ^{1}*H NMR* [$CDCl_3$, 250 MHz] δ 5.74 [m, 1H], 5.02 [br d, J = 15.3 Hz, 1H], 5.01 [br d, J = 11.4 Hz, 1H], 3.14 [br d, J = 10.6 Hz, 2H], 2.32–2.20 [m, 1H], 1.92–1.79 [m, 1H], 1.47 [br s, 1H, OH], 0.80 [s, 9H]; *IR* (neat) 3435 (br), 3075, 2985, 2909, 2870, 1640, 1480, 1433, 1395, 1364, 1293, 1210, 1070, 1007, 990, 910, 861, 770 cm^{-1}; R_f 0.52 [3 : 1 hexane-ether; I_2]

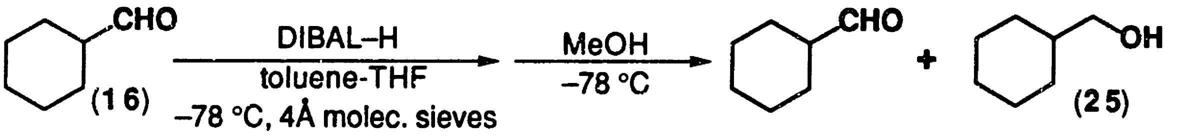
The enantiomeric excess of (S)-(**22**) was determined (i) by integration of the signals from ^{19}F NMR (282.2 MHz) analysis of the corresponding (R)-MTPA ester derivative:[9] (R,S)-isomer δ −71.09, (R,R)-isomer δ −71.41. (ii) Analysis and direct resolution of (S)-(**22**) by chiral capillary GC.[13]

Data for (R)-Tridec-1-en-4-ol (23): (Obtained in 86% yield) $[\alpha]^{20}_{D}$ +5.3° (c = 1.17, $CHCl_3$); ^{1}*H NMR* [$CDCl_3$, 250 MHz] δ 5.89–5.73 [m, 1H], 5.11 [dt, J = 1.1 Hz, 13.9 Hz, 2H], 3.61 [br m, 1H], 2.35–2.23 [m, 1H], 2.17–2.08 [m, 1H], 1.54 [d, J = 3.9 Hz, 1H], 1.50–1.35 [br m, 3H], 1.35–1.20 [br m, 13H), 0.86 [t, J = 6.1 Hz, 3H]; *IR* (neat) 3360 (br), 3080, 2935, 2860, 1645,1465, 900 cm^{-1}; R_f 0.44 [3 : 1 hexane-ether; I_2, PMA/char]

The enantiomeric excess of (S)-(**23**) was determined by integration of the H(2) signals from ^{1}H NMR (400 MHz) analysis of the corresponding (R)-MTPA ester derivative:[9] (R,R)-isomer δ 5.70–5.57 (m), (R,S)-isomer δ 5.84–5.71 (m).

Data for (R)-Pentadeca-1,5-dien-4-ol (29): (Obtained in 46% yield using (S,S)-(**13**); the reaction was run in THF) $[\alpha]^{20}_{D}$ +1.7°, $[\alpha]^{20}_{546}$ +2.7° (c = 0.52, $CHCl_3$); ^{1}*H NMR* [$CDCl_3$, 300 MHz] δ 5.86–5.72 [m, 1H], 5.70–5.60 [m, 1H], 5.51–5.44 [dd, J = 9.0 Hz, J = 15.0 Hz, 1H], 5.16–5.10 [m, 2H], 4.15–4.08 [br m, 1H], 2.36–2.20 [m, 2H], 2.02 [q, J = 7.20 Hz, 2H], 1.56 [d, J = 4.5 Hz, 1H], 1.38–1.26 [m, 10H], 0.88 [t, J = 6.0 Hz, 3H]; *IR* (neat) 3440 (br), 3079, 2980, 2960, 2929, 2859, 1740, 1641, 1601, 1469, 1376, 1255 (br), 1105 (br), 995, 970, 911, 825, 721 cm^{-1}; *HRMS* [CI] for $C_{13}H_{24}O$ *M – 1 calcd.*: 195.1749, *obsvd.*: 195.1756; *M – 17 calcd.*: 179.1800, *obsvd.*: 179.1797; R_f 0.35 [3 : 1 hexane-ether; PMA/char]

The enantiomeric excess of (R)-(**29**) was determined by integration of the H(1) signals from ^1H NMR (400 MHz) analysis of the corresponding (R)-MTPA ester derivative:[9] (R,R)-isomer δ 5.05–4.96 (m), (R,S)-isomer δ 5.17–5.06 (m).

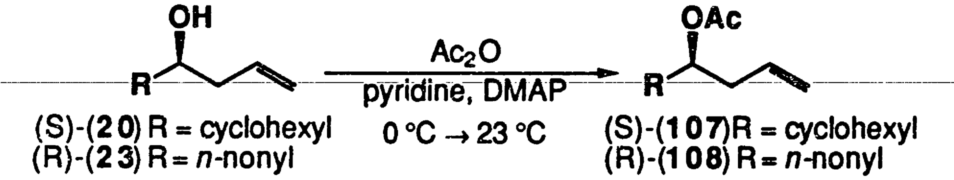


Control Experiment for the Quenching of Unreacted Aldehyde with DIBAL-H.

Procedure: A mixture of 1 mL of dry toluene and 0.5 mL of dry THF was cooled to –78 °C and then 0.04 mmol of cyclohexanecarboxaldehyde was added. The resulting mixture was treated with 0.2 mmol of DIBAL–H [1.0 M in hexane]. After being stirred for a specific duration (1, 5, and 30 min; three separate experiments), the reaction mixture was quenched with 3.2 mmol of dry MeOH then stirred for another 30 min and then added to 1 : 1 Et_2O–1 M NaOH. The organic layer was separated and dried over anhydrous Na_2SO_4. The organic phase was analyzed by capillary GC [50 m x 0.25 mm Bonded FSOT Carbowax 20M; 100 °C/4 min → 10 °C/min → 190 °C] for detection of cyclohexanecarboxaldehyde (**16**) [t_R 4.21 min] and cyclohexanemethanol (**25**) [t_R 7.65 min]. The results indicated that cyclohexanecarboxaldehyde had been reduced to the extent of 97% after 1 min and 98% after 5 min. The efficiency of

MeOH to quench unreacted DIBAL-H at –78 °C was determined by changing the order of addition of the reagents: A solution of 0.2 mmol of DIBAL–H [1.0 M in hexane] in a mixture of 1 mL of dry toluene and 0.5 mL of dry THF was treated with 3.2 mmol of dry MeOH at –78 °C. After a period of time (1 min and 5 min; two separate experiments), 0.04 mmol of cyclohexanecarboxaldehyde was added. The mixture was stirred for 30 min before being worked up according to the procedure described above. The results from these experiments revealed that > 98% of aldehyde survived reduction even after only a 1 min exposure of the DIBAL-H solution to MeOH. These control experiments are discussed more fully in Section 2.2.1.

Correlation Studies.



(S)-(**20**) R = cyclohexyl
(R)-(**23**) R = *n*-nonyl

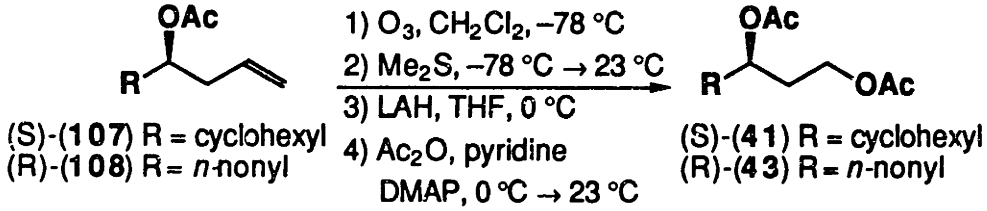
(S)-(**107**) R = cyclohexyl
(R)-(**108**) R = *n*-nonyl

1. Procedure for the Acylation of Homoallylic Alcohols (20) and (23).

Procedure: A solution of (S)-1-cyclohexylbut-3-en-1-ol (**20**) (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. After being stirred overnight, the reaction mixture was concentrated *in vacuo* followed by repeated concentration *in vacuo* from heptane to remove residual pyridine and acetic acid. The crude product so obtained was purified by PTLC (2 x 0.5 mm plates) using 3 : 1 hexane–Et$_2$O as eluant to give 45 mg (50% yield) of (S)-(**107**) as a clear, colorless liquid. Acetate (R)-(**108**) was prepared in 88% yield from (R)-(**23**) using the above procedure.

Data for (S)-1-Acetoxy-1-cyclohexylbut-3-ene (107): $[\alpha]^{25}_{D}$ +15.7°, $[\alpha]^{25}_{546}$ +18.2° (c = 1.15, $CHCl_3$); *^1H NMR* [$CDCl_3$, 300 MHz] δ 5.80–5.66 [m, 1H], 5.08–5.01 [m, 2H], 4.80–4.72 [m, 1H], 2.39–2.19 [m, 2H], 2.02 [s, 3H], 1.76–1.41 [series of m, 6H], 1.29–0.92 [series of m, 5H]; *IR* (neat) 3070, 2930, 2850, 1740, 1640, 1445, 1365, 1235, 1015, 910 cm^{-1}; *HRMS* [CI] for $C_{12}H_{20}O_2$ *M + 1 calcd.*: 197.1541, *obsvd.*: 197.1585; *M – 59 calcd.*: 137.1330, *obsvd.*: 137.1325; R_f 0.59 [3 : 1 hexane-ether; I_2]

Data for (R)-4-Acetoxytridec-2-ene (108): *^1H NMR* [$CDCl_3$, 300 MHz] δ 5.80–5.66 [m, 1H], 5.08-5.02 [m, 2H], 4.89 [quint, 1H], 2.36–2.21 [m, 2H], 2.02 [s, 3H], 1.56–1.46 [br m, 2H], 1.24 [br s, 14H], 0.86 [t, J = 6.0 Hz, 3H]; *IR* (neat) 3078, 2925, 2858, 1744, 1642, 1466, 1372, 1239, 1020, 914 cm^{-1}; *HRMS* [CI] for $C_{15}H_{28}O_2$ *M + 1 calcd.*: 241.2167, *obsvd.*: 241.2166; R_f 0.63 [3 : 1 hexane-ether; I_2]


OAc
R
(S)-(107) R = cyclohexyl
(R)-(108) R = n-nonyl
1) O₃, CH₂Cl₂, –78 °C
2) Me₂S, –78 °C → 23 °C
3) LAH, THF, 0 °C
4) Ac₂O, pyridine
DMAP, 0 °C → 23 °C
OAc
R
OAc
(S)-(41) R = cyclohexyl
(R)-(43) R = n-nonyl

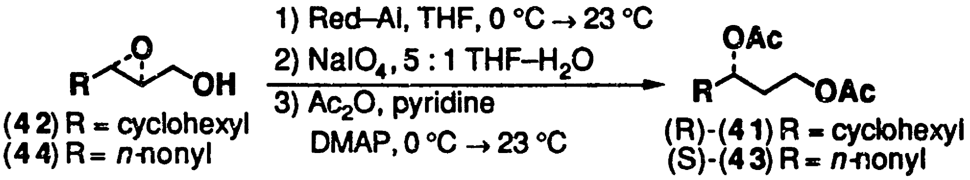
2. Procedure for the Synthesis of 1,3-Diacetates (S)-(41) and (R)-(43) from Homoallylic Acetates (S)-(107) and (R)-(108).

Procedure: A solution of 0.19 mmol (37 mg) of (S)-(**107**) in 10 mL of dry CH_2Cl_2 at –78 °C 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 [marked by the disappearance of the blue coloration]. Dimethylsulfide (1 mL, 13.6 mmol) was added, and the mixture was allowed to warm to room temperature.

Solvent was removed *in vacuo*, and then the ozonide was redissolved 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 mixture was allowed to warm to room temperature. 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 which was dissolved in 1 mL of pyridine. The mixture was treated with DMAP and cooled to 0 °C before 5.3 mmol of acetic anhydride was added. After being stirred for 14 h, the reaction mixture was concentrated *in vacuo* followed by repeated co-evaporation with heptane to remove pyridine and acetic acid. The resulting crude product was purified by PTLC (0.5 mm silica gel plate) using 3 : 1 hexane–Et_2O as eluant. This provided 20 mg [47% overall yield] of the desired diacetate (S)-(**41**). Diacetate (R)-(**43**) was similarly prepared in 54% yield starting from (R)-(**108**).

Data for (S)-3-cyclohexyl-1,3-diacetoxypropane (41): $[\alpha]_D^{20}$ –24.9° (c = 0.35, CH_2Cl_2); *^1H NMR* [$CDCl_3$, 300 MHz] δ 4.86–4.79 [m, 1H], 4.07–4.02 [m, 2H], 2.02–0.82 [series of overlapping s and m, 21H]; *IR* (neat) 2920, 2850, 1740, 1450, 1365, 1230, 1040 cm^{-1}; *HRMS* [CI] for $C_{13}H_{22}O_4$ *M + 1 calcd.*: 243.1596, *obsvd.*: 243.1604; R_f 0.36 [3 : 1 hexane-ether; PMA/char]

Data for (R)-1,3-Diacetoxydodecane (43): $[\alpha]_D^{20}$ –6.90°(c = 1.07, CH_2Cl_2); *^1H NMR* [$CDCl_3$, 300 MHz] δ 4.96 [quint, 1H], 4.07 [t, J = 6.0 Hz, 2H], 2.01 [s, 6H], 1.92–1.88 [m, 2H], 1.60–1.16 [series of br m, 16H], 0.86 [t, J = 6.0 Hz, 3H]; *IR* (neat) 2920, 2850, 1740, 1465, 1365, 1230, 1040 cm^{-1}; *HRMS* [CI] for $C_{16}H_{30}O_4$ *M - 59 calcd.*: 227.2011, *obsvd.*: 227.2007; R_f 0.29 [3 : 1 hexane-ether; PMA/char]

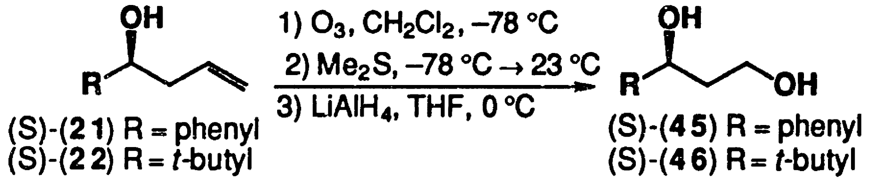


3. Procedure for the Synthesis of 1,3-Diacetates (R)-(41) and (S)-(43) from Epoxyalcohols (42) and (44).

Procedure: A solution of 108 mg (0.53 mmol) of epoxyalcohol (44) [(R,R)-DIPT derived][32, 33] 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. After being stirred for another 2 h, the reaction was quenched by the addition of 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 which was taken up in 6 mL 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 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 co-evaporation with heptane [4 x 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 (S)-(**43**) that was enantiomeric to the sample produced from homoallylic alcohol (R)-(**23**). An authentic reference sample of (R)-(**41**) was similarly prepared from (R,R)-DIPT derived (**42**) (50% overall yield). The sample of (R)-(**41**) so obtained was enantiomeric to (S)-(**41**) prepared by degradation of homoallylic alcohol (S)-(**20**).

Data for (R)-3-cyclohexyl-1,3-diacetoxypropane (41): $[\alpha]^{20}_D$ +31.1° (c = 0.83, CH_2Cl_2); *^1H NMR* [$CDCl_3$, 300 MHz] δ 4.86–4.80 [m, 1H], 4.07–4.02 [m, 2H], 2.07–0.91 [series of overlapping s and m, 21H]; *IR* (neat) 2930, 2850, 1740, 1450, 1365, 1240, 1040 cm^{-1}; *HRMS* [CI] for $C_{13}H_{22}O_4$ *M + 1 calcd.*: 243.1596, *obsvd.*: 243.1593; R_f 0.32 [3 : 1 hexane-ether; PMA/char]

Data for (S)-1,3–Diacetoxydodecane (43): $[\alpha]^{20}_D$ +11.0° (c = 0.95, CH_2Cl_2); *^1H NMR* [$CDCl_3$, 300 MHz] δ 4.96 [br quint, 1H], 4.08 [t, J = 7.2 Hz, 2H], 2.03 [s, 6H], 1.94–1.79 [m, 2H], 1.62–1.43 [br m, 14H], 0.86 [t, J = 6.0 Hz, 3H]; *IR* (neat) 2929, 2857, 1742, 1467, 1367, 1240, 1044, 1020 cm^{-1}; *HRMS* [CI] for $C_{16}H_{30}O_4$ *M + 1 calcd.*: 287.2222, *obsvd.*: 287.2234; *M – 59 calcd.*: 227.2011, *obsvd.*: 227.2010; R_f 0.29 [3 : 1 hexane-ether; PMA/char]



(S)-(**21**) R = phenyl
(S)-(**22**) R = *t*-butyl

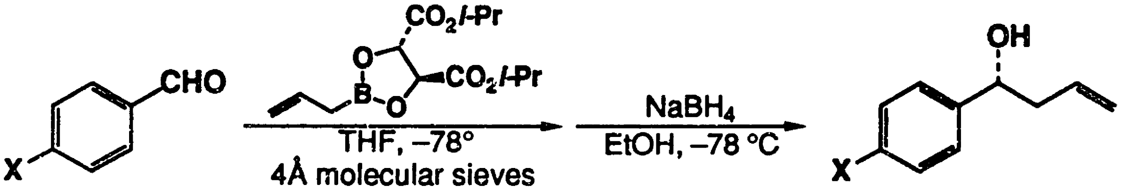
(S)-(**45**) R = phenyl
(S)-(**46**) R = *t*-butyl

Procedure for the Preparation of 1,3-Diols (S)-(45) and (S)-(46) from Homoallylic Alcohols (S)-(21) and (S)-(22).

