Arylboronic Acids Catalyzed Upgrade of Glucosamines for Deoxyfructosazine and Insights on Reaction Mechanism

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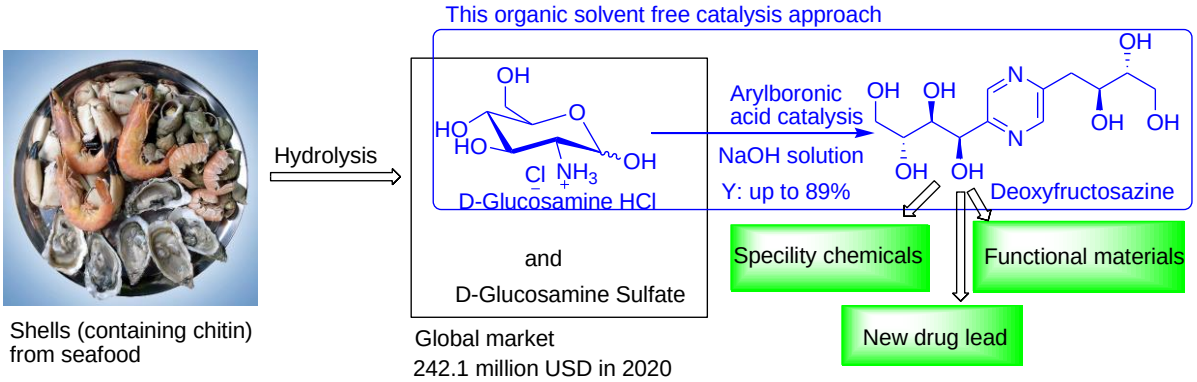
Abstract

Chitin is the most abundant N-containing polysaccharides in nature and D-glucosamine is one of most successful commercial monomer products in current market. Here we reported an arylboronic acids catalyzed upgrade of glucosamines in aqueous solution for deoxyfructosazine which is an important high-value compound in pharmaceutical and food industries, as well as a promising bio-based platform molecule for speciality chemicals and sustainable functional materials. Such direct integration of deoxyfructosazine into development of renewable chemicals/functional materials might be a practical way for utilization of chitin as a renewable nitrogen source. A mechanism focusing on catalytic cycle of arylboronic acid via a boron transfer was also proposed.

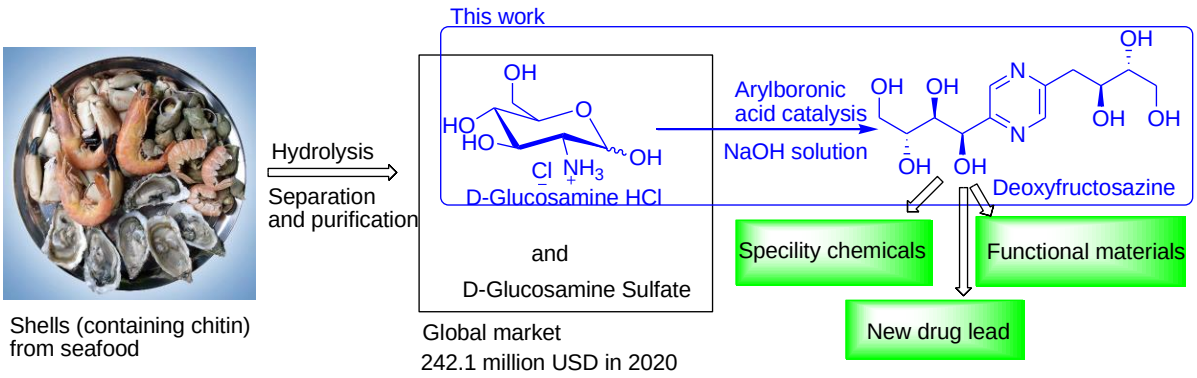


Introduction

Chitin is the second most abundant biopolymer in nature following cellulose, and the most abundant N-containing polysaccharide excluding proteins. Because only a few natural amines are available and their importance as key intermediates in chemical industry, chitin is promising to be the largest renewable amine source in the future, contributing to decarbonization for sustainability.[1,2] However, utilization of chitin or its deacetylation product chitosan is rather limited mainly because high purity of chitin is not accessible economically with current purification methods; in addition, structures of chitin are also not same from different sources, which led to more difficulty in followed modifications for derivatives.[3,4,5] Such recalcitrant structure usually led to complex products in direct conversion of chitin into chemicals, and not surprisingly its hydrolysed monomer N-acetyl-D-glucosamine (NAG) was frequently used for preparation of bio-based chemicals such as 3-acetamidofuran, 3-acetamido-

5-acetylfuran (3A5AF), acetamidoacetaldehyde, pyridine and so on.[6] Very recently bio-based cyclic and short-chained aliphatic amines were also produced from NAG by selectively removing the oxygenated group over Ru/C, and an acid co-catalyst H_3PO_4 is proved to be vital for retaining the amino group in NAG by protonation.[7] Although significant progress was achieved in reported literatures, new catalytic systems to synthesize high-value-added N-containing chemicals from NAG or deacetylated monomer D-glucosamine (HCl salt or sulfate salt) are still highly desired for better nitrogen cycle. Here we reported an arylboronic acids catalyzed dimerization of glucosamine forming deoxyfructosazine (**Scheme 1**); the reaction could be completed in a few hours and yield of sole product was excellent. Deoxyfructosazine is widely used in food industry and also showed therapeutic potential in treatments of diabetes[8] and immunological diseases[9] as well as DNA strand breakage activity[10]; its unique structure containing pyrazine moiety[11] and multiple hydroxyls[12] make it very promising platform molecule for speciality chemicals and new smart materials.

