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The Enantioselective Synthesis of α-Amino Acid Derivatives via Organoboranes

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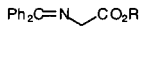
New methods for preparing optically active α-amino acids, the "building blocks of life", continue to attract considerable attention.[1,2] The benzophenone imines of glycine esters (**1** and **2**) have been used as glycine anion and cation equivalents in solution and on-resin for the synthesis of optically active α-amino acids.[2] The



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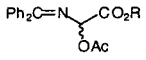

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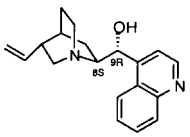
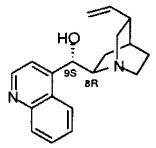
methods involve chiral catalysts, reagents, or auxiliaries, as well as racemic synthesis followed by resolution. In 1985, we reported the synthesis of racemic α-amino acids from organoboranes by the reaction of **2a** (R = Et) with *B*-alkyl-9-BBN derivatives,[3] which provides a method for "appending" the α-amino acid subunit onto functional groups such as alkenes or alkyl halides that can be readily converted into organoboranes.[4−6] We now report that this reaction can be used to prepare optically active α-amino acids by employing the inexpensive and readily available *Cinchona* alkaloids, cinchonidine (**3**) or cinchonine (**4**),[7] to control the stereochemistry at the α-carbon center.



3 (Cinchonidine, CdOH)
5 (CdOLi)

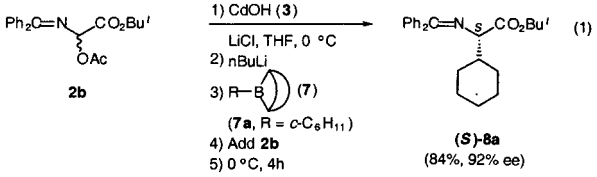


4 (Cinchonine, CnOH)
6 (CnOLi)

Preliminary studies focused on the enantioselective synthesis of the benzophenone imine of cyclohexylglycine *tert*-butyl ester (**8a**) by reaction of **2b** with *B*-cyclohexyl-9-BBN (**7a**) in the presence of the lithium alkoxide of cinchonidine (**5**) (eq 1). When the reaction was carried out in THF at 0 °C for 4 h, **(*S*)-8a** was isolated in 77% yield and 61% ee. The enantiomeric product (**(*R*)-8a**) was prepared (73%, 61% ee) using the alkoxide from cinchonine (**6**). Next, several reaction variables were studied: (a) esters that were either less or more sterically demanding than the *tert*-butyl ester **2b** gave poorer results,[8] (b) THF was the optimal solvent,[9] (c) best results were obtained at 0 °C,[10] and (d) the product was not racemized under the reaction conditions.[11]

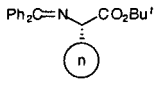
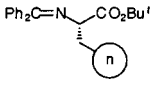
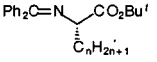
A dramatic increase in the enantioselectivity (61% ee to 92% ee) was achieved by the addition of lithium chloride to the reaction mixture.[12,13]

On the basis of these early results, the optimal procedure (eq 1) used in subsequent studies involved addition of *n*-BuLi (1.3 equiv) to a solution of the alkaloid **3** or **4** (1.3 equiv) containing anhydrous lithium chloride (5 equiv) at 0 °C. The *B*-alkyl-9-BBN (**7**, 1.2 equiv) in THF was then added, followed by a solution of **2b** (1.0 equiv) in THF. The reaction mixture was stirred for 4 h at 0 °C and then subjected to an aqueous workup followed by flash chromatography.



Using conditions developed for the enantioselective boron alkylation to form the cyclohexylglycine **(*S*)-8a**, we prepared a number of homologous cycloalkylglycine derivatives (Table 1, **(*S*)-8a**−**(*S*)-8f**). Such amino acids, which contain a secondary β-carbon, can be difficult to obtain from a glycine anion equivalent because of competing elimination. The *B*-alkyl-9-BBN reagents **7a** and **7d**−**7f** were readily prepared by hydroboration of the corresponding cycloalkene with 9-BBN, while the cyclopropyl and cyclobutyl reagents, **7b** and **7c**, were obtained by reaction of the organolithium derivative with *B*-methoxy-9-BBN. While the enantioselectivity for the three- and four-membered ring analogues was only moderate, products containing a five-, six-, seven-, or eight-membered ring were obtained with excellent enantioselectivity (89−95% ee). Three homologous cycloalkylmethylglycine derivatives (Table 1, **(*S*)-8g**−**(*S*)-8i**) were prepared by hydroboration of

Table 1. Enantioselective Alkylation of Acetate **2** with Organoboranes **7**[a]

Product (8)	% Yield	%ee (Config)	Product (8)	% Yield	%ee (Config)
Cycloalkylglycines :			*Cycloalkylmethylglycines* :		
					
