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Rationally Improved Chiral Brønsted Acid for Catalytic Enantioselective Allylboration of Aldehydes with an Expanded Reagent Scope

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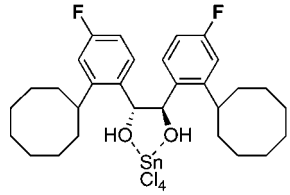
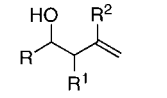


p-F-vivol (**4b**) • $SnCl_4$



up to 97% ee, >98% dr

R = aliphatic
R^1 = H or CH_3
R^2 = H, CH_3 , or Br

One of the most useful reactions in organic synthesis, the stereocontrolled addition of allylic metal reagents to carbonyl compounds, provides access to enantiomerically enriched homoallylic alcohols related to the acetate, propionate, and other oxygen-containing functionalities present in a large number of biologically active natural products and pharmaceutical drugs. In the search for an ideal carbonyl allylation methodology, the catalytic enantioselective allylboration presents numerous advantages such as a high chemo-, diastereo-, and enantiocontrol with stable and nontoxic pinacol allylic boronates. This article reports a rationally improved diol•$SnCl_4$ complex as chiral protic acid catalyst, which provides unprecedented levels of enantioselectivity in the catalytic allylation, methallylation, crotylation, and 2-bromoallylation of aliphatic aldehydes. The new diol, p-F-Vivol (**4b**), enables a more active diol•$SnCl_4$ catalyst that can compete more effectively with the background uncatalyzed allylboration. The usefulness of this optimized catalytic allylboration methodology was demonstrated with an efficient synthesis of the naturally occurring pyranone (+)-dodoneine and to the preparation of biologically important exomethylene-γ-lactones.

Introduction

The search for an ideal carbonyl allylation methodology has been going on for decades,[1,2] fueled by the usefulness of this reaction as a means to access the acetate, propionate, and other oxygen-containing functionalities present in a large number of biologically active natural products and pharmaceutical drugs. In producing the desired homoallylic alcohols, an ideal allylation method would have to demonstrate all of the following attributes: mildness and chemoselectivity, ease of operation at low cost with simple allyl donors, low environmental impact ("greenness"), broad substrate generality (for both allylmetal reagent and carbonyl substrate), high and predictable diastereoselectivity, and high enantioselectivity. With regard to enantioselectivity, an ideal carbonyl allylation methodology would circumvent the use of stoichiometric chiral auxiliaries through a simple and efficient chiral catalyst.[3] Catalytic enantioselective aldehyde allylation methods based on allylic trialkoxy- and trialkylsilanes,[4] trihalosilanes,[5] trialkylstannanes,[6] halides,[7] and acetates[8] have been reported. Arguably, none of these methods meet all of the above-mentioned attributes. For example, several methods perform well only with aromatic

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aldehydes, whereas others require expensive transition-metal catalysts or employ highly toxic trialkylallylic tin reagents or chromium-based catalysts. Several very effective and popular aldehyde allylation methods based on boron reagents have been developed, but they all require a stoichiometric chiral inductor.[9] Our laboratory has advocated the development of a catalytic enantioselective allylboration as an attractive alternative.[10] Indeed, pinacol allylboronates are air- and water-stable, nontoxic, and readily formed reagents whose additions to aldehydes are characterized by very high levels of chemo-, regio-, and diastereoselectivity. Moreover, a plethora of efficient methods are available for the preparation of functionalized allylic boronates.[11,12] Recently, we discovered that both Lewis acids[13] and Brønsted acids[14] can catalyze additions of allylboronates to aldehydes. These mechanistically novel allylboration procedures[15] have matured into an efficient enantioselective Brønsted acid-catalyzed allylation and crotylation of aliphatic aldehydes, producing homoallylic alcohol products in up to 95% ee (Figure 1).[16] This system, based on Yamamoto's elegant concept of "Lewis acid assisted Brønsted acidity" with chiral diol−$SnCl_4$ complexes,[17] provides useful selectivities, but the scope of useful substrates remains quite limited with the optimal diol Vivol (**4a**) (Figure 1). Here, we report the design and applications of an improved catalyst that provides significantly higher ee's with useful aliphatic aldehydes and a wider range of allylic boronates including the unprecedented 2-bromoallylboron pinacolate. As demonstrated in a total enantioselective synthesis of (+)-dodoneine, the resulting catalytic enantioselective allylation methodology can match or surpass the efficiency of the popular Brown[9b] and Keck[6b] allylation reactions.

