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New preparative methods for allylic boronates and their application in stereoselective catalytic allylborations*

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Abstract: Stereocontrolled additions of allylic metal reagents to carbonyl compounds constitute one of the most useful classes of transformations in organic synthesis. The recent development of Lewis and Brønsted acid-catalyzed manifolds for the allylboration of carbonyl compounds has opened doors toward an ideal carbonyl allylation methodology using stable and nontoxic allylic boronates as reagents. This paper describes the development of acid-catalyzed allylborations, mechanistic investigations of these new processes, and ongoing efforts toward general catalytic enantioselective allylboration methodologies. The preparation of optically enriched α-substituted allylic boronate reagents is discussed, as well as their applications in Lewis acid-catalyzed additions to afford skeletally diverse products like propionate units, polysubstituted furans, vinylcyclopropanes, and larger ring systems.

Keywords: aldehydes; allylation; boron; catalysis; Lewis acids; stereocontrol.

INTRODUCTION

In the past two decades, carbonyl allylation chemistry has become an invaluable tool for the stereocontrolled formation of carbon–carbon bonds in the field of organic synthesis (Fig. 1) [1]. The usefulness and popularity of aldehyde allylation methods in the context of natural product synthesis is matched only by asymmetric aldol methodologies.

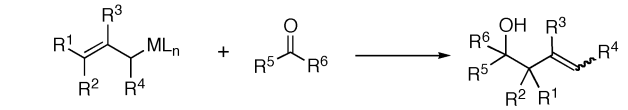

Fig. 1 General approach to substituted homoallylic alcohols from the addition of allylmetal reagents to carbonyl compounds.

Several excellent methodologies have been described for carbonyl allylation using stoichiometric chiral directors based on reagents of boron, silicon, tin, and titanium [1]. A number of substoichiometric (catalytic) methods have been reported for allylic reagents of silicon, tin, and chromium [2]. Of all possible allylic metal reagents, however, the use of allylic boron reagents has dominated the field of natu-

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ral product synthesis [3]. This reaction process was discovered in 1964 by Mikhailov and Bubnov, who observed the formation of a homoallylic alcohol product from the reaction of triallylborane with aldehydes [4]. The first example of allylation using an allylic boronate was disclosed by Gaudemar and coworkers in 1966 [5]. However, it is only in the late 1970s that the true beginnings of this chemistry in terms of practical synthetic applications can be traced back, with Hoffmann's crucial realization of the regio- and diastereospecific nature of the additions of both crotylboronate isomers to aldehydes [6]. It is only in the next decade, the 1980s, that highly efficient methods appeared for the control of absolute stereoselectivity [6]. The most notable contributions in terms of efficiency and utility are the methods of Brown, using pinane-derived reagents [7], the borolane derivatives of Masamune [8], the bis(sulfonamide) derivatives of Corey [9], the tartrate boronates of Roush [10], and more recently, another class of highly efficient dialkylboranes reported by Soderquist and coworkers [11].

A mechanistic description of allylic metal reagents helps us understand the popularity of allylic boron reagents. A classification system for carbonyl allylation reagents based on the postulated nature of the mechanism was proposed by Denmark in the early 1980s [12]. Allylic boron reagents belong to the Type I class (Fig. 2, M = B), which involves closed cyclic, six-membered chair-like transition states characterized by internal activation of the carbonyl by the boron atom [13]. This mechanism contrasts with the Type II reagents, exemplified by allylic trialkylsilanes and allylic trialkylstannanes (M = Si or Sn), which generally react with aldehydes under the activation of an external Lewis acid, and proceed by way of open transition structures [14]. Allylic trialkyltin reagents may also behave as Type I reagents in the absence of a Lewis acid, albeit only at high temperatures [15].

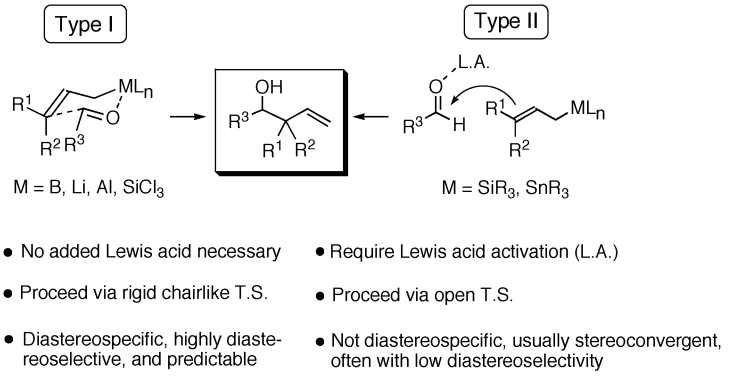


Fig. 2 Mechanistic classification for allylic metal reagents of Types I and II.

The reactivity of allylic boranes and boronates can be modulated quite easily by varying the two remaining boron substituents (i.e., L_n in Figs. 1 and 2). Moreover, as a result of the Type I mechanism, diastereoselection with γ-substituted reagents is generally very high. This important observation was first noted by Hoffmann and Zeiss [6] and constitutes a significant advantage of boron reagents over all Type II reagents such as trialkysilanes and trialkylstannanes. Unfortunately, the means to control absolute stereoselectivity in the additions of allylic boron reagents to carbonyl compounds have long been restricted to stoichiometric approaches because Lewis acids were thought unsuitable for catalyzing allylborations. Consequently, even in today's age of substoichiometric enantiocontrol, the Brown pinene-based allylation reagents have remained a method of choice in the toolbox of synthetic chemists [1b,3a,7c]. Yet, there are other disadvantages to the Brown allylation aside from the need for a stoichiometric chiral director. These allylic dialkylboranes are unstable to air and moisture and must usually be prepared and reacted in situ at low temperatures.