Procedure: A solution of 55 mg (0.37 mmol) of (S)-1-phenylbut-3-en-1-ol (**21**) in 1 mL of dry CH_2Cl_2 was cooled to –78 °C. The reaction vessel was then flushed sequentially with N_2 followed by O_2. Ozone was bubbled through the solution for a few min at a time; the progress of the reaction was monitored closely by TLC. When all the starting material had been consumed, 1.9 mmol of Me_2S were added, and the reaction mixture was allowed to warm slowly to room temperature. Solvent and excess Me_2S were stripped off *in vacuo*. The resulting crude material was taken up in 5 mL of dry THF before cooling to 0 °C. The mixture was then treated with 6.85 mmol (260 mg) of $LiAlH_4$. After stirring for 2 h, the mixture was quenched with 1 mL of H_2O and 3 mL of 1 N NaOH. The resulting granular solids were removed by filtration; the filtrate was concentrated *in vacuo*. The crude material was purified by PTLC (0.5 mm silica gel plate) using Et_2O as eluant, giving 7 mg (12% yield) of (S)-(**45**). The diol so obtained was found to be identical to (S)-(**45**) reported in the literature.[36] Similarly, (S)-(**46**) was prepared from (S)-(**22**) (65% yield) and was identical to (S)-(**46**) reported in the literature.[25]

Data for (S)-1-Phenylpropane-1,3-diol (45): $[\alpha]^{20}_{D}$ −20.5° (c = 0.66, $CHCl_3$); *1H NMR* [$CDCl_3$, 300 MHz] δ 7.41–7.29 [m, 5H], 5.03–4.99 [m, 1H], 3.92 [q, J = 5.1 Hz, 2H], 2.73 [d, J = 3.3 Hz, 1H], 2.28 [t, J = 5.1 Hz, 1H], 2.09–1.98 [m, 2H]; *IR* ($CHCl_3$ solution) 3610 (sharp), 3600 (sharp), 3490 (br), 3010, 2930, 2850, 1450, 1050 cm^{-1}; *HRMS* [CI] for $C_9H_{12}O_2$ M^+ *calcd.*: 152.0837, *obsvd.*: 152.0841; R_f 0.12 [3 : 1 hexane-ether; UV, PMA/char]

Data for (S)-4,4-Dimethylpentane-1,3-diol (46): $[\alpha]^{20}_{D}$ −15.0°, $[\alpha]^{20}_{546}$ −17.7° (c = 2.49, $CHCl_3$); *1H-NMR* [$CDCl_3$, 300 MHz] δ 3.89–3.84 [m, 2H], 3.50 [d, J = 10.2 Hz, 1H], 2.62 [br s, 1H], 1.73–1.57 [overlapping m, 2H], 0.92 [s, 9H]; *IR* ($CHCl_3$ solution) 3630 (sharp), 3450 (br), 2960, 2870, 1055; *HRMS* (Submitted); *Elemental analysis* (Submitted); R_f 0.30 [Et_2O; I_2]



(47) X = Me
(48) X = MeO
(49) X = Br
(50) X = NO_2

(R)-(51) X = Me
(R)-(52) X = MeO
(R)-(53) X = Br
(R)-(54) X = NO_2

Allylborations of *p*-Substituted Benzaldehydes (47)–(50).

Procedure: The procedure described for the allylboration of cyclohexanecarboxaldehyde was followed, with the exception that the reactions were run in THF rather than toluene.

Data for (R)-1-(4'-Methylphenyl)but-3-en-1-ol (51):[40] (Obtained in 70% yield using (S,S)-(**13**)) $[\alpha]^{20}_{D}$ +41.4°, $[\alpha]^{20}_{546}$ +49.5° (c = 1.10, $CHCl_3$); *^1H NMR* [$CDCl_3$, 300 MHz] δ 7.24 [d, J = 7.20 Hz, 2H], 7.14 [d, J = 7.20 Hz, 2H], 5.87–5.72 [m, 1H], 5.18–5.10 [m, 2H], 4.72–4.66 [m, 1H], 2.50 [t, J = 6.0 Hz, 2H] 2.33 [s, 3H], 1.94 [d, J = 3.0 Hz, 1H]; *IR* (neat) 3380 (br), 3075, 3010, 2978, 2920, 1640, 1515, 1105, 1042, 992, 912, 870, 815 cm^{-1}; *HRMS* [CI] for $C_{11}H_{14}O$ *M – 17 calcd.*: 145.1017, *obsvd.*: 145.1010; *M - 18 calcd.*: 144.0939, *obsvd.*: 144.0938; R_f 0.28 [3 : 1 hexane-ether; UV, PMA/char]

The enantiomeric excess of (R)-(**51**) was determined by integration of the signals from ^{19}F NMR (282.2 MHz) analysis of the corresponding (R)-MTPA ester derivative:[9] (R,R)-isomer δ –71.74, (R,S)-isomer δ –71.94. (ii) Analysis and resolution of the corresponding methyl ether derivative by chiral capillary GC.[13] The (R)-enantiomer is faster eluting (t_R 8.2 min) than its (S)-

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[40] Smith, G. G.; Voorhees, K. J. *J. Org. Chem.* **1970**, *35*, 2182.

enantiomer (t_R 11.1 min; 90 °C/30 psi; Ni-4-pin).

Data for (R)-1-(4'-Methoxyphenyl)but-3-en-1-ol (52):[40] (Obtained in 80% yield using (S,S)-(**13**)) $[\alpha]^{20}_{D}$ +40.9°, $[\alpha]^{20}_{546}$ +49.5° (c = 1.55, $CHCl_3$); *^{1}H NMR* [$CDCl_3$, 250 MHz] δ 7.30–7.23 [m, 2H], 6.92–6.85 [m, 2H], 5.88–5.70 [m, 1H], 5.19–5.09 [m, 2H], 4.68 [td, J = 2.9 Hz, J = 7.08 Hz,1H], 3.81 [s, 3H], 2.48 [t, J = 7.08 Hz, 2H], 1.94 [br d, J = 2.9 Hz]; *IR* (neat) 3404 (br), 3075, 3002, 2938, 2910, 2839, 1640, 1612, 1586, 1522, 1465, 1442, 1302, 1248, 1175, 1035, 1000, 917, 870, 831 cm^{-1}; *HRMS* [CI] for $C_{11}H_{14}O_2$ *M – 18 calcd.*: 160.0888, *obsvd.*: 160.0877; R_f 0.17 [3 : 1 hexane-ether; UV,PMA/char]

The enantiomeric excess of (R)-(**52**) was determined by integration of the signals from ^{19}F NMR (282.2 MHz) analysis of the corresponding (R)-MTPA ester derivative:[9] (R,R)-isomer δ –71.46, (R,S)-isomer δ –71.69.

Data for (R)-1-(4'-Bromophenyl)but-3-en-1-ol (53):[41] (Obtained in 82% yield using (S,S)-(**13**)) $[\alpha]^{20}_{D}$ +37.5°, $[\alpha]^{20}_{546}$ +45.2° (c = 2.52, $CHCl_3$); *^{1}H NMR* [$CDCl_3$, 300 MHz] δ 7.46 [d, J = 7.90 Hz, 2H], 7.21 [d, J = 8.1 Hz, 2H], 5.83–5.69 [m, 1H], 5.18–5.11 [m, 2H], 4.67 [t, J = 6.47 Hz, J = 5.9 Hz, 1H], 2.51–2.34 [m, 2H], 2.30 [br s, 1H]; *IR* (neat) 3380 (br), 3078, 2979, 2932, 2905, 1641, 1592, 1490, 1405, 1100, 1070, 1010, 919, 870, 825, 775, 738, 716 cm^{-1}; *HRMS* [CI] for $C_{10}H_{11}BrO$ *M – 17 calcd.*: 210.9946 (^{81}Br), *obsvd.*: 210.9949; *M – 17 calcd.*: 208.9966 (^{79}Br), *obsvd.*: 208.9961; *M – 18 calcd.*: 207.9887 (^{79}Br), *obsvd.*: 207.9888; R_f 0.25 [3 : 1 hexane-ether; UV, PMA/char]

The enantiomeric excess of (R)-(**53**) was determined by integration of the signals from ^{19}F NMR (282.2 MHz) analysis of the corresponding (R)-MTPA ester derivative:[9] (R,R)-isomer δ –71.62, (R,S)-isomer δ –71.81. (ii) Analysis and resolution of the corresponding methyl ether derivative by chiral capillary GC.[13] The (R)-enantiomer is faster eluting (t_R 5.1 min) than its (S)-enantiomer (t_R 7.0 min; 90 °C/30 psi; Ni-4-pin).

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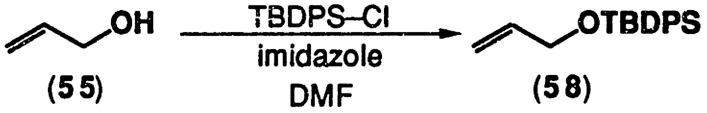
[41] Ropp, G. A.; Coyner, E. C. *J. Am. Chem. Soc.* **1950**, *72*, 3960.

Data for (R)-1-(4'-Nitrophenyl)but-3-en-1-ol (54): (Obtained in 73% yield using (S,S)-(**13**)) $[\alpha]_D^{20}$ +44.5°, $[\alpha]_{546}^{20}$ +52.8° (c = 1.89, CHCl$_3$); *^1H NMR* [CDCl$_3$, 250 MHz] δ 8.20 [d, J = 8.33 Hz, 2H], 7.53 [d, J = 8.33 Hz, 2H], 5.86–5.69 [m, 1H], 5.21–5.14 [m, 2H], 4.85 [quint,1H], 2.60–2.37 [m, 2H], 2.18 [d, J = 4.17 Hz, 1H]; *IR* (neat) 3420 (br), 3069, 2980, 2938, 2910, 1641, 1607, 1520, 1347, 1107, 1054, 1011, 992, 920, 855, 752, 700 cm^{-1}; *HRMS* [CI] for $C_{10}H_{11}NO_3$ *M + 1 calcd.*: 193.0817, *obsvd.*: 194.0813; R_f 0.12 [3 : 1 hexane-ether; UV, PMA/char]

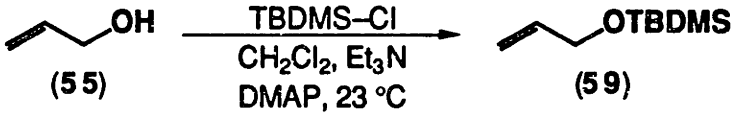
The enantiomeric excess of (R)-(**54**) was determined (i) by integration of the aromatic proton signals (α to the NO$_2$ group) from ^1H NMR (300 MHz) analysis of the corresponding (R)-MTPA ester derivative:[9] (R,R)-isomer δ 8.21 (d), (R,S)-isomer δ 8.15 (d).



Synthesis of 1-(*t*-Butyldiphenylsilyloxy)prop-2-ene (58).

Procedure: A solution 29 mmol (1.7 g) of allyl alcohol (**55**) in 20 mL of dry DMF was treated with 36 mmol (2.5 g) of imidazole and 30 mmol (8.8 g) of TBDPS-Cl. Stirring was continued for 4 h during which the reaction mixture turned cloudy. The mixture was then filtered, and the clear filtrate was added to saturated

NaCl–Et_2O. The aqueous phase was separated and extracted with Et_2O (3 x 25 mL). The combined organic layers were dried over anhydrous Na_2SO_4. The extracts were filtered and then concentrated *in vacuo*. The crude material (11.4 g) was purified by chromatography on a column of silica gel [70 x 200 mm] using 60 : 1 hexane–Et_2O as eluant, giving 7.08 g (82% yield) of TBDPS ether (**58**): *^1H NMR* [$CDCl_3$, 300 MHz] δ 7.72–7.68 [m, 4H], 7.47–7.36 [m, 6H], 6.00–5.88 [m, 1H], 5.40 [dq, J = 17.3 Hz, J = 1.95 Hz, J = 1.91 Hz, 1H], 5.13 [dq, J = 10.6 Hz, J = 2.04 Hz, J = 2.09 Hz, 1H], 4.24–4.21 [m, 2H], 1.08 [s, 9H]; *IR* (neat) 3060, 2950, 2920, 2850, 1470, 1425, 1110, 820, 700 cm^{-1}; *HRMS* [CI] for $C_{19}H_{24}OSi$ *M - 40 calcd.*: 256.1283, *obsvd.*: 256.1240; R_f 0.45 [3 : 1 hexane-ether; UV, I_2]



Synthesis of 1–(*t*-Butyldimethylsilyloxy)prop-2-ene (59).

Procedure: A solution of 29 mmol (1.7 g) of allyl alcohol (**55**) in 50 mL of dry CH_2Cl_2, containing 36 mmol (4.4 mL) of dry triethylamine was treated with 33 mmol (5 g) of TBDMS-Cl and a few crystals of DMAP. The reaction mixture turned cloudy orange after a few minutes and was stirred overnight. It was then filtered through a pad of silica gel, and the filtrate was concentrated *in vacuo*. The resulting crude substance was purified by chromatography on a column of silica gel [50 x 150 mm] using 25 : 1 hexane–Et_2O, giving 4.09 g [82% yield] of the TBDMS ether (**59**):[42] *^1H NMR* [$CDCl_3$, 300 MHz] δ 5.93–5.88 [m, 1H], 5.27 [dq, J = 17.2 Hz, J = 6 Hz, J = 2.1 Hz, 1H], 5.09 [dq, J = 10.2 Hz, J = 3.6 Hz, J = 1.5 Hz, 1H], 4.19–4.16 [m, 2H], 0.92 [s,

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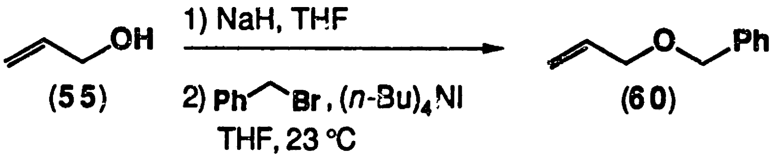
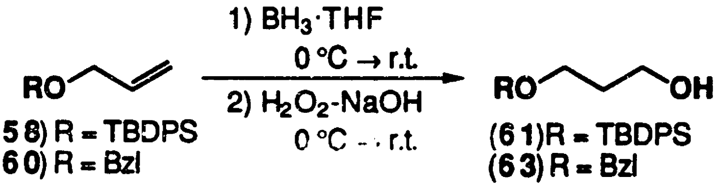
[42] Scheller, M. E.; Frei, B. *Helv. Chim. Acta* **1986**, *69*, 44.

9H], 0.08 [s, 6H]; *IR* (neat) 2960, 2930, 2870, 1645, 1470, 1465, 1365, 1255, 1140, 1085, 835 cm^{-1}; *HRMS* [CI] for $C_9H_{20}OSi$ *M - 57 calcd.*: 115.0579, *obsvd.*: 115.0594; R_f 0.75 [3 : 1 hexane-ether; I_2, PMA/char]



Synthesis of 1-Benzyloxyprop-2-ene (60).

Procedure: An excess of NaH [56.8% in oil] was added to 29 mmol (1.7 g) of allyl alcohol (**55**) in 50 mL of dry THF. This solution was then treated with 34 mmol (5.75 g) of benzyl bromide and a few crystals of tetrabutylammonium iodide, and stirred overnight at room temperature. The reaction mixture was quenched with 25 mL of H_2O. The two layers were separated, and the aqueous phase was saturated with NaCl prior to extracting with Et_2O (3 x 25 mL). The combined organic layers were dried over anhydrous Na_2SO_4, and then filtered. Removal of solvent *in vacuo* gave 5.68 g of crude material which was purified by chromatography on a column of silica gel [50 x 150 mm] using hexane followed by 10 : 1 hexane–EtOAc. The benzyl ether (**60**) was isolated as a clear, pale yellow liquid (3.15 g, 73% yield): *^{1}H NMR* [$CDCl_3$, 300 MHz] δ 7.38–7.27 [overlapping m, 5H], 6.03–5.91 [m, 1H], 5.33 [dd, J = 18.7 Hz, J = 3.2 Hz, 1H], 5.22 [d, J = 11.3 Hz, 1H], 4.55 [s, 2H], 4.05 [d, J = 5.4 Hz, 2H]; *HRMS* [EI] for $C_{10}H_{12}O$ *M – 43 calcd.*: 105.0340, *obsvd.*: 105.0311; R_f 0.47 [5 : 1 hexane-ether; UV, I_2]

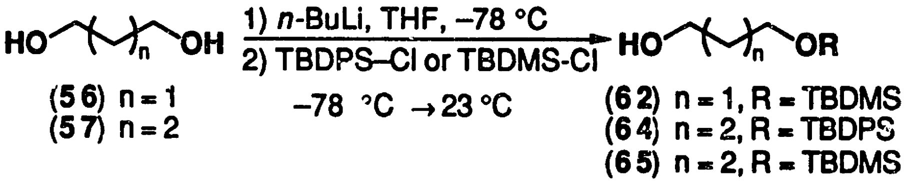


Procedure for the Hydroboration of Allyl Ethers (58) and (60): Synthesis of 3-(*t*-Butyldiphenylsilyloxy)propanol (61) and 3-Benzyloxypropanol (63) .

Procedure: A solution of 5.8 mmol (1.72 g) of 1-(*t*-butyldiphenylsilyloxy)prop-2-ene (**58**) in 10 mL of dry THF was cooled to 0 °C and 1.9 mmol of BH_3·THF (1 M solution in THF) was added dropwise. The resulting mixture was allowed to warm to room temperature and was stirred for 3 h. It was then cooled to 0 °C, and 5 mL of MeOH was added. Effervescence was observed. When the bubbling had subsided, 5 mL of H_2O_2 (30% aq. solution) and 5 mL of 3 M NaOH were added simultaneously. The reaction mixture turned cloudy. Et_2O (5 mL) was added, and the two-phased mixture was stirred for 1.5 h before being separated. The aqueous layer was extracted with Et_2O (2 x 20 mL). The combined organic layers were washed sequentially with brine and sat. $NaHSO_3$ before being dried over anhydrous Na_2SO_4. The extracts were filtered and concentrated by rotary evaporation. The crude material was purified by column chromatography (50 mm x 140 mm column) using 3 : 1 hexane-ether as eluant to provide 0.58 g (32% yield) of the desired alcohol (**61**). Alcohol (**63**) was similarly prepared in 30% yield starting from (**60**).

Data for 1-(*t*-Butyldiphenylsilyloxy)propan-3-ol (61): *^1H NMR* [$CDCl_3$, 300 MHz] δ 7.67 [d, J = 8.0 Hz, 4H], 7.45–7.33 [m, 6H], 3.71–3.63 [m, 4H], 2.00 [br s, 1H], 1.72–1.56 [m, 4H], 1.06 [s, 9H]; *IR* (neat) 3320 (br), 3065, 2930, 2855, 1470, 1428, 1390, 1110, 820, 700 cm^{-1}; R_f 0.25 [3 : 1 hexane-ether; UV, I_2]

Data for 1-Benzyloxypropan-3-ol (63):[43] *^1H NMR* [$CDCl_3$, 300 MHz] δ 7.35–7.27 [m, 5H], 4.52 [s, 2H], 3.83–3.75 [m, 2H], 3.70–3.63 [m, 2H], 2.28 [t, J = 5.0 Hz, 1H], 1.93–1.83 [m, 2H]; *IR* (neat) 3360 (br), 3075, 3050, 3020, 2930, 2860, 1495, 1455, 1360, 1200, 1095, 1025, 735, 695 cm^{-1}; *HRMS* [CI] for $C_{10}H_{14}O_2$ *M + 1 calcd.*: 167.1072, *obsvd.*: 167.1076; *M^{+} calcd.*: 166.0994, *obsvd.*: 166.0978; R_f 0.20 [3 : 1 hexane-ether; UV, PMA/char]



Procedure for the Preparation of Alkoxyalcohols (62), (64), and (65).

