Asymmetric Synthesis of α-Alkylproline Derivatives from a Chiral Borane−Amine Adduct: Inversion of Enantioselectivity in the Presence of a Crown Ether

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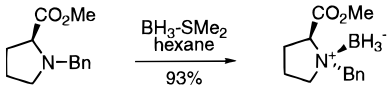
In recent years, α-alkylprolines have been used in the synthesis of peptides having increased stability toward proteases[1] and of peptidomimetics containing a *β*-turn mimic.[2] Several procedures have been described to gain access to these compounds.[3] Herein we report the preparation of enantiomerically enriched α-alkylproline derivatives, using a method that relies on several successive chirality transfers *via* a chiral borane−amine adduct.[4]

(*S*)-*N*-Benzylproline methyl ester **1**,[5] a compound having an easily removable protecting group on the nitrogen atom, was chosen as the starting material (Scheme 1).

Scheme 1



1 **2**

Treatment of methyl ester **1** with borane−methyl sulfide complex in 3/1 hexane/CH_2Cl_2 afforded the borane−amine adduct **2** as a single diastereomer. Its structure

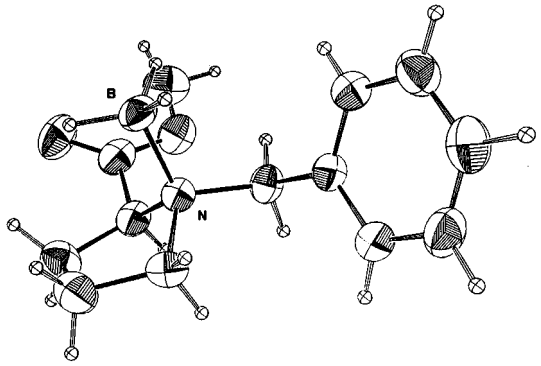
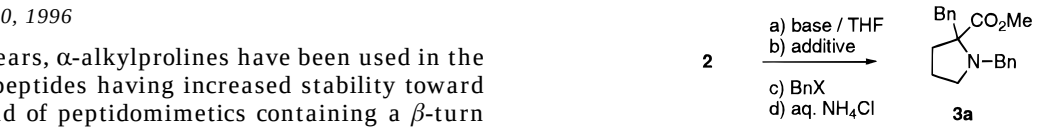


Figure 1. Crystal structure of the borane−amino ester adduct **2**.

Table 1. α-Benzylation of 2[a]



3a

entry	base	additive (equiv)	BnX	major enant	yield (%)	ee[b] (%)
1	LDA	none	BnBr		0	
2	KHMDS	none	BnBr	(*S*)	54	45[c]
3	KHMDS	none	BnBr	(*S*)	64	54[d]
4	LDA	HMPA (2)	BnI	(*R*)	56	82
5	LDA	HMPA (3)	BnI	(*R*)	74	88[e]
6	LDA	HMPA (5)	BnI	(*R*)	82	76
7	KHMDS	18-crown-6 (0.2)	BnBr	(*R*)	67	36
8	KHMDS	18-crown-6 (0.5)	BnBr	(*R*)	63	60
9	KHMDS	18-crown-6 (1)	BnI	(*R*)	74	80

[a] See the text for conditions; the reaction was usually performed on a 0.3−0.5-mmol scale. [b] The enantiomeric excess was determined by ^{1}H NMR spectroscopy of **3a** in C_6D_6 in the presence of (+)-Eu(hfc)$_3$ (see the supporting information for details). [c] $[\alpha]^{23}_D = -19$ ($c = 1.9$ in CH_2Cl_2). [d] The alkylation was performed at 0 °C. [e] $[\alpha]^{23}_D = +39$ ($c = 2.0$ in CH_2Cl_2).

was ascertained by a single-crystal X-ray analysis (Figure 1),[6] which showed that the boranato group and the carboxylate function are *cis* to each other.

We then studied the α-alkylation of adduct **2** with benzyl halides under various conditions[7] (Table 1). The enolate derived from ester **2** was generated by treatment with LDA or KHMDS for 15 min at −23 °C in THF; the electrophile was added at −78 °C and the reaction mixture was stirred at this temperature for 2−3 h and then either hydrolyzed directly or after being warmed to room temperature if the alkylation was not complete; in all cases, after the hydrolysis with a saturated NH_4Cl aqueous solution, no borane−amine adduct was obtained. The lithium enolate proved unreactive toward benzyl bromide (Table 1, entry 1) unless HMPA was added prior to the electrophile, and the yield in adduct **3a** improved as more HMPA was used (Table 1, entries 4−6). On the

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(4) For the enantioselective synthesis of α-alkylalanine derivatives (having an unremovable *N*-methyl group) using such a strategy, see: Ferey, V.; Toupet, L.; Le Gall, T.; Mioskowski, C. *Angew. Chem.* **1996**, *108*, 475; *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 430.

(5) Corey, E. J.; McCaully, R. J.; Sachdev, H. S. *J. Am. Chem. Soc.* **1970**, *92*, 2476. In this paper , the synthesis of (*R*)-*N*-benzylproline methyl ester ($[\alpha]^{24}_D = +73.8$; $c = 2.15$ in $CHCl_3$) is described; starting from (*S*)-proline, we prepared **1** ($[\alpha]^{23}_D = -70.5$; $c = 2.1$ in $CHCl_3$) in the same manner.

