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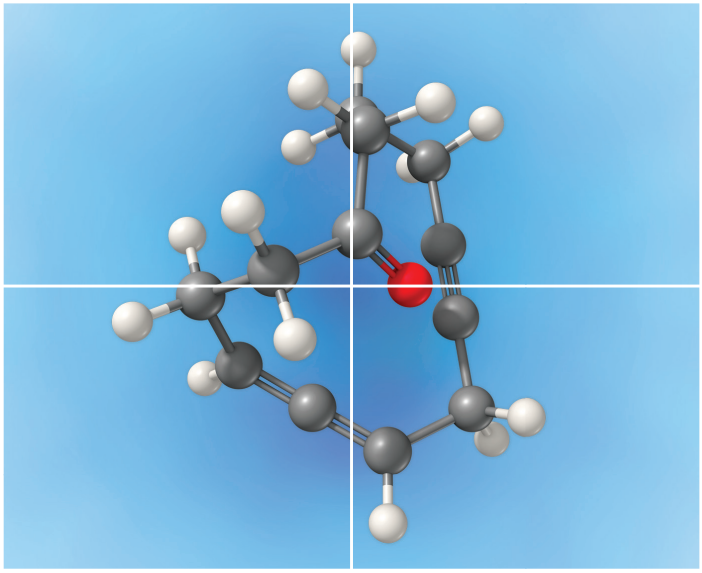

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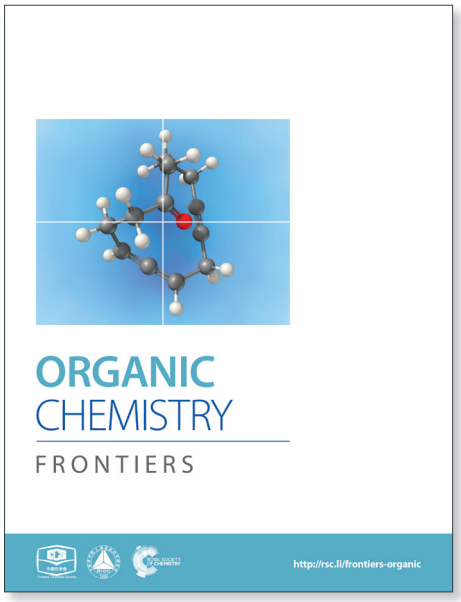

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Asymmetric Synthesis of γ-Aryl-substituted GABA Derivatives via a Highly Diastereoselective Rh-Catalyzed Boronic Acid Addition at Room Temperature

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P. Veeraraghavan Ramachandran,* Wataru Mitsuhashi and Bidyut Biswas

A highly diastereoselective Rh-catalyzed boronic acid addition to enantiopure sulfinylimine providing γ-aryl GABA derivatives has been described. The reaction proceeds in protic solvents at room temperature and the starting material is readily prepared. The novel protocol enables the introduction of a variety of aryl substituents onto an unactivated sulfinylimine under mild conditions.

"GABA (γ-aminobutyric acid) is the main inhibitory neurotransmitter in the adult mammalian central nervous system (CNS)."[1] It is critical in balancing neuronal excitation and inhibition, and has been involved in a large number of GABAergic diseases,[2] which include neurological disorders such as Huntington's and Parkinson's disease, musculoskeltal and pain disorders, addiction and drug-withdrawal syndromes, epilepsy and seizures, anesthesia, liver diseases and hepatic encephalopathy, cognition, learning and memory disorders, premenstrual and other hormonal disorders, and many other related conditions.[3] The therapeutic applications of GABA derivatives are limited by the inability of GABA to cross the blood-brain barrier, thus preventing oral administration. The preparation and pharmacological effect of many structural analogs of GABA for the treatment of CNS disorders has drawn attention of medicinal chemists (Figure 1).[4] Examples of these medicines are the β-(4-chloro)phenyl GABA analog baclofen,[5] the β-substituted GABA analog gabapentin (Neurontin®, Pfizer, NY, USA) and pregabalin (Lyrica©, Pfizer) that are effective in the treatment of neuropathic pain via a mechanism which involves binding to the $\alpha_2\delta$ subunit of voltage-gated Ca^{2+} channels.[6] Also, γ-vinyl GABA analog vigabatrin (Sabril®, Lundbeck, Copenhagen, Denmark), an effective inhibitor of GABA transaminase, is prescribed for treating epileptic seizures.[7]

