

Organic Reactions

VOLUME 51

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PREFACE TO THE SERIES

In the course of nearly every program of research in organic chemistry the investigator finds it necessary to use several of the better-known synthetic reactions. To discover the optimum conditions for the application of even the most familiar one to a compound not previously subjected to the reaction often requires an extensive search of the literature; even then a series of experiments may be necessary. When the results of the investigation are published, the synthesis, which may have required months of work, is usually described without comment. The background of knowledge and experience gained in the literature search and experimentation is thus lost to those who subsequently have occasion to apply the general method. The student of preparative organic chemistry faces similar difficulties. The textbooks and laboratory manuals furnish numerous examples of the application of various syntheses, but only rarely do they convey an accurate conception of the scope and usefulness of the processes.

For many years American organic chemists have discussed these problems. The plan of compiling critical discussions of the more important reactions thus was evolved. The volumes of *Organic Reactions* are collections of chapters each devoted to a single reaction, or a definite phase of a reaction, of wide applicability. The authors have had experience with the processes surveyed. The subjects are presented from the preparative viewpoint, and particular attention is given to limitations, interfering influences, effects of structure, and the selection of experimental techniques. Each chapter includes several detailed procedures illustrating the significant modifications of the method. Most of these procedures have been found satisfactory by the author or one of the editors, but unlike those in *Organic Syntheses* they have not been subjected to careful testing in two or more laboratories.

Each chapter contains tables that include all the examples of the reaction under consideration that the author has been able to find. It is inevitable, however, that in the search of the literature some examples will be missed, especially when the reaction is used as one step in an extended synthesis. Nevertheless, the investigator will be able to use the tables and their accompanying bibliographies in place of most or all of the literature search so often required.

Because of the systematic arrangement of the material in the chapters and the entries in the tables, users of the books will be able to find information desired by reference to the table of contents of the appropriate chapter. In the interest of economy the entries in the indices have been kept to a minimum, and, in particular, the compounds listed in the tables are not repeated in the indices.

The success of this publication, which will appear periodically, depends upon the cooperation of organic chemists and their willingness to devote time and effort to the preparation of the chapters. They have manifested their interest already by the almost unanimous acceptance of invitations to contribute to the work. The editors will welcome their continued interest and their suggestions for improvements in *Organic Reactions*.

Chemists who are considering the preparation of a manuscript for submission to *Organic Reactions* are urged to write either secretary before they begin work.

Correction: Volume 50 of *Organic Reactions* lists the names of those who contributed to the editing and publication of Volumes 26–50. Although the name of Professor Barry M. Trost appears in the table at the top of page x in Volume 50, his picture was inadvertently omitted from those on pages xi–xv.



WILLIAM G. DAUBEN

November 6, 1919–January 2, 1997

Bill Dauben, Professor Emeritus of Chemistry at the University of California, Berkeley, and Editor-in-Chief of *Organic Reactions* from 1969 to 1988, died at his home January 2, 1997.

Bill was born in Columbus, Ohio, and received his B.A. degree from Ohio State University in 1941. His graduate work was at Harvard University under Louis Fieser, where he received his M.A. degree in 1942 and Ph.D. in 1944. He joined the faculty at Berkeley in 1945 as an instructor and became a full professor in 1957. His arrival at Berkeley was contemporary with the start of two other distinguished Berkeley careers, those of Professors James Cason and Henry Rapoport. These three brilliant young scientists launched what would soon become a world-class program in organic chemistry at Berkeley. On his retirement from active teaching in 1990, Bill was awarded the Berkeley Citation in special recognition of his outstanding career in teaching, research, and University service.

He maintained an active research program throughout his career, even until the time of his death. During his more than 50-year academic career at Berkeley, Bill directed the research of more than 200 undergraduate, graduate, and post-doctoral students. Bill's research interests were unusually diverse, and they had a profound impact on the development of synthetic organic and natural products chemistry, physical organic chemistry, and photochemistry in the second half of the 20th century. Dauben's early work on the biosynthesis of steroids influenced not only the development of the squalene hypothesis but also our current understanding of the complex photochemistry of vitamin D derivatives. Dauben was a seminal figure in the field of diene and polyene photochemistry, the solvolyses of bridgehead carbinols and amines, and the stereoselective synthesis of complex polycyclic steroids and terpenes. He developed the use of CrO_3 -pyridine for

allylic oxidations and was the leading exponent of the catalysis of organic reactions by high pressures. In recent years, his group completed a series of extremely challenging natural product syntheses, including kempene, crassin methyl ester, spatol, and the ceroplastin nucleus.

