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COMMUNICATIONS

Published on Web 09/06/2002

Dramatic Rate Enhancement with Preservation of Stereospecificity in the First Metal-Catalyzed Additions of Allylboronates

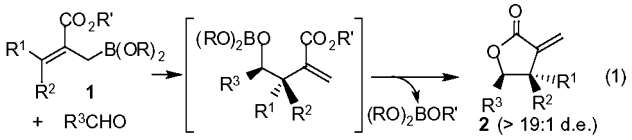
Jason W. J. Kennedy and Dennis G. Hall*

Department of Chemistry, University of Alberta, Edmonton, AB T6G 2G2, Canada

Received June 25, 2002

Allylboronates constitute a very useful class of synthetic intermediates for accessing functionalized homoallylic alcohols.[1] They belong to the type I class of allylation reagents[2] (Figure 1, $ML_n = B(OR)_2$), whose additions onto aldehydes are believed to occur via closed, six-membered cyclic chairlike transition states characterized by internal activation of the aldehyde by the boron center.[3] This mechanism contrasts with the type II reagents exemplified by the popular allylsilane and allylstannane analogues ($M'L_n = SiR_3$, SnR_3), which react with aldehydes generally under the activation of an external Lewis acid catalyst and proceed by way of open transition structures. Because of their compact and organized transition structure, allylborations with γ-substituted reagents tend to demonstrate a level of stereoselectivity superior to that of type II reagents and in a highly predictable fashion.

There are no reports on the use of Lewis acids to catalyze the addition of allylboronates to aldehydes.[4] Because the carbonyl is activated by the allylboronate itself, there is no apparent reason to believe that these reactions could be accelerated by added Lewis acids. Moreover, by potentially inducing a changeover from a type I mechanism toward open transition structures, the use of Lewis acids could be detrimental to the reaction's stereoselectivity. *Herein, we challenge the prevailing perception that allylboronates are not suited to Lewis acid catalysis*. Using our recently described isomerically pure tetrasubstituted allylboronates **1** (eq 1),[5] we now report that some metals allow these reagents to add onto aldehydes to yield γ-lactone products **2** at temperatures almost 100 °C lower than the corresponding uncatalyzed reactions. Moreover, the stereospecificity observed in the uncatalyzed allylborations is preserved, suggesting that type I behavior is maintained in this unprecedented catalytic reaction manifold.



(1)

Our design approach takes advantage of the 2-alkoxycarbonyl group of allylboronates **1** and is based on the premise substantiated by the work of Brown and co-workers[6] that boron electrophilicity is determinant to the reactivity of allylboronates. We envisioned that formation of a metal ion chelate (for example, **3** in Figure 3) between the carboxyester and one of the boronate's oxygens could increase the acidity of boron and, in turn, strengthen its interaction with the aldehyde at the transition state level. In fact, recent ab initio MO calculations conclude that the strength of B−O coordination is the main factor lowering the activation energy in the addition of allylboronates to aldehydes.[7]

* To whom correspondence should be addressed. E-mail: dennis.hall@ualberta.ca.

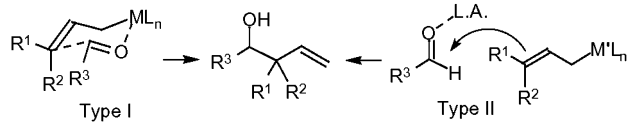
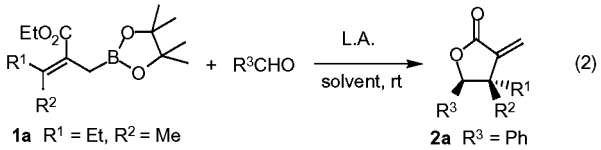


Figure 1. Accepted mechanisms for type I and II allylation reagents.



(2)

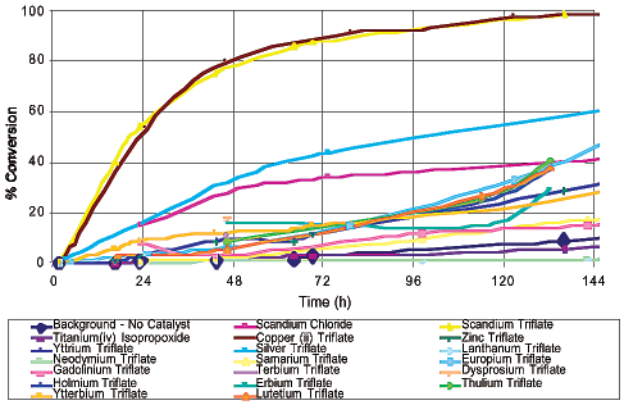


Figure 2. Comparative reaction speed for different Lewis acids. Conversion of **1a** into lactone **2a** (%) is plotted against time.

