

### **Alkoxyamine-cyanoborane adducts: efficient cyanoborane transfer agents†**

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We report the synthesis of the hitherto unknown zwitterionic alkoxyamino cyanoboranes by reduction of O-alkyloximes with sodium cyanoborohydride; unprecedented cyanoboronated N-alkoxyformamidines were also isolated as by-products. Boronated alkoxyamines were found to be efficient cyanoborane transfer agents towards more basic amines , including aminosugars; they were also successfully transformed into neoglycoconjugates by the neoglycorandomization reaction with reducing sugars .

Much effort has been devoted to the preparation of organoboron compounds ; such derivatives exhibit unique structural and chemical profiles which make them valuable intermediates and catalysts in organic synthesis,<sup>1</sup> including asymmetric processes. Boron-containing compounds are widely used in hydroborations ,<sup>2</sup> reductions ,<sup>3</sup> cross-coupling reactions (e.g. Suzuki–Miyaura reaction),<sup>4</sup> or cycloadditions ,<sup>5</sup> among others.

Organoboron derivatives are also of great interest from a biological and pharmacological point of view.<sup>6</sup> In this context,  $\alpha$ -aminoboronic acids, considered as isoelectronic analogues of amino acids , have been reported as inhibitors of proteases;<sup>7</sup> aminocarboxyboranes, and their precursors amine -cyanoboranes<sup>8</sup> have shown antifungal, antibacterial, antiarthritic, and antiinflammatory properties.<sup>9</sup> Some cyanoboronated nucleosides have been reported to act as potent antitumor agents in mammalian cell lines, and to possess antiinflammatory and hypolipidemic activities.<sup>10</sup>

Furthermore, numerous organoboron derivatives have been assayed in imaging studies<sup>11</sup> and radiotherapy, as boron carriers to tumor cells for the boron neutron capture therapy (BNCT),<sup>12</sup> which has been demonstrated to be a successful treatment against some tumoral malignancies, with efficiency comparable to conventional radiotherapy. Therefore, new effective methods to prepare boron-containing amino derivatives are of relevance in synthetic, bioinorganic, and pharmaceutical chemistry.

Herein we report the synthesis of the first examples of N-alkoxyamine-cyanoboranes by an experimentally-simple procedure and their use as cyanoborane transfer agents towards aliphatic amines .

O-Alkyloximes 1 and 2 were prepared by condensation of chloroacetaldehyde diethylacetal with N-alkyl(methyl, benzyl)oxyamine hydrochlorides in water medium (Scheme 1). For the oxime 3, the N-benzyloxamine hydrochloride was previously transformed into the N-benzyloxamine sulfate in order to avoid mixtures of 2 and 3, in situ produced by nucleophilic displacement of Br by chloride when reacting bromoacetaldehyde diethylacetal with N-benzyloxamine hydrochloride. The liquid oximes 1–3 were obtained in high yields (81, 84, 74%, respectively) as mixtures of the E/Z isomers in roughly 2[thin space (1/6-em)]:[thin space (1/6-em)]1 ratios, as deduced from the NMR spectra .

We have accomplished the reduction of O-alkyl oximes 1–3 with sodium cyanoborohydride in glacial acetic acid, conditions commonly used for reducing oximes . Surprisingly, the expected N-alkyloxy-N-(2-haloethyl)amines 4 and 5 were obtained as minor compounds after chromatographic purification (the volatile methoxy derivative was not isolated). The hitherto unknown zwitterionic N-cyanoboronated-N-alkoxyamines 6–8 were isolated as the major compounds (29–62%), obtained as crystalline derivatives stable to air and silica purification . To our knowledge, no boronated derivatives have been previously reported in the reduction of O-alkyloximes with boron-containing reducing agents.

Boronated derivatives 6–8 were characterized by NMR spectroscopy , including <sup>11</sup>B-NMR , MS, and single crystal X-ray crystallography ‡ (Fig. 1 depicts ORTEP drawing of 6 showing thermal ellipsoids at the 50% probability level). <sup>1</sup>H-NMR spectra of compounds 6–8 showed a broad signal located at roughly 2 ppm, and associated to the BH<sub>2</sub>CN protons ; furthermore, the benzylic protons of 7 and 8 appeared as diastereotopic signals, due to the chiral nitrogen . <sup>11</sup>B-NMR spectra of 7 exhibited a broad triplet at –21 ppm, with a coupling constant of 90 Hz, which agrees with the proposed structure. X-Ray diffraction structures of 6–8 confirmed that they crystallize as racemic compounds.

Remarkably, cyanoboronated N-benzyloxy-N-(2-haloethyl)formamidines 9 and 10 were also isolated in modest yields (8% and 6%, respectively) upon reduction of 2 and 3 (Scheme 1). The high coupling constants between the protons of the amidino group (16.2 and 15.9 Hz, respectively) indicate a trans arrangement of such protons . No previous reports on cyanoboronated amidines can be found in the literature.

