

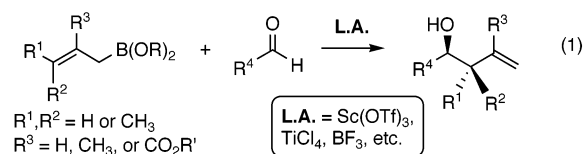
Lewis Acids Catalyze the Addition of Allylboronates to Aldehydes by Electrophilic Activation of the Dioxaborolane in a Closed Transition Structure

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The quest for new catalytic methods to accelerate chemical reactions is of utmost importance to expand substrate scope or to allow control of the absolute stereochemistry of products. Equally crucial to this endeavor is an understanding of the mechanisms by which these catalysts operate. Such information allows the design of improved chiral catalyst–ligand complexes, as well as applications to other reaction processes. We^{1,2} and others³ have recently reported the first examples of Lewis acid-catalyzed additions of allylboronates onto aldehydes (eq 1).



Further to the remarkable rate enhancement observed, it is significant that this novel catalytic manifold preserves the diastereospecificity of uncatalyzed allylboration. These findings paved the way to more effective methods to access aldol-like adducts with high stereocontrol² and may unveil similar opportunities for catalyzing other reactions involving organoboronates. Here, we report our investigation on the intriguing mechanism of this novel Lewis acid-catalyzed allylboration reaction with the best catalyst found, Sc(OTf)₃, and we provide substantial evidence to explain the nature of the activation provided by the metal ion.

Foremost, the general mechanistic nature of this allylation reaction, that is, Type I (closed transition structure) or Type II (open),^{4,5} must be addressed (Figure 1). Allyl boranes and boronates react with aldehydes to give homoallylic alcohols through a highly diastereoselective Type I mechanism (ML_n = BR₂, B(OR)₂), which involves a closed six-membered chairlike transition state characterized by internal activation of the aldehyde by the boron center.⁶ This “self-activation” mechanism, which is at the origin of the earlier perception that allylboronates were not suited to catalysis by external Lewis acids, contrasts with the type II reagents exemplified by the popular allylsilane and allylstannane analogues (M'L_n = SiR₃, SnR₃).⁵ These reagents react with aldehydes under the activation of an external Lewis acid catalyst and proceed by way of open transition structures that tend to provide lower diastereoselectivity in the case of 3-substituted reagents.

The fact that the diastereospecificity of noncatalyzed additions with *Z*- and *E*-crotylboronates (**1** and **2** in eq 2) is preserved under Sc(OTf)₃ catalysis^{2,3} gives a strong indication that a Type I mechanism may be at play. The corresponding crotylstannanes, for example, show the expected Type II behavior by reacting with aldehydes in a stereoconvergent fashion in the presence of BF₃·OEt₂.⁷ Surprisingly, crotylstannations were never reported under Sc(OTf)₃ catalysis. It was necessary to rule out the remote possibility that this particular Lewis acid could be an intrinsic promoter of Type I stereoselectivity regardless of the allylmetal reagent. To this end, we ran test reactions (with hydrocinnam-

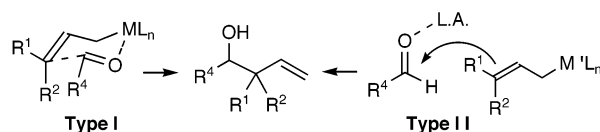
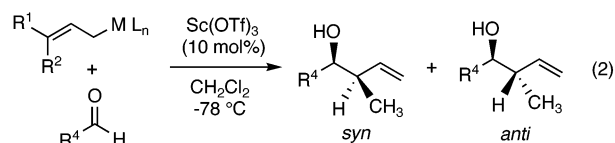


Figure 1. Postulated mechanisms for Type I and II allylation reagents.