Scheme 1. A "drop-in" upgrade of D-glucosamine with arylboronic acid catalysis on current utilization of chitin.



A good conversion of D-glucosamine hydrochloride to deoxyfructosazine in the presence of excess amount (2.5 to 5 equivalents) of phenylboronic acid and excess amount of NaOH in water was initially reported by J. A. Peters *et.al*[13], which was a cleaner transformation and a significant progress based on pioneer works in alkali hydroxide solution only[10] or pyridine solution only[14]. Further optimization on this conversion with phenylboronic acid as a promoter[15] or boric acid as an additive with 1-ethyl-3-methylimidazolium acetate ($[C_2C_1Im][OAc]$) as a catalyst[16] or in deep eutectic solvents[17] was also reported, however yield of deoxyfructosazine was generally low to moderate although more clues were achieved in mechanism investigation[16,17]. In these literatures (**Scheme 1**), excess amount of phenylboronic acid or boric acid is still a must for achieving a good yield of deoxyfructosazine. It was generally proposed that phenylboronic acid or boric acid masked diols on glucosamine and then subsequent dimerization reaction occurred.

Arylboronic acids as organocatalysts were widely used in various organic transformations[18-20] for pharmaceutical intermediates, forming reversible covalent bond with hydroxyl groups of carboxylic acids or alcohols. However, their application as catalysts in selective transformations for glycosides was less explored and very few progress was reported. D. Takahashi and K. Toshima found aromatic boronic acids could catalyze glycosylation of both protected[21] and unproctected[22] sugar acceptors with epoxide ring in a regioselective manner via S_Ni-type mechanism in the presence of water. Site-selective sulfonation unprotected

monosaccharides catalyzed by chiral benzazaborole in MeCN[23] and site-selective acylation catalyzed by Shimada's boronic acid catalyst in dioxane[24] were also reported very recently. Encouraged by this progress and our previous knowledge[25] on arylboronic acid catalyzed amide formation from carboxylic acids and amines, we envisaged that arylboronic acids might be possible to act as a catalyst instead of a reagent in upgrade of glucosamines for deoxyfructosazine under a suitable condition.

Experimental Section

1. General procedure and yield calculation

1.1 General procedure for Table 1.

D-Glucosamine hydrogen chloride (107.8 mg, 0.50 mmol) and $PhB(OH)_2$ (24.4 mg, 0.20 mmol) were added into different volumes of aqueous NaOH (0.1N) solution; the reaction mixture was stirred for 36 hrs at room temperature. Then the reaction mixture was acidified (pH value = 1-3) by dropwise addition of 2N HCl aqueous solution, and subsequently the mixture was stirred for another 30 mins. After then, 1 mL of the reaction mixture was taken out to another flask mixing with ethanol for fast evaporation under reduced pressure at 33℃. Further drying in *vaccum* gave a crude product for ^{1}H NMR to determine a yield (In most samples, ethanol was difficult to be fully removed due to strong hydrogen bonding with DOF, however, its existence didn't affect yield calculation; see Ref 26).

1.2 General procedure for Table 2.

D-Glucosamine hydrogen chloride (107.8 mg, 0.50 mmol) and $ArB(OH)_2$ (0.20 mmol) were added into aqueous NaOH (0.1N, 6.5 mL) solution and the reaction mixture was stirred for 36 hrs at room temperature; then the reaction mixture was acidified (pH value = 1-3) by dropwise addition of 2N HCl aqueous solution, and subsequently the mixture was stirred for another 30 mins. After then, 1 mL of the reaction mixture was taken out to another flask mixing with ethanol for fast evaporation under reduced pressure at 33℃. Further drying in *vaccum* gave a crude product for ^{1}H NMR to determine a yield.

1.3 Procedure for Table 3.

D-Glucosamine hydrogen chloride (107.8 mg, 0.50 mmol) and $ArB(OH)_2$ (24.4 mg, 0.20 mmol) were added into NaOH (0.1N, 6.5 mL) aqueous solution and the reaction mixture was stirred for 6 hrs or 12 hrs at 40℃ or 60℃. Then the reaction mixture was acidified (pH value = 1-3) by dropwise addition of 2N HCl aqueous solution, and subsequently the mixture was stirred for another 30 mins. After then, 1 mL of the reaction mixture was taken out to another flask mixing with ethanol for fast evaporation under reduced pressure at 33℃. Further drying in *vaccum* gave a crude product for ^{1}H NMR to determine a yield.

1.4 Method to determine yields based on ^{1}H NMR for all tables.

Integration of unique peak of DOF product at δ 5.20 and integration of unique peak of D-glucosamine at δ 3.50 (similar protons of both alpha-form and beta-form are at the same position) were used to determine yield because both of the peaks were clearly or mostly separated from neighbour peaks (very small overlapped area in some entries). An analysis of sample spectra see supporting information.

1.5 Procedure for quantitative ^{1}H NMR analysis for entries 7 and 8 in Table 3.

D-Glucosamine hydrogen chloride (107.8 mg, 0.50 mmol) and $PhB(OH)_2$ or 3-$NH_2C_6H_4B(OH)_2$ (0.20 mmol) were added into a solution of NaOH (0.1N, 6.5 mL), the mixture was stirred for 6 hours at 60℃. Then the reaction mixture was acidified (pH value = 1-3) by dropwise addition of 2N HCl, and subsequently the mixture was stirred for another 30 mins. After acidification respectively, the reaction mixture was mixed with ethanol and was evaporated to dryness under reduced pressure at 33℃. Removal of residual solvent in *vaccum* gave a crude product. Their weights were 166.3 mg and 158.4 mg, respectively. The yield of DOF was quantitatively analysed by ^{1}H NMR using pyrazine as an internal standard substance: the crude product was mixed with pyrazine (0.05mmol), and D_2O (1 mL), after mixing thoroughly, partial mixture was transferred to an NMR tube for ^{1}H NMR measurement.