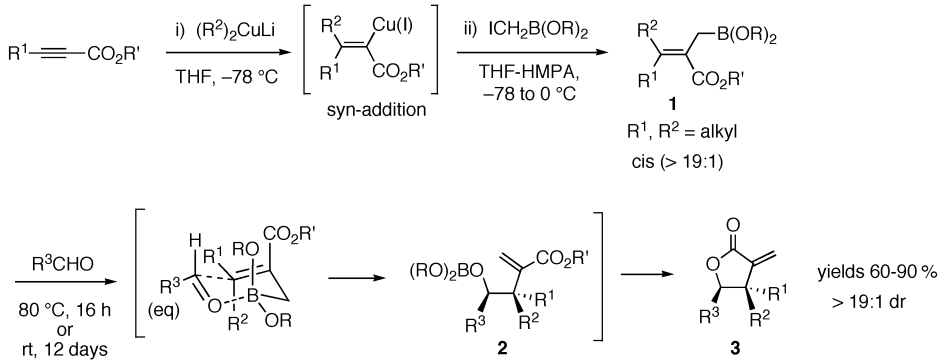
Despite extensive efforts by numerous research groups over the course of more than two decades [1,2], there is still no aldehyde allylation methodology that possesses all of the following attributes:

mildness and chemoselectivity, substrate generality (for both allylmetal reagent and aldehyde substrate), high levels of diastereo- and enantioselectivity, and high practicality (ease of use, low cost, and low environmental impact). Very importantly, the ideal enantioselective allylation methodology would circumvent the use of a chiral auxiliary through a simple and efficient chiral catalyst. In this regard, a catalytic enantioselective allylboration would be a very attractive method. Indeed, pinacol allylic boronates are air- and water-stable nontoxic reagents whose additions to aldehydes are characterized by very high levels of chemo-, regio-, and diastereoselectivity. This article relates our laboratory's discovery of the Lewis and Brønsted acid-catalyzed allylboration, our mechanistic investigations of these new processes, and the ongoing efforts toward a general catalytic enantioselective allylboration methodology.

DISCOVERY AND DEVELOPMENT OF CATALYZED ALLYLBORATIONS

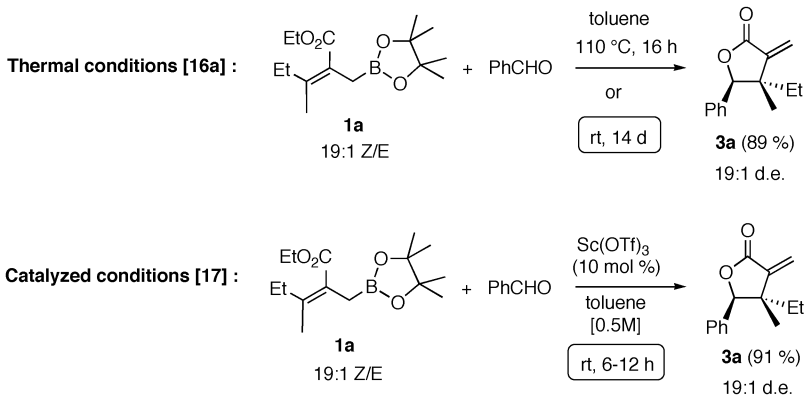
Lewis acid-catalyzed allylborations

The simple idea of accelerating carbonyl allylborations with Lewis acids was counter-intuitive on a mechanistic standpoint because the carbonyl is internally activated by the boron atom in the transition state for this reaction (cf. Fig. 2). Moreover, by potentially inducing a changeover from a Type I mechanism toward open transition structures, the use of Lewis acids would be detrimental to the reaction's diastereoselectivity. However, there were no reports in the literature to confirm these apprehensions, and we were presented with an opportunity to test the idea. We had successfully developed an efficient approach to access 3,3-disubstituted 2-alkoxycarbonyl allylboronates **1** through a stereoselective carbocupration of acetylenic esters followed by electrophilic trapping with halomethylboronates (Scheme 1) [16]. These allylic boronates **1** were found to add to aldehydes stereospecifically to afford, through the intermediacy of open intermediates **2**, α-exomethylene butyrolactones **3** embedding a quaternary carbon center [16a].



Scheme 1 Approach to *exo*-methylene γ-lactones using tetrasubstituted 2-alkoxycarbonyl allylboronates **1**.

