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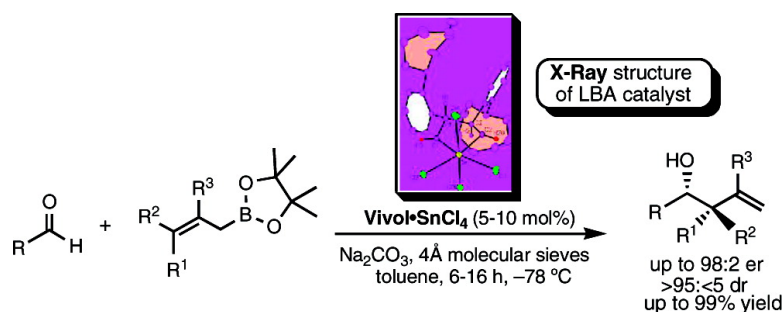
Catalytic Enantioselective Allyl- and Crotylboration of Aldehydes Using Chiral Diol•SnCl Complexes. Optimization, Substrate Scope and Mechanistic Investigations

Vivek Rauniyar, Huimin Zhai, and Dennis G. Hall

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Catalytic Enantioselective Allyl- and Crotylboration of Aldehydes Using Chiral Diol·SnCl₄ Complexes. Optimization, Substrate Scope and Mechanistic Investigations

Vivek Rauniyar, Huimin Zhai, and Dennis G. Hall*

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

Received March 7, 2008; E-mail: dennis.hall@ualberta.ca

Abstract: We report a novel class of C_2-symmetric chiral diols derived from the hydrobenzoin skeleton. The combination of these diols with $SnCl_4$ under Yamamoto's concept of Lewis acid assisted Brønsted acidity (LBA catalysis) leads to high levels of asymmetric induction in the allylboration of aldehydes by commercially available allylboronic acid pinacol ester **1a**. The corresponding homoallylic alcohol products of synthetically useful aliphatic aldehydes are obtained in excellent yields with up to 98:2 er. This combined acid manifold is also efficient in catalyzing the diastereo- and enantioselective crotylboration of aldehydes, thus providing the propionate units in >95:5 dr and up to 98:2 er. The X-ray crystal structure of the optimal diol·SnCl₄ complex, Vivol (**4m**)·SnCl₄, unambiguously shows the Brønsted acidic character of this LBA catalyst and its highly dissymmetrical environment. Further controls have ruled out a possible boron transesterification mechanism with the chiral diol and point to LBA catalyst-derived activation of the pinacol allylic boronates **1**. Due to slow dissociation of the diol·SnCl₄ complex, a small excess of diol is required in order to suppress a competing racemic cycle catalyzed by free $SnCl_4$.

Introduction

Carbonyl allylations constitute an important class of carbon—carbon bond forming reactions[1] and in this context; aldehyde allylations (eq 1) have served as important surrogates for the aldol reaction.[2] During the past two decades, an extensive repertoire of allylation methods have emerged to answer the needs of the synthetic community. Indeed, the products of aldehyde allylation, i.e., homoallylic alcohols, are very useful building blocks for elaboration into polyacetate and propionate units commonly found in numerous biologically interesting marine macrolides and other natural products. Additionally, possibilities for the post-allylation transformation of homoallylic alcohols have been greatly empowered by the recent development of alkene metathesis.
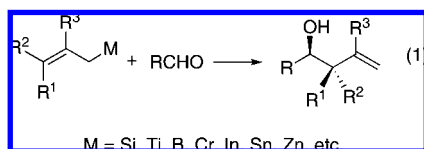

The majority of aldehyde allylation reagents are based on main group metals and metalloids such as silicon,[3] titanium,[4] boron,[5] chromium,[6] indium,[7] tin,[8] and zinc.[9] These reagents have been classified as type I, type II, or type III, based on their proposed mechanism and the stereoselectivity observed with γ-substituted reagents, i.e., *cis* and *trans*-crotyl reagents.[1e] Type I allyl and crotyl reagents based on boron and electrophilic silicon operate by coordinating and activating aldehydes via a rigid chair like Zimmerman—Traxler transition state,[10] which ensures a high stereochemical transfer of the reagent's olefinic geometry. On the other hand, type II and III reagents require activation of aldehydes with external Lewis acids and operate through open transition states, giving *syn* and *anti* products irrespective of the starting olefinic geometry.[1e] As a consequence, allyl transfer reactions based on type I reagents have gained utmost importance because they are stereospecific, highly diastereoselective, and predictable with *cis* and *trans* crotyl reagents providing *syn* and *anti* propionate products, respectively.

Since the inception of methods based on stoichiometric chiral directors by the groups of Hoffmann,[5a,b] Masamune,[5c,d] Brown,[5e,f] Roush,[5g,h] and Corey[5i,j] in the 1980s, and recent reports by Soderquist,[5k] Chong,[5l] and our group,[5m,n] allylboration of aldehydes has remained a dormant field in the modern era of

(1) For reviews, see: (a) Denmark, S. E.; Almstead, N. G. In *Modern Carbonyl Chemistry*; Otera, J., Ed.; Wiley-VCH: Weinheim, 2000; Chapter 10, pp 299−402. (b) Chemler, S. R.; Roush, W. R. In *Modern Carbonyl Chemistry*; Otera, J., Ed.; Wiley-VCH: Weinheim, 2000; Chapter 11, 403−490. (c) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207−2293. (d) Helmchen, G.; Hoffmann, R.; Mulzer, J.; Schaumann, E. In *Stereoselective Synthesis. Methods of Organic Chemistry (Houben-Weyl)*, 21st ed.; Thieme Stuttgart: New York, 1996; Vol *3*, pp 1357−1602. (e) Denmark, S. E.; Fu, J. *Chem. Rev.* **2003**, *103*, 2763−2793.

(2) Mahrwald, R. *Chem. Rev.* **1999**, *99*, 1095–1120.

(3) (a) Wang, Z. G.; Wang, D.; Sui, A. *Chem. Commun.* **1996**, 2261–2262. (b) Wang, D.; Wang, Z.; Wang, M. W.; Chen, Y. J.; Liu, L.; Zhu, Y. *Tetrahedron: Asymmetry* **1999**, *10*, 327–328. (c) Kinnaird, J. W. A.; Ng, P. Y.; Kubota, K.; Wang, X.; Leighton, J. L. *J. Am. Chem. Soc.* **2002**, *124*, 7920–7921. (d) Kubota, K.; Leighton, J. L. *Angew. Chem., Int. Ed.* **2003**, *42*, 946–948. (e) Denmark, S. E.; Fu, J. *J. Am. Chem. Soc.* **2001**, *123*, 9488–9489. (f) Denmark, S. E.; Fu, J. *Chem. Commun.* **2003**, 167–170.

(4) Hafner, A.; Duthaler, R. O.; Marti, R.; Rihs, G.; Rothe-Streit, P.; Schwarzenbach, F. *J. Am. Chem. Soc.* **1992**, *114*, 2321–2336.

catalytic enantioselective synthesis.[11] The difficult challenge that represents a catalytic allylboration is exemplified by the instantaneous additions of most allylic boron derivatives at low temperatures, and as such, effective catalysis is rendered very difficult because of a significant background reaction to be competed with (even at −78 °C).[12] In this context, the most convenient achiral allylboron reagent appears to be the air- and water-stable, nontoxic, and commercially available allylboronic acid pinacol ester (**1a**), which has been shown to possess negligible allyl transfer activity at −78 °C.[12] Another key issue with catalysis of allylboration was the perception that incorporating Lewis acidic catalysts would interfere with the intrinsic type I nature of the reaction and turn it into a type II process, thereby destroying its highly diastereoselective nature. Our group,[13,14] and others[15] addressed this issue in 2002. We reported that Lewis acid catalysts dramatically accelerate the allylboration of aldehydes and, more importantly, retain the diastereoselectivity of the reaction. In their report, Miyaura and co-workers showcased the first example of a catalytic enantioselective and diastereoselective crotylboration of benzaldehyde, albeit with moderate enantioselectivity (51% ee).[15] Subsequently, our group garnered significant evidence that pointed
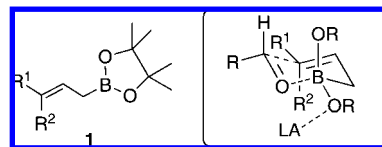

Figure 1. Proposed transition state for the Lewis acid activation of pinacol allylic boronates (**1**).

toward an electrophilic activation of the allylic boronate by coordination of the Lewis acid to one of the oxygens of the boronic ester in the type I transition state (Figure 1).[16] Other beneficial effects of this new mode of activation have been observed in the much improved *E/Z* selectivity of the homoallyl alcohol products when employing chiral α-substituted allylboronates as well as the large rate acceleration of deactivated allylic boronates.[17] Until recently, however, all efforts by our group and others only led to modest levels of enantioselectivities for the catalytic manifold using chiral Lewis acids. This can be partially attributed to the sterically crowded nature of the dioxaborolane in reagents **1**, which prevents efficient coordination of the large chiral Lewis acids (Figure 1).

