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Acyclic Stereoselective Boron Alkylation Reactions for the Asymmetric Synthesis of β-Substituted α-Amino Acid Derivatives

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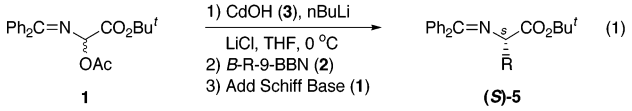
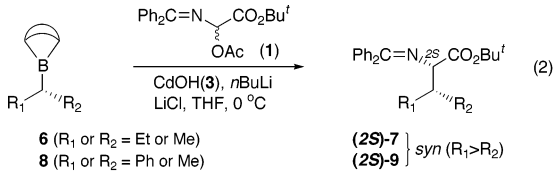
The enantioselective synthesis of α-amino acid derivatives via organoboranes was recently reported from this laboratory.[1] The methodology involves reaction of the α-acetoxy derivative of the benzophenone imine of glycine *tert*-butyl ester (**1**) with an achiral *B*-alkyl-9-BBN (**2**) in the presence of a *Cinchona* alkaloid and added lithium chloride (eq 1). Either enantiomer of the product α-amino



acid (**5**) was prepared by simply changing the alkaloid: cinchonidine (**3**, CdOH) gave (*S*)-**5**, while cinchonine (**4**, CnOH) led to (*R*)-**5**. The highest enantioselectivity (95% ee) was obtained in the preparation of the β-substituted α-amino acid derivative of cyclopentylglycine [**(*S*)-5**, R = *c*-C_5H_9]. We hypothesized that the enantioselective protonation was controlled by complexation of the enolate to the alkaloid, with delivery of the proton from the less sterically hindered face.

β-Substituted α-amino acids, of interest as conformationally constrained α-amino acid analogues,[2] have been the focus of numerous synthetic studies.[3] We report a novel route to these important targets, the stereoselective boron alkylation of **1** with chiral, nonracemic *B*-substituted-9-BBN's[4] (eq 2).



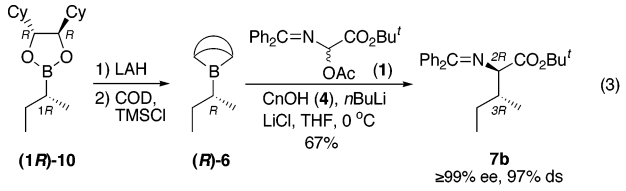
Two representative β-alkyl-substituted α-amino acid targets were chosen for this study, the isoleucines (**7**) and the β-methylphenylalanines (**9**). Stereochemical control in the preparation of each of the four stereoisomers of the two targets will depend on: (a) stereoselective preparation of the latent β-center via the corresponding chiral, nonracemic organoborane (**6** or **8**) and (b) final protonation of the boron enolate intermediate to set the α-stereocenter, which follows the organoborane alkylation to form the $C_\alpha-C_\beta$ bond.[1]

(*2S,3R*)-7 (**7a**) (shown)
(*2R,3R*)-7 (**7b**)
(*2S,3S*)-7 (**7c**)
(*2R,3S*)-7 (**7d**)

(*2S,3R*)-β-MePhe (**9a**) (shown)
(*2R,3R*)-9 (**9b**)
(*2S,3S*)-9 (**9c**)
(*2R,3S*)-9 (**9d**)

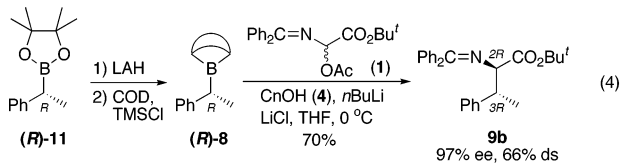
The inherent diastereoselectivity[5] in the final protonation step of the boron alkylation sequence was addressed first by reaction of **1** with racemic *B*-(*s*-butyl)-9-BBN [(±)-**6**] in the presence of an achiral proton source.[6] The product racemic diastereomers **7** were obtained with low *syn*-diastereoselectivity [60% ds, 3:2 dr of (**7a**+**7d**):(**7b**+**7c**)], which is not surprising due to the similar size of ethyl vs methyl.[7] Replacement of the ethyl with a larger phenyl group[7] in the *B*-alkyl-9-BBN (±)-**8** increased the *syn*-diastereoselectivity substantially (91% ds, 10:1 dr) for products **9**.[6]

Matteson asymmetric homologation chemistry[8] with DICHED boronic esters (**10**) was used to establish the latent β-stereocenter in the enantiomers of **6** [R_1,R_2 = Et,Me for (*R*)-**6**; or Me,Et for (*S*)-**6**] (eq 3) because of the potential for the homologation



methodology to be applied to the construction of α-amino acid derivatives containing multiple stereogenic centers in the side-chain. Boronic esters (**10**) were converted to the *B*-alkyl-9-BBN derivatives (**6**) for use in the asymmetric boron alkylation reaction by the reduction/hydroboration methodology of Brown and Singaram.[9] The organoborane alkylation reaction with an expected poor selectivity was chosen as a test case. Thus, use of cinchonine, which typically gives 2*R* stereochemistry,[1] together with the (*R*)-organoborane **6** gave the inherently disfavored (2*R*,3*R*)-*anti*-product **7b** in high enantio- and diastereoselectivity (eq 3 and Table 1, entry b). The other stereoisomers of **7** were formed in equally high stereoselectivity (Table 1, entries a, c, and d).[6]