Procedure: To a solution of 28 mmol (2.5 g) of 1,4-butanediol (57) in 50 mL of dry THF at –78 °C was added 28 mmol of *n*-butyllithium [1.6 M in hexane] followed by 28 mmol (7.7 g) of TBDPS-Cl. Stirring was continued for 15 min at –78 °C then the reaction mixture was allowed to warm to room temperature and then was heated to 45 °C. After being stirred for 4 h, the cooled mixture was concentrated *in vacuo*, then added to Et_2O–saturated NaCl. The aqueous layer was separated and extracted with Et_2O (3 x 25 mL). The combined organic layers were dried over anhydrous Na_2SO_4. Filtration to remove the drying agent followed by solvent removal *in vacuo* gave 10.5 g of clear, pale yellow liquid which was purified by chromatography on a column of silica gel [40 x 190 mm] using 7 : 1 hexane–Et_2O, giving 8.48 g [92% yield] of the desired product (64).[44] Alcohols (62) (90% yield starting from 1,3-propanediol (56)) and (**65**) (94% yield starting from 1,4-butanediol (**57**)) were prepared in a similar manner.

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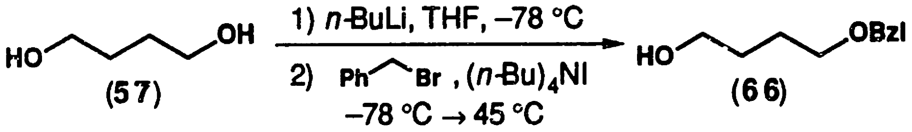
[43] Gennari, C.; Cozzi, P. G. *J. Org. Chem.* **1988**, *53*, 4015.

[44] (a) Roush, W. R.; Gillis, H. R.; Essenfeld, A. P. *J. Org. Chem.* **1984**, *49*, 4674. (b) Roush, W. R.; Blizzard, T. A. *Ibid.* **1984**, *49*, 1772. (See in particular ref. 23 cited therein) (c) McDougal, P. G.; Rico, J. G.; Oh, Y. I.; Condon, B. D. *Ibid.* **1986**, *51*, 3388.

Data for 1-(*t*-Butyldimethylsilyloxy)propan-3-ol (62):[45] *1H NMR* [$CDCl_3$, 300 MHz] δ 3.85–3.77 [m, 4H], 2.60 [t, J = 6.0 Hz, 1H], 1.82–1.74 [q, 2H], 0.93 [s, 9H], 0.10 [s, 6H]; *IR* (neat) 3370 (br), 2940, 2860, 1470, 1255, 1090, 840, 775 cm^{-1}; *HRMS* [CI] for $C_9H_{22}O_2Si$ *M + 1 calcd.*: 190.1467, *obsvd.*: 191.1463; R_f 0.36 [3 : 1 hexane-ether; PMA/char]

Data for 1-(*t*-Butyldiphenylsilyloxy)butan-4-ol (64): *1H NMR* [$CDCl_3$, 300 MHz] δ 7.67 [d, J = 8.0 Hz, 4H], 7.45–7.33 [m, 6H], 3.71–3.63 [m, 4H], 2.00 [br s, 1H], 1.72–1.56 [m, 4H], 1.06 [s, 9H]; *IR* (neat) 3320 (br), 3065, 2930, 2855, 1470, 1428, 1390, 1110, 820, 700 cm^{-1}; R_f 0.25 [3 : 1 hexane-ether; UV, I_2]

Data for 1-(*t*-Butyldimethylsilyloxy)butan-4-ol (65):[46] *1H NMR* [$CDCl_3$, 300 MHz] δ 3.69–3.63 [m, 4H], 2.57 [br s, 1H], 1.68–1.61 [m, 4H], 0.90 [s, 9H], 0.07 [s, 6H]; *IR* (neat) 3040, 2920, 2850, 1470, 1250, 1110, 835, 775 cm^{-1}; *HRMS* [CI] for $C_{10}H_{24}O_2Si$ *M + 1 calcd.*: 204.1624, *obsvd.*: 205.1611; R_f 0.08 [5 : 1 hexane-ether; PMA/char]



Procedure for the Preparation of 1-Benzyloxybutan-4-ol (66) from 1,4-Butanediol (57).

Procedure: A solution of 10.3 mmol (0.93 g) of 1,4-butanediol (**57**) in 50 mL of dry THF was cooled to –78 °C and then treated with 10.3 mmol *n*-BuLi (as a 1.6 M solution in hexane). After stirring for 15 min, 10.1 mmol (1.73 g) of benzyl bromide was added followed by a few crystals of $(n\text{-Bu})_4NI$. The reaction mixture was allowed to warm to room temperature and then heated to 45 °C. The reaction mixture was stirred overnight then concentrated *in vacuo* and added to 1 : 1 Et_2O-sat. NaCl. The aqueous layer was separated and extracted with Et_2O (3 x 25 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude liquid was purified by column chromatography (30 mm x 140 mm) using 2 : 1 ether-hexane as eluant, giving 0.76 g (42% yield) of the alcohol (66):[47] *^{1}H NMR* [$CDCl_3$, 300 MHz] δ 7.39–7.16 [m, 5H], 4.53 [s, 2H], 3.66 [q, J = 6.4 Hz, 2H], 3.53 [t, J = 6.4 Hz, 2H], 2.18 [t, J = 5.6 Hz, 1H], 1.76–1.68 [m, 4H]; *IR* (neat) 3380 (br), 3090, 3070, 3030, 2940, 2860, 1495, 1455, 1355, 1095, 1060, 735, 695 cm^{-1}; *HRMS* [CI] for $C_{11}H_{16}O_2$ *M + 1 calcd.*: 181.1228, *obsvd.*: 181.1217; *M^{+} calcd.*: 180.1150, *obsvd.*: 180.1159; R_f 0.15 [1 : 1 hexane-ether; UV, PMA/char]

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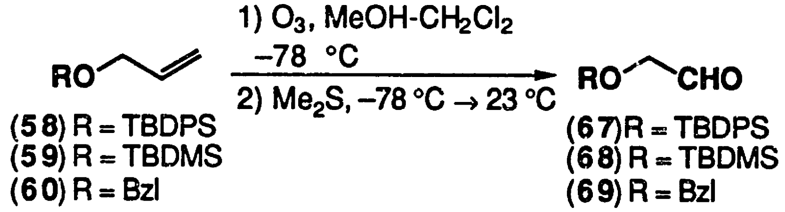
[45] Trost, B. M.; Verhoeven, T. R. *J. Am. Chem. Soc.* **1980**, *102*, 4743. See also ref. 44c

[46] Ikeda, Y.; Ukai, J.; Ikeda, N.; Yamamoto, H. *Tetrahedron* **1987**, *43*, 731 and refs. cited therein.



(58) R = TBDPS
(59) R = TBDMS
(60) R = Bzl

(67) R = TBDPS
(68) R = TBDMS
(69) R = Bzl

Procedure for Ozonolysis of Allyl Ethers (58)–(60): Preparation of α-Alkoxyaldehydes (67)–(69).

Procedure: A solution of 6.1 mmol (1.05 g) of 1-(*t*-butyldimethylsiloxy)prop-2-ene (59) in 13 mL of MeOH and 4 mL of CH_2Cl_2 was cooled to –78 °C, and treated with a stream of O_3 in O_2 until all of (59) had been consumed (TLC analysis). The reaction vessel was then flushed with N_2 to remove excess O_3, and 30.6 mmol (2.25 mL) of Me_2S was added. The reaction mixture was allowed to warm to room temperature, and then it was poured into 1 : 1 sat. NaCl-Et_2O. The two phases were separated, and the aqueous layer was extracted with Et_2O (2 x 20 mL). The combined organic phases were dried over anhydrous Na_2SO_4 and filtered to remove the drying agent. Concentration of the filtrate by rotary evaporation gave the crude aldehyde that was subsequently purified by chromatography on a column of silica gel (40 mm x 90 mm) using 3 : 1 hexane-ether to give 1.0 g (94% yield) of **(68)**. Aldehydes **(67)** and **(69)** were similarly prepared in 99% and 61% yields by ozonolysis of **(58)** and **(60)**, respectively.

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[47] Parker, K. A.; Iqbal, T. *J. Org. Chem.* **1987**, *52*, 4369.

Data for 2-(*t*-Butyldiphenylsilyloxy)ethan-1-al (67): *^1H NMR* [$CDCl_3$, 300 MHz] δ 9.73 [s, 1H], 7.74–7.61 [m, 4H], 7.46–7.34 [m, 6H], 4.22 [s, 2H], 1.08 [s, 9H]; *IR* (neat) 3060, 3040, 2960, 2930, 2890, 2850, 2700 (w),1740, 1600, 1470, 1430, 1360, 1110, 820, 740, 700, 610 cm^{-1}; *HRMS* [CI] *M – 57 calcd.*: 241.0685, *obsvd.*: 241.0659; R_f 0.37 [3 : 1 hexane-ether; UV, vanillin/char]

Data for 2-(*t*-Butyldimethylsilyloxy)ethan-1-al (68): *^1H NMR* [$CDCl_3$, 300 MHz] δ 9.70 [s, 1H], 4.22 [s, 2H], 0.93 [s, 9H], 0.11 [s, 6H]; *IR* (neat) 2960, 2930, 2880, 2860, 2710, 1740, 1470, 1250, 1125, 835, 775 cm^{-1}; *HRMS* [CI] for $C_8H_{18}O_2Si$ *M + 1 calcd.*: 175.3254, *obsvd.*: 175.1151; R_f 0.28 [3 : 1 hexane-ether; vanillin/char]

Data for 2-Benzyloxyethan-1-al (69):[48] *^1H NMR* [$CDCl_3$, 300 MHz] δ 9.73 [s, 1H], 7.38–7.30 [m, 5H], 4.64 [s, 2H], 4.13 [s, 2H]; *IR* (neat) 3060, 3030, 2920,

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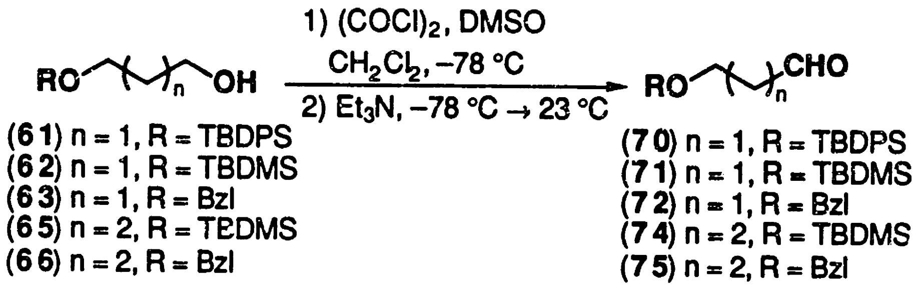
[48] Arndt, H. C.; Carroll, S. A. *Synthesis* **1979**, 202.

2860, 1725, 1495, 1450, 1270, 1100, 740, 700 cm^{-1}; *HRMS* [CI] for $C_9H_{10}O_2$ *M – 43 calcd.*: 107.0497, *obsvd.*: 107.0496; R_f 0.24 [1 : 1 hexane-ether; UV, PMA/char]


1) (COCl)2, DMSO
CH2Cl2, –78 °C
2) Et3N, –78 °C → 23 °C
RO
OH
n
CHO
(61) n = 1, R = TBDPS
(62) n = 1, R = TBDMS
(63) n = 1, R = Bzl
(65) n = 2, R = TBDMS
(66) n = 2, R = Bzl
(70) n = 1, R = TBDPS
(71) n = 1, R = TBDMS
(72) n = 1, R = Bzl
(74) n = 2, R = TBDMS
(75) n = 2, R = Bzl

Procedure for the Swern Oxidation of β– and γ–Alkoxyalcohols: Preparation of 3-Alkoxypropan-1-als (70)–(72) and 4-Alkoxybutan-1-als (74)–(75).

Procedure: A –78 °C solution of 0.75 mmol (95 mg) of distilled oxalyl chloride in 0.8 mL of dry CH_2Cl_2 was treated with 0.94 mmol of dry DMSO. The solution was stirred for 15 min, then alcohol (**61**) (102 mg, 0.32 mmol) was added dropwise as a solution in 0.4 mL of dry CH_2Cl_2. One hour later, 1.44 mmol (0.2 mL) of dry triethylamine was added. The mixture was then allowed to warm slowly, the progress of the reaction being monitored by TLC. When the bath temperature had reached –15 °C, the reaction was judged to be over, and the mixture was poured into 1 : 1 H_2O–CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2 (2 x 4 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The resulting crude mixture was triturated with Et_2O to remove insoluble amine hydrochloride. Solvent was removed from the triturate to give 112 mg of a pale yellow liquid which was purified by PTLC (2 x 0.5 mm silica gel plates) using 3 : 1 hexane-ether as eluant, giving 96 mg [96% yield] of aldehyde (**70**).

Data for 3-(*t*-Butyldiphenylsilyloxy)propan-1-al (70): *^1H NMR* [$CDCl_3$, 300 MHz] δ 9.83 [t, J = 2.4 Hz, 1H], 7.748–7.64 [m, 4H], 7.47–7.35 [m, 6H], 4.03 [t, J = 5.7 Hz, 2H], 2.61 [td, J = 2.4 Hz, J = 5.7 Hz, 2H], 1.05 [s, 9H]; *IR* (neat) 3070, 2960, 2930, 2890, 2860, 2730 (w), 1725, 1690, 1470, 1425, 1110, 820, 740, 700 cm^{-1}; *HRMS* [CI] for $C_{19}H_{24}O_2Si$ *M + 1 calcd.*: 313.1624, *obsvd.*: 313.1647; R_f 0.37 [3 : 1 hexane-ether; UV]

Data for 3-(*t*-Butyldimethylsilyloxy)propan-1-al (71):[49] (Obtained in 75% yield by oxidation of (**62**)) *^1H NMR* [$CDCl_3$, 300 MHz] δ 9.80 [t, J = 1.9 Hz, 1H], 3.99 [t, J = 6.7 Hz, 2H], 2.60 [td, J = 1.9 Hz, J = 6.7 Hz, 2H], 0.88 [s, 9H], 0.06 [s, 6H]; *IR* (neat) 2950, 2920, 2880, 2850, 1725, 1470, 1255, 1095, 885, 775 cm^{-1}; *HRMS* [CI] for $C_9H_{20}O_2Si$ *M – 57 calcd.*: 131.0528, *obsvd.*: 131.0524; R_f 0.41 [3 : 1 hexane-ether; PMA/char]

Data for 3-Benzyloxypropan-1-al (72):[40] (Obtained in 82% yield by oxidation of (**63**))*^1H NMR* [$CDCl_3$, 300 MHz] δ 9.78 [s, 1H], 7.34–7.28 [m, 5H], 4.52 [s, 2H], 3.80 [t, J = 6.0 Hz, 2H], 2.68 [td, J = 6.0 Hz, J = 3.0 Hz, 2H]; *IR* ($CHCl_3$ solution) 3030, 3005, 2960, 2930, 2870, 1720, 1450, 1090, 700 cm^{-1}; *HRMS* [CI] for $C_{10}H_{12}O_2$ *M + 1 calcd.*: 165.0915, *obsvd.*: 165.0933; *$M^{+\cdot}$ calcd.*: 164.0837, *obsvd.*: 164.0842; R_f 0.14 [3 : 1 hexane-ether; UV, PMA/char]

Data for 4-(*t*-Butyldimethylsilyloxy)butan-1-al (74):[43] (Obtained in 75% yield by oxidation of (**65**))*^1H NMR* [$CDCl_3$, 300 MHz] δ 9.77 [t, J = 1.6 Hz, 1H], 3.64 [t, J = 6.2 Hz, 2H], 2.51–2.44 [m, 2H], 1.88–1.80 [m, 2H], 0.08 [s, 3H], 0.02 [s, 3H]; *IR* (neat) 2950, 2925, 2860, 1715, 1470, 1255, 1110, 835,

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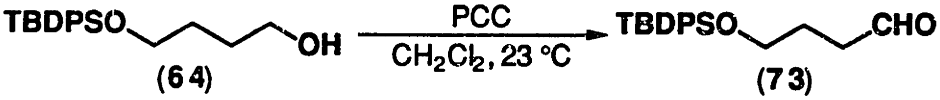
[49] Vijn, R. J.; Hiemstra, H.; Kok. J. J.; Knotter, M.; Speckamp, W. N. *Tetrahedron* **1987**, *43*, 5019.

775 cm^{-1}; R_f 0.52 [3 : 1 hexane-ether; vanillin/char]

Data for 4-Benzyloxybutan-1-al (75):[50] (Obtained in 86% yield by oxidation of (66))*^1H NMR* [$CDCl_3$, 300 MHz] δ 9.79 [t, J = 1.4 Hz, 1H], 7.36–7.31 [m, 5H], 4.49 [s, 2H], 3.51 [t, J = 5.7 Hz, 2H], 2.56 [td, J = 2.4 Hz, J = 7.6 Hz, 2H], 1.95 [quint, 2H]; *IR* (neat) 3060, 3030, 2930, 2860, 2720 (w), 1725, 1495, 1450, 1360, 1100, 735, 700 cm^{-1}; *HRMS* [CI] for $C_{11}H_{14}O_2$ *M + 1 calcd.*: 179.1072, *obsvd.*: 179.1071; Rf 0.53 [2 : 1 ether-hexane; UV, PMA/char]



Synthesis of 4-(*t*-Butyldiphenylsilyloxy)butan-1-al (73) by PCC Oxidation of (64).

Procedure: To a well-stirred solution of 13.5 mmol (4.44 g) of alcohol (64) in 35 mL of dry CH_2Cl_2 was added 16.6 mmol (3.57 g) of PCC. The dark brown solution was diluted with 35 mL of Et_2O after 2.5 h and stirred for another 0.5 h. The resulting mixture was filtered through a pad of Celite, concentrated *in vacuo*, then taken up in 3 : 1 hexane–Et_2O [200 mL]. The solution was filtered through silica gel. Solvent was removed *in vacuo* to give 3.35 g [72% yield] of (73) as a clear, colorless liquid: *^1H NMR* [$CDCl_3$, 300 MHz] δ 9.80 [br s, 1H], 7.67–7.64 [m, 4H], 7.45–7.37 [m, 6H], 3.70 [t, J = 6.0 Hz, 2H], 2.57 [td, J = 7.2 Hz, J = 3.0 Hz, 2H], 1.90 [quint, 2H], 1.06 [s, 9H]; *IR* (neat) 3070, 2950, 2930, 2890, 2860, 2720 (w), 1725, 1470, 1430, 1110, 820, 740, 700 cm^{-1}; R_f 0.39 [3 : 1 hexane-ether; UV, I_2]

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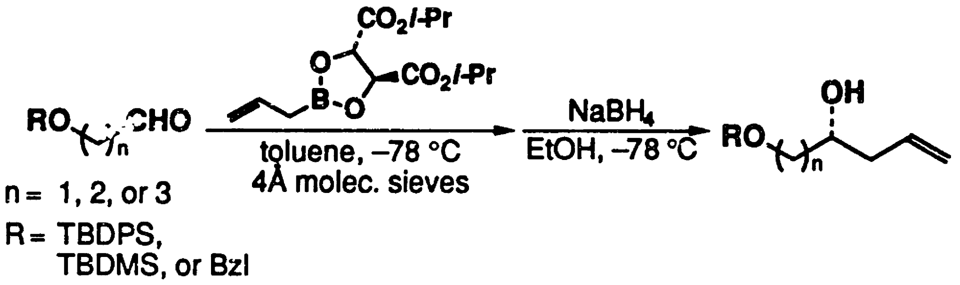
[50] Dawson, M. I.; Vasser, M. *J. Org. Chem.* **1977**, *42*, 2783.



