Allylation

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Catalytic Enantioselective and Catalyst-Controlled Diastereofacial-Selective Additions of Allyl- and Crotylboronates to Aldehydes Using Chiral Brønsted Acids**

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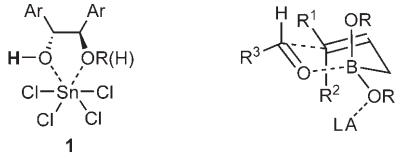
Despite the extensive efforts of numerous research groups over the course of more than two decades, there is still no methodology for the allylation of aldehydes that possesses all of the following attributes: mildness and chemoselectivity, substrate generality (for both the allyl–metal reagent and aldehyde substrate), high levels of diastereo- and enantioselectivity, and high practicality (ease of use, low cost, nontoxicity, and low environmental impact).[1] Very importantly, the ideal enantioselective allylation methodology would circumvent the use of a chiral auxiliary through a simple and efficient chiral catalyst.[2] The recent discovery of Lewis and Brønsted acid catalyzed allylboration manifolds[3] has opened doors towards an ideal methodology for the allylation of carbonyl compounds. Indeed, pinacol allylboronates are air- and water-stable nontoxic reagents whose additions to aldehydes are characterized by very high levels of chemo-, regio-, and diastereoselectivity. Efforts by us and others[3b] to develop catalytic enantioselective additions with chiral Lewis acids have led only to low levels of enantioselectivity in model allylborations of aldehydes. Herein, following our recent report of Brønsted acid catalyzed allylborations,[3e] we demonstrate that the use of the Yamamoto chiral diol–$SnCl_4$ complexes[4] (Scheme 1) provides a significant advance towards a general catalytic enantioselective allylboration process. The current conditions are particularly advantageous in promoting efficient diastereofacial control in additions to α-chiral aldehydes.



Scheme 1. Left: diol–$SnCl_4$ chiral Brønsted acid complex **1**.[4] Right: Proposed transition state in the Lewis acid (LA) catalyzed allylboration.[5]

Mechanistic studies of the Lewis acid catalyzed allylboration point to a cyclic bimolecular transition state with boronate activation through coordination of an oxygen atom of the hindered pinacolate to the metal center (Scheme 1).[5] In this perspective, the use of a smaller activator, a proton, seemed ideal and prompted us to investigate a number of chiral Brønsted acid catalysts.[6] Among several systems tested for the model reaction between hydrocinnamaldehyde and pinacol allylboronate at −78 °C, the concept of "Lewis acid assisted Brønsted acidity" with diol–$SnCl_4$ complexes, developed by Yamamoto and co-workers,[4] was found to be the most promising (Scheme 2).

As shown in Table 1, basic 1,2-diphenyl-1,2-ethanediol (**1a**) provided product **4a** with 37% *ee* (entry 1). Further optimization of the diol, catalyst stoichiometry, and additives led to the current optimal conditions shown in entry 12 with commercially available (*R*,*R*)-(+)-1,2-di(1-naphthyl)-1,2-ethanediol (**1j**). No other diol derivatives, including electronically modulated diaryl glycols (**1e**,**f** and **1i**) and various mono-O-alkylated diols (**1b**,**c**), led to higher enantioselectivities.[7] In all cases, the *ee* values were slightly higher in anhydrous toluene than in dichloromethane. Interestingly, $SnCl_4$ alone promotes an allylboration at a comparable rate, although in a non-enantioselective fashion. Thus, the use of a slight excess of diol was found to be desirable (compare

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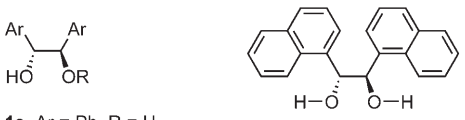
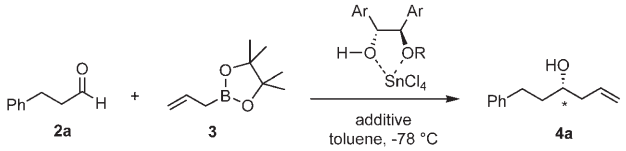
Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.