IntDOF: Integration of unique peak of DOF product at δ 5.20 (1H);

IntPy: integration of pyrazine peak at δ 8.60 (4H);

Mol of DOF (2 × D-Glucosamine) = (IntDOF/IntPy) × 4 × 0.05 mmol;

DOF yield regarding on D-Glucosamine hydrogen chloride was calculated as:

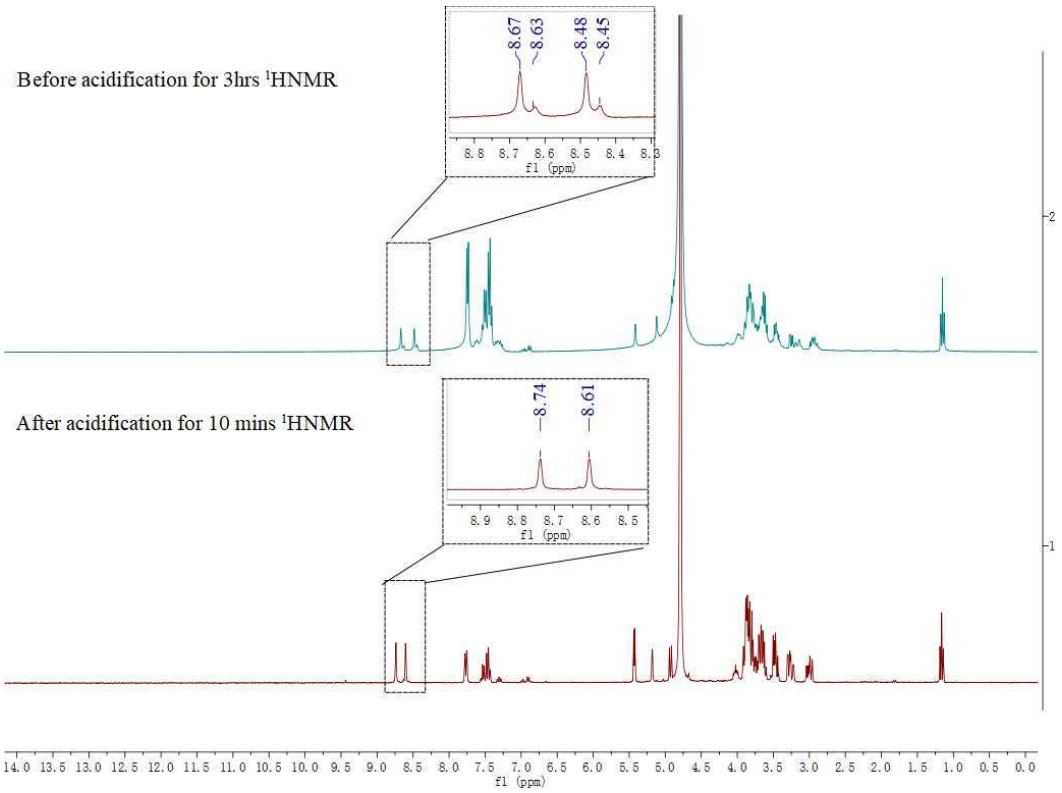
$$\text{Yield}=2\times\frac{(\text{IntDOF/IntPy})\times 4\times 0.05\ \text{mmol}}{0.5\ \text{mmol}}\times 100\%$$

(Integrated ^{1}H NMR Spectra sees supporting information).