Bill was elected to the National Academy of Sciences in 1970, and from 1977–1981 chaired the Chemistry Section. He received numerous honors from the American Chemical Society, including the California Section Award, the Ernest Guenther Award, and the Arthur C. Cope Scholar Award. Among the numerous international awards Bill received are a Senior U.S. Scientist Award from the Alexander von Humboldt Foundation, an honorary doctorate from the University of Bordeaux, a Japan Society for the Promotion of Science Award, and honorary membership of the Pharmaceutical Society of Japan.

Bill's service to the organic chemistry community was profound. He served on the Medicinal Chemistry Study Section of the National Institutes of Health, the Chemistry Panel of the National Science Foundation, the editorial boards of the *Journal of Organic Chemistry*, *Organic Syntheses*, and *Steroids*, and chaired the American Chemical Society Committee on Publications. Bill's role in directing the publication and operation of *Organic Reactions* spans nearly 30 years and cannot be overestimated. He joined the Editorial Board as Editor-in-Chief in 1969 and as President of Organic Reactions Inc. He held both positions for 19 years! In 1988, he relinquished these posts but remained an active member of the Board of Directors until his death. Bill's leadership over the above 28-year period helped define the very nature of today's *Organic Reactions*. He recruited many of the Editors and Directors currently active, and was instrumental in appointing Robert Joyce and Robert Bittman as current Editorial Coordinator and Secretary, respectively. It is regrettable that Bill just missed seeing the Golden Anniversary Volume, *Organic Reactions, Volume 50*, reach the organic chemistry community to which he has dedicated his entire illustrious career.

Bill Dauben is survived by his wife, Carol, his daughters Barbara Baumer of Portland, Oregon and Ann Klaus of College Station, Texas, and two grandchildren.

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CHAPTER 1

ASYMMETRIC ALDOL REACTIONS USING BORON ENOLATES

CAMERON J. COWDEN AND IAN PATERSON

University Chemical Laboratory, Cambridge, England

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INTRODUCTION

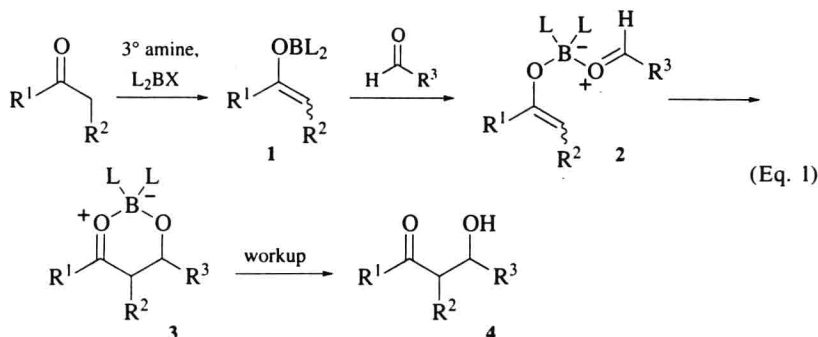
The directed aldol reaction allows the construction of new carbon-carbon bonds in a regio-, diastereo-, and enantioselective manner. The kinetically controlled, boron-mediated aldol reaction is particularly powerful for the efficient synthesis of β -hydroxy carbonyl compounds. Compared to other metal enolates, the boron-oxygen bond in boron enolates is relatively short which, on addition to aldehydes, leads to tight cyclic transition states and highly stereoselective carbon-carbon bond formation. Moreover, variation of the steric demands of the ligands on boron allows discrimination between competing transition states. Chiral auxiliaries attached to the boron enolate are frequently employed to control the relative and absolute stereochemistry of the aldol products. Asymmetric reactions using chiral ligands on boron are also possible and these produce useful enantiomerically enriched adducts. The utility of boron-mediated aldol reactions has been demonstrated in numerous total syntheses of complex polyoxygenated natural products, and several of these are highlighted in the Application to Synthesis section of this chapter.