Rhodium-catalyzed asymmetric hydroboration of styrene[10] was used to establish the stereogenic center in the preparation of **8**. Once again (eq 4 and Table 1, entry f), the case with an expected poor



stereoselectivity, the formation of the *anti*-diastereomer, was studied. In this case, an eroded diastereoselectivity (66% ds) was observed while an excellent enantioselectivity (97%) was maintained. The other three stereoisomers of **9** (Table 1, entries e, g, and h) were prepared with high enantioselectivity but variable diastereoselectivity. In the case of the *syn*-products (**9a** and **9d**) the diastereoselectivity was high (98% and 97% ds, respectively), while for the other *anti*-product (**9c**) the diastereoselectivity was again moderate.[6]

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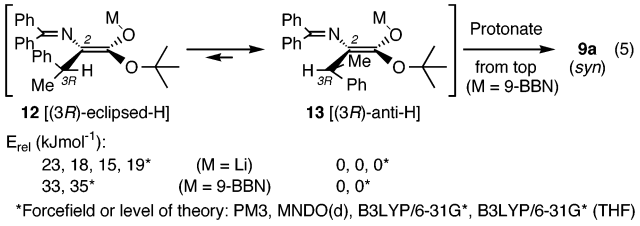
Table 1. Stereoselective Alkylation of **1** with Organoboranes **6** or **8**

entry	β-R*-9-BBN	alkaloid	product[a]	ratio of stereoisomers	% ee[b]	% ds
			7a:7b:7c:7d			
a	(*R*)-**6**	CdOH (**3**)	**7a** (*syn*)	97:1:2:0	≥99	97
b (eq 3)	(*R*)-**6**	CnOH (**4**)	**7b** (*anti*)	0:97:0:3	≥99	97
c	(*S*)-**6**	CdOH (**3**)	**7c** (*anti*)	0.5:0:98.5:1	≥99	98
d	(*S*)-**6**	CnOH (**4**)	**7d** (*syn*)	0.5:0:1:98.5	99	99
			9a:9b:9c:9d			
e	(*R*)-**8**	CdOH (**3**)	**9a** (*syn*)	96:1:1:2	96	98
f (eq 4)	(*R*)-**8**	CnOH (**4**)	**9b** (*anti*)	23:65:1:11	97	66
g	(*S*)-**8**	CdOH (**3**)	**9c** (*anti*)	9:1:65:25	97	66
h	(*S*)-**8**	CnOH (**4**)	**9d** (*syn*)	3:2:1:94	94	97

[a] % yield, not optimized, for entries a−h: 27%, 67%, 33%, 53%, 65%, 70%, 70%, 63%. [b] % ee of major stereoisomer.

The stereochemical outcome of the boron alkylation reaction is dependent on two key factors. First, the inherent diastereoselectivity (substrate control) favors formation of the *syn*-products (vide supra). This is in contrast with studies[11] of the diastereoselective reaction of simple acyclic alkenes containing a β-stereogenic center with electrophiles (in this case, protonation of lithium enolates) where *anti* products are favored. These earlier results were rationalized using the "Houk model," in which the electrophile approached from the least hindered face of the most stable enolate conformation. Calculations predicted that, to minimize $A_{1,3}$-strain, the smallest group (H) on the β-stereogenic center eclipsed the alkene or enolate double bond.[11] In the present case, with the bulky diphenylketimine group at the α-carbon, the Houk conformer (**12**) was calculated to be less stable than the *anti*-conformer (**13**), in which steric interaction between the two non-hydrogen groups on the β-center and the α-$Ph_2C{=}N$ has been minimized.[12,13] Protonation of the more stable conformer (**13**) from the least hindered top face then leads to the observed *syn*-products (eq 5). Calculations of the 9-BBN boron enolates by semiempirical methods [PM3 and MNDO(d)] predicted the same preference for conformation **13**.



The second important factor in determining the stereochemistry of the products in these reactions is the relative importance of the two steric control elements in the chiral protonation: the stereogenic β-center (substrate control) and the *Cinchona* alkaloid (reagent control). Insight into this is gained from the β-methylphenylalanine products **9** (eq 4 and Table 1, entries e−h). In the matched case for formation of *syn*-products (entries e and h), the diastereoselectivity is high because the inherent preference for *syn*-diastereoselectivity is reinforced by the preference of cinchonine to yield 2*S*- and cinchonidine to give 2*R*-products. In contrast, for the mismatched case to yield *anti*-products (entries f and g), these two factors are in opposition; the preference of the substrate is for formation of the *syn*-product, while the reagent (*Cinchona* alkaloid) favors the *anti*-product. The preferred formation of the *anti*-product demonstrates substantial reagent control is obtained in these reactions.

In summary, the stereoselective organoborane alkylation for the synthesis of optically active β-substituted α-amino acids has been realized. This novel reaction, in combination with demonstrated methodology[8−10] for the preparation of chiral, nonracemic organoboranes, will provide access to a variety of α-amino acids containing multiple stereogenic centers. Future studies will focus on application of this methodology, improvement of the diastereoselectivity in the mismatched case, and gaining further insight into the mechanistic details of the reaction.

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Supporting Information Available: Full experimental procedures and analytical data as well as stereoviews and Cartesian coordinates of **12** and **13** (M = Li, 9-BBN), and absolute energies of **12** and **13** (M = Li) (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) A conformational search of the lithium enolates corresponding to (**3*S***)-**9** and (**3*S***)-**7** was conducted by the Monte Carlo method, generating over 400 initial structures using MMFF94 in Spartan v. 5.1.3. The four lowest-energy conformers spanning an energy range of 12 kJ/mol were refined independently at PM3 and MNDO(d), and the geometries were then optimized at B3LYP/6-31G* using Jaguar. See Supporting Information for full details.
(13) The lithium enolate generated by addition of (S)-**6** to **1** was calculated, and showed the same preference for the *anti* conformation by the four computational treatments.

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