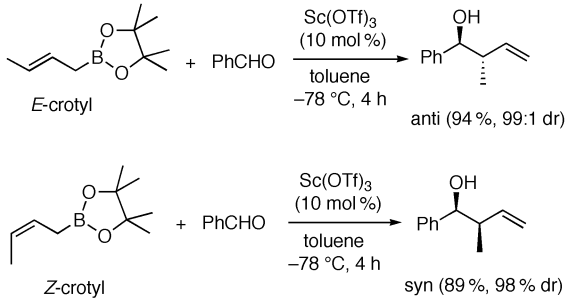
The nucleophilicity of reagents **1**, however, is greatly attenuated by the 2-alkoxycarbonyl substituent, and by the steric effect from the two substituents on carbon 3 (i.e., R^1, R^2). Not surprisingly, reaction times were very long: as much as two full weeks at room temperature! An attempt to accelerate these reactions was made by screening several dozen metal salts for catalysis, in particular, metal triflates, using a qualitative NMR-based experiment. To our surprise, both $Sc(OTf)_3$ and $Cu(OTf)_2$ led to a dramatic rate acceleration [17]. A side-by-side comparison of a model uncatalyzed and catalyzed allylboration between **1a** and benzaldehyde was set up. The outcome, highlighted in Scheme 2, con-



Scheme 2 Comparison of thermal uncatalyzed and Sc(III)-catalyzed allylborations with model substrates.

firmed that the allylborations of reagents **1** could be catalyzed with a dramatic rate acceleration and with preservation of the stereospecificity displayed by the uncatalyzed variant [17].

Our original communication also reported control experiments, such as the reaction of an esterless allylic boronate, which provided an indication that the 2-alkoxycarbonyl substituent of allylic boronates **1** was not necessary and that the catalytic manifold could be generalized to many other reagents. This observation was further confirmed in a subsequent report by Miyaura and coworkers (Scheme 3), who showed that additions of the pinacol crotylboronates can be accelerated by not only $Sc(OTf)_3$ but also by classical hard Lewis acids like BF_3, $TiCl_4$, and $AlCl_3$ [18].



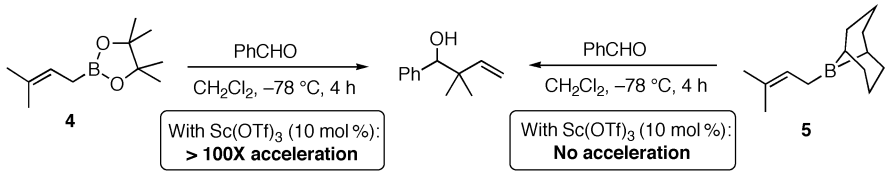
Scheme 3 Demonstration of diastereospecificity in the Sc(III)-catalyzed additions of crotylboronates.

Mechanistic considerations

At the outset, the fact that the additions of crotylboronates are still stereospecific provided us with a strong indication that the catalytic allylboration is probably proceeding through the usual chairlike transition state characteristic of Type I allylation reagents. Further evidence for this mechanism was obtained by the measurement of rate orders [19], which confirmed the bimolecularity of the process, that is, a rate equation proportional to K[allylboronate]^1[aldehyde]^1. This important result left two possibilities for the site of coordination of the Lewis acid: aldehyde double coordination (**A**) or coordination to one of the boronate oxygens (**B**) (Fig. 3).

Fig. 3 Possible mechanisms of activation by the Lewis acid.

This intriguing question was addressed by comparing the effect of $Sc(OTf)_3$ on the 3,3-dimethyl allylboronate **4** and its borabicyclononane analog **5** (Scheme 4). Whereas the boronate is accelerated over 100-fold, the Lewis acid had no effect on the dialkylborane: no rate acceleration nor any decomposition [19]. Other control experiments ruled out the possibility of transmetallation of the allylboronate, as well as catalysis by adventitious triflic acid.

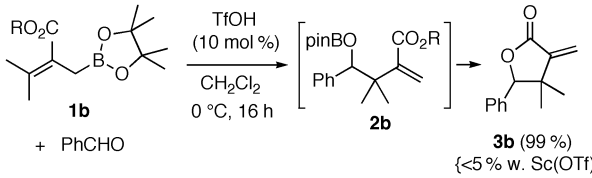


Scheme 4 Control experiments to elucidate the mode of activation of the Lewis acid-catalyzed allylboration.

Altogether, these experiments are consistent with a mechanism of catalysis based on electrophilic activation of the boron atom through coordination of one of the boronate oxygens (i.e., **B** in Fig. 3). This mechanism of activation is in accord with an experimental study by Brown and coworkers, who concluded that the "reactivity of boron-based allylation reagents can be rationalized in terms of the relative availability of lone pairs of electrons on the oxygen atoms attached to the boron" [20]. At this time, one can only speculate as to which of the four lone electron pairs of the boronic ester is involved in the coordination. It is most likely that this interesting fundamental issue will be addressed successfully only with the help of high-level calculations. To the best of our knowledge, this mechanism represents the first example of a Lewis acid-promoted electrophilic activation of a boronic ester in a way analogous to the activation of carbonyl-containing substrates in numerous organic reactions.

Brønsted acid-catalyzed allylborations

Shortly after initiating an investigation on the scope of substrates, we quickly found limits to the new Lewis acid-catalyzed conditions. The problem was in the form of electron-rich aromatic aldehydes and sterically hindered aliphatic ones, which provided low yields with $Sc(OTf)_3$ at room temperature [21]. To address these shortcomings, strong protic acids were attempted as catalysts despite our apprehension that the allylic boronates would undergo protodeboronation or cationic oligomerization. Nevertheless, a triflic acid-catalyzed reaction between allylboronate **1b** and benzaldehyde was attempted (Scheme 5). To our satisfaction, it provided a near-quantitative yield of the lactone product, at 0 °C, a temperature at which $Sc(OTf)_3$ was essentially useless (<5 % yield) [22]. Moreover, this result came with an added bonus: the open intermediates (e.g., **2b**) lactonized spontaneously in the presence of TfOH so that there was no longer a need to treat some of the crude reaction mixtures with a separate toluenesulfonic acid-catalyzed cyclization.

