Asymmetric Catalysis

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Catalytic Enantioselective Preparation of α-Substituted Allylboronates: One-Pot Addition to Functionalized Aldehydes and a Route to Chiral Allylic Trifluoroborate Reagents**

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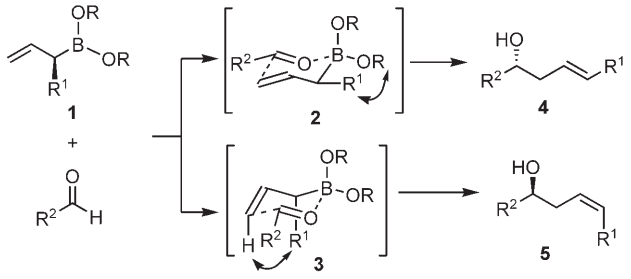
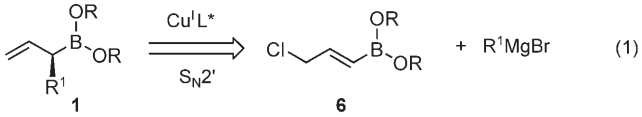
Additions of allylic boron reagents to aldehydes have evolved into one of the most popular methods for stereoselective C–C bond formation.[1] Compared to dialkyl allylic boranes, allylic boronic esters are often more advantageous as a class of reagents because of their superior stability. Three strategies have been developed for the control of enantiofacial selectivity in additions of allylic boronates to achiral aldehydes: 1) the use of a chiral diol or a diamine auxiliary as the two nonallylic substituents on the boron center;[2] 2) the use of chiral Lewis and Brønsted acid catalysis with achiral boronates;[3] and 3) the use of optically pure α-substituted reagents (so-called α-chiral allylboronates).[4] The preparation of chiral α-substituted allylboronates **1** and their additions to aldehydes were pioneered by Hoffmann and co-workers.[4] Regrettably, these reagents have remained underused in part because of their stepwise preparation based on a Matteson asymmetric homologation of chiral alkenylboronates.[5,6] The reagent-controlled additions of **1** to aldehydes proceed with near-complete transfer of chirality to give two diastereomeric products **4** and **5** (Scheme 1). These *Z* and *E* allylic alcohols are epimeric, and their ratio is highly dependent on the nature of the α substituent R^1 and the nature of the boronic ester.[4] The ratio of **4** and **5** can be explained in terms of steric and dipolar effects on the two competing transition structures **2** and **3**. With a nonpolar alkyl substituent R^1, steric interactions play a dominant role. The chairlike transition structure **2** can be destabilized by a steric interaction between a large boronic ester and the pseudoequatorial α substituent R^1. On the other hand, the transition structure **3** features unfavorable allylic interactions that result from the pseudoaxial position of the R^1 substituent. The common use of a hindered ester, such as pinacolate, aggravates the interactions between R^1 and the methyl groups of the pinacol moiety in **2**. Thus, in this case transition structure **3** is more probable and leads to mixtures of products **4** and **5** in modest selectivities.[7]



Scheme 1. Competing transition structures in the allylation of aldehydes with chiral α-substituted allylboronates (**1**).

In our view, two major issues need to be resolved to render chiral α-substituted allylboronates attractive reagents: a simple catalytic enantioselective method for their preparation and full diastereocontrol of the ratio **4**/**5** by a suitable optimization of reagent (R^1, $(OR)_2$) and reaction conditions. Here, we report an approach that successfully addresses these two issues and provides a simple and efficient method for enantioselective aldehyde allylation.

Prompted by the recent report of Alexakis and coworkers[8a] on the copper-catalyzed S_N2' allylic alkylation of cinnamyl chloride using chiral phosphoramidite ligands (L*),[8,9] we envisioned that 3-halopropenylboronates **6**[10] could be suitable substrates in this reaction [Eq. (1)]. With



these substrates, however, the noncatalyzed (that is, background) allylic Matteson homologation may pose a serious threat to the enantioselectivity of this process.[11]

The effect of the solvent and the nature of the Grignard reagent were first examined on substrate **6a** by using 2 mol% of copper catalyst with the ligand **7a** (Table 1). It should be noted that the nature of R^1 is often inconsequential, as in its most common synthetic application the residual alkene of **4**/**5** is cleaved oxidatively to reveal an aldehyde intermediate. In the event, it was found that the highest enantioselectivity is

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Supporting information (including general section, full experimental details, and NMR spectra for novel compounds) for this article is available on the WWW under http://www.angewandte.org or from the author.

