Organic Reactions

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Organic Reactions

INTRODUCTION TO THE SERIES
ROGER ADAMS, 1942

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*.

INTRODUCTION TO THE SERIES
SCOTT E. DENMARK, 2008

In the intervening years since "The Chief" wrote this introduction to the second of his publishing creations, much in the world of chemistry has changed. In particular, the last decade has witnessed a revolution in the generation, dissemination, and availability of the chemical literature with the advent of electronic publication and database services. Although the exponential growth in the chemical literature was one of the motivations for the creation of *Organic Reactions*, Adams could never have anticipated the impact of electronic access to the literature. Yet, as often happens with visionary advances, the value of this critical resource is now even greater than at its inception.

From 1942 to the 1980's the challenge that *Organic Reactions* successfully addressed was the difficulty in compiling an authoritative summary of a preparatively useful organic reaction from the primary literature. Practitioners interested in executing such a reaction (or simply learning about the features, advantages, and limitations of this process) would have a valuable resource to guide their experimentation. As abstracting services, in particular *Chemical Abstracts* and later *Beilstein*, entered the electronic age, the challenge for the practitioner was no longer to locate all of the literature on the subject, but rather how to critically efficiently digest it. *Organic Reactions* chapters are much more than a surfeit of primary references; they constitute a distillation of an avalanche of information into the knowledge needed to correctly implement a reaction. It is in this capacity, namely to provide focused, scholarly, and comprehensive overviews of a given transformation, that *Organic Reactions* takes on even greater significance for the practice of chemical experimentation in the 21st century.

Adams' description of the content of the intended chapters is still remarkably relevant today. The development of new chemical reactions over the past decades has greatly accelerated and has embraced more sophisticated reagents derived from elements representing all reaches of the Periodic Table. Accordingly, the successful implementation of these transformations requires more stringent adherence to experimental details and conditions. The suitability of a given reaction for an unknown application is best judged from the informed vantage point provided by precedent and guidelines offered by a knowledgeable author.

As Adams clearly understood, the ultimate success of the enterprise depends on the willingness of organic chemists to devote their time and efforts to the preparation of chapters. The fact that well into the 21st century the series continues to thrive is fitting testimony to those chemists whose contributions serve as the foundation of this edifice. Chemists who are considering the preparation of a manuscript for submission to *Organic Reactions* are urged to contact the Editor-in-Chief.

PREFACE TO VOLUME 73

Volume 73 represents another example in the *Organic Reactions* series in which a single chapter constitutes the volume. In the 66 year history of the series, this has happened six times before, most recently in Volume 71 which featured the chapter "Ionic and Organometallic-Catalyzed Organosilane Reductions" by Gerald L. Larson and James L. Fry. Such single-chapter volumes represent definitive treatises on extremely important chemical reactions. The organic chemistry community owes an enormous debt of gratitude to the authors of such chapters for the generous contribution of their time, effort, and insights on reactions that we clearly value.

The allylation of carbonyl compounds is universally recognized as one of the premier methods for carbon-carbon bond formation. The most prominent reasons for the popularity of the method include the high degree of both diastereo- and enantioselectively observed and the latent functionality in the homoallylic alcohol product which makes the reaction ideal for synthetic planning. Moreover, the reactions are mechanistically intriguing and their utility stimulates a synergy between fundamental studies of stereochemistry and applications in target-oriented synthesis. Among the most often employed methods for carbonyl allylation, the allylboration reaction holds a prominent position. This landmark chapter by Hugo Lachance and Dennis G. Hall provides a comprehensive survey of the various classes of allylic (propargylic and allenic) boron reagents that have been developed in the three decades since their introduction into the portfolio of synthetic methods. The chapter covers the practical features (stability, reactivity, and workup) that practitioners need to select among the available reagents. More importantly, Lachance and Hall have thoroughly covered the most significant aspects of allylboration, namely the stereochemical control elements including relative diastereoselection with crotylboranes, induced (internal) diastereoselection with chiral carbonyl compounds, auxiliary-controlled enantioselective allylations with chiral borane reagents, and the most recent advances in catalysis of allylboration.