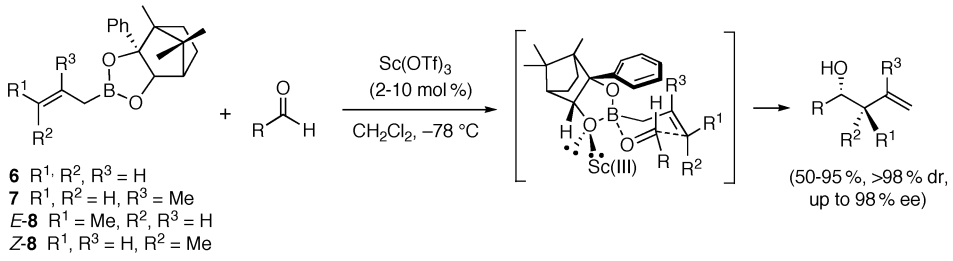


Scheme 5 Comparison of triflic acid-catalyzed and Sc(III)-catalyzed allylborations.

ENANTIOCONTROLLED ACID-CATALYZED ALLYLBORATION OF ALDEHYDES

Stoichiometric approaches

The most important practical implication of the new catalyzed conditions is the possibility to react pinacol allylic boronates and other hindered boronates at temperatures much lower than previously possible. For example, pinacol crotylboronates react slowly at 0 °C in the absence of a Lewis acid, and they are essentially unreactive with most aldehydes at –78 °C. The Lewis acid-catalyzed conditions now allow these additions to proceed within a few hours at –78 °C. We tried to use this increase of reactivity to the benefit of improved stereoselectivities in the additions of chiral allylic boronates. Existing methodologies like the Brown pinene-based system tend to show lower enantioselectivities in crotylation reactions compared to simple allylations [1]. Given the importance of the products of allylation, methallylation, and particularly crotylation reactions, we set out to develop the first general, highly enantio- and diastereoselective system for the allylation of aldehydes based on conveniently handled and stable boron-based reagents. Of several chiral diol auxiliaries investigated, we were surprised to discover that the original camphordiol boronates developed by Hoffmann and coworkers were actually the most stereoselective ones (Scheme 6) [23]. When reported in 1978, these camphordiol-derived reagents were the first ever examples of chiral allylic boron reagents [24]. Unfortunately, their stereoselectivity is only modest under noncatalyzed conditions. Upon using the $Sc(OTf)_3$-catalyzed procedure at –78 °C, however, the stereoselectivities raised uniformly to levels over 95 % in the simple allylation, methallylation, and both *E*- and *Z*-crotylations of a wide range of aldehydes with reagents **6–8** (Fig. 4) [23]. Moreover, these reactions were proven on gram-scale with high yields of recovery for the camphordiol auxiliary. It is also noteworthy that the use of triflic acid as catalyst led to lower enantioselectivities compared to $Sc(OTf)_3$.



Scheme 6 Enantiocontrolled $Sc(OTf)_3$-catalyzed allylboration with camphordiol-derived reagents **6–8**.

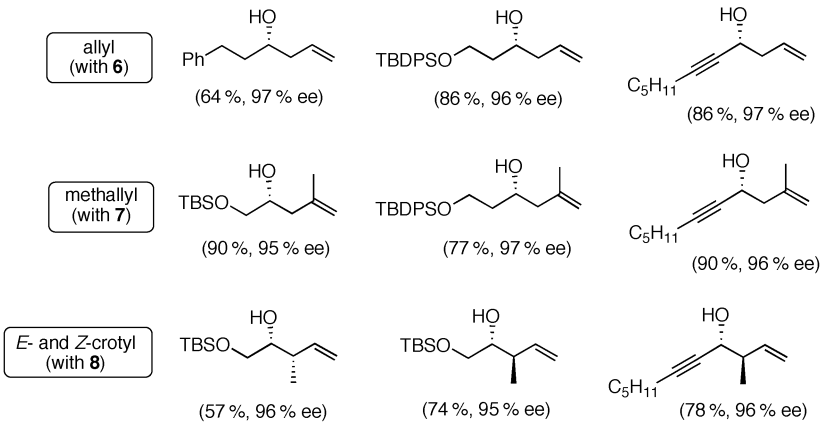
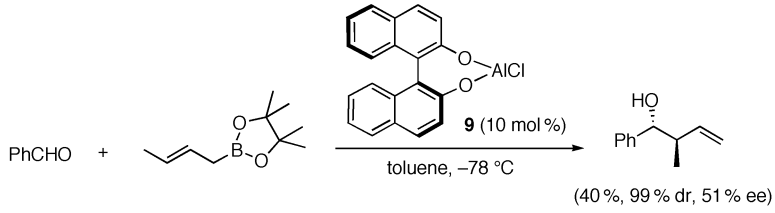


Fig. 4 Examples of synthetically useful intermediates made using the $Sc(OTf)_3$-catalyzed additions of reagents **6–8**.

