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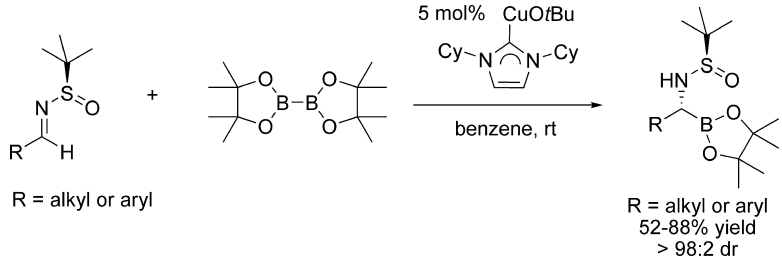

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Asymmetric Copper-Catalyzed Synthesis of α-Amino Boronate Esters from *N-tert*-Butanesulfinyl Aldimines

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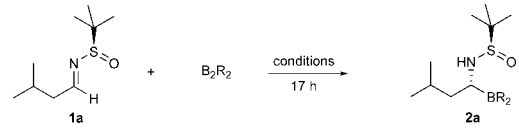
α-Amino boronic acids have emerged as key mechanism-based pharmacophores for serine protease inhibition and have been incorporated into inhibitors of numerous therapeutically important proteases, including thrombin,[1a] elastase,[1b] and dipeptidyl peptidase IV.[1c] Indeed, bortezomib (Velcade), was the first FDA approved proteasome inhibitor drug and is in clinical use for the treatment of multiple myeloma and mantle cell lymphoma.[2]

Despite the clear biological importance of α-amino boronic acids, few methods are currently available for their asymmetric synthesis. In fact, the only reported syntheses of enantioenriched α-amino boronic acids have relied on Matteson's protocol.[3] This method utilizes chiral pinanediol boronate esters in a homologation reaction to prepare α-chloroboronate esters that are further transformed to α-amino boronic acids. While Matteson's chemistry has been extensively used in both academia and industry,[1–3] the α-amino boronic acid side chain is derived from an alkyl boronic acid input, few of which are commercially available. Herein, we report a new and more direct approach for the asymmetric synthesis of diverse α-amino boronic acids by the highly diastereoselective copper-catalyzed addition of bis(pinacolato)diboron to *N-tert*-butanesulfinyl aldimines[4] at ambient temperature. We further report on the synthetic utility of the *N*-sulfinyl α-amino boronate ester addition products by the efficient asymmetric synthesis of bortezomib.

Few reports have appeared in the literature on the addition of boron to a carbon heteroatom double bond.[5,6] However, Baker and co-workers demonstrated diborylation of a very limited number of *N*-aryl aromatic aldimines with bis(catecholato)diboron (B_2cat_2) in the presence of a platinum catalyst to afford racemic α-amino boronate esters.[6] We therefore began by examining the platinum-catalyzed diborylation of *N-tert*-butanesulfinyl aldimines. Unfortunately, no reaction was observed using this catalyst system (Table 1, entry 1). Recently, Sadighi and co-workers reported the addition of bis(pinacolato)diboron (B_2pin_2) across aldehydes using a catalytic amount of (1,3-dicyclohexylimidazol-2-ylidene)copper(I) *tert*-butoxide ((ICy)CuO*t*Bu).[7] Gratifyingly, the addition of B_2pin_2 to *tert*-butanesulfinyl aldimines with Sadighi's catalyst proceeded in 78% yield (Table 1, entry 2). A very high diastereomeric ratio of >98:2 was achieved as determined by ^{19}F NMR analysis of the corresponding (+)- and (−)-MTPA amides prepared by acidic deprotection of the *N*-sulfinyl group followed by treatment with either (+)- or (−)-MTPACl.[8] A control reaction was performed to demonstrate that in the absence of catalyst no reaction was observed (Table 1, entry 3). Performing the reaction at lower temperatures required extended times for reaction completion (entry 4), and at higher temperatures, a lower yield was observed (entry 5). Using toluene, dioxane, or THF as the solvent (entries 6−8) gave lower yields but diastereoselectivity comparable to that obtained with benzene (entry 2).