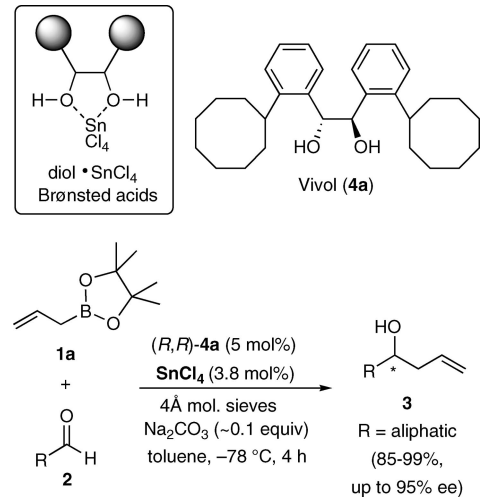

FIGURE 1. Vivol·$SnCl_4$-catalyzed allylboration of aldehydes.

Results

Design and Evaluation of an Improved Chiral Diol·$SnCl_4$ Catalyst. While developing an optimal chiral diol for the diol·$SnCl_4$ catalysis of the prototype allylation reaction between hydrocinnamaldehyde (**2a**) and allylboron pinacolate (**1a**), we realized that the slow background uncatalyzed allylation competed non-negligibly with the catalytic process. In the course of 4−5 h, approximately 3−4% of racemic **3a** was formed, consequently eroding the enantioselectivity by a few percent of ee.[16c]

We rationalized that a more acidic diol and thus more active Brønsted acid was required in order to shorten the reaction times and suppress the background uncatalyzed reaction. In this regard, it was expected that electron-withdrawing substituents on the diol's aryl units could decrease the pK_a of the hydroxylic protons in the diol·$SnCl_4$ complex. It was also deemed preferable to place the substituent in the para position as opposed to the ortho or meta positions because the X-ray crystallographic structure of the vivol·$SnCl_4$ complex shows an intimate steric relationship between the cyclooctyl unit and the aryl group of adjacent carbons, which appear to stack with one another.[16c] Upon inspection of the crystal structure, modulating electronic effects at the para position of the aryl groups appeared to least disrupt the catalyst's spatial arrangement. To this end, diols **4b** and **4c** with respective *p*-fluoro and trifluoromethyl substituents were targeted (Figure 2). In order to support the hypothesis of electronic modulation of catalyst acidity, diol **4d** with electron-donating methoxy substituents was also planned. Diols **4b** and **4c** were prepared using a previously published sequence,[16c] whereas diol **4d** required an alternative route (see the Supporting Information). The synthesis of the optimal diol, **4b**, is outlined in Scheme 1 and features an efficient sequence of six high-yielding steps similar to that reported for the nonfluorinated analogue **4a**. Starting from commercially available 2-bromo-4-fluorobenzaldehyde, a stereoselective McMurry coupling yielded the corresponding *trans*-stilbene **5** in 76% yield.[18] Sharpless asymmetric dihydroxylation under the influence of

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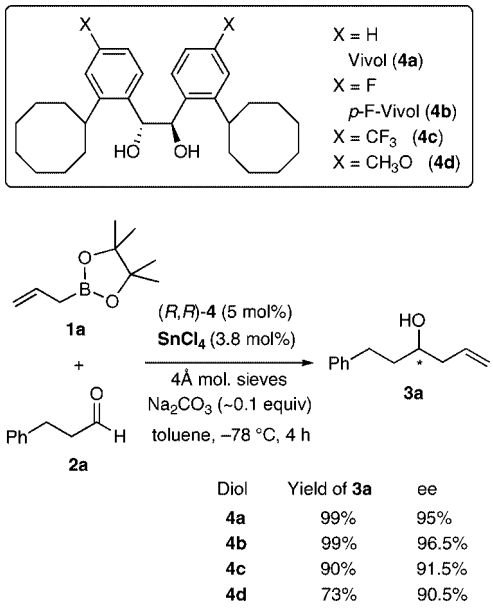

Diol	Yield of **3a**	ee
4a	99%	95%
4b	99%	96.5%
4c	90%	91.5%
4d	73%	90.5%

FIGURE 2. Comparison between a set of electronically modulated diols in the diol·$SnCl_4$-catalyzed model allylboration of hydrocinnamaldehyde (**2a**) with allylBpin (**1a**).

