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Catalytic Enantioselective One-pot Aminoborylation of Aldehydes: A Strategy for Construction of Nonracemic α-Amino Boronates

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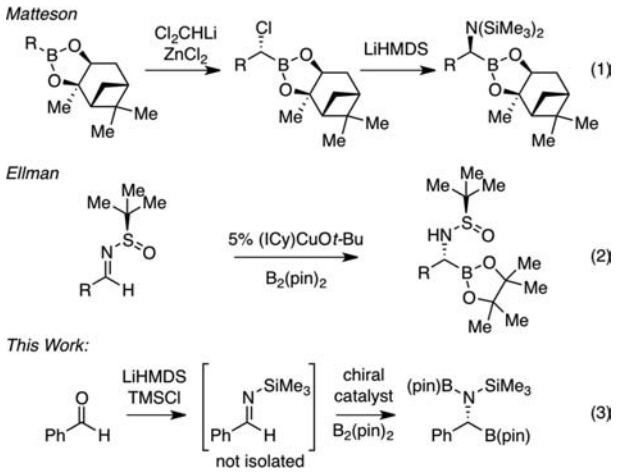
Supporting Information

ABSTRACT: We report a strategy for the conversion of aldehydes to enantiomerically enriched α-amino boronates through the intermediacy of *in situ*-generated silylimines. This transformation is brought about by Pt-catalyzed asymmetric addition of $B_2(pin)_2$ across the imine double bond. An attractive feature of the intermediate diboration adduct is that it can be acylated directly and provides convenient access to important *N*-acyl α-amino boronic ester derivatives.

Chiral α-amino boronic acids have found widespread use as pharmacologically active agents, most notably as protease inhibitors, and have appeared as motifs in clinically relevant therapeutics for the treatment of multiple myeloma.[1,2] These structures have also found use as chiral intermediates in asymmetric synthesis, thereby further extending their importance in organic chemistry.[3] As important as *N*-acyl α-amino boronic acids are, there are only two effective methods available for their synthesis in an asymmetric fashion. Matteson has established a diastereoselective homologation of pinanediol-derived boronic esters that is accomplished by treatment with dichloromethyllithium; the product of this reaction is a chiral α-chloro boronic ester that may undergo stereospecific substitution with amine nucleophiles providing α-amino boronates (eq 1, Scheme 1).[4] In another approach, Ellman has introduced a copper-catalyzed diastereoselective borylation of chiral sulfinylimines that furnishes α-amino boronic esters (eq 2).[5,6] We considered that a catalytic enantioselective approach that employs readily available substrates and reagents may streamline access to these important motifs. Along these lines, we describe herein the direct conversion of aldehydes to α-amino boronic esters in a catalytic asymmetric fashion (eq 3). An important feature of this reaction strategy is that acylation of the amino boronic ester occurs after C−B bond formation such that diverse arrays of peptidic α-amino boronates may be accessed in a simple fashion.

Scheme 1



Recent studies conducted in our laboratory have demonstrated that chiral platinum−phosphonite complexes can catalyze the enantioselective addition of $B_2(pin)_2$ across the π systems found in isolated terminal alkenes and in conjugated dienes.[7,8] It was considered that analogous enantioselective addition of $B_2(pin)_2$ across imine double bonds would provide a straightforward route to α-amino boronic acid derivatives.[9] As design criteria, we targeted a reaction where (a) substrates are readily available and (b) the reaction product is readily converted to *N*-acyl α-amino boronic acid derivatives. These criteria obviated the use of *N*-aryl and *N*-sufonyl imines as suitable substrates. Initially, we considered that *N*-acyl imines, compounds that are isoelectronic with dienes, might participate in enantioselective diboration and directly provide *N*-acyl α-amino boronates. However, studies with a range of such substrates provided reaction products with moderate levels of selectivity and yield. *N*-Silyl imines also appeared to satisfy the reaction design criteria. To develop a broadly useful method, studies were focused on the reaction of substrate **1** (Table 1) wherein it was reasoned that the lability of the N−Si bond might enhance the versatility of the reaction products.[10] While it was later determined (*vide infra*) that *in situ*-prepared silylimines are suitable substrates, initial exploratory efforts employed purified silylimine **1**, conveniently prepared from benzaldehyde and LiHMDS.[11] As depicted in Table 1, a small collection of substituted taddol-derived phosphonite ligands was surveyed in the Pt-catalyzed diboration of **1**. After 14 h of reaction, the mixtures were concentrated and, to facilitate purification, treated with pivaloyl chloride. This set of experiments revealed that efficient reactivity and good levels of stereoselection could be obtained with many Pt−phosphonite catalysts. Notably, in contrast to alkene and diene diboration, there is relatively little dependence of stereoselectivity on the size of the meta substituents in taddol-based phosphonite ligands; however, it was clear that