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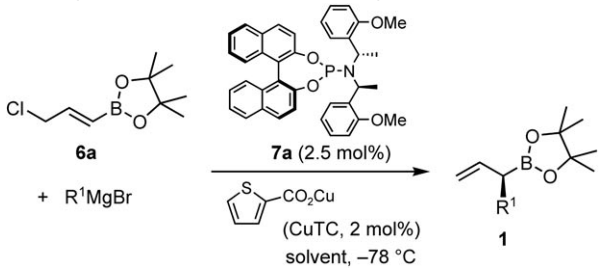
Table 1: Optimization of solvent and nucleophile.[a]



Entry	R^1MgX[b]	Solvent	Rate of R^1MgX addition	*ee* [%][c]
1	EtMgBr	toluene	40 min	18
2	EtMgBr	CH_2Cl_2	40 min	84
3	EtMgBr	CH_2Cl_2	4 h	87
4	EtMgCl	CH_2Cl_2	4 h	41
5	MeMgBr	CH_2Cl_2	4 h	49
6	*i*PrMgBr	CH_2Cl_2	4 h	44[d]

[a] Reaction conditions: **7a** and CuTC were premixed at RT, then **6a** was added followed by R^1MgX at −78 °C. Typical reaction scale: 1.0 mmol at 0.3 M. [b] From halide-free 3 M solutions in Et_2O. [c] Measured by HPLC of an isocyanate derivative (after oxidation of **1**) on a chiral stationary phase. [d] Opposite enantiomer.

obtained using methylene chloride as solvent and slow addition of ethylmagnesium bromide as nucleophilic reagent (Table 1, entry 3). By using these conditions, we examined various phosphoramidite ligands (**7a**–**e**, Figure 1) and various cyclic boronate groups in **6** (Table 2).

These fine-tuning experiments unveiled that the most enantioselective combination of ligand and boronic ester was ligand **7d** with 2,2-dimethylpropanediol boronate (**6d**) to afford allylboronate **1d** in 93% *ee* (Table 2, entry 9). In the end, the use of a catalyst loading of 5 mol% succeeded in achieving the desired level of enantioselectivity in the preparation of **1d** (95.5% *ee*, Table 2, entry 11). Although other ligands provided better ratios of S_N2' to S_N2, the reaction conditions shown in entry 11 provide the desired S_N2' product **1d** with acceptable regioselectivity. It is noteworthy that the corresponding 3-bromopropenylboronates gave lower enantioselectivity and lower S_N2'/S_N2 ratios. Reagent **1d** is less robust than pinacolate **1a**, but we have been able to use it successfully without the need for silica gel purification.

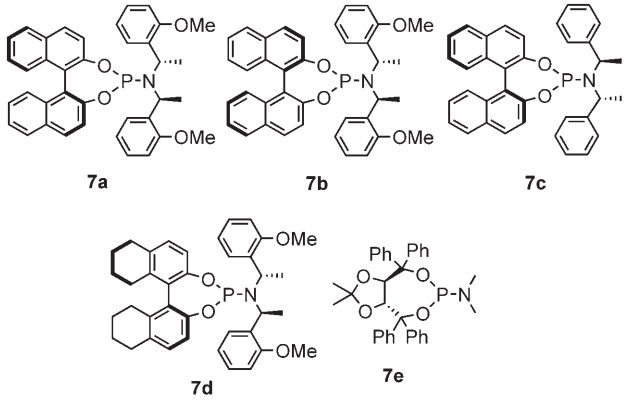
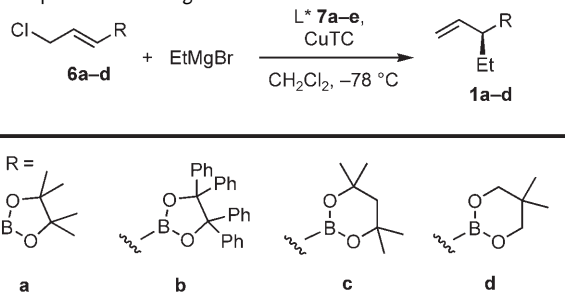


Figure 1. Chiral phosphoramidite ligands evaluated in the allylic alkylation of **6**.

Table 2: Optimization of ligand **7** and boronic ester **6**.[a]



Entry	L*	Prod.[b]	L*/Cu	S_N2/S_N2'[c]	*ee* [%][d]
1	**7a**	**1a**	2.5:2.0	1:9	87
2	**7a**	**1b**	2.5:2.0	1:12	52
3	**7a**	**1c**	2.5:2.0	1:8	86
4	**7a**	**1d**	2.5:2.0	1:19	91
5	**7b**	**1a**	2.5:2.0	1:11	77
6	**7c**	**1a**	2.5:2.0	1:4	84
7	**7d**	**1a**	2.5:2.0	1:7	92
8	**7e**	**1a**	2.5:2.0	1:5	46[e]
9	**7d**	**1d**	2.5:2.0	1:12	93
10	**7a**	**1d**	5.5:5.0	1:30	94
11	**7d**	**1d**	5.5:5.0	1:7	95.5

[a] Reaction conditions: see Table 1, entry 3. [b] Not isolated, but characterized as an isocyanate derivative after oxidation. [c] Measured by ^1H NMR spectroscopy of an aliquot of the crude reaction mixture. [d] Measured by HPLC analysis of an isocyanate derivative on a chiral stationary phase. [e] Opposite enantiomer.