$(DHQD)_2PHAL$ provided the required hydrobenzoin **6** in >99.9% ee after recrystallization from CH_2Cl_2/hexanes.[19] The diol unit was transformed into acetonide **7** using standard conditions and subsequent bidirectional Suzuki−Miyaura cross-coupling using cyclooctenylpinacol boronate[16c,20] led to the formation of **8** in 95% yield. The acetonide moiety was then deprotected under acidic conditions to yield cycloalkenylhydrobenzoin **9**, which was then subjected to hydrogenation under Pd/C. The requisite *p*-F-Vivol **4b** was thus obtained in quantitative yield and further recrystallized from CH_2Cl_2/hexanes to afford the desired diol as a white amorphous solid.

All four diols were tested in the prototypic allylation of hydrocinnamaldehyde under previously described conditions employing molecular sieves and insoluble Na_2CO_3 as precautionary scavengers of adventitious water and HCl, respectively.[16c] The fluorinated diol **4b** led to the highest yield and enantioselectivity (Figure 2). Although *p*-F-Vivol (**4b**) provided a relatively small increase of enantioselectivity over **4a** in the simple allylation of hydrocinnamaldehyde, its effect on other aliphatic aldehydes and substituted allylboronates is significant and appears to be general (cf., Figure 3). It should be noted that simple allylations with the commercially available reagent **1a** as well as methallylations (with **1b**) and crotylations (with **1c**) are performed with a minimal excess of the reagent (i.e., 0.1 equiv in excess) and with a relatively low catalyst loading of 2.5−5 mol %. In line with the previous Vivol·$SnCl_4$-catalyzed allylborations,[16c] the optimal *p*-F-Vivol/$SnCl_4$ ratio was found to be 1.2−1.3 (see the Supporting Information). We have also noted that this allylboration system functions efficiently at very high concentrations, even beyond 1.0 M, which makes it very advantageous from the viewpoint of green chemistry (i.e., solvent economy). The superior efficiency of *p*-F-Vivol (**4b**) was highlighted with the examples of Figure 3.

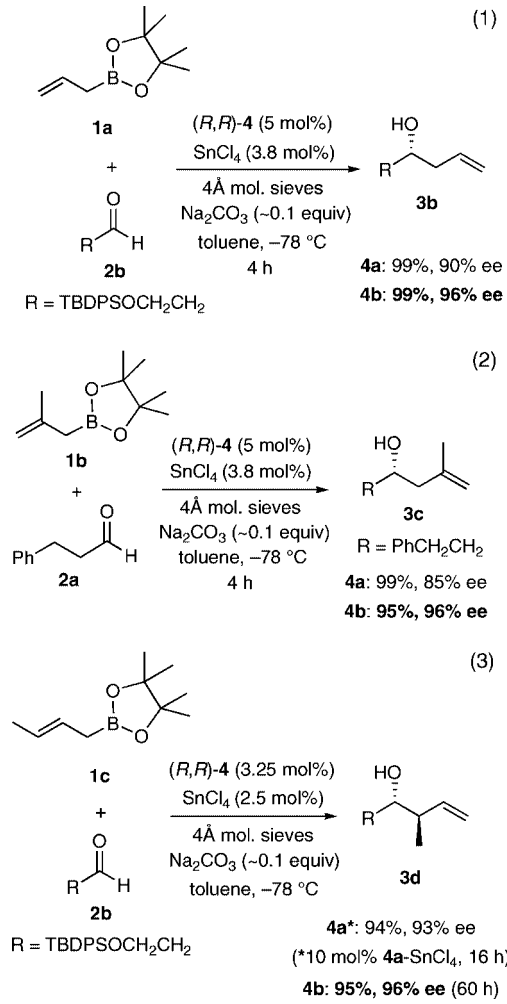

FIGURE 3. Comparison between Vivol·$SnCl_4$ and *p*-F-Vivol·$SnCl_4$-catalyzed allyl-, methallyl-, and (*E*)-crotylboration of representative aliphatic aldehydes.