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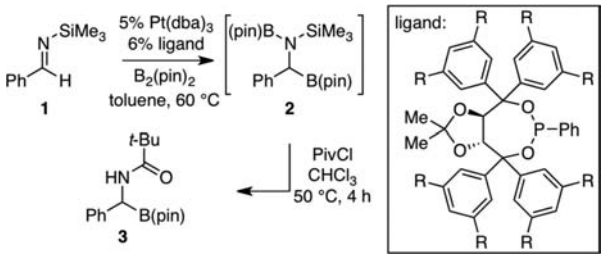
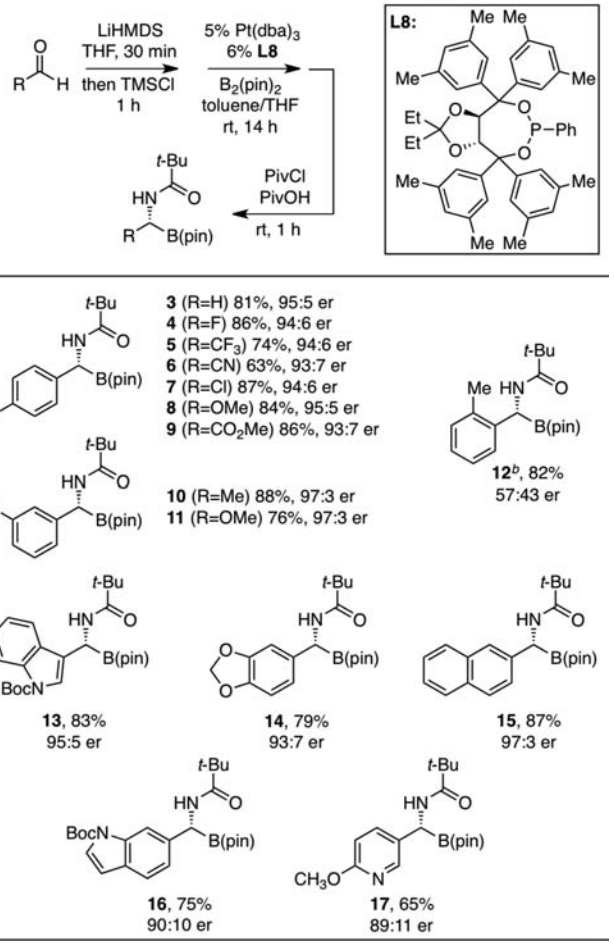
Table 1. Catalytic Enantioselective Diboration of 1[a]



entry	ligand	R	yield (%)	e.r.
1	**L1**	H	76	84:16
2	**L2**	Me	80	89:11
3	**L3**	F	64	83:17
4	**L4**	Et	79	90:10
5	**L5**	*i*-Pr	70	89:11
6	**L6**	Ph	71	73:27
7	**L7**	*t*-Bu	72	81:19

[a]Reactions were conducted as described in the text. The percent value given refers to the isolated yield of purified material and is an average of two experiments.

Table 2. Catalytic Enantioselective Aminoborylation of Aldehydes[a]



[a]Reactions were conducted as described in the text. The percent value given refers to the isolated yield of purified material and is an average of two experiments. [b]Purified silylimine was used as the starting material for this experiment.

the readily available *meta*-xylyl derivative **L2** (entry 2) was among the most effective.[12]