With optimal reaction conditions identified, the scope of the methodology was investigated by the borylation of various *N-tert*-butanesulfinyl aldimines (Table 2). Additions to unbranched aliphatic aldimines proceeded in good yields and with high diastereoselectivities to provide the *N*-sulfinyl-α-amino boronate esters corresponding to leucine, phenylalanine, and homophenylalanine, respectively (entries 1−3). The addition reaction is not sensitive to sterics as demonstrated by the syntheses of the analogues of valine, α-cyclohexylglycine (entries 4 and 5), and, most dramatically, *tert*-leucine (entry 6). Addition of B_2pin_2 to *N-tert*-

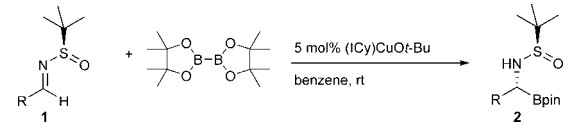
Table 1. Catalyst Screen for α-Amino Boronate Ester Synthesis



entry	B_2R_2	catalyst[a]	temp (°C)	solvent	yield (%)[b]	dr[c]
1	B_2cat_2	$Pt(cod)Cl_2$	rt	C_6H_6	NR	
2	B_2pin_2	(ICy)CuO*t*Bu	rt	C_6H_6	78	>98:2
3	B_2pin_2	none	rt	C_6H_6	NR	
4[d]	B_2pin_2	(ICy)CuO*t*Bu	10	C_6H_6	71	>98:2
5	B_2pin_2	(ICy)CuO*t*Bu	50	C_6H_6	54	97:3
6	B_2pin_2	(ICy)CuO*t*Bu	rt	toluene	69	>98:2
7	B_2pin_2	(ICy)CuO*t*Bu	rt	dioxane	62	98:2
8	B_2pin_2	(ICy)CuO*t*Bu	rt	THF	50	99:1

[a] With 5 mol % of catalyst used. [b] Yields were determined by ^1H NMR of the crude material relative to 1,3,5-trimethoxybenzene as an internal standard. [c] Diastereomeric ratio was determined by ^{19}F NMR of the corresponding (*R*)- and (*S*)-MTPA amides. [d] The reaction time was 30 h.

Table 2. Synthesis of Functionalized α-Amino Boronate Esters



entry	R	product	yield (%)[b]	dr
1	$(CH_3)_2CHCH_2-$	**2a**	74	>98:2[c]
2	$PhCH_2-$	**2b**	59	>98:2[c]
3	$PhCH_2CH_2-$	**2c**	70	99:1[c]
4	$(CH_3)_2CH-$[a]	**2d**	88	>98:2[d]
5	cyclohexyl−	**2e**	81	97:3[d]
6	$(CH_3)_3C-$	**2f**	75	96:4[d]
7	Ph−[e]	**2g**	(66[f]) 54	99:1[c]
8	4-methoxyphenyl−[e]	**2h**	(74[f]) 57	>98:2[c,g]
9	4-chlorophenyl−[e]	**2i**	(77[f]) 61	99:1[c]
10	2-chlorophenyl−[e]	**2j**	(79[f]) 52	>97:3[g]
11	4-(CF_3)-phenyl−[e]	**2k**	(66[f])	>95:5[g]
12	$TBDPSOCH_2-$	**2l**	75	>99:1[c]

[a] Absolute configuration was determined by X-ray crystallography. [b] Isolated yields after silica gel chromatography. [c] See footnote c, Table 1. [d] Determined by ^1H and ^{13}C NMR after preparation of an authentic mixture of diastereomers. [e] Reaction was run in toluene at 0 °C for 48 h with 2.0 equiv of B_2pin_2 and 10 mol % of catalyst. [f] See footnote b, Table 1. [g] No minor diastereomer detected by ^1H and ^{13}C NMR.

