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Synthesis of benzylcyanoborane adducts of amines and separation of their enantiomers; S_N2 substitution at boron atom†

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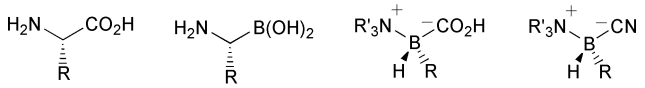
Benzylcyanoborane adducts of several amines were prepared in four steps from toluene, their enantiomers were separated using chiral phase HPLC and an S_N2 pathway was evidenced in the reaction of a trimethylamine-derived enantiomer with pyridine.

Several methods for the synthesis of enantiomerically pure α-amino acids **1** have been reported.[1] These compounds, either

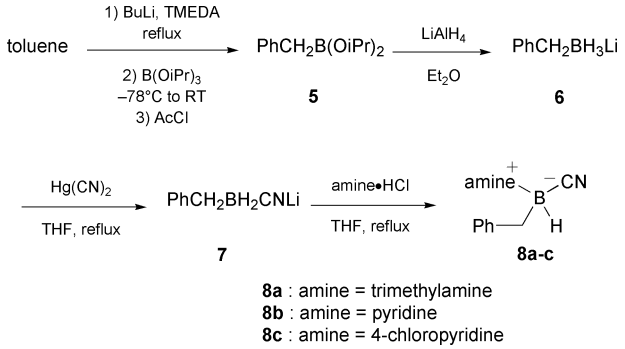


1 **2** **3** **4**

naturally occurring or not, may then be employed as building blocks for the preparation of biologically active products. Among various analogues of amino acids, boron-containing species have been prepared.[2] α-Aminoboronic acids **2**, in which the carboxylic acid moiety is replaced by a boronic acid moiety, have been employed to prepare peptides modified at the C-terminal amino acid and several enantioselective accesses to them have been described.[3] Boron analogues **3**, in which a tetravalent boron atom replaces the α-carbonyl carbon atom, may be used to modify the N-terminal amino acid of a peptide. The synthesis of **3** and the corresponding esters, amides and nitriles has also been investigated.[4] However, although general pathways to amine–alkylcyanoborane adducts **4** have been designed, only glycine analogues (**3**, R = H) can be prepared efficiently, due to the difficult hydrolysis of the cyano group of substituted analogues. Nevertheless, compounds **4** (R = alkyl) may find use as precursors to dipeptides isosteres. To the best of our knowledge, such compounds have never been obtained in enantiomerically pure form.

In this Communication, we describe the preparation of several amine–benzylcyanoborane adducts and the separation of their enantiomers by chiral phase HPLC. A ligand exchange study was also performed starting from one enantiopure adduct, which suggests the occurrence of an S_N2 mechanism.

The syntheses of quinuclidine and trimethylamine adducts of benzylcyanoborane were described by Todd *et al.*[5] These adducts were obtained from the complex of benzyllithium and TMEDA which was then converted to lithium benzylcyanodihydroborate–TMEDA. A modest overall yield was obtained, probably because of the presence of TMEDA in the reaction mixture during the complexation of the amine. In order to avoid this, benzyllithium–TMEDA was reacted with triisopropyl borate to yield boronate **5**,[6] which was purified by distillation (85% yield) and then reduced to lithium benzyltrihydroborate free from TMEDA (Scheme 1).[7] Treatment of **6** with mercury(II) cyanide[8] yielded lithium benzylcyanodihydroborate **7**,



Scheme 1 Preparation of benzylcyanoborane adducts of amines.

which was reacted with the hydrochlorides of trimethylamine, pyridine and 4-chloropyridine to afford benzylcyanoborane adducts **8a**, **8b**, **8c**, respectively. The adducts were obtained as crystals with 27, 69 and 51%, overall yield, respectively, from boronate **5**. They are stable to air and moisture, and are not hydrolyzed by contact with slightly acidic or basic aqueous solutions. The structures of compounds **8a** and **8c** were confirmed by X-ray analyses (Fig. 1 and 2).[9]

The enantiomers of adducts **8a**–**c** were separated by HPLC over Chiracel columns using hexane–alcohol mixtures or subcritical CO_2–methanol as eluents (Table 1). However the absolute configuration of the enantiomers was not determined.