Catalytic approaches

The ultimate application of the acid-catalyzed allylboration is the development of a general, catalytic enantioselective methodology for the simple allylation and crotylations of aldehydes and ketones. Current methods of general use are based on stoichiometric chiral directors with rather unstable reagents that cannot be isolated and must be formed and used in situ under air- and moisture-free conditions. It would represent an important advance to develop an effective and general method using stable allyllic boronates, such as the pinacol-based reagents, that could be performed with a substoichiometric amount of a simple chiral catalyst. In their 2002 communication, Miyaura and coworkers reported that chiral binol-aluminium Lewis acid **9** provides 51 % ee in the *E*-crotylation of benzaldehyde (Scheme 7) [18]. Though modest, this example constituted the first example of a catalytic enantioselective allylboration and set the stage for more work to come.



Scheme 7 Binol-AlCl-catalyzed crotylboration of benzaldehyde by Miyaura and coworkers.

Following our own original report of catalytic allylborations [17], we tried several chiral ligand systems for scandium, copper, and many other metals in simple allylations using allylboron pinacolate. None of these attempts were successful, providing either low ee or no rate acceleration over the background uncatalyzed reaction. We suspect that these chiral metal complexes are simply too hindered to coordinate effectively to the hindered boronic ester. In 2005, our realization that protic acids could be effective catalysts led us to consider chiral Brønsted acids [25]. At that time, the literature featured an increasing number of reports describing such catalytic systems. Our attention focused on Yamamoto's ingenious concept of Lewis acid-assisted Brønsted acidity [26]. This concept was elegantly demonstrated with the diol-$SnCl_4$ complexes of type **10**, which were employed in several reactions (Fig. 5) [27].

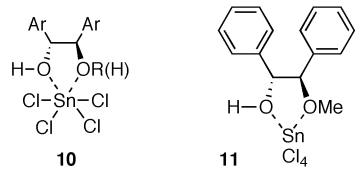
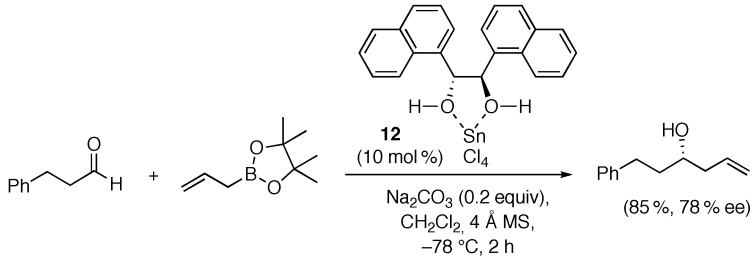


Fig. 5 Yamamoto's diol-$SnCl_4$ complexes used as chiral Brønsted acids.

We first aimed at optimizing a procedure for the simple allylation of aliphatic aldehydes, which tend to be the most difficult examples with existing catalytic enantioselective allylation methodologies [2]. With a modest ee of 32 % in the allylation of hydrocinnamaldehyde, our very first attempt with simple complex **11** left much room for improvement but was nonetheless promising. A careful optimization of diol and conditions improved the ee up to 80 % using complex **12**, made from a bis(naphthyl) diol, and a solid carbonate salt as a scavenger of adventitious HCl (Scheme 8) [28].



Scheme 8 Example of enantioselective chiral Brønsted acid-catalyzed allylboration of aliphatic aldehydes.

This procedure represents the most efficient catalytic enantioselective allylboration of aldehydes to date. Although it is not yet practically applicable in the control of absolute stereochemistry, it was found useful in doubly diastereoselective additions, especially in the matched manifold where the diastereomeric ratio can be substantially improved [28,29]. The search for a broadly effective catalytic enantioselective allylboration continues in our laboratory. Other groups have made excellent contributions in the past few years, particularly in the allylboration of ketones [30,31].

LEWIS ACID-CATALYZED ADDITIONS OF α-SUBSTITUTED ALLYLIC BORONATES

Acyclic α-substituted allylic boronates

Two strategies have been developed for controlling enantiofacial selectivity in additions of allylic boronates to achiral aldehydes: 1. The use of a chiral diol or a diamine derivative as boron's two nonallylic substituents (B-chiral allylic boronates), and, 2. The use of optically pure, α-substituted reagents (C-chiral, or α-chiral allylic boronates) [32].

The preparation of optically enriched α-substituted allylic boronates **13** and their additions to aldehydes were pioneered by Hoffmann [32]. These reagent-controlled additions proceed with almost perfect transfer of chirality to give two diastereomeric products **16** and **17** (Fig. 6). The *Z*- and *E*-allylic alcohol products are epimeric, and their ratio is highly dependent on the nature of the α-substituent (R^1) and the nature of the boronic ester [32]. The ratio of **16** and **17** can be explained in terms of steric and dipolar effects on the two competing transition structures **14** and **15**. With a nonpolar alkyl substituent R^1, steric interactions play a dominant role in the relative energies of these putative transition structures. Transition structure **14** is destabilized by a steric interaction between the boronic ester and the pseudoequatorial substituent R^1. On the other hand, chairlike transition structure **15** features unfavorable al-