We initiated our investigation by screening a large number of representative Lewis acids of moderate strength. Most metals were employed as their triflates for optimal solubility in the apolar noncoordinating solvents typically used in allylboration reactions. These experiments were carried out in NMR tubes using equimolar amounts of pinacol allylboronate **1a** and benzaldehyde with 0.5 equiv of the Lewis acid as a dilute solution in CD_2Cl_2 (0.07 M concentration) at 25 °C (eq 2).

While a number of Lewis acids induced a modest acceleration over the background uncatalyzed reaction, two of them, $Cu(OTf)_2$ and $Sc(OTf)_3$, provided a dramatic rate enhancement (Figure 2).

Several assays involving Lewis acids of limited solubility in CD_2Cl_2 were repeated in 1:1 CD_2Cl_2/THF-d_8 to rule out the influence of solubility. The outcome was similar,[8] except for $Yb(OTf)_3$, which was later found to be efficient in THF and toluene. Further evaluation of the three best metals (Yb(III), Cu(II), Sc(III)) was carried out in different solvents, and the use of $Cu(OTf)_2$ or $Sc(OTf)_3$ in either dichloromethane or toluene were the combinations found to provide the fastest rate of formation of α-exomethylene γ-lactone **2a**. Some of these experimental conditions were validated

10.1021/ja027453j CCC: $22.00

Table 1. Lewis Acid Catalyzed Formation of γ-Lactones **2** (Eq 2)[a]

entry	boronate (R^1,R^2)	aldehyde (R^3)	L.A.[b]	solvent[c]	product[d]	yield (%)[e]
1	**1a** (Et, Me)	C_6H_5	$Sc(OTf)_3$	CH_2Cl_2	**2a**	72
2	**1a**	C_6H_5	$Sc(OTf)_3$	toluene	**2a**	93
3	**1a**	C_6H_5	$Cu(OTf)_2$	toluene	**2a**	67
4	**1a**	C_6H_5	$Yb(OTf)_3$	toluene	**2a**	91
5	**1b** (Me, Bu)	3-I-C_6H_4	$Sc(OTf)_3$	toluene	**2b**	55
6	**1b**	C_6F_5	$Sc(OTf)_3$	toluene	**2c**	53
7	**1a**	$PhCH_2CH_2$	$Sc(OTf)_3$	toluene	**2d**	64
8	**1a**	$PhCH_2CH_2$	$Yb(OTf)_3$	toluene	**2d**	66
9	**1b**	Bu	$Sc(OTf)_3$	toluene	**2e**	62
10	**1b**	CH_2-i-Pr	$Sc(OTf)_3$	toluene	**2f**	53
11	**1a**	C_6H_{11}	$Cu(OTf)_2$	toluene[f]	**2g**	54

[a] Reaction scale: approximately 0.4 mmol (>100 mg) of **1**, and 1.0−1.5 equiv of aldehyde, room temperature, 6−24 h.[8] [b] 10 mol %. [c] Typically 0.5−1.0 M concentration in allylboronate.[8] [d] The dr was usually over 19:1 (determined by ^{1}H NMR). In some cases, allylboronate of lesser isomeric purity was employed, but the final lactones were of identical dr. [e] Unoptimized yields of pure products isolated after flash chromatography. [f] Performed at 60 °C for 16 h.

and further optimized on a practical scale with 10% catalyst loading at 0.5−1.0 M concentration (Table 1, entries 1−4). Lactone **2a** was isolated in high yield, thereby confirming the capacity of the Lewis acids to turnover in these reactions. The stereoselectivity reflected the isomeric purity of allylboronates **1** and was usually equal or superior to a 19:1 ratio favoring the indicated diastereomer, the same as in the uncatalyzed process.[5] Unbranched aliphatic aldehydes, notorious for self-condensing in the presence of Lewis acids, provided good yields of products (entries 7−9). Gratifyingly, branched aldehydes that were ineffective without metal activation are now suitable substrates (for example, cyclohexanecarboxaldehyde, entry 11). It is noteworthy that reactions catalyzed by $Sc(OTf)_3$ are tolerant of moisture; rates and yields were not appreciably affected by the addition of up to 1 equiv of water. Most reaction examples of Table 1 were complete within 12 h at room temperature, a feature viewed as a significant practical improvement over the previous uncatalyzed process. Indeed, to reach completion without a catalyst, the allylboration between **1a** and benzaldehyde necessitated 14 days at room temperature or 16−24 h at 110 °C![5] Here, comparative kinetic experiments with the same substrates showed that while $Sc(OTf)_3$-catalyzed runs are over within 6 h at room temperature, the background uncatalyzed reaction reaches only 3−4% completion. This issue of rate enhancement has important repercussions toward the eventual use of chiral catalysts.