Asymmetric Allylboration of α-, β-, and γ-Alkoxyaldehydes (67)–(75).

Procedure: The asymmetric allylborations of (**67**)–(**75**) were performed using the previously described procedure.

Data for (R)–1–(*t*-Butyldiphenylsiloxy)–2–hydroxypent–4–ene (76): (Obtained in 30% yield from (**67**) and (S,S)-(**13**)) $[\alpha]^{20}_{D}$ +0.8°, $[\alpha]^{20}_{436}$ +2.7°, $[\alpha]^{20}_{365}$ +6.8° (c = 1.0, $CHCl_3$); *^1H NMR* [$CDCl_3$, 300 MHz] δ 7.74–7.66 [overlapping d, J = 7.2 Hz, J = 7.2 Hz, 4H], 7.45–7.37 [m, 6H], 5.87–5.74 [m, 1H], 5.12–5.05 [overlapping d, J = 18.6 Hz, J = 9 Hz, 2H], 3.82–3.77 [br m, 1H], 3.70–3.66 [dd, J = 10.8 Hz, J = 3 Hz, 1H], 3.59–3.53 [dd, J = 10.8 Hz, J = 7 Hz, 1H], 2.48 [d, J = 2.6 Hz, 1H], 2.25 [t, J = 6.51 Hz, 2H], 1.08 [s, 9H]; *IR* (neat) 3565, 3430 (br), 3070, 3045, 2960, 2855, 1640, 1589, 1110 cm^{-1}; *HRMS* [CI] for $C_{21}H_{28}O_2Si$ *M – 17 calcd.*: 323.1831, *obsvd.*: 323.1808; R_f 0.39 [3 : 1 hexane-ether; UV, PMA/char]

The enantiomeric excess of (R)-(**76**) was determined by integration of the following signals from ^1H NMR (500 MHz) analysis of the corresponding (R)-MTPA ester derivative:[9] H(1) (R,R)-isomer δ 5.14–5.03 (m), (R,S)-isomer δ 5.02–4.91 (m); H(2) (R,R)-isomer δ 5.77–5.64 (m), (R,S)-isomer δ 5.63–5.49 (m).

Data for (S)–1–(*t*-Butyldimethylsilyloxy)–2–hydroxypent–4–ene (77): (Obtained in 42% yield from **(68)** and (R,R)-**(13)**) $[\alpha]^{20}_{D}$ +1.7° (c = 0.24, $CHCl_3$); *^{1}H NMR* [$CDCl_3$, 300 MHz] δ 5.91–5.76 [m, 1H], 5.14–5.05 [m, 2H], 5.75–3.65 [m, 1H], 3.63 [dd, J = 10.8 Hz, J = 4.8 Hz, 1H], 3.44 [dd, J = 10.8 Hz, J = 6.0 Hz, 1H], 2.42 [d, J = 4.8 Hz, 1H], 2.24 [t, J = 7.2 Hz, 2H], 0.90 [s, 10 H], 0.07 [s, 6H]; *IR* (neat) 3450 (br), 2960, 2930, 2860, 1730, 1642, 1470, 1465, 1255, 1110, 910, 835, 775, 735 cm^{-1}; *HRMS* [CI] for $C_{11}H_{24}O_2Si$ *M + 1 calcd.*: 217.1624, *obsvd.*: 217.1623; R_f 0.38 [2 : 1 hexane-ether; vanillin/char]

The enantiomeric excess of (S)-**(77)** was determined by integration of the signals from ^{19}F NMR (376.3 MHz) analysis of the corresponding (R)-MTPA ester derivative:[9] (R,S)-isomer δ –72.10, (R,R)-isomer δ –72.19.

Data for (R)–1–Benzyloxy–2–hydroxypent–4–ene (78):[51] (Obtained in 58% yield from **(69)** and (S,S)-**(13)**) $[\alpha]^{20}_{D}$ +1.7°, $[\alpha]^{20}_{546}$ +1.8° (c = 2.27, $CHCl_3$); *^{1}H NMR* [$CDCl_3$, 300 MHz] δ 7.37–7.32 [m, 5H], 5.90–5.77 [m, 1H], 5.16–5.08 [overlapping d, J = 18 Hz, J = 10.8 Hz, 2H], 4.56 [s, 2H], 3.94–3.85 [m, 1H], 3.55–3.51 [dd, J = 10 Hz, J = 3.68 Hz, 1H], 3.41–3.56 [dd, J = 9.3 Hz, J = 7.4 Hz, 1H], 2.37 [d, J = 3.52 Hz, 1H], 2.28 [t, J = 6.6 Hz, 2H]; *IR* (neat) 3435 (br), 3060, 3025, 2910, 2855,1720,1640, 1495, 1451, 1271, 1110, 915, 735, 697 cm^{-1}; *HRMS* [CI] for $C_{12}H_{16}O_2$ *M^+ calcd.*: 192.1150, *obsvd.*: 192.1153; R_f 0.25 [1 : 1 hexane-ether; UV, vanillin/char]

The enantiomeric excess of (R)-**(78)** was determined by integration of the following signals from ^{19}F NMR (376.3 MHz) analysis of the corresponding (R)-MTPA ester derivative:[9] (R,R)-isomer δ –72.17, (R,S)-isomer δ

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[51] Takano, S.; Sekiguchi, Y.; Sato, N.; Ogasawara, K. *Synthesis* **1987**, 139.

–71.95.

Data for (R)–1–(*t*-Butyldiphenylsiloxy)–3–hydroxyhex–5–ene (79):[52] (Obtained in 98% yield from (**70**) and (S,S)-(**13**)) $[\alpha]^{20}_{D}$ +2.2°, $[\alpha]^{20}_{436}$ +5.3°, $[\alpha]^{20}_{365}$ +8.8° (c = 0.49, $CHCl_3$); *^1H NMR* [$CDCl_3$, 300 MHz] δ 7.68 [d, J = 7.2 Hz, 4H], 7.47–7.37 [m, 6H], 5.92–5.78 [m, 1H], 5.13–5.08 [overlapping d, J = 17.1 Hz, J = 10.3 Hz, 2H], 4.0–3.92 [br m, 1H], 3.92–3.79 [m, 2H], 3.25 [br s, 1H], 2.28 [t, J = 6 Hz, 2H], 1.77–1.64 [m, 2H], 1.05 [s, 9H]; *IR* (neat) 3470 (br), 3070, 2930, 2860, 1640, 1590, 1472, 1430, 1110, 910, 820, 735, 700 cm^{-1}; *HRMS* [CI] for $C_{22}H_{30}O_2Si$ *M – 17 calcd.*: 337.1987, *obsvd.*: 337.1983; R_f 0.36 [3 : 1 hexane-ether; UV, PMA/char]

The enantiomeric excess of (R)-(**79**) was determined by integration of the following signals from ^1H NMR (500 MHz) analysis of the corresponding (R)-MTPA ester derivative:[9] H(2) (R,R)-isomer δ 5.67–5.57 (m), (R,S)-isomer δ 5.81–5.70 (m); H(1) (R,R)-isomer δ 5.03–4.96 (m), (R,S)-isomer δ 5.14–5.06 (m).

Data for (S)–1–(*t*-Butyldimethylsilyloxy)–3–hydroxyhex–5–ene (80): (Obtained in 48% yield from (**71**) and (R,R)-(**13**)) $[\alpha]^{20}_{D}$ –4.8°, $[\alpha]^{20}_{436}$ –9.3°, $[\alpha]^{20}_{365}$ –14.5° (c = 0.91, $CHCl_3$); *^1H NMR* [$CDCl_3$, 300 MHz] δ 5.92–5.78 [m, 1H], 5.14–5.08 [overlapping d, J = 18.6 Hz, J = 12 Hz, 2H], 3.94–3.78 [overlapping m, 3H], 3.40 [br s, 1H], 2.31–2.20 [m, 2H], 1.70–1.64 [m, 2H], 0.90 [s, 9H], 0.08 [s, 6H]; *IR* (neat) 3420 (br), 3068, 2950, 2925, 2850, 1638, 1468, 1250, 1085, 998, 908, 830, 770 cm^{-1}; *HRMS* [CI] for $C_{12}H_{26}O_2Si$ *M + 1 calcd.*: 231.1780, *obsvd.*: 231.1773; R_f 0.32 [3 : 1 hexane-ether; vanillin, PMA/char]

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[52] Clive, D. L. J.; Murthy, K. S. K.; Wee, A. G. H.; Prasad, J. S.; da Silva, G. V. J.; Majewski, M.; Anderson, P. C.; Haugen, L. D.; Heerze, L. D. *J. Am. Chem. Soc.* **1988**, *110*, 6914.

The enantiomeric excess of (R)-(**80**) was determined by integration of the following signals from ^{1}H NMR (500 MHz) analysis of the corresponding (R)-MTPA ester derivative:[9] H(1) (R,S)-isomer δ 5.15–5.08 (m), (R,R)-isomer δ 5.06–5.00 (m); H(2) (R,S)-isomer δ 5.83–5.71 (m), (R,R)-isomer δ 5.71–5.60 (m).

Data for (R)-1-Benzyloxy-3-hydroxyhex-5-ene (81):[53] (Obtained in 44% yield from (**72**) and (S,S)-(**13**)) $[\alpha]^{20}_{D}$ +1.5°, $[\alpha]^{20}_{436}$ +3.8°, $[\alpha]^{20}_{365}$ +7.8° (c = 1.12, $CHCl_3$); *^{1}H NMR* [$CDCl_3$, 300 MHz] δ 7.38–7.28 [m, 5H], 5.91–5.78 [m, 1H], 5.14–5.08 [overlapping d, J = 16.3 Hz, J = 10.3 Hz, 2H], 4.53 [s, 2H], 3.92–3.84 [m, 1H], 3.76–3.61 [m, 2H], 2.89 [br s, 1H], 2.25 [t, J = 7.2 Hz, 2H], 1.82 [m, 2H]; *IR* (neat) 3440 (br), 3060, 3030, 2920, 2860, 1745, 1640, 1496, 1454, 1364, 1100, 1026, 995, 910, 732, 698 cm^{-1}; *HRMS* [CI] for $C_{13}H_{18}O_2$ M^{+} *calcd.*: 206.1307, *obsvd.*: 206.1282; R_f 0.36 [1 : 1 hexane-ether; UV, PMA/char]

The enantiomeric excess of (R)-(**81**) was determined by integration of the following signals from ^{1}H NMR (400 MHz) analysis of the corresponding (R)-MTPA ester derivative:[9] H(1) (R,R)-isomer δ 5.06–4.98 (m), (R,S)-isomer δ 5.14–5.08 (m); H(2) (R,R)-isomer δ 5.71–5.58 (m), (R,S)-isomer δ 5.83–5.72 (m); H(benzylic) (R,R)-isomer δ 4.50–4.44 (q), (R,S)-isomer δ 4.43–4.35 (q).

Data for (R)-1-(*t*-Butyldiphenylsiloxy)-4-hydroxyhept-6-ene (82): (Obtained in 52% yield from (**73**) and (R,R)-(**13**)) $[\alpha]^{20}_{D}$ +1.6°, $[\alpha]^{20}_{546}$ +2.0° (c = 0.76, $CHCl_3$); *^{1}H NMR* [$CDCl_3$, 300 MHz] δ 7.67 [dd, J = 7.4 Hz, J = 1.56 Hz, 4H], 7.47–7.36 [m, 6H], 5.92–5.77 [m, 1H], 5.16–5.11 [overlapping d, J = 15.6 Hz, J = 11.7 Hz, 2H], 3.71 [t, J = 2.26 Hz, J = 3.6 Hz, 3H],

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[53] Majewski, M.; Clive, D. L. J.; Anderson, P. C. *Tetrahedron Lett.* **1984**, *25*, 2101.

2.34–2.14 [m, 3H], 1.74–1.45 [overlapping m, 4H], 1.06 [s, 9H]; *IR* (neat) 3400 (br), 3068, 2930, 2855, 1640, 1590, 1472, 1429, 1110, 910, 820, 735, 700 cm^{-1}; *HRMS* [CI] for $C_{23}H_{32}O_2Si$ *M + 1 calcd.*: 369.2250, *obsvd.*: 369.2295; R_f 0.52 [2 : 1 hexane-ether; UV, PMA/char]

The enantiomeric excess of (R)-(**82**) was determined by integration of the H(2) signals from ^{1}H NMR (500 MHz) analysis of the corresponding (R)-MTPA ester derivative:[9] (R,R)-isomer δ 5.81–5.70 (m), (R,S)-isomer δ 5.69–5.57 (m).

Data for (S)–1–(*t*-Butyldimethylsilyloxy)–4–hydroxyhept–6–ene (83): (Obtained in 49% yield from (**74**) and (R,R)-(**13**)) $[\alpha]^{20}_{D}$ +5.1° (c = 1.0, $CHCl_3$); *^{1}H NMR* [$CDCl_3$, 300 MHz] δ 5.91–5.77 [m, 1H], 5.15–5.08 [overlapping d, J = 16.9 Hz, J = 10.4 Hz, 2H], 3.68–3.60 [m, 3H], 2.64 [br s, 1H], 2.32–2.14 [m, 2H], 1.69–1.41 [overlapping m, 4H], 0.90 [s, 9H], 0.08–0.04 [m, 6H]; *IR* (neat) 3380 (br), 2930, 2860, 1645, 1475, 1255, 1095, 1005, 910, 835, 775 cm^{-1}; *HRMS* [CI] for $C_{13}H_{28}O_2Si$ *M + 1 calcd.*: 245.1937, *obsvd.*: 245.1935; R_f 0.18 [3 : 1 hexane-ether; vanillin, PMA/char]

The enantiomeric excess of (R)-(**83**) was determined by integration of the following signals from ^{1}H NMR (500 MHz) analysis of the corresponding (R)-MTPA ester derivative:[9] H(2) (R,R)-isomer δ 5.04–4.94 (m), (R,S)-isomer δ 5.14–5.05 (m); H(3) (R,R)-isomer δ 2.39–2.33 (m), (R,S)-isomer δ 2.46–2.40 (m).

Data for (R)-1-Benzyloxy-4-hydroxyhept-6-ene (84): (Obtained in 39% yield from (**75**) and (R,R)-(**13**)) $[\alpha]^{20}_{D}$ +5.2°, $[\alpha]^{20}_{436}$ +9.6°, $[\alpha]^{20}_{365}$ +13.9° (c = 1.05, $CHCl_3$); *^{1}H NMR* [$CDCl_3$, 300 MHz] δ 7.38–7.27 [m, 5H], 5.91–5.77 [m, 1H], 5.16–5.09 [m, 2H], 4.52 [s, 2H], 3.71–3.63 [m, 1H], 3.52 [t, J = 5.8 Hz, 2H], 2.40–2.14 [overlapping m, 3H], 1.80–1.60 [overlapping m, 2H]; *IR* (neat) 3420 (br), 3070, 3030, 2930, 2860, 1640, 1495, 1455, 1360, 1205, 1100, 1025, 995, 913, 735, 695 cm^{-1}; *HRMS* [CI] for $C_{14}H_{20}O_2$ *M + 1 calcd.*: 221.1542, *obsvd.*: 221.1545; R_f 0.16 [2 : 1 hexane-ether; UV, PMA/char]

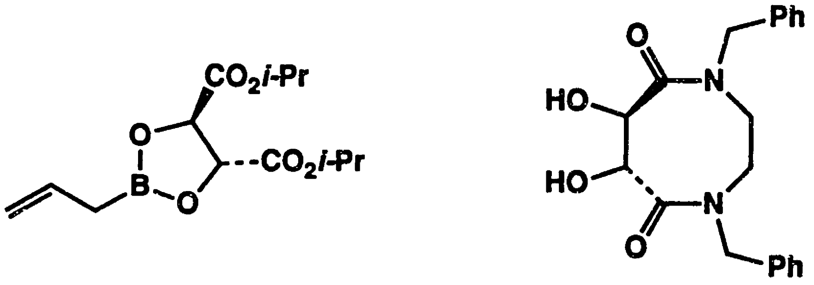
The enantiomeric excess of (R)-(**84**) was determined by integration of the H(2) signals from ^{1}H NMR (500 MHz) analysis of the corresponding (R)-MTPA ester derivative:[9] (R,R)-isomer δ 5.75–5.65 (m), (R,S)-isomer δ 5.62–5.57 (m).

CHAPTER 3

Studies Toward the Development of Second Generation Chiral Auxiliaries with Improved Enantioselectivity

3.1 Introduction.

A transition state model was presented in the previous chapter that accounts for the experimentally observed enantioselectivity of the reactions of aldehydes and the tartrate modified allylboronate (**1**).



(R,R)-(1) (R,R)-(2)

Figure 1

Based on this transition state model, a coworker, Dr. L. Banfi, initiated studies designed to probe the origin of asymmetric induction and, in the process, develop reagents with improved enantioselectivity. As a result of this study, the diol auxiliary (**2**) was developed and allylboronate (**3**) was shown to be substantially more enantioselective than (**1**) (Figure 2).[1]

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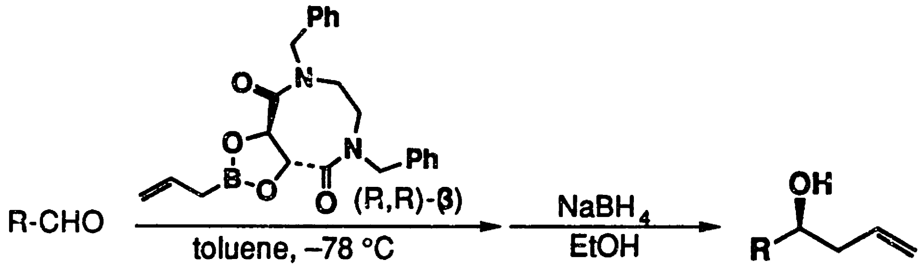
[1] Roush, W. R.; Banfi, L. *J. Am. Chem. Soc.* **1988**, *110*, 3979.