Following our first report on the Brønsted acid catalyzed allylboration,[18a] we unveiled the utility of Yamamoto's chiral diol•SnCl₄ combined acid catalyst system[19] in the enantioselective addition of allylboronic acid pinacol ester to aldehydes.[20] We first aimed at optimizing a procedure for the simple allylation of aliphatic aldehydes, which tend to be the most difficult substrates with existing catalytic enantioselective allylation methodologies.[3e,f] Under this first-generation catalyst system, homoallylic alcohols were obtained in moderate to good er and excellent dr. Thereafter, we undertook an extensive optimization of the chiral diol and arrived at a novel one, hereafter named Vivol (**4m**), which was found to be very efficient in the diol•SnCl₄ catalyst system for the enantioselective addition of pinacol allyl- and crotylboronates onto aliphatic aldehydes.[21] With this second-generation catalyst, homoallylic alcohols are now obtained in very good to excellent er and

(5) (a) Hoffmann, R. W.; Ladner, W. *Tetrahedron Lett.* **1979**, *20*, 4653–4656. (b) Hoffmann, R. W.; Zeiss, H.-J. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 306–307. (c) Garcia, J.; Kim, B.; Masamune, S. *J. Org. Chem.* **1987**, *52*, 4831–4832. (d) Short, R. P.; Masamune, S. *J. Am. Chem. Soc.* **1989**, *111*, 1892. (e) Brown, H. C.; Bhat, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 1892–1894. (f) Brown, H. C.; Jadhav, P. K. *J. Am. Chem. Soc.* **1983**, *105*, 2092–2093. (g) Roush, W. R.; Ando, K.; Powers, D. B.; Palkowitz, A. D.; Halterman, R. L. *J. Am. Chem. Soc.* **1990**, *112*, 6339–6348. (h) Roush, W. R.; Walts, A. E.; Hoong, L. K. *J. Am. Chem. Soc.* **1985**, *107*, 8186–8190. (i) Corey, E. J.; Yu, C.-M.; Kim, S. S. *J. Am. Chem. Soc.* **1989**, *111*, 5495–5496. (j) Corey, E. J.; Yu, C.-M.; Lee, D.-H. *J. Am. Chem. Soc.* **1990**, *112*, 878–879. (k) Burgos, C. H.; Canales, E.; Matos, K.; Soderquist, J. A. *J. Am. Chem. Soc.* **2005**, *127*, 8044–8049. (l) Wu, T. R.; Shen, L.; Chong, J. M. *Org. Lett.* **2004**, *6*, 2701–2704. (m) Lachance, H.; Lu, X.; Gravel, M.; Hall, D. G. *J. Am. Chem. Soc.* **2003**, *125*, 10160–10161. (n) Gravel, M.; Lachance, H.; Lu, X.; Hall, D. G. *Synthesis* **2004**, 1290–1302.

(6) (a) Okude, Y.; Hirano, S.; Hiyama, T.; Nozaki, H. *J. Am. Chem. Soc.* **1977**, *99*, 3179–3181. (b) Chen, C.; Tagami, K.; Kishi, Y. *J. Org. Chem.* **1995**, *60*, 5386–5387. (c) Wan, Z.-K.; Choi, H.-w.; Kang, F.-A.; Nakajima, K.; Demeke, D.; Kishi, Y. *Org. Lett.* **2002**, *4*, 4431–4434. (d) Fürstner, A.; Shi, N. *J. Am. Chem. Soc.* **1996**, *118*, 12349–12357. (e) Bandini, M.; Cozzi, P. G.; Umani-Ronchi, A. *Angew. Chem., Int. Ed.* **1999**, *38*, 3357–3359. (f) Xia, G.; Yamamoto, H. *J. Am. Chem. Soc.* **2006**, *128*, 2554–2555.

(7) Loh, T.-P.; Zhou, J.-R.; Yin, Z. *Org. Lett.* **1999**, *1*, 1855–1857.

(8) (a) Costa, A. L.; Piazza, M. G.; Tagliavini, E.; Trombini, C.; Umani-Ronchi, A. *J. Am. Chem. Soc.* **1993**, *115*, 7001–7002. (b) Keck, G. E.; Tarbet, K. H.; Geraci, L. S. *J. Am. Chem. Soc.* **1993**, *115*, 8467–8468. (c) Furuta, K.; Mouri, M.; Yamamoto, H. *Synlett* **1991**, 561–562. (d) Aoki, S.; Mikami, K.; Terada, M.; Nakai, T. *Tetrahedron* **1993**, *49*, 1783–1792. (e) Casolari, S.; Cozzi, P. G.; Orioli, P. A.; Tagliavini, E.; Umani-Rochi, A. *Chem. Commun.* **1997**, 2123–2124. (f) Hanawa, H.; Kii, S.; Asao, N.; Maruoka, K. *Tetrahedron Lett.* **2000**, *41*, 5543–5546. (g) Yanagisawa, A.; Nakashima, H.; Ishiba, A.; Yamamoto, H. *J. Am. Chem. Soc.* **1996**, *118*, 4723–4724.

(9) (a) Pu, L.; Yu, H.-B. *Chem. Rev.* **2001**, *101*, 757–824. (b) Hong, B.-C.; Hong, J.-H.; Tsai, Y.-C. *Angew. Chem., Int. Ed.* **1998**, *37*, 468–470.

(10) Zimmerman, H. E.; Traxler, M. D. *J. Am. Chem. Soc.* **1957**, *79*, 1920–1923.

(11) Ojima, I. *Catalytic Asymmetric Synthesis*, 2nd ed.; Wiley-VCH: Weinhein, 2004.

(12) Brown, H. C.; Racherla, U. S.; Pellechia, P. J. *J. Org. Chem.* **1990**, *55*, 1868–1874.

(13) Hall, D. G. *Boronic Acids: Preparation and Application in Organic Synthesis and Medicine*; Wiley-VCH: Weinheim, 2005.

(14) (a) Kennedy, J. W. J.; Hall, D. G. *J. Am. Chem. Soc.* **2002**, *124*, 11586–11587. (b) Kennedy, J. W. J.; Hall, D. G. *J. Org. Chem.* **2004**, *69*, 4412–4428.

(15) Ishiyama, T.; Ahiko, T.-a.; Miyaura, N. *J. Am. Chem. Soc.* **2002**, *124*, 12414–12415.

(16) Rauniyar, V.; Hall, D. G. *J. Am. Chem. Soc.* **2004**, *126*, 4518–4519.

(17) (a) Carosi, L.; Lachance, H.; Hall, D. G. *Tetrahedron Lett.* **2005**, *46*, 8981–8985. (b) Peng, F.; Hall, D. G. *J. Am. Chem. Soc.* **2007**, *129*, 3070–3071. (c) Carosi, L.; Hall, D. G. *Angew. Chem., Int. Ed.* **2007**, *27*, 5913–5915. (d) Kabalka, G. W.; Venkataiah, B.; Dong, G. *J. Org. Chem.* **2004**, *69*, 5807–5809. (e) Kabalka, G. W.; Venkataiah, B.; Dong, G. *Tetrahedron Lett.* **2005**, *46*, 4029–4211. (f) Ramachandran, P. V.; Pratihar, D.; Biswas, D.; Srivastava, A.; Reddy, M. V. R. *Org. Lett.* **2004**, *6*, 481–484. (g) Ramachandran, P. V.; Pratihar, D.; Biswas, D. *Org. Lett.* **2006**, *8*, 3877–3879. (h) Ramachandran, P. V.; Pratihar, D. *Org. Lett.* **2007**, *9*, 2087–2090. (i) Selander, N.; Sebelius, S.; Estay, C.; Szabó, K. J. *Eur. J. Org. Chem.* **2006**, 4085–4087. (j) Lira, R.; Roush, W. R. *Org. Lett.* **2007**, *9*, 4315–4318.

(18) (a) Yu, S.-H.; Ferguson, M. J.; McDonald, R.; Hall, D. G. *J. Am. Chem. Soc.* **2005**, *127*, 12808–12809. (b) Elford, T.; Yu, S. H.; Arimura, Y.; Hall, D. G. *J. Org. Chem.* **2007**, *72*, 1276–1284. (c) Selander, N.; Kipke, A.; Sebelius, S.; Szabó, K. J. *J. Am. Chem. Soc.* **2007**, *129*, 13723–13731.