1a Ar = Ph, R = H
1b Ar = Ph, R = Me
1c Ar = Ph, R = Bn
1d Ar = 3,5-$(CH_3)_2$-C_6H_3, R = H
1e Ar = 3,5-$(CF_3)_2$-C_6H_3, R = H
1f Ar = 4-CH_3O-C_6H_4, R = H
1g Ar = 2-CH_3-C_6H_4, R = H
1h Ar = 2-Ph-C_6H_4, R = H
1i Ar = 2-CH_3-4-CH_3O-C_6H_3, R = H

Scheme 2. Chiral *R,R* diols evaluated in the enantioselective allylboration catalyzed by diol–$SnCl_4$ complexes.

Table 1: Optimization of the diol–$SnCl_4$ catalyst system.[a]



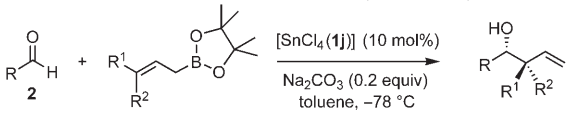
Entry	Diol [mol%]	$SnCl_4$ [mol%]	Additive	*ee* [%][b]
1	**1a** (11)	(10)	Na_2CO_3	37
2	**1b** (11)	(10)	none	34
3	**1c** (11)	(10)	Na_2CO_3	62
4	**1c** (10)	(20)	Na_2CO_3	0
5	**1d** (11)	(10)	Na_2CO_3	38
6	**1e** (11)	(10)	Na_2CO_3	34
7	**1f** (11)	(10)	Na_2CO_3	45
8	**1g** (11)	(10)	Na_2CO_3	69
9	**1h** (11)	(10)	Na_2CO_3	33
10	**1i** (11)	(10)	Na_2CO_3	74
11	**1j** (11)	(10)	none	70
12	**1j** (11)	(10)	Na_2CO_3	78
13	**1j** (11)	(10)	Ag_2CO_3	75
14	**1j** (11)	(10)	K_2CO_3	74

[a] Conditions: all reactions were performed with aldehyde **2a** (0.25 mmol), allylboronate **3** (0.275 mmol), *R,R* diol **1** (0.0275 mmol), $SnCl_4$ (0.025 mmol), Na_2CO_3 (0.05 mmol), and 4-Å molecular sieves (50 mg) in toluene (1 mL) at −78 °C for 12 h. [b] The absolute configuration was determined by comparison with known compounds;[7] all *ee* values were measured through the formation of Mosher esters and ^{19}F NMR spectroscopic analysis.[7]

entries 3 and 4). Because of worries that adventitious HCl (e.g., residual HCl in commercial $SnCl_4$) could lead to an erosion of the stereoselectivity, mildly basic additives were tested as precautionary HCl scavengers (entries 11–14). The use of Na_2CO_3, insoluble in toluene, afforded the highest enantioselectivity.[8] Other allylboronic esters, such as those made from 1,2-cyclohexanediol, 1,2-cyclopentanediol, and tetraphenylethanediol, provided much lower enantioselectivities, even with the optimal diol **1j** (results not shown[7]).

The substrate scope of the catalytic enantioselective allylborations was studied with a panel of model aldehydes under the optimal conditions of Table 1[7] (the results are summarized in Table 2). In contrast with several other reported catalytic allylation systems,[1] aliphatic aldehydes give higher enantioselectivities in the current allylboration process. Whereas aromatic and unsaturated aldehydes gave

Table 2: Enantioselective additions of allyl- and crotylboronates.[a]