These compounds were shown to be configurationnally stable by chiral HPLC analysis, after storage for several weeks as crystals or in ethanolic solution. CD spectra were recorded for each pure enantiomer of trimethylamine–benzylcyanoborane **8a** and pyridine–benzylcyanoborane **8b**, showing symmetrical bands which proved opposite chirality. Numerous peaks were split in the ^{1}H NMR spectrum of racemic **8b** in C_6D_6, in

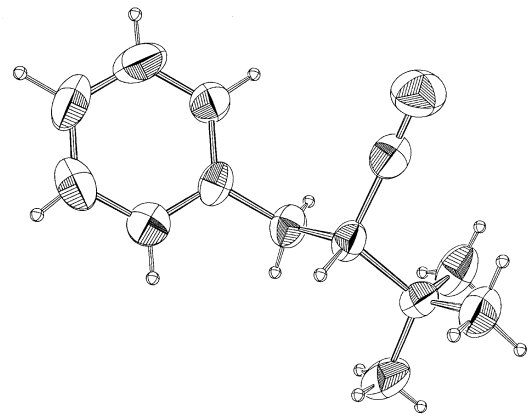


Fig. 1 X-Ray structure of adduct **8a**.

† Experimental procedures and characterization data for compounds **5**, **6**, **7**, **8a**–**c** as well as HPLC profiles are available as supplementary data. For direct electronic access see http://www.rsc.org/suppdata/cc/b0/b006265k

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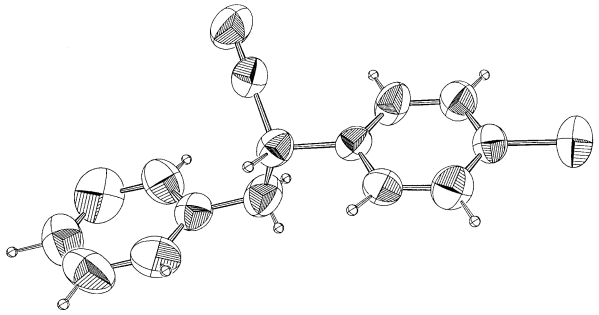

Fig. 2 X-Ray structure of adduct **8c**.

Table 1 Separation of the enantiomers of benzylcyanoborane adducts **8a–c** by chiral phase HPLC

Adduct	Column	Eluent/flow rate	R_t/min
8a	Chiracel OD	95:5 hexane–EtOH 1.2 mL min^{-1}	23.2, 29.1
8a	Chiracel OD	CO_2, 1 mL min (180 bars) MeOH, 0.2 mL min^{-1}	9.4, 10.6
8b	Chiracel OD	95:5 hexane–EtOH 1.2 mL min^{-1}	26.8, 29.0
8b	Chiracel OD	CO_2, 2 mL min^{-1} (250 bars) MeOH, 0.15 mL min^{-1}	8.7, 9.8
8c	Chiracel OC	90:10 hexane–*i*PrOH 1 mL min^{-1}	54.1, 56.3

the presence of Eu(hfc)$_3$‡ (2.4 eq.). In the same conditions, single sets of peaks were observed for separated enantiomers.

Direct evidence of an S_N2 substitution at the boron atom was observed in our laboratory in the reaction of a diastereomerically pure monoisopinocampheylcyanoborane adduct of triphenylphosphine with a more nucleophilic phosphine, dimethylphenylphosphine.[10,11]

Having pure amine–benzylcyanoboranes enantiomers in hand, we also studied similar substitution. Thus, one enantiomer of trimethylamine–benzylcyanoborane **8a** was dissolved in pyridine, at rt or at 70 °C, and the reaction was monitored by chiral HPLC. After 2 h at rt, one enantiomer of pyridine–benzylcyanoborane **8b** was formed, and after a longer time the second enantiomer appeared, probably because of the racemization of the first one in the presence of the excess of pyridine. At 70 °C, the same phenomenon occurred, but faster. The fact that one enantiomer of reactant was transformed into one enantiomer of product is indicative of an S_N2 mechanism occurring at the boron atom.

In conclusion, several benzylcyanoborane adducts of amines were prepared in four steps from toluene and separated using chiral phase HPLC. The occurrence of an S_N2 pathway at a tetravalent boron atom was evidenced by the formation of a single adduct in the treatment of an enantiopure trimethylamine adduct with pyridine.

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Notes and references

‡ Eu(hfc)$_3$ = Europium tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorate].

1 (*a*) R. M. Williams, *Synthesis of Optically Active α-Amino Acids*, Pergamon Press, Oxford, 1989; (*b*) R. O. Duthaler, *Tetrahedron*, 1994, **50**, 1539.

