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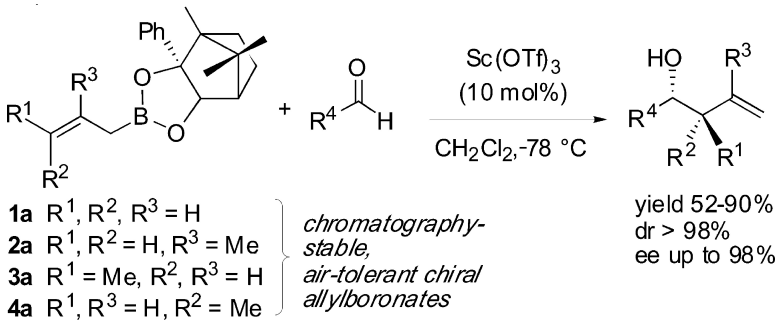

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Scandium-Catalyzed Allylboration of Aldehydes as a Practical Method for Highly Diastereo- and Enantioselective Construction of Homoallylic Alcohols

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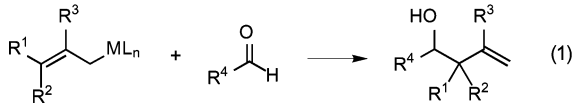
Carbonyl allylation chemistry is one of the most useful tools in modern organic synthesis.[1] Despite extensive investigations, there is yet no general method using simple and stable allylation reagents for the stereocontrolled formation of a wide variety of homoallylic alcohol products (eq 1). Of particular significance is the challenging



(1)

problem of controlling both diastereo- and enantioselectivity in aldehyde crotylation, a process allowing the elaboration of syn and anti propionate units ubiquitous in several classes of natural products (eq 1, R_1,R_2 = H,CH_3 or CH_3,H). Reagents of boron, silicon, and tin have emerged as the most popular crotyl transfer agents for achiral aldehydes.[1] The most stereoselective methods,[2−9] however, suffer from one or many drawbacks such as air or moisture sensitivity, the need for a multistep preparation of chiral reagents, or incompatibility with aliphatic aldehydes. Thus, the search continues for an efficient, practical solution to the problem of stereoselective aldehyde crotylation and allylations in general.

We[10] and others[11] have recently reported the first examples of metal-catalyzed additions of allylboronates. Further to the remarkable rate enhancement, there are significant implications to the fact that this novel catalytic manifold preserves the diastereospecificity of uncatalyzed allylborations. These findings pave the way to the development of more effective methods to access aldol-like adducts with high enantiocontrol. Herein, we describe a general approach for the allylation of aldehydes using stable, air-tolerant chiral allylboronates under $Sc(OTf)_3$ catalysis. This practical methodology provides both syn and anti propionate units and other homoallylic alcohols with very high diastereo- and enantioselectivity for several substrates, including functionalized aliphatic aldehydes useful toward the elaboration of complex natural products.

There are no chiral allylboronic esters known to afford practical levels of enantioselectivity (>95% ee) in additions to achiral aldehydes under typical low-temperature conditions (−78 °C).[1] On the basis of the potential beneficial effect of a lower reaction temperature and the different mechanistic nature of the metal-catalyzed manifold on the enantioselectivity, we planned to revisit a number of known chiral diol auxiliairies for boronic acids. At the outset, the allylation of benzaldehyde was investigated using different solvents, temperatures, and Lewis acids identified from our previous studies.[10] A small set of allylboronates **1** derived from chiral diol precursors **a**−**e** was compared under these variables (Figure 1).

Using allylboronate (−)-**1a**, these investigations revealed that $Sc(OTf)_3$ is significantly more active than other Lewis acids and provided the highest enantiomeric excess in the formation of homoallylic alcohol **5** (Table 1, entries 1−7). A pronounced solvent effect was observed, with dichloromethane standing out as the most

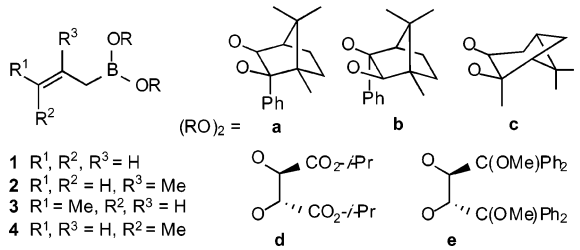
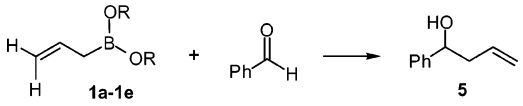


Figure 1. Chiral allylboronates evaluated for enantioselective Lewis acid-catalyzed additions onto aldehydes.