3 R^1, R^2 = H
5 R^1 = Me, R^2 = H
7 R^1 = H, R^2 = Me

4a R = $Ph(CH_2)_2$, R^1, R^2 = H
4b R = $CH_3(CH_2)_8$, R^1, R^2 = H
4c R = C_6H_{11}, R^1, R^2 = H
4d R = TBDPSO$(CH_2)_2$, R^1, R^2 = H
4e R = Ph, R^1, R^2 = H
4f R = PhCH=CH, R^1, R^2 = H
4g R = $CH_3(CH_2)_4CC$, R^1, R^2 = H
6a R = $Ph(CH_2)_2$, R^1 = Me, R^2 = H
6b R = $CH_3(CH_2)_8$, R^1 = Me, R^2 = H
8a R = $Ph(CH_2)_2$, R^1 = H, R^2 = Me
8b R = $CH_3(CH_2)_8$, R^1 = H, R^2 = Me

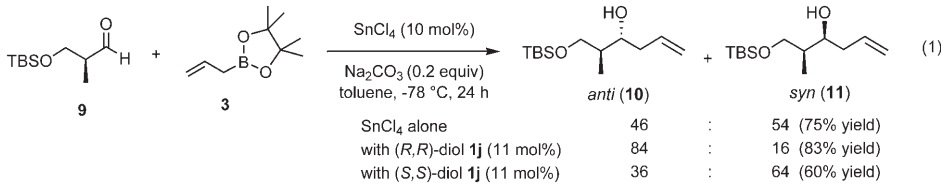
Entry	Aldehyde (R)	Boronate	Product	Yield [%][b]	e.r.[c]
1	**2a** $PhCH_2CH_2$	**3**	**4a**	85	89:11
2	**2b** $CH_3(CH_2)_8$	**3**	**4b**	76	90:10
3	**2c** C_6H_{11}	**3**	**4c**	90	85:15
4	**2d** TBDPSO$(CH_2)_2$	**3**	**4d**	90	83:17
5	**2e** Ph	**3**	**4e**	99	55:45
6	**2f** PhCH=CH	**3**	**4f**	72	60:40
7	**2g** $CH_3(CH_2)_4CC$	**3**	**4g**	99	56:44
8	**2a** $PhCH_2CH_2$	**5**	**6a**	99	86:14
9	**2b** $CH_3(CH_2)_8$	**5**	**6b**	70	86:14
10	**2a** $PhCH_2CH_2$	**7**	**8a**	87	70:30
11	**2b** $CH_3(CH_2)_8$	**7**	**8b**	70	73:27

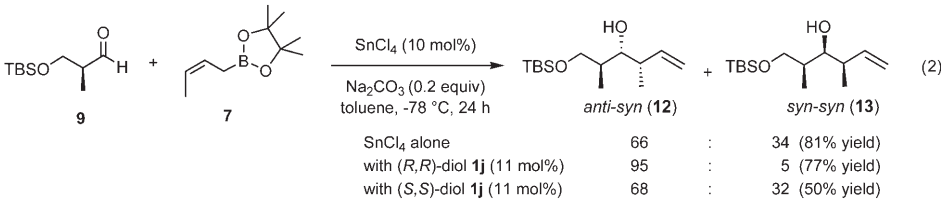
[a] Reaction conditions: all entries were performed with aldehyde (0.25 mmol), allylboronate (0.275 mmol), **1j** (0.0275 mmol), $SnCl_4$ (0.025 mmol), Na_2CO_3 (0.05 mmol), and 4-Å molecular sieves (50 mg) in toluene (1 mL) at −78 °C for 12 h (entries 1–7) or 24 h (entries 8–11). [b] The yields are for the isolated product and are an average of two runs. [c] All the e.r. values were measured by chiral HPLC (Chiralcel OD), except for entries 3, 7, 9, and 11, which were measured through the formation of Mosher esters and ^{19}F NMR spectroscopic analysis.[7] TBDPS = *tert*-butyldiphenylsilyl.

modest selectivities (entries 5–7), the enantiomeric ratio in allylations of aliphatic aldehydes rose to 90:10 (80% *ee*; entry 2). The e.r. values of prototypic crotylborations (entries 8–11) were slightly lower than those obtained in the simple allylborations, with *trans*-crotyl reagent **5** giving higher selectivities. The diastereoselectivities of the crotylations are very high (> 98:2 d.r.) and consistent with the corresponding uncatalyzed allylborations.