GABA receptors are categorized into three major classes: $GABA_A$, $GABA_B$, and $GABA_C$. $GABA_A$ and $GABA_C$ receptors are ligand-gated ion channels, on the other hand, $GABA_B$ receptors are G protein coupled receptors. $GABA_C$ receptors differ considerably from $GABA_A$ receptors in terms of its agonist and antagonist structural profiles. Both sub-families of GABA-activated ligand-gated ion channels are targets for drug development.[8] The area of GABAergic drugs is growing rapidly in the field of medicinal chemistry and neurodegenerative diseases. Although there are several procedures for the preparation of α- and β-substituted GABA derivatives,[9] the corresponding γ-substituted derivatives have not received similar attention.

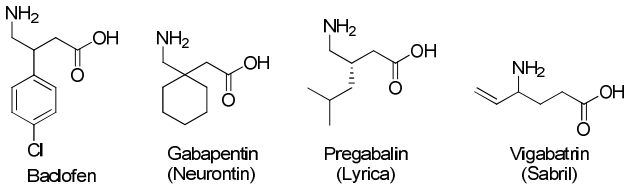
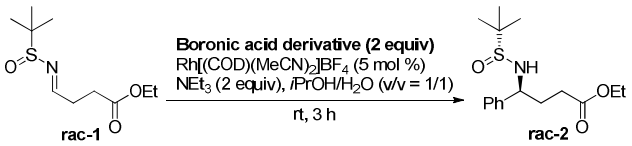


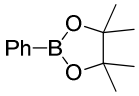
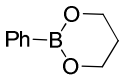
Fig. 1 GABAergic drugs.

A number of useful protocols to synthesize chiral α- and β-amino acids have been developed using a *t*-butanesulfinamide.[10] On the basis of the initial report by Miyaura and co-workers on the addition of arylboronic acids to sulfonylimine,[11] Ellman and co-workers described the first Rh-catalyzed diastereoselective aryl boronic acid addition to sulfinyl imines,[12] and further expanded the methodology for the synthesis of α-amino acids.[13] In addition to the above high temperature protocols, the first boronic acid addition to sulfinylimines at room temperature was reported by Bolshan and Batey.[14] Excellent yields have been achieved with activated sulfinylimines and boronic acids. However, the reaction with unactivated aliphatic sulfinylimines has remained a challenge. A diastereoselective synthesis of γ-substituted γ-amino acids by using a sulfinamide via the sequence of sulfinylimine formation and diastereoselective reduction has been reported recently.[15] Additionally, the syntheses of α-methylene γ-substituted γ-amino acids have been reported by Lin[16] and Yus[17] and their co-workers.

We have been interested in the synthesis of GABA derivatives, and have reported a protocol involving the asymmetric allylation of *N*-alumino- or -boryl imines, prepared from commercially available nitriles, followed by hydroboration and oxidation.[18] Considering the importance of γ-substituted γ-amino acids,[7] it is surprising that a direct synthesis has not been reported. We envisaged that the application of the above Rh-catalyzed addition of arylboronic acids to 4-sulfinylimino butanoate can lead to the preparation of γ-substituted GABA derivatives, thus providing a useful and powerful method to access this important class of compounds. The inherent lower reactivity of the aliphatic sulfinylimine was a concern. Allylation of these types of inactivated sulfinylimines is known.[19] However, to the best of our knowledge, Rh-catalyzed addition of boronic acids[14] remains a challenge. Herein we describe the successful preparation of the target molecules using the Ellman protocol.

Table 1. Optimization of boronic acid derivatives.