Preliminary investigations were carried out to gain insight on the possible mode of activation in these metal-catalyzed allylborations. Control reactions with Bu_4NOTf, and with $Sc(OTf)_3$ in the presence of a base (DIPEA), ruled out the possibility that either triflate ion or adventitious TfOH are the activating species.[8] Allylboronate **4** (Figure 3)[9] lacking the 2-alkoxycarbonyl group was reacted with benzaldehyde, and although the rate of product formation was enhanced in the presence of $Sc(OTf)_3$, it was found to be small as compared to the case of allylboronates **1**.[8,10] These results clearly highlight the crucial role of the ester group and the metal ion at providing optimal rate acceleration. NMR studies on mixtures of **1a** and $Sc(OTf)_3$ provided evidence for the formation of a defined 1:1 complex, and proton chemical shift data lend support to a chelate of type **3** implicating coordination of scandium both to the carboxyester and to the boronate groups.[8] These observations and the fact that the catalyzed reactions preserve the stereospecificity of the uncatalyzed type I process led us to propose hybrid transition structure model A (Figure 3). This model involves a seven-membered metal-activated complex assembled within the usual chairlike transition structure of type I allylmetal reagents. In

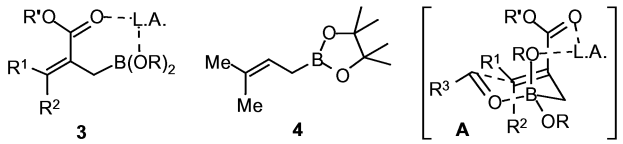


Figure 3. Mechanistic studies and postulated transition structure.

principle, coordination of the metal to one of the alkoxy groups increases boron's acidity, which in turn compensates through increasing its interaction with the aldehyde and concomitantly lowering the reaction's activation barrier.[6,7] Further support for electrophilic boronate activation and for ruling out open transition structures comes from the corresponding allylsilanes, which are unreactive with $Sc(OTf)_3$ and react slowly even with a strong multivalent Lewis acid like $TiCl_4$ to give mixtures of diastereomeric lactones.[8,11] Another potential mode of activation, acting alone or in concert with the above, may arise from twisting the ester out of conjugation with the alkene, thereby increasing the nucleophilicity of the allylboronate's γ-carbon.

In summary, this work on 2-alkoxycarbonyl allylboronates reports the first examples of Lewis acid-catalyzed additions of allylboronates to aldehydes. The huge rate enhancement over the uncatalyzed reaction provides a highly improved practical approach to access aldol-like adducts with a stereogenic quaternary carbon center. This novel catalytic reaction manifold opens exciting possibilities for the development of substoichiometric methods of absolute stereocontrol. Moreover, further to the remarkable rate enhancement, the fact that the stereospecificity observed in the uncatalyzed process is preserved raises intriguing mechanistic questions. Ongoing investigations on the nature of this unprecedented mode of allylboronate activation may unveil similar opportunities for catalyzing other reactions of organoboronates.

Acknowledgment. This work was funded by the Natural Sciences and Engineering Research Council (NSERC) of Canada and the University of Alberta. J.W.J.K. thanks NSERC and the Alberta Heritage Foundation for Medical Research (AHFMR) for graduate scholarships. The authors thank Glen Bigam, Gerdy Aarts, and Lai Kong for the NMR analyses.

Supporting Information Available: Additional NMR screening (^{1}H and ^{11}B) of the best catalysts, spectra and details of ^{1}H and ^{11}B NMR studies of the **1a**-$Sc(OTf)_3$ complex, full experimental details for all entries of Table 1 and control compound **4**, characterization data and spectra for all new lactone products **2** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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JA027453J