Several reviews of the directed aldol reaction are available,¹⁻⁸ including the *Organic Reactions* chapter by Mukaiyama in 1981.⁹ The material covered in this review concerns only the asymmetric formation of β -hydroxy carbonyl compounds using boron enolates and surveys the literature from 1981 until the end of 1995.¹⁰

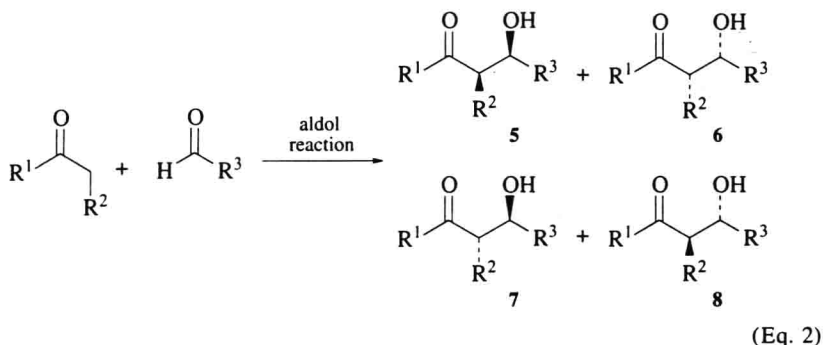
MECHANISM AND STEREOCHEMISTRY

In the boron-mediated aldol reaction, enolization of a carbonyl compound with a Lewis acidic boron reagent (L_2BX ; $X = OTf, Cl, Br$) generates a boron

enolate **1**, which combines with an aldehyde to form a reactive ate-complex **2** (Eq. 1). This complexation then facilitates bond reorganization via a six-membered cyclic transition state, thus affording the boron aldolate **3** which, upon hydrolytic workup, gives the aldol product **4**.



A stereorandom aldol reaction between a carbonyl compound ($R^2 \neq H$) and an aldehyde ($R^3 \neq H$) creates a new carbon-carbon bond and two stereocenters and gives rise to four possible products: a pair of syn stereoisomers (**5** and **6**) and a pair of anti stereoisomers (**7** and **8**) (Eq. 2). If the R^1 , R^2 , and R^3 groups do not

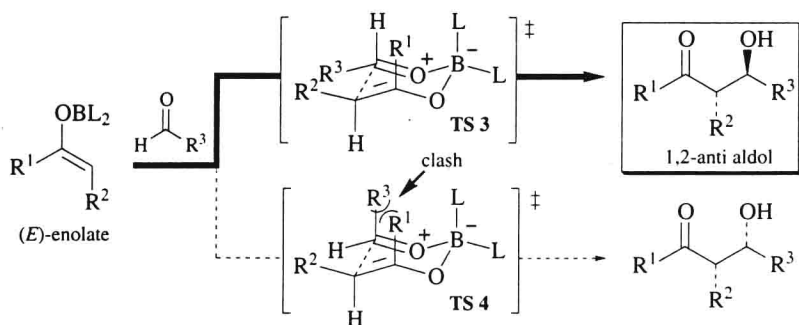
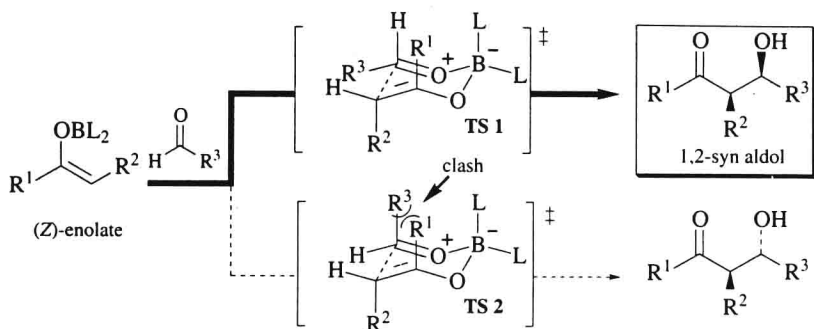


contain any further stereocenters, then compounds **5** and **6** will be enantiomers, as will compounds **7** and **8**. The selective formation of any one of these four stereoisomers constitutes an asymmetric process. In such an aldol reaction there will be two stereochemical issues operating: relative and absolute stereocontrol.