Together with the chapter of allylsilanes by Ian Fleming, Jacques Dunoguès, and Roger Smithers (Volume 37) and the chapter of allylstannanes by Benjamin W. Gung (Volume 64) this chapter completes an outstanding triumvirate on this most important of chemical transformations.

It is appropriate here to acknowledge the expert assistance of the entire editorial board, in particular Scott D. Rychnovsky who shepherded this immense chapter, and Robert Bittman, the secretary responsible for processing this chapter. In addition, the *Organic Reactions* enterprise could not maintain the quality of production without the dedicated efforts of its editorial staff, Dr. Linda S. Press and Dr. Danielle Soenen. Insofar as the essence of *Organic Reactions* chapters resides in the massive tables of examples, the authors' and editorial coordinators' painstaking efforts are highly prized.

SCOTT E. DENMARK
Urbana, Illinois

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CHAPTER 1

ALLYLBORATION OF CARBONYL COMPOUNDS

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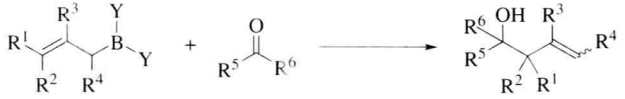
INTRODUCTION

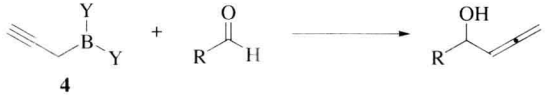
Allylic boron compounds have gained a prominent position as a useful class of synthetic reagents in the past 25 years. Their general structures, **1** and **2**, and their utility in carbonyl additions are shown in Eq. 1. The main use of these reagents is in the stereoselective synthesis of homoallylic alcohols **3** by an allyl-transfer reaction to carbonyl compounds. In this process, a new carbon–carbon bond is formed, and up to two new stereogenic centers are created. Moreover, the residual allylic unit can be manipulated through a number of different transformations such as oxidative cleavage, olefin metathesis, and many others. Although less prevalent, the propargyl and allenyl reagents typified by **4** and **5** have also been described (Eqs. 2 and 3). Most examples of allylic boron reagents used in carbonyl additions belong to one of two main classes, boranes (structure **1**, Y = alkyl) and boronate derivatives (structure **2**, Y = OR or NR_2 for bis(sulfonamide) derivatives). This chapter focuses on describing and comparing both classes, and when needed, they will be discussed separately. A chart of ligand structures with the acronyms used in this text can be found preceding the Tables.



1 Y = alkyl
2 Y = O-alkyl(aryl)
or N-alkyl(aryl)

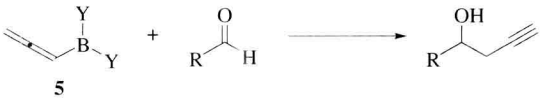
3

(Eq. 1)



4

(Eq. 2)



5 (Eq. 3)

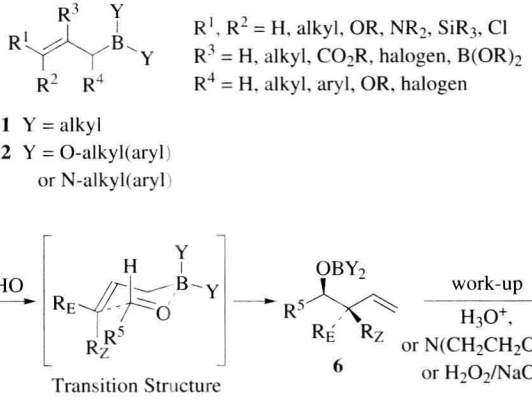
Allylic boron reagents react with several classes of carbonyl compounds and their derivatives, including imines. Their most common use, however, is in nucleophilic additions to aldehydes to produce homoallylic secondary alcohols (i.e., the process of Eq. 1 where $R^5 = H$). This reaction process was discovered by Mikhailov and Bubnov in 1964, who observed the formation of a homoallylic alcohol product from the reaction of triallylborane with aldehydes.[1] The first example of allylboration using an allylic boronate was disclosed by Gaudemar and coworkers in 1966.[2] The true beginnings of this chemistry in terms of practical synthetic applications can be traced back to the late 1970's, with Hoffmann's crucial realization of the regio- and diastereospecific nature of the additions of both crotylboronate isomers to aldehydes (see "Mechanism and Stereochemistry").[3] In the following two decades, the work of Hoffmann, Brown, Roush, and Corey was determinant in maturing carbonyl allylboration chemistry into one of the primary methodological tools in stereoselective synthesis. In particular, numerous syntheses of polyacetate and polypropionate natural products feature stereoselective allylborations as key steps (see "Applications to the Synthesis of Natural Products"). The discovery of the Lewis acid catalyzed manifold by Hall and Miyaura recently opened new doors for further development of this important reaction.