Entry	R	R-CHO	Reaction conditions[2a]	Product	% Conv.[2b]	% e. e. (via (3))[2c]	$\Delta\Delta G^\ddagger$	% e. e. (via (1))[2d]
1	Cyclohexyl	(4)	−78 °C, 47 h	(7)	80	97	−1.61	(87)
2			−50 °C, 17 h		84	94	−1.53	(82)
3			25 °C, 2 h		97	87	−1.55	(50)
4	Phenyl	(5)	−78 °C, 47 h	(8)	75	85	−0.97	(60)
5	*t*-Butyl	(6)	−78 °C, 67 h	(9)	60	96	−1.50	(86)

Figure 2

Although (3) exhibited excellent enantioselection in reactions with representative chiral and achiral aldehydes, the exceedingly long times required for the reactions to go to completion diminished its synthetic utility. The prolonged reaction times are a consequence of the limited solubility of (3) in toluene, especially at low temperatures. This, in turn, led to inefficient stirring and for best results the reactions had to be performed at relatively low concentrations (typically 0.03 M).

As a result of these problems, we began studies toward the development of reagents with improved solubility characteristics while retaining the high enantioselectivity of (3). These investigations are described in the following sections.

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[2] (a) Reactions were performed in toluene (typically 0.03 M) using 1–1.3 equiv. of (3). Reactions were quenched with $NaBH_4$ in EtOH to reduce any unreacted aldehyde. (b) The % conversions were determined by capillary GC method described in Chapter 2. (c) The enantiomeric purities of the homoallyl alcohols were determined by the chiral capillary GC method described in Chapter 2. (d) Values are those obtained using (R,R)-(1).

3.2 Studies Toward the Development of Auxiliaries with Improved Solubility Characteristics

3.2.1 Cyclic Tartramide Auxiliaries.

At the outset of our investigations, we decided that the most convenient way to obtain a more soluble reagent was to modify the N-alkyl substituent of the diol auxiliary (**2**). Indeed, during his initial investigations, Banfi attempted to synthesize (**13**) (Figure 3).

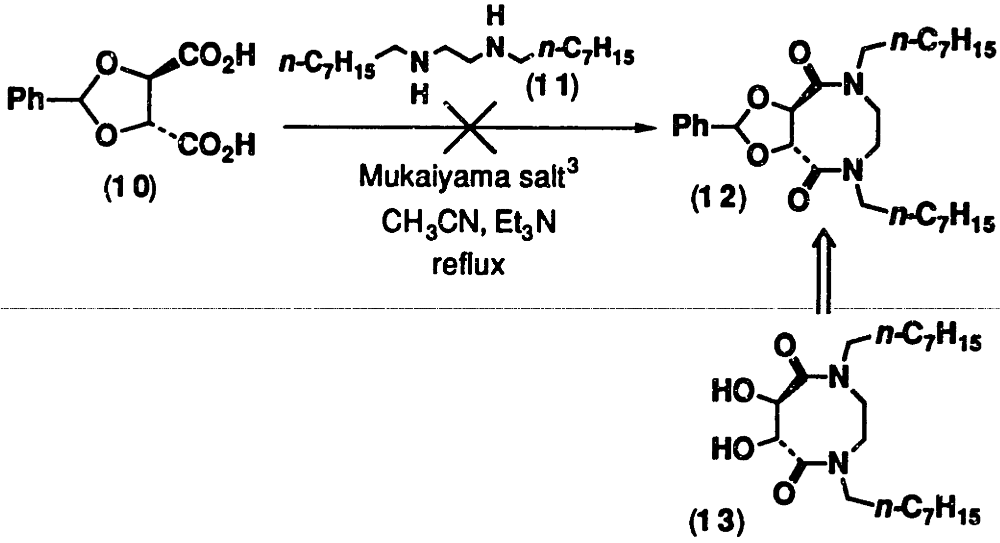

Figure 3.

Unfortunately, when the benzylidene tartaric acid (**10**) was treated with diamine (**11**) during the macrocyclization step, the diamine-diacid salt precipitated from the reaction mixture.[4] We elected to use other N-alkyl substituted amines (**19**)–(**22**) in our studies, hoping that the oxygenated side chains would impart more favorable solubility characteristics. These compounds were prepared in a straightforward manner starting from N,N-dibenzylethylenediamine (**14**) via standard functional group transformations (Figure 4). Unfortunately, attempts to prepare (**22**) were thwarted by O to N acyl migration during the catalytic

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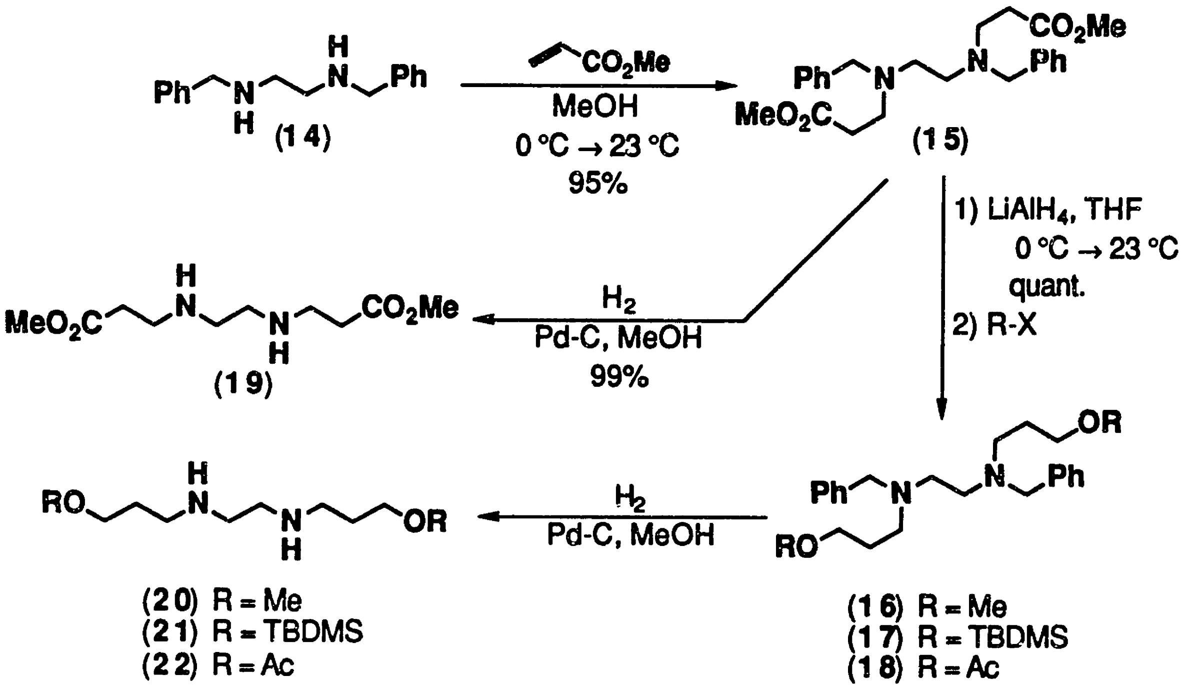
[3] (a) Mukaiyama, T.; Usui, M.; Saigo, K. *Chem. Lett.* **1976**, 49. (b) Bald, E.; Saigo, K.; Mukaiyama, T. *Ibid.* **1975**, 1163.

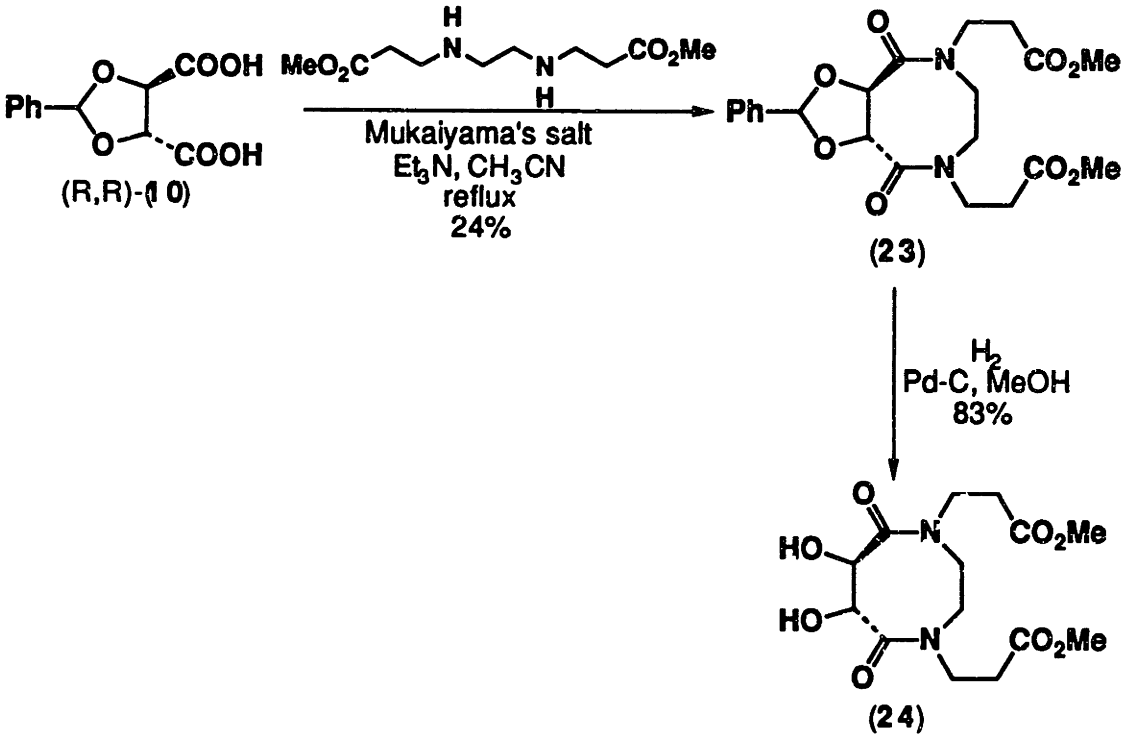
[4] Roush, W. R.; Banfi, L. Unpublished research results.

hydrogenolysis of (**18**), and none of diamine (**22**) was obtained. Moreover, attempts to induce diamines (**20**) and (**21**) to participate in Banfi's macrocyclization protocol were unsuccessful (Figure 5). Diamine (**20**) was insoluble under the reaction conditions, precipitating as its amine salt, paralleling the behavior of (**11**), while no product was detected in the attempted reaction with (**21**). We had better success with diamine (**19**), and the cyclic tartramide (**23**) was obtained in 24% yield. Removal of the benzylidene protecting group by hydrogenation gave diol auxiliary (**24**) in 83% yield. Standard conversion of (**24**) to the corresponding allylboronate (**25**), by treatment with triallylborane, followed by treatment with cyclohexanecarboxaldehyde (–78 °C, toluene) resulted in a disappointing conversion of only 14% after 36 h (Figure 6). The reagent (**25**) did not appear to be appreciably soluble in toluene even at room temperature and consequently did not provide a solution to our problem.



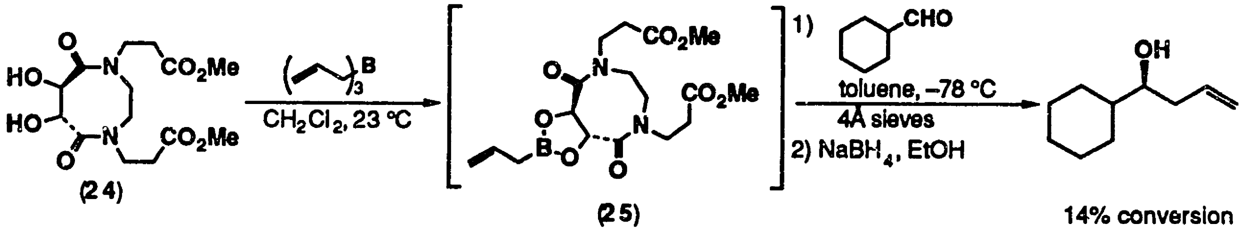
(14)
CO2Me
MeOH
0 °C → 23 °C
95%
(15)
1) LiAlH4, THF
0 °C → 23 °C
quant.
2) R-X
H2
Pd-C, MeOH
99%
(19)
H2
Pd-C, MeOH
(20) R = Me
(21) R = TBDMS
(22) R = Ac
(16) R = Me
(17) R = TBDMS
(18) R = Ac

Figure 4.



Ph
COOH
COOH
(R,R)-(1 0)
MeO2C
CO2Me
Mukaiyama's salt
Et3N, CH3CN
reflux
24%
CO2Me
CO2Me
(23)
H2
Pd-C, MeOH
83%
HO
HO
CO2Me
CO2Me
(24)

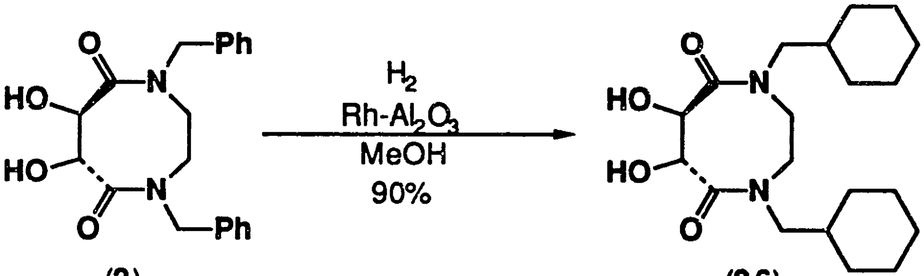
Figure 5.



HO
HO
CO2Me
CO2Me
(24)
CH2Cl2, 23 °C
CO2Me
CO2Me
(25)
1)
CHO
toluene, -78 °C
4Å sieves
2) NaBH4, EtOH
OH
14% conversion

Figure 6.

In view of these disappointing results, we decided to change our approach to the problem. Since diol (**2**) is relatively easy to prepare (the yield of the Mukaiyama salt mediated condensation of N,N'-dibenzylethylenediamine and benzylidene tartaric acid is 52–56%),[1] we decided to explore modifications of the N-substituents by using (**2**) as the starting material. Thus, the diol auxiliary (**26**) was prepared in excellent yield (90%) via direct hydrogenation of (**2**) (Figure 7).

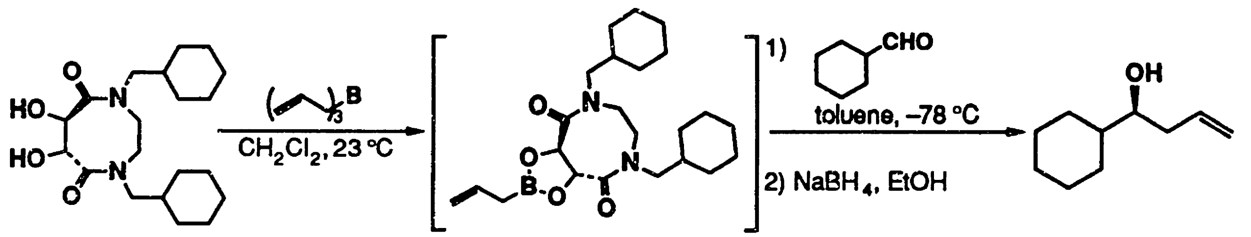


(2)

(26)

Figure 7.

Allylboronate (27) was prepared from (26) via standard procedures[1] (Figure 8) and was found to be completely soluble in toluene at –78 °C at concentrations of 0.44 M (higher concentrations have not been explored). This enabled the allylborations to be carried out at higher concentrations, resulting in significantly shortened reaction times (entries 1–3, Figure 7). By way of comparison, attempts to perform the allylborations using the Banfi reagent (3) at higher concentrations, comparable to those with (27), did not prove successful since the limited solubility of (3) precluded effective stirring. This situation was exacerbated when 4Å molecular sieves were employed. Indeed, the higher conversions we observed with (3) in our studies without sieves suggest that the significantly lower conversions observed by Banfi using sieves may be due to inefficient stirring caused by the sieves. As expected, there was no apparent difference in enantioselectivity between (3) and (27) in experiments carried out side by side (entries 1–3). The lower % e. e.'s observed with both (3) and (27) in these experiments, compared to Banfi's earlier experiments (Figure 2) may be attributed to the fact that our experiments were performed under unoptimized conditions (i. e., in the absence of sieves).



(26) (27)

Entry	Reaction time	Reagent (27)			Reagent (3)		
		Conc.	Conversion	% e. e.	Conc.	Conversion	% e. e.
1	1.5 h	0.15 M	46%	92	0.03 M	33%	91
2	6		83	90		65	91
3	24		90	91		85	91
4	7	0.44	96	92			

Figure 8[5]

In spite of these improved results, the rates of these allylborations were still slower than those observed with the tartrate ester modified allylboronate (**1**). While (**27**) remains a promising candidate for further study, we decided to focus our efforts on the development of an auxiliary that was ester-like in nature in the hopes of increasing the reaction rates even further.

3.2.2 Reagents based on Cyclic Tartrate Esters.

We first endeavored to prepare the auxiliary precursor (**31**) via the macrolactonization reaction of benzylidene tartaric acid (**10**) and ethylene glycol (**28**) (Figure 9).[6] Despite our efforts and those of an earlier coworker, Don Cha,[7] we only managed to obtain dimeric product (**30**) and higher oligomers. Lactonization procedures attempted included use of 2-chloro-1-methylpyridinium iodide (Mukaiyama salt conditions),[3] dipyridyl disulfide-triphenylphosphine (Corey procedure),[8] and a mixed anhydride protocol (pivaloyl chloride, Et_3N).[9] This result was not unexpected as the initially formed monoester (**29**) presumably exists in the preferred s-trans conformation, thereby highly disfavoring the formation of the eight-membered heterocycle (**31**) in the final lactonization step.

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[5] (a) Reactions were performed in toluene at –78 °C without molecular sieves. The reactions were quenched with excess $NaBH_4$-EtOH. (b) The % conversions were determined by capillary GC according to the procedure described in Chapter 2. (c) The % e. e.'s were determined by capillary GC analysis of the (R)-MTPA ester derivative of the homoallyl alcohol.

[6] For a review of macrolactonization reactions, see: (a) Nicolaou, K. C. *Tetrahedron* **1977**, *33*, 683. (b) Masamune, S.; Bates, G. S.; Corcoran, J. W. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 585. (c) Back, T. G. *Tetrahedron* **1977**, *33*, 3041.

[7] Roush, W. R.; Cha, D. Unpublished research, 1986.