(19) (a) Ishihara, K.; Kaneeda, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1994**, *116*, 11179–11180. (b) Nakamura, S.; Kaneeda, M.; Ishihara, K.; Yamamoto, H. *J. Am. Chem. Soc.* **2000**, *122*, 8120–8130. (c) Ishihara, K.; Nakamura, S.; Kaneeda, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1996**, *118*, 12854–12855. (d) Ishihara, K.; Nakamura, H.; Nakamura, S.; Yamamoto, H. *J. Org. Chem.* **1998**, *63*, 6444–6445. (e) Ishihara, K.; Nakashima, D.; Hiraiwa, Y.; Yamamoto, H. *J. Am. Chem. Soc.* **2003**, *125*, 24–25. (f) Ishihara, K.; Nakamura, S.; Yamamoto, H. *J. Am. Chem. Soc.* **1999**, *121*, 4906–4907.

(20) Rauniyar, V.; Hall, D. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 2426–2428.

(21) Preliminary portions of this work have been presented at the 14th OMCOS Conference held in Nara, Japan during August 2−6, 2007: Abstract # P-102.
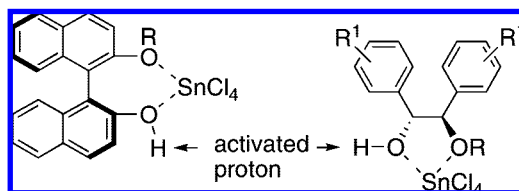
Figure 2. Yamamoto's Lewis acid assisted Brønsted acid (LBA) catalyst system based on chiral diol•SnCl₄ complexes.

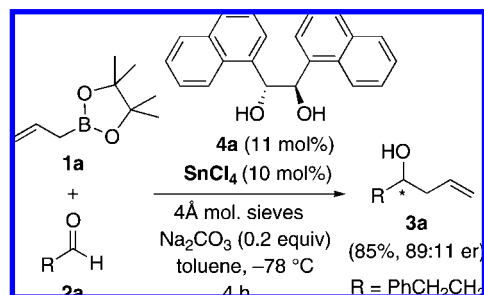**Figure 3.** First-generation catalytic enantioselective allylboration using diol **4a**.

consistently high dr. Moreover, we have obtained a snapshot of the putative active catalyst in the form of a crystal structure of a 1:1 complex of Vivol•SnCl₄, which clearly shows the Brønsted acidic character of this LBA catalyst and its highly dissymmetrical environment.

Results

Initial Evaluation of Chiral Brønsted Acids. Having realized the ability of strong Brønsted acids as superior catalysts for the addition of deactivated allylic boronates,[18] we examined the effectiveness of simple chiral Brønsted acids (e.g., camphorsulfonic acid, tartaric acid, etc.) for the enantioselective addition of allylboron pinacolate (**1a**) onto hydrocinnamaldehyde at −78 °C (see Supporting Information). Unfortunately, most of these simple chiral Brønsted acids were ineffective at promoting the reaction. We then turned our attention to conceptually novel types of chiral Brønsted acids. In this context, Yamamoto and co-workers have designed numerous combined acid catalyst systems, including LBA[19] and BLA[22] approaches. In particular, their concept of Lewis acid assisted Brønsted acid catalysis (LBA) has been shown to be remarkably effective for the enantioselective protonation of prochiral silyl enol ethers and silyl ketene acetals, and also for the protonation induced enantioselective polyene cyclization.[19a–f] In this catalyst system, coordination of SnCl₄ to the oxygens of chiral alcohols generates rigid complexes that restrict the directional orientation of the hydroxylic protons and concurrently increases their acidity (Figure 2). The characteristics of this LBA catalyst system were demonstrated in the single crystal X-ray structure derived from a complex between a 1:1 mixture of monomethylated hydrobenzoin (R^1 = H, R = Me) and SnCl₄.[19e]

When applied to the simple allylboration of aldehydes, we found that electronic or steric manipulation at the para or the meta position of the aromatic rings of the hydrobenzoin-derived diols did not provide any beneficial effect (see Supporting Information). However, placement of substituents at the ortho position seemed to imply dramatic effects. After extensive screening, we identified the commercially available (*R*,*R*)-1,2-dinaphthyl ethanediol **4a** as the most effective diol under the present LBA catalyst system for the addition of **1a** onto the model aliphatic aldehyde, hydrocinnamaldehyde (**2a**) (Figure 3).[20]

In this system, the active catalyst was generated in situ by addition of a 1.0 M CH₂Cl₂ solution of anhydrous SnCl₄ to a slight excess of chiral diol in anhydrous toluene at room temperature and cooled to −78 °C.[19e] This was followed by addition of a toluene solution of **1a** and, after 15 min, a dropwise addition of **2a**. After 4 h, any unreacted amounts of **2a** were quenched by addition of DIBAL-H at −78 °C, and the borate ester was hydrolyzed to release the product **3a** by addition of 1.0 M HCl.[23] Thereafter, we explored other sources of Lewis acid in conjunction with **4a**, including SnBr₄, TiCl₄, TiF₄,

Cu(OTf)₂, Zn(OTf)₂, Yb(OTf)₃, Sc(OTf)₃, and others; however, they all failed in comparison to SnCl₄, giving dismal conversions and/or er's.

Effect of Additives on the Diol•SnCl₄ Catalysis. During the course of optimization, we reasoned that trace amounts of HCl, a potentially strong activator of the non-enantioselective reaction, could be generated from the combination of SnCl₄ and adventitious water in the reaction system or be present in trace amounts in commercially available SnCl₄.[20] We thus screened for additives that could provide anhydrous reaction conditions and sequester adventitious HCl. Gratifyingly, under the original reaction conditions of Yamamoto and co-workers, introduction of 4 Å molecular sieves and anhydrous Na₂CO₃ (which is insoluble in the reaction media) as additives led to a noticeable improvement in the enantioselectivity of product **3a**. It was found that freshly distilled SnCl₄ in the absence of any dehydrating agent does provide similar er of the product; however, the addition of 4 Å molecular sieves and sodium carbonate assures reproducibility.

Optimization of a Second-Generation Catalyst.[21] This first-generation LBA catalyst with diol **4a** (Figure 3) became the benchmark for the catalytic asymmetric allylboration of aldehydes and provided a platform to seek further advancements. The addition of **1a** to hydrocinnamaldehyde under a stoichiometric loading of the **4a**•SnCl₄ catalyst system only led to a modest increase in selectivity, namely 91.5:8.5 vs 89:11 er under catalytic conditions.[20] This result implied that enantioselectivity of the catalytic reaction was not limited by the intrinsic background reaction between **1a** and hydrocinnamaldehyde. Since the stoichiometric and the catalytic reactions provided comparable er's, this observation led us to believe that there certainly was room for improvement in the catalyst's efficiency. To this end, we tried to look for correlation between the er of the product and the substitution pattern of the chiral diol unit. As mentioned earlier, we had already noticed a dramatic change in the er of the product by replacing the ortho-hydrogen with an ortho-methyl or -phenyl group in the hydrobenzoin skeleton (see ref 20 and Supporting Information). Pursuing along this direction and taking into account electronic and steric factors, we prepared a select group of ortho substituted hydrobenzoin derived diols, namely **4b−i** (Table 1). Most of the diols employed in this study are readily obtained by the Sharpless asymmetric dihydroxylation[24] of the corresponding *trans-*

(22) (a) Furuta, K.; Miwa, Y.; Iwanaga, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1988**, *110*, 6254–6255. (b) Ishihara, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1994**, *116*, 1561–1562. (c) Ishihara, K.; Kurihara, H.; Matsumoto, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1998**, *120*, 6920–6930. (d) Ishihara, K.; Kurihara, H.; Yamamoto, H. *J. Am. Chem. Soc.* **1996**, *118*, 3049–3050. (e) Ishihara, K.; Miyata, M.; Hattori, K.; Tada, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1994**, *116*, 10520–10521.