With the above-described observations in hand, a number of modifications were probed to improve the reaction. First, high efficiency was still observed when the reaction temperature was lowered to 22 °C. Second, it was found that the diethyl ketal analog (**L8**, see Table 2) of ligand **L2** furnished enhanced selectivity compared to the dimethyl ketal with the latter converting the benzaldehyde-derived imine to the α-amino boronate in 95:5 er. Third, pivalic acid was found to enhance the rate of the acylation reaction resulting in shortened reaction times and improved yield.[4a] In the absence of pivalic acid, acylation of the diboron intermediate required 4 h at 50 °C; however, when one equivalent of pivalic acid was employed, the reaction time was shortened considerably such that the product was generated in one hour at ambient temperature. Control experiments (use of benzoic acid in place of pivalic acid) suggested that the function of pivalic acid is not to generate pivalic anhydride *in situ*, but to convert the diboron intermediate to a more reactive species perhaps through protodeboronation and/or protodesilylation. Lastly, it was found that unpurified silylimines could be used in the reaction such that direct conversion of aldehyde substrates to α-amino boronic acid derivatives could be accomplished in a single-flask process, without isolation of any intermediates and without solvent-swapping operations. In connection with this last feature, it was found that addition of TMSCl to the unpurified silylimine mixture was critical to high yields and selectivity; it is reasoned that addition of TMSCl converts LiOTMS (generated in the imine synthesis) into less reactive LiCl and TMS_2O. As the data in Table 2, indicates, these improvements applied to a range of substrates allowing direct conversion of aldehydes to chiral α-amino boronates in an asymmetric fashion. Notably, the reaction is insensitive to substrate electronic effects with both electron-rich and electron-poor substrates performing similarly. While both meta and para substituted aryl aldehydes were converted to aminoboronates with high stereoselection, an *ortho*-substituted aryl aldehyde reacted in a near-racemic fashion. Fused-ring substrates also reacted with good selectivity (compounds **13**−**16**). Importantly, while the products are often hydrolytically sensitive, the reaction mixtures could often be purified with water-deactivated silica gel chromatography (see Supporting Information for these details).[13]

As alluded to above, one feature of this strategy for construction of α-amino boronates is that the amino group can be acylated with a variety of different acyl donors. To explore the possibility of coupling with activated amino acid derivatives that might be used in peptide synthesis, a tandem diboration/acylation sequence employing α-amino acid derivatives was examined. It was considered that configurationally stable α-amino acid fluorides might replace pivaolyl chloride used in Table 2. As depicted in eqs 4 and 5, this strategy proved highly effective and delivered peptidic amino boronates **17** and **18** in good yield and without significant epimerization of stereogenic centers. An additional important feature in considering the utility of the amino borylation reaction is the proclivity of the pinacol boronate to undergo conversion to the derived boronic acid. As depicted in eq 6, this transformation is readily accomplished by treatment with BCl_3.

In addition to serving as a simple route to α-aryl aminoboronic ester derivatives, the aminoborylation strategy described herein can offer accelerated routes to chiral enantiomerically enriched benzhydryl amines. A recent report

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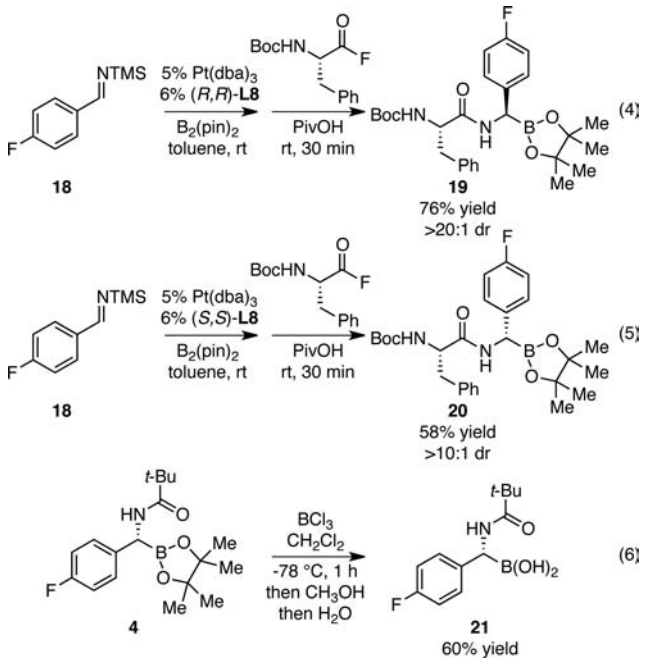
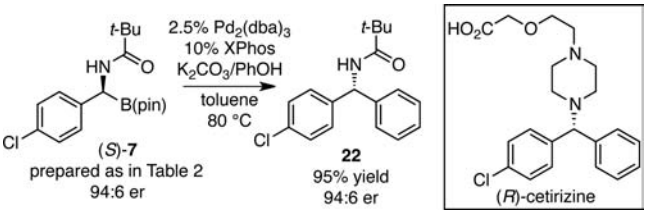


by Ohmura and Suginome described the stereoinvertive cross-coupling of *N*-pivaloyl protected α-aminoboronates.[3] As depicted in Scheme 2, this strategy was easily combined with aminoborylation to give nonracemic **22**, a potential precursor to the more active enantiomer of the antihistamine agent cetirizine (Zyrtec).

Scheme 2



In summary, we report a catalytic enantioselective method for the α-amino borylation of aldehydes. This transformation can serve as a starting point for the construction of amino boronic acid-derived peptides. Further studies addressing the scope and utility of this process are in progress.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Procedures, characterization and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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