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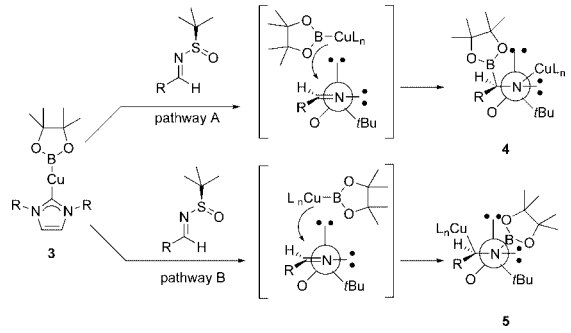
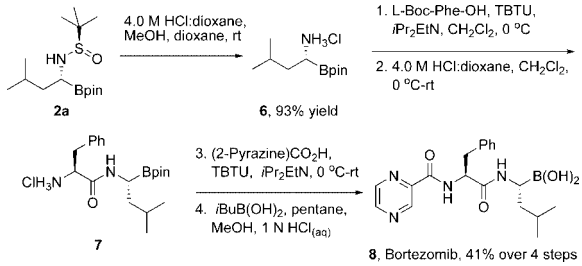
Scheme 1. Rationale for the Observed Sense of Induction



Scheme 2. Asymmetric Synthesis of Bortezomib



butanesulfinyl aromatic aldimines could also be achieved to produce the boronate ester analogues of arylglycines, but the best yields were obtained when the temperature was lowered to 0 °C, reaction times were increased, and the catalyst loading and equivalents of B_2pin_2 were increased (entries 7−11). Both electron-donating (entry 8) and -deficient (entries 9−11) substituents were tolerated on the aryl ring, but protodeborylation occurred readily during chromatography, particularly for electron-deficient addition product **2k**. The success of the method for functionalized α-amino boronic acid analogues was demonstrated by the preparation of the α-amino boronate ester corresponding to *O*-TBDPS-protected serine (entry 12).

The sense of induction can best be understood by considering Sadighi's preliminary investigations on the Cu-catalyzed diborylation of aldehydes with B_2pin_2 where he demonstrated that **3** is generated upon mixing a copper NHC complex with B_2pin_2 (Scheme 1). From **3**, two pathways for the stereodetermining step are possible.[9] In pathway A, direct boron−carbon bond formation occurs, while in pathway B, an organocopper intermediate is first generated, which is expected to undergo transmetalation with retention of configuration to give the boronate ester product.[10] For both pathways, the sense of induction is consistent with an open transition state with the reagent delivered from the least hindered face.[11]

Upon establishing broad substrate scope, we sought to demonstrate the versatility of the *N*-sulfinyl α-amino boronate esters **2** by the efficient synthesis of bortezomib. Selective removal of the *N*-sufinyl group under acidic conditions afforded the amine hydrochloride **6** in 93% yield (Scheme 2). *N*-Boc-L-phenylalanine was coupled with **6** using 2-(1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU) according to the procedure by Millenium Pharmaceuticals,[12] and without purification, treatment with HCl then provided the amine hydrochloride **7**. Coupling of 2-pyrazinecarboxylic acid to crude **7** provided the penultimate intermediate, the pinacol boronate of bortezomib. This unpurified material was subsequently hydrolyzed under biphasic conditions utilizing *iso*-butylboronic acid as a pinacol sequestering agent.[12] Purification by reverse phase chromatography produced analytically pure bortezomib, **8**, in an overall yield of 41% from **6** for the four-step process.

In conclusion, we have achieved the first asymmetric addition of boron to a carbon heteroatom double bond, enabling the practical production of highly enantioriched α-amino boronic acid derivatives form readily accessible *N*-sulfinyl imine inputs **1** using a very inexpensive Cu/ligand catalyst system. This transformation proceeds in good yields and with very high diastereoselectivities for both hindered and unhindered *N*-sulfinyl imine substrates. Moreover, the *N*-sulfinyl α-amino boronate pinacol ester products **2** are perfectly packaged for direct incorporation into α-amino boronic acid-based protease inhibitors as demonstrated by the efficient synthesis of bortezomib, a potent proteasome inhibitor approved for the treatment of cancer.

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

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