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Convenient Synthesis of Stable Aldimine–Borane Complexes, Chiral δ-Amino Alcohols, and γ-Substituted GABA Analogues from Nitriles

P. Veeraraghavan Ramachandran* and Debanjan Biswas

Herbert C. Brown Center for Borane Research, Department of Chemistry, Purdue University, 560 Oval Drive, West Lafayette, Indiana 47907-2084

chandran@purdue.edu

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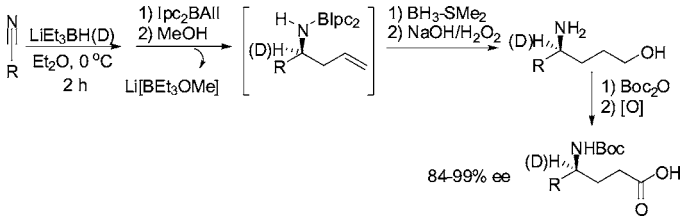
ABSTRACT



A one-pot synthesis of stable aldimine–trialkylborane adducts, the first synthesis of *C*- and *N*-deuterated imine–borane complexes, and their application for a highly enantioselective (84–99% ee) synthesis of δ-amino alcohols and γ-substituted γ-aminobutyric acids, including deuterated amino acids from nitriles, are described.

γ-Aminobutyric acid (GABA) and GABA-associated receptors play a vital role in numerous central nervous system disorders.[1] GABA analogues, such as γ-vinyl-GABA, are selective and irreversible inhibitors of GABA-transaminase.[2] Several other GABA analogues, such as gabapentin[3] and pregabalin,[4] are widely used in studies related to CNS disorders, such as anxiety, addiction, and neuropathic pain.[5] Further development of this primary class of biomolecule analogues and their isotopomers capable of crossing the blood−brain barrier is important for structure−activity relationship (SAR) and pharmacokinetic studies and therapy.[6,7]

As part of our research involving amino acid synthesis,[8] we undertook the synthesis of optically active GABA analogues. Nucleophilic addition to imine derivatives provides a simple route to amino acids.[9] Most of the frequently used azomethines are substituted with benzyl, sulfinyl, sulfonyl, trialkylsilyl, or metals on the nitrogen, necessitating their removal.[10] Itsuno and co-workers originally reported the allylboration of silylimines and, subsequently, alumino- and borylimines in low yields and variable ee.[11] We have reported high yields and ee for the asymmetric allylboration of *N*-silyl- and *N*-aluminoimines with allyldiisopinocam-

(1) (a) Lu, H. J.; Silverman, R. B. *J. Med. Chem.* **2006**, *49*, 7404. (b) Chen, G.; Kittler, J. T.; Moss, S. J.; Yan, Z. *J. Neurosc.* **2006**, *26*, 2513. (c) Farrant, M.; Nusser, Z. *Nature Rev.* **2005**, *5*, 215.

(2) (a) Dewey, S. L.; Morgan, A. E.; Ashby, C. A., Jr.; Horan, B.; Kushner, S. A.; Logan, J.; Volkow, N. D.; Fowler, J. S.; Gardner, E. L.; Brodie, J. D. *Synapse* **1998**, *30*, 119. (b) γ-Vinyl GABA is commercialized as Sabril by Aventis.

(3) Pfizer tradename for gabapentin: Neurontin.

(4) Pfizer tradename for pregabalin: Lyrica.

(5) Yogeeswari, P.; Ragavendran, J. S.; Sriram, D. *Recent Pat. CNS Drug Discovery* **2006**, *1*, 113.

(6) For a review on SAR of selective GABA uptake inhibitors, see: Hog, S.; Greenwood, J. R.; Madsen, K. B.; Larsson, O. M.; Frolund, B.; Schousboe, A.; Krogsgaard-Larsen, P.; Calusen, R. *Curr. Top. Med. Chem.* **2006**, *6*, 1861.

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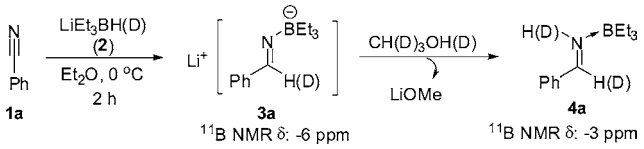
pheylborane and a proton source, such as water or methanol.[12] Herein we report a convenient, room-temperature (rt) preparation of stable aldimine−borane adducts from nitriles and their allylboration for a general synthesis of chiral γ-substituted GABA analogues. A detailed ^{11}B NMR spectroscopic study, the first synthesis of *C*- and *N*-deuterated imine−borane complexes, and a one-pot conversion of nitriles to δ-amino alcohols via these complexes are included.