Table 1. Further Evaluation of Ortho-Substituted Diols for the LBA Catalysis of a Model Allylboration Reaction[a]
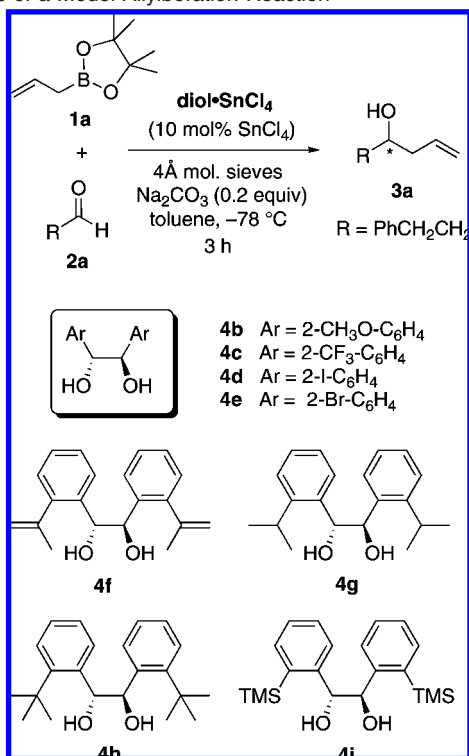
entry	diol	yield (%)	er
1	**4b**	75	84.5:15.5
2	**4c**	96	56:44
3	**4d**	99	79.5:20.5
4	**4e**	94	88.5:11.5
5	**4f**	nd	nd
6	**4g**	71	89.5:10.5
7	**4h**	18	58.5:41.5
8	**4i**	55	69.5:30.5

[a] Reaction conditions: All reactions were performed with 0.250 mmol of **2a**, 0.275 mmol of **1a**, 0.0275 mmol of diol, 0.025 mmol of SnCl$_4$, 0.050 mmol of anhydrous Na$_2$CO$_3$, 50 mg of 4 Å molecular sieves, and 1.0 mL of toluene at − 78 °C for 3 h. Er of **3a** was determined by chiral HPLC.

stilbenes, which are in turn obtained by a McMurry coupling[25] reaction of the corresponding aldehydes (see Supporting Information).

Upon subjection of **4b**−**4i** as diol•SnCl$_4$ catalysts for the model allylboration reaction, it appeared that large nonpolar substituents had a beneficial effect on the enantioselectivity of the reaction (Table 1). Although **4e** led to an encouraging er for product **3a** (entry 4), its iodo-counterpart **4d** failed to provide a similar er (entry 3). Surprisingly, diol **4f** failed to give an acceptable level of catalysis under the LBA system. A plausible explanation for this failure may be attributed to the isopropylene π-electrons, which can potentially sequester the Brønsted acidity of the activated proton via an OH−π interaction[21] or even form a cyclic ether via a benzylic tertiary carbocation (a dead-end

(23) The procedure in ref 5m and 5n was followed for the workup of the reaction.
(24) (a) Jacobsen, E. N.; Marko, I.; Mungall, W. S.; Schröder, G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 1968–1970. (b) Kolb, H. C.; Van-Nieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483–2547.
(25) McMurry, J. E.; Fleming, M. P. *J. Am. Chem. Soc.* **1974**, *96*, 4708–4709.

for catalysis). Gratifyingly, when we subjected diol **4 g** (equipped with ortho-isopropyl substituents) to the model reaction, we observed a significant improvement in the enantioselectivity, i.e., 89.5:10.5 vs 84.5:14.5 er observed with the methyl analogue.[20] Moreover, this result was comparable to the best diol **4a** of our first-generation catalyst system. From there on, the obvious direction was to increase the steric bulk at the ortho-position by substitution of the isopropyl group of diol **4g** with a tertiary butyl group as in diol **4h** and its analogous TMS-counterpart in diol **4i**. The Sharpless asymmetric dihydroxylation of the corresponding *trans*-stilbenes which was so reliable for the preparation of other diols failed to yield **4h** and **4i**. This failure stems from the steric hindrance of the *tert*-butyl group and the TMS group of the corresponding stillbene precursors. However, these diols were made through alternative routes requiring multiple synthetic steps (see Supporting Information for details), and they were subjected to LBA catalysis of the model allylboration reaction. Unfortunately, it was disappointing to observe slow reaction rates and, more importantly, significantly diminished er's of the isolated product **3a** (entries 7 and 8). We reasoned that the slow reaction rates were a consequence of inefficient accessibility of the activated proton in these more hindered catalyst complexes **4h**•SnCl$_4$ and **4i**•SnCl$_4$. As such, we concluded that there should be at least one benzylic hydrogen in the ortho-subtituent of the diol unit for maintaining a desirable level of activity in the LBA catalyst.
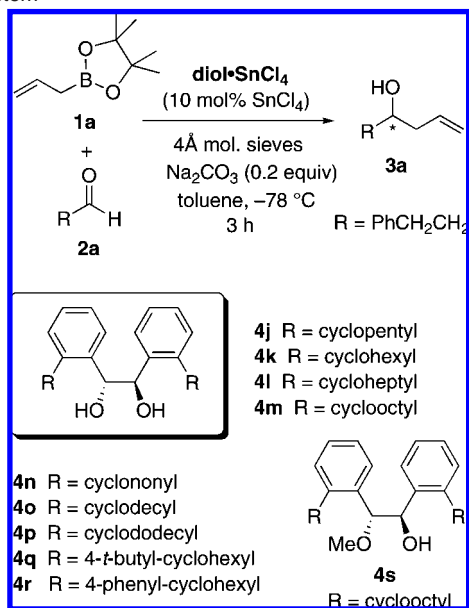
To this end, we decided to re-examine the best current diol, **4g**, and extend the isopropyl framework further in space. Subsequent design in this direction called for elaboration of the isopropyl framework through the use of various cycloalkyl rings. Accordingly, diols **4j**−**4r** were prepared and subjected under the LBA catalyst system to the model allylboration of **2a** (Table 2). To our satisfaction, we observed a gradual increase in the enantioselectivity of the reaction with increasing ring size. For example, whereas diol **4j** containing cyclopentyl rings in the ortho-position gave 90:10 er, diol **4k** containing cyclohexyl rings gave a 94:8 er, diol **4l** containing cycloheptyl ring gave 95.5:4.5 er, and diol **4m** equipped with cyclooctyl rings provided an optimal 96.5:3.5 er of product **3a** (entry 4). However, further increase in the ring size led to a gradual decrease in the er of the product along with diminished reaction rates. Diol **4n** containing cyclononyl groups gave 70% conversion and 94.5:5.5 er, diol **4o** containing cyclodecyl groups gave 50% conversion and 91.5:8.5 er, and diol **4p** containing cyclododecyl groups gave a dismal 20% conversion and 86:14 er of the desired product **3a** (entries 5−7). Substitution within the ortho-cyclohexane rings such as in diols **4q** and **4r** also gave encouraging results (entries 8 and 9). However, since these diols were obtained as a mixture of diastereomers from their precursors (see Supporting Information), they were not pursued. Interestingly, protection of one of the hydroxy group of diol **4m** leads to significantly diminished reaction rates and lower er of the product (entry 10). Overall, the most performant diol stood out to be diol **4m**, named Vivol, and as such we proceeded with this diol for the study of substrate scope.

Synthesis of Diol 4m (Vivol). During our optimization of the diol component of the catalyst, we needed to have rapid access to the above-mentioned diols. Although the Sharpless asymmetric dihydroxylation[24] of the corresponding *trans*-stilbene does provide diols **4j**−**m**, the reaction failed to provide diols **4o**−**p**. Moreover, the synthesis of the stilbene precursors, namely the corresponding aldehydes, is linear (see Supporting Information). As such, we designed a convergent approach for the

Table 2. Evaluation of Ortho-Cycloalkyl Substituted Diols in the LBA System[a]

entry	diol	% conversion	er
1	**4j**	100	90:10
2	**4k**	100	91:9
3	**4l**	100	95.5:4.5
4	**4m**	100	96.5:3.5
5	**4n**	70	94.5:5.5
6	**4o**	50	91:9
7	**4p**	20	86:14
8	**4q**	100	95.5:4.5
9	**4r**	100	95.5:4.5
10	**4s**	50	92.5:7.5

[a] Reaction conditions: All reactions were performed with 0.250 mmol of **2a**, 0.275 mmol of **1a**, 0.0275 mmol of diol, 0.025 mmol of SnCl4, 0.050 mmol of Na2CO3, 50 mg of 4 Å molecular sieves and 1.0 mL of toluene at − 78 °C for 3 h. Er of **3a** was determined by chiral HPLC.