Relative Stereocontrol Arising From Enolization Selectivity

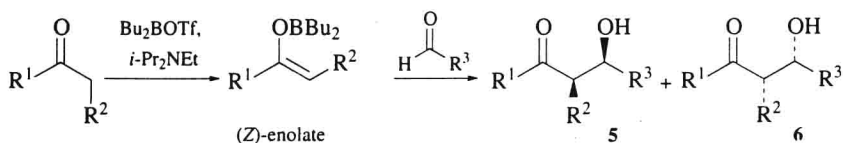
Most boron-mediated aldol reactions are considered to proceed through a chair-like transition state, where (*Z*)-boron enolates* give syn aldol products (Eq. 3) and (*E*)-boron enolates* afford anti aldol products (Eq. 4).^{10a,b} The controlling in-

*To simplify discussion, (*Z*)- and (*E*)- enolates are assigned whereby the oxygen-metal substituent is designated a higher priority than R^1 (see Eqs. 3 and 4).

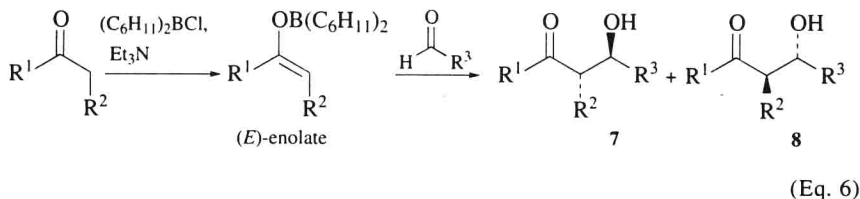


fluence in these reactions is the avoidance of severe 1,3-diaxial interactions in the cyclic transition states (TS 1 vs. TS 2 and TS 3 vs. TS 4). It is also unlikely that transition states such as TS 2 and TS 4 would be accessible because this requires the formation of an unfavorable cis geometry about the ate-complex 2.

As the boron enolate geometry is faithfully translated into aldol product stereochemistry, enolization selectivity is crucially important. In the case of direct boron enolate formation, it is usually possible to selectively prepare either (*E*)- or (*Z*)-boron enolates by enolization of simple ethyl ketones ($R^2 = \text{Me}$).¹⁰⁻¹³ A combination of small ligands on boron (e.g., *n*-butyl), a good leaving group (e.g., triflate), and a bulky amine base (e.g., diisopropylethylamine) usually leads to (*Z*)-selective enolization (Eq. 5). On the other hand, use of sterically demanding



ligands on boron (e.g., cyclohexyl), a poor leaving group (e.g., chloride), and a small amine base (e.g., triethylamine) usually promotes (*E*)-enolate formation (Eq. 6).^{11,12,14-17} Two explanations have been proposed for this enolization behavior.^{18,19}



Absolute Stereocontrol Arising From π -Facial Selectivity

In an aldol reaction, absolute stereocontrol is the selective production of either syn aldol products **5** or **6** and, similarly, the production of either anti products **7** or **8**. Control of the absolute stereochemistry requires facial discrimination of either the boron enolate or aldehyde π -systems. This π -facial discrimination can be achieved by one or more of the following methods:

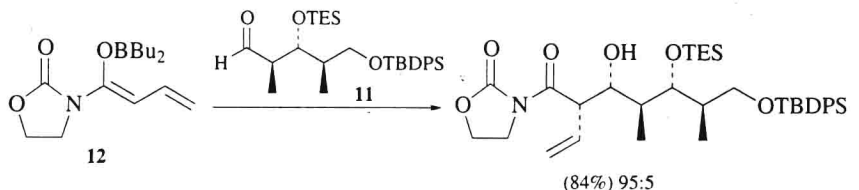
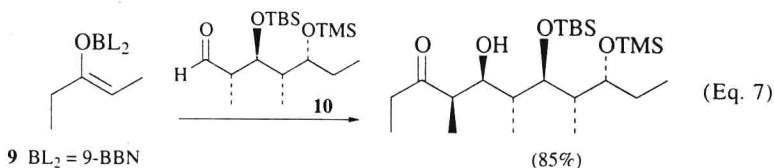
1. The use of chiral aldehydes where R^3 is a stereogenic group
2. The use of auxiliary control from the enolate where R^1 is a stereogenic group and is subsequently removed
3. The use of substrate control from a chiral enolate where R^1 is a stereogenic group but is retained in subsequent steps
4. Reagent control by the use of chiral boron reagents

A more detailed discussion of these individual effects and their combined influence is outlined in the following section.

SCOPE AND LIMITATIONS

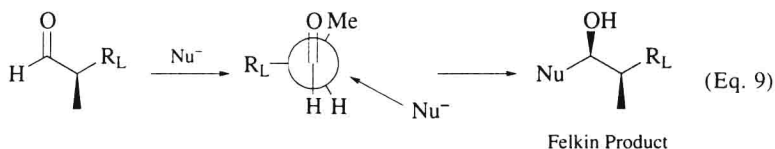
Asymmetric Induction From Chiral Aldehydes

Reactions of achiral enolates with chiral aldehydes represents the simplest method of asymmetric aldol synthesis. Control of the boron enolate geometry generally determines the syn versus anti diastereoselectivity; it therefore follows that if a good level of facial selectivity can be imparted by a chiral aldehyde, a useful asymmetric aldol reaction will be possible. The selectivity induced by a chiral aldehyde can fluctuate, and changing either the ligands on boron,²⁰ the solvent used,²¹ or the protecting group on a β -oxygenated stereocenter²⁰ can have a significant effect. When these variables are optimized, a synthetically useful reaction can result. For example, reaction of boron enolate **9** with aldehyde **10** proceeds in high yield to afford a single observed syn aldol adduct (Eq. 7).²² Interestingly, the aldol reaction of aldehyde **11** was initially performed using a chiral auxiliary, but it was subsequently found that the facial bias of the aldehyde was enough to use the achiral enolate **12** (Eq. 8).²³

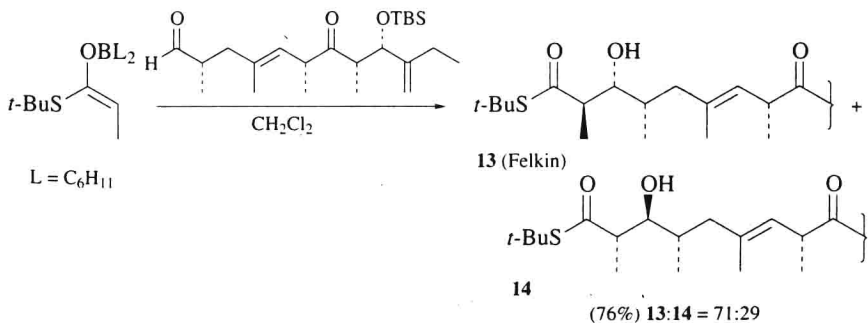


(Eq. 8)

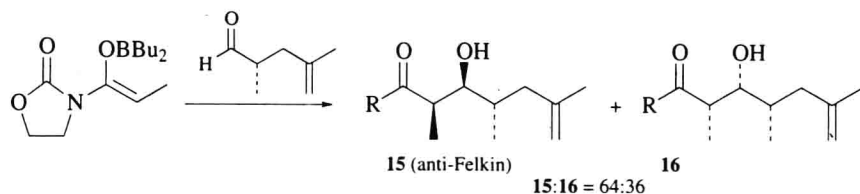
α -Chiral Aldehydes and Influence of Enolate Geometry. Aldol reactions of achiral boron enolates and α -substituted chiral aldehydes are the most thoroughly studied systems. The Felkin–Anh model for nucleophilic attack on α -chiral aldehydes predicts the product stereochemistry indicated in Eq. 9, where R_L is either the largest group or the group with the lowest lying σ^* orbital.^{24,25}