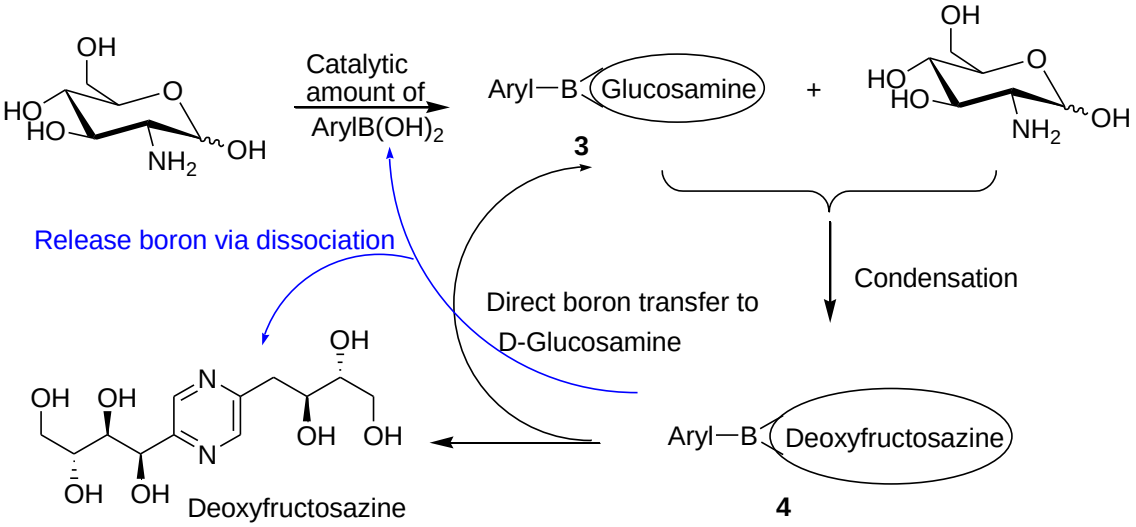
Results and discussion

Because arylboronic acids can be handled in air without special precautions and mostly are chemically stable for long periods of time, we revisited an experiment in literature[13] with phenylboronic acid as a sole promoter (Glucosamine hydrogen chloride to phenylboronic acid = 1:1), and surprisingly both free deoxyfructosazine and its boronic acid ester form were both observed in crude ^{1}H NMR (**Figure 1**)[26]. From the spectra, clear two more small peaks (δ = 8.63, 8.45) appeared near to two big peaks (δ = 8.67, 8.48), and likely they represented two types of pyrazine moieties; after acidification (HCl solution), two small peaks disappeared along with some peaks in aromatic range indicated that the two small peaks likely belong to phenylboronic acid protected deoxyfructosazine. And most of deoxyfructosazine (DOF) were actually in free form under our revisited condition. Encouraged by this finding, we envisaged that a catalytic cycle might be realized if boronic acid could transfer from protected deoxyfructosazine to a free glucosamine directly or be released to be a free acid via a dissociation as proposed in **Scheme 2** by tuning reaction conditions. Arylboronic acid might react with one molecular of D-glucosamine forming ester intermediate **3**, then activated ester intermediate **3** further cyclized themselves or with another one molecular of D-glucosamine forming boronic acid protected DOF **4**. Subsequently a boron transfer might occur between product **4** and D-glucosamine regenerating ester intermediate **3** for next catalytic cycle or release free arylboronic acid. After all or most of D-glucosamines are consumed, a mixture of protected product **4** and free deoxyfructosazine will be achieved at the end.

Figure 1. Crude ^{1}H NMR spectra for revisited reaction (phenylboronic acid to glucosamine hydrochloride is 1:1).



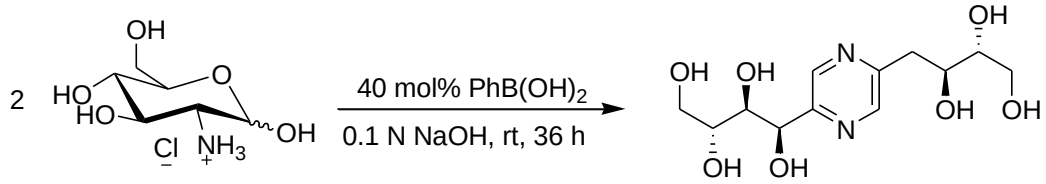
Scheme 2. Proposed catalytic cycle via boron transfer.



Based on this hypothesis, we initially investigated effect of base on deoxyfructosazine formation with 40 mol% phenylboronic acid as a catalyst in different volume of 0.1 N NaOH solution for 36 hrs at room temperature. Because at least 1 equiv. base was necessary in order to neutralize hydrogen chloride within the starting material D-glucosamine hydrogen chloride, we selected a range of 1.0 to 1.5 equiv. of NaOH (equivalent to D-glucosamine hydrogen chloride) for the parallel study (**Table 1**). The increase of base till 1.3 equiv. led to increase on deoxyfructosazine yield (Entries 1 - 4, **Table 1**). Yield of deoxyfructosazine decreased slightly with an increase of base use over 1.3 equiv. (Entries 4 - 6, **Table 1**) and obvious amount of byproduct fructosazine appeared, probably because of the presence of more base accelerated further oxidization of deoxyfructosazine to fructosazine. The best yield (68%) of

deoxyfructosazine was achieved in the presence of 1.3 equiv. NaOH (Entry 4, **Table 1**) although the difference was not significant within the range (1.1 to 1.5). The yield was much over 40% (Usage of phenylboronic acid), which indicated the catalytic cycle indeed occurred as expected.

Table 1. Investigation on Base Effect.



D-Glucosamine hydrogen chloride

Deoxyfructosazine

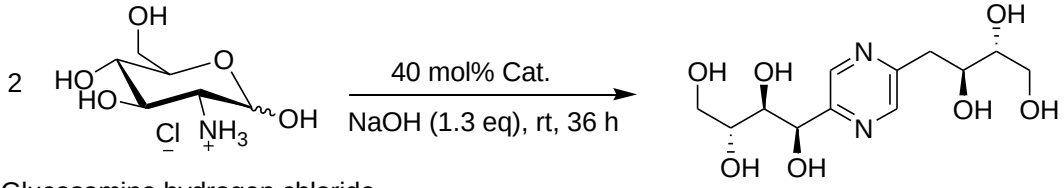
Entry	NaOH(equiv.)	Yield[%][a]
1	1.0	56
2	1.1	64
3	1.2	65
4	1.3	68
5	1.4	59
6	1.5	60

[a] Determined by crude ^{1}H NMR.