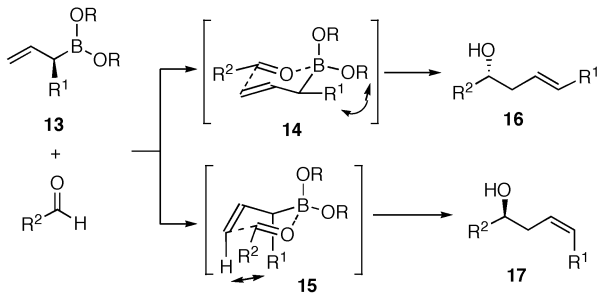
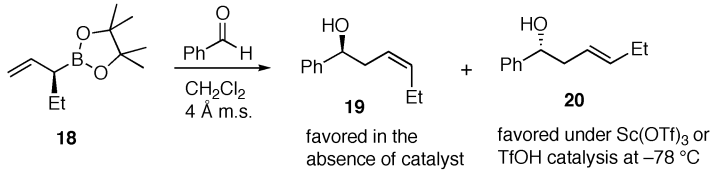


Fig. 6 Postulated competing transition structures in the allylation of aldehydes with α-substituted allylic boronates (**13**). Note: A stereodefined reagent is shown to emphasize the stereochemistry of the reaction and the epimeric relationship between products **16** and **17**.

lylic interactions due to the pseudo-axial position of the R^1 substituent. The use of a hindered ester, such as pinacolate, aggravates interactions between R^1 and the pinacol methyls in **14**, and tends to favor transition structure **15** leading to the *Z*-configured product **17** [33]. With a polar R^1 substituent (halogen, alkoxy), dipolar effects tend to dominate and further favor transition structure **15** with the pseudo-axial C–R^1 bond oriented anti to the axial B–O bond [32].

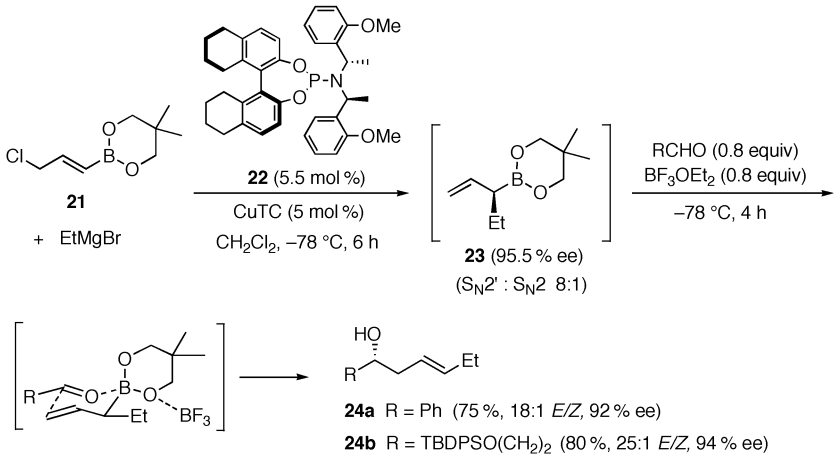
More surprising results were observed in a recent study on the scope and stereoselectivity of additions of α-substituted allylboronates promoted by the low-temperature Lewis and Brønsted acid-catalyzed conditions. The stereoselectivity of additions of four model α-substituted allylboronates to benzaldehyde was examined under the standard thermal (uncatalyzed) conditions and the Lewis and Brønsted acid-catalyzed conditions [34]. With either $Sc(OTf)_3$ or triflic acid as catalysts, an α-ethyl allylboronate, **18**, led to a surprising inversion of stereoselectivity (Scheme 9). This inversion can be tentatively rationalized by invoking subtle differences in the geometry of the allylboration transition state between the uncatalyzed and catalyzed pathways, which are suggestive of a more advanced transition structure in the catalyzed variants. Thus, a transition state with a shorter B–O(aldehyde) bond and a longer B–C bond would relieve the R^1–OR interaction of structure **14**, and further favor the corresponding product **16** (i.e., **20** in Scheme 9).



Scheme 9 Inversion of selectivity between thermal and acid-catalyzed allylborations of α-substituted reagent **18**.

Our results with reagent **18** suggested that careful optimization of the nature of the alkyl substituent and the boronate's diol unit in an optically pure α-substituted allylic boronate could provide very high stereoselectivities. At the same time, we were motivated to develop an efficient catalytic enantioselective methodology for the preparation of α-alkyl allylic boronates. The starting point to such a method was a report by Alexakis and coworkers of catalytic enantioselective allylic alkylation using Grignard reagents [35]. The same transformation, when applied to 3-halopropenyl boronates as substrates, required extensive fine-tuning to achieve the desired levels of regiochemistry and enantioselectivity. In the event, the use of a semi-hydrogenated chiral phosphoramidite ligand, **22**, along with dioxaborinane **21** and ethylmagnesium bromide as the optimal reagents, led to the formation of reagent **23** in 8:1 regioselectivity and over 95 % ee (Scheme 10) [36]. Concurrent to this work, a "one-pot" pro-

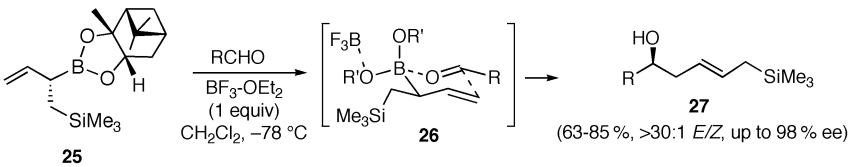
tocol was optimized where the aldehyde and the Lewis acid, BF_3OEt_2, are added after the allylic alkylation. The products of allylboration (**24**) were obtained not only with excellent transfer of chirality (up to 94 % ee), but also in surprisingly high *E*/*Z*-selectivity up to 25:1. Considering that selectivities of about 3:1 are obtained in the absence of a Lewis acid, this outcome is most satisfying and provides yet another evidence of the tremendous benefits of Lewis acid catalysis in additions of allylic boronates to carbonyl compounds.