Table 3. Optimization of diol vs. SnCl4 stoichiometry[a]
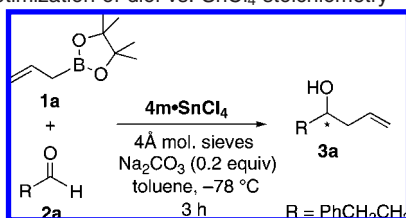
entry	**4m** (mol%)	SnCl4 (mol%)	conversion (%)	er
1	10	10	100	95:5
2	11	10	100	97:3
3	12.5	10	100	97.2:2.8
4	13	10	100	97.5:2.5
5	20	10	90	95:5

[a] Reaction conditions: All reactions were performed with 0.250 mmol of **2a**, 0.275 mmol of **1a**, 0.025 mmol of SnCl4, 0.050 mmol of Na2CO3, 50 mg of 4 Å molecular sieves, and 1.0 mL of toluene at −78 °C for 3 h. Er of **3a** was determined by chiral HPLC.

synthesis of diols **4j** and **4m−4r**, which branches out from common precursor **6** and requires three steps to reach the final diol Scheme 1. A representative example is the preparation of Vivol (**4m**), which is outlined in Scheme 1. The dibromo-acetal **6** is rapidly prepared in three simple operations in 50% combined yield from commercially available 2-bromobenzaldehyde **5**.[26] The cycloalkenylboronic acid **8** is then prepared

Table 4. Optimization of Reaction Concentration and Catalyst Loading[a]
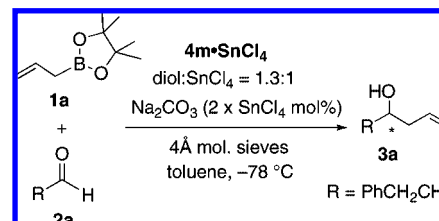
entry	(mol%) SnCl4	[aldehyde] (M)	time (h)	% conversion	ee
1	10	0.25	4	100	95
2	10	1.0	4	100	95.3
3	5	0.5	4	100	95.1
4	5	1.0	4	100	95.6
5[b]	3.85	1.0	5	100	95
6	2	0.5	16	100	94
7	2	1.0	16	100	94.3

[a] Reaction conditions: All reactions were performed with 0.250 mmol of **2a**, 0.275 mmol of **1a**, and the indicated amount of **4m**, SnCl4, and Na2CO3, with 50 mg of 4 Å molecular sieves and 0.25–1.0 mL of toluene at −78 °C for 3 h. Ee of **3a** was determined by chiral HPLC. [b] 5 mol % **4m** was used in this example.

following a Shapiro reaction protocol[27] from cyclooctanone (**7**) and assembled together with dibromide **6** in a high yielding bidirectional Suzuki−Miyaura cross-coupling reaction. The alkene protons of the corresponding product **9** appear misleadingly upfield as broad singlets and show correlation in the 2D-COSY NMR only upon heating the sample to 60 °C. The next step called for hydrogenation of the intermediate **9** followed by deprotection of the acetal to provide the requisite diol **4m**. However, in our hands, hydrogenation failed to yield any desired product, probably because of the sterically hindered nature of the molecule.[28] We then decided to reverse the sequence. After rigorous optimization, we were able to deprotect the acetal **9** in an acceptable yield to afford intermediate **10** and prevent side-products resulting from etherification of the alkene. Hydrogenation of the unsaturated diol **10** was then attempted. Surprisingly, hydrogenation of **10** required 50 wt % of Pd/C per double bond. Although we could lower the loading of Pd/C to 25 wt %, this protocol required high pressure and temperature, during which, we observed hydrogenolysis of the benzylic alcohol functionality.[29]

Having identified the optimal diol **4m** (Vivol) and prepared multigram amounts, we turned our attention to optimization of reaction parameters, including reaction solvent, diol/SnCl4 stoichiometry, and the concentration of the reaction.

Optimization of Solvent and Fine-Tuning of Catalyst Stoichiometry. Allylboration reactions are known to operate best in polar noncoordinating solvents.[12] Accordingly, we screened several polar noncoordinating solvents including mixed solvent systems that do not freeze at −78 °C (see Supporting Information). In the event, toluene was found to be the solvent of choice, just as in our first-generation conditions.[20] With toluene as the optimal solvent, we then proceeded to optimize the stoichiometry

(26) Wyatt, P.; Warren, S.; McPartlin, M.; Woodroffe, T. *J. Chem. Soc., Perkin Trans. 1* **2001**, 279–297.
(27) (a) Passafaro, M. S.; Keay, B. A. *Tetrahedron Lett.* **1996**, *37*, 429–432. (b) Rauniyar, V.; Zhai, H.; Hall, D. G. *Synth. Commun.*, in press.
(28) Other hydrogenation conditions using Crabtree's catalyst, Wilkinson's catalyst, Adam's catalyst, Pearlman's catalyst, and diimide reduction failed to yield the desired product.
(29) Hydrogenation under 2000 psi and 80 °C led to 40−50% of dehydroxylated product.

Scheme 1. Synthesis of Vivol (**4m**)
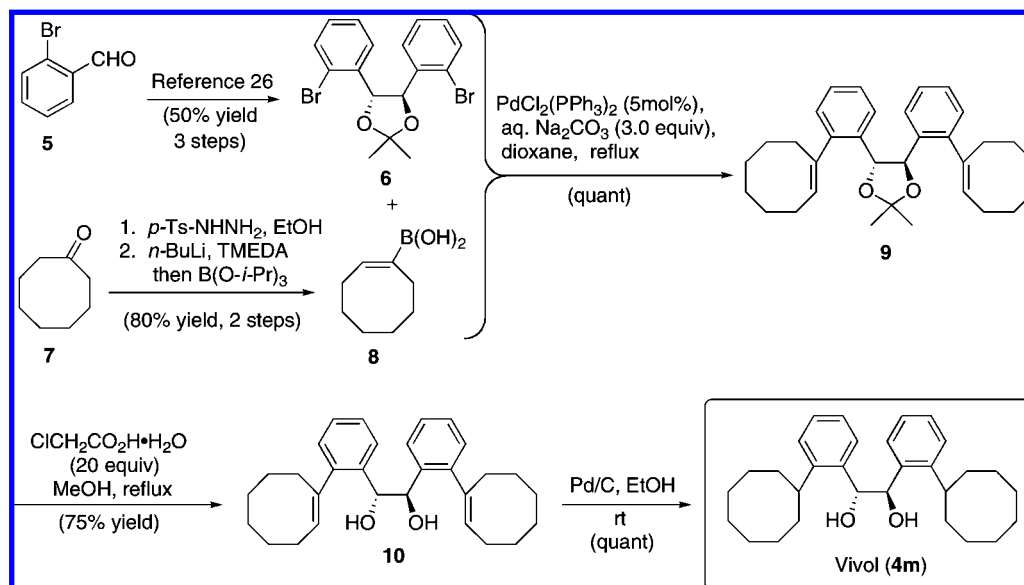
of the catalyst components. Along this line, it was found that SnCl$_4$ alone is a strong activator of the non-enantioselective reaction. A 10 mol % loading of SnCl$_4$ provides a 70% conversion of the model allylboration reaction after 4 h. As such, we had previously utilized a slight excess of diol over SnCl$_4$, i.e., 11 vs 10 mol %. However, upon further optimization of the **4m**/SnCl$_4$ ratio in this present second-generation system, increased enantioselectivities were observed reproducibly with a slightly higher loading of diol, which was optimal at a 1.3: 1.0 ratio of **4m**/SnCl$_4$ (Table 3, entry 4).

Optimization of Reaction Concentration. In our first report, we performed the catalytic reaction at a 0.25 M concentration of aldehyde substrate.[20] With the **4m**•SnCl$_4$ complex, an increase in the operating reaction concentration led to faster reactions and a slight increase in the er of the product (Table 4). Moreover, we can now lower the loading of the catalyst to 5 mol % of diol **4m** without a negative impact in the product er (entry 5). Remarkably, it was found possible to lower the loading of SnCl$_4$ down to 2 mol % and observe a similar product er (entry 7).

Substrate Scope for Allylation and Methallylation. Having optimized reaction parameters with the Vivol **4m**•SnCl$_4$ complex, we explored the substrates scope of the simple allylboration of aldehydes at 1 M concentration (Table 5). Once again, the preferred substrates for this second-generation LBA catalyst system were found to be aliphatic aldehydes. The reaction gave near quantitative yields for the majority of reactions, including aromatic substrates, and high er's for the aliphatic substrates. Synthetically useful homoallylic alcohol products from functionalized aldehydes were obtained in excellent enantioselectivity with er's up to 98:2 (entries 5−7, 9−11). Straight chain aliphatic aldehydes also gave the corresponding products in high er (entry 16). For oxygenated aliphatic aldehydes, insulation of the coordinating group by protection with bulky silyl groups gave better er's than when using benzyl protection (compare entries 5−7 vs 8). Catalytic allylation of phenylacetaldehyde, however, was more efficient with **4k** (entry 2) as the diol component of the LBA catalyst compared to diols **4m** (entry 4) or **4j** (entry 3). For hindered or branched aldehydes possessing α-substituents, we had to

employ a 10 mol % loading of SnCl$_4$ and employ a less hindered diol with a smaller ring size (entries 2, 12−15). For the allylation of cyclohexanecarboxaldehyde, diol **4m** gave moderate results, i.e., 87:13 er and 50% yield (entry 15). However, by switching to diols with smaller ring sizes, a gradual increase in the product er was observed, with diol **4j** providing optimal er and yield (entry 12). The present catalytic manifold gives comparably diminished er's for the allylation of protected α-hydroxy aldehydes (entries 17 and 18).