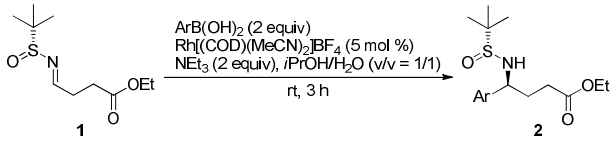


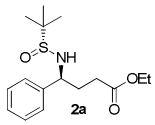
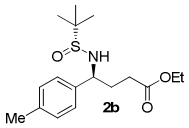
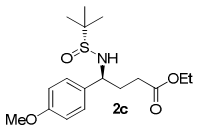
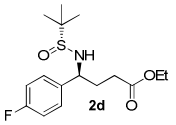
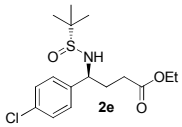
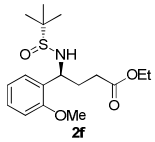
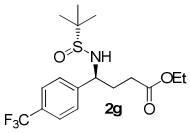
Entry	Boronic acid derivatives	Yield[a] (%)	dr[b]
1	$PhB(OH)_2$	75	97:3
2		71[c]	94:6
3		71	96.5:3.5
4	$PhBF_3K$	23[d,e]	92:8

[a]Isolated yield. [b]Determined by comparing ^{1}H NMR of diastereomers prepared according to literature.[20] [c]The yield of product (**rac-2**) was estimated by the ratio by ^{1}H NMR since it was difficult to separate from pinacol. [d]Recovered starting material was a mixture with impurities which were difficult to separate. [e]The amount of recovery is estimated by ^{1}H NMR of the crude product (**rac-1**: **rac-2** = 73:27).

We began the investigation by using racemic sulfinylimine (**rac-1**), prepared as described[21] (see ESI), as the substrate. $PhB(OH)_2$ (2 equiv) was chosen as a model reagent along with 10 mol% of $Rh[(COD)(MeCN)_2]BF_4$ and 2 equiv of Et_3N in dioxane/H_2O (v/v = 1/2) at room temperature. The reaction was monitored by TLC and provided **rac-2** in 43% isolated yield after purification. We then optimized for catalyst loading, solvent, temperature, additives, and boron source. The most common solvent for the Rh-catalyzed boronic acid addition is dioxane. However, less harmful[22] 2-propanol gave an improved yield of **rac-2**, with decreased catalyst loading (5 mol%) during the phenyl boronic acid addition to rac-**1**. Other alcoholic solvents, such as MeOH, *n*PrOH, *n*BuOH and *t*BuOH did not improve the yield further. The equivalencies of phenylboronic acid and triethylamine were also varied, but the yield did not improve further. Seeking more efficient conditions, several phenyl boronic acid derivatives were screened to optimize the reaction. As can be seen from Table 1, all of these derivatives, except the potassium trifluoroborate salt gave similar yields. However, due to its performance in diastereoselectivity and lower molecular weight, commercially available boronic acids were used for further reactions.

Table 2. Preparation of γ-aryl GABA derivatives.



Entry	Product	Yield[a] (%)	dr[b]
1		77	97.5:2.5
2		81	97:3
3		64	96:4
4		49 (63)[c]	97:3
5		43 (52)[c]	97:3
6		28 (52)[c]	97:3
7		21 (54)[c]	97:3

[a]Isolated yield. [b]Determined by comparing ^{1}H NMR (NH or benzylic H) (and ^{19}F NMR) of diastereomers prepared according to literature.[20] [c]Yield on the basis of recovered starting material.

Having standardized the condition for the preparation of **rac-2**, we attempted the reaction of phenylboronic acid with enantiopure (*R*)-isomer of the sulfinylimine (**1**). The reaction was complete as before and the product **2a** was isolated in 77% yield. The diastereomeric ratio was determined by ^{1}H NMR (and/or ^{19}F NMR) spectroscopy analysis of the NH and/or benzylic protons by comparing with epimers prepared according to the literature.[20] We were pleased to observe a diastereomeric ratio 97.5:2.5. The absolute configuration of the product (**2a**) was confirmed by the rotation of the lactamized product [(-)-(*S*)-5-phenylpyrrolidin-2-one] reported in the literature.[23] On the basis of analogy with **2a**, we believe that we have obtained the (4*S*)-isomer for all of the GABA derivatives **2b-g** described subsequently.