Scheme 10 Catalytic enantioselective preparation of an α-substituted allylboronate and its one-pot addition to aldehydes.

Application to a boron/silicon double-allylation reagent

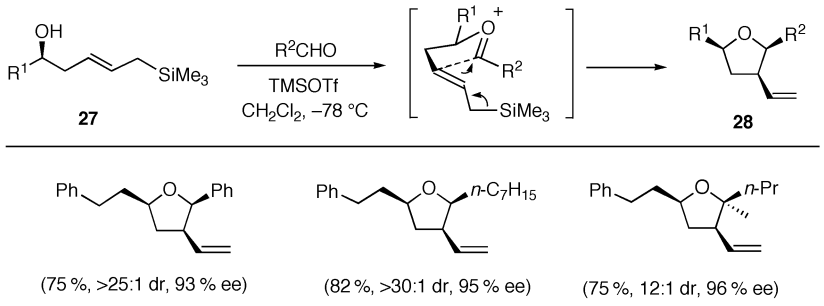
All our new knowledge on the catalytic allylboration of α-substituted allylic boronates could be exploited in the design of new allylation reagents, including the attractive family of double allylation reagents. A number of double-allylation reagents have been made with boron and silicon [37]. We have recently unveiled a new class of double-allylation reagents exemplified by the optically pure α-trimethylsilylmethyl pinanediol allylboronate **25** (Scheme 11) [38].



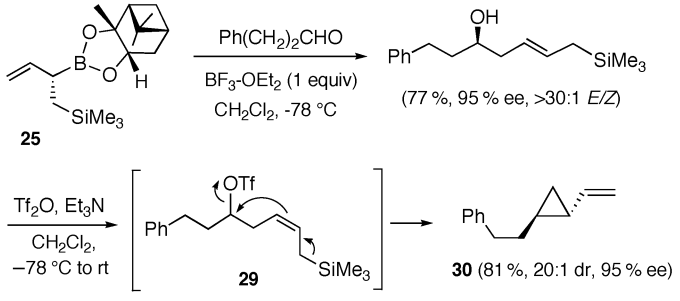
Scheme 11 Enantio- and diastereocontrolled BF_3-promoted additions of α-trimethylsilylmethyl reagent **25** to aldehydes.

Initially, it was found that double-allylation reagent **25** adds onto aldehydes under uncatalyzed conditions, at ambient temperature, to give the expected homoallylic alcohols with a disappointingly low *E*/*Z* selectivity. To our satisfaction, the low-temperature Lewis acid-promoted allylboration manifold provided products **27** in very high selectivity (>30:1) and excellent enantioselectivities up to 98 % ee [38]. The outstanding *E*-selectivity obtained with $BF_3{\cdot}OEt_2$ is of crucial importance because the *Z*-isomer of **27** is epimeric at the carbinol, and would require a separation in the event of a lower selectivity. This issue is avoided with the Lewis acid-promoted conditions, and remarkably, no double-

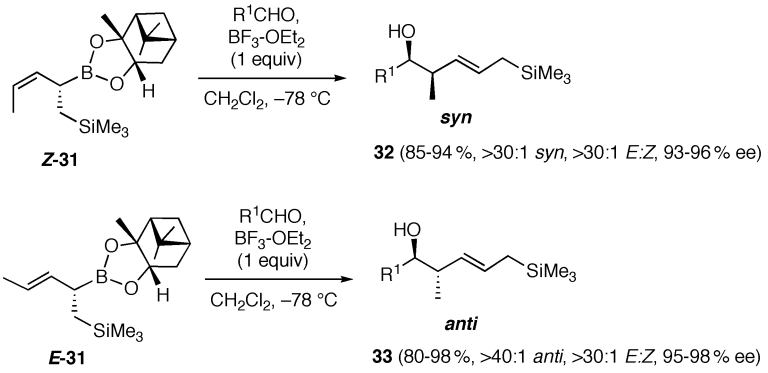
allylation products from further reaction of the allylic silane **27** were observed. A wide range of aliphatic and unsaturated aldehydes are suitable substrates. As depicted in transition structure model **26**, the enantiofacial selectivity is controlled by the configuration of the reagent's α-carbon center and the preference for a pseudo-equatorial orientation of the substituent. The influence of the pinanedioxy unit is likely negligible [23b]. The high degree of *E*/*Z*-selectivity can be tentatively explained by a late transition state [34] involving coordination of the Lewis acid to a boronate oxygen [19]. All of the allylic silane products such as **27** are very useful intermediates that can be transformed, in one simple operation, into polysubstituted furans [39], vinylcyclopropanes [40], and larger carbocycles. As shown in Scheme 12, addition of a second aldehyde, with trimethylsilyl triflate as promoter for oxonium ion formation, leads to the formation of tri- and tetrasubstituted furans **28** in excellent stereoselectivities [38]. Transformation of the secondary hydroxyl group into a leaving group, like triflate **29**, triggers an intramolecular substitution that provides vinylcyclopropane products **30** (Scheme 13). Similar methylated furans and cyclopropanes can be accessed from **32** and **33**, which originate from the equally efficient crotylboronate homologs ***Z*-31** and ***E*-31** (Scheme 14). With dicarbonyl substrates, the second allylation is intramolecular and can lead to the isolation of oxabicyclic products, such as **34**, embedding a medium ring (Scheme 15) [38].