Table 1. Lewis Acid-Catalyzed Allylboration of Benzaldehyde[a]



entry	boronate	L. A.[b]	solvent[c]	temp (°C)	time (h)	conv.[d] (%)	ee[e] (%)
1	**1a**	none	CH_2Cl_2	25	72	50	11
2	**1a**	$AlCl_3$	CH_2Cl_2	−78	2	14	63
3	**1a**	$TiCl_4$	CH_2Cl_2	−78	2	22	78
4	**1a**	TfOH	CH_2Cl_2	−78	2	72	84
5	**1a**	$Cu(OTf)_2$	CH_2Cl_2	−40[f]	2	4	52
6	**1a**	$Yb(OTf)_3$	CH_2Cl_2	−40[f]	2	4	38
7	**1a**	$Sc(OTf)_3$	CH_2Cl_2	−78	2	90	92
8	**1a**	$Sc(OTf)_3$	toluene	−78	2	30	46
9	**1a**	$Sc(OTf)_3$	hexanes	−78	2	20	8
10	**1b**	$Sc(OTf)_3$	CH_2Cl_2	−78	2	62	84[g]
11	**1c**	$Sc(OTf)_3$	CH_2Cl_2	−78	2	100	9
12	**1d**	$Sc(OTf)_3$	CH_2Cl_2	−78	2	100	7
13	**1e**	$Sc(OTf)_3$	CH_2Cl_2	0	2	0	-

[a] Reaction scale: approximately 0.4 mmol (>100 mg) of (−)-**1** (1.1 equiv), and PhCHO (1 equiv). [b] Lewis acid, 10 mol %. [c] Typically 0.5 M concentration in allylboronate. [d] Measured by integration of representative signals by ^{1}H NMR on crude product obtained after an appropriate workup. [e] Measured by chiral HPLC (see Supporting Information for details). [f] No reaction observed at −78 °C. [g] Opposite enantiomer is predominant.

efficient one both in terms of conversion and ee (entries 7−9). Whereas pinanediol-derived **1c** and the tartrate-based reagents **1d**[12] and **1e**[13] gave disappointing results (entries 11−13), the Hoffmann camphor-based allylboronates **1a** and **1b**[14] gave high enantioselectivities under $Sc(OTf)_3$ catalysis (entries 7, 10). Further optimization confirmed that molecular sieves are not required and that the preferred order of addition involves mixing the aldehyde with $Sc(OTf)_3$ in CH_2Cl_2 at −78 °C, followed by the allylboronate.

Developed more than two decades ago, the Hoffmann camphor-based allylboronates were the first chiral allylboron reagents ever reported.[14] The advantages of the new, low-temperature catalytic manifold are remarkable. In the absence of a catalyst (e.g., entry 1), **1a** and **1b** are unreactive at −78 °C and afford modest ee's (<75%) at higher temperatures.[14] Interestingly, the diol precursor of our most effective allylboronate, **1a**, has been by far the least

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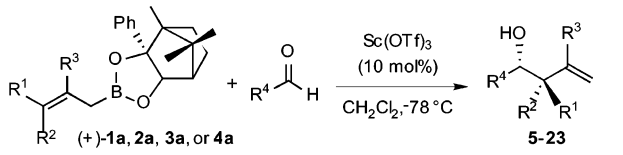
Table 2. Substrate Scope for the $Sc(OTf)_3$-Catalyzed Enantioselective Addition of Allylboronates **1a**−**4a** with Model Aldehydes[a]



entry	allylboronate (R^1, R^2, R^3)	aldehyde (R^4)	product [b]	yield [c] (%)	ee [d] (%)
1	**1a** (H, H, H)	Ph	**5**	85	92
2	**1a**	$PhCH_2CH_2$	**6**	64	97
3	**1a**	$TBDPSOCH_2CH_2$	**7**	86	93
4	**1a**	$BnOCH_2$	**8**	62	77
5	**1a**	$TBDMSOCH_2$	**9**	76	90
6	**1a**	$TBDPSOCH_2$	**10**	61	90
7	**2a** (H, H, Me)	Ph	**11**	64	98
8	**2a**	$PhCH_2CH_2$	**12**	76	97
9	**2a**	$TBDPSOCH_2CH_2$	**13**	77	97
10	**2a**	$BnOCH_2$	**14**	70	97
11	**2a**	$TBDMSOCH_2$	**15**	90	95
12	**3a** (Me, H, H)	Ph	**16**	60	97
13	**3a**	$PhCH_2CH_2$	**17**	71	96
14	**3a**	$TBDPSOCH_2CH_2$	**18**	63	94
15	**3a**	$TBDMSOCH_2$	**19**	74	95
16	**4a** (H, Me, H)	Ph	**20**	53	59
17	**4a**	$PhCH_2CH_2$	**21**	52	96
18	**4a**	$TBDPSOCH_2CH_2$	**22**	57	96
20	**4a**	$TBDMSOCH_2$	**23**	57	96

[a] Standard conditions: reaction scale: approximately 0.4 mmol of aldehyde in CH_2Cl_2 (0.4−0.6M) with 10 mol % $Sc(OTf)_3$ at −78 °C followed by addition of allylboronate (entries 1−10: 1.1 equiv, entries 11−14: 1.5 equiv). Entry 15 is with 3 equiv of aldehyde, entries 16−20 are with 1.5 equiv of aldehyde. Reaction times: 12−24 h. [b] The dr for **16**−**23** was always over 49:1 (determined by ^1H NMR). [c] Unoptimized yields of pure products isolated after flash chromatography. [d] Measured by chiral HPLC on the free alcohol or a derivative thereof (see Supporting Information for details), or through NMR analysis of Mosher esters (entries 3,5,9,11). The absolute configuration was determined by comparison of optical rotation with known compounds.

studied of the two isomers in the literature. This diol is easily made without chromatographic purifications in four steps from camphorquinone,[14] which is commercially available in both enantiomeric forms. Allylboronates **1a**−**4a** are noticeably stable and can be purified by chromatography and conveniently handled without any special precautions.

The scope of suitable aldehyde substrates in the $Sc(OTf)_3$-catalyzed manifold was investigated using **1a** and **2a**, and both *E*- and *Z*-crotylboronates **3a** and **4a**. Allylboronate **1a** and methallyl derivative **2a** reacted with model aromatic and aliphatic aldehydes to give the corresponding homoallylic alcohols **5**−**15** in good to excellent yields and up to 98% ee (Table 2). Most significantly, the *E*- and *Z*-crotylboronates **3a** and **4a** gave comparably high levels of enantioselectivity (94−97% ee) to provide the respective anti and syn propionate products **16**−**23** in good yields (52−74%) and very high diastereoselectivity (>98%).

Compared to **1a** and **2a**, additions of crotylboronates **3a** (*E*) and **4a** (*Z*) are slower and usually required the use of an excess of one substrate to provide acceptable yields.[15] Reactions of α-branched aliphatic aldehydes provided only low yields of products.[15] Despite these current limitations, it is particularly significant that functionalized aliphatic aldehydes such as $TBDPSOCH_2CH_2CHO$ and $TBDMSOCH_2CHO$ effectively provide addition products with great utility as early intermediates in the synthesis of complex natural products. To demonstrate the potential of this methodology in practical-scale preparation, the reaction of entry 9 was carried out with a gram quantity of **2a**. Using only 5 mol % of $Sc(OTf)_3$, alcohol **13** was obtained in a satisfying 71% yield and 96% ee. To the best of our knowledge, this method represents the most effective system for enantioselective methallyl transfer onto aldehydes,[16] which suggests that a new generation of highly enantioselective β-substituted allylating agents could be developed.

At this time, the precise mechanistic nature of this Lewis acid-catalyzed process and the mode of stereoinduction are unknown. On the basis of preliminary arguments presented earlier[10] and the fact that the diastereospecificity of the noncatalyzed reaction is preserved, the allylboration is thought to proceed via the usual cyclic transition state, with electrophilic boron activation by metal coordination to the boronate oxygens.

In conclusion, we have reported a remarkably general and practical aldehyde allylation methodology based on the $Sc(OTf)_3$-catalyzed reaction of stable chiral allylboronates. This approach is unrivaled in many ways, in particular, its efficient control of both diastereo- and enantioselectivity. We anticipate that this new metal-catalyzed allylboration process will find use in the synthesis of complex natural products, thereby giving new life to the camphor-based allylboronates.

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Supporting Information Available: Full experimental details, characterization data, and spectral reproduction for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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