Next in the presence of 1.3 equiv. NaOH (0.1 N) aqueous solution, we screened a few arylboronic acids commercially available in order to investigate effect of functional groups on aromatic moiety (**Table 2**). In the absence of any boronic acid, the reaction gave no desired product deoxyfructosazine and only small amount of fructosazine was observed (Entry 1, **Table 2**), which proved the catalysis role of arylboronic acid. Electron-donating groups of OMe and O^{i}Pr on arylboronic acids led to an obvious drop on reaction yield (Entries 2 - 4, **Table 2**). Electron-deficient groups of CF_3 on 2-position and penta-fluoridation also had negative effect on catalytic efficiency (Entries 5 and 7, **Table 2**). Meanwhile comparable yield was observed surprisingly when 3,5-di(trifluoromethyl)arylboronic acid or 2-fluoroarylboronic acid was employed as a catalyst (Entries 6 and 8, **Table 2**). It was concluded that inductive electronic effect had influence on reaction yield, but definitely was not the only dominated factor. A favoured fluoride bonding (H-F bonding, F-B bonding) also likely played an important role. Subsequently some arylboronic acids with interactive groups on aromatic moiety were also evaluated (Entries 9 - 12, **Table 2**) in order to investigate potential hydrogen bonding assistant effect. The existence of carboxylic acid group on 3-position or hydroxyl group on 4-position both slowed down the self-condensation reaction rate and lower yields of deoxyfructosazine were observed (Entries 9 and 10, **Table 2**). To our delight, amino group on 3-position did benefit the conversion and 76% yield of deoxyfructosazine was obtained with which as a catalyst under the same conditions (Entry 11, **Table 2**); pyridyl boronic acid delivered a similar

good catalytic efficiency (Y: 78%) (Entry 12, **Table 2**) although the mechanism in detail on how pyridyl group and amino group assist the self-condensation is still unknown.

Table 2. Screening Catalysts of Aryl Boronic Acids[a]



D-Glucosamine hydrogen chloride

Deoxyfructosazine

Entry	Cat. [$ArB(OH)_2$]	Yield[b]
1	None	0[c]
2	Phenyl	68
3	2,5-$(MeO)_2C_6H_3$	60
4	4-^{i}PrOC_6H_4	57
5	2-$CF_3C_6H_4$	46
6	3,5-$(CF_3)_2C_6H_3$	69
7	2,3,4,5,6-F_5C_6	39
8	2-FC_6H_4	71
9	3-$HOOCC_6H_4$	59
10	4-$HOCH_2C_6H_4$	69
11	3-$NH_2C_6H_4$	76
12	4-Pyridyl	78

[a] Reaction conditions: D-Glucosamine hydrochloride (0.5 mmol) and $ArB(OH)_2$ (0.2mmol) were stirred in NaOH solution (6.5 mL; 0.1N) for 36 h at room temperature.

[b] Determined by crude ^{1}H NMR.

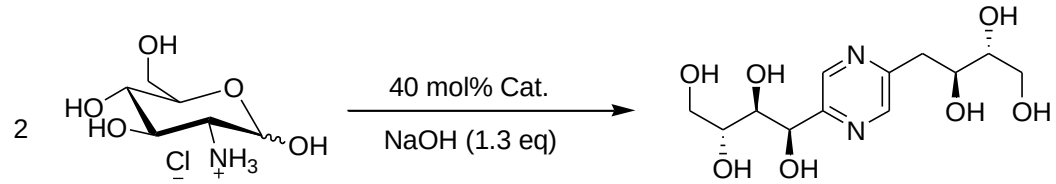
[c] Contains trace fructosazine.

Since catalyst optimization indicated that catalyst **1** and **2** showed better activity (**Table 2**), we further optimized reaction temperature in the presence of the two best catalysts as well as phenylboronic acid (**Table 3**). Initially a parallel study of self-condensation reactions with the three catalysts respectively (Entries 1 - 3, **Table 3**) was performed at 40℃ for 6 hours (Optimization of catalyst loading of $PhB(OH)_2$ at 40℃ sees STable 1 in supporting information); and yields of deoxyfructosazine were comparable to these achieved at room temperature for 36 hours (Entries 1, 10 and 11, **Table 2**). Prolonged reaction time to 12 hours only slightly improved yields for all reactions with three catalysts (Entries 4 - 6, **Table 3**). A further increase of temperature to 60℃ had remarkable impact on reaction efficiency and excellent yields of deoxyfructosazine (Entries 7 - 9, **Table 3**) were achieved for all three parallel reactions in 6 hours. To our excitement, the reactions still kept clean at 60℃; no fructosazine or other side products from decomposition of D-glucosamine was observed. Even though pyridylboronic acid catalyst **2** still showed the highest activity (Y: 89%), yield difference with either of catalyst **1** (Y: 86%) and phenylboronic acid (Y: 85%) became very

narrow. A further optimization on base use at 40℃ or 60℃ with 40 mol% $PhB(OH)_2$ and 40 mol% 3-$NH_2C_6H_4B(OH)_2$ as a catalyst showed similar trend with previous optimization at room temperature (detail sees **STable 2** in supporting information).

Because all yields of deoxyfructosazine were measured by crude ^{1}H NMR without internal standard, another two repeated reactions were carried out and their crude products were measured with pyrazine as internal standard for comparison. We repeated reactions in entry 7 as shown (with phenylboronic acid) and entry 8 (with 3-aminophenylboronic acid) in **Table 3** (the detail sees quantitative ^{1}H NMR Spectra in experimental section). The recalculated yield of repeated reaction in entry 7 with internal reagent was 74% (Y: 78% without internal reagent); the recalculated reaction yield of repeated reaction in entry 8 with internal reagent was 90% (Y: 84% without internal reagent). The little difference between yield measured w/o internal standard and that with internal standard for these two cases indicated the data obtained in the absence of internal standard is acceptable in accuracy for this particular condensation reaction. The excellent yields obtained under optimized conditions indicated this catalytic condensation in the presence of arylboronic acids are very promising for upgrade of D-glucosamine hydrogen chloride to value-added product deoxyfructosazine.

Table 3. Optimization on Reaction Temperature.