We postulate that the formation of formamidine derivatives can take place by reaction of the cyanoborohydride anion with cyanoborane (Scheme 2) to afford adduct 13; further reaction

with acetic acid can lead to the intermediate 16, which can be trapped by N-alkoxyamines 4 and 5 to furnish formamidines 9 and 10.

The presence of a haloalkyl moiety in compounds 6–8 makes them suitable for being transformed into a variety of derivatives; compound 7 was subjected to nucleophilic displacement of the chlorine atom with sodium azide in DMF to give a separable mixture of cyanoboronated derivative 12 (53%) and benzyloxyamine 11 (22%), obtained by a partial deboronation reaction.

We have also explored the ability of cyanoboronated N-alkoxyamines to behave as new boron transfer agents towards amines ; for that purpose we chose as model compounds cyanoboronated benzyloxyamines 7 and 8, which were subjected to reaction with benzylamine and tetra-O-acetyl- $\beta$ -D-glucosamine under mild conditions to give 18 and 19 in a 57–93% yield (Scheme 3). Alkoxyamine cyanoborane 7 was regenerated (63% yield) by treatment of 4 with sodium cyanoborohydride in acetic acid. The number of aminoboranes derived from carbohydrates is scarce, limited to oxazaborolidine<sup>13</sup> and cyanoborane-nucleoside adducts.<sup>10</sup>

These results suggest that cyanoboronated N-alkoxyamines act as effective cyanoborane transfer agents probably due to the lower basicity of alkoxyamines compared to amines . The reaction can be performed at rt, in contrast with reported procedures involving the use of other transfer agents in refluxing diethyl ether or dimethoxyethane.<sup>14</sup>

We have also accomplished the preparation of neoglycoconjugates 20–25 from cyanoboronated N-benzyloxyamines 7, 8 and 12 by an N-glycosylation reaction with D-glucose, D-xylose and D-galactose in methanolic acetic acid (Scheme 4). The distribution of isomeric N-glycosides was found to be dependent on the nature of the carbohydrate .

Such a chemoselective reaction, originally developed by Peri and co-workers<sup>15</sup> and currently known as neoglycorandomization,<sup>16</sup> is a very robust glycosylation methodology which involves treatment of an alkoxyamine with a non-activated reducing sugar . We have simplified the original conditions used by Peri, by replacing DMF and the acetic/acetate buffer by greener MeOH and catalytic amounts of glacial acetic acid to furnish the corresponding  $\beta$ -glycopyranosides 20–23 in a totally stereoselective fashion in short reaction times and from good to almost quantitative yields (55–94%), starting from D-glucose or D-xylose and cyanoboronated N-alkoxyamines 7, 8 and 12 (Scheme 4).

Similarly, by coupling D-galactose with 7, a separable mixture of  $\beta$ -D-galactopyranoside 24 (52%) and  $\beta$ -D-galactofuranoside 25 (9%) was obtained (Scheme 4); remarkably, no equilibration was observed in solution.

The syntheses of N-glycosides 20–25 constitute the first examples of cyanoboronated N-alkoxyamines being transformed into N-glycosides via the neoglycorandomization reaction; the outcome of the reaction proved to be compatible with alkoxyamines bearing a cyanoborane moiety and a variety of functional groups such as halides and azido .

The same kind of reaction was assayed on non-boronated alkoxyamine 4 (Scheme 4), obtained either by reduction of 2, as indicated in Scheme 1, or by removal of the cyanoborane moiety of 7 by refluxing in aqueous THF. For D-mannose, a non-separable mixture of  $\alpha$ - and  $\beta$ -D-

mannopyranosides 26, 27 and  $\alpha$ -D-mannofuranoside 28 were obtained in a 2:1 ratio and in a 76% yield after chromatographic purification. The same ratio was obtained starting from alkoxyamine cyanoborane 7.

We have also extended the previous reactions to carbohydrate-derived alkoxyamines. In this context, reaction of partially-protected xylo-configured aldehyde 29 with BnONH<sub>2</sub>·HCl afforded the corresponding oxime 30 (Scheme 5) as a stereoisomeric E/Z mixture (87% yield). NaBH<sub>3</sub>CN-mediated reduction of 30 using the same conditions as indicated in Scheme 1 furnished a separable mixture of alkoxyamine 31 and alkoxyamine cyanoborane 32 (5:1 diastereoisomeric ratio) in almost quantitative overall yield (68% and 22%, respectively). No formamide was detected.