2 For a review on boron analogues of biomolecules, see: C. Morin, *Tetrahedron*, 1994, **50**, 12 521.

3 Selected references: (*a*) D. S. Matteson, K. M. Sadhu and G. E. Lienhard, *J. Am. Chem. Soc.*, 1981, **103**, 5241; (*b*) C. A. Kettner and A. B. Shenvi, *J. Biol. Chem.*, 1984, **259**, 15 106; (*c*) T. A. Kelly, V. U. Fuchs, C. W. Perry and R. J. Snow, *Tetrahedron*, 1993, **49**, 1009; (*d*) P. Mantri, D. E. Duffy and C. A. Kettner, *J. Org. Chem.*, 1996, **61**, 5690; (*e*) C. Lebarbier, F. Carreaux and B. Carboni, *Synthesis*, 1996, 1371; (*f*) C. S. Brosz, J. C. Calabrese, C. A. Kettner and C. A. Teleha, *Tetrahedron: Asymmetry*, 1997, **8**, 1435.

4 Selected references: (*a*) B. F. Spielvogel, L. Wojnowich, M. K. Das, A. T. McPhail and K. D. Hargrave, *J. Am. Chem. Soc.*, 1976, **98**, 5702; (*b*) P. Wisian-Neilson, M. K. Das and B. F. Spielvogel, *Inorg. Chem.*, 1978, **17**, 2327; (*c*) B. F. Spielvogel, F. U. Ahmed, G. L. Silvey, P. Wisian-Neilson and A. T. McPhail, *Inorg. Chem.*, 1984, **23**, 4322; (*d*) A. Sood and B. F. Spielvogel, *Main Group Met. Chem.*, 1989, **12**, 143; (*e*) C. H. Sutton, M. W. Baize and L. J. Todd, *Inorg. Chem.*, 1994, **33**, 4221; (*f*) W. J. Mills, C. H. Sutton, M. W. Baize and L. J. Todd, *Inorg. Chem.*, 1991, **30**, 1046.

5 (*a*) W. J. Mills, C. H. Sutton, E. Libby and L. J. Todd, *Inorg. Chem.*, 1990, **29**, 302; (*b*) W. J. Mills, L. J. Todd and J. C. Huffman, *J. Chem. Soc., Chem. Commun.*, 1989, 900.

6 H. C. Brown, M. Srebnik and T. E. Cole, *Organometallics*, 1986, **5**, 2300.

7 B. Singaram, T. E. Cole and H. C. Brown, *Organometallics*, 1984, **3**, 774.

8 J. Emri and B. Györi, *J. Chem. Soc., Chem. Commun.*, 1983, 1303.

9 Crystal data for racemic adduct **8a**: $C_{11}H_{17}BN_2$, M = 188.08, colourless, orthorhombic, a = 11.645(5), b = 16.506(3), c = 9.074(4) Å, β = 95.07(2)°, T = 294 K, space group $P2_12_12_1$, Z = 4, μ(Mo-Kα) 0.586 cm^{-1}, 1222 reflections measured, 761 reflections observed [$I > \sigma(I)$], final wR = 0.048. Selected bond distances (Å): B–N 1.619(7), B–CN 1.60(8). Crystal data for racemic adduct **8c**: $C_{13}H_{12}BN_2Cl$, M = 242.52, colourless, monoclinic, a = 8.539(2), b = 11.828(3), c = 12.989(4) Å, T = 293 K, space group $P2_1/n$, Z = 4, μ(Mo-Kα) 2.68 cm^{-1}, 2592 reflections measured, 1180 reflections observed [$I > \sigma(I)$], final wR = 0.061. Selected bond distances (Å): B–N 1.578(8), B–CN 1.60(1). CCDC 182/1804.

10 P. Vedrenne, V. Le Guen, L. Toupet, T. Le Gall and C. Mioskowski, *J. Am. Chem. Soc.*, 1999, **121**, 1090.

11 For other recent studies on substitution at a boron atom, see: (*a*) S. Toyota and M. Oki, *Bull. Chem. Soc. Jpn.*, 1990, **63**, 1168; (*b*) S. Toyota, T. Futawaka, H. Ikeda and M. Oki, *J. Chem. Soc., Chem. Commun.*, 1995, 2499; (*c*) S. Toyota, T. Futawaka, M. Asakura, H. Ikeda and M. Oki, *Organometallics*, 1998, **17**, 4155; (*d*) T. Imamoto and H. Morishita, *J. Am. Chem. Soc.*, 2000, **122**, 6329; (*e*) E. Vedejs, S. C. Fields, S. Lin and M. R. Schrimpf, *J. Org. Chem.*, 1995, **60**, 3028; (*f*) E. Vedejs, S. C. Fields, R. Hayashi, S. R. Hitchcock, D. R. Powell and M. R. Schrimpf, *J. Am. Chem. Soc.*, 1999, **121**, 2460.