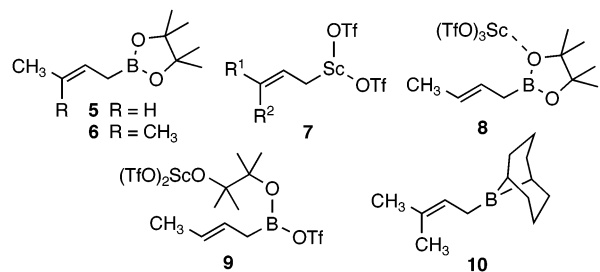
aldehyde; R⁴ = PhCH₂CH₂) that confirmed the Type II stereochemical behavior of Sc(OTf)₃-catalyzed crotylations with **3** and **4**, an outcome clearly distinct to that of crotylboronates (eq 2). Thus, it is most likely that a Type I mechanism is operative in additions of allylboronates catalyzed by Lewis acids such as Sc(OTf)₃.



- | | |
|---|--------|
| 1 M L _n = B(OR) ₂ , R ¹ = H, R ² = CH ₃ | 98 : 2 |
| 2 M L _n = B(OR) ₂ , R ¹ = CH ₃ , R ² = H | 2 : 98 |
| 3 M L _n = SnBu ₃ , R ¹ = H, R ² = CH ₃ | 98 : 2 |
| 4 M L _n = SnBu ₃ , R ¹ = CH ₃ , R ² = H (80% E) | 98 : 2 |

The next important issue concerns the exact role of scandium. Control reactions (*E*-crotylboron pinacolate **5** and PhCH₂CH₂CHO) with Bu₄NOTf, and with Sc(OTf)₃ in the presence of an acid scavenger ([1,8-bis(dimethylamino)-naphthalene]), ruled out the possibility that either triflate ion or adventitious TfOH are promoters. These experiments confirm that the activation is provided by the metal ion. Transmetalation of the allylboronate to a reactive allyl-scandium species (**7**) is highly improbable. Otherwise, the Sc(OTf)₃-catalyzed additions of camphor-based allylboronates, which provide homoallylic alcohols with >95% ee's, would not be enantioselective.² Thus, the allyl transfer agent is truly a boronate.

To gain more information on the nature of the rate acceleration observed, we performed low-temperature NMR spectroscopic studies. At the temperature of the reaction (−78 °C), and also at higher temperatures, no complex between **5** and Sc(OTf)₃ was observed by ¹H and ¹¹B NMR in all solvents examined.⁸ These results undermine the possible formation of a stable allylboronate–Sc(OTf)₃ complex of putative structure **8** in the rate-limiting step. It also makes less probable an activation mode involving dioxaborolane opening and formation of a highly electrophilic boron triflate of type **9**.



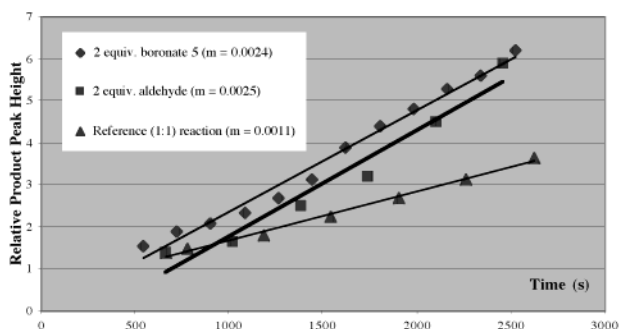


Figure 2. Graph of initial reaction rates between **5** and *p*-tolualdehyde.¹⁰

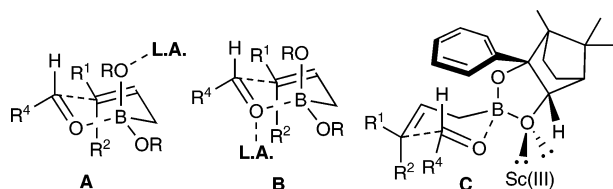


Figure 3. Possible closed transition structures with Lewis acid activation.