8a (n=6)	84%	92% ee (*S*)	**8g** (n=4)	74%	65% ee (*S*)
8b (n=3)	84%	54% ee (*S*)	**8h** (n=5)	89%	62% ee (*S*)
8c (n=4)	57%	55% ee (*S*)	**8i** (n=6)	69%	62% ee (*S*)
8d (n=5)	78%	95% ee (*S*)		83%	59% ee (*R*)
	80%	92% ee (*R*)	*α-Alkylglycines* :		
8e (n=7)	81%	89% ee (*S*)			
8f (n=8)	79%	90% ee (*S*)	**8j** (n=4)	80%	80% ee (*S*)
			8k (n=6)	74%	85% ee (*S*)
				85%	82% ee (*R*)
			8l (n=8)	92%	75% ee (*S*)

[a] See eq 1 and text for reaction procedure.

the methylenecycloalkanes, followed by the standard organoborane alkylation (eq 1), while the straight-chain derivatives **(*S*)-8j**−**(*S*)-**

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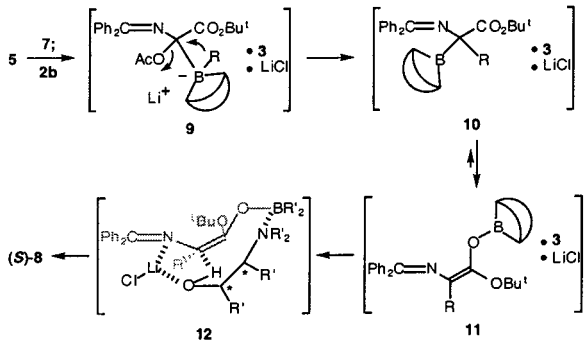
8l were prepared by using the corresponding *B*-(*n*-alkyl)-9-BBN (**7**). The enantiomeric products (**(*R*)-8d**, **(*R*)-8i**, and **(*R*)-8k**) were prepared using cinchonine (**4**).[14]

While the full mechanistic and stereochemical details of the enantioselective organoborane alkylation are complex and remain to be elucidated, a number of points are noted. The use of lithium halide additives to improve selectivity in enolate reactions is well known.[15] The *Cinchona* alkaloid plays two crucial roles in this reaction: as the lithium alkoxide (**5** or **6**),[16] it deprotonates the starting acetate **2b**, which then reacts with the *B*-alkyl-9-BBN reagent **7** to give the ate complex **9**. Migration of the alkyl group with loss of acetate yields the α-boryl ester **10**, which tautomerizes[17] to the boron enolate **11**. The final step in the sequence is the crucial enantioselective protonation (**12**),[18−23] which is mediated by the parent alkaloid, to give the product **8**.[24]



In summary, the enantioselective synthesis of α-amino acids from organoboranes has been realized in up to 95% ee. The versatile and well-established chemistry of the organoboranes, combined with their structural variability, holds considerable promise for the application of this new methodology to the synthesis of optically active α-amino acids. Future work will expand the studies reported here, as well as explore the use of chiral, nonracemic organoboranes for the preparation of optically active α-amino acids containing multiple stereogenic centers.

Acknowledgment. This work is dedicated to Professor H. C. Brown on the occasion of his 90th birthday. We acknowledge the National Institutes of Health (GM 28193) for support. We thank Dr. Mary Mader for detailed discussions.

Supporting Information Available: Experimental procedures and analytical data for products **8** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) Ester *R* group, % yield, % ee: Me, 76%, 26% ee; Et, 72%, 42% ee; *tert*-Bu, 77%, 61% ee; Et_3C−, 52%, 14% ee.

(9) Solvent, % yield, % ee: THF, 77%, 61% ee; CH_2Cl_2, 29%, 75% ee; THF/CH_2Cl_2 (1:1), 76%, 58% ee; PhMe, 76%, 58% ee; DME, 83%, 49% ee; *tert*-BuOMe, 31%, 24% ee; Et_2O, 64%, 23% ee.

(10) Temp, % yield, % ee: 25 °C, 79%, 43% ee; 0 °C, 77%, 61% ee; −20 °C, 60%, 27% ee; −40 °C, 88%, 34% ee; −78 to 0 °C, 76%, 46% ee.

(11) Rx time, % ee: 1 h, 62% ee; 2 h, 63% ee; 4 h, 62% ee; 6 h, 62% ee; 16 h, 63% ee.

(12) LiCl (eq), % yield, % ee: 0, 77%, 61% ee; 0.5, 83%, 89% ee; 1, 78%, 89% ee; 2, 73%, 91% ee; 5, 84%, 92% ee.

(13) Additive (eq), % yield, % ee: LiCl (5), 84%, 92% ee; LiBr (5), 85%, 62% ee; LiCl (4) + LiBr (1), 81%, 67% ee.

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(24) A control experiment involving reaction of the enolate from **8a** (88% ee) with 9-Cl-9-BBN followed by treatment with cinchonidine (**3**) gave product **(*S*)-8a** in 14% ee; see Supporting Information for experimental details.

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