In addition to the predominant allyl and crotyl reagents, a large number of allylic borane **1** and boronate derivatives **2** (Eq. 1) with various substituents (R^1–R^4) have been reported. Interested readers can refer to the comprehensive Tabular Survey at the end of this monograph, which covers the literature up to the end of 2005. Several reviews on allylic boron compounds and other allylmetal reagents and their additions to carbonyl compounds and imines have been written prior to this one,[4–14] and these sources may be consulted if a more in-depth historical perspective is desired.

MECHANISM AND STEREOCHEMISTRY

Thermal Uncatalyzed Reactions

Mechanistically, allylic boron reagents belong to the Type I class of carbonyl allylation reagents.[15] Type I reactions proceed through a rigid, chairlike transition structure which requires a synclinal orientation of reacting π systems. Although catalytic variants for additions of allylic boronates have been reported recently, the reaction between most allylic boron reagents and aldehydes is spontaneous, irreversible, and requires no external activator. The uncatalyzed reactions of these Type I reagents proceed by way of a six-membered, chairlike transition structure that features a dative bond between the boron and the carbonyl oxygen of the aldehyde (Scheme 1).[16–20] Competitive kinetics in the addition of



Scheme 1. Overall aldehyde allylboration process.

an allylboronate to benzaldehyde and deuterobenzaldehyde in different solvents revealed a negative secondary deuterium kinetic isotope effect, which rules out a single-electron transfer mechanism.[20] Theoretical studies using ab initio MO and DFT methods strongly suggest that the strength of the dative bond between the boron and the aldehyde carbonyl oxygen in the transition structure is the dominant factor in determining the rate of the reaction.[19,20] Indeed, whereas the B–O bond is short (~1.6 Å) and very advanced in the transition state, the incipient C–C bond between the carbonyl carbon and the allylic unit has merely initiated (~2.4 Å) (Fig. 1). A weakly bound B–O coordinated complex was detected as an early intermediate in the calculated reaction pathway.[19] Not surprisingly, allylboration reactions tend to proceed faster in non-coordinating solvents, and the most electrophilic boron reagents react faster.[21]

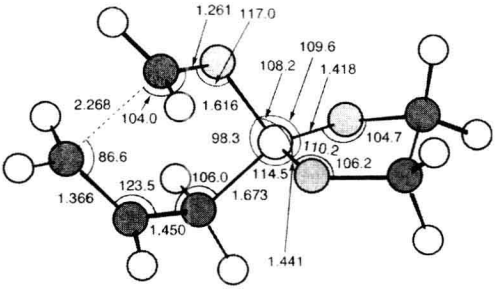
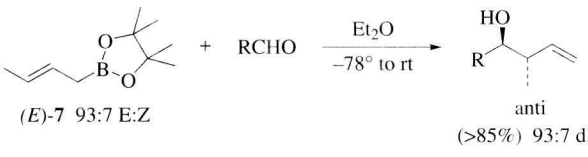


Figure 1. Calculated transition structure for the allylboration reaction between *B*-allyl-1,3,2-dioxaborolane (CH_2=$CHCH_2B[OCH_2]_2$) and formaldehyde at the MP2/6-31G** level of theory. Indicated bond distances are in angstrom. Reprinted with permission from *J. Org. Chem.* **1998**, *63*, 8331.[19] Copyright 1998 American Chemical Society.