The rate law governing the $\text{Sc}(\text{OTf})_3$ -catalyzed allylboration was studied by ^1H NMR spectroscopy using the initial rate method.⁹ To this end, we employed **5** and *p*-tolualdehyde as model substrates at -78°C in CD_2Cl_2 , the preferred solvent for this reaction. Unfortunately, it was not possible to obtain a relevant rate order for the catalyst because of its low solubility in dichloromethane. In the event, the reaction was found to be first order in each substrate (Figure 2),¹⁰ which negates the formation of a unisubstrate-scandium complex (e.g., **8**) in the rate-limiting step, and further supports the closed Type I transition structure involving both reactants.

The last but perhaps the most fundamentally important question to address concerns the binding site of the metal ion in a putative Type I transition structure. Electrophilic boronate-activation via coordination of the oxygen atom(s) (A) or double complexation of the aldehyde carbonyl (B) both appear as reasonable possibilities (Figure 3).

In the first hypothesis (A), coordination of the Lewis acid to one of the dioxaborolane oxygens would suppress $n_{\text{O}}-p_{\text{B}}$ overlap and increase the acidic character of boron, which would compensate by strengthening its interaction with the aldehyde in the transition state. This assumption is in agreement with Brown's experimental demonstration that the electrophilicity of boron parallels reactivity in the allylboration of aldehydes.¹¹ Further support also comes from recent MO calculations concluding that the strength of boron-carbonyl coordination is the main factor lowering the activation energy of allylboration.^{12,13} Double coordination of the aldehyde in structure B would "superactivate" the carbonyl to facilitate formation of the new carbon-carbon bond and concomitantly accelerate the reaction. At first sight, this second hypothesis appears less likely, as calculations show very little C-C bond development in the allylboration transition state.^{11,12} To discriminate between these two possibilities, we needed to test the effect of $\text{Sc}(\text{OTf})_3$ on an allylboron reagent lacking the boronate oxygens, that is, a dialkylallylborane. The latter reagents, however, tend to be very reactive even at -78°C , which would make kinetic studies difficult. To our satisfaction, we found that prenyl-BBN **10**¹⁴ reacts slowly enough (within hours at -78°C) to allow an accurate comparison of relative rates between the uncatalyzed and $\text{Sc}(\text{OTf})_3$ -catalyzed reactions under conditions identical to the prenylboronate **6**. In this key experiment, $\text{Sc}(\text{OTf})_3$ was found to accelerate the reaction between **6** and hydrocinnamaldehyde by a factor of >100 (based on $t_{1/2}$ extrapolations), whereas no appreciable acceleration was

observed in the case of **10**. These results indicate that the boronate oxygens are required for the activation, which is consistent only with transition structure A.¹⁵ As it is unlikely that the two oxygens each coordinate with a molecule of Lewis acid, one leftover question is "which oxygen?": the more accessible pseudo-equatorial one, or the more basic (anomeric) pseudo-axial one (as shown in A, Figure 3)? Future high level calculations may help unravel this last issue. Nonetheless, a possible interpretation comes from the enantioselective $\text{Sc}(\text{OTf})_3$ -catalyzed allylation with camphordiols boronates.² From the accepted stereoselection model based on a $\pi_{\text{phenyl}}-\pi_{\text{C=O}}$ attraction,¹⁶ proposed structure C (Figure 3) implicates coordination of $\text{Sc}(\text{III})$ to the least hindered lone pair (syn to H) of the pseudo-equatorial oxygen, thereby suppressing $n_{\text{O}}-p_{\text{B}}$ conjugation and maximizing boron-carbonyl bonding.

This study sheds light on the mechanistic intricacies of the Lewis acid-catalyzed manifold for additions of allylboronates to aldehydes. Strong evidence points to electrophilic boron activation by coordination of the metal ion to one of the boronate oxygens in a closed bimolecular transition state. Future work will address the nature of this boronate-metal interaction and its implications in enantioselective catalysis.

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Supporting Information Available: Experimental details and spectral reproductions for all experiments (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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