The synthetically useful β-siloxy aldehyde **2b** was allylated to give product **3b** with a substantially improved ee of 96% (compared to 90% ee with diol **4a**)[16c] (eq 1). The new diol **4b** was particularly beneficial when used with the methallylboronate **1b** (eq 2) and with the *E*-crotyl boronate **1c** (eq 3). In the latter example, the crotylation of aldehyde **2b** was realized with only 2.5 mol % of catalyst on a scale providing 7.3 g of the synthetically useful propionate product **3d** from a reaction using only 20 mL of solvent (1.0 M concentration). Moreover, the chiral diol **4b** can be recovered with ease with a remarkable yield of 80−90%. This allylation system was optimized for aliphatic aldehydes; therefore, it is not surprising that *p*-F-Vivol (**4b**) does not fare better than Vivol (**4a**) for unactivated aromatic aldehydes: the addition of **1a** to benzaldehyde gives the homoallylic alcohol product in only 60% ee (not shown). Likewise, as exemplified with the addition of **1a** to cyclohexanecarbaldehyde (70% yield and 80% ee with **4b** vs 50% yield and 74% ee with **4a**), α-branched aldehydes are more difficult substrates, but the use of a diol with smaller cycloalkyl substituents is expected to improve the enantioselectivity.[16c]

Applications

Target oriented-synthesis of natural products or pharmaceutical drugs constitutes a recognized way of validating new

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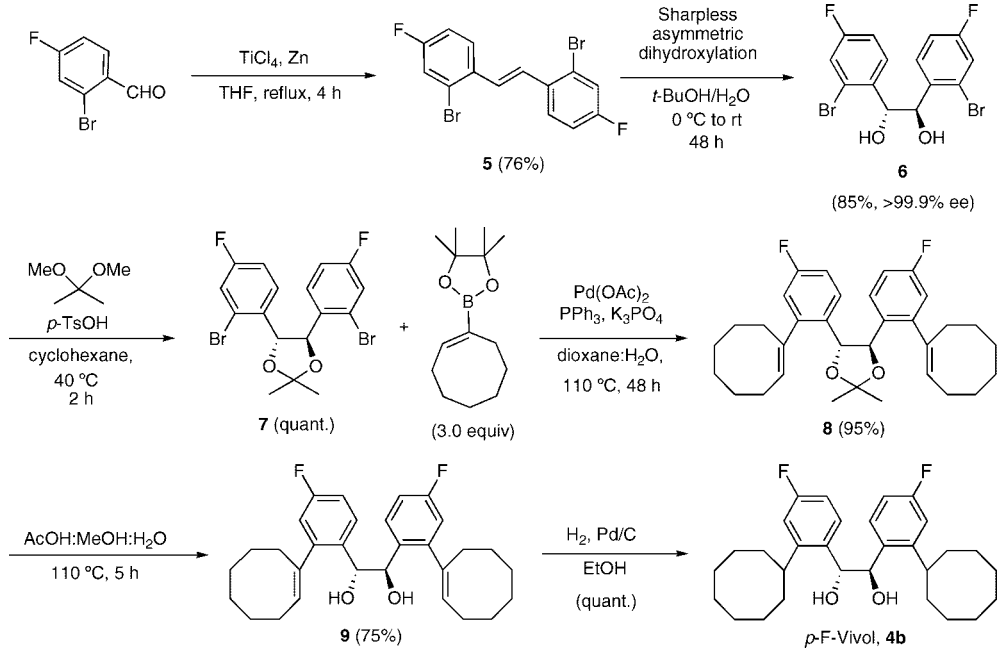
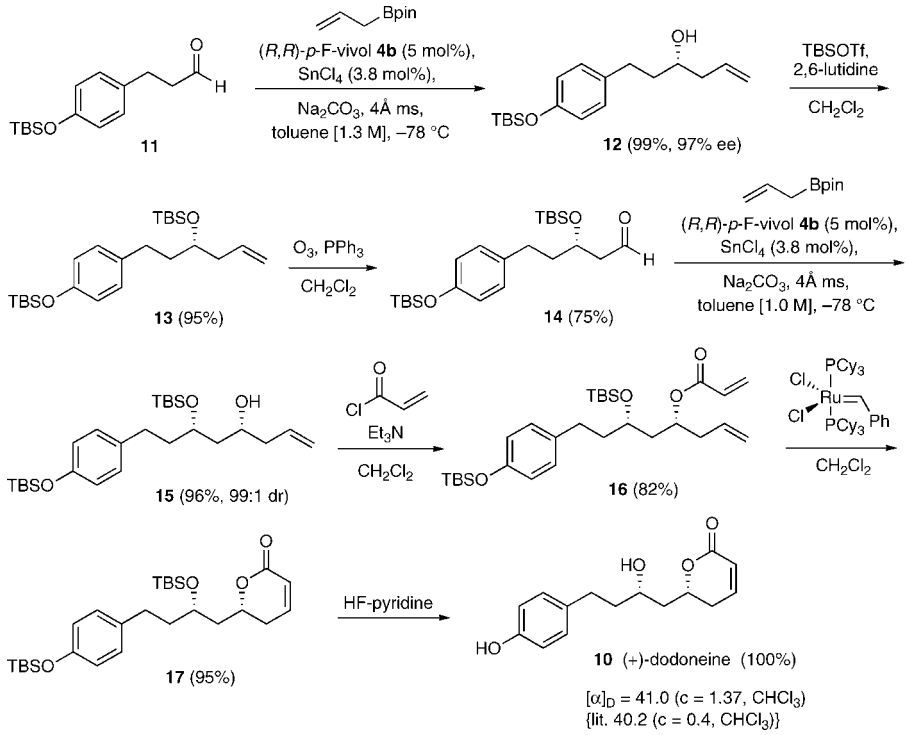
SCHEME 1. Preparation of *p*-F-Vivol, 4b