Coupling of 31 with reducing sugars (D-glucose, D-xylose and D-galactose) under glycosylation conditions led to the corresponding  $\beta$ -D-glycopyranosyl pseudodisaccharides 33–35 (85–90%) in a totally stereoselective fashion. Remarkably for 35, no furanosyl glycoside was detected, unlike the previous reaction of 7 with D-galactose, which indicates that stereoselectivity of the glycosylation reaction is strongly dependent on the aglycone nature.

In conclusion, we have developed a novel procedure for the preparation of the hitherto unknown cyanoboronated N-alkoxyamines by reduction of O-alkyloximes with sodium cyanoborohydride in acetic acid. Title compounds were efficiently used as cyanoborane transfer agents towards aliphatic amines, including aminosugars under mild conditions. The novel and efficient preparation of N-glycosides from cyanoboronated N-alkoxyamines under glycorandomization conditions is also reported.

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## Footnotes

† Electronic supplementary information (ESI) available: Experimental details, NMR spectra , X-ray structures showing unit cells of compounds 6–8. CCDC 816969–816971. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c1cc11345c

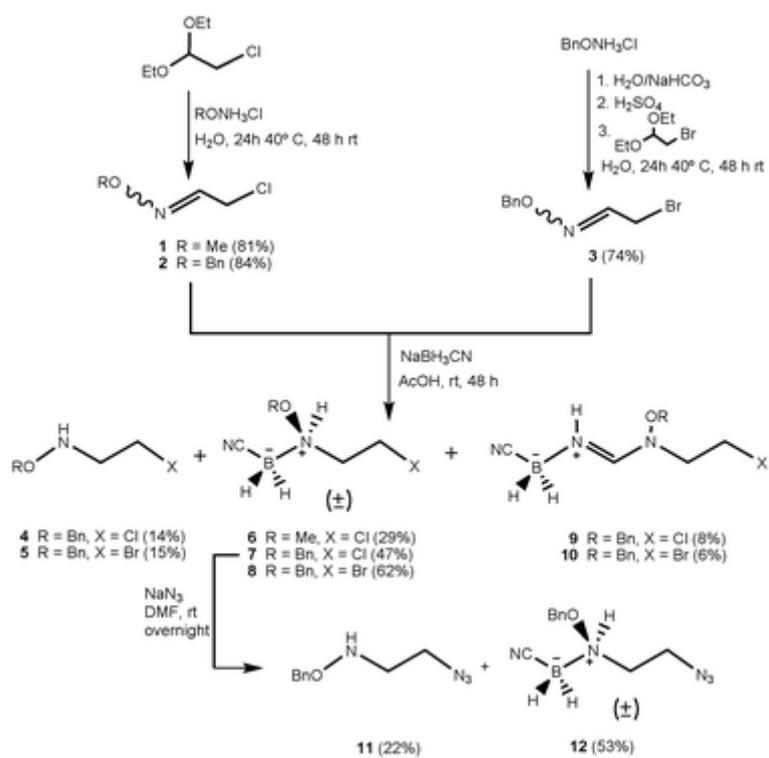
‡ Crystal data for 6: C<sub>4</sub>H<sub>10</sub>BClN<sub>2</sub>O, M = 148.40, triclinic, a = 6.2785(6) Å, b = 6.5034(6) Å, c = 9.6048(9) Å, α = 83.088(3)°, β = 87.368(4)°, γ = 78.440(3)°, V = 381.34(6) Å<sup>3</sup>, T = 173(2) K, space group P[1 with combining macron], Z = 2, μ(MoKα) = 0.424 mm<sup>-1</sup>, 6575 reflections measured, 2301 independent reflections (R<sub>int</sub> = 0.0335). The final R<sub>1</sub> values were 0.0405 (I > 2σ(I)). The final wR(F<sub>2</sub>) values were 0.0956 (I > 2σ(I)). The final R<sub>1</sub> values were 0.0566 (all data). The final wR(F<sub>2</sub>) values were 0.1140 (all data). The goodness of fit on F<sub>2</sub> was 1.095. Crystal data for 7: C<sub>10</sub>H<sub>14</sub>BClN<sub>2</sub>O, M = 224.49, monoclinic, a = 9.5051(4) Å, b = 12.3772(5) Å, c = 9.9685(4) Å, α = 90.00°, β = 92.1500(10)°, γ = 90.00°, V = 1171.93(8) Å<sup>3</sup>, T = 173(2) K, space group P2(1)/c, Z = 4, μ(MoKα) = 0.300 mm<sup>-1</sup>, 33074 reflections measured, 3579 independent reflections (R<sub>int</sub> = 0.0320). The final R<sub>1</sub> values were 0.0317 (I > 2σ(I)). The final wR(F<sub>2</sub>) values were 0.0851 (I > 2σ(I)). The final R<sub>1</sub> values were 0.0412 (all data). The final wR(F<sub>2</sub>) values were 0.0893 (all data). The goodness of fit on F<sub>2</sub> was 1.047. Crystal data for 8: C<sub>10</sub>H<sub>14</sub>BBrN<sub>2</sub>O, M = 268.95, monoclinic, a = 9.6308(3) Å, b = 12.4411(4) Å, c = 9.9555(4) Å, α = 90.00°, β = 92.716(2)°, γ = 90.00°, V = 1191.51(7) Å<sup>3</sup>, T = 173(2) K, space group P2(1)/c, Z = 4, μ(MoKα) = 3.425 mm<sup>-1</sup>, 15111 reflections measured, 3094 independent reflections (R<sub>int</sub> = 0.0399). The final R<sub>1</sub> values were 0.0369 (I > 2σ(I)). The final wR(F<sub>2</sub>) values were 0.0736 (I > 2σ(I)). The final R<sub>1</sub> values were 0.0632 (all data). The final wR(F<sub>2</sub>) values were 0.0829 (all data). The goodness of fit on F<sub>2</sub> was 1.025.