The generality of the Rh-catalyzed addition of aryl boronic acids to chiral sulfinylimine (**1**) was demonstrated with a series of boronic acids under the optimized condition (Table 2). Good yields were observed with electron neutral and rich aryl boronic acids (entry 1-3). Weakly deactivated 4-halogenated arylboronic acids resulted in moderate yields and the starting material was also recovered (entry 4 and 5). A sterically hindered (entry 6) and inductively deactivated boronic acid (entry 7), were less reactive and gave lower yields with the recovery of more starting material (~50% on the basis of recovered starting material). Extending the reaction time for those in entries 4-7 did not improve the yield, but rather adversely affected the dr. This was attributed to the electron-withdrawing group at the 4-position affecting the benzylic proton of the product. Overall, the diastrereoselectivities are excellent (96:4-97.5:2.5), but the yields are strongly affected by the (sterically or electronically) deactivating functional groups in boronic acids. The optimized reaction time was 3 h since longer reaction time negatively affected the diastereoselectivity. Under this condition, the byproducts which decreased the product yields were mostly the hydrolyzed imine (aldehyde and sulfinamide). We also attempted the reaction of a heteroaromatic boronic acid, 2-thiophenylboronic acid. Unfortunately, the reaction, monitored by TLC, did not proceed.

Conclusions

In conclusion, we have reported a diastereoselective synthesis of GABA derivatives via a Rh-catalyzed boronic acid addition to enantiopure *t*-butanesulfinyl imine. A variety of aryl boronic acids, including those with a sterically hindered and electron-withdrawing substituent were applicable to the methodology. The simple preparation of the chiral imine, coupled with the facile diastereoselective addition of boronic acids makes this reaction attractive for the preparation of a variety of γ-aryl γ-amino acids. Further work to improve the yields and include the addition of alkylboronic acids is in progress.

Acknowledgements

We thank the Herbert C. Brown Center for Borane Research for financial assistance and Mr. Eric Jones for some preliminary experiments.

Experimental

General. All reactions were performed at room temperature and under a nitrogen atmosphere in either flame or oven-dried glassware unless otherwise noted. All TLC analysis was performed using aluminum-backed Thin-Layer Chromatography Plates (Dynamic Absorbent Inc., 200 μm thickness, F-254 Indicator). Flash chromatography was performed using 230-400 mesh, 60Å pore diameter flash chromatography gel. All chromatography elutions were gradient in nature, eluting first with hexanes, followed by incorporating more polar solvents as appropriate. ^{1}H, ^{13}C, and ^{19}F spectra were recorded at room temperature, on Varian INOVA 300 MHz or Bruker 400 MHz. Chemical shifts (δ values) are reported in parts per million, and are referenced to tetramethylsilane. ^{19}F NMR is referenced internal to the spectrometer. Data are reported as: δ value, multiplicity, and integration, (s=singlet, d=doublet, t=triplet, q=quartet, p=pentet, h=hextet, br=broad). ^{1}H NMR (and/or ^{19}F NMR) was used as the measurement of dr by comparing the relative integration values of the benzylic or NH protons. Optical rotations were measured on an Autopol III automatic polarimeter, and are reported against the "Sodium D" line at 25 °C ($[\alpha]_D^{25}$).

General procedure for Rh-catalyzed arylboronic acids. To $ArB(OH)_2$ (0.4 mmol) and $Rh[(COD)(MeCN)_2]BF_4$ (3.8 mg, 0.01 mmol) in a 1-dram vial, **1** (0.2 mmol) in degassed *i*PrOH/H_2O (1 mL, v/v = 1:1) and triethylamine (56 μL, 0.4 mmol) at 0 °C. After stirring for 3 h at rt, the crude product was diluted with water (5 mL) and extracted with EtOAc (3×10 mL). The combined organic layers were then washed with brine (15 mL) and filtered through Na_2SO_4, and the solvent was removed under reduced pressure. The crude product was purified by column chromatography to provide the addition products **2**.