SCHEME 2. Application of *p*-F-Vivol·$SnCl_4$ Allylboration to the Total Synthesis of (+)-Dodoneine



synthetic methods. To measure the efficiency of our new allylation variant in this context, we chose (+)-dodoneine as target (**10**, Scheme 2), which requires two aldehyde allylation reactions for its elaboration. Dodoneine is a naturally occurring dihydropyranone recently isolated from a parasitic plant in Burkina Faso.[21] It displays a vasorelaxant effect on preconstricted rat aortic rings, thus suggesting a potential toward cardiovascular disorders. (+)-Dodoneine was previously synthesized by the groups of Marco[22] and Cossy[23] using established aldehyde allylation methods. Our planned synthesis followed similar routes so as to allow a direct comparison with the *p*-F-Vivol·$SnCl_4$-catalyzed allylboration. The requisite *p*-siloxy aldehyde **11** was prepared in just a few steps from commercial material.[22] To our satisfaction, the *p*-F-Vivol·$SnCl_4$-catalyzed allylboration of **11** proceeded in near-quantitative yield to afford alcohol **12** in 97% ee. Brown allylation of the same aldehyde

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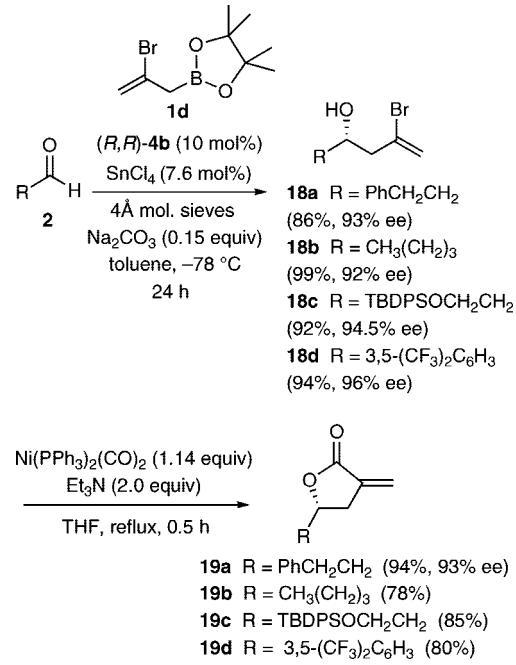
employed in the Marco synthesis of dodoneine was reported to give a significantly lower ee of 90%.[22] A Keck allylation of the same aldehyde was reported to provide 95% ee, however, in a considerably lower yield.[24] Thus, the example of aldehyde **11** shows that the *p*-F-Vivol·$SnCl_4$-catalyzed allylboration system can compare favorably with some of the most popular and effective aldehyde allylation methodologies. The secondary hydroxyl group of product **12** was silylated to give **13**, which was then transformed into aldehyde **14**. This β-siloxy aldehyde was treated under the same allylation conditions to give the alcohol product **15** in a very high diastereoselectivity of 99:1 in favor of the monoprotected syn diol. The level of catalyst-controlled diastereoselectivity obtained in this reaction is truly remarkable because the uncatalyzed allylation provides a nearly equal diastereoselectivity ratio of 56:44. Marco and co-workers employed a stereochemically matched Brown allylation for this transformation,[22] obtaining a similarly high diastereoselectivity, albeit, in a much lower yield compared to the *p*-F-Vivol·$SnCl_4$ catalyzed allylboration. From **15**, the remainder of the synthesis of (+)-dododeine (**5**) was performed using a sequence similar to that of Marco and co-workers.[22]