When a reaction takes place through an acyclic transition state, the Felkin–Anh model generally holds. However, boron-mediated aldol reactions usually proceed through a highly ordered cyclic transition state where other factors have an influence on the selectivity. Thus, while (*E*)-boron enolates usually favor formation of the Felkin adduct, as in Eq. 10,^{21,26} (*Z*)-boron enolates normally lead to anti-Felkin products, as in Eq. 11.²⁷



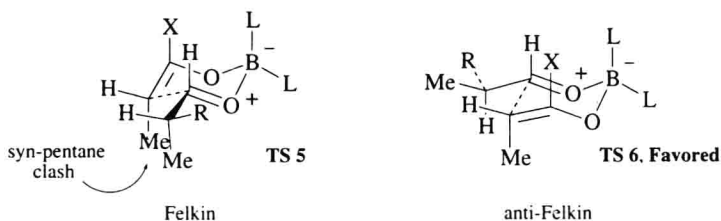
(Eq. 10)



(Eq. 11)

This anomalous behavior of (*Z*)-boron enolates has been attributed to a destabilizing syn-pentane steric interaction in the cyclic chair transition state **TS 5** leading to the Felkin product (Fig. 1).^{28,29} This interaction is avoided in the diastereomeric transition state **TS 6** leading to a preference for anti-Felkin attack. For (*E*)-boron enolates, the aldol addition favors the Felkin-type **TS 7** over **TS 8**.

Transition State Model for (*Z*)-Enolates with α -Chiral Aldehydes



Transition State Model for (*E*)-Enolates with α -Chiral Aldehydes

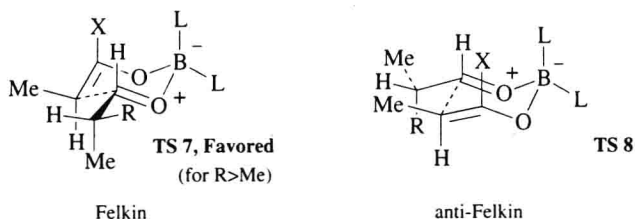
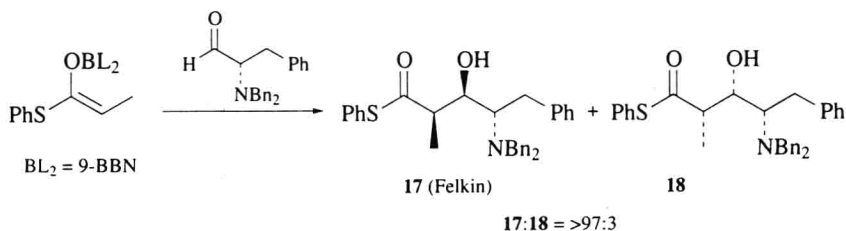


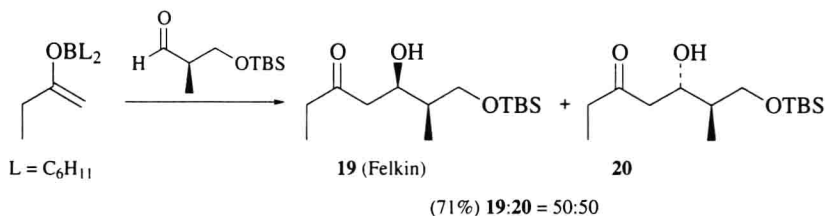
FIG. 1

There are exceptions to this generalization; for example, an α -heteroatom may provide an especially strong facial bias leading to Felkin-type selectivity (Eq. 12).³⁰



(Eq. 12)

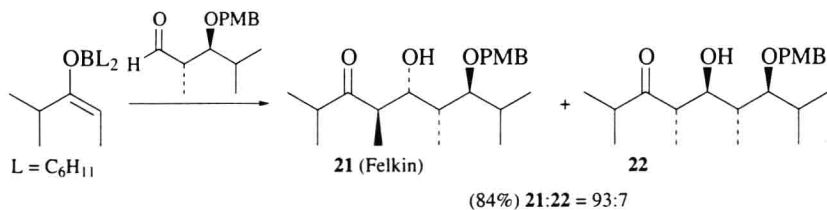
Few examples of boron-mediated aldol reactions of methyl ketones or thioesters with α -chiral aldehydes which do not possess a β -stereocenter have been reported.³¹ It would appear, however, that the asymmetric induction from an α -methyl group alone is negligible (Eq. 13).³²