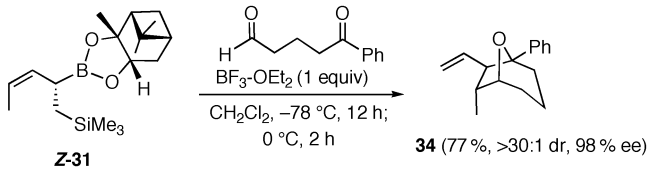
Scheme 12 Synthesis of polysubstituted furan derivatives using allylic silane intermediates **27**.



Scheme 13 Example of stereoselective preparation of a vinylcyclopropane product from reagent **25**.



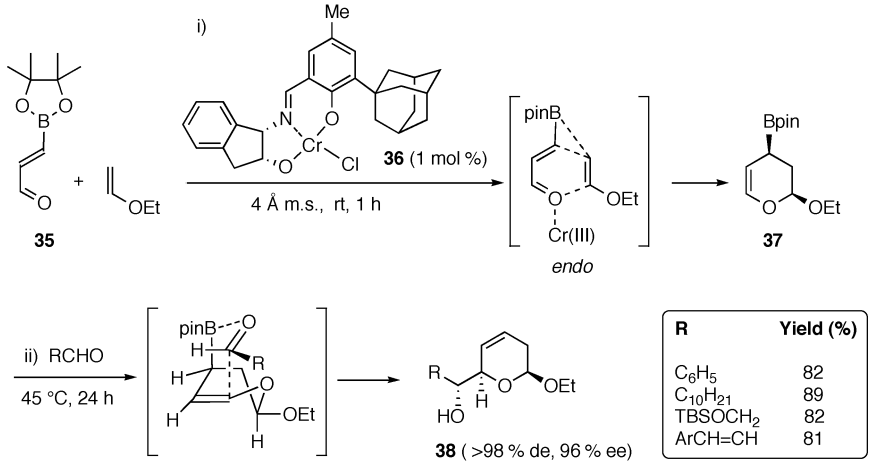
Scheme 14 Additions of crotylboronates **31** giving propionate products.



Scheme 15 Example of preparation of an oxabicyclic product by addition to a ketoaldehyde.

Cyclic α-substituted allylic boronates

Cyclic α-substituted allylic boronates are equally attractive to their open-chain analogs, but examples have been scarce probably because of a lack of effective preparative methods. Although the Lewis acid-catalyzed allylboration conditions were never required in the additions of allylboronate **37**, its preparation did exploit a catalytic enantioselective inverse electron-demand hetero Diels–Alder cycloaddition using Jacobsen's Cr(III) catalyst, **36** [41]. Here, 3-boronoacrolein pinacolate (**35**) was found to be an outstanding heterodiene, and required as little as 0.5 mol % of the catalyst for an effective one-pot three-component hetero[4+2]cycloaddition/allylboration that provides α-hydroxyalkyl dihydropyrans **38** in very high diastereo- and enantioselectivities (Scheme 16) [42]. This efficient chemistry was applied to



Scheme 16 Preparation of diydropyrans **38** using a hetero[4+2]cycloaddition/allylboration reaction.

the first total synthesis of a thiomarinol antibiotic [43]. The polysubstituted pyran unit of this natural product was assembled using the same three-component reaction, however with a 2-substituted enol ether as dienophile.

CONCLUSION

For more than two decades, allylic boron reagents have been invaluable tools for the stereocontrolled formation of carbon–carbon bonds in the field of organic synthesis. These "green", nontoxic reagents add to carbonyl compounds with very high regio- and diastereoselectivity. Unfortunately, the means to control absolute stereoselectivity in the additions of allylic boron reagents had long been restricted to stoichiometric approaches because Lewis acids were thought unsuitable for catalyzing allylborations. Such a catalytic enantioselective allylboration was elusive up until the recent discovery of the Lewis and Brønsted acid-catalyzed allylboration reactions. Of particular significance is the identification of a unique mode of electrophilic activation of boronic esters based on the coordination of the metal ion to an oxygen atom on the boronate group. The discovery of catalytic allylborations opens doors toward an ideal catalytic enantioselective carbonyl allylation methodology with air- and water-stable nontoxic reagents such as pinacol allylic boronates.

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14. The Type III reagents, not illustrated in Fig. 2, are stereoconvergent reagents that react via a six-membered cyclic transition state like Type I reagents, however, by providing the same diastereomeric product regardless of the geometry of the γ-substituted allylic metal reagent. Thus, these reagents, exemplified by allylic chromium species, undergo isomerization of the *Z*-alkene to the *E*-isomer prior to the carbonyl addition [1a].
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