The *p*-F-Vivol·$SnCl_4$-catalyzed methallylation with boronate **1b** is remarkably efficient (cf. eq 2, Figure 3), and we were hopeful that other 2-substituted allylboronate reagents could be equally successful. The unprecedented pinacol 2-bromoallylboronate **1d** (Scheme 2) was prepared via the bromoboration of allene according to a literature procedure.[25] Reagent **1d** is very attractive for the possibility of functionalizing the alkenylbromide unit in the resulting addition products **18**. For example, a nickel-promoted carbonylative cyclization[26] would provide the exomethylene γ-lactones **19**, which are a compelling class of compounds known to display a wide range of biological properties.[27] To our satisfaction, reagent **1d** adds to a variety of aldehydes with very good enantioselectivity under similar chiral Brønsted acid-catalyzed conditions described above (Scheme 3). The subsequent carbonylation provides an expedient preparation of lactones **19** with preservation of stereochemistry.

SCHEME 3. Application of 2-Bromoallylboronate 1d to the Enantioselective Preparation of α-Exomethylene-γ-lactones 19



Discussion

The results of Figures 2 and 3 clearly demonstrate the superiority of the new diol **4b**, *p*-F-Vivol, as a component of a chiral Brønsted acid for the catalytic enantioselective allylboration of aliphatic aldehydes. Diol **4b** with *p*-fluorine substituents on the diol's aryl units was designed on the premise of increased catalyst activity through a more acidic diol component in the chiral diol·$SnCl_4$ complex compared to the parent unsubstituted diol, **4a**. As hypothesized at the outset, this improvement may be attributable to a more acidic thus more active **4b**·$SnCl_4$ catalyst. The results of a semiquantitative kinetic analysis of a model allylboration reaction comparing **4a**·$SnCl_4$ and **4b**·$SnCl_4$ shows a small increase of catalytic activity for **4b**·$SnCl_4$. Specifically, when ran for only 1.0 h at 0.5 M concentration, the model allylation of Figure 2 gave 40% conversion with **4b**·$SnCl_4$ compared to 34% for **4a**·$SnCl_4$. In comparison, the catalyst from the negative control diol **4d**, electronically enriched thus less acidic, led to only 17% conversion, which appears to support the anticipated catalyst acidity-activity relationship. Although the small increase of about 15−20% conversion rates provided by **4b**·$SnCl_4$ over **4a**·$SnCl_4$ may be sufficient to help decrease the erosion of enantioselectivity caused by the competing background uncatalyzed reaction, it is also possible that a subtle change in the structure of the complex plays a role. Indeed, the previously reported X-ray crystallographic structure of the Vivol(**4a**)·$SnCl_4$ complex shows an intimate steric relationship between the cyclooctyl unit and the aryl group of adjacent carbons, which appear to stack with one another. The small fluorine atoms in **4b** are essentially isosteric to the hydrogen atoms they replaced in **4a**, which would avoid any significant change in the catalyst's structure. In this regard, an opposite trend may be at play with diol **4c**. Even though this diol contains *p*-trifluoromethyl substituents expected to increase the activity of the resulting catalyst **4c**·$SnCl_4$, the use of the larger *p*-CF_3 substituent on the aryl units of the diol may cause a significant disruption of the catalyst's structure. Such a change could possibly lead to a lessened discrimination between the two competing transition states leading to the respective enantiomers of the homoallylic alcohol products.