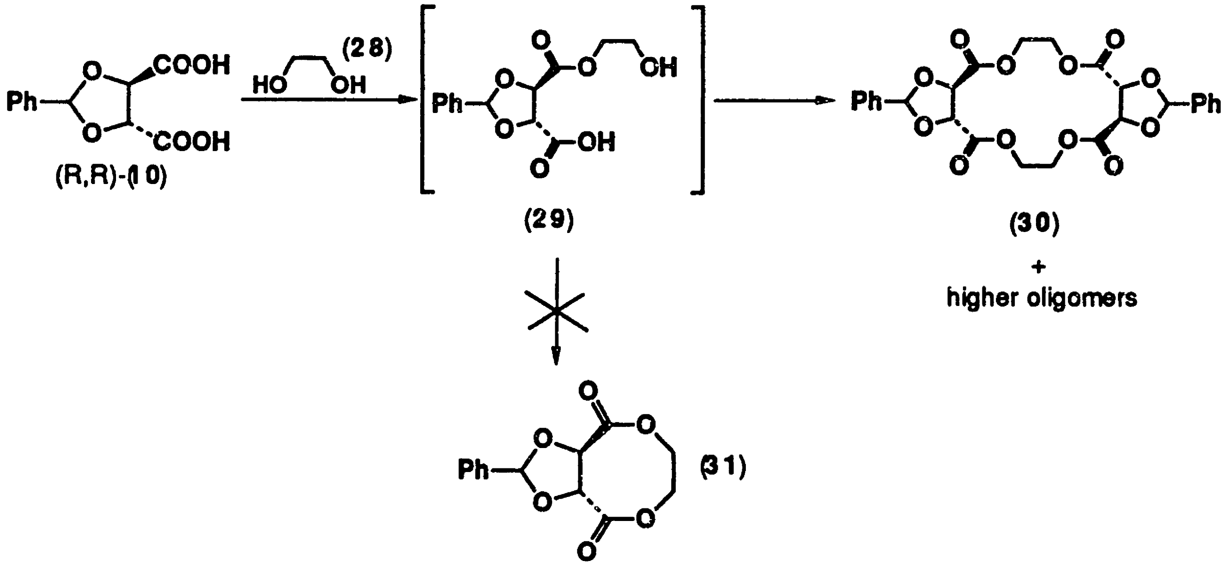

Figure 9.

Consequently, we turned our attention towards the preparation of cyclic benzylidene tartrate ester (**36**) (Figure 11). Inspection of molecular models suggested to us that the conformation of the auxiliary in allylboronate (**32**) (Figure 10) derived from (**36**) would be very similar to that of the Banfi auxiliary in (**3**).

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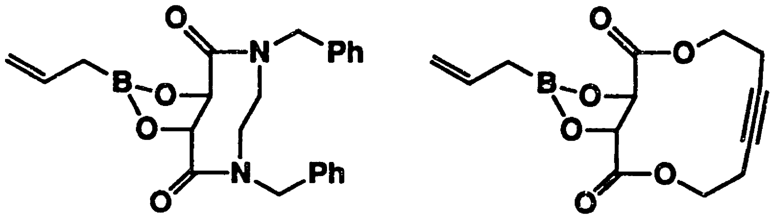
[8] Corey, E. J.; Nicolaou, K. C. *J. Am. Chem. Soc.* **1974**, *96*, 5614.

[9] Roush, W. R.; Blizzard, T. A. *J. Org. Chem.* **1984**, *49*, 1772.



(R,R)-(3) (R,R)-(32)

Figure 10.

While the twelve-membered ring in (**32**) is more flexible than the eight-membered ring of the tartramide based reagents, the minimum energy conformation appears to be that depicted here. In this structure, both esters adopt favored s-trans conformations, and each — $OCH_2CH_2{-}C\equiv C$ unit adopts a staggered gauche conformation. No significant transannular interactions are present due to the acetylene unit that forms one edge of the macrocycle. The latter consideration together with the more favorable (larger) ring size led us to expect that the synthesis of (**36**) would be less problematic than the synthesis of (**31**).

The synthesis of (**36**) is summarized in Figure 11. Condensation of hex-3-yn-1,6-diol (**33**) and benzylidene tartaric acid, using our standard Mukaiyama salt procedure, provided the desired product (R,R)-(**36**), as we had hoped. However, much to our dismay, (R,S)-(**37**) was also produced. The ratio of the two readily separated diastereomers was 72 : 28 and were obtained in a combined yield of 33%. The condensation of (**10**) and (**33**) was also attempted using the Corey-Nicolaou procedure but (**36**) was obtained in only 26% yield under these conditions. None of (**36**) was obtained when we attempted to use the Blizzard mixed anhydride protocol.

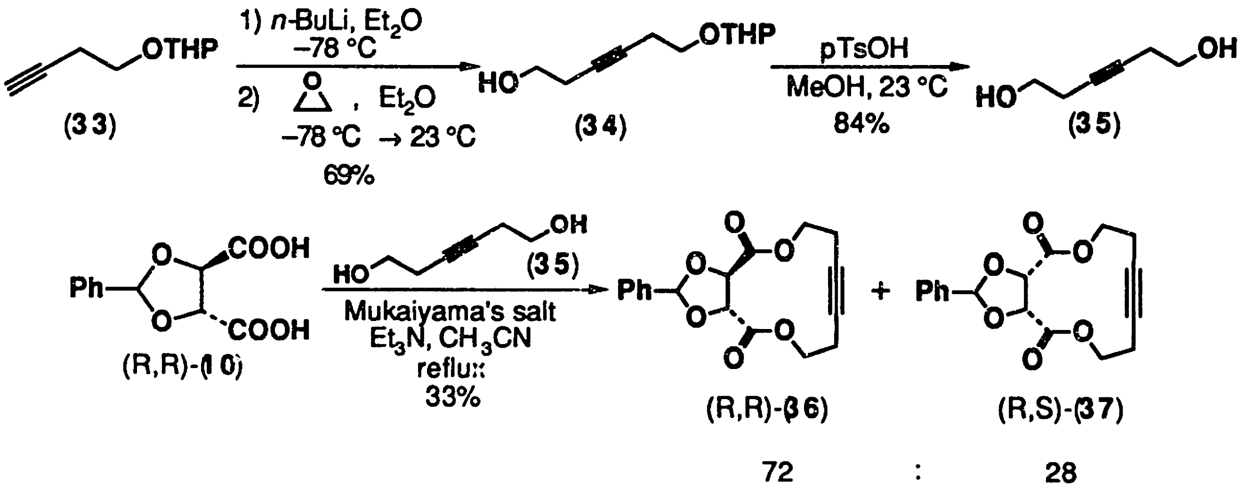

OTHP
(33)
1) n-BuLi, Et2O
-78 °C
2) Et2O
-78 °C → 23 °C
69%
HO
OTHP
(34)
pTsOH
MeOH, 23 °C
84%
HO
OH
(35)
Ph
COOH
COOH
(R,R)-(10)
HO
OH
(35)
Mukaiyama's salt
Et3N, CH3CN
reflux
33%
Ph
(R,R)-(36)
+
Ph
(R,S)-(37)
72
:
28

Figure 11.

The possibility that (**37**) arises by epimerization of (**36**) was ruled out by resubjecting (R,R)-(**36**) to the reaction conditions. No evidence for the formation of the *meso*-diastereomer was found by NMR analysis. Consequently, we suspect that the epimerization occurs via a ketene intermediate (**40**) which can lead to either (R,R)-(**36**) or (R,S)-(**37**) depending on whether protonation of the intermediate (**41**) occurs from the α- or the β-face (Figure 12).[10] If this hypothesis is correct, then the enantiomeric purity of (R,R)-(**36**) should be the same as (**10**). Attempts to ascertain the enantiomeric purity of (R,R)-(**36**) by conversion to (**43**) (Figure 14) and subsequent conversion to its (R)-MTPA derivative, however, gave only elimination products.

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[10] For the generation of ketenes from carboxylic acids and Mukaiyama's salt, see: Funk, R. L.; Novak, P. M.; Abelman, M. M. *Tetrahedron Lett.* **1988**, *29*, 1493.

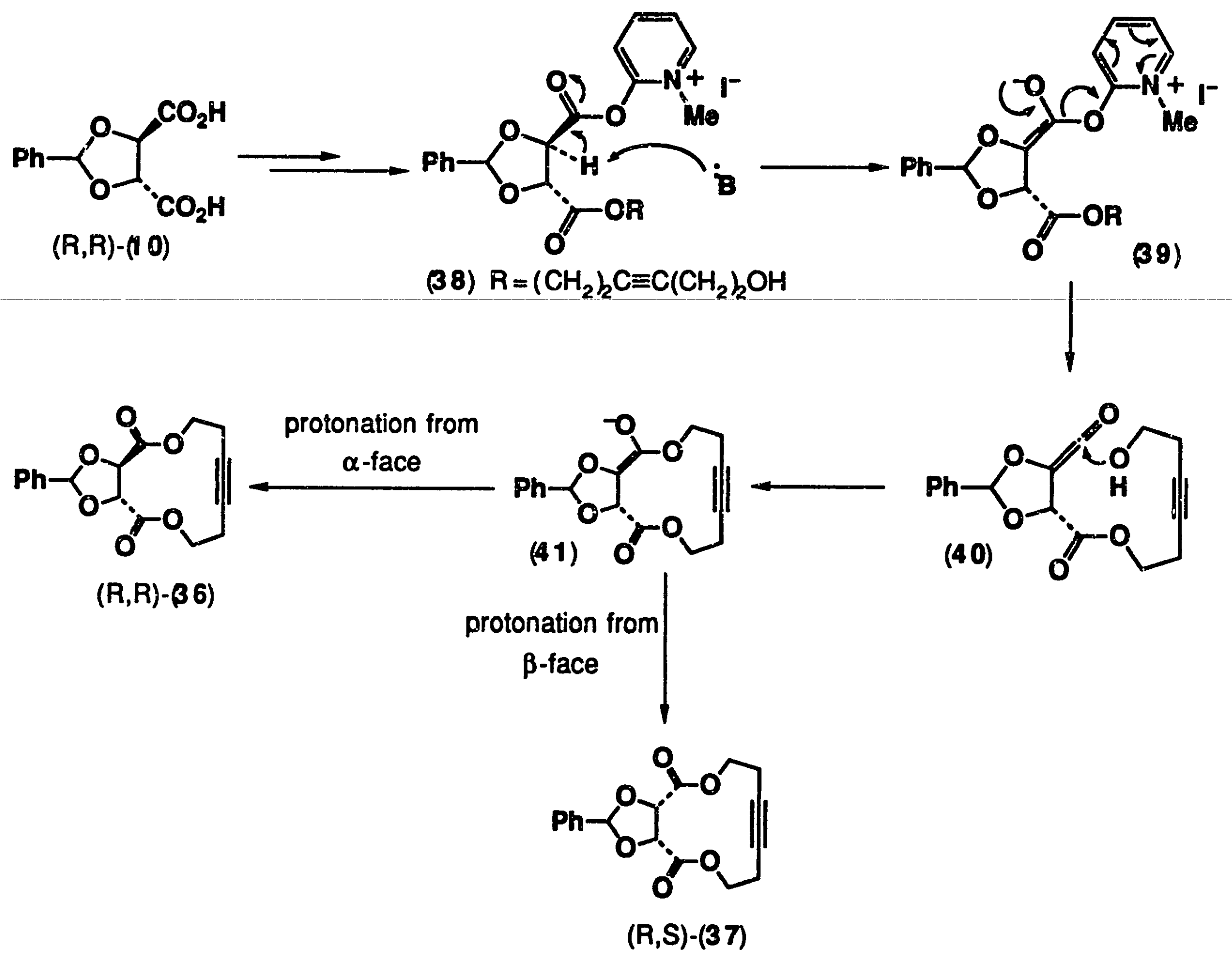
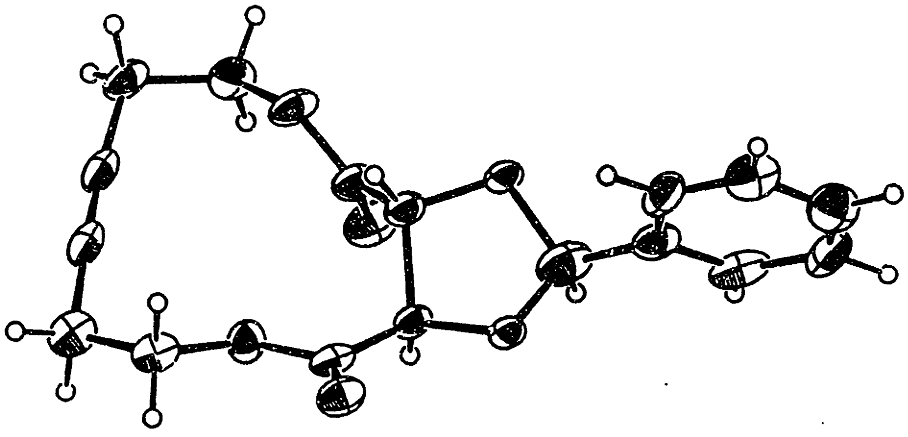
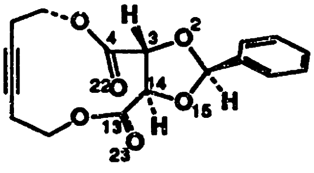

(R,R)-(10)
(38) R=(CH2)2C≡C(CH2)2OH
(39)
protonation from α-face
(41)
(40)
(R,R)-(36)
protonation from β-face
(R,S)-(37)
Ph
B
N+
Me
I-
OR

Figure 11.

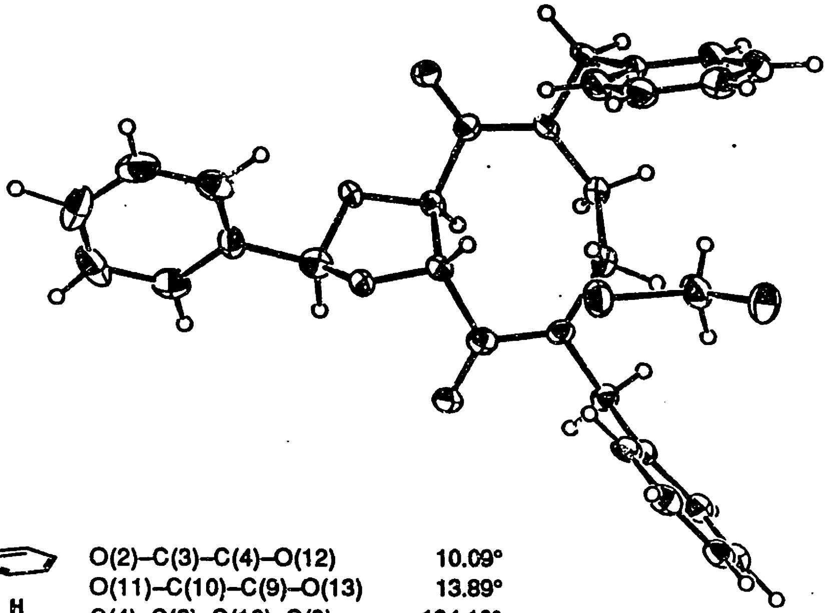
The stereochemistry of (R,R)-(**36**) and (R,S)-(**37**) was confirmed by X-ray crystallography. Examination of the results of this analysis revealed that only one of the carbonyl groups in (R,R)-(**36**) is in the desired syn coplanar arrangement with the adjacent alkoxy unit (O(15)–C(14)–C(13)–O(23) = 0.39°) (Figure 12). The orientation of the remaining carbonyl group deviates significantly from this desired arrangement (O(2)–C(3)–C(4)–O(22) = 71.92°). As a comparison, an X-ray analysis of (R,R)-(**42**), the ORTEP of which is given below (Figure 13), indicated that the conformation of (**42**) as well as the orientation of the carbonyl groups relative to the α-alkoxy units were exactly as we had anticipated: (O(2)–C(3)–C(4)–O(12) = 10.09°; O(11)–C(10)–C(9)–O(13) = 13.89°).

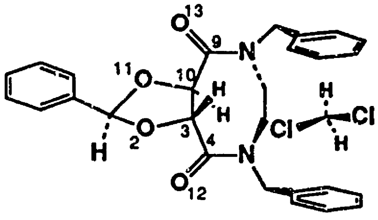



H
O
4
3
2
22O
14
15
H
13
H
O
23

(R,R)-(36)

O(2)–C(3)–C(4)–O(22)	71.92°
O(15)–C(14)–C(13)–O(23)	–0.39°
C(4)–C(3)–C(14)–C(13)	–99.01°
O(2)–C(3)–C(14)–O(15)	21.67°




O13
9
N
11
O
10
H
H
H
Cl
Cl
H
2
O
3
4
N
H
O12

(R,R)-(42)

O(2)–C(3)–C(4)–O(12)	10.09°
O(11)–C(10)–C(9)–O(13)	13.89°
C(4)–C(3)–C(10)–C(9)	–124.10°
O(2)–C(3)–C(10)–O(11)	–2.34°
C(4)–C(3)–C(10)–O(11)	118.15°
O(2)–C(3)–C(10)–C(9)	115.41°

Figure 12. ORTEP Structures for (R,R)-(36) and (R,R)-(42).

Although the synthesis of (R,R)-(36) was not as efficient as we would like, and while the question of the enantiomeric purity of (36) remained, we decided to proceed with the conversion of (R,R)-(36) to the corresponding allylboronate (R,R)-(32) (Figure 14) as a probe of the solubility and reactivity characteristics of this reagent. This would allow us to ascertain whether additional effort to improve the synthesis of (36) was warranted. Thus, the benzylidene acetal (36) was hydrolyzed by heating in 80% HOAc. Diol (R,R)-(43) was obtained in 60% yield following recrystalization (Figure 14).