The immediate products of additions between carbonyl substrates and allylic boranes **1** or boronate derivatives **2** are borinate or borate esters, respectively. To cleave the covalent B–O bond in these intermediates (structure **6**, Scheme 1) and to obtain the desired free alcohol, a hydrolytic or oxidative work-up is required. This issue is discussed in detail in the section "Work-Up Conditions". In the interest of simplifying chemical equations, specific work-up conditions are not included in most of the examples highlighted in this chapter.

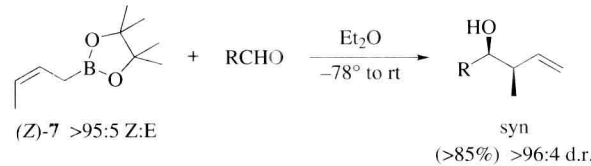
One of the main reasons for the popularity of allylic boron reagents in stereocontrolled synthesis is that their additions to aldehydes are reliably highly stereoselective and the outcome is predictable. The diastereospecificity of the reaction was first recognized by Hoffmann and Zeiss using both E- and Z-crotylboronates **7** (Eqs. 4 and 5).[3,22] For both crotylboranes and crotylboronates, the additions generally proceed with near-perfect reflection of the olefin geometry of the reagent into the configuration of the product. Specifically, the E-crotylboron reagents (Scheme 1, $R_E = Me$, $R_Z = H$) lead to anti-propanoate products and the Z-crotyl reagents (Scheme 1, $R_E = H$, $R_Z = Me$) lead to syn-products. In both instances, of the two possible chairlike transition structures the favored one places the aldehyde substituent (R^5) in a pseudo-equatorial orientation. This model, which has been reproduced computationally for both crotylborane[17] and crotylboronate[18] derivatives, accounts for the high diastereospecificity of most allylborations. Even highly functionalized reagents and most intramolecular additions follow the same trend.



(*E*)-**7** 93:7 E:Z

anti
(>85%) 93:7 d.r.

(Eq. 4)



(*Z*)-**7** >95:5 Z:E

syn
(>85%) >96:4 d.r.

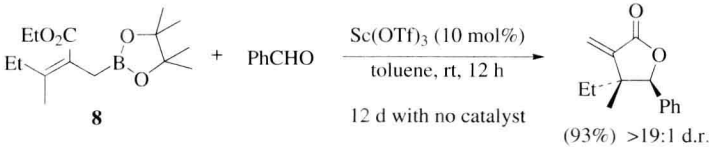
(Eq. 5)

It is well accepted that the high diastereospecificity of aldehyde allylboration reactions is a consequence of the compact cyclic transition structure. Theoretical calculations have shown that the chairlike transition structure shown in Scheme 1 and Fig. 1 is the lowest in energy relative to other possibilities such as the twist-boat conformation.[16] With boronate reagents, it has also been suggested that a weak hydrogen bond between the axial boronate oxygen and the hydrogen of the polarized formyl unit contributes to the preference for the transition structure with the aldehyde substituent in the pseudo-equatorial position.[23]

Lewis Acid Catalyzed Reactions

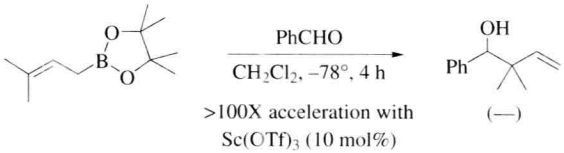
As described above, allylic boron reagents are self-activating, Type I reagents where the allylation is effected by coordination of the aldehyde carbonyl oxygen

to the boron atom within a cyclic six-membered transition structure. Because of this self-activation mechanism, there would appear to be no advantage to using an external promoter such as a Lewis or Brønsted acid. Furthermore, one could expect an added Lewis acid to compete with the boron atom for the basic aldehyde oxygen, potentially leading to a switch from the highly diastereospecific Type I mechanism to a less selective, open-chain Type II mechanism.[15] Recent publications, however, show that the additions of allylic boronates can be efficiently and beneficially catalyzed by several Lewis acids.[24–28] Allylic boranes are not subject to this catalytic effect.[29] For additions of allylic boronates, the rate enhancements observed in the presence of these catalysts are quite dramatic.[24,29] For example, the addition of 2-ethoxycarbonyl allylboronate **8** to benzaldehyde to give an exo-methylene butyrolactone requires almost two weeks at room temperature, but only 12 hours in the presence of a catalytic amount of $Sc(OTf)_3$ (Eq. 6).[24] Note that in this example the resulting homoallylic alcohol intermediate cyclizes in situ with the carboxy ester group to form a lactone product.