To achieve a simple and general route to chiral GABA derivatives from nitriles, we sought a rt preparation of aldimine−borane adducts. Accordingly, reduction of benzonitrile (**1a**) with Super-Hydride ($LiEt_3BH$, **2**),[13] at rt, examined using ^{11}B NMR spectroscopy, revealed the quantitative formation of lithium *B*-iminotriethylborate (**3a**) (δ −6 ppm). Addition of 1 equiv of methanol converted the covalent N−B bond in **3a** to a dative bond in the aldimine−triethylborane complex (**4a**) (^{11}B NMR, δ −3 ppm), with the concurrent elimination of LiOMe. Filtration and removal of solvents provided pure **4a**, whose spectral characteristics were identical to those reported earlier[14] (Scheme 1). This

Scheme 1. One-Pot Preparation of Benzaldimine−Triethylborane Complex

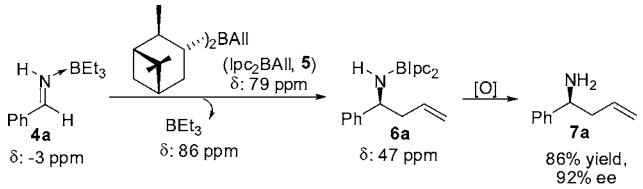


provided the new route for stable aldimine−boranes to achieve GABA analogue synthesis.

A series of aromatic aldimine−triethylborane complexes (**4a**−**e**) were readily prepared from the corresponding nitriles (**1a**−**e**) using our protocol (see the Supporting Information for ^{11}B, ^{1}H, and ^{13}C NMR spectra).

To prepare the GABA derivatives, allylboration of the imine−boranes was examined (Scheme 2). *B*-Allyldiisopinocampheylborane (**5**, ^{11}B NMR δ 79 ppm) competes with triethylborane (^{11}B NMR δ 86 ppm) on **4a** (^{11}B NMR δ −3 ppm) and eventually displaces it by converting the complex into an amine (^{11}B NMR δ 47 ppm) via the allyl transfer. The ^{11}B NMR spectrum revealed the conversion of the tetracoordinated boron to the tricoordinated species within 12 h at rt. Oxidation provided 86% yield of 1-phenyl-3-butenamine (**7a**) in 76% ee. Decreasing the reaction temperature to −78 °C increased the time to 16 h, with a corresponding increase in ee to 88%. Further lowering the temperature to −100 °C resulted in a very slow reaction.

Scheme 2. Allylboration of Benzaldimine−Triethylborane Complex with *B*-Allyldiisopinocampheylborane



Initiating the reaction at −100 °C for 6 h and warming to −78 °C over 16 h provided 92% ee for the homoallylamine, thus establishing a direct correlation between temperature and enantioselectivity for the allylboration of **4a**. We then examined *B*-allyldiiso-2-caranylborane (**8**)[15] for the allylboration of **4a** and obtained 85% ee for **7a**.[16]

The successful preparation of **7a** in high ee prompted us to investigate a one-pot allylboration of in situ generated **4a** as described in Scheme 1. A ^{11}B NMR spectroscopic study revealed the displacement of Et_3B by **5** from **4a** as the LiOMe complex (δ 1 ppm, Figure 1) (Scheme 3).

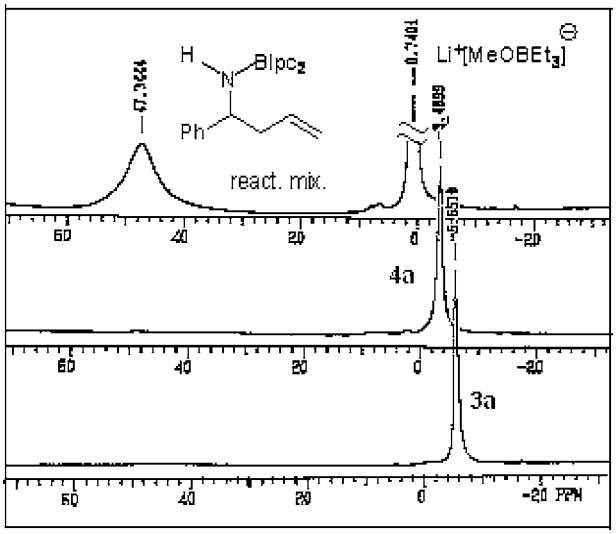


Figure 1. ^{11}B NMR spectra showing the reaction progress: reduction of benzonitrile with $LiEt_3BH$, methanolysis, and allylboration.

Comparable yield and ee was achieved for **7a**, and we extended this protocol to a series of substituted benzaldimines, including fluorobenzaldimines. The corresponding 1-phenyl-3-butenamines were obtained in 82−89% yield and 81−99% ee (Table 1). Representative imine−borane intermediates were allylborated in one pot with **8** also to show the generality of this process (entries 14−17).

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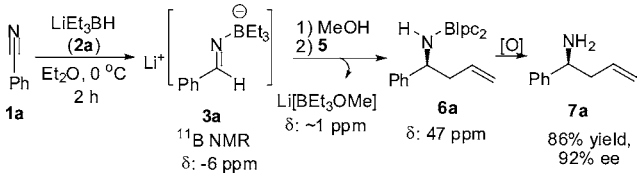
(16) Comparing this result with the 10% ee reported (ref.11c) for the allylboration of **3** with **8**, we find that there was no reaction of **3** with **5** or **8** as reported, as confirmed by ^{11}B NMR spectroscopy.