D-Glucosamine hydrogen chloride — Deoxyfructosazine

Entry	Cat. [$ArB(OH)_2$]	Temperature	Time (h)	Yield[a]
1	Phenyl	40℃	6	62
2	3-$NH_2C_6H_4$	40℃	6	69
3	4-Pyridyl	40℃	6	74
4	Phenyl	40℃	12	69
5	3-$NH_2C_6H_4$	40℃	12	70
6	4-Pyridyl	40℃	12	78
7	Phenyl	60℃	6	85
8	3-$NH_2C_6H_4$	60℃	6	86
9	4-Pyridyl	60℃	6	89

[a] Determined by crude ^{1}H NMR

Global glucosamine market (mainly D-glucosamine hydrogen chloride and D-glucosamine sulfate) was valued at 242.1 million USD in 2020[27], largely driven by supplement industry. Not surprisingly D-glucosamine hydrogen chloride was priced at only 131 USD for 500 g from TCI Chemicals (Aug. 23, 2021), meanwhile deoxyfructosazine was priced at 1695 USD for 50 mg (Aug. 23, 2021) from Toronto Research Chemicals. The huge price gap makes this arylboronic acids catalysis in water for upgrade of D-glucosamine for deoxyfructosazine very attractive. Although no online data is available for annul market size of deoxyfructosazine, we

estimated current market should be small from a fact that most of deoxyfructosazine was marketed at mg package online; however, the market is promising to grow quickly in the future regarding deoxyfructosazine's strong potential as a drug precursor and a raw material for speciality chemicals/smart functional materials (**Scheme 1**).

Reaction mechanism

Although boron acid-diol complexation[28,29] and arylboronic acid-monosaccharides[30,31] was extensively investigated in several recent reports, D-glucosamine was rarely included for these study and experimental data on complex of D-glucosamine-arylboronic acid was not yet known to our best of knowledge. Mechanistic understanding on how arylboronic acid interacts with D-glucosamine and subsequent interacts with condensation product deoxyfructosazine as well as dissociation/tranfer from deoxyfructosazine would be of much important to future design of more efficient arylboronic acid catalystic system.

For condensation pathway, It was proposed that an intermolecular nucleophilic cyclization of D-glucosamine in the presence of catalyst/promoter generates a dihydrofructosazine [2,5-bis(d-arabino-tetrahydroxybutyl)dihydropyrazine] intermediate via a dehydration process[13,14], and this intermediate was detected via mass spectrometry analysis[10,32] and ^{13}C NMR[32]. A subsequent dehydration and isomerization formed final product deoxyfructosazine. This pathway was initially proposed when deoxyfrutosazine was discovered[10] and was widely accepted as a consensus. All reported mechanistic study focused on boric acid, but it is well known that arylboronic acids and boric acid were very different on interaction of monosaccharides[33]. Regarding mechanistic understanding on the role of arylboronic acids catalysts in each step of condensation pathway is not yet studied, here some insights were achieved mostly from ^{1}H NMR study.

NaCl effect

Most of commercial D-glucosamine is available in salt form and D-glucosamine hydrogen chloride was usually used for self-condensation in the presence of NaOH in water; and it means 1 equivalent NaCl would be in-situ generated in aqueous solution. Our recent study on ^{1}H NMR elucidation of sugar-NaCl-water complexes[34] indicated both sodium cation and chloride anion played important role in perturbing hydrogen bonding network of monosaccharides and bulk water. In this study we also observed clear shifts on crude ^{1}H NMR spectra (page 14, supporting information) from control reaction with only D-glucosamine hydrogen chloride (page 6, supporting information) in NaOH solution (Entry 1, **Table 2**). Meanwhile a much bigger peak at δ 4.96 (proton of anomer position for beta-form) was observed proved that both NaCl and NaOH promoted anomerization of alpha-form to beta-form.

Interaction of arylboronic acid and D-glucosamine

^{1}H NMR tracking reaction at 40°C with phenylboronic acid or 3-$NH_2C_6H_4B(OH)_2$ or 4-Pyridyl$B(OH)_2$ as a catalyst (40 mol%) respectively at 30 mins, 3 hrs and 12 hrs as well as 30 mins after acidification was performed in order to get some clues on arylboronic acid-glucosamine complex (Spectra see 5.0 in supporting information). An obvious decrease on proton peak at anomer position of alpha-D-glucosamine was observed after 30 mins for three parrel reactions; meanwhile an obvious increase on proton peak at the same position after acidification. It suggested that proton at anomer position of alpha-form along with adjacent NH_2 group likely participated 1,2-*cis*-boronated ester bonding with one molecule of arylboronic acid; and such similar bonding at 1,2-*cis* position was determined in crystal of $(PhB)_2$(β-D-ArapH_4)[35] prepared with D-arabinose in the presence of two equivalents of phenylboronic acid. Very recently a 1:1 chelated chelated boron complex of alpha-D-glucosamine and boric acid at 1,2-*cis* position was also detected in d_6-DMSO via ^{1}H/^{13}C

NMR.[36] However, co-existence of alpha-anomer chelated boronic ester at 3,4-*cis* position was also highly possible although concentration might be much lower that of 1,2-*cis* chelated one due to stability difference. Interaction of arylboronic acid and beta-D-glucosamine was not observable in our ^{1}H NMR tracking reactions due to proton at anomer position overlapped with big water peak, a chelation at 3,4-*cis* position is more probably because two *cis*-hydroxyls are more favorable to form ester bonds[30,35] with phenylboronic acid.