Conclusion

Compared to the previous Vivol(**4a**)·$SnCl_4$ complex, the new *p*-F-Vivol(**4b**)·$SnCl_4$ catalyst consistently provides higher yields and higher enantioselectivities in the allylation, methallylation, and *E*-crotylation of model aliphatic aldehydes. While only a small panel of aldehydes was employed, all examples gathered thus far have led to an increase of enantioselectivty with **4b**·$SnCl_4$, suggesting that its benefit is general and applicable to other aldehydes previously tested with **4a**·$SnCl_4$.[16c] It is remarkable that the aldehyde additions can be performed at a relatively low catalyst loading of 2.5−5 mol %, at a very high concentration, and that most of the diol **4b** can be recovered. Moreover, these allylation reactions are very clean, with easy

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purification of products. When used with 2-bromoallylboronate **1d**, the new catalyst provides the first examples of catalytic enantioselective 2-bromoallylation, which leads to an efficient route to optically enriched exomethylene γ-lactones through an intramolecular carbonylation reaction. As demonstrated in a synthesis of the naturally occurring pyranone (+)-dodoneine, this allylation methodology can outperform some of the most popular allylation reactions currently in use in organic synthesis. Further applications of this carbonyl allylation methodology in the synthesis of complex molecules will be reported in due course.

Experimental Section

Typical Catalytic Allylboration Procedure: (*R*)-1-[4-(*tert*-Butyldimethylsiloxy)phenyl]pentan-3-ol (12). To a flame-dried 50 mL round-bottom flask equipped with a stirbar was added 213 mg (0.454 mmol, 0.05 equiv) of *R*,*R*-diol **4b**, 74 mg (0.70 mmol, 0.08 equiv) of anhydrous Na_2CO_3, and 50 mg of 4 Å molecular sieves (previously dried under high vacuum at 100 °C and stored in an oven). The flask was capped with a rubber septum and placed under argon followed by the addition of 7.0 mL of freshly distilled toluene. The mixture was stirred for 2 min followed by addition of 349 μL of a 1.0 M CH_2Cl_2 solution of $SnCl_4$ (0.349 mmol, 0.038 equiv). This mixture was stirred at room temperature for 5 min, cooled to −78 °C, and maintained at this temperature for 15 min, which was followed by the addition of 1.91 mL (9.98 mmol, 1.10 equiv) of allylboronic acid pinacol ester **1a**. This mixture was then stirred for an additional 30 min after which, 2.4 g (9.08 mmol, 1.00 equiv) of aldehyde **11** was added to the reaction mixture. The reaction was allowed to stir for 12 h at −78 °C after which, 10.0 mL of a 1.5 M toluene solution of DIBAL-H was added to quench any unreacted aldehyde. The reaction mixture was allowed to stir for an additional 15 min at −78 °C, after which time 25 mL of 1 N HCl was added. The reaction mixture was then allowed to warm to room temperature and allowed to stir for 30 min. The resulting mixture was extracted with 3 × 50 mL of Et_2O, and the combined organic extracts were washed with brine (30 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo to give an oily residue that was purified by flash chromatography (5% EtOAc/hexanes) to provide the requisite homoallylic alcohol product **12** in quantitative yield. The ee of the product was determined by formation of diastereomeric esters by condensation with (*S*)-Mosher acid chloride and was judged to be 97%: $[\alpha]^{25}_D$ −11.96 (*c* 1.02, $CHCl_3$); IR (neat) 3367, 2956, 2930, 2859, 1610, 1472, 1259, 917, 84, 780 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.05 (d, J = 8.0 Hz, 2H), 6.76 (d, J = 8.4 Hz, 2H), 5.77−5.88 (m, 1H), 5.12−5.17 (m, 2H), 3.64 (tt, J = 4.4, 7.6 Hz, 1H), 2.70−2.78 (m, 1H), 2.59−2.66 (m, 1H), 2.29−2.35 (m, 1H), 2.15−2.22 (m, 1H), 1.73−1.79 (m, 2H), 1.65 (s, 1H), 0.99 (s, 9H), 0.19 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.7, 134.7, 134.6, 129.4, 119.9, 118.2, 70.0, 42.0, 38.6, 31.2, 25.7, 18.2, −4.4; HRMS-EI (*m*/*z*) $[M]^+$ calcd for $C_{18}H_{30}O_2Si$ 306.20151, found 306.20148.

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Supporting Information Available: Full experimental conditions for the preparation of diols **4a**−**d** and carbonyl allylation reactions; characterization data for all new compounds, including NMR spectral reproductions and chiral HPLC chromatograms. This material is available free of charge via the Internet at http://pubs.acs.org.

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