Compared to our first-generation LBA system,[20] products of aromatic aldehydes are now obtained with much improved er's. In particular, electron-poor aromatic aldehydes give better er's than electron-rich ones. We were particularly delighted to see a high er for the allylation of 3,5-bis-trifluoromethyl benzalde-hyde (entry 19). A limitation to the current methodology lies in the allylation of deactivated aromatic aldehydes (e.g., entry 21). The present catalytic manifold is also applicable to the methallylboration reaction and provides good to excellent er and excellent yields of the corresponding products (entries 25−27).

Substrate Scope in the Crotylboration of Aldehydes. We then explored the analogous crotylboration of aliphatic aldehydes. Freshly prepared reagents **1c** and **1d** of >95% isomeric purity were reacted with aliphatic aldehydes under Vivol•SnCl$_4$ catalysis (Table 6). The results correlate with our previous report, i.e., that the trans-crotyl boronate **1c** affords better er than the cis-crotyl boronate **1d**.[20] Er's as high as 98:2 are observed, and more importantly, the *E/Z* geometry of the reagent is completely transferred diastereospecifically to the product. Since the reaction is significantly slower than simple allylboration, we chose to use a 10 mol % catalyst loading. Lower catalyst loading does provide the requisite product in a slightly diminished yield and comparable er (entry 2). The corresponding cis crotylboration reaction also provides improved er's of the product when compared to the first-generation catalyst system (entries 8−10). Furthermore, it is remarkable that the stereoselectivity of this catalytic

Table 5. Substrate Scope in the Catalytic Enantioselective Allyl and Methallylboration of Aldehydes[a]
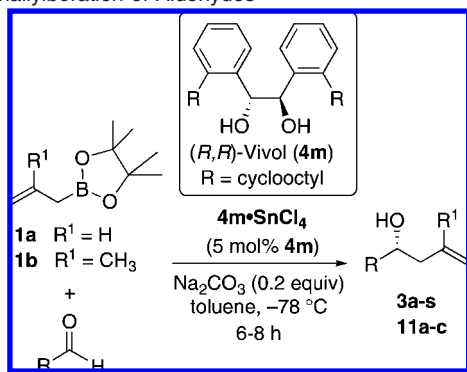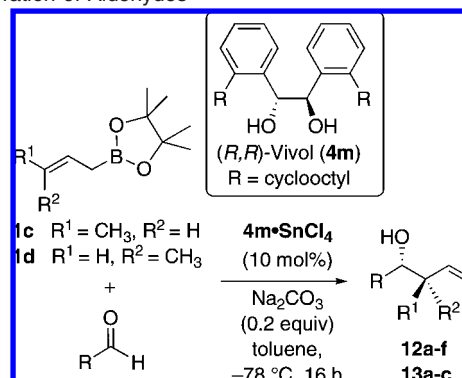

entry	R¹	aldehyde	product	yield (%)	er
1	H	Ph(CH₂)₂CHO	**3a**	99	97.5:2.5
2	H	PhCH₂CHO	**3b**	99	96.5:3.5[b,e]
3	H	PhCH₂CHO	**3b**	99	91:9[c]
4	H	PhCH₂CHO	**3b**	99	87:13
5	H	TBSO(CH₂)₂CHO	**3c**	98	97.5:2.5
6	H	TIPSO(CH₂)₂CHO	**3d**	99	97.5:2.5
7	H	TBDPSO(CH₂)₂CHO	**3e**	99	95:5[e]
8	H	BnO(CH₂)₂CHO	**3f**	99	90:10
9	H	TBDPSO(CH₂)₃CHO	**3g**	95	96.5:5
10	H	TBSO(CH₂)₃CHO	**3h**	85	96:4
11	H	TIPSO(CH₂)₃CHO	**3i**	99	96:4
12	H	C₆H₁₁CHO	**3j**	94	95.5:4.5[c,e]
13	H	C₆H₁₁CHO	**3j**	91	91:9[b,e]
14	H	C₆H₁₁CHO	**3j**	90	90:10[d,e]
15	H	C₆H₁₁CHO	**3j**	50	87:13[e]
16	H	CH₃(CH₂)₂CHO	**3k**	90	97.5:2.5
17	H	TBDPSOCH₂CHO	**3l**	99	88.5:11.5[e]
18	H	BnOCH₂CHO	**3m**	99	85:15[e]
19	H	3,5-(CF₃)₂C₆H₃CHO	**3n**	99	97:3
20	H	2-F-C₆H₄CHO	**3o**	99	90:10
21	H	4-OMe-C₆H₄CHO	**3p**	45	56.5:43.5
22	H	2-Br-C₆H₄CHO	**3q**	99	80:20
23	H	2-CF₃ C₆H₄CHO	**3r**	95	87.5:12.5
24	H	C₆H₅CHO	**3s**	99	85.5:14.5
25	CH₃	TBDPSO(CH₂)₂CHO	**11a**	99	96:4
26	CH₃	Ph(CH₂)₂CHO	**11b**	99	92:8
27	CH₃	TBDPSO(CH₂)₃CHO	**11c**	95	92.5:7.5

[a] Reaction conditions: Unless noted, all reactions were performed with 1.10 mmol of boronate, 1.00 mmol of aldehyde, 3.85 mol% of SnCl₄, 5.00 mol% of **4m**, 0.077 mmol of Na₂CO₃, 50 mg of 4 Å molecular sieves, and 1.0 mL of toluene at −78 °C for 6−8 h. Er was determined by chiral HPLC and/or ¹⁹F-NMR analysis of diastereomeric Mosher esters. [b] Diol **4k** was used. [c] Diol **4j** was used. [d] Diol **4l** was used. [e] 10 mol% of catalyst was used.

enantioselective trans-crotylboration is superior to that of the most popular stoichiometric reagents.[5]

Mechanistic Studies

How Bad Is the Background Reaction? The first mechanistic issue to address was the extent of the absolute background (uncatalyzed) reaction between allylboronate **1a** and model aldehyde **2a** at −78 °C and its impact on the enantioselectivity of the catalytic cycle. Although Brown and co-workers have reported that there is no reaction between **1a** and benzaldehyde at −78 °C for 12 h,[12] we found that this is not the case with aldehyde **2a**. In our studies of the low temperature (−78 °C) reactivity of **1a** with hydrocinnamaldehyde, we did observe trace amounts (2%) of the borate ester of the product at a 0.2 M concentration of aldehyde **2a** after a 5 h time period. This result implies that during the 6−8 h allylation run, the background reaction can possibly

Table 6. Substrate Scope in the Catalytic Enantioselective Crotylboration of Aldehydes[a]

entry	aldehyde	R¹	R²	product	yield (%)	er
1	Ph(CH₂)₂CHO	CH₃	H	**12a**	93	98:2
2[b]	Ph(CH₂)₂CHO	CH₃	H	**12a**	80	96.5:3.5[b]
3	TBDPSO(CH₂)₂CHO	CH₃	H	**12b**	94	96.5:3.5
4	TBSO(CH₂)₂CHO	CH₃	H	**12c**	99	95.5:4.5
5	TBSO(CH₂)₃CHO	CH₃	H	**12d**	93	95.5:4.5
6	CH₃(CH₂)₃CHO	CH₃	H	**12e**	74	97.5:2.5
7	3,5-(CF₃)₂C₆H₃CHO	CH₃	H	**12f**	99	95:5
8	PhCH₂CH₂CHO	H	CH₃	**13a**	78	92:8
9	TBDPSOCH₂CH₂CHO	H	CH₃	**13b**	75	90:10
10	TBDPSOCH₂(CH₂)₂CHO	H	CH₃	**13c**	70	94:6

[a] Reaction conditions: All reactions were performed with 0.275 mmol of boronate, 0.250 mmol of aldehyde, 0.0325 mmol of **4m**, 0.025 mmol of SnCl₄, 0.050 mmol of Na₂CO₃, 50 mg of 4 Å molecular sieves, and 1.0 mL of solvent at −78 °C for 16 h. Er was determined by chiral HPLC and/or ¹⁹F-NMR analysis of diastereomeric Mosher esters. [b] 5 mol% of SnCl₄ was used.