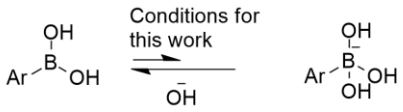
Interaction of arylboronic acid and deoxyfructosazine

Although three types of borate esters (1,2-bidentate, tridentate and 1,2-bidentate with interaction to nitrogen) were detected in solution of disodium tetraborate (excess)/glucosamine hydrogen chloride via ^{11}B/^{13}C NMR spectroscopy[13] in reported literature, in our study majority of deoxyfructosazine was in free form and only small portion of deoxyfrutosazine chelated with arylboronic acids based on crude ^{1}H NMR after 12 hrs before acidification (Figure 1) (5.0 in supporting information). There are three possible reasons for the observed difference: 1) only 40 mol% arylboronic acid was used in our systems meanwhile excess amount of disodium tetraborate was used in reported system; 2) arylboronic acids has less affinity compared to boric acid in chelation with monosaccharides according to results from known study;[30] 3) coordination of either arylboronic acids or boric acid with monosaccharides are very dependable on pH value of aqueous solution.[31,33]

Active arylboronic species

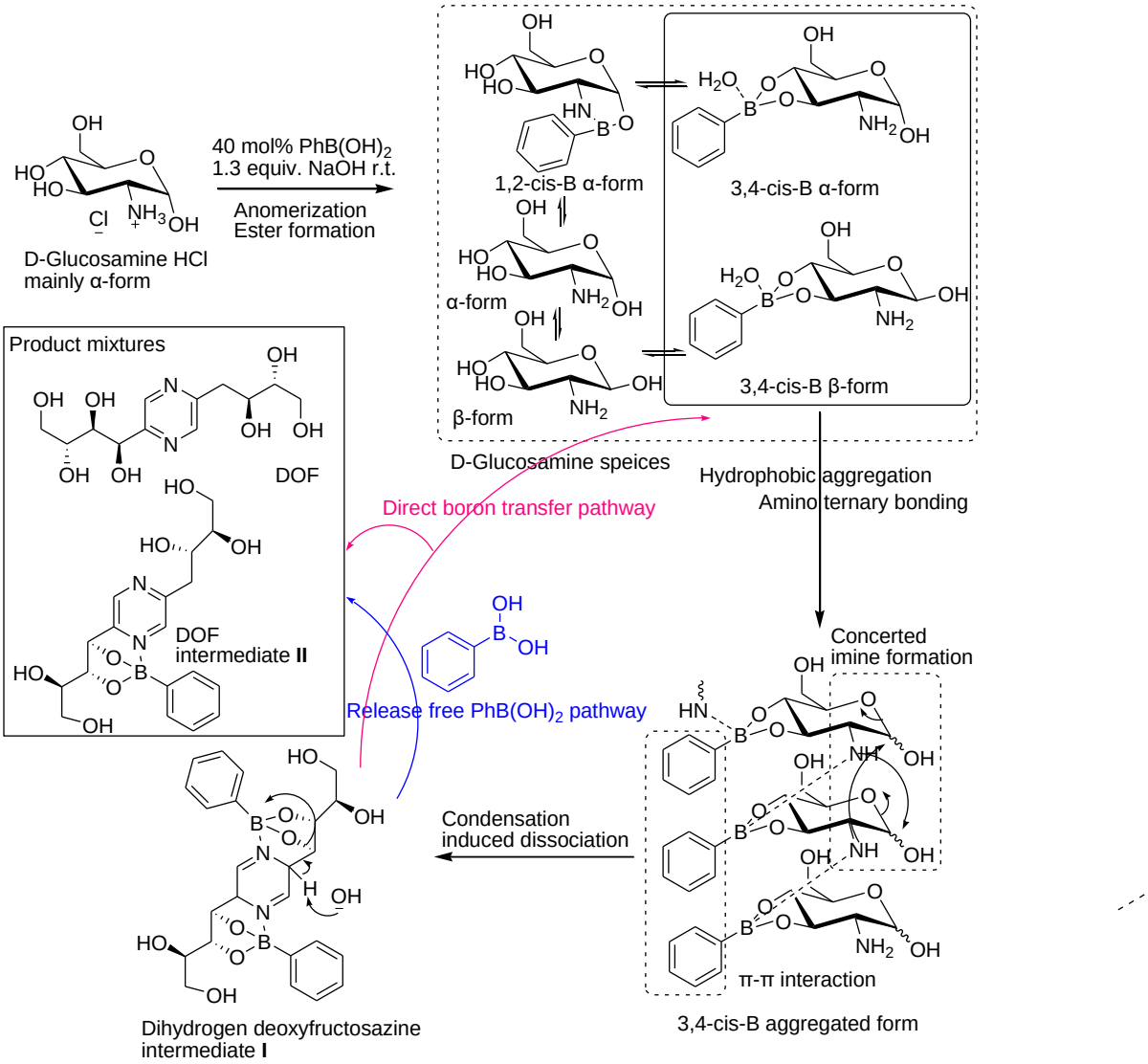
It is well known that arylboronic acids could switch from free acid form into their boronates form under basic condition, and the latter forms might also act as catalysts. In order to figure out which forms were the real active catalytic species, pH values were measured with pH meters for reaction media at 30 mins, after 3 hours and after 12 hours respectively when the reactions were stopped in the parallel reactions under 40°C (Entries 4 - 6, **Table 3**). pH Values ranging at 8.35 – 8.21 at 30 mins, values ranging at 8.07 – 8.00 at 3 hours and values ranging at 8.06 – 7.97 at 12 hours were obtained, and the results indicated reactions proceeded in neutral–alkaline solution (**Scheme 3**). According to pioneering mechanistic study between arylboronic acids and diols in aqueous solution by K. Ishihara[37], in neutral–alkaline solution order of kinetic reactivities of free boronic acid and its' hydroxyl form is $ArylB(OH)_2$>$ArylB^-(OH)_3$ (sometimes $ArylB(OH)_2$ > > $ArylB^-(OH)_3$). Hence arylboronic acids instead of their boronates were proposed as active catalytic species in glucosamine self-condensation although an equilibrated mixture of both forms existed dynamically in the aqueous solutions. The amount of NaOH in solution was crucial to enable occurrence of a catalytic cycle and overuse of NaOH could lead to formation of fructosazine byproduct.