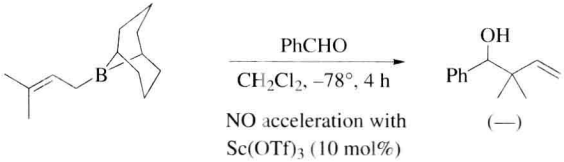


(Eq. 6)

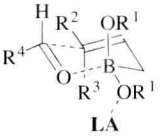
It is noteworthy that the stereospecificity observed in the thermal reaction is fully preserved under this new catalytic manifold. Furthermore, the presence of a 2-alkoxycarbonyl substituent on the allylic boronate is not necessary for the metal-promoted activation to occur (Eq. 7).[24,25] According to mechanistic studies, a chairlike bimolecular transition structure similar to the thermal additions can be proposed for these catalyzed allylborations.[29] Control experiments have confirmed the inefficiency of Lewis acids with dialkylallylboranes (Eq. 8). Hence, the catalytic effect is thought to derive from an increase in the electrophilicity of the boron atom through binding of the metal ion to one of the boronate oxygens [transition structure (T.S.) **9**], as opposed to coordination of the carbonyl oxygen (T.S. **10**).[29]



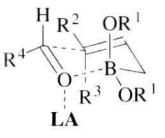
(Eq. 7)



(Eq. 8)



9

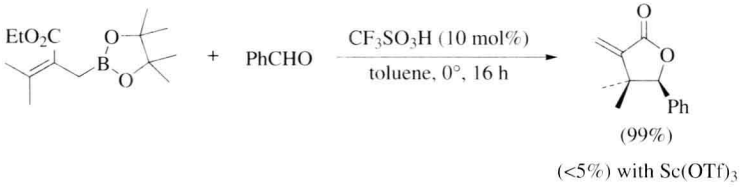


10

Coordination of the Lewis acid to the boronate oxygens is thought to decrease the overlap between the oxygen lone electron pairs and the vacant p-orbital of the boron atom. Consequently, the boron center is rendered more electron-deficient, and compensates by strengthening the key boron–carbonyl oxygen interaction and concomitantly lowering the activation energy of the reaction. This idea is consistent with theoretical calculations of the non-catalyzed allylboration[19] and from an experimental study consisting of a quantitative survey of steric and electronic effects in the reactions of different allylboronates.[21] The latter results led to the conclusion that the rate of a given allylboration can "be rationalized in terms of the relative availability of lone pairs of electrons on the oxygen atoms attached to the boron".

Brønsted Acid Catalyzed Reactions

In line with the effect of Lewis acids, the huge rate acceleration in the additions of allylic boronates to aldehydes by strong protic acids such as triflic acid was recently reported.[30] In the example of Eq. 9, the reaction yield is almost quantitative after 16 hours at 0° under conditions where the use of $Sc(OTf)_3$ gives less than 5% of the product. Interestingly, additions with geometrically defined allylic boronates are not always stereospecific. Although definitive mechanistic studies have not yet appeared, it can be presumed that the origin of the acceleration could be similar to that of Lewis acid catalysis, with activation by protonation of a boronate oxygen in the cyclic chairlike transition structure.



(99%)

(<5%) with $Sc(OTf)_3$

(Eq. 9)

SCOPE AND LIMITATIONS

Preparation of Allylic Boron Reagents

Unlike aldehydes and ketones, allylic boron compounds are not ubiquitous, commercial organic substrates. There are several methods for the preparation of allylic boronates, however, and many of these have been developed in the past decade. This topic has been reviewed recently[14] so only the most common methods are emphasized in this section. As a result of the lesser stability of allylic boranes, methods to access these reagents are more limited and it is generally easier to prepare allylic boronates with a wide range of functional groups.