Scheme 3. One-Pot Allylboration of Aldimine−Triethylborane Complex with (−)-*B*-Allyldiisopinocampheylborane



Contrary to the reported lack of reduction of aliphatic nitriles with **2**,[13] we also achieved the reduction of representative aliphatic nitriles, cyclohexanecarbonitrile (**4f**) and isobutyronitrile (**4g**), as evidenced by the preparation of the corresponding homoallylic amines in 42% and 40% yields and 84% and 80% ee, respectively.[17] We are currently investigating procedures to improve the yields.

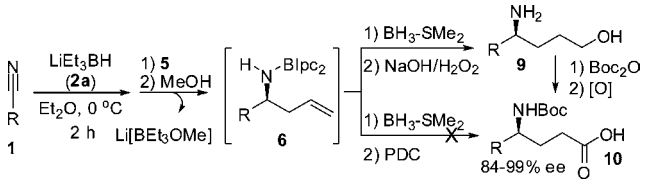
Initially, the *N*-protected γ-substituted GABA derivatives were synthesized in 72% yields from these homoallylic amines without any loss of optical activity using three steps: (i) protecting them as the BOC derivative, followed by (ii) hydroboration using dicyclohexylborane and (iii) oxidation with PDC. A successful one-pot synthesis of the δ-amino alcohols in ~75% yields was then achieved, avoiding the protection−deprotection steps, from the nitriles wherein the intermediates **6a**−**k** were hydroborated with $BH_3{\cdot}SMe_2$[18] and oxidized with alkaline H_2O_2. Attempted oxidation of the hydroboration product directly to the GABA derivatives with PDC resulted in a mixture of products. Therefore, representative examples of the BOC-protected δ-amino alcohols (**9**) were oxidized to the corresponding GABA derivatives (**10**) in 70−72% yields by utilizing PDC (Scheme 4).

Table 1. Allylboration of Aldimine−Borane Complexes

	imine−BEt_3				homoallylamine		
entry	no.	R	reagent	T, °C	no.	yield,[a] %	ee,[b] %
1	**4a**	Ph	**5**	25	**7a**	86	76
2	**4a**	Ph	**5**	−78	**7a**	80	88
3	**4a**	Ph	**5**	−100	**7a**	79	92
4	**4b**	4-Tol	**5**	−100	**7b**	86	94
5	**4c**	4-$MeOC_6H_4$	**5**	−100	**7c**	90	94
6	**4d**	4-$NO_2C_6H_4$	**5**	−78	**7d**	64	81
7	**4e**	2-Thioph	**5**	−100	**7e**	82	99
8	**4f**	Chx	**5**	−78	**7f**	42	84
9	**4g**	*i*-Bu	**5**	−78	**7g**	40	80
10	**4h**	3-FC_6H_4	**5**	−60	**7h**	63	91
11	**4i**	4-FC_6H_4	**5**	−60	**7i**	69	90
12	**4j**	2,6-$F_2C_6H_3$	**5**	−60	**7j**	57	93
13	**4k**	3,4-$F_2C_6H_3$	**5**	−60	**7k**	60	90
14	**4a**	Ph	**8**	25	**7a**	71	76
15	**4a**	Ph	**8**	−60	**7a**	62	85
16	**4b**	4-Tol	**8**	−60	**7b**	61	88
17	**4c**	4-$MeOC_6H_4$	**8**	−60	**7c**	70	84

[a] Isolated yield after chromatography. [b] Determined by ^{19}F NMR of Mosher amides.

Scheme 4. One-Pot Conversion of Benzonitriles to δ-Amino Alcohols and γ-Substituted GABA



Extending this protocol, the *C*-deuterated, *N*-deuterated, or *C*- and *N*-dideuterated benzaldimine-triethylborane complexes were prepared from benzonitrile using Super-Deuteride and CH_3OH or Super-Hydride and CD_3OD, or a combination of Super-Deuteride and CD_3OD, respectively (Scheme 1). The *C*-deuterated homoallylic amine provided the corresponding γ-deuterated γ-phenyl GABA.

In conclusion, we have achieved an efficient highly enantioselective synthesis of γ-substituted GABA derivatives via a one-pot preparation of a variety of δ-amino alcohols from nitriles using a sequential reduction with trialkylborohydrides, methanolysis, allylboration, hydroboration, and oxidation. We are further examining the applications of the imine−borane complexes in organic synthesis.

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Supporting Information Available: Experimental details and spectral data of compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) The ^{11}B NMR spectrum reveals the formation of the imine−borane complex.

(18) Hydroboration with 9-BBN and Chx_2BH gave complex mixtures.