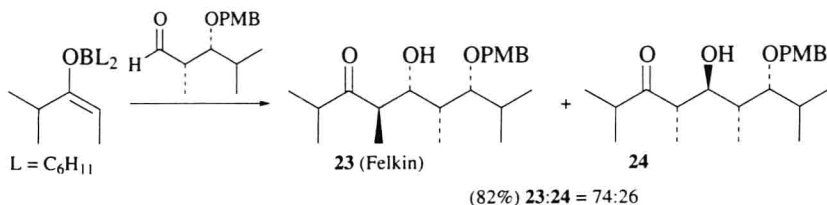
(Eq. 13)

Stereochemical Trends for β -Alkoxy Aldehydes. The boron-mediated aldol reactions of ketones with chiral aldehydes having a β -alkoxy substituent have been studied in detail.^{20,33–39} In the majority of cases, the aldehyde also possesses an α stereocenter which complicates the analysis. For dialkyl boron reagents, a chelation-controlled reaction is not possible, but the β -alkoxy stereocenter has steric and electronic contributions. There are many variables in these reactions, including the β -oxygen protecting group, the choice of ligands on boron and, of course, the structure of the enolate concerned.

The β -alkoxy stereocenter of an aldehyde may exert an electronic or opposed dipoles effect resulting in the production of a 1,3-anti diol relationship.^{37,39} Such an effect is strongest for reactions that proceed through an open transition state, such as the Mukaiyama aldol reaction. In the examples of Eqs. 14 and 15, the se-



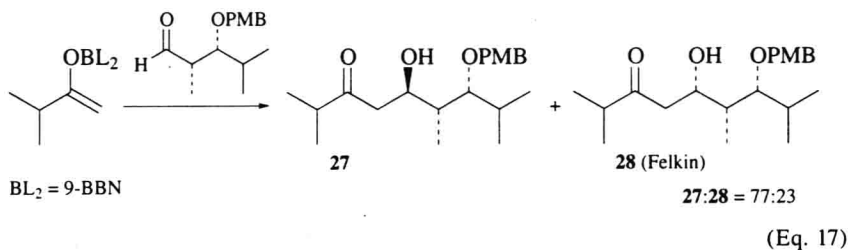
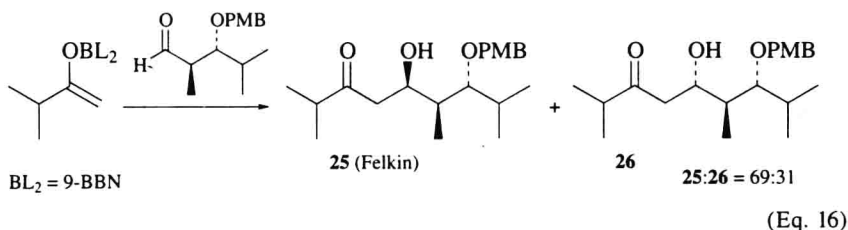
(Eq. 14)



(Eq. 15)

lectivity of the aldol reaction deteriorates when the aldehyde β -stereocenter is inverted, indicating some contribution to the reaction.³⁸ The bias of the aldehyde is still dominated by the α -chiral methyl group however, showing that the effect of the β -stereocenter is only moderate.

The analogous methyl ketone aldol reaction of α -methyl- β -alkoxy aldehydes has been extensively studied.^{20,34,35,38-40} As already indicated (Eq. 13), boron-mediated aldol reactions of methyl ketones are not greatly influenced by the α -chiral methyl group of an aldehyde, and from the results reported to date, the β -stereocenter can play a significant role. For example, the 1,3-anti product is obtained independent of the configuration of the α -methyl group of the aldehyde (Eqs. 16 and 17).³⁹



In contrast, the reaction of boron enolate **29** with aldehydes **30** and **31** leads to a small preference for the 1,3-syn product (Eqs. 18 and 19).³⁴