(*S*)-ethyl 4-[(*R*)-1,1-dimethylethylsulfinamido]-4-phenylbutanoate (2a).[15] 77% yield, 97.5:2.5 dr. $[\alpha]_D^{25}$ = -121 (c 0.86, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 7.38 – 7.26 (m, 5H), 4.43 (td, *J* = 6.8, 2.7 Hz, 1H), 4.09 (q, *J* = 7.1 Hz, 2H), 3.79 (d, *J* = 2.7 Hz, 1H), 2.39 – 2.07 (m, 4H), 1.23 (t, *J* = 7.1 Hz, 3H), 1.19 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 172.9, 141.0, 128.3, 127.5, 127.3, 60.5, 58.7, 55.5, 33.2, 30.7, 22.5, 14.1. Mass (ESI+): calc. for $[M+H]^+$ 312.2, found 312.2; for $[M+Na]^+$ 334.2, found 334.3.

(*S*)-ethyl 4-[(*R*)-1,1-dimethylethylsulfinamido]-4-(4-methylphenyl)butanoate (2b). 81% yield, 97:3 dr. $[\alpha]_D^{25}$ = -82.9 (c 2.43, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 7.23 – 7.04 (m, 4H), 4.37 (dt, *J* = 6.8, 2.7 Hz, 1H), 4.07 (q, *J* = 7.2 Hz, 2H), 3.75 (d, *J* = 2.7 Hz, 1H), 2.32 (s, 3H), 2.28 – 2.00 (m, 4H), 1.22 (d, *J* = 7.2 Hz, 3H), 1.17 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 172.9, 137.8, 137.2, 129.0, 127.2, 60.5, 58.3, 55.4, 33.2, 30.7, 22.5, 21.1, 14.1. Mass (ESI+): calc. for $[M+H]^+$ 326.2, found 326.1; for $[M+Na]^+$ 348.2, found 348.2.

(*S*)-ethyl 4-[(*R*)-1,1-dimethylethylsulfinamido]-4-(4-methoxyphenyl)-butanoate (2c). 64% yield, 96:4 dr. $[\alpha]_D^{25}$ = -78.6 (c 1.66, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 7.21 (d, *J* = 8.7 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 4.46 – 4.31 (m, 1H), 4.09 (q, *J* = 7.1 Hz, 2H), 3.80 (s, 3H), 3.73 (d, *J* = 2.1 Hz, 1H), 2.33 – 2.02 (m, 4H), 1.23 (t, *J* = 7.1 Hz, 3H), 1.18 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 173.2, 159.2, 133.0, 128.7, 113.9, 60.6, 58.1, 55.5, 55.2, 33.3, 30.8, 22.6, 14.2. Mass (ESI+): calc. for $[M+Na]^+$ 364.2, found 364.1; for $[M+K]^+$ 380.1, found 380.0.

(*S*)-ethyl 4-[(*R*)-1,1-dimethylethylsulfinamido]-4-(4-fluorophenyl)butanoate (2d). 49% yield (63% on the basis of recovered starting material), 97:3 dr. $[\alpha]_D^{25}$ = -82.7 (c 1.48, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 7.34 – 7.20 (m, 2H),

7.03 (m, 2H), 4.43 (m, 1H), 4.10 (q, J = 7.2 Hz, 2H), 3.81 (s, 1H), 2.40 – 2.18 (m, 2H), 2.18 – 2.00 (m, 2H), 1.24 (t, J = 7.2 Hz, 3H), 1.19 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 173.2, 162.3 (d, $J_{C\text{-}F}$ = 246.1 Hz), 137.0, 129.2 (d, $J_{C\text{-}F}$ = 8.1 Hz), 115.5 (d, J = 21.5 Hz), 60.7, 58.0, 55.6, 33.3, 30.7, 22.6, 14.2. ^{19}F NMR ($CDCl_3$) δ -115.71. Mass (ESI+): calc. for $[M+H]^+$ 330.2, found 330.1; for $[M+Na]^+$ 352.1, found 352.2; $[M+K]^+$ 368.1, found 368.1.