Scheme 3. Active arylboronic species.



Reaction after 30 mins at 40°C; pH = 8.35 - 8.21
Reaction after 3 hrs at 40°C; pH = 8.07 - 8.00
Reaction after 12 hrs at 40°C; pH = 8.06 - 7.97

Scheme 4. Proposed boron transfer mechanism.



Proposed boron transfer mechanism

With clues in hand, here we proposed an arylboronic acid catalysis mechanism (**Scheme 4**) in which pH enabled boron transfer is a key for a catalytic cycle. Initially moderate water-soluble arylboronic acid (solubility in water: 10g/L, 20°C) reacted with highly hydrated D-glucosamine[34] forming three types of arylborate esters (1,2-*cis* chelated alpha-form, 3,4-*cis* chelated alpha-form and 3,4-*cis* chelated beta-form), in which anomerization of alpha-form to beta-form promoted mainly by NaCl and NaOH (arylboronic acid may also participate in promotion) occurred simultaneously. 1,2-*cis* chelated alpha-form was very stable and as a rest intermediate it was likely not involved in the condensation as depicted in literature[38]. These newly generated arylborate esters would become amphiphilic because of hydrophobic nature of aryl moieties, and they tend to aggregate due to hydrophobic effect and potential aromatic π-π interaction; ternary complexes might likely also form via intermolecular of amino functional group of glucosamine and such intermolecular coordination was known in literature[39]. Such hydrophobic aggregation might explain the accelerated rate of condensation in aqueous solution by arylboronic acid. In addition, the amino group or pyridine group of arylboronic acid moiety may also contribute to aggregation via intermolecular hydrogen bonding, lowering energy barrier. It might explain why with 3-$NH_2C_6H_4B(OH)_2$ or 4-pyridyl$B(OH)_2$ yield of deoxyfructosazine was remarkable higher at room temperature than that with any of other aryboronic acids; while the difference became much narrow when

temperature was increased to 60℃ (hydrogen bonding would be much weaker at high temperature). Such closer complexes would likely lead to imine condensation of two adjacent glucosamine moieties (they could be both alpha-forms or both beta-forms or a mixture) likely in a concerted manner because aldehyde peak from acyclic form of glucosamine was never observed in all ^{1}H NMR tracking reactions (5.0 in supporting information); however, we cannot rule out the possibility on reactions occurred in acyclic form[13,30] because open forms of monosaccharides were much more reactive even though in very low concentration. Then the newly generated six-membered ring of dihydrofructosazine [2,5-bis(d-arabino-tetrahydroxybutyl)dihydropyrazine] intermediate **I** may break the two arylborate esters from aggregated complexes because of steric effect. A subsequent chem-selective dehydration directed by arylboronic ester[40] occurred and this arylboronic acid may dissociate to be a free acid form or transfer to D-glucosamine raw material regenerating a glucosamine arylborate ester; then a followed isomerization generated arylboronic acid protected deoxyfructosazine intermediate **II**. Because of better water-soluble pyrazine moiety and seven hydroxyls, arylboronic acid protected deoxyfructosazine would have a stronger hydrate effect in water and tend to stay in bulk water; that could favor equilibration to an arylborate ester via direct boron transfer or dissociation to a free arylboronic acid followed with a chelation to glucosamine, completing a catalytic cycle. The existence of arylboronic acid is a key to push dihydrofructosazine intermediate to dehydration[40] (to deoxyfructosazine) rather than dehydrogenation (to fructosazine).

Conclusion

In summary, we developed an arylboronic acids catalyzed upgrade from D-glucosamine hydrogen chloride for DOF in aqueous media. DOF is proposed to be a promising bio-based platform molecule for new drug lead and design of speciality chemicals/functional materials in the future because of its unique structure containing pyrazine moiety and multiple hydroxyls. Regarding broad use of high-end speciality chemicals/functional materials, we envisage that this catalysis development could accelerate utilization of chitin via organic solvent free upgrade of its most commercially available monomer (D-glucosamine). Due to current difficulty and relatively high cost in hydrolysis of chitin and subsequent purification process, the price of D-glucosamine is still too high as a renewable nitrogen source to prepare most of amine raw materials in chemical industry; this proposed integration of DOF with renewable nitrogen into high-end speciality chemicals/functional materials looks more practical in the near future toward decarbonation in chemical industry.

Mechanistic study including NaCl effect, interaction of arylboronic acid with D-glucosamines, intermediates and DOF was also investigated for the first time. The hydrophobic aggregation promoted by boronic acids might explain the accelerated condensation rate and a pH enabled boron transfer via direct transfer or dissociation was a key for the catalysis cycle. Such new insights might be of much important for further improvement of this condensation process and design of new arylboronic acid for catalyzing selective monosaccharides transformations in aqueous media.

Supporting Information

The Supporting Information is available free of charge on this website.

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Author Contributions

L. Gu designed concept; M. Wang and G. Zhu carried out all experiments as well as collected all experimental data; both L.Gu and Y. Li supervised this project; L. Gu analyzed the data and drafted manuscript; All authors edited manuscript and had given approval to the final version of the manuscript.

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