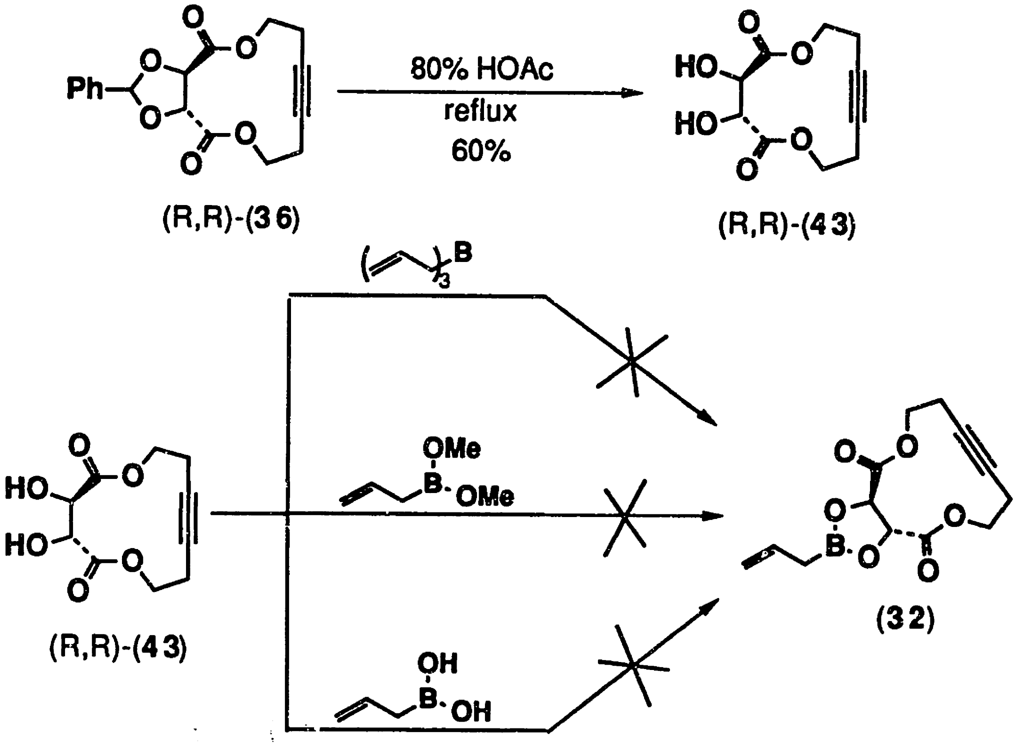


Figure 14

Much to our surprise, subsequent attempts to prepare allylboronate (32) via a number of methods were unsuccessful (Figure 14). Thus, treatment of (43) either with triallylborane (CH_2Cl_2), allylboronic acid (CH_2Cl_2, Et_2O, toluene) or with dimethyl allylboronate (CH_2Cl_2 or THF, 4Å sieves) failed to provide (32) as determined by ^1H NMR analysis and the failure to obtain significant amounts (> 10%) of homoallylic alcohol products upon treatment with cyclohexanecarboxaldehyde at room temperature. Similar reactions using (R,R)-DIPT or

(R,R)-(**2**) in side-by-side experiments led cleanly to (**1**) and (**3**), respectively. Experiments to prepare the acetonide derivative (**44**) were equally unsuccessful even under forcing conditions (PPTS, neat 2,2-dimethoxypropane, 23 °C) (Figure 15). However, we were able to prepare the diacetate derivative (**45**).

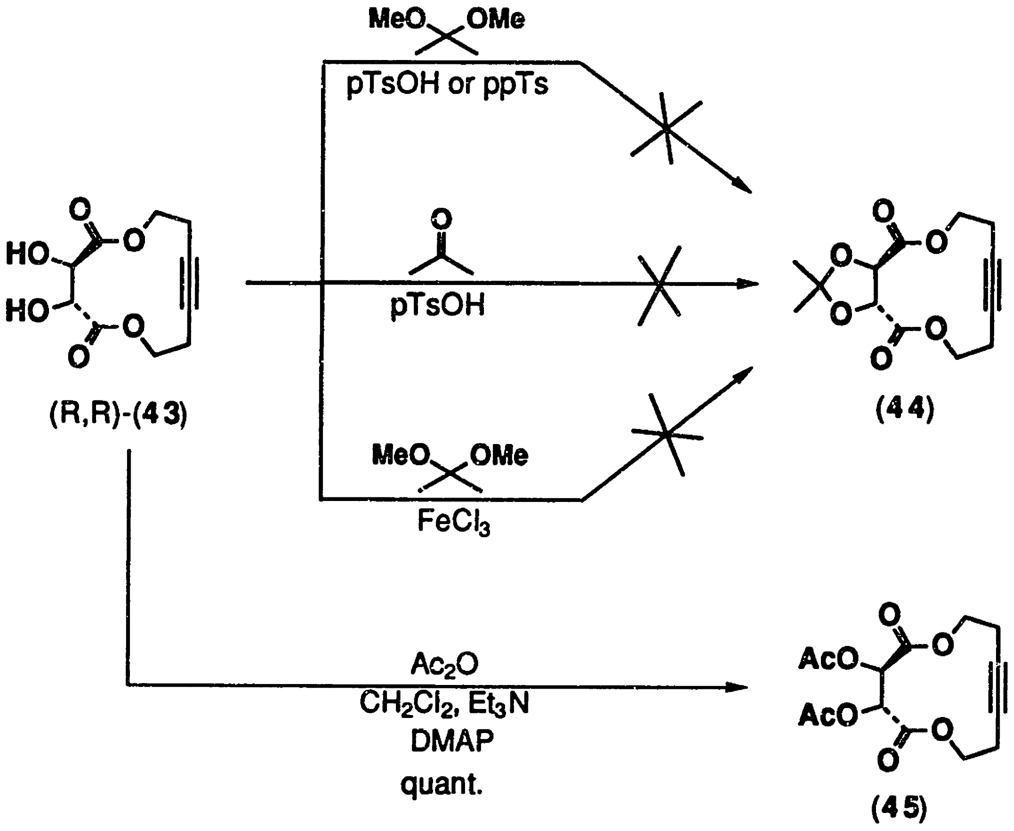
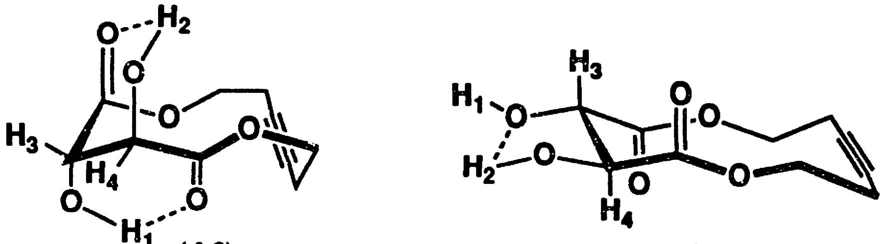


Figure 15

The lack of diol reactivity of (**43**) is indeed surprising. We initially speculated that the inability of (43) to form cyclic derivatives (e. g., (**32**), (**44**)) may be due to the preference of (**43**) to exist in a conformation with the vicinal hydroxy groups in a trans diaxial arrangement (e.g., (**46**), Figure 16). In this conformation, each –OH is hydrogen bound to the carbonyl two positions removed. The presence of two such hydrogen bonds would be expected to create a substantial barrier to conformational interconversion to the diequatorial conformation, since both hydrogen bonds must be broken before conformational flipping can occur.



(46) **(47)**

Conformation favored in $CDCl_3$
$J_{1,3} = J_{2,4} = 8.5$ Hz
$J_{3,4} = 4.3$ Hz
MMX energy –9.3 kcal/mol
$\Delta H_{formation}$ –299.8 kcal/mol

Conformation favored in THF and DMSO
$J_{1,3} = J_{2,4} = 6.6$ Hz
$J_{3,4} = 8.6$ Hz
MMX energy –8.7 kcal/mol
$\Delta H_{formation}$ –299.1 kcal/mol

Figure 16

Unfortunately, attempts to obtain X-ray quality crystals of (**43**) were unsuccessful. However, MM2 calculations (gas phase) performed by using Gajewski's MMX program[11] indicated that the diaxial conformer (**46**) (MMX energy –9.3 kcal mol^{-1}; ΔH_{form} –229.8 kcal mol^{-1}) is lower in energy than the diequatorial conformer (**47**) (MMX energy –8.7 kcal mol^{-1}; ΔH_{form} –229.1 kcal mol^{-1}). These structures were obtained only when π-calculations were perfromed as part of the MMX minimizations (this is necessary for the program to recognize that the ester carbonyls are more Lewis basic, hence better hydrogen bond acceptors, than normal ketone carbonyls that define the normal hydrogen bond acceptor properties in MMX). In spite of the amplification provided by the π-calculations, the parameters for hydrogen bonds to a carbonyl oxygen acceptor are too weak in MMX and the ***calculated energy difference*** between the diaxial and diequatorial conformations is expected to be smaller than in reality.[12]

In addition, inspection of the ^1H NMR spectrum of (**43**) measured in THF-d_8 and $CDCl_3$ revealed an AA'XX' pattern for the —CH(OH)–CH(OH)— unit (Figure 17).

---

[11] (a) Molecular mechanics calculations were performed using MMX on an IBM PC-XT. MMX is derived from the Allinger MM2 force field (1977 version QCPE 395) with the VESCF π subroutines from MMP1 (QCPE 318): Gilbert, K. E.; Gajewski, J. J. Serena Software, P. O. Box 3076, Bloomington, IN 47402–3076.
(b) We would like to thank Prof. Gajewski for his assistance in obtaining the minimized structures.

[12] Personal communication from Prof. Gajewski.

Computer simulation[13] of the pattern in THF (Figure 17) provided $J_{3,4}$ = 8.6 Hz which is consistent with the diequatorial conformation (**47**). In contrast, an analogous simulation of the AA'XX' pattern obtained in $CDCl_3$ showed $J_{3,4}$ = 4.3 Hz which corresponds to the diaxial, doubly hydrogen bonded conformation (**46**). The conformational difference of (**43**) in THF-d_8 relative to $CDCl_3$ is explained by the ability of THF to serve as a hydrogen bond acceptor, thereby disrupting the intramolecular hydrogen bonds that occur in and stabilize the diaxial conformation (**46**). Indeed, when an ^1H NMR spectrum of (**43**) was measured in DMSO, which also is able to act as a hydrogen bond acceptor, an AA'XX' pattern was obtained that was identical to the one obtained in THF. These data suggest that the formation of cyclic derivatives of (**43**) may be successfully carried out if the cyclizations are performed in solvents (e.g, THF) which favor the diequatorial conformer (**47**). Unfortunately, due primarily to time constraints, we were unable to pursue this issue further.

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[13] Computer simulation of ^1H NMR spectra were performed using PCPMR on an IBM PC-XT. PCPMR is available from Serena Software, PO Box 3076, Bloomington, IN 47402.

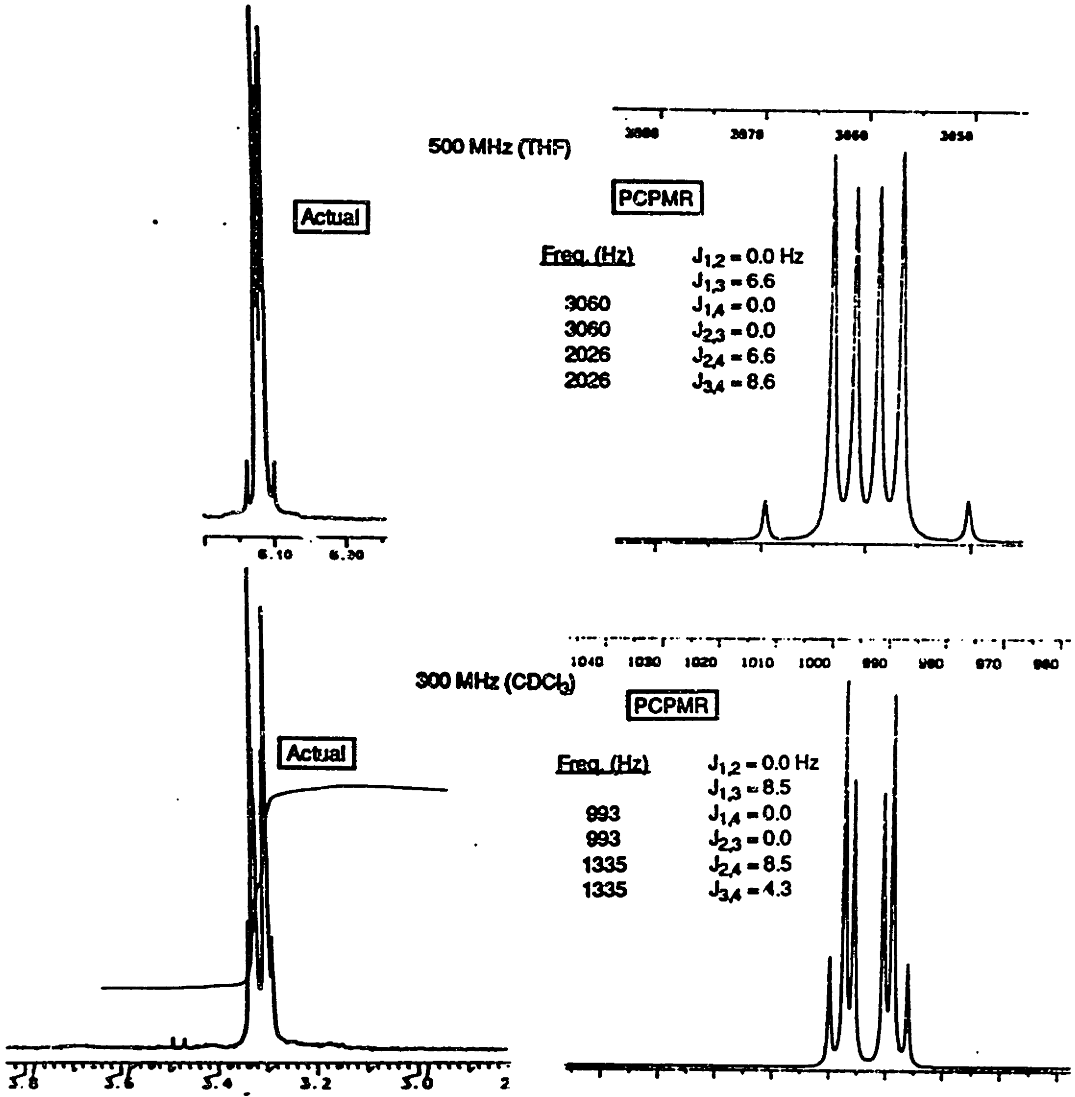

Figure 17
Comparison of Actual and Simulated AA'XX' pattern of (43) in THF-d_8 and CDCl$_3$

3.3 Conclusion.

Although our studies with the cyclic tartrate derivative (43) did not prove fruitful, the initial results obtained with the tartramide based reagent (27) are very encouraging. Further studies with (27) may eventually provide an acceptable solution to the problems discussed at the outset, namely the development of a synthetically accessible reagent that is both highly enantioselective and soluble at low temperatures. Further developmental studies with (27) have recently been initiated by a coworker, and we will eagerly await the results of those efforts.

Experimental Section

General. ^{1}H NMR spectra were measured in $CDCl_3$ at 250 MHz on a Bruker WM 250 instrument, at 300 and 400 MHz on Varian XL-300 and XL-400 instruments, at 360 MHz on a Nicolet 360 instrument, and at 500 MHz on a Bruker AM 500 instrument. Residual chloroform (δ 7.26 ppm) was used as internal reference. ^{13}C NMR spectra were recorded at 75.4 MHz on the XL-300 and were referenced with the δ 77.0 ppm resonance of $CDCl_3$. ^{19}F NMR spectra were obtained at 376.3 MHz, 338.7 MHz, or 282.2 MHz on the XL-400, Nicolet 360, or XL-300 instruments respectively and were referenced with external 4-bromobenzotrifluoride [Aldrich; δ –63.31 ppm in $CDCl_3$]. ^{11}B NMR were recorded at 115.8 MHz on a Nicolet 360 instrument and were referenced with external $BF_3{\cdot}Et_2O$ (δ 0.0 ppm). Infrared spectra were recorded on a Perkin-Elmer Model 1420 Infrared Spectrophotometer and were referenced by the 1601 cm^{-1} absorption of polystyrene. Optical rotations were measured on a Rudolph Autopol III Automatic Polarimeter using a 1 cm^3 quartz cell (10 cm path length). Mass spectra were measured at 70 eV on a Varian MAT 44 or a Finnegan MAT 8200 instrument. High-resolution mass spectra were measured at 70 eV on the Finnegan MAT 8200.

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 % e.e.'s via the separation of diastereomeric MTPA esters, were carried out using a Shimadzu GC-9A Gas Chromatograph equipped with 50 m x 0.25 mm Bonded FSOT Carbowax 20M. Chiral capillary GC % e.e. determinations of methyl ethers were performed on a Hewlett Packard 5890A Gas Chromatograph equipped with 25 m x 0.25 mm 10% nickel (II) bis(3-heptafluorobutyryl-(1R)-camphorate)/OV-1 [Ni-R-Cam] or 25 m x 0.25 mm 10% nickel (II) bis (heptafluorobutyryl-(1R, 2S)-pinan-4-oate)/OV-1 [Ni-4-Pin] chiral capillary columns.

Analytical thin-layer chromatography (TLC) was performed by using 2.5 cm x 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 x 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,[14] using Kieselgel 60 (230–400 mesh) or Kieselgel 60 (70–230 mesh). Compounds were visualized by charring with ethanolic vanillin/H_2SO_4, phosphomolybdic acid (PMA), ammonium molybdate/ceric sulfate (Ce-Mo) or by staining with iodine vapor. Unless otherwise noted, all compounds purified by chromatography are sufficiently pure (> 95% by ^{1}H NMR analysis) for use directly in subsequent transformations.

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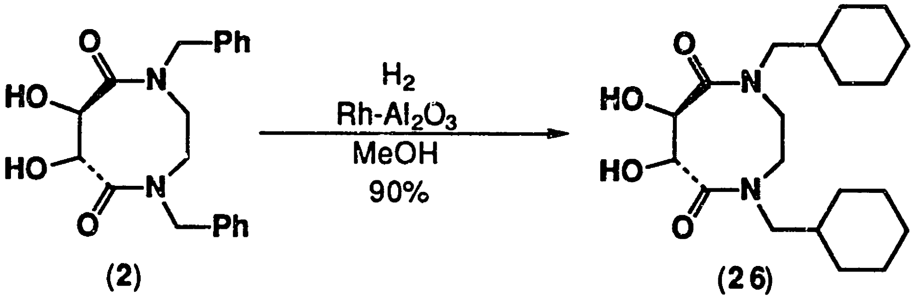
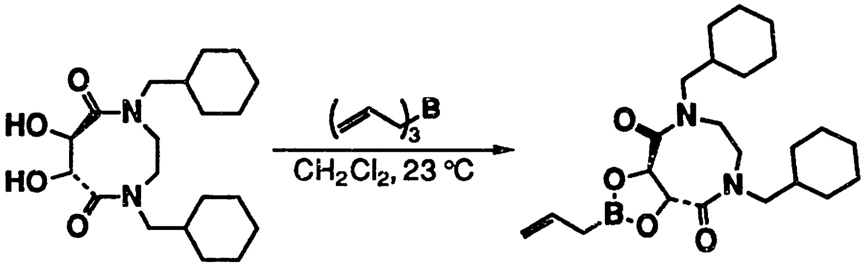
[14] Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.



Preparation of N,N'-Di(cyclohexylmethyl)-N,N'-ethylene Tartramide (26).