(*S*)-ethyl 4-[(*R*)-1,1-dimethylethylsulfinamido]-4-(4-chlorophenyl)butanoate (2e). 43% yield, (52% on the basis of recovered starting material), 97:3 dr. $[\alpha]_D^{25}$ = -82.4 (c 1.19, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 7.32 (d, J = 8.5 Hz, 2H), 7.24 (d, J = 8.5 Hz, 2H), 4.42 (td, J = 6.9, 2.5 Hz, 1H), 4.10 (q, J = 7.2 Hz, 2H), 3.85 (d, J = 2.2 Hz, 1H), 2.39 – 2.19 (m, 2H), 2.19 – 2.00 (m, 2H), 1.24 (t, J = 7.2 Hz, 3H), 1.19 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 173.1, 139.8, 133.4, 128.8, 128.7, 60.7, 58.0, 55.5, 33.0, 30.6, 22.5, 14.1. Mass (ESI+): calc. for $[M+Na]^+$ 368.1, found 368.2; $[M+K]^+$ 384.1, found 384.1.

(*S*)-ethyl 4-[(*R*)-1,1-dimethylethylsulfinamido]-4-(2-methoxyphenyl)-butanoate (2f). 28% yield, (52% on the basis of recovered starting material), 97:3 dr. $[\alpha]_D^{25}$ = -56.9 (c 0.93, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 7.31 – 7.20 (m, 2H), 7.00 – 6.76 (m, 2H), 4.73 (m, 1H), 4.10 (t, J = 7.1 Hz, 2H), 3.83 (s, 3H), 2.50 – 2.02 (m, 4H), 1.23 (t, J = 7.1 Hz, 3H), 1.17 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 173.3, 156.6, 129.5, 128.3, 127.8, 120.3, 110.5, 60.4, 55.6, 55.2, 55.1, 31.8, 31.0, 22.5, 14.2. Mass (ESI+): calc. for $[M+Na]^+$ 364.2, found 364.3; $[M+K]^+$ 380.1, found 380.1.

(*S*)-ethyl 4-[(*R*)-1,1-dimethylethylsulfinamido]-4-(4-trifluoromethylphenyl)butanoate (2g). 21% yield, (54% on the basis of recovered starting material), 97:3 dr. $[\alpha]_D^{25}$ = -74.2 (c 0.75, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 7.61 (d, J = 8.1 Hz, 2H), 7.44 (d, J = 8.1 Hz, 2H), 4.52 (td, J = 6.8, 2.6 Hz, 1H), 4.11 (q, J = 7.2 Hz, 2H), 4.05 – 3.92 (m, 1H), 2.45 – 2.23 (m, 2H), 2.13 (m, 2H), 1.24 (t, J = 7.2 Hz, 3H), 1.21 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 173.2, 145.7, 130.1 (q, J = 32.7 Hz), 127.9, 125.6 (d, J = 3.5 Hz), 122.7, 60.9, 58.4, 55.8, 33.1, 30.7, 22.6, 14.2. ^{19}F NMR ($CDCl_3$) δ -64. Mass (ESI+): calc. for $[M]^+$ 381.2, found 381.0; $[M+Na]^+$ 402.1, found 402.3.

Notes and references

[a] *Herbert C. Brown Center for Borane Research, Department of Chemistry, Purdue University, 560 Oval Dr. West Lafayette, IN 47907, USA. Fax: +1 765 494 5303; Tel: +1 765 494 0239; E-mail: chandran@purdue.edu*

† Electronic Supplementary Information (ESI) available: Synthesis of **1** and additional experimental details, ^{1}H and ^{13}C NMR spectra of all products, and ^{19}F NMR spectra of **2d** and **2g** are included. See DOI: 10.1039/c000000x/

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