Scheme 2. Control Reaction with Fully Protected Diol **4t**
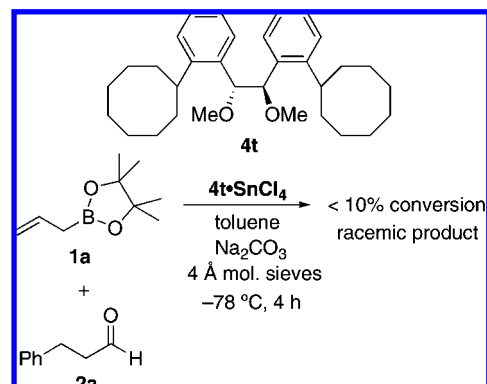

account for at least 2% of the opposite enantiomer (especially at higher reaction concentration). Consequently, the current LBA catalyst can only provide a maximum of approximately 98:2 er.

Truly a Brønsted Acid Catalyst? Given the complexity of the diol•SnCl₄ system, it seemed appropriate to ask whether the active catalyst is truly a Brønsted acid or a bisalkoxy-dichloro-tin species. To this end, we synthesized the dimethoxy ether derivative **4t** of the diol **4m**, which is devoid of hydroxylic protons. In the event, the addition of **1a** into hydrocinnamaldehyde **2a** under **4t**•SnCl₄ catalysis led to low yields of the desired product in racemic form (Scheme 2). Similar results were obtained when using the SnCl₄ complex of diol **4a** fully protected as its dimethyl ether. These results strongly suggest the important role of hydroxylic protons for efficient catalysis and facial selectivity of the aldehyde substrates. As indicated by the moderate activity of the

Scheme 3. Control Reactions That Rule out a Trans-Esterification Mechanism
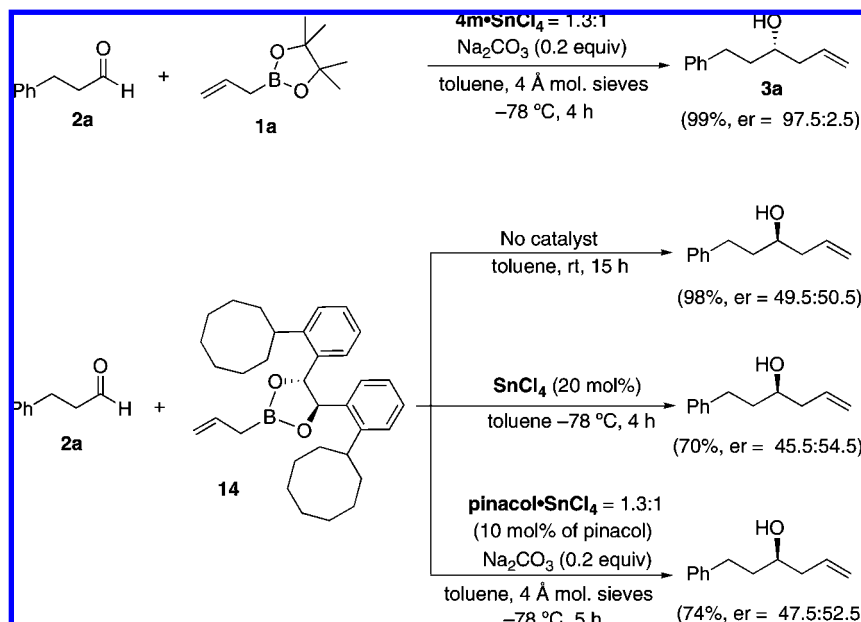
complex of monomethyl ether **4s** (entry 10, Table 2), a single hydroxylic proton suffices for enantioselective catalysis although it is not as efficient as two protons (compare with **4m**, entry 4).

A similar outcome was also observed when replacing anhydrous Na$_2$CO$_3$ with a soluble base, Et$_3$N. Addition of Et$_3$N (2.0 equiv vs **4a**) inhibits the allylation by most likely leading to a bisalkoxide tin species, which is a weak Lewis acid compared to the strongly Lewis acidic SnCl$_4$.[30] Additionally, based on ^{119}Sn NMR studies, the complex of **4a**•SnCl$_4$ in toluene-d_8, with or without added anhydrous Na$_2$CO$_3$, exhibits octahedral geometry around the tin atom. In these experiments, we observed only a single peak at −572.70 ppm, a region associated with hexacoordinated tin complexes.[31] We also ran the model reaction under the presence of a proton sponge and failed to observe any catalysis. All these observations clearly point to a Brønsted acid activation manifold for the allylboration reaction with the diol•SnCl$_4$ LBA catalyst system. An analogous Brønsted acid activation of the boron center has been proposed in the elegant ketone allylboration work of Schaus and co-workers.[32]

Is Trans-Esterification between 4m and 1a a Possibility? If the kinetic barrier for trans-esterification is low enough, boronic esters can exchange with free diols.[13] We wanted to address the possibility that a Lewis or a Brønsted acid catalyzed trans-esterification process could lead to the chiral allylboron intermediate **14**, which could be responsible for the observed enantioselectivity in the product. To this end, we independently synthesized authentic reagent **14** appended with a (R,R)-Vivol (**4m**) scaffold.[33] To our surprise, subjecting this chiral reagent under Lewis acid catalysis or combined acid catalysis (pinacol•SnCl$_4$) provided products in a much lower er and with

opposite absolute stereochemistry (based on HPLC retention times) (Scheme 3). Such a low level of enantioselectivity is in line with previously reported aldehyde allylation results from Roush and co-workers when employing chiral hydrobenzoin derived auxiliaries.[34] *It is truly remarkable that chiral diol 4m functions much better when acting as a component of the LBA catalyst than when used stoichiometrically as a chiral auxiliary reagent.*

The possibility of boron-to-tin transmetalation to form an allylic tin reagent is equally unlikely as it would be hard to reconcile with the lack of activity of the fully protected diol (cf., Scheme 2). Moreover, low-temperature (−78 °C) NMR experiments between equimolar **1a** and **4a**•SnCl$_4$ hint to complexation of the boronate unit, however, with a negligible change of chemical shift for the methylene protons (CH_2B). Altogether, these results confirm that the role of the LBA catalyst is to accelerate by noncovalent interactions the addition of allylboronate **1a** onto aldehydes and at the same time provide asymmetric bias for the enantiofacial selectivity.

Why is Excess Diol Needed? The optimal conditions in this second-generation catalytic system employ slightly different diol/SnCl$_4$ stoichiometry compared to the first-generation catalyst system. Although there is not a highly significant variation of er's going from a 1.1:1 to 1.3:1 ratio (Table 3), we felt the need to understand the seemingly anomalous use of up to 0.3 additional equiv of diol in the in situ catalyst preparation. During the course of this study, we have found that the (R,R)-1,2-dinaphthyl ethanediol **4a** slowly catalyzes the addition of **1a** onto hydrocinnamaldehyde, giving rise to homoallylic alcohol product **3a** in 70% conversion and −17%

(30) Iwasaki, F.; Maki, T.; Nakashima, W.; Onomura, O.; Matsumura, Y. *Org. Lett.* **1999**, *1*, 969–972.
(31) Harris, R. K.; Kennedy, J. D.; McFarlane, W. In *NMR and the Periodic Table*; Harris, R. K., Mann, B. E., Ed.; Academic Press: London, 1978; Chapter 10, pp 309−377.
(32) (a) Lou, S.; Moquist, P. N.; Schaus, S. E. *J. Am. Chem. Soc.* **2006**, *128*, 12660–12661. (b) Lou, S.; Moquist, P. N.; Schaus, S. E. *J. Am. Chem. Soc.* **2007**, *129*, 15398–15404.
(33) The reagent was made through condensation of triallylborane with **4m** under catalytic Et$_3$N in THF for 2 h at reflux. See Supporting Information for more details.
(34) Roush, W. R.; Banfi, L.; Park, J. C.; Hoong, L. K. *Tetrahedron Lett.* **1989**, *30*, 6457–6460.
(35) See Supporting Information for full details.
(36) CCDC-679578 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
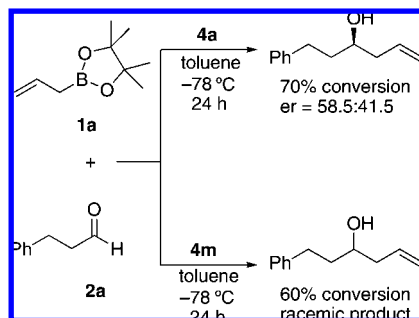
ee after 24 h. In contrast, Vivol (**4m**) was found to catalyze the same reaction to give the product in 60% conversion in racemic form (Scheme 4). Hence, in order to avoid aggravating any erosion of enantioselectivity, it is logical that the first-generation catalyst system functions well with a minimal excess of diol **4a** vs SnCl₄. The second-generation catalyst system, however, can accommodate a slightly higher excess of the diol **4m**, and indeed the product er gradually rose from 95:5 to 97.5:2.5 by going from a 1.1 to 1.3:1 ratio of diol vs SnCl₄ (see Table 3).