(6) Atomic coordinates for the structure reported in this paper have been deposited at the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Center, 12 Union Road, Cambridge CB2 1EZ, UK.

(7) Compound **3a** obtained from a reaction performed with LDA/HMPA was converted to (*R*)-2-benzylproline dimethylamide in two steps: i) Me_2NLi, THF, −78 °C, 25 min, 81%; (ii) HCO_2NH_4, $Pd(OH)_2$, MeOH, reflux, 20 min, 78%. Its specific rotation was $[\alpha]^{23}_D = -49$ ($c = 2.2$ in CH_2Cl_2) (lit.[3b] $[\alpha]^{23}_D$ −52.4 ($c = 2.2$ in CH_2Cl_2)). The absolute configuration of the major enantiomer in each run then followed from the measured specific rotations and/or the pattern of the ^{1}H-NMR spectra in presence of Eu(hfc)$_3$.

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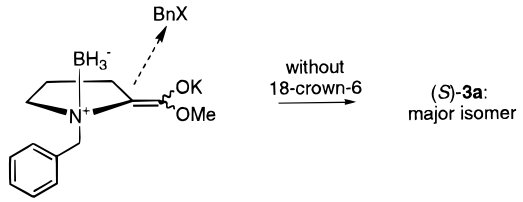
Scheme 2



contrary, the potassium enolate reacted with benzyl bromide without the need of an additive (Table 1, entries 2 and 3); however, the yield of the product **3a** improved by adding 18-crown-6 prior to the halide (Table 1, entries 7−9).

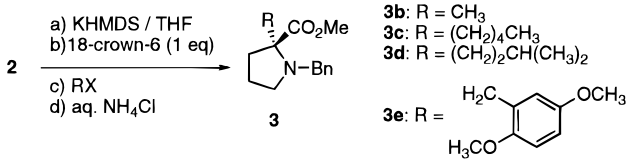
The quantity of additive used had a great impact on the level of enantioselectivity. Thus, 3 equiv of HMPA in conjunction with the lithium enolate gave the best observed enantiomeric excess (Table 1, entry 5); in this case, the lithium cation might be chelated by three molecules of HMPA; hence, the enolate would be a very well-organized species, having a tetrahedrally coordinated lithium. Starting from the potassium enolate, the best enantiomeric excess was obtained using 1 equiv of 18-crown-6.

The most striking observation was the *inversion of enantioselectivity* in the reaction of the potassium enolate in the absence (Table 1, entries 2 and 3) *versus* in the presence (Table 1, entries 7−9) of 18-crown-6. Few examples have been reported in the literature in which the addition of a crown ether produces a reversal of diastereoselectivity,[8,9] and as far as we are aware, only one of them involves an intermolecular reaction.[8c]

An approach of the electrophile by the less crowded enantioface of the potassium enolate, e.g. the side of the smaller boranato group (Scheme 2), can be postulated to explain the stereochemical outcome of the reaction in the absence of additive.

To account for the preferential formation of the (*R*)-enantiomer when 18-crown-6 was added, one must envision that a close interaction exists between the crown ether and the enolate.[10] We suggest that the O−K bond of the enolate lies out of its plane and that the bulky crown ether can interact with either the boranato or the benzyl group. For steric reasons, it should rather place itself on the side of the smaller boranato group, thus

Table 2. α-Alkylation of 2[a]



entry	RX	product	yield (%)	ee[b] (%)
1	CH_3OTf	**3b**	76	88[c]
2	$CH_3(CH_2)_4OTf$	**3c**	64	92
3	$(CH_3)_2CH(CH_2)_2OTf$	**3d**	60	86
4	$2,5\text{-}(MeO)_2PhCH_2I$	**3e**	55	91

[a] See the text for conditions; the reaction was usually performed on a 0.3-0.5 mmol scale. [b] The enantiomeric excess was determined by ^1H NMR spectroscopy of **3** in C_6D_6 in the presence of (+)-Eu(hfc)$_3$ (see the supporting information for details). The absolute configurations of compounds **3b**−**e** have not been determined; in each case, the selectivity should be the same as the one observed when benzyl iodide was used as electrophile. [c] Precision of the ee: only ±5%. The splitting signals from the two enantiomers were not completely separated.

preventing the approach of this side by the incoming electrophile. A similar reasoning may also apply to the reaction of the lithium enolate in combination with HMPA.

The α-alkylation of borane−amino ester **2** with other electrophiles was then performed using KHMDS and 1 equiv of crown ether (Table 2). While 2,5-dimethoxybenzyl iodide gave rise to compound **3e** with 91% ee (Table 2, entry 4), several experiments using alkyl or allyl iodides afforded the corresponding adducts only with low ee's. However, it was possible to obtain good enantioselectivities when the more reactive trifluoromethanesulfonates[11] were used as electrophiles (Table 2, entries 1−3). For instance, compound **3b** was obtained with 88% ee, *versus* 44% ee, using methyl triflate instead of methyl iodide.

In summary, we have shown that our method relying on the use of a chiral, nonracemic borane−amino ester in the enantioselective construction of a carbon−carbon bond can be applied to the preparation of α-alkylproline derivatives. The occurrence of a reversal of diastereoface selection produced by a crown ether in the alkylation of a chiral enolate has been demonstrated; whether this effect can also be observed with acyclic substrates or not remains to be evaluated.

Supporting Information Available: Experimental procedures and characterization data are provided for compounds **2** and **3a**−**e** (4 pages).

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