**Figure captions**

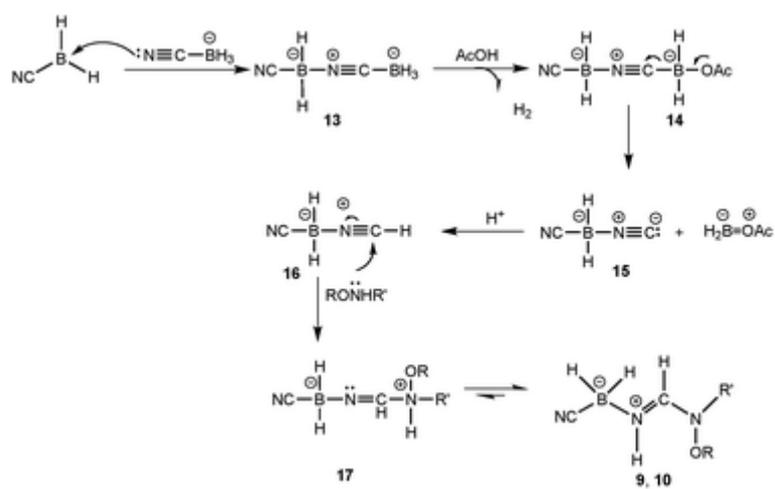
**Figure 1.** ORTEP drawing of 6.



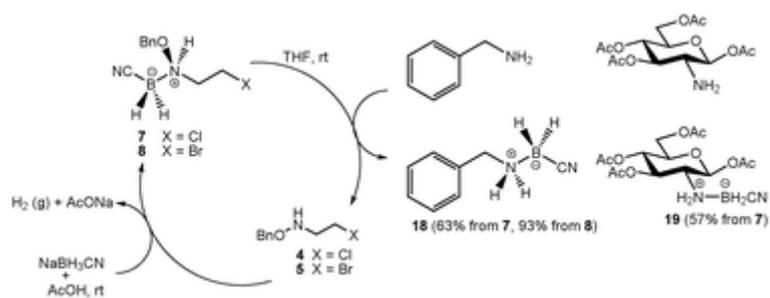
Scheme 1



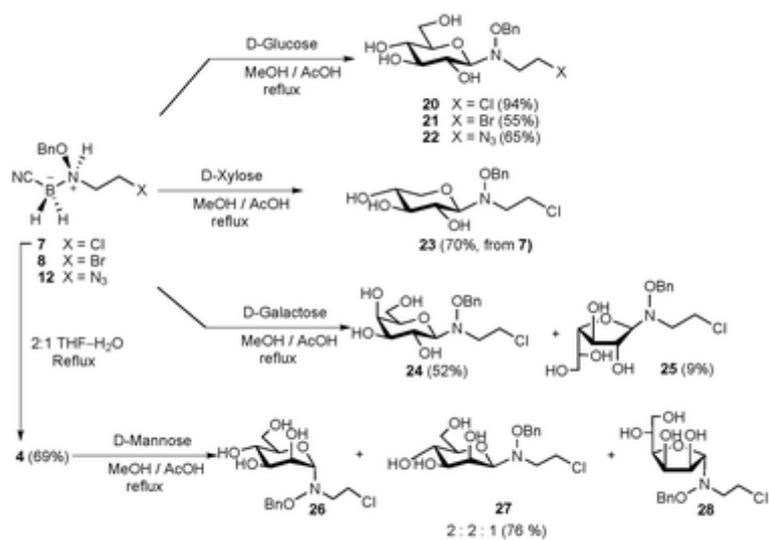
Scheme 2



### Scheme 3



Scheme 4



## Scheme 5