We reasoned that this slightly higher loading of diol **4m** is required in order to sequester any uncomplexed SnCl₄ (which can act as a strong achiral Lewis acid catalyst for the same reaction). To probe this assumption, we subjected a preformed (1:1) complex of (*R,R*)-Vivol **4m•SnCl₄** at −78 °C with 1 equiv of (*R,R*)-hydrobenzoin. After a 3 h time period, we could see up to 6% exchange of SnCl₄ from the (*R,R*)-Vivol **4m•SnCl₄** complex to the (*R,R*)-hydrobenzoin•SnCl₄ complex by ¹¹⁹Sn NMR spectroscopy. The reverse exchange experiment also provided similar results with an even larger amount of SnCl₄ exchange (see Supporting Information). Along the same line, Yamamoto and co-workers have mentioned the phenomenon of reversible complexation of diols with SnCl₄ as a reason for difficulty in obtaining diol•SnCl₄ crystals.[19e] As such, any free-floating SnCl₄ in the reaction medium would be detrimental to the product er; hence the presence of excess diol is needed for sequestering this strong racemic activator. These observations are summarized in Figure 4.

Catalyst Structure, Origin of Enantioselectivity. To shed light onto the structure of the active catalyst, crystallization of a 1:1 mixture of (*R,R*)-Vivol (**4m**) and SnCl₄ in toluene and methylene chloride was attempted. After extensive optimization of the crystallization conditions and numerous failed attempts, we were fortunate to obtain clear and colorless
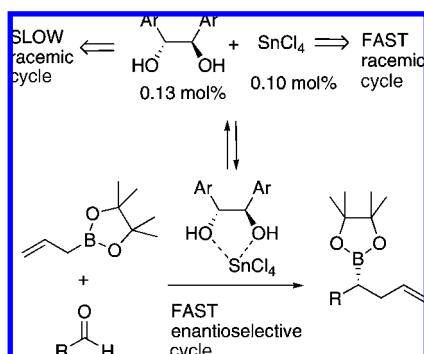
Figure 4. Schematic representation of diol•SnCl₄ exchange phenomenon and its implications on the reaction's enantioselectivity.
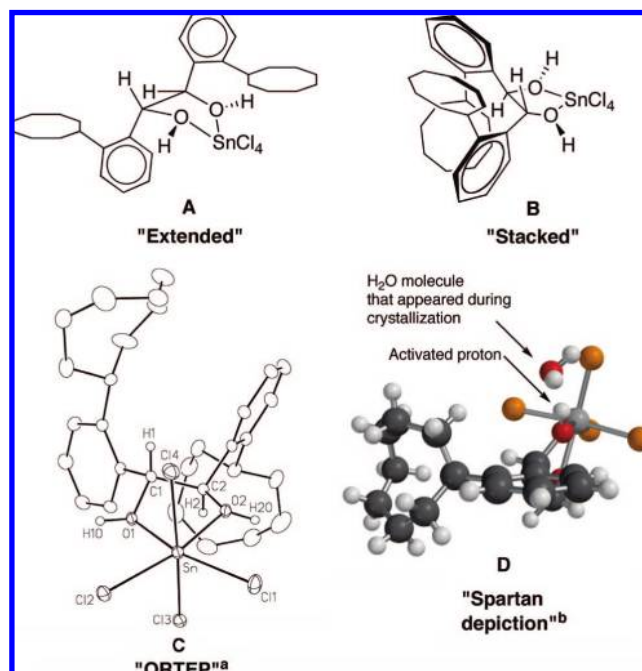
Figure 5. Possible structural motifs of (*R,R*)-Vivol (**4m**)•SnCl₄ complex including ORTEP representation of X-ray crystallographic structure. [a] Selected interatomic bond lengths of **C** (Å): H10−O1= 0.86, H20−O2 = 0.86, intermolecular H10•••O1S = 1.67, intermolecular H20−Cl3 = 2.42, Sn−Cl1 = 2.3401(8), Sn−Cl2 = 2.3571 (8), Sn−Cl13 = 2.4262 (8), Sn−Cl4 = 2.3698 (9). Selected interatomic bond angles (deg): Cl2−Sn−O1 = 92.96(6), Cl1−Sn−O2 = 89.37 (6), O1−C1−C2 = 105.8 (2), O2−C2−C1 = 104.5, intermolecular O2−H2•••Cl3 = 149.2. [b] Spartan representation (unminimized) of the X-ray structure (the cyclooctyl-aryl fragment of the distal carbon is omitted for clarity).

needles from a 1:1 mixture of Vivol (**4m**) and SnCl₄ during a 2 month period at −15 °C.[35] Single crystal X-ray diffraction analysis of this LBA catalyst provided the structure shown in Figure 5.[36] Surprisingly, the complex does not exhibit the extended conformation (**A**) that would minimize steric interactions between the two substituents. Instead, it prefers a stacked structure (**B**) where the cyclooctyl group of one aryl substituent piles over the arene unit of the other substituent, and vice versa. Although this conformation may simply result from crystal packing, it would explain the subtle effect observed with respect to the ortho substituent's ring size and the asymmetric environment of the activated protons. The ORTEP representation (**C**) shows hydrogen-bonding interactions of the activated protons H-20 and H-10 with apical Sn−Cl-3 and includes an adventitious water molecule that presented itself during the crystallization event (see Supporting Information). It is likely that H-10 is also the point of electrophilic activation of reagent **1** through hydrogen bonding interaction with one of the oxygens of the dioxaborolane, as proposed previously in the case of Lewis acid activation (c.f. Figure 2).[16] Another key observation concerns the direction of the activated protons, i.e., H-10 and H-20. Both potential Brønsted acids are pointing outward in a pseudoequatorial direction from the five-membered chelated ring system of Vivol (**4m**)•SnCl₄. This observation depicts the rigidity, i.e., lack of orientational flexibility of the activated H-10 and H-20, and as such, these hydroxylic protons bear chiral information of the diol scaffold. From the Spartan structure of the crystal structure (**D**), a highly dissymmetric environment is evident around both activated protons. The edge of the cyclooctyl ring along with the

equatorial and apical chlorine atoms, Cl-2 and Cl-4, block several directions around both activated protons and are the most likely elements that influence the stereochemical outcome of the reaction. In this model, the plane of the aryl group may thus provide a surface for the transition state assembly, and its precise orientation, which is potentially influenced by the adjacent cyclooctyl group, could be critical to the selectivity of the catalyst.

Conclusion

We have reported a very efficient catalyst system for the enantioselective allyl- and crotylboration of aliphatic aldehydes that provides useful homoallylic alcohol products in very good to excellent enantioselectivity. Remarkably, the products of trans-crotylboration are obtained with superior er's than that of the well-established stoichiometric allylboration methods. Using control reactions and X-ray crystallographic analysis of the optimal Vivol (**4m**)−SnCl$_4$ complex, we have also shown that the active catalyst in this reaction is a Brønsted acid that is rigidly held in a highly dissymmetrical environment. We also uncovered the unusual requirement for a small excess of diol in the in situ preparation of the catalyst and its likely role as a sequestering agent for free SnCl$_4$, which may act as a racemic catalyst that arises in small amounts from the dynamic nature of the diol•SnCl$_4$ complex. As we have noted that the background uncatalyzed reaction is limiting the product er's in the simple allylation reaction, diols based on the Vivol (**4m**) scaffold with increased acidity could be designed and provide more active diol•SnCl$_4$ complexes. Moreover, diols **4a−4r** can potentially find application in other reactions susceptible to LBA catalysis.[19]

Supporting Information Available: Full experimental details, additional data and tables for catalyst optimization, compound characterization, copies of ^{1}H and ^{13}C NMR spectra for all new compounds, and X-ray crystallographic data for **4m**•SnCl$_4$ in CIF format are included. This information is available free of charge via the Internet at http://pubs.acs.org.

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