Our next objective was to develop a practical one-pot procedure for the stereoselective aldehyde allylation with reagent **1d**. Critical for this goal is the isolation of a very high proportion of one of the two possible diastereomers (**4** or **5**, Scheme 1), which would circumvent the need for their separation and avoid an erosion of the overall enantioselectivity of this allylation process. We were delighted to find that use of **1d** gave outstanding stereocontrol under the new low-temperature reaction conditions promoted by a Lewis acid [Eq. (2); TBDPS = *tert*-butyldiphenylsilyl, TBS = *tert*-butyldimethylsilyl].[3a,12] Compared to the corresponding pinacolate **1a**,[11b,13] the high *E*/*Z* selectivity may be explained by the low temperature of the reaction,[14] and also by minimal non-bonded interactions between the pseudoequatorial ethyl group and the boronate in the ternary[15] transition structure. Using $BF_3{\cdot}OEt_2$ at −78 °C, model reactions afforded the alcohol products **8** in good yields for the one-pot two-step process.[16] All the aldehydes tested led to products in enantioselectivities similar to the optical purity of reagent **1d**, which is indicative of a near-perfect chirality transfer from reagent **1d**. The formation of functionalized products **8c** and **8d** clearly indicates the potential of this one-pot allylation procedure in the construction of complex synthetic intermediates. Furthermore, the extension of this method to other primary aliphatic Grignard reagents in the allylic substitution of **6**, followed by oxidative workup on intermediates **1**, could provide access to useful chiral allylic alcohols.

Allylic trifluoroborate salts have demonstrated significant potential in carbonyl allylation chemistry.[17] These species are thought to react in a closed transition state through the in situ generation of the highly reactive allylic difluoroboranes.

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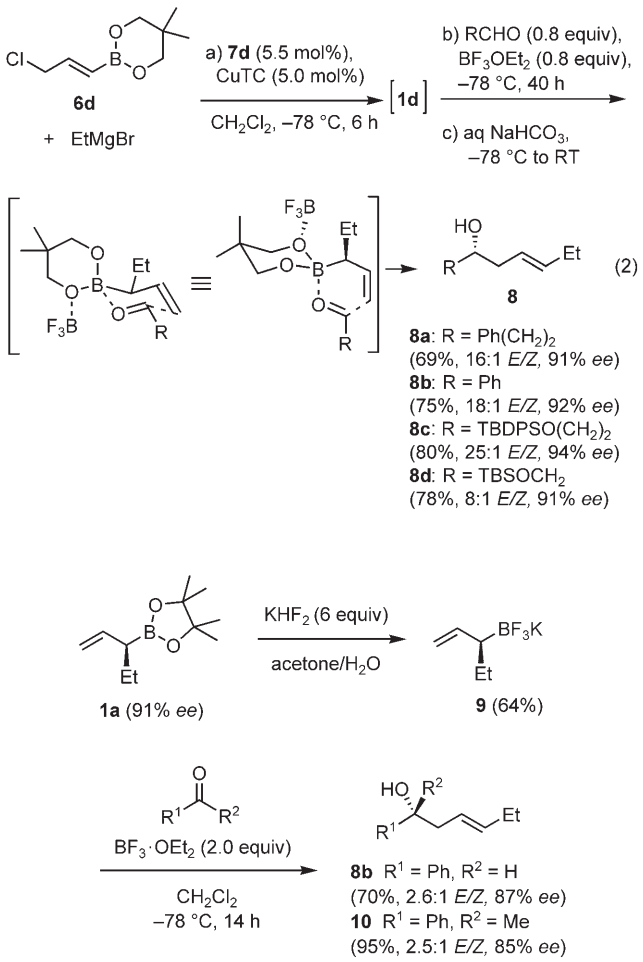

Scheme 2. Formation of **9** and its addition to a model aldehyde and ketone.

Unfortunately, there is little opportunity for using these species in enantioselective additions because the fluoride substituents cannot be readily modified to incorporate chiral directing groups.[18] Herein, we report promising preliminary results for the first chiral α-substituted allylic trifluoroborate salts. We were delighted to find that the preparation of salt **9** from the corresponding pinacolate **1a** occurs with ease[19] and without racemization as shown by its addition to a model aldehyde and ketone (Scheme 2). Ongoing efforts to increase the *E*/*Z* selectivity may lead to an efficient class of highly reactive ketone allylation agents.

In summary, we have developed a simple and efficient catalytic enantioselective preparation of a chiral α-substituted allylic boronate reagent. It was further demonstrated that this reagent can add with very high diastereoselectivity to aldehydes in a convenient one-pot fashion using a low-temperature procedure promoted by a Lewis acid. This preparative method also provides an efficient route to reactive allylic trifluoroborate salts. Further studies will aim to extend this approach to carbonyl crotylation reactions and additions to imines.

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