Procedure: A solution of 0.87 mmol (308 mg) of N,N'-dibenzyl-N,N'-ethylene tartramide (2) in 45 mL of MeOH was treated with a catalytic amount of 5% Rh-Al_2O_3. The reaction vessel was then flushed with N_2 followed by H_2. Stirring was begun. A slow, steady stream of H_2 was bubbled through the well-stirred reaction mixture overnight. When the reaction was judged to be complete by TLC analysis, the crude mixture was filtered to remove the hydrogenation catalyst. Solvent was removed *in vacuo* to give 271 mg (88% yield) of (R,R)-(26) as a white solid: R_f 0.55 [EtOAc; I_2, Ce-Mo/char]; m.p. 149–151 °C; $[\alpha]^{20}_{D}$ -43.8°, $[\alpha]^{20}_{546}$ –51.5° [c = 0.98, $CHCl_3$]; *^{1}H-NMR* [$CDCl_3$, 300 MHz] δ 4.33 [s, 2H], 3.74–3.47 [m, 5H], 3.31–3.08 [br m, 5H], 1.75–0.79 [series of br m, 22H]; *IR* ($CHCl_3$ solution) 3400 (br), 3000, 2920, 2850, 1660, 1450, 1400, 1105, 1075, 1040 cm^{-1}; *HRMS* [CI] for $C_{20}H_{34}N_2O_4$ *M + 1 calcd.*: 367.2597, *obsvd.*: 367.2567; *M^+ calcd.*: 366.2518, *obsvd.*: 366.2504

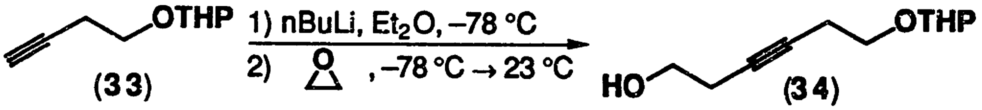


(26) (27)

Preparation of Allylboronate (R,R)-(27).

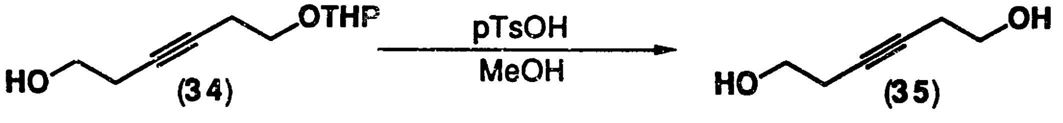
Procedure: A solution of 0.29 mmol (105 mg) (R,R)-(**26**) in 3 mL of dry CH_2Cl_2 was treated with 0.28 mmol (50 µL) of triallylborane at 23 °C. After stirring for 3 h, solvent was removed *in vacuo,* and the residue was placed under vacuum (0.25 mmHg) overnight. The crude reagent was then dissolved in 2.0 mL of dry toluene. A 0.4 mL aliquot of the solution was titrated with cyclohexanecarboxaldehyde (0.056 mmol, 6.3 mg) at 23 °C according to the procedure described in Chapter 3. This showed the concentration of (**27**) to be 0.12 M (83% yield).

Data for Allylboronate (R,R)-(31):^{1}*H-NMR* ($CDCl_3$, 500 MHz) δ 5.98–5.90 [m, 1H], 5.29–5.05 [m, 2H], 4.98 [s, 2H], 3.63–3.51 [m, 4H], 3.43 [dd, J = 6.8 Hz, J= 13.5 Hz, 2H], 3.16 [dd, J = 5.8 Hz, J = 13.5 Hz, 2H], 1.98–1.96 [m, 2H], 1.73–1.48 [overlapping m, 12H], 1.24–1.14 [m, 6H], 1.05–0.91 [m, 4H]



Preparation of 1-(Tetrahydropyranyloxy)hex-3-yn-6-ol (34).

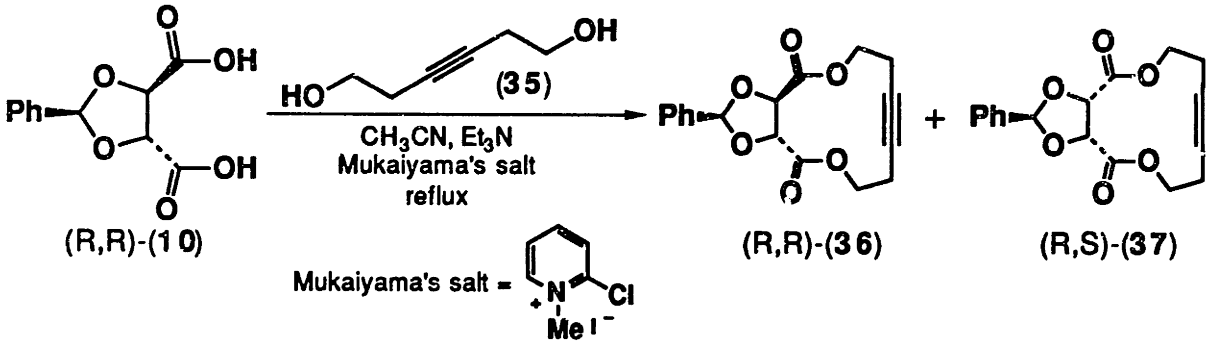
Procedure: A solution of 92.2 mmol (14.2 g) 1-(tetrahydropyranyloxy)but-3-yne (**33**) in 230 mL of dry Et_2O was cooled to –78 °C and then was treated dropwise with 111 mmol of *n*-butyllithium [2.5 M in hexane]. Precipitation was observed during the addition. The solution was stirred for 1 h at –78 °C, then 140 mmol (7 mL) of ethylene oxide [condensed at –78 °C and transferred rapidly via cannula] was added. The resulting cloudy mixture was stirred at –78 °C for 2 h then allowed to warm slowly to room temperature. Stirring was continued overnight. The mixture was poured into saturated NH_4Cl–Et_2O; the aqueous layer was separated and extracted with Et_2O (3 x 100 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated to give 14.9 g of clear, yellow liquid. The material was purified on a column of flash silica gel [60 x 130 mm] using 1 : 1 hexane–Et_2O to give 6.44 g of recovered (**33**) along with 6.86 g of (**34**) [38% yield; 69% yield based on consumed (**33**)]: R_f 0.17 [1 : 1 hexane-ether; PMA/char]; *^{1}H–NMR* [$CDCl_3$, 300 MHz] δ 4.65–4.62 [m, 1H], 3.91–3.76 [series of m, 2H], 3.67 [q, J = 5.8 Hz, 2H], 3.59–3.48 [series of m, 2H], 2.50–2.39 [m, 4H], 2.12 [br s, 1H], 1.83–1.49 [series of m, 6H]; *IR* (neat) 3430, 2940, 2870, 1440, 1385, 1350, 1200, 1120, 1050, 970, 905, 870, 810 cm^{-1}; *HRMS* [CI] for $C_{11}H_{18}O_3$ *M + 1 calcd.*: 199.1334, *obsvd.*: 199.1333



HO
OTHP
(34)
pTsOH
MeOH
HO
OH
(35)

Preparation of Hex-3-yne-1,6-diol (35).

Procedure: To a solution of 6.66 mmol (1.32 g) of (**34**) in 200 mL of methanol was added a few crystals of pTsOH. Stirring was continued overnight. Solvent was removed *in vacuo* to give 0.64 g of crude solid which was taken up in 60 mL of warm Et_2O. Recrystallization from Et_2O gave 0.64 g [84% yield] of the desired diol (**35**): m.p. 76–78 °C; *^1H-NMR* [$CDCl_3$, 300 MHz] δ 3.71 [t, J = 6.4 Hz, J = 5.7 Hz, 4H], 2.47–2.43 [m, 4H], 2.10 [s, 2H]; *IR* ($CHCl_3$ solution) 3600 (sharp), 3400 (br), 3000, 2940, 2880, 1420, 1380, 1040 cm^{-1}; *HRMS* [CI] for $C_6H_{10}O_2$ M^{+} *calcd.*: 114.0681, *obsvd.*: 114.0697



O
OH
Ph
O
O
OH
O
(R,R)-(10)
HO
OH
(35)
CH3CN, Et3N
Mukaiyama's salt
reflux
Mukaiyama's salt =
N
Cl
Me I⁻
Ph
(R,R)-(36)
+
Ph
(R,S)-(37)

Preparation of 3,4-O-Benzylidene-(3R,4R)-1,6-dioxacyclododec-9-yn-2,5-dione (36) and 3,4-O-Benzylidene-(3R,4S)-1,6-dioxacyclododec-9-yne-2,5-dione (37).

Procedure: To a solution of 0.018 mol (4.3 g) of benzylidene (R,R)-tartaric acid (**10**) and 0.27 mmol (37 mL) of dry Et_3N in 350 mL of dry CH_3CN was added 0.018 mol (2.0 g) of hex-3-yne-1,6-diol (**35**) as a solution in 100 mL of dry CH_3CN. The resulting clear solution was transferred to an addition funnel, and the contents were then added dropwise, over a period of 11 h, to 0.14 mol (37 g) of Mukaiyama's salt [N-methyl-2-chloropyridinium iodide] in 1 L of refluxing CH_3CN. The dark brown mixture was then refluxed for another 10 h before cooling to room temperature. It was then added to 1 : 1 sat. NaCl-Et_2O. The aqueous layer was separated and extracted with Et_2O (4 x 100 mL). The combined organic layers were dried over anhydrous Na_2SO_4 before being filtered and concentrated *in vacuo* to give 7.24 g of crude dark brown liquid. The crude material was then purified on a column of silica gel [60 x 130 mm] using 1 : 1 hexane-Et_2O, giving a total of 1.9 g (33% yield) of (R,R)-(**36**) and (R,S)-(**37**) in a ratio of 72 : 28.

Data for 3,4-O-Benzylidene-(3R,4R)-1,6-dioxacyclododec-9-yn-2,5-dione (**36**): R_f 0.37 [1 : 1 hexane-ether; UV, PMA/char]; m. p. 126–129 °C; $[\alpha]_D^{20}$ +25.5°, $[\alpha]_{546}^{20}$ +30.7° (c = 2.39, $CHCl_3$); *^1H NMR* [$CDCl_3$, 300 MHz] δ 7.60–7.56 [m, 2H], 7.42–7.39 [m, 3H], 6.27 [s, 1H], 4.72 [d, J = 8.5 Hz, 1H], 4.62 [d, J = 8.5 Hz, 1H], 4.61–4.50 [m, 2H], 4.13–4.02 [m, 2H], 2.66–2.61 [m, 2H], 2.46–2.39 [series of m, 2H]; *IR* ($CHCl_3$, solution) 3030, 2960, 2920, 1755, 1460, 1410, 1350, 1110 cm^{-1}; *HRMS* [CI] for $C_{17}H_{16}O_6$ M^+ *calcd.*: 316.0947, *obsvd.*: 316.0924;

X-ray Crystal Data for (R,R)-(**36**) $C_{17}H_{16}O_6$:[15] space group: $P\bar{1}$; cell dimensions (at −155°C): a = 9.837(2) Å, b = 9.966(2) Å, c = 8.198(2) Å, α = 111.85(1)°, β = 99.45(1)°, γ = 89.51(1)°; Z (molecules/cell): 2; volume: 734.66 Å^3; calculated density: 1.430 g/cm^3; wavelength: 0.71069 Å; linear absorption coefficient: 1.019 cm^{-1}. The structure was solved using a combination of direct methods and Fourier techniques, and was refined to final residuals R(F) = 0.0557 and R_W(F) = 0.0719 for 1813 independent reflections (F > 2.33Σ(F)) of 1922 unique intensities collected in the range 6.0°

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[15] X-ray crystallography was carried out by Dr. John C. Huffman at the Indiana University Department of Chemistry Molecular Structure Center, Indiana University, Bloomington, IN 47405

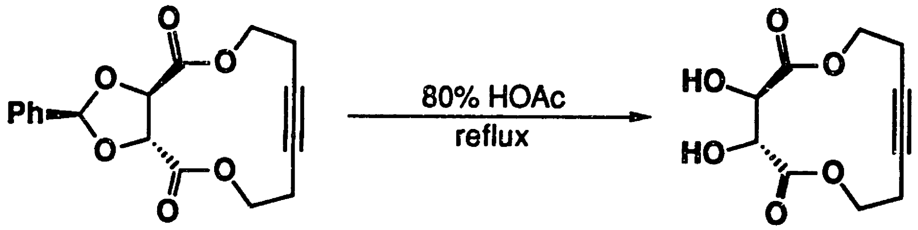
$\leq 2q \leq 45^\circ$. Details of the data collection and structure solution, atomic positional and thermal parameters, complete bond distance and bond angle data, and a listing of F_{obs} vs. F_{calc} may be obtained directly from the Indiana University Molecular Structure Center. Request report No. 88215.

Data for 3,4-O-Benzylidene-(3R,4S)-1,6-dioxacyclododec-9-yn-2,5-dione (37): R_f 0.17 [1 : 1 Hexane-ether; UV, PMA/char]; m.p. 132–135°; *^{1}H-NMR* [$CDCl_3$, 300 MHz] δ 7.68–7.64 [m, 2H], 5.98 [s, 1H], 4.98 [s, 2H], 4.49–4.44 [m, 2H], 4.25–4.19 [m, 2H], 2.59–2.45 [m, 4H]; *^{13}C-NMR* [$CDCl_3$, 75.6 MHz] δ 168.24, 135.34, 129.76, 128.29, 126.69, 106.04, 78.78, 76.59, 62.84, 19.25; *IR* ($CHCl_3$ solution) 3020, 2960, 2910, 1760, 1601, 1455, 1390, 1340, 1285, 1105 cm^{-1}; *HRMS* [CI] for $C_{17}H_{16}O_6$ M^{+} *calcd.*: 316.0947, *obsvd.*: 316.0946;

Crystal Data for (R,S)-(**37**):[15] space group: $P2_1/a$; cell dimensions (at –155°C): a = 11.698(3) Å, b = 11.249(2) Å, c = 14.093(3) Å, β = 125.56(1)°; Z (molecules/cell): 4; volume: 1508.71 Å^3; calculated density: 1.393 g/cm^3; wavelength: 0.71069 Å; linear absorption coefficient: 0.992 cm^{-1}. The structure was solved using a combination of direct methods and Fourier techniques, and was refined to final residuals R(F) = 0.0361 and $R_W(F) = 0.0421$ for 2392 independent reflections ($F > 2.33\Sigma(F)$) of 2662 unique intensities collected in the range $6.0^\circ \leq 2q \leq 50^\circ$. Details of the data collection and structure solution, atomic positional and thermal parameters, complete bond distance and bond angle data, and a listing of F_{obs} vs. F_{calc} may be obtained directly from the Indiana University Molecular Structure Center. Request report No. 88213.

Crystal Data for (R,R)-(42): *Crystal Data for* (R,R)-(**42**):[15] space group: $P2_1/a$; cell dimensions (at –155°C): a = 11.698(3) Å, b = 11.249(2) Å, c = 14.093(3) Å,

$\beta = 125.56(1)°$; Z (molecules/cell): 4; volume: 1508.71 Å^3; calculated density: 1.393 g/cm^3; wavelength: 0.71069 Å; linear absorption coefficient: 0.992 cm^{-1}. The structure was solved using a combination of direct methods and Fourier techniques, and was refined to final residuals R(F) = 0.0361 and $R_W(F) = 0.0421$ for 2392 independent reflections ($F > 2.33\Sigma(F)$) of 2662 unique intensities collected in the range $6.0° \leq 2q \leq 50°$. Details of the data collection and structure solution, atomic positional and thermal parameters, complete bond distance and bond angle data, and a listing of F_{obs} vs. F_{calc} may be obtained directly from the Indiana University Molecular Structure Center. Request report No. 89059.

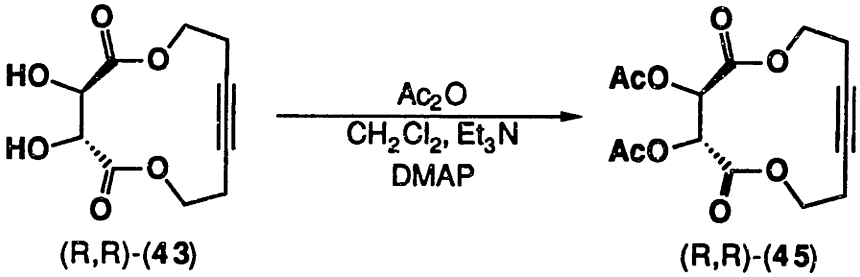


(R,R)-(36) (R,R)-(43)

Preparation of (3R,4R)-3,4-Dihydroxy-1,6-dioxacylododec-9-yn-2,5-dione (43).

Procedure: A solution of (R,R)-(**36**) (1.61 mmol, 0.51 g) in 40 mL of 80% HOAc was heated to reflux and stirred for 21 h. After being cooled to room temperature, solvent was removed by repeated co-evaporation with heptane and benzene. The resulting crude substance was then placed under vacuum [0.5 mmHg; 4 h] to remove residual acid and H_2O. The remaining 0.452 g of crude product was recrystallized from EtOAc-hexane, to give 0.22 g (60% yield) of the desired diol (**43**): R_f 0.60 [EtOAc; vanillin/char]; $[\alpha]^{20}_{D}$ +1.8°(c = 3.3, THF), $[\alpha]^{20}_{436}$ +2.0°; ^{1}*H-NMR* [$CDCl_3$, 300 MHz] δ 4.52–4.43 [series of m, 4H], 4.37–4.30 [m, 2H], 3.33–3.29 [m, 2H], 2.59–2.46 [m, 4H]; [DMSO, 500 MHz] δ 6.14–

6.11 [m, 2H, OH], 4.35–4.28 [m, 2H], 4.07–4.05 [m, 2H], 3.99–3.96 [m, 2H], 2.47–2.41 [m, 4H]; *^{13}C-NMR* [THF d_8, 75.6 MHz] δ 171.6, 79.6, 74.3, 62.6, 19.9; *IR* ($CHCl_3$ solution) 3530 (br), 2980, 1750, 1270, 1235, 1110 cm^{-1}; *HRMS* [CI] for $C_{10}H_{12}O_6$ *M^+ calcd.*: 228.0634, *obsvd.*: 228.0629



Preparation of (3R,4R)-3,4-Diacetoxy-1,6-dioxacylododec-9-yn-2,5-dione (45).

Procedure: To a solution of 0.016 mmol of diol (**43**) in 2 mL of dry CH_2Cl_2 was added 0.05 mmol (7 μL) of Et_3N and 0.08 mmol (4 μL) of dry, distilled acetic anhydride along with a few crystals of DMAP. The reaction mixture was stirred overnight then concentrated *in vacuo*. The crude material was purified by chromatography on a 0.25 mm PTLC plate using 1 : 1 hexane-EtOAc to provide the desired diacetate (**45**) in quantitative yield: R_f 0.40 [1 : 1 hexane-EtOAc; PMA/char]; *^{1}H-NMR* [$CDCl_3$, 300 MHz] δ 5.47 [s,2H], 4.40–4.30 [m, 2H], 4.29–4.25 [m, 2H], 2.51–2.48 [m, 4H], 2.18 [s, 6H]; *IR* ($CHCl_3$ solution) 2960, 2920, 1755, 1370, 1130, 1005 cm^{-1}; *HRMS* [CI] for $C_{14}H_{16}O_8$ *M + 1 calcd.*: 313.0923, *obsvd.*: 313.0886