Uncatalyzed additions of pinacol allylboronates are known to proceed very slowly at −78 °C. Nonetheless, we carried out control experiments with hydrocinnamaldehyde (**2a**), which confirmed the lack of a background reaction (namely, < 2% conversion) in the absence of the diol–$SnCl_4$ catalyst. The addition of allylboronate **3** to aldehyde **2a** in the presence of 100 mol% of [$SnCl_4$(**1j**)] led only to a modest improvement, from 78 (10 mol% [$SnCl_4$(**1j**)]) to 83% *ee*. These observations suggest that in the case of aliphatic aldehydes the current level of enantioselectivity is not limited by a competitive racemic background reaction, thus superior diols could possibly be found. Satisfactorily, the current conditions were found to be effective for the diastereocontrolled additions of allyl- and crotylboronates to chiral α-methyl aldehyde **9**, thus providing the very useful propionate units of **10** and **11** and dipropionate "triads" of types **12** and **13**

[Eqs. (1) and (2)]. There has been huge interest in the construction of these units for applications in the total synthesis of bioactive polypropionate natural products.[9] Current methods, however, require chiral allylation reagents to effect a high diastereofacial selective addition (namely, double diastereoselection).[10] Herein, we have demonstrated that diol–$SnCl_4$ catalysis of allylations and *cis*-crotylations of chiral aldehydes can be successfully employed with convenient, stable achiral pinacolate esters. The catalyst was found to exert a strong influence on the diastereofacial selectivity. In both the allylation [Eq. (1)] and *cis*-crotylation with **9** [Eq. (2)], the [$SnCl_4$(**1j**)] catalyst system improved the





intrinsic selectivity preference of the $SnCl_4$-catalyzed reactions in the matched combination, and even improved the selectivity of the disfavored diastereomer when using the antipode of diol **1j**. For example, selectivity in favor of the *anti–syn* unit **12** was improved from a modest 2:1 ratio to 19:1 using [$SnCl_4${(*R*,*R*)-**1j**}] [Eq. (2)]. For reasons not yet understood, the *trans* crotylations with **5** were less successful, thus giving low conversions, even after 24 h. The [$SnCl_4$(**1j**)]-catalyzed additions of **3** and **7**, however, are particularly impressive considering that pinacol allyl- and crotylboronates react very slowly and unselectively in the absence of a catalyst.[10] Combined with the commercial availability of diol **1j**, this new system is operationally simple and could find immediate use in the diastereoselective construction of several types of propionate units found in bioactive natural products.

The unusual conditions of this allylation system using an insoluble basic additive (Na_2CO_3) warrant a brief mechanistic discussion. We believe that catalysis is due to Brønsted acid activation and not through a Lewis acid activation mechanism, which could possibly occur by the base-promoted formation of tin alkoxides.[11] Indeed, structural studies of the [$SnCl_4$(**1a**)] and [$SnCl_4$(**1j**)] complexes by variable temperature (VT) NMR spectroscopic analysis reveal the same species at −78 °C with or without added Na_2CO_3.[7] This tin(IV) complex does show the presence of activated hydroxy protons and, according to ^{119}Sn NMR shift data, is unambiguously hexacoordinated. The enantioselectivities in the absence of Na_2CO_3 tend to be lower and irreproducible. A soluble base, such as Et_3N, however, shuts down the activating effect of the catalyst. These observations are consistent with a passive role in which the basic additive Na_2CO_3 simply acts as a scavenger of adventitious HCl, which is likely a strong but non-enantioselective activator of this reaction.

This novel chiral Brønsted acid catalyzed enantioselective allylation system constitutes the most efficient catalytic enantioselective allylboration reported thus far. It represents a significant advance that demonstrates the great potential of chiral Brønsted acid catalysis towards the development of an ideal methodology for the allylation of carbonyl compounds. The current diol–$SnCl_4$ catalyst system is readily applicable to catalyst-controlled double diastereoselective allylations to access, with improved selectivities, polypropionate units of the